

Focus on EB Simplex – a treatment in sight?

What is Epidermolysis Bullosa Simplex (EBS)?

EBS is a group of inherited disorders in which the skin blisters extremely easily. It is caused by a fault in the genes which hold the instructions necessary for production of certain proteins in the top layer of skin. The result is that the top layer of skin does not “stick” securely to the layer beneath it, and where the two layers separate a blister develops.

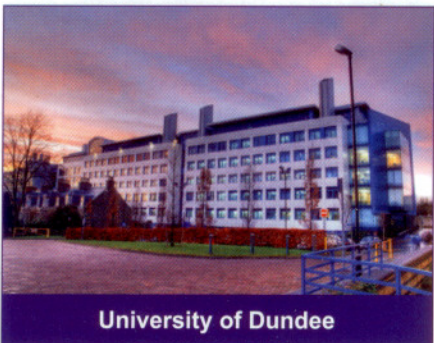
Approximately 70% of people with EB suffer from EBS. The most common form of EBS has blistering confined to hands and feet but in some forms of EBS blistering can occur all over the body.

Management involves identifying new blisters, lancing them with a sterile needle, or snipping with a sharp pair of scissors to release the fluid and prevent spread. Blisters can be very painful and limit mobility.

For many years, DebRA has funded research into Epidermolysis Bullosa Simplex (EBS) with the aim of identifying the genes that cause the condition and developing an effective treatment. Recently, the project has secured new funding for the next five years from the Medical Research Council. We catch up with Professor McLean and find out where the research is at and how close we are to finding an effective treatment for EBS.

Can you give us a brief overview of the work you have undertaken in the last few years?

DebRA has been funding work on EBS since the early nineties. I was one of the first post-doctoral scientists employed and funded by DebRA back in 1992, when the genes were being discovered that cause EBS.



University of Dundee

We're chipping away at the genetics. We can pinpoint the defective gene in around 90% of EBS patients. It's very important to know which gene it is as some of the treatments being developed now are dependent on knowing what particular gene is faulty.

Most patients with EBS have mutations in either their keratin 5 or keratin 14 genes. We know that if you can somehow switch off this faulty gene then the one normal gene will produce enough keratin to give you normal skin. That gave us a great incentive. The big challenge for us over the last decade or more has been to find a way to do that. And that's a pretty tall order!

What DebRA has been funding particularly over the last five years has been the development of a therapy for EBS and that's really the main area of our research now. The gene hunting side has become a secondary priority. We have tried several different approaches and we look to have hit on something that looks really hopeful. It is a new technology called siRNA which is something new and different. It's not a gene therapy and it's not quite a drug either. It's somewhere in the middle.

To our great surprise and delight, it's turned out to be possible to use



Irwin McLean

Irwin McLean is Professor of Human Genetics at The University of Dundee. His group has identified the causative genes for more than 20 human diseases. In particular, he has a long-standing interest in the genetics of Epidermolysis Bullosa Simplex (EBS) and development of therapy for this and closely related keratin disorders.

Prof McLean has recently relocated to the Division of Molecular Medicine, College of Life Sciences, University of Dundee, where he is Head of Division. This new Life Sciences/Medicine joint research division is aimed at translating discoveries in basic research into new medicines, mainly focusing on skin diseases and cancer. He was elected as a Fellow of The Royal Society of Edinburgh in 2005 and a Fellow of the Academy of Medical Sciences in 2009.

Irwin works closely with DebRA and has even produced a CD which he sold around the University with all proceeds coming to the charity. He claims to have a large catalogue on unreleased material so we may well see another CD very soon!

siRNA to switch off the mutated defective copy of the keratin gene and not affect the normal copy. If you had asked me five years ago if that would have been achievable I probably would have said no or bet the other way! But remarkably, it can, so over the last couple of years we've been working on this for EBS.

Has a trial been done on humans?

There has been one clinical trial conducted in the USA in the last year or so on a single patient with a condition called PC, which is also caused by a genetic fault in a keratin gene, using exactly the same method that we are developing for EBS. This trial was successful on a very small scale. They injected a lesion on the foot of the patient with siRNA on one side and water on other side. The lesions on the side that got the siRNA shrunk and disappeared whereas the other side remained the same. That was the first proof of concept in humans that siRNA can be used to treat a keratin disorder. It doesn't really matter which keratin defect it is, the principle is the same for all of them.

That's given us really strong hope. The big challenge is to get the siRNA into the skin and that PC trial was delivered by injection into the skin which is, first of all, a very crude and inefficient way of delivering treatment into the skin, but it was the only thing we knew at the time would definitely get the stuff in. It was injected into a blistering lesion so it was a very brave lady who undertook this painful treatment!

The field of siRNA is really focussing on how to deliver this stuff into the skin and we're looking at a special kind of 'gene cream'. There is a patented formulation for this 'gene cream' but it still needs a lot of refinement.

How long do you think it will take to develop this delivery method?

Both sides of the Atlantic are working closely together to solve this delivery problem and we are pretty optimistic

we will have some results in the next year or two. Then we can get on to the part of designing clinical trials on people.

One of the things we are doing is collecting skin cells from patients that have certain mutations that we know we can treat so that we have a bank of material to validate the therapy all ready to go. We're working with a small number of EBS families to get cells and test that the siRNA really works to pave the way for clinical trials. We're starting to gear up for them with the hope that the 'gene cream' will be ready over the next couple of years.

If this is a successful treatment what percentage of people with EBS will potentially benefit?

It will be applicable to about 90% of the EBS population, which is about 4,500 people in the UK. It's a very exciting couple of years as we get closer and closer to actually trying something out on patients. We don't want to raise false hopes but we are closer than we have ever been to having a successful treatment.

Will the siRNA be classified as a drug?

Yes, at the moment it is. Assuming everything goes according to plan we envisage it to be a cream which you would rub on the affected areas to prevent the blistering. We don't know how often it would have to be



Daisy May Pearson and her brother Joseph

applied but we imagine daily or weekly. And that's something we would have to learn from the human trials. It does seem to work for quite a long time in cell culture.

Are we looking at the siRNA being an effective treatment or a cure?

Not a cure. It would have to be applied as a treatment. The cure as such will probably come from gene manipulation and that is proving extremely difficult. siRNA is inherently safer.

An effective treatment is really the goal because EBS is not life-threatening like the more severe forms of EB. If it works the way we hope it's going to work it will be pretty good.

If you would like to donate to DebRA's Research programme please visit www.debra.org.uk.



Daisy's hands and feet showing blisters caused by EBS