

## G'day Everyone!

Welcome to our brief update on the company's activities over the past quarter. As you will see in the content, we have been quite busy indeed. By the time you receive this the Australian holiday season will be upon us.

Imagene continues to be hard at work whilst you hopefully are enjoying the sun and lifestyle on offer throughout December and January in Australia. As our gastric cancer trial sites open up at the oncology centers in the Eastern Asian centers, there will be little rest for us but we consider this great news. I do not hesitate to say that our team here and overseas have chosen to commit all our resources, including time, to bring forth the promise and potential that our HER-Vaxx therapy could bring to gastric cancer patients as the trial progresses.



As our work commitment continues to grow, so will my involvement in all aspects of the company's development. In light of that, I have recently been greatly humbled by our board of directors decision to appoint me as the chief executive officer of the company.

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Their confidence in me strengthens my resolve and conviction to continue the work of growing Imugene into the formidable biotech company that I know it to be. I hesitate to tell you what our chairman, Paul Hopper, said on my appointment but as it reflects more on the company than my modest contribution he said:

"We are delighted to announce Leslie's enhanced role in the company. Over the past year she has

demonstrated a clear understanding of the nuances of the Australian market for life sciences. She has developed a strong rapport with our investors and led the recent and successful capital raising with great aplomb."

I am incredibly fortunate to have a chairman, board and management who complement and support the strategic goals of growing and developing Imugene. We make a formidable team.

Once the New Year is upon us I look forward to further updates on the trial and the company's development.

I would like to take this opportunity to thank you for your continued and active support of Imugene and to wish you all a very warm holiday greeting. May this season bring you health, happiness, spirit and success.

Warmest regards,

Leslie

# Imugene files new patent application for the mimotopes!

Imugene has filed four new patent application with IP Australia that if granted, will provide cover until 2037.

The patents filed under the name of Imugene Ltd specifically protect new mimotope B-cell vaccine compositions which are directed to commercially validated immunooncology targets. Each of the targets already has a monoclonal antibody synthetic drug on market generating sales in the hundreds of millions treating cancers such as melanoma, non-small cell lung cancer, multiple myeloma and bladder cancer. A fourth patent filed under the name of the Medical University of Vienna protects a broad technology platform related to identifying mimotopes from available monoclonal antibodies.

have measure and potential. We are also very proud to have Private Portfolio Managers (PPM) on our registry. At the time, our CEO, Ms. Chong, said,

# "Successful Capital Raising!"

The acquisition of funding necessary to carry on the funding of cancer research is a self-evident but difficult task for companies in the sector. Achieved, it is both a practical requirement and an acknowledgement that a company has potential.

We are proud that both these considerations have been met in our recent placement to institutions and sophisticated investors. There was a strong demand and we in fact were oversubscribed in the \$3.2 million raising.

A now substantial shareholder in the company is The Platinum Asset Management Fund, one of Australia's most respected investment houses. Attracting the calibre of such a fund is an affirmation that our efforts on your behalf

"I am delighted that two highly regarded and prominent funds have taken the majority of the placement, one of which becomes the largest shareholder in Imugene."

The level of demand speaks to genuine investor interest and support for the company's technology and development. The majority of the funds will be used to support the new trials for gastric cancer in Thailand, Taiwan and Hong Kong."

" Maintaining and strengthening our already strong international intellectual property position is a key area of focus in maintaining the competitive advantage of our B-cell mimotope peptide vaccine portfolio. We are extremely pleased with the progress made from our expert scientific team in 2016." Leslie Chong



# **HER-Vaxx** goes to Asia!

One of the unfortunate realities of international cancer research is that geography may play a part in the susceptibility factor of the many different types of cancer. Imagene strategically chose gastric cancer for HER-Vaxx clinical development plan, where overexpression of HER2+ (a particular protein found on the surface cells) plagues about 20-25% of cases and there is a high rate of incidence of gastric cancer in Asia. When one views the global patient size, gastric cancer is the second most common cause of cancerrelated death in the world with a large percentage in Asia. We are conducting Phase1b/2 trials in Hong Kong, Taiwan and Thailand.

The clinical trial is being conducted in two parts, Phase1b is an open label, multicentre dose escalation study designed to assess the safety, tolerability and immunogenicity of HER-Vaxx in metastatic gastric cancer patients who are HER2+. We are enrolling up to 18 patients who will be treated with HER-Vaxx in combination with chemotherapy to interrogate three dose levels.

The larger open label Phase 2 clinical trial will recruit 68 patients with metastatic gastric cancer overexpressing the HER2 receptors. It will be randomised into two groups, one a combination of HER-Vaxx and chemotherapy and the other in the standard of care, chemotherapy arm so comparisons can be made.

As you know, HER-Vaxx works by targeting the same receptors as Herceptin and Perjeta, the leading monoclonal antibody drugs currently available with annual sales of \$US 8.2 billion.

Immunotherapies have taken the cancer research field by storm, across all disciplines including ours and are predicted to generate sales of \$US 36 billion by the year 2025.

The currently available cancer treatments come at a great cost so one of the advantages of our therapy is the low cost of goods that will enable flexibility in the pricing. You can imagine for HER-Vaxx combination therapies, this is a huge advantage and a key factor in determining market cost.

We have set our sights to help those in the Asian region who are afflicted with gastric cancer.

Our CEO, Leslie Chong recently commented, "the mortality rate for gastric cancer in Asia is substantially higher than the world average and unfortunately adding to that statistic is the reality that there is currently a difficulty for Asian patients to obtain treatments readily available in other countries be it financially or availability."

"That is why we are pushing forward with great vigour to build on our significant clinical and commercial potential in the Asian region," she said.





# Why are we Running our Clinical Trial in Asia?

Good question – straightforward answer. Less than a century ago gastric or stomach cancer was the most common cancer in the world. Despite its incidence decline in the western world it is in fact worsening in the Asian region.

It's the 4<sup>th</sup> most common cancer in the world but more than 70% of cases occur in the developing world, particularly Asia.

It remains a significant public health and economic burden in Asia and it is difficult to assess any systemic review of gastric cancer incidence and mortality.

## It is the most common cause of cancer death in Asia.

That's a sobering statistic. Asia is the world's largest and most populous continent with more than 4.3 billion people. Its growth rate is high and has quadrupled in the last hundred years.

## "Out and About!"

Our hard working and hard travelling CEO, Leslie Chong was recently asked to participate in an important gathering of biotech and healthcare executives gathered together under the banner of, "Women in Pharma and Medical, Leadership Summit 2016."

The summit was held in Sydney and covered many aspects of the business cycle including topics such as, "the influential leadership journey and lessons learned,"

through to "strategies on the transition from technical to management expertise and the importance of strategic networking."

Workshops on, "developing resilience in times of turbulence," "managing transitions and boosting leadership roles," and "work/life balance," were key focus points.

Just another acknowledgement that the company is fortunate to have attracted the calibre of executive personified by Ms. Chong. (editor note – my observation, not hers)



Ms. Chong was on a panel discussion with fellow executives, Josie Downey, director of the oncology business unit, Merck Sharp and Dohme; Dr. Kathy Kociuba, director customer experience, oncology at Baxter Healthcare and Michele Blanshard, business director, ANZ Diabetes.

# Gastric Cancer – An International Update

Three prominent, clinical associations in The United States, The College of American Pathologists; American Society For Clinical Pathology and The American Society of Clinical Oncology have collaborated on a much needed clinical practice guideline.

It will help establish standards in HER2 testing, improve the accuracy of the test interpretation, guide HER2 targeted therapies (ourselves included) and in the final analysis provide accurate, personalised care for patients with gastric cancer.

This is not just a group of scientists presenting more data, it's an industry guideline that is evidence based and reflects well upon our activities in the field and indicates that we are on the right track.

Their collective efforts and findings flow from 969 peer level reviews and 116 studies.

Amongst its findings is that 22% of patients with gastric cancer in the USA are HER2+ and that HER2 directed treatment has shown to improve the life span of patients with advanced gastric cancer.

We have always been hopeful and confident that our research and development is leading us in the right direction but to receive third party validation from such prestigious bodies is heartening indeed.

### **Forward Looking Statement**

Any forward looking statements in this newsletter have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside Imugene Limited's control. Important factors that could cause actual results to differ materially from any assumptions or expectations expressed or implied in this brochure include known and unknown risks. As actual results may differ materially to any assumptions made in this brochure, you are urged to view any forward looking statements contained in this brochure with caution. This presentation should not be relied on as a recommendation or forecast by Imugene Limited, and should not be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.

# **Immuno-Oncology in Numbers!**

### **Global Cancer Treatments**

At the moment immunotherapies only comprise 3% of cancer treatments globally, but... that number is set to jump to 60% by 2023. Six years is a brief span in cancer research and the economics parallel to that growth figure are staggering indeed.



## **Cost of Cancer Drugs**

" We believe this market will generate sales of up to \$35 billion (a year) over the next 10 years and be used in some way in the management of up to 60 percent of all cancers," Citi analyst Andrew Baum stated

#### **Alliances**

The immuno-oncology alliances between big pharma, big biotech and small enterprise grew from 6 in 2013 to 58 in 2015. Figures like that speak louder than words.



## **Economics**

The economics are equally staggering by proportion. Analysts have estimated the cost of an immuno-oncology treatment could be in the excess of \$US 500,000 per patient likely in the combination.

Currently, Opdivo approved for certain kinds of melanoma and lung cancer is priced at 12,500 a month or about 150,000 per year of treatment. Yervoy, approved in 2011 (with Dr. Axel Hoos

as a clinical lead) for certain kinds of melanoma, costs 130,000 for a 12-week course. This works out to be around \$U.S. 157.46 per mg per dose.



That's 4000 times the price of gold.

Are we in the right sector of cancer research?



Sources: reuters.com/article/us-cancerimmunotherapy-idUSBRE94L0CF20130522 "Cure", July, 2015



# Imugene's Significant Collaboration with Baker IDI!

In August 2015 a very important paper was published in Nature Reviews Drug Discovery. The title of this seminal review was Big Opportunities for Small Molecules in Immuno-Oncology and our non-executive director, Dr Axel Hoos, co-authored it<sup>1</sup>.



Professor David Kaye, Head of Hypertension and Cardiac Disease at Baker IDI and senior cardiologist at the Alfred Hospital.



Axel's review highlighted the conspicuous absence of small molecule drugs with application to cancer therapy in the new era of immuno-oncology. Modulating the immune system through a small-molecule approach offers several unique advantages that are complementary to, and potentially synergistic with, biologic modalities. The review highlighted immuno-oncology pathways and mechanisms that can be targeted by small-molecule medicines. Agents aimed at these mechanisms modulation of the immune response - are poised to significantly extend the scope of immuno-oncology applications and enhance the opportunities for combination with immunotherapies.

Our own Chief Technology Officer Dr Nick Ede upon sitting down with a coffee to read the review immediately noticed something that raised his pulse rate. The review highlighted a key mechanism of cancer escape resulting from the depletion of the amino acid arginine in the tumor microenvironment. In Figure 2b of the review he excitedly read that depletion of intracellular and extracellular arginine results in impaired T-cell performance resulting in an impaired immune response to the growing cancer. Small molecule drugs that increase the availability of arginine in the tumor microenvironment therefore have great promise both as single agents and in combination with other cancer medicines.

The reason Nick was so excited was that in his previous role as Chief Scientific Officer at Mimotopes Pty Ltd

in Melbourne, he designed and tested in collaboration with Professor David Kaye at the Baker Heart Research Institute, a set of compounds that did exactly what he had just read in Axel's review! The application was in cardiovascular research since an increase in arginine in blood vessels results in dilation of blood vessels, and blood pressure lowering. Professor Kaye has continued his research at the renamed Baker IDI and one of the best compounds from this set has advanced closer to human trials.

A conversation between Nick and Axel followed and plans for a proof of concept (POC) were quickly laid down. Importantly the research is inexpensive to initiate meaning POC will come quickly in 2017. The upshot of this is that last week we announced an exclusive and worldwide material transfer agreement with the Baker IDI to access these arginine modulating compounds in the field of cancer and specifically immuno-oncology. We have filed a patent

protecting the use of the compound set in the field of oncology and treatment of proliferative disorders such as cancer.

Getting back to the science, the field of tumor immunology is focused on developing agents that activate the body's own immune system to attack and kill tumors. Imugene's new preclinical program in tumor immunology will be focused on developing modulators of arginine bioavailability in the tumor microenvironment where arginine is often depleted. By increasing the availability of arginine in and around the tumor, it may be possible to restore the tumor killing

activity of cytotoxic T cells by preventing the depletion of arginine. A recent publication in the prestigious journal Cell supports our hypothesis where Swiss researcher's found that T-cells with increased arginine levels display improved anti-tumor activity<sup>2</sup>.

There are several pharma and biotech companies active in developing small molecule immune modulators but like us, they are all preclinical.

Big pharma will pay a handsome premium for these immune modulating small molecule drugs.

In 2015 BMS snapped up a preclinical immuno-oncology small molecule asset from CA-based Flexus for US\$1.25Bil with US\$800Mil cash upfront. We are particularly excited about this agreement because we believe we can apply our core expertise in tumor immunology to rapidly advance our potent and selective small-molecule arginine modulators into the clinic to develop a first-inclass immuno-oncology therapy for cancer patients.

"There is ever increasing evidence that the biology of inflammation that contributes to heart failure is also relevant to the biology that drives cancer. Our collaboration with Imugene supports our internal research programs to find new and more effective treatments for heart failure,"said Dr. Kaye.

## **Board and Management**

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<sup>1-</sup> Adams JL, Smothers J, Srinivasan R, Hoos A. Big opportunities for small molecules in immuno-oncology. Nat Rev Drug Discov. 2015 Sep;14(9):603-22

<sup>&</sup>lt;sup>2</sup> Geiger, R etal. L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity, Cell, 2016, 167, 829-842