

## Qu Biologics Developing CDx for Immunomodulator Drug to Treat Inflammatory Bowel Disease

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NEW YORK (GenomeWeb) — Qu Biologics, a Canadian firm developing a series of therapies for inflammatory bowel disease called site-specific immunomodulators, has discovered in a Phase 2 clinical trial that certain genetic traits predict a positive response in patients.

The firm is now working on a companion diagnostic test to tailor its follow-on trial and is seeking collaborators to develop an easy-to-use multiplex PCR-based diagnostic.

Founded in 2007, Vancouver, British Columbia-based Qu's therapies aim to repair the immune system in order to treat certain illnesses. Its site-specific immunomodulators (SSIs) are made from inactivated bacteria which happen to be endogenous to certain organs or tissues of the body.

"When the immune system responds to acute infection, it responds through the adaptive immune system, which is the basis of vaccination, but it also responds through the innate immune system," Qu's founder and CEO, Hal Gunn, explained in an interview.

The innate immune system is considered the body's first line of defense and, in a sense, has pre-programmed responses at the ready to pathogens that humans have been exposed to during evolution, Shirin Kalyan, the firm's director of scientific innovation, said. Yet the innate system might be less well understood than the lock-and-key antibody-based adaptive system, so it has historically been more of a challenge to modulate.

"It is our discovery that this [innate] response [to SSIs] occurs in an organ-specific way — instead of sending activated immune cells everywhere in the body, the innate immune system sends them to the organ or tissue in which that bacteria normally causes infection," Gunn said. Because of this feature of the immune system, the firm was able to create SSIs from specific bacteria that are both endogenous in people and also pathogenic in the organ or tissue where disease is occurring.

Any type of chronic inflammation typically suppresses innate immune function, he noted, so a wide range of diseases that might be considered very different from the perspective of the adaptive immune system all share this same feature of dysregulation of the innate immune system.

"Our goal is to restore the innate immune system in these diseases, and then once that is restored, the adaptive immune system dysfunction begins to resolve," Gunn said.

For example, to treat diseases in the gastrointestinal tract, the firm makes its immunotherapy from *Escherichia coli*. A therapy for asthma — the subject of a recently-published pre-clinical study in *Scientific Reports* co-authored by researchers at the University of British Columbia — was developed from *Klebsiella pneumoniae* bacteria. In the

study, mice treated prophylactically with the therapy prior to exposure to allergens showed reduced allergic response.

The company is undertaking clinical trials in Crohn's disease and ulcerative colitis — two types of inflammatory bowel disease — and has used patient samples to discover a subset of genetic changes that seem to influence response to SSI therapy in IBD patients.

Work on the genetic aspect of the studies, which was led by collaborator Dermot McGovern, director of translational research in the inflammatory bowel and immunobiology research institute at Cedars-Sinai, suggests the potential of a personalized medicine approach by using a companion diagnostic to identify IBD patients likely to respond and go into remission with treatment, said Gunn.

To discover the genetic changes associated with treatment response, the team analyzed approximately 250 different SNPs and mutations that were previously associated with IBD using an Illumina Omni human gene chip and focusing on IBD-related targets, Kaylan said.

The firm was inspired to examine these SNPs and genetic changes through literature analysis, and used a bioinformatics algorithm to parse difference in responders and non-responders. The company is now hoping to develop a companion diagnostic for the IBD treatment, preferably one that is multiplex PCR-based for about five to seven SNPs, and it is seeking collaborators for this aspect of the project. "If we could make it as practical as possible for patients and physicians, that would be great," Gunn said.

The SNPs are outside of coding regions, Kaylan said, so they may play more of a regulatory function. Coupled with the CDx, the therapy "may provide, for the first time, personalized medicine in IBD," Gunn said. And interestingly, the SNPs are also correlated with other immune-related diseases as well, so the CDx may prove to be more broadly useful in the future.

Unlike Qu's approach, therapies that are immune-based tend to focus on the adaptive immune response, while ignoring the innate response, Gunn said. Such is the case for the common current treatments for IBD, Remicade (infliximab) and Humira (adalimumab), which are monoclonal antibodies that act by suppressing the adaptive immune system.

"What is emerging in our understanding of IBD is that there is dysbiosis, or overgrowth of pathogenic bacteria in the GI tract, and chronic infection with a range of bacteria," Gunn said. Of the known SNPs and polymorphisms that predispose people to IBD, "Many of those relate to genes that impact innate immune function and the clearance of bacterial infection," he added, suggesting the possibility that an innate immune system dysregulation in patients may lead to the dysbiosis, and this bacterial overgrowth causes an adaptive immune response which leads to further damage.

"When you suppress the adaptive immune system, it does not help clear chronic bacterial infections, if anything, it makes that worse rather than better," Gunn said. "We're hoping that by treating IBD in a different way ... we're treating upstream, at the point where the genetics are impacting the disease," he said. If the genetic correlation is confirmed, the firm will be specifically be able to select for the 60 percent of Crohn's patients highly likely to go into remission with the drug.

"This would be a real advance, because currently with Remicade and Humira there is about a 50 percent chance of response and 35 percent chance of remission," Gunn noted, and the drugs are also associated with significant side effects because they act by suppressing immune function. "We're excited about it because the genes we've identified as correlated

to SSI function are highly relevant to recruitment of activated innate immune cells to clear bacterial infection."

Along with the optimal timing to restore mucosal health, the validity of the CDx test will be assessed in a follow-on to the Phase 2 trial. This will help determine the optimal patient group to move forward into Phase 3 trials and regulatory approval, Gunn said.

Qu is also evaluating its inactivated *K. pneumonia* suspension in a trial as a potential treatment for adenocarcinoma following resection of stage I non-small cell lung cancer. And a recent presentation by the firm noted that preclinical studies showed repeated subcutaneous administration of SSI therapy in animal models of lung cancer significantly reduced lung tumor burden at day 16 post-inoculation.

The firm will also be publishing animal model-based research this year using its therapies to treat chronic obstructive pulmonary disease, IBD, and lung cancer, and it plans to publish its clinical work in IBD and lung cancer as well. It is moving forward with a randomized control trial for a treatment for pancreatic cancer, also using the *E. coli*-based drug, and is developing treatments for immune-based skin disorders using inactivated *Staphylococcus aureus*.

Gunn initially discovered SSIs in his clinical practice, and has since obtained a number of intellectual property protections around it. As a clinician, he also founded supportive cancer treatment centers in Canada called Inspire Health. These centers are funded by the Canadian government, providing no-cost health and immune system support for cancer patients.

Qu Biologics has been supported by individual funders with C\$23 million (US\$17.2 million) to date, and is continuing to raise money. Gunn said he is hoping that the publication on Crohn's disease and SSIs will really launch the company and aid its mission to restore normal immune function to patients.

The treatments are considered drugs, Gunn said, and will be submitted to Health Canada for regulatory approval. Qu Biologics also plans to submit to the US Food and Drug Administration, and will include US sites in its upcoming clinical trials.

"The large majority of the most significant chronic diseases share suppression of innate immune function, so we think our treatment is potentially broadly applicable," Gunn said, including, potentially, ailments such as Alzheimer's disease or multiple sclerosis.