New microscope enables 'super' science

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Using the only microscope of its kind in Australia, medical scientists have seen for the first time the inner workings of T-cells, the front-line troops that alert our immune system to go on the defensive against germs and other invaders in our bloodstream.

The discovery overturns prevailing understanding, identifying the exact molecular 'switch' that spurs T-cells into action - a breakthrough that could lead to treatments for a range of conditions from auto-immune diseases to cancer.

The findings, by researchers at the University of New South Wales (UNSW), are reported this week in the high-impact journal *Nature Immunology*.

Studying a cell protein important in early immune response, the researchers led by Associate Professor Katharina Gaus from UNSW's Centre for Vascular Research at the Lowy Cancer Research Centre, used Australia's only microscope capable of super-resolution fluorescence microscopy to image the protein molecule-by-molecule to reveal the immunity 'switch'.

The technology is a major breakthrough for science, Dr. Gaus said. Currently there are only half a dozen of the 'super' microscopes in use around the world.

"Previously you could see T-cells under a microscope but you couldn't see what their individual molecules were doing," Dr. Gaus said.

Using the new microscope the scientists were able to image molecules as small as 10 nanometers. Dr. Gaus said that what the team found overturns the existing understanding of T-cell activation.

"Previously it was thought that T-cell signalling was initiated at the cell surface in molecular clusters that formed around the activated receptor.

"In fact, what happens is that small membrane-enclosed sacks called vesicles inside the cell travel to the receptor, pick up the signal and then leave again," she said.
Dr. Gaus said the discovery explained how the immune response could occur so quickly.

"There is this rolling amplification. The signalling station is like a docking port or an airport with vesicles like planes landing and taking off. The process allows a few receptors to activate a cell and then trigger the entire immune response," she said.

PhD candidate David Williamson, whose research formed the basis of the paper, said the discovery showed what could be achieved with the new generation of super-resolution fluorescence microscopes.

"In conventional microscopy, all the target molecules are lit up at once and individual molecules become lost amongst their neighbours - it's like trying to follow a conversation in a crowd where everyone is talking at once.

"With our microscope we can make the target molecules light up one at a time and precisely determine their location while their neighbours remain dark. This 'role call' of all the target molecules means we can then build a 'super resolution' image of the sample," he said.

The next step was to pinpoint other key proteins to get a complete picture of T-cell activity and to extend the microscope to capture 3-D images with the same unprecedented resolution.

"Being able to see the behaviour and function of individual molecules in a live cell is the equivalent of seeing atoms for the first time. It could change the whole concept of molecular and cell biology," Mr Williamson said.

Other research team members were physicist Dr. Dylan Owen, cell biologists Dr Jérémie Rossy and Dr Astrid Magenau, from the Center for Vascular Research, and Professor Justin Gooding and

Matthias Wehrmann, from UNSW's School of Chemistry and the Australian Centre for Nanomedicine.

Provided by University of New South Wales