Coeliac Vaccine Research Update

Written by: Ruth Hoarau, Marketing & Communications Manager, Coeliac Queensland
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On Monday 22nd January, representatives from Coeliac Queensland attended a Brisbane-based information seminar regarding the research progress into a vaccination for coeliac disease. This interesting and complex subject has been summarised for our members below.

Dr Bob Anderson *(Chief Scientific Officer ImmusanT* - well known for his decades of research into coeliac disease) and Leslie Williams (*Founder, President and Chief Executive Officer ImmusanT),* both normally based in the USA, provided an update into the coeliac disease vaccine research while briefly in Australia. Queensland-based Gastroenterologist and coeliac disease expert, Dr James Daveson, facilitated the event, which was jointly hosted by QPharm and QIMR.

The vaccine in development – named **Nexvax2**® - is based on the same principles as desensitization therapy for allergies. The most important outcome of the session is that Nexvax2® is showing **excellent promise** as a genuine, future solution for people with coeliac disease. Whilst dozens of medical research projects are embarked upon globally, relatively few progress through Phase 1 and into Phase 2. Nexvax2® however, has successfully completed *four* Phase 1 stages (which have to some extent all been conducted in Brisbane at QPharm),and will shortly enter Phase 2. Phase 2 has an estimated research cost of $50m+, which indicates the level of confidence in the vaccine's potential.

Projected timeframe - The most pressing question for people with coeliac disease was regarding the likely timeframe of the vaccine being available. Understandably, the researchers were unable to commit to an estimated launch date due to the multiple variables and hurdles involved with medical research. As a guide however, Coeliac Queensland's interpretation of the information presented - assuming the research continues to progress as hoped - is that a commercially available vaccine is only **6-10** years away. Whilst this may sound dishearteningly distant to many, when you consider that an 8yo child with coeliac disease today may potentially have the opportunity to enter adulthood with reduced/eliminated coeliac disease symptoms, it puts into perspective the Nexvax2's potential to dramatically change the future of the disease.

Australian coeliac disease participants have been key to every stage of the vaccine research to date. For those eager to see the research progress as quickly as possible, further trials will require many willing participants to maintain the research momentum. We believe further clinical participant recruitment will likely commence this year, and we will inform members once this is known, for further consideration. Interested participants will need to meet a set of criteria necessary for the research outcomes, such as their gene type.

Gene Types – an important aspect of the vaccine is the gene type targeted by Nexvax2®. Earlier coeliac disease research identified that there are different **genes** that make an individual susceptible to developing coeliac disease. Of these, **DQ2** is the most common, identified in over 90% of coeliac disease patients. Other patients carry the gene **DQ8**, or even DQ2 and DQ8 combined. The immune systems of all three types of gene carriers react to different sets of gluten peptides. **Nexvax2® is designed to work for people with DQ2** being the most common gene type. However, it is hoped that future development will then logically extend to a vaccine variation for DQ8 gene carriers.

Among the other points of interest noted by Coeliac Queensland included the years of painstaking research that pre-empted the development of the vaccine prototype. Dr Bob Anderson and his group have studied no less than **17,000+** peptide fragments of gluten. Gluten is a group of proteins and in turn, proteins are composed of **peptides**. Their discovery that particular peptides cause the T-cell* (immune cell) response of an individual with coeliac disease to react, was integral to the development of the vaccine. *(*a T-cell is a type of white blood cell of vital importance to the immune system, as it acts in response to a specific pathogen (or in the case of coeliac disease, a gluten peptide)).*

What we know so far about the Nexvax2® vaccine:

o The **Nexvax2®** injection is intended to **reduce reactiveness** to gluten.

o Currently, the vaccine is delivered through a **series of injections.** The Phase 1 trial used a series of injections, with the dosage gradually increased to build tolerance to gluten. It was found that by starting with a very low dose, symptoms that people may experience when exposed to gluten were abolished. Although the first injections of Nexvax2® did cause some symptoms similar to those experienced by the participants when previously exposed to gluten, by later starting at a much lower dose these symptoms were largely abolished. Importantly, the series of injections at the Phase 1 dosage did not cause gastrointestinal damage and in fact showed trend towards an improvement.

o By injection number 16, the equivalent gluten dose delivered into the patient – without triggering any immune or symptom response – was the equivalent of approximately **two full loaves of standard bread**!

o After each injection, the body's immune reaction to the vaccine or to gluten exposure can be measured via a blood test. The subsequent increase in certain cytokines# can be tracked as peaking between **2 to 4 hours** after the injection *(#a cytokine is secreted by certain immune cells).* It appears that the cytokine increase corresponds with the symptoms experienced by some people with coeliac disease when exposed to gluten. Interestingly this response was turned off after the series of injections with the vaccine.

o **Will it give lifelong protection?** It is not yet clear if the vaccine will provide life-long protection like other vaccines currently do, or require an ongoing daily/weekly/monthly dosage; or at minimum, boosters at various stages throughout life. This will become clearer in time as the research progresses.

o **What's next? Stage 2** is projected to commence **this year**, and conclude next year. If all progresses as hoped, Stage 3 will be embarked upon immediately. At or after Stage 3, the vaccine will need to undergo the process of approval by the **FDA** (Food & Drug Administration in the USA). Following this, approval by the **TGA** (Therapeutic Goods Administration, here in Australia) will also be required.

o **Potential affordability** - Coeliac Queensland enquired on behalf of our members whether the researchers anticipated any challenges bringing an *affordable* vaccine to market. Whilst there is currently no tangible indication nor guarantee of pricing, and any product brought to market does need to be profitable in order for medical research and development to be viable, it was pleasing to learn that the Nexvax2® formulation components themselves currently do not contain any exorbitantly expensive molecules. This hopefully means a cost-effective solution is possible (unlike some other vaccines where the active ingredients are extremely rare or expensive to produce).

o **Coeliac disease is a whole-body ("systemic") condition** - the ill feeling caused by ingesting gluten probably isn't a result of damage to the digestive tract. In fact, the gluten triggers the body to produce T-cells, which in turn trigger an immune response. Although this can cause harm to the digestive tract (which can be seen under the microscope), as these cells are located in the bloodstream they seem to be able to affect other organs of the body, which adds to the ill feeling often experienced. Therefore, coeliac disease affects the whole body, such as other organs, muscles, bones and brain, which may vary between sufferers. This goes someway to explaining the 'brain fog' some patients describe, or muscle aches others experience after ingesting gluten.

o **Potential diagnostic applications** - a further benefit of the **Nexvax2®** research is its potential future application for aiding in the diagnosis of coeliac disease. In a person with coeliac disease, the cytokine "IL-2" will rise after about two hours; however, no such rise occurs in a non-coeliac gluten-intolerant patient. This means a person who hasn't been formally tested and diagnosed with coeliac disease - but has been following a gluten-free diet, or someone who may have been diagnosed many years ago and is following a gluten free diet though wondering if that original diagnosis was actually correct, could be (subject to further clinical trials) diagnosed as either having coeliac disease or not, based on this test. This would remove the need to expose patients to a lengthy gluten challenge, which is currently a deterrent for many.

o **Further information** is available on the ImmusanT website: http://www.immusant.com/clinical-development/celiac-disease-programs.php

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· *Daveson AJM, Ee HC, Andrews JM, King T, Goldstein KE, Dzuris JL, MacDougall JA, Williams LJ, Treohan A, Cooreman MP, Anderson RP. Epitope-Specific Immunotherapy Targeting CD4-Positive T Cells in Celiac Disease: Safety, Pharmacokinetics, and Effects on Intestinal Histology and Plasma Cytokines with Escalating Dose Regimens of Nexvax2 in a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study. EBioMedicine. 2017;26:78-90.*

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