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Circadian Technologies Limited (ASX: CIR) recently announced it had demonstrated the ability to produce the VGX-300 protein in cell culture at gram quantity yields. How does this advance your VGX-300 cancer therapeutics program?

**CEO & MD Robert Klupacs**

This is a major advance for the program. When we began the program, one of the key go/no-go points was whether the protein could be sufficiently produced. Soluble receptor proteins are a relatively new class of biological drugs. As such, there are few general methods to produce them. So the ability to produce VGX-300 in gram quantities is significant, allowing us to now move forward into the next phase of extensive pre-clinical testing and is a major step along the pathway for developing current Good Manufacturing Practice (cGMP) grade drug material for human clinical trials.

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VGX-300 is a soluble form of Vascular Endothelial Growth Factor Receptor 3 (VEGFR-3) and is intended to bind and neutralise the proteins VEGF-C and VEGF-D thereby starving cancer tumours of oxygen and preventing the spread of the cancer. What are the next major milestones that investors should look forward to in this program, and how far away from clinical trials is VGX-300?

**CEO & MD Robert Klupacs**

The most important near term milestones for the program will be testing the protein in animal models of cancer as well as further improving our manufacturing

system. Over the next 6 to 12 months we will conduct a series of studies to build on the previously published anti-cancer effects of this molecule and its utility as a therapeutic agent for cancer. If this can be demonstrated, it will add further significant value to the program. Following this, we will be developing the specific formulations for ultimate clinical delivery of the drug and then developing large-scale manufacturing processes (this is all part of the cGMP process). If all continues to go well, we're targeting late 2011/early 2012 for an investigational new drug (IND) filing to commence clinical studies of VGX-300.

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VGX-300 is similar to the highly successful drug Avastin in that it is intended to treat tumours by inhibiting blood supply. How is VGX-300 positioned against Avastin?

**CEO & MD Robert Klupacs**

First of all, it's important to emphasise that VGX-300 is not intended as a competitor of Avastin. Rather, it's a drug that would be used alongside chemotherapy to achieve more complete tumour control particularly in cases where Avastin treatment is ineffective. The key compelling advantage of VGX-300 is that it is able to bind and inactivate two separate factors (VEGF-C and VEGF-D) that stimulate the processes of blood vessel and lymphatic vessel development in cancer. Avastin only blocks the protein VEGF-A. We believe that VGX-300 would therefore potentially have the advantage of inhibiting both tumour growth and tumour spread. This potentially represents a significant benefit for cancer patients in the treatment of their tumours.

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One of your other in-house programs, around VEGF-C antibody VGX-100, is focused around addressing resistance and non-responsiveness to anti-angiogenic therapies, and you've targeted lodgement of an IND application for VGX-100 in the US in 2011. How might the focus of the VGX-300 program differ?

**CEO & MD Robert Klupacs**

VGX-100 and VGX-300 are different molecule types: VGX-100 is an antibody and VGX-300 is a receptor and the fact that VGX-300 has the ability to block both VEGF-C and VEGF-D suggests that subtle differences will emerge in the indications they'll be suited for as we move down the clinical development pathway. We'll make the call on the preferred indications for both in the next couple of years, on the basis of our findings in the pre-clinical studies.

In the pre-clinical phase however the development of both molecules will be very similar. We need to test them in animal models of cancer and potentially other diseases, develop formulations for their clinical delivery and develop processes for ongoing large scale manufacture.

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Is it your intention to continue developing VGX-300 in-house or to partner it? What is the expected cost of the program in the pre-clinical phase?

### **CEO & MD Robert Klupacs**

As we've previously stated, our strategy is to partner our programs at certain stages of their development so that we share in the risks and costs that are associated with clinical drug development but preserve significant upside on their success. VGX-300 has already attracted interest from potential partners. We have estimated that the total cost to conduct the pre-clinical phase of the VGX-300 program would be around \$5 million to \$6 million.

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In August, Circadian announced it had been granted exclusive rights to the VEGF-C protein, gene and antibodies in Japan. Why did you seek specific patents in Japan and what is the significance of the patents for Circadian's intellectual property portfolio and its development?

### **CEO & MD Robert Klupacs**

The Japanese market is very significant: on a single-country basis it's the second largest pharmaceutical market after the US. As such, patent protection in that market is vitally important. Having the Japanese rights gives us a position of strength from which we can now engage directly with major Japanese pharmaceutical companies for potential partnering in that market. These patents in Japan confirm our very strong, world leading position around the VEGF-C target.

We now have patent coverage for our molecules VGX-100 (VEGF-C antibody), VGX-200 (VEGF-D antibody) and VGX-300 in all the major pharmaceutical markets, including the US and Europe.

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You also recently announced an agreement to provide US life and analytical sciences company PerkinElmer Inc a worldwide licence to market research products incorporating Circadian's VEGF technology. What was the rationale for granting this license and what level of income is it expected to generate?

### **CEO & MD Robert Klupacs**

PerkinElmer approached us because it recognised our strong patent position around VEGF-C and VEGF-D, and needed a licence from us to make a proposed new research product. The product will use a new technology platform from PerkinElmer to develop an improved diagnostic assay for VEGF-C and VEGF-D. It is a win-win for both entities. The PerkinElmer product will assist researchers who are working on VEGF-C and VEGF-D and support their efforts to further elucidate the role of these proteins in disease. In addition to the financial benefits, an improved understanding of the function of these proteins will support our drug development activities over the next two to three crucially important development years.

The financial aspects of this non-exclusive deal are confidential and as such I cannot disclose them. This deal does however illustrate the strength of our IP portfolio. While our core focus is our therapeutics program, which targets large markets, we have the opportunity to license out other rights to develop complementary technologies and bring in modest recurring revenue streams in niche or research markets. For example, through this deal with PerkinElmer and

through other existing licenses we have with international research reagent companies such as R&D Systems in US and Reliatech GmbH in Germany.

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As at the end of June 2009, Circadian had cash of \$38.8 million and cash outflow from operations for the June 2009 year was \$6.6 million. What is your expected cash spend as your VGX-100, VGX-200 and VGX-300 programs move forward and how are you positioned to fund them?

**CEO & MD Robert Klupacs**

As at the end of June, in addition to cash in bank of \$38.8 million, we had listed investments with a market value of \$5 million (a combined value of \$43.8 million).

Based on our current budgets and prevailing foreign exchange rates, we're expecting a net spend of \$13 million to \$15 million in the current year ending June 2010.

To give you some context, most of our R&D costs in 2009 were around the VGX-100 program, including the start-up of manufacturing. Our activities will ramp up significantly in FY2010, when a large part of our VGX-100 manufacturing will actually be done and when we'll also commence the VGX-100 toxicology testing. Our other programs will also be ramping up, with ongoing activities linked to the achievement of predetermined milestones.

Having said that, we have strict go/no-go criteria for our programs: if things aren't progressing satisfactorily we won't spend. Similarly, we have strong disciplines around the decision to partner our programs so that, as I said earlier, we share in the risks and costs that are associated with clinical drug development but preserve significant upside on their success. We think we're very well positioned to make the necessary investment to release value for our shareholders.

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Thank you Robert.

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For more information about Circadian Technologies, visit [www.circadian.com.au](http://www.circadian.com.au) or call Robert Klupacs on +61 3 9826 0399.

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