Graeme Macluskie

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Expert Spotlight: Improving precision medicine strategies with human tissue testing

Graeme joined REPROCELL in 2011 as a human tissue scientist, and is now Director of Precision Medicine. He has over two decades of experience preclinical research and development and has established several human fresh tissue models during his time at REPROCELL.

At our Centre for Predictive Drug Discovery and Research, Graeme leads the R&D team, who develop new and innovative ways of testing drugs using human fresh tissue. Recently, he has taken on the responsibility of leading REPROCELL's Precision Medicine initiatives, which aim to stratify patient populations earlier in the drug development process.

Graeme has worked with several human tissue types during his time at REPROCELL specializing in inflammatory conditions, such as psoriasis, acne, and inflammatory bowel disease (IBD).

He is credited with developing our innovative induced skin disease models, which use a cocktail of inflammatory compounds to induce a skin disease phenotypes in healthy biopsies. Graeme is also responsible for establishing our IBD permeability model, which uses gastrointestinal tissues from IBD patients to estimate drug permeability.

Outside of this vital R&D work, Graeme often participates in company webinars and helps our clients understand and interpret the data behind their projects. He has also written for a number of publications about the benefits of human fresh tissue research, the most recent being European Biopharmaceutical Review.

Publications

Combining explainable machine learning, demographic and multi-omic data to identify precision medicine strategies for inflammatory bowel disease (2021)

Application of pharmacogenomics and bioinformatics to exemplify the utility of human ex vivo organoculture models in the field of precision medicine (2019)

P142 Topical MTX-GNPs reduce IMQ-induced inflammation in mice (2018)

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In 2019, Graeme co-authored a paper exploring the use of human fresh tissue testing to stratify patient populations pre-clinically. This research used lung tissue from COPD patients to identify genes that may contribute to inter-patient variation in drug response.

What inspired REPROCELL to pursue this ambitious project?

At REPROCELL, we've known for decades that human fresh tissues predict inter-patient variation more accurately than any other model. Over the years, several clients have approached us looking to test their drugs in human fresh tissue because the clinical adverse effects of their treatment were not detected in other models. Our thought was, if human tissues can predict drug response more accurately because they account for genetic variation, could we identify these genes at an early stage? Doing so would save pharma companies a considerable amount of money, as non-responders could be excluded from clinical testing, therefore reducing attrition.

> **"Human fresh tissues predict inter-patient variation more accurately than any other model."**

What experimental methods did you use?

We used an *ex vivo* model and human lung tissue from chronic obstructive pulmonary disease (COPD) patients to estimate inter-individual differences in drug response. Once we had quantified this variation in the patient population, we collaborated with a bioinformatics company to stratify the patient population based on this efficacy data, and then determine which genes, if any, could be a cause of this variation.

Results of the study suggested that two genes had a significant impact on drug response. Can you discuss whether the literature supports this finding?

The two genes that were linked to variations in drug response were Smad3 and CYP2E1. In the literature, cellular pathways containing these components have been linked to COPD pathology and drug mechanisms. For example, the Smad3 pathway had been linked to COPD pathology previously. One of the drugs we used to measure inter-patient variation in drug response, Roflumilast, has also been found to reduce Smad3 activity by inhibiting TGF-β release.

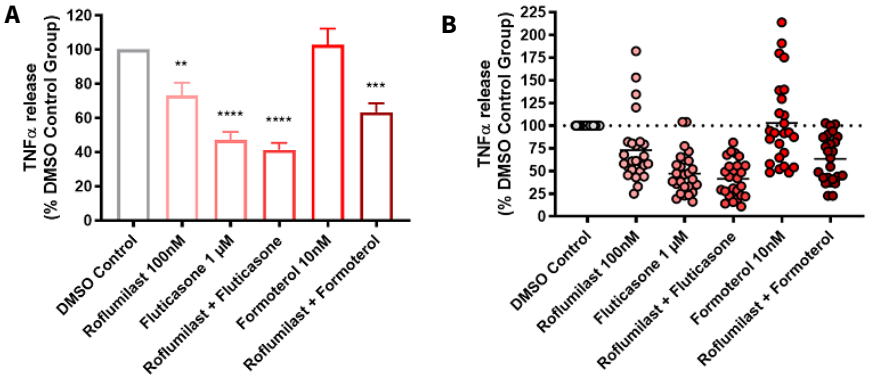

Figure 1: Graphs showing the effects of test articles on TNFα release from LPS stimulated human lung parenchyma biopsies, n = 25 donors diagnosed with COPD. Data is displayed as a percentage of the corresponding DMSO control group in both graphs. A: Bar graph depicting mean + SEM TNFα release. B: Scatter graph depicting individual patient (dots) and mean (black line) TNFα release.

For further information on REPROCELL's human fresh tissue studies, visit www.reprocell.com