

>>> endocrine mimetics – an opportunity for novel oral diabetes and cancer drug development

>>>market opportunity

Diabetes affects over 150 million people worldwide with the number of diabetics increasing rapidly. The estimated direct cost of the disease in the USA is over US\$100 billion annually.

Traditional therapies remain expensive, invasive and not as effective as needed. These also require constant close monitoring.

There is an urgent market need for a treatment that is non-invasive, stable in formulation, inexpensive and long acting. Treatments should be as effective as insulin, but avoid its side effects. The global diabetes drug market reached US\$11 billion in 2001 and is predicted to rise at an average annual rate of 28% over the next 10 years.

Cancer causes 25% of all deaths in the western world and is estimated to cost over US\$100 billion annually in the USA.

Most treatments are relatively non-specific, often with poor therapeutic indices when compared to treatments for other diseases.

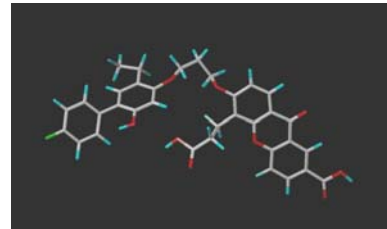
The worldwide market for anti-cancer therapies was over US\$8 billion in 2000, and is expected to grow at a high rate to US\$20 billion by 2010.

>>> project description

This project has utilised computer-aided drug design (CADD) to design compounds based on the atomic structures of insulin and insulin-like growth factor (IGF-1) molecules. These similar proteins are implicated in diabetes and certain cancers, respectively. The technology involves using 3D molecular maps (pharmacophores) to interrogate pharmaceutical libraries for leads.

Agonists and antagonists of insulin and IGF-1 receptors have been determined. In a recent trial, one compound (IM140) lowered blood glucose in diabetic mice. CADD has been used to design new compounds employing an insulin receptor homology-modelled on the published IGF-1 receptor atomic structure to accelerate lead compound identification, lead optimisation and drug design. Another compound (IM175) shows promise as a

template for developing novel anti-cancer agents, particularly breast and prostate cancers.



IM 140

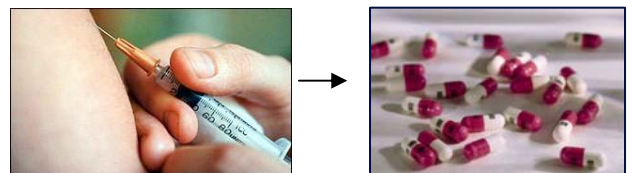
- > Privileged substructures
- > MicroM affinity
- > Binds to IR
- > Lowers blood glucose

Recently commissioned synthesis of compounds as "insulin mimetics" were prioritised for their "developability". These compounds are expected to have nanomolar binding affinities and other important qualities.

Expected Outputs of the Project:

- > *Orally available drug for type I and some type 2 diabetics.*
- > *Anti-cancer drug focussing on the IGF-1 pathway.*
- > *Insulin antagonist drug to block insulin action to treat insulinomas, congenital and adult hyperinsulinism (nesidioblastosis) and gastric dumping syndrome.*

>>>commercial application



A long-acting orally available glucose-lowering drug for Type I and Type II diabetes

>>>proposed 'go to market' strategy

The strategy is to add value to its IP by successfully completing pre-clinical studies of a number of drug candidates for the treatment of diabetes and cancer. Following successful Phase I clinical trials, EM will seek to partner major pharmaceutical drug companies to manage the financial and development risks associated with bringing drugs to market.

>>>competition

Diabetes: There is significant competition in diabetes with most attention placed on non-invasive delivery of insulin. Strategies include pumps, inhalers, nasal sprays, patches and capsules. All have their limitations and none have yet become viable, marketable products. Other approaches - transplantation of the pancreas and the insertion / cell graft of islet cells - have considerably more risk.

The most promising developments in recent times are the insulin promoters and sensitisers - "the Type 2 drugs". The shortcoming of these treatments is they cannot replace the effects of insulin and are therefore not suitable for Type 1 diabetes.

Insulin antagonist drugs: Only 2 drugs are presently used. Neither is specific in targeting the conditions; both have undesirable side effects.

Cancer: A number of different chemotherapeutic agents are presently in use but they all are relatively non-specific and this explains their severe side effects. The anti-cancer drugs being developed in this project will be designed to be more specific in their mode of action.

>>>intellectual property

An International Patent Application PCT/AU99/00786 (WO 0016798; 2000) is presently in the national / regional phase (priority date of 22 September 1998). Applications under review in the US aim to protect both the pharmacophore approach, the general design of molecules and matters of substance for the treatment of diabetes and insulin-related illnesses. Curtin University of Technology is the sole applicant of the patent. All the rights to exploit the technology vest with the Western Australian Biomedical Research Institute through Curtin University of Technology.

>>>progress

This project is focusing on a long-acting oral drug that acts like natural insulin by turning on the insulin receptor and lowering blood glucose. The IM140 compound has been used to design and commission new compounds. Target criteria have been set for drug compounds. Target binding affinity is < 500 nM, with > 50:1 affinity ratio for IR over IGF-1R. Target compounds are expected to have a logP > 1.5, serum stability ($t_{1/2}$ > 4 hrs), have "drug-like chemical sub-structures" and be able to lower blood glucose to below 3.5 mM in normal rats with a tolerable dose. These steps will provide clear proof of principle and will enable EM to design, commission and test second (and if required third generation) anti diabetic drug compounds.

Efficacy in animal models of diabetes will be evaluated. The STZ model is in-house; collaborations for other models exist. Safety evaluations to demonstrate that the compounds and metabolites are no more toxic than insulin will be pursued in both short-term and longer-term studies with a CRO.

>>>investment

EM is currently seeking investors and partners to assist in the development of these "break-through" products for the treatment of diabetes and cancer.

>>>further information

- > Associate Professor Erik Helmerhorst, Chief Investigator:
erik.helmerhorst@curtin.edu.au
- > Professor Simon Carroll, Director Western Australian Biomedical Research Institute:
simon.carroll@wabri.org.au
Tel: 61-8-9266 2133.