Q&A with Professor Alexandra Sinclair

Co-Founder, Executive Director & Chief Scientific Officer, Invex Therapeutics Ltd
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Background

Invex Therapeutics Ltd (Invex; the Company) is a biopharmaceutical company focused on the repurposing of an already approved drug, Exenatide, for efficacious treatment of neurological conditions characterised by raised intracranial pressure, such as Idiopathic Intracranial Hypertension (IIH), acute stroke and traumatic brain injury.

Invex successfully completed an Initial Public Offering (IPO) to raise A$12 million and commenced trading on the Australian Securities Exchange (ASX) on 5 July 2019.

The Company's focus is on developing and commercialising more than ten years of scientific discovery and technology development by Professor Sinclair and her team at the University of Birmingham into treatments for reducing intracranial pressure.

Q&A

Can you please briefly explain what IIH is?

IIH is a condition of unknown cause but associated with obesity, younger age and females. The condition results in raised pressure in the brain and can cause disabling headaches and loss of sight by compressing the optic nerve (papilloedema).

Patients with IIH may also suffer from other symptoms that include pulsatile tinnitus, back pain, dizziness, neck pain, visual blurring, cognitive disturbances, radicular pain and horizontal diplopia.

Current therapies lack efficacy leaving patients with chronic disability and its incidence is increasing rapidly as seen by a more than three-fold increase between 2005-2017.

What is Exenatide?

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist which was first approved for therapeutic use by humans by the European Medicines Agency (EMA) in 2006 and the U.S Food & Drug Administration (FDA) in 2005 for the treatment of type II diabetes.
The GLP-1 receptor is a receptor found on the surface of certain cell types, including the beta cells of the pancreas where it is involved in the control of blood sugar levels. GLP-1 receptor agonists have been widely developed for diabetes and a number have reached the market in

this indication and are in widespread use. They are well tolerated and don't cause hypoglycaemia.

Recent publications from my research group at The University of Birmingham, UK, have demonstrated that the GLP-1 receptor agonist exendin-4 (Exenatide is a synthetic form of the 39 amino acid peptide exendin-4) reduces cerebrospinal fluid (CSF) secretion in-vitro. In particular, tissue sections and cell cultures were used to demonstrate the expression of the GLP-1 receptor in the choroid plexus, the signalling pathway through Cyclic Adenosine Monophosphate, (cAMP), Protein Kinase A and ultimately effecting the Na^+K^+APTase ion channel (a principle ion exchanger responsible for driving secretion of cerebrospinal fluid). When Exendin-4 was given to rodents with markedly raised intracranial pressure the pressure dropped significantly with both acute and chronic dosing.

Invex is focused on reformulating Exenatide, which is largely off-patent in the major territories (US and EU), to deliver it in a way that enables exploitation of its previously unknown ability to reduce cerebral spinal fluid secretion in the choroid plexus of the brain to treat conditions involving raised intracranial pressure.

Invex is also aiming to broaden its patent protection through disease informed repurposing of Exenatide and thereby position it for use in indications other than type II diabetes.

How will the A$12 million in funds raised from the IPO be used?

Invex plans to use the funds to support the expansion of its intellectual property portfolio, complete the repurposing of Exenatide for the treatment of neurological conditions characterised by raised intracranial pressure and finalise an on-going Phase II clinical study in IIH - the IIH:Pressure trial.

What is the benefit to your research of listing Invex in Australia?

It means that our research into IIH and other raised intracranial pressure conditions can advance and enable us to fast track development success more rapidly towards commercialisation. Recognising that the success of Invex will ultimately provide widespread help for those suffering from these debilitating conditions.

Is the University of Birmingham involved in an ongoing basis with your research now that Invex has the intellectual property and patent portfolio?

My research group at Birmingham is fully focussed on exploring the basic science of raised intracranial pressure conditions. I have a track record of successfully delivering more randomised clinical trials in IIH than any other research group internationally. This year I was voted onto the board of the International Headache Society and will be leading the drafting of the first guidelines for clinical trial outcomes in Idiopathic Intracranial hypertension. I also sit on the European Headache Federation board and the research Committee for the North American Neuro-ophthalmology Society. These key international leadership roles ensure I am at the forefront of science, clinical research and policy. My expertise and leadership will be key to delivering successful clinical trials with Invex in the future.

As a clinician and global leader in the treatment and pathophysiology of IIH, your extensive preclinical research has demonstrated that Exenatide, already approved for treatment of type 2 diabetes, can reduce intracranial pressure in animal models – as published in 2017 in leading scientific journal *Science Transitional Medicine*. What are you now doing under Invex?

I am the CSO of Invex and am therefore intimately involved in the process of repurposing Exenatide to optimise the delivery of the drug for patients with diseases involving raised intracranial pressure. I bring my knowledge of the basic science as well as my clinical insights into the development process as well as in the patenting of our discoveries to underpin the company's commercialisation efforts. In addition, I am the Chief Investigator on our randomised double blinded Phase II study of Exenatide in IIH (IIH:Pressure), which is currently progressing to plan and where we expect to publish data in the first half of 2020.

In my role as Professor of Neurology at University of Birmingham, I published the first International IIH disease management guideline in the Journal of Neurology, Neurosurgery, and Psychiatry. I work closely with the patient community and was the lead clinician for the IIH research priority setting exercise which highlighted the absolute importance of bringing through new drugs to treat IIH (British Medical Journal Open 2019).

When are results expected from this Phase II study?

The study has progressed ahead of schedule and we have enrolled all 16 required patients. The last patient was enrolled on 15 October 2019. Having completed recruitment and dosing ahead of schedule the Company is pleased to confirm the last patient is likely to receive the final dose in early 2020. If that remains the case then the Company will report full results of the clinical trial in the first half of calendar year 2020 which is very exciting, and Invex will keep all shareholders and stakeholders informed of progress.

Does Invex have an Intellectual Property Portfolio?

The Company is actively pursuing patent applications at both the European and the US patent offices. On 7 October 2019 the Company announced that patent number 2017-512008 had been granted by the Japanese Patent Office. This patent relates to the treatment of undesirable increased intracranial pressure. Elevated intracranial pressure is observed in subjects with IIH as well as a broader group of diseases including, but not limited to, secondary pseudotumour cerebri, hydrocephalus, normal pressure hydrocephalus, meningitis, brain trauma, brain injury and venous sinus thrombosis.

This is a significant first step in securing world-wide protection for Invex's drug candidates and we will continue to work with the patent offices of other jurisdictions to secure similar protection in other territories.

What led to your focus on Exenatide as a possible treatment for IIH?

My inspiration to evaluate the role of Exenatide (a GLP-1 receptor agonist) in regulating intracranial pressure stems from data highlighting the ability of this class of drugs to regulate fluid transport in the kidney. As such I investigated this pathway in the fluid secreting structure that produces brain fluid and our discovery subsequently proved correct.

Can you expand more on the strategy of repurposing of an already approved drug?

Drug repurposing is a well-established and relatively lower risk approach to drug development. It is defined as identifying and developing new uses for existing drugs.

By utilising a repurposing process, rather than undertaking novel drug discovery, the time required to develop the drug is usually shorter, the costs are lower, and the process is less risky.

By exploiting the excellent safety record of Exenatide and successfully repurposing the drug to address disease specific challenges, Invex intends to progress expediently to clinical evaluation and undertake the registration of different formulations of Exenatide optimised to treat different neurological conditions.

Are there other raised intracranial pressure conditions which are applicable to your research?

There are a number of neurological conditions derived from or involving intracranial pressure, these include IIH, acute stroke, hydrocephalus, venous sinus thrombosis, brain tumours, meningitis, secondary pseudo tumour cerebri and traumatic brain injury. Invex will initially focus on its Phase II clinical study in IIH (IIH:Pressure), followed by proof of concept studies in other conditions.

NASA has shown an interest in your research for reducing intracranial pressure. Can you please tell us about your relationship with NASA?

The University of Birmingham and my research group hosted a high profile visit from NASA in June 2019. NASA is interested in our expertise on raised intracranial pressure stemming from our leading IIH clinical service at University Hospital Birmingham coupled with my translational science portfolio at the University of Birmingham. Astronauts develop raised intracranial pressure with prolonged spaceflight. My recent discovery of the novel use of GLP- 1 receptor agonists like Exenatide to reduce intracranial pressure are of particular interest to the NASA team in their quest to reduce brain pressure during long duration space travel and allow them to go beyond the Moon.

What are the commercial opportunities in finding a treatment(s) for raised intracranial pressure?

Invex believes there are a number of significant commercial opportunities in developing a drug for IIH sufferers including:

• a large market underpinned by a pool of poorly treated existing patients coupled with accelerating incidence in-line with growing obesity in Western countries;
• repurposing of an already approved drug, Exenatide, which has a record of safe use over extended periods in significant numbers of diabetic patients (Byetta®) and with which regulators in the EU and the US are already familiar, thereby enabling the Company to potentially decrease development costs, speed up development and reduce the Company's overall development risk;
• novel formulations (of Exenatide) to extend the period of patent protection, improve efficacy and safety; and
• other related indications to diversify the Company's development portfolio, reduce risk and create further value.

What is Invex's growth strategy?

Invex intends to, subject to conducting successful clinical trials, drive growth by exploiting the wealth of data already available on the safety of Exenatide combined with its proprietary knowledge of diseases caused by raised intracranial pressure to expediently get a first product to market in IIH.

In order to diversify the Company's operations, Invex also intends to pursue other disease indications with the same drug repurposed specifically to match the needs of each disease. Commercialisation and growth could be further accelerated through establishing key partnerships for manufacturing, as well as marketing, rather than establishing these capabilities within the Company itself.

This growth strategy is underpinned by Invex's commitment to ongoing technology and product development, which aims to maintain and develop the Company's position in the biopharmaceutical and therapeutics space and continuously develop and improve the performance of the Company's products.

How will Invex commercialise and generate revenue?

When and if Invex is successful in establishing safety and efficacy of a repurposed Exenatide in clinical trials agreed with regulatory authorities, it plans to seek marketing partnerships with major pharmaceutical companies for commercialisation in large markets, such as the EU and US. The Company will also consider developing a direct sales capability in Australia.

This approach is a well-established, and generally successful, route to market for smaller biopharmaceutical companies. It will serve as a means of developing a return for shareholders either through revenue generation under licensing agreements (upfront, milestone and royalty payments) or through the outright sale of the Company (or its assets).

Should the Company proceed to commercialisation of a repurposed Exenatide, it intends to secure manufacturing capacity for its product(s) with potential commercial contract manufacturers. The Company believes this is a well-established approach within the pharmaceutical industry and will help to reduce capital expenditure.

What are the next steps for Exenatide, IIH and Invex?

Invex has the necessary commercial strategy, partnerships, leadership and a world class scientific team in place to make a difference and provide real solutions for patients of diseases involving raised intracranial pressure. Our research is ongoing and we aim to publish findings in prestigious scientific journals. Our relationships with organisations such as NASA and IIH UK will also continue to thrive and drive further research and potentially successful outcomes.

We will continue our efforts to repurpose Exenatide and optimise the delivery of the drug for patients with diseases involving raised intracranial pressure and we are progressing our randomised double blinded Phase II study of Exenatide in IIH (IIH:Pressure) where we have already enrolled all 16 patients required.

Results of our repurposing development and Phase II trial will be released when completed and we will keep all stakeholders informed of progress on a regular basis. There is still a lot of work to be done but we are confident in our team, abilities and knowledge and will continue to work hard to achieve positive results for patients, shareholders and all our stakeholders.

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