THREE CHALLENGES IN UNLOCKING THE GENOME'S THERAPEUTIC POTENTIAL

At the NextGen Omics UK Series, we sat down with an advisory group of leading experts to gain their thoughts on the state of the genome editing and synthetic biology industries. The therapeutic potential of genomic technology is virtually unlimited, but there are significant challenges in trying to harness it.

Genetic studies have been around for over a century. Since Mendel's observation on the inherited characteristics of peas in his gardens (1865), scientists have worked towards systematising spontaneous genetic mutations. The 1970s and 1980s brought the first targeted genomic changes in yeast and in mice. Increasingly rapid sequencing technologies in the 1990s paved the way for whole genome sequencing in the 2000s. The rise of CRISPR/Cas9 since then has made gene editing accessible and cost-efficient in research. These exponential advances in genomics have brought us to a stage where we can anticipate the transformative potential of genome editing. It is a technology which will significantly disrupt any market that deals with organisms. Genome editing will greatly increase the world's food supply, combat climate change, and cure – or prevent – previously unmanageable diseases.

Our line of conferences is especially interested in the therapeutic potential of gene editing applications. We – along with many others – are very excited about the ways in which genomics could transform medicine from drug development to the prevention of congenital disorders. However, in discussing this potential with our advisory board, we found that investment is currently focused in more basic applications. Nigel Saunders, Professor of Systems & Synthetic Biology at Brunel University, noted that "*industrial biotech and microbial are by far the largest sectors in terms of current revenue and scale in pharma*". Biotech and Pharma Companies segment was valued at USD 1.4 billion in 2017.

Additionally, the animal genetic engineering segment was valued at USD 785.4 million in 2017 and considerable revenue size can be associated with the extensive demand for dairy and livestock. Plant genetic engineering is also seeing a rise with increasing agricultural demands. Investment in these industries is notably free of the risk associated with gene editing in humans. Research institutes, however, accounted for only 30.2% revenue share in 2017. Though there is demand for efficient drugs, the development of these drugs using genome editing is a riskier investment than that into industrial biotech or animal or plant gene editing. There is a great disparity in terms of scope between the research being done in academic labs and the applications of gene editing then taken up within industry.

This is because three types of obstacles stand between current genomic technology and its apparently limitless therapeutic applications. The first is the difficulty of communication within the scientific community. As Robert Hindges, Professor of Developmental Neurobiology at King's College London points out, in "*trying to build a bridge between basic science and translational and clinical science, one of the most important or most difficult things is to speak the same language in terms of what we're doing*". Gene editing is used internationally by a diverse range of scientists, but not everyone has the same methodology, technology or aims in their research.

The biggest gene editing story of 2019 illustrated the consequences of this challenge. He Jiankui shocked the scientific community when he announced at a conference in Hong Kong that he had created genetically modified twin sisters, and that a third child was on the way. Many scientists denounced He's experiments on grounds that CRISPR is still unsafe to try on humans, especially when it comes to germline edits (changes to the DNA which are passed to future generations). In an interview with The Guardian in November 2018, Julian Savulescu, a professor of practical ethics at the University of Oxford went so far as to say, "*If true, this experiment is monstrous*". Yet Jiankui's intention to disable a gene called CCR5 that forms a protein doorway that allows HIV, the virus that causes Aids, to enter a cell, was not itself the problem. Discussion on the use of gene editing has entered the bioethical and public realms, with no present sign of a consensus on how to move the technology forward.

A great uncertainty in the effects of the gene editing lies at the heart of bioethical and public discussion. Gene therapy is a hot topic at the moment, and discussion surrounding its use has focused on ethical perspectives in reaction to Jiankui's experimentation. But, because people do not know what to expect if gene editing is allowed to be performed on humans, there is no widespread support of advancing the field. The technology is still imprecise enough to entail doubts regarding its safety, manageability and targetability. The main challenge with therapeutic applications of genome editing is therefore a scientific one. "*Off-target integration, oncogenic gene activation, vector challenges, contained use challenges*" are still the most important obstacles for translation and delivery according to Nigel Saunders. These issues are inseparable from questions regarding whether gene editing ought to be applied in humans. For gene editing to be a clinically relevant technology, it must be proven to pass tests of security and efficacy even before it faces ethical or regulatory evaluation.

Toni Cathomen, Full Professor and Director of the Institute for Transfusion Medicine and Gene Therapy at the University of Freiburg, pinpoints specificity as the key to progressing the technology to the next step. High specificity would ensure that gene editing does not produce off-target effects or unforeseen and unwanted changes in patients later in their lives. Toni told us that what is really needed in the field to ensure this is the development of "*biological assays that tell us whether CRISPR/Cas induced off-target effects have a negative impact on the edited cell, such as its transformation, in the long run*". Moreover, current assays are not geared towards quantitively assessing off-target effects in clinically relevant cells – they generally focus on surrogate cell lines. Clinical risk assessment needs to involve primary cells, and not everyone

working in the gene editing field has access to the types of assays that can produce clinically relevant specificity data.

So what's holding researchers in the field from using such an assay? A key area mentioned was cost. In the industry of drug development, specificity is less important than in academic research. All that is needed to validate a drug target on an industrial scale is to control for off-target effects. Additionally, pharmaceutical companies are avoiding the potentially costly unwanted effects of gene editing with Cas9 by simply not using it in their drug development pipeline. This means that pharmaceutical investment – which has been seen is the lion's share – is not going into developing biological assays for clinically relevant human cells.

Given the three challenges discussed so far, it seems understandable that investment into human gene editing is lagging behind more stable applications of CRISPR. Beyond these key challenges lie even more deterrents to investment in human gene editing. Not only are there regulatory and IP barriers to using gene editing technology but the disciplines involved in discussing and developing gene editing are also widely varied and fast-moving. Between human-animal chimerism, stem cell new organ tissue generation, and the vast potential of synthetic biology, Nigel Saunders points out that "*We work in disciplines which need two or three yearly big trainings*". There is not just a technological cost to the capital required for progressing genetic therapeutics – there is also the human cost associated with training and funding researchers.

All these barriers can be surmounted through communication and collaboration. Lin Wu, Director of the Genome Modification Facility at Harvard University, reassured us that, in weighing up the costs and benefits of gene editing going forward, "*there's a good balance of a group of people talking about both sides*". Lin's driving force at her facility has been on basic science with an eye paving the road to the clinic. She has collaborated with several research groups who do not have the same facilities available at Harvard. It is this collaboration between clinicians and those working in basic science that gives cause for optimism regarding progression in genetic therapies. Everyone is, after all, working towards the same goal: cost-efficient, safe and efficacious treatment and prevention of illness.

At Oxford Global, we share Lin's optimism. The significance of the goal of gene editing has led pioneers in the gene editing field such as CRISPR Therapeutics, IDT, Sangamo Therapeutics, Addgene, Allele Biotech, Bio-Rad and Takara Bio to invest in comprehensive gene libraries, assay development and novel Cas proteins. More attention – and more money – is being paid to overcoming the challenges outlined in this article. A constructively critical approach within the scientific community regarding the types of discussion which can help with the challenges is focusing their approach to clinical translation. CRISPR, TALEN and ZFN technology is actively being used by pharma companies to develop new gene-edited therapies. Our NextGen Omics UK Series this November displayed the application of such technology as well as the basic science behind developing the next clinical breakthroughs. With your help, we are hoping to facilitate efficient analysis of the challenges in the field going forward.

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Lin Wu, Director, Genome Editing Facility, Harvard University

Lin Wu received her Ph.D. from Columbia University in Molecular and Cellular Developmental Biology, and her Postdoctoral training from The Rockefeller University in Biomedical Genetics and Metabolic diseases. After working many years as an associate director at the Transgenic and Gene Targeting Facility of Massachusetts General Hospital, Harvard Medical School, Lin become the director of the Genome Modification Facility (GMF) at Harvard University in 2012. The GMF provides transgenic, gene targeting, and other services to investigators of Harvard University and its affiliated institutions, as well as to investigators within the US and abroad. For more details, please Click Here.

Toni Cathomen, Full Professor and Director of the Institute for Transfusion Medicine and Gene Therapy, University of Freiburg

Toni Cathomen is Professor of Cell and Gene Therapy at the University of Freiburg, Germany, and Director of the Institute for Transfusion Medicine and Gene Therapy at the University Medical Center. After receiving his Ph.D. from the University of Zurich, Switzerland, Toni was a postdoctoral fellow at the Salk Institute in San Diego, Assistant Professor of Molecular Virology at Charité Medical School in Berlin, and Associate Professor of Experimental Hematology at Hannover Medical School. His research focuses on the application of TALEN and CRISPR-Cas nucleases for gene editing in hematopoietic stem cell and CAR T cells, with the goal to develop novel therapies to treat patients suffering from HIV infection, primary immunodeficiencies and certain types of cancer.

Robert Hindges, Professor of Developmental Neurobiology, King's College London

Robert Hindges is a Professor of Developmental Neurobiology. He graduated from the University of Zürich Switzerland, where he also obtained his Doctoral Degree in Molecular Biology. He subsequently joined the Molecular Neurobiology Laboratory at the Salk Institute in La Jolla, USA, before moving to King's College London in 2006. He has made fundamental contributions to the field of vertebrate visual system development, in particular on the formation of binocular vision, orientation-selective circuits and visual maps in the brain. Some of his work is now described in basic neuroscience textbooks. His recent studies focus on synaptic gene families, where mutations have been linked to several disorders, including mental disabilities, epilepsy, schizophrenia and bipolar disorder. In addition to his position as a principle investigator, Prof. Robert Hindges is the Academic Head of the Genome Editing and Embryology Core Facility at King's, which offers state-of-the-art technologies to the research community.

Nigel Saunders, Professor of Systems & Synthetic Biology, Brunel University

Professor Saunders is a medically and PhD trained microbiologist with extensive experience in comparative and functional genomics, addressing bacteria ranging from pathogens to industrially applicable species. Formerly a member of the molecular infectious diseases group at the Institute of Molecular Medicine, and PI the Bacterial Pathogenesis and Functional Genomics Group at the Sir William Dunn School of Pathology at Oxford University (including two Wellcome Trust Fellowships); he moved to Brunel University to take up the newly created Chair of Systems and Synthetic Biology in 2011. Since moving into Synthetic Biology he has focussed upon a new bottom-up strategy to develop the biological and analytical tools and resources necessary for knowledge-based design of bacterial systems. Comparative and evolutionary biology approaches have been taken, based upon newly robust and consistent bioinformatics and strain-collection foundations, to identify behavioural determinants: strains, genes, gene-variants, that can be identified for strain selection and engineering; leading to a range of capabilities and resources. These have been applied to parts discovery, enzyme variant identification for pathway engineering, targeted strain selection and process-optimization for bio-enhanced concrete, improved product-tolerant chassis strains, evolved communities for waste remediation, overcoming catabolite repression, and more. Professor Saunders was also a founding manager of the Oxford University Computational Biology Research Group, providing bioinformatics and computational biology to Life Sciences and the Medical School at Oxford; Lecturer and Senior Research Fellow at Somerville College, Oxford; Fellow of University College, Oxford; and is currently the Theme Leader of the Synthetic Biology Research Theme at Brunel University London.