Eye drug finds new life in Geelong diabetes trial: background, 23 April 2010

A drug used to treat eye disease in the 1970s is now undergoing clinical trial as therapy for type 2 or adult onset diabetes. The compound was unearthed as a potential treatment for diabetes by researchers at Deakin University's Metabolic Research Unit (MRU) using a clever new approach that monitors impacts on gene levels.

The repurposed drug, now known as VVP808, represents a new class of medicines to treat Type 2 diabetes, a chronic condition from which about 900,000 Australians suffer. In Type 2 diabetes, the body loses its sensitivity to insulin, the hormone that controls the ability of cells to take up sugar from the blood and process it. At its worst, the condition can lead to blindness, kidney failure, heart problems and amputations.

VVP808 has shown promise in restoring sensitivity to insulin both in cells in the laboratory and in mice—so much so that Verva Pharmaceuticals Ltd, a clinical-stage company based in Geelong, is sponsoring a Phase 2a trial at the Geelong Hospital to see whether the compound is safe and effective in humans. Several Melbourne hospitals are likely to join the trial in the coming months.

"Insulin sensitisers are important tools in diabetes therapy," says Verva CEO, Vince Wacher, "but significant side effects with existing products mean there is a market demand for a new sensitiser with improved safety and a different mode-of-action."

"With an appropriate development partner, and if VVP808 is effective in all of its trials, it could be in clinical use as early as six years from now," says Wacher.

Deakin and Verva's new approach to drug discovery

Verva was established in December 2007, by merging the diabetes interests of another Geelong-based company, ChemGenex Pharmaceuticals (ASX: CSX), with Brisbane obesity-focused biomedical company Adipogen Pharmaceuticals.

It was good timing. Many experts say diabetes is reaching epidemic proportions. Its incidence is increasing dramatically worldwide, in concert with the growth of obesity. The number of patients with diabetes in Australia is expected to double in the next 20 years. According to business information company Datamonitor, the multi-billion dollar worldwide market for diabetes therapy is expected to double faster than that—in only seven years.

The clinical trial of VVP808 will also be a test of the company's Gene Expression Signature (GES) drug-discovery technique. MRU researchers took technology originally developed for cancer research and applied it to diabetes, says the Unit's deputy director, Dr Ken Walder. The approach depends on microarrays, a means of assessing the levels thousands of genes simultaneously.

"We basically took cells in culture and made them insulin resistant," Walder said, "and then we reversed the insulin resistance using a cocktail of known anti-diabetic drugs." With microarray technology, the researchers could then compare the differences in levels between genes when cells were in a diabetic state and later, when insulin sensitivity was restored. Collective changes in the levels of a set of 7 to 13 genes were related to this.

Using this "gene expression signature", compounds can be screened for their effect on insulin-resistant cells. Their potential as diabetes medicines is measured by how closely they move the gene expression signature toward that of insulin sensitivity.

In this case, the technology was employed to screen a small group of drugs with a history of medical use. By virtue of their prior application, these compounds had already been tested for safety and side effects. VVP808 itself was used to treat eye disease in the 1970s, Walder said, but was superseded. Significantly, the researchers have found that VVP808 activity in diabetes does not occur through modulating any previously known diabetes targets.

One of the differences between the new GES approach and traditional studies, says Walder, is that it doesn't necessarily come up with a single protein as a target for treatment. "Diabetes is very complex. It's caused by hundreds of different genes and environmental factors, and they all conspire differently in different patients to cause insulin resistance. If you find an individual protein in a pathway and then you target a drug against it, the disease is so complex that there are often unexpected results. [At the MRU], we are trying to use the GES technology to classify the sub-type of diabetes each patient has and therefore to optimise treatment."

About the trial

Typically, diabetes is diagnosed by GPs, who manage the condition, at least initially, in the gentlest way possible—by diet and exercise. Only if that does not work, do they switch patients onto medication. Those overseeing the clinical trial are looking for about 80 people in Geelong and Melbourne who are now at that stage; approximately 40 people from the Geelong area.

The trial will involve participants taking VVP808 or a placebo for 24 weeks, during which time they will attend nine visits to a clinic to be weighed and tested. "It's a randomised, double-blind, placebo-controlled trial in people who have diabetes but have not been on any other medication," says Dr Geoff Nicholson, head of the Department of Clinical and Biomedical Sciences at the Geelong Hospital and leader of the study in Geelong.

"Geelong is internationally known as a particularly good area in which to undertake clinical trials," Wacher says. "It is the right size and diversity, and serves as a therapeutic hub for a regional population from which we can recruit trial participants. Geelong Hospital has good facilities, and the investigators and clinical team with whom we work have extensive laboratory and clinical experience with large international pharmaceutical companies."

The trial will be looking in particular at the impact of VVP808 therapy on blood glucose and HbA_{1c}, the standard markers for diabetes therapies. If VVP808 is effective, it will lower the levels of these markers in the blood. In addition, the researchers will monitor changes in weight, blood pressure and in the quantity and quality of fats in the bloodstream. They will also be checking, of course, for any possible side effects.

Next steps

With appropriate patient recruitment, the trial will run until early 2011.

Verva is already investigating how the structure of VVP808 can be modified and used to build whole families of drugs which are effective against diabetes under different circumstances. Wacher and his Board hope that a range of treatments, put together with the capacity of GES technology to split the diabetes community into sub-groups of different gene profiles, will prove a more efficient strategy for treating the condition than the one-size-fits-all medicinal approaches of the past.

Written by Tim Thwaites, Science in Public for Verva Pharmaceuticals.

Contacts

For further information: Niall Byrne, +61 (3) 9398-1416, niall@scienceinpublic.com.au and at www.vervapharma.com.

For interview: Vince Wacher PhD, CEO Verva Pharmaceuticals, +61 (448) 871 479, vwacher@vervapharma.com

Potential study participants or medical professional interested in learning more about the VVP808 clinical study, including risks and potential side effects, may call the study coordinator in Geelong on (03) 5226 7884.

For information on other study sites as they open please visit www.vervapharma.com.