



**BUY \$0.51**

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# Cytopia (CYT)

## Ex-CYT-ing Year Ahead For Cytopia

### Company Data

ASX Code	CYT
Price	\$0.51
12 month price target	\$1.00
Implied return	95%

Shares on issue	84.6m
Market capitalisation	\$43.1m
12 Month price range	\$0.45–\$0.74
Monthly turnover (shares)	0.9m

### Cash Flow Summary

Yr to 30 June (A\$m)	2007A	2008F	2009F	2010F
License Fees	3.1	4.2	4.2	0
Grants	0.6	0.9	1.1	0
Interest	1.1	0.6	0.3	0
Oper. Cash Inflow	4.8	5.7	5.6	0
Oper. Cash Out	(12.5)	(15.3)	(20.1)	(19.0)
<b>Net Oper Cash</b>	<b>(7.6)</b>	<b>(9.6)</b>	<b>(14.5)</b>	<b>(19.0)</b>
Net Inv. Cashflow	2.8	0	0	0
Net Fin. Cashflow	0	5.0	0	0
<b>Inc/(Dec) Cash</b>	<b>(4.9)</b>	<b>(4.6)</b>	<b>(14.5)</b>	<b>(19.0)</b>
Opening Cash	19.0	14.1	9.6	(4.9)
<b>Closing Cash</b>	<b>14.1</b>	<b>9.6</b>	<b>(4.9)</b>	<b>(23.9)</b>

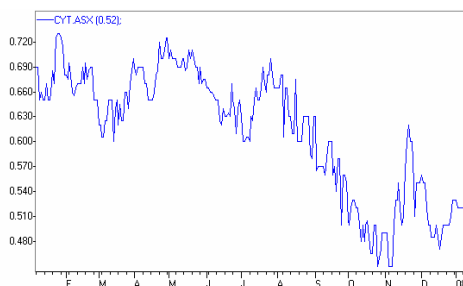
### Board of Directors

Robert Watson	Chairman
Andrew Macdonald	MD
Kevin Healy	Non-Exec. Dir.
Roderick Lyle	Non-Exec. Dir.
Mark Rowsthorn	Non-Exec. Dir.
Geoffrey Vaughan	Non-Exec. Dir.

### Substantial Shareholders

Mark Rowsthorn	13.8%
Acorn Capital	12.7%
Robert Watson	11.7%
<b>Top 20 Shareholders</b>	<b>57.5%</b>

### Share Price Chart



Source: Iress Market Technology

### Investment Summary

CYT is one of the standout buying opportunities in the biotechnology sector. In our view, the current price of \$0.51 does not reflect the underlying value of the company's technology, drug pipeline and partnerships.

The next year will see a significant transformation of CYT as all of its projects make material progress and achieve major value-creating milestones which we believe support a **price target of \$1.00 for CYT**.

Thus, CYT offers investor upside from both a re-rating by the market to reflect the value of its current technology and further value growth over the next year as several significant milestones are achieved.

### Lead Anti-Cancer Product In Phase-II

CYT's most advanced product, CYT997, is an exciting new class of anti-cancer drug called Vascular Disrupting Agents (VDA) that work by destroying the blood supply to tumours. This blood supply is essential for tumours to grow and survive. We believe that CYT has the only VDA in clinical development that is being administered orally (ie: as a pill) as well as intravenously. This has the potential to open up unique market opportunities for CYT's VDA that could allow treatment regimes which reduce the number of clinic visitations for cancer patients.

Phase-I clinical data for CYT997 have shown that the drug is safe, well-tolerated and able to stabilise disease in late-stage cancer patients who have failed standard treatments. With this encouraging data in hand, the company has commenced its first Phase-II trial for CYT997 with plans to undertake a further 2-3 Phase-II clinical trials.

The commercial potential of VDAs is substantial. Avastin, an anti-angiogenesis drug (which also works by reducing blood supply to tumours) had sales of US\$2.4B in 2006. In April 2007, Novartis entered into a US\$890m deal, which included a US\$75m upfront payment, to acquire a VDA after it had completed Phase-II clinical testing.

### Two Other Leads Heading To The Clinic

CYT also has very potent and selective inhibitors against two validated drug targets (JAK2 and FMS) in advanced preclinical development. These drugs are expected to enter into Phase-I clinical testing in late-08/early-09. CYT's inhibitors to these drug targets are likely to have a number of clinical applications. Thus the company is well-positioned to establish partnerships around these compounds while progressing the compounds itself for cancer indications.

### Partnership with Novartis

In 2006, CYT announced one of the most significant licensing deals by any company in the Australian biotechnology sector. CYT's deal with Novartis for the development of inhibitors to the JAK3 kinase drug target provides the company with R&D payments (up to \$13m), the potential to earn up to \$274m in milestone payments and a royalty on sales. While the progress of this project remains confidential, the company potentially could receive a milestone payment during 2008.

With these opportunities ahead and a currently low valuation, we believe that CYT offers a standout investment opportunity in the sector.

## Investment Thesis

*CYT offers good near term upside for investors*

CYT is a high quality biotechnology company developing novel small molecule drugs which have applications for the treatment of cancer and autoimmune-related disorders. With one drug having commenced the first trial in an extensive Phase-II clinical trial program, two further drug candidates entering clinical development in late-08/early-09, and other drug candidates in a significant partnership with Novartis, CYT provides a very attractive investment opportunity from two perspectives:

- **Undervalued:** current price does not reflect existing value in the company
- **Near-Term Milestones:** progress in 2008 should transform the profile of the company

### Why We Think CYT Is Undervalued

*CYT's lead product belongs to a new class of anti-cancer drugs*

CYT's most advanced drug CYT997, belongs to a exciting new class of anti-cancer drugs called Vascular Disrupting Agents (VDAs). CYT997 is unique in that it is the only VDA in development that is being administered to patients orally (ie: as a tablet) as well as intravenously. CYT997 has been in Phase-I clinical trials and is expected to commence its Phase-II program within 3 months. A UK company, Antisoma, recently secured a US\$890m licensing deal with Novartis for its VDA after it had completed Phase-II testing.

*Has two other drugs in preclinical development*

CYT also has two further compounds in late-stage preclinical development which are very potent and highly selective inhibitors of two drug targets (JAK2 and FMS). These targets have been validated for a variety of cancer and autoimmune/inflammatory disorders. CYT plans to complete preclinical development of its JAK2 and FMS inhibitors during 2008 and IND submissions to commence Phase-I clinical testing are expected late-08/early-09. As these compounds have potential to be used for several therapeutic applications, they provide opportunities for both licensing and internal development.

*And a partnership with Novartis*

Finally, the company has an established partnership with Novartis for the development of compounds against another validated drug target called JAK3. This partnership currently generates revenues from R&D payments and has the potential to deliver up to A\$274m in milestone payments and royalty revenue on sales.

*Value of this portfolio not reflected in current price*

CYT's price of \$0.51 means the market is currently valuing the company at \$43.2m and an enterprise value of \$28.7m (based on 30 June '07 cash balance of \$14.1m, cash burn of \$750K per month and capital raising of \$5.0m). On both a fundamental basis and a comparative basis, we believe this significantly undervalues a company with a promising drug in Phase-II, two further drugs with strong licensing potential 12-15 months from the clinic and an established partnership with the 4th largest pharmaceutical company in the world.

In view of the low current valuation, we believe CYT has limited downside risk. The risk profile is further reduced by the company having a portfolio of projects (rather than a single project) that may provide the value-creating events over the next 12 months.

### What Is Expected To Happen In 2008

*Several value-creating milestones expected in 2008*

Each of CYT's programs are expected to provide significant, value-creating milestones over the next 12 months. We anticipate that by the end of 2008, the company will have:

- **Multiple Phase-II clinical trials** in progress for CYT997 (both oral and intravenous)
- **Preliminary clinical efficacy data** from at least one of the Phase-II clinical trials
- **Two further drugs** (JAK2 and FMS inhibitors) about to commence clinical testing
- **One additional licensing partnership** in place with a major pharma/biotech
- **A development milestone payment** from the Novartis JAK3 partnership

Each of these events should represent a major value-inflection point for the company. Furthermore, this profile would place CYT well within the top tier of Australian biotechnology companies and would support a valuation that is significantly greater than its current market capitalisation.

Thus, as an investment opportunity, CYT provides significant potential upside from both a re-rating by the market that more fully reflects the value of the company's current portfolio and from the achievement of several material milestones over the next year.

## Valuation

We have a price target for CYT of \$1.00, a >95% premium to the current share price of \$0.51. Our price target implies a market capitalisation of \$85m for CYT which we believe reflects a conservative valuation for the company's drug portfolio. The development over the next 12 months (ie: to end of 2008) should see this portfolio mature considerably.

*Two approaches to valuation support price target of \$1.00*

As all of CYT's drugs are at a stage where it is too early to clearly define specific therapeutic markets on which sales projections can be made, we have used two approaches to provide valuation guidance for the company's technology:

- Value Of Potential License Opportunities
- Comparable VDA Companies

Both of these approaches support our valuation of approximately \$85m for CYT suggesting the company is currently trading at a discount to the underlying value of its technology.

### Value of Potential License Opportunities

CYT has three internal lead programs in place: CYT997 which is a VDA has commenced Phase-2 clinical testing, JAK2-inhibitors and FMS-inhibitors which are expected to enter clinical development programs in late-08/early-09. CYT997 is primarily focused on cancer applications however the JAK2- and FMS-inhibitors have potential additional indications (autoimmune diseases, inflammatory disorders and, in the case of FMS, osteoporosis). These additional indications provide earlier stage licensing opportunities for CYT.

CYT's management valued the Novartis deal for JAK3 inhibitors at US\$32m (based on their risk-adjusted DCF at the time of signing). While the deal terms for earlier stage compounds have improved over the past few years, our risk-adjusted NPV for an early stage licensing deal for a novel kinase inhibitor with preclinical data demonstrating good pharmaceutical potential falls in the range of \$16m-\$26m using the assumptions set out below.

**Table 1: Risk Adjusted NPVs Of Typical Early Stage Licensing Deals For Kinase Inhibitors**

Milestone	Deal 1	Deal 2	Likelihood	Timeframe
Upfront	\$5m	\$10m	100%	1yr
Commencement of Phase-II	\$15m	\$25m	60%	3yr
Commencement of Phase-III	\$25m	\$35m	24%	5yr
Completion of Phase-III	\$40m	\$50m	14%	8yr
Marketing Approval	\$60m	\$80m	11%	10yr
Headline Value	\$145	\$200		
<b>Risk Adjusted NPV*</b>	<b>\$16.1m</b>	<b>\$26.4m</b>		

SOURCE: Lodge analysis, Discount Rate = 16%, Discounted to assume license in 12 months time.

*We estimate preclinical licensing deals for kinase inhibitors are worth \$16m to \$26m*

Our risk-adjusted NPV valuations are lower than the those implied by actual, reported early stage licensing deals for kinase inhibitors that have occurred in the market:

**Table 2: Early stage licensing deals for kinase inhibitors**

Licensee	Licensor	Date	Headline Value	Specific Payments	Stage
Roche	Plexxikon	Dec'06	US\$660m	US\$25m upfront, \$6m R&D over 2yrs	Preclinical entering clinic
Novartis	SGX	Mar'06	US\$515m	\$25m in upfront and equity investment	Discovery with IND expected in 2H'08
Serono	Rigel	Oct'05	US\$160m	US\$10m upfront & US\$15m equity investment	Preclinical
Genentech	Exelixis	Jun'05	US\$40m + Option	US\$40m on signing and submission of IND	Preclinical entering clinic
Merck	Vertex	Jun'04	US\$350m	US\$20m upfront, US\$14m R&D, US\$130m for first indication	Preclinical

SOURCE: Company announcements

*Market data on actual deals indicate that this estimate is conservative*

With respect to valuing CYT997 (a VDA entering Phase-II), Novartis licensed Antisoma's VDA compound in a deal that included a US\$75m upfront payment, US\$25m on commencement of a Phase-III trial, additional milestones payments of up to US\$790m and Antisoma receiving royalties on sales and the right to co-commercialise the product in the US.

*Novartis recently entered into a significant deal for a VDA*

*JAK3 deal worth at least \$21m*

We have valued the existing Novartis JAK3 license at \$21.6m based on our risk-adjusted NPV of \$26.4m less the \$4.8m that CYT has already received as R&D payments. In this case we have used the higher pro-forma valuation as we know that the cumulative milestone payments are \$274m (vs our higher pro-forma headline value of \$200m).

Using these licensing deals as benchmarks, we believe a conservative valuation estimate for CYT's portfolio of drugs under development is \$71.6m, or \$0.85 per share. In addition, the cash reserves held by the company (\$14.5m) provide \$0.17 per share.

**Table 3: Breakdown Valuation of CYT Based On Licensing Deals**

Technology	Basis for Valuation	Valuation
CYT997 – Phase-II	Antisoma/Novartis upfront (US\$75m) discounted 3yrs with 60% prob.adj.	\$33.9m
JAK2 & FMS – Preclinical	Taken as a single proforma licensing deal for one program	\$16.1m
JAK3 – Novartis Deal	Proforma deal 2 (\$200m headline) less \$4.8m cash received to date	\$21.6m
<b>Total</b>		<b>\$71.6m</b>

SOURCE: *Lodge Estimates*

We believe there is potential for significant upside beyond our breakdown valuation. First, we have valued CYT997 based on a single upfront payment of US\$75m in 3 years time assuming successful completion of several Phase-II clinical trials. We have assumed a 60% probability that CYT997 will successfully complete the Phase-II program. As our deal valuation equates only to the upfront component of the Novartis/Antisoma deal (which had a headline value of \$890m), we believe this is a very conservative approach to valuing this asset. Second, our valuation of the preclinical compounds is based on only a single early stage license with terms less favourable than what has been seen for other compounds. Third, our valuation of the Novartis/JAK3 deal is based on a headline value that is less than the company reported for the deal.

*Estimate of value of potential licenses support valuation of at least \$85m for CYT*

In view of this, we believe the company's drug assets plus cash can comfortably support a valuation of \$85m (\$1.00) and has the potential to deliver significant upside beyond this valuation.

**Comparable VDA Companies**

A comparison with listed companies developing VDAs also supports a valuation of in excess \$85m for CYT based solely on CYT997 as a VDA about to commence Phase-II testing.

**Table 4: Market Capitalisation of Companies Developing VDAs**

Company	Market Cap	Stage of Development
Bionomics	A\$86m	VDA (IV only) in preclinical development with Phase-I scheduled to commence in early 2008 providing results in 1Q 2009.
OxiGene	US\$102m/A\$114m	Zybrestat in pivotal trial only for niche indication (thyroid cancer). Commencing Phase-II development for other cancer types
Antisoma	£138m/A\$281m	Completed Phase-II trials in lung, prostate and ovarian cancers. Licensing deal with Novartis and commencing Phase-III trials

SOURCE: *Company announcements*

*Comparison with other VDA companies reinforces \$85m valuation is conservative*

All of these companies have other compounds under development however, as with CYT, their VDA program is their most advanced program and thus key driver of market value.

CYT997 has completed its Phase-I clinical trial for IV administration and is soon to complete the oral Phase-I trial and commence an extensive Phase-II clinical program. Thus, in terms of development, CYT997 is considerably more advanced than Bionomic's VDA for which an IND was only recently granted and results from its Phase-I trial are not expected until early 2009. While OxiGene has a registration trial in progress for anaplastic thyroid cancer, this is a niche application (1,000 to 4,000 patients per year) and the drug is only commencing Phase-II trials for other cancer indications. OxiGene's follow-on VDA, Oxi4503, is currently in a Phase-I trial. Antisoma's VDA is more advanced than CYT997 and thus does not provide an appropriate basis for direct comparison.

Taking these into account, we believe our valuation for CYT of \$85m falls at the low end of market comparables and thus is conservative. We believe that both the licence opportunity and comparable approaches highlight the fact that the underlying value of CYT's portfolio is not fully factored into the current market capitalisation and that a significantly higher valuation for the company can easily be justified.

## Underlying Technology And Product Pipeline

### Technology

CYT has established an integrated series of technologies and capabilities for the discovery and optimisation of small molecule drugs.

*High quality technology platform for generation of new small molecule drugs*

- **Virtual Screening:** using an internally developed software system called ChemoPhore for “in silico” identification and optimisation of new drug candidates
- **Medicinal Chemistry:** a team of 18 medicinal chemists able to synthesise hundreds of variants of candidate drugs to optimise for pharmaceutical properties (probably the best single team of medicinal chemists in the Australian biotechnology sector)
- **Screening and Biological Testing:** established high-throughput assays and models to measure the biological and pharmaceutical activity of drug candidates

The company has used these technologies to focus on one of the leading classes of drug targets called kinases. Over 500 different kinases have been identified which have a variety of roles in cell signalling pathways which control processes such as cell division and tissue growth. Due to their critical role in regulating these processes, kinases have been one of the most effective classes of drug targets particularly for diseases such as cancer and AIID (autoimmunity and inflammatory disorders).

### Pipeline

Using this technology platform, CYT has four active drug discovery and development programs currently in progress.

*That has generated a good pipeline of drugs candidates*

- **CYT997:** Vascular Disrupting Agent (VDA) for cancer entering Phase-II (oral & IV)
- **JAK2 inhibitor:** Phase-I for cancer/MPD expected late-'08.
- **FMS Inhibitor:** Phase-1 for cancer expected early'09
- **JAK3 inhibitors:** collaboration with Novartis for transplantation and autoimmune disorders (progress confidential).

Figure 1: CYT's Drug Pipeline – Progress from 2007 to 2008

Drug	Indications	Preclinical	Phase-I	Phase-II	Comments
CYT997 (IV)	Cancer - VDA				First Phase-II trial in multiple myeloma to commence in 4Q'07 with preliminary results in 3Q'08.
CYT997 (oral)	Cancer - VDA				Oral Phase-I near completion with results in 1Q'08 and at least one Phase-II trial commencing in '08.
JAK2 Inhibitor	MPD/AIID				Finalisation of preclinical data package and scale-up. Phase-I to commence late-08.
FMS Inhibitor	Cancer/ Osteoporosis				Optimisation of lead candidates targeting IND in early 2009.
JAK3 Inhibitors	Transplantation/ RA/AIID				Partnership project with Novartis. Status confidential however could earn milestone payment in 2008

SOURCE: Company presentations; VDA = Vascular Disrupting Agent, AIID = Autoimmune and Inflammatory Diseases, RA = Rheumatoid Arthritis

In addition to cancer indications that are the focus of CYT's internal drug development program, JAK2 is important in autoimmunity and inflammation and FMS has important roles in osteogenesis (bone growth and modelling). These indications provide additional product and licensing opportunities for these drugs.

**CYT997 – In Clinical Development**

*Most advanced product has commenced Phase-II clinical testings*

CYT's most advanced program is a Vascular Disrupting Agent (VDA) called CYT997 that is being used to treat cancer by the destroying blood supply to tumours. Unlike other VDAs in development, this drug can be administered both orally and intravenously which may allow additional uses of the drug such as in-home maintenance dosing.

CYT997 has completed an intravenous (IV) Phase-I clinical trial and should complete the oral Phase-I trial by the end of CY08 with results expected in Q1'08. The results from the Phase-I IV trial showed that the drug is safe, well tolerated and was able to stabilise disease in advanced cancer patients who had failed to respond to standard anticancer treatments.

Furthermore, a number of different biomarkers (dynamic contrast-enhanced MRI, plasma von Willibrand factor) indicated that CYT997 was reducing tumour bloodflow in these patients by damaging the tumour blood vessels. Thus, in addition to the safety data that was the primary focus of the trial, there is good evidence that CYT997 is able to provide a therapeutic benefit to cancer patients through its vascular disrupting activity.

The company is planning a program of Phase-II trials for both the oral and IV administration of CYT997. The first of these trials commenced in December 2007 and is a single arm study for a blood cancer called multiple myeloma where CYT997 has shown very good activity against cancer cells isolated from patients. Interim data from this trial should be announced in 3Q 2008

*Another two preclinical drugs expected to enter the clinic within 15 months*

During 2008, the company should commence an additional 2-3 Phase-II trials (oral and IV) against solid tumours (glioma, melanoma, and/or GIST) which will focus on CYT997's VDA activity.

**JAK2 & FMS Inhibitors – Completing Preclinical and Manufacture**

CYT has potent and specific inhibitors to the kinase enzymes FMS and JAK2. Both of these targets are validated in cancer and other indications. CYT is planning to complete the preclinical development of these compounds during 2008 and take them into Phase-I trials for cancer applications in late-'08/early-'09. Other therapeutic applications, such as osteoporosis and anti-inflammatory immunological disorders (AIID), could provide opportunities for the company to secure licensing partnerships.

**JAK3 Inhibitors – Funded Collaboration with Novartis**

*Strong news flow driven by Phase-II program*

In June 2006, CYT executed a landmark deal (headline value of A\$274m) with Swiss pharmaceutical giant Novartis for the development of JAK3 inhibitors to prevent transplantation rejection and for autoimmune diseases such as rheumatoid arthritis. Due to confidentiality, CYT is unable to disclose the development status of drug candidates in this program.

We believe the progress of CYT's drug candidates over the next 12 months should provide significant news flows for the company. The key near term value driver will be the commencement of the Phase-II program for CYT997 with interim results from the first of these trials expected in 3Q 2007. This should be followed by JAK2 and FMS inhibitors progressing to clinical testing in late-08/early-09. In addition, during the course of 2008, the company may receive a development-based milestone payment from Novartis for the JAK3 program and there is scope for CYT to secure licensing deals around the non-cancer applications for the JAK2 and FMS inhibitors.

## VDA's –A Bloody Good Way To Treat Cancer

*VDA's are a class of anti-cancer drugs that work by depriving tumours of their blood supply*

Vascular Disrupting Agents (VDA's) are the next generation of anti-cancer drugs that act on tumours by destroying their blood supply. The loss of blood supply deprives tumours of oxygen and nutrients, which prevents them from growing and spreading, and leads to necrosis or tissue death. Pharmaceutically, there are two ways to deprive tumours of the blood supply:

- **Angiogenesis Inhibitors** – which prevent new blood vessels from forming
- **VDAs** – which destroy the blood vessels that are already established in the tumour

The reason that these agents can work is that the architecture of the blood vessels which supply tumours is different from the other blood vessels in the body. Structurally, the blood vasculature that is formed to supply tumours is weaker than regular vasculature. As a consequence, angiogenesis inhibitors and VDAs can selectively act on tumour blood vessels without affecting the normal blood vessels in the body.

### Angiogenesis Inhibitors –Death By Starvation Works

*Angiogenesis inhibitors have proven this approach works*

Tumours, like any other tissue in the body, require a blood supply to provide oxygen and nutrients and to remove waste products. As tumours grow, they secrete various growth factors which stimulate the growth of new blood vessels. The formation of new blood vessels is a process that is called angiogenesis.

Angiogenesis inhibitors act by blocking the signals that stimulate the formation of new blood vessels. This prevents the tumour from being able to grow further and makes it more susceptible to cytotoxic anti-cancer drugs (drugs that are toxic to dividing cells). However, angiogenesis inhibitors only prevent formation of new blood vessels and do not have any effect on the tumour blood vessels that are already established

*The only angiogenesis inhibitor on market had sales of US\$2.4B in 2006*

The effectiveness and commercial value of this approach has been highlighted by the antibody drug Avastin which binds to a protein called Vascular Endothelial Growth Factor (or VEGF). VEGF is one of the key signalling molecules that tumours secrete in order to stimulate the formation of new blood vessels. Avastin is used to treat a range of solid tumours including colorectal cancer, breast cancer and non-small cell lung cancer. While Avastin was only launched in 2004, by 2006 it generated sales of US\$2.4B.

### Vascular Disrupting Agents – Death By Destruction Even Better

*VDAs work by destroying the blood supply to tumours*

VDA's go one step further than angiogenesis inhibitors in that they trigger the destruction of blood vasculature that is established and already supplying the tumour. While the underlying principle of depriving the tumour of blood supply is the same as with angiogenesis inhibitors, VDAs act more rapidly by causing the collapse of blood vessels which supply the tumour. In animal models, VDAs have been shown to cause a significant reduction in tumour blood flow within 5–15 minutes of administration and complete vascular shutdown after only 30 minutes.

As this is a relatively new approach to cancer treatment, there are currently no VDAs on the market. However a few VDAs have been tested in clinical trials (Zybrestat owned by OxiGene and ASA404 owned by Antisoma/Roche). The results from these trials have been very encouraging, showing significant improvements in key indicators such as mean survival times, tumour response rates and times to tumour progression.

The mechanism of vascular disruption by these compounds is complex and is likely to involve several cellular factors. However, one key effect of these compounds is the disruption of components of the cytoskeleton, such as tubulin, which provide structural support for the endothelial cells. Even within this, the VDAs appear to differ in how and where they bind to these components which may result in differences in activity and also the ability to overcome drug resistance when it develops.

## Lethal Combinations

*VDA's are likely to be most effective in combination with cytotoxic drugs*

Angiogenesis inhibitors are usually used in combination with other agents such as cytotoxic anti-cancer drugs currently used for chemotherapy. This is because, while angiogenesis inhibitors prevent further tumour growth, they usually have limited ability to kill the tumour directly. On the other hand, VDAs can destroy the blood supply to tumours and effectively starve the tumour leading to necrosis (death) of the tumour tissue. Thus, VDAs have the potential to be used either as a monotherapy or in combination with a cytotoxic agent.

Cells on the outside of the tumour often are able to access oxygen and nutrients from the surrounding tissue and, in some cases, normal blood system. Thus, while VDAs can cause the death of most of the tumour cells, the greatest effect for VDAs will still result from combining their use with cytotoxic agents. This strategy is to effectively kill or weaken cells inside the tumour through starvation. Cytotoxic agents then act on any remaining internal cells and will also poison the rapidly dividing cells which are present on the outside of the tumour.

Phase-II clinical trials for VDAs have typically included combination therapies (VDA plus cytotoxic) once the safety profile of the VDA has been established from Phase-I clinical trials. Due to both the trial design and to the mode of operation, Phase-I trial results for VDAs usually do not provide any indication of clinical efficacy.

## VDAs – Putting Money Where Your Mouth Is

*We believe that CYT997 is the only VDA that is being given both orally and intravenously*

Given the therapeutic potential of using VDA's to treat cancers, a number of companies have started developing new vascular disrupting agents. However, as this is still a relatively new approach, none of these agents are in the market and only two of them (Zybrestat and ASA404) have completed Phase-II efficacy trials.

Cytopia's VDA, CYT997, is unique in that, to our knowledge, it is the only VDA in clinical development that can be given both intravenously and orally (ie: in a capsule). This may provide unique market opportunities by reducing the need for patients to attend a clinic in order to receive medication. Furthermore, CYT997 has good pharmaceutical properties in that it is well tolerated and is very potent in its activity. Data from CYT's preclinical studies indicate that CYT997 also has cytotoxic activity in addition to its VDA activity. Thus we believe that CYT997 currently has a very competitive profile against other VDA's that are in development.

**Table 5: VDAs in Development**

VDA	Company	Stage
ASA404	Antisoma / Roche	Completed Phase-II trials in lung, prostate & ovarian cancers
Zybrestat	OxiGene	In Phase-II/III trials for rare thyroid cancer
Azixa	Myriad	Phase-II for metastatic brain cancer initiated in May'07
<b>CYT997</b>	<b>Cytopia</b>	<b>IV Phase-I complete, oral Phase-I complete early 2008</b>
ZD6126	AstraZeneca	Phase-II studies suspended
ARENEGYR	MolMed S.p.A	Phase-I to establish high dose and MTD for VDA activity
OXI4503	OxiGene	In Phase-I dose escalation trial
NPI-2358	Nereus Pharmaceuticals	Phase-I trial initiated in June'06
EPC2407	EpiCept	Phase-I trial initiated in Dec '06
BNC105	Bionomics	Completing preclinical development

SOURCE: *Company websites*

*CYT997 is one of the more advanced VDAs in development*

CYT997 is one of the more advanced VDAs currently under development. As with cytotoxic drugs, we expect that a number of VDAs will end up being used in the clinic for the treatment of cancer. This is because the differences in their mechanisms of action (ie: how they cause the vascular disruption) will result in different activities against various types of cancer. These differences can also be used to overcome the resistance that tumours often develop to specific drugs.

## CYT997 – Ready for Phase-II

CYT997 has completed its Phase-I intravenous trial and is expected to complete its oral Phase-I trial in early 2008. The company commenced first trial in an extensive program of Phase-II clinical trials at the end of 2007. The first trial is for the intravenous formulation of CYT997 with further trials for both intravenous and oral formulations expected to commence during the course of 2008.

### Completion of Phase-I Trials

In November 2007, CYT reported the final data for its 31-patient Phase-I dose escalation trial for intravenously administered CYT997. The primary objective of this study was to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) for the drug. The study achieved these aims and demonstrated that the drug is well tolerated in cancer patients.

*Phase-I trial for IV CYT997 successfully completed*

The Phase-I intravenous trial took longer than was originally anticipated simply because the drug was so well tolerated that it was necessary to keep increasing the dose to higher levels before any toxic effects could be seen. While it is usually preferable not to experience delays, experiencing them because a drug is safer than expected is quite a good thing.

Of the 22 patients evaluable for tumour response measurement, 17 showed disease stabilisation (ie, the tumour stopped growing). This is a particularly impressive result because all of the subjects in this trial were late stage patients who had failed to respond to standard anticancer treatments and had very limited life expectancy. Furthermore, the biomarker data that was collected in the trial indicated that CYT997 had reduced bloodflow to the tumour sites and had caused damage to the blood vessels, supporting its mode of action as a VDA.

*Oral CYT997 trial should be completed by early in 2008*

CYT also has a Phase-I dose escalation trial in progress for the oral formulation of CYT997. This trial, which is partly funded by a \$3.0m Commercial Ready grant, is expected to conclude early in 2008 with results expected 2–3 months after dosing is completed.

### Extensive Phase-II Program Planned For 2008

CYT plans to initiate 3–4 Phase-II clinical trials for CYT997 during 2008. The trial designs are planned to include single-arm studies (in which all patients receive the drug) and randomised studies (in which patients either receive the drug along with the standard treatment or just receive the standard treatment). Each trial will focus on specific patient groups with cancers such as myeloma, glioma, gastrointestinal cancer and melanoma.

*Expect 3-4 Phase-II trials for CYT997 will be initiated in 2008*

Single arm studies are typically smaller (between 20–40 patients) and are of shorter duration. The results of these studies provide an initial indication of the effectiveness of the drug. While no control arm is included in these studies, for diseases where limited treatment options are available, any significant improvement over standard treatments (using historical data from the same patient group) is considered beneficial. Typically an interim analysis is undertaken half-way (10–20 patients) in single-arm studies. Thus, we would expect to see some initial results from such trials during the course of 2008 and early in 2009.

*Interim results from one of these trials should be available in 3Q 2008*

Randomised studies are typically larger (100–120 patients) and of longer duration. Furthermore, because randomised trials are usually “blinded” (ie: it is not known until the end of the study which patients received the drug and which did not), the undertaking of an interim analysis has to be specifically included in the design of these trials and usually requires testing in larger patient numbers.

The company has announced that it commenced the first single-arm Phase-II clinical trial in December 2007 for a blood cancer called multiple myeloma. In preclinical studies, CYT997 has shown good cytotoxic activity against myeloma cells isolated from patients. This trial has a two stage design with an interim analysis after 14 patients and a maximum enrolment of 24 patients. The company is expected to release the interim data from this study in 3Q 2008.

The company is expected to initiate 2-3 another Phase-II trials during 2008 for various solid tumours. CYT plans to focus on niche solid tumours for which there are limited treatment options such as melanoma, glioma and GIST. This approach has been used for a number of drugs (including Avastin, Sutent and Nexavar) and as it facilitates more rapid initial approval from the regulators with the opportunity to expand into other indications in the future.

From an investment perspective, we believe the initiation of the Phase-II program, which will provide interim results during 2008, should result in strong news flow that will generate greater market interest for CYT.

## Two More Drugs In The Clinic Within 18-Months

*Two more drugs entering the clinic in late 2008 or early 2009*

In addition to CYT997, CYT has two drugs in preclinical development against specific kinase targets called JAK2 and FMS. The preclinical testing and scale up manufacture of these two drugs will be completed in 2008. These drugs are expected to commence clinical testing in late-'08/early-'09.

### JAK 2 Inhibitor – Opportunities in MPD and Cancer

CYT has a potent, highly-specific inhibitors to a kinase called JAK2. This target has been validated in Myeloproliferative Diseases (MPDs), some cancers and inflammatory diseases.

*Specific mutation in JAK2 causes several diseases called MPDs*

MPDs are a group of disorders that are characterised by the cellular proliferation of one or more cell types found in blood and include diseases such as polycythemia rubra vera (PV), essential thrombocythemia (ET) and agnogenic myeloid metaplasia (AMM). Mutations in JAK2 appear to be one of the primary causes of certain MPDs with one particular gain-of-function mutation, called V617F, being present in a large number of patients. This is similar to another MPD called chronic myeloid leukaemia (CML) in which a specific mutation called Ph<sup>+</sup> is the primary cause of CML in most patients.

**Table 6: Frequency Of The JAK2 V617F Mutation In Myeloid Disorders**

Type of Myeloproliferative Disease (MPD)	Frequency That Patients Have Mutation in JAK2
Polycythaemia vera	81 – 99%
Essential thrombocytosis	41 – 72%
Primary myelofibrosis	39 – 57%
Chronic myeloid leukaemia (CML)	3 – 9%
Myelodysplasia	3 – 5%
Acute myeloid leukaemia	<5%

SOURCE: *Nature Review Drug Discovery*

While the incidence of MPD is relatively low (approximately 10,000 new cases per year in the US of which 5,000 are CML), the ability to target a specific mutation that causes the disease provides an attractive therapeutic opportunity. From a commercial perspective, most of the MPDs are chronic diseases requiring long term treatment. As a comparison, Novartis's Gleevec, which is the mainline treatment for CML, has generated significant sales (2006 sales US\$2.6B) despite the low incidence of new cases. As the condition is not lethal, it is estimated that there are currently up to 100,000 people with non-CML MPD in the USA.

*Potential applications for cancer and inflammatory diseases*

In addition to MPD, JAK2 inhibitors are likely to have applications for treating other proliferative disorders such as cancer and inflammatory diseases including rheumatoid arthritis and psoriasis. As with CYT's FMS program, the company will focus on MPD and cancer-like applications with a view to seeking licensing partners for other indications. CYT is targeting for preclinical work on this compound to be completed during 2008 with clinical trials for MPD and/or cancer commencing in late-'08/early-'09.

With the discovery of the V617F mutation in several of the MPDs, a number of companies have initiated JAK2 inhibitor programs including Targegen (TG101348), Incyte (INCB18424), Exelixis (XL019) and Astex (AT9283 & discovery). To date, only Incyte's compound has entered Phase-I clinical testing.

*CYT's JAK2 inhibitor is highly selective which is important*

Specificity to JAK2 will be critical for any of these compounds as activity against the closely related JAK3 kinase is likely to lead to side-effects and potential safety problems. As CYT's JAK2 inhibitors are highly specific and have a very low affinity for JAK3, we believe they will be very competitive against compounds under development by other companies.

### Potent Inhibitors of FMS

*FMS target has been validated for cancer and osteoporosis*

The drug target FMS is a kinase that acts as the cell surface receptor for a cytokine (a type of potent signalling molecule in the body) called macrophage colony-stimulating factor or M-CSF. M-CSF stimulates the formation of cells called osteoclasts that are involved in turnover of bone tissue and, consequently, have a role in the establishment of metastases (secondary tumours) in bone tissue. The role of FMS has been validated by several studies in animal models which have shown that inhibition of FMS dramatically reduces the growth of metastases that have become established in bone.

In addition to reducing the growth of metastases, inhibitors of FMS are likely to have

program is focussed on the cancer applications of its FMS inhibitors, and thus their use in other therapeutic areas could provide out-licensing opportunities for the company.

CYT has potent and highly selective inhibitors of FMS which act on the “closed” form of the enzyme. The “closed” form of FMS is inactive and is the form in which the enzyme is normally found in cells. This inhibitor essentially locks FMS into this inactive “closed” configuration. The high selectivity of CYT’s FMS inhibitors means they are less likely to have “off-target” activity which can result in undesirable side-effects.

*CYT has a very potent and specific inhibitor to FMS*

There are a few compounds that are in development that inhibit FMS but the majority of these compounds are non-specific in that they also inhibit other kinase enzymes. The Pharmaceuticals Division of Kirin Breweries (Japan) is developing an inhibitor of FMS called Ki20227. This compound appears to be reasonably specific for FMS but is still in preclinical development. Other potential inhibitors, such as Plexxikon’s PLX647 and Pfizer’s Axnitib also have activity against other drug targets (cKit and VEGF respectively) which will result in a different activity and safety profile compared with a highly specific inhibitor.

Formulation and preclinical development of CYT’s FMS inhibitor is scheduled for completion in 2008 with the compound scheduled to enter clinical development in early-’09. CYT’s compound is likely to be one of the first specific inhibitors of FMS to enter clinical development.

### Valuable Partnership With Novartis For JAK3

In June 2006, CYT announced a license and R&D collaboration with Novartis to develop inhibitors of JAK3 kinase for the prevention of transplant rejection and treatment of autoimmune diseases such as rheumatoid arthritis. The terms of this deal included R&D payments totalling A\$13m over 3yrs (to fund R&D undertaken by CYT), potential milestone payments totalling A\$274m (for multiple indications) and a royalty on end sales.

*Partnership with Novartis provides both financial and strategic benefits*

As well as being one of the largest deals signed by any Australian biotechnology company, especially for a preclinical program, this partnership is significant for four reasons

- **Deal-making:** demonstrates CYT’s ability to secure good deals with big pharma
- **Cash-generating:** reduces cash burn for CYT through R&D payments
- **Expertise development:** collaboration enhances skills and expertise within CYT
- **Validation:** confirms CYT’s technology can generate commercially attractive leads

The deal demonstrates the ability of CYT’s management to negotiate and finalise a commercially attractive deal with a big pharma partner. This achievement should not be underestimated as it is a significant challenge to maintain momentum and ongoing support of internal stakeholders within large pharma companies while ensuring that the needs of both parties are met in the final agreement. On this basis, we have added confidence on CYT’s ability to secure further licensing deals for its lead compounds.

Since signing the deal, CYT has received \$4.8m as upfront and R&D payments to 30 June 2007 and thus should receive a further \$8.2m in R&D payments over the next two years which represents around 35% of the company’s current operating costs.

The collaboration provides continued dialogue and meetings between the R&D teams of CYT and Novartis to manage the JAK3 program and evaluate data. As a consequence, CYT’s scientists are getting access to expertise and training from one of the largest pharmaceutical companies in the world. The skills and expertise that CYT’s scientists are gaining from this collaboration should assist in the development of the company’s own drugs.

Finally, we view the fact that Novartis entered into the collaboration as a strong endorsement of CYT’s skills in developing specific kinase inhibitors and also of the quality of the JAK3 inhibitors that it had already developed. Novartis owns the biggest selling kinase inhibitors in the market (Gleevec) and also has a number of internal programs targeting specific kinases as drug targets.

Novartis is a significant player in the \$3.3B transplantation market in which three products account for 80% of sales: Prograf (Astella, US\$1B), Cellcept (Roche, US\$945m) and Neoral (Novartis US\$650m). While Neoral has come off patent, sales are not expected to decline in the near future. However, the development of new immunosuppressants will be essential for Novartis to maintain market share in this area. Novartis currently has a limited presence in the autoimmune market but has active programs in psoriasis, rheumatoid arthritis,

inflammatory bowel disease, systemic lupus erythematosus and multiple sclerosis.

Under the confidentiality terms of the agreement with Novartis, CYT is not permitted to disclose the stage of development of any of the JAK3 inhibitors. Thus, in the near term, updates on this program will be limited to milestone payments as the program achieves specific development milestones.

## Cash Position

CYT had a cash balance of \$14.1m on 30 June 2007. During FY07, operating cash outflows were \$12.5m (\$11.1m for operations and \$1.5m for tax) however, the company received \$3.1m in payments from the Novartis deal, \$0.65m from grants, \$1.1m from interest and also \$3.4m from the sale of its remaining shares in Alchemia (held as a result of the company's previous PDF structure when it was Medica Holdings).

*Cash and expected receipts will support current development plan into 2009*

In December 2007, CYT raised \$5.1m in a placement of 11m shares at \$0.46 to institutional and sophisticated investors. As well as providing additional funds to support the planned Phase-II clinical trials for CYT997, the placement attracted several new institutional investors significantly strengthening the company's share register. In combination with the cash, we believe the company has sufficient cash reserves for the next 15 months.

## Ongoing Cash From Novartis and Grants

Under the collaboration with Novartis, CYT is eligible to receive a further \$8.2m in R&D payments over two years commencing 30 June 2007. The company also has a \$3.0m Commercial Ready grant for the development of CYT997. We estimate that the company has received \$1m of this grant to date and so is eligible to receive a further \$2m from this grant. We also expect the company to receive between \$0.3m–\$0.6m/yr in interest over the next two years

## Cash Requirements Will Expand With Clinical Trial Program

In FY07, the operating cash requirements for CYT were \$11.1m. However, with the company planning to initiate 3–4 Phase-II clinical trials during 2008, we expect that the cash burn rate will increase over the next 12 months.

*Estimated cost of Phase-II is \$6m–7m over the next 18–24 months*

The company is currently planning two types of clinical trials for CYT997. The single arm trials (which do not include a control arm) will involve up to 24 patients. Depending on the data collected during these trials (ie: use of Dynamic Contrast–MRI for tumour imaging), these trials are expected to cost \$0.5m–\$1.0m each. The randomised Phase-II trials will involve 100–120 patients and are likely to cost around \$2.5m each. Thus, we expect the initial Phase-II program for CYT997 will add a further \$6.0m–\$7.0m in costs over the next 18–24 months.

We also expect the expenditure on the preclinical compounds CYT645 and JAK2 inhibitor to increase as they will require scale-up GMP manufacturing and animal toxicity studies which will be done by external providers. As these are completed, the company will have to initiate Phase-I safety studies which we estimate would cost \$0.5m each.

Table7: Four Year Base Case Cash Projection For CYT

	FY07A	FY08E	FY09E	FY10E
License Fees	3.1	4.2	4.2	0
Grants	0.6	0.9	1.1	0
Interest Received	1.1	0.6	0.3	0
<b>Operating Cash Inflow</b>	<b>4.8</b>	<b>5.7</b>	<b>5.6</b>	<b>0</b>
Suppliers & Employees	(11.1)	(12.8)	(14.1)	(15.5)
Tax	(1.3)	0	0	0
Clinical Trial Costs - VDA	0	(2.5)	(4.5)	0
Clinical Trial Costs - Others	0	0	(1.5)	(3.5)
<b>Operating Cash Outflow</b>	<b>(12.5)</b>	<b>(15.3)</b>	<b>(20.1)</b>	<b>(17.0)</b>
<b>Net Operating Cash</b>	<b>(7.6)</b>	<b>(9.6)</b>	<b>(14.5)</b>	<b>(17.0)</b>
Net PP&E	(0.6)	0	0	0
Sale of Assets (ACL)	3.4	0	0	0
<b>Net Inv. Cashflow</b>	<b>2.8</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Net Fin. Cashflow</b>	<b>0</b>	<b>5.0</b>	<b>0</b>	<b>0</b>
Inc / (Dec) Cash	(4.9)	(4.6)	(14.5)	(17.0)
Opening Cash	19.0	14.1	9.6	(4.9)
<b>Closing Cash</b>	<b>14.1</b>	<b>9.6</b>	<b>(4.9)</b>	<b>(23.9)</b>

SOURCE: *Lodge Estimates*

*Additional cash may come in from grants or further licensing deals*

Our cash flow summary for the next four years is a base case which assumes no additional cash receipts other than the existing Commercial Ready grant and the committed R&D payments from Novartis. We anticipate during the next 12 months, the company may receive a milestone payment from Novartis from the JAK3 program and also could secure an additional licensing deal for one of its other lead compounds. In addition, with two of its leads likely to enter clinical development programs in the next 12-15 months, the company will be well positioned to secure additional grants for these programs.

Based on these estimates, the current cash reserves plus receipts from Novartis and grants will support the current plans for clinical and preclinical development of its compounds for a further 12-15 months (to the end of 2008). As the company is planning to out-license non-cancer applications for its drugs, it may be able to secure further licensing revenues in the near-to-medium term.

## Management and Board

Mr Andrew Macdonald was appointed CEO of Cytopia in June 2006 having been employed as CFO since August 2005. Prior to joining CYT, Mr Macdonald was CFO at Biota for 3yrs. His previous roles include CFO and CEO for IT companies and also extensive experience in global finance. He holds a BSc and BBus and is a member of AICD and a CPA.

*Management team provides expertise in drug discovery and development*

CYT's senior management team includes Dr Andrew Wilks (Chief Scientific Officer) who discovered JAK1 and JAK2 kinases as a researcher at the Ludwig Institute in Melbourne, Dr Chris Burns (Research Director) who spent 5yrs at Pfizer Central Research in the UK, Dr Gregg Smith (Director, Drug Development) who has over 10yrs in drug development experience including 5yrs in product development, and Dr Shreefal Mehta (Vice President, Business and Corporate Development) who was previous CEO and co-founder of the US private company Myomatrix which CYT acquired in January 2005.

The company has recently appointed Dr Jim Palmer as Head of Chemistry. Dr Palmer has extensive industry experience having worked at Marion Lab (now part of Sanofi Aventis), Prototek, Celera and Rigel working on developing drugs against kinase targets.

*Highly credible Board with extensive commercial experience*

CYT's Board is chaired by Mr Robert Watson who joined the Board in June 2003 and became non-executive Chairman in November 2006. Mr Watson has been CEO of several corporations (Mayne Nickless, Computer Services, Data Sciences International and Lend Lease Employer Systems) and is also a director of SEEK and Virgin Blue. Mr Watson has extensive experience in M&A and capital raising. He currently holds 14.1% of CYT.

The other Board members are Dr Kevin Healey who has extensive industry experience and established Medica Holdings that was the PDF that eventually became CYT, Mr Roderick Lyle (a M&A lawyer), Mr Mark Rowsthorn (ex-Toll Holdings, previously chairman of Virgin Blue and holds 15.9% of CYT), Dr Geoffrey Vaughan (Victorian College of Pharmacy, TGA and IR&D Board), and Mr Macdonald (CEO).

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**Hold:** Expected Total Return between 0% and 15% over a 1 year period.

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