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In this edition...
Progen's PI-88 compound is a potential cancer drug with multiple modes of action. PI-88 has steadily advanced into later stage clinical trials. It may come as a surprise to some that the company has received consent from the FDA to conduct a Phase III trial in liver cancer, and drop a second planned Phase II trial. This is good news because it will speed PI-88's progress to market. Dire unmet meet is the driver for this green light by the FDA

We also note positive changes that have occurred at Clinuvel Pharmaceuticals and discuss cancer biomarker development and three companies working in that area.

The editors

Companies covered: CUV, FER, HTX, PGL, PXL

	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)	-1.7%
Cumulative Gain	**173%**
Average Annual Gain	**23.6%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd. The company also provides market and company analysis of the Australian pharmaceutical and biotech industries for local and international funds management institutions, venture capital funds and other related industry groups. For further details contact David Blake (see details below).

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Bioshares

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

Pivotal Milestones Approaching For Progen With Four Shots On Goal

Progen Industries (PGL: $3.75), which has recently been added to the Bioshares Model Portfolio, held its AGM this week and gave an exceptionally in-depth description of the company's business and the path to market for its lead product. It's worth reading and can be found on the ASX website.

Progen is a specialty oncology drug development business. Its lead compound, PI-88, is an angiogenesis inhibitor, currently in four Phase II trials with a Phase III trial set to begin in mid 2007.

Current Phase II programs

Progen is currently evaluating PI-88 in four oncology applications. These are liver cancer, lung cancer, metastatic melanoma and prostate cancer. The liver cancer trial results are due to be released in the first quarter of 2007; the lung cancer study results should be released before mid 2007, and the melanoma and prostate studies should be completed by the end of 2007 with results anticipated in early 2008.

What the company has learnt is that if it is to be successful in licensing this drug out, it requires not just standalone date for the compound, but data comparing the efficacy in blinded trials against existing treatments. While there is anticipation of a licensing deal, which may be responsible for the recent share price rise, its difficult to understand why Progen might license the compound ahead of the release of pivotal data which will emerge over the next four to 15 months.

Liver Cancer

The Phase II liver cancer trial was conducted by Progen's partner, **Medigen Biotechnology Corporation**, in Taiwan. Primary liver cancer is much more prolific in Asia because of the high hepatitis infection rates in that area. It involved 172 patients, post liver resection surgery, split into three arms: a placebo, and two different doses on PI-88. The trial started in mid 2004 and recruitment finished in January this year. The trial endpoint will look at two measurements, disease-free survival after 12 months and cancer recurrence rate.

An additional Phase II trial was to be conducted however because of the dire unmet need for this condition (the five year survival rate is only 40% for liver cancer compared to 90% for breast cancer), the FDA has agreed that Progen can conduct one Phase III trial in liver cancer and if the results are positive, it can register the drug. Another boon for the company was receiving accelerated approval, meaning the company did not need to measure life extension but the surrogate marker of disease-free survival. This is a significant outcome. Both events mean the drug may reach market between two to three years earlier. The company is to be congratulated for actually setting an antici-

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pated launch date for PI-88, if all goes well, of 2011. Although this is still over four years away, a major licensing deal or the sale of the company should occur well before that date at a multiple of its current valuation if clinical trials proceed well.

Liver cancer is one of the strongest applications for this technology because of the mechanism of action of PI-88, which prevents angiogenesis in the liver (growth of new blood vessels) and cancer metastasis (secondary cancers are transported through the blood stream which is filtered by the liver) by inhibition of heparanase, which are both mechanisms that contribute to mortality in this disease.

Lung cancer

The Phase II lung cancer trial involves 100 patients and is testing PI-88 in conjunction with and in comparison to an existing oncology drug, Taxotere. Lung cancer is an extremely difficult therapeutic area, and our view is that a spectacular outcome should not be anticipated.

Melanoma

In contrast, the current Phase II melanoma study may produce an exciting result for the company. The trial involves up to 118 patients. Importantly it is being tested as a first-line therapy in conjunction to and in comparison with an existing chemotherapy drug, dacarbazine. The reason that this trial result may produce a pivotal result in 2008 is that in a previous Phase II study in 44 patients, very positive results were achieved in patients with Stage 4 melanoma, patients who had exhausted all other treatment options, with an 80% survival after six months. This compares to historical figures, for patients with Stage 3 and 4 melanoma (who were less sick), of 51% median survival in treatment with dacarbazine. The current Phase II study should generate considerably informative data on the potential of this drug to treat metastatic melanoma.

Prostate cancer

This is a physician-sponsored study in up to 90 patients. It is testing PI-88 in combination and in comparison to Taxotere. Our view is that this is not a pivotal program for the company although it will add to the data package for this drug candidate.

Other developments

The therapeutic hurdle for oncology drugs is not high. In the CEO's AGM presentation, Justus Homburg listed four oncology drugs that were approved on the basis of providing between 2 and 4.7 months of survival improvement. Avastin, delivered patients with bowel cancer with 4.7 months extra life and has now been extended to a number of other indications. There are more than 250 trials underway or planned for the Avastin in over 20 different therapeutic areas. It is currently generating sales in excess of US$1 billion a year.

Avastin, a monoclonal antibody angiogenesis inhibitor, has helped add US$68 billion in market value for Genentech since the drug delivered positive Phase III results in 2003 and triggered a resurrection in the global biotech industry as a result. Being a biological, the drug potentially has an exceedingly long regulatory protection available from competition with generic biologics yet to be approved in the US (and so the attraction of biological drugs).

PI-88 is a semi-biologic, where the final manufacturing step uses cell-based fermentation. Any generics that may want to compete with this drug when the patents expire will need to demonstrate equivalence of the process, and bridging studies may be required to help establish equivalence. It will present some obstacles to generic competitors; not as much as with monoclonal antibody drugs but not as easy as for small molecule drugs.

Chemistry, Manufacturing & Controls (CMC) in place

From a CMC perspective, Progen confirmed with the FDA that its facility complies with FDA requirements and the company has the capacity to manufacture the PI-88 active pharmaceutical ingredient to meet all Phase III requirements and also for initial launch requirements. It's another valuable aspect that contributes to the package for a potential partner or acquirer.

License Obligations

Progen has an 8.5% of revenue license obligation to the **Australian National University** pertaining to PI-88. Under an alliance agreement with Medigen Biotechnology Corporation, Progen is required to pay 15% of future PI-88 revenues generated from sales of PI-88 in oncology or cardiovascular applications.

Summary

Progen is capitalised at $152 million with $15.9 million in cash at June this year. It is entering a pivotal 15 month period in which it should receive results from four Phase II programs, a Phase III trial in about 1000 patients with liver cancer should begin, and a licensing deal should be negotiated over this time.

Key trial results to look out for are the Phase II liver cancer trial, expected in the first quarter of 2007, and the Phase II melanoma study in early 2008. The company has the potential to generate a high multiple return for investors and cement its position as a Tier-1 biotech. However, technical or product development risks exist and further capital will be required in the next six months to fund the upcoming Phase III trial.

Bioshares recommendation: **Speculative Buy Class A**

Clinuvel Charts A Better Course

One stock that has previously failed to generate the interest of this newsletter has been Clinuvel Pharmaceuticals (CUV: 53 cents), formerly Epitan. Since listing on the ASX in 2000, Clinuvel had a string of investment issues from the outset. Its core technology emanated from research conducted in the early 1990s and as a consequence, its key patents were going to expire between 2001 and 2008, well before any of its potential products might reach the market! Its management team was very thin, and its product applications – an injectible pharmaceutical to reduce skin cancers and to promote cosmetic tanning use – was a confused and risky approach into an non-established market.

To compound difficulties for the company, in July 2004, it decided to in-license a range of dermatology pharmaceuticals that it would distribute in Australia. This has been an unsuccessful business model for listed biotechs in Australia and in September this year the company divested this asset to **Genepharm Australasia** for $1 million.

The product – CUV1647

Clinuvel's CEO, Philippe Wolgen, correctly refers to the simplicity of the company's compound, CUV1647, compared to the complexity of the business of commercialising the product. The drug candidate is a synthetic peptide analogue of the naturally occurring melanocyte stimulating hormone, which is responsible for skin pigmentation (darkening) in the body. It reduces the absorption of ultra violet light through the production of melanins and eumelanin. CUV1647 is a more potent version which causes more than 1000-fold greater skin pigmentation. It is delivered as a depot injection under the skin.

The turnaround begins

So what has changed with this company? Over the last 12 months, the company has undergone a sizeable transformation, and one that is not yet complete. In October 2005, Clinuvel appointed a new chairman, Roger Aston, and at the same time a new director, Philippe Wolgen. Within two months of that board change, the company's existing CEO, Ian Kirkwood, who was hired in January that year, was asked to make way for Wolgen who would take over the helm as CEO.

The group behind this management change appeared to be one of Clinuvel's European institutional investors, **Absolute Capital Management**, which committed to an additional $10 million in funding to Clinuvel concurrent with the management change.

Wolgen was previously a cranio-facial surgeon who had moved into pharmaceutical management and then into investment analysis before he was scouted for the Clinuvel appointment. Seriously committed to turning the business around, Wolgen has helped steer the company quickly into a more appropriate direction for commercialising its assets.

Distribution business divested & product application extended

As mentioned above, in September this year, the company made the sensible decision to divest its pharmaceutical distribution business, EpiPharm. Over the period August/September this year, Clinuvel has extended its patent position and product application of CUV1647 into three other pharmaceutical areas: the prevention of skin cancer in patients undergoing organ transplant (the immunosuppression drug regime makes patients significantly more susceptible to skin cancer), and two rare skin disorders called 'solar urticaria' and 'erythropoietic protoporphyria (EPP)' that manifest in severe skin damage when exposed to direct sunlight.

Previously, the company had identified the disorder polymorphous light eruption (PLE) and the prevention of precancerous skin lesions (actinic keratosis) as areas of focus. It now gives the company four different therapeutic applications for which to seek regulatory approval. This is now an improved strategy with the concept of developing a 'tanning drug' appearing to have been sidelined almost completely.

PLE is also a skin condition triggered by sunlight exposure, predominantly in the northern hemisphere. Whilst these sunlight exposure allergy-type conditions are generally unknown in Australia, in Germany the condition is better known following the suicide of the wife of the former German Chancellor, Helmut Kohl, in 2001, who suffered from EPP. Hannelore Kohl's sunlight allergy prevented her from being in direct sunlight and resulted in the onset of severe depression.

$35 million capital raising with major European institutional support

In what has been a very busy second half of the year for Clinuvel, in November the company announced it would be raising $35 million through an underwritten rights issue and private placement, with about 10 European institutional investors taking up the offer.

Board changes

Most recently, the company's founder and non-executive director, Wayne Millen has stepped down from the board. This is a very positive sign that the company is being transformed as it evolves its commercialisation process. More refreshment at board level would be welcome in view of some of the poor corporate decisions in the past.

Busy 12 month period ahead

The next year is shaping up to be just as busy. There are two Phase II trials set to begin (for prevention of AK in immunocompromised patients and in patients with Solar Urticaria in four trials in Australia, the UK, the US and France) and

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two Phase III trials are expected to start in 2007 as well (in AK with immunocompromised patients and in patients with PLE). This is in addition to Phase II studies in EPP which are expected to begin in Australia and Switzerland in 2006 (now started).

Risks

A major risk remains the regulatory pathway, and whether bodies such as the FDA will accept the current approach of developing CUV1647 a a treatment for various clinically recognised conditions, although evidence is mounting that it will. The product has a far greater chance of success for four different disease applications than being developed as a sun tanning product or as a treatment for sunburn. Other risks include product risk, with only one compound in development and a less than ideal patent position (composition of matter patents will expire before the product reaches market), although it is improving with the recent filing of 'use' patents for particular applications.

Summary

A positive characteristic of Clinuvel is that the company has placed itself in a position where it can generate substantial shareholder value if it can successfully meet major milestones over the next 12 – 18 months by progressing its compound through later stage clinical milestones. The company has a much improved business plan, is well funded to achieve its objectives, although more funds will likely need to be raised, and its management has been bolstered with the appointment of Wolgen as CEO. The company is seeking regulatory approval for niche pharmaceutical applications, for which the company would benefit in further elucidation of these potential markets.

Moving forward, the company needs to be fully committed to its new direction. The technology risk remains, although there is evidence of activity that has been established to date. Its patent position has been strengthened over the last 12 months. A key risk remains negotiating the regulatory pathway for its compound. The company is capitalised at $147 million with approximately $40 million in cash assets.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares Model Portfolio (1 December 2006)

Company	Price (current)	Price added to portfolio
Acrux	$0.82	$0.83
Alchemia	$0.90	$0.67
Avexa	$0.25	$0.15
Bionomics	$0.21	$0.210
Biosignal	$0.17	$0.22
Cogstate	$0.20	$0.18
Cytopia	$0.68	$0.46
Chemgenex Pharma.	$0.61	$0.38
Evogenix	$0.54	$0.47
IDT Australia	$1.71	$1.80
Optiscan Imaging	$0.46	$0.35
Mesoblast	$1.61	$1.27
Metabolic Pharmaceuticals	$0.77	$0.53
Neuren Pharmaceuticals	$0.40	$0.70
Peptech	$1.31	$1.31
Prima Biomed	$0.054	$0.09
Progen Industries	$3.75	$3.40
Sirtex Medical	$2.84	$1.95
Sunshine Heart	$0.18	$0.19

The Bioshares 20 Index

Change from June 30, 2005	**-1.9%**
Change from June 30, 2006	**17.6%**
Change - week ago	**1.1%**

Nasdaq Biotech Index

Change from June 30, 2005	**18.5%**
Change from June 30, 2006	**10.1%**
Change - week ago	**-1.7%**

The Oncology Biomarker Companies: Proteome Systems, HealthLinx and Fermiscan Holdings

There are several ASX companies that are in the business of developing biomarkers for applications in oncology, including HealthLinx, Proteome Systems and Fermiscan Holdings.

What are biomarkers?
Biomarkers are measurable physiological characteristics that can be used to depict or describe normal states, disease states, disposition to develop a disease (predictive power), or the response to interventions made to a disease.

Biomarkers are often narrowly defined to include single protein biomarkers, for example prostate specific antigen (PSA), that are obtained from blood or urine samples. However, biomarkers can also be more broadly defined to include single genetic markers, panels of genes or panels of proteins, and images of diseased tissue and cells.

Biomarker discovery is of great interest in a number of disease areas, but in particular in oncology. The development of therapies to treat cancers is limited and slowed down by a clinical trials process that seeks to assess response to treatments according to factors such as progression-free survival and overall survival. The prospect of conducting clinical trials of new therapies where lengthy clinical trials are required can thwart the development of potentially effective and better medicines. The discovery and confirmation of biomarkers that confirm the presence of a disease in early, mid and late stages and then measure the effect of interventions as they take place has the potential to speed up the clinical trials process and speed up the advance of new drugs into the market.

What are the challenges in developing biomarkers?
There are a number of challenges that confront biomarker developers. Performance, cost and economic benefit are key issues. For protein biomarkers, abundance is also important. A biomarker could be found that is highly sensitive and specific. However, if the abundance (occurrence) of the marker falls below the current detection capacity of available technology, then the biomarker is not likely to be commercialised.

However, it would appear that one of the most significant challenge for biomarker developers is establishing or accessing sample collections of tissue and cells, blood or urine from patients, both healthy and those with disease conditions. Sample collections are necessary for initial research and subsequent validation activities. Furthermore, the collection of *sufficient* numbers of samples is also critical to ensure that the right number of samples exist for the generation of statistically significant results. This may mean thousands of samples must be collected. And this could be a time consuming task. Storage of samples and patients' records is another consideration, along with the ability of investigators to efficiently and cheaply analyse samples on a retrospective basis. In the following section we review three Australian cancer biomarker companies.

HealthLinx
HealthLinx (HTX: $0.025) is developing a serum based ovarian cancer diagnostic, OvPlex. (Serum is the component of blood plasma from which clotting factors have been removed.) OvPlex is a panel of five markers that together seek to detect ovarian cancer. OvPlex is being developed to detect mid to late stage ovarian cancer. The technology that underlies OvPlex has been licensed from the **University of Melbourne** and the **Royal Women's Hospital**, Melbourne.

The OvPlex technology is being developed around a new diagnostic platform, BioPlex, developed by **BioRad**. While risk always exists with the aligning of a test with new platform, the fact that an established industry player such a BioRad is involved decreases the cause for concern. According to BioRad, BioPlex is the first clinical diagnostics platform to offer multiplexing technology on a fully-automated, fully-integrated random access platform. The system received marketing approval from the FDA in January 2005.

HealthLinx is conducting a validation trial of OvPlex in 3000 women, in collaboration with the **Women's Cancer Foundation** and **ARL Pathology Pty Ltd**. The trial was launched in May 2006. To date, 700 samples from individuals have been collected and to fast track collection, the company is looking to add another hospital to increase the collection rate. The sample collection target of 3000 was chosen because the samples will also be used to study the power and validity of OvPlex (or other related future tests) in testing for cervical and breast cancer, inflammatory disease and for uterine fibroids.

HealthLinx is capitalised at $5.5 million. It held cash of $1.0 million as of September 30, 2006. While HealthLinx appears to have the most advanced and organised biomarker program amongst the listed biomarker companies, management has a challenge to drive the company with a strong commercial intent.

Bioshares recommendation: **Speculative Buy Class B**

Proteome Systems
Proteome Systems (PXL: $0.28) has developed a rapid diagnostic platform, DiagnostiQ, for which a first application is for testing wheat. Agricultural applications of the technology have been licensed to **Bayer CropScience**. A second diagnostic program is well underway to develop a panel of proteins with which to build a tuberculosis diagnostic.

In the area of oncology, Proteome Systems (PSL) has partnered with **Egenix** from the US, to develop a diagnostic to test for the presence of a protein (Human Carcinogen Antigen) that is correlated with the presence of prostate cancer. HCA is a glycoprotein, which means that is protein that has sugar molecules attached to it. PSL has particular strengths in the analysis of glycoproteins. Egenix has licensed HCA from **Harvard Medical School**. However, under the alliance agreement Egenix and PSL would share intellectual property stemming from the program.

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There is a clear opportunity for Egenix and PSL to develop a prostate cancer biomarker that could outperform the current prostate specific antigen (PSA) test. At best, sensitivity of the PSA test is 70%, which is relatively poor. This level of performance can lead to unnecessary surgery and intervention.

HCA is found in blood. However, it is found in much more significant quantities in semen, which has encouraged PSL to consider semen as the most appropriate sample media to build the test around. However, this may be an issue for a potential PSL/Egenix HCA test because of collection issues.

Reflecting the early stage of the program, the clinical development path for a HCA prostate cancer specific diagnostic has not been mapped out by the company. However, it likely that a pathway would need to include several validation studies that include the collection of 1,000 to 2,000 patient samples.

While PSL and Egenix may be able to develop a superior test that detects prostate cancer, the asset is of lesser value until it is properly validated in large patient studies and is shown that the test can comfortably conform to existing testing procedures, platforms and reimbursement programs.

PSL is capitalised at $43 million. It held cash of $5 million as of September 30, 2006. The company's cash position is a concern, and it is very likely that it will need to conduct a capital raising in the near future. In Bioshares 191, we reported that PSL recorded a Survival Index measure of 0.7, or a little more than six months of cash to cover operations.

Bioshares recommendation: **Sell**

Fermiscan Holdings

Fermiscan (FER: $0.625) is aiming to develop a breast cancer screening technology using hair samples that are subjected to low angle X-ray diffraction analysis. The company claims the technology is capable of delivering 100% sensitivity in detecting breast cancer.

The Fermiscan business model is subject to several challenges. The company expects to price its test at $249 and has said that it is not seeking reimbursement. It is questionable that at that price, without reimbursement, the company could generate sales of its product as a widely available and widely acceptable screening service. It is possible the test may be more successfully positioned and sold as a 'comfort factor' product to healthcare consumers with high disposable income, but this would constitute a smaller market.

A second and quite major challenge for Fermiscan is its reliance on synchotron facilities. There are in the order of 20 such facilities around the globe, although one is under construction in Victoria. Such facilities are generally used by researchers and are also subject to long maintenance periods. It is not clear how Fermiscan could ensure regular and reliable service from such a facility that is not set up to perform volume analysis for commercial customers. Therefore test processing is a major risk for this company.

The company may have to undertake further validation studies to ensure that its technology is indeed able to detect specific cancers. In addition, it is our view that the company needs to strenghthen its experience in diagnostic product development.

Fermiscan is capitalised at $80 million. Following its back-door listing through Olympus Resources in August, and subsequent capital raising of $2.3 million, we estimate the company holds cash resources of $8.9 million.

Bioshares recommendation: **Sell**

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

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