Institution: University College London

Unit of Assessment: 5 - Biological Sciences

Title of case study: Healing chronic wounds with Nexagon

1. Summary of the impact

Professor David Becker and colleagues at UCL's Department of Anatomy (now Cell & Developmental Biology) identified the gap junction protein Connexin43 (Cx43) to be a new therapeutic target for wound healing. Becker then developed Nexagon™, a topically applied antisense gel that knocks down Cx43 production, and both accelerates the healing of acute wounds as well as stimulating healing in chronic wounds. He co-founded a company, CoDa Therapeutics, to develop this technology. The company has raised $42m in finance and has completed good manufacturing practice (GMP) manufacture, toxicity testing and Phase 1 safety trials for both skin and eye indications. It has recently completed both Phase 2a and 2b clinical trials for venous leg ulcers. Nexagon has been given approval for compassionate use on a number of occasions and, in 2009, Nexagon gel was granted Orphan Drug Designation by the Food and Drug Administration in the US for treatment of persistent epithelial defects of the eye.

2. Underpinning research

In 1994 David Becker obtained a Royal Society University Research Fellowship to investigate gap junction proteins, in collaboration with Colin Green (formerly UCL, currently University of Auckland). Initial findings of his research showed that the gap junction protein Cx43 normally down-regulates in wound edge keratinocytes and fibroblasts in the first 24 hours after wounding as they become migratory, but it increases in blood vessels in and around the wound site as they become inflamed and leaky.

Becker therefore tested the hypothesis that down-regulation of Cx43 would accelerate wound healing, and found this to be the case **[1, 2]**. Because of the obvious therapeutic relevance, the discoveries were covered by a series of patents (listed in Section 5 below) starting in 1999.

Becker and colleagues developed Nexagon, a topically-applied antisense gel that down-regulates Cx43 protein production and by this means accelerates the healing of acute wounds, reducing inflammation and scar formation.

Wound healing in diabetic patients is notoriously slow, and Becker and colleagues then showed that Cx43 was abnormally up-regulated at the edge of wounds in the streptozotocin-diabetic rat model. This abnormal Cx43 expression is responsible for the failure of wound-edge cells to migrate and close the wound. Becker showed that reducing the Cx43 expression using Nexagon restored healing rates to normal or better **[3]**.

Wellcome Trust (Catalyst Biomedica) provided seed funding for proof of concept studies with Nexagon (2001-3). Becker and Green then founded CoDa Therapeutics (NZ) Ltd in 2003. Three years later (2006) they co-founded CoDa Therapeutics, Inc, which is based in San Diego CA. Becker continued preclinical studies at UCL in collaboration with CoDa, and found that that biopsy samples from a wide variety of human chronic wound samples all have a striking over-expression of Cx43 protein over a wide area of the wound edge epidermis and dermis, which is likely to contribute to lack of migration and healing **[4, 6, 7]**.

3. References to the research

[1] Qiu C, Coutinho P, Frank S, Franke S, Law LY, Martin P, Green CR, Becker DL. Targeting connexin43 expression accelerates the rate of wound repair. Curr Biol. 2003 Sep 30;13(19):1697-703. http://dx.doi.org/10.1016/j.cub.2003.09.007

[2] Mori R, Power KT, Wang CM, Martin P, Becker DL. Acute downregulation of connexin43 at wound sites leads to a reduced inflammatory response, enhanced keratinocyte proliferation and wound fibroblast migration. J Cell Sci. 2006 Dec 15;119(Pt 24):5193-203. http://dx.doi.org/10.1242/jcs.03320

[3] Wang CM, Lincoln J, Cook JE, Becker DL. Abnormal connexin expression underlies delayed wound healing in diabetic skin. Diabetes. 2007 Nov;56(11):2809-17. http://dx.doi.org/10.2337/db07-0613

[4] Cronin M, Anderson PN, Cook JE, Green CR, Becker DL. Blocking connexin43 expression reduces inflammation and improves functional recovery after spinal cord injury. Mol Cell Neurosci. 2008 Oct;39(2):152-60. http://dx.doi.org/10.1016/j.mcn.2008.06.005

[5] Becker DL, Thrasivoulou C, Phillips AR. Connexins in wound healing; perspectives in diabetic patients. Biochim Biophys Acta. 2012 Aug;1818(8):2068-75. http://dx.doi.org/10.1016/j.bbamem.2011.11.017

[6] Mendoza-Naranjo A, Cormie P, Serrano AE, Wang CM, Thrasivoulou C, Sutcliffe JE, Gilmartin DJ, Tsui J, Serena TE, Phillips AR, Becker DL. Overexpression of the gap junction protein Cx43 as found in diabetic foot ulcers can retard fibroblast migration. Cell Biol Int. 2012 Jul;36(7):661-7. http://dx.doi.org/10.1042/CBI20110628

[7] Mendoza-Naranjo A, Cormie P, Serrano AE, Hu R, O'Neill S, Wang CM, Thrasivoulou C, Power KT, White A, Serena T, Phillips AR, Becker DL. Targeting Cx43 and N-cadherin, which are abnormally upregulated in venous leg ulcers, influences migration, adhesion and activation of Rho GTPases. PLoS One. 2012;7(5):e37374. http://dx.doi.org/10.1371/journal.pone.0037374

Peer reviewed grants that underpinned research:

- Catalyst Biomedica (Wellcome Trust 064024). Antisense connexins and wound healing £363,089 (2001-2003)
- AMRC Project grant AP 1055 – Diabetic wound healing £159,108 (2006-2009)
- BBSRC Industrial Case Studentships x2 £168,000 (2010-2014)
- BBSRC Pathfinder Follow on Fund £34,051 Novel target in wound healing. (2010)
- BBSRC Follow on Fund £153,000 Circadian clock and wound healing. (2011-2012)

Evidence of quality of the research:

Becker won the Nomura Award for Best Biotech Innovation at the Medical Futures Awards in 2003: http://www.medicalfutures.co.uk/2003.php

Becker was a BBSRC Innovator of the Year finalist in 2010: http://www.bbsrc.ac.uk/news/people-skills-training/2011/110125-f-profile-david-becker.aspx

4. Details of the impact

Most acute wounds heal without issue, but as we get older our bodies become compromised by poor blood circulation and conditions such as diabetes, leading to slower healing. This can result in stalled or hard-to-heal chronic wounds or ulcers. Currently about two per cent of the Western population develop a chronic leg or foot ulcer, and this figure will rise as the population ages and diabetes becomes more prevalent. Unfortunately a significant proportion of these chronic wounds fail to respond to conventional treatment and result in amputation of the lower limb. To date, there have been no effective therapeutic agents available to treat these wounds. A key feature of the Nexagon technology is that it is able to kick-start the healing of chronic wounds where healing has stalled, thus addressing a widespread unmet clinical need.

Commercial impacts: Coda Therapeutics

CoDa Therapeutics was founded in 2003 by Becker and Green to develop Nexagon technology. In October 2006 CoDa Therapeutics raised $23m in series A financing, and with this they completed GMP manufacture and toxicity testing. In July 2012 CoDa Therapeutics raised series B funding of about $38m for venous leg ulcer and diabetic foot ulcer trials.

CoDa Therapeutics has 11 Biotech team members in New Zealand, including five scientists based at the University of Auckland. There are around seven staff members at the San Diego site, from where clinical trials are organised **[a]**.

Thus far there are 11 patents relating to Nexagon at different stages of being granted worldwide and two more in preparation **[b]**.

Compassionate use of Nexagon:

In 2008, CoDa Therapeutics were given approval for compassionate use of Nexagon on an amputee patient with a below-the-knee wound that had not healed for 18 months. The patient was scheduled for amputation above the knee, but just two treatments with Nexagon, a week apart, triggered healing and saved his leg from further amputation.

Nexagon has also been granted compassionate use approval from the New Zealand regulatory authorities for treatment of persistent epithelial defects following corneal burns. So far Nexagon treatment has saved the eyes of over a dozen people when given for compassionate use **[c]**.

Orphan drug designation:

In 2009, CoDa Therapeutics were awarded FDA Orphan Drug designation for Nexagon for treatment of persistent epithelial defects (PED) following corneal burns. Orphan Drug Designation entitles CoDa to seven years of market exclusivity in the treatment of PED patients in the event of market approval for this indication **[d]**.

Results of clinical trials with Nexagon:

Clinical trials with Nexagon were started in 2008. Nexagon successfully completed Phase 1 safety trials for both skin (NCT00736593) and eye (NCT00654550) indications. In the Phase 1 trial for skin wounds, Nexagon was found to be safe and well-tolerated following administration to 43 healthy volunteers given punch biopsy wounds. Phase 2 trials are now in progress or completed for both skin and eye indications.

Nexagon has also shown positive results in Phase 2a and 2b clinical trials for venous leg ulcers, treated by a topical once-weekly application. The 98-patient Phase 2a clinical trial of Nexagon (NCT00820196) showed that venous leg ulcers treated with Nexagon healed five times faster than the current standard of care, with 31% healing completely within four weeks, compared to 6% with the current standard of care **[e]**. One participant in this study, who had suffered from debilitating leg ulcers for three years, described this trial as "*the answer to my prayers… I tried everything possible and this is the only thing that worked*" **[f]**.

The 300-patient randomised, vehicle-controlled, double-blind Phase 2b trial (NCT01199588) was completed in December 2012 and showed Nexagon was both safe, and showed an increase in complete healing of leg ulcers. CoDa is preparing a paper describing the results of this trial that will be submitted to a peer-reviewed medical journal.

A Phase 2 double-blind randomised vehicle-controlled clinical trial to investigate the safety and clinical effect of Nexagon as a topical treatment for subjects with a diabetic foot ulcer (DUNE; NCT01490879) was started in July 2012, and expects to enrol 160 patients and complete in August 2013.

Persistent Corneal Epithelial Defects occur following corneal damage, particularly burns or chemical damage, when healing of the cornea does not occur and eyesight is often lost. An efficacy and safety double-blinded study of Nexagon for Persistent Corneal Epithelial Defects (NCT01165450) started in November 2011, and is due for completion in October 2014. It is being run by Dr B Jeng, University of California, San Francisco and expects to enrol 72 patients.

Media coverage

Nexagon has received international media coverage due to its wide potential importance **[g]**.

5. Sources to corroborate the impact

[a] http://www.codatherapeutics.com/index.html

[b] Patent applications, granted and pending. All available on request.

- D.L. Becker and C.R. Green. Patents filed relating to formulations for use in therapeutic and/or cosmetic treatments particularly those in which localized disruption in direct cell to cell communication is possible (1999). New Zealand NZ500190, PCT No. WO 00/44409 USA No. PCT/GB00/00238
- D.L. Becker and C.R. Green. Formulations comprising antisense nucleotides to connexins. New Zealand patent 513154 awarded 2004, Australia 21193, USA09/890363, Canada 2361251, Europe 901236 and Japan 00/595711.
- CoDa Therapeutics NZ (Ltd); WO/2005/053600 Antisense compounds targeted to connexins and methods of use thereof.
- D.L. Becker and C. Thrasivoulou; GB0611356.78-6-6 Imaging method and apparatus. Multiphoton second harmonic imaging for defining the borders of skin cancers.
- D.L. Becker 11-12-2006 Treatment of chronic wounds with formulations comprising antisense nucleotides to connexins. United states provisional application No.: 60/874,404
- D.L. Becker, C.R. Green and B.J. Duft; WO/2008/060622A2; Methods and compositions for wound healing and tissue repair.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/085270A2; Use of inhibitors of connexin43 for treatment of Fibrotic conditions.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/085269A2; Use of anti-connexin polynucleotides, peptides or antibodies for the treatment of orthopedic conditions.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/085277A2; Use of anti-connexin 43 polynucleotides for the treatment of abnormal or excessive scars.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/085272A2; Improved medical devices.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/085273A2; Use of anti-connexin polynucleotides for the treatment of surgical adhesions.
- D.L. Becker, C.R. Green and B.J. Duft; WO/2009/075881A3; Impaired wound healing compositions and treatments.

[c] http://www.auckland.ac.nz/webdav/site/central/shared/for/the-media/publications/Auckland%20Now/Auckland%20Now%20Issue%208.pdf (See p.5)

[d] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=279609

[e] http://www.codatherapeutics.com/news-nexagon.html

[f] Article describing patient's positive experience of taking part in the trial: http://usatoday30.usatoday.com/news/health/2010-08-14-wounded-heal_N.htm

[g] Example of press coverage: http://www.huffingtonpost.com/2010/08/12/nexagon-new-gel-could-spe_n_679753.html