Interview with Co-founder and Scientific Board Member of Cynata, Professor Igor Slukvin

Melbourne, Australia; 11 January 2018: Australian stem cell and regenerative medicine company, Cynata Therapeutics Limited (ASX: CYP), is pleased to provide the market with an interview with Cynata Co-founder and Scientific Advisory Board member, Professor Igor Slukvin.

In this Q&A, Professor Slukvin focuses on the unique benefits of Induced Pluripotent Stem Cells (iPSCs), the importance of iPSCs in Cynata's Cymerus™ manufacturing process, and their significance more broadly in stem cell medications.

Professor Igor Slukvin is Professor of Pathology and Laboratory Medicine and Cell and Regenerative Biology at the University of Wisconsin-Madison, School of Medicine and Public Health. His work has elucidated the developmental pathway for mesenchymal stem cells including identifying a novel precursor for endothelial and mesenchymal stem cells, mesenchymoangioblasts (MCAs). He completed postdoctoral and medical residency training at the University of Wisconsin, has published over 85 peer reviewed research papers, and serves on several editorial boards. Professor Slukvin holds key patents in the area of haematovascular cell production from human pluripotent stem cells, several of which form the core of Cynata's intellectual property portfolio, and is a co-founder of Cynata and of Cellular Dynamics International, previously listed on Nasdaq but acquired by FUJIFILM in 2015 for US$307m.

Q&A with Professor Igor Slukvin

What are iPSCs?

iPSCs are cells that that have been reprogrammed by treatment with defined factors back into an embryonic-like pluripotent state. Pluripotency means the ability to develop into an unlimited source of any type of adult human cell.

How are iPSCs derived/sourced?

iPSCs may be derived from nearly any cell in the body; typically cells from the skin or from blood are used. The process to derive iPSCs was the result of ground-breaking discoveries in 2006 by researchers in Japan and here at the University of Wisconsin – Madison. One of the researchers in Japan, Shinya Yamanaka, was awarded the Nobel Prize in 2012 for his role in describing the process to derive iPSCs. The discovery has been a game-changer for stem cell research and therapeutic product development. iPSCs have been central in making the manufacture of Cynata's Cymerus™ mesenchymal stem cells (MSCs) possible.

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What makes them so unique?

What makes iPSCs unique is their embryonic-like properties, their ability to be cultured (the process of growing cells in an artificial environment) indefinitely and to be developed into almost any type of human cell. This makes iPSCs the ideal source material for the development of therapeutic stem cell treatments. It is this unique ability of iPSCs that make them the optimal starting material for our MSCs and this also enables us to overcome the existing challenges faced by stem cell therapies, which require multiple donations using invasive procedures, such as bone marrow aspiration – limiting the scalability and expandability.

What is the difference between embryonic stem cells and iPSCs?

iPSCs are derived from adult cells that have been turned into an embryonic-like state. Embryonic stem cells, on the other hand, are derived from embryos.

Are the ethical challenges associated embryonic stem cells relevant to iPSCs?

No, iPSCs are not affected by the controversy surrounding embryonic stem cells. The perceived issue with the use of embryonic stem cells is that the embryo is destroyed in the process of isolating the stem cells, and some people take the view that a fertilised embryo is a human life in its own right. While many others strongly disagree with that view, especially within the scientific community, the vociferous opposition from some quarters continues to hamper progress with embryonic stem cell research. Conversely, iPSCs are derived from adult cells, and iPSC production does not involve the use of embryos. Importantly, whilst iPSCs are derived from a totally different source than embryonic stem cells, both cell types have very similar properties, hence the enormous worldwide interest in their use in therapeutic applications.

Why are iPSCs so important to the Cymerus process?

IPSCs are the starting material to manufacture our therapeutic MSC products. The pluripotent state of the iPSCs means they can be expanded (grown) indefinitely, making them an effectively limitless raw material. Cynata's proprietary Cymerus process then causes the iPSCs to differentiate into MSCs.

How are MSCs created from iPSCs?

MSCs have unique and valuable therapeutic properties that are not shared by iPSCs. So, we developed a novel way of culturing the iPSCs, using special growth medium supplemented with particular growth factors, which causes the cells to differentiate into MSCs. This involves first producing important precursor cells called mesenchymoangioblasts (MCAs). This is the core of Cynata's unique Cymerus technology: the ability to cause pluripotent cells like iPSCs to differentiate into MSCs. The Cymerus platform has unique intellectual property that enables the creation of MSCs for therapeutic use. It can produce consistent, economical and virtually limitless quantities of MSCs, which means we won't need to constantly seek fresh stem cell donors or massively expand the MSCs themselves to fuel manufacturing demands.

Why do you believe allogeneic iPSC-derived MSCs could be significantly more useful than bone-marrow derived MSCs?

The process for deriving MSCs from bone marrow requires a donor who is prepared to undergo a bone aspiration, a surgical procedure that involves pain and risk to the donor. The MSCs in the donation are present only in very small amounts and have to be massively expanded in culture to produce sufficient product for even a small number of doses. Therefore, to manufacture even a modest quantity of product for allogeneic use (i.e. when the product comes from another person) requires many donors (all of whom are different and so have different MSCs) and/or even greater expansion in culture. Culture expansion has been shown in scientific studies to be problematic for MSCs as they appear to have a limited capacity to do this before they lose their medically useful properties; this process is called replicative senescence. The use of iPSCs as a starting material in the Cymerus process addresses all of these profound shortcomings, as this facilitates the production of an effectively limitless number of doses from a single blood donation, without the need for excessive MSC culture expansion.

What is unique about the GvHD trial?

This is the first formally-conducted allogeneic iPSC clinical trial in the world. Never before have iPSC-derived cells been used in a human clinical trial. Given the enormous interest in iPSCs it is not surprising that much international attention is focused on Cynata and this trial.

Are iPSCs being used in other trials?

The therapeutic potential of cells derived from MSCs is the subject of intense investigation around the world. A clinical study is presently underway in Japan using a type of eye cell derived from iPSCs and it is likely more trials will get underway this year, for example in Parkinson's disease.

Tell us about the work you and the team were doing that led to the ground-breaking discovery that MSCs could be differentiated from pluripotent cells such as iPSCs?

My team is focused on studying vascular and hematopoietic differentiation from iPSCs with the goal to advance the clinical use of stem cells for blood transfusion and regeneration, cancer immunotherapy, and vascular repair. Identification of MSC precursors and developing methods for MSC generation from iPSCs was very critical for us, because MSCs contribute to the formation of vascular wall, the hematopoietic stem cell niche in bone marrow and connective tissues. In addition, MSCs are widely used for cellular therapies and tissue engineering. Studies by Dr. Maxim Vodyanik in my laboratory revealed that MSCs in iPSC cultures develop from a common endothelial and MSC progenitor, MCAs. This discovery was really critical because it allows the generation of well-defined and uniform MSC lines that can be expanded (ie proliferated) many times in culture.

What were the next steps after the invention?

After we filed patent applications and published our scientific paper on MCAs in the journal *Cell Stem Cells* in

2010, I got an email from Ian Dixon, an entrepreneur from Australia. Ian realized the advantages and enormous potential of our iPSC technologies for MSC production, especially the potential to overcome the clear shortcomings of MSC production from adult stem cells, such as derived from bone marrow. Ian proposed to start a company with the goal to commercialise our discovery which eventually led to the establishment of Cynata Therapeutics.

Where do you believe iPSCs could take us in the future?

iPSCs offer a platform for industrial manufacture of off-the-shelf cellular products for tissue repair and immunotherapies. The iPSC field is rapidly evolving and the energy (and capital) going into iPSC research is extraordinary. Methods for scalable production of different types of cells, including blood, heart, vascular and connective tissue cells, all derived from iPSCs, have been already developed. Based on these advances numerous venture-financed companies pursuing iPSC technologies have been established. The most significant task at current stage is to establish the safety of cells manufactured from iPSCs and guidelines to determine their quality. It is also important to determine the setting in which allogeneic iPSCs can be used and conditions which will require autologous iPSCs. I believe that within next decade several iPSC products will be approved for clinical use and became commercially available.

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About Cynata Therapeutics (ASX: CYP)

Cynata Therapeutics Limited (ASX: CYP) is an Australian clinical stage stem cell and regenerative medicine company that is developing a therapeutic stem cell platform technology, Cymerus™, originating from the University of Wisconsin-Madison, a world leader in stem cell research. The proprietary Cymerus™ technology addresses a critical shortcoming in existing methods of production of mesenchymal stem cells (MSCs) for therapeutic use, which is the ability to achieve economic manufacture at commercial scale. Cymerus™ utilises induced pluripotent stem cells (iPSCs) to produce a particular type of MSC precursor, called a mesenchymoangioblast (MCA). The Cymerus™ platform provides a source of MSCs that is independent of donor limitations and provides an "off-the-shelf" stem cell platform for therapeutic product use, with a pharmaceutical product business model and economies of scale. This has the potential to create a new standard in the emergent arena of stem cell therapeutics and provides both a unique differentiator and an important competitive position