

# cytopics

CYTOPIA'S OFFICIAL NEWSLETTER

APRIL 2008

## Robots at Cytopia!

There is a new addition to Cytopia's Burnley laboratories – a state-of-the-art robotic pipetting system. The robot, called a Zephyr® Compact Liquid Handling Workstation, is made specifically for the drug discovery industry by US robotics and instrumentation company Caliper Life Sciences. This is the first installation of this robot in Australia.

The multi-functional robot can pipette solutions from one container to another with high speed and accuracy and can repeat this process many times per hour. The robot adds an extra dimension to our drug discovery process by replacing a number of manipulations currently performed manually, including multiple repetitive pipetting processes, and thus increases throughput and reproducibility whilst improving laboratory safety. It can also perform complex sequences of transfer, dilutions, replicating and reagent dispensing.

Head of Biology, Dr Emmanuelle Fantino, said "the Zephyr system will allow us to significantly increase the number of assays we can perform per week, thereby giving us the opportunity to screen more drug compounds against more biological targets".

The system is programmable and can be run under sterile conditions, further enhancing its utility in the laboratory. The robot is now fully deployed and is being used in all Cytopia's research projects.

## Cytopia reaches Phase II milestone – more Phase II studies to come

Cytopia reached an important milestone earlier this year with the commencement of dosing in its first Phase II efficacy trial – a study in patients with multiple myeloma.

This study is the first of a suite of Phase II studies designed to determine the activity of CYT997 in particular cancer types. In addition, the company has finalised preparations for its second Phase II study, concluded its first Phase I study where CYT997 was given as an intravenous infusion and continued its Phase I oral capsule study during the recent months.

As reported in the previous edition of Cytopics, multiple myeloma is an incurable cancer of specialised cells in the bone marrow which divide in an uncontrolled manner and invade both the marrow and the solid bone tissue. To be eligible for the study, patients must have failed at least one previous line of approved therapy. The company anticipates releasing interim data for this study in the third quarter of 2008.

The potential activity of CYT997 in multiple myeloma extends the utility of the drug beyond the company's core focus of Phase II studies in solid tumours. Cytopia intends to file an Orphan Drug Designation (ODD) application in the USA within three months.

ODD will give a range of development benefits including extended patent life and the opportunity for increased consultation and assistance from regulatory agencies, including the FDA.

Cytopia is also scheduled to commence a Phase Ib/II study in glioblastoma multiforme (GBM) in the second quarter of this year. GBM is an aggressive brain tumour commonly treated with radiotherapy, surgical resection and chemotherapy. Unfortunately many patients with GBM relapse after these therapies and subsequently have poor prognoses.

This study will initially investigate the optimal safe dose for CYT997 when administered with standard chemotherapy. Following that initial safety assessment, the Phase II efficacy study will commence. It is estimated that some 25 to 30 patients will be enrolled into the study at sites in Australia and overseas.

The company is also undertaking feasibility analysis for a study in mesothelioma. It is anticipated that appropriate regulatory submissions to support this study will be filed in the fourth quarter of 2008.

### Key clinical milestones to Dec 2008

CYT997	Conclude Ph. I IV clinical trial	3Q-2007	✓
CYT997	Announce Ph. I IV clinical data	4Q-2007	✓
CYT997	Commence Ph II multiple myeloma trial	4Q-2007	✓
CYT997	Second Ph II clinical trial commences	2Q-2008	
CYT997	Conclude Ph. I Oral clinical trial (est.)	3Q-2008	
CYT997	Interim results multiple myeloma trial	3Q-2008	
CYT997	Third Phase II clinical trial commences	3Q-2008	
CYT997	Conclude Ph. II multiple myeloma trial	4Q-2008	
JAK2	Lodge IND, commence Ph. I studies	4Q-2008	



## Chairman and CEO 's message



Dear shareholders,

Welcome to our latest issue of Cytopics. In the last communication to shareholders, we outlined our expectations for 2008 and during the first quarter have delivered excellent news on the progress of two of our major programs. This progress has without doubt added to the value of our overall drug development portfolio and the value should be further enhanced as we move through the year.

Our core expertise is in the development of JAK kinase inhibitors, and we have a very strong IP portfolio behind our JAK2 inhibitors, including patents over our drug candidates as well as patents covering the enzyme as a drug target. We are therefore very excited to have nominated CYT387, a JAK2 inhibitor, as our clinical candidate to treat a series of blood diseases known as myeloproliferative disorders (MPDs).

These diseases affect over 300,000 patients worldwide and currently, there are no effective long term treatments available on the market. A best-in-class drug has the potential to deliver blockbuster sales. Other targeted kinase inhibitor drugs like Gleevec, Iressa and Tarceva have already demonstrated billion dollar sales on niche markets.

The results of an in-vivo model of MPDs recently carried out at Oregon Health and Science University in the USA with CYT387 were very encouraging, delivering data which gives us confidence that the drug will be effective in treating patients in the clinic.

Over the next six months CYT387 will be taken through formal preclinical studies, including toxicology studies, which will support the lodgment of an Investigational New Drug application in Q4 2008 with the US FDA. If approved, the company will be able to commence its third Phase I clinical study.

Our business strategy is to partner our oncology programs after establishing proof of efficacy in clinical studies, and to seek earlier stage partners for non-oncology programs. We have established

a high calibre relationship with Novartis to progress our JAK3 program, and the JAK2 MPD program is also a contender for partnering in the near term.

The exciting aspect of the JAK2 signalling pathway as a drug target is that is implicated in different diseases. In addition to MPDs, our scientists are also generating other JAK2 compounds to treat diseases such as cancer and pulmonary hypertension (PAH). PAH is yet another disease for which there is an unmet medical need.

Another key event during the quarter was the commencement of our first Phase II clinical study with our vascular disrupting agent, CYT997. In this trial, our compound is being used to treat patients with relapsed or refractory multiple myeloma, a cancer of the bone marrow. Although the core Phase II studies for CYT997 will be in highly vascularised solid tumours, the multiple myeloma trial highlights the potentially broader utility of the drug for the treatment of cancer.

The first in what will be a series of core Phase II clinical studies will commence during Q2 2008, dosing patients with a particularly aggressive form of brain tumour known as glioblastoma multiforme (GBM). Both the multiple myeloma trial and the GBM trial are discussed in more detail on page 1.

It is important that the activities of the company are being properly profiled and to the right audiences. To achieve this, we have an extensive schedule of attendance and presentations during 2008 at key international biotech and investor

conferences. We were particularly pleased to have been accepted for an oral presentation of the Phase I study of CYT997 to be made in June 2008 at the annual ASCO General Meeting, the world's largest conference for cancer clinicians, being held in Chicago.

We have continued to deliver on the majority of our milestones, regardless of the recent events on world and local markets and the generally negative sentiment towards biotechnology stocks in particular. A summary of these milestones for 2008 is provided elsewhere in Cytopics.

It was pleasing to welcome new investors to the share register in December 2007 and we remain focused on achieving key scientific and commercial goals for all of our shareholders during this year and onwards.

Lastly, in past editions we have encouraged shareholders to register for electronic communications from the company and we would again ask shareholders who have not done so to register through the Link Market Services website (details provided below). By doing so, shareholders will be able to more efficiently receive all relevant communications from the company.

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

“ We are highly encouraged by Cytopia’s compound in this model of myeloproliferative disease which clearly indicates significant amelioration of symptoms and disease remission. The favourable data from this in vivo model augers well for activity of the compound in the clinic. ”

**Michael WN Deininger, MD, PhD**  
Associate Professor Head,  
Hematologic Malignancies Section  
Oregon Health & Science  
University

## Excellent Data for Cytopia JAK2 Inhibitor



We recently announced that our lead JAK2 inhibitor CYT387 is progressing into formal preclinical toxicology studies after completion of extensive laboratory testing. An Investigational New Drug (IND) Application will be filed with the US Food and Drug Administration (FDA) in late 2008, after successful completion of formal toxicology studies.

CYT387 is the culmination of a number of years research within the company and possesses an excellent potency and safety profile in our laboratory tests. Most recently we have demonstrated activity of the compound in an in vivo model of Myeloproliferative Diseases (MPDs).

In humans it was recently found that many MPD patients possess a genetic abnormality in their JAK2 enzyme which causes it to be permanently ‘switched on’. This in turn leads to over-production of particular cells in the bloodstream, such as red blood cells.

The in vivo model of MPD, performed by clinical haematologist Dr Michael Deininger at the Oregon Health and Science University, USA, is extremely complicated and involves genetically altering the JAK2 enzyme to be identical with the mutation found in humans. The model developed the classical symptoms of human MPDs, however when dosed orally with CYT387 an almost complete reversal of the disease symptoms occurred.

Dr Deininger said, “We are highly encouraged by Cytopia’s compound in this model of myeloproliferative disease which clearly indicates significant amelioration of symptoms and disease remission. The favorable data from this in vivo model augers well for activity of the compound in the clinic.”

These encouraging results follow on from data reported earlier this year where, in conjunction with US and Australian MPD clinicians, we demonstrated that CYT387 blocks the activity of the mutant JAK2 enzyme present in samples taken from MPD patients. The formal preclinical studies and toxicology studies currently underway are required by the US FDA, and other regulatory bodies around the world, before the drug can be dosed to patients.

## Shareholder Communications

Shareholder communication is something we take very seriously at Cytopia. We do this through 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](http://www.linkmarketservices.com.au). Non-shareholders can also receive these announcements by forwarding your details to [info@cytopia.com.au](mailto:info@cytopia.com.au).

## Patent Update

Cytopia continues to progress its patent families towards grant or issue in a number of key pharmaceutical markets. The table below outlines the granted patents at the time of printing.

### Cytopia's Granted Patents

TITLE	APPLICATION #	COUNTRY	PRIORITY DATE	FILING DATE
Tubulin inhibitors*	2006/02664	South Africa	3 Dec 2003	3 Dec 2004
<b>Pyrazine-based tubulin inhibitors</b>	<b>2005/4052</b>	<b>South Africa</b>	<b>11 Dec 2002</b>	<b>11 Dec 2003</b>
Pyrazine-based tubulin inhibitors	540035	New Zealand	11 Dec 2002	11 Dec 2003
<b>Pyrazine-based tubulin inhibitors</b>	<b>2412372</b>	<b>UK</b>	<b>11 Dec 2002</b>	<b>11 Dec 2003</b>
Protein kinase signalling	2002226196	Australia	30 Jan 2001	30 Jan 2002
<b>Protein kinase inhibitors</b>	<b>2004/9341</b>	<b>South Africa</b>	<b>23 May 2002</b>	<b>23 May 2003</b>
Protein kinase inhibitors	7122550	USA	23 May 2002	23 May 2003
<b>Protein kinase inhibitors</b>	<b>537155</b>	<b>New Zealand</b>	<b>23 May 2002</b>	<b>23 May 2003</b>
Protein kinase inhibitors	2392154	UK	23 May 2002	23 May 2003
<b>Protein kinase inhibitors</b>	<b>1513821</b>	<b>Europe</b>	<b>23 May 2002</b>	<b>23 May 2003</b>
Method of inhibiting kinases	2002226197	Australia	30 Jan 2001	30 Jan 2002
<b>Kinase inhibitors</b>	<b>2004/9346</b>	<b>South Africa</b>	<b>23 May 2002</b>	<b>23 May 2003</b>
Kinase inhibitors	7259179	USA	23 May 2002	23 May 2003
<b>Kinase inhibitors</b>	<b>2398781</b>	<b>UK</b>	<b>23 May 2002</b>	<b>23 May 2003</b>
Azole-based kinase inhibitors	2423083	UK	3 Dec 2003	3 Dec 2004

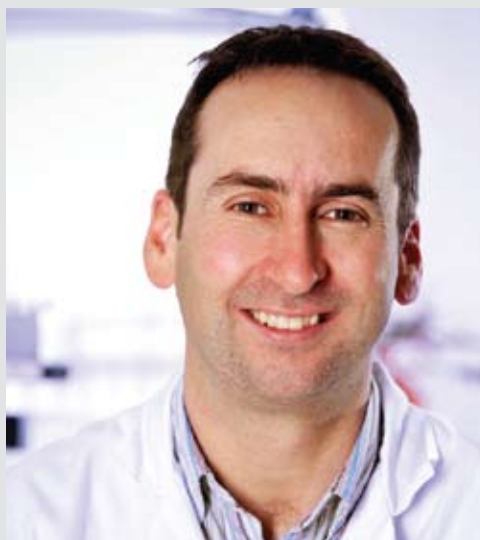
\*The first of the family of Patent Applications covering CYT997

## Staff Profiles

### Michael Harte

A native of Melbourne, Michael undertook a Bachelor of Science with Honours at the University of Melbourne followed by a PhD in Organic Chemistry which he completed in 1998 investigating the total synthesis of fungal natural products. Michael then moved to the chemistry department at Monash University where he undertook two postdoctoral research projects in medicinal chemistry working on collaborative projects with the Australian biotech company AMRAD and the Baker Heart Research Institute.

In 2001 Michael joined start-up company NSL Health Ltd as Senior Chemist developing technology for the transfer of laboratory based biochemical allergy assays to portable hand-held test kits.



Michael joined the chemistry team at Cytopia in 2002 working on the anti cancer program and completed the first synthesis of CYT997 in 2003. Following the entry of CYT997 into clinic trials Michael became lead chemist on the FMS project and is now leader of the FMS kinase cancer program.

## Recruitment

Specific job openings will be posted on the Cytopia website from time to time. Please refer to the following link for details: [www.cytopia.com.au](http://www.cytopia.com.au)

## cytopics

Further copies of cytopics are available from the company website:  
[www.cytopia.com.au](http://www.cytopia.com.au)

## Conferences and Presentations

Currently and in the coming months, Cytopia is participating at a number of Australian and international conferences & investor presentations, including:

### SBS 14TH INTERNATIONAL CONFERENCE

St Louis, USA  
April 6-10

### AACR ANNUAL MEETING 2008

San Diego, USA  
April 12-16

### PROTEIN KINASES IN DRUG DISCOVERY

San Diego, USA  
May 5-6

### IP MANAGEMENT IN PRACTICE

Sydney  
May 18-21

### 2008 BIO INTERNATIONAL CONVENTION

San Diego, USA  
June 17-20

### CHI PROTEIN KINASE TARGETS

Boston, USA  
June 23 - 25

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