CELLMID 🔘

Newsletter - March 2014

From the CEO



Dear Shareholder,

We have recently reported on a very successful first half to the 2014 financial year making a profit of \$242,000. While a significant portion of our revenue was the result of one off items, such as licensing fees, we continue to work on increasing regular revenues for Cellmid.

The financial result of the last six months clearly demonstrates that our strategy of reducing risk by building revenue producing assets is working.

MK antibody program is becoming clinic ready

We are at a pivotal point in our therapeutic antibody program with our 'first in class' MK antibodies expected to become clinic-ready by the end of 2014. We are currently progressing through lead selection and choosing the manufacturer of our drug. Discussions with clinical sites are ongoing and IND-enabling studies should be completed as previously announced. All of these represent significant value increasing milestones for Cellmid and we will report to you on our progress as we achieve them.

Pacific Edge is kicking goals with Cxbladder®

We continue to be impressed with our licensing partner, Pacific Edge, and the speed with which they have been able to achieve access to market in the USA and also in New Zealand. We also understand that there is a time lag between market access and significant sales, but Pacific Edge is making all the right moves to become market leader and be in prime revenue position in the coming years. This will of course be particularly exciting when Cellmid starts receiving royalty revenues.

BJP midkine review the most significant validation of our technology yet

In the biotechnology industry we continually work towards validating our technologies, whether they are diagnostic tests or drugs for diseases with unmet needs. We do this to gain the recognition of the scientific community, to get acceptance from the regulators, but most importantly to get buy-in of the clinical community which ultimately represents our market.

We have foreshadowed in the October newsletter that the British Journal of Pharmacology has agreed to publish a complete review edition on midkine. Representing the most significant, and most exciting, validation yet of midkine as a disease target, the review edition has since been published with contribution from several clinicians, in addition to eminent scientists showing new research.

Revenue growth is expected from the consumer health division by late 2014

With the boosting of the Japanese distribution we expect to deliver marked revenue increase towards the end of 2014. We continue to develop "own-brand" products for our customers in the salon and beauty markets as well. Our entry into the salon market in Australia is expected to deliver growth locally in addition to the new products we are developing for the retail market.

Our Chinese distributor will commence sales once their product specific website is fully developed. We continue to actively work with them on optimising their product positioning strategy and marketing.

We have a great team in Australia and Japan and we are now looking to boost our resources in international markets to take advantage of overseas opportunities.

This is a transforming period for Cellmid on many fronts. Our consumer health business is poised for growth, and I am looking forward to the exciting journey of taking our antibodies into the clinic.







Market potential for MK therapeutics and diagnostics in cancer

Oncology therapeutics and in vitro diagnostics currently dominate sales in the pharmaceutical and medical technology sectors respectively. The anti-cancer treatment market alone is worth an estimated 77.4 billion dollars and is expected to reach 143.7 billion dollars within the next ten years. Cellmid's MK technology has strong potential for a firm positioning in both of these markets.

Cellmid's MK antibody is designed to inhibit MK, which is highly expressed in over 25 cancers and enhances the survival, migration, chemo-resistance and regenerative activity of tumour cells. This makes Cellmid's anti-MK technology an ideal and potent candidate for the treatment of numerous cancers. Additionally, recent research has confirmed that MK signals via two important oncology pathways; Notch2 and ALK. Since MK works upstream of both these pathways, anti-MK therapeutics might represent a more effective approach in controlling cancer (FIG 1).



FIG 1 Targeting MK blockades multiple tumorigenic pathways. MK works upstream of many significant oncology pathways inducing a range of tumorigenic effects.

Cellmid's MK antibody is first-in-class with no competition. The clinical development pipeline in the oncology industry is currently congested around a few targets, as shown in FIG 2. While having precedents can be an advantage, there are also various risks such as difficulty obtaining market share, strong competition for patient access and regulatory risks such as having a higher bar for approval. Novel treatment targets offer increased clinician interest and don't face the "me too" resistance.

Having an appropriate companion biomarker test has become vital for any oncology therapeutic. Regulators and clinicians now demand that only patients who are likely to respond are treated, and the treatment needs to be appropriately monitored for response and relapse.



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Cellmid's validated MK ELISA is ready to become the companion diagnostic for anti-MK therapeutics. It will be used to stratify patients for MK targeted therapy, as well as monitoring for response and relapse after treatment.

Importantly, the MK ELISA can be adapted to various platforms used in the diagnosis of cancer, including multiplexing MK with other biomarkers. Enhancing screening this way increases sensitivity and can substantially reduce rates of false detection and over treatment, subsequently presenting physicians with safer and more effective options for diagnosis and treatment.



FIG 2 Collective industry pipeline for oncology targets in preclinical stages and beyond. *Source: Defined Health, 2013*

Cellmid's MK antibody for cancer therapy is in late preclinical development. Cellmid has out-licensed MK for inclusion in two cancer diagnostic tests already.

Pacific Edge has developed Cxbladder using MK as one of five biomarkers in a urine-based detection and monitoring test for bladder cancer in patients presenting with haematuria. This product is already on market in the USA, Australia & New Zealand.

Quest Diagnostics is developing Lung Dx, a blood test for the early detection of lung cancer. We expect an update on their progress in the coming weeks.

We are close to finalising a license with Fujikura Kasei for a latex based MK test for the early diagnosis of cancer. Once licensed the test is expected to enter clinical validation in Japan.

With a "first in class" drug and a validated companion diagnostic Cellmid is in an outstanding position to access the rapidly growing oncology market.





Solid progress on the MK diagnostic programs

Cellmid has a number of diagnostic collaborations underway (Table 1) in addition to the Pacific Edge Biotechnology, Celera-Quest and Fujikura deals.

In support of these collaborations, Cellmid has recently completed its CK3000 study into normal serum MK levels in 574 healthy subjects. Knowing the normal MK range in healthy people is critical to detecting elevated MK levels, and determining how to interpret the result of a MK blood test.

FIG 3 shows how data from CK3000 (along with control data from other smaller studies) might be used to define a screening strategy for early detection of disease. Most significantly, when this screening strategy was applied to the CK3000 study data, apparently healthy subjects who had suffered from cancer, autoimmune or inflammatory diseases were successfully identified. The Study was the

result of two years of sample collection by our research partners at Kumamoto University and analysis at our diagnostic labs in Newcastle.

| Indication | Project aims | Collaborator |
|--|---|---|
| Colorectal cancer | Does MK monitoring in healthy subjects effectively detect early asymptomatic disease? | Abcodia, UK |
| | Does monitoring serum MK levels detect recurrence of metastatic disease earlier and/or more frequently than the current standard of care (CEA blood test)? | Calvary Mater Newcastle Hospital, Australia |
| Liver | Is MK an effective biomarker for early detection of cancer, particularly in at-risk individuals? Does MK out-perform other recently described novel biomarkers? | Westmead Millennium Institute, Westmead Hospital and University of Sydney, Australia |
| Prostate | Is the measurement of urinary MK helpful in disease detection? Can urinary MK differentiate aggressive from benign cancer? | Norwich Medical school, University of East Anglia, UK |
| | Does MK expression correlate to the more deadly androgen-independent form of cancer? | Institute of Clinical Sciences , Gothenburg University, Sweden |
| Bladder | Is measurement of urinary MK protein helpful in cancer detection? | Undisclosed international diagnostics company |
| Glioblastoma multiforme | Do MK levels correlate with treatment resistance? | Undisclosed European pharma company |
| Any kidney injury or disease | Does MK elevation correlate to kidney damage, inflammation, poor function and/or poor patient outcomes? | Nambour Hospital, Australia |
| Veterinary: canine/feline cancer and kidney disease | Exploratory studies to determine whether MK is a useful diagnostic and/or disease monitoring biomarker for managing veterinary cancer and kidney disease | Undisclosed multinational veterinary pharma company |

Table 1: Midkine diagnostic collaborations



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FIG 3: Screening strategy based on CK3000 data, MK ELISA validation data and previously published studies.



Getting closer to Cxbladder royalties

Cellmid licensee Pacific Edge has gained momentum in rolling out its Cxbladder[®] test in New Zealand with the commercial agreement between the Health Innovation Hub (HIH) and the District Health Boards. The agreement means that the test is now accessible for half of all New Zealanders.

The agreement with HIH builds on a momentous 12 months for Pacific Edge during which Cxbladder[®] has been commercially launched in the United States, achieved sales and signed agreements with several large provider networks giving access to more than 50 million Americans.



In addition, Cxbladder[®] is now being marketed in Australia by Healthscope, a leading healthcare provider, and is due to be launched in Spain this year.

About Cxbladder®

Cxbladder[®] is a non-invasive test designed to detect and monitor the recurrence of bladder cancer. Patients that have undergone treatment currently require regular cystoscopy, which is an invasive and painful method to monitor for recurrence. As a novel non-invasive test, Cxbladder[®] has the potential to replace cystoscopy over time as a preferred tool for patient monitoring.

For more information on *Cxbladder*[®] please visit <u>www.cxbladder.com</u>.

Less than four weeks to the 3rd Midkine Symposium in Kyoto

With less than a month to the most significant scientific event on midkine biology an exciting program has been finalised, with world-class presenters. This time around the program has a particularly strong cancer component but other areas of MK biology are also well represented.

Highly anticipated speakers include Dr Ryuichi Sakai, Chief of the Division of Metastasis & Invasion Signalling at Japan's National Cancer Center Research Institute. Dr Sakai is a recognised global leader in understanding how cancers metastasize and spread. Also attending is Professor Herman Rohrer from the Max Planck Institute



for Brain Research in Germany, who will share ground-breaking research on how MK influences cells in cancer and other diseases via signalling. Dr Satoshi Kishida from Nagoya University Graduate School of Medicine, and Dr Guillermo Velasco of the Department of Biochemistry and Molecular Biology at Complutense University in Madrid, will both report on their studies of anti-MK antibodies and aptamers in brain cancers. For the first time some of our commercial collaboration partners have been invited to gain further insight into our joint programs.

The full program can be viewed at http://www.cellmid.com.au/content_common/pg-2014-mk-symposium-program.seo





Consumer Health division delivers new opportunities

Increasing the number of profitable sales channels in Australia

We have recently conducted an independent market survey in Australia of women over 35 and asked several questions about hair loss. The results were surprising and enlightening about how many women are concerned about hair loss and what they do about it. Over and above our original expectations more than

38% of women reported suffering from hair loss. Of these women more than half (55%) have not sought advice for various reasons. Some of the women assumed that they can't do anything about it, while others didn't want to talk about it for fear of embarrassment.

38% of women over 35 have hair loss concerns

This has given us the incentive to develop an opportunity for women to come forward with their problem without embarrassment, letting them know that they are not alone. We asked our brand ambassador, Brynne Edelsten, to spearhead our "Put Your Hand Up" campaign for women with hair loss. The first event was our media launch in December 2013 with participation from The Daily Telegraph, Sunday Telegraph, The Morning Show, Daily Edition and Nine MSN just to name a few. In March the campaign received further boost and media coverage on Nine MSN, Sunrise, The Carousel and many other publications.

As a result of the campaign, and for the first time since product launch, our website exceeded sales pharmacy sales in December. This is great news for Cellmid as we have significantly better margins on these sales without the below the

55% of women with hair loss do not seek help for fear of embarrassment or not knowing that they may be able to find a solution

line marketing costs of the pharmacy channel. This represents a clear message to us to continue to expand marketing efforts in the most profitable channels.

Another message from our market research was that a large percentage of women with hair loss concerns went to their hairdresser for help. We have since dedicated resources to this channel, hired and trained a salon sales team in NSW and expect to roll out the model to other states later on this year subject to performance.

Australia is our home market and we continue to invest into new sales channels and products, including "own brand" opportunities for distribution partners with synergistic existing brands.

New Japanese distribution agreements hold the key to revenue increase in 2014

Since the May 2013 acquisition of Advangen Inc. we have been working on boosting the relationships with existing distributors and opening up new opportunities in addition to existing orders. Our marketing team has been working closely with our customers to individualise product concepts, which are expected to form

extensions to existing orders. We will start manufacturing to fill some of these new orders in August and, with a three months manufacturing cycle, sales are expected to increase as a result in the last quarter of 2014.

"Put Your Hand Up" campaign aims to remove the stigma attached to female hair loss

Chinese distribution agreement is expected to start delivering revenue in late 2014

We continue to work closely with our Chinese distribution partner to finalise their product specific commercial website and assist with the training of the more than 100 sales people who will be involved in the Jo-Ju® and Lexilis® program. Subject to receiving government licenses in a timely manner sales in China are expected to commence in the latter part 2014.

In addition to our Australian, Japanese and Chinese distribution we are actively working on other international markets, which are expected to deliver revenue growth in the next 12-18 months.





British Journal of Pharmacology features midkine in special edition



Pre-eminent researchers published 16 cutting edge reviews on MK in the latest review edition of the BJP, one of the most prestigious pharmacology journals. The BJP feature includes comprehensive up-to-date articles covering advances in MK biology and the role of MK in disease including various cancers. kidney diseases. cardiovascular disease.

multiple sclerosis and neurodegenerative disorders.

The articles validate the importance of MK in health and disease and endorse Cellmid's strong MK portfolio and pipeline. The following is a brief selection of notable reviews from BJP's MK feature.

Midkine: an emerging target of drug development for treatment of multiple diseases

An editorial by the discoverers of MK, Takashi Muramatsu and Kenji Kadomatsu, that reflects the current understanding of MK biology and advances in applications targeting MK for the treatment of cancer, cardiovascular, inflammatory and autoimmune diseases.

Pancreatic cancer Güngör et al, University Hospital Hamburg-Eppendorf, Germany

Pancreatic cancer remains one of the most lethal solid tumours due to its resistance to treatment and difficulty in diagnosis. Elevated MK expression and secretion has been found to promote survival, proliferation and support of pancreatic cancer cells escaping chemotherapy treatment. The precise mechanism of how MK induces chemo-resistance is shown in FIG 4. Targeting MK provides a rational new strategy to circumvent pancreatic resistance cancer to chemotherapy.



FIG 4 MK promotes chemo-resistance in pancreatic cancer. MK-mediated Notch-2 activation is highly linked to chemoresistance and migration of cancer cells, whereas MK depletion promotes increased chemo-sensitivity and decreased migratory potential allowing for treatment of pancreatic cancer. By Gungor et al. *Br J Pharmacol*, 2014

Midkine in nephrogenesis, hypertension and kidney diseases Sato et al, Nagoya University Graduate School of Medicine, Japan

MK is involved in the development of acute kidney injury and the progression of chronic kidney disease, often accompanied by high blood pressure and diabetes. This process becomes evident when MK recruits inflammatory cells, which trigger high blood pressure and ultimately leads to progressive renal failure. These actions of MK open up new avenues for targeted approaches to treating various kidney diseases.

Midkine as a regulator of B cell survival in health and disease Cohen et al, Weizmann Institute of Science, Israel

Lymphomas are solid tumours of the immune system often affecting B cells and are sometimes referred to as lymph or blood cancers. Knowledge regarding the role of MK in regulating B cell survival has been expanding rapidly. MK has recently been shown to be involved in proliferation, differentiation and the programmed cell

The full table of contents and the BJP articles themselves can be viewed at the following web address http://onlinelibrary.wiley.com/doi/10.1111/bph.2014.171.issue-4/issuetoc





British Journal of Pharmacology features midkine in special edition

death of B cell malignancies. Thus, novel therapeutics aimed at interrupting the MK survival pathway may offer a new strategy for targeting B cell malignancies. Furthermore, because MK is elevated in both early and advanced malignancies MK can also serve as a prognostic marker.

Therapeutic potential of midkine in cardiovascular disease Kadomatsu et al, Nagoya University Graduate School of Medicine, Japan

Heart attack is a life-threatening event that occurs when the blood vessels supplying heart tissue are suddenly restricted. Acute treatment with MK induces tissue protection when blood supply is restricted in the heart, thereby reducing the extent of tissue death resulting in long-term benefits in the prevention of heart failure (FIG



FIG 5 Cardio-protective effects of MK.

(A) Viability of cultured heart muscle cells after a 4 h of simulated blood supply restriction followed by 2 h of simulated blood supply restoration. MK applied during simulated restriction increases cell viability. (B) Data on tissue damage size in a restriction model. MK administered 5 min before the induction of restriction significantly decreases the size and area of tissue damage. by Kadomatsu et al, *Br J Pharmacol*, 2014.

5). This provides strong supporting evidence for the use of MK therapy in the treatment of heart attack and the prevention of heart failure.

Involvement of midkine in neuroblastoma tumourigenesis *Kishida et al, Nagoya University Graduate School of Medicine, Japan*

Neuroblastoma is one of the most malignant solid tumours occurring in children, with nearly half of all

cases are children under two. MK was found to be expressed in every neuroblastoma cell line tested and the knockdown of MK alone was sufficient to suppress tumour growth. This indicates that neuroblastoma cells are highly dependent on MK and that a MK-targeted therapy could serve as a significant treatment option.

Midkine and multiple sclerosis *Hideyuki Takeuchi, Nagoya University, Japan*

Multiple sclerosis is a disease of the brain and spinal cord in which the protective sheath that covers nerve cells becomes inflamed, swollen and detached. It has



FIG 6 MK negatively regulates autoimmune tolerance. MK activates a pathway that leads to the suppression of DCreg development and Treg expansion critically suppressing autoimmune tolerance. Therefore, blockade of MK can effectively suppress autoimmunity by enhancing DCreg development and Treg expansion. by Takeuchi et al, *Br J Pharmacol*, 2014.

been demonstrated in animal models that removal of MK suppresses brain inflammation. This removal of MK increases DCreg cell numbers which are important in driving development and expansion of inducible regulatory T-cells (Treg) as well as a decrease in the numbers of auto-reactive cells (FIG 6). Thus, inhibition of MK signalling may provide an effective therapeutic strategy against autoimmune diseases including multiple sclerosis.

Access to the **full version** of these reviews and others In the BJP special issue can be found at the Wiley Online Library. Link provided at the bottom of page 6.





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Brand ambassador Brynne Edelsten teams up with évolise in the latest Put Your Hand Up! campaign reaching out to women suffering from hair loss.

One in three Australian women suffer from hair loss or are worried about losing their hair. This can have a negative impact on their selfesteem, self-perception and confidence.

Brynne Edelsten has been courageous enough to open up about this topic and assist with uniting women to show hair loss issues are



Cellmid - Fast Facts

Listings Australian Securities Exchange (ASX)

ASX Code: CDY

Issued Capital - Ordinary Shares 735,585,702

(Listed) Options 290,542,770 (exercise price \$0.034 exp. 23 October 2016)

Market Capitalisation A\$21M (19 March 2014)

Cash Position A\$4.1M (last reported 31 December 2013)

Board

| Dr David King | Chairman |
|----------------|--|
| Maria Halasz | Chief Executive Officer and Managing Director |
| Graeme Kaufman | Director |
| Martin Rogers | Director |

Senior Management

| /laria Halasz | Chief Executive Officer and Managing Director |
|-----------------|---|
| Darren Jones | Head of Product Development |
| licholas Falzon | Financial Controller and Company Secretary |
| Emma Chen | Advangen General Manager |

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