Minimizing Iatrogenic Effects of Clioquinol in the Treatment of Neurodegenerative Disease

[Ref No. T02343]

**Novelty** | University of Tasmania researchers have developed a therapeutic protocol to minimise the development of adverse side effects of a drug being developed as a treatment of neurodegenerative disease (i.e. iatrogenic minimisation).

Clioquinol was a registered antimicrobial drug that was taken off the market in 1970 due to peripheral neuropathy and blindness associated with its use. The mode of adverse action was however unknown. Recently, there has been renewed interest in the drug for the treatment of neurodegenerative diseases such as Huntington’s and Alzheimer’s disease.

The University of Tasmania has recently discovered that clioquinol and its derivatives appear to be inhibitors of a particular reductase (R1). R1 plays an important detoxifying role in the body and any impairment of this protein’s function poses significant risks to patients receiving therapies that require metabolic detoxification. An inactivating form of the R1 protein (a polymorphism) has been associated with the onset several forms of cancer, and carriers of the polymorphism are reported to have heightened sensitivity to environmental toxins.

The University of Tasmania has discovered an association between the cellular levels of R1 activity and cells’ sensitivity to clioquinol. While experiments continue, it is our expectation that this hypothesis explains why Asian populations (with naturally high R1 polymorphism) experienced the most clioquinol-dependent neurotoxicity (manifesting as blindness given the normally high level of R1 expression in the eye) when treated with clioquinol.

Further, as patients that have a polymorphic R1 or low R1 activity can be identified there is an opportunity to develop an assay that allows a more appropriate dosage regime to be designed or counter-indications to be recognised.

In order to minimise adverse side effects from administration of the drug, the University has filed for patent protection over a therapeutic protocol for treating a subject including determining the activity levels of R1 and whether or not the patient expresses functional R1 which is not substantially inhibited by the drug.

There are published assays to determine the activity of R1 that are easily adaptable for low cost point of care use, therefore when combined with the protocol offer low cost solution to minimise iatrogenic outcomes.

**Value Proposition** | The combination of known assays to determine the activity of R1 (that are easily adaptable for low cost point of care use) with the current protocol will avoid or minimise iatrogenic side effects likely to be suffered by at risk patient populations being treated for certain neurodegenerative diseases.

The present technology will also allow drug developers to reduce the time, cost and failure rates otherwise likely to be observed in clinical trials by tailoring the administration of a promising drug for neurological disease patients to the individual, based on R1 activity levels.
To provide potential licensees with commercial advantage, the University has protected the therapeutic protocol and method for determining the potential pharmacoefficiency of a drug via a patent application. This protection provides access to a defensive patent position that if granted, may delay entry of competitors into the market.

**Market** | The incidence of Alzheimer’s and Huntington’s disease is increasing. Alzheimer’s is the most common form of dementia. According to the World Alzheimer’s Report 2012, approximately 36 million people worldwide have Alzheimer’s disease; with 1 in 4 people over 85 having dementia. Similarly, Huntington’s disease typically begins later in life and is currently without a treatment. Following onset of symptoms, the average life expectancy is 15-25 years.

To date, the activity levels of R1 in those populations are unknown although there are some reports that they might be altered in AD. However, the inactivating polymorphism has been found to be frequent in Asia. In China, up to 50% of people have a polymorphism where they possess two different alleles for the gene responsible for R1 (heterozygous) which means protein activity is reduced by ~50% whereas 15% of the population have both alleles modified leading to extremely low levels of residual protein activity (i.e. homozygous), which means they are particularly sensitive to iatrogenic side effects from clioquinol and its derivatives.

**Technical Details** | The research team has *in vitro* data from human embryonic kidney cell lines (with the same genetic background (HEK293)) that sensitivity to clioquinol toxicity depends on the activity of R1.

Using mass spectrometry the research team has also confirmed that R1 does not detoxify clioquinol and have shown instead that *in vitro* clioquinol at a range of 10-100µM inhibits the enzymatic activity of the R1 (which does play a key role in detoxification). This inhibition occurs at the plasma clioquinol concentrations of patients using therapeutic doses of clioquinol. Further work is underway to demonstrate the dependence of clioquinol-induced toxicity on R1 activity in an *in vivo* model.

**Business Opportunity** | This technology is available for licensing or development opportunities to interested industry partners.

**Stage Development** | Early stage

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**Patent** | Australian Provisional Patent Application No. 2014904633

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