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Garvan Institute develops first-ever biologically stable antibodies

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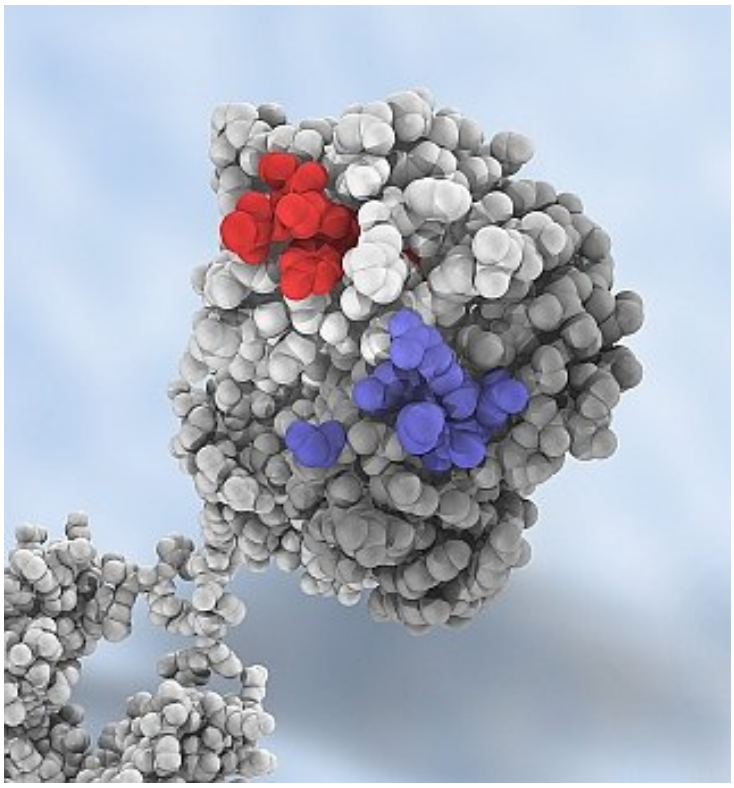

Singapore: One of the most challenging tasks ahead of pharmaceutical companies is to create antibodies that are stable enough to meet stringent requirements necessary for production in large quantities, injection into patients and long-term storage.

Antibodies often display limited stability and succumb to the stresses imposed during their manufacture, storage and use. In particular, protein aggregation often leads to failures in formulation of otherwise promising drugs. Until now such problems had to be handled on a case-by-case basis, with many monoclonals ultimately failing formulation studies. Dr Daniel Christ, director, antibody development laboratory, Garvan Institute of Medical Research; Dr Kip Dudgeon, post-doctoral research fellow, Garvan Institute of Medical Research; and Romain Rouet have developed specific mutations that increase the stability of antibody molecules.

In a conversation with *BioSpectrum*, Dr Christ and Dr Dudgeon talk about the importance of this breakthrough in the antibodies field. "Monoclonal antibodies have come of age and now represent more than half of all drugs entering clinical studies. Recent research in our laboratory has outlined a general strategy to overcome the limited stability and high aggregation propensity of human antibodies."

"More specifically, we have identified specific positions within antibody variable domains that control aggregation. Importantly, these mutations are independent of antibody sequence variation at other positions and compatible with antigen binding. We have been able to successfully apply these mutations not only to antibody libraries, but also managed to retrofit existing drugs such as the breast cancer drug Herceptin (Trastuzumab).

Our mutations allow the proteins to withstand extreme conditions (such as heating to 90°), while simultaneously increasing expression, purification and concentration yields," they added.

The team used high-throughput methods (phage display) to screen many different mutations for increased aggregation resistance. This unbiased approach revealed many surprising findings including, mutations in antibody heavy and light chains are in completely different regions, despite the fact the two chains are structurally very similar.

Both the members of the antibody development lab said that "Collaboration is an essential part of the process. Although our initial work was carried out in the academic environment of the Garvan Institute of Medical Research, we have had significant input from industry collaborators to examine and apply the technology."

Talking about the challenges involved in the production of antibodies, the researchers mentioned that "there are significant failure rates of lead molecules during pre-clinical development due to low stability or aggregation leading to failures in formulation. This places a large burden on pre-clinical development programs. This is further complicated by the move towards high concentration preparations for self-injection, as many antibodies aggregate under such conditions. Formulation changes alone are often not sufficient to overcome the problem. In contrast, we were able to show that a limited number of specific mutations can significantly increase the stability of human antibodies."

The next step for the researchers is to further apply the findings to real-world problems. For this, the researchers are currently working with partners in industry to apply this approach to clinical candidates.