



## The DEBRA International Research Strategy 2015 – 2019

*“from strong research foundations to therapy development”*

### Executive Summary

- DEBRA supports world-class research, worldwide, to increase understanding of the causes and consequences of epidermolysis bullosa, and to develop the evidence base for development of better clinical care and disease-modifying therapies for those with epidermolysis bullosa (EB).
- DEBRA International's research strategy for the period 2015-2019 has been developed to take into account the notable recent advances in both knowledge of EB and therapy technologies, and the increasing number of early-stage clinical trials of promising treatments both planned and underway.
- The purpose of this document is to outline our strategy over the next 5 years for supporting and promoting EB research and ensuring its translation from laboratory to clinical application. The ultimate goal of the strategy is to ensure that research will benefit the estimated 500,000 to 700,000 – possibly more as mild forms are underdiagnosed – people living with EB worldwide.
- Over the next 5 years, we will build on our research achievements towards two clear goals. One is to translate the promising research outcomes from our supported research projects to date into clinical application. Another is to continue funding basic research that leads to a better understanding of the causes and consequences of EB, thus allowing us to identify new therapeutic targets and concepts.
- DEBRA International is dedicated to helping people with EB, and invests in research to improve the lives of people living with EB now, and those in generations to come. As a patient organisation, the unmet medical needs and welfare priorities of people with EB determine our priorities. In revising our strategy for the previous period (2010-2014), we have consulted people with EB and their carers, EB researchers, clinicians, and other stakeholders in healthcare development and delivery, about their perspectives and priorities. We have addressed in this strategy the particular emphasis given by both clinicians and people with EB to increased support for symptom-relief research concurrently with support for curative-therapies research.
- These consultations have enabled us to create a balanced, yet flexible, strategy for the next five years. There are clear criteria for focusing our financial support, and for evaluating research achievements and outcomes. Furthermore, we are able to develop measurable goals against which we can assess our progress, engendering our accountability to our supporters, and our preparedness to potential future partners.

The key **Aims** of our research strategy for 2015-2019 are to:

- 'Improve our understanding of EB to create new concepts for treatment'
  - 'Improve clinical-care and symptom-relief through research'
  - 'Develop disease-modifying and curative therapies'
  - 'Develop our future EB research community'
  - 'Foster partnerships to develop, and deliver treatments'
- To achieve our strategic aims, we will promote targeted funding support for three key fields of research (discovery, symptom-relief and disease-modifying therapies) of research, and a portfolio of actions to build research capacity and partnerships with external stakeholders.

## Background

- As yet, there is no cure, nor effective targeted treatment either to offer sustained symptom relief, or modification of the natural course of EB, or to increase longevity in severe forms of EB. Nearly 1 in 5 people with EBS still have no identified mutation, and squamous cell carcinoma will still lead to a premature death in an estimated 80% of people with severe RDEB by age 40.
- The policy which underpins our research strategy is that DEBRA International exists to improve the quality of life experienced by people with any form of EB, by supporting and promoting EB research and its clinical translation to better treatments and cures, while simultaneously encouraging adoption of best-practice clinical care. With our distinct perspective as an EB patient-centred organisation, DEBRA will act to facilitate the work of our national member DEBRAs interested in research support, and all stakeholders sharing our research interests.
- DEBRA International enables its 50 or so national autonomous DEBRA member organisations to network and collaborate in areas of mutual interest, including research support. DEBRA International coordinates the research funding contributed to DEBRA International by member DEBRAs, to ensure support of the best-quality research worldwide, without fragmentation of funding or effort.
- On behalf of its national members interested in research support, DEBRA International set up and manages a dedicated Medical & Scientific Advisory Panel (MSAP). MSAP membership is drawn from senior researchers and clinicians worldwide recognised for their expertise, and advises DEBRA International on research matters, including peer-review of research proposals and progress of funded research projects.
- DEBRA International also manages a biopharma industry-led group of advisers which provides strategic advice to DEBRA on actions needed to accelerate research translation, and ad-hoc advisory expert groups on specific topics, as required.
- DEBRA has led the way in supporting EB research for over 30 years, and funded research that identified many genes and the respective mutations that cause pathology. Our funding has led to an understanding of the mechanisms of EB, the development of diagnostics, and the creation of a dedicated cohort of researchers and clinicians.
- Outcomes of successful DEBRA-funded research are now entering clinical trials, and the biopharma industry is initiating programmes of research to develop specific treatments.
- Worldwide, DEBRA International and its research-active national DEBRA members have together invested approximately \$/ €35 million in research to date, and spend is expected to grow as laboratory research outcomes progress into clinical trials.

## Strategic Aims 2015 – 2019

We have 5 strategic Aims in our research strategy:

- **‘Improve our understanding of EB to create new concepts for treatment’**
  - Through ‘discovery and therapeutic-concept’ research
- **‘Improve clinical-care and symptom relief through research’**
  - By expanding the evidence-base for clinical practice and symptom relief through research
- **‘Develop disease-modifying and curative therapies’**
  - Through research and clinical studies to develop therapies that target the underlying disease mechanism in EB
- **‘Develop our future EB research community’**
  - By attracting the best researchers and clinicians, creating the infrastructure to support their work, and supporting young investigators in their early careers, we will strengthen the future the EB research community

- **‘Foster partnerships to develop and deliver treatments’**
  - By increasing our research capacity by working in partnership with other stakeholder organisations and funding bodies wherever possible.
  - By working to increase awareness of our research and opportunities for clinical development with bio/pharmaceutical and healthcare industries, providing appropriate support for those developing clinical trials, and aiming to develop and deliver therapies, including through commercialisation.

### The rationale for these strategic aims

- DEBRA’s programmes of research support will prioritise increased understanding of the causes and consequences of EB to identify new or better therapeutic targets and the clinical development of curative therapies and safe, effective treatments for symptom relief.
- An increased emphasis on symptom relief research is a key change in the strategy for 2015-2019, in response to the wishes of the international DEBRA membership. As part of the strategy review, consultation with people who have EB and their families and carers (James Lind Alliance study of 2013, supported by DEBRA Spain; patient survey DEBRA AGM, Rome 2013; UK patient survey members’ day, 2014), has indicated that better treatments addressing symptom relief and quality of life are considered as part of the cure for EB.
- In addition to direct funding of research, DEBRA recognises the need to drive development of EB research and therapy development in other ways: these include ‘capacity-building’ and ‘partnership development’.
- There will also be increased emphasis on ‘capacity building’ to recruit and develop the next generation of EB researchers, providing appropriate early-career support for young investigators, and infrastructural and project support to also attract established researchers from other disciplines.
- Support for research will be from early-stage basic ‘discovery and therapy-concept’ research through to clinical trials, though direct sole funding or in collaboration with partners. The recognition of the major costs and time-demands of an increased focus on clinical translation anticipated over the next five years will necessitate the involvement of external partners (major sponsors, collaboration with the biopharma industry, and healthcare providers, for example). Partnership development will thus be crucial to enabling clinical trials and delivery of improved therapies to be planned.

### Implementation Plan: strategic Actions to achieve our Aims

1. **‘Discovery’ means research that aims to provide a better understanding of EB – there is still a great deal that is unknown, which may provide better ways of managing EB or new concepts for treatment.**
  - i. We will continue to fund research to elucidate unknown mechanisms by which known EB mutations exert their effects (‘genotype-phenotype’ studies); identification of new genes and mutations that cause EB; identification of ‘modifier’ genes which may not be the ultimate cause of EB but exacerbate or ameliorate symptoms, and are therefore possible therapeutic targets; identification of any other causes of EB and its symptoms.
  - ii. ‘Blue-sky’ or ‘fishing expedition’ studies will not be funded: all research must be hypothesis-driven based on some preliminary published research evidence.

2. **‘Symptom-relief’ means research to gain a better understanding of the consequences of EB which restrict quality of life, and lead to accrued disability, with the goal of developing better treatments.**
- i. The consequences of tissue fragility in EB are diverse and disabling: chronic inflammation and failed wound healing leading to contractures, with resulting pseudosyndactyly, and oesophageal stenosis, for example. Itch and pain are symptoms which have been identified by people with EB as a major concern, but little is known of the underlying mechanisms and this hampers the ability to develop effective treatments. It is expected that researchers from other disciplines (e.g. neuropharmacology, neurophysiology) will be needed to address most symptoms: targeted calls for research proposals to the wider research community would benefit from supported by a coordinated approach from the EB research/ clinical community through EB-CLINET.
  - ii. Consultation with the EB research and clinical community (e-mail survey June 2014, together with reference to DEBRA advisers, and DEBRA International’s Medical and Scientific Advisory Panel (MSAP) and published outcomes from the ‘EB2012’ triennial research conference) has identified some reasons why symptom relief research is difficult, and DEBRA will work with the research and clinical community to overcome these as far as possible.
  - iii. Increased communications between researchers and clinicians to identify clinical priorities will be a first step, brokered largely through EB-CLINET.
  - iv. Targeted research project funding, including both small (6 months – 1 year) clinical feasibility studies and clinical trials in collaboration with other funding partners, will be considered.
3. **‘Disease-modifying’ means research which aims to develop treatments which directly aim to address the underlying mechanistic defect in EB – generally considered to be ‘cure’ therapies – and may be at the protein, gene or cellular level, for example.**
- i. Such therapies may be whole-body (systemic) or localised, and may be one-off treatments (e.g. a transplant) or lifelong (e.g. repeated topical delivery or oral drugs). This would include therefore also therapies that compensate for the EB fault or suppress effects sufficiently for the person with EB to lead a largely normal life (e.g. small-molecule drugs or biologicals that reduce production of faulty EB proteins, or suppress damaging effects (signalling or structural interactions) of those proteins, or enhance production of normal or compensatory proteins).
4. **‘Capacity-building’ means DEBRA investment aiming at strengthening the EB research and clinical community, and its ability to carry out research and develop better treatments, as effectively and quickly as possible.**
- i. Activities in this area will be diverse: **development of the next generation of EB researchers** is seen as a priority, and the most promising young researchers will be attracted into EB research and supported in their early careers by new funding.
    - Specific calls, for example, for PhD studentships, clinical fellowships, young independent researcher awards, and nurse PhD studentships are anticipated: some calls may be international, and others geographically restricted, to meet the research and clinical career structures that are region or country-specific, and will be offered either by DEBRA International or national DEBRAs.

- Consultation with the research and clinical community has identified additional support (e.g. 'rolling fellowships' to assist with the logistics of clinical trial development; clinical fellowships to backfill clinical duties and allow senior researcher-clinicians time to dedicate time to research and clinical trials), and these will be considered for funding, too.
- ii. Capacity-building also includes activities where DEBRA as the patient organisation, and the EB clinical community (EB-CLINET), are uniquely placed to carry out, or initiate in partnership with others, activities that will accelerate or expand research and therapy development.
- iii. A priority, which has proved to be a logistical and financial challenge over the past 5 years, but is increasingly urgent with the advent of clinical trials, is the development of a sustainable, high-quality, international **patient register**, or linked national registers, to support both research and recruitment to clinical trials.
- iv. Further existing examples are the commissioned **study on the natural history**, and validated clinical endpoints of RDEB for therapy evaluation (a retrospective comprehensive literature review and prospective patient study aiming to document the natural course of symptom development, and thereby identify and validate clinical endpoint measures; patient study to be expanded to additional EB reference centres); and the DEBRA-led working group evaluating and documenting suitability of clinical measures of disease severity and quality of life. While some biopharma companies are carrying out similar studies for their own purposes, DEBRA's advisers from bioindustry noted that the regulatory authorities place great value on such studies led by the relevant patient organisation and clinical community.

**5. 'Partnership development' means DEBRA investment into activities that will interest, encourage and facilitate support for DEBRA-led EB research and therapy development.**

- i. Cultivation of partnerships with other research charities, either dedicated to EB, or with overlapping disease mechanisms or symptoms (chronic inflammation, itch, pain), is important to get new perspectives on possible therapies, as well as linking resources to undertake expensive preclinical research and clinical trials.
- ii. Potential partners also include the bioindustry, from small biotech through to big pharma: the rapid increase in interest from the sector in EB research has been remarkable over the past five years, and has led to direct funding of research and clinical trials. Whether individual companies are in a position of 'watch and wait', to collaborate, or to initiate their own EB R&D programmes, all wish to have some degree of contact with DEBRA as patient organisation and associated clinical community, both for information and access to patients. A strong programme of communication and engagement with these stakeholders is essential.
- iii. Future partners with whom DEBRA needs to engage include healthcare providers – whether provision will be funded either publicly or privately. DEBRA International, together with EB-CLINET, is in a position to support national DEBRAs by developing policy and health-economic arguments, which can be reinforced by information gathered by DEBRA, a strong research communications programme and cooperation with transnational and international lobbying and policy bodies such as EURORDIS, NORD, CORD or Rare Diseases International.