Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Gene therapy for immunodeficiency diseases

1. Summary of the impact

Research at the UCL Institute of Child Health (ICH) has led to the successful treatment of children with primary immunodeficiency diseases for whom there was little chance of "cure" by the only other possible means: haematopoietic stem cell transplantation (HSCT). Beginning in 2002, we have treated 32 patients with four different primary immunodeficiency disorders. In total we have treated 12 patients with severe combined immunodeficiency (SCID-X1), 13 patients with adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID), 5 patients with chronic granulomatous disease (CGD) and 2 patients with Wiskott-Aldrich syndrome (WAS). Most of the patients have been successfully treated and are at home, off all therapy. We are now starting to develop this technology to treat a wider range of related disorders.

2. Underpinning research

Primary immunodeficiency disorders are a heterogeneous group of rare, inherited diseases, where children are born with defective immune systems. In the most severe forms children are unable to fight off even very mild infections and, without treatment, will usually die within the first 2 years of life.

With the discovery of the causative genes for several primary immunodeficiencies by our group and others came the possibility of developing new and improved forms of treatment for these life-threatening diseases **[1]**. Although earlier clinical trials of gene therapy had been conducted, these had been largely unsuccessful.

Our strategy was to develop efficient methods for introducing therapeutic genes into haematopoietic stem cells (HSCs). To this end we developed gammaretroviral vectors to transduce HSCs, using technology that we had developed in-house (selection of HSCs using anti-CD34 monoclonal antibodies and novel vectors). Using CGD as a model disorder, we showed functional correction of the defect in in vitro models **[2]**. At the same time we developed immunodeficient mouse models for testing functional correction in vivo. By 2000 we had developed gammaretroviral vectors that were capable of delivering therapeutic genes under the control of constitutive viral promoters that could transduce HSCs with high efficiency and which could be used for clinical trials of gene therapy **[3]**.

Following scale-up of these methods we initiated our first clinical trial of gene therapy for SCID-X1, followed by clinical trials for ADA-SCID and CGD using gammaretroviral vectors in the early 2000s. By measuring the quantity and quality of immune reconstitution using cellular and molecular techniques we evaluated the success of these treatments, comparing them to the only other alternative, HSCT. We have also analysed these patients using novel molecular methods for investigating and mapping gene integration sites to assess the efficiency of transduction **[4, 5]**.

Overall these clinical trials have been judged to be largely successful. However, following the development of a T-cell leukaemia-like disease in 4 of 10 SCID-X1 patients in a French clinical trial, there were concerns regarding the safety profile of the use of gammaretroviral vectors. Of these patients 3 were successfully treated by chemotherapy and HSCT while unfortunately 1 patient died. One of our patients was similarly affected but responded to chemotherapy treatment. These studies demonstrated that while gene correction of autologous HSCs was highly effective, the use of gammaretroviral vectors utilising the viral promoter had a finite risk of insertional mutagenesis **[6]**.

Further research has shown that relatively simple modifications to design, such as the use of self-

inactivating (SIN) vectors in which viral promoters are deleted and transcription is under the control of an internal mammalian promoter, may significantly improve safety **[7]**. To this end, we have developed new SIN gammaretroviral vectors which incorporate additional safety features, including self-inactivation and tissue specific promoters, and we have also developed SIN lentiviral vectors based on HIV. Current clinical trials using these new vectors are being conducted for SCID-X1, ADA-SCID, CGD and WAS.

3. References to the research

[1] Vetrie D, Vorechovský I, Sideras P, Holland J, Davies A, Flinter F, Hammarström L, Kinnon C, Levinsky R, Bobrow M, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993 Jan 21;361(6409):226-33. http://dx.doi.org/10.1038/361226a0

[2] Thrasher AJ, Casimir CM, Kinnon C, Morgan G, Segal AW, Levinsky RJ. Gene transfer to primary chronic granulomatous disease monocytes. Lancet. 1995 Jul 8;346(8967):92-3. http://dx.doi.org/10.1016/S0140-6736(95)92116-8

[3] Demaison C, Brouns G, Blundell MP, Goldman JP, Levinsky RJ, Grez M, Kinnon C, Thrasher AJ. A defined window for efficient gene marking of severe combined immunodeficient-repopulating cells using a gibbon ape leukemia virus-pseudotyped retroviral vector. Hum Gene Ther. 2000 Jan 1;11(1):91-100. http://dx.doi.org/10.1089/10430340050016184

[4] Gaspar HB, Parsley KL, Howe S, King D, Gilmour KC, Sinclair J, Brouns G, Schmidt M, Von Kalle C, Barington T, Jakobsen MA, Christensen HO, Al Ghonaium A, White HN, Smith JL, Levinsky RJ, Ali RR, Kinnon C, Thrasher AJ. Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. Lancet. 2004 Dec 18-31;364(9452):2181-7. http://dx.doi.org/10.1016/S0140-6736(04)17590-9

[5] Gaspar HB, Bjorkegren E, Parsley K, Gilmour KC, King D, Sinclair J, Zhang F, Giannakopoulos A, Adams S, Fairbanks LD, Gaspar J, Henderson L, Xu-Bayford JH, Davies EG, Veys PA, Kinnon C, Thrasher AJ. Successful reconstitution of immunity in ADA-SCID by stem cell gene therapy following cessation of PEG-ADA and use of mild preconditioning. Mol Ther. 2006 Oct;14(4):505-13. http://dx.doi.org/10.1016/j.ymthe.2006.06.007

[6] Howe SJ, Mansour MR, Schwarzwaelder K, Bartholomae C, Hubank M, Kempski H, Brugman MH, Pike-Overzet K, Chatters SJ, de Ridder D, Gilmour KC, Adams S, Thornhill SI, Parsley KL, Staal FJ, Gale RE, Linch DC, Bayford J, Brown L, Quaye M, Kinnon C, Ancliff P, Webb DK, Schmidt M, von Kalle C, Gaspar HB, Thrasher AJ. Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. J Clin Invest. 2008 Sep;118(9):3143-50. http://dx.doi.org/10.1172/JCI35798

[7] Thornhill SI, Schambach A, Howe SJ, Ulaganathan M, Grassman E, Williams D, Schiedlmeier B, Sebire NJ, Gaspar HB, Kinnon C, Baum C, Thrasher AJ. Self-inactivating gammaretroviral vectors for gene therapy of X-linked severe combined immunodeficiency. Mol Ther. 2008 Mar;16(3):590-8. http://dx.doi.org/10.1038/sj.mt.6300393

Selected research grant support

Wellcome Trust Senior Fellowship in Clinical Science. Development of novel therapeutic approaches for primary immunodeficiency. 1999-2014. Over £4 million. Thrasher

Department of Health. Clinical trials of gene therapy for primary immunodeficiency. 2005-10. £1,033,723. Thrasher, Kinnon & Gaspar

MRC Project Grant. Clinical trial of self-inactivating vectors for gene therapy of X-linked severe combined immunodeficiency (SCID-X1). 2006-12. £727,647. Thrasher & Gaspar

4. Details of the impact

Impact on patients

The majority of our patients are well and off all prophylactic therapy. One SCID-X1 patient who was atypical (adolescent at time of treatment and had previously undergone HSCT, which was failing) was treated on compassionate grounds, but did not reconstitute. As discussed, we have had one serious adverse event (leukaemia). This patient was successfully treated by chemotherapy and HSCT **[a]**.

The only alternative treatment for our patients would have been HSCT. Many patients who have undergone this treatment suffer from additional complications such as long-term effects related to chemotherapy, usually with alkylating agents (e.g. lack of growth, compromised fertility, secondary malignancy, hearing loss, hypodontia). Our recent study suggests a high incidence of cognitive and behavioural abnormalities in SCID patients following HSCT. Since many of our gene therapy patients have not received chemotherapy we can reasonably expect to see a reduction in the appearance of such debilitating side effects and a consequent improved quality of life compared to patients who have had chemotherapy.

One parent whose child underwent gene therapy said:

> "*Guy is now doing brilliantly; he can do all of the things his friends can do and more. He is able to play football and ride a pony. He wouldn't be here if it wasn't for the option of gene therapy treatment. We are incredibly grateful to the whole team at Great Ormond Street Hospital, but especially Adrian Thrasher and Bobby Gaspar who pioneered this work. To other parents who find themselves in our situation we would say 'go for it'*" **[b]**.

Economic benefits

The cost of gene therapy compared to the only other comparable treatment, HSCT, is reduced because the patient has a significantly shorter stay in hospital (4-6 weeks for gene therapy compared to 8 weeks on average for HSCT). The cost of enzyme replacement for ADA-SCID is estimated at £350,000 p.a. minimum cost for the life-time of a patient. A significant number of our patients are now off enzyme replacement treatment, with gene therapy thus offering an overall total cost saving of £5 million to date.

Input into guidelines and policy

Gaspar has been Chairman of the BMT and Gene Therapy Working Party of European Society for Immunodeficiencies (ESID), Chairman of the Inborn Errors Working Party of the European Blood and Marrow Transplantation Society (EBMT). He has been involved in developing the current guidelines for the treatment of PIDs **[c, d]**. In 2006 we contributed to the European Primary Immunodeficiency Consensus Conference and their guidelines, which are still current **[e]**.

Thrasher has acted in an advisory capacity to the US Recombinant DNA Advisory Committee (RAC), the US Federal Drugs Administration (FDA), the UK Gene Therapy Advisory Committee (GTAC) **[f]**, the Medicines Control Agency (MCA) and the European Medicines Evaluation Agency (EMEA).

Public engagement

We have worked extensively with national and international patients' groups including the Primary Immunodeficiency Association (PIA) **[g]**, the CGD Society, the International Patient Organisation for Primary Immunodeficiency (IPOPI) and Rare Disease UK **[h]**. This has included speaking at their meetings and contributing to newsletters. For example, Gaspar is Chairman of the IPOPI Medical Advisory panel and is a member of the advisory panels for PID-UK and the Ataxia Telangiectasia society.

We have publicised our work to the general public through our interactions with the GOSH

Children's Charity fundraising work, through talks, films and other promotional material. We have also worked closely with the Jeans for Genes Campaign in schools and at other fundraising events, speaking and appearing in films to raise awareness of our work. Our work has been presented as part of a living exhibition to promote the public understanding of science. The exhibition, "Health Matters", has been on continuous display in the Science Museum throughout the 2008-13 period. Our work also appears as part of a science exhibition at Bristol Museum.

We have worked extensively with the media to publicise our work. We have promoted our research through films, newspapers and television, including BBC News, Newsnight and Radio 4, ITN News and Channel 4 News and also in numerous scientific documentaries, including BBC Horizon **[i]**. We have worked with the Science Media Centre in educating journalists about our work.

We are very active in scientific societies which relate to our work such as the British Society for Gene and Cell Therapy (BSGCT). Thrasher has recently retired as the President of the BSGCT, and has organised education days for junior scientists and the general public. We are hosting at tent at the forthcoming Bloomsbury Festival to showcase our work. We have talked about our work in schools, to students of all ages from primary through to 'A' Level students. We have hosted school children to visit our labs and to hear presentations on our work. We offer one week work experience placements to students in our labs on a biannual basis.

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

[a] Patient data can be verified by Senior Consultant Immunologist, Chair of Research Governance Advisory Committee, GOSH. Contact details provided.

[b] Patient testimonies available from Senior Press Officer, Great Ormond Street Hospital. Contact details provided.

[c] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766674/?tool=pubmed

[d] http://www.esid.org/downloads/BMT_Guidelines_2011.pdf

[e] http://ec.europa.eu/health/ph_projects/2005/action1/docs/action1_2005_frep_01_en.pdf

[f] Corroboration can be obtained from former Chair of the Gene Therapy Advisory Committee (GTAC). Contact details provided.

[g] Letter of testimony from David Webster, past Chairman of Trustees of the Primary Immunodeficiency Association available on request.

[h] Corroborating testimony as to our work with patient groups can be obtained from the Chronic Granulomatous Disease Society (CGD Society). Contact details provided.

[i] Media coverage:

- 2011 article marking 10 years since the boy received treatment : http://bbc.in/pqXemq
- http://www.bbc.co.uk/news/health-11451810
- http://www.bbc.co.uk/news/health-17209287
- http://www.channel4.com/news/has-a-cure-been-found-for-boy-in-the-bubble-syndrome 2011 report on overall trial results and Science Translational Medicine paper
- http://www.gosh.org/gen/news/latest-news/2011-archive/gene-therapy-success-for-children-born-without-functioning-immune-system/
- YouTube video discussing the Science Translational Medicine paper http://www.youtube.com/watch?v=3IGKoh6-o7I [578 views at 22 Sep 2013]
- YouTube video 'Rhys' story - a Genetic Disorders UK / Jeans for Genes Day film' http://www.youtube.com/watch?v=8fcXB0cf9DU [10,529 views at 22 Sep 2013]