Institution: The University of Edinburgh

Unit of Assessment: UoA5: Biological Sciences

Title of case study:

12. Prospect of a cure for Rett syndrome has driven the formation of a charity and underpins new clinical trials.

1. Summary of the impact

Impact on society (non-profit organisations) and public attitudes: The discovery of the reversibility of Rett syndrome in a mouse model for the disease has changed attitudes and awareness amongst families of sufferers and has led directly to the formation of two new charities: the Rett Syndrome Research Trust (US) and ReverseRett (UK).

Impact on health and welfare: Two new clinical interventions are being trialled with Rett syndrome patients.

Beneficiaries: Families living with Rett syndrome worldwide.

Significance and Reach: The research has given hope to thousands of families world-wide and has prompted an active philanthropic drive to fund research into a cure based on the UoE findings. The RSRT has raised $15 million since 2008. The incidence of Rett syndrome is 1 in 10,000 females. Some 16,000 individuals have Rett syndrome in the USA, and an estimated 2,400 in the UK.

Attribution: The research was carried out at UoE led by Adrian Bird. The critical underpinning paper was the UoE demonstration of reversibility (2007).

2. Underpinning research

DNA methylation is a post-synthetic modification of DNA that does not alter its coding potential but affects the activity of genes. Methylation sites occur predominantly at the cytosine in CpG (cytosine-phosphate-guanine) dinucleotides that are mainly located in CpG islands (CGIs) near gene promoters. CGIs are not usually methylated, unlike the bulk of the genome; however if methylation of the CGIs occurs, transcription of the related gene is almost always silenced.

Adrian Bird and his team at UoE discovered the methyl CpG binding protein 2 (MeCP2) and in 1997 showed that it can act as a transcriptional repressor [1]. The clinical significance of the MeCP2 protein was made clear in 1999 when a group working in the USA [Amir et al. (1999) *Nature Genetics* 23, 185–188] showed that many mutations in the *MeCP2* gene are associated with the autism spectrum disorder Rett syndrome. This syndrome is a single gene disorder with the mutated MeCP2 protein the cause of pathology. In 2001 the Bird group developed a mouse model for Rett syndrome by introducing a mutation into the mouse *MeCP2* gene [2]. Heterozygous female mice carrying this mutation had behavioural characteristics similar to those of girls with Rett syndrome, including poor motor coordination, behavioural deficits, breathing arrhythmia and, in males, early death. This mouse model is currently used in hundreds of labs across the world in Rett syndrome research.

In 2007 the Bird group introduced a new modified version of the *MeCP2* gene into their Rett syndrome mouse model. This allowed controlled expression of normal MeCP2 protein. Mutant female mice carrying this modified gene exhibited the characteristics of Rett syndrome until normal MeCP2 expression was activated, after which they rapidly regained normal behaviour [3]. This striking result indicated that Rett syndrome is not an irreversible developmental or degenerative disease, and overturned previous understanding of the disease. It is this dramatic result, building on the underlying research elucidating the function of MeCP2 that has led to the impact described.

Key personnel, all at UoE: Professor Adrian Bird (1990-present); Xinsheng Nan, PDRA (1991-1998) and (2004-2005); Javier Campoy, PDRA (1992-1995); Jacky Guy, PDRA (1997-present); Brian Hendrich, PDRA (1994-2001); Jim Selfridge, PDRA (2000-present). Others contributing to the research were medical researchers Megan Holmes (University of Edinburgh) [2] and Jian Gan

and Stuart Cobb (University of Edinburgh) [3].

3. References to the research

1. Nan, X., Campoy, F.J., and Bird, A. (1997). MeCP2 is a transcriptional repressor with abundant binding sites in genomic chromatin. *Cell* **88**, 471-481. *doi*:10.1016/S0092-8674(00)81887-5

   595 Scopus citations on 19/09/2013

2. Guy, J., Hendrich, B., Holmes, M., Martin, J.E., and Bird, A. (2001). A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. *Nature Genetics* **27**, 322 - 604 (2001). doi:10.1038/85899

   573 Scopus citations on 19/09/2013

3. Guy, J., Gan, J., Selfridge, J., Cobb, S., and Bird, A. (2007). Reversal of neurological defects in a mouse model of Rett syndrome. *Science* **315**, 1143-1147. DOI: 10.1126/science.1138389

   305 Scopus citations on 19/09/2013

4. Details of the impact

Rett syndrome is a severe autistic-spectrum disorder with delayed onset that affects 1 in 10,000 girls. It is a childhood-onset regressive disease that causes loss of speech and hand movement, coupled with autistic behaviour, microencephaly, and growth retardation. In most cases the disease is due to mutations in the gene coding for MeCP2. Affected females carry a single copy of the mutation, they are heterozygous. Males that inherit a mutant gene almost always die. Affected girls develop normally for around 18 months then regress, losing abilities they once had and requiring increasing levels of care as they age. Rett syndrome was believed to be a developmental or neurodegenerative disease because of its early onset and the gradual deterioration of those affected. A cure or therapy was thought to be most unlikely and Rett charities focussed on family support; the care given to sufferers was palliative.

In 2007 UoE researchers published the landmark paper that established the principle of reversibility for Rett syndrome even in late stages of the disease [3]. This work was immediately featured widely in communications amongst Rett syndrome support groups and infused Rett families with hope and urgency. For the first time the focus was switched from symptom management to the realistic hope of finding a cure for Rett syndrome.

The work of a charity has been substantially influenced by this research:

As a direct result of the 2007 results, a small group of parents of children with Rett syndrome, led by Monica Coenraads, formed the **Rett Syndrome Research Trust** (RSRT), a highly efficient non-profit charity devoted to finding a cure for Rett Syndrome [a, b]. The RSRT was established purely because these parents believed there was now a real prospect of a cure for Rett syndrome. Monica Coenraads states:

> *"The elegant execution of Professor Bird's experiment and the unexpected results has forever changed the way Rett Syndrome is perceived. No longer confined to symptom management, it is now realistic and urgent to focus on a cure. I formed the Rett Syndrome Research Trust to pursue the vital next steps from this milestone".*

The RSRT was launched in September 2008 and has so far raised over $15M, 93% of which has been committed to funding research projects seeking to cure Rett Syndrome. Adrian Bird is a trustee of the RSRT and sits on their scientific advisory board. As such, he has influenced the practice and policy-making of the charity. The RSRT seeks to identify, evaluate and prioritise novel and ambitious research projects. It is an example of venture philanthropy, which is becoming an engine for innovation in biomedical research. Venture philanthropies are adopting the techniques of venture capital finance and the strategies of business management to build networks of scientists to work through early findings and develop promising ideas for new experiments. The RSRT is a member of The Research Acceleration and Innovation Network (TRAIN), a group of 55 unique non-profit foundations created by patients and their families. These are organisations with a

singular focus on, and a significant stake in, getting promising therapies from the laboratory bench to the patient's bedside as rapidly as possible.

In July 2010, the UK charity '**ReverseRett**' (originally RSRT-UK) was formed in collaboration with RSRT by families across the UK who wanted to contribute to RSRT's efforts to accelerate treatments for Rett Syndrome [c,d]. Two 'Reverse Rett' London Gala Fundraisers, in 2010 and 2011, addressed by Adrian Bird, raised a total of £425,000. The charity won the **'Best New Charity'** Award at the UK Just Giving Awards in March 2012.

The UK charity has raised a total of £1.5M since 2010 and 95% of all funds generated have been delivered to support RSRT's research projects. The charity now uses the name 'ReverseRett' to emphasise the prospects which arise from the underpinning research. The charity succinctly demonstrates the impacts of UoE research on the families living with Rett Syndrome with its statement:

> *"For families living with Rett syndrome, the prognosis has always been poor until the reversal experiments of 2007 catapulted the disorder into new realms of possibility, positioning Rett Syndrome to become the world's first curable brain disorder. We believe that Rett Syndrome is reversible. Everything we do every day stems from this belief".*

Public debate has been stimulated or informed, and the awareness, attitudes and understanding of sections of public have been informed by the research:

The RSRT launched a campaign in November 2011 to boost awareness of Rett syndrome and the possibility of a cure presented by the UoE research. Their public service announcement ran in Times Square, New York for three months and it is estimated that 1.5 million people per day, viewed the 6000 square foot display. This powerful campaign, showing that Rett Syndrome is curable, has increased the public awareness of Rett syndrome [a,e].

A documentary film that has increased awareness of Rett syndrome, '**RETT: there is hope**' [f], was recently honoured with a Rising Star Award by the 2012 Canada International Film Festival and won the Awareness Film Festival, USA, in 2012. It has also been selected for the New Hope, We Care (India), DC Independent, Culture Unplugged and Focus film festivals. Filmmaker Jason Rem was inspired to make the documentary, which features the UoE research, after attending an RSRT charity event. Rem says:

> *"The goal of the film is solely to assist fundraising efforts to help bring about a cure as soon as possible".*

The UoE research has given hope to thousands of families world-wide that there is a cure for Rett Syndrome where previously there was none. Rett syndrome is also connected to other genetically complex disorders, such as autism. The transformational results of this research influenced the international neuroscience community to re-evaluate their approach to research in this overall area [e.g. Silva AJ & Ehringer, D. *Adult reversal of cognitive phenotypes in neurodevelopmental disorders.* J Neurodev Disord. 2009 Jun; 1(2):150-7]. Interviewed in the February 2012 edition of BioWorld Insight, Monica Coenraads traced the realisation that developmental disorders do not necessarily mean a lifetime of disability to the 2007 reversal of Rett syndrome in a mouse model [a, g]. She stated:

> *"It changed the perspective, not just for Rett syndrome, but for other developmental disorders".*

Impact on health: new clinical interventions are being trialled with patients with funding from RSRT

The RSRT has committed to funding drug trials to treat Rett Syndrome. A two-centre Phase 2 clinical trial of Copaxone, an immunomodulator drug, is being carried out by Children's Hospital at Montefiore, Bronx, USA and at the Sheba Medical Center in Ramat Gan, Israel. It is currently recruiting twenty patients. This trial marks the beginning of a trend toward drug treatments seeking to modify the underlying mechanisms of neurological dysfunction in Rett syndrome, rather than just

treat symptoms, and our research [3] is cited as underpinning this rationale [h]. In a separate development, Children's Hospital Boston commenced a Phase 2 clinical trial of Insulin-like Growth Factor-1 (IGF-1) in January 2013 with thirty girls with Rett syndrome [i]. IGF-1 is indirectly regulated by MeCP2 and has been shown to ameliorate several features of Rett-like disease in mice. Our research [3] is referenced as underpinning the rationale behind this clinical trial [i,j]

5. Sources to corroborate the impact

The Tiny URLs provide a link to archived web content, which should be accessed if the original web site links don't work

a) Corroboration for the influence and impact of the UoE research on the formation of the US charity and its aims can be provided by the founder and Executive Director of RSRT

b) RSRT charity website which has extensive references to UoE research: http://www.rsrt.org/ or http://tinyurl.com/pkxmvw2

c) Corroboration for the influence and impact of the UoE research on the formation of the UK charity and its aims can be provided by the founder and Executive Director of ReverseRett (RSRT-UK).

d) ReverseRett UK charity website: http://www.reverserett.org.uk/ or http://tinyurl.com/p84zer4

e) Details of RSRT awareness campaign: http://www.rsrt.org/about-rsrt/press-releases/rett-syndrome-research-trust-launches-awareness-campaign-in-iconic-times-square-location/ or http://tinyurl.com/oo2wrk3

f) Details of 'RETT: there is hope' documentary: http://www.rsrt.org/about-rsrt/press-releases/new-documentary-on-rett-syndrome-released/ or http://tinyurl.com/qc3vkhn

g) BioWorld Insight interview describing the influence of the research on the RSRT aims and the wider impact on the view of neurological disorders and treatments http://rettsyndrome.files.wordpress.com/2012/02/bioworld.pdf or available on request

h) Copaxone Clinical Trial: http://www.einstein.yu.edu/departments/neurology/clinical-research-program/rett/Clinical_Trials_Research.aspx or available on request

i) IGF-1 Clinical Trial Press release: http://www.prnewswire.com/news-releases/clinical-trial-for-rett-syndrome-launched-112027039.html or available on request

j) IGF-1 Clinical Trial: http://clinicaltrials.gov/ct2/show/NCT01777542?term=rett+syndrome&rank=3 or available on request