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In this edition...
Mesoblast has entered the record books by raising the largest sum of cash by an Australian biotech. It is a testament to the skill of its CEO, Dr Silviu Itescu, to raise these funds. The funding means Mesoblast's extensive clinical programs can be properly supported.
Companies with pivotal events ahead in the next 12-18 months include Sirtex Medical, Antisense Therapeutics, Circadian Technologies and Tissue Therapies. Circadian may have, courtesy of a meeting with a leading physician at ASCO in 2012, uncovered a new drug development opportunity in the area of lymphodema. The program may be the basis of a turnaround in that company's stock price.
SIM VSE listed Telezon is seeking funding for its plastic needles program.
Companies Covered: AHZ, ANP, CIR, MSB, POH, SRX, TIS, Telezon

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - current)	6.7%
Cumulative Gain	**268%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

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

Mesoblast Enters Agreement for Record Capital Raising for Australian Biotech Sector

Mesoblast (MSB: $6.40) has reached agreements with investors to raise $170 million. This is a landmark capital raising for the Australian biotech sector, being the largest on record. Of particular interest also is that the capital will be raised at only a slight 2.2% discount, at $6.30 a share, to its last traded price.

The funds will be raised to help fund Phase III spinal therapy trials, which includes spinal fusion and the earlier intervention called intervertebral disc repair. Mesoblast has a completed a Phase II trial in spinal fusion and results from the company's Phase II trial in intervertebral disc repair are due mid year, with the final patients expected to reach their six month endpoint next month.

The funds will also be used to expand into Phase II trials of systemic therapies using the company's stem cell therapy technology. Mesoblast has eight Phase II trials either underway, planned or pending.

The funds being raised will give the company $332 million, placing it in a very strong position to fully leverage the potential of its stem cell therapies. This places less emphasis on the company's relationship with Teva Pharmaceutical Industries, which Mesoblast is waiting on to initiate a Phase III study for the treatment of congestive heart failure.

This capital raising also places pressure on those investors short in the stock, which at 4 March totaled 18.3 million shares representing a value of $117 million at the current price. Mesoblast may have just gained the upper hand in the battle with its short sellers.

Investment Analysis

For the last two years, Mesoblast shares have largely traded been in a range between $5-$8. The stock is currently in the middle of that trading range. The current capital raising may see some short sellers covering their positions resulting in increased demand for the stock. Investors with trading strategies may look to buy at the lower end, or below, of its trading range, if the opportunity arises. Mesoblast's capitalisation at $2.0 billion assumes very high success rates across its diverse portfolio which are not consistent with industry rates of clinical and regulatory success as well as the time it takes to meet performance milestones.

Bioshares recommendation: **Take Profits/Reduce Exposure**

Companies With Pivotal Events Ahead – Part 2

This week we continue looking at companies with major regulatory and clinical inflexion points in the year ahead (or in the case of Sirtex Medical, the next 18 months). This analysis will continue into the next edition of Bioshares.

Sirtex Medical

Sirtex Medical (SRX: $11.55) is planning for 2020, the year when it anticipates a step change in demand for its live cancer ablation therapy. That leap in demand is dependent on results from a large Phase IV clinical trial underway.

To get adoption of a new cancer therapy, there are four things required, according to Sirtex's Chief Medical Officer, Dr David Cade. The first is clinical development, the second is regulatory approval, the third is reimbursement by payors, and the fourth is Level 1 evidence of effectiveness, testing the new treatment against the existing standard of care.

With that goal in mind, Sirtex is conducting five large studies involving over 2,100 patients. The most advanced of these studies is the SIRFLOX trial with 518 patients to be recruited. This trial is being managed by Sirtex. The study is 94% complete. This study will complete enrolment in coming weeks and results are expected to be available at the earliest in late 2014.

This will be a pivotal clinical milestone for Sirtex. The trial is comparing the company's Sir-Spheres treatment with the current standard of care treatment, against the standard of care treatment alone in patients with colorectal cancer that has spread to the liver. If successful, it should aid in shifting Sir-Spheres treatment up from being used as a salvage therapy to a first line therapy in some cases.

The end point in this trial is progression-free survival (PFS). A statistically significant result in PFS will be enough to convince the newer brigade of oncologists, believes Dr Cade. These younger oncologists are more open to multi modality treatment practising a more personalised medicine approach. The older oncologists will be looking for overall survival data.

That tougher measure of overall survival is an endpoint in the second trial called FOXFIRE. This trial is being run independent of Sirtex, although Sirtex is funding one third of the costs. That trial will recruit 490 patients with metastatic colorectal cancer (the same indication as above) and is currently 35% recruited. This trial is expected to see recruitment completed in mid-2014. Final data from this trial should coincide with overall survival data from the first trial, giving the company data from more than 1,000 patients, with both providing data on survival advantages from SirSpheres as a first line therapy over existing treatments.

There are three other trials underway that are between 20%-43% recruited. These are all in the treatment of primary liver cancer, where overall survival is the primary measure. We expect results from trials two-five will be between three-five years away.

While waiting for these results, Sirtex expects growth in sales to be maintained at around 24% a year. The results at the end of 2014 have the capacity for a moderate effect on the company's share price. We rate the chances of achieving statistical significance ($p<0.05$) in PFS to be reasonably good. Oncologists will be very focused on that p-value according to Dr Cade.

Sirtex Medical is capitalised at $644 million.

Bioshares recommendation: **Hold**

Circadian Technologies Uncovers Lymphedema Indication

Circadian Technologies (CIR: $0.27) has become a clinical stage company with its lead antibody drug candidate, VGX-100, almost having completed Phase I clinical testing. However Circadian has a strategy to accelerate its clinical development progress.

The very successful cancer drug Avastin works by starving tumours of a blood supply, blocking the VEGF-A pathway. Circadian has built up a proprietary position around blocking other associated pathways, VEGF-C and VEGF-D. Blocking other pathways as well may be a more effective process in sustaining cancer therapy.

The Phase I trial with VGX-100 is expected to be completed in the next month and results are anticipated in June this year. That trial is in healthy volunteers and the key metric is safety of the drug candidate. If it is shown to be safe, then Circadian can move into Phase II studies.

Lymphedema Treatment Potential

However, there is another potential application for VGX-100 which could move through to market faster than in the treatment of cancer. That indication is in lymphedema.

Other drugs have shown that inhibiting the VEGF-C pathway can treat lymphedema, for which there are no current therapies. It is thought that by restricting lymphatic growth for long enough, the lymphatic system can organise itself to grow properly. The problem with other drugs trialed is that they are too toxic and not appropriate for a patient population that is largely healthy. If VGX-100 is shown to be very safe, then it may be usefully applied to treat lymphedema

If that is the case, then the company plans to start a Phase II trial in lymphedema around August this year with initial results in December. The trial is expected to be completed in April next year.

If the results are positive, then the company could raise funds to complete a Phase III/registration trial. Under the FDA's Breakthrough Therapy provision, treatment for such an unmet need could be rapidly progressed through the clinic.

We expect there to be a reasonable chance of the Phase II trial in lymphedema returning positive results. The impact of the trial's results on the company's share price has the potential for a large gain.

Circadian is capitalised at $13 million with $12.2 million in cash at the end of last year, which in other words shows the company is trading at close to cash backing and by implication with very little value being ascribed to the company's non-cash assets.

Circadian will be covered in more depth in the next edition of *Bioshares*.

Bioshares recommendation: **Speculative Buy Class B**

Antisense Therapeutics ATL1103 Trial

Antisense Therapeutics (ANP: $0.012) is due to commence a trial in 24 patients with acromegaly with its antisense compound ATL1103. The patients will be treated over three months with one of two doses.

The trial is expected to be completed at the end of this year, with final results out in the first quarter of 2014. There is the potential for some interim results to become available because the trial is not blinded.

The aim of the trial is to reduce IGF-1 levels. Given that IGF-1 is the end point but is also a biomarker, a quick and accurate readout should be achievable in this trial. To have an effective therapeutic, IGF-1 levels will need to drop by more than 25%. Just as important will be the safety profile of the drug in this trial.

Last month, biotech company Chiasma signed a US$595 million deal with Roche in this acromegaly field. That deal included a US$65 million up front payment. The license was around an oral form of the acromegaly drug Octreotide, called Octreolin. That program has moved into a Phase III trial.

For Antisense, this deal confirms the interest in this disease area from larger pharmaceutical companies.

Antisense Therapeutics is capitalised at $17 million. A positive trial outcome should have a major impact on the company's share price. We rate the chances of success in this trial as moderate.

Bioshares recommendation: **Speculative Buy Class C**

Allied Healthcare Group

Allied Healthcare Group (AHZ: 3.2 cents) is commercialising several assets. The most advanced development asset is the CardioCel tissue repair implant for the treatment of heart defects and a myriad of other types of tissue repairs.

This week the company announced that after four years following implant of Cardiocel in children with heart abnormalities, there was still no calcification of the tissue observed. This is an impressive result given calcification normally starts to appear after six months with existing products.

The product is already in use at the Mater Hospital in Brisbane under a special access scheme. A second surgeon is seeking access at the Royal Childrens' Hospital in Melbourne under an Authorised Prescriber scheme. In June last year the company filed for regulatory approval in Europe. Approval is expected in three to four months time.

Should Allied get approval in Europe, the potential exists for a strong share price gain to occur. We ascribe a high chance of approval this year but with the caveat that decisions of regulators can be very difficult to predict. One of the appeals of this technology is the demand by surgeons for better tissue implant products.

A second asset the company is commercialising is a novel vaccine technology pioneered by Ian Frazer and his team, who was one of the inventors of Gardasil. This vaccine technology seeks to not only immunize but also to treat infected patients. Phase I trials are expected to start this year. Allied currently owns 48% of the Coridon, where the technology resides. Allied has an option to increase its stake to over 50%.

Positive results in patients in generating both an antibody and a T-cell response has the potential for a very meaningful result for the company and its share price. However, the technical challenges are very high.

Allied Healthcare is capitalised at $33 million.

Bioshares recommendation: **Speculative Buy Class A**

Tissue Therapies Chasing EU Approval

Tissue Therapies (TIS: $0.255) has addressed its capital requirements by raising $8.7 million through a placement. Along with a fully underwritten rights issue, which is expected to raise $4.5 million, the company will be in more a comfortable cash position as it passes through the final stages of approval in Europe for its wound healing product VitroGro ECM. The price of both raisings was executed at a relatively steep discount of ~25%.

We expect European approval (anticipated mid 2013) to be a modest catalyst for Tissue Therapies' share price. Tissue Therapies has product and sales infrastructure in place to immediately begin sales in the UK, Germany, Switzerland, Austria, Belgium, the Netherlands, Sweden, Norway and Denmark.

However, Tissue Therapies must first complete trials aimed at gaining reimbursement in the UK and Germany, which will dampen sales until completed and results are submitted to the relevant hospitals and insurance bodies.

Tissue Therapies is capitalised at $60 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (8 March 2013)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	$0.270	$0.270	March 2013
Tissue Therapies	$0.255	$0.255	March 2013
Allied Healthcare	$0.032	$0.026	February 2013
Psivida	$2.28	$1.550	November 2012
Benitec	$0.013	$0.016	November 2012
Nanosonics	$0.480	$0.495	June 2012
QRxPharma	$1.22	$1.66	October 2011
Somnomed	$1.16	$0.94	January 2011
Cogstate	$0.400	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.64	$6.60	September 2007
Universal Biosensors	$0.82	$1.23	June 2007

Portfolio Changes – 8 March 2013

IN:

Circadian Technologies has been included in light of the potential for VGX-100 in treating lymphedema.

Tissue Therapies has been added back now that short term funding concerns have been addressed.

OUT:

We will take some profits with Osprey Medical also noting the delay in commencing its 600 patient pivotal trial. (A start was planned for December 2012)

Phosphagenics Extends Pain Product Lineup

Phosphagenics (POH: $0.14) has added a new pain product to its transdermal drug product portfolio. The company will develop a patch that delivers oxymorphone, a potent opioid, across the skin for the treatment of chronic pain. Oxymorphone is 3.5 times more powerful than oxycodone.

The best known oral form of oxymorphone is Opana, marketed by Endo Pharmaceuticals. Opana was first marketed in 2006 and a reformulated version became available in 2011. Annual sales of Opana have reached US$1 billion. There is currently no transdermal patch product that delivers oxymorphone across the skin, owing to irritation caused by the active drug. Phosphagenics' phosphorylated tocopherol, the core of its transdermal technology, ameliorates the irritation because of its ant-inflammatory properties as well as acting as a penetration enhancer.

Extended release pain products are sought for patients with chronic pain e.g. cancer patients.

However, a drawback of (opioid) pain drugs is tolerance, which occurs when patients find they must use increasingly higher doses to address pain. Phosphagenics argues that its transdermal pain patch products can lessen the tolerance problem because they are better able to deliver steady-state levels of drug.

It is argued that the peaks and troughs of pain relief observed with oral pain drugs are a major factor with the problem of tolerance. Another advantage of opioid pain patch products, such as those in development by Phosphagenics, is that they eliminate gastrointestinal effects, including constipation.

Lessons from Oxycodone Patch Program

Phosphagenics has been able to develop an oxymorphone patch product relatively quickly because of the development of its oxycodone patch. The oxycodone program has experienced many different design and manufacture challenges and has run behind schedule. About 250 different prototype oxycodone patch were created. However, lessons learnt have been applied to the oxymorphone product, enabling rapid development of that product.

Phosphagenics has completed the dosing phase in its Phase I trial of its oxymorphone patch product, which has been designed for 72 hour delivery. The results of this trial are still being analysed and are due shortly.

Update on Oxycodone Patch and Trial Design

Due to many product design improvements to its oxycodone patch, Phosphagenics must complete a small pharmacokinetic study in 12-15 healthy volunteers before commencing a larger proof-of concept study (Phase II/III) later in 2013. This trial will commence this month.

Phosphagenics will use an enriched trial design for its proof-of-concept study. This type of study involves a run-in period in order to discover and remove subjects that do not experience any pain relief. Patients would be individually titrated by investigators to levels that afford pain relief. Once the run-in is completed then the trial would be randomised. The challenge in pain trials is to test pain drugs in an homogenous group so as to properly tease out the placebo effect, which would be biased if non-responders were included.

Gel Product for Skin Pain

An additional product in the pain space being developed by Phosphagenics is a gel formulation of oxycodone. Such a product could find use in treating pain that is localised in the skin, for example, in conditions such as diabetic neuralgia and shingles. A Phase II trial of the gel product is planned for commencement in 2013 Q3.

Phosphagenics' TPM technology is very versatile, enabling different parameters of alpha-tocopherol to be manipulated to control or limit the release of active drug only to certain depths in the skin as desired.

Summary

Phosphagenics' broadening of its pain portfolio is positive. However, the stock appears to be trading on the the blue sky of its TPM platform and is not reflecting key risks in its drug programs.

Phosphagenics is capitalised at $143 million and retained cash of $16.9 million at December 31, 2012.

Bioshares recommendation: **Speculative Hold Class A**

Telezon's Plastic Needles Offer Benefits in Third World Markets

Telezon (SIM VSE – TLZ: $0.07) is commercialising a plastic (polymer) needle technology. Its lead product is the SoloFlow Medical Transfer Canula. Other products in development include the DuoDraw Canula and the Polydermic Injection Needle.

The SoloFlow Medical Transfer Canula received CE Mark certification in December 2012. This product is used where a drug solution stored in a vial must be transferred to a syringe for administration into a patient via a needle of another gauge (or perhaps through an intravenous canula). The use of a larger gauge needle to draw up solution offers efficiency in terms of time and decrease in waste of drug solution. Efficacy is also an advantage where the proper dose is correctly drawn up into the syringe

Advantages of Plastic Needles

One of the attractions of plastic needles is that they can be easily disabled and also disposed of or recycled. The tip of a plastic needle can be sealed with a simple flame. The benefit of this is that reuse is prevented. A major health problem exists in third world countries because of needle re-use. Disposal by low temperature incineration – at one-tenth of the temperature needed to melt steel – also eliminates the risk of infection that occurs through the recycling of metal needles components, which also takes place in third world countries.

Telezon cites World Health Organisation data that indicates 1.3 million deaths occur each year from unsafe needle injections. The WHO is planning to create a sub-category based on the SoloFlow canula. This would benefit Telezon with its attempts to interact with larger medical device companies that also have devices prequalified by the WHO.

Telezon has developed know-how and expertise to design and manufacture needles with the tensile strength and dimensional attributes (e.g. length) that allow the same functional performance of a range of needles and canulas. It is possible that Telezon's design of a hypodermic needle means that less pain is experienced by eliminating an effect called coring, in which the skin is cut and pulled (the plastic needle has its opening on the side near the tip, and is not open at the tip like the metal needles). The SoloFlow is currently manufactured by a contract manufacturer in Germany. That relevant expertise does not exist in Australia.

History

Telezon's polymer needle technology dates back to 1994. SSB Technology Pty Ltd was formed by John Stevens, Jack Bartlett and Trevor Smith. SSB was acquired by Telezon in 2005. (Telezon was a shell company at the time.) Telezon listed on the SIM VSE (Singapore) in December 2011, at the same time discontinuing its eight year old ASX listing. The foundation patent for the company's technology expires in 2014. However, subsequent patents expire in 2028 and 2030. In addition to patents, know-how and trade secrets form part of a barrier around Telezon's intellectual property.

Serum Institute of India Agreement

Telezon signed supply agreements with the Serum Institute of India and Hindustan Syringes and Medical Devices in 2012, for the supply of SoloFlow Medical Transfer Canulas. The Serum Institute is also evaluating the SoloFlow product in clinical trials. These commercial agreements are breakthrough events for the company, indicating the potential for the products. The company has supplied 100,000 Soloflow units to the Serum Institute.

Capital Raising

Telezon issued a prospectus in 2012 where it set out a capital raising objective to secure up to $6 million, of which $2 million has been earmarked for the four-fold expansion of its manufacturing capacity for the SoloFlow product, from a four mold unit to a 16 mold unit. Other funds are earmarked for the Blunt SoloFlow Soft Transfer Canula, the Polydermic Injection Needle and the DuoDraw Multi-Application Solution.

Model

Telezon will ultimately seek to license its technology and products and secure royalty income. Currently the company is demonstrating commercial proof-of-concept, including the development of manufacturing capabilities which contribute to proof-of-concept. It also wants to 'seed' markets with product in order to understand customer views on polymer needles. Its marketing pitch is to spell out the end-to-end costs in needle use as opposed to simple unit costs or prices.

Summary

Telezon's plastic needles offer several clear advantages over steel needles in third world countries. A reason for investors to pay some attention to Telezon is because its agreement with the Serum Institute of India. The benefit of the deal at this stage is that it provides a degree of validation of the technology.

Telezon is capitalised at $3 million and retained cash of $0.2 million at December 31, 2012. Investors should note that the current levels of cash in the company are very low and that liquidity on the SIM VSE exchange is low relative to that offered by the ASX.

Bioshares recommendation: **Under Review pending Completion of Capital Raising**

Bioshares

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. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

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: Pharmaxis, Starpharma Holdings, Cogstate, Bionomics, Biota Holdings, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phosphagenics, Immuron, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Bioniche, Atcor Medical, Invion