A versatile mouse that can teach us about many diseases and drugs

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Scientists from the UK and Australia have created a mouse that expresses a fluorescing 'biosensor' in every cell of its body, allowing diseased cells and drugs to be tracked and evaluated in real time and in three dimensions.

This biosensor mimics the action of a target molecule, in this case a protein known as 'Rac', which drives cell movement in many types of cancer. Rac behaves like a switch, oscillating on the molecular level between two states – active or inactive.

When Rac is active, the biosensor picks up chemical cues and glows blue. When Rac is inactive the biosensor glows yellow.

Using sophisticated imaging techniques, it is possible to follow Rac activation in any organ at any time, or watch moment-by-moment oscillation of Rac activity at the front or back of cells as they move in the body. This technology has been used to monitor Rac activity in many organs in response to drug treatment.

The biosensor is a single molecule probe named 'Raichu-Rac' and was invented by Japanese scientist, Professor Miki Matsuda, in 2002.

Although many researchers have used Raichu-Rac since 2002, this is the first time a mouse has been genetically modified successfully to express the molecule throughout the body without affecting cell function. The mouse can be used to study any cancer type by crossing it with other

models, limiting expression of Raichu-Rac to specific cell or tissue types. The mouse can also easily be adapted to study diseases other than cancer by expressing the biosensor in different disease models.

Dr Paul Timpson began the study with colleagues from the Beatson Institute for Cancer Research in Glasgow and completed it at Sydney's Garvan Institute of Medical Research. He collaborated closely throughout the process with Dr Heidi Welch from the Babraham Institute in Cambridge – the creator of the mouse – who uses it to study the movement of immune cells, known as neutrophils. The study, now online, has been published in the prestigious journal *Cell Reports*.

"The great thing about this mouse is its flexibility and potential for looking at a broad range of diseases and molecular targets," said Dr Paul Timpson.

"It allows us to watch and map, in real time, parts of a cell or organ where Rac is active and driving invasion. In cancers, a lot of blue indicates an aggressive tumour that is in the process of spreading."

"You can literally watch parts of a tumour turn from blue to yellow as a drug hits its target. This can be an hour or more after the drug is administered, and the effect can wane quickly or slowly. Drug companies need to know these details - specifically how much, how often and how long to administer drugs."

Dr Heidi Welch is very modest about her role in creating the mouse, viewing it mostly as a tool that will help other scientists to understand Rac and work out how to stop cancer cells from moving.

"The credit must go to Professor Miki Matsuda, the genius who invented the biosensor in the first place 12 years ago," she said.

"He made his discovery freely available to the scientific community, and has been very open about his findings since."

"Miki Matsuda was super-helpful in suggesting the expression levels we should be looking for, and in recommending the exact biosensor we should use, out of many he developed. He was superb."

According to Welch, competition is growing rapidly in this area, with Matsuda himself making biosensor mice for a variety of target molecules.

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