Executive Summary

- EB is a heterogenous condition and the genetic defect that underlies the condition varies with subtype. Additionally, the same genotype can give rise to different clinical presentations. Therefore, there is a need for better understanding of the correlation between genotype and phenotype in EB.
- As well as structural proteins, the number of stem cells, immune functioning and inflammatory responses can also all vary with subtype.
- We need to understand the unique natural history of EB wounds both anatomically and temporally. The biological mechanisms involved in wound development, the formation of blisters, healing, soft tissue fibrosis and scarring need to be investigated, and it is important to establish whether there are variations across the wound on the surface and at different depths in the wound.
- The biology of the deeper dermis should be established including bacterial load.
- Inflammatory processes need to be elucidated for all skin compartments.
- We need to consider the invading microbes as well the host’s responses. Eliminating microbes is not a simple, clear-cut consideration. Some bacteria produce beneficial agents, such as antibiotics.
- We need to consider the roles of commensal and pathological bacteria as well as host responses to these organisms. The influence of pH in the surface compartment on the bacteria needs to be understood.
- Wounds show a complex interplay between organisms, inflammation and tissue response. Inflammatory responses need to be elucidated in greater detail.
- We need to appreciate the differences between acute and chronic wounds and what switches an acute wound into chronicity.
- The processes that result in the development of squamous cell carcinoma need to be understood. There is a need for long term monitoring of selected wounds to obtain more information on malignant transformation.
- There are differences between responses to bacteria and the healing processes in mucosal and cutaneous lesions. We need to understand the oral microbiome and the nature of the fibrosis that occurs in the mouth.
- Current definitions of outcomes and endpoints for clinical trials may not be helpful. More informed clinical opinion and importantly, patient perceptions of what is a ‘successful’ outcome need to be presented to regulators to inform outcome measures that are robust, meaningful and practical.
There are opportunities for biobanking of tissues (blistcr fluid, biopsies and exudate) and standardizing the methodology for investigations of wounds at different stages. There needs to be uniformity in what we are documenting in terms of anatomical site, history, clinical work-up etc. and proper consent obtained for using tissue. Detailed photographic documentation of wounds over time could be very valuable.

Prospective banking of samples may have advantages over retrospective review of stored tissue.

Itch is by far the most distressing symptom for EB for patients. We do not understand itch but there is evidence to suggest it shares common pathways with pain.

We should consider ‘personalised’, multimodal treatment - taking into account both the differences in the types of EB and the types of wound. Personalised treatment of itch and pain may be especially useful and should encompass behavioural as well as pharmacological interventions.

The group is in a strong position to collect data on the efficacy and acceptability of wound dressings that can underpin further research.

While cure is usually not possible, it should still remain an ultimate long-term goal. However, in the interim small but incremental changes can be achieved in the short-term to benefit patients more immediately. Goals should be set for 1 year, 3-5 years and 5+ years.

Changes in skin seen in puberty and in pregnancy are indicative of hormonal actions on skin metabolism that need to be understood more fully.

Keratinocytes are important cells to investigate both for their functional role and the cytokines they produce. A potential rich source of keratinocytes is the outer root sheath of hair follicles.

Important advances are being made in the technology of applying mesenchymal stem cells to wounds. Spraying on cells or using supportive matrix preparations are being investigated. Adequate wound bed preparation is essential prior to using cellular therapy.

Gene corrected cells or HLA antigen compatible cells are the way forward in trying to cure EB. There are many genetic manipulations being pursued in EB research. These are providing exciting opportunities with safety being paramount.

Use of agents such as gentamicin for genetic manipulation or use of antisense oligonucleotides are other techniques in development.

Patients should be stratified as to their suitability for gene therapy. Having a minimal expression of mutated proteins identifies good candidates since they will be less prone to developing antibodies.

Familial analysis, with HLA antigen mapping can identify family members who could be potential donors of cells expressing normal skin proteins.

Delivery systems for stem cells and small molecules are important and should be a focus for EB research.

This meeting has demonstrated the values of sharing data and experience across different disciplines that are involved in wound care and healing and has opened up opportunities for collaborative research.
Meeting Aims

This meeting aimed to bring together senior researchers and clinicians who specialize in EB research and clinical management alongside researchers and experts from other disciplines specialized in wound healing to pool and share expertise and thus gain further insight into the biology and treatment of EB wounds.

The meeting had the following objectives:

- To evaluate current knowledge and challenges in EB wound healing
- To interact with and learn from experts from associated disciplines
- To develop consensus on unmet clinical-research priorities in EB wound healing
- To identify fresh concepts from expertise of the wider wound-healing community
- To set priorities for a 2017 call for research proposals with a view to considering proposals that include different but complementary disciplines
- To widen the net of experts who may be able to advise DEBRA on research priorities and generate innovative research proposals

Meeting participants: See Appendix 1

Session 1: Skin fragility and blistering: similarities and differences compared with other acute and chronic conditions

This session was opened with a presentation by Professor Jo-David Fine ‘Setting the scene – life with EB’, which outlined the genetic, cellular and tissue characteristics of the four major classes of EB and the serious clinical complications of chronic non-healing wounds, the most serious of which is the development of aggressive, and frequently fatal, squamous cell carcinoma (SCC). The challenges of clinical management were considered.

Key points of the discussion

- EB differs from other conditions where wounds are a prominent feature, since EB is a genetic condition where lack of structural proteins, especially collagen VII, gives rise to constant blisters, acute and chronic wounds and scarring. These problems are present from birth and persist throughout life. By contrast, conditions such as diabetes, venous ulcers and burns are associated with chronic illness or severe trauma and wound problems which may be an isolated incident although recurrences can be frequent.
- The genetic defect underlying EB differs with subtype and thus the characteristics of the wounds and their development differs. Structural protein profiles, underlying conditions (e.g. multifactorial anaemia), availability of stem cells, immune function and inflammatory responses can all vary with subtype. We need to understand the correlation between genotype and phenotype in greater depth.
- Similarly, there may not be one treatment of blisters and wounds that is appropriate for wounds of different aetiologies or for lesions in different EB subtypes.
While infection and inflammation are important contributors to wound development, and immune responses are important in healing, we need to understand if these processes are different in EB from other conditions.

There is a lack of knowledge of how wounds develop and heal both temporally and anatomically. Therefore, there is a need for greater understanding of the processes involved both over time, and at different depths in the wound. The contribution of different cell types and the signaling cytokines they release needs to be understood as well as the role of pH, ions (Zn\(^{++}\) Ca\(^{++}\)) and micronutrients in allowing bacterial colonisation.

There are differences between acute and chronic wounds that we do not fully appreciate. Acute EB wounds do tend to heal and only in a minority of cases do they persist and become chronic lesions; we need to understand what precipitates this switch.

We need to understand the nature of scarring over both acute and chronic wounds.

Wounds may respond to treatment initially and then stop or progress suggesting multiple sequences in wound healing that need to be elucidated. There may also be differences within a single wound since parts may heal while another area is breaking down.

Understanding these processes can inform treatment; for example, topical agents may control processes at the surface but not at the level of the deep compartment, so there is a need to differentiate between anti-microbial agents that can penetrate the surface and those that need to used systemically.

Being able to access and understand the biology of deep layers of skin, especially deep dermal layers, is important for treatment and for employing agents that help ameliorate scarring. Laser capture and DNA microarray analysis could be used to investigate areas at different levels throughout the entire lesion.

The contributory role that repeated and persistent wounds make to the development of SCC needs to be understood. Areas prone to chronic wounds are also the sites of SCC but whether there is a causal relationship is not clear; we need to understand the nature and duration of prolonged inflammation, whether due to infective organisms or host factors, and if these are contributory factors to malignant transformation. We need to follow specific wounds for prolonged periods to establish the relationship.

Inflammation may be good or bad for healing. It has been shown in venous ulcers that lymphocytic infiltration was associated with healing but the presence of polymorphic cells was associated with more bacterial infection and decreased healing. Inflammatory markers can also vary within different tissue layers and venous ulcers and diabetic foot ulcers have demonstrated different cytokine profiles in the wound exudates.

Patient age and skin type may also influence tissue responses. People of Afro-Caribbean origin often have skin that is more permeable and carries huge numbers of inflammatory cells and inflammation which often gives rise to keloid scarring. However, EB patients rarely develop keloids and different skin types do not show differences in behaviour, but atrophic scarring may get worse with age.
Session 2: Mechanism of skin inflammation in wounds and wound healing

Dr Ardeshir Bayat spoke on ‘Tissue integrity, repair and regeneration in wound healing’. This presentation considered inflammation and fibrosis and the similarities and differences between EB and other complex wounds. Acute wounds, chronic wounds and scarring were considered. The differences between keloids and scars were considered. Treatment options were outlined as well as emerging techniques for improving both diagnosis and management.

Key points of the discussion

• There are issues around how success is defined in treating wounds. The FDA requirement for complete wound closure that lasts seven days was considered unhelpful. Wounds may close and remain ‘healed’ for seven days but then break down after that period. It was questioned whether that can really be considered as ‘healed’ -there may be coverage but not healing.
• EB is a genetic disorder (with the exception of EB acquista, a severe autoimmune condition) so cure must rely on gene therapy, which is mostly not possible or affordable. So, while genetic cure is undoubtedly a desirable long-term goal that must not be ignored, patients need effective interventions now. Defining realistic and attainable goals that can be achieved in a stepwise manner and shorter timeframe was considered a more valuable approach.
• In line with other diseases, such as arthritis and cancer, enabling patients to live well is a valid outcome even if it falls short of cure.
• Inclusion of cost into definitions of outcome can also be misleading since looking at costs of consumables alone does not encompass staff costs and does not value quality of life.
• Outcome measures need to tailored to EB type and parameters such as decreased pain and decreased surface area of open wounds may be more meaningful to patients. A survey showed that that patients would consider a 20% decrease in wound area a successful and worthwhile achievement. Other desirable outcomes were a decrease in time for dressing changes and less wound exudate.

Session 3: Complications of EB wounds

José Duipmans gave a talk on ‘Aetiology of pain and itch: is EB special?’ which considered the implications of chronic wounds, the itch-scratch cycle and its management and the aetiology of pain and management of dressing changes. While the aetiology of pain and itch seems common to all pathological conditions, these issues are special for EB since
they are life-long, unpredictable, lead to anticipatory symptoms, and establish vicious cycles which are difficult to break, all of which contribute to impaired wound healing.

**Professor Jan Maarten van Dijl** presented the ‘**Implications of infection on wound healing**’, covering the skin biome, managing chronic open wounds and infection, and tracking infection, including the implications for management. EB was compared with other chronic infection situations.

**Key points of the discussion**

- By far the most distressing symptom for patients, occurring in 85% of patients and placed first by patients in a survey, is itch. Itching not only causes distress, but scratching wounds or even areas of intact skin, in response can be detrimental to healing and overall skin integrity, possibly promoting new wounds. Moreover, a vicious circle of stress, itch and pain can develop which may lead to hypersensitivity. Itching in the absence of an identifiable stimulus and anticipatory itch and pain can also occur.
- Currently, there is no evidence to suggest that the mechanisms of pain differ in EB from those in other conditions.
- Interventions for pain relief in non-EB patients include transcutaneous electrical nerve stimulation (TENS), which has been used to stimulate vagal fibres causing release of acetylcholine which attenuates cytokine release from macrophages. Yoga/mindfulness can also help pain control and this too may rely on vagal stimulation. These may not be appropriate or effective in EB.
- The mechanisms of itch are poorly understood.
- The fact that treatments for neuropathic pain seem to work for itch suggest that they are utilizing the same neurological pathways.
- Itch has been relieved by gabapentin in EB patients.
- Relief from itch has been experienced in EB with cooling of creams/ointments and dressings, ondansetron (a 5HT3 receptor antagonist), and aprepitant (an NK-1 antagonist), both of which are anti-emetics.
- Cannabis has demonstrated activity in decreasing both itch and pain in EB patients. Access to cannabis has been reported as the main request for symptom control from EB patients and is becoming widely used in some countries (USA).
- Biofeedback has some utility, but is time consuming and expensive so access to such services is limited. There are suggestions that multi-modality approaches combining pharmacological agents with behavioural interventions can bring relief from pain and itch.
- There are no absolute definitions of ‘chronic wound’ but it is generally taken to mean those lasting >3 months.
- A definition of biofilm is a complex mixture of bacteria, extracellular proteins and DNA which derive from both the bacteria and the host; they can be dissolved by DNA-ases and proteases. Biofilms can be barriers to drugs and oxygen and may invade deeper compartments so can be problematic in wound healing.
- Commensal bacteria may help prevent colonization by pathogenic bacteria so there must be a balance between cleaning wounds and not removing all bacteria. Some bacteria produce antibiotics and a low levels of *s. aureus* can enhance wound healing.
In wounds, there is a complex inter-play between organisms, inflammation and tissue response. The invading organisms (staphylococci, pseudomonas) also varies between individuals and different types of wounds and well as their distribution within the wound itself.

There is a greater need for understanding the make-up of the oral microbiome. The mouth has a different inflammatory status to skin and there are differences in the bacterial clearing mechanisms. Blisters will heal much quicker, but fibrosis can be problematic.

The gut also shows differences in tolerance and immune responses. In general, there is little scarring in the mucosa, of the mouth. Peridontal problems do occur and there are differences in the biology of the tongue and mucosa.

Oesophageal strictures can be common in some types of EB (DEB and Kindler syndrome). Their aetiology probably varies with where they are located; lower oesophageal strictures are likely to be associated with damage due to acid reflux, whereas more proximal strictures probably result from damage from ingested food and possibly could be due Plummer-Vinson syndrome caused by low iron.

There was no consensus on what bacterial profile should determine whether wounds are treated or not and also the nature of the treatment; eliminating the bacteria or treating the host response. The NERDS system (Non-healing, Exudate, Red and bleeding, Debris and Smell) recommends treatment of the organisms if 3 or more of the signs are present, otherwise no treatment of organisms is given.

Mucosal tissue does not seem to develop blisters and ulcers, but wounding results in fibrosis that can be problematic. The periodontal region should also be investigated since it can harbour significant bacterial loads.

Session 4: New directions for EB wound management – learning from other research

Associate Professor Peter Marinkovich presented his talk ‘Care versus cure: translating EB research into improved wound care’ looking at how autologous mesenchymal cells that have been undergone retroviral transduction to overexpress collagen VII could be delivered as autografts and improve healing in EB patients.

Professor Anthony Metcalf presented ‘Wound healing research in 2016: translation to EB?’ to explore the advances in wound healing and management in burn wounds. He considered the recent and developing scientific research and how this information is applicable to EB.

Key points of the discussion

- Autografts are showing great promise in wound healing but host antibodies are a problem since they may compromise the graft.
• Controlled clearance of stem cells from the wound bed before introducing the graft improved outcome.

• The outcome in the dermis is currently under investigation.

• Hair follicles can be a valuable source of keratinocytes which could be used for transduction and grafting.

• Methodology is important since results for antibody presence and titre differs between indirect immunofluorescence, ELISA and Western blotting. Different epitope expression by the patient can influence local rejection of the graft and auto immune responses. For patients who have residual collagen VII the propensity for antibody formation to the collagen is lower.

• Preventative tacrolimus may be useful in patients with no collagen VII as an immunosuppressant. Plasmapheresis has been tried but antibody clearance is followed by a rebound spike in antibody production. Use of immunosuppression should always take into account the potential increased risk of SCC.

• Tacrolimus can help local contain local rejection. Ointment is preferable to cream and the problematic thick viscous nature of some formulations can be overcome by applying to the dressing rather the graft.

• Patients can become sensitive to preservatives in topical creams. Although the vehicle for tacrolimus cream may be important for penetration into skin, it also contains a lot of preservative. Alternating applications with anti-bacterial agents (e.g. mupirocin, bacitracin) may avoid microbial growth.

• The use of photographic systems for obtaining comprehensive data on wound progression was welcomed. In clinics, wounds may only be visually inspected after several weeks, tattooing the edges of wounds allows patients to take frequent photographs (e.g. using an iPhone or similar device) which can be compared with Canfield or similar images used in the research setting. In this way, a more detailed documentation of wound progress is obtained. This is important as wounds are not static entities and photography can be especially useful where wounds heal in one area but not another or where wounds seem to ‘move’ from one skin area to another.

• It is important that the status of the patient is good before grafting; attention must be given to pain and nutrition, correction of anaemia, ensuring that haemostasis is good and the wound bed is prepared adequately with signs of active wound granulation.

• There are several novel developments for wounds resulting from burns. Wound pH and glycaemic levels have been shown to be important and loading dressings with buffers, ions and insulin can address these problems.

• Several matrices (collagen/elastin matrix preparations) are available, and these materials can act as a vehicle for various therapeutic agents

• There is always a balance between leaving dressings in place to assist wound healing and the possibility that an uninspected wound may be developing infection. Infection-detecting dressings have been developed that contain nanoparticles which release auto fluorescent material in response to infection, alerting people to problems beneath the dressings.

• ‘Spray-on’ cell preparations were of great interest as an alternative to grafts. These sprays contain spheres of fibroblasts that are protected from degradation by a keratinocyte coat. They are effective but keeping them in place can be problematic. They have been used in EB.

• Matriderm (a collagen elastin matrix) can be used as a carrier to allow cells to be applied to wounds.
Hyperbaric oxygen was considered controversial. While there is evidence that it has efficacy in diabetic foot ulcers its role in other wound types is uncertain, also it is a costly intervention, requires multiple treatment cycles, is only effective at high O2 pressures and effects may cease when treatment stops with subsequent wound breakdown.

Similarly, negative pressure bandages were not universally accepted as effective in wound healing.

It was discussed whether clinical responses necessarily lead to corresponding changes in molecular markers. Changes in microbiology might not necessarily correlate with wound progression.

HLA analysis of siblings might facilitate using cells from family members for grafting.

There is a lot of work that needs to be done before gene therapy can be widely used in EB and it might be best to stratify patients for suitability for this type of treatment. Good candidates will have minimal expression of mutated proteins – to avoid complications of antibody formation, but further work is needed to identify the biomarkers that suggest wounds will show a positive response to grafting. HLA familial analysis could form part of the stratification criteria.

Gene therapy should be directed towards very young children who have not yet developed chronic wounds and bacterial superinfections. This will not only prevent problems developing but is more likely to produce a successful outcome than treating adults.

Session 5: Topical agents and delivery mechanisms – opportunities in EB

Professor Keith Harding shared ‘Patient studies in wound healing’ to consider the relevance of new and active dressings to EB patients and the opportunities for novel topical agents. The challenges involved in study design were considered.

Professor Andrew Baird considered ‘Drug delivery for wound healing’ addressing drug discovery, development and deployment for injury and tissue repair and considering their applicability to EB.

Key points of the discussion

- When trying to design clinical trials for wound healing, patient preferences must be taken into account. Patients have strong preferences for how their wounds are managed and their dressings of choice, consequently getting them to comply with a protocol will be very difficult if it differs significantly from what experience has shown is effective in their situation. This will inevitably introduce considerable heterogeneity in the data produced since patients with similar clinical profiles may pursue very different treatment regimens.
• Patients change dressings at home so it is difficult to be sure that they have adhered to a protocol and they will reject any interventions they find painful. Fear of pain can also cause patients to be reluctant to try new interventions.
• These considerations make investigating optimal wound dressings in EB difficult, if not impossible.
• Issuing patients with ‘treatment toolkits’ has been shown to be beneficial. The toolkit provides advice on what to do for specific problems such as itch, pain, exudate, smell. The patient can then self-manage quite successfully with less dependency on healthcare professionals. Kits would need to be tailored to different types of EB.
• Anecdotally, some treatments given for other pathologies can produce improvements in skin condition. Examples include cyclophosphamide and anti-TNF biologic treatment.
• There was discussion of whether anti-interleukins, especially IL-1, could be candidates for anti-inflammatory therapy. Experience with biological agents and immunosuppression in wound healing is limited. However, IL-1, although it drives the inflammatory response, also drives skin closure, therefore, using antagonists may be counter-productive.
• Immunosuppression is used to treat skin conditions such as psoriasis. It is becoming evident that the epidermis plays a bigger role in psoriasis than previously thought and there may be value in trying to stimulate immune feedback loops in superficial skin layers and avoiding systemic immunosuppression.
• Biological agents also have the problem that patients may respond initially but over time antibodies develop and the effect attenuates. So these agents can ‘buy time’ but are not a long-term solution.
• Various sheet matrix preparations such as hydrogels e.g. Actiform Cool, Aquace® (carboxymethylcellulose) and Puridon (cross-linked hydroxymethylcellulose) were suggested as effective dressings but there was little consensus on which was best. There are issues with dressing adhering to wounds and trying to keep optimal moisture balance.
• A topical local anesthetic, such as pramoxine when used as a spray that has been kept refrigerated relieves wound discomfort.
• A database using the experience of this group could be constructed that collects experience of what helps with pain, itch and smell of EB wounds. This could provide a platform for considering which products, biomaterials or techniques could be investigated further.
• It has been demonstrated in a conditional knock-out mouse model that collagen has a half-life of about 4 weeks. It is not known if this applies to exogeneously supplied collagen.
• Microneedles, either steel or biodegradable have been used to deliver transformed mesenchymal cells into wounds. The needle length and spacing can be adjusted to allow precise delivery of cells to different skin layers and across precise areas.
• It was questioned whether such needles could be used to deliver biological vectors that can then introduce the collagen VII gene into the local cells. However, there are many considerations in introducing biologically active vectors. Not being able to control the distribution and activity of such vectors once inside
the body is a potential problem and regulatory agencies would probably not approve such systems.

- It was suggested that other systems using adenovirus transfection to correct oncogenes have been allowed by the FDA so it is not certain that regulatory approval would be denied.
- Lasers have been used to deliver drugs to the skin of patients with Leishmania. The laser seems to open microholes in the skin for a few seconds which allows drugs to penetrate – the skin of these patients has shown cosmetic improvement.
- In using in vivo viral transfection of cells for gene correction there is a risk that alongside the required gene correction there may be a random inappropriate gene insertion in other cells.
- Transfecting cells in vivo may also significantly increase the risk of immune rejection of the new skin cells. If the transfection takes place in vitro these issues can be examined before cell replacement.
- A lot of technical work is also required to ensure that we are targeting the correct cell types and that the resultant cells are capable of maintaining long-term responses.
- There are many genetic manipulations being explored in EB that are showing great promise in correcting the defects in collagen VII production. These include using aminoglycoside antibiotics, such as gentamicin, which can suppress premature termination codons thus permitting translation to continue to the normal end of the transcript producing a functional protein. Introducing gentamicin into the fibroblasts of the dermis via microneedles might be a technique to consider since there are toxicity issues in using gentamicin on large areas of open wounds due to systemic absorption.
- Exon skipping of certain mutations may also allow production of functional collagen VII. Exon skipping can be achieved with antisense molecules, which may also provide a valuable technique for correcting or restoring missing gene products without the problems of gene manipulation.

Opportunities for research

Important aims of this meeting were to develop consensus on unmet clinical-research priorities in EB wound healing and to draw together a wider net of experts who may be able to advise DEBRA on research priorities. By so doing it was hoped that fresh concepts and innovative research proposals would be generated that would give rise to suitable projects that DEBRA might fund in 2017.

The following list is a brief summary of potential research opportunities mentioned in the discussions. It is not exhaustive and the lively discussion no doubt generated other ideas that researchers can bring to the table in response to DEBRA’s call for proposals.

- Collectively, the EB treaters contributing to the is meeting care for a large number of EB patients – this presents important opportunities for data collection on a significant scale and it was agreed that there could be valuable sharing of data regarding biobanking of tissues (blister fluid, exudate and biopsies) and experience in treatment interventions such as dressings, that could contribute to several of the projects.
below. Tissues are no doubt already stored that could be used for retrospective review but prospective banking may be more useful. Setting up any biobank should include proper documentation of the clinical history of the patient for correlation with molecular findings and as many photographic records as is practical. Informed consent must also be recorded to allow current and subsequent use of tissue.

- While we have detailed understanding of the subtypes of EB and the perturbations in the structural proteins of the skin that are produced by the lack of, or mutation of, protein genes, we do not fully understand the interactions between genotype and phenotype that result in patients with the same type of EB showing different clinical pictures. So, genotype-phenotype correlations need to be explored. Investigating differences in severity in affected family members may reveal relative expression of modifying genes.

- EB can only be cured by genetic intervention and this remains the ideal, major goal for EB treaters. However, this can only be achieved through complex and expensive interventions (if at all) and realistically is a long-term aim. Efforts should be made therefore to identify smaller, more achievable incremental changes that benefit EB patients in the immediate future. Priorities need to be set and projects identified that can address each issue. Examples discussed include:
  - Itch. Itch is the most distressing symptom for the majority of EB patients. The physiology of itch is poorly understood and basic biological research is needed. But for EB patients the immediate priority should be practical interventions that can alleviate itch. Identifying effective interventions can then be followed by elucidating the mechanisms that give rise to itch.
  - Pain. Wounds are painful and changing dressings can precipitate particularly painful intervals. This can give rise to anticipatory pain. Drawing on current knowledge of treating pain, we need to identify those interventions that are effective for EB pain and the best dressings for managing wounds and minimizing the pain associated with dressing changes.
  - Exudate. More copious exudate requires more frequent dressing changes. Some treaters had developed methods to overcome this – such a piercing the dressing and covering with absorbent materials that could be changed without disturbing the dressing. Such techniques for coping with exudate and minimizing pain could be shared and evaluated.
  - Smell. Similarly, techniques for reducing the smell that accompanies anaerobic bacterial colonisation could be shared and investigated further.

- The group could conduct a survey of the most overall effective dressings to identify those that warrant more detailed investigation.

- Specialised wound dressings have been developed for burns patients and their applicability to EB wounds could be investigated further.

- The relative benefits of topical and systemic wound treatments need to investigated further.

- Blistering and wounding of the skin in response to even gentle trauma is a hallmark of all types of EB but the development of wounds over time is poorly understood. There is a need to investigate the anatomical distribution of wounds and whether different areas of the body are more prone to wounding, which may be related to the amount of trauma to the area but could include other factors and how wounds develop over time.

- There is a need to understand the differences between acute and chronic wounds and the biological switch that makes an acute wound become a non-healing chronic wound.
The differences between acute and chronic wounds in EB may not be the same as for other wounds. Chronic EB wounds may sometimes behave more like 'persistent acute wounds'.

There is a need to evaluate and standardise the tools by which we measure wound healing in EB. The detailed photographic documentation of wounds demonstrated at the meeting could be developed to assist data collection. For example, patients could be engaged to photograph their own wounds on a regular basis.

The development of scar tissue needs to be investigated further and could be compared with scarring after burns and in different skin types.

The oral mucosa behaves differently from the skin; while blisters heal more rapidly there is a problem with fibrosis. There is a need to understand more about the oral microbiome and the healing processes in oral and/or gut mucosae.

Outcome measures need to be more practical and defined in terms of what matters to patients. The FDA end-point for clinical studies of complete wound closure that lasts 7 days is not helpful and does not reflect real world experience. Significant, but incomplete, closure of wounds still may improve patients’ quality of life and closure is not synonymous with healing; wound cover may be achieved but be followed by breakdown within a short time-period. There needs to be collaboration between patients, clinicians and regulators to define outcome measures and meaningful endpoints.

There is a need for a more detailed understanding of the microbiome of wounds. Bacterial involvement is not simple and we need to consider both the nature and behaviour of the colonising bacteria and the inflammatory responses of the host. Examples of the data that could be collected include:
- the distribution of bacteria across the wound and at different depths within the wound.
- the positive role of commensal bacteria and the bacterial species that can help wound healing.
- the inflammatory cell types and mediators that are seen in different skin compartments and the biology of the deeper dermis.
- host characteristics that promote or hamper wound healing.
  - the role of pH and ions in wound behavior.

Such information could provide more information to inform treatment interventions.

EB patients are at a high risk of developing SCC but the relationships between blisters, wounds and malignant transformations are not known. Following specific wounds over the long term could give insight into the relationship between skin lesions and SCC formation.

Sophisticated flow cytometry techniques can allow cytokine challenge of patient leukocytes to look at pro- and anti-inflammatory responses of cells involved in the host response to bacterial colonization of wounds.
Appendix 1: Meeting Participants

Expert Faculty

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