Institution: BRUNEL UNIVERSITY (H0113)

Unit of Assessment: 3 – Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Engaging with Premature Ageing: Families, Community and Society

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

The Progeria Research Team at Brunel has been researching Progeria for over 10 years. Interestingly, they have close contact with Progeria families and support them by helping parents make decisions about drug treatments available in clinical trials and providing scientific information about the disease and the team's research. The Progeria research has allowed the team to engage directly and positively with individuals and communities that raise money and awareness for Progeria research in interesting and entertaining ways. The team have raised public understanding and awareness of Progeria locally, nationally and globally. This has been done directly, and also by facilitating the production of a film and a TV programme about the disease.

2. Underpinning research (indicative maximum 500 words)

Drs Kill (Senior Lecturer) and Bridger (Reader) brought Progeria research back to the UK in 2002 by combining their expertise to work on the premature ageing disease when it was discovered that Progeria was caused by a mutation in lamin A, a protein in the cell nucleus. This resulted in a seminal publication in 2004 (cited 92). The data showed that Progeria cells behaved differently from what was expected and help explain why the children age so rapidly. Based on this research and the interest it generated, the team has expanded with 4 more group leaders being incorporated into the team (Drs Eskiw, Makarov, Tree, Vagnarelli), with 8 PhD students and a fully funded post-doctoral scientist (Clements) analysing the effect of different drugs on Progeria cells. Brunel's research into Progeria spans from the control of individual gene expression to a whole organism model for Progeria; from basic understanding to developing a cure.

The research has been funded by the Brunel Progeria Research Fund (established 2003), the US Progeria Research Foundation and the children's medical research charity Sparks. The team have published 10 articles describing a Drosophila model of Progeria (2008), how Progeria cells are hyperproliferative and surcumb to suicide (2004, 2007), how the genome does not behave properly in Progeria nuclei (2005, 2007, 2011), that structures are aberrant in Progeria cells (2007, 2008, 2010) and how this is corrected by a drug in the US clinical trial (2010, 2011). There are 5 manuscripts in preparation on gene expression changes in Progeria, how the gene is regulated and the behaviour of stem cell populations in the fly model. Unpublished data from these studies has been presented at national and international conferences (2013, 2012, 2009).

The research remit of the team is to understand the basic biology of Progeria, test the safety and efficacy of drugs, identify and develop new treatments and work towards a cure. The team has on-going successful projects that address all these aspects of their vision.

The work funded by Sparks recapitulates *in vitro* on-going and current proposed drug trials. There are already very interesting results that have been disseminated to researchers at the 6th Nuclear Envelope and Chromatin Organisation meeting held at Brunel, September 2013, showing Pravastatin as a drug that has positive benefits on Progeria cells. Other data have the potential to alter on-going drug trials. Research from Kill and Makarov groups promise a cure to Progeria by understanding how the toxic protein in Progeria can be degraded by the cell or by controlling the expression of the toxic protein, presented in 2013 to clinicians, families and researchers. Our Progeria research has impact on the study and treatment of normal ageing since Progeria arguably is the best model for normal ageing. Progress in this field also has value for the future treatment of conditions such as cancer since many cancers have Progeria lamin A. Understanding the basic biology of the ageing process supports the strategic aim of UK Research Councils, the European Commission and the National Institute for Aging in the USA.

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

1) Bridger J.M. and Kill I.R. (2004) Ageing of Hutchinson-Gilford Progeria Syndrome fibroblasts is characterised by hyperproliferation and increased apoptosis. *Experimental Gerontology* 39 717-724.
2) Farnesyltransferase inhibitor treatment restores chromosome territory positions and active

chromosome dynamics in Hutchinson-Gilford progeria syndrome cells. Mehta IS, Eskiw CH, Arican HD, Kill IR, Bridger JM. Genome Biol. 2011 Aug 12;12(8):R74. (REF2).
3) Progeria, the nucleolus and farnesyltransferase inhibitors. Mehta IS, Bridger JM, Kill IR. Biochem Soc Trans. 2010 Feb;38 (Pt 1):287-91. (REF2)
4) Towards a Drosophila model of Hutchinson-Gilford progeria syndrome. Beard GS, Bridger JM, Kill IR, Tree DR. Biochem Soc Trans. 2008 Dec;36(Pt 6):1389-92.
5) Xioning He; Bridger JM; Kill IR (2008). Too Old Too Soon. *The Biochemist* *http://www.biochemist.org/bio/default.htm?VOL=30&ISSUE=5*
6) Nuclear motors and nuclear structures containing A-type lamins and emerin: is there a functional link? Mehta IS, Elcock LS, Amira M, Kill IR, Bridger JM.Biochem Soc Trans. 2008 Dec;36(Pt 6):1384-8.
7) Primary laminopathy fibroblasts display altered genome organization and apoptosis. Meaburn KJ, Cabuy E, Bonne G, Levy N, Morris GE, Novelli G, Kill IR, Bridger JM. Aging Cell. 2007 Apr;6(2):139-53. Epub 2007 Feb 5.

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

Supporting the Families

The team at Brunel helps and supports the children and their families, primarily by continuing to ensure that the research into Progeria progresses and keeping the families informed of the progress. Members of the Progeria research team are proactively involved with families of Progeria sufferers. Dr Bridger is in active contact with The Okines and The Crowther families, and monitors how Hayley Okines (http://en.wikipedia.org/wiki/Hayley_Okines) is progressing both at home and on her medical visits to the US. The team are also members of the Progeria Family Circle, informing them of their progress (https://www.facebook.com/#!/familycircleprogeria?fref=ts) and the Atypical Progeria Group. The team have presented their work and findings to families of Progeria suffers in the UK (2011), the US (2013, 2010, 2008) at the Progeria Research Foundation workshops and Italy (2012) at the Progeria Family Meeting.

Figure 1

On April 15th 2011 Dr Kill organised the 1st UK Progeria Research Day at Brunel (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3324340/pdf/nucl-2-517.pdf) where scientists and clinicians spoke and mingled with The Okines and The Crowthers. Hayley Okines, who has Progeria, spoke to the scientists about her life (Figure 1) and Harry Crowther who suffers from an even rarer form of Progeria wrote on his website how much he enjoyed his day at Brunel. (A) In order to help Progeria suffers such as Harry, Dr Bridger has set up a new collaborative cross-Europe consortium to decipher how Harry's lamin works differently to Hayley's so that drug treatments for suffers of Progeria that make a different toxic protein can have some hope of a treatment. The initial meeting of the network has been funded by Sparks.

However, the most significant interactions and support that the team has had is when The Okines family came to Brunel University to film one of the TV documentaries on the family "*The-96-year old schoolgirl*" (http://www.channel5.com/shows/extraordinary-people/episodes/extraordinary-people-hayley-the-96-year-old-schoolgirl, Figure 2).


Figure 2

An excerpt from the book "*Old Before My Time; Hayley Okines' Life with Progeria*" written by Hayley and Kerry Okines reveals that Dr Kill helped the Okines make a potentially life-changing decision by demonstrating how the new drugs suggested to the family by the US clinical trial team might help Hayley's Progeria (B). After talking to Dr Kill the family made the decision to commit to the new combinatorial 3 drug trial, which seems to have had positive results for Hayley.

During this same visit the team learnt that Hayley's mother was seeking funding for a reunion event

of children with Progeria after the one in the US had been cancelled. The Development Office at Brunel University was able to identify a sponsor who agreed to fund the event at the Ashford Hotel in Kent in 2010 for ~ 20 families with Progeria children staying for 1 week.

Engaging with Individuals and Communities

The research conducted by the team at Brunel has also impacted on the activities of numerous individuals and organisations that have learnt about Progeria through the dissemination of the research, internet searches or media articles and programmes that highlight the team and its research. Individuals decide to take part in sporting events such as marathons to help fund the work, school children find inventive ways to raise money for the team and a retirement group make Christmas decorations to fund the work. Individuals from Brunel itself have got behind the team as a home-made charity it can support. They raise thousands of pounds by hosting social evenings and baking cakes. Other individuals have donated prizes for the best undergraduate and Masters' projects in Progeria research – that have led to local press releases. Dr Bridger has been invited to give many talks over the years to the laypeople describing Progeria and Brunel University's role. Hundreds of people have been exposed to and have actively taken part in raising the awareness of Progeria by doing something positive and fun for themselves. Organisations such as the *Royal Anti-Diluvean Order of the Buffaloes* (2008), the *Freemasons* (2013), and Ruislip St Martin's Lodge have each raised over £5,000 for Progeria research (C). Drs Bridger and Kill spent time with the Buffaloes in Epping Forest at a number of their social events – chatting about their work and Progeria (2008); and provided images and information for a presentation of their work to 500 Freemasons at a special dinner (2013). Other organisations that have requested talks and information are the *Soroptomists* (D), which represent a powerful female voice in international awareness and lobbying and the *Athena* group of female professional and business women. Dr Kill took part in the University's series of public lectures as one of three presenters contributing to a lecture entitled "*Can We Live Forever*" and highlighted the work of the research team (E). There were over 200 members of the public in the audience who participated in a lively debate.

Figure 3

In March 2010, the team took part in a public presentation of their research at a local science fair in Uxbridge, Middlesex (Figure 3), speaking to local shoppers about Progeria and their findings.

On June 8th 2013 Drs Bridger and Kill, along with Prof Shananan of Kings College London presented to a paying audience "*Ageing Fast and Slow*" a topic at The Times Cheltenham Science Festival. There were nearly 100 members of the public at the event and it was actively tweeted about. The audience asked some well-informed questions and showed a lot of interest in Progeria (F).

The team are also acting as consultants for Sparks to train individuals from this organisation about Progeria and the research happening at Brunel. They have run 2 training sessions this year already (April and November), where Dr Bridger gives a presentation and other members of the team run "lab tours".

Raising Awareness and Promoting Public Understanding

The original underpinning work research findings were taken up by the media and the team was interviewed for articles, radio and international television programmes. HRH Prince Philip also requested to meet the team in 2008. Since 2008, the team continue to be involved in informing the UK and the world about their work and Progeria. Dr Clement's arrival at Brunel has been championed by Sparks to raise public awareness of Progeria and there have been local press releases in the area around Brunel and where Dr Clements lives (G). Dr Lynda Shaw a local neuroscientist has adopted Brunel's Progeria research to highlight and fundraises for Progeria research at Brunel (http://www.drlyndashaw.com/#!progeria/c1oan) and she has recently been in a number of high profile magazines discussing Progeria (H).

In 2005, a PhD student with the team, met with the Khan family in Kolkata, India to initiate contact and to commence a research study; 4 of 6 children in the Khan family suffer from a rare form of

Progeria. (http://news.bbc.co.uk/1/hi/world/south_asia/4286347.stm) Incidentally, as a consequence of this meeting, his sister featured as a wardrobe designer in the Bollywood movie about Progeria called *Paa* (English: Father) in 2009; this film has educated many thousands of people about Progeria.

In 2010 The Brunel team helped James Routh of Rabbit productions to film "*Hayley-The 96-year old schoolgirl*" for the Extraordinary People series (I) by providing information and film footage of flies with Progeria. This had ratings of 1.43million on the night. Dr Ian Kill was also featured in the programme. In 2011 Hayley was filmed at Brunel University at the 1st UK Progeria Research Day, giving a speech – a topic she mentioned a lot in the documentary as she ticked off the days on her calendar. This programme was "*Hayley – the World's oldest Teenager*" (J). These shows reach an international audience.

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

A. Atypical Porgeria Syndrome: Harry's Story blog – Brunel University & Alton Towers (!9 Apr 2011) http://sharron-harrysstory.blogspot.co.uk/2011/04/brunel-university-alton-towers.html
B. Excerpt from "Old Before my Time" Hayley and Kerry Okines. Accent Press Ltd, Bedlinog 2011: *"To help us learn more we visited a Progeria expert at Brunel University in the UK. Dr Ian Kill and his team of scientists were studying the effects of ageing in Progeria children and normal adults…Dr Kill then sat us down and explained how the FTI drugs, which Hayley had been taking for two years, were able to block the pathway of the Progeria cells in the body. But he told us that sometimes this happened late in the process and that's why his team of scientists were trying to find ways of starting the blocking earlier…He showed Mark and I a diagram with arrows pointing to lots of long names. It meant nothing to us, but the long and the short of what he was telling us was that statins, which are taken by people with high cholesterol, could be used to treat Progeria…Armed with this new information, Mark and I decided it was worth a try."*
C. Ruislip St. Martin's Lodge, Charity Award Boosts Lodge University Link: http://www.ruislipstmartinslodge.com/page7.html
D. Soroptimist International, Open Council Meeting (10 March 2012): http://sigbi.org/london-chilterns/open-council-meeting-10-march-2012/
E. Brunel Public Lecture Series, 'Can we live forever? – The Social and Biological Challenges of Ageing' (08 Mar 2010): http://www.brunel.ac.uk/news-and-events/public-lectures-2013/videos/2010/can-we-live-forever
F. Ageing Fast and Slow (8 June) http://www.cheltenhamfestivals.com/science/whats-on/2013/ageing-fast-and-slow/
G. '"Dream Come True" Medical Funding' (27 Feb 2013) Uxbridge Gazette
H. 'Dr Lynda Shaw helps with vital Progeria research' (27 March 2013), Mature Times http://www.maturetimes.co.uk/health/health-news/5380-dr-lynda-shaw-helps-with-vital-progeria-research.html
'Understanding unexpected ageing' (27 Mar 2013) 50Connect: http://www.50connect.c'o.uk/articles/understanding-unexpected-ageing
I. Channel 5 – Extraordinary People: 2010 – Hayley: The 96 Year Old Schoolgirl http://www.channel5.com/shows/extraordinary-people/episodes/extraordinary-people-hayley-the-96-year-old-schoolgirl
'Five's Extraordinary People watched by 1.43m', The Guardian (14 June 2010): http://www.theguardian.com/media/2010/jun/15/extraordinary-people-channel-five-tv-ratings
J. Channel 5 – Extraordinary People: 2011 – Hayley: World's Oldest Teenager http://www.channel5.com/shows/extraordinary-people/episodes/extraordinary-people-hayley-worlds-oldest-teenager

Contactable

- Founder of Progeria UK (Father of Hayley Okines) http://www.progeria.co.uk/
- Founder of The Progeria Family Circle
- Chief Executive of Sparks, children's medical research charity.
- Founding Director, Rabbit Productions for the Extraordinary People series
- Dr Lynda Shaw, Neuroscientist