Made to measure sugar-like molecule could improve cancer-fighting antibodies

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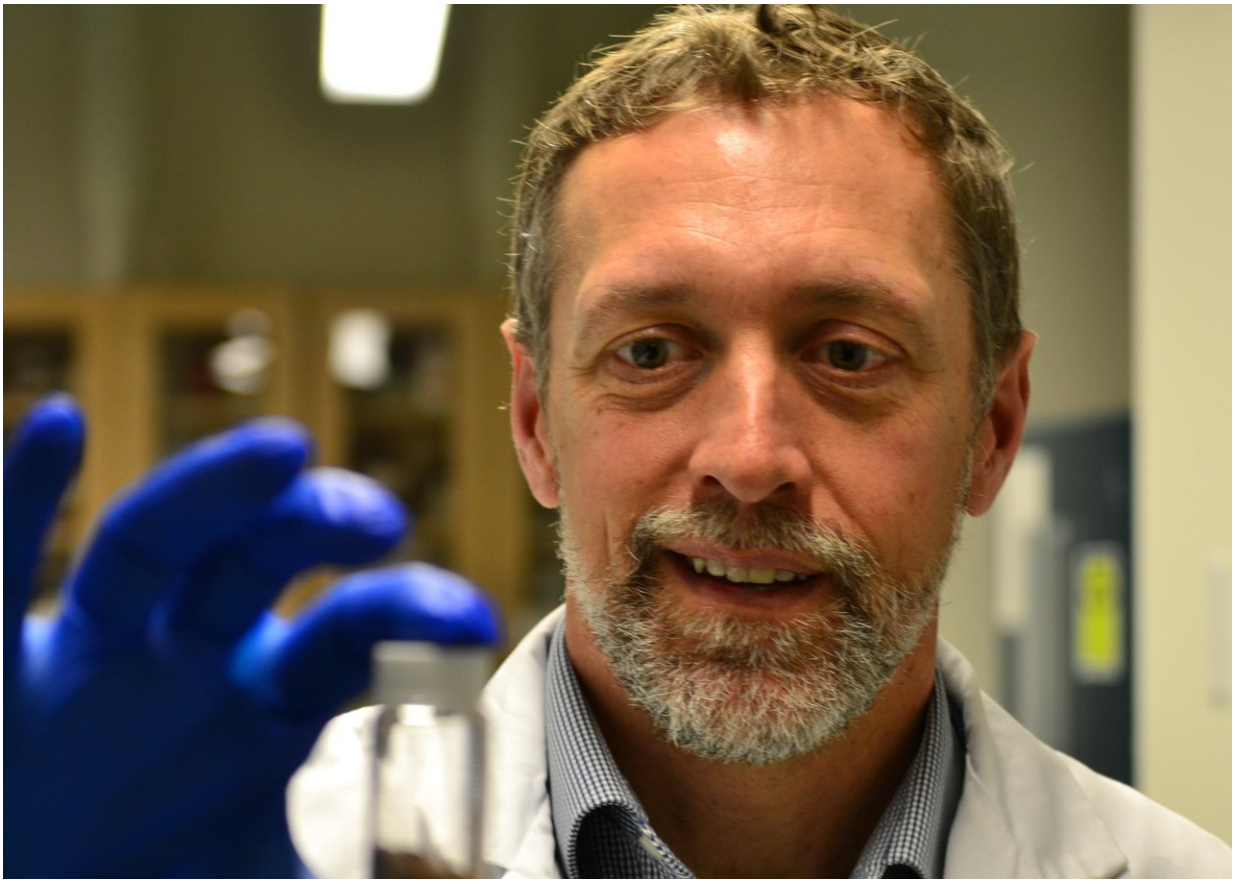

Dr. Robert Britton in his Simon Fraser University lab in Burnaby, BC. Credit: B. Poitras, GlycoNet

Dr. Robert Britton firmly believes every molecule is important. This

chemist doesn't want any molecule sitting unused on a laboratory shelf or in a fridge.

"I want every molecule to have a purpose—that's my ethos for our lab," says Britton, a GlycoNet network investigator and professor at Simon Fraser University.

With that spirit in mind, Britton has embarked on an ambitious project to develop carbohydrate mimics to assist cancer therapies by making them more selective in how they target and kill cancer cells.

In the 80s and 90s, it was recognized that traditional chemotherapies were limited as a result of the high systemic toxicity associated with targeting rapidly dividing cells. Researchers began to look at alternative approaches to specifically targeting cancer cells, including the development of antibodies which recognized and bound to proteins expressed on cancer cells.

This research led to the development and approval of the first two monoclonal antibodies (mAbs) for use in cancer therapy: rituximab (Rituxan) for non-Hodgkin's lymphoma in 1997 and trastuzumab (Herceptin) for breast cancer in 1998. Herceptin changed HER2+ breast cancer from a fatal disease where patients had a small chance of survival to one that is highly treatable

Britton's work focuses on the binding of the antibody to the cancer cell which leads to the recruitment of Natural killer cells and results in Antibody-Dependent Cell-mediated Cytotoxicity (ADCC). ADCC is a critical mechanism underlying the clinical efficacy of therapeutic anticancer antibodies. After the cancer cell is terminated, the human body will naturally get rid of it.

However, researchers have now identified that when antibodies have

fucose molecules attached (i.e. are fucosylated), they have lower levels of ADCC as the antibody's ability to attract immune cells is impeded, and studies have shown that removal/prevention of the fucosylation from antibody therapeutics elicits high ADCC.

"There has been a lot of effort and investment into ways to prevent fucosylation of antibodies so you can improve cytotoxicity," says Britton.

"The challenge in creating these molecules is that, while some companies are successful in inhibiting the transfer of fucose to the antibody, the inhibitor itself becomes attached to the antibody which may represent an imunogen and presents significant drug consistency risks"

Britton explains the goal of his project is to develop fucosylation inhibitors that do not transfer themselves to the antibody.

These molecules, fucosylation inhibitors, are what Britton and his research group are trying to identify and create. GlycoNet funding will provide the means to develop this set of inhibitors in the form of a Catalyst grant.

"These aren't simple molecules to make," says Britton. "They take real expertise, so GlycoNet funding allows us to hire highly qualified personnel to work on this project for one year. We couldn't do this without GlycoNet—it takes a lot of time, energy and expertise."

"We're excited by the prospect of Dr. Britton's research and we see the potential to translate this research into a practical, medical application," says Dr. Todd Lowary, Scientific Director of GlycoNet. "Dr. Britton's lab has the expertise and knowledge to produce these inhibitors and make this project a success."

While Britton's lab has a defined expertise in creating new molecules—20 researchers strong and a long history in chemical synthesis—producing these inhibitors for medicinal chemistry is a new direction for them.

Scaling up the synthesis will be a challenge, but if his lab is successful Britton hopes to attract industrial partners to test the inhibitors with antibodies for stability and cytotoxicity.

Once that happens, Britton says the next step is to license the inhibitors for commercialization.

"Because these molecules are going into the production of antibodies, there is a much clearer path from discovery to commercialization," says Britton. "If we can produce a good inhibitor, we anticipate a quick uptake from companies that would use it to produce these cancer-fighting antibodies."

Provided by Canadian Glycomics Network

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