# IMU Shareholder Newsletter

**Melbourne, Australia, 13 April 2016:** Imugene Limited (ASX: IMU), a clinical stage immuno-oncology company, provides the following market update via a shareholder newsletter.

## About Imugene

Imugene (ASX: IMU) is a clinical stage immuno-oncology company headquartered in Melbourne, Australia. Its lead product is HER-Vaxx, a B Cell peptide vaccine for the treatment of gastric cancer. The company is also developing mimotope-based immunotherapies against validated and new oncology targets.

HER-Vaxx is a cancer immunotherapy designed to treat tumours that over-express the HER-2/neu receptor, such as gastric, breast, ovarian, lung and pancreatic cancers. This unique immunotherapy, developed by leading scientists at the Medical University of Vienna in Austria, is a peptide vaccine constructed from various B cell epitopes of HER-2/neu. It has been shown in pre-clinical work and in one Phase 1 study to stimulate a potent polyclonal antibody response to HER-2/neu, a well-known and validated cancer target. HER-Vaxx's successful Phase 1 study was in patients with breast cancer and the next stage of development will be a Phase 1b/2 study in patients with gastric cancer initiating in 2016.

In January 2016 Imugene announced a new partnership with the Medical University of Vienna to discover and develop mimotope-based immunotherapies against validated and new oncology targets. This partnership has the potential to create game-changing B Cell peptide vaccines that would replace or augment conventional monoclonal antibodies.

For further information, please visit www.imugene.com.
Sign up to follow @TeamImugene on Twitter at http://www.twitter.com/TeamImugene.
To follow Imugene on Facebook visit www.facebook.com/imugene.

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**INVESTOR NEWSLETTER**
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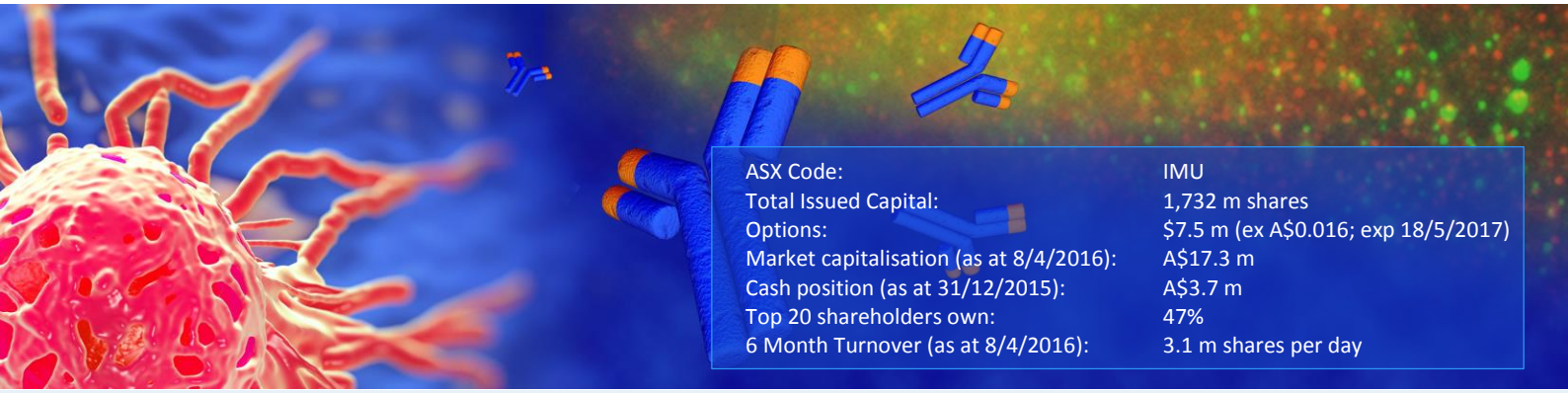

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| ASX Code: | IMU |
| Total Issued Capital: | 1,732 m shares |
| Options: | $7.5 m (ex A$0.016; exp 18/5/2017) |
| Market capitalisation (as at 8/4/2016): | A$17.3 m |
| Cash position (as at 31/12/2015): | A$3.7 m |
| Top 20 shareholders own: | 47% |
| 6 Month Turnover (as at 8/4/2016): | 3.1 m shares per day |

## IMU (Imugene) is developing B Cell peptide vaccines for immuno-oncology therapy. Clinical-stage vaccine, HER-Vaxx now entering Phase 1b/2 for the treatment of gastric cancer

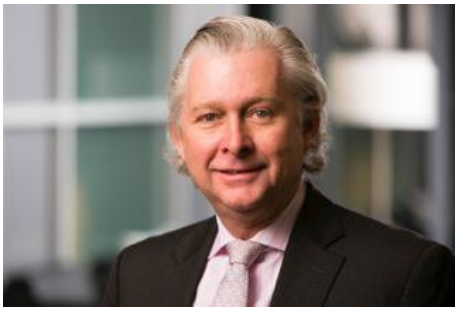
# From the Chairman

Dear Fellow Shareholders,

Welcome to Imugene's first shareholder newsletter for 2016. This year is set to be a particularly exciting one for our company. Our clinical-stage B Cell peptide vaccine, HER-Vaxx, will soon commence its long-awaited Phase 1b/2 study in gastric cancer. Meanwhile, following on from our landmark 20 January agreement with the Medical University of Vienna, our scientists will be working through the year to create a pipeline of mimotope vaccines based on validated monoclonal antibody targets. Both of these developments, in our view, represent significant steps forward not just for Imugene but for the field of immuno-oncology.

With the HER-Vaxx gastric cancer study we will join the ranks of immunotherapy companies with products in mid-stage development, giving us an advantage over other players still at the conceptual or benchtop stage (many of which have market capitalisations considerably greater than ours). More importantly, HER-Vaxx's re-entry into the clinic will represent the completion of a period where our product has been considerably optimised. The HER-Vaxx that we started with in late 2013 had shown that a B Cell peptide vaccine could generate a strong polyclonal antibody response against a cancer target, with antibodies apparently more potent than comparable monoclonal antibodies. The HER-Vaxx we are now working with has been shown in animal models to be capable of an antibody response at least twenty times as powerful as the original HER-Vaxx from three years ago. It also has patent life potentially stretching out to 2036.

We think HER-Vaxx is a big deal for the cancer immunotherapy field because we are one of the few companies globally working on B Cell peptide vaccines for immunotherapy. Up until now companies and laboratories developing cancer immunotherapies have tended to focus on T Cells, and we believe that this approach has had certain shortcomings that our B Cell approach, as exemplified by HER-Vaxx, may be able to overcome. The proof of the pudding will be the results of the upcoming Phase 1b/2 study that we're about to start. We look into the difference between B Cells and T Cells, and the 'epitopes' they recognise on immune system targets, later in this newsletter.



*Executive Chairman, Paul Hopper*

With our new mimotopes programme we will, in conjunction with our colleagues at the Medical University of Vienna, seek to build a valuable pipeline of HER-Vaxx-like B Cell peptide vaccines. HER-Vaxx prompts a polyclonal antibody response to the cancer antigen HER2. This antigen is already targeted by two successful monoclonal antibody drugs from Roche - Herceptin and Perjeta – which between them registered US$8.2bn in net sales for Roche in 2015. However, by 'reverse engineering' of HER2, scientists at Medical University of Vienna were able to create a mimotope – a 'mimic' of the epitopes – targeted by Herceptin and Perjeta. The resulting HER-Vaxx product is potentially superior and more cost-effective than the monoclonals. Under our 20 January agreement with Medical University of Vienna we're now using the same broad approach to develop new mimotopes. That this reverse engineering of monoclonal antibodies has significant upside is

suggested by the current size of the global market for monoclonals. In 2015 it was US$72bn, having grown 13% pa since 2009, with more growth to come given that potential blockbusters like Merck's Keytruda and BMS's Opdivo are still fairly new.

Leslie Chong joined Imugene as our new Chief Operating Officer in September 2015. Leslie brings to Imugene around twenty years' experience in clinical development of new drugs, gained in part at three very successful pharmaceutical companies - GlaxoSmithKline, Exelixis and Genentech/Roche. For Imugene to have attracted an executive of Leslie's calibre says a lot about the potential our technology and programmes. Since joining Imugene Leslie's major focus has been on preparing HER-Vaxx for its re-entry into the clinic in 2016, and I am very pleased with the progress she and her team have made to date.

Imugene in its present form has been a listed company since October 2013. As I look back over the last two and a half years I am satisfied that our progress with HER-Vaxx and our new mimotopes have laid the foundations for significant future growth in shareholder value. I want to thank you for your support so far and encourage you to continue following us in 2016 as we further develop the potential of our B Cell peptide vaccines.

Sincerely

Paul A. Hopper

## From our Chief Operating Officer

Dear Fellow Shareholders

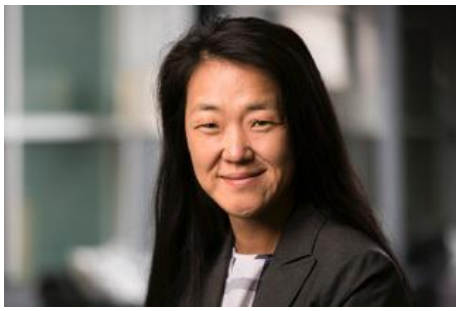
In the six months since I joined Imugene, our company has made great strides towards getting our clinical program HER-Vaxx back into the clinic for patients who need it while diligently working on building our franchise and pipeline.

In December of 2015 we announced Novotech as our lead Contract Research Organisation (CRO) to run the Phase 1b/2 study with HER-Vaxx in the HER2-positive gastric cancer trial. Novotech was selected primarily due to their experience in the Asia region and we believe they are a good fit with Imugene. We have advanced to the point where we will shortly announce our first regulatory and ethics review submissions in Asia. In the 2nd half of 2016, I look forward to announcing our first active site and then see us move on to the much-anticipated patient recruitment.

The HER-Vaxx gastric cancer study will be conducted in two parts. The initial Phase 1b will be up to 18 patients with HER-Vaxx in combination with chemotherapy to interrogate three dose levels. This first stage is simply to obtain data on safety and immunogenicity (a measure of how many of the HER2 antibodies are produced), as well as evaluate the booster schedule and determine the optimal dose to take into the Phase 2 study or recommended phase 2 dose (RP2D). The larger open label Phase 2 study will recruit around 68 patients randomised into two arms of either HER-Vaxx plus standard-of-care or standard-of-care alone.

As you may have noticed, we have changed the region to conduct our clinical trial. Prior to my arrival, Imugene had indicated that the study would be conducted in Australia and Eastern Europe. Upon my joining Imugene and after conducting a review of the clinical development plan, it was clear that Asia was the region to conduct our HER-Vaxx gastric cancer study given the incidence of the disease and the availability issues around existing anti-HER2 drugs in the region.

The average incidence rate globally for gastric cancer in 2012 was about 13.5 per 100,000 people (source: Globocan). In Australia it was 8.9 per 100,000. In contrast we saw an incidence rate in Japan, South Korea and China of 85, 64 and 30 per 100,000 respectively and in China it was 30 per 100,000. The incidence in Asia for gastric cancer alone made a strong case to conduct our study in this region, but additionally, in many parts of Asia the lack of availability and reimbursement for current HER2 therapies is an issue which made conducting our study there much more attractive.



*Chief Operating Officer, Leslie Chong*

We believe that HER-Vaxx could fill an unmet medical need in gastric cancer, which is the second most common cause of cancer-related death in the world and the fourth most commonly diagnosed cancer, with ~950,000 new cases annually. Estimated Western world five-year survival for gastric cancer across all stages of the disease is only ~30%. Herceptin, which targets HER2, is known to be effective in HER2-positive gastric cancer (around 20% of all cases) but in many countries, especially in Asia, it is not available or widely reimbursed, leaving the standard of care as two very old chemotherapies - Cisplatin and 5-FU. We see potential for HER-Vaxx to make a difference in this setting.

Building on HER-Vaxx, B-Cell peptide vaccines offer a unique opportunity to intervene at multiple points in the immune system and create immune memory which could enhance not only the response but the durability of that response. With our mimotope technology, we expect to invoke many facets of the complicated tumor micro-environment. This technology greatly increases our B-Cell antibody invoking peptide franchise, and our pipeline. Watch this space for much more to come in the near future on our mimotope technology.

***We believe that HER-Vaxx can fill a strong area of unmet medical need in gastric cancer***

I would like to echo our Chairman in thanking shareholders for their support as we seek to build shareholder value through the imminent return of HER-Vaxx to the clinic and through our exciting mimotopes programme.

Sincerely

Leslie Chong

# On B Cells, T Cells and epitopes – The science behind Imugene

The last five years have witnessed a revolution in the treatment of cancer. Up until recently oncologists only had surgery, radiotherapy and chemotherapy with which to attack tumours. However, since 2011 they have also had immunotherapy, where the patient's own immune system has been harnessed to generate an anti-cancer immune response. The breakthrough drug for the cancer immunotherapy field was Yervoy (ipilumimab), FDA approved in March 2011, whose clinical development was overseen by Imugene director Dr Axel Hoos when he was at Bristol-Myers Squibb. Yervoy was the first of the 'checkpoint inhibitors' which work by targeting molecules that serve as checks and balances in the regulation of immune responses. By blocking inhibitory molecules, checkpoint inhibitors help to unleash or enhance pre-existing anti-cancer immune responses.

Two other checkpoint inhibitors gained FDA approval in 2014 – Merck & Co.'s Keytruda (pembrolizumab) and Bristol-Myers Squibb's Opdivo (nivolumab). The clinical success of the checkpoint inhibitors, by proving that cancer immunotherapy was no longer 'science fiction', prompted a rush of capital into the field and led to the rise of many companies developing different immunotherapy approaches such as 'adoptive T cell therapy', 'T cell activating bispecific antibodies' and 'oncolytic viruses'. In this section of our newsletter we'd like to explain why we think our B Cell peptide vaccines represent a promising new cancer immunotherapy approach that can compete alongside these other approaches.

***Our B Cell peptide vaccines represent a promising new cancer immunotherapy approach***

Before we do so, however, let's cover a little immunology. The immune system is a collection of various white blood cells, all with specialised functions that contribute towards dealing with **antigens**, which the immune system is designed to recognise as foreign and proceed to eliminate. The immune system recognises antigens by molecular 'signatures' or 'motifs' associated with them called **epitopes**. One of the ways in which the immune system recognises the antigen or epitope is when **antigen-presenting cells** present the epitopes to **T cells** so as to produce the appropriate immune system response. T cells come in two basic forms – **Cytotoxic T cells**, whose job is to kill cells bearing the antigen, and **Helper T cells**, one of whose jobs is to help another group of cells called the **B Cells**.

T and B Cells make up the two basic 'arms' of the immune system – the cellular arm, handled by the Cytotoxic T cells, and the humoral arm, which is handled by B cells. The latter cells produce **antibodies**. These are Y-shaped molecules that circulate freely in the body and can attach themselves to antigens with exquisite specificity, enabling the antigen-bearing cell to be neutralised. The neutralisation happens because once an antibody has bound to an antigen, the resulting immune complex is engulfed by cells such as neutrophils and macrophages which then send out hormones called **cytokines**, whose role, broadly speaking, is to signal to the rest of the immune system that more help is needed to deal with the foreign antigen. This cytokine activity is what we call inflammation.

We mentioned earlier that cancer immunotherapy is a recent development. However, in one sense medicine has been harnessing the immune system to treat disease for a long time because of the **monoclonal antibody** drugs which have been coming on to the market since the late 1990s. These are formulations of antibodies cloned from one individual antibody that researchers

found to be particularly specific for a certain target antigen in the body. So, for example, Herceptin (trastuzumab) targets a cancer antigen called HER2 that overexpresses in breast and gastric cancers as well as other cancers.

The difference between anti-cancer monoclonal antibodies and the current generation of cancer immunotherapies is that the monoclonals represent **passive immunotherapy** from one small part of the immune system whereas checkpoint inhibitors and other products under development represent **active immunotherapy** that seeks to prompt the patient's own immune system to respond with its considerably more diverse repertoire.

Which brings us to what Imugene is seeking to do with its B Cell peptide vaccines. Traditionally vaccines have been used prophylactically, as in influenza or tuberculosis vaccines. They are administered in order to protect the vaccinated subject against disease. Such vaccines often work through the generation of a B Cell response to antigens from the microbe being vaccinated against, so that when the body encounters the real thing it has antibodies that can prevent disease. These protective antibodies are '**polyclonal antibodies**' in the sense that B Cells from the response can help bind the relevant target in different ways by producing multiple 'clones' of target-engaging antibodies.

Imugene is seeking with its B Cell peptide vaccines to create similar kind of vaccines, but for the treatment of disease rather than for prevention. We identify epitopes on known, therapeutically relevant targets where those epitopes generate a B Cell response by the immune system – that is, create antibodies rather than T Cells. We create an antibody-producing vaccine by joining together several of these epitopes in a long **peptide**, that is, a string of amino acids like one would find in any protein. And we then formulate our vaccine with other known immune-boosting substances that prompt T Helper Cells to boost the polyclonal antibody response.

Our clinical stage B Cell Peptide vaccine, HER-Vaxx, illustrates Imugene's approach. The target of the vaccine, HER2, was already known from the monoclonal antibody drug Herceptin to be therapeutically relevant in a number of cancers including breast cancer. We originally identified three B Cell epitopes from HER2 that generated a strong anti-HER2 polyclonal antibody response. After some work we created a vaccine in which all three epitopes came together in a single peptide, and that peptide was combined with CRM197, a so-called 'carrier protein' that provides an immunogenic kick for the Prevnar vaccine which is routinely given to prevent pneumococcal infections. More recently we've experimented in our vaccine formulation with **adjuvants**, which are other substances known to turn up an immune response. What we've looked for in the animal models as we've gone along is increasing numbers of antibodies targeting HER2, and as our Chairman noted above we now have vaccines at least twenty times as powerful as those we started with.

One significant reason why we think this approach has merit, with the potential to lead to great outcomes for cancer patients as well as significant creation of shareholder value, is because we think we can go one better than the monoclonal antibodies, in terms of killing cancer cells. Peptides are inexpensive to manufacture compared to monoclonal antibodies. More importantly, with our vaccines we can go after more than one B Cell epitope at a time with multiple different types of antibodies, giving us the opportunity to hit cancer cells harder than a monoclonal could. The commercial potential of all this is suggested by the high sales for leading monoclonals – Herceptin peaked at US$6.85bn in net sales for Roche in 2014.

Another reason why we believe our approach has merit has to do with an advantage of B Cells over T Cells. In their attempts to generate a T Cell response, cancer vaccine developers often face a problem called 'MHC restriction'. Put very simply, MHC restriction means that each person's Cytotoxic T Cell response is genetically determined (Australia's Peter Doherty figured this out in the early 1970s and won the Nobel Prize for Medicine in 1996 for his efforts). Consequently, many patients won't respond to certain types of T Cell epitopes, limiting the vaccine to a certain class of patients. B Cell epitopes don't have this problem and therefore our kind of vaccine is universal.

***B Cell peptide vaccines don't have an MHC restriction problem***

Finally, we think our B Cell vaccines have an advantage in the issue of immune 'memory.' With many prophylactic vaccines, you only need to get them once because the antibodies continue to circulate for decades afterwards. We believe our vaccines, being oriented towards antibody production, have a similar memory effect. Consequently, there is potential our vaccine could help

many patients remain in remission for a long time after their initial treatment.

Our forthcoming Phase 1b/2 study in HER2-positive gastric cancer will allow us to gather valuable data to see if our theories on the clinical benefits of B Cell peptide vaccines are valid. Success here opens large horizons for Imugene given that we are one of the few companies globally working on B Cell vaccines.

## Imugene's new mimotypes venture

Imugene announced on 20 January 2016 an extension of its partnership with the Medical University of Vienna (MUW) to discover and develop new mimotope-based immune-oncology therapies.

A mimotope is simply a peptide which mimics an epitope known to be able to generate an immune response. Imugene's HER-Vaxx B Cell peptide vaccine is a mimotope derived from three B Cell epitopes of the cancer antigen HER2. Imugene's 20 January agreement with MUW now extends the mimotope approach that led to the creation of HER-Vaxx to other tumor antigens and immune regulators such as checkpoints.

The potential upside for our mimotopes technology is significant. In 2015 global sales of monoclonal antibodies was US$72bn and our mimotopes antibody platform enables us to 'reverse engineer' any of these antibodies and develop a B Cell peptide vaccine with potentially greater efficacy, possibly at lower toxicity and cost of manufacturing. However, the platform isn't limited to validated monoclonal antibody targets. Any therapeutic antibody could be a target of one of Imugene's mimotopes.

Imugene's partnership with MUW comes at an opportune time for the company. Recently the MUW scientists, led by our Chief Scientific Officer, Professor Ursula Wiedermann, have started using more advanced approaches for the identification of mimotopes than they have traditionally employed, opening up the potential for more rapid epitope selection for B Cell peptide vaccine products to take into pre-clinical development.

Work is now well underway in Vienna to develop Imugene's pipeline of mimotope vaccines. Imugene will own the Intellectual Property in the mimotope vaccines generated under the partnership, but it also retains the right to use the platform to generate additional mimotope vaccines independent of MUW. We will be periodically updating shareholders further on our progress with mimotopes, with an expectation that a number of vaccine candidates will be unveiled before the end of 2016.

*Dr. Anton Uvarov*

## Interview with Dr Anton Uvarov, Imugene's new director

Imugene announced on 5 January that Dr Anton Uvarov had joined its board as a Non-Executive Director.

Prior to moving to Perth, WA, where he currently resides, Anton worked in the US biotechnology research team at the investment bank Citigroup in New York. Anton completed his PhD in Biochemistry and Medical Genetics at the University of Manitoba in 2008. He gained an MBA from the University of Calgary in 2010.

### Q. WHAT DO YOU SEE AS IMUGENE'S KEY STRENGTHS AT THE MOMENT?

A. The focus on B Cells in vaccines, which is pretty unique. As our colleague Professor Wiedermann likes to say, T Cell vaccines have been exhaustively researched whereas but B Cell vaccines are an open frontier for immunotherapy. If we're right on the advantages of B Cell vaccines, patients and shareholders will do very well. Imugene can become a breakthrough company in the B Cell area in a same way Juno Therapeutics (Nasdaq: JUNO) became a breakthrough company in the T Cell space back in 2013.

### Q. AND JUNO HAS A HIGHER MARKET CAPITALISATION THAN IMUGENE, RIGHT?

A. It most certainly does, at least at the moment. At the 8 April close on Nasdaq it was valued at US$4.5bn, of which only US$1.2bn was cash.

### Q. AS AN ANALYST BY BACKGROUND, WHAT DO YOU LIKE TO SEE IN BIOTECH COMPANIES WORTHY OF INVESTOR INTEREST?

A. Great people. Great technology. And products in the clinic or near to it. And reasonable valuations. With plans well underway to start the gastric cancer study this year, we at Imugene now have the people, technology and products but are valued way below peers in the space.

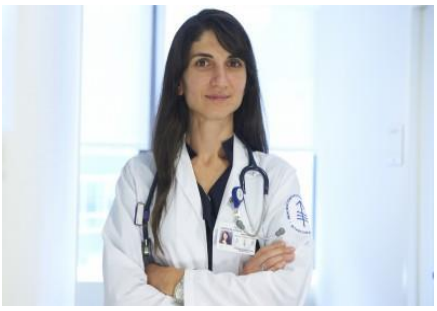
I'm also happy when I see a lot of progress has been made on a relatively small budget.

Q. CAN YOU ELABORATE ON THE LAST POINT ABOUT BUDGETS?

A. It's less common these days, but historically the biotech industry has gone through what are called 'nuclear winters' where capital is more difficult to raise. The winners in this environment have been companies that can get a lot done with limited resources. The classic case was Amgen in the early days, when all it took was one guy – Dr Fu-Kuen Lin – to effectively create what became their first blockbuster, Epogen. Highly cost-effective product development is a hallmark of emerging companies like Imugene. When I think what has been achieved in just two years on our low burn rate in terms of optimising HER-Vaxx, I am very pleased.

Q. IMUGENE IS CURRENTLY CAPITALISED ON ASX AT ONLY A$17m. WHY SO SMALL?

A. Sometimes the ASX underprices biotech companies compared to other markets, but that's our opportunity. Once upon a time Amgen was a small cap by US standards. Now it's worth over US$100bn and is the world's 12th largest pharma company. For Imugene, some good early data from the Phase 1b/2 can change market perceptions markedly, but most importantly, with new data in a completely new area, our company will surely be on the radar of bigger players.



*Dr Yelena Janjigian*

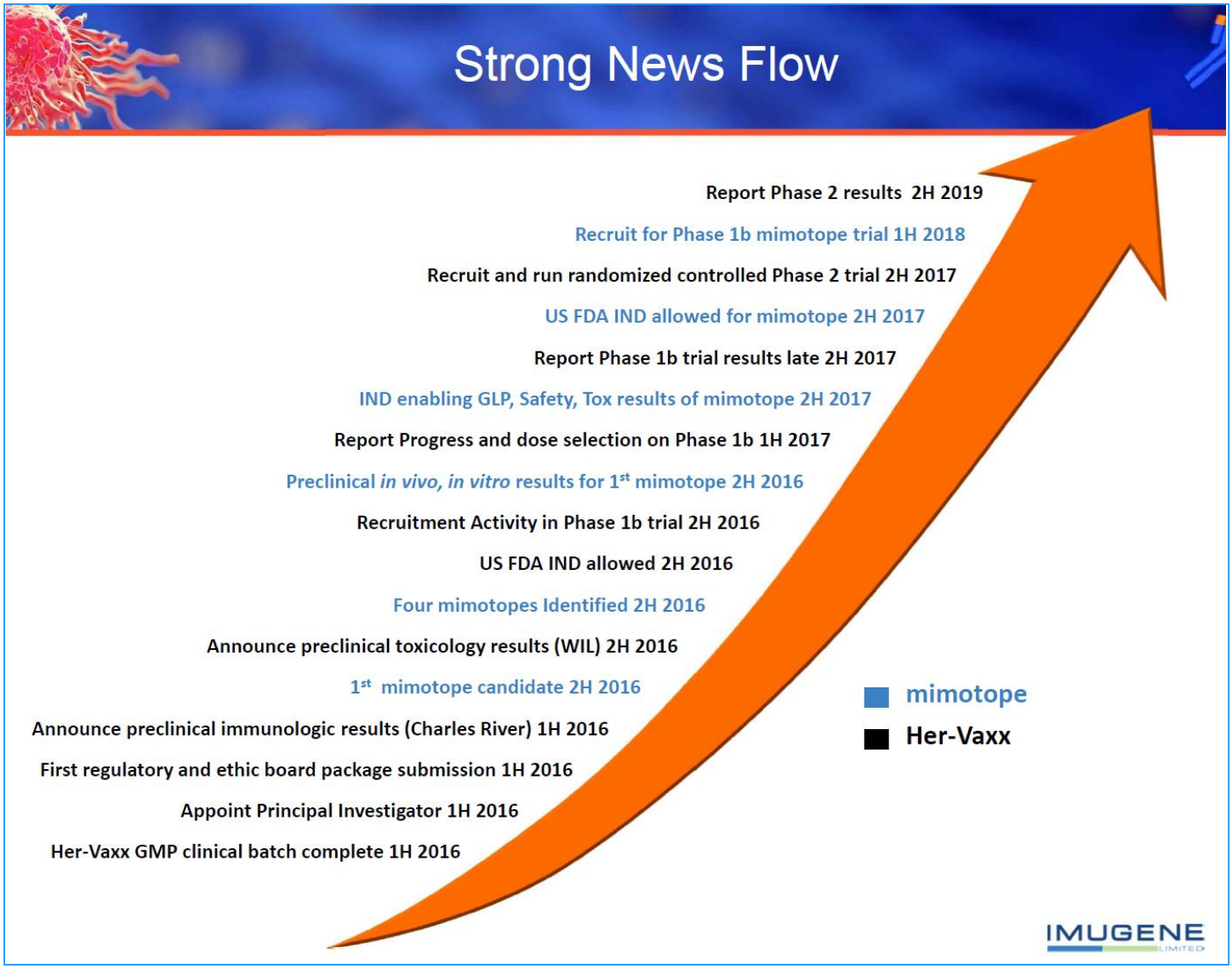
## Imugene secures a new Scientific Advisory Board member from Memorial Sloan-Kettering

We are pleased to announce that Dr Yelena Janjigian of Memorial Sloan Kettering Cancer Center in New York, the oldest and largest private cancer centre in the US, has joined Imugene's Scientific Advisory Board. Dr Janjigian is a medical oncologist who specializes in the treatment of malignancies of the gastrointestinal tract, including oesophageal and gastric cancer. Her research focuses on the development of new treatments for patients with these kinds of cancers, particularly 'personalised' therapies where the best treatments for patients are based on the molecular characteristics of their tumour specimens. Dr Janjigian has run clinical and translational studies designed to develop a better prevention, early diagnosis, staging, and treatment strategies and has been Principal Investigator on a number of clinical trials conducted at Memorial Sloan-Kettering. Imugene's SAB now comprises Dr Janjigian plus Professors Christophe Zielinski and Ursula Wiedermann of the Medical University of Vienna, who did the initial development of the science behind B Cell peptide vaccines, and Dr Neil Segal, also an oncologist at Memorial Sloan-Kettering.

## Hearing from us electronically

Many of our shareholders have lodged their email address with our share registry, Automic Registry Services, in order to receive shareholder communication electronically. However, we estimate around 16% of the Imugene-specific email addresses recorded at Automic are now out of date. You can notify Automic of your current email address by accessing Automic's investor online portal or calling 1300 288 664. The URL for the online portal is http://automic.7g.com.au/registration.aspx.

There are a number of other ways you can stay in touch with us. You can subscribe to our mailing list at imugene.com/contact. You can sign up to follow Imugene on Twitter at twitter.com/TeamImugene. And you can follow Imugene on Facebook at facebook.com/Imugene.

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