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Singapore: Australian scientists have overcome one of the most pressing problems facing the pharmaceutical industry, how to create antibodies that are stable enough to meet stringent requirements necessary for production in large quantities, injection into patients and long-term storage.

Members of the Antibody Engineering Laboratory at Sydney's Garvan Institute of Medical Research, Dr Daniel Christ and PhD students Kip Dudgeon and Romain Rouet, have developed specific mutations that universally increase the stability of antibody molecules. The breakthrough finding has been published in the early online edition of the Proceedings of the Academy of Science (PNAS), the journal of the United States National Academy of Sciences.

"When we talk to collaborators in industry, we find that 30-50 percent of the antibody-based drugs they develop have to be put on hold because they don't meet quality tests that the companies or regulatory agencies such as the US Food and Drug Administration, require before marketing or approving these molecules," said Dr Christ.

"Until now, the issue of antibody instability has been tackled on a case-by-case basis, which is only tinkering with the problem. When you're dealing with such a diverse population of molecules, you have to make sure that the method you develop is generally applicable - and that's what we've done."

Produced by the immune system in response to infection, there can be as many as 100 million different kinds of antibodies in the circulation of a single human being.

Antibodies have 'constant regions' and 'variable regions', the latter determining the binding specificity of the molecule. The shape of the variable region will exactly match the 'antigen', or invader, in the same way as a lock matches a key.

With infinite variability of antibody structure comes varying levels of stability. It is fairly common, therefore, to have an antibody that is very good at binding to a specific antigen, but which is also very unstable. The mutations created by the Garvan team fix the stability problem without compromising the antigen binding properties of an antibody. â€¨â€¨Antibodies

consist of two chains - a heavy and a light chain - and Dr Christ emphasises that mutations have to work with each chain individually and both chains in combination.

"Typically you'd have both chains present in a therapeutic molecule, as well as additional biological activity, such as the ability to bind to a cancer target," he said.

"Our challenge was to maintain biological activity under very unnatural conditions, for which antibodies were not optimised by evolution. It is really when you take these molecules out of their natural environment, purify and concentrate them, that stresses become apparent. When used as a drug, antibodies are formulated at very high concentrations, for instance for delivery in a small syringe. You end up with an almost honey-like, highly viscous preparation. Under these conditions, antibodies can stick to surfaces like tubing and become entangled with one another. Our mutations make them much less sticky, much less entangled. They also make the antibodies more robust against common storage methods such as freeze drying." â€¨â€¨

The next step for the Garvan team will be to work with colleagues in the pharmaceutical industry to improve the stability of antibody therapeutics for the treatment of cancer and inflammatory conditions.