EB Research Network

Aiming for a world where EB is curable

Annual Report #2021

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June 2022

eb Research Network.

CONTENT

1. Summary

The year 2021 was again dominated by the Coronavirus (Covid-19) pandemic. In addition to the challenges for EB sufferers and EB research, one thing became apparent: international collaboration in science is key to accelerating research. EB Research Network stands for collaboration. The network aims to connect EB patient organisations active in EB research to facilitate joint support for research, to pool results, and to share knowledge. Currently, there are 125 EB research projects in our project database – both active and completed and publicly available to all. It is remarkable that, since 2007, almost 17 million Euros have been invested into EB research only through the international funding rounds of DEBRA International and EB Resnet joint calls. Additional funding was provided by national EB patient groups and trusts worldwide.

The All Priorities (AP) Call 2021 was the 25th research funding round implemented since 2007, reviewed by the Medical and Scientific Advisory Panel (MSAP). This time EB Resnet member DEBRA Austria organised and funded the AP Call. Out of the five projects recommended by MSAP, the three top-ranked will be funded.

This report gives an insight into the statistics of the funding rounds since 2007. The first international funding by member DEBRAs goes back even further to the early 1990s. Here you can find out where most project applications came from and where most funding went. One thing becomes evident: although USA and UK have a strong presence, funding has always been awarded very internationally.

The current era holds a window of opportunity for combatting EB as never before. Since the 1990s, funds have been invested into EB basic research to understand the disease better and explore potential therapeutic approaches. The high number of clinical trials (more than 30 active studies worldwide) for EB results directly from this long-term investment. The challenge now is to translate these results as quickly as possible. EB sufferers have little time, as the impact of their disease can, at best, only be alleviated, and too many patients develop life-threatening consequences too early. Closer cooperation will be needed financially and in terms of scope of effort and organisation. Even though there are many active clinical trials, there is also a need for targeted coordination with the patient organisations, pharmaceutical companies, clinicians, healthcare providers and regulatory authorities. Two potential treatments have reached the approval process at the end of 2021; 2022 will show whether these studies have been successful. EB Resnet aims to work with its members and partners to improve coordination of clinical translation. One way would be to strengthen the IPP (Industry Partnering Panel), implementing activities to overcome barriers already identified by industry, to drive forward development and adoption of therapies.

Thematically, EB Resnet remains true to its established priorities for therapy development. However, we also recognise the potential opportunities from drug repurposing. Consequently, we anticipate a funding focus here in 2022/23 in addition to a standard AP Call 2022.

2. EB Research Network

THE EB RESEARCH NETWORK IS AN ALLIANCE OF PATIENT ORGANISATIONS WORKING TOGETHER AND IN COOPERATION WITH PARTNERS TO DEVELOP AND DELIVER EFFECTIVE THERAPIES FOR ALL PEOPLE LIVING WITH EPIDERMOLYSIS BULLOSA (EB).

EB Resnet always aims to show the current state of EB research, its challenges – including gaps in knowledge or technology that hinder progress - and opportunities to develop therapies and advance their introduction into the clinic. Researchers, clinicians, patients, but especially partners from industry, all have an important role to play.

The EB Resnet website provides information on current EB research projects worldwide and highlights cooperation opportunities with, and for, industry. In addition, international funding rounds for EB research are announced and processed via EB Resnet.

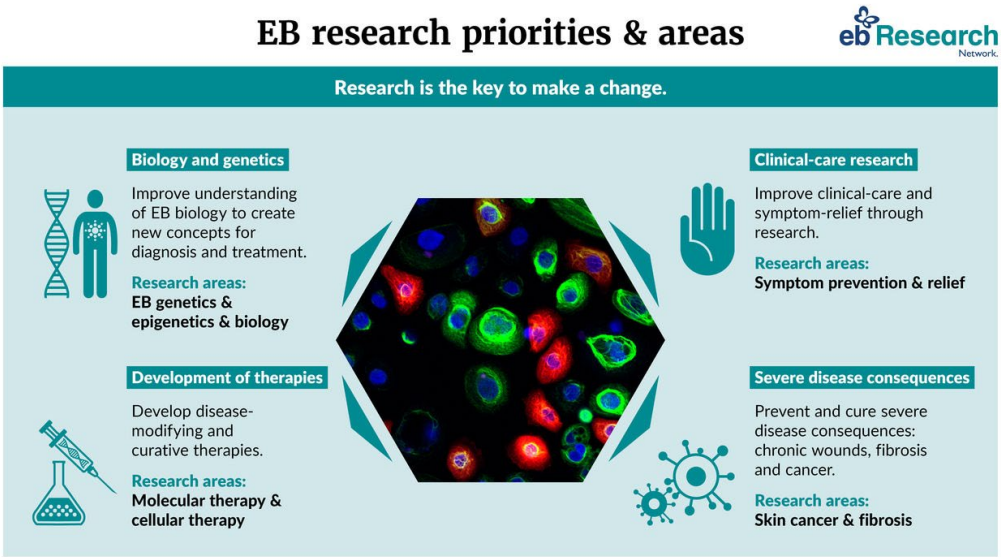
Our Mission

Translating successful research into patient benefit.

Strategic goals

In the current EB Resnet strategy (2020-2024) three strategic aims are defined:

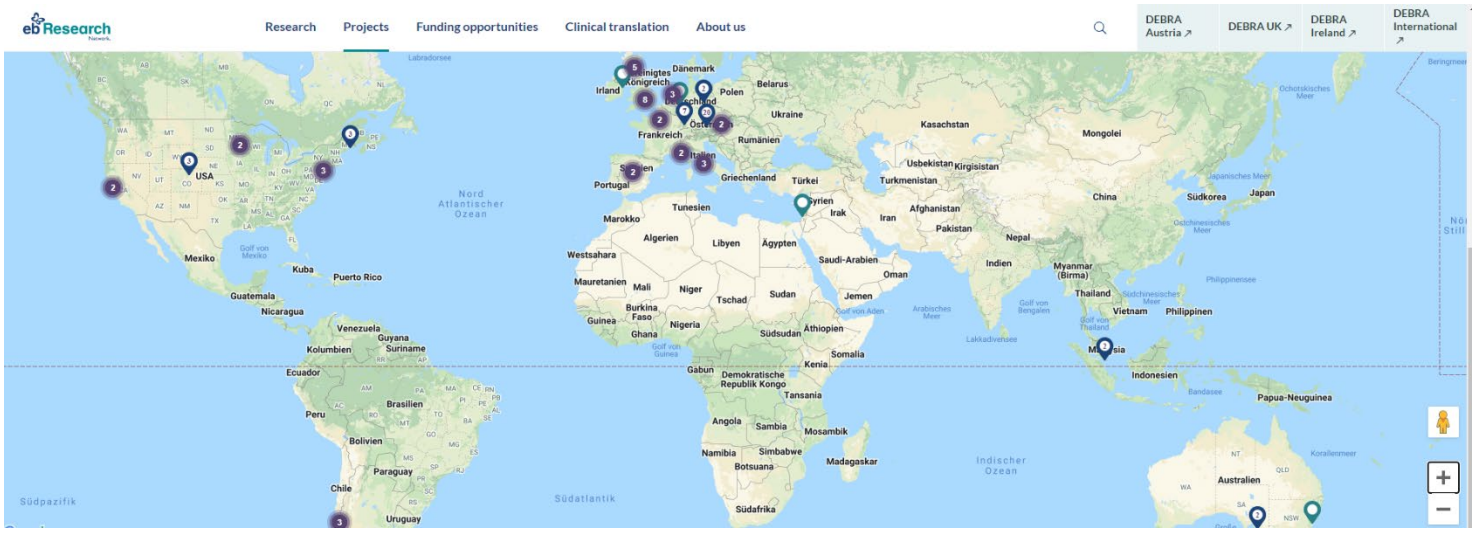
1. **To support research to develop effective and safe treatments**
2. **To develop partnerships to expand research**
3. **To drive clinical translation and the adoption of treatments internationally**



Current research prorities and areas (EB Resnet 2022)

3. Project Overview

THE EB RESNET PROJECT DATABASE RANGES FROM NATIONAL PROJECTS IN THE NATIONAL MEMBER GROUP STATES TO INTERNATIONALLY FUNDED PROJECTS IN OVER 50 RESEARCH INSTITUTIONS WORLDWIDE. THE PROJECTS COVER ALL CURRENT RESEARCH PRIORITIES AND ALL EB TYPES.



EB Resnet Project Map shows current and completed projects worldwide.

Project Database & Project Map

There are 125 projects in the EB Resnet project database. Of these, 78 projects have been recommended for funding through international funding rounds since 2007 (Research Grants). All other projects were recommended by individual peer-review of national member groups and funded via national funding channels of EB Resnet members & partners.

35 projects in the database are ongoing and being conducted at 27 different research institutions worldwide. Again, 18 of these are active Research Grants, where three new ones have been added in 2021 (AP Call 2021).

EB Resnet members and partners fund research projects, either jointly or individually.

The Google Map on the EB Resnet website shows the geographic location of all projects. Our database provides a lay summary, a short scientific summary, the strategic relevance for EB, related publications, and a short impact report for each project.

Search our database or Search our Google map

Recently completed projects

Several internationally funded Research grants have been completed in the reporting period 2021, and the final reports have undergone review – EB Resnet website provides short impact reports:

Uitto 2 - Implementation and clinical utility of transcriptome sequencing by RNA-seq in EB
Project details on EB Resnet

Calvo 1 - Neurotrophic factors and neuropathic pain in RDEB
Project details on EB Resnet

Uitto 3 - Implementation of non-invasive, next-generation sequencing-based early prenatal diagnosis for Epidermolysis Bullosa
Project details on EB Resnet

Bruckner-Tuderman 5: REFLECT (symptom-RElieF with Losartan - EB Clinical Trial): A dual-center prospective phase II trial to establish safety, tolerability and efficacy of losartan in children with recessive dystrophic EB (RDEB).
Project details on EB Resnet

Hovnanian 7 - CRISPR/Cas9–based editing to treat recessive dystrophic epidermolysis bullosa (Extension underway - funded by DEBRA France)
Project details on EB Resnet

4. Research Funding

EB RESNET SUPPORTS AND COORDINATES RESEARCH FUNDING ON BEHALF OF ITS MEMBER ORGANISATIONS AND PARTNERS. IT CURRENTLY OFFERS THREE FUNDING SCHEMES: RESEARCH GRANTS THROUGH SCHEDULED CALLS FOR PROPOSALS, AD-HOC GRANTS (OUR FLEXIBLE FUNDING SCHEME TO ACCOMMODATE CO-FUNDING OPPORTUNITIES WITH OTHER FUNDERS), AND CO-FUNDING FOR INDUSTRY-PARTNERING PROJECTS.

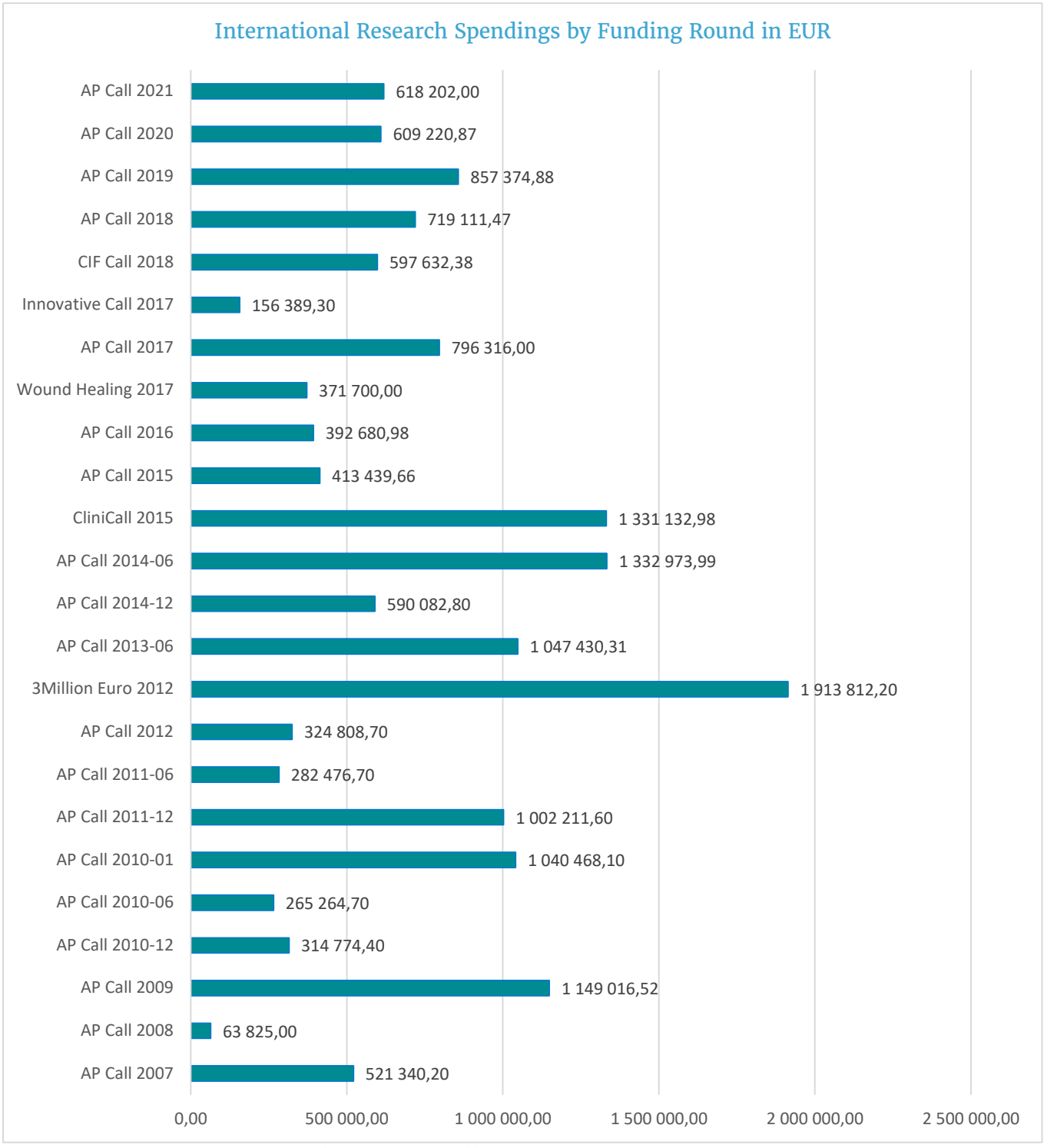
EB Resnet welcomes proposals for innovative research and clinical development of treatments or diagnostics. All proposals are evaluated for scientific excellence, feasibility, and value for money, and whether they address the priority needs of people with EB. We undertake peer review to ensure that only the best research is funded.

The actual funding contribution can vary widely from year to year owing to several factors: first, the number of funding rounds held in any year varies (while usually two, it has varied from one to three, depending on funding availability from contributing DEBRAs or other funders, and other commitments); second, the number of research grant applications to any call has varied, usually in the range of 12-25; and third, as MSAP recommendations for funding are based solely on research quality and importance for patient benefit, the proportion of project applications funded has ranged from ~10% - 50%, usually around 25%.

Research Grants

Facts and figures since 2007

The first international EB research funding rounds took place back in the early 1990s. The calls organised by DEBRA International were reviewed by the Medical and Scientific Advisory Panel (MSAP), which has since met once or twice annually to review the best research proposals received, as it did in 2021. The review process is based on a standardisd peer-review procedure, followed by a funding recommendation from MSAP. The International EB Research funding rounds include the All Priorities Calls (AP Calls) and the Special Calls. AP Call means that project topics must fit one or more of EB Resnet's four strategic research priorities (see page 2). Alternatively, a Special Call may be issued to solicit proposals for important unresolved research questions, technology needs, or clinical consequences of EB (e.g., chronic inflammation and fibrosis). Since 2007, 20 AP Calls and 5 Special Calls have been organised, and approximately €16.7 million has been invested in international EB research in the form of Research Grants. These funds have been raised primarily by national DEBRA groups and occasional other EB patient organisation funding partners.



Research grants approved in Euros by research funding round since 2007

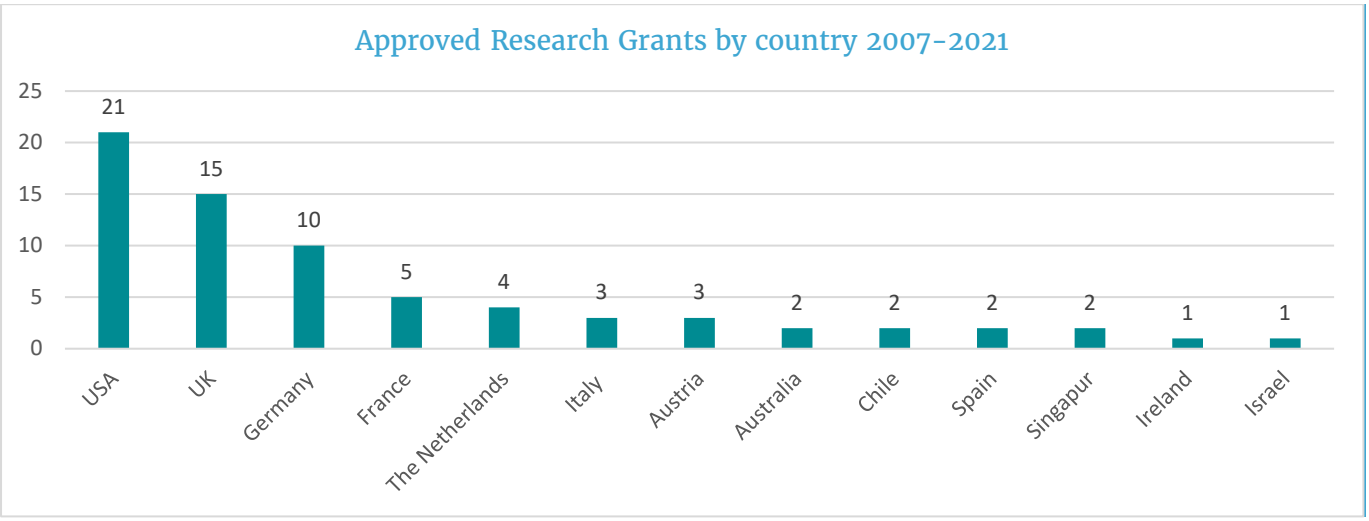
Not all data are known about the early funding rounds from the early 1990s, as some paper records were lost to flooding in storage by the funding member. Since 2007, EB Resnet has been able to keep reasonably good statistics with committed funding.

It also needs to be remembered that the budget required for a project is quite variable, with late-stage preclinical research generally more expensive than early-stage lab research; clinical trials may be an order of magnitude higher still. In 2012, the highest annual distribution was just

under 2 million euros. This peak came about due to a Special Call in Spring 2012, the '€ 3 M fund for collaborative EB therapy research'. A special Expert Panel, involving additional experts from industry and translational medicine was convened to discuss the strategic importance of the many large-budget clinical trial proposals received.

Since 2019, we have seen a decrease in annual funding. Other national DEBRAs that previously contributed to DEBRA International joint calls have shifted their focus to national EB research. In addition, several DEBRAs are increasingly struggling with fundraising and hence research budget shortages owing to the Covid-19 pandemic. For this reason, there has only been one funding round per year since the start of the pandemic: these have been funded and administered by EB Resnet member DEBRA Austria, with MSAP meetings held very successfully online. Increasingly, we are seeking, through EB Resnet, to widen collaborations with other EB patient organisations – notably, this has led to two sizeable grants being co-funded with a Belgian charity 'Vlinderkindje' (Flemish for 'butterfly children') focused on severe EBS to develop iPSC derived gene-cell therapies.

The number of International Research Grants approved per year since 2007.



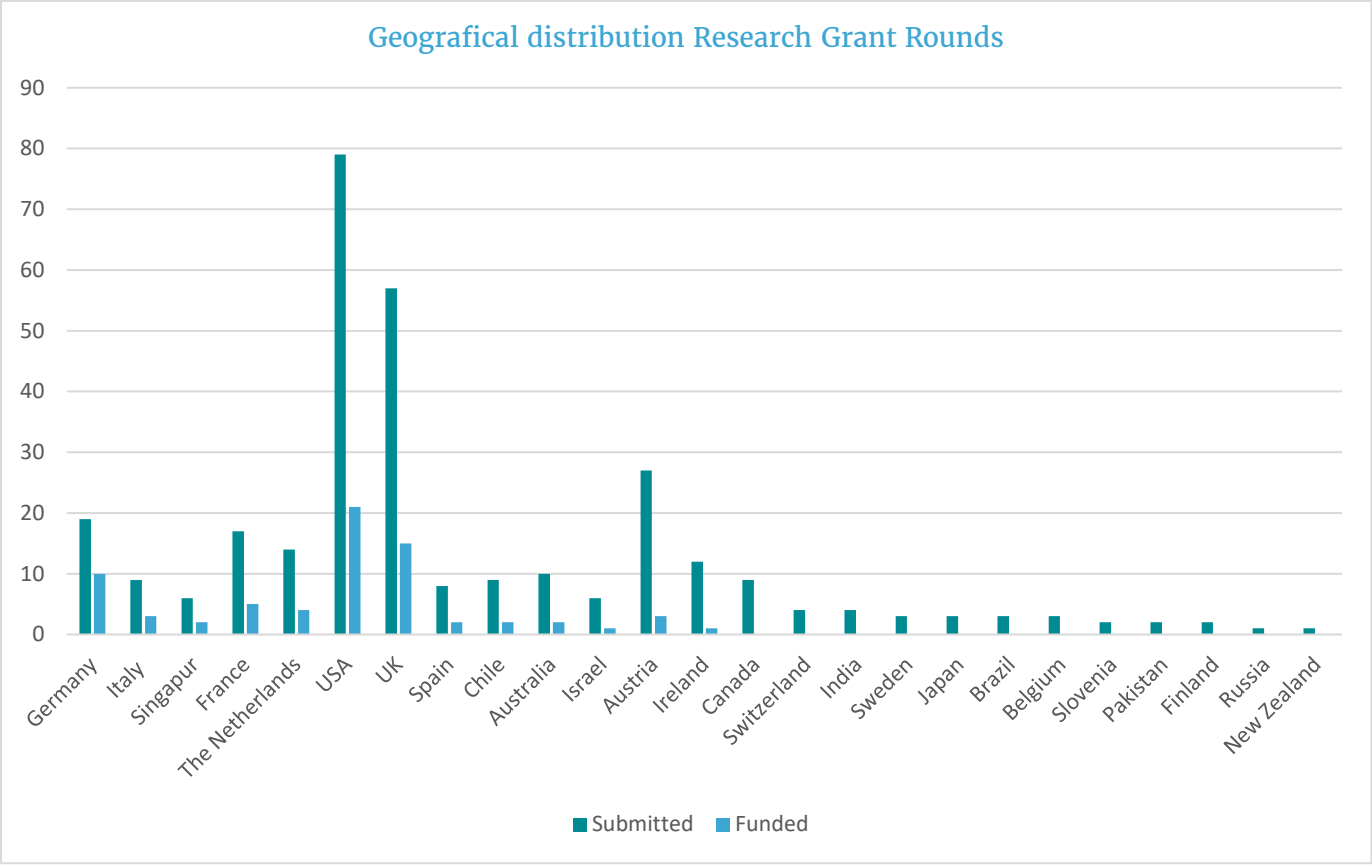
The number of international research grants approved per country of the research institution since 2007.

With 21 projects, the USA ranks top among the countries that have received the most project funding, with the UK and Germany following. Researchers from other European countries, Australia, South America, and Asia, have received funding. In principle, the approved projects reflect those countries with particularly strong EB research and clinical groups with a long track record, and countries with the greatest number of grant applications submissions. The majority of grant applications came from the USA and the UK - where it is notable that many of the established groups are led by researchers and clinicians supported by DEBRA at early stages of their careers in the period from the late 1980s – the turn of the Millenium.

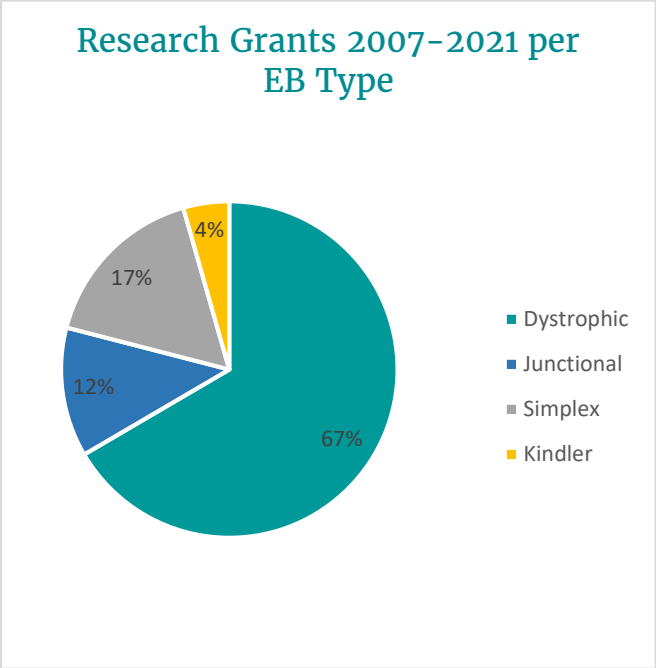
Germany is the most successful country (as measured by successful grant applications compared to the number of grant applications), with 20 submissions and ten approved projects.

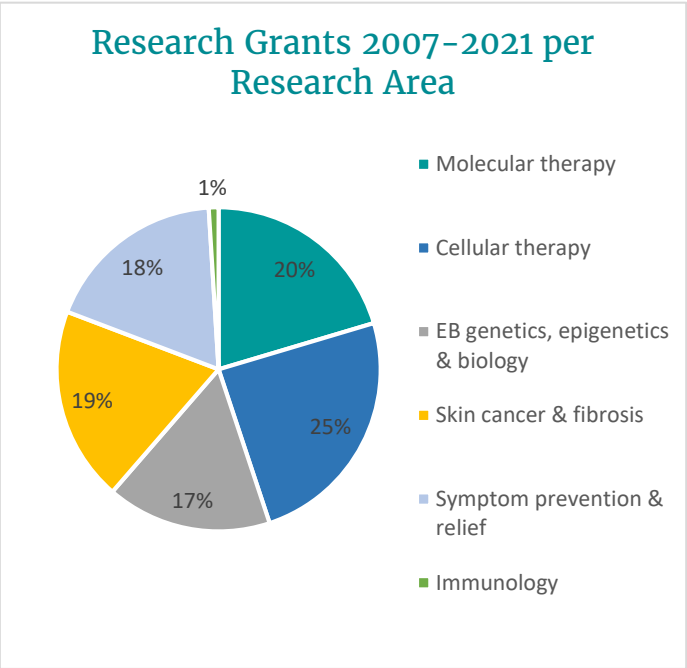
It is important to emphasise that EB research supported via DEBRA International and EB Resnet has never been geographically restricted. The data show that there are excellent EB researchers worldwide. In taking forward research into the clinic, partnerships with companies will be increasingly required, and in EB – just as in the wider biopharma and healthcare industries - there is a preponderance of such companies in the USA, which will require increased international thinking.

More than 330 project submissions have already been reviewed by the MSAP or an international expert panel since 2007.



The number of submitted and approved international research projects (2007-2021) by country of research institution; ranked by the success rate of submissions. Only submissions from DEBRA International / EB Resnet funding rounds are included.





Looking at the expenditure in relation to the EB types, we see an evident dominance by RDEB among research projects. This reflects the focus on patients with RDEB as being among the most severely affected. The nature of the biology of RDEB and the status of research creates opportunities for therapy development. This is in contrast to, for example, severe (Herlitz) JEB, where the nature of the disease and the extreme fragility of children have hindered the investigation of therapeutic approaches developed to date. More recent, less invasive, technologies may in future enable treatment of such highly fragile patient groups.

The research areas of the 84 research projects studied are quite diverse and evenly distributed. Molecular and cellular approaches together account for almost half of the projects. Often, projects cannot be assigned to just one area - there are overlaps – especially in these two areas. The general understanding of the disease and the background of EB is addressed in EB genetics, epigenetics, and biology, which accounts for 17%. Equally important is the area of cancer research and fibrosis, which with 19% has a similar share as the no less essential research areas of symptom control and relief.

Funding Round 2021: AP Call 2021

The 2021 funding round was opened at the beginning of June 2021 and was promoted via the EB Research Network website and handled via Grant Tracker (online Grant Management Software).

We could not organise an in-person MSAP meeting owing to the COVID-19 pandemic. To allow focused discussion of the most promising proposals during the on-line meeting of MSAP on December 14, we again introduced a triage step following external peer-review, as in 2020, to shortlist proposals. For this triage, MSAP members were grouped according to their areas of expertise, with each group assigned 4-6 proposals together with the associated external reviews for consideration. The process was conducted via anonymous voting in Grant Tracker.

A total of 21 project proposals were submitted; one of which was a resubmission. Seven projects were excluded due to serious deficiencies (consensus decision by MSAP). The remaining 14 projects were submitted by research institutions operating in 8 different countries. One project reached the 'international importance' standard for funding and four the 'national importance' standard for funding. Owing to the limited budget, only the first three projects will be funded.

Contract negotiations are finalised and all projects will start in 2022.

Projects recommended for funding and covered by budget 2021

León 1: Characterization of novel fibrosis modulators in Recessive Dystrophic EB

Dr. Carlos Léon (University Carlos III de Madrid, Spain), 2 years, EUR 135 500 (Funded by DEBRA Austria, co-financing by EB Loppet and by DEBRA Sweden)

Carlos León and Fernando Larcher studied fibroblasts from two RDEB siblings with a very different clinical presentation of the disease. Preliminary results from this team show that the protein prolargin/PRELP is enriched in the fibroblasts of the sibling with milder symptoms, suggesting a plausible role for this protein in modulating RDEB fibrosis. This project aims to 1) characterize fibroblasts from mild and severe RDEB siblings with single cell resolution and 2) investigate the pro-adhesive, anti-fibrotic and anti-tumor properties of prolargin/PRELP in reconstituted skin equivalents and hypomorphic mice, a well-established model for RDEB. This molecule may be an important modulator of disease severity in RDEB and a potential target for amelioration of this disease.

Potential Impact for EB Patients: The chronic, non-healing wounds of RDEB are characterisd by inflammation and the formation of scar tissue (fibrosis), leading to pain and disability and posing a higher risk of developing cancer. The goal of this project is to find new drug targets that reduce inflammation and fibrosis. Detailed analysis of fibroblast skin cells from RDEB patients with widely varying symptom severity has identified some potential drug targets that will be further explored in this project. The treatment of chronic inflammation and fibrosis is a clinical priority and a focus of EB Resnet support.

Projectdetails on EB Resnet

Kopecki 1: A stimuli responsive dressing for treatment of wound infection in Epidermolysis Bullosa

Dr. Zlatko Kopecki (University of South Australia, Adelaide, Australia), 27 months, EUR 212 602 (Funded by DEBRA Austria)

Infections are a daily problem for patients with severe EB. Treatment of EB wounds relies heavily on antiseptics, topical antimicrobials, and silver dressings, but their success is limited. This project addresses the problem of high cytotoxicity of silver dressings by developing a stimuli-responsive silver dressing and validating its efficacy in small and large animal models of wound infection. By developing a temperature- and pH-responsive dressing for the delivery of ultrasmall silver nanoparticles to wounds, the team hopes to develop a safe and effective approach for treating infections and facilitating healing in EB in preparation for clinical trials.

Potential Impact for EB Patients: The non-healing wounds of EB are constantly inflamed and need to be well controlled to promote wound healing and prevent whole-body infections and sepsis. Silver dressings are commonly used and are effective in fighting infections, but can cause dangerous silver toxicity as a result of long-term use in EB wounds. The group has already developed technology in the lab that responds to the increased temperature and decreased pH of infected wounds to release less silver overall; this project will further develop the technology. A dressing that can be relied upon to respond only when needed could be clinically very valuable for treating large chronic EB wounds in severe types of EB.

Pojectdetails on EB Resnet

Magin 5: Repurposing compound 1 to a therapy for Epidermolysis Bullosa Simplex (EBS)

Prof. Thomas Magin (University of Leipzig), 3 years, EUR 270 100 (Funded by DEBRA Austria)

KRT5 and KRT14 mutations cause EBS accompanied by keratin aggregates that make the epidermis brittle and itchy. After screening 5000 agents (Magin 3), Thomas Magin identified the kinase inhibitor C1 as an agent that significantly reduces keratin aggregation and improves epithelial resistance by reducing EBS-associated hyperphosphorylation of keratins and desmoplakin. Based on solid preliminary evidence, the research team hypothesizes that systemic or topical administration of C1 may be a viable strategy for the treatment of EBS. This project will provide data necessary for a clinical trial using a panel of EBS keratinocytes with various KRT5 and KRT14 mutations in combination with state-of-the-art functional assays. This includes optimization of C1 application in primary and immortalized EBS keratinocytes as well as in EBS keratinocytes transplanted to humanized mice.

Potential impact for EB patients: Mutant keratins in EBS form clumps. They can no longer form the filaments that give skin cells strength, leading to tissue fragility. In a drug screen (Magin 3, funded by EB Resnet member DEBRA Austria), Thomas Magin has identified a molecule that can reverse this effect *in vitro*, using tissue from patients with

EBS mutations. He now wants to demonstrate whether this compound is also active in more complex disease models, including work in mice and commercial human skin explants. In addition, there are extensive data on toxicity and side effects associated with the primary disease indication for which this molecule is used. Currently, the drug is administered orally, but Prof. Bishr Omary, a collaborator at the University of Michigan, is working on a topical formulation (cream).

Projectdetails on EB Resnet

Funding Rounds 2022/23

EB Resnet launched an All Priorities Call (AP Call 2022) in June with a deadline for submissions in early September. The MSAP meeting is expected to take place again in December. In addition to the AP Call 2022, this year EB Resnet member DEBRA Austria has agreed to provide an additional funding stream to support proof-of-concept projects aimed at exploring possible repurposing opportunities that tackle the following EB's unmet medical needs: Chronic inflammation and fibrosis, Pain, Itch, and Cutaneous squamous cell carcinoma (cSCC). The Call is named 'Special Ad-Hoc Call 2022 - 'Repurposing drugs for EB'.

The topic of drug repurposing holds tremendous potential and is also a high priority: if drugs with established safety profiles and demonstatrated efficacy in disease targets relevant to EB can be identified, this can reduce both time and cost in developing new treatments for EB.

For a possible Special Call 2023 organised together with our partner LifeArc will start in 2022. The starting point will be a survey among experts to consider additional druggable disease targets in EB, and in other inflammatory and/or fibrotic conditions that may point to novel treatments for EB. Similar to the Chronic Inflammation & Fibrosis Call, we would like to start the discussion with experts and ask specifically about conditions, pathways, and molecules that would be worth further investigating. A structured questionnaire circulated among experts will help gather crucial information for discussion at a (virtual) round table. Identification of drugs already marketed for other conditions but with evidence of possible value to EB may be the first step to approach industry or to publish a targeted call for proposals (Repurposing Call 2023).

Ad-hoc Grants

The Ad-hoc funding channel enables small funding grants to be awarded quickly and flexibly. The aim is to enable, for example, co-financing opportunities, new project ideas or proof-of-concept projects. Of course, all ad hoc projects proposals undergo rigororus review. Academic researchers, clinicians, and the industry can contact us outside the official funding rounds to submit research proposals.
In 2022 we will use the Ad-hoc Channel to open the above mentioned Special Ad-Hoc Call 2022 - Repurposing drugs for EB.

Overview Ad-hoc Grants

Medical and Scientific Advisory Panel (MSAP)

The Medical and Scientific Advisory Panel (MSAP) was created by DEBRA International more than 30 years ago. Its members are senior EB researchers and clinicians who jointly reflect the breadth of EB research. For Special Calls for research proposals, which may focus on a particular unmet research need or novel technology, we convene Expert Panels with expertise specifically relevant to the topic of the call, which can involve selected MSAP members and additional experts chosen for their specific area of knowledge. MSAP and other members of our Expert Panels work to act as a guardian of scientific quality and relevance to people with EB of the research that EB Resnet funds. MSAP members review both proposals and progress of research funded by EB Resnet members: this peer-review process is central to maintaining our reputation as a research funder among the academic and clinical research community, bioindustry, and research sponsors and donors.

Sacher Torte for the Medical and Scientific Advisory Panel (MSAP)

As a thank you for the many years of volunteer service by MSAP members, 25 Artist Collection Sacher cakes were shipped in December 2021. The shipment was timed to coordinate with the virtual MSAP meeting on December 14, 2021. MSAP member Prof. Jo-David Fine was also very pleased with the surprise.

MSAP member Prof. Jo-David Fine is delighted with the Austrian delicacy

Useful links

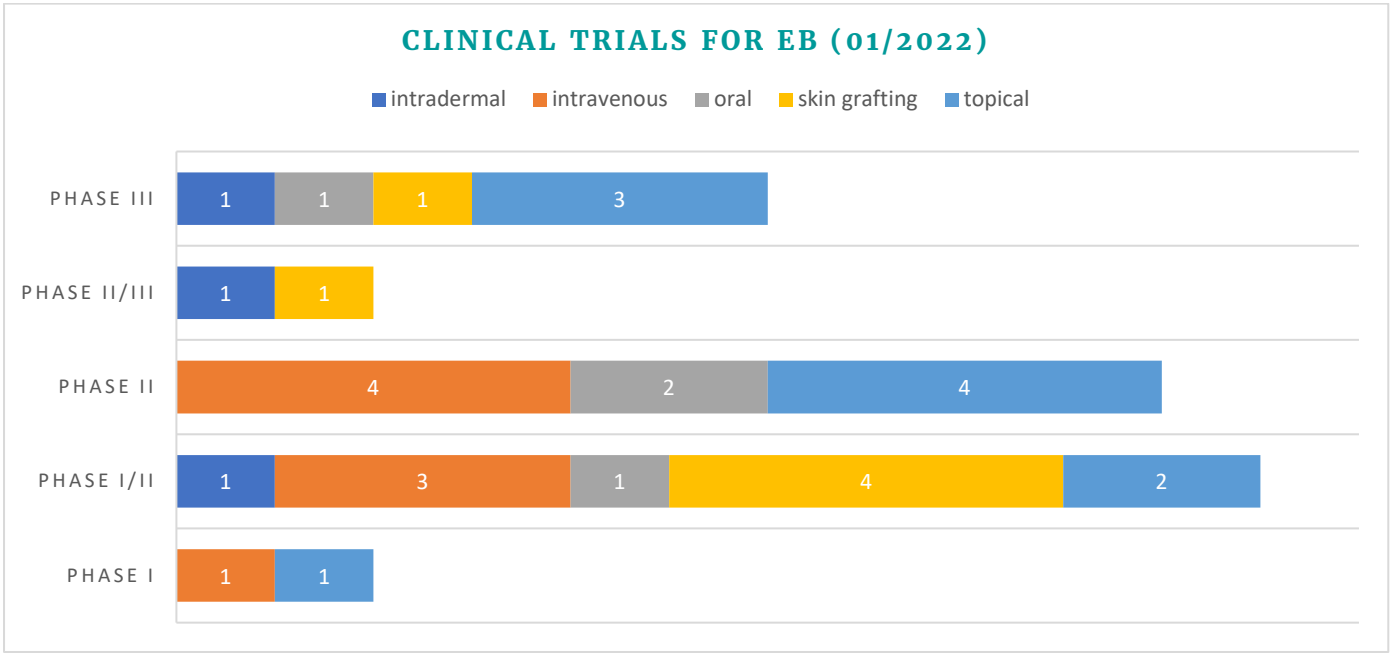
- Review-Process
- Overview Research Grants
- Overview Ad-hoc Grants

5. Clinical trials for EB

NEVER BEFORE HAVE THERE BEEN SO MANY ACTIVE CLINICAL STUDIES FOR EB. OVER 30 ARE REGISTERED ON CLINICALTRIALS.GOV, OF WHICH 6 ARE ALREADY IN PHASE 3. TWO ARE POSSIBLY CLOSE TO APPROVAL IN THE US AND THE EUROPEAN UNION, ALTHOUGH SOME QUESTIONS STILL REMAIN.

Current clinical trials for EB

Currently, six phase 3 clinical trials for EB are ongoing worldwide. Twenty-five additional studies are active or recruiting patients. As clinical trials are dynamic, with new trials being registered, completed, or withdrawn, or protocols modified, we can only here provide a snapshot at a particular point in time. We have listed those intervention studies that are currently enrolling patients or, to our knowledge, will start/continue soon (01/2022).



The number of active clinical trials by phase and type of application. Status 01/2022.

Some of the treatments address the underlying genetic fault of EB, such as that being developed by Krystal Biotech, a non-invasive repeat-application topical gene therapy for dystrophic EB, which is the only gene-targeting approach for treating dystrophic EB that has completed a Phase 3 trial. Other treatments are not specific to EB but should aid wound healing: Amryt Pharma believes it is very close to the market authorization of FILSUVEZ® which is a topical therapeutic gel to help faster healing of wounds in RDEB.

All studies are listed below. The identification number takes you directly to the study on clinicaltrial.gov.

Active cinical trials for EB worldwide (01/2022)						
Therapeutic strategy	**Trial description**	**Route**	**EB Subtype**	**Stage of clinical trial**	**Identification number Trial name**	**Sponsor**
Gene therapies and Combined Gene/cell therapies	Topical application of a gel of non-integrating, replication-deficient HSV-1 vector expressing collagen VII (KB103)	topical	RDEB	Phase II	NCT03536143	Krystal Biotech, Inc.
	Topical application of a gel of non-integrating, replication-deficient HSV-1 vector expressing collagen VII (KB103)	topical	RDEB, DDEB	Phase III	NCT04491604	Krystal Biotech, Inc.
	Topical application of Beremagene Geperpavec (B-VEC) expressing collagen VII protein	topical	DEB	Phase III	NCT04917874	Krystal Biotech, Inc.
	Grafting of epidermal sheets containing epidermal stem cells, corrected with a retroviral vector carrying LAMB3 cDNA	skin grafting	JEB	Phase II/III	NCT05111600 HOLOGENE 5	Holostem Terapie Avanzate s.r.l.
	Grafting of epidermal sheets containing epidermal stem cells, corrected with a retroviral vector carrying COL17A1 cDNA	skin grafting	JEB	Phase I/II	NCT03490331 HOLOGENE 17	Holostem Terapie Avanzate s.r.l.
	Grafting of epidermal sheets containing kertinocytes (EB-101) corrected with a gamma-retroviral vector carrying COL7A1 cDNA	skin grafting	RDEB	Phase III	NCT04227106 VIITAL	Abeona Therapeutics, Inc
	Grafting of epidermal sheets containing epidermal stem cells, corrected with a retroviral vector carrying COL7A1 cDNA	skin grafting	RDEB	Phase I/II	NCT02984085 HOLOGENE 7	Holostem Terapie Avanzate s.r.l.
	Transplantation of COL7A1-SIN retroviral engineered autologous tissue-engineered skin	skin grafting	RDEB	Phase I/II	NCT04186650 GENEGRAFT	INSERM, France
	Grafting of epidermal sheets containing kertinocytes corrected with a gamma-retroviral vector carrying COL7A1 cDNA	skin grafting	RDEB	Phase I/II	NCT01263379	Stanford University
	Injection of COL7A1-genetically modified autologous fibroblasts into wounds (FCX-007)	intradermal	RDEB	Phase I/II	NCT02810951	Castle Creek Biosciences, LLC.
	Injection of COL7A1-genetically modified autologous fibroblasts into wounds (FCX-007)	intradermal	RDEB	Phase III	NCT04213261	Castle Creek Biosciences, LLC.
Cell- and extracellular vesicle-based therapies	Wound dressing of allogeneic MSC (ALLO-ASC-SHEET)	topical	DEB	Phase II	NCT05157958	Anterogen Co., Ltd.
	Systemic infusion of allogeneic hematopoietic stem cells and and serial sonor MSC	intravenous	EB	Phase II	NCT02582775	Masonic Cancer Center, University of Minnesota
	Systemic infusion of allogeneic hematopoietic stem cells and "off-the-shelf" MSC	intravenous	EB	Phase II	NCT01033552	Masonic Cancer Center, University of Minnesota
	Systemic infusion of allogeneic ABCB5+ MSC	intravenous	RDEB	Phase I/II	NCT03529877	RHEACELL GmbH & Co. KG
	Grafting of epidermal cells (harvested via CelluTome) onto wounds after hematopoietic cell transplantation	skin grafting	EB	N/A	NCT02670837	Masonic Cancer Center, University of Minnesota
	Grafting of bioengineered Self-Assembled Skin Substitute (SASS) onto chronic skin wounds	skin grafting	DEB	Single patient treatment	NCT04171661	University Hospital Quebec-University Laval
	Topical application of MSC-derived extracellular vesicles for COL7A1 mRNA or C7 delivery (AGLE102) onto wounds	topical	DEB	Phase I/II	NCT04173650	Aegle Therapeutics
Drug therapies	Topical application of Thymosin beta 4 0.03% (RGN137) gel onto wounds	topical	JEB, RDEB	Phase II	NCT03578029	Lenus Therapeutics, LLC
	Topical application of Oleogel S10 (betulin: birch bark triterpene derivate) onto wounds	topical	EB	Phase III	NCT03068780	Amryt Research Limited

	Topical application of Cannabinol (INM-755) cream onto wounds	topical	EB	Phase II	NCT04908215	InMed Pharmaceuticals Inc.
	Topical application of TolaSure gel, 5% w/w Targeting Aggregated Mutant Keratin onto wounds	topical	EBS	Phase I	NCT05062070	BioMendics, LLC
	Infusion of Gentamicin	intravenous	RDEB	Phase I/II	NCT03392909	University of Southern California
	Infusion of Gentamicin and topical application of Gentamicin ointment onto wounds	intravenous and topical	JEB	Phase I/II	NCT03526159	University of Southern California
	Topical application of Gentamicin ointment (GENTELBULL) onto wounds	topical	EB	Phase I/II	NCT04644627	Oslo University Hospital
	Palmar injection of botulinic toxin	intradermal	EBS	Phase II/III	NCT03453632	University Hospital Toulouse
	Oral application of Serlopitant (neurokinin-1 receptor antagonist)	oral	EB	Phase II	NCT03836001	Stanford University
	Oral application of Pregabalin (inhibititor of calcium currents)	oral	RDEB	Phase III	NCT03928093	The Hospital for Sick Children
	Injection of Ixekizumab (IL-17A inhibitor)	Subcutaneous	EBS	Phase II	2020-001542-19	University Hospital Nice
	Oral application of rigosertib for advanced squamous cell carcinoma	oral	RDEB	Phase I/II	NCT03786237	Prof. Johann Bauer, SALK
	Infusion or oral application of Rigosertib for advanced squamous cell carcinoma	intravenous, oral	RDEB	Early Phase I	NCT04177498	Thomas Jefferson University
	Systemic infusion of Nivolumab (anti-tumor PD-1 inhibition)	intravenous	Patients with cutanous SCC	Phase II	NCT03834233	Instituto do Cancer do Estado de São Paulo
	Systemic infusion of Nivolumab (anti-tumor PD-1 inhibition)	intravenous	Patients with cutanous SCC	Phase II	NCT04204837	Salzburger Landeskliniken
	Transvamix (100mg/mL THC / 50mg/mL CBD)	oral	EB	Phase II	2021-000103-20	University Medical Center Groningen
Wound dressings	BIOOPA wound dressing	wound dressing	EB and chronic wounds	Phase I/II	2018-003890-91	Medical University of Warsaw
Observational Studies	Gynecological Follow-up	observational	DEB	Cohort	NCT04757727	Centre Hospitalier Universitaire de Nice
	Genotype-phenotype correlation	observational	JEB	N/A	NCT04727268	University Hospital Birmingham NHS Foundation Trust
	Evaluate characteristics of RDEB patients and their cells in order to develop new strategies of therapy	observational	RDEB	Cohort	NCT01019148	Stanford University
	Characterize the molecular signatures in the cSCC occurring in RDEB patients	observational	RDEB	N/A	NCT04285294	Assistance Publique - Hôpitaux de Paris
	Explore the role of gut flora in EB	observational	EB	Cohort	NCT04213703	ProgenaBiome
	Determine the state of sexual development in patients	observational	EB	Cohort	NCT05033574	National Medical Research Center for Children's Health, Russian Federation
	Evaluate the Long-Term Safety of the Krystal Biotech, Inc. Gene Therapy Products Using HSV-1 Backbone	observational	DEB	Cohort	NCT04917887	Krystal Biotech, Inc

Ongoing clinical studies for EB incl. links to the study register. Studies in phase 3 are highlighted in blue.

Update on selected studies

Update Amryt Study PHASE 3

FDA approval for the drug was initially expected in mid-December 2021 but was delayed until late February 2022. The US Food and Drug Administration (FDA) has rejected the application seeking Filsuvez (Oleogel-S10) approval for

treating skin wounds in people with junctional and dystrophic EB.

In its complete response letter, the FDA stated that the company's application could not be approved in the present form. Particularly, the agency has asked for more evidence of Filsuvez's effectiveness in treating EB. Amryt now intends to discuss the nature of the requested data with the FDA again.

On 22 April 2022, Amryt Pharma announced a remarkable milestone for EB patients. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) announced a recommendation for the approval of the Filsuvez® gel. The therapeutic ointment would be the first approved treatment for EB sufferers in Europe (decision point end of June 2022). EB Resnet member DEBRA Austria initiated a letter to the EMA due to the approval process of FILSUVEZ® (Oleogel) in Europe. More than 20 European DEBRA groups have supported the initiative.

Update Abeona Study: PHASE 3

Abeona has completed patient enrollment in the EB-101 Phase 3 VIITAL™ study, with the publication of the first data planned for the third quarter of 2022. The Abeona study is a gene therapy in the US designed to help patients with dystrophic EB via transplantation of genetically corrected pieces of skin.

Update Krysta Studyl: PHASE 3

US pharmaceutical company Krystal Biotech announced positive results from its phase 3 trial. The bulky name VYJUVEKTM is a non-invasive and topical gene therapy for EB patients with dystrophic EB.

The treatment introduces a copy of the C7 gene into the cells, where it produces the C7 protein. Because the treatment is designed to provide additional, correct C7 protein, not correct the mutation, it should work for any RDEB mutation. Because the C7 gene is not permanently integrated into the patient's DNA, it is eventually lost (e.g., when the cell into which it was introduced dies), so re-treatment is required.

The study's primary endpoint examined the improvement in wound healing using topical VYJUVEKTM compared to placebo at six months. The study reached statistical significance. 31 EB patients were included in the study. At three months, 71% of wounds treated with the agent achieved complete wound closure, compared with 20% of wounds treated with the placebo. At six months, 67% of wounds treated with the agent achieved complete wound closure compared to 22% of wounds treated with the placebo.

The treatment is transient and requires repeated administration. It is a more patient-friendly treatment and can treat large areas as a topical product.

Update Inmed Study: PHASE 2

InMed Pharmaceuticals Inc., a leader in the manufacturing and clinical development of rare cannabinoids, announced that it has initiated its Phase 2 clinical trial of INM-755 (cannabinol) cream for the treatment of Epidermolysis Bullosa. This is the first time cannabinol has entered a Phase 2 clinical trial to be evaluated as a therapeutic option to treat a disease. (October 2021)

This study is being conducted at eleven sites in seven countries, including Austria Germany, Greece, France, Italy, Israel and Serbia.

INM-755 is a cannabinol (CBN) cream intended as a topical therapy to treat EB and potentially other dermatological conditions. Preclinical data show that INM-755 (cannabinol) cream can help relieve typical EB symptoms such as inflammation and pain and may also help restore skin integrity in a subset of EB simplex patients.

Update Rigosertib Study: PHASE 1/2

This EB Resnet member DEBRA UK funded Phase 1/2 trial is the first clinical trial of a so-called 'targeted' cancer therapy that is based on scientific data obtained from studying RDEB SCC. There are two clinical trials registered for 'Rigosertib'. A European study, where EB House Austria serves as the study center, which DEBRA UK funds. The first EB patient was treated there successfully in 2021.

In the USA, at Thomas Jefferson University, there is a second study of rigosertib funded by DEBRA of America.

The retrospective pooling of the data must then be arranged by the PIs (also taking into account the contracts between the sites and the funders).

EB Resnet project details

An online overview of all active EB studies is currently in progress and will be available on EB Resnet's website in the second half of 2022.

Useful links:

- US-based ClinicalTrials.gov: **clinicaltrials.gov**
- EU Clinical Trials Register (EUDRACT): **clinicaltrialsregister.eu**
- International Clinical Trials Registry Platform (ICTRP): **apps.who.int/trialsearch**

6. Support us

JOINING FORCES TO FIND A CURE AND THERAPIES FOR EB.

There are several ways to support EB Resnet's activities

- Join the network as a funding member: assist EB Resnet in managing and funding the grant schemes.
- Join the network as an ordinary member: share your national research projects and provide small research funding for EB Resnet funding channels and profit from peer-reviewing process provided by EB Resnet.
- Join the network as a partner: share your research knowledge on EB, your EB projects and/or profit on EB patients' access.
- Join the network as a strategic partner: to help driving research outcomes into clinical application for patient benefit.
- Help building up the Industry Partnering Panel - IPP.
- Donate to increase funds for EB research.

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