

cytopics

CYTOPIA'S NEWSLETTER

APRIL 2009

Swiss-Australian Academic Network (SAAN) Presentation

Cytopia and global pharmaceutical giant Novartis joined forces in 2006 to develop novel drugs for the treatment of transplant rejection and autoimmune disorders. The collaboration is delivering potent and selective inhibitors of JAK3, initially to deliver "second generation" drugs for transplantation that do not have the side effect profile of the current transplantation medications.

Mr Andrew Macdonald, CEO of Cytopia, Dr Martin Missbach, Head of Chemistry Autoimmune Diseases and Transplantation, and Dr David Cox, Strategic Alliance Manager of Novartis Institute for BioMedical Research, presented an overview of the current research program and joint vision to a gathering of members and guests of the Swiss-Australian Academic Network in late March 2009. This presentation was well attended and provided different perspectives of the collaboration from each of the parties.

Bottom photo from left to right, Mr Andrew Macdonald (Cytopia), Dr Martin Missbach (Novartis) and Dr David Cox (Novartis)

CYT997 and CYT387 Medicinal chemistry and biology data presented at the 237th American Chemical Society National Meeting and Exposition

Salt Lake City, Utah, USA March 22-26, 2009

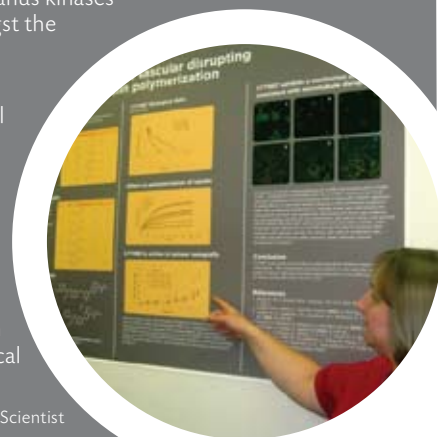
At the 2009 spring meeting of the American Chemical Society in Salt Lake City, Utah, Dr Tracy Nero presented two posters on the medicinal chemistry and associated biology for Cytopia's vascular disrupting agent CYT997 and the JAK2 kinase inhibitor CYT387.

The poster titled "Discovery of CYT997, a potent vascular disrupting agent and inhibitor of tubulin polymerization" was presented in the Division of Medicinal Chemistry poster session on Sunday March 22 from 7:00-9:00pm. The poster generated a great deal of interest, particularly in the clinical trials progress.

On the evening of Wednesday March 25 in the Division of Medicinal Chemistry poster session, the poster titled "Small molecule inhibitors of Janus kinases" was presented and generated enormous interest amongst the conference attendees.

The poster outlined the medicinal chemistry program undertaken by Cytopia to identify CYT387, a novel small molecule inhibitor of JAK2 kinase with good potency, selectivity, and oral bioavailability. CYT387 has shown cellular efficacy in MPD patient derived samples and in vivo efficacy in an in vivo disease model, supporting Cytopia's progression of this compound into clinical trials for the treatment of MPDs. CYT387 is undergoing rigorous IND-enabling toxicology studies and we anticipate filing appropriate regulatory applications with the US FDA and Australian TGA shortly to support clinical studies in the United States and Australia.

Photo: Dr Tracy Nero, Senior Scientist



2009 Key program milestones

CYT997	Conclude Phase I oral safety trial	Q1-2009	✓
CYT387	Conclude pre-clinical toxicology program	Q2-2009	
JAK3	Conclusion of initial three year research term	Q2-2009	
CYT387	Lodge IND for Phase I trial - MPD	Q2-2009	
CYT387	Commence Phase I trial - MPD	Q3-2009	
CYT997	Conclude dose esc./preliminary efficacy assessment glioma trial	Q3-2009	
CYT997	Commence further Phase II single arm trial - niche market	Q4-2009	
CYT997	Interim analysis Phase II trial - multiple myeloma	Q4-2009	
CYT387	Interim results for Phase I study - MPD	Q4-2009	

Chairman and CEO's message

Dear shareholders,

Welcome to our latest issue of *Cytopics*. Since the last time we wrote to you, there has been considerable activity at Cytopia as we work to deliver on our strategy of building a sustainable drug development company. The global external environment in which we are operating has been harsh, particularly in the US and Europe, and may stay that way for some time, but this has not halted the progress on our research, development and corporate goals. We trust that this issue will highlight key aspects of this progress in the business as well as provide general information about operations here at Cytopia.

Our preclinical and clinical projects are tracking very well, with our JAK2 inhibitor anticipated to move into the clinic in the second half of 2009. Before this can occur and prior to lodging an Investigational New Drug (IND) application with the US Food and Drug Administration, we must complete a body of work known as formal preclinical studies. During this process, in-vivo studies are conducted on the nominated compound with thorough investigation of various toxicology and pharmacokinetics aspects of the drug candidate. The outputs of these studies are used in the IND application.

Our JAK2 drug candidate, CYT387, designed specifically for the treatment of blood diseases known as myeloproliferative disorders is approaching the end of such studies. Extensive work on the compound in contract research organisations in Scotland and Canada is anticipated to conclude by early June. This should allow us to lodge the CYT387 IND late June 2009 and move into a Phase I myelofibrosis study in the Mayo Clinic at Rochester, Minnesota shortly thereafter.

We have recently opened enrolment at the Royal North Shore Hospital for our Phase II clinical study with anti-cancer vascular disrupting agent CYT997 in glioma and expect to have enrolment commence at other sites over the next quarter. This will help recruitment by accessing a much wider pool of patients suffering this severe and usually fatal disease.



Andrew Macdonald, CEO

Whilst it is only one of a number of solid, highly vascularised

tumours which potentially could be treated with CYT997, glioma is currently an area of unmet medical need for which an effective treatment is being urgently sought. Just recently, an FDA advisory committee recommended that Genentech's drug Avastin be approved as a treatment for this disease despite a lack of compelling evidence that the drug worked for that use. In the event that some efficacy were demonstrated in the current CYT997 trial, it is likely that the compound could be "fast tracked" through a registration enabling trial to meet this need.

Recently, Cytopia and Novartis made a joint presentation to a Swiss Australian Academic Network event hosted by the Victorian State Government, talking to our collaboration. Most shareholders will be aware that we have a joint collaboration and development agreement with Novartis based around JAK3 inhibitors for the treatment of organ transplant rejection and other autoimmune disease.

The agreement between the two companies is structured around an initial joint research effort at both Cytopia and Novartis, and once this has delivered suitable compounds, promising JAK3 inhibitors are then taken through into formal preclinical studies and clinical trials and ideally through to market. We are approaching the end of the initial three year research period where internal research has been funded at Cytopia. Many new JAK3 compounds have arisen from this work and we are looking forward to the further development of some of these compounds within Novartis. Novartis also have an option over a further year of Cytopia funding for further compound development and we expect to receive confirmation on whether this will be forthcoming around mid 2009.

One of the growth planks of our strategy has been the consideration of merger and acquisition opportunities. For much of this financial year, we have been engaged in an attempt to merge Cytopia with Progen



Bob Watson, Chairman

Pharmaceuticals Ltd, another cancer focused, small molecule biotech company in which Cytopia has been an investor.

We have communicated regularly with our shareholders regarding the detail of this attempt, particularly over recent months. Although unsuccessful in having our nominees appointed to the Progen board, we will continue to explore similar opportunities that may allow us to substantially grow our existing business.

Clearly, to deliver on all of the above, the support of our shareholders is critical to us, but support for Cytopia, and the broader biotech sector, from the Federal Government is also very important. The biotech industry is the delivery arm of the medical research sector and to turn the government's large investment in research into products that save lives and create jobs and wealth, Australia needs a strong and successful biotech sector.

We believe that the Federal Government should better recognise the benefits that the sector has provided to date, as well as the potential for the future, and provide more tangible support and investment to Australian biotech. Cytopia is working with local industry bodies to further this view and we would encourage our Australian shareholders to reinforce this message where possible by either speaking or writing to their local Member of Parliament.

We look forward to providing you with a further update in the next quarter.

Andrew Macdonald **CEO**
Bob Watson **Chairman**

Shareholder Communication

Shareholder communication is something we take very seriously at Cytopia. We do this in various ways, including the latest issues of *Cytopics* and general announcements to the market and press.

To ensure you receive these communications via email, please update your details with our registry, Link Market Services at: www.linkmarketservices.com.au.

Non-shareholders can also receive these announcements by forwarding your details to info@cytopia.com.au

Phase I oral study concluded



Cytopia's clinical development programme for CYT997 reached another important milestone recently with the successful conclusion of the company's oral capsule dosing Phase I study.

The primary objectives of this study were to determine safety and tolerability of the compound when administered in capsule form every two weeks to cancer patients with a diverse range of malignancies.

Patients entering the trial had advanced cancer that had failed to respond to other therapies or for which no other therapy exists. Each was eligible to receive a maximum of six cycles of CYT997 therapy, subject to clinical status. One patient continued to receive the drug beyond their initial six cycles due to prolonged disease stabilisation. No patients currently remain on study.

CYT997 was generally well tolerated in this study with maximal plasma concentrations some two-fold higher than those observed in the Phase I intravenous infusion study at comparable doses, indicating favourable oral absorption.

The demonstration of oral activity of CYT997 represents a key advantage over most other vascular disrupting agents which can only be administered intravenously. The oral activity of CYT997 should markedly improve its clinical and commercial value.

The findings of this study support data obtained in the company's first Phase I study where CYT997 was administered intravenously. Together, these studies suggest that the CYT997 is a potent and selective vascular disrupting agent which is well tolerated at doses which perturb tumour blood vessels. This oral trial was partly funded under the company's \$3 million Commercial Ready grant.

Patent Update

Cytopia continues to progress its Intellectual Property Portfolio by protecting its inventions using the patent system in key pharmaceutical markets.

The process of obtaining a patent for an invention is reasonably lengthy. When an invention is first identified, a provisional patent application is filed as a place holder to obtain a "priority date" for the invention. During the next 12 month period, the invention is refined and further data obtained so that a full application can be filed, usually an international application, under the Patent Cooperation Treaty (PCT). This application does not result in a world patent, but rather allows the applicant to defer the cost of filing in each country or region by a further 18 months. Therefore it is only 30 months after the filing of the original provisional application that each country must be selected (called National Phase Entry) to progress the application.

Once an application has entered national phase, each country will follow their national process for examining the application, and terminology for different stages will vary from country to country. The time taken for a country to commence examining an application after national phase entry is typically anywhere from 1-5 years.

The examination process involves an examiner at the intellectual property office deciding whether the application complies with the laws of that country, and if it doesn't, writing to the applicant to explain why.

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Scientific Publications

Information about Cytopia's scientific progress and achievements is disseminated in a number of different ways. For example it occurs through media releases and ASX announcements, shareholder presentations and newsletters such as Cytopics, business partnering presentations and by publication in scientific journals.

Once novel aspects of our science are protected through patents, it is important for Cytopia's scientific work to be published in scientific journals. As a consequence of the rigorous peer-review process scientific papers undergo, this acts as independent validation of our research. Furthermore, the publication of key results in these journals raises the profile of the company and our specific programs, particularly amongst potential partners and clinicians.

Given the development of our patent portfolio over the last few years, we are now in a position to publish key aspects of some of our research. In this last quarter there have been five separate papers published from Cytopia scientists and collaborators.

Work on our JAK2 inhibitor CYT387, conducted in collaboration with scientists at the Mayo Clinic in the US, has been published in the prestigious journal *Leukemia*. This work describes the impressive activity of CYT387 against cells isolated from patients with myeloproliferative disorders, supporting the clinical development of this compound for treatment of these diseases.

Another important publication described the world-first determination of the precise three-dimensional structure of JAK1, a protein involved in cancer and immune function, by Cytopia scientists and collaborators at Monash University. This information has allowed Cytopia scientists to design more effective drugs targeting this protein.

Collaborative work with scientists from Melbourne's Baker Institute has been published describing the activity of an experimental compound discovered at Cytopia in models of atherosclerosis. This work is the subject of an ongoing relationship with the Baker Institute, and is consistent with our approach to working with partners in non-cancer indications.

Related research with collaborators from Queensland's Institute of Molecular Bioscience has been published that demonstrates a link between inflammation and cardiovascular disease, indicating a potential utility of selected compounds from our laboratory in the treatment of these diseases.

Research on inhibitors of the protein FMS, which is involved in cancer progression, metastasis and the bone degradation associated with many cancers, has been published. This work describes our 'first generation' compounds and is the first disclosure of our chemistry research in this area.

Further papers describing our science are in preparation and will be noted in future editions of Cytopics as they are published.

Details of the above publications are as follows:

'CYT387, a selective JAK1/JAK2 inhibitor: in vitro assessment of kinase selectivity and preclinical studies using cell lines and primary cells from polycythemia vera patients' A. Pardani, T. Lasho, G. Smith, C.J. Burns, E. Fantino, and A. Tefferi *Leukemia*. 2009 Mar 19.

'Dissecting specificity in the Janus kinases: The structures of JAK-specific inhibitors complexed to the JAK1 and JAK2 Protein Tyrosine Kinase Domain' N.K. Williams, R.S. Bamert, O. Patel, C. Wang, P.M. Walden, E. Fantino, J. Rossjohn, I. S. Lucet *Journal Molecular Biology* 2009, 387, 219.

'The pyrido-pyrimidine derivative CYC10424 inhibits glycosaminoglycan changes on vascular smooth muscle-derived proteoglycans and reduces lipoprotein binding' M.L Ballinger, N. Osman, A.F Wilks, S. Su, C.J Burns, X. Bu, P.J Little, J. *Cardiovascular Pharmacology* 2008, 52, 403.

'Colony Stimulating Factor-1 (CSF-1) stimulation delivers a pro-atherogenic signal to human macrophages' K.M. Irvine, K. Schroder, M. Andrews, C.J. Burns, S.Su, A. Wilks, D.A. Hume, M. Sweet. *Journal Leukocyte Biology* 2009, 85, 278.

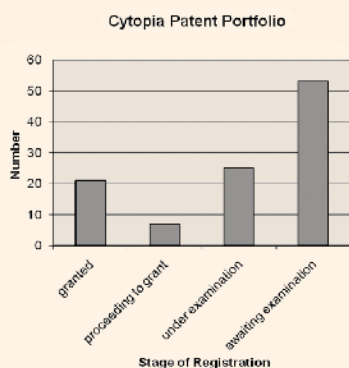
'Discovery of 2-(α -Methylbenzylamino) Pyrazines as Potent Type II Inhibitors of FMS' C. J. Burns, M.F. Harte, X. Bu, E. Fantino, M. Giarrusso, M. Joffe, M. Kurek, F.S. Legge, P. Razzino, S. Su, H. Treutlein, S. Wan, J. Zeng, A.F. Wilks, *Bioorganic Medicinal Chemistry Letters* 2009, 19, 1206.

Patent Update (Continued)

The applicant may respond in a variety of ways including presenting reasons why the examiner's assessment is not correct under the local law, providing additional experimental data to demonstrate that the invention is new or legally patentable, or amending the application. Frequently the examination process in many countries will involve a combination of these strategies, and it typically takes 1-4 years from issuance of the first examination report before a patent is granted.

Once the examiner determines that the patent application complies with all of the laws of the country, the application is accepted. There are then a number of administrative processes which may be required in each country before the patent is granted. It is after issuance or grant that an invention can legally be labeled as "patented" and the owner of the patent can stop other people from using the invention. Therefore the entire process from first identification of the invention to obtaining a patent is typically between 4 and 10 years on a country by country basis, and may be longer in specific circumstances.

The accompanying chart outlines the breakdown of Cytopia's patent portfolio by process stage. The applications in the far right column are those that have been filed as a provisional application, an international application or a national application and have not yet been examined. The second column from the right is the number of applications which are currently within the process of examination. The two columns on the left demonstrate the number of applications which have been granted (i.e. are in force) and those that have been deemed by the examiner as being in order for grant, but are currently going through the process to be formally granted.



Staff news

Andrew Donohue, Senior Scientist at Cytopia, celebrated his 100th game with the Oakleigh Cricket club by winning the Grand Final in the South-East Group of the Victorian Sub District Cricket Association (VSDCA). Local newspaper, the Oakleigh Leader, enthused "Oakleigh saved its best performance for the Grand Final and, in doing so, became the VSDCA South-East Group champions." Andrew, who has been playing club cricket for 25 years, said "It was especially nice for me as I have played in four losing semi finals previously."

Andrew undertook a Bachelor of Science with Honours at Monash University followed by a PhD in Organic Chemistry examining novel efficient methods for the synthesis of asthma drugs such as salbutamol, which he completed in 1997. He then held post-doctoral positions in synthetic organic chemistry at CSIRO Molecular Sciences and the Dyson Perrins Laboratory, University of Oxford, UK. After returning to Australia, Andrew joined The Walter and Eliza Hall Institute (WEHI) investigating the modulation of apoptosis by the inhibition of protein-protein interactions with small molecules. In 2004 Andrew joined start-up company Chirogen as head of the

organic chemistry section working on chiral radical technology.

Andrew joined the chemistry team at Cytopia in June 2005 working on the JAK2 project exploring analogues of CYT387 and has subsequently moved onto the JAK3 project in collaboration with Novartis.

Andrew, pictured below with son Hamish, is also an avid cyclist, and regularly joins with other Cytopia staff in competing in team triathlons and cycling events.



Recruitment

Specific job openings will be posted on the Cytopia website from time to time. Please refer to the following link for details:

<http://www.cytopia.com.au/careers.html>

Cytopics

Further copies of Cytopics are available from the Company website:

<http://www.cytopia.com.au/cytopics.html>

Conferences and Presentations

Cytopia continues to participate in a number of Australian and international conferences and investor presentations. In recent months, these have included:

JP MORGAN HEALTHCARE CONFERENCE
SAN FRANCISCO, CALIFORNIA
January 12 to 15

7TH BIOPARTNERING NORTH AMERICA
VANCOUVER, CANADA
February 6 to 8

ACS NATIONAL CONFERENCE
SALT LAKE CITY, UTAH
March 22 to 26

Future conferences in 2009 include:

AACR MEETING – DENVER, COLORADO
April 18 to 22

BIO INTERNATIONAL CONVENTION - ATLANTA, GEORGIA
May 18 to 21

ASCO MEETING – ORLANDO, FLORIDA
May 29 to June 2

5TH BIOSHARES BIOTECH SUMMIT - THREDBO, AUSTRALIA
August 28 to 29

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