Institution: University of Dundee

Unit of Assessment: 5: Biological Sciences

Title of case study: Identification of the genetic basis of inherited keratin skin disorders leading to advances in diagnosis for patients.

1. Summary of the impact (indicative maximum 100 words)

Keratins are major cytoskeletal proteins of epithelial cells. Pioneering research at the University of Dundee led by Prof Irwin McLean FRSE and Prof Birgit Lane FRSE showed the association of keratin mutations with genetic skin fragility disorders. This has dramatically changed the diagnosis of inherited skin disorders and has directly translated into improved clinical management of patients both in the UK and internationally. Further work on this disease has resulted in the first clinical trial using siRNA for a skin condition.

2. Underpinning research (indicative maximum 500 words)

Epithelia are barrier tissues that protect the body from physical and chemical damage, dehydration, infection and heat loss. The epidermis is the largest of the epithelial tissues and forms the first line of defence against the outside world. The function of the keratinocyte cells of the epidermis is to maintain epidermal integrity and withstand the mechanical and chemical forces that the skin is subjected to every day. Much of its strength comes from a dense meshwork of cytoplasmic intermediate filaments composed of keratin proteins.

Epidermolysis bullosa (EB) is an inherited disease causing blisters in the skin and mucosal membrane caused by a defect in anchoring between the epidermis and dermis which results in skin fragility. Its severity ranges from mild to lethal. In the 1990's, **Prof Irwin McLean FRSE FMedSci** (then Honorary Lecturer at the CRC Cell Structure Research Group, College of Life Sciences from 1992-1996) and **Prof Birgit Lane FRSE FMedSci** (then Professor of Anatomy and Cell Biology, College of Life Sciences from 1990-2009) used a combination of candidate gene analysis and genome-wide genetic linkage analysis to show, for the first time, the linkage of keratin gene mutations with several severe skin disorders. This work was published in a succession of high impact publications (1-5). In 1993, mutations in keratin 5 and 14 were implicated by the Dundee team in the skin fragility syndrome Weber-Cockayne Epidermolysis Bullosa Simplex (EBS-WC), the mildest form of the EB keratinizing disorders (1). In 1995, they then described a null mutation in keratin 14 that results in severe epidermal blistering due the complete absence of keratin 14 expression (2). Profs Lane and McLean also discovered mutations in keratins 1 and 10 in bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis), an inherited condition that causes severe blistering and thickening of the skin (3). In a further study, McLean and Lane discovered a mutation in the gene for plectin, a cytoskeleton-membrane anchorage protein and showed that the absence of plectin protein in skin and muscle cells caused a combination of muscular dystrophy with epidermolysis bullosa (4).

A further skin disease that has been transformed by the work of the University of Dundee is pachyonychia congenita (PC). PC is an inherited skin disorder characterised by thickened toenails, calluses, blistering, thickened skin, and plantar pain. Plantar pain is the most important feature of PC affecting quality of life, as it can severely limit mobility. In 1995, a team involving McLean and Lane identified the first causative mutations for this disease in keratin genes 16 and 17 (5). Identification of pathogenic mutations in these genes, and the subsequent discovery of additional mutations in keratins 6A and 6B, was pivotal in establishing genetic testing as the key criteria for diagnosis of PC.

More recent work by McLean (appointed as Prof of Human Genetics at the College of Life Sciences in 2008) has focused on the development of therapeutic siRNAs for genetic disorders in a variety of cell and animal models (6) and this has resulted in the first skin disease siRNA clinical trial (for PC).

3. References to the research (indicative maximum of six references)
Publications:

1. Rugg, E.L., Morley, S.M., Smith, F.J., Boxer, M., Tidman, M.J., Navsaria, H., Leigh, I.M. and **Lane, E.B.** (1993) Missing links: Weber-Cockayne keratin mutations implicate the L12 linker domain in effective cytoskeleton function. Nat Genet. *5*, 294-300. (doi:10.1038/ng1193-294). (Citations 64, Scopus Nov 2013).

2. Rugg, E.L., **McLean, W.H.I.**, **Lane, E.B.,** Pitera, R., McMillan, J.R., Dopping-Hepenstal, P.J., Navsaria, H.A., Leigh, I.M. and Eady, R.A.J (1994). A functional 'knock-out' of human keratin 14. Gen. Dev. *8*, 2563-2573. (doi:10.1101/gad.8.21.2563) (Citations 109, Scopus Nov 2013).

3. **McLean, W.H.I.**, Eady, R.A.J., Dopping-Heppenstal, P.J.C., McMillan, J.R., Leigh, I.M., Navsaria, H.A., Higgins, C., Harper, J.I., Paige, D.G., Morley, S.M., and **Lane, E.B.** (1994) Mutations in the rod 1A domain of keratins 1 and 10 in bullous congenital ichthyosiform erythroderma (BCIE). J. Invest.Dermatol. *102*, 24-30. (doi:10.1111/1523-1747.ep12371726) (Citations 65, Scopus Nov 2013).

4. Smith, F.J.D, Eady, R.A.J, Leigh, I.M., McMillan, J.R., Rugg, E.L., Kelsell, D.P., Bryant, S.P., Spurr, N.K., Geddes, J.F., Kirtschig, G., Milana, G., de Bono, A.G., Owaribe, K., Wiche, G., Pulkkinen, L., Uitto, J., **McLean, W.H.I** and **Lane, E.B**. (1996) Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. Nat. Genet. *13*, 450-7 (doi:10.1038/ng0896-450) (Citations 251, Scopus Nov 2013).

5. **McLean, W.H.I.**, Rugg, E.L., Lunny, D.P., Morley, S.M., **Lane, E.B.**, Swensson, O., Dopping-Hepenstal, P.J.C., Griffiths, W.A.D., Eady, R.A.J., Higgins, C., Navsaria, H.A., Leigh, I.M., Strachan, T., Kunkeler, L., and Munro, C.S. (1995) Keratin 16 and keratin 17 mutations cause pachyonychia congenita. Nat. Genet. *9*, 273-278 (doi:10.1038/ng0395-273) (Citations 209, Scopus Nov 2013).

6. Smith, F.J.D., Hickerson, R.P., Sayers J.M., Reeves, R.E., Contag, C.H., Leake, D., Kaspar, R.L., and **McLean, W.H.I.** (2008) Development of therapeutic siRNA for pachyonychia congentia. J. Invest. Dermatol. *128*, 50-58. (doi:10.1038/sj.jid.5701040) (Citations 34, Scopus Nov 2013).

4. Details of the impact (indicative maximum 750 words)

Beneficiaries:
Inherited genetic skin disease patients and their clinicians.

Benefits and impacts:
(a) New diagnostics for several genetic skin diseases.
(b) Significant contribution to international patient registry and support.
(c) Initiation of the first human clinical trial for siRNA therapy of pachyonychia congenita.

Background
The identification by the University of Dundee of many of the genes that underlie keratinizing disorders, such as Epidermolysis Bullosa (EB) and pachyonychia congenita (PC) has impacted on the diagnosis, clinical genetic management and support of patients and families with these disorders. Epidermolysis Bullosa can give rise to significant disability and is thought to affect 1 in 17,000 live births. Pachyonychia congenita is classified as an ultra-rare genetic skin disease but its effects on patients are profound, causing painful blistering and calluses on the feet, thickened nails and cysts.

Impacts:

Diagnosis

The major impact of this research has been to transform the diagnosis for several keratin disorders. Prior to the discovery of the genetic basis of these diseases, several clinical classification schemes were proposed. Unfortunately classifications by clinical criteria were hindered by significant variability of the phenotype, even within affected members of the same family. In the case of PC, the average general practitioner might only see one or two cases in an entire career. Failure to correctly diagnose keratin disorders due to the diversity in the clinical features often resulted in incorrect or inadequate treatment. The advent of mutational screening avoided the ambiguity of diagnosis, permitting classification of the subtype, as well as the providing the option for prenatal genetic diagnosis. Thus, while clinical diagnosis is important, genetic testing has transformed the ability to verify the patient's condition.

The UK Genetic Testing Network (UKGTN) advises the NHS on genetic testing and assesses whether providing a test is likely to be of benefit to patients. In 2003, as a direct result of the discovery of the causative mutations by the team in Dundee, UKGTN approved a genetic test for Epidermolysis Bullosa. As a consequence, the National Services Division of the NHS has funded a UK-wide genetic testing service for Epidermolysis Bullosa since 2007 (1). This genetic testing service is run in the NHS-Tayside Molecular Genetics Unit at Ninewells Hospital in Dundee, which has become the primary centre in the UK for genetic diagnosis for all keratin disorders. Over 200 individuals have been identified with Pachyonychia congentia by the genetic diagnosis service in Dundee over the REF assessment period (2). The University of Dundee also runs the international molecular diagnostic service for PC where state-of-the-art sequencing methodologies are used to identify causative mutations. In the case of PC, >1000 patients have been identified worldwide to date.

In addition to an earlier and more accurate diagnosis, a further impact of approved genetic diagnosis for these disorders has been the opportunity for disease prevention through pre-implantation diagnosis for couples concerned about transmitting an inherited disease to their children. Pre-implantation diagnosis detects a specific disease-causing genetic mutation within an embryo before it is transferred to the womb.

Genetic diagnosis of PC by the laboratory of Prof McLean was highlighted in the public domain in a recent episode of the Channel 4 show *Embarrassing Bodies* on 16th April 2012 (3).

Creation of international patient registry and patient support

Often in rare diseases, individuals are widely scattered throughout the world. As a consequence, little progress can be made on treatment. Research in Dundee has directly resulted in the creation of an approved patient registry, the International Pachyonychia Congenita Research registry (IPCRR). Established in 2004, the registry collects clinical and genetic data on patients with PC worldwide and is funded by the organisation Pachyonychia Congentia Project, a public charity, founded to support the development of treatments for PC (www.pachyonychia.org) (4). Patients have now been identified in over 50 countries with over 750 patients registering on the IPCRR during the REF assessment period (5). Genetic testing to confirm PC, genetic counselling and consultations with dermatologists specialising in keratin disorders are all coordinated by the PC project and are provided free of charge to patients internationally.

Clinical Trials

In 2006-2008, Prof McLean and his team made significant progress in the development of therapeutic siRNAs for PC. As a consequence of this and the creation of the PC research registry, the first clinical trial using siRNA for PC commenced in January 2008. Funded by the PC Project, this is the first phase 1b clinical trial for a skin condition and for specific silencing of a mutant gene to successfully demonstrate the clinical efficacy and safety of siRNA treatment (6).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. UK genetic diagnostic service for Epidermolysis Bullosa and other keratin disorders
   Molecular Genetic Laboratory, East of Scotland Regional Genetics Service
   http://humangenetics.org.uk

2. External corroboration can be obtained from the Director of the Pachyonychia Congenita Project.

3. *Embarrassing Bodies,* Channel 4
   http://www.channel4embarrassingillnesses.com/episodes/episode-guides/embarrassing-bodies-series-5/episode-7--brighton/excessive-skin-regrowth-on-feet/

4. International Pachyonychia Congenita Research registry (IPCRR)
   http://www.pachyonychia.org/patient_registry.php

5. http://www.pachyonychia1.org/GRAPHS/IPCRRGrowthCount.pdf

6. First clinical trial for a treatment for pachyonychia congentia
   Leachman, S,A., Hickerson, R.P., Schwartz ME, Bullough, E.E., Hutcherson, S.L., Boucher, K.M., Hansen, C.D., Eliason, M.J., Srivatsa, G.S., Kornbrust, D.J., Smith, F.J.D, McLean, W.H.I., Milstone, L.M., Kaspar, R.L. (2010) First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder. Mol Ther. *18*, 442-6 **ClinicalTrials.gov Identifier:** NCT00716014 http://clinicaltrials.gov/ct2/show/NCT00716014?term=pachyonychia&rank=1