ISSN 1679-4508

ALBERT EINSTEIN
INSTITUTO ISRAELITA DE
ENSINO E PESQUISA

einstein

volume 24, supplement 2, 2026

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International Congress EB 2026 Brazil,

January 20-22, 2026

SUPPLEMENT 2

e-ISSN: 2317-6385

einstein

Official Publication of the Instituto Israelita de Ensino e Pesquisa Albert Einstein

Instituto Israelita de Ensino e Pesquisa Albert Einstein
Sociedade Beneficente Israelita Brasileira Albert Einstein
Avenida Albert Einstein, 627/701 - building A, 2nd sub-basement, einstein journal - Morumbi
Zip code: 05652-900 - São Paulo - SP - Brazil
e-mail: revista@einstein.br Site: https://journal.einstein.br
Phone: (55 11) 2151-1233 - ext.: 70904/70902

Indexed in SciELO
Indexed in LILACS
Indexed in Emerging Sources Citation Index (Web-of-Science)
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Indexed in MEDLINE

Periodicity: continuous publication

einstein (São Paulo), v. 24, supplement 2, pages S1-S122, 2026

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einstein (São Paulo) - e-ISSN: 2317-6385 is a continuous publication journal published by the *Instituto Israelita de Ensino e Pesquisa Albert Einstein* - IIEP. Our journal publishes supplements. The statements and opinions contained in articles are solely responsability of the individual authors and not of the publisher or editors. Total or partial reproduction of manuscripts is allowed, once the source is cited. The electronic format, e-ISSN 2317-6385, is continuously published.

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Cover: Rudolf Serviços Gráficos

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Contents

einstein (São Paulo), v. 24, supplement 2, pages S1-S122, 2026

Welcome Address

CONTENTS

The EB 2026 Congress was held at the World Trade Center São Paulo, in São Paulo, Brazil, from January 20 to 22, 2026, marking the first edition of this international meeting to take place in South America. Organized by DEBRA Brasil, in partnership with DEBRA International and EB-CLINET, the congress represented a strategic milestone for the global Epidermolysis Bullosa (EB) community. Its realization in the Southern Hemisphere underscored the growing role of emerging regions in EB care, research, and advocacy, while reinforcing the importance of decentralized, collaborative, and globally inclusive scientific initiatives.

The congress brought together clinicians, researchers, patient organizations, and advocates from more than 50 countries, reflecting the successful execution and broad international reach achieved under the leadership of DEBRA Brazil. Collaboration with EB-CLINET – an international network dedicated to improving clinical standards, professional education, and multidisciplinary care in EB – was central to fostering scientific exchange and strengthening consensus-driven approaches to patient management. In parallel, DEBRA International played a key role in aligning global advocacy efforts, supporting professional consensus initiatives, and connecting national DEBRA organizations worldwide around shared priorities in research, access, and policy.

Following the main congress, the Innovation Arena took place on January 23, 2026, at the *Centro de Ensino e Pesquisa Albert Einstein*, as a strategically designed post-congress activity. This forum was conceived to synthesize key insights generated during EB 2026 and to identify the most relevant scientific, clinical, and structural themes likely to shape EB research, care models, and therapeutic innovation over the next ten years. By focusing on future-oriented discussions, the Innovation Arena aimed to highlight priority solutions and emerging directions for the EB field.

The Innovation Arena included the Rapid Fire session, designed to gather concise, high-impact perspectives from a diverse group of stakeholders across the EB value chain. Participants included healthcare professionals, academic and medical experts, biotechnology innovators, contract research organizations, industry representatives, investors, regulators, as well as patients, families, and advocates. A central element of the discussion was the contribution of the DEBRA Youth Council, which brought forward the perspective of young people living with EB, emphasizing lived experience, long-term disease burden, and expectations regarding future therapies. Complementarily, the perspectives of families and caregivers highlighted the daily challenges of care and the importance of holistic, patient-centered approaches.

Discussions during the Innovation Arena reinforced that, despite major advances in science and therapeutic development, effective interdisciplinarity in EB care and research remains a significant unmet challenge. The complexity of EB requires coordinated efforts across dermatology, pediatrics, surgery, pain management, nutrition,

psychology, rehabilitation, oncology, regulatory science, and health policy. Advancing truly interdisciplinary and integrated models of care and research was identified as essential for translating innovation into meaningful and sustainable clinical impact and for improving long-term outcomes for individuals and families affected by EB.

Organizers of EB 2026

Editorial

CONTENTS

Epidermolysis bullosa and global challenges in translational research for rare diseases

Priscila Keiko Matsumoto Martin [1,2], Laurent Ketlen Leão Viana[1], Mel Dominici Sanfins[3]

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DOI: 10.31744/einstein_journal/2026Suppl_2ED0001

Rare diseases collectively affect hundreds of millions of individuals worldwide; however, each condition individually faces substantial barriers to research, innovation, and equitable access to therapies. Accelerating and promoting research in rare diseases is therefore not only a scientific necessity but also a public health and ethical imperative. Limited funding, small patient populations, fragmented expertise, and complex regulatory and reimbursement pathways frequently delay the translation of scientific advances into tangible clinical benefits, particularly outside high-income regions. Even when innovative therapies receive regulatory approval, access often remains restricted to a small number of countries, reinforcing global disparities. Epidermolysis Bullosa (EB) exemplifies these challenges while simultaneously serving as a paradigmatic model for advances in gene therapy, regenerative medicine, and precision therapeutics.

Epidermolysis Bullosa is a group of rare, inherited genetic disorders characterized by marked skin and mucosal fragility, leading to blistering and erosions following minimal mechanical trauma. EB results from pathogenic variants in genes encoding structural components of the dermal–epidermal junction, including *KRT5* and *KRT14* (EB simplex), *LAMA3*, *LAMB3*, and *LAMC2* (junctional EB), *COL7A1* (dystrophic EB), and *FERMT1* (Kindler syndrome), among others. According to the level of tissue cleavage, EB is classified into four major types: EB simplex, junctional EB, dystrophic EB, and Kindler syndrome, each associated with distinct molecular mechanisms and clinical phenotypes.[1-3]

EB is a multisystem disorder with significant extracutaneous involvement, affecting the gastrointestinal tract, oral cavity, eyes, musculoskeletal system, kidneys, and cardiovascular system. Severe forms, particularly recessive dystrophic EB (RDEB) and junctional EB, are associated with chronic non-healing wounds, recurrent infections, malnutrition, progressive fibrosis, and a markedly increased risk of aggressive cutaneous squamous cell carcinoma, a leading cause of premature mortality in this population.[4,5]

Although the majority of EB research, clinical trials, and advanced therapeutic development remains concentrated in

How to cite this article:
Martin PK, Viana LK, Sanfins MD. Epidermolysis bullosa and global challenges in translational research for rare diseases [editorial]. einstein (São Paulo). 2026;24(Suppl 2):eED0001.

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North America and Europe, Latin America has made relevant progress in genetic mapping, molecular diagnosis, and clinical characterization of EB patients. Regional reference centers and collaborative initiatives have contributed to improved genotype–phenotype correlations and the establishment of patient cohorts. Despite these advances, patients from Latin America still face substantial barriers to inclusion in global clinical trials and early access to innovative therapies. Ongoing regional efforts seek to integrate these patients into international research networks and to facilitate the introduction of new therapeutic solutions.

Over the past two decades, EB research has expanded considerably, encompassing basic disease mechanisms, wound healing biology, fibrosis, carcinogenesis, and pain and itch pathways. Translational efforts include gene replacement and gene editing strategies, RNA-based therapies, protein- and cell-based approaches, and the development of viral and non-viral delivery platforms.[6-12] These advances have positioned EB at the forefront of cutaneous gene therapy research.

Clinical development has recently led to the approval of the first disease-modifying gene-based therapies for EB. However, these achievements have also highlighted profound global inequities. Vyjuvek™ (beremagene geperpavec), a topical gene therapy for dystrophic EB, was approved by the U.S. Food and Drug Administration in 2023, yet it remains unavailable to most patients in the Southern Hemisphere. Zevaskyn™ (prademagene zamikeracel), an autologous ex vivo cell-based gene therapy, is currently approved only in the United States and has an estimated cost exceeding three million US dollars per patient. In addition to cost, this therapy requires highly specialized manufacturing infrastructure, complex logistics, and prolonged hospitalization, representing major barriers to implementation in low- and middle-income countries. To date, scalable solutions enabling broad deployment of these therapies outside high-income regions remain limited.[13-15]

Promoting and valuing research in regions such as Latin America – through targeted funding, genuine international collaboration, capacity building, and regulatory alignment – represents a critical strategy to reduce these disparities. Facilitating access to therapies already approved in the United States and Europe may help bridge the gap between scientific innovation and patient benefit while strengthening local healthcare systems and regulatory pathways.[16]

Within this context, the EB2026 Congress was conceived as a platform to foster discussion on accelerating research, innovation, and access in EB. Its objectives included bringing together experienced investigators and researchers from other scientific disciplines, promoting interdisciplinary dialogue, and organizing forums involving clinicians, researchers, allied health professionals, and patient advocates. A central goal was to position the EB community as active protagonists in defining unmet needs and priorities, thereby contributing to the development of more inclusive, equitable, and globally relevant strategies for EB and other rare diseases.

DATA AVAILABILITY

The content is already available.

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CONTENTS

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The Scientific Committee would like to express its sincere appreciation to the invited reviewers who generously contributed their time, expertise, and scientific rigor to the evaluation of abstracts submitted for oral presentations. Their commitment was essential to ensuring the high scientific quality of the program and the excellence of the selected works.

We gratefully acknowledge the following reviewers:

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CONTENTS

Scientific Program

January 20st 2026 | 7:30-22:30

Start	End		
07:30	08:00	**Registration**	
08:00	08:30	**Opening of EB2026** |Leandro Rossi, Ritu Jain and Sophie Kitzmuller **(Theater)** **Acknowledgement Sponsors / Organizers / Partners / Scientific Committee / Invited Reviewers**	
08:30	10:10	**1st Session Genetics and Diagnostics (Theater)** • Diagnostic challenges of rare forms of EB | **Cristina Has** • Importance of genetic diagnosis for disease management | **Ghada El-Kamah** • The diagnostic journey in epidermolysis bullosa: the Dutch experience | **Peter van den Akker** • TEM and IEM in diagnosis and therapy responses of DEB | **Douglas R. Keene** • Atypical and rare variants of epidermolysis bullosa simplex: clinical and genetic insights | **Liat Samuelov** • Oral Abstract: Immunofluorescence Mapping vs. Electron Microscopy in Epidermolysis Bullosa Comparative Retrospective Study in 84 Genetically Confirmed Patients in Australia | **Nicole Tomas** • Oral Abstract: Genotype-Phenotype Correlations in Dystrophic Epidermolysis Bullosa| **Kun Zhan** Discussion | **all speakers**	**Debra International: Ibero-American Voice (Curitiba Room)** This session, *"The Ibero-American Network,"* will present the organic development of a virtual support network that connects DEBRA organizations, medical specialists, caregivers, and people living with EB across Ibero-America. Panel: • **Evanina de Morcillo Makow (Debra Spain)** • **Setsuko Shiraishi (Debra Mexico)** • **Graciela Manzur (Argentina)** • **Ana Maria Gonzalez (Debra Chile)** • **Liliana Consuegra (Debra Columbia)** • **Jeanine Magno (Brazil)**
10:10	10:20	**Diamond sponsor: CHIESI (Theater)** Giacomo Chiesi, Executive Vice president of Chiesi Global Rare Diseases	
10:20	10:40	**Coffee Break**	
10:40	12:40	**Open FORUM: Active health promotion in EB** (until 12:40) **(Theater)** • **Jennifer Chan**	**Professionals FORUM: Nutrition in EB (Curitiba Room)** • **Nutritional Management of Pediatric EB patients: Brazilian Experience and Clinical Cases** **Ana Paula Caio Zidorio**, PhD – Brazil EB Dietitian and President of Multidisciplinary Team for Care of People with EB/ Hospital Universitario de Brasília Debra Brazil Volunteer • **Nutritional Aspects of Epidermolysis Bullosa in Adults: Clinical Experience in a Brazilian Tertiary Hospital** **Maria Efigênia de Queiroz Leite** – Brazil EB Dietitian Universidade Federal da Bahia • **Nutrition and EB: Perspectives and Clinical Experiences Body Image, Appetite, and Sensory Perception in People with EB: What Nutrition Still Fails to See** **Marcela Peres Rodrigues Madureira** – Brazil EB Dietitian PhD student/ Universidade Estadual Paulista • **Assessing the Need for Gastrostomy in Children with EB** **Rosie Jones** – United Kingdom EB Dietitian/Birmingham Women's and Children's Hospital NHS • **Swallowing the Truth: Are Supplements the Secret Sauce** **Marie Fitzpatrick** - United Kingdom Principal Dietitian for Epidermolysis Bullosa at Guy' and St Thomas' Hospital NHS • **Living with EB: A Personal Experience with Food and Nutrition** **Anna Carolina Rocha** – Brazil Person with EB and Researcher
12:40	13:10	**DEBRA International: International EB Community Advisory Board (EB CAP)** • **Rainer Riedl**	

Start	End		
13:10	14:25	**Conference Lunch: Sponsored by Abeona** **Pz-cel (prademagene zamikeracel):** **An autologous cell sheet-based gene therapy with proven wound healing in recessive dystrophic EB (RDEB) | Dr. James Gow** SVP, Clinical Development & Medical Affairs Clin Ops	
14:25	15:25	**DEBRA International: Priority Settings Networking Session** & **JLA overview** (Theater) **Networking session** Started at EB Congress in Cairo 2024, to regularly question and define the top 10 Priorities in EB for attendees of International EB Congresses. Group lived experience with clinical, research and others. • **Ignacia Fuentes**, Ph.D., supported by Debra International Executive Directors and Debra International Youth Council **JLA Review** Research priorities based on key unanswered EB questions shared by the global EB community for EB Simplex (EBS), Dystrophic EB (DEB), Junctional EB (JEB) and Kindler (KEB). What's next? Project lead by Debra UK, and supported by Cure EB, Debra Ireland, Debra Canada, EB Research Partnership and Debra International. • **Dr. Irene Lara-Corrales, (Sick Kids** & **Debra Canada)**	
15:25	18:25	**Open FORUM: Philanthropic research support for future cures in EB** (Theater) • A global collaboration for people living with EB| **Martin Steiner and Francis Palisson** • DEBRA Research; Strategy and progress | **Christoph Coch** • The pre-clinical opportunity | **Emanuel Rognoni** • The role for a disease atlas in rare disease | **Ines Sequeira** • Driving drug development |**Cristina Daniele and Christoph Coch** • Panel discussion| **Martin Steiner and Francis Palisson** • Big steps forward with data | **Hubert Truebel and Anna Bruckner** • Outcome measures and planning for the regulators | **Marieke Bolling and Nicky Bush** • From local to global data – registry and patient platform | **Anna Bruckner, Jemima Mellerio, Peter Walton, Caroline Collins, Michael Hund and Ritu Jain** • Panel discussion and call to action | **Hubert Truebel and Anna Bruckner**	**Professional FORUM: Psychological support in EB** (Curitiba Room) • **Jodie Fellows and Michelle Lahat** **Presentations by Gudrun Salamon and Petra Hitthaler-Waigner, Diedre Callis, Alejandra Livschitz and Joanna Willen**
16:30	16:50	**Coffee Break –** in between forums	
20:00	22:00	**Welcome Cocktail Reception**	

January 21st 2026 | 8:00-19:00

Start	End		
08:00	10:30	**DEBRA International (Theater)** **8h00** **Empowering Voices Forum Caring Together: Patients, Families & Clinicians** This forum highlights the voices of those living with EB and their caregivers, as well as their interaction with healthcare professionals. Bringing these perspectives together shows how care decisions are balanced between families and healthcare professionals, and how country-specific conditions (access to specialists, materials, referral centers, and psychological support) shape the experience of EB. • **Ritu Jain** (President Debra International, Debra Singapore) Panel: • Caregiver's Perspective: **Angelique Sauvestre** (Debra France/International) and **Ryan Hultman** (Debra Canada/International) • Lived Experience: **David Santiago Vargas** (Colombia RDEB), **Martin Guadalupe** (Mexico DDEB). **8h35** **Youth Council Forum** This session brings together DEBRA Jovem Brazil and the DEBRA International Youth Council for a dynamic, youth-led conversation about what it means to live beyond the skin and how young advocates are shaping the future of EB community. **Youth Leaders – Toni Roberts, Imtishan Rafiq, Lena Riedl, Rodrigo Sousa, Emily Boros-Rausch, Giulia Victoria, Ida Steinlein and Paulina Verdugo.** **9h10** **CPG Status and future prospects** Overview of project current, past and next steps. Progress and importance of information to reach high, medium and low resource medical systems. • **Dr. Irene Lara-Corrales** (Sick Kids & Debra Canada) • support by **Sophie Kitzmuller**, PhD. (EB Academy & EB Clinet) **9h20** **Pharma and Research Perspectives** **From Participants to Partners: Empowering Patients in EB Clinical Trials.** Provide diverse views and perspectives for Debra/EB to support future care in EB. • Introduction: **Elena Pope** • The patient perspective: **Lena Riedl** (Debra Austria, DIYouth), • The patient organization perspective **Ignacia Fuentes** *(DEBRA Chile)* • The Clinician perspective: **Anna Bruckner** • The Industry perspective: Rachele Berria (**Chiesi)** • The Biotech perspective: **Helene Hartman** (CEO Xinnate)	**Professionals FORUM: Wound care and Nursing in EB (Curitiba Room)** Types of EB & Diagnosis Skin & Wound Care Pain, Nutrition & Blood Tests Psychosocial Support & Transition Sexual Health & Cultural Care Workforce & Collaboration Group Discussion & Forum • **Kalsoom Begum and Catalina Hubner** • **María Helena S. Mandelbaum, Annette Downe and Janet Hanson**
10:30	10:50	**Coffee Break**	

Start	End		
10:50	12:30	**2nd Session EB skin, mucosae and its challenges (Theater)** • Concordance Between Next-Generation Sequencing and Conventional Clinical/Lab based Diagnostic Approaches in Epidermolysis Bullosa | **Rahul Mahajan** • Dupilumab in RDEB: Breaking the Cycle of Pruritus and Skin Fragility | **Renata Rodrigues and Jeanine Magno** • Skin care and wound management in EBS | **Anna Bruckner** • Laparoscopic-assisted gastrostomy in EB | **Giampiero Soccorso** • Amelogenesis imperfecta in EB | **Susanne Krämer** • Oral abstract: Mental Health in Epidermolysis Bullosa Psychological Care for Patients and Their Families | **Gudrun Salamon Petra Hitthaler-Waigner** • Oral abstract: Low-level laser therapy in Junctional Epidermolysis Bullosa | **Susanne Krämer** • Discussion | **all speakers**	**DEBRA International: EB without borders, how to go further together (Curitiba Room)** This workshop is designed to present History, present and future goals of this Debra International group. Define continued outreach and program viability. • **Evanina de Morcillo Makow** • **(Debra Spain), Emeline Baillargeault (Debra France), Vlasta Zmazek (Debra Croatia) and Ritu Jain (Debra Singapore)**
12:30	13:45	**Conference Lunch: Sponsored by Chiesi** **CHIESI-SPONSORED LUNCH PANEL** **From Voices to Vision: Building the Future of EB Together** **Join us for an engaging session** featuring a live interview with a Brazilian patient and a healthcare professional, exploring the daily care burden, psychological impact of EB, significant comorbidities such as squamous cell carcinoma, nutritional issues, and the need for multidisciplinary support. Gain practical insights into resilience and collaboration with care teams, then hear from a multi-stakeholder panel as they address systemic gaps and share solutions to improve diagnosis, shared decision-making, and patient involvement in future research priorities. **Be part of this conversation and help shape a more inclusive future for EB care.** **Agenda** Welcome and Introduction | **Su Lwin** Living with EB: Rodrigo's Story| **Su Lwin** & **Rodrigo Sousa** Together for EB: Panel Discussion | **All panelists** Closing Remarks | **Su Lwin** & **all panelists** **Chair: Dr Su Lwin** (St John's Institute of Dermatology, Kings College London, UK) **Leandro Rossi** (President of DEBRA Brazil and Treasurer of DEBRA International **Rodrigo Sousa** (Advocate living with EB) **Dr Lara Wine Lee** (Dermatology and Dermatologic Surgery, Medical University of South Carolina, USA) **Stuart Siedman** (Vice President, Global Patient Advocacy, Chiesi GRD)	
13:45	15:25	**3rd Session Basic Science for the Understanding of EB (Theater)** • From observations to improvements: pre-clinical models in translational EB fibrosis research | **Alexander Nyström** • Utilizing discarded dressings to understand wound resolution in EB | **Ignacia Fuentes** • Notch signaling in RDEB fibrosis| **Angelo Condorelli** • Airway involvement in JEB and potential therapeutic approaches | **Robert Hynds** • Lessons from basement membrane biology | **Peter Marinkovich** • Oral abstract: The EB Cell Atlas: A Framework for Translational Drug Discovery | **Christina Guttmann-Gruber** • Oral abstract: Improving skin regeneration in JEB by targeting the integrin αvβ6 | **Viktorija Lapinska** • Discussion | **all speakers**	**DEBRA International: Medium resource groups (Curitiba Room)** To foster growth and sharing of ideas to enable established and potential member DEBRA/EB groups to benchmark, develop and strengthen their organizations. Enhance a strong international network in EB for advocacy, healthcare, social support and national membership needs. • **Erin Hoyos (moderator – Debra Canadá)** • **Vlasta Zmazek (Debra Croatia)** • **Emeline Baillargeault (Debra France)** • **Leandro Rossi (Debra Brazil)**
15:25	15:45	**Coffee Break**	

Start	End		
15:45	17:30	**4th Session Preclinical studies Part 1 (Theater)** • Base-Editing Gene Therapy Development for the Most Common Pathogenic COL7A1 Variant in Brazil | **Priscila Matsumoto** • Targeting inflammation in DEB with biologics and cellular therapies | **Yanling Liao** • Readthrough therapies for DEB and JEB - a critical update | **Yanling Liao** • Systemic administration, yet skin-selective therapy for DEB | **Tero Järvinen** • Keratinocyte Dysfunction as a Driver of Chronic Pain in RDEB | **Margarita Calvo** • Oral abstract: KLHL24 Mutation Drives Intermediate Filament Degradation, Mitochondrial Dysfunction and Fibrosis in heart failure patients | **Veronika Ramovs** • Oral abstract: Identifying Molecular Signatures of Disease Heterogeneity in Epidermolysis Bullosa | **Priya Garcha** • Discussion | **all speakers**	**Professionals FORUM: Palliative and end-of-life care in EB (end: 18:15) (Curitiba Room)** • Demystifying Palliative and End-of-Life Care: Optimizing Quality of Life | **Mark Popenhagen** • End-of life care across-cultures, and beyond EB | **Nicholas Schräder**
17:30	17:45	**Award Presentation:** The Jouni Uitto, MD, PhD, international Visiting Professorship Lectureship in Molecular Dermatology • **Dr. Andrew P South**	
17:50	19:10	**Poster Viewing Session Day 1: Networking with drink and snacks**	

January 22nd 2026 | 8:30-20:30

Start	End		
08:30	10:15	**5th Session Preclinical studies Part 2 (Theater)** • Biofilm and wound infection in Epidermolysis Bullosa | **Zlatko Kopecki** • Patient-Derived Samples as a Prerequisite for Pre-Clinical Research | **Christina Guttmann-Gruber** • Gene editing for type XVII collagen deficient JEB | **Ulrich Koller** • Autologous iPSC derived skin grafts for DEB treatment | **Anthony Oro** • Prime-edting for treatment of DEB | **Mark Osborn** • Splice modulation strategies using antisense oligonucleotides for Recessive Dystrophic Epidermolysis Bullosa | **Matthias Titeux** • Oral abstract: N-Acetylcysteine as a therapeutic candidate for RDEB wound healing | **Evelyng Catalán** • Discussion | **all speakers**	**DEBRA International: High resource groups Curitiba Room** To foster growth and sharing of ideas to enable established and potential member DEBRA/EB groups to benchmark, develop and strengthen their organizations. Enhance a strong international network in EB for advocacy, healthcare, social support and national membership needs. • **Angelique Sauvestre** (moderator) • **Rainer Riedl (Debra Austria)** • **Anita Gonzales (Debra Chile)** • **Deirdre Callis (Debra Ireland)** • **Oral presentation:** Living with Dystrophic Epidermolysis Bullosa in Poland First National Assessment of Quality of Life and Clinical Burden |**Natalia Bien**
10:15	10:40	**Coffee Break**	
10:40	12:40	**6th Session Cancer Therapies (Theater)** • Mechanisms underlying aggressiveness of RDEB-associated cSCCs| **Andrew P. South** • Squamous Cell Carcinoma in Chilean EB patients: A retrospective study of 27 years | **Francis Palisson** • Using Artificial Intelligence for SCC detection in RDEB | **Antonia Reimer-Taschenbrecker** • Current treatment standards for EB-SCC treatments | **Jemima Mellerio** • cSCC in Kindler syndrome - underlying pathomechanism | **Valerie Brunton** • Walking on Glass: Safely Delivering Cancer Therapy in EB | **Erica Koch** • Emerging Therapies for RDEB-SCC: a US Adult EB Clinic Experience | **Andrew P. South** • Oral abstract: Towards a minimally invasive diagnostic for early detection of cancer in Recessive Dystrophic | **Albert Mellick** • Discussion | **all speakers**	**DEBRA International: Low resource groups Curitiba Room** To foster growth and sharing of ideas to enable established and potential member DEBRA/EB groups to benchmark, develop and strengthen their organizations. Enhance a strong international network in EB for advocacy, healthcare, social support and national membership needs. • **Jimmy Fearon (moderator)** • **Graciela Manzur (Argentina)** • **Lilliana Consuegra (Debra Colombia)** • **Setsuko Shiraishi (Debra Mexico)** • **Toni Roberts (Debra South Africa)**
12:40	13:00	**COSEB Project** **Peter van den Akker and Dimitra Kiritsi**	
13:00	14:15	**Conference Lunch**	
14:15	15:45	**7th Session Clinical Trials Part 1, Corrective Therapies (Theater)** • Clinical Trials for RDEB Using Skin Grafts Modified with SIN Retroviral Vectors | **Alain Hovnanian** • Gene therapies for EB | **Peter Marinkovich** • Clinical trial for treating eye manifestation in DEB patients by delivering COL7A1 gene| **Suma Krishnan-** • Oral abstract: COL7A1 c.6527dupC (insC) A translational Journey from early Diagnosis to Prime Editing | **Fernando Larcher** • Oral abstract: Highly efficient correction of recurrent pathogenic variants in COL7A1 using Cytosine or Adenine Base editing to treat recessive dystrophic epidermolysis bullosa | **Araksya Izmiryan** • Oral abstract: Development of a Dual CRISPRCas9 Nickase Strategy for COL7A1 Correction in a Prevalent Brazilian Pathogenic Variant of Recessive Dystrophic Epidermolysis Bullosa | **Laurent Ketlen Leão Viana** • Discussion | **all speakers**	**Youth Council Workshop Curitiba Room** Additional Activities for youth EB community
15:45	16:05	**Coffee Break**	

Start	End	
16:05	18:00	**8th Session Clinical Trials Part 2, Symptomatic Therapies (Theater)** • Systemic disease-modifying options for EB: use of losartan and ABCB5+ mesenchymal stem cells | **Dimitra Kiritsi** • Currently tested agents for itch relief | **Elena Pope** • Challenges and Updates on EBS Clinical Trials | **Joyce Teng** • Oleogel-S10 real life experience | **Mauricio Torres** • TCP-25, an immunomodulatory peptide in phase 2/3 clinical development targeting dysregulated inflammation in EB wounds | **Artur Schmidtchen** • Oral abstract: Pilot Study of ELK-003 Eye Drops for Treating Ocular Manifestations of Epidermolysis Bullosa (GOTAS-ELK-EB) | **Francis Palisson** • Oral abstract: Repurposed treatment with losartan in children with severe forms of epidermolysis bullosa: effect on nutritional, growth, and hematological parameters, and iScorEB | **Mariana Rivera-Salazar** • Discussion | **all speakers**
18:00	18:45	**Special Closing Session: Harnessing global policies for improved healthcare access (Theater)** A policy-focused panel discussion on the integration of EB in the planning of national healthcare and social services worldwide; leveraging recent international policy frameworks (Universal Health Coverage, the UN Resolution on Rare Diseases, and the recent WHA Resolutions on Rare Diseases, Skin Diseases, and Diagnostics) and policy models in countries with advanced EB care and health access. • **Yann Le Cam (Moderator),** Founder & Past-CEO of EURORDIS – Rare Diseases Europe, Co-Founder of Rare Diseases International, Vice President of the UN NGO Committee for Rare Diseases • **Ritu Jain,** President of DEBRA International, Council member of Rare Diseases International • **Leandro Rossi,** President DEBRA Brazil, Executive Board member for DEBRA International • **Antoine Daher,** President of Casa Hunter, Council member of Rare Diseases International • **Mariangela Pellegrini,** Executive Director of DEBRA International
18:45	19:00	**Closing session** • **Leandro Rossi**
19:00	20:30	**Poster Viewing Session Day 2: Networking, drink and snacks**

January 23rd, 2026 | 9:00-13:00

Innovation Arena
Venue: Albert Einstein Educational and Research Center
Camila Bueno Theater – 2nd floor
Adress: Rua Comendador Elias Jaffet, 755 – Morumbi - São Paulo/SP

Start	End	
09:00	09:10	**Introduction** **Leandro Rossi, Jemima Mellerio and Peter Marinkovich**
09:10	10:00	**Rapid-Fire Stakeholder Insights: What Must We Achieve in the Next 5 Years to Enable Curative EB Solutions by 2035?** **Lena Riedl, Alex Hersham, Ignacia Fuentes, Robert Ryan, Ricardo Weinlich, Cristina Danielle, Michael Hunt, Sharmila Nikapota**
10:00	10:30	**Q&A session**
10:30	11:00	**Coffee break**
11:00	12:30	**What are the keycurrent blockers in the fly wheel and how are we going to address them in the next 5 years?** **Moderator: Alex Hersham**
12:30	13:00	**Our Call to Action: The Strategic Framework for the EB Ecosystem** **Moderator: Peter Marinkovich and Jemima Mellerio**

CONTENTS

Presentation Abstracts

001

A novel *KRT5* variant in a multi-generational family affected by epidermolysis bullosa simplex

Iyla Draw[1], Beth Moeves[2], Kalyani Marathe[2], Sarah Crawford[3]

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ABSTRACT

Epidermolysis bullosa simplex (EBS) is the most common subtype of inherited epidermolysis bullosa, a group of inherited skin and fragility disorders characterized by non-scarring bullae and erosions in response to minor mechanical trauma. The blistering occurs within the basal epidermis due to keratinocyte cytoskeletal instability. The *KRT5* gene encodes keratin 5, which partners with keratin 14 (*KRT14*) to form type II intermediate filaments in basal keratinocytes. Pathogenic variants in *KRT5* destabilize this network, leading to intraepidermal blistering. This study reports a familial case of EBS related to a *KRT5* intronic deletion that has not been previously described in the literature.

An 11-month-old male presented with blistering localized to the great toes, fifth toes, and arches of the feet without involvement of the hands. Symptoms began at 5-6 months of age and occurred in the absence of secondary infection. On clinical examination, the patient exhibited well-defined bullae without evidence of scarring or mucosal involvement. He demonstrated no other systemic symptoms such as poor growth or developmental issues. The family history was notable for a strong multigenerational pattern of similar bullae involving the hands, feet, and occasionally the knees and elbows, with at least five generations reportedly affected. Genetic testing with a comprehensive EB gene panel identified a variant of uncertain significance (VUS) in *KRT5 c.928-7_928-3del*, an intronic deletion predicted to impact the canonical splice acceptor site. While insufficient evidence currently exists to classify this variant as pathogenic, the combination of its predicted effect on gene function and the extensive family history suggest it underlies the EBS phenotype in this family. Familial cascade testing demonstrated that the proband's father, paternal grandmother, and paternal great-grandfather harbored the same variant. The pedigree pattern was consistent with autosomal dominant inheritance. This case highlights the clinical and molecular significance of a novel intronic deletion in *KRT5* associated with EBS. Mutations in *KRT5* are well-established as causative for EBS, with the majority being missense variants. However, deletions remain less frequently reported and their genotype-phenotype correlations are incompletely characterized. The *KRT5 c.928-7_928-3del* variant has not been previously reported in the literature. Although classified as a VUS, its predicted impact on splicing, strong family history, and phenotype consistent with EBS supports a pathogenic role. Continued documentation and functional characterization of such variants are essential for refining genotype-phenotype correlations and improving patient care in EBS.

Presentation Abstracts

CONTENTS

002

A validated human skin wound healing model as a basis for developing an epidermolysis bullosa disease platform

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ABSTRACT

Epidermolysis bullosa (EB) is a group of inherited blistering disorders caused by mutations in structural proteins of the dermal–epidermal junction, leading to skin fragility, recurrent blistering, and impaired wound healing. Progress in therapeutic development is limited by the lack of robust preclinical models that accurately reproduce EB pathology while enabling safe and scalable drug testing.

At REVIVO BioSystems, we have established a validated wound healing model based on REVskin, our proprietary full-thickness human skin equivalent. This model employs a standardized 3 mm blister-like wound that preserves dermal integrity and reliably mimics the structural and healing context of EB lesions. It has already been used to demonstrate the efficacy of selected active compounds in promoting wound closure, confirming its translational relevance. Barrier restoration is quantitatively assessed through on-chip caffeine permeation assays, providing dynamic and sensitive readouts of stratum corneum recovery during healing.

We now propose to extend this platform into an EB-specific disease model. The model can be established either by incorporating patient-derived keratinocytes and fibroblasts, by genetically modifying wild-type cells using CRISPR-Cas9 technology to introduce disease-causing mutations, or by using existing reconstructed skin models that simulate EB. This will enable precise recreation of patient phenotypes, including delayed wound closure, blister persistence, and defective barrier repair, within a controlled and reproducible setting. Such a system will support the screening of drug libraries and large-scale preclinical studies, offering a safe and scalable alternative to early-stage patient exposure and minimizing risks from adverse side effects.

By bridging a validated wound model with advanced genetic engineering and functional barrier assays, our proposed EB disease model offers a powerful tool to accelerate drug discovery, provide mechanistic insights into disease progression, and de-risk therapeutic development for EB patients.

003

Access to atraumatic dressings and supply needs in epidermolysis bullosa care in Alagoas, Brazil: findings from a cross-sectional survey with pain and quality-of-life measures

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ABSTRACT

Introduction: Regular access to atraumatic dressings is essential to minimize iatrogenic trauma and pain in EB care. In Brazil, supply through the public health system (SUS) is inconsistent and often depends on litigation or donations.

Objective: To describe access to atraumatic dressings and related supplies, estimate consumption patterns, and report pain and quality-of-life outcomes among individuals with EB in Alagoas.

Methods: A cross-sectional survey was conducted with 13 respondents identified through the state reference service. Data included sociodemographics, access to dressings (SUS, litigation, donations), frequency and quantity of dressing changes, and validated instruments: QoLEB (adults), CDLQI (children), Visual Analog Scale (VAS), and Brazilian McGill Pain Questionnaire (Br-MPQ). Descriptive statistics were applied.

Results: Nine of 13 participants (69.2%) reported access to atraumatic dressings; all seven who received supplies from SUS were in this group, and 8/9 (88.9%) required litigation. One case relied on NGO donations. Most reported daily changes (7/9), with a median of seven dressings per change; estimated median consumption was 42 dressings per patient per week (≈399/week for the group). Common products were Mepilex Transfer and Mepilex AG; frequent complementary items included hypochlorous acid or PHMB antiseptics and tubular bandages. QoLEB scores (adults, n=9) had a median of 40 (severe to very severe impact), and CDLQI (children, n=4) had a median of 19. Pain assessment: VAS median 0 (mean 1.85), IAD median 0 (mean 0.85). McGill Total median was 23 (mean 22.1; n=11), with domain medians: Sensory 11, Affective 3, Evaluative 3, Miscellaneous 3. Participants with access showed higher McGill and VAS scores (e.g., McGill Total 25 *versus* 17), likely reflecting greater clinical severity. Correlations between McGill Total and VAS/IAD/QoLEB were nonsignificant.

Conclusion: Access to atraumatic dressings in Alagoas is heavily dependent on litigation, with high weekly consumption that demands structured procurement and standardized care protocols. Incorporating these products into state-level guidelines and monitoring pain and quality-of-life indicators are critical to reducing inequities.

Keywords: Epidermolysis bullosa; Atraumatic dressings; Pain; Quality of life; Wounds

Presentation Abstracts

CONTENTS

004

Alginate hydrogels encapsulation of lentiviral vector for enhanced deliviry on 3D skin model

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ABSTRACT

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe genetic disorder, currently with no cure, caused by mutations in the COL7A1 gene, leading to chronic skin fragility, blistering, and fibrosis, impacting patients quality of life. Lentiviruses (LV) are gene therapy vectors engineered to ensure safety and large cargo capacity, enabling the delivery of genetic material. Alginate hydrogel is a biocompatible biomaterial used in drug delivery and tissue engineering, able to encapsulate biological agents like viral vectors. This study aims to develop a new treatment platform for skin diseases, combining LV and biomaterials, for potential gene therapy applications for RDEB. To enhance transduction, alginate hydrogels were used to encapsulate LV (carrying the GFP gene), providing controlled release and protection, improving stability and delivery. The LV-alginate hydrogel system was tested in a 3D skin model in four conditions: negative control (only skin), positive controls (skin only with alginate hydrogel and skin only with virus), and the test group (skin with LV-alginate system). Immunofluorescence assay confirmed GFP transgene presence, indicating transduction efficiency. The presence of green cells was quantified and Welch's ANOVA was utilized due to unequal variances (Levene's test, $p < 0.001$), revealing significant differences between the groups ($p = 0.020$). Subsequent Games-Howell post-hoc analysis showed that the mean difference in GFP between the control groups and the LV-alginate was substantial, indicating higher transduction efficiency. These results suggest that alginate hydrogel encapsulation enhances the efficiency of lentiviral transduction in 3D skin models, increasing it up to five times. In this study we developed a system using LVs encapsulated in biomaterials to enhance gene delivery, offering a platform for future research in gene therapy, potentially used for new therapeutic strategies for genetic skin disorders like RDEB.

Keywords: Epidermolysis bullosa; Lentivirus; Alginate; Skin model

005

Application of the TLC-Ag Matrix in Wound Management for Epidermolysis Bullosa: Lessons and Reflections from the Nursing Perspective

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ABSTRACT

Introduction: Wound management in Epidermolysis Bullosa (EB) is one of the most complex challenges for nursing, requiring utmost scientific rigor and deep sensitivity.

Objective: To describe the experience of implementing the Regenerating Tissue Matrix Based on Cellulose and Silver (TLC-Ag), highlighting transformative lessons from the nursing perspective.

Methods: Experience report based on the nurse's work in a quaternary-level teaching hospital complex with children and adolescents.

Results: Practical observation revealed multidimensional impacts. In healing, the matrix created a moist and protected microenvironment, promoting autolytic debridement, stimulating granulation tissue, and efficiently controlling bacterial load with its sustained-release silver, accelerating the transformation of the wound bed. The most revolutionary lesson was in pain and trauma management: the concept of selective adherence of the matrix, which adheres to the wound bed but not to healthy skin, made dressing removal practically painless, without bleeding or new injuries, significantly reducing iatrogenic suffering and anxiety for both patients and their families. Operationally, the ability to extend intervals between dressing changes, guided by clinical assessment rather than a rigid schedule, optimized resources and reduced skin manipulation. This allowed nursing to reorganize care, dedicating more time to emotional support and health education instead of an exhausting routine of traumatic dressings. The lessons learned consolidate essential principles: *Primacy of Non- Aggression*, which is absolute in EB care, where dressing choice must prioritize, above all, minimizing physical and emotional trauma; Individualization of Care, recognizing that there is no rigid protocol—the frequency of dressing changes must be a clinical decision based on careful assessment of each wound and each patient, valuing the nurse's expertise and clinical judgment; Empowerment of Practice, the incorporation of TLC-Ag empowers the nursing team and provides a concrete tool to positively impact quality of life, transforming care from a sometimes frustrating task into a practice with visible and rewarding results; Person-Centered Care, with experience beyond the wound—by relieving pain and reducing the frequency of procedures, the focus of care expands and holistically improves quality of life.

Conclusion: Technological innovation, when combined with accurate clinical assessment and compassionate care, can revolutionize the prognosis of complex wounds and the patient experience. The lessons learned establish a new gold standard for nursing care in patients with Epidermolysis Bullosa, scientifically robust and deeply humane.

Presentation Abstracts

CONTENTS

006

Bespoke antisense oligomer-mediated splice modulating therapies for recessive dystrophic epidermolysis bullosa patients

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ABSTRACT

Objective: Design tailored antisense oligomers to reframe/restore collagen 7 protein expression in recessive dystrophic epidermolysis bullosa patient-derived cells, utilizing: Splice-modulating antisense oligomers to remove exons carrying null mutations to reframe the *COL7A1* transcript, creating an internally truncated yet functional collagen 7 protein isoform. Splice-correcting antisense oligomers to rectify aberrant splicing induced by mutations, either by including skipped exons or correcting cryptic splicing.

Methods: Antisense oligomers were designed to rescue either full-length or internally truncated collagen 7 protein expression. In the initial screen, antisense oligomers were delivered into normal or patient- derived cells. COL7A1 gene transcripts were amplified to assess alterations in COL7A1 expression, including changes in transcript levels and splicing patterns. Functional collagen 7 protein restoration was assessed after antisense oligomer treatment by immunohistochemistry and/or western blotting.

Results: Diverse splicing patterns were occasionally induced by antisense oligomers, including excision of adjacent non-targeted exons and/or retention of nearby introns in some transcripts. In proof-of- concept experiments, our lead candidates demonstrated the exclusive elimination of a mutation- containing exon in patient-derived cells, restoring collagen 7 protein expression.

Our next step involves the validation of the antisense oligomers. This will initially occur in an *in vitro* organotypic-engineered skin model. Subsequently, we plan to extend our validation efforts to patient-derived engineered skin grafted to an immunodeficient mouse to assess our lead candidates' delivery, efficacy, and safety.

Conclusion: This comprehensive approach marks a significant step towards advancing therapeutic interventions for individuals with recessive dystrophic epidermolysis bullosa. Tailored therapies hold the potential to reach patients rapidly through n-of-1 trials.

007

Beyond the primary mutation: the role of genetic modifiers in epidermolysis bullosa and related genodermatoses

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ABSTRACT

The introduction of large-scale molecular analysis methods in recent years has enabled a broader understanding of genetically determined diseases and the identification of additional co-occurring genetic variants that may modulate disease severity and progression. Epidermolysis Bullosa (EB) is a monogenic disorder, and diagnostic efforts have traditionally focused exclusively on analyzing causal genes. For many years, research in EB has aimed to define genotype-phenotype correlations and identify genetic modifiers that influence disease severity and clinical variability.

In the present study, we performed a retrospective analysis of the results from targeted gene panel sequencing in 75 individuals referred for genetic evaluation due to suspected skin fragility and sensitivity disorders. Initially, genetic testing focused exclusively on a panel of genes associated with the primary clinical manifestation—blistering. The current analysis has been expanded to include an extended panel comprising an additional 100 genes implicated in genodermatoses, allowing for a more comprehensive molecular assessment.

In 8 cases of patients with molecularly confirmed RDEB, SEB and APSS pathogenic heterozygous variants in genes *FLG*, *WNT10A*, *TGM1*, *C2* and *AP1S1* were detected. Also in two cases (RDEB and SEB), heterozygous variant in *TGM5* was detected.

Among the identified variants, the most compelling are those in the *FLG* and *WNT10A* genes. The *FLG* variants are associated with autosomal dominant (AD) atopic dermatitis, whereas variants in *WNT10A* underlie selective tooth agenesis type 4 (STHAG4) and related ectodermal dysplasia, often with clinical features overlapping epidermolysis bullosa in some respects.

In contrast, variants in the *C2* gene lead to complement component 2 deficiency (C2D), inherited in an autosomal recessive (AR) manner. Similarly, pathogenic variants in *TGM1* cause autosomal recessive ichthyosis due to loss of function in transglutaminase-1. Additionally, *AP1S1* mutations result in MEDNIK syndrome (AR). These variants typically result in impaired production or complete loss-of-function of the corresponding proteins.

Functionally, AD variants (e.g., *FLG*, *WNT10A*) may predispose to the onset or exacerbation of clinical symptoms, whereas AR variants (e.g., *C2, TGM1, AP1S1*) likely disrupt epidermal homeostasis. This disruption may compromise skin barrier function, delay wound healing, or promote inflammatory states.

Importantly, these findings are preliminary and warrant validation in a larger cohort with comprehensive phenotypic characterization. Our observations also suggest a potential phenotypic convergence, particularly in the context of AD conditions, indicating that overlapping manifestations could hold additional clinical significance. Moreover, our data support improved accuracy and personalization of genetic counseling in the context of genodermatoses.

Presentation Abstracts

CONTENTS

008

Bridging science and care to transform epidermolysis bullosa treatment at the EB Research Institute, Salzburg

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ABSTRACT

Epidermolysis bullosa (EB) is a rare genetic skin fragility disorder marked by severe wounds, fibrosis, and cancer risk. Despite progress in gene and molecular therapies, translating discoveries into effective treatments remains a critical challenge.

The EB Research Institute (EB-RI) in Salzburg was founded as a non-profit biotech to accelerate EB therapy development by bridging academia, clinics, and industry. Our mission is to deliver a comprehensive translational R&D platform that systematically integrates: i) biobanking with high-dimensional profiling of biosamples including technologies like single-cell RNA-seq, ii) validated preclinical models such as 3D skin equivalents, xenografts, and inducible mouse models, and iii) computational and phenotypic workflows linking omics signatures to drug response profiles. This integrated approach aims to accelerate compound discovery, drug repurposing, and biomarker identification.

To date, we have generated an EB Cell Atlas from patient samples, providing a valuable framework for target identification and model benchmarking.

By combining patient-derived resources, advanced profiling, and translational models under one roof, EB-RI aims to de-risk therapy development and accelerate progression toward the clinic. With international accessibility and strong clinical integration, EB-RI intends to serve as a global R&D partner for academia, biotech, and pharma, driving transformative treatments for EB patients.

009

Bridging the gap in neonatal care for epidermolysis bullosa: The "First Package" Program in Poland as a model for non-systemic intervention

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ABSTRACT

Epidermolysis bullosa (EB) is a rare and severe genetic skin disorder that represents one of the greatest challenges in neonatal care, especially in countries without systemic healthcare solutions or specialized national reference centers. A particularly dramatic scenario occurs when a child with EB is born into a family with no prior history of the disease. For parents, this moment brings profound shock and emotional burden, while for hospital staff, it creates a situation of uncertainty and difficulty. In most cases, the medical team has never encountered EB before and may lack the knowledge, training, or resources to provide appropriate and urgent care.

When no national referral center is available and transportation of the newborn is impossible, hospitals are left to manage the situation on their own, sometimes for weeks. This gap in care highlights the urgent need for rapid, practical strategies to ensure safe, evidence-based neonatal management of EB.

In response, the EB Polska Foundation developed the "First Package" program in Poland, implemented outside the state healthcare system. Designed as a practical, emergency intervention, the program provides immediate support for newborns with EB, their families, and the healthcare teams responsible for their care. Between 2016 and 2025, ten newborns in Poland were included in this initiative.

The program's core components included: Rapid provision of specialized wound dressings tailored for EB care. Deployment of trained professionals (nurse or physician) to hospital wards to offer direct instruction and hands-on support. Immediate access to remote consultation, enabling staff and families to receive expert guidance without delay.

The timeline of interventions illustrates the program's effectiveness. The interval between a hospital's first contact with the Foundation and its response ranged from as little as 24 hours to a maximum of three weeks. Delivery of specialized dressings took between a few hours and 48 hours. The arrival of a nurse or physician at the hospital occurred within several hours to four days. Importantly, telephone consultations were always available on the same day, offering crucial reassurance and guidance to both families and medical staff.

Our experience demonstrates that the "First Package" program is a feasible and effective emergency model for EB neonatal care in the absence of systemic solutions. The rapid supply of materials, combined with expert support, enables hospitals to stabilize newborns, reduce the risk of life-threatening complications, and ease the emotional strain on families and medical teams.

This initiative also highlights the vital role of non-governmental organizations in rare disease care. By addressing systemic gaps, they can create scalable interventions that are adaptable to other countries facing similar challenges. Ultimately, providing a responsive support system during the critical first days of life not only saves time and resources but also significantly improves survival chances and quality of life for infants with EB.

The program shows that collaboration between healthcare providers, patient organizations, and families can lead to flexible, effective solutions that improve outcomes in rare diseases, even without formal national infrastructure.

Presentation Abstracts

CONTENTS

010

Butterfly Kit – clinical and logistical support for newborns with epidermolysis bullosa: an 8- year review

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ABSTRACT

Introduction: Epidermolysis bullosa (EB) is a rare, genetically determined, and currently incurable disease characterized by skin and mucosal fragility, leading to recurrent blister formation due to defective structural proteins. The neonatal period represents a critical challenge for both families and healthcare providers. Delays in diagnosis and in establishing appropriate care guidelines can significantly worsen prognosis and increase morbidity and mortality.

Objective: This study aimed to evaluate the implementation of the *Butterfly Kit*, which provides: Non-adherent dressings for newborns with EB, Educational materials for healthcare teams and families, Multidisciplinary technical and scientific support during hospitalization and after discharge.

We compared outcomes related to early access to the kit and the morbidity and mortality rates observed over the eight years of the project.

Methods: Based on the 2017 International Consensus on Wound Care, a standardized kit was developed containing non-adherent dressings for the first three months of life, donated by partner companies. The kit also included: Infographics and simplified educational materials for families; A copy of Good Clinical Practice (GCP) guidelines for healthcare professionals; A symbolic plush butterfly representing the team's care; Online support from DEBRA's volunteer team (pediatric dermatologist, nurse, and a trained mother volunteer; The *Butterfly Kit* was implemented nationwide in January 2018; Upon notification of a birth, the volunteer team provides immediate technical guidance for neonatal management and ensures the supply of special dressings for in-hospital care.

Results: Brazil, with an EB incidence of 19 cases per million live births, faces challenges due to the lack of awareness among neonatal teams and limited access to adequate supplies. The *Butterfly Kit* addressed these gaps by enabling: Timely access to specialized dressings and care protocols; Reduction of new skin injuries, pain, and secondary complications; Improved neonatal quality of life.

Greater visibility of EB within the medical community and Strengthened family and healthcare team confidence.

Over the eight years, the initiative has become a recognized symbol of support for newborns with EB, expanding disease awareness, facilitating earlier case notifications, and improving neonatal outcomes. The mortality has decreased by almost 30% over the years, as we have increased the project's reach to a large proportion of newborns, with increased birth notifications.

Conclusion: The *Butterfly Kit* project has provided effective clinical and logistical support for newborns with EB in Brazil. Over its 8-year trajectory, it has contributed to earlier diagnosis, improved quality of care, enhanced survival during the first year of life, and strengthened the trust of families and healthcare professionals. This initiative demonstrates the impact of organized volunteer support in rare disease management and serves as a replicable model for other countries.

011

Climatic and environmental challenges of epidermolysis bullosa care in Brazil's Unified Health System (SUS): a narrative review

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ABSTRACT

Introduction: Epidermolysis bullosa (EB) is a rare genodermatosis marked by skin fragility and blistering after minimal trauma, caused by mutations affecting dermoepidermal adhesion proteins. In Brazil, a tropical country with wide climatic variation, environmental factors can aggravate the clinical course — heat and humidity intensify lesions, delay healing, and increase infection risk by promoting maceration and bacterial colonization, whereas cold, dry climates exacerbate fissuring. Although the environment is recognized as a modulator of cutaneous disease progression, few Brazilian studies have explored its influence on EB or its implications for management within the Unified Health System (SUS).

Objective: To analyze how climatic conditions affect clinical management, complications, and quality of life in EB, emphasizing implications for SUS-based care, in Brazil.

Methods: Narrative review of articles published between January 2019 and September 2025 in Portuguese or English, prioritizing observational and qualitative studies given the scarcity of clinical trials and systematic reviews. Included papers addressed climatic or environmental effects on EB management, particularly within the SUS. Excluded were in vitro or animal studies, non-clinical reviews, and non-peer-reviewed documents. Descriptors "Epidermolysis Bullosa," "Climate," "Humidity," "Temperature," "Wound Healing," "Quality of Life," "Brazil," and "Unified Health System" (DeCS/MeSH) were combined with Boolean operators AND/OR in PubMed, SciELO, and LILACS. Selection involved screening titles, abstracts, and full texts, followed by qualitative synthesis of relevant findings.

Results: The SUS faces major challenges in EB care across Brazil's vast and climatically diverse regions. Environmental conditions affect supply logistics, dressing-change frequency, and costs, demanding local adaptation of care. A national study of 278 patients in São Paulo found frequent anemia, malnutrition, and skin infection, noting that heat and humidity intensify sweating and maceration, increasing dressing use and household expenses. Hot, humid climates hinder dressing adherence and pain control, whereas cold, dry weather exacerbates fissures and chronic pain. Thermal discomfort limits mobility, leisure, and school activities, heightening emotional burden in children and caregivers; climatic vulnerability compounds SUS structural barriers, impacting quality of life and continuous access to care. International studies also show that high temperature and humidity weaken the dermoepidermal junction, increasing the risk of secondary infection. In tropical regions, management requires breathable dressings, frequent changes, and hydration to prevent friction and infection. In cold and dry climates, low humidity leads to fissures and neuropathic pain, requiring more occlusive and emollient care. The combination of climatic and socioeconomic factors leads to poorer quality-of-life scores and higher hospitalization rates, especially in low-income hot regions. In Brazil, rapid dressing deterioration under heat and humidity increases costs and regional inequities, making climate a further determinant of health vulnerability within the SUS.

Conclusion: Brazil's climatic diversity significantly influences EB management, intensifying infection,

pain, and emotional distress. Findings align with global evidence yet reveal a lack of multicenter Brazilian research including environmental variables. Region-specific adaptation of materials, protocols, and educational strategies is vital to ensure equitable, effective EB care in the SUS.

Keywords: Epidermolysis bullosa; Climate; Quality of lfe; Unified Health System

Presentation Abstracts

012

Clinical outcomes of epidermolysis bullosa skin lesions treated with a highly conformable lipido-colloid contact layer, assessed in clinical trials

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ABSTRACT

Introduction: Epidermolysis bullosa (EB) is a heterogeneous group of rare, inherited skin diseases characterized by recurrent painful skin lesions, often induced by minor trauma resulting in dermal-epidermal separation or split with main implications on the physical, psychological and social wellbeing of the affected patients and their families.

Objective: To assess the acceptability, tolerance and efficacy of a new lipido-colloid contact layer in the management of EB skin lesions, two clinical trials were conducted in Dermatology Departments, being part of French national references in that skin disease. The first study was the largest ever conducted in EB with dressings.

Methods: Both clinical trials were open-label non comparative ones, involving 20 EB patients in the first one suffering from EB simplex or dystrophic EB and 5 dystrophic EB patients (on the 78 patients in total) for the second one. Boths dressings are lipido-colloid ones, the second being the same but mesh free, leading to a higher conformability of this dressing.

Patients were selected from the register of EB patients at the investigating centers and included subjects were presented with at least one skin lesion treated with the study dressing for a maximum period of four weeks. All dressing changes, wound parameters, pain and effect on quality of life were recorded.

Results: All the patients completed the trials. At the end of the study period, 22/25 EB lesions have healed after hundreds of nursing cares performed with those two dressings. Following the dressing applications always considered very easy or easy, the dressing removals were also documented as 'easy' or 'very easy' in 98% of changes and more that 90% of the dressing changes did not cause any pain. A very good safety profile was reported by the investigators. All these acceptability parameters were leading to an improvement of the quality of life of those patients.

Conclusion: These trials support the use of this TLC non-adherent contact layer for an optimal management of skin disorders treatment of EB, showing good tolerance and excellent conformability of this new contact layer, along with its efficacy, justifying its availability to health care professionals and patients for use in this EB indication. The painless character of the dressing changes with this dressing improves patients' quality of life and makes nursing procedures dramatically easier.

Presentation Abstracts

CONTENTS

013

Clinical study landscape in epidermolysis bullosa: a living scoping review

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ABSTRACT

Background: Epidermolysis bullosa (EB) comprises a group of rare, inherited disorders characterized by hyperfragility of epithelialized tissues with prototypic blistering, erosions and healing deficits in skin and mucous membranes upon mechanical trauma. To date, no consolidated overview of clinical research activities for EB exists, limiting the ability to learn from past lessons and shape a successful research landscape.

Objective: This project aims to systematically map all (commercial and non-commercial) registered and published clinical studies in EB on a yearly basis, in order to provide a structured overview of therapeutic approaches, reported efficacy and safety outcomes, as well as disclosed reasons for trial discontinuation, screening failures, or lack of study completion. By further comparing the available trial data with patient-reported needs, we seek to define current evidence gaps to guide future research initiatives.

Methods: Public clinical trial registries, commercial development - and literature - databases will be screened according to PRISMA guidelines to identify EB studies registered and published after 1991. The first iteration of this living review will capture studies identified before November 2025 and re-iterated every 12 months. Extracted data, including trial phase and status (e.g. completed, ongoing, on hold, discontinued), will be incorporated into a development trajectory of individual treatment approaches across different trial stages. Reported treatment outcomes will be documented and compared with patient-reported priorities as identified in previous studies. Due to the expected heterogeneity of EB trials, a comprehensive landscape will be created. While no formal meta-analysis will be performed, data will be synthesized descriptively.

Conclusion: By consolidating the global clinical study landscape in EB, this living review will provide a reference of past, ongoing and future therapeutic activities and summarize reported outcomes. It will further highlight unmet patient needs, recurrent causes of trial discontinuation and failures to outcome capture. The resulting evidence map is intended to inform clinicians, researchers, regulators, industry and patient organizations in planning and designing efficient and patient-centered EB trials.

Keywords: Epidermolysis bullosa; systematic review; clinical studies

014

Co-occurrence of KRT5 and TGM5 mutations in one family: a rare observation linking epidermolysis bullosa simplex and acral peeling skin syndrome

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ABSTRACT

Introduction: Epidermolysis bullosa simplex (EBS) is most commonly associated with autosomal dominant mutations in the KRT5 or KRT14 genes, resulting in intraepidermal skin fragility and blister formation, predominantly on the feet and hands. Acral Peeling Skin Syndrome (APSS) is a distinct autosomal recessive genodermatosis caused by biallelic pathogenic variants in TGM5, characterized by superficial peeling of acral skin. To date, the co-occurrence of pathogenic variants in KRT5 and TGM5 within the same family has rarely been documented.

Case description: We report a familial occurrence of epidermolysis bullosa simplex (EBS) affecting a father and his daughter, with no previous family history of similar disease. Genetic testing revealed that both individuals carried a heterozygous pathogenic variant in *KRT5* (c.556-16C>G). In addition, they harbored a heterozygous *TGM5* variant (p.Gly113Cys), which is known to cause acral peeling skin syndrome (APSS) only in the biallelic stateThe daughter had a history of acral skin fragility and blistering since early childhood, although no active lesions were present at the time of examination. The father reported a similar disease course, characterized by recurrent plantar blistering and erosions; at admission, he presented with painful superficial erosions localized to the plantar surfaces of both feet. Neither mucosal involvement nor nail dystrophy was observed in either case. In the past, episodes of secondary bacterial superinfection of blisters and erosions had been managed exclusively with topical corticosteroids and antibiotics. During the current hospitalization, local wound care with non-adhesive dressings was recommended as the main therapeutic approach.

Conclusion: These findings reinforce the pathogenic significance of *KRT5* variants in the clinical expression of epidermolysis bullosa simplex (EBS), whereas the heterozygous *TGM5* mutation appears clinically silent. The co-occurrence of both variants within a single family highlights the necessity of comprehensive genetic profiling to delineate the contribution of individual alleles. Such integrative approaches are crucial not only to avoid misdiagnosis but also to refine disease classification, improve genotype–phenotype correlations, and ultimately guide precision-based management of overlapping keratinization disorders.

Presentation Abstracts

CONTENTS

015

Cutaneous Squamous Cell Carcinoma in Epidermolysis Bullosa: A monocentric retrospective analysis of disease course and management

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ABSTRACT

Background: Recessive dystrophic Epidermolysis bullosa (RDEB) is a multi-system disease causing significant morbidity and mortality. Affected individuals are particularly prone to the development of cutaneous squamous cell carcinoma (cSCC). These tumors show a distinct biological behavior, with an onset as early as in the patients' 20s as well as a strikingly aggressive course accounting for cSCC to be the leading cause of death in this patient cohort.[1-3] While representing a major disease burden, systematic data on prognostic factors and treatments remain scarce.

Objective: This retrospective analysis aims to collect data on cSCC development, course and treatment outcomes to identify key endpoints that may potentially serve as prognostic factors. Conclusive results could further inform research initiatives to address current research gaps and policies to improve disease management.

Methods: Data are retrieved from medical records of eligible patients registered at the EB House Austria. Extracted items for each cSCC, reported and stratified according to EB-subtype, include age at first cSCC occurrence, clinical presentation and localization; treatment regimens and response rates; recurrence, progression, metastatic spread and survival outcomes; histological features as well as molecular markers. Additionally, longitudinal photographic documentation from follow-up visits will be analyzed to characterize lesional evolution. Treatment efficacy and outcomes will be assessed statistically referring to the identified end points.

Results: We pre-identified a total of 25 patients (13 female, 12 male) diagnosed for at least one cSCC. The study cohort includes individuals with severe (n=19) and intermediate (n=2) RDEB as well as junctional Epidermolysis Bullosa (JEB, n=4), with ages at first cSCC occurrence ranging from 15 to 47 years, 23 to 50 years and 45 to 71 years, respectively. 11 patients are currently in active follow-up. Investigations to gather information on individual treatment modalities and disease courses as well as statistical analysis are ongoing with results pending.

Conclusion: We anticipate correlations between disease severity, age of cSCC onset, progression, and survival as well as differences in disease courses between RDEB and JEB patients. Given the scarce clinical data on cSCC treatment in EB, which are mainly based on methodologically heterogeneous case reports/series, this systematic approach should provide insights to better characterize the oncological burden of EB-associated cSCC and serve as guidance for clinicians to improve therapeutic strategies.[4-6]

Keywords: Epidermolysis Bullosa, Recessive Dystrophic Epidermolysis Bullosa, Squamous cell carcinoma, Junctional Epidermolysis Bullosa, retrospective data analysis

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Presentation Abstracts

CONTENTS

016

DEBRA Colombia: collaborative model of comprehensive health care, social inclusion, and legal support for people with epidermolysis bullosa

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ABSTRACT

DEBRA Colombia: DEBRA Colombia was founded in 2009, dedicated to improving the quality of life of people with Epidermolysis Bullosa (EB).

Mission: To provide comprehensive and specialized care for patients with Epidermolysis Bullosa through strategic alliances that ensure access to fundamental rights such as health, nutrition, and education.

Interdisciplinary Care Model: DEBRA Colombia integrates multiple specialties for comprehensive care: Dermatology: Specialized care, early diagnosis counseling, treatment access pathways; Nursing; Nutrition; Psychology; Sexology; Dentistry; Comprehensive Physical Therapy; Genetics.

Social Inclusion – "DEBRA Aprende" Program: An educational initiative that promotes inclusion and empowerment of people with EB and their families, fostering their participation in educational and political frameworks. It ensures access to education and social participation with reasonable accommodations according to the unique needs of individuals with EB.

Administrative Support: Coordinates and manages human and financial resources to fulfill the mission.

Support Programs: Delivery of kits for nutritional and wound care, as well as Medivaric® copper-fiber garments, which have improved the quality of life of our beneficiaries.

Results and Achievements: 6 national meetings (1 virtual during the pandemic) and 34 regional meetings of education and specialized interdisciplinary care across different regions of the country, benefiting 140 patients since 2009, with 85 active patients in 2025.

Telemedicine and in-person/virtual interdisciplinary support on demand.

Access to molecular diagnosis and specific treatments, including the vital non-available drug Filsuvez®, through the Colombian health system.

Awards and Recognition: Liliana Consuegra nominated for Mujer Cafam 2024 for female leadership; DEBRA Colombia recognized by the Bogotá City Council.

Legislative Impact: International process following a successful case before the Inter- American Commission on Human Rights (IACHR) to ensure fundamental rights for EB patients (ongoing).

Clinical Guidelines: National skin care guidelines for EB patients developed by the DEBRA.

Colombia team; treatment guidelines for EB certified by the Colombian Ministry of Health with the participation of DEBRA professionals (pending publication).

Conclusion: The DEBRA Colombia care model demonstrates that interdisciplinary collaboration in health care, the "DEBRA Aprende" social inclusion program, and national and international legislative processes enable individuals with EB to access early molecular diagnosis, treatments, community empowerment, and a pathway to secure their fundamental rights, positively impacting their quality of life in a biopsychosocial context.

Keywords: DEBRA Colombia; Interdisciplinary care; Epidermolysis bullosa; Quality of life; Education; Legal support; Social impact

017

DEBRA Peru: first national registry of peruvian patients with epidermolysis bullosa

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ABSTRACT

Patient registries for rare or orphan diseases (RODs) are tools obtained with the help of patient associations to comprehensively understand the impact of these diseases on quality of life. They also facilitate the development of research projects, the optimisation of genetic diagnostics, the design of advanced therapies, and public health policies. In Peru, 546 RODs are recognised out of the more than 7000 identified worldwide, and it is estimated that there are 2 million affected individuals. Despite this significant population, the country lacks a public national registry that systematises information for its research. Epidermolysis bullosa (EB) is a rare multisystemic genetic disease characterised by skin fragility, blister formation, and difficult wound healing; it also lacks a national registry. In this context, the objective of this project was to develop the first Peruvian national registry for patients with EB, based on the members of DEBRA Peru. A questionnaire (69 questions in 9 sections) was developed, discussed, and validated by DEBRA Peru and previous surveys on RODs and EB. An informed consent form was signed, complying with the data protection and bioethics laws established in Peru. Each patient was assigned a code for identification; the analyses and graphs were performed in RStudio. 18 questionnaires were obtained (2 from adults and 16 from guardians of minors) from the 59 patients who are members of the association. There are 50% (9) affected females and 50% (9) affected males. 89% (16) of the patients are <18 years old. 50% of the cases are in Lima (3 patients had to emigrate from their regions due to a lack of reference hospitals). The most abundant types were Dystrophic EB (DEB) (72%, 13), Simplex EB (EBS) (22%, 4), and one particular case that had a VUS and whose result was both EBS and DEB (6%,1). 39% (7) were able to access genetic diagnosis. Only 1 out of the 13 individuals with DEB who need surgery accessed hand surgery. On average, accessing a skin biopsy and genetic study takes 6 months and 3 years, respectively, without considering one atypical case. The professionals who predominate in the diagnosis are dermatologists (63%), while the involvement of geneticists is limited (11%). On average, 75% of the families' monthly income is allocated to treating EB, and 89% consider that they do not have sufficient financial income; this is considered a catastrophic situation that impoverishes the family, limits access to education, limits access to medication, and harms mental health. It is concluded that the preliminary data show a critical and unfavourable situation faced by patients and families of patients with EB. It is hoped that this information will be used by health institutions in Peru and research groups to take action and promote EB projects by collaborating with international groups. We recommend promoting the dissemination of the disease to society to increase its visibility and we commit to strengthening the data with greater patient participation.

Keywords: Epidermolysis bullosa; Patient registry; Rare disease; DEBRA Peru

Funding: Self-funded

Presentation Abstracts

CONTENTS

018

Dental treatment needs in epidermolysis bullosa - a cross-sectional study

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ABSTRACT

Introduction: Oral health in Epidermolysis Bullosa (EB) is reported to be severely affected, particularly in types with high-risk or oral disease such as Recessive Dystrophic EB (RDEB), Junctional EB (JEB) and Kindler EB (KEB). Previous studies have shown a higher caries prevalence in RDEB, accompanied by poorer oral hygiene indexes, while KEB presents early signs of periodontal disease. Efforts have been made to improve their oral health status, but to date, it is still unclear what particular needs regarding dental treatment these patients face.

Objective: This research aims to assess the oral health status and dental treatment needs in a large cohort of patients living with EB.

Methods: A total of 101 participants living with EB (EB Simplex n=26, JEB=6, DDEB=20, RDEB=47, KEB=2) were assessed extra and intraorally during their regular dental appointments, including simplified debris index (DI-S), stage and severity of periodontal disease and Decay-Missing-Filled teeth index (DMF/def index). After the assessment, and according to referral parameters, the treatment needs were determined as: preventive, periodontics, restorative, endodontics, orthodontics, prosthodontics, oral surgery, oral pathology, oral radiology, speech therapy and others. Descriptive and statistical analysis was performed.

Results: People living with EB show a median of 3 referrals to different dental specialities, being the most prevalent restorative dentistry (n=55, 54.5%), prosthodontics (n=52, 51.5%) and speech/oral function therapy (n=43, 42.6%). By EB type, JEB (3.67±0.52) and RDEB 3.34±1.03 showed the highest number of referrals. When analyzed by risk of oral disease, a significant difference was observed between the groups "high" v/s "moderate" risk of oral disease (Kruskal–Wallis; $p<.05$). Endodontics, prosthodontics, speech therapy, and preventive and restorative dentistry showed significant differences ($p<.05$, Fisher's exact test) between the risk groups. Age and gender showed no significant correlation with the total number of referrals.

Discussion: This research confirms that patients living with a type of EB considered high risk of oral disease require at least 3 different dental specialities. Even though that recommendation was made as an expert's statement position, this research confirms that classification. The importance of early and multidisciplinary dental care for these patients it has been previously stated, as they require complex treatments, sometimes difficult to provide due to the orofacial characteristics expressed in each type/subtype. Health providers should consider specific references for each type, for example, including oral rehabilitation to patients with JEB due to associated syndromic Amelogenesis Imperfecta, or periodontal treatment to patients with KEB.

Keywords: Epidermolysis bullosa; Oral health; Treatment needs

019

Development and validation of a nutritional deficiency assessment scale in patients with congenital epidermolysis bullosa

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ABSTRACT

Background: Severe forms of congenital epidermolysis bullosa (CEB) frequently present with nutritional deficiency among other complications, yet no standardized algorithm for identifying such nutritional disorders is currently available despite existing international guidelines.

Objective: The objective of this study was to develop and initially validate a comprehensive scale for assessing nutritional deficiency in CEB, integrating clinical, laboratory, and instrumental parameters that best reflect the nutritional status of these patients.

Methods: The study included 50 patients (23 males and 27 females) with CEB, aged 5 to 17 years and 11 months. Development of the Nutritional Deficiency Assessment Scale (NDAS) was based on the Birmingham Epidermolysis Bullosa Severity (BEBS) index, as well as laboratory and anthropometric indicators. Cronbach's alpha coefficient was employed to evaluate internal consistency, while intraclass correlation was used to determine reliability by comparing scale results upon patient admission and 10 days later. Criterion validity was assessed using Pearson's correlation coefficient (r) between the NDAS and the BEBS and THINC scales.

Results: Internal consistency (Cronbach's $\alpha=0.85$) and test-retest reliability (ICC=0.88) confirm its stability and uniformity. Criterion validity, assessed through correlation with existing scales (BEBS, THINC), revealed significant positive relationships ($r>0.70$; $p<0.001$).

Conclusion: The NDAS integrates both objective measures and disease-specific clinical features, reflecting a comprehensive approach to evaluating the nutritional status of patients with CEB. The present study supports the NDAS as a reliable and easy-to-use tool for diagnosing and predicting nutritional risks in patients with CEB.

Full Name		Medical record number	
Age			
Diagnosis		Date of completion	
			Point
Extent of Skin Involvement	1–10% (2 points)	31–49% (8 points)	
	11–30% (5 points)	>50% (11 points)	

Type of Skin Lesions	No lesions (0 points)	Erosions (1 point)	Blisters (1 point)	Erosions with purulent discharge (2 points)
Head				
Neck				
Anterior trunk				
Posterior trunk				
Upper limbs				
Lower limbs				
Buttocks				

Chronic Wounds Present for More Than 6 Months (as a percentage of body surface area, 1% = palm size)	<1% (1 point)	5–10% (4 points)
	1–2% (2 points)	> 10% (5 points)
	2–5% (3 points)	
Presence of Microstomia	No (0 points)	Yes (2 points)
Presence of Ankyloglossia	No (0 points)	Yes (2 points)
Presence of Esophageal Stricture	No (0 points)	Yes (2 points)
	Episodic dysphagia (1 point)	
Presence of Anal Fissures	No (0 points)	Yes (2 points)
Assessment of Hand Condition	Not altered (0 points)	Grade 3b (4 points)
	Grade 1 (1 point)	Grade 4a (5 points)
	Grade 2 (2 points)	Grade 4b (5 points)
	Grade 3a (3 points)	
Albumin Concentration (g/L)	≥35 (0 points)	<25 (3 points)
	26–35 (2 points)	
Calcium Concentration (mmol/L)	≥2.3 (0 points)	<2.2 (2 points)
Iron Concentration (µmol/L)	≥13 (0 points)	<9.3 (3 points)
	9.4–13 (2 points)	
Vitamin B12 Concentration (pg/mL)	≥350 (0 points)	<196 (3 points)
	196–349 (2 points)	
Vitamin D Concentration (ng/mL)	> 30 (0 points)	10–19 (3 points)
	20–29 (2 points)	<10 (4 points)
Z-Score Osteodensitometry	> -2.0 SD (0 points)	< -3 SD (5 points)
	-2.1 to -2.9 SD (3 points)	

< 15 points: Normal nutritional status
16–35 points: Risk of nutritional deficiency
36 points: Presence of nutritional deficiency

Total score

Table 1. Scale for assessing the risck of nuctritional deficiency in children with congenital epidermolysis bullosa

Presentation Abstracts

020

Development of cellular platforms to study type VII collagen deficiency in recessive dystrophic epidermolysis bullosa

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ABSTRACT

Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe genetic skin disorder characterized by extreme fragility of the skin and mucosa, leading to chronic blistering and erosions even after minor trauma. The disease is caused by biallelic mutations in the *COL7A1* gene, located on chromosome 3, which encodes type VII collagen (C7), the major component of anchoring fibrils that connect the epidermis to the dermis. The absence or dysfunction of C7 results in dermal–epidermal separation, manifesting as lifelong tissue damage, chronic wounds, fibrosis, and an increased risk of aggressive squamous cell carcinoma. Patient-derived fibroblasts and keratinocytes are valuable tools for modeling RDEB, as they display molecular and functional alterations that reflect disease pathology. However, simplified two-dimensional cultures fail to reproduce key pathophysiological parameters such as tissue architecture, extracellular matrix organization, and cell–cell interactions. To address these limitations, we sought to generate and characterize cell models carrying the pathogenic c.5047C>T mutation in COL7A1, with the ultimate goal of applying them in three-dimensional (3D) culture systems for translational and therapeutic research.

The BJ-hTERTc.5047C>T cell line was generated by nucleofecting immortalized neonatal foreskin fibroblasts (BJ-hTERT) with a Cas9/gRNA complex targeting exon 54 of COL7A1 and a single-stranded donor oligonucleotide containing the c.5047C>T substitution. Following genome editing, single-cell clones were isolated by flow cytometry, expanded, and validated by genotyping and Sanger sequencing. A confirmed clone, designated BJ-hTERTc.5047C>T, was expanded to establish master and working cell banks. In parallel, primary fibroblasts derived from RDEB patients homozygous for the same mutation (SBEB02) were cultured. Immortalized BJ-hTERT fibroblasts served as healthy controls. Cells were maintained under standard conditions in DMEM supplemented with 10% fetal bovine serum, and subcultured every three days.

Phenotypic characterization focused on the analysis of C7 expression. Immunofluorescence revealed strong, diffuse cytoplasmic staining in BJ-hTERT controls, consistent with robust protein production, whereas BJ-hTERTc.5047C>T cells showed markedly reduced intracellular C7 levels, mirroring the molecular phenotype of RDEB. Similar reductions were observed in immortalized SBEB02 fibroblasts. To evaluate extracellular secretion, cultures were stimulated with ascorbic acid (50 mg/ml). Western blot analysis of cell lysates initially revealed low-intensity, degraded bands. Optimization using NC1-C7 antibody the robust detection of full-length C7 (~290 kDa) in BJ-hTERT controls. However, detection of secreted C7 in supernatants remains under development and requires further methodological refinement.

The establishment of this engineered fibroblast line represents a significant advance in RDEB research. By faithfully reproducing the c.5047C>T-associated phenotype, BJ-hTERTc.5047C>T provides a stable and renewable cellular resource for functional studies, including the analysis of disease mechanisms, protein

trafficking, and degradation pathways. Moreover, it offers a robust platform for testing gene-editing and gene-replacement strategies aimed at restoring C7 expression. Future directions include the incorporation of these cells into 3D organotypic skin equivalents, which will allow the study of cell–matrix interactions and anchoring fibril formation in a physiologically relevant context.

Presentation Abstracts

021

Early and particular cutaneous features in Kindler syndrome

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ABSTRACT

Kindler syndrome (KS) is a rare autosomal recessive epidermolysis bullosa (EB), related to loss-of-function mutations in the kindlin-1 gene (*FERMT1*), characterized by skin and mucosal involvement. The first clinical manifestations are described as a particular acral blistering but the disease is poorly characterized in infancy. We report here particular and similar early erosions in 2 unrelated newborns with Kindler syndrome.

Two unrelated male neonates presented with congenital remarkably similar large patchy erosions on the legs or buttocks, without any reported trauma. They were born from 2 unrelated parental couples from Senegal and Mali respectively. Lesions healed within few days, evolving first towards milia and then, before the age of 1 year, towards skin atrophy. While growing, the skin fragility of the infants was moderate, but were observed a characteristic diffuse poikiloderma, skin atrophy, periodontitis, anal pain in both and bloody diarrhea in one. Molecular diagnosis confirmed two homozygous mutations in respectively exon 3 and exon 6 of *FERMT1*, leading to a premature stop codon for each patient.

Large patchy erosions of buttocks and legs evolving towards milia and atrophic scarring might be characteristic early signs of Kindler syndrome, allowing an early recognition of this rare and potentially severe EB form.

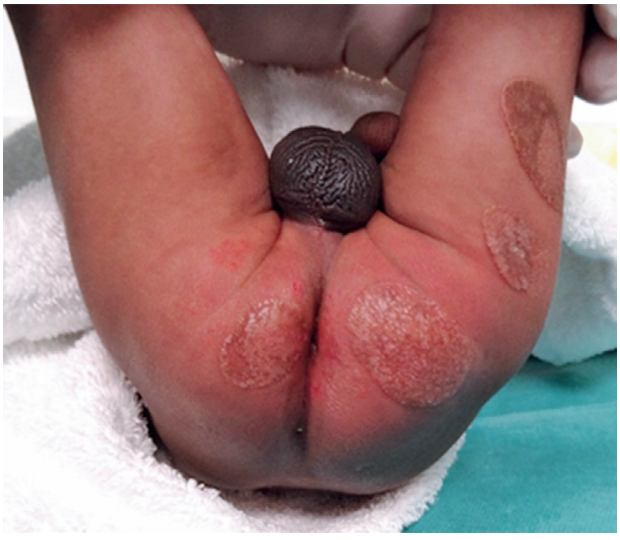

Figure 1. Large patchy congenital erosions of the buttocks and thighs at birth

Presentation Abstracts

CONTENTS

022

Effects and mechanism of exosomes derived from urine-derived stem cells compositing with ZIF and SIS hydrogel on the recessive dystrophic epidermolysis bullosa

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ABSTRACT

Background: Recessive dystrophic eermolysis bullos (RDEB) is one of the most severe and lethal subtypes of epidermolysis bullosa caused by the gene mutation of *COL7A1*. Currently, there is no cure for RDEB. Exosomes from stem cells emerging as a new direction for cell-free therapy strategies for RDEB but also facing application bottlenecks like low yield and delivery efficiency. Small intestinal submucosa (SIS) hydrogel possesses a natural extracellular matrix structure and load exosomes could protect them from being rapidly cleared. However, the pores of the SIS hydrogel are at the micrometer scale, and the ability to release nanometer-sized exosomes needs to be further improved. Zeolitic imidazolate framework-8 (ZIF-8) is a subclass of metal-organic frameworks not only could help reduce the pores of SIS hydrogel, but also possessed anti-inflammatory and antibacterial properties. Based on the above, this study intends to incorporate ZIF-8 into SIS hydrogel via physical blending and then loaded USCs-exosomes. Then the effectiveness, safety and mechanism of the USCs-exosomes composite ZIF-8/SIS hydrogel in treating RDEB mice in vitro and in vivo were explored.

Methods: Primary urine-derived stem cells (USCs) were isolated from the urine samples of healthy male adult donors (aged 20–30), then exosomes of USCs were isolated through a meticulous ultracentrifugation process. SIS was digested with 0.1% pepsin, freeze-dried, and reconstituted in phosphate buffered saline (PBS) to make SIS hydrogel. Different concentrations of ZIF-8 (0.03mg, 0.05mg, 0.08mg) were added to 30mg SIS powder and dissolved in 1 mL PBS. In vitro release of exosomes from different group of ZIF-8/SIS hydrogels were also performed. 10μg/mL USCs-exosomes was added to the final selected ZIF-8/SIS hydrogel to obtain the composite hydrogel. Effects of USCs-exosomses composite ZIF-8/SIS hydrogel on human umbilical vein endothelial cells (HUVECs), keratinocytes and fibroblasts from RDEB, peripheral blood mononuclear cells (PBMCs) and murine RAW264.7 cell line in vitro were explored. Finally, observation of in vivo therapeutic effects of USCs-exosomes composite ZIF-8/SIS hydrogel on RDEB mice and also the mechanisms explored via single-cell RNA sequencing analysis were also performed.

Results: USCs were successfully isolated. Flow cytometry showed USCs expressed CD29 and CD73 while lacked expression of CD34 and CD45. USCs also holding the capability for tri-lineage differentiation into osteogenic, adipogenic, and chondrogenic pathways.

Transmission electron microscopy (TEM) revealed that the USCs-exsomes exhibited cup-shaped morphologies with intact vesicular membranes. Nanoparticle tracking analysis demonstrated that the size distributions of exsomes are comparably 128±22.67nm; Western blotting showed USCs-exosomes expressed protein of CD63, TSG101, but not Calnexin. 3% SIS hydrogel showed porous structure under scanning electron microscope (SEM); ZIF-8 showed dodecahedral rhombic structure under TEM. The ZIF/SIS hydrogel was prepared by the physical blending method. SEM showed ZIF-8 dispersed in SIS pores; TEM showed ZIF-8 dispersed among network fibers. Emission spectrum element analysis

showed the main elements of ZIF/SIS hydrogel were C, O, N, Zn. Rheological properties of ZIF-8/SIS hydrogels were significantly higher than SIS alone, with 0.05mg/mL ZIF-8+3% SIS performing best. Degradation resistance of ZIF/SIS hydrogel was increased with ZIF-8 concentration. CCK-8 showed the extracts of 0.05mg/mL ZIF-8+3% SIS could promoted keratinocytes proliferation. Antibacterial assays showed 3% SIS had no antibacterial effect, while 0.05mg/mL ZIF-8+3% SIS showing excellent antibacterial performance (>90% inhibition rate). The hydrogel's efficacy for the sustained release of exsomes showed 0.05mg/mL ZIF-8+3% SIS hydrogels have the best sustained-release effect. So 0.05mg/mL ZIF-8+3% SIS hydrogel was choosed as the final ratio. 10μg/mL USCs-exosomes were added to 0.05mg/mL ZIF-8+3%SIS to form the final composite hydrogel (USCs-exos+ZIF-8/SIS). Keratinocytes from RDEB mouse showed cobblestone morphology, with positive of CK14 antibody. Fibroblasts from RDEB mouse were spindle-shaped or triangular with positive of α-SMA antibody. Tube formation of HUVECs showed USCs-exos+SIS and USCs-exos+ZIF-8/SIS groups could significantly promote HUVECs forming intricate tubular networks than USCs-exosomes. Scratch assay and transwell migration assay showed USCs-exos+ZIF-8/SIS significantly promoted keratinocytes and fibroblast migration. After co-culture of keratinocytes and fibroblasts with composite hydrogel, expression of IL-6, TNF-α, IL-1β, IFN-γ, MMP-9, MMP-2 from keratinocytes were significantly decreased ($p<0.05$). The expression of L-6, TNF-α, TGF-β1, MMP-13 and MMP-1 of fibroblasts were significantly decreased while VEGF were increased ($p<0.05$). As for the immunomodulatory effects of composite hydrogel. CCK-8 showed USCs-exos+ZIF-8/SIS decreased PBMC absorbance ($p<0.05$). ELISA assay showd USCs-exos+ZIF-8/SIS groups significantly downregulated IL-6, IL-18, IL-1β of PBMCs ($p<0.05$). Flow cytometry showed compared to RAW264.7 stimulated with lipopolysaccharide, USCs-exos+ZIF-8/SIS groups decreased expression of CD86 but increased expression of CD206. Quantitative polymerase chain reaction (Q-PCR) analysis showd USCs-exos+ZIF-8/SIS group significantly downregulated TNF-α and upregulated IL-10 mRNA levels in RAW264.7. In vivo therapeutic effects in RDEB mice, Kaplan-Meier survival curve shoewd median survival time for USCs-exos+ZIF-8/SIS treated group was increased to 7 days compared to 2 days of RDEB group. H&E staining showed improved dermal-epidermal junction in USCs-exos+ZIF-8/SIS group. Immunofluorescence detected discontinuous collagen VII (C7) expression at the basement membrane zone in USCs-exos+ZIF-8/SIS groups. Immunofluorescence showed the expression of CD206 of the skin from RDEB mouse treated with USCs-exos+ZIF-8/SIS were increased, but CD86 expression was downregulated. Immunohistochemistry of CD31 showed the expression of CD31 of USCs-exos+ZIF-8/SIS treated skin were increaed. Sirius Red staining showed the lowest ratio of Type I to Type III collagen in USCs-exos+ZIF-8/SIS group. Q-PCR of the skin from different group at day 7 showed compared to RDEB group, USCs-exos+ZIF-8/SIS group downregulated the expression of TGF-β1, IL-6, TNF-α, MMP-13, and upregulated the expression of IL-10 and VEGF genes ($p<0.05$). Through single-cell RNA sequencing analysis, the keratinocytes and fibroblasts overall increased in USCs-exos+ZIF-8/SIS group compared to RDEB froup. M1 macrophages significantly decreased and M2 macrophages overall showed an upward trend in USCs-exos+ZIF-8/SIS group. In M1 macrophages, toll-like receptor-2 signaling (TLR-2) was further inhibited. In upregulated keratinocytes and fibroblasts, VEGF signaling was upregulated compared to control. Protein-protein interaction analysis suggested a significant potential interaction between ADGRA2 and *COL7A1*. Safety analysis showed normal tissue structure in major organs from USCs-exos+ZIF-8/SIS group.

Conclusion: This study developed a novel USCs-exosomes composite ZIF-8/SIS hydrogel system. The composite hydrogel promoted RDEB keratinocyte and fibroblast migration, accelerated HUVECs tube formation in vitro; simultaneously inhibited inflammatory and MMPs-related gene expression in RDEB keratinocytes and fibroblasts, and upregulated *VEGF* expression. Additionally, the composite hydrogel inhibited mouse PBMC proliferation and inflammatory cytokine secretion, while promoting macrophage polarization from M1 to M2. Application of the composite hydrogel on RDEB mice effectively repaired skin lesions, improved dermal-epidermal separation, promoted C7 expression at the basement membrane zone and anchoring fibril generation; it also suppressed tissue inflammation, promoted vascularization, and improved extracellular matrix remodeling. Based on histological and omics analyses, the specific mechanisms may involve: the composite hydrogel providing C7 via USCs-exosomes, directly targeting the cause of RDEB to improve skin C7 expression; in inflammation repair, it modulates macrophage polarization from M1 to M2 and inhibits TLR-2 signaling to ameliorate lesion inflammation; simultaneously, it promotes keratinocyte and fibroblast proliferation and upregulates the VEGF signaling pathway to promote lesion vascularization and epithelial repair.

Keywords: Recessive dystrophic epidermolysis bullosa; Urine-derived stem cells; Exosomes; Small intestinal submucosa; Metal-organic framework

Presentation Abstracts

CONTENTS

023

Efficacy, tolerance, and acceptability of a TLC dressing in the treatment of epidermolysis bullosa skin lesions

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ABSTRACT

Objectives: To evaluate the efficacy and safety of a 100% lipid-colloid, extra-flexible dressing in the healing of skin lesions in patients with Epidermolysis Bullosa (EB). Secondary objectives include assessing pain upon dressing removal, treatment tolerance, the condition of perilesional skin, and the acceptability of the dressing by healthcare professionals and patients.

Methods: This case series study included 15 patients diagnosed with EB. Treatment with the 100% lipid-colloid, extra-flexible dressing was applied for up to 4 weeks, with 12 scheduled evaluation visits to document healing progress, pain, and tolerance. Parameters such as wound condition and the ease of dressing application and removal were assessed.

Results: A high percentage of lesions showed favorable progress over 4 weeks, defined as a reduction of at least 40% of the initial wound surface area. Additionally, adherence to treatment was high, with reduced pain upon dressing removal.

Conclusion: The 100% lipid-colloid, extra-flexible dressing provided a safe and effective treatment for EB lesions, promoting healing and improving patients' quality of life by reducing pain and trauma during the healing process.

024

Evaluation of the effect of iron therapy on nutritional and hematological parameters, disease extension, and patient-reported outcomes in pediatric patients with epidermolysis bullosa

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) is a systemic genodermatosis causing fragile skin, chronic wounds, and multisystemic involvement including chronic anemia. Patients frequently suffer anemia due to multiple factors: decreased intake, increased anabolism, malabsorption, active bleeding from wounds, chronic inflammation; among others. Current guidelines for treatment of anemia in EB recommend oral (PO) iron supplementation from infancy, and if hemoglobin (Hb) falls below 9mg/dL, begin intravenous (IV) iron infusions. We aimed to assess the change in nutritional and hematological parameters, as well as the patient-reported outcome measure Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB), in children with EB and anemia treated with iron, either IV or PO according to severity of their anemia and/or preference.

Methods: This was a retrospective, observational study at the National Institute of Pediatrics that analyzed clinical and laboratory data of children aged 0-18 with EB before and ≥6 months after initiation of iron therapy, from 2018-2024. We measured parameters such as body mass index (BMI), hemoglobin (Hb), hematocrit (Hct), and body surface area (BSA) affected by wounds; as well as iscorEB at a baseline visit and a follow up visit ≥6 months after. Descriptive statistics were used.

Results: We included 15 patients with a mean age of 9.2±5.7 years, 8 were male. Most (12, 80%) had recessive dystrophic EB. Six patients received IV iron. At baseline, their BMI was 13.6±1.9kg/m^2, 3 (50%) patients had <29% BSA by wounds, Hb was 8.2±1.9g/dL, Htc 26.1±4.9%, and iscorEB was 33.6±20.6. After treatment with 2.3±1.9 doses of IV iron, BMI increased to 15±2.8kg/m^2, 4 (64%) patients had <29% BSA by wounds, Hb increased to 10±1.2g/dL, Htc to 31.1±3.6 %, and iscorEB improved to 26±13.2. Nine patients received PO iron. At baseline, their BMI was 13.3±2.3kg/m^2, 8 (88%) patients had >29% BSA by wounds, Hb was 10±1.3g/dL, Hct was 31.5±2.7 %, and mean iscorEB 29.3±8.5. After treatment, BMI was 13.3±1.5kg/m^2, 7 (77%) had >29% BSA by wounds, Hb decreased to 9.5±1.6g/dL, Hct to 30.7±4.3 %, but iscorEB improved to 27.1±13.2.

Conclusions: Treatment with iron is essential to improve multifactorial anemia in all patients with EB, especially those with severe subtypes (RDEB, JEB). Whether treatment is done PO or IV depends on severity of the anemia, but other factors are taken into account such as age and patient preference. In this study, all patients who received iron treatment had improvement of the BSA affected by wounds and grade of anemia categories, regardless of treatment mode. The iscorEB measure also improved in all patients during the study period. Patients who received IV therapy additionally had improved BMI, Hb and Htc. This pilot study highlights the importance of iron supplementation to optimize clinical parameters and outcomes in patients with EB. Further studies of the benefit of iron supplementation in EB patients are required.

Keywords: Epidermolysis bullosa; Patient outcome assessment; Iron, anemia

Presentation Abstracts

CONTENTS

025

From fragile skin to stronger systems: insights from Ireland's EB butterfly review

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ABSTRACT

Background: Epidermolysis bullosa (EB) is a rare, life-limiting genetic condition characterised by skin and mucosal fragility. In Ireland, an estimated 300 people live with EB, yet systemic challenges persist in healthcare access, community support, and welfare provision. To address these gaps, Debra Ireland commissioned the EB Butterfly Review in 2024, a comprehensive national study of lived experience and service provision.

Methods: A mixed-methods approach integrated qualitative and quantitative data from 93 survey respondents, 31 stakeholder interviews, and a validation workshop with 14 EB experts (people with a lived experience of EB). A Research Advisory Group, including people with EB and carers, advised during the process to ensure patient-centred outcomes.

Results: Key challenges were identified including weakly structured care transitions across life stages, limited EB knowledge in community healthcare, workforce shortages and variability in home nursing, inconsistent access to wound care products and medicines, gaps in psychological and dental services, burdensome welfare processes, geographic inequities, unclear accountability in policy implementation. Despite these barriers, specialist centres provided highly valued, compassionate care.

Recommendations: Twelve evidence-based actions were proposed across five themes: (A) strengthening foundational care through policy alignment and workforce resourcing; (B) enhancing awareness, education, and research; (C) improving care coordination and life-stage transitions; (D) ensuring equitable access to wound care and financial support; and (E) improving accessibility and patient experience in hospital and community care.

Conclusion: The EB Butterfly Review provides the first holistic analysis of EB care in Ireland, highlighting systemic barriers and offering a clear roadmap for reform. Implementation of these recommendations has informed Debra Ireland's 2025–2028 strategy and has the potential to significantly improve the quality of life, dignity, and hope for people living with EB and their families.

026

From research to advocacy and action: Ireland's EB butterfly review launch

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ABSTRACT

Background: Epidermolysis bullosa (EB) is a rare, life-limiting genetic condition characterised by extreme skin and mucous membrane fragility. In Ireland, approximately 300 people live with EB, yet significant challenges remain in healthcare access, community support, and welfare provision. To address these gaps, Debra Ireland commissioned the *EB Butterfly Review* in 2024—a comprehensive national study examining lived experiences and service provision.

The review identifies areas where EB care is strong, where it falls short, and where urgent improvements are needed. It provides clear recommendations to ensure that everyone in the EB community receives the support they deserve. This research does not standalone; its launch serves as a foundation for advocacy, enabling Debra Ireland to push for better services and supports at every stage of life. The launch coincided with EB Awareness Week, an optimum time to transform research into tangible action.

Objectives: Highlight systemic gaps in EB care and support; Identify key advocacy messages; Maintain pressure on government for policy change and enhanced services; Raise public and political awareness and Foster collaboration across stakeholders.

Methods: A government TD (Member of Parliament in Ireland) sponsored the report launch, which included a briefing for TDs and Senators in government buildings. Invitations were extended to: All TDs and Senators (via invitations, follow-up emails, calls, and social media outreach); Individuals with lived experience of EB, who were supported to share their stories at the event and Research contributors and key funders.

The launch was supported by a robust media and social media campaign, including press releases, national and regional print coverage, radio interviews, and TV appearances. Key messages focused on: Coordinated community care with dedicated EB nurses; Fully resourced specialist hospital and outreach teams; Financial relief through initiatives like a National Bandage Scheme and Education, awareness, and seamless transition between paediatric and adult services.

Results: The event reached full capacity, with over 60 stakeholders in attendance, including more than 30 government TDs/Senators and key decision-makers. There was strong political engagement, including a commitment to establish an All-Party Interest Group to advance the EB agenda. Individuals with lived experience played a central role, sharing powerful testimonies. Extensive media coverage (print, radio and TV) amplified the message nationally and regionally.

Post launch, there have been parliamentary questions to keep the issues on the government agenda, New relationships have been built, and there has been ongoing engagement with TDs and Senators, meetings with the Department of Health and healthcare professionals, families and other key stakeholder, all aimed at turning the research into advocacy and action.

Conclusion: The EB Butterfly Review launch successfully highlighted critical gaps, proposed actionable solutions, and fostered collaboration among government, healthcare providers, and the EB community. It created a strong advocacy platform for implementing recommendations that can significantly improve quality of life, dignity, and hope for people living with EB and their families.

Presentation Abstracts

CONTENTS

027

Genetic and clinical spectrum of epidermolysis bullosa simplex in Argentina: experience from 1G5 patients in a reference center

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ABSTRACT

Background: Clinical diagnosis of EBS is often challenging due to overlapping features with other forms of epidermolysis bullosa. Molecular diagnosis is essential, as it enables the identification of specific genetic variants, confirming the diagnosis, facilitating appropriate patient management, and providing accurate genetic counseling, ultimately improving quality of life.

Methods: We studied 195 patients from 125 families who were referred to CEDIGEA (Center for research in genodermatosis and Epidermolysis Bullosa, School of Medicine, University of Buenos Aires) by dermatologists within our national network with clinical suspicion of EBS. Sanger sequencing was performed for exons 1 and 9 of the *KRT5* gene and exons 1 and 6 of the *KRT14* gene. If no variants were identified, clinical exome sequencing was subsequently carried out.

Results: A molecular diagnosis was achieved in 160 patients (82.05%). Of these, 144 were confirmed with EBS: 93 harbored pathogenic variants in *KRT5*, 49 in *KRT14*, one in *PLEC*, and one in *KLHL24*. Notably, 50% of patients with *KRT14* variants carried a variant affecting arginine 125, which was consistently associated with a severe generalized phenotype. In addition, we identified a significant number of patients with EBS-PM who shared the same *KRT5* variant (c.1649del), allowing us to characterize its clinical and molecular features. Overall, we detected 50 distinct pathogenic variants across these genes, 21 of which had not been previously reported in the literature.

Discussion: The most relevant contribution of this study lies in analyzing a large cohort of EBS patients, which enabled us to describe the genetic landscape of the disease in our population. This knowledge is particularly valuable for designing cost- effective molecular diagnostic algorithms, tailored to regional variant distributions.

Conclusion: Our nationwide network of dermatologists, in collaboration with CEDIGEA, has proven effective in enabling the molecular diagnosis of EBS. This approach underscores the value of coordinated national efforts in rare diseases, where timely and precise genetic identification can guide clinical management and improve patient care.

Presentation Abstracts

028

GMEB-SASS: first-in-human trial of bilamellar gene-corrected skin substitutes for the treatment of recessive dystrophic epidermolysis bullosa

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ABSTRACT

Background: Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited life- limiting skin disorder caused by mutations in the COL7A1 gene, which encodes type VII collagen, a key structural protein of anchoring fibrils at the dermal–epidermal junction. Loss of functional collagen VII results in skin fragility after minor skin trauma, chronic wounds, scarring, and a high lifetime risk of aggressive squamous cell carcinoma. Current treatments are limited to palliative wound management, which is burdensome, costly, and fails to address the underlying genetic defect. Recently the US Food and Drug Administration (FDA) approved two topical treatments (Vyjuvek and (Filsuvez), however, the wounds treated by these two drugs were mostly small and both treatments required repeated application.

Methods: GMEB-SASS clinical trial phase I/II is conducted at the LOEX (CHU de Québec- Université Laval) and investigates an ex vivo gene therapy strategy combined with tissue engineering for EB treatment. Autologous keratinocytes and fibroblasts are isolated from a small skin biopsy from RDEB patients and transduced with a self-inactivated retroviral vector carrying full-length COL7A1 cDNA. The corrected cells are expanded and used to generate GMEB-SASS, a gene-modified epidermolysis bullosa-self assembled skin substitute. These autologous bilayered dermo-epidermal skin substitutes will be surgically grafted onto chronic, non-healing wounds of enrolled patients. The preclinical studies were achieved, and regulatory approval was obtained from Health Canada.

Results: Comprehensive preclinical studies have been completed both in vitro and in murine models, demonstrating stable vector integration, sustained type VII collagen expression, correct localization at the basement membrane zone, and ultrastructural reconstitution of anchoring fibrils. Rigorous biosafety assessments confirmed absence of replication competent retrovirus or malignant transformation. Following these data, Health Canada has granted regulatory approval to initiate GMEB-SASS clinical trial consisting in the production of a gene modified epidermolysis bullosa-self assembled skin substitute (GMEB-SASS) and aims to assess safety, feasibility, and preliminary efficacy of genetically corrected skin grafts to treat RDEB permanently. Expected clinical outcomes include durable wound closure, reduced blistering frequency, and enhanced dermal–epidermal stability. Secondary endpoints encompass pain reduction, improved mobility, and better overall quality of life. From a health economics perspective, graft-based correction is anticipated to significantly reduce the daily costs of specialized dressings, hospital

admissions, and nursing care associated with chronic wound management. At present, GMEB-SASS clinical trial is in the patient recruitment phase, following completion of all preclinical studies and regulatory authorization by Health Canada.

Conclusion: GMEB-SASS clinical trial represents a highly innovative and promising therapy for an unmet clinical need for patients suffering from RDEB and could be a valuable treatment option to include within the Canada's health system once clinical trial is completed.

029

Hand reconstruction in a pediatric patient with recessive dystrophic epidermolysis bullosa: case report

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) is a rare, non-contagious genetic disease with no cure until now, characterized by alterations in the production of proteins responsible for binding the skin layers, such as collagen and elastin. It is characterized by skin fragility and blister formation after minimal trauma. Pseudosyndactyly is one of the most disabling manifestations of recessive dystrophic EB, associated with severe functional morbidity, scarring, and hand deformities, which profoundly impair function.

Objective: To report the case of a pediatric patient with recessive dystrophic EB submitted to corrective hand surgery, highlighting the surgical technique, wound dressing strategy, and postoperative outcomes.

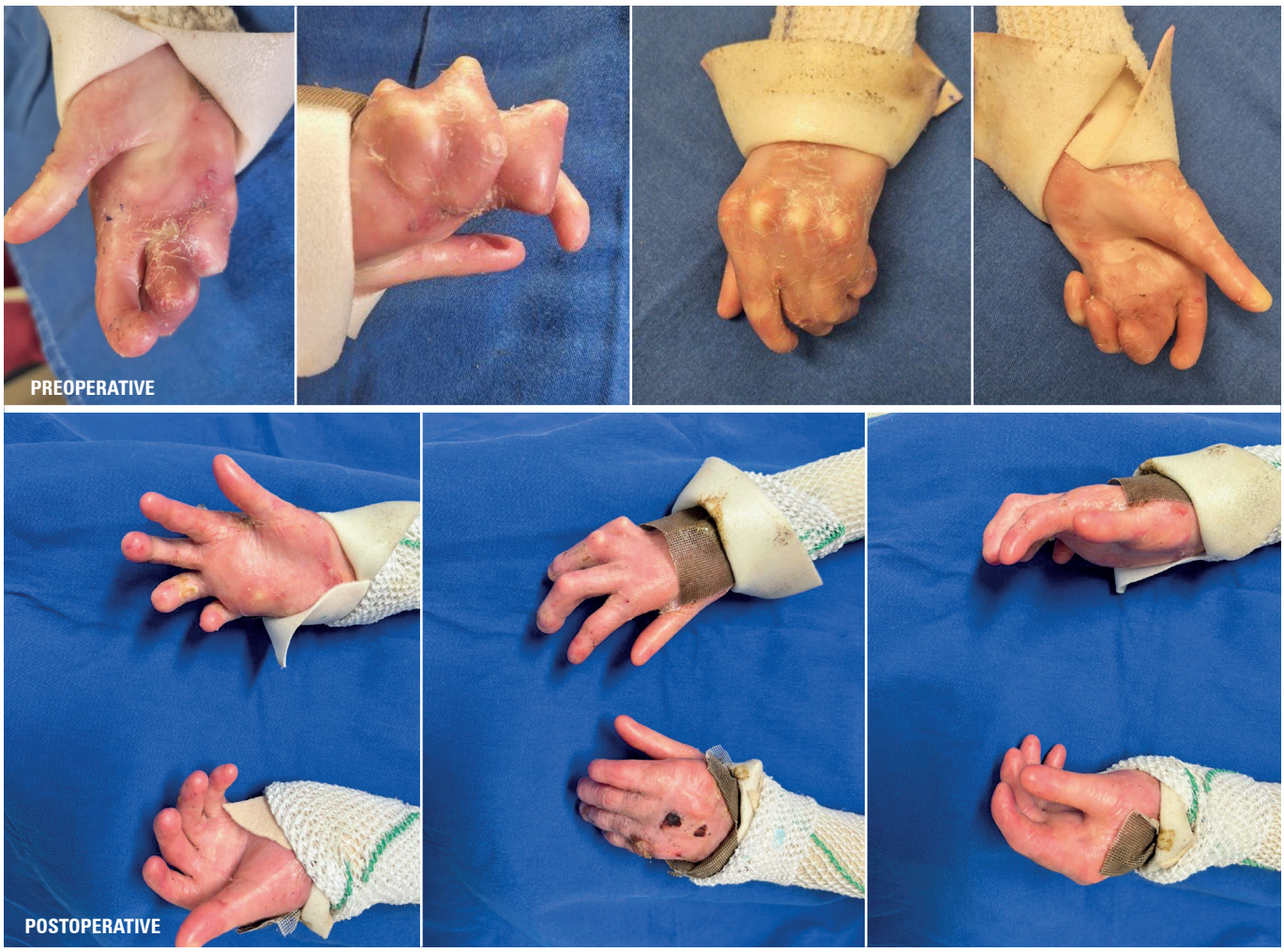
Methods: A 10-year-old female patient presented with multiple syndactylies and finger flexion contractures underwent adhesion release, digital separation, stabilization with Kirschner wires, and positioning of the fingers in extension/abduction using a metallic "racket" splint were performed. For wound care, a polyester non-occlusive mesh impregnated with a lipidocolloid matrix and silver salts (TLC-Ag) was applied. Upon contact with wound exudate, the dressing forms a gel while silver ions are released in a sustained manner within the matrix, ensuring antimicrobial protection and preventing adherence to the surgical site, thus allowing atraumatic removal. Dressing changes were performed every 7 days in the operating room.

Results: Postoperative dressings were changed weekly. The polyester mesh with TLC-Ag proved advantageous, as it did not adhere to the wound, facilitated dressing changes, reduced pain and risk of additional trauma, and provided antimicrobial effect. Kirschner wires and the orthosis were removed after 4 weeks, with a complementary orthosis maintained for up to 4 months. Functional improvement was observed, with increased range of motion and better digital positioning, without infectious complications.

Conclusion: Despite challenges, hand surgery in patients with Epidermolysis Bullosa is a feasible option for restoring manual function. The use of advanced dressings, such as TLC-Ag Healing Matrix, allowed for optimal moisture balance, enhanced wound healing, provided comfort, prevented infection, reduced the costs of prolonged hospitalization, and served as an important adjuvant in postoperative management. Improvement in motor function, digital mobility, and preservation of functional independence resulted in better quality of life, enabling the resumption of daily activities that had been compromised, such as drawing, playing, brushing teeth, and eating.

Six patients with recessive dystrophic epidermolysis bullosa (RDEB) underwent surgical treatment (12 hands). All presented multiple pseudosyndactylies, flexion contractures and functional impairment of grasp and pinch. Postoperative follow-up demonstrated improvement in interdigital opening, correction of contractures and functional hand use. One recurrence was observed and treated surgically. Figure 1 illustrates the preoperative deformity, intraoperative release of pseudosyndactyly, and the postoperative functional outcome in a representative patient.

Keywords: Epidermolysis bullosa; Syndactyly; Hand surgery; Advanced dressings; Case report



Note: Images shared with family consent. Do not distribute without the authors' permission.

Figure 1. Surgical correction of hand deformities in recessive dystrophic epidermolysis bullosa. (A) Preoperative appearance showing pseudosyndactyly and flexion contractures. (B) Intraoperative release of pseudosyndactyly and stabilization with Kirschner wires. (C) Postoperative result demonstrating restoration of finger separation and improved hand function

030

IL-4 inhibitors for pruritus in dystrophic epidermolysis bullosa: a systematic review

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ABSTRACT

Background: Dystrophic epidermolysis bullosa (DEB), caused by COL7A1 mutations, results in chronic skin fragility and disturbing pruritus. Although emerging evidence suggests IL-4 related signaling pathways plays a potential role in DEB-related pruritus, therapeutic effect of IL-4 inhibitors is heterogenous.

Objective: Synthesizing demographic and DEB-related clinical characteristics in DEB patients treated with IL-4 inhibitors, to optimize therapeutic management strategies.

Methods: We systematically reviewed PubMed, Web of Science, Scopus, and Embase for IL-4 inhibitor-treated DEB studies from inception to August 2025. Subgroup analyses compared outcomes by DEB subtype, age, IgE/eosinophil levels, and gender using longitudinal visual analogue scale (VAS) scores.

Results: 74 dupilumab-treated DEB patients (19 studies) were identified but no prior stapokibart cases were reported. We included 50 patients (16 studies) with extractable individual pre- and post-treatment VAS scores for efficacy analysis. Pruritus significantly decreased in the first 5 treatment months, followed by a transient rebound. Pruriginosa dominant DEB (DDEB-Pr) patients exhibited significant improvement than recessive DEB-Pr (RDEB-Pr) after 3 months of treatment ($p=0.002$, P.adjusted$=0.022$ by Bonferroni correction). No significant differences were observed across gender, age, IgE and eosinophils groups ($p>0.05$).

Conclusion: IL-4 inhibitors including dupilumab and stapokibart effectively reduce pruritus in DEB, with dominant DDEB-Pr showing greater VAS score improvement than RDEB-Pr. Further large-scale studies are needed to optimize T-helper type 2 (Th2)-targeted therapy for DEB-related inflammation.

Keywords: Epidermolysis bullosa; Pruritus; Dupilumab; Stapokibart; IL-4 receptor

Presentation Abstracts

CONTENTS

031

Immune response and clinical severity are shaped by skin-adapted *Staphylococcus aureus* in chronically infected patients

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ABSTRACT

Objective: Despite the well-described association of skin lesions with *Staphylococcus aureus*, the distinct ability of clinical isolates to influence the local and systemic inflammatory response in a patient-specific manner is insufficiently characterized. In this study, we analyzed clinical Recessive Dystrophic Epidermolysis Bullosa (RDEB), which is characterized by wounds chronically colonized with *S. aureus,* to explore the relationship between inflammatory immune response and strain diversity.

Methods: Children with RDEB (moderate phenotype n=5; severe phenotype n=10) and controls (n=18) were enrolled in the study. Profiling of plasma proteins (n=800), immune cells (n= 30 subsets and cytokine-producing cells) and cytokines (n=38) identified specific inflammatory signature in severe patients.

Results: Patients with severe RDEB presented high frequency of IL-17A+ cells among CD4+ and Mucosal-Associated invariant T (MAIT) lymphocytes. Positive *S. aureus* cultures from the skin of patients with RDEB allowed whole-genome sequencing of patient's strains and assessment of primary keratinocyte immune response upon bacterial challenge. Notably, *S. aureus* secretome and conditioned media from keratinocytes challenged with *S. aureus* strains from patients with severe but not from moderate RDEB promoted strong activation and pro-IL-17 response in both CD4+ and MAIT cells.

Conclusion: Our findings show that *S. aureus* strains isolated from patients with severe RDEB induce an IL-17-skewed immune response and pave the way for precision microbiology to explain and predict the highly variable virulence potential of bacterial clinical isolates.

032

Immunological and microbiological factors influencing the effectiveness of local gene therapy in patients with recessive dystrophic epidermolysis bullosa: results of a pilot study

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ABSTRACT

Introduction: Recessive dystrophic epidermolysis bullosa (RDEB) is the most severe form of congenital epidermolysis bullosa, for which local gene therapy is considered a promising treatment modality. It is known that chronic erosions may be colonized by opportunistic microorganisms, although clinical signs of secondary infection are often absent. Even subclinical colonization can influence local inflammation and the epithelialization process.

Objective: To evaluate the impact of microbial environment and cytokine profile on the effectiveness of local gene therapy in patients with RDEB.

Methods: Seventy patients treated with beremagene geperpavec (B-VEC) are under follow-up by the "Butterfly Children" Foundation. Twelve patients (aged 5–17 years) with severe RDEB who received treatment at the Foundation's Gene Dermatology Centers were included in this study. The focus was on chronic wound surfaces; patients with erosions presenting with purulent exudate and clear signs of secondary infection were excluded. An AAV vector encoding COL7A1 was applied topically to 18 chronic erosions. The following parameters were assessed before treatment and at week 8: rate of epithelialization and duration of remission, cytokine profile of wound exudate (IL-1β, TNF-α, IL-6, IL-10), and microbial environment of wound surfaces (culture, MALDI-TOF, PCR).

Results: Microbiological analysis revealed opportunistic microorganisms at low concentrations: *Staphylococcus aureus* (75%), *Pseudomonas aeruginosa* (33%), *Acinetobacter baumannii* (17%), *Stenotrophomonas maltophilia* (8%). In patients with Gram-negative colonization, higher levels of IL-1β (+38%) and TNF-α (+32%) were observed and persisted until week 8. IL-10 levels increased less markedly (+8% *versus* +20% in the group without Gram-negative flora). Mean epithelialization time in patients without Gram-negative flora was 5.0 weeks, compared to 7.3 weeks in those with colonization ($p<0.05$). Despite delayed healing, epithelialization occurred in some patients even with persistent *P. aeruginosa* colonization, highlighting the complex interplay between microorganisms, immune response, and reparative processes.

Conclusion: Local gene therapy in RDEB demonstrates clinical efficacy; however, the presence of Gram-negative non-fermenting bacteria in erosions—even at low concentrations and without clinical signs of infection—is associated with delayed healing and a predominance of proinflammatory cytokine profiles. These findings emphasize the need for regular microbiological monitoring and immunological assessment in clinical trials of gene therapy.

Presentation Abstracts

CONTENTS

033

Modulation of digit deformation and inflammation by unrestricted somatic stem cells (USSCs) in mice with recessive dystrophic epidermolysis bullosa

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ABSTRACT

Background: Recessive dystrophic epidermolysis bullosa (RDEB) is a blistering disorder secondary to mutations in the *COL7A1* gene encoding type VII collagen (C7), which results in chronic inflammation, impaired wound healing, and mutilating fibrosis. Unrestricted somatic stem cells (USSCs) are suggested to be a primitive mesenchymal stem cell population derived from umbilical cord blood that exhibit immunomodulatory properties.

Design: USSCs were injected intraperitoneally in each $C7^{hypo}$ mouse per week, which were collected for digit measurements, complete blood count (CBC), protein lysate, and plasma along with controls.

Results: Systemic administration of USSCs mitigated severe digit deformation and inflammation in $C7^{hypo}$ mice, exemplified by restoration of shortened digit length in $C7^{hypo}$ mice and lowering of the neutrophil and monocyte blood counts (Figure 1A-C). We found that USSCs significantly increased ratios of IL-1Ra to IL-1α in RDEB mouse skin (Figure 1D) which may relate to the reduced inflammation. This effect is likely attributable to leukemia inhibitory factor (LIF) production by USSCs, which was detectable in treated $C7^{hypo}$ mice (Figure 1E).

Conclusion: Our results demonstrate that digit deformation, inflammation, and cytokine dysregulation are attenuated by USSC administration in $C7^{hypo}$ mice.

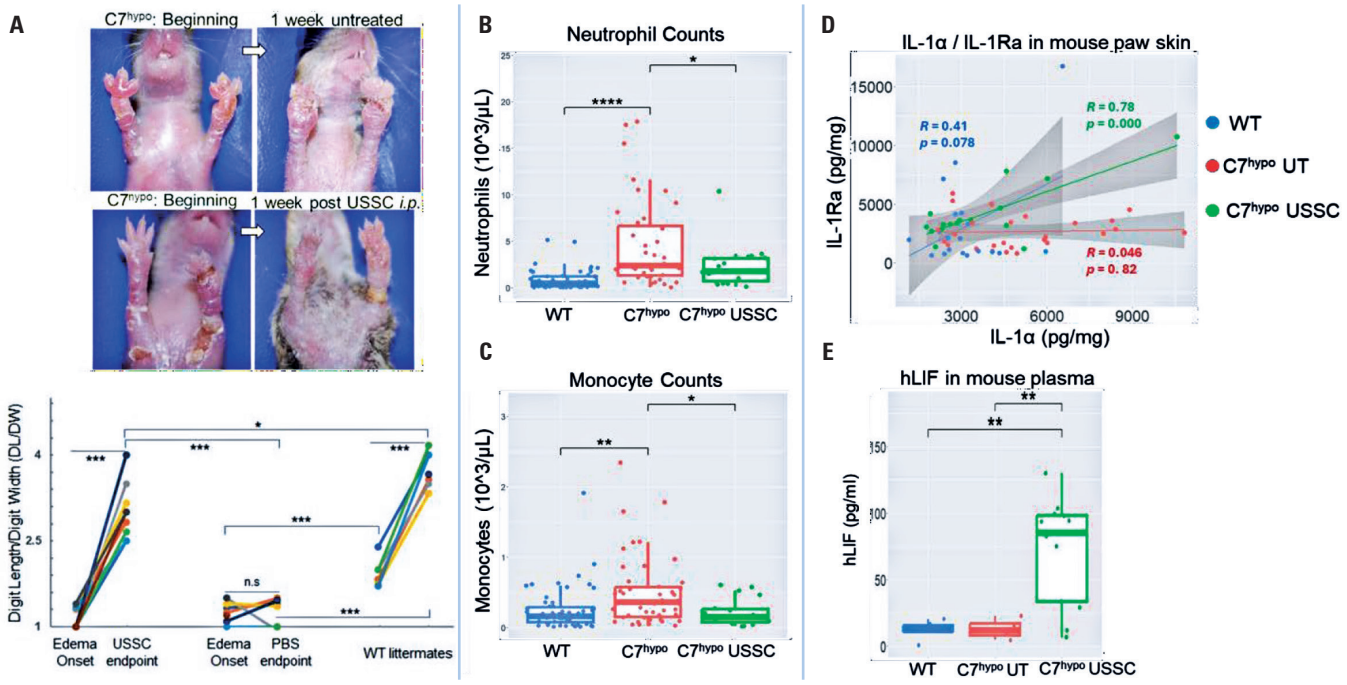

Figure 1. Digit deformation, inflammation, and IL-1α dysregulation were ameliorated by USSC treatment in C7^{hypo} mice. (A) Digit deformation measured by digit length / digit width (DL/DW) ratios in C7hypo paws at the start and a week after phosphate-buffered saline (PBS) or USSC administration, together with the age-controlled wild type (WT). (n ≥10 per group). Significances were calculated by two- tailed unpaired Student's t test. (B-C) Systemic inflammation measured by blood counts of neutrophils and monocytes in WT, untreated C7^{hypo} mice, and C7^{hypo} mice treated with USSCs. Significances were calculated by Tukey's HSD. (D) Relationship between IL-1Ra and IL-1α protein concentrations in paw skin lysates of WT, C7^{hypo}, and C7^{hypo} mice treated with USSCs with correlation (R) and p-value (p) calculated by Pearson's correlation. Human leukemia inhibitory factor (hLIF) concentrations in the plasma of WT, C7^{hypo} untreated, and C7^{hypo} mice treated with USSCs 1 day before collection. Significances were calculated by Tukey's HSD. p-value<0.05 (*), p-value<0.01 (**), p-value<0.0001 (****)

Presentation Abstracts

CONTENTS

034

Investigating chronic pain and itch mechanisms in a skin fragility disorder epidermolysis bullosa

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ABSTRACT

Epidermolysis Bullosa (EB) is a group of rare blistering disorders caused by mutations in genes essential for maintaining the dermal-epidermal junction (DEJ), resulting in extreme skin fragility. Chronic pain and itch arise even in the absence of visible skin damage, causing significant discomfort to EB patients. Effective analgesics for these symptoms are currently lacking and are critically needed to improve the lives of EB patients. Dystrophic EB (DEB), a subtype of EB, arises from COL7A1 gene mutations affecting collagen VII, a key DEJ structural component that stabilises the skin. We recently developed and characterised a mouse model of Dominant DEB (DDEB) that recapitulates the clinical phenotype of EB patients. In this study, we investigated chronic pain and itch phenotypes in DDEB mice and performed anatomical characterisation of neuroimmune networks in the skin. Mechanical allodynia, especially a major clinical concern in EB, and thermal sensitivity were assessed in male and female DDEB mice using von Frey and Hargreaves tests, respectively (thermal: 8-12 weeks, n=12/group; mechanical: separate cohorts across 10-24 weeks, n=12/group) to examine the development of mechanical hypersensitivity over time. The efficacy of clinical analgesics (n=6/group), including amitriptyline, buprenorphine, gabapentin, paracetamol, and meloxicam, and Phytocannabinoids (n=6/group), including cannabichromene (CBC), cannabigerol (CBG), and cannabidiol (CBD), was evaluated using von Frey assays.

Spontaneous scratching was measured at baseline (8-16 weeks, n=12) and following administration of pruritogens (n=4/group), histamine, serotonin, and chloroquine, to characterise itch via distinct pathways. Hind paw skin sections from DDEB mice (n=8) were stained with immunomarkers to quantify nerve fibre crossings at the dermal-epidermal junction. DDEB mice showed increased thermal hypersensitivity ($p<0.0001$) and peak mechanical allodynia at 12-14 weeks ($p<0.0001$) compared to WT controls, but differences in mechanical allodynia were not observed in older mice. Treatment with clinical analgesics produced a dose-dependent reduction in mechanical allodynia, with maximal effect at 1 h ($p<0.001$). Phytocannabinoids selectively reduced mechanical hypersensitivity in male DDEB mice, with peak efficacy at 5 h ($p<0.001$). In contrast, DDEB mice exhibited no itch phenotype at baseline or following pruritogen administration, when compared to WT mice across all groups. Immunostaining of skin sections revealed no differences in the frequency of nerve fibre crossings at the DEJ between DDEB and WT skin. Our DDEB mouse model reproduces the thermal and mechanical hypersensitivity reported in EB patients but shows no change in pruritus. Mechanical

sensitivity peaks at 12-14 weeks, consistent with the onset of blistering, whereas the lack of differences in older DDEB mice compared to WT mice may reflect fibrotic changes in the skin. Mechanical hypersensitivity was attenuated by clinically used analgesics spanning acute, neuropathic, and inflammatory pain classes, highlighting the multifaceted nature of EB pain. Phytocannabinoid treatment also reduced mechanical hypersensitivity in a sex-specific manner. The lack of anatomical changes in cutaneous innervation suggests EB pain may arise from altered nociceptive signalling rather than structural differences in peripheral nerves. Further characterisation using imaging and other approaches will be critical to elucidate EB-specific pain pathways and guide the development of targeted analgesics to improve the lives of EB patients.

Presentation Abstracts

CONTENTS

035

Symptom burden in recessive dystrophic epidermolysis bullosa: focus on pain and pruritus

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ABSTRACT

Introduction: Pain and pruritus are constant and debilitating manifestations in individuals with Recessive Dystrophic Epidermolysis Bullosa (RDEB), frequently associated with extensive and difficult-to-manage skin lesions (Figure 1-A and 1- B).

Objective: To assess the intensity of these symptoms in patients followed at referral centers in Espírito Santo, Brazil.

Methods: This observational, descriptive study was approved by the Research Ethics Committee of the *Universidade Federal do Espírito Santo* (CAAE: 41764921.4.0000.5060). Six individuals with clinically and genetically confirmed RDEB completed a structured questionnaire developed by the authors, consisting of ten specific questions on pain and pruritus, combined with a visual analog scale. Pruritus was classified as mild, moderate, or severe. Pain was assessed in three situations: take a shower, put on shoes and change bandages.

Results: Most participants (83.3%) reported moderate pruritus (Figure 1-C). Regarding pain, 66.6% indicated moderate intensity during bathing and dressing changes, whereas shoe-wearing was most frequently associated with severe pain (Figure 1-D). No participant reported an absence of pain or pruritus.

Conclusion: These findings highlight that pain and pruritus significantly affect the quality of life in individuals with RDEB. In the absence of a cure, interventions that lessen symptom intensity are essential for comprehensive care.

Keywords: Epidermolysis bullosa dystrophica; Pain; Pruritus

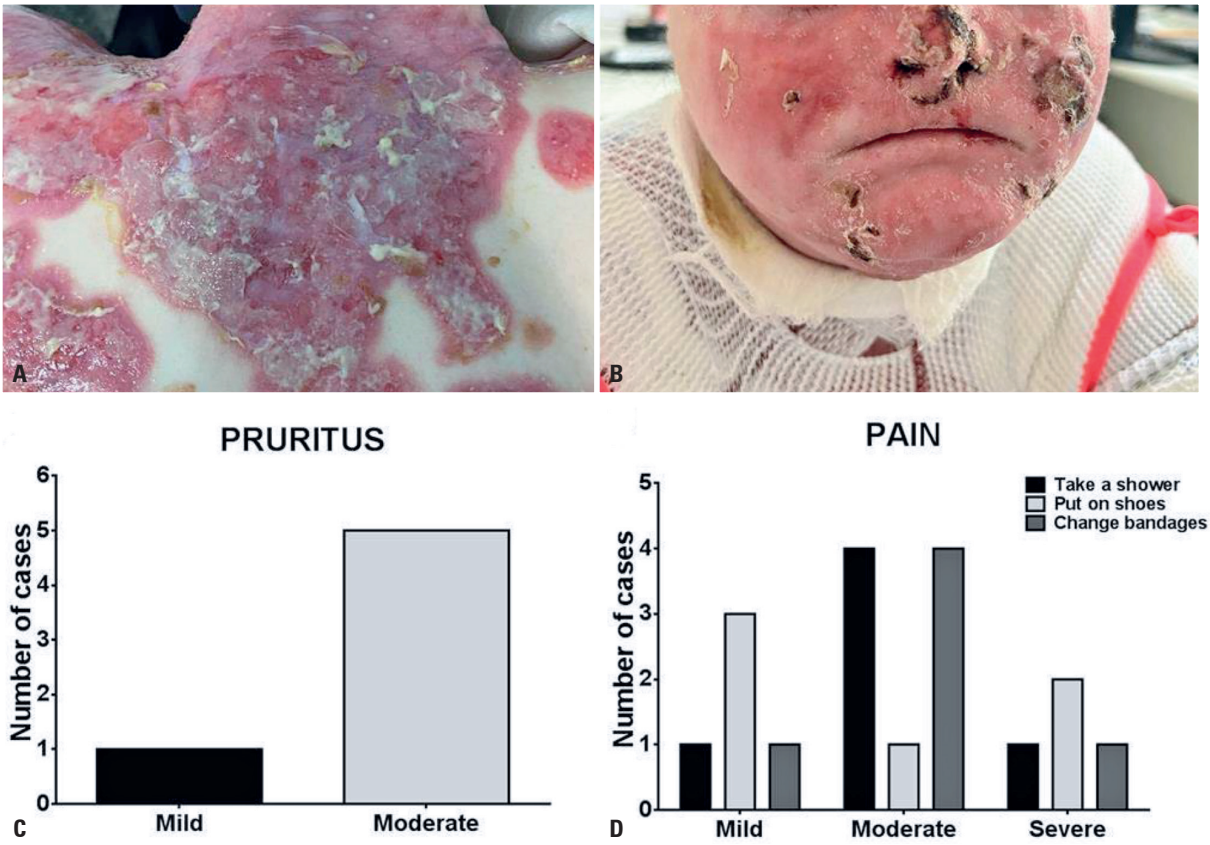

Figure 1. Clinical aspects and symptom intensity in individuals with RDEB. (A, B) Extensive and recurrent cutaneous lessions characteristic of RDEB. (C) Intensity of pruritus reported by participants. (D) intensity of pain in different daily situation

Presentation Abstracts

CONTENTS

036

Therapeutic research and evaluation for advancing treatments for epidermolysis bullosa (TREAT-EB)

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ABSTRACT

Epidermolysis Bullosa (EB) is a family of rare, incurable, inherited disorders that are characterised by extreme skin and mucosal fragility. The two most severe forms are recessive dystrophic EB (RDEB), caused by mutations in the gene encoding type VII collagen, and junctional EB (JEB), caused by mutations in genes encoding the skin basement membrane proteins laminin 332 (α3, β3, γ2), type XVII collagen or integrin α6β4. Despite similarities between the disease pathology of JEB and RDEB, there are dramatic differences in life expectancies of these subtypes of EB. RDEB patients survive to early or mid-adulthood, comparatively JEB patients rarely survive beyond the first year of life. The reason for this disparity in survival is poorly understood and therapeutic development has largely focused on individual EB subtypes.

Building on the pre-clinical expertise in EB research at QMUL (https://www.bci.qmul.ac.uk/our-research/epidermolysis-bullosa/) we have developed a preclinical analysis pipeline running from transcriptomic data through to in vivo EB disease models. Transcriptomic data from over 40 patients with RDEB, DEB and JEB are combined with highly scalable 2D/3D EB culture models and clinically relevant EB in vivo disease models of the main EB subtypes, allowing for the first time to directly dissect and compare different EB pathogenesis mechanisms.

Knockdown of the disease causing EB genes in keratinocytes display key features of EB subtypes such as deregulated, JAK/STAT, YAP and TGFβ signalling. 3D cell culture models of the different EB subtypes are able to recapitulate the EB subtype specific proliferation, differentiation and cell signalling defects. Further we have established EB in vivo disease models for JEB, RDEB and DEB and characterised their unique disease phenotype and wound healing response. While all EB disease models show a delay in wound healing, this is most severe in *Lama3* depleted wounds whereas mutations in *Col7a1* lead to changes in angiogenesis and extracellular matrix remodelling.

Importantly, the TREAT-EB pipeline not only enables to dissect the EB disease heterogeneity but also to simultaneously screen new drug candidates in different EB subtypes, compare treatment effects and quickly generate preclinical data for multiple EB indications. TREAT-EB is a novel approach to accelerate translational research in the rare disease field.

037

Topical Oleogel-S10 in real-life management of dystrophic and junctional epidermolysis bullosa: a case series

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ABSTRACT

Background: Epidermolysis bullosa treatment landscape was limited to wound bandages until very recently. Supportive care remains the mainstay of treatment. Triterpenes derived from birch bark, with anti-inflammatory and regenerative properties, represent the first therapy approved in Europe for EB. However, real-life evidence regarding their effectiveness in daily clinical practice remains limited.

Objective: To describe the real-life experience with a topical triterpene cream in patients with dystrophic and junctional EB.

Methods: We conducted an observational case series including 11 patients (9 recessive dystrophic EB, 2 junctional EB) treated in routine clinical practice. The cream was in each bandage change in target wounds, alongside standard wound care. Endpoints were lesion closure, size and patient/caregiver satisfaction at 3 and 6 months. No formal disease severity score (e.g., EBDASI) was used given the real-world setting.

Results: Among the 11 patients, 2 discontinued treatment: one due to local pain and inflammation upon application, and another because of lack of perceived benefit. 67% of the lesions were located on limbs and 44% of patients had also wound on trunk. Of the 9 patients who continued, 6 achieved complete closure of at least one treated lesion at 3-6 months, while the remaining 3 experienced partial improvement with wound area reduction and symptomatic relief. Satisfaction was reported by patients or caregivers in 7 out of 9 evaluable cases. No systemic adverse events were recorded, and the topical cream was generally well tolerated.

Conclusion: In a real-life clinical setting, topical triterpene cream showed to be helpful in lesion closure and high patient/caregiver satisfaction in both dystrophic and junctional EB. Despite the small sample size and lack of a control group, these results support its consideration as an adjuvant therapy in EB wound management while waiting for the regulatory approval of gene therapy.

Keywords: epidermolysis bullosa, triterpenes, real-world practice, topical therapy, wound healing

Presentation Abstracts

CONTENTS

038

Unraveling Inflammation in RDEB: Insights from COL7A1-Knockout human fibroblasts

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ABSTRACT

Epidermolysis Bullosa (EB) is a group of rare, inherited disorders that affect the dermo- epidermal junction, leading to blistering, erosions, and skin wounds. The severity of EB varies, with the most severe forms being disabling or even fatal. Recessive Dystrophic Epidermolysis Bullosa (RDEB) is characterized by deficient or absent production of type VII collagen, caused by a mutation in the COL7A1 gene. This results in repeated wound healing and chronic inflammation, altering pro-fibrotic pathways. Current treatment is mainly palliative, and its limitations highlight the need for new approaches that improve patients' quality of life. A promising alternative is the modulation of gene expression in genes involved in fibrosis. Thus, the aim of this study was to investigate the behavior of BJ-hTERT fibroblasts with COL7A1 knockout (BJ-hTERT-KO) and compare them with wild-type BJ-hTERT cells (control group); to evaluate the impact of the mutation on proliferation, viability, cell migration, and wound healing; to perform a dose-response curve with LPS to assess cytotoxicity; to quantify IL-6 expression after treatment with Losartan and Angiotensin II; and to verify AGTR1 expression by qPCR.

To achieve these goals, fibroblast cell lines (BJ-hTERT), both knockout for COL7A1 and wild-type, were cultured in DMEM supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Cell proliferation was assessed by flow cytometry. Migration assays were conducted using a scratch assay, with wound closure monitored under bright - field microscopy and analyzed with ImageJ software. A dose-response curve for lipopolysaccharide (LPS) was performed at concentrations of 0.01–10μg/mL to assess cytotoxicity, with cell viability determined by MTT assay. Finally, IL-6 quantification was performed by ELISA after treatment with Losartan and Angiotensin II.

Results showed that the wild-type lineage had significantly higher proliferation, approximately 2.3 times greater than the knockout group ($p<0.05$), as measured by flow cytometry in triplicate. MTT assays confirmed that the cell multiplication rate was significantly lower in knockout cells ($p<0.05$). In the migration assay, knockout cells took longer to close the wound (~96 h) compared to wild-type cells, which fully closed the wound in about 80 h. The LPS dose-response curve showed no cytotoxicity at the tested concentrations (0.01–10μg/mL, $p>0.05$). IL-6 expression did not differ significantly between groups ($p>0.05$), indicating that the isolated absence of type VII collagen does not influence the inflammatory response under the tested conditions.

In conclusion, the data demonstrate a significant difference in cellular behavior between knockout and wild-type fibroblasts, particularly in proliferation and metabolic rate. The absence of type VII collagen does not alter IL-6 expression. Continued research on gene modulation is essential to support the development of novel anti-fibrotic drugs and gene therapies to improve patient well-being.

Presentation Abstracts

039

Immunofluorescence mapping *versus* electron microscopy in epidermolysis bullosa: comparative retrospective study in 84 genetically confirmed patients in Australia

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) subtypes can be diagnosed and distinguished by three internationally recognized methods: immunofluorescence mapping (IFM), electron microscopy (EM) and genetic testing (current gold standard). Each method has its limitations and is not equally available worldwide, as some are more cost-effective and require specific expertise. Given the rarity of EB, our aim was to compare these diagnostic tools in a relatively large cohort covering a broad age range, to evaluate their diagnostic accuracy and limitations.

Methods: We conducted a retrospective cohort study of 84 genetically confirmed EB patients (41 males, 43 females; mean age 22 years, range 3 days–62 years) who underwent both IFM and EM. Diagnostic success was also evaluated by biopsy site, quality (blistered *versus* non-blistered), and source (EB center *versus* external facility).

IFM was performed at St. George Hospital (Sydney). Skin biopsies were shipped in Michel's Medium (2–8°C), processed, and stained with 15 monoclonal antibodies against EB-related proteins, followed by fluorescently tagged secondary antibodies. Fluorescent signal patterns were assessed under a UV microscope. EM was primarily carried out at the Royal Children's Hospital (Melbourne). Biopsies were fixed in 2.5% glutaraldehyde buffered with 0.1 M sodium, sectioned into ultrathin slices (70–90nm), and examined with a TEM at 80kV to assess ultrastructural morphology. Genetic testing of an EB panel was performed at the Royal Brisbane and Women's Hospital. Blood samples (3–5mL in EDTA) were stored at 4°C and sequenced using Sanger sequencing until 2021, and thereafter NGS (Illumina NovaSeq 6000). Variant classification followed ACMG guidelines, ACGS Best Practice Guidelines v1.2, and SVI recommendations.

Results: IFM outperformed EM in overall accuracy (71.4% *versus* 58.3%) and sensitivity for EB simplex (EBS) (81.1% *versus* 56.6%) and junctional EB (JEB) (100% *versus* 70%). Dystrophic EB (DEB) (39.1% *versus* 43.5%) was the most challenging subtype. EM showed higher accuracy for RDEB than for DDEB (70.8% *versus* 60.9%). IFM, on the other hand, showed slightly lower accuracy for RDEB compared with DDEB (56.5% *versus* 69.6%). Biopsy referred from external facilities were more often non-blistered (17.6%

IFM, 53% EM) than those from EB centres (11.3% IFM, 38% EM). Foot and arm were the most common sites, both with good diagnostic yield. On average, IFM results were confirmed after 72 hours of biopsies and EM within 4 weeks, whereas for genetic results the average was 10-24 weeks.

Conclusion: Genetic testing with NGS remains the gold standard for EB diagnosis, but is still not routinely funded in many countries and has the longest turnaround time, making it suboptimal for neonates, where a rapid diagnosis is essential. IFM proved to be the most accurate method overall, has the lowest turnaround time, is widely accessible including in resource-limited settings, and requires relatively less technical expertise than EM or genetic testing. Its limitations in certain subtypes can be mitigated by complementing it with EM. Proper biopsy technique remains a key determinant of diagnostic outcome, highlighting the importance of performing biopsies correctly.

040

Genotype-phenotype correlations in dystrophic epidermolysis bullosa

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ABSTRACT

Background: Dystrophic epidermolysis bullosa (DEB), caused by COL7A1 mutations, encompasses a spectrum of inherited mucocutaneous fragility disorders. It is subclassified into localized, inversa, pruriginosa, intermediate, severe and self-improving subtypes. Despite advances in genetic diagnostics, genotype-phenotype correlations remain incompletely understood.

Objective: This study aimed to systematically investigate the relationship between mutation types and clinical manifestations in DEB, with emphasis on their role in determining disease severity across different anatomical sites.

Methods: We analyzed cross-sectional data from 91 genetically confirmed DEB patients including 46 with dominant (DDEB) and 45 with recessive (RDEB). Mutations were classified by type - glycine substitution (GS), non-glycine substitution (NGS), frame shift (FS), slicing (SP) and nonsense (NS) – as well as by domain location and presence of premature termination codon (PTC). RDEB genotypes were categorized as: biallelic PTC, PTC+FS, PTC+SP, PTC+GS, PTC+NGS and Others. Disease severity was quantified using the Epidermolysis Bullosa Disease Activity Scoring Index (EBDASI), covering skin, mucosa, scalp, nails, and other epithelialized surfaces for both activity and damage. Non-parametric tests including Kruskal–Wallis and Dunn's post-hoc with Bonferroni correction were applied to compare EBDASI scores across different mutation types.

Results: No significant differences in EBDASI activity or damage scores were observed across RDEB mutation groups for skin, mucosa, scalp, or other epithelialized surfaces. However, nail activity was higher in PTC+GS compared to PTC+SP ($Z=2.92$, $p.adj=0.018$) and Others ($Z=3.34$, $p.adj=0.013$). In DDEB, significant differences were detected in mucosa activity (Eyes: $p=0.020$; Nose: $p=0.020$; Oral cavity: $p=0.035$), mucosa damage (Eyes: $p=0.020$; Anogenital region: $p=0.020$; Oral cavity: $p=0.027$), and nail activity ($p=0.043$). FS were associated with higher mucosa activity and damage than all other types, while NGS correlated with elevated nail activity (FS: $Z=2.98$, $p.adj=0.012$; GS: $Z=3.01$, $p.adj=0.032$; NS: $Z=2.89$, $p.adj=0.021$).

Conclusion: This study demonstrated genotype–phenotype relationships in DEB. In RDEB, the PTC+GS genotype correlated with severe nail activity. In DDEB, FS were linked to increased activity and damage in mucosal sites including eyes, nose, oral cavity and anogenital region, as well as heightened nail activity.

Keywords: Dystrophic epidermolysis bullosa; premature termination codon; genotype-phenotype correlation

Presentation Abstracts

CONTENTS

041

Mental health in epidermolysis bullosa: psychological care for patients and their families

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ABSTRACT

Background: Beyond the severe physical burden, EB significantly impacts patients' and their relatives' emotional well-being, social participation and mental health. In recognition of the multifaceted nature of the condition, many EB expertise centres have psychologists or psychotherapists in their multidisciplinary care teams. However, structured knowledge regarding challenges and strategies of psychological and psychotherapeutic support in EB remains limited.

Objective: This study aims to explore psychological and psychotherapeutic approaches currently used in EB care. By analysing the perspectives of international experts working with EB patients and their families, common themes in psychological treatment and effective interventions are identified.

Methods: We conducted 15 expert interviews with psychologists and psychotherapists working with EB families in 13 different countries. In addition, socio-demographic data was obtained via an online questionnaire. The interviews were transcribed verbatim and subjected to thematic analysis, allowing for inductive theme development and cross-country comparison of practices.

Results: International comparison revealed a highly diverse landscape of psychological support for people living with EB. Across settings, three primary modes of care emerged: brief consultations within multidisciplinary "carousel" clinical appointments, separate ambulatory or inpatient consultations, and – less frequently – long-term psychotherapeutic support.

The most central topics addressed in psychological consultations reflect the psychosocial challenges faced by patients and relatives, including emotion regulation, self-esteem, the search for meaning, practical limitations, pain management, sexuality, the balance between attachment and autonomy, social integration and exclusion, and confronting cancer, amputation, and death. Relatives also often deal with marital conflict, grief, uncertainty about the future, and feeling overwhelmed. The broader context highlights the importance of supporting siblings and of ensuring that institutions such as schools and kindergartens are adequately informed to facilitate transitions.

Interventions cover psychoeducation, emotion regulation, building resilience, and adapting behavioural or trauma-informed methods to suit the realities of EB. Overall, experts agreed that psychological support for EB patients must be highly individualised, taking into account factors such as age, EB type and personal coping strategies.

A consistent finding was the importance of the therapeutic relationship. For building trust with patients who often face frequent medical interventions and profound emotional vulnerability as well as ambivalence about addressing difficult feelings, experts emphasised the need for flexibility, patience and creativity. Furthermore, therapists highlighted the importance of systemic work and engaging with parents, siblings, schools and the wider care network.

Conclusion: This study provides the first empirically informed insights into psychological and psychotherapeutic practice in supporting EB patients and their relatives. It identifies the key issues that need to be addressed, as well as the most effective methods for doing so.

Keywords: Epidermolysis bullosa; Mental health; Psychology; Psychotherapy, Family support; Multidisciplinary care

042

Low-level laser therapy in junctional epidermolysis bullosa

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ABSTRACT

Photobiomodulation using low-level laser therapy (LLLT) is a non-invasive strategy to improve healing and reduce the symptoms associated with chronic granulation tissue wounds, surgical wounds and amelogenesis imperfect, with the potential to improve the quality of life in patients with Epidermolysis Bullosa.

Here we present the use of LLLT in three patients with JEB. Laser used for treating the patients we Therapy DMC and Therapy AC DMC.

Patient 1, a 16 year old female patient with severe JEB presents a chronic wound on her tongue. The mother reports the wound has been present since the age of 2. The lesion was treated with 660nm continuous light laser, 6 J per point, 2 mm distance from the wound, 4 application points. Three sessions every 48 hours. The patient reported a significant change in pain and oral functions. She could now eat tomato, orange and lemon without pain and bleeding, brushing the teeth was no longer painful. Pain on her tongue reduced on a VAS from 10 to 0.

Patient 2, 5 year old female patient with intermediate JEB presents unrestored and very hypersensitive permanent lower incisors with severe hypoplastic AI and granulation tissue wounds on her nostrils. Laser was applied on the teeth to reduce hypersensitivity (4J red laser 660nm and 4J infrared laser per point, 2mm distance from the cervical area of each lower incisor. The same protocol was applied on the right nostrils and hyperplastic gingivae of the upper arch. Five sessions were conducted. Patient reported outcome: Pain caused by the air/water syringe reduced from 5 to 1, pain when brushing the teeth reduced from 4 to 1 and pain while eating chocolate reduced from 3 to 0. Dental fear decreased from 4 to 0.

Patient 3, 13 year old female patient with intermediate JEB presents chronic granulation tissue on her neck. LLLT was applied, reducing the local inflammation, itch, and wound exudate, while promoting healing.

LLLT is a promising strategy for granulation tissue wounds, tooth sensitivity and gingival inflammation in JEB.

Presentation Abstracts

CONTENTS

043

The EB cell atlas: a framework for translational drug discovery

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ABSTRACT

Single-cell RNA sequencing (scRNA-seq) enables systematic dissection of tissue complexity and is ideally suited to uncover disease-driving mechanisms. This is particularly powerful for recessive dystrophic epidermolysis bullosa (RDEB), a rare genetic disorder marked by skin fragility, chronic wounds, fibrosis, and cancer predisposition. Despite advances in care, there is an urgent need for disease-modifying therapies, underscoring the value of scRNA-seq for elucidating pathogenic mechanisms and identifying therapeutic targets.

To accelerate drug discovery in EB, we established the first large-scale EB Cell Atlas, profiling over 300,000 cells collected across different EB subtypes and diverse tissues, including intact and wounded skin, squamous cell carcinoma (SCC), wound-dressing derived cells, blood, alongside matched healthy control samples. Integration into a unified atlas enables us to perform cross- sample and stage-resolved comparisons, creating a platform for target discovery, biomarker development, and therapeutic innovation. In the present study, we focused on RDEB as a disease model to explore the utility of the atlas and to identify potential pathogenic mechanisms and novel targets. Differential gene expression (DEG) analysis across disease stages, from healthy skin to RDEB wounds and SCC, revealed progressive transcriptional changes in both structural and immune compartments. Gene set enrichment analysis (GSEA) showed that with advancing disease stage, immune-mediated processes and metabolic pathways became more strongly enriched. Notably, fibroblasts showed these same pathway enrichments without an increase in overall abundance, indicating that transcriptomic reprogramming, rather than expansion, drives their altered function. Cell–cell communication analysis confirmed fibroblasts as a major signaling hub in RDEB. Deeper analysis of fibroblast states revealed marked transcriptional shifts enriched for TNFα signaling, epithelial-to-mesenchymal transition, hypoxia, and oxidative phosphorylation. Subclustering resolved a disease-specific fibroblast cluster expanded in RDEB skin, alongside stage-dependent subtypes including inflammatory, matrix-remodeling (mCAF), and immunomodulatory (iCAF) fibroblasts in wounded and SCC tissue. Finally, pseudotime analysis connected these states into continuous differentiation trajectories from homeostatic to inflammatory and cancer-associated states, mapping fibroblast evolution through the course of fibrosis, chronic wound repair, and tumorigenesis. These findings demonstrate that the EB Cell Atlas can uncover disease-driving mechanisms and dissect dynamic changes across cell types and disease stages.

Presentation Abstracts

044

Improving skin regeneration in JEB by targeting the integrin αvβ6

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ABSTRACT

Introduction: Epithelial integrin αvβ6 has many important roles in skin repair in particular the activation of latent TGFβ and its abnormal activity has been associated with chronic wounds. αvβ6 integrin is transiently upregulated in blistered skin, however it becomes chronic in epidermolysis bullosa skin blistering diseases such as Recessive Dystrophic Epidermolysis Bullosa (RDEB) and Junctional EB (JEB). Here we explore how pathological integrin αvβ6 upregulation in EB is driving defective wound healing, chronic inflammation, and fibrosis and if its targeted inhibition improves skin EB symptoms using an inducible JEB disease mouse model.

Methods: A Tamoxifen-inducible JEB disease model with epidermis-specific LAMA3 knock-out (JEB eKO) was utilized for identifying the αvβ6 integrin signalling changes by immunofluorescent staining and flow-cytometry during skin homeostasis and wound healing. To inhibit αvβ6 signalling in JEB skin in vivo a novel αvβ6 integrin blocking antibody 264RAD was injected intraperitoneally for two weeks prior skin analysis.

Results: αvβ6 integrin expression is significantly upregulated in epidermis of JEB eKO mice, especially in the blistering areas in comparison to controls. The increased expression of αvβ6 correlates with enhanced inflammatory and fibrosis markers in blistered and wounded skin, suggesting a key role in the pathological mechanisms driving skin disease.

The 264RAD treatment showed a strong decrease in integrin αvβ6 expression and a modest increase in skin cell proliferation, angiogenesis and immune cell infiltration in particular FoxP3+ Treg cells. Importantly a reduction in fibrosis around skin blisters, less skin blistering and an overall improvement in wound healing was observed in JEB eKO mice treated with 264RAD.

Conclusion: The obtained preclinical data reveals abnormal expression of αvβ6 integrin in JEB and indicates that inhibition of αvβ6 is a potential novel therapeutic target to improve skin health and regeneration in JEB and possibly other EB subtypes.

Presentation Abstracts

CONTENTS

045

KLHL24 Mutation Drives Intermediate Filament Degradation, Mitochondrial Dysfunction and Fibrosis in heart failure patients

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ABSTRACT

A striking aspect of epidermolysis bullosa patients with a *KLHL24* mutation (*KLHL24*^{mut}) is their life-threatening deterioration of heart function. KLHL24 is part of the ubiquitin-proteasome system, acting as a substrate-specific adaptor protein for E3 ubiquitin ligase. *KLHL24*^{mut} is a gain-of-function mutation causing cardiac and skin pathologies through excessive degradation of target proteins. Although reduced desmin levels in cardiomyocytes (CMs) have been documented, additional mechanisms in *KLHL24*^{mut}-driven heart pathology remain unexplored. To better understand the pathophysiology of KLHL24^{mut}-driven heart failure, we integrated proteomic analyses of heart tissue of two *KLHL24*^{mut} patients with human induced pluripotent stem cell (hiPSC) models. Mass spectrometry analysis of CMs derived from patient hiPSCs mirrored the proteomic profile of their left ventricle tissue. We uncovered that KLHL24^{mut} mediates the excessive degradation not only of desmin, but also of synemin and vimentin. In cardiac tissue, the effects of *KLHL24*^{mut} extend beyond CMs or IF proteins, affecting cardiac fibroblasts and a wide array of proteins. This leads to impaired PKA signaling, disrupted mitochondrial function and localization, alterations in autophagy and sarcomere structure, and a pronounced fibrosis.

Importantly, close similarity between hiPSC-derived CMs and patient cardiac explants validates hiPSC-derived CMs as a relevant model for future mechanistic and therapeutic studies.

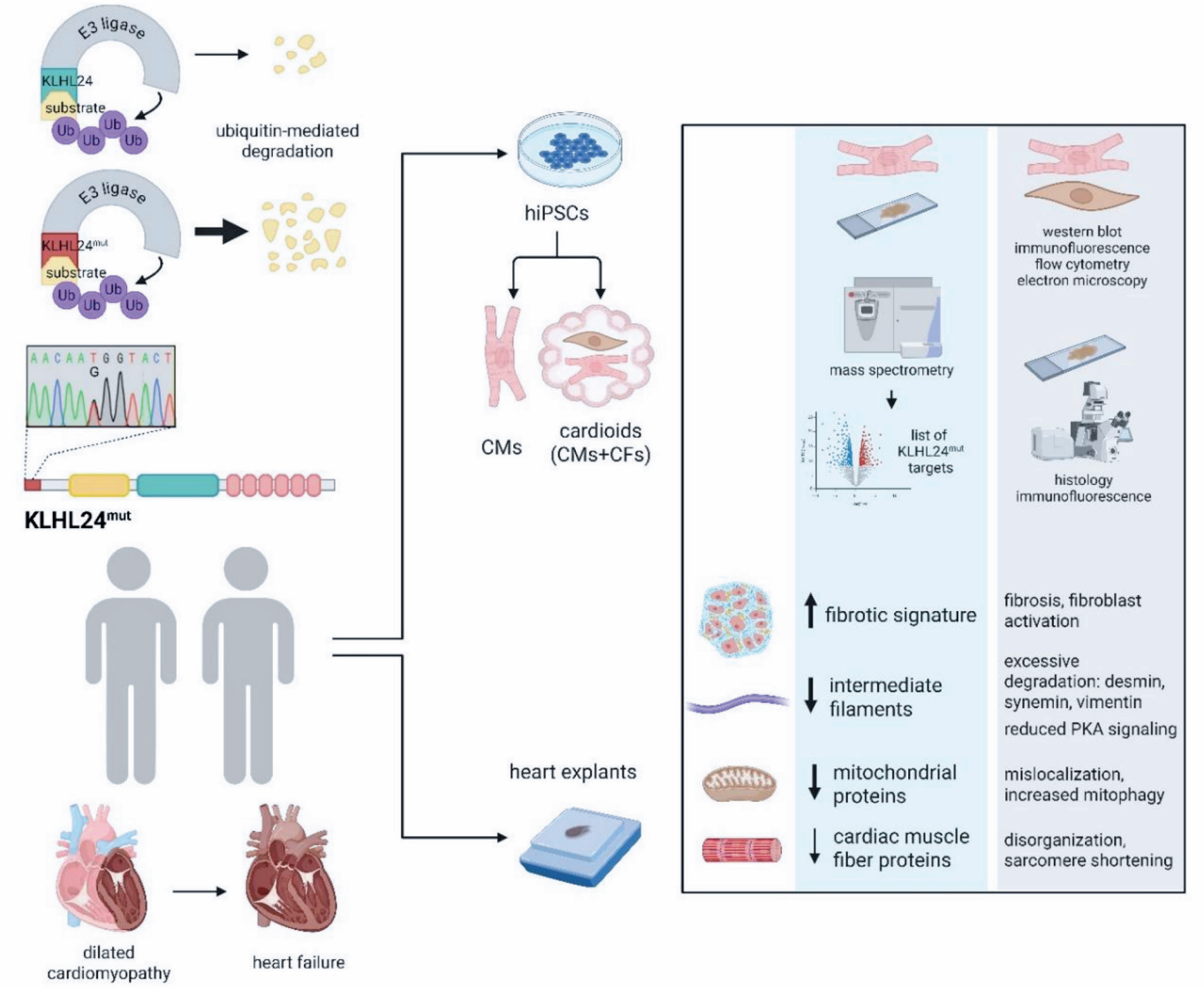

Figure 1. Graphical abstract

Presentation Abstracts

CONTENTS

046

Identifying Molecular Signatures of Disease Heterogeneity in Epidermolysis Bullosa

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ABSTRACT

Epidermolysis Bullosa (EB) is a family of rare, incurable, inherited disorders characterised by extreme skin and mucosal fragility. The most severe forms are recessive dystrophic EB (RDEB), caused by loss of type VII collagen, and junctional EB (JEB), caused loss of the skin basement membrane proteins laminin 332, type XVII collagen or integrin α6β4.

Despite similarities between these disease pathologies, there are dramatic differences in life expectancy. RDEB patients survive to early or mid-adulthood, JEB patients rarely survive beyond the first year of life. The reason for this disparity is poorly understood.

To investigate this, we performed bulk RNA-Sequencing on 22 DEB and 19 JEB patient skin biopsies with the aim to identify molecular changes underpinning the differences in these diseases. Immunohistochemistry was used to validate these findings in patient-matched samples and models of EB.

Pathway and Gene Ontology (GO) analysis of DEGs indicated an upregulation in cell death, proinflammatory pathways and interleukins (IL1, IL11, CXCL12, and β-defensins) which stimulate the adaptive immune response in JEB compared to DEB. In addition, an abundance of transcriptional factors linked to angiogenesis and wound healing (MMP2, COL1A1), collagen remodelling (LOX), fibrosis (TGFβ) and epidermal development (EPPK1, TGM1, FLG and KRT14) were upregulated in JEB patients compared to DEB. This has been validated in mouse models of EB, through the use of single cell RNA-seq and immunofluorescent staining of a JEB mouse model (*Lama3*$^{flx/flx}$K14^{CreERT}) which recapitulates all key features of JEB. We have confirmed the changes in angiogenesis, ECM remodelling and increased immune infiltration using multiplexed imaging of patient tissue using a CellDive microscope.

We have identified and validated significant changes between EB subtypes. The use of pathway and GOterm analysis identified altered pathways and molecular drivers that could be used as a novel approach for therapeutic treatments for EB.

047

School management strategies for the inclusion of children with epidermolysis bullosa: overcoming barriers and educational challenges

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ABSTRACT

Background: Epidermolysis bullosa (EB) is a rare genetic condition that causes extreme skin fragility, posing significant barriers to the inclusion of affected children in regular schools. School management plays a central role in developing inclusive strategies, coordinating pedagogical adaptations, and fostering collaboration with families and healthcare professionals. This study aimed to analyze the strategies adopted by school management to promote the inclusion of children with EB, identifying barriers, evaluating practices, and proposing improvements.

Methods: A qualitative approach was employed through semi-structured questionnaires applied to one school principal and two pedagogical coordinators from three schools located in Curitiba (Paraná) and São José/Palhoça (Santa Catarina), Brazil. Data collection occurred in October 2024. Closed-ended responses were tabulated and analyzed descriptively, while open-ended responses were examined using content analysis. Results were cross-validated with the existing literature on inclusive education and rare diseases.

Results: The most frequent barriers reported were lack of specific training for educators (66.7%), insufficient financial resources (33.3%), limited knowledge about EB (33.3%), and difficulties with social acceptance among peers. Despite these challenges, school management demonstrated significant commitment to inclusion. The most cited strategies included teacher training and professional development (66.7%), partnerships with healthcare professionals (33.3%), and continuous family involvement (33.3%). Most participants considered these strategies effective (66.7%) or very effective (33.3%). Suggested improvements included adapted spaces for medical care, proper classroom furniture, and continuous training on EB-specific care.

Conclusion: This study highlights both the challenges and advances in the inclusion of children with EB in Brazilian schools. Effective inclusion requires not only physical or curricular adaptations but also an integrated approach involving families, educators, and healthcare professionals. Teacher training, family engagement, and institutional partnerships emerged as essential elements for reducing barriers. Strengthening public policies, expanding resources, and encouraging further research are crucial steps toward ensuring equitable access to quality education for children with rare conditions.

Keywords: Epidermolysis bullosa; School management; Inclusion; Educational strategies; Rare diseases

Presentation Abstracts

CONTENTS

048

DEBRA Colombia: book inside out story

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ABSTRACT

Introduction: Introducing the book: Inside Out is a story written by Nicole Cubillos Prieto, a special education teacher and researcher in EB, inspired by children with epidermolysis bullosa from Debra Colombia.

Interdisciplinary Care.

Objective: To raise awareness, raise awareness, and educate about the condition, using language relevant to children and families.

Added value: It is interactive and links developmental milestones, allowing it to be used in both educational and therapeutic contexts.

The symbolism of the narrative.

Main character: Dino → represents the experience of a child with EB, who explores their environment, recognizes their differences, and faces physical and emotional pain.

Meeting Yellow: symbolizes the importance of friendship, empathy, and feeling supported in their differences.

The use of metaphors—the egg, changing skin, and the colors of emotions—allows EB to be explained using accessible and sensitive language.

Pedagogical and Therapeutic Resources.

The book proposes movements, gestures, games, and questions that promote:

- Fine and gross motor development; Language stimulation; Identification and expression of emotions; Body and skin recognition.
- This makes it a teaching material adaptable to inclusive classrooms, speech therapy, psychology, or special education settings.
- 5 National Meetings (1 virtual during pandemic) and 33 Regional Interdisciplinary Care Events, benefiting 140 patients since 2009 and 85 active patients in 2025.
- Pedagogical consultancies to guide educational processes and desensitization in school.

Conclusion: Conclude with the key phrase from the book: “Feeling is the best way to cope with the pain in our skin.” Propose reading as a tool for community awareness in schools, hospitals, libraries, and families. Emphasize that this is a story that is just beginning, as is the path to inclusion and recognition for people with EB. Expand on the cycle of emotional security provided by school and the stages of trauma that comes with having an orphaned, rare condition, as proposed by diverse network 5.5, The Layers of Psychological Trauma in Children with Rare Diseases. The book “Inside Out” has a profound impact in addressing epidermolysis bullosa with empathy. It serves as a mirror for children with EB, helping them feel understood and less alone. For families, it becomes an invaluable tool for explaining the condition, promoting open dialogue about emotions and challenges. By including educational resources, the book not only educates but also strengthens emotional bonds, helping children develop a positive body image and communicate their feelings effectively. In essence, it facilitates acceptance and emotional well- being.

Keywords: Reasonable adjustments; Inclusive education; Empathy

Presentation Abstracts

049

Dermal papillary fibroblasts promote persistent granulation tissue formation in junctional epidermolysis bullosa

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ABSTRACT

The skin dermis is composed of multiple fibroblast subpopulations with different functions in skin homeostasis and repair, but their role in skin diseases is largely unknown. Junctional epidermolysis bullosa (JEB) is a hereditary skin disorder characterised by severe skin fragility and aberrant granulation tissue formation, caused by loss of function mutations in basement membrane proteins including laminin-332.

Here we developed JEB organotypic (OT) cultures with distinct fibroblast subpopulations and explored their role in an inducible JEB in vivo disease model, mimicking key features of the human disease. JEB OTs with papillary fibroblasts showed deregulated epidermal growth and cytokine signalling compared to reticular fibroblasts. Mechanistically, papillary fibroblasts are highly increased in granulation tissue of blistered JEB skin promoting pathological αvβ6 integrin expression and TGFβ signalling in JEB keratinocytes. Treatment with the TGFβ receptor inhibitor RepSox not only normalised aberrant cell proliferation, differentiation and cytokine signalling in JEB OTs, but also reduced aberrant granulation tissue formation, αvβ6 integrin expression and skin blistering in laminin-332 depleted mice.

Collectively, our study reveals that papillary fibroblasts promote JEB pathogenesis through aberrant avb6 integrin -TGFβ signalling leading to increased epidermal proliferation, inflammation, angiogenesis and persistent granulation tissue formation. Disrupting the pathological signalling interactions by inhibiting TGFβ signalling significantly improved skin health and regeneration in JEB.

Presentation Abstracts

CONTENTS

050

Laboratory abnormalities in recessive dystrophic epidermolysis bullosa: a retrospective single-center study

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ABSTRACT

Background: Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genodermatosis characterized by skin fragility and systemic complications, including anemia, inflammation, and nutritional deficiencies. The prevalence and age of onset of these laboratory abnormalities remain poorly defined in the current literature.

Objective: To characterize the frequency of nutritional deficiencies and earliest age of laboratory abnormalities in a cohort of RDEB patients.

Methods: A retrospective chart review of 122 patients with RDEB seen at a tertiary care EB center (2010–2021) was conducted. Laboratory and anthropometric data from initial visits were stratified by age group and compared to institutional reference ranges.

Results: Inflammatory markers were frequently elevated: C-reactive protein (CRP) (100%, 74/74) and ESR (81%, 71/88), including in patients <2 years. Anemia (86%, 98/114) and iron deficiency (84%, 80/95) were highly prevalent. Hypoalbuminemia was present in 69% of patients (77/112), particularly among those younger than 16 years. Thrombocytosis occurred in 41% (49/120). Anthropometric measures revealed early declines in weight-for-age and height-for-age percentiles and persistently low BMI. Mean height-for-age percentile decreased sharply from the 61st to the 30th %ile between ages 0–1.99 and 2–3.99 years. Vitamin D deficiency (using a 30ng/mL cutoff) affected 49% (44/90), especially those >8 years. Zinc and carnitine levels declined with increasing age, but the majority of patients had values within normal limits. Magnesium, selenium, and phosphorus were generally within normal limits for most patients.

Conclusion: Nutritional, hematologic, and inflammatory abnormalities are common and often present, even in infancy, among patients with RDEB. These findings underscore the need for standardized, age-specific laboratory monitoring protocols beginning in early childhood. Early recognition. of and intervention for abnormalities may improve long-term outcomes in this medically complex population.

Keywords: Epidermolysis bullosa; Laboratory: Nutrition; Micronutrient, Preventative care

051

Linking senescence and fibrosis in recessive dystrophic epidermolysis bullosa

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ABSTRACT

Introduction: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe genetic skin disorder characterized by chronic wounds and progressive fibrosis. Persistent wound microenvironment may drive the accumulation of senescent fibroblasts, which secrete a senescence-associated secretory phenotype (SASP) that could exacerbate tissue remodeling and fibrosis. This study aimed to characterize senescence features in fibroblasts derived from distinct RDEB cutaneous microenvironments and to explore their relationship with fibrotic markers.

Methods: Fibroblasts were isolated from chronic wounds, acute wounds, and non- lesional skin of RDEB donors, as well as from healthy controls. Cells were analyzed for senescence- associated features including DNA damage foci (53BP1, γH2A.X), nuclear morphology, and SA-β-gal activity. Transcriptomic data (RNA-seq) were used to evaluate SASP-related gene expression. In addition, different skin tissues from the RDEB mouse model were analyzed by immunofluorescence for p21 (senescence marker) and Tenascin-C (TNC, fibrosis marker).

Results: Fibroblasts from RDEB chronic wounds showed increased senescence features, including enlarged nuclei, accumulation of DNA damage foci, and elevated SA-β-gal activity, compared with fibroblasts from acute wounds and non-lesional skin. RNA-seq analysis revealed upregulation of SASP-related genes in chronic wound fibroblasts, indicating a distinct senescence signature. Immunofluorescence in RDEB mouse skin demonstrated elevated p21 expression in highly fibrotic areas (marked by TNC), supporting an association between senescent cells and fibrotic matrix deposition.

Discussion: Our results indicate that fibroblast senescence is a hallmark of RDEB chronic wounds, characterized by SASP gene expression and fibrotic remodeling. The correlation between p21 and TNC expression supports the hypothesis that senescent fibroblasts may contribute to fibrosis in RDEB through SASP-mediated extracellular matrix alterations. These findings provide mechanistic insights into the interplay between senescence and fibrosis in RDEB chronic wounds.

Acknowledgements: FONDECYT 1220704 granted to IF.

Presentation Abstracts

CONTENTS

052

Longitudinal improvement in epidermolyis bullosa simplex patients with De Novo *KRT5* mutations

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ABSTRACT

Background: Epidermolysis bullosa simplex (EBS) is a genodermatosis characterized by blistering and erosions following minimal trauma.[1] Many cases result from dominant mutations in the keratin 5 (KRT5) or keratin 14 (KRT14) genes, though some arise from de novo events. De novo *KRT5* mutations are often associated with severe EBS subtypes, with affected individuals typically presenting at birth with widespread blistering, mucosal involvement, feeding difficulties, and a high risk of death. This early severity has historically led some providers to recommend withdrawal of care in infancy; however, clinical observation shows that infants who survive this period experience substantial improvement over time, with the potential for normal life expectancy. Despite this, existing literature largely emphasizes initial presentation, with limited longitudinal data.

Objectives: To describe the long-term clinical course of patients with de novo *KRT5* mutations and identify key milestones of clinical improvement.

Methods: A retrospective chart review was performed for four patients with genetically confirmed de novo *KRT5* mutations. Clinical data from birth through the most recent visit were reviewed to describe longitudinal changes in skin, nails, mucosa, nutrition, growth, development and supportive interventions. Observations are presented descriptively.

Results: All four patients presented at birth with widespread blistering, aplasia cutis, mucosal involvement, and feeding difficulties, requiring prolonged hospitalizations ranging from 26 days to 3 months. Within the first year of life, all developed palmoplantar hyperkeratosis, nail dystrophy, and motor delays. Additional complications included ophthalmologic involvement (n=2), esophageal narrowing (n=1), significant pain requiring daily opioids (n=1), and language delay (n=2, one resolved during infancy). Early interventions included gastrostomy tube placement (n=3), occupational/physical therapy (n=4), tracheostomy placement (n=1), skin grafting (n=1), and contracture release surgery (n=1). Among the three patients with follow-up beyond infancy, clinical improvement and the emergence of new features began in early childhood. Around age 2, blistering became more localized and generally non-scarring. Between ages 2-4, all patients developed EB nevi and a widespread reticular skin pigmentation pattern, while hyperkeratosis and nail dystrophy persisted. Developmental delays gradually improved, and by age 4, two patients could walk independently. Pain also decreased, allowing discontinuation of opioid therapy, and nutritional support was reduced, with one patient transitioning to partial gastrostomy tube use and another achieving full oral intake by age 5.

From ages 6 to 9, further improvement was noted. Blistering became increasingly rare and localized, and reticular hyperpigmentation lightened. Nail dystrophy and palmoplantar hyperkeratosis became less pronounced, with near resolution in some cases. Additionally, motor function normalized in most patients, allowing full participation in school and recreational activities. In the patient followed into early adolescence, dyspigmentation continued to fade, and the skin healed without further blistering or erosions.

Conclusion: Although patients with EBS caused by de novo *KRT5* mutations often present with severe, life-threatening disease at birth, long-term follow-up demonstrates marked clinical improvement in skin integrity, mobility, pain management, and functional independence. Families and providers should be counseled on this disease trajectory and the potential for normal life expectancy with the appropriate supportive care.

Presentation Abstracts

CONTENTS

053

Managing pain in epidermolysis bullosa: insights from a systematic review and meta-analysis

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ABSTRACT

Background: Pain is among the most burdensome symptoms in patients with Epidermolysis bullosa (EB). Its impact extends beyond physical suffering, contributing to functional impairment, emotional distress, and social isolation, leading to reduced quality of life. Best practice care guidelines for pain in EB were last updated in 2014. However, since then, various treatments with analgesic effects have been reported, ranging from pharmacological interventions to advanced wound care strategies. The inconsistent use of generic measurement instruments further complicates the comparison of these treatment outcomes.

Objective: The aim of this study is to provide a comprehensive literature overview and meta-analysis of studies reporting pain treatment options for EB and their effects, emphasizing the variability in pain assessment and challenges in evaluating treatment efficacy.

Methods: Following the PRISMA guidelines for reporting, articles from six bibliographical databases were screened and reviewed by two independent reviewers. Articles published from 1991, after the implementation of the first consensus classification of EB, up to 16th October 2024, investigating any type of treatment in EB patients with reported effects on EB-associated pain, were considered eligible.

Results: A total of 48 articles, comprising 1005 EB patients, were identified and included. Of these 36 reported on the analgesic effect of local treatments and 12 on systemic treatments. Significant pain reduction was shown in 11 studies for topical regimens and four studies for systemic regimens. Nine randomized controlled trials were included in the meta-analysis, showing a trend favoring the experimental groups: eight investigated local and one systemic treatment approaches. A statistically significant improvement was observed after three months of therapy with a MD of -0.71 with a 95% confidence interval of -1.40 to -0.01 (p=0.046). Across all trials a total of 13 different measurement tools were used.

Conclusion: This systematic review and meta-analysis identified 15 articles reporting on 13 different treatment modalities with statistically significant analgesic effect on patients with EB. However, of all 48 studies, only three studies have been included in the best practice care guidelines for EB published in 2014, omitting a variety of different treatment modalities have been published since then. The use of 13 different pain assessment tools poses a significant challenge for comparative evaluation and interpretation of the effects. Implementation of an EB-specific pain questionnaire could enhance outcome comparability of outcomes across different trials and support informed evidence-based decision-making in EB pain management.

Keywords: Epidermolysis bullosa; Meta-analysis; Systematic review; Pain management; Pain assessment; Pain measurement tools; Analgesics

054

Micro-costing of hospital care for patients with recessive dystrophic epidermolysis bullosa in the UK

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ABSTRACT

Background: Recessive dystrophic epidermolysis bullosa (RDEB) is one of the most severe forms the group of inherited skin fragility/blistering disorders known epidermolysis bullosa (EB). RDEB severity varies greatly by sub-type. To date no therapy is curative. Care is life-long, often intensive, and delivered in home and hospital settings. The lifetime cost of care is high, both financially and in negative impact on quality of life for affected individuals and carers. To date various methodologies have been applied to costing care for patients with EB, but no study has looked specifically at the costs of hospital care for RDEB by sub-type. The UK National Health Service (NHS) provides a tariff of costs, but these are thought inaccurate when applied to rare diseases. Designated EB-specialist centres in the UK have an individually agreed tariff although this is not publicly available.

Objective: To develop reference costs for UK hospital care for EB-specialist clinics and interventions which could be applied to individuals with RDEB.

Methods: An iterative process was used to quantify common EB-specialist clinics and interventions at the two London, UK, EB services. EB experts at each centre were approached in person or by email or telephone to detail all personnel involved and estimate the time each member of staff spent EB-specialist clinics and interventions, including preparation, procedure and after-care. Experts were given 3-4 opportunities to review data. The most experienced EB experts were the final arbiters. Personnel costs (contact and non-contact time) were calculated using the 'Unit Costs of Health and Social Care' (2022). Costs of hospital stay (inpatient and day case) included an average cost for EB dressing change (materials and labour) taken from the PEBLES community care costs paper (Jeffs et al, 2024).

Results: Six EB-specialist clinics were identified: EB multidisciplinary team (MDT) clinic (most severe RDEB), EB mini-MDT clinic and EB half day clinic (milder RDEB), EB podiatry clinic, EB clinical nurse specialist (CNS) Clinic, intravenous iron infusion clinic. Appointment costs ranged from £112 for podiatry to £2134 for the MDT clinic attended by the most severely affected patients. Of note, the NHS Payment Scheme 2023-24 quoted only £201 for an MDT dermatology appointment.

Ten common EB-specialist interventions were identified: oesophageal dilatation; release of hand and digit contractures and associated change of dressings in theatre, ward or outpatients; biopsy for cutaneous squamous cell carcinoma (SCC); SCC removal; dermatology admission for symptom management; gastrostomy tube insertion. The costs for the individual stages of each intervention ranged from £32 - £798 for pre-procedure preparation, £197-£3049 for the procedure, £117-£228 for post-procedure specialist review and, where appropriate, £152-£273 for ward

rounds. The bed stay was £587/day with an additional £253/day for EB wound dressings changes applied for stays of 2 or more days.

Conclusion: Specialist EB care is expensive and moreover is lifelong with little respite from the intensity of required care.

Keywords: Recessive dystrophic epidermolysis bullosa; Costs of hospital care; Micro-costing

055

Mucosal involvement as a defining feature of recessive dystrophic epidermolysis bullosa inversa

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ABSTRACT

Background: Recessive dystrophic epidermolysis bullosa inversa (RDEB-I) is a rare subtype of epidermolysis bullosa characterized by blistering, erosions and scarring predominately in body flexures and mucosal surfaces. While mucosal involvement is recognized as a feature of RDEB-I, detailed descriptions of its involvement, progression, and complications across different mucosal sites remain limited.[1,2]

Objective: To characterize the natural history of mucosal involvement across oral, esophageal, anorectal, and genitourinary sites.

Methods: We conducted a retrospective chart review of ten patients with RDEB-I at our institution. Data regarding clinical histories, exam findings, and procedures involving mucosal sites were collected and summarized descriptively.

Results: Mucosal disease was universal, often presenting at birth or early infancy and persisting throughout follow-up. Oral involvement affected all patients, with onset as early as six months of age. Manifestations included recurrent blistering and painful wounds that frequently impaired eating (n=5) and contributed to progressive microstomia (n=5) and ankyloglossia (n=2), requiring surgical intervention in two patients.

Esophageal involvement was also universal, with reported symptoms of dysphagia (n=10) and choking (n=7), often necessitating dietary modifications (n=8). Strictures requiring dilation occurred in eight patients, typically beginning in childhood between the ages of 5 and 12, though one patient did not require intervention until age 32. The esophageal mucosa was very delicate, and patients experienced complications such as mucosal tearing or bleeding during dilations. Esophageal disease was chronic and recurrent, with repeated dilations required at intervals ranging from 4 months to 5 years, with some undergoing >20 procedures over their lifetime. Anorectal disease was highly prevalent (n=6) and caused significant functional impairment. Involvement began as early as infancy for some patients and persisted throughout follow-up. Most experienced painful bowel movements, anorectal fissures, rectal bleeding, and perianal tissue sloughing that was exacerbated by defecation and wiping. Ongoing mucosal fragility required repeated management throughout follow-up, including intensive bowel regimens and Botox injections.

Genitourinary involvement was observed exclusively in female patients (n=5) and was characterized by painful blistering, erosions, and extensive scarring in the vulvar and vaginal regions. Friction from underwear usage, menstrual pads, and sexual intercourse often triggered new blistering and wounds. Progressive scarring of the labia and vagina became apparent in adulthood, limiting sexual activity, routine pelvic examinations, and vaginal delivery, with two patients requiring cesarean delivery. Two additional patients required surgery due to genitourinary complications: one underwent vaginoplasty and another required intervention for anuria due to urethral obstruction.

Conclusion: In patients with RDEB-I, fragile mucosa leads to chronic, recurrent blistering and erosions that lead to progressive scarring and structural complications such as microstomia, ankyloglossia, esophageal strictures, rectal sloughing/fissures, and

vaginal stenosis. These findings highlight the need for proactive, multidisciplinary management and close longitudinal monitoring to prevent long-term functional impairment.

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056

Multiplex engineered gamma delta T cells as allogenic micropharmacies with homing capability for systemic correction of dystrophic epidermolysis bullosa

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ABSTRACT

To date, no therapy has demonstrated durable improvement in the systemic pathophysiology of recessive dystrophic epidermolysis bullosa (RDEB). At a minimum, an effective treatment will need to persistently deposit therapeutic levels of collagen VII (C7) diffusely throughout a large portion of the body, including both cutaneous and extracutaneous sites. Human gamma delta (γδ) T cells are migratory immune cells that have broad tissue accessibility and are particularly prevalent in barrier sites and mucosal tissues. This subtype of T cells is not MHC-restricted and has been successfully utilized in allogeneic therapies, making it a viable off-the-shelf treatment option. Our research has developed protocols for the *ex vivo* expansion of γδ T cells combined with targeted CRISPR engineering to induce C7 overexpression (C7-γδT cells). This inherently allo-compatible therapy utilizes natural γδ homing to target specific tissues affected by RDEB, while secreting therapeutic levels of C7.

Additionally, simultaneous gene knock-in and multiplex gene knockout can be achieved in γδT cells with high efficiency by utilizing Cpf1 nuclease in combination with Cas9 base editing. This enables us to explore options such as increasing homing to the skin via induced expression of CCR10, a chemokine receptor whose main ligands, CCL27 and CCL28, direct homing to keratinocytes in the epidermis near the dermal-epidermal junction. In RDEB, the skin is locked in a chronic, IL-1-rich inflammatory state that fuels tissue damage. Engineering the C7-γδT cells to also secrete a natural IL-1 receptor antagonist (Anakinra) may dampen the IL-1 signalling cascade and suppress the counterproductive inflammation. Potential limitations of this strategy include diminished persistence due to host-versus-graft elimination of the allogeneic cells and the inherent capability of γδ T cells to mediate cellular cytotoxicity and inflammation. Multiplex gene knockout with base editor can be leveraged to overcome these limitations by targeting genes such as MHC class I and II to improve persistence and simultaneously disrupt key mediators of inflammation, such as perforin (PRF1), Granzyme B (GZMB), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ).

Presentation Abstracts

CONTENTS

057

Mupirocin resistance of staphylococcus aureus isolated from patients with epidermolysis bullosa

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ABSTRACT

Epidermolysis Bullosa (EB) is a group of genetic skin conditions associated with skin fragility. Most patients have multiple open wounds that may become colonized or infected, commonly with *Staphylococcus aureus* (*S. aureus*). While mupirocin has been an established agent for methicillin-resistant *S. aureus* (MRSA) treatment, there is growing awareness of mupirocin resistance in MRSA. We aimed to determine the prevalence of mupirocin resistance among *S. aureus* specimens in EB patients. Retrospective chart reviews from 2019-2024 were completed on all patients with any type of EB who had at least one wound culture grow *S. aureus* and information on mupirocin Minimum Inhibitory Concentrations (MICs). A total of 50 patient charts met inclusion criteria. Susceptibility to mupirocin was categorized into three groups: susceptible (MIC <4mcg/mL), low-level (MIC 6-256mcg/mL), and high-level resistance (MIC ≥512mcg/mL). Forty-two percent of patients had at least one wound culture which grew *S. aureus* with high level resistance, 20% had low level resistance, and 38% maintained susceptibility (Figure 1). Resistance to mupirocin was associated with erythromycin resistance (p=0.037). Some patients did not maintain mupirocin resistance over time. Mupirocin may not be effective for *S. aureus* in up to 58% of EB patients.

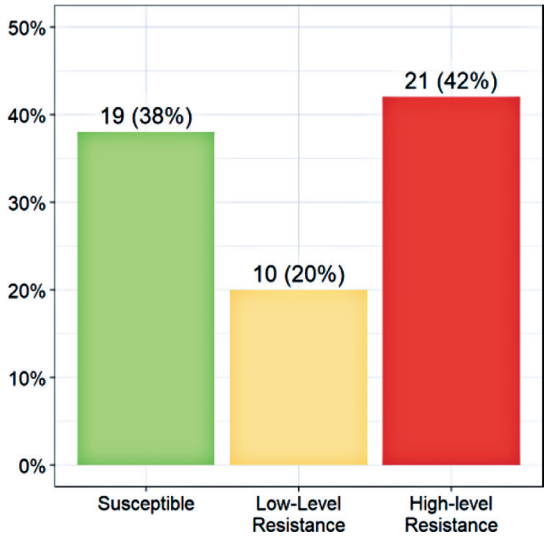

Figure 1. Percentage of patients with each highest level of mupirocin resistance of s. aureus

058

National registry of epidermolysis bullosa – 10-year analysis

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ABSTRACT

Introduction: Hereditary Epidermolysis Bullosa (EB) is a rare genetic disorder with an estimated prevalence of 11 per million individuals. Treatment requires multidisciplinary care and generates high costs, reinforcing the need for public policies supported by reliable epidemiological data. Only a few countries, such as the USA and the UK, have official EB registries that allow incidence and prevalence estimates. In Brazil, there are no official publications on the number of patients. The Brazilian branch of the Dystrophic Epidermolysis Bullosa Research Association (DEBRA Brasil) has been consolidating a national registry, aiming to provide a unified database to support public health policies and improve access to new therapies.

Objective: To determine the epidemiological profile of EB in Brazil over the last 10 years and compare it with international data.

Methods: Data were collected from the DEBRA Brasil registry between January 2014 and April 2024. Sources included online forms, regional associations, social media, patient support groups, and dermatology services. Information was organized in a business intelligence system with data protection compliant with the General Data Protection Law (LGPD). Descriptive statistics were applied, with variables analyzed by means, standard deviations, and proportions. Shapiro-Wilk, chi-square, and Fisher's exact tests were used where appropriate. Analyses were performed using GraphPad Prism®, with significance set at $p<0.05$.

Results: A total of 1540 cases were registered, with 239 reported deaths. No significant gender differences were observed. Epidermolysis bullosa simplex was the most frequent clinical subtype, followed by recessive dystrophic EB, although a considerable proportion of patients still lack confirmed clinical or molecular diagnosis. The prevalence until 2024 was 3.73 cases per 1,000,000 inhabitants—lower than global estimates but increasing in recent years as registry coverage expanded. The incidence in 2023 was 23 cases per 1,000,000 live births, comparable to international reports.

Conclusion: The Brazilian EB registry reveals prevalence rates below those described globally, suggesting underreporting of older cases. However, the incidence is in line with international data, likely due to increased awareness of DEBRA's work among maternity hospitals and pediatric centers. Expanding patient identification strategies and increasing the registry's visibility are essential. Publishing these data will contribute to patient care planning, stimulate EB research in Brazil, and support the development of public health policies.

Presentation Abstracts

CONTENTS

059

Negative-pressure wound therapy associated with fat grafting in the treatment of complex lower-limb wounds in patients with recessive dystrophic epidermolysis bullosa (RDEB): five years of technical evolution and clinical follow-up

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ABSTRACT

Background: The management of complex wounds has challenged medicine since its origins. Among the major technological innovations of the 21st century are negative pressure wound therapy (NPWT) and autologous fat grafting (AFG). NPWT has shown evidence of effectiveness in exudate removal, edema reduction, wound-size decrease, protection, neovascularization, and stimulation of granulation tissue. AFG has traditionally been used to correct deformities and for soft-tissue augmentation; however, few studies have reported the isolated use of autologous "in natura" adipose tissue in wound treatment. The application of fat grafting for the coverage of complex wounds, including those with exposure of internal fixation materials, is even more scarcely documented.

Objective: To present a case series reporting the use of NPWT combined with AFG in the treatment of complex lower-limb wounds in patients with Epidermolysis Bullosa following excision of squamous cell carcinoma.

Methods: A case-series study (N=2) was conducted with a descriptive, prospective, and observational design, involving patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) who presented with acute and complex lower-limb wounds. All participants had previously undergone conventional therapeutic measures without adequate clinical response.

Results: The combination of NPWT and AFG was successful in treating complex lower-limb wounds in patients with Epidermolysis Bullosa after resection of squamous cell carcinoma.

Discussion: A probable synergistic effect between NPWT and AFG was observed. The properties of both techniques as stimuli for wound healing and neoangiogenesis were demonstrated. The capacity of lipoaspirated adipose tissue to serve as a biological matrix for complex-wound coverage became evident. The filling and contour-regularization effects of AFG when associated with NPWT were also noted.

Conclusion: The association of NPWT with AFG proved to be an effective option for managing a complex wound described as refractory to conventional methods. The approach demonstrated low morbidity, innovation, efficiency, and good tolerance, particularly in scenarios where flap options were unavailable.

Keywords: Wound Healing; Wounds and Injuries; Lower Limb; Adipose Tissue; Autologous Transplantation; Negative-pressure wound therapy; Wound closure techniques

060

Neither fully inside nor fully outside: school experiences of adolescents with recessive dystrophic epidermolysis bullosa

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ABSTRACT

Introduction: Inherited epidermolysis bullosa (EB) is characterized by mucosal and skin fragility, and visible impairment, often leading to social isolation. In severe forms such as recessive dystrophic EB (RDEB), pain and progressive loss of motor skills have major repercussions on schooling and peer interactions. School dropout (SD) is frequent and compromises both socialization and professional integration.

Objective: To explore the perceptions of adolescents with RDEB regarding their educational pathways. and to identify risk and protective factors of potential SD .

Methods: The criteria of inclusion in this multicentric prospective study (IRB11928) were patients aged 12–25 years with molecularly confirmed RDEB. Semi-structured individual interviews were recorded, transcribed and analyzed through thematic coding (NVIVO 5, double-blind). Psychological and psychomotor testing, including WISC-V, MDI-C, Rorschach, and TAT, were performed. Medical and educational data were collected from parental questionnaires.

Results: Sixteen patients (8 males, mean age 16 years) completed interviews and testing. Four main themes arose: social relationships, health, social integration, and schooling. Nine out of fifteen patients were in SD or at risk. Intellectual efficiency appeared correlated with disease severity. Emotional difficulties were present but comparable to the general population. Persistent challenges in socialization and learning (60%) limited high school attendance.

Discussion: Transition to middle school was identified as a critical turning point for young EBDR patients who experience it as a real academic and social "shift" where they no longer have their bearings. SD reflected a process of progressive disaffiliation, marked by absences, isolation, educational fatigue, and loss of belonging. School adaptations were often insufficient, hindered by poor institutional knowledge of the disease. However protective factors emerged, including the central role of mothers in daily care, family support, and positive relationships with peers and teachers. Adolescents also developed coping strategies (social withdrawal, reliance on school assistants) that temporarily safeguarded mental health but weakened long-term integration. Social and territorial inequalities further amplified disparities.

Conclusion: School dropout among RDEB adolescents is common, multifactorial, and part of a broader process of social withdrawal. A specific integration program for each affected adolescent based on recognition of their experiences and focused on sustainable school inclusion can foster their sense of belonging to a social group and self-confidence. It should involve early multidisciplinary interventions. It will help to develop their autonomy not despite but with their EB. School being experienced as a space of emancipation.

Presentation Abstracts

CONTENTS

061

New orofacial myofunctional therapeutic approach for the treatment and prevention of dysphagia in epidermolysis bullosa with involvement oral and oesophagel mucosa

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ABSTRACT

Introduction: The genetic manifestation of oral involvement EB is blister and retractable scar on the oral and oesophageal mucosa from birth, without musculoskeletal alterations of the Stomatognathic System (SS) or quantity and quality of saliva. It is proposed to use these resources, stimulating them with myofunctional treatment to improve salivary management and preparation of food in mouth to avoid oesophageal lesions.

Objectives: Saliva management: Saliva is a fluid, it must remain in the mouth, moistens and protects hard and soft tissues and participates in the formation of the food bolus. The management of saliva in patients with EB with oral lesions is altered, causing choking or aspiration. Regardless of where patients are feeding (oral, gastrotomy), they will continue to produce saliva and will need to manage salivary swallowing oesophageal. Bolus of food that does not hurt the oesophagus: Chronic dysphagia and oesophageal stricture, common especially in RDEB, due to food-induced trauma. To form a food bolus that does not hurt, it is suggested to prepare the food with coordinated movements of the SS including teeth and saliva.

Prevent orofacial malformations: SS located in the cranio-cervical-facial region allows respiratory, swallowing, masticatory, speech, etc.

The patient with EB is born with a normal SS, over time he suffers anatomical and functional alterations due to lack or misuse.

Dolorous blisters and scars on the oral mucous membranes that prevent and limit the normal mobility of the SS trigger dysfunctions, atypical swallowing and dysphagia (dolorous processes and insufficient feeding), these produce lack of growth and development of the SS that deepen dysfunctions.

The goal of treatment is to increase muscle strength and maintain musculoskeletal mobility of the SS so that it is functional and does not atrophy.

Methods: Speech therapist, professional trained in the diagnosis and treatment of swallowing anomalies (dysphagia, atypical swallowing). It performs orofacial myofunctional treatment so that the patient can handle saliva, form the food bolus that does not damage the oesophagus, educate patients and caregivers about food consistencies and processing in the mouth. Treatment consists of oral and facial exercises; and stimulation (massages) of the muscles of the SS, tongue, lips, cheeks.

We suggest using a vehicle to perform the stimulation treatment without damaging the mucous membranes. The Curefini ointment vehicle meets 3 fundamental characteristics for EB: Apply at any age while being safe and non-toxic.

Suitable for long-term use, and High adhesion and remanence in soft tissues.

Curefini® natural formula contains cod, sunflower and sweet almond liver oils, has local analgesic and anti-inflammatory action (polyunsaturated fatty acids), beeswax (antimicrobial peptides of local action).

Curefini in the oral cavity provides a temporary barrier, protects and reduces inflammation of the oral mucosa. This lipid interface facilitates the performance of the exercises.

Conclusion: Orofacial myofunctional therapy for proper functioning of the SS, facilitating oesophageal and nutritional functions. Improving the quality of life of patients with EB.

Presentation Abstracts

CONTENTS

062

Novel Aggregation-Induced Emission (AIE) Photosensitizers-Enhanced Casein Nano- Fabrics for Wound Management in *Epidermolysis Bullosa*

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ABSTRACT

Fragile skin disorders continueto present a major challenge globally both in clinical care and biomedical research. Among them, *Epidermolysis Bullosa* (EB) is a debilitating hereditary disorder of the skin causing blistering, persistent inflammation and disrupting healing. In theabsence of a curativetreatment, current research is focused on efficient wound management with the aim of decreasing complications and improving quality of life. These wounds are often complicated by bacterial infections, thus significantly increasing patient morbidity. Commercial dressings available, such as silver-loaded or synthetic polymer membranes, can provide only limited protection and in cases may adhere to skin, cause delayed healing, or cytotoxicity upon frequent replacement, especially for these individuals with delicate skin.

In light of these challenges, this project explored the potential of nature-derived polymers for wound care due to their biocompatibility, cost-effectiveness, and the potential of support the healing process. Casein, a milk-derived amphiphilic protein, was selected as a promising wound dressing material due to its low immunogenicity, ability to reduce pro-inflammatory cytokines, and support for fibroblast adhesion and growth—addressing key challenges in EB management. In parallel, aggregation-induced emission photosensitizers (AIE PSs) have been introduced as protective barrier coatings for wound treatments, since they offer low toxicity and its antibacterial mechanism involves reactive oxygen species (ROS) generation under visible light. Integrating an AIE PS coating onto the outer surface of casein/PVA nanofibrous dressings presents a promising strategy for preventing bacterial infections in EB patients.

Electrospinning was selected for its capacity to produce highly porous, and to mimic extracellular matrix (ECM) structures that encourage epithelial cell growth. A multi-nozzle electrospun setup was employed to fabricate a multilayer construct, enhancing mat thickness and surface porosity. The optimal 40:60 casein/PVA ratio produced in sequential electrospinning showed bead-like casein micelles, while glutaraldehyde crosslinking improved mechanical integrity and water resistance; these micelles may serve as reservoirs for future drug delivery. Structural and surface characterization using SEM, FTIR, contact angle analysis, and fluorescence spectroscopy confirmed the successful formation of each layer. Swelling and *in vitro* tests for the nanofibrous mats demonstrated balanced exudate absorption and their moderate biodegradation in PBS. Surface modification via plasma polymerization created distinct wettability layers, with a hydrophobic PDMS outer coating serving as both a durable barrier and immobilization platform for AIE molecules.

The MTT assay demonstrated high cell viability in both HaCaT and HDF skin cell lines across all samples, confirming that the coated nanofibers were non-cytotoxic and biocompatible. CFU counts and Live/Dead fluorescence assays confirmed the photodynamic antibacterial performance upon illumination against

key EB-associated pathogens, with AIE-coated samples showing survival rates below 22.2% and 15.8% for *S. aureus* and MRSA, respectively.

Overall, this study consisted on the design of a photoactive, multilayer wound dressing composed of casein/PVA nanofibers, plasma-modified surface coatings, and AIE photosensitizers to enhance both healing and antibacterial performance, representing a promising advance in wound care strategies for EB.

Keywords: Casein nanofibers; Electrospinning; AIE photosensitizers; Photodynamic antibacterial therapy; ROS; Epidermolysis Bullosa; Wound management.

Presentation Abstracts

CONTENTS

063

Novel *DST* Variants Causing Late-Onset Epidermolysis Bullosa Simplex: First Reported Case in Australia

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ABSTRACT

Introduction: Epidermolysis bullosa simplex (EBS) is the most common type of inherited epidermolysis bullosa, characterized by intraepidermal blistering due to basal keratinocyte fragility. While most cases are caused by autosomal dominant mutations in *KRT5* and *KRT14*, variants in other genes such as *PLEC*, *EXPH5*, and *DST* define rarer subtypes. The *DST* gene encodes dystonin, a hemidesmosomal linker protein essential for epidermal stability. We describe the first Australian case of late-onset EBS associated with novel *DST* variants.

Methods: A 30-year-old Caucasian female was referred for a second opinion with blistering that began at age 10, predominantly affecting her hands and feet. The blisters were painful, slow to heal, and had a substantial impact on her quality of life. She had normal sensation and no muscle weakness. Her father reported a history of blistering but had never undergone diagnostic evaluation. Her mother and three half-siblings were unaffected. Medical history included depression, a suspected heart murmur pending evaluation, a congenital nevus on the left dorsal foot, and multiple atypical nevi. A punch biopsy of a fresh blister from the left sole was performed for immunofluorescence mapping (IFM) and electron microscopy (EM). Whole exome sequencing (WES) was subsequently undertaken.

Results: Serological tests for BP180, BP230, Dsg1, Dsg3, envoplakin, and collagen VII antibodies were all negative. IFM demonstrated a subcorneal split with reduced intensity of keratins 5 and 14, consistent with EBS. EM did not reveal structural abnormalities, a finding reported in milder forms. WES identified two novel heterozygous *DST* variants: c.3818T>A (p.Leu1273*) and c.4464_4467del (p.Asp1488Glufs*8). Both are nonsense variants located in the penultimate exon (23 of 24) of the epithelial isoform of *DST*. The genetic report classified them as protein-coding changes predicted to introduce premature termination codons, with nonsense-mediated mRNA decay (NMD) and loss-of-function as the proposed mechanism. However, because premature stop codons in the penultimate exon may escape NMD, these variants could instead produce truncated dystonin protein, providing an alternative explanation for the milder phenotype and later-onset of EBS. These findings are consistent with autosomal recessive EBS and indicate the need for further pedigree investigation and parental genetic testing to fully clarify the underlying mechanism in this case.

In Australia, genetic testing for adults is not routinely funded, leading to diagnostic delays. After negative *KRT5* and *KRT14* panel testing, whole exome sequencing was performed, prolonging the diagnostic process.

Conclusion: This case highlights the importance of WES in uncovering atypical or late-onset forms of EBS, particularly when family history suggests a misleading autosomal dominant pattern. The identification of

recessive *DST* mutations indicates that the patient is highly unlikely to transmit EBS to her offspring. So far, *DST*-EBS cases have not shown cardiac or neuromuscular complications in the literature, with the exception of a single patient who also had CADASIL. This case further expands the known variants and phenotypes of *DST*-EBS and reinforces the value of integrating clinical, histopathological, and molecular approaches to achieve accurate diagnosis in adult-onset or non-classical blistering disorders.

Presentation Abstracts

CONTENTS

064

Nursing care for children with epidermolysis bullosa: a multidimensional approach focused on pain relief and quality of life

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) is a rare group of genetic diseases characterized by extremely fragile skin and mucous membranes, which form blisters and erosions with minimal trauma. When it manifests in childhood, it requires complex and continuous care, impacting the quality of life of the child and their family. Nurses play a central role, acting as educators. This study aims to analyze nursing interventions in EB, promoting humane and evidence-based clinical practices.

Development: Wound and Dressing.

Management: Trauma and Infection Prevention: Wound care is essential for the management of EB, and nursing technical expertise is crucial. The use of low-adhesion materials, such as silicone mesh and non-adhesive foam, helps minimize trauma during dressing changes. The technique of immersing the patient in a warm bath before dressing removal is also recommended to reduce pain and bleeding. Furthermore, continuous wound assessment for signs of infection is a vital responsibility of the nurse. Pain Management: Beyond Pharmacology: Pain in EB is both acute and chronic, making a stepped, multimodal approach essential for its management. While pain from exacerbations is treated with medication, pain from dressings requires non-pharmacological strategies, such as distraction with toys or relaxation techniques. The nurse, as the person responsible for the procedure, must evaluate the effectiveness of these interventions and adapt them as needed. Family Education and Empowerment: Due to the high complexity of care, parents assume much of the responsibility for daily procedures. Nurses play a key role in family empowerment, providing ongoing training in dressing techniques, pain management, and general care. Educational programs have been shown to increase caregiver confidence and improve treatment adherence. Psychosocial Support and Rights Advocacy: EB has a significant psychosocial impact, with the child dealing with constant pain and social stigma. The family also faces emotional and financial burden. Nurses, in constant contact with the family, must provide emotional support, referring patients to psychological or social services when necessary. They must also act as advocates for the patient's rights, ensuring access to healthcare, inclusive education, and a dignified life.

Conclusion: Nursing care for children with EB is a multidimensional process that involves clinical and emotional skills. By applying science-based protocols and adopting a family-centered approach, nurses are essential for preventing complications and managing pain. Continuous training of nursing professionals and further research on EB are essential to further improve the care provided to this vulnerable population.

065

Oral health status, treatment needs and Oral health-related quality of life in patients with Epidermolysis Bullosa (EB): A mixed-methods pilot study

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ABSTRACT

Introduction: People living with EB can present a variety of orofacial features and conditions, such as oral strictures, high caries prevalence and poor oral hygiene; that can become a major physical and psychological burden, which is not always assessed or understood by professionals or covered by health services. Over the past decades, intensive efforts by the patient organization DEBRA Austria have created a unique support structure for affected individuals in the country. However, to date, no EB-specific dental care pathway has yet been established in Austria. The present study aims to explore the relationship between oral health status, oral health treatment needs and quality of life (QoL) in Austrian patients with EB, and to provide an overview of the diversity of dental situations and individual experiences within this population.

Methods: Combining purposive sampling with a mixed-methods design, the study aimed to capture a wide range of dental manifestations of EB in Austria. Standardized information on oral health and quality of life, was obtained. Extraoral and intraoral assessments were conducted to capture the lived experiences of Austrian EB patients in relation to their oral health, including evaluation of oral functions and PhOX, as well as oral treatment needs. Quantitative data were analysed descriptively, while qualitative data were subjected to reflexive thematic analysis to explore recurring patterns and themes in participants' experiences.

Results: A total of 13 participants with a genetic diagnosis of EB were included in the study: EB simplex (EBS, n=3) and dystrophic EB (DDEB, n=1; RDEB, n=9). The need for specialized dental care was particularly pronounced, with participants often required to travel long distances to access EB-specific dental services. Participants living with RDEB exhibited poorer quality of life results across all indexes (OHIP-14: 15.7; COHIP: 53.5, iscorEB-p: 38.8, QOLEB: 15.6) compared to EBS (OHIP-14: 5; COHIP: 69.5, iscorEB-p: 17.3, QOLEB: 10.3), as well as worse oral health parameters such as PhOX (RDEB: 53.2, EBS: 80.5) and DMFT (EBS: 5.3, RDEB: 14.3) and higher dental treatment needs, ranging between one (preventive treatment) to five (preventive/periodontics, restorative, prosthodontics/implants, surgery and speech therapy). Compromised oral function was an important factor in QoL results and oral health assessment, as all RDEB participants reported that most oral health problems are related to functional limitations, but their improvement did not necessarily correspond to oral treatment needs. Most of the EB patients required preventive dentistry (84.6%), restorative dentistry (76.9%), or speech therapy (69.2%). Future interventions should seek to establish country-adapted guidelines for proper oral health care.

Conclusion: EB, particularly RDEB, has a significant impact on oral health and quality of life in Austrian EB

patients. Compromised oral function strongly influences outcomes, but improvements do not always match treatment needs. These findings highlight the importance of individualized, EB-specific dental care in Austria. Multidisciplinary oral health management, including a speech therapist, is essential for EB patients to improve, not only oral health, but also their oral health-related quality of life.

066

Oral use of medicinal cannabidiol oil in the healing process in patients with epidermolysis bullosa – a clinical case report

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ABSTRACT

In recent years, studies with medicinal cannabidiol (CBD) have been growing in dermatological disorders due to its multiple pharmacological properties such as antioxidant, anti-inflammatory, moisturizing, healing, and anti-aging effects, but there are still few of them. In addition, they help reduce the process of chronic pain and itching.

In this study, premium quality full-spectrum cannabidiol oil with 200mg/ml of CBD and 0.2% THC was introduced in patients with recessive dystrophic epidermolysis bullosa to improve their quality of life as well as anxiety, sleep, and pain.

A 26-year-old patient, with recessive dystrophic epidermolysis bullosa, used full-spectrum cannabidiol with 200mg/ml of CBD and 0.2% THC, totaling 10 drops every 12 hours. After one month of oral use of cannabidiol oil, the patient reported a reduction in pain, itching, and anxiety, improved mood and sleep, and noticeable improvements in the healing process and skin hydration (Figure 1).

Considering that cannabinoid signaling regulates fibroblast functions, the proliferation and differentiation of epidermal keratinocytes, as well as skin inflammation, influencing the complex process of skin wound healing and angiogenesis.

Thus, it can be concluded that the use of oral medicinal cannabidiol in the healing process helps reduce the time, risk of biofilm formation and infection of lesions, as well as improving skin hydration. Reduction of local pain and itching. It helped reduce anxiety and pain, and there was an improvement in sleep, which contributed to the healing process and quality of life of these patients. Thus, the use of cannabidiol is promising in the healing process, improving skin and mood in patients with epidermolysis bullosa.

Keywords: cannabidiol; CBD; Cannabinoids; Wound healing; Skin; Pain, Itching; Anxiety; Epidermolysis bullosa

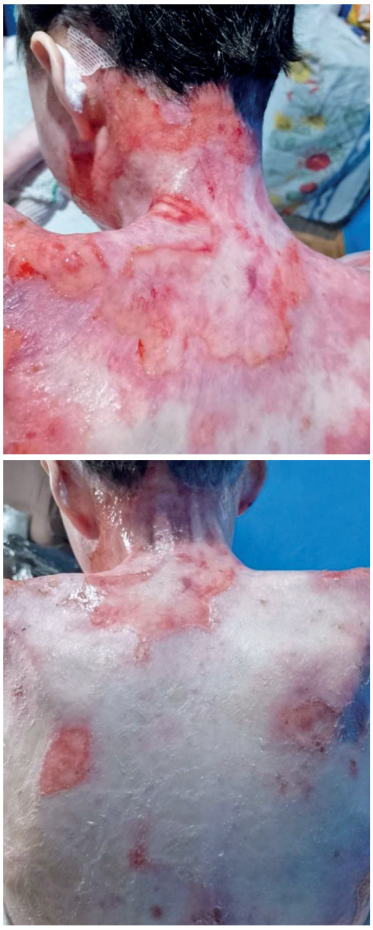

Figure 1. Before and after photo of one month of oral cannabidiol use

Presentation Abstracts

CONTENTS

067

Orthodontic treatment in patients with epidermolysis bullosa (EB)– Clinical Practice Guidelines (CPG)

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ABSTRACT

Introduction: Orthodontics in epidermolysis bullosa (EB) is scarce, underreported, challenging for the specialist and difficult for the patients to access, despite being included in the referral pathways of those types with high risk of oral disease, such as recessive dystrophic EB and junctional EB. The aim of this Clinical Practice Guidelines (CPG) is to provide information regarding best practice for orthodontic diagnoses and treatment for people living with EB.

Methods: A systematic literature review was performed, finding one cross-sectional study, five case-control studies and eight case reports and a panel of experts was invited to provide additional information based on their experience through an open-ended form. Later, a Delphi panel with dental experts (n=12), including orthodontists, paediatric dentists and special care dentists, sought agreement regarding recommendations, with a consensus threshold at 75%. Members of the medical team (n=4) and patient representatives (n=2) revised the final document and provided their perspective.

Results: A total of 15 recommendations were obtained, divided into three categories: general information, orthodontic diagnoses, and orthodontic treatment.

Orthodontic treatment is possible in people with EB, but proper risk-benefit assessment should be performed, as not all patients will benefit from it. These treatments are not the same in complexity compared to the general population, and must be adapted according to several factors, including oral characteristics, patients' barriers and facilitators/enablers, and the health care system. Patients should be assessed by a specialist before the age of 7.

The most prevalent malocclusions are crowded teeth and posterior crossbite. Intraoral photographs and impressions/ intraoral scanning can be limited due to microstomia, vestibule obliteration or ankyloglossia. Orthodontic treatment must be realistic, patient-

centred and planned in stages. Treatment takes more time (dental chair and full treatment), increasing the risk of caries. Different therapeutic approaches have been successfully used including early/selective tooth extraction, removable and fixed orthopaedic devices, fixed braces, mini-implants and aligners; each one requiring specific adaptations for its use. Retention is highly recommended, especially in patients with an imbalance of orofacial forces. Benefits of orthodontic treatment include enhanced aesthetics and self-perception, easier oral hygiene and fewer traumatic ulcers caused by misplaced teeth. Complications may include oral ulcers, transitory pain, poor oral hygiene, recurrent debonding of the brackets, and an increased number of caries. A multidisciplinary approach should include speech therapy and other dental specialities. Patients with EB looking for orthodontic treatment can face barriers such as limited access, funding and scarce training in EB by orthodontists. Patients and other members of the medical team agreed that orthodontic treatment can improve oral health, function, and quality of life in the EB population, but barriers should be properly addressed in order to improve this.

Discussion: Orthodontic CPG for patients living with EB are presented, including general aspects of EB, orthodontic diagnosis, and orthodontic treatment. These recommendations are intended to decrease patients' barriers, as people living with rare diseases present a high prevalence of malocclusions, but limited access to proper treatment.

Keywords: Epidermolysis Bullosa, Orthodontics

Presentation Abstracts

CONTENTS

068

Podiatric problems and needs in individuals with epidermolysis bullosa: a neglected care and its impact

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ABSTRACT

Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous group of rare and currently incurable inherited disorders characterized by fragility of the skin and mucous membranes. This results in blistering and wounds in response to seemingly disproportionate mechanical forces as pressure, friction and shear, specially in the feet, in all types of EB, resulting in a great impact in mobility and quality of life on affected persons, their families and caregivers, and healthcare systems In this experience report, our objective is to raise awareness among professionals about the importance of foot assessment, problem identification, and the planning of preventive, recovery, and rehabilitation care for the feet through guidance and education, podoprophylaxis, offloading, proper management of injuries, use of appropriate footwear with a focus on self-care, patient and family engagement, and greater attention from professionals. This is a qualitative study conducted with 11 patients and their families in which the main spontaneous complaints of the individuals were identified, followed by a foot examination conducted by a specialist nurse and dermatologist. The results highlighted the significant impact of foot pathologies and podiatric manifestations on all participants, which were classified into five groups: blisters and ulcerations, pain in the feet and other areas, biomechanical alterations, mobility and autonomy, infections and complications. Results demonstrated that the feet and legs are commonly affected, and neither patients and professionals, include the evaluation and foot care as an important condition in the their protocol and routine of care, showing a neglected care for people Improved foot care in EB requires comprehensive insight into the lived experiences and beliefs of patients, carers and healthcare professionals of holistic foot care management in patients with EB, as the psychosocial consequences of physical symptoms impacted quality of life more than the presence of physical symptoms alone. Frustration arising from poor access to healthcare professionals with knowledge of EB coexisted the foot is an engineering miracle combining grace, durability, and sensitivity, but is perhaps one of the most neglected parts of the body, generally hidden from sight, and its importance is only fully appreciated when something goes wrong. Healthy feet in good working order give us the joy of movement. Painful unhealthy feet make one feel tired and irritable, and take the pleasure out of life. These findings indicate a need for actions to reduce this gap, and to inform a reorientation and update of current EB foot care guidelines that includes also cultural, social and political aspects to provide changes and acess in the management of podiatric care in multiprofissional team with nurses, doctors, phisioterapy, podiatry and podologist and industries.

Keywords: Epidermolysis bullosa; Podiatry; Nurse; Woundcare

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Presentation Abstracts

069

Pre-clinical Development of Gene Therapy for RDEB to Restore Collagen VII

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ABSTRACT

Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe genetic disorder characterized by extreme fragility of the skin and mucous membranes, leading to recurrent blistering and chronic, hard-to-heal wounds. It significantly impairs quality of life and may cause early mortality in affected individuals. RDEB is caused by mutations in the *COL7A1* gene, which encodes collagen VII (C7), a protein essential for adhesion and stability between the dermis and epidermis. In Brazil, the most frequent mutation (c.5047C>T) is located in exon 54, leading to reduced or absent expression of C7. This project aims to develop an innovative gene-editing protocol to restore functional C7 expression in cells from individuals carrying the c.5047C>T mutation. The approach focuses on precise correction of the pathogenic variant using next-generation adenine base editors (ABEs). By converting adenine to guanine at the targeted site, ABEs enable accurate repair of the mutated nucleotide, thereby reinstating normal C7 expression. Our preliminary results demonstrated the successful optimization of the gene-editing protocol using fibroblast cell lines containing the mutation. The combination of ABE8e-mRNA with gRNA achieved high delivery efficiency while maintaining cell viability. At the c.5047 site, one of the guides (gRNA-05) reached correction rates exceeding 90%. The optimized protocol was subsequently successfully applied to patient-derived fibroblasts, bringing the study closer to a clinically relevant context. Immunofluorescence assays confirmed C7 expression restoration in edited cells. Skin 3D equivalents are being generated with the edited cells to interrogate whether C7 is properly localized in the basal membrane. By the conclusion of this project, the goal is to establish a safe and efficient gene-editing protocol for functional C7 expression in fibroblasts and keratinocytes, as well as to validate its application in generating C7-expressing skin fragments. If successful, this work will provide the foundation for further development of a gene therapy for individuals with RDEB.

Presentation Abstracts

CONTENTS

070

Prevalence of Epidermolysis Bullosa in Argentina: Insights from a Unified Patient Registry

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ABSTRACT

Introduction: Epidermolysis Bullosa is considered a rare disease, and to date, there is no unified patient registry in Argentina. Given the significant variation in prevalence reported in different countries (5–55 per million inhabitants), the estimated number of patients in Argentina could range from 250 to 2500. The objective of this study is to provide an accurate estimate of the prevalence of EB in Argentina. Preliminary results of this work were presented at the World Congress of Pediatric Dermatology 2025 in Buenos Aires. Given the strong interest it generated, we decided to present it at EB2026, incorporating additional patients enrolled in our registry and providing an estimate of the annual incidence along with the evolution of the time to achieve an accurate diagnosis.

Methods: A cross-sectional study was conducted based on a unified patient database constructed from anonymized records provided by four EB-specialized centers in Argentina involved in care, follow-up, molecular diagnosis and/or enrollment for clinical studies. Prevalence was estimated using capture-recapture methods.

Results: The Center for Research on Genodermatoses and Epidermolysis Bullosa (CEDIGEA) provided a list (L1) of 469 patients (2009–present). Four different healthcare centers in the city of Córdoba contributed a list with 44 patients (L2). A registry initiated by DEBRA Argentina (2010–2019) and continued by Fundación Respirar included 432 patients (L3). Lastly, the Garrahan National Pediatric Hospital's Dermatology department provided a list (L4) of 138 patients seen at least once (2013–present). These sources were combined into a final registry of 674 living, likely unique patients (313 EBS, 305 DEB [104 dominant, 201 recessive], 36 indeterminate EB, 15 JEB, and 5 KEB), with only 60.83% having confirmatory molecular studies. Preliminary calculations showed L2 was not independent, so the final estimation was based solely on L1, L3, and L4. The total number of cases in Argentina was estimated at 1203, with a 95% CI [1079, 1356], resulting in an estimated prevalence of 25.55 per million inhabitants.

Conclusion: This study provides an accurate estimate of the prevalence of EB in Argentina using a capture-recapture approach based on records from four specialized centers. The estimated prevalence is consistent with data reported in other countries. The identification of only 60.83% of cases with confirmatory molecular diagnoses underscores the urgent need to improve access to genetic testing and enhance diagnostic accuracy. Furthermore, the absence of a unified registry highlights the importance of establishing a centralized data collection system to better monitor prevalence and improve medical care for EB patients in Argentina.

Presentation Abstracts

071

Profile of Brazilian adults with epidermolysis bullosa: a nationwide cross-sectional study on socio-demographic, clinical, and nutritional characteristics

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) is a rare, genetic skin fragility disorder with a profound impact on quality of life. In Brazil, reliable epidemiological data is scarce, fragmented, and often focused on the pediatric population, leaving adults with EB largely underrepresented. This study aimed to characterize the socio-demographic, clinical, and nutritional profile of Brazilian adults with EB.

Methods: A nationwide cross-sectional online study was conducted from April to October 2024, in partnership with patient associations (DEBRA Brazil, APPAPEB). A total of 111 adults (≥18 years) with a self-reported EB diagnosis completed a structured form. Data included socio-demographics, clinical characteristics, and self-reported weight and height for BMI calculation.

Results: Participants were mean aged 33.1±11.0 years, predominantly female (67%), white (68%), unmarried (73%), and residing in urban areas (89%). Geographically, participants resided primarily in the Southeast (54%) and South (25%) regions. Socioeconomic data revealed that 43% reported a monthly family income between USD 200-600. Over half (55%) were employed, predominantly in remote or hybrid work models. Clinically, the dystrophic subtype was most prevalent (63%), followed by simplex (36%). Medication use was high (71%), with analgesics and antibiotics being most common. Nutritional supplement use was widespread. Nutritional status was a critical finding: 36% were underweight, 14% overweight and 13% obesity. History of hospitalizations and blood transfusions varied significantly.

Conclusion: This pioneering study provides the first comprehensive portrait of adults with EB in Brazil. It reveals a predominantly young population facing significant socioeconomic challenges and a high burden of disease management. The complex bimodal nutritional status calls for a paradigm shift in nutritional care.

Keywords: Epidermolysis bullosa; Rare diseases; Brazil; Adult; Cross-sectional studies; Socioeconomic factors; Nutritional status

Presentation Abstracts

CONTENTS

072

Psychosocial impact of epidermolysis bullosa on patients and relatives: a systematic review

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ABSTRACT

Background: Epidermolysis bullosa is a rare chronic condition, resulting in a high skin fragility. In addition to its physical impact, EB poses a profound psychosocial challenge to patients and their families, impacting daily functioning, social interactions, mental health and overall quality of life. According to the biopsychosocial model, psychosocial factors directly impact pain perception and physical health. Stress, emotional strain, and social isolation can impair wound healing, exacerbate chronic symptoms, and weaken immune responses. Despite their importance, systematic knowledge of the psychosocial burden, coping resources, and supportive strategies in EB is scarce, and the psychosocial effects of EB are often only considered in addition to its physical impact. Addressing psychosocial aspects is crucial for the development of comprehensive care concepts that improve the quality of life of patients and their relatives and move beyond the management of physical symptoms.

Objective: To address this gap, the aim of the systematic review is to synthesize existing evidence on the psychosocial consequences of EB for patients and their families.

Methods: A protocol was registered in PROSPERO (registration number: CRD42024604288). Following PRISMA 2020 guidelines, we conducted a systematic search across 15 databases. Studies with a qualitative, quantitative or mixed-methods design, that published empirical research in English, German, French, Dutch, Italian or Portuguese before October 30th, 2024 were eligible. Case reports, case series with less than three EB participants, reviews, and conference abstracts were excluded. Study selection and data extraction were performed independently by two reviewers, with discrepancies resolved by consensus. Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists.

Results: From an initial pool of 5.076 studies, 240 met the inclusion criteria after title/abstract screening and 108 met the inclusion criteria after full-text screening, including conflict resolution, duplicate removal and post-sampling. The included studies covered a broad range of psychosocial themes across physical, emotional, social and functional dimensions.

Reported burdens included chronic pain, itch, visibility of the disease, dependency on caregivers, and social stigma, often associated with anxiety, depression, and reduced quality of life. Families and relatives reported high emotional strain and financial challenges. At the same time, resilience, family cohesion, social support and disease-specific coping strategies emerged as important protective factors. Several studies highlighted unmet needs in psychosocial care and insufficient integration of psychological support into clinical management.

Conclusion: EB imposes a significant psychosocial burden on patients and their relatives, with wide-ranging emotional, mental and social implications. Coping strategies and supportive resources can play a protective role. This review underscores the need for integrated, multidisciplinary care that explicitly addresses psychosocial well-being alongside and in combination with medical treatment. Future research should focus on developing evidence-based psychological support

programs and improving access to psychosocial services in EB care pathways.

Keywords: Epidermolysis bullosa; Psychosocial impact; Quality of life; Coping; Systematic review

Presentation Abstracts

CONTENTS

073

Quality of life in recessive dystrophic epidermolysis bullosa: findings of the Prospective Epidermolysis Bullosa Longitudinal Evaluation Study (PEBLES)

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ABSTRACT

Background: Individuals with epidermolysis bullosa (EB) present with different manifestations of severity which may significantly impair health-related quality of life (HRQoL). The impact of recessive dystrophic EB (RDEB) and differing disease severity across the subtypes on HRQoL has not been studied in depth.

Objective: To measure HRQoL in a large cohort of individuals with RDEB, explore differences in physical functioning and emotional/psychosocial health scores, separately report findings by RDEB subtype to identify potential correlation with disease severity.

Methods: Individuals of all ages with RDEB were recruited (2014-2021) to the Prospective EB Longitudinal Evaluation Study (PEBLES), a register study of children and adults with RDEB. Data collection occurred every 6 months (under 10 years) or annually (10 years and above) including measurement of disease severity, using Birmingham EB Severity score (BEBS) and the Instrument for Scoring Clinical Outcomes for EB (iscorEB), and assessment of HRQoL. Adults participants completed the EB-specific Quality of Life in Epidermolysis Bullosa questionnaire (QOLEB), and child participants and their parents completed the Pediatric Quality of Life Inventory (PedsQL) generic core scales, version 4.0.

Results: 47 adults and 14 children reported HRQoL in 335 reviews over a maximum of seven years, including 26 participants with severe RDEB (RDEB-S), 21 with intermediate (RDEB-I), 9 with inversa (RDEB-Inv), 4 with pruriginosa (RDEB-Pru) and 1 with pretibial RDEB.

QOLEB scores showed severe impact of RDEB on HRQoL for all 47 adults with RDEB, particularly in RDEB-Pru and RDEB-S. The total QOLEB scores and functioning subscores for all RDEB correlated with iscorEB and BEBS disease severity scores. Those with RDEB-S reported a statistically higher HRQoL impact compared to the milder subtypes, RDEB-I and RDEB-Inv.

Worse HRQoL (PedsQL) was also reported by children with greater disease severity (iscorEB) and by their parents.

HRQoL related to physical functioning (adults) and physical health (children) was more severely impacted than emotions (adults) and psychological health (children). HRQoL generally improved with age.

Conclusion: We reported HRQoL by age and disease subtype for a large cohort of individuals with RDEB. Our findings highlighted a significant impact on HRQoL which generally correlates with disease severity for all ages and all RDEB subtypes. Functioning/physical health was more severely impacted than emotions/psychosocial health suggesting psychological adaptation

from living with RDEB since or shortly after birth with ongoing adaptation throughout life.

Keywords: Epidermolysis bullosa; Health-related quality of life; Disease severity; Natural history

Presentation Abstracts

CONTENTS

074

Recessive dystrophic epidermolysis bullosa and kidney involvement

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ABSTRACT

Instroduction: Renal manifestations in RDEB patients due to collagen VII deficiency have only been described in case series and could thus be underestimated.

Objectives: To find out how common kidney disease is in patients with RDEB and to describe the different types of kidney involvement they can face.

Methods: Retrospective study in an EB French expert center (MAGEC-Necker-St Louis) including RDEB patients with at least two concurrent blood and urine analyses. Kidney disease was defined as either glomerular with elevated albuminuria or tubulointerstitial with elevated β2-microglobulinuria.

Results: We included 120 RDEB patients between 2005 and 2021. The patients' median age was 18.5 years [11–30], 57 (47.5%) were younger than 18 years, 36 (30%) exhibited kidney disease. Of these, 15 (12.5%) displayed glomerular disease, most commonly due to IgA nephropathy, and 21 (17.5%) presented with a tubulointerstitial presentation, often associated with complex hydroelectrolytic disorders. The immunohistochemistry study with anti-collagen VII antibody was positive on glomerular and tubular basement membranes in controls and negative in patients with complete collagen VII deficiency. In multivariate analysis, kidney disease was significantly associated with disease severity ($p=0.002$). Overall survival was reduced in RDEB patients with kidney involvement.

Discussion: Given the unexpectedly high frequency of kidney involvement in RDEB patients, we propose the following recommendations, to be validated in prospective studies:

a) First assessment and monitoring of kidney manifestations in RDEB patients. For all patients with non-severe RDEB: annual urine test: proteinuria ? hematuria,? along with blood pressure measurement. Any abnormalities: screening recommended for patients with severe RDEB. Patients with severe RDEB : systematic screening at least once a year: *blood pressure* measurement, *blood tests*: creatinine, cystatin C, compared eGFR rates based on creatinine and cystatin C, electrolytes (Na^+, K^+, Ca^{2+}, P, and Mg^{2+}), glucose, CRP, and albumin; *urine tests:* creatinine, total protein, albumin, and tubular proteinuria markers like retinol-binding protein, beta-2 microglobulin, and/or alpha-1 microglobulin, depending on test availability at each center. Additional urine assessments should comprise Na^+, K^+, urea, Ca^{2+},

P, and glucose, as well as urine sediment analysis.

b) Systematic nephrology consultation whenever these conditions are encountered: Glomerular proteinuria and/or reduced eGFR; Tubular proteinuria, with or without electrolyte imbalances: insights.

c) Early management and prevention of renal manifestations. Standard nephroprotective principles should be adapted to the RDEB population: Nephrotoxic antibiotics should be avoided when possible, with dosage adjustments based on kidney function assessed by creatinine, cystatin C, or measured GFR, as necessary. Recurrent monitoring of antibiotic levels recommended in cases of prolonged therapy, as the distribution volume can significantly vary among patients; The common episodes of dehydration require proactive management, which potentially involves increased salt intake *(e.g.,* sodium chloride capsules or hydration via gastrostomy); For glomerular proteinuria, renin–angiotensin–aldosterone system (RAAS) blockade could be considered. This strategy requires a close monitoring for hypotension and dehydration, with immediate treatment cessation should these issues arise.

Conclusion: Kidney disease is common, correlates with disease severity, and impacts the prognosis of patients with RDEB. Systematic screening is recommended in this population.

Presentation Abstracts

CONTENTS

075

Squamous cell carcinomas associated with epidermolysis bullosa: experience of treatment

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ABSTRACT

Introduction: Epidermolysis bullosa (EB), especially RDEB the severe dystrophic form with a recessive type of inheritance, associated with a high risk of developing invasive squamous cell carcinoma of the skin and mucous membranes. This cohort of patients often develops multiple primary and metachronous tumors, characterized by aggressive course and a tendency to metastasize. Moreover SCC is the main cause of death in patients with RDEB.

Objective: demonstration of experience in management and treatment of patients with severe forms of epidermolysis bullosa and squamous cell skin cancer.

Methods: From 2019 to 2025, 16 patients with SCC as a result of RDEB were identified. The average age at first manifestation SCC was 29 years (age range 17.7 - 60 years), the gender ratio was the same: 8 men and 8 women. In 31% (n=5) of cases, the malignant skin lesion was of a primarily multiple nature of distribution. Three patients at the time of initial treatment had a tumor lesion for which radical surgery was not possible, one patient refused a mutilating volume of surgery. In total, 39 surgical interventions were performed during the observation period, 46 foci of SCC were removed, two amputations of lower limb were performed. Four patients underwent systemic therapy, EGFR inhibitors, PD1 inhibitors, as well as metronomic regimens of polychemotherapy for palliative purposes were used. At the time of publication, 6 patients died, 5 of them due to the progression of SCC, one due to the development of systemic amyloidosis. Currently, 10 patients are under observation: 9 are in remission, one patient is receiving immunotherapy. In addition, 5 patients from this group, during the observation period, demonstrated the development of both metachronous tumors and local relapses of SCC.

The study was conducted using data from the "Register of Genetic and Other Rare Diseases" of the BELA. Butterfly Children Charitable Foundation (https://deti-bela.ru).

Results: overall and event-free survival of patients was 62.5% and 25%, median follow-up was 28.8 and 11.8 months, respectively.

Conclusion: Squamous cell skin cancer against the background of RDEB has a chronic course, with a high risk of developing synchronous and metachronous tumor foci. The most effective treatment method is radical removal of the tumor, but this is possible in early detection of primal tumor. In case of locally advanced relapse, PD-1 inhibitors have demonstrated efficacy. The prognosis of SCC is characterized by high mortality in the group of patients with RDEB. Currently, there are no specific methods for preventing SCC in patients of this cohort, since the pathogenetic options for treating RDEB are limited.

Keywords: Epidermolysis bullosa; Dystrophic form of epidermolysis bullosa; Squamous cell carcinoma of the skin

076

Targeting cytokine pathways for drug repurposing in epidermolysis bullosa: a comprehensive systematic review

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ABSTRACT

Objective: Epidermolysis bullosa (EB) is rare inherited blistering disorder of the skin characterised by fragile skin and mucous membranes that blister easily. As a result of the large heterogeneity of EB, individualised symptom management and prevention of secondary complications are currently the best options for patients with this debilitating disease. Whilst these strategies have been useful in managing the disease, the need for new therapeutic approaches remains a priority. This review examines the inflammatory profile of EB and drug repurposing as a potential treatment pathway.

Methods: A comprehensive search was performed across PubMed, Embase and Cochrane Clinical Trials databases to identify relevant articles focused on potential cytokine targets and current examples of drug repurposing in inherited EB patients.

Results: As a result, 47 papers met the eligibility criteria. Cytokines were measured in serum (n=15) and skin (n=5) in 1 to 92 patients. Importantly, cytokine expression varied between individuals, rather than by EB subtype. The review highlights the key involvement of cytokines in the EB inflammatory process such as IL-6, TGF-ß and IL-1ß. It also suggests possible involvement of TNF-α and the Th1 and 2 pathways, though their exact contributions remain unclear. The results suggest that targeting these cytokines could potentially play a role in the treatment of EB, while acknowledging that the diverse clinical manifestations of the disease may limit the identification of precise therapeutic targets. Furthermore, this review identified 19 current examples of repurposed drugs targeting specific cytokines and their related pathways, such as diacerein, dupilumab, thalidomide and secukinumab, which demonstrated clinical and score-related improvements, although most did not assess cytokine profiles before treatment. Other treatments, such as broader anti-inflammatory medications, like colchicine, were also highlighted in this review, along with various drugs like phenytoin, gentamicin and dapsone.

Conclusion: The varied findings emphasise the need for personalised medicine approaches, such as measuring cytokines before deciding on treatments, and for more extensive research to understand the cytokine profile of each EB subtype. Large-scale clinical trials to validate the effectiveness of such treatments to ultimately improve the quality of life for EB patients is essential.

Presentation Abstracts

CONTENTS

077

Targeting pain for a better quality of life in EB: a transdisciplinary approach

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ABSTRACT

Background: Epidermolysis bullosa (EB) is associated with a variety of physical and psychosocial burdens. While a curative treatment remains elusive, patients and their families must address the challenges posed by EB, including the discomfort associated with wound care and the psychosocial impact of the condition on their daily lives. A comprehensive understanding of EB requires not only attention to medical aspects but also to the psychosocial and psychotherapeutic dimensions of living with the condition.

To address this need, the research project "Visions of Quality of Life with Epidermolysis Bullosa – A Transdisciplinary Approach to Identify, Measure and Improve Quality of Life with Epidermolysis Bullosa", funded by the Austrian Academy of Sciences (ÖAW), integrates medical, psychological, and psychotherapeutic expertise to provide a comprehensive view of EB and its impact.

Within the multidimensional burden of EB, pain stands out as one of the most debilitating and pervasive symptoms, affecting up to 91% of patients. Pain in EB is complex, comprising neuropathic and non-neuropathic qualities, and arises from wounds, wound care and due to daily life activites as e.g. eating or walking. It is often accompanied by burdensome itch and has cascading effects on sleep, psychological well-being, and daily functioning. However, despite its central role in shaping quality of life, no validated instrument exists to capture all dimensions of pain in EB.

Objective: This project aims to develop a disease-specific pain questionnaire for EB integrating medical, psychological, and psychotherapeutic perspectives and to provide a basis for interventions that address the multidimensional impact of the disease and improve patients' and families' quality of life.

Methods: Our interdisciplinary team combines medical, psychological, and psychotherapeutic expertise. By employing a transdisciplinary approach with methodological triangulation, combining qualitative, quantitative, and mixed-method designs, we aim to develop tools and interventions that move beyond isolated symptom management to address the broader impact of EB on patients and their families.

Results: A systematic review on psychosocial aspects of EB and a meta-analysis on pain treatments form the scientific foundation of our project. The review highlights the considerable psychosocial burden of EB, including impacts on identity, mental health, and social participation, while the meta-analysis shows that current pain lack standardized outcome measures. Additionally, 34 semi-structured interviews with patients and relatives provide qualitative insights into daily life and suffering. Building on these findings, and in collaboration with patients, representatives, and EB experts, we are developing a disease-specific pain questionnaire capturing the physical, emotional, and social dimensions of EB-related pain. In an international survey, interview findings on pain, itch, health identity, and psychosocial support needs are applied to a larger sample to assess the multidimensional impact of EB, and the questionnaire is subsequently statistically validated. The instrument will improve intra- and inter-

trial comparability and strengthen the evaluation of therapeutic interventions.

Conclusion: Overall, the research project shall provide a validated pain questionnaire for EB and multidisciplinary access points to improve quality of life of EB patients and their relatives already in the now.

Keywords: Epidermolysis bullosa; Pain; Burden; Resources; Psychosocial aspects

Presentation Abstracts

CONTENTS

078

The Bulgarian pathway to beremagene geperpavec access and reimbursement

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ABSTRACT

Introduction: Epidermolysis bullosa (EB) is a rare, debilitating genetic disorder for which few disease-modifying therapies exist. Beremagene geperpavec (Vyjuvek) is a non-integrating, replication-deficient HSV-1 vector that delivers functional COL7A1 to restore type VII collagen in dystrophic EB wounds. It became the first EMA-approved topical gene therapy for dystrophic EB in April 2025, representing a paradigm shift in management. However, the therapy's high cost and regulatory novelty present major challenges for reimbursement and access across Europe. Bulgaria was among the first countries to secure access to Vyjuvek, providing a unique early example of policy responsiveness in rare disease care.

Methods: In Bulgaria, access to innovative therapies for rare diseases is possible through established legal mechanisms for exceptional reimbursement. Applications are initiated by treating physicians through hospital commissions, validated by the hospital director, and reimbursed by the National Health Insurance Fund (NHIF) after initial hospital payment. Protocols are renewed every three months. This pathway was first applied to severe EB in 2023, when Birch triterpenes (Filsuvez) became available for patients under 18 years of age (Fund for Treatment of Children, NHIF). Later, Vyjuvek followed the same framework.

Results: A 3-year-old Bulgarian male with severe recessive dystrophic EB carrying two nonsense COL7A1 variants (c.2005C>T, p.Arg669Ter & c.6994C>T, p.Arg2332Ter) received Vyjuvek in the United States in April 2024, following an application process initiated in mid-2023. Unfortunately, disease activity worsened rapidly when therapy was interrupted upon his return to Bulgaria, prompting urgent actions. Under the established mechanisms of Ordinance №10/2011, which allows exceptional use of non-authorized medicinal products, the Bulgarian Drug Agency approved import of Vyjuvek in January 2025. Reimbursement by the NHIF followed immediately, and the first doses were delivered nationally in February 2025 – several months before the official EMA approval of Vyjuvek. This made Bulgaria one of the first countries in Europe to provide funded access to the gene therapy, demonstrating how existing legislation can be leveraged to integrate breakthrough treatments ahead of formal European authorization.

The introduction of Filsuvez in 2023 catalyzed the establishment of EB DEBRA Bulgaria, which created a platform for international collaboration, national advocacy, and structured support for EB families. This experience strengthened the dialogue between clinicians, patients, and health authorities, laying the groundwork for the much more complex integration of Vyjuvek.

Conclusion: While Filsuvez opened the door for therapy access in EB, Vyjuvek marked the first gene therapy adopted through this mechanism, testing the limits of financial sustainability but proving the effectiveness of patient-driven advocacy combined with existing legal frameworks. For the international EB community, Bulgaria's case illustrates a replicable model for persuading governments to reimburse novel therapies.

Keywords: Epidermolysis bullosa; Gene therapy; Beremagene geperpavec; Health policy; Orphan drugs; Funding; Bulgaria

079

Therapeutic use of Botulinum toxin in the orofacial region in patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB)

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ABSTRACT

Introduction: Patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) present diverse orofacial complications secondary to the scarring process, which hinder the delivery of standard treatment strategies for common conditions, such as providing occlusal splints (OS) for Bruxism. Botulinum toxin type A (BTX-A) has emerged as a treatment option for bruxism. We present the preliminary outcomes of administering BTX-A in the orofacial region in patients with RDEB.

Case 1: In 2017, a 15-year-old female patient with severe RDEB (homozygous c.6527insC in *COL7A1)* referred nocturnal awakenings due to pain (VAS 8/10), sensation of tooth mobility, grinding, muscular stiffness and difficulty to chew. Bruxism was diagnosed but microstomia (13 mm maximal mouth opening) hindered providing OS. She was treated with 50U of BTX-A (Reage®). From 2017 to 2021 the patient received yearly infiltrations of BTX-A, increasing the dosage to 100U and adding the temporalis muscle into the infiltration scheme. The patient reported a decrease in the symptoms 48 hours after the punctures and maximal efficacy two weeks after. Absence of bruxism-related pain lasted 5 to 8 months. Adverse events were minimal and localised. Patient reported reduction in pain and an improvement in her quality of life. She has not needed new interventions since 2021.

Case 2: In 2021, a 19 old female patient with severe RDEB (homozygous c.7708delG in *COL7A1)* complained of facial pain, mainly in the temporomandibular joint (TMJ) area, with trigger points in the masseter muscles. OS was not possible due to microstomia (23mm). Treatment included 100U of BTX-A (Botox®), with 14 infiltration sites distributed in masseter and temporalis muscles. In 2023, the patient returned to treatment, referring that BTX-A infiltrations improved her facial skin, reducing her sweat-worsened blistering episodes. She requested facial BTX-A infiltration. A new scheme was used, with 100U divided into 10 facial points. A similar scheme was applied in March 2024. The patient reported that the effect starts fading after 6 months. No adverse reactions were reported, only a slight change in the upper lip movement, but not clinically relevant. By January 2025, the patient reported reduced sweetening but did not need a new infiltration. Patient reported that pain was successfully treated and facial infiltrations reduced her sweat-worsened facial blisters. She rates her treatment as a 10/10 score, her face is not burning anymore and changes in facial expression are minimal.

Discussion: TBX-A infiltrations reduced bruxism-triggered orofacial pain and other associated symptoms with minimal adverse effects. Remarkably, patient 2 experienced a reduction in facial sweat-worsened blistering after the facial infiltration scheme. The use of TBX-A in patients living with EB has been previously reported for plantar blistering, including sweat-worsened plantar blisters. In patients with RDEB, it has only been reported as a therapeutic option for chronic anal fissures and anal sphincter spasm. Botulinum toxin is a promising alternative for managing both bruxism in patients with severe microstomia and sweat-worsened facial blisters. Further studies are needed to confirm these findings.

CONTENTS

080

Topical use of cannabidiol foam and phytoactives in the healing process of patients with epidermolysis bullosa – case report

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ABSTRACT

We know that epidermolysis bullosa has a reduced microbiota and altered angiogenesis, causing the healing process to be altered and slow, leading to the appearance of biofilm on the lesions, hindering the healing of these patients.

Recent studies have shown that topical medicinal cannabidiol (CBD) activates endocannabinoid receptors in the skin, helping in the healing process, reducing oxidative stress, improving angiogenesis, and reducing inflammation in the lesion.

Thus, the topical use of Nubescare foam with CBD and phytoactives was performed once a day, on alternate days, due to the difficulty of performing daily dressings, with an excellent response in healing. There was a reduction in biofilm and a balance of the lesion's microbiota, facilitating healing and thus reducing pain and itching in these patients who used the foam in a short time.

Attached is a photo of patient, 16 years old, with recessive dystrophic epidermolysis bullosa with a lesion showing biofilm and improvement after 4 uses of the foam (Figure 1).

Thus, CBD foam came to help the healing and hygiene process of wounds in patients with epidermolysis bullosa, reducing the time of lesions and healing them, making life easier for these patients and improving their quality of life with fewer lesions.

Keywords: cannabidiol, CBD, cannabinoids, wound healing, skin, pain, itching, healing, epidermolysis bullosa

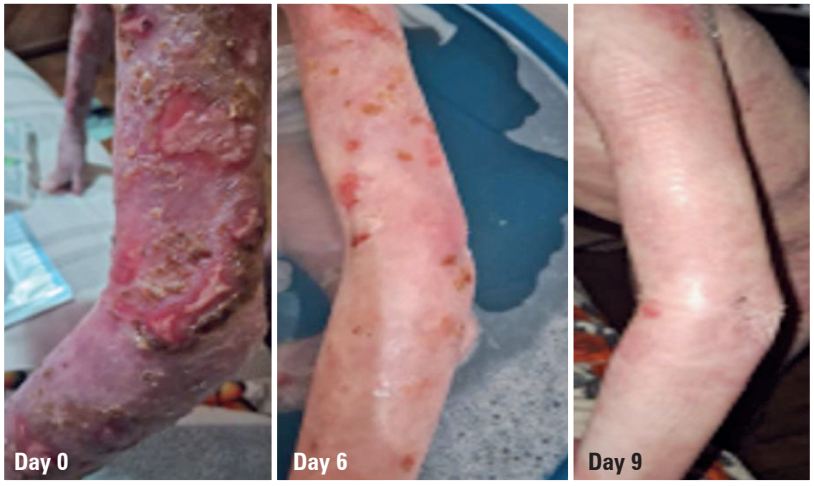

Figure 1. Healing progression of a RDEB lesion following topical CBD foam application (Day 0, Day 6, and Day 9)

Presentation Abstracts

081

Treatment of dystrophic epidermolysis bullosa with gene therapy: scientific advances and current challenges

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ABSTRACT

Introduction: Dystrophic epidermolysis bullosa (DEB) is a rare hereditary dermatosis characterized by mucocutaneous fragility, with the formation of severe dermal blistering in response to minor trauma or friction. Currently, DEB has no cure, and conventional wound care methods are only minimally effective. In this context, new potentially effective therapeutic approaches, such as gene therapies, are being investigated, and their benefits and disadvantages are being assessed to promote a better quality of life for patients with DEB.

Objective: To evaluate the progress of gene therapy in the treatment of DEB and its current obstacles.

Methods: This literature review included only original articles and systematic reviews in English, published between 2020 and 2025 in the PubMed database. The descriptors used were: "epidermolysis bullosa dystrophica," "treatment," "gene therapy," and "advances," focusing on the main advances and challenges related to gene therapy in DEB.

Discussion: DEB is caused by mutations in the COL7A1 gene, which encodes type VII collagen (C7), the main component of the anchoring fibrils that attach the epithelial lamina densa to the underlying dermis. Among new treatments for DEB, in vivo gene replacement therapy using the topical drug Vyjuvek™ has gained prominence during clinical trials. This therapy employs a modified, non-integrating, non-replicating herpes simplex virus type 1 (HSV-1) vector to replace the defective COL7A1 gene with two functional complementary DNA copies of this gene in keratinocytes and fibroblasts present in DEB wounds. Results showed complete healing of 71% of lesions over a 3-month period, with the production of functional C7 and anchoring fibrils. Moreover, this therapy presented a reduced risk of triggering an immune response and promoted a decrease in pain and infections. However, some limitations were noted, such as the need for long-term weekly applications and the high production cost, which prevents this treatment from being accessible to all patients.

Conclusion: Among emerging treatments, gene therapy based on gene replacement, although expensive, is highly effective for wound healing in DEB and contributes to improving the well-being of affected individuals.

Presentation Abstracts

CONTENTS

082

Wound precede my being: a personal narrative study on the suffering experiences of individuals with Hereditary Epidermolysis Bullosa

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ABSTRACT

Background: Hereditary Epidermolysis Bullosa (EB) is a rare genetic skin disorder that causes chronic wounds and vulnerability. Beyond the medical perspective, there is a need to understand how individuals live with and narrate their suffering.

Methods: This study adopted a narrative research approach and applied Critical Narrative Analysis to the case of "A-Wan," an individual with hereditary EB. Over one and a half years of long-term companionship and repeated in-depth interviews, we explored how A-Wan copes with the effects of wounds and illness, narrates his personal story, and constructs meaning and social positioning.

Results: Findings show that suffering emerges not only from bodily fragility but also from medical discourse and social interactions. The interplay between rarity and social alterity produced multiple marginalities in A-Wan's subjectivity. To preserve internal order and coherence, he set strict psychological boundaries and behavioral rules, while finding belonging mainly within the peer community. Illness profoundly shaped his temporal experience: normative life timelines became unattainable, and he relied on repetitive daily rhythms to maintain control, resulting in a fragmented sense of self.

Conclusion: A-Wan's predicament is both physiological and socio-cultural, reflecting broader neglect of subjectivity in rare disease contexts. Addressing such needs requires moving beyond medical care toward relational presence, narrative witnessing, and ethical responsiveness to lived suffering.

Keywords: Critical narrative analysis; Epidermolysis bullosa; Rare disease; Suffering experience; Subjectivity; Narrative research

Presentation Abstracts

083

N-Acetylcysteine as a therapeutic candidate for RDEB wound healing

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ABSTRACT

Introduction: RDEB is characterized by chronic wounds and progressive fibrosis. Fibroblasts from RDEB chronic wounds exhibit hallmarks of cellular dysfunction, including reduced viability, senescence, and abnormal contractility, which together contribute to impaired healing. Importantly, fibroblasts isolated directly from wounds provide a relevant cellular model of wound healing, as they nay better recapitulate the pathological microenvironment compared to fibroblasts derived from non-lesional skin. This model allows the identification of candidate drugs capable of modifying key parameters of wound chronicity. In this context, we explored the effects of N-acetylcysteine (NAC), a clinically repurposed compound with anti-inflammatory and antioxidant properties. Previous studies have shown that NAC can act through the TGF-β pathway in RDEB fibroblasts, but those experiments were limited to non-lesional cells. Here, we investigated whether NAC could modulate wound-derived fibroblast dysfunction *in vitro* and promote wound healing and symptom relief *in vivo* through topical application.

Methods: Fibroblasts derived from chronic wounds, non-lesional skin of RDEB patients, and skin from healthy donors were treated *in vitro* with different NAC concentrations. Cell senescence, viability and contractility were assessed, and mitochondrial morphology and dynamics were visualized by immunofluorescence. In parallel, a topical NAC-containing gel was applied to chronic wounds in two RDEB patients. Wound closure kinetics, as well as changes in pruritus and pain, were monitored over time.

Results: High concentrations of NAC (≥1 mM) selectively reduced the viability of chronic RDEB fibroblasts, without affecting fibroblasts from non-lesional RDEB skin or healthy controls. At 1 mM, NAC did not alter cell viability but downregulated contractility-associated genes, resulting in reduced fibroblast contractile capacity in collagen I gels. Furthermore, 1mM NAC decreased the proportion of senescent cells and restored normal mitochondrial morphology in chronic wound fibroblasts. Clinically, topical application of a NAC-containing gel to chronic RDEB wounds (>6 months wound duration) yielded heterogeneous outcomes. In one patient, NAC treatment led to rapid and complete wound closure within days. In the second patient, although no significant improvement in wound closure was observed, NAC application was associated with a notable reduction in pruritus and pain, highlighting a potential symptomatic benefit independent of closure.

Discussion: These findings demonstrate that NAC ameliorates key features of fibroblast dysfunction in RDEB, including senescence, excessive contractility, and mitochondrial abnormalities. Clinically, NAC showed promising effects not only by promoting wound closure in one case but also by alleviating pruritus and pain in another, suggesting broader therapeutic potential. The use of wound-derived fibroblasts strengthens the translational relevance of these results, as this model more faithfully represents the RDEB wound microenvironment. Together, these data support NAC as a promising candidate for wound-targeted therapy in RDEB. Future studies in larger cohorts are warranted to validate these observations and to

establish optimal dosing strategies for chronic wound management in RDEB.

Acknowledgements: FONDECYT 1220704 and FONDEF ID24I10119 granted to IF.

084

Towards a minimally invasive diagnostic for early detection of cancer in recessive dystrophic epidermolysis bullosa

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ABSTRACT

Objective: If they survive into young adulthood, patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) almost always develop an aggressive and lethal formof of aggressive squamous cell carcinoma (SCC). Early and effective detection, as well as timely intervention is the key to effective treatment. However, lack of well-defined biomarkers and the trauma associated with biopsy excision can make compliance to a regular screening regime, challenging. The aim of our work has been to identify biomarkers of malignancy in RDEB and apply them to the development of a minimally invasive diagnostic that will improve quality of life for patients.

Methods: To do this we have applied novel methods in fluorescent multivariate histochemistry and filtration-based circulating tumour cell (CTC) isolation (Gasch *et al*. *Sci. Reports*, 2015), using a unique collection of patient derived keratinocyte, fibroblast and cell lines, to identify novel SCC biomarkers; and applied these methods to cells isolated from the blood of patients.

Results: In this way we have identified certain small RNAs (miRNAs) markers of malignancy in aggressive SCCs [Cell Commun Signal 18:61]. We have also determined that one of these markers, the small miR-10b imparts a stem cell-like phenotype to noncancerous cells, preferentially marks, the nonadherent fraction in culture, and can be used to mark putative CTCs in the blood of advanced SCC patients. We have also identified non small RNA novel markers of malignancy in SCCs, including most recently the chondroitin sulfate proteoglycan 4 (CSPG4) [Chen K, et al. (2022) Cancers (Basel). 14:5564] and used methods in image analysis and machine learning to incorporate both RNA and nonRAN markers into the development of a minimally invasive diagnostic of disseminated disease.

Conclusion: This work, spanning has used cutting edge methods in molecular biology and blood/cell -based diagnostics to provide the basis of a minimally invasive diagnostic that may be applied at point of care and has the potential to dramatically improve the quality of life of cancer patients. At the same time the basis for the development of a minimally invasive diagnostic that has the potential to While tragic for patients and families, RDEB represents a unique population to study malignancy in SCCs, with valuable information that can be used to inform treatment in the general community and drive the development of minimally invasive diagnostic methods.

Presentation Abstracts

CONTENTS

085

Splice modulation strategies using antisense oligonucleotides for recessive dystrophic epidermolysis bullosa

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ABSTRACT

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare autosomal recessive skin disorder characterised by recurrent blisters and erosions of the skin and mucous membranes leading to major local and systemic complications. It is caused by loss-of-function variants in the *COL7A1* gene encoding type VII collagen (C7), the main component of the anchoring fibrils. Abnormalities in the structure and/or expression of C7 lead to abnormal, rare or absent anchoring fibrils, resulting in the loss of dermo-epidermal adhesion and the formation of skin and mucosal detachments. To date, more than 1,200 distinct pathogenic variants of all type have been reported in the 118 exons of *COL7A1*, 19% of which being deleterious splicing variants. Importantly, exons 28 to 112 encoding the central collagenous domain are in the same open reading frame. Therefore, splice modulation, including exon skipping using antisense oligonucleotide (ASO), is a promising approach to treat RDEB. We have developed several strategies aiming at modulating *COL7A1* splicing. First, we have developed a palmitoylated tricyclo-DNA ASO which induces efficient exon 73 skipping and C7 re-expression *in vitro* after transfection in primary RDEB keratinocytes and fibroblasts and *in vivo* upon intravenous or subcutaneous injections in RDEB mice models. Transcript analyses of disease relevant tissues (skin, eyes, and oesophagus) revealed variable levels of exon 73 skipping *in vivo*, consistent with ASO biodistribution. Immunostaining and transmission electron microscopy demonstrated restoration of C7 expression and formation of mature anchoring fibrils (AF) at the dermal-epidermal junction upon intravenous and subcutaneous injections in immunodeficient murine model grafted with reconstructed skin from C7-deficient RDEB patient cells. No adverse reactions were observed *in* pre-toxicology studies in mice and non-human primates. Second, we report successful *in vitro* splice defect correction of *COL7A1* transcripts induced by novel deep intronic variants. Transfection of ASOs restored normal *COL7A1* mRNA splicing (up to 94%) and strong re-expression of C7 at a level sufficient to reverse the phenotype (up to 56% of the normal expression level). Thus, we demonstrated both re-expression of a wild-type C7 protein using ASO targeting deep intronic variants *in vitro*, and successful *in vivo r*estoration of functional C7 protein upon *in vivo* systemic delivery of ASO inducing exon 73 skipping. Overall, our data indicate that systemic administration of palmitoylated tricyclo-DNA ASO restores C7 expression and AF formation by skipping exon 73 of *COL7A1* pre-mRNA, which holds therapeutic potential for about 10% of RDEB patients carrying variants in this exon. Targeting several other exons could expand the patient population likely to benefit from this approach. We also demonstrated that splicing modulation applied

to deep intronic variants in *COL7A1* represents a promising therapeutic strategy for personalised medicine in RDEB, as first demonstrated for Batten disease, ataxia-telangiectasia and amyotrophic lateral sclerosis for which three mutation-specific ASOs have been approved by the FDA.

Presentation Abstracts

CONTENTS

086

COL7A1 c.6527dupC (insC): a translational journey from early diagnosis to prime editing

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ABSTRACT

Mutations in *COL7A1* spanning the entire gene are responsible for dystrophic epidermolysis bullosa (DEB), encompassing both dominant (DDEB) and recessive (RDEB) forms. To date, approximately 1,000 different mutations have been characterized, most of which are intrafamilial and non-recurrent, although exceptions exist. In 2007, our group initiated genetic diagnosis of EB in Spain and soon identified a remarkably recurrent frameshift mutation, c.6527insC (dupC) in the Spanish RDEB population. Subsequent studies revealed that this mutation, that originated in the Sephardic population of Spain more than 1000 years ago, spread to several countries in Latin America and the United States through historical migration during the colonial era. Based on available data, we estimate that more than 300 RDEB patients worldwide may carry this mutation. The unexpectedly high prevalence of c.6527insC prompted us to explore targeted correction strategies. Beginning in the pre-CRISPR era, our efforts have evolved through successive technological advances, progressively achieving increasingly efficient and precise genome editing approaches. In parallel, patients harboring the c.6527insC mutation have been enrolled in a clinical trial testing systemic mesenchymal stromal cell (MSC) therapy, further expanding therapeutic opportunities for this subgroup. These discoveries underscore the clinical applicability of our work: identifying recurrent founder mutations enabled the design of mutation-specific therapeutic strategies with high translational potential. Our results not only provide a framework for the development of targeted genome editing in DEB but also highlight how historical and population genetic insights can directly inform precision medicine approaches for rare diseases.

Presentation Abstracts

087

Highly efficient correction of recurrent pathogenic variants in *COL7A1* using cytosine or adenine base editing to treat recessive dystrophic epidermolysis bullosa

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ABSTRACT

This study investigated the therapeutic potential of base-editing–mediated correction of three recurrent pathogenic *COL7A1* variants in primary skin cells from individuals with Recessive Dystrophic Epidermolysis Bullosa (RDEB), a severe and life-threatening genetic disorder affecting the skin and mucosa.

Base editing enables precise single-nucleotide conversion of cytosine to thymine (C-to-T) or adenine to guanine (A-to-G) using Cytosine and Adenine Base Editors (CBEs, ABEs), respectively. We achieved efficient correction of the following variants: c.425A>G (p.Lys142Arg), c.6187C>T (p.Arg2063Trp), and c.6508C>T (p.Gln2170*) in primary RDEB keratinocytes (KCs) and fibroblasts (FCs).

Up to fourteen gRNAs were designed, and *in vitro* transcribed mRNAs encoding CBEs and ABEs were delivered by nucleofection to patient KCs and FCs. For the c.425A>G variant (exon 3), gRNA-N1 and gRNA-N2 achieved 73% and 91% editing in keratinocytes and fibroblasts, respectively, with minimal bystander effects as determined by high-throughput sequencing. mRNA analysis confirmed accurate *COL7A1* transcript expression. Restoration of type VII collagen (C7) protein using gRNA-N2 together with TAD-CBE_dV106W was shown by western blot and immunocytochemistry.

For the c.6187C>T variant (exon 74), two gRNAs combined with ABE_8eSprY achieved up to 79% correction in homozygous patient cells. For the c.6508C>T variant (exon 80), six gRNAs were tested with three ABEs (ABE_8e, ABE_Max, ABE_8eNG). The highest correction (91%) was obtained with gRNA-N5 or gRNA-N6 in combination with ABE_8eNG, without bystander activity. Other conditions also yielded high correction efficiencies (up to 86%) but introduced up to four bystander edits, ranging from 13% to 95%, none of which predicted alteration of the amino acid sequence.

Currently, genetically corrected 3D skin equivalents and epidermal organoids are being generated to assess functional rescue and validate this strategy for future *ex vivo* clinical applications. Notably, at least 16.5% of patients registered in the international DEB database carry one of these three recurrent variants and could directly benefit from this approach.

In summary, by demonstrating the feasibility and efficiency of base editing for selected *COL7A1* variants, this study supports clinical translation of gene-editing strategies to treat RDEB individuals.

Presentation Abstracts

CONTENTS

088

Development of a dual CRISPR/Cas9 nickase strategy for *COL7A1* correction in a prevalent Brazilian pathogenic variant of recessive dystrophic epidermolysis bullosa

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ABSTRACT

Epidermolysis Bullosa is a rare genetic disorder affecting the skin, characterized by the formation of blisters and erosions resulting from minimal trauma, due to extreme skin fragility. Recessive Dystrophic Epidermolysis Bullosa is one of the most severe subtypes, caused by mutations in the *COL7A1* gene. This gene encodes type VII collagen (C7), a key protein in the formation of anchoring fibrils, which are essential for dermal-epidermal adhesion. In Brazil, one of the most frequent pathogenic variants is c.5047C>T, which leads to the formation of a premature stop codon, resulting in translation interruption and a deficiency of functional C7 production. This study aims to establish an *ex vivo* gene correction strategy in immortalized neonatal foreskin fibroblasts harboring the variant (BJ-hTERTc.5047C>T), by using the Dual CRISPR/Cas9 Nickase (Cas9n) platform. This approach utilizes a Cas9 enzyme with its catalytic RuvC domain inactivated by the D10A mutation, which generates only single-strand breaks (nicks). To induce a double-strand break with high specificity, a pair of single-guide RNAs (sgRNAs) is designed to bind to complementary sequences on opposite DNA strands. The coordinated generation of nicks by the two Cas9n results in a double-strand break, significantly reducing the off-target event rate relative to wild-type Cas9. Initially, sgRNA pairs were designed to flank the mutation site and subjected to *in silico* analysis for the prediction of potential off-target effects. The selected sgRNAs were synthesized and complexed with Cas9n protein to form ribonucleoproteins (RNPs). The RNP complexes were then delivered into the healthy fibroblast BJ-hTERT and BJ-hTERTc.5047C>T cell lines via nucleofection, using the Nucleofector 4D system (Lonza). To optimize the protocol, transfection efficiency was first assessed by delivering GFP-encoding mRNA, achieving 94% GFP+ cells 24 hours post-nucleofection in both cell lines. Once high transfection efficiency was confirmed, the individual delivery of each sgRNA complexed with Cas9n was tested; however, it did not generate significant levels of indels detected by NGS sequencing. We then proceeded to co-transfect the sgRNA pairs. Cell viability was assessed, and genomic DNA was extracted 5 days post-nucleofection. The target region was amplified by PCR and sequenced by NGS. Data analysis was performed using the CRISPResso2 software to quantify the indel percentage. Notably, one pair demonstrated high efficiency, inducing indels in 76% of alleles in the BJ-hTERT line and 75% in the BJ-hTERTc.5047C>T line. The next stages of this work include:

(i) optimization of RNP concentrations to maximize editing efficiency; (ii) introduction of DNA donor molecules, such as single-stranded oligonucleotides and 5'OH oligonucleotides, containing the genomic sequence to promote the correction of the target mutation via Homology-Directed Repair; (iii) comparison of the correction efficiency mediated by each donor type; (iv) selection and expansion of edited cellular clones; and (v) functional characterization of C7 protein expression and localization. Subsequently,

the strategy will be adapted and validated in Full-Thickness Skin. This project aims to develop the first Cas9n-based gene therapy for patients carrying the *COL7A1* c.5047C>T mutation, thereby contributing to the advancement of safer and more efficient gene editing platforms.

Presentation Abstracts

CONTENTS

089

Pilot study of ELK-003 eye drops for treating ocular manifestations of epidermolysis bullosa (GOTAS-ELK-EB)

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ABSTRACT

Background: Epidermolysis bullosa (EB) frequently affects the ocular surface leading to recurrent painful corneal lesions that may progress to scarring and irreversible vision loss. Current management is supportive highlighting the urgent need for therapies that enhance epithelial stability and promote repair. ELK-003 is an investigational biologic eye drop derived from a standardized amniotic fluid secretome and specifically formulated for ocular application.

Objective: To evaluate the safety and efficacy of topical ELK-003 in patients with junctional (JEB) and dystrophic epidermolysis bullosa (DEB) presenting with recurrent corneal lesions.

Methods: GOTAS-ELK-EB (ClinicalTrials.gov: NCT06713434) is a single-center, open-label, non-randomized trial conducted in Chile. The study has two sequential phases: an Observational Phase of up to 6 months to document the natural history of ocular symptoms in patients with EB, followed by a 6-month Treatment Phase evaluating ELK-003 eye drops (administered up to six times daily). Each participant serves as their own control with outcomes compared between phases.

Key assessments are performed at baseline, month 4, and end of treatment, and include slit-lamp examination with photography, optical coherence tomography, keratograph analysis, visual acuity, tear osmolarity, InflammaDry testing, superficial punctate keratitis (SPK) scoring, Schirmer testing, and corneal opacity scoring. Participants also complete weekly questionnaires to capture symptoms, quality of life, and abrasion events. When symptoms suggest a corneal lesion, healthcare personnel conduct a home visit to confirm and document the event using fluorescein staining.

Results: Seven patients have completed the trial with no drug-related adverse events and data from this first cohort is under analysis. Another seven patients are currently enrolled and additional participants are expected before the end of the year.

Discussion and Anticipated Impact: This trial is essential both for defining the natural history of ocular disease in EB and for deepening our understanding of a potential new therapy to address this significant unmet medical need. The findings will also provide the foundation for the design of future controlled studies.

Keywords: Epidermolysis bullosa; Corneal abrasion; Corneal erosion; Corneal ulcer; Ocular surface; Amniotic fluid secretome; ELK-003

090

Repurposed treatment with losartan in children with severe forms of epidermolysis bullosa: effect on nutritional, growth, and hematological parameters, and ISCOREB

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ABSTRACT

Introduction: Epidermolysis Bullosa (EB) is a systemic genodermatosis characterized by fragile skin, chronic wounds, and multisystemic involvement. Management strategies include wound care, nutritional support, and treatment of disease-related complications such as esophageal stenosis and pseudosyndactyly. In recent years, therapeutic approaches for recessive dystrophic EB (RDEB) and junctional EB (JEB) have advanced significantly, with available new drugs although costly and unavailable for most patients. There is also increasing evidence on the benefits of repurposed anti-inflammatory and antifibrotic treatments, such as losartan, for these patients. Losartan is safe, inexpensive, widely available, and has been reported to improve wound healing, disease severity, and quality of life in patients with EB. We sought to study effects of losartan on laboratory and clinic parameters in patients with severe EB.

Methods: These are preliminary results of a retrospective, descriptive study at the National Institute of Pediatrics (2023-2025). We analyzed growth parameters, body surface affected (BSA), hematological parameters, and disease severity score iscorEB of patients 0 to 18 years old with severe forms of EB (8 with RDEB and 1 with JEB) treated with losartan (0.7mg/kg/day) who had a follow-up visit ≥6 months later. Non-parametric analysis was used to compare parameters between visits.

Results: We included 9 patients (6 female), with a mean age of 8.52±5.13 years. The baseline mean BMI was 13.91±1.81kg/m^2, 4 (44%) had BSA>50%, mean iscorEB was 22±13.45, hemoglobin 9.68±2.02, hematocrit 30.86±4.89, platelets 512.33±134.3, and leucocytes 10.69±3.38. At the follow-up visit, BMI was 13.07±2.12kg/m^2 (p=0.05), 3 (33%) had BSA>50%, iscorEB decreased to 13.5±9.05 [p=0.02, mean % change (Δ) -31.59±37.11], hemoglobin and hematocrit increased to 10.37±2.04 (Δ 7.99±34.58) and 32.25±5.02 (Δ 4.15±26.23), respectively, and platelets and leucocytes decreased to 464.5±78.76 (Δ -6.38±16.29) and 11.58±2.19 (Δ 19.5±38.32), respectively.

Conclusion: In this pilot study, pediatric patients with EB treated with losartan had significant improvement in disease severity measured by iscorEB after ≥6 months. Hematological parameters and BSA tended to improve; longer follow-up time may confirm this tendency. BMI significantly decreased between visits, which is a frequent consequence of known disease-related complications as patients treated with losartan included in this study had severe forms of EB and may suffer malnutritiom and esophageal strictures. Further studying widely available and inexpensive repurposed drugs, such as losartan, and the effect of their anti-inflammatory and/or anti-fibrotic properties in outcomes of patients with EB for longer periods of time is advocated for.

Keywords: losartan; Epidermolysis bullosa; Patient outcome assessment

Presentation Abstracts

CONTENTS

091

Living with dystrophic epidermolysis bullosa in Poland: first national assessment of quality of life and clinical burden

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ABSTRACT

Introduction: Dystrophic epidermolysis bullosa (DEB) is a rare, severe, hereditary mechanobullous disorder characterized by chronic skin fragility, recurrent blistering, erosions, and progressive scarring. These clinical manifestations are often associated with persistent pain and pruritus, leading to marked impairment in health-related quality of life (HRQoL). Despite the considerable disease burden, patient-reported outcomes in DEB remain insufficiently studied, particularly at the national level. The present study aimed to assess HRQoL and symptom burden in individuals with DEB in Poland using validated dermatology-specific and generic assessment instruments.

Methods: A cross-sectional, anonymous online survey was conducted using Google Forms and disseminated via email to patients. The questionnaire included: (i) sociodemographic and basic clinical data, (ii) information on current symptoms, comorbidities, and previous treatments, and (iii) HRQoL instruments including the Dermatology Life Quality Index (DLQI) for adults, Children's DLQI (CDLQI) for pediatric patients, numeric rating scales (NRS) for pain and pruritus, the SkinIndex-29, and the Short Form-36 (SF-36). Parents completed the survey on behalf of children unable to do so independently. All instruments were administered in their validated Polish versions and scored according to standardized protocols. Descriptive and inferential statistical analyses were performed on the collected data.

Results: A total of 33 participants (25 females, 8 males), including 16 children, were enrolled. The mean age was 23.7 years (range: 5 weeks to 43 years). All participants reported disease onset within the first year of life. Clinical manifestations included dysphagia in 16 patients (47.1%), malnutrition in 9 (26.5%), alopecia in 7 (20.6%), syndactyly in 13 (38.2%), and nail dystrophy in 27 (79.4%). Genetic confirmation of DEB was available in 24 individuals (70.6%). The most commonly reported treatments included non-adhesive dressings (100%) and wound-healing adjuvants (79.4%). The mean self-rated quality of life score (on a 0–10 scale) was 5.74. Mean NRS scores for pain and pruritus over the past week were 5.57 and 5.94, respectively. The mean CDLQI score was 14.3, while the mean DLQI score was 13.9, both reflecting moderate to severe impairment in quality of life.

Conclusion: To the best of our knowledge, this is the first study to systematically evaluate health-related quality of life and symptom burden in Polish patients with DEB. Our findings demonstrate a profound negative impact on HRQoL, characterized by high levels of pain, pruritus, and functional impairment. These results highlight the urgent need for comprehensive, multidisciplinary management strategies and the development of targeted interventions to address both the physical and psychosocial challenges associated with DEB. However, given the relatively small study cohort, further research involving larger patient populations is warranted to confirm and expand upon these findings.

einstein
Official Publication of the Instituto Israelita de Ensino e Pesquisa Albert Einstein

e-ISSN: 2317-6385

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Books
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Pinheiro LL. Avaliação da aorta torácica de brasileiros tabagistas por tomografia de tórax de baixa dose: diâmetros e prevalência de aneurismas [tese]. São Paulo: Faculdade Israelita de Ciências da Saúde Albert Einstein; 2021.

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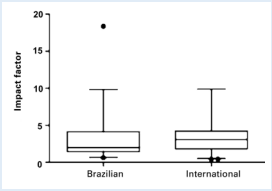
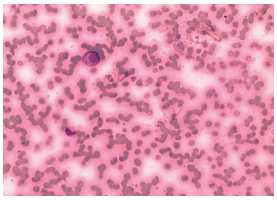
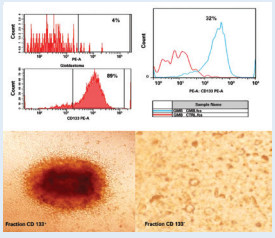
Line art	An image composed of lines and text, which contains no tonal or shaded areas		tif or eps	Monochrome 1 bit or RGB	900 to 1,200 dpi
Halftone	A continuous tone photograph containing no text		tif	RGB or Grayscale	300 dpi
Combo	Image contains halftone plus text or line art elements		tif or eps	RGB or Grayscale	500 to 900 dpi

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