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In this edition...
Whilst the Tier-1 biotechs have been streaming ahead this financial year, there is reason to look at companies that are seeking to join this group. Over the next two weeks, we will examine some overlooked smaller biotech stocks that are providing some strong investment appeal.

Cytopia is one such stock and is set for a busy year with major milestones approaching. Similarly, Phylogica is approaching some major crossroads with respect to external validation of its technology.

We also update readers on Acrux's second deal with Organon in as many weeks.

The editors
Companies covered: ACR, BTA, CYT, PYC

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.0%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (from 5 May '06)	13.4%
Cumulative Gain	**216%**
Average Annual Gain	**26.1%**

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Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.

22 Million Reasons for Cytopia to Hit Milestones in 2007

Cytopia (CYT: 64 cents) is a biotech company that has failed to unlock the potential of its drug discovery assets as recognised by the investment market. A licensing and collaboration deal with Novartis last year, valued as much as $274 million in future potential milestone payments, sent the share price into a tailspin, falling by almost 40%. Will 2007 be a turnaround year for Cytopia and its investors?

There are four main projects the company is currently focused on.

Novartis collaboration

The first is the collaboration with **Novartis**, developing compounds that inhibit the JAK3 signal transduction pathway, an area of expertise for Cytopia. Modulating this pathway is expected to have an effect on autoimmune disorders and also help prevent rejection of organs during transplants. The organ rejection market is worth about US$3 billion a year and Novartis is a leading player in this market with its products Sandimmune and Neoral.

Since the deal with Novartis was signed in June last year, Cytopia has received $3 million in licensing fees from $13 million payable in the first three years of the collaboration in R&D and licensing fees. We anticipate another milestone payment may be triggered this year, which could be for the selection of a lead candidate from the collaboration.

CYT997 clinical trials

In July 2006 Cytopia started a Phase I trial with an intravenous formulation of its lead compound CYT997. The objective of this trial is to test the safety of the compound and to evaluate the drug's maximum tolerable dose. The trial involves patients with advanced solid tumours who have failed at least one course of first-line therapy or where no therapy options exist.

CYT997 is a vascular targeting agent that disrupts blood vessel formation in tumours which makes it potentially suitable to treatment of solid tumours.

It's expected that close to 30 patients with 12 different tumour types will be recruited for this trial which should be closed around June this year. The trial stops when two or more patients experience a maximum tolerable dose. Results are expected early in Q3 2007. Results should also include details of pharmacokinetic profile of the drug and MRI scans will provide some interesting information on the effect on tumour vasculature. As early patients were receiving a low dose, it's likely that significant signs of efficacy across the board will be established in this trial.

A Phase II trial should begin in the second half of 2007 in 50 – 100 patients with similar disease profiles. The company will likely seek to partner this program at the completion of Phase II studies.

A trial with an oral formulation of CYT997 started in December 2006 in 12 – 15 patients, also with solid tumours. This trial is expected to be completed in Q3 2007.

Second partnering deal potential – JAK2

Cytopia is looking to secure a second partnering deal with a major pharmaceutical company. The likely program to be partnered next is the JAK2 project focusing on myeloproliferative disorders (MPDs). MPDs occur when the body makes an excess of red blood cells or platelets increasing the likelihood of unwanted blood clots in the body. Cytopia's area of expertise is in JAK signaling pathways. It owns an exclusive license to the JAK2 enzyme, which has recently been independently linked to the overproduction of red blood cells in MPD. There are over 50,000 people in the world with MPD. The program is currently at the lead optimization stage.

Other JAK2 programs

The JAK2 pathway is also implicated in other disorders such as pulmonary hypertension, chronic heart failure and leukemia. The company is conducting in *vivo* efficacy studies in these areas with its JAK2 small molecule inhibitor leads.

FMS program

Cytopia has discovered compounds that have shown high potency in inhibiting a kinase enzyme, FMS, that may restrict the spread of cancer metastases. A lead candidate is expected to move into preclinical studies this year.

Summary

An achievable objective for Cytopia is to have three clinical programs underway within 18 months and two major licensing deals completed (including the Novartis deal). Cytopia is in a position to generate significant shareholder value over the next 12 months. It remains undervalued and an attractive investment option. The company now has 50 employees, with $18 million cash at the end of last year and is capitalised at $48 million. It's worth noting that the company's PDF status will be rescinded in June 2007 and this may pave the way for increased investor interest in this stock (PDF companies have not generated strong appeal for investors in the past).

And with 22 million $1 options due to expire in November this year, which could bring in $22 million of funding for the company, there's plenty of motivation to achieve major milestones this year.

Milestones for 2007

- Completion of CYT997 Phase I intravenous study
- Results from CYT997 intravenous study
- Completion of CYT997 Phase I oral study
- Results from CYT997 Phase I oral study
- Start of Phase II trial for CYT997
- First milestone payment from Novartis
- Second licensing deal, for JAK2 in MPDs

Bioshares recommendation: **Speculative Buy Class A**

Acrux Signs Second Licensing Deal

Acrux (ACR: $1.26) has followed up last week's announcement of a deal with **Akzo Nobel's** healthcare business **Organon** covering the application of Acrux's drug delivery technology to contraceptive compounds, with another deal with the same firm. This time it covers the delivery of a non-hormone compound. Potentially, Acrux can receive up to $US12 million in milestone payments, in addition to royalty payments.

The deals were announced separately because the second deal came to fruition as a by-product of the first deal, about two thirds of the way through commercial discussions and due diligence.

The second deal is significant because the compound covered by the deal that is not a hormone, and it is also proprietary, at least at the moment. Previously the focus of Acrux's drug delivery technology has been on hormones, a class of signalling molecules that have proved more amenable than large proteins to delivery across the skin. While the compound associated with the second deal has not been revealed, it is a sign that the Acrux technology is capable of being broadened in scope

With these two deals, Acrux has effected very specific licensing terms. The first deal is exclusive with Organon and is limited to the extent to that Organon selects a specific contraceptive compound. It doesn't stop Acrux's existing contraceptive drug delivery programs. The second deal covers a specific compound for a specific indication. The upside over the longer term is that with this technology, Acrux can roll out similar very specific deals and build a solid royalty income base.

Correction: In edition 206 we said that the royalty rate pertaining to Acrux's license deal with Organon would lie between 3% and 5%, when in fact the royalty rate for the deal(s) with Organon is more likely to lie in the standard industry rates of 5% to 8% range, according to general guidance previously provided by the company.

Acux is capitalised at $180 million.

Bioshares recommendation: **Speculative Buy Class A**

Key Milestones Approaching for Phylogica

Phylogica (PYC: 35 cents) is moving towards major commercial validation crossroads. The company has two commercial research agreements, one with **Johnson & Johnson** and the second with **Opsoma Therapeutics** in Ireland. Over the coming six months it is expected that both partners will be in positions to decide on substantial extensions of their respective relationships with Phylogica.

Opsoma collaboration

In March last year Phylogica signed a research collaboration with Opsoma. The agreement involved Phylogica delivering up to 20 Phylomer drug candidates (peptides) that hit inflammatory dis-

Cont'd over

ease targets, more specifically Toll-Like Receptor targets and T-regulatory cells.

Phylogica has delivered 37 peptides from its first screen using its proprietary library. Opsoma is currently completing cell culture testing of the potential drug leads with results expected shortly. If positive, it will be the first third party confirmation and validation of the technology that the company will announce. It's anticipated that a three way larger commercial collaboration may then eventuate, possibly involving a major pharmaceutical group.

Johnson & Johnson collaboration

In June last year Phylogica entered into a research collaboration with Johnson & Johnson, for Phylogica to provide specific peptides for an undisclosed target. It's expected that this program will be completed in the next six months after which time Johnson & Johnson may consider broadening the drug discovery collaboration.

Results to date

Phylogica has shown some of its Phylomers to be effective in preclinical studies in two models for the treatment of stroke and burns. In the burns study, preclinical results showed that its peptide was able to significantly increase the time to healing over a control, with significantly less scarring. The company is talking to potential licensees for the stroke compound and is considering whether it may take the burns treatment product into the clinic independently.

Novel protein library companies becoming a scarce resource

Acquisitions of protein library companies over the last few years has reduced the number of such companies to collaborate with big pharma. In December 2005 antibody company **Abgenix** was acquired by **Amgen** for US$2.2 billion; **Cambridge Antibody Technology** was bought by **AstraZeneca** for US$1.3 billion last year; and most recently single domain antibody group **Domantis** was acquired by **GlaxoSmithKline** for $575 million in December 2006.

This increases the potential demand for companies such as Phylogica. Should Phylogica's technology prove to be successful, then a potential trade sale of the company to one of its collaborators is a distinct possibility. The initial research collaborations that Phylogica has entered can be viewed as expressions of interest in the technology. It's expected that if the compounds supplied prove to be effective, then deeper alliances may be formed.

Phylogica is capitalised at $42 million. It had $4 million in cash at the end of last year and may raise $5.5 million through the exercise of 25 cent options expiring at the end of August this year.

Bioshares recommendation: **Speculative Buy Class A**

Concerns Emerge Over Tamiflu Safety

As the stockpile of influenza antiviral drugs Tamiflu and Relenza continues, some concerns are emerging in Japan over the safety of Tamiflu. Tamiflu is owned by Roche although is sold in Japan by Chugai Pharmaceutical Co. Relenza is owned by GlaxoSmithKline. Biota Holdings (BTA: $1.59) receives royalties from sales of Relenza, which are becoming significant for the company ($12.7 million in the first six months of this financial year).

Tamiflu continues to enjoy the lion's share of this market and its use is widespread in Japan for the treatment of seasonal flu strains. However according to the Japanese Health Ministry, 54 people have died so far taking the drug although there is still no proven link. It's believed by some that Tamiflu causes abnormal behaviour in children.

If this issue progresses, it could have implications for Biota. To our knowledge no such health concerns have been experienced with Relenza and the dose of Relenza is only 30% of that in a course of Tamiflu. Relenza is also administered to the site of infection through inhalation where Tamiflu is taken systemically as an oral drug.

Bioshares recommendation: **Buy**

Bioshares Model Portfolio (9 March 2007)

Company	Price (current)	Price added to portfolio
Acrux	$1.26	$0.83
Alchemia	$1.04	$0.67
Bionomics	$0.30	$0.21
Cogstate	$0.18	$0.18
Cytopia	$0.65	$0.46
Chemgenex Pharma.	$0.74	$0.38
Optiscan Imaging	$0.48	$0.35
Neuren Pharmaceuticals	$0.48	$0.70
Peplin	$0.80	$0.83
Peptech	$1.66	$1.31
Phylogica	$0.35	$0.42
Probiotec	$1.06	$1.12
Progen Industries	$6.05	$3.40
Sunshine Heart	$0.22	$0.19
Tissue Therapies	$0.56	$0.58
Ventracor	$0.91	$0.92

How Bioshares Rates Stocks

For the purpose of valuation, *Bioshares* divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, *Bioshares* grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Phylogica, Neuren Pharmaceuticals, Pharmaxis, NeuroDiscovery, Prima Biomed, Biotech Capital, Cygenics, Cytopia, Biodiem, Peptech, Starpharma Holdings, Cogstate, Xceed Biotechnology, Healthlinx, Incitive, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Medical Therapies

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