

A novel screen for product molecule compatibility with the production cell that accounts for intracellular toxicity

The Challenge

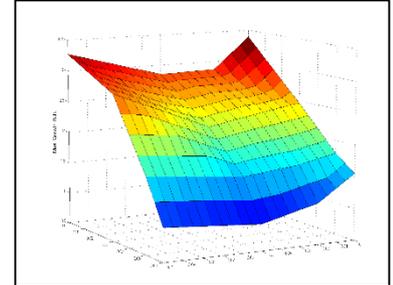
Industrial Biotechnology increasingly uses genetically-enhanced production cells to biosynthesise non-native chemical products. Being non-native and high concentration, such products often are toxic to the production cell.

This being so, many putative products applied *externally* to test for compatibility with the production cell will not cross the membrane, so *intracellular* cytotoxicity – the key IB question - is not assayed.

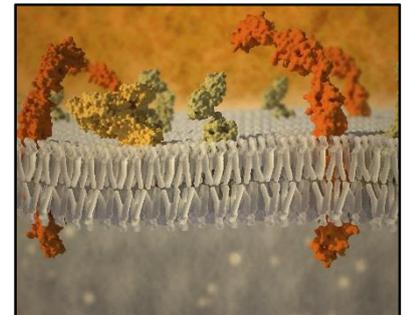
The Research

Dr Jagroop Pandhal is a Lecturer in Biological Engineering at the University of Sheffield. The research in his laboratory focusses mainly on metabolic engineering and biomanufacturing, for example, for therapeutic protein production.

Dr Pandhal applied for CBMNet Proof-of-Concept funding with Croda and The Centre for Process Innovation. The project aimed to develop superior cell toxicity screen exploiting a membrane disruption methodology in cells to achieve product uptake.



A response surface curve of DMSO/Ethanol concentrations



CBMNet Proof of Concept
Funding

The Result

The new screen worked. Two anonymous industrial bio-products were tested with both the traditional screen and the new test.

The new screen demonstrated a specific level of toxicity, missed by the present screen, and therefore these findings could link to productivity levels for the compounds.

With this knowledge, the aim would be to improve productivity with process improvements or cell engineering. Moreover, this methodology could be developed for application to different industrially relevant host cell organisms.

The Future

The industrial collaborators are interested in the test for clients who want to test toxicity of products and also the response of cells to inhibitory compounds in complex feedstocks and are looking to progress this very soon.

The data from this project will be used to apply for funding through the Engineering and Physical Sciences Research Council's Impact, Innovation and Knowledge Exchange Proof of Concept funding scheme to undertake these tests on more molecules.

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"Being able to develop an improved screen within the laboratory was a key aim and interesting to undertake. However, using it to test real-life industrial biotechnology products and discovering potential toxicity, which manufacturers don't see, was a revelation."

Dr Jagroop Pandhal

"Toxicity of products is a significant concern when developing products using IB and, especially, Synthetic Biology where the product is non-native and may be new to nature. The approach devised at Sheffield through this project shows significant potential. Availability of a robust test method, which accounts for trafficking across the membrane, represents a valuable tool for industry."

Dr Doug Cossar