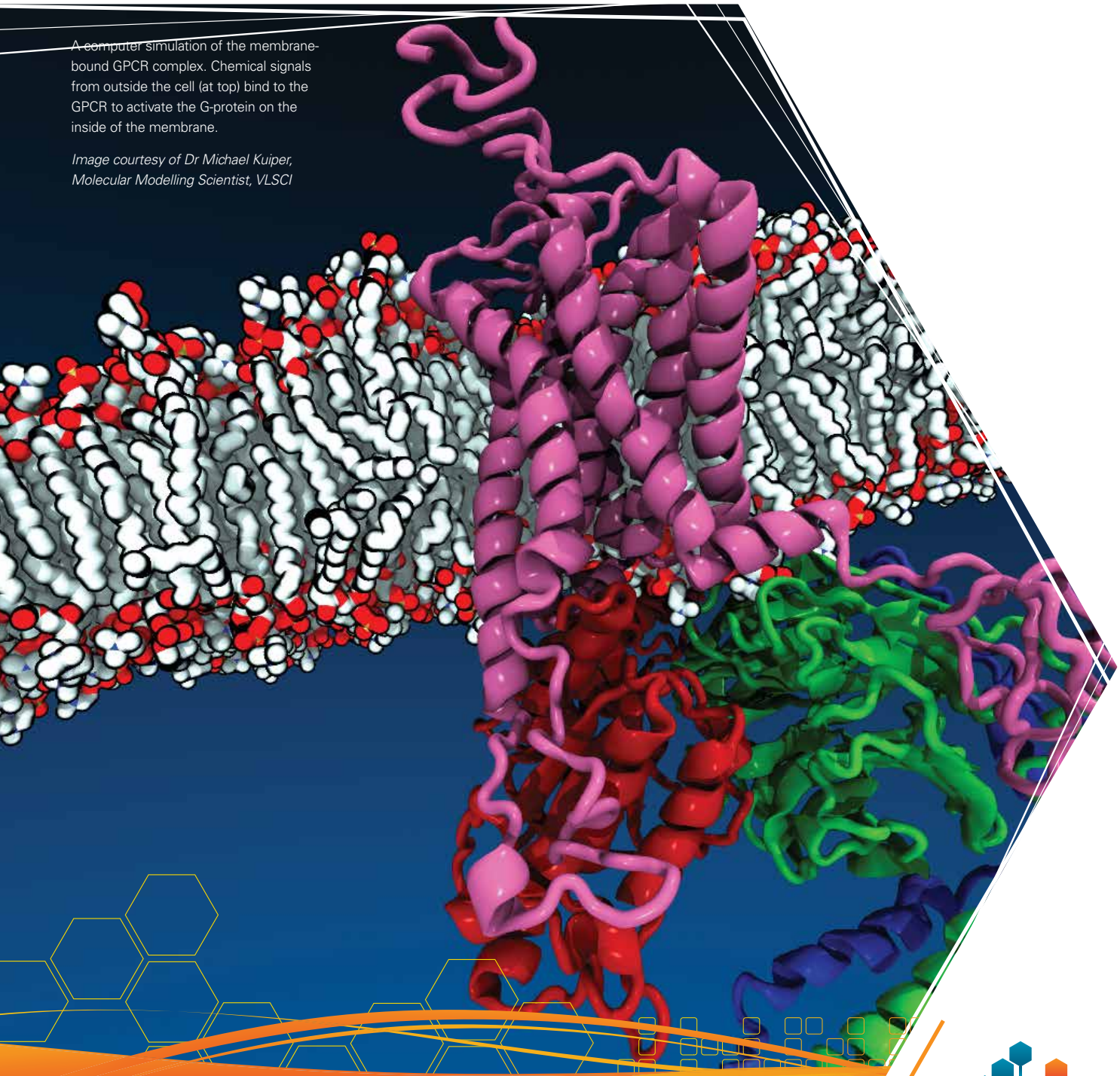
VLSCI SCIENCE STORY 10

UNDERSTANDING DRUG INTERACTIONS AT THE MOLECULAR LEVEL

Almost half of the currently available medicines act on a single group of molecules - G protein-coupled receptors (GPCRs), which can trigger cellular responses to a wide range of ailments such as heart disease, infections, respiratory disorders, digestive and other conditions. New drugs are predicted to emerge from a deeper understanding of GPCRs at the molecular level. The race is on.

Tim Thwaites, Science Writer



A computer simulation of the membrane-bound GPCR complex. Chemical signals from outside the cell (at top) bind to the GPCR to activate the G-protein on the inside of the membrane.

Image courtesy of Dr Michael Kuiper, Molecular Modelling Scientist, VLSCI

vlsci
LIFE SCIENCES COMPUTATION

"These computer simulations to test different docking models used to take six weeks – now they take a couple of days."

Dr Thomas Coudrat (left) is a Post Doctoral Fellow who has come from France to join Professor Sexton's group in Melbourne to carry out the complex computational modelling work for this project. He is seen here getting advice from Dr Michael Kuiper, VLSCI's Molecular Modelling Scientist.
Image credit: VLSCI

Melbourne researchers are using the unique number-crunching power of supercomputers to look at aspects of GPCRs in a way that would have been unimaginable even a few years ago. And the research has attracted the interest of the large European pharmaceutical group, Servier.

The body's capacity to adapt to environmental conditions such as heat and cold are well understood at the physiological level – shivering heats up the muscles, sweating cools them down. That is Biology 101. But what happens at the cellular level is less obvious: how is information about the external environment transmitted to the cells to trigger a response that can adapt the whole body to the ambient temperature? The story of how this is done, and the role played by this large and complex class of proteins (GPCRs) formed the substance of the 2012 Nobel Prize for Chemistry. GPCRs form a communication link between the external and internal environment of cells and as such are targets of nearly 50% of current pharmaceuticals. Drugs outside the cell can act on GPCRs sitting within the membrane to stimulate internal cellular responses and treat many common health complaints.

Prof. Patrick Sexton, Theme Leader, Drug Discovery Biology, Professor of Pharmacology, Monash Institute of Pharmaceutical Sciences (MIPS)
Image credit: MIPS

What makes the development of new drugs difficult is getting that ground level understanding of these proteins is hard, due to their complex crystal structure. GPCRs are made up of a set of seven linked helices each of which spans the cellular membrane and this complexity has meant that most of the thousands of GCPRs encoded by the human genome have remained a mystery.

A research group at the Monash Institute of Pharmaceutical Sciences (MIPS) in Parkville, advised by 2012 Nobel Laureate Professor Brian Kobilka who won the Prize for his work in GPCRs, is using the supercomputing resources of the Victorian Life Sciences Computation Initiative (VLSCI) to expand our knowledge of these complex molecules and their interactions.

"We're hoping to create predictive models of GPCRs which allow us to understand how certain ligands (binding molecules) bind to them," says Professor Patrick Sexton, leader of the Drug Discovery Biology group at MIPS. "That could allow us to predict other ligands that might bind, and possibly to pick out new drug leads."

Building and testing those models demands a lot of computer power. Previously, running computer simulations to test different docking models could take six weeks – now with the VLSCI supercomputers, this computing time has been slashed to a couple of days. All of this work has not gone unnoticed. In 2012, MIPS signed a significant agreement with Les Laboratoires Servier, to collaborate on GPCRs research. The agreement provides researchers with access to substantial funding and resources, while allowing them to apply their expertise to identify novel GPCRs targets and design new ligands to modify the activity of drugs already of interest to the company.

For further information about this research contact Professor Patrick Sexton at patrick.sexton@med.monash.edu.au.

To contact VLSCI go to www.vlsci.org.au

This article first appeared in the October 2013 edition of Australasian Biotechnology.