SPEAKER SPOTLIGHT:

CRISPR Screens For Drug Discovery

As pharmaceutical companies give more and more attention to genome editing technologies, the potential for CRISPR to play a role in drug discovery and development is beginning to be realised. We talked to Ricky Trigg from GlaxoSmithKline about the use of CRISPR for target screening.

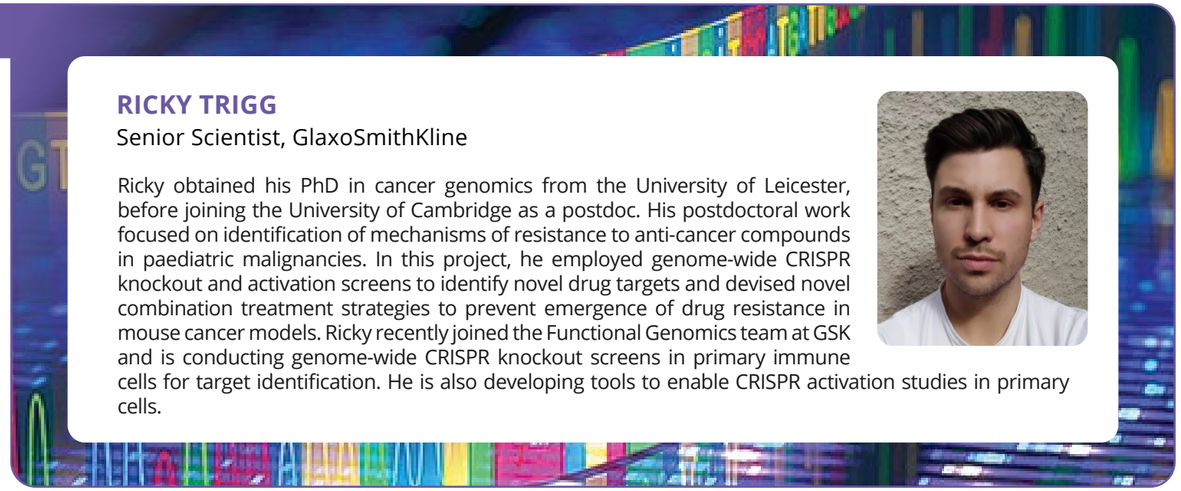
What is your role at GSK and what are you currently working on?

I work as a Senior Scientist in a team specialising in genome editing in primary immune cells to identify drug targets for a range of immune-mediated diseases. Currently, I am working on the design and execution of genome-wide CRISPR knockout screens in primary T cells. A significant component of my work lies in the development of methodology for editing CD4+ T cells in a screening context, which involves extensive optimisation of protocols for lentiviral transduction, Cas9 protein electroporation and cell enrichment. Additionally, I am leading collaborative efforts to develop CRISPR-based transcriptional modulation technologies (CRISPR activation and interference) for use in primary cell types. When matured, these technologies will be used as orthologous and complementary tools to improve the robustness of our target discovery workflows.

How are genome editing technologies impacting drug discovery and development in the pharma industry?

I think it's fair to say that the mass investment in genome editing technologies and expertise in the pharma industry is driving a revolution in drug discovery. For example, in mid-2019, GSK entered into a five-year collaboration with CRISPR pioneers Jennifer Doudna and Jonathan Weissman at the University of California to launch the Laboratory for Genomic Research. This partnership aims to accelerate research that will facilitate the development of technologies to screen for new drug targets.

CRISPR has made genome editing more tractable, and its versatility is enabling us to efficiently and cost-effectively identify drug targets on a genome-wide scale while providing insights into disease-relevant biological processes. Whereas simple drug candidates bind to and interfere with a protein encoded by a disease-associated gene, we are now able to use CRISPR to uncover more subtle targets in complex regulatory networks and potentially devise more sophisticated, multi-targeted approaches to treatment. Recently developed genome editing tools are also being used to generate complex animal models of disease in which to conduct preclinical studies for assessing drug safety and efficacy. The precision of CRISPR enables generation of models that faithfully recapitulate the genetic features of a disease while avoiding the use of exogenous DNA elements associated with traditional genetic engineering approaches.



RICKY TRIGG
Senior Scientist, GlaxoSmithKline

Ricky obtained his PhD in cancer genomics from the University of Leicester, before joining the University of Cambridge as a postdoc. His postdoctoral work focused on identification of mechanisms of resistance to anti-cancer compounds in paediatric malignancies. In this project, he employed genome-wide CRISPR knockout and activation screens to identify novel drug targets and devised novel combination treatment strategies to prevent emergence of drug resistance in mouse cancer models. Ricky recently joined the Functional Genomics team at GSK and is conducting genome-wide CRISPR knockout screens in primary immune cells for target identification. He is also developing tools to enable CRISPR activation studies in primary cells.

What challenges are you aiming to overcome in your work?

There is major interest in the development of genome editing strategies for disease-relevant primary cell types. However, primary cells are often resistant to transfection, and immune cells have an innate mechanism to resist entry of foreign genetic material. Primary cells also have a finite growth potential and lifespan in culture, which limits the extent to which they can be manipulated. My team use a combination of published and novel strategies to enable high-efficiency editing in primary immune cells, but several issues still remain. For example, inefficient lentiviral transduction means we must transduce very high cell numbers. We are currently exploring ways of reducing the required cell numbers for our screening experiments while maintaining sufficient coverage of our guide RNA libraries.

Where do you think the genome editing field is heading?

Progress in the field has been rapid and the potential applications of CRISPR and related technologies in research, medicine and biotechnology are becoming increasingly evident. But before these applications can be demonstrated, we first need to sharpen our current tools. I think a lot of effort will be focused on improving the efficiency of existing genome editing technologies and addressing the safety aspect of using these tools clinically, particularly relating to off-target activity. Of course, we must continue to consider the social, ethical and legal implications of genome editing when applied to human therapeutics.

What would you like to achieve at the 6th Annual Genome Editing Congress? What kind of work are you most excited to see?

I look forward to presenting my work and receiving feedback. It will be a great opportunity to meet academic and industry colleagues working in the genome editing space to discuss the challenges and opportunities of working with current and next-generation tools. In particular, I am excited to hear about the latest developments in precision editing technologies such as prime editing and base editing, and how they may be applied in the context of cell and gene-based therapies.