

## Understanding & manipulation of peptide transporters using chemical & structural biology

### The Challenge

Industrial scale fermentations used in Industrial Biotechnology and Bioenergy, where media account for a large proportion of the overall cost, often use cheap complex substrates with organic nitrogen sources such as yeast extract & corn steep liquor. The peptide transporters that take up these nutrients are secondary transporters that are poorly studied at the biochemical & structural level & hence have not yet been targets of rational engineering.

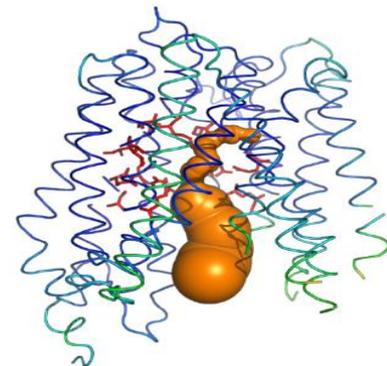
The Global Deodorants industry valued at around €10 billion and Unilever is the market leader, driven by sales of its 3 main brands, Rexona (Sure), Axe (Lynx) and Dove. Current product technology is based mainly on aluminium-containing antiperspirant salts (which also act as antimicrobials), antimicrobial solvents (ethanol, glycols) and fragrance. There is a demand for more targeted interventions, such as interfering directly with the formation of malodour at the molecular level. In this context, inhibiting the bacterial transporter responsible for the uptake of the key precursor to thiol-based malodour represents a completely novel approach that holds great potential. One particular member of the peptide transporter family is involved in the production of human malodour by *Staphylococcus* bacteria.

### The Research

Dr Gavin Thomas is a Reader in Microbiology at the University of York. The research in his laboratory focusses mainly on membrane transport proteins in a range of bacteria.

Dr Thomas applied for CBMNet Proof-of-Concept funding along with Unilever and colleagues at The University of Sheffield & University of Oxford to develop a collaborative project aimed at using a chemistry-based approach to investigate the space of peptide-based inhibitors for these transporters, combined with a structural biology approach, in the odour-forming bacterium *Staphylococcus hominis*.

The project will lead to improved understanding of peptide transporter function & through their manipulation there is the potential to remove yield restrictions in large scale fermentations.



CBMNet Proof-of-Concept  
Funding

## The Result

In this short Proof-of-Concept grant the team made significant progress in developing peptide transporters as targets for inhibition in biotechnological processes, completing all of its milestones.

The team was able to identify a number of small molecules that inhibit the function of our experimental system, a Cys-Gly-3M3SH transporter relevant to Unilever, giving them structural leads to the design of improved inhibitors.

They also made a significant breakthrough in solving the structure of this membrane transporter to 2 Å resolution, which gives unprecedented insight into how the protein is likely to recognise the substrate and how to rationally design further inhibitors.

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## The Future

The successful solution of the structure of the key protein involved in transporter of malodour precursors into *S. hominis* is an important result for Unilever. Further work will be needed beyond the project to try and co-crystallise the protein with relevant ligands and Unilever are in discussion with the University of Oxford to fund time to continue this work.

It is also likely that Unilever will patent some of these ideas and both York and Oxford will likely feature as inventors on this patent. Work will also be published in a high-impact journal late in 2017.

Dr Gavin Thomas has been awarded a 3-year BBSRC LINK grant with Unilever, which started April 2016, to continue to study the transporter and other enzymatic steps involved in thioalcohol production.

The team will also continue this work through the BBSRC iCASE scheme via the White Rose DTP scheme.

*"The project was phenomenally successful due to our ability to combine our biochemical and genetic studies with the crystal structure of the transporter, which came from work in Prof. Simon Newstead's lab in Oxford. Together we now understand precisely how the malodour precursor compound is recognised and therefore how we might potentially inhibit its function and more generally more about bacteria peptide transporter function and substrate recognition".*

Dr Gavin H Thomas, Project lead.

*"This CBMNet Proof-of-Concept project has proved pivotal in progressing our understanding of a bacterial transporter involved in body odour, and crucially how to target it with small molecule inhibitors. Key outputs have been a patent filing, scientific paper, and follow-up collaborations with partners at York and Oxford."*

Dr Gordon James, Science Leader,  
Unilever