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In 2018 FightMND will commit another $7.6 million into MND research. Projects were assessed by a panel of both national and international MND experts and the research projects selected for funding include:

- Phase III clinical trial of TWOO1 (Oral Edaravone)
- Phase II clinical trial of Copper(II)ATSM
- Phase I clinical trial of mEphA4-Fc
- 2 Drug Development Projects
  + LAUR-301
  + GRT-X
- National Precision Medicine Program for MND
- Biomarker Facility at Flinders University, South Australia

OUR IMPACT

A snapshot of how the money has been invested to fight MND since 2014:

$28.6 million
Committed to research initiatives

$10 million
Seven new clinical trials

$8.7 million
Nine drug development research grants

$3.4 million
Other research grants, scholarships and initiatives

$4.5 million
World-first drug screening project

$2 million
Precision medicine program

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Clinical Trials

PHASE III CLINICAL TRIAL OF TW001 (AN ORAL FORMULATION OF EDARAVONE)

Background

The drug, edaravone is a free radical scavenger that targets oxidative stress, a process known to play an important role in the pathogenesis of MND. Analysis from clinical trials of edaravone have shown that it slows disease progression in a sub-group of patients who have been recently diagnosed and have lesser disability [for more info]. In 2015, the intravenous formulation of edaravone, known as Radicut®, was approved in Japan for the treatment of MND and in the USA it was approved under the name Radicava® in May 2017. Currently, it is not approved in Australia.

Radicut® and Radicava® are administered intravenously (like an intravenous drip) and the dosing regimen consists of 10 days of treatment, over a period of two weeks, followed by a 16-day drug holiday, a period in which the patient is not given edaravone. This method of administration is very taxing for patients who need to visit clinics/hospitals on treatment days and for doctors/nurses who need to administer the drug.

The Project.
Phase III TW001 trial

In 2015, Treeway, a biotechnology company in the Netherlands, demonstrated in clinical trials that adequate levels of edaravone can be obtained in the blood by oral administration of edaravone. At Treeway, orally administered edaravone is referred to as TW001. Treeway is developing edaravone as a formulation so patients can take it via the mouth (oral) each day as a sustained delivery medicine.

The clinical trial of TW001 is a large international phase III trial, with FightMND funding the Australia component. The trial will commence towards the end of 2019. The trial sites are still to be determined.

PHASE 2 CLINICAL TRIAL OF CUATSM ORAL SUSPENSION

Background

The development of copper(II)ATSM (CuATSM) as a treatment option for MND started around 15 years ago when it and related compounds were tested in animal models of neurodegenerative disease. Over the years, the laboratory-based evidences supportive of CuATSM being an effective treatment accumulated to the extent where clinical testing in MND patients became a legitimate possibility.

In 2016, FightMND helped to support the phase I clinical trial where CuATSM was given to MND patients as a therapeutic for the first time. Results from the phase I trial indicated that CuATSM was safe and well tolerated in MND patients and a dose was identified that would be used in the next phase of testing.

In addition to confirming that the drug is safe, reporting on the phase I trial also included descriptions of efficacy, however this result should be taken with caution as the number of patients included in phase 1 testing (for any drug) is kept small by necessity, and phase 1 trials are not designed to demonstrate efficacy. For example, all patients in the phase 1 trial knowingly receive the drug and there is no placebo control group for direct comparison. So, while the phase 1 results support progressing CuATSM to a phase 2 trials, there is still a considerable amount of work to do before it can be confirmed that CuATSM is an effective treatment for MND.

The Project.
Phase II CuATSM trial

This phase II study is being run by the company Collaborative Medicincal Development and will test an oral suspension of CuATSM in MND patients in both Australia and the USA. This study will be larger than the phase I study and has been designed as a placebo-controlled trial where both participants and doctors will be blinded to whether the participant

is in the placebo or drug group. These factors, plus a number of other important aspects of the study design are vital when investigating the efficacy of a new drug. Outcomes from this phase II trial will confirm that CuATSM can be safely administered to MND patients and provide evidence of the efficacy of CuATSM in slowing disease progression.

PHASE I TRIAL OF MEPHA4-FC IN MND PATIENTS

Background

The molecule EphA4 plays an essential role in both the formation and function of the locomotor system where nerve cells connect with muscles to control movements. Work from Prof Bartlett's laboratory has shown that blocking EphA4 with a drug called mEphA4-Fc improved functional performance and life span in an MND mouse model by preventing the death of motor neurones. Researchers propose the drug mEphA4-Fc may be able to slow disease and protect motor neurons in MND patients.

In 2017, FightMND awarded Prof Perry Bartlett's team a grant to fund a project focused on preparing this new compound for testing in a phase I trial. This project included scaling up the manufacturing of mEphA4-Fc, quality control to ensure the drug is high-quality and suitable for clinical testing as well as safety and toxicology studies and mEphA4-Fc is now ready for testing in a phase I trial.

The Project. Phase I mEphA4-Fc trial

This project, led by Prof Perry Bartlett at the Queensland Brain Institute, is a phase I safety trial that will examine the safety and tolerability of mEphA4-Fc in MND patients. This study is the first time that mEphA4-Fc will be tested in humans. The study is expected to begin in the middle of 2019 and be completed in late 2021. Positive outcomes from this trial will support mEphA4-Fc to be progressed through to the next phase of testing.

Drug Development Projects

V-SMART® NANOMEDICINE FOR THE TREATMENT OF ALS/MND (LAUR-301)

Background

GDNF is a protein that supports the health of neurones and has been shown to protect dying motor neurones in MND mice. However, GDNF does not have good drug-like properties for treating MND as it cannot penetrate the brain and reach its target cell, the diseased motor neurones.

Lauren Sciences LLC, a private New York biotechnology company, has developed an innovative nanovesicle platform technology, called V-Smart®, to encapsulate and deliver non-brain penetrant molecules across the blood-brain-barrier (BBB), target sites in the brain and selectively release molecules at these target sites. Importantly, V-Smart® nanomedicines developed with this technology can be administered non-invasively.

Lauren Sciences has shown that their V-Smart® Nanomedicine LAUR-301: encapsulates GDNF, maintains GDNF activity, targets cells, delivers and selectively releases dose-dependent amounts of GDNF in the central nervous system (CNS, i.e., brain and spinal cord) of normal mice, without toxicity.

The Project. Pre-clinical testing of LAUR-301 in MND mice

The researchers will now test whether LAUR-301 can deliver GDNF in MND mice, protect dying motor neurones, reverse or slow down progression of

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MND disease and increase lifespan. Successful results from this project will lead directly to future development of LAUR-301 to be progressed towards a phase I clinical trials.

INVESTIGATING THE THERAPEUTIC POTENTIAL OF GRT-X IN HUMAN AND MOUSE MODELS OF MND

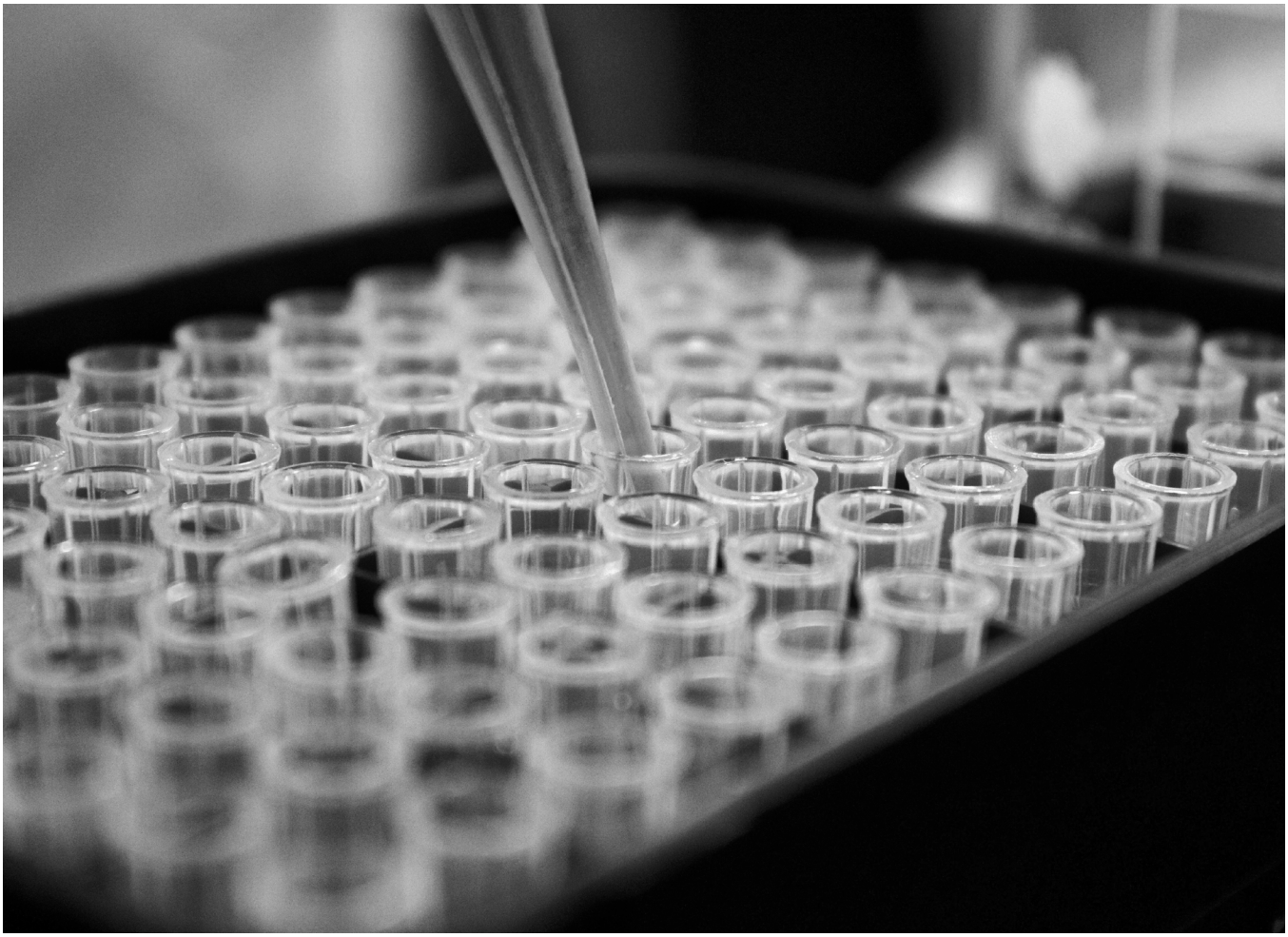
Background

This project brings together 3 academic researchers with differing but internationally acclaimed expertise in MND and a pharmaceutical company with a unique a promising drug, GRT-X.

GRT-X is a promising therapeutic as it acts simultaneously on two neuroprotective mechanisms that can reduce the rate of motor neurone loss, which will hopefully slow the progression of the disease. GRT-X has been shown to reduce hyperexcitability, commonly seen in MND motor neurons, and reduces inflammation and inflammatory pathways.

The Project.
Pre-clinical testing of GRT-X in human and mouse models of MND

This project will test the ability of this new drug GRT-X, to slow MND disease progression in MND mice. It will also investigate how the drug is having protective effects on motor neurons and determine if GRT-X is a good drug to be advanced into the clinic.



National Precision Medicine Program

This is a large scale national collaborative project that aims to accurately classify/group MND patients according to their genetic, molecular and clinical profiles using innovative stem cell models and systems biology approaches to predict and tailor treatment options for each individual patient.

This project involves a vital collaboration between:

- MND patients and clinics
- the Centre for Eye Research (CERA) led by Associate Professor Alice Pebay
- the Australian MND Registry (AMNDR) led by Associate Professor Paul Talman
- the Sporadic ALS Australia Systems Genomics Consortium (SALSA-SGC) led by Professor Naomi Wray, and
- the FightMND Drug Screening Program at the Florey Institute of Neuroscience and Mental Health led by Associate Professor Brad Turner

The Project workflow

MND patient and control subject blood will be collected for genomic analysis by SALSA-SGC. Skin cells will also be collected and reprogrammed into stem cells which are differentiated into motor neurons in the dish. MND and healthy control motor neurons will be profiled using genetic, protein and metabolism approaches to construct disease pathways and networks. Genetic, molecular and clinical data obtained from AMNDR will be integrated using systems biology and big data analysis. Disease signatures will be generated and used to subtype MND patients according to genetic, molecular and clinical profiles. Patient motor neurons will then be subject to targeted and personalised drug screening guided by disease signatures and subtypes, in an effort to advance drug candidates to clinical trials in MND patients.

Expected outcome: This project will lead to a better understanding of the Australian MND population and improved recruitment of patients into clinical trials: the right drug for the right patient at the right time.

This project is supported by the Australian Government through the Medical Research Future Fund.

MND Biomarker Facility

FightMND is providing the funding for the purchase of cutting-edge robotics to fast-track the assessment of MND biomarkers in patient samples from both Australian and international Clinical Trials. Biomarkers help to track disease progression and aid in the development of therapies by providing a read out of whether or not the therapy is effective. Flinders University have developed a world-first urine test (biomarker) that can reliably be used to determine MND disease progression.

Expected outcome: This will establish a high-through screening facility to assess MND patients' response to new therapeutics.