patrys

# ANNUAL REPORT 2018 (Extract)

patrys

# Company Profile

Patrys is a therapeutic antibody development company with operations in Australia and the United States of America.

Patrys' expertise and assets target antibody therapeutics in the field of oncology with both IgM antibodies and IgG antibody fragments under development.

Patrys has successfully out-licensed a clinical candidate, PAT-SC1 for the Chinese oncology market and has conducted two clinical trials with another lead candidate from its IgM platform, PAT-SM6. Patrys has in-licensed from Yale University a suite of novel, nucleus-penetrating antibodies (Deoxymabs 3E10 and 5C6) and Deoxymab 3E10 conjugated to nanoparticles which it will progress through development. Patrys has now humanized Deoxymab 3E10 and its lead candidate PAT-DX1 is currently being evaluated in a number of pre-clinical settings. Patrys will continue to advance lead candidates from both its technology platforms towards the market.

Patrys Limited is an ASX listed company (ASX:PAB) with corporate headquarters in Melbourne, Australia.

For further information on Patrys, visit www.patrys.com

# Operations

- Corporate headquarters in Melbourne, Australia
- Preclinical work conducted in multiple Australian and overseas sites, including Yale School of Medicine, Beth Israel Deaconess Medical Center (BIDMC) in United States of America and Garvan Institute and Walter and Eliza Hall Institute in Australia.
- Patrys Limited trades on the Australian Securities Exchange (ASX:PAB)

# Milestones

## 2H 2017

- Granted first US patent for Deoxymab portfolio
- Reported activity of PAT-DX1 in pre-clinical cancer models
- PAT-DX1 conjugated to nanoparticles shown to selectively target tumours
- U.S. patent granted for IgM pre-clinical candidate PAT-LM1
- Awarded Innovation Connections Grant with Garvan Institute of Medical Research for PAT-DX1 work on pancreatic cancer
- Collaboration with the Walter and Eliza Hall Institute of Medical Research
- Data showing synergy of PAT-DX1 with PARP inhibitor olaparib
- Research coverage initiated by NDF Research

## 1H 2018

- Oversubscribed Rights Issue raised $2.4 million
- PAT-DX1 targets delivery of nanoparticles to breast cancer tumors in animal model
- PAT-DX1-NP localises to lymph node metastases
- Publication of scientific paper and reporting of patent filing for humanized version of Deoxymab 3E10
- PAT-DX1 crosses blood brain barrier to reduce tumor size in animal model of glioblastoma
- PAT-DX1 improves survival in animal model of glioblastoma
- Patrys collaborators present at AACR conference
- NDF Research continues analysis and reporting on Patrys programs completed
- $4.6 million capital raise
- Announcement of collaboration with Beth Israel Deaconess Medical Center
- PAT-DX1 targets and kills brain cancer stem cells

# Assets

- **PAT-SC1** is an immunoglobulin M (IgM) type antibody which targets an isoform of the membrane-bound CD55 (DAF-B). This isoform has been shown to be significantly over-expressed on the membrane of gastric cancer tissues (74%), while no expression was detected on healthy cells and tissues. In September 2015, Patrys signed an exclusive development and commercialization license agreement for all oncology indications in China for PAT-SC1 with the Chinese company Hefei Co-source Biomedical Co.

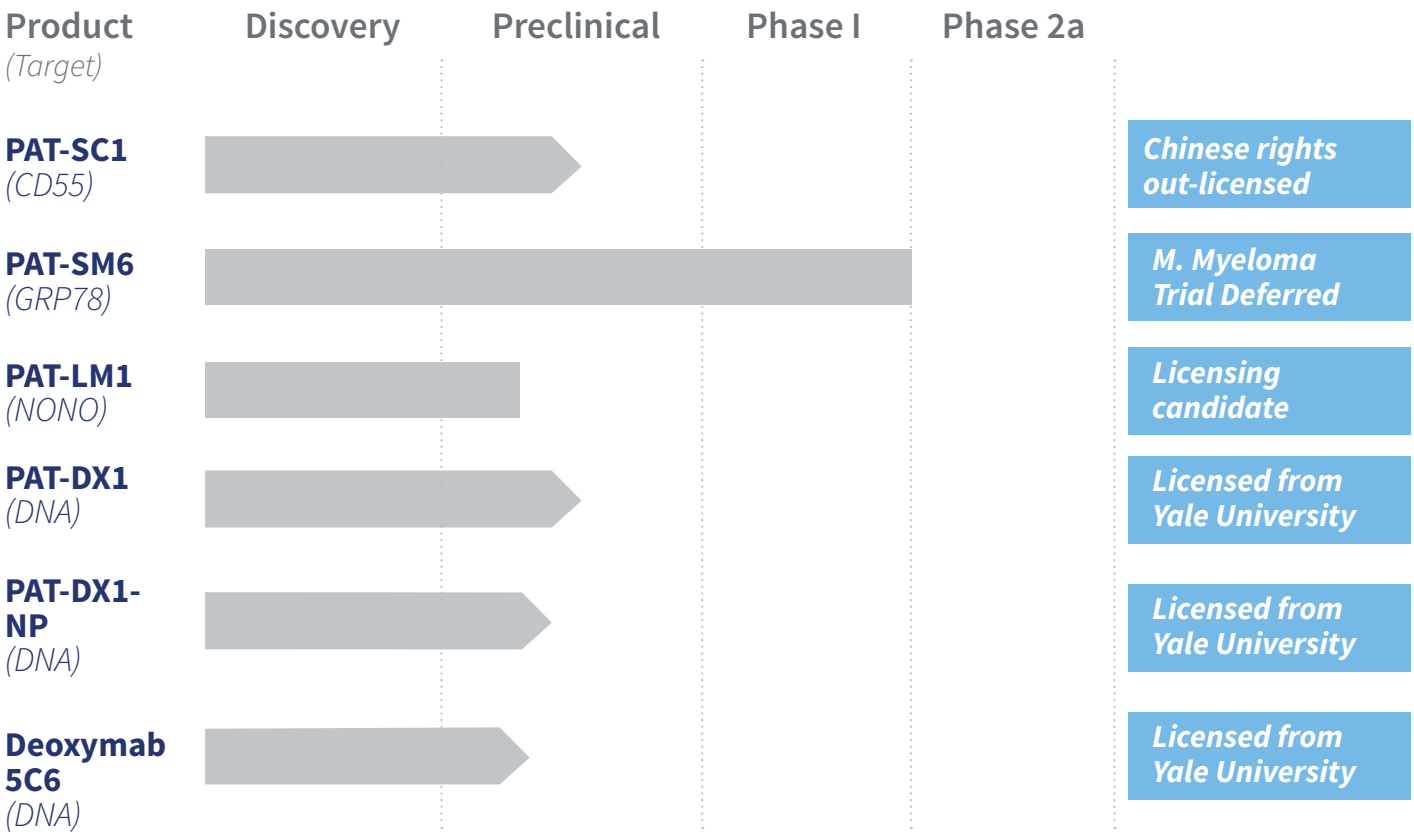
- **PAT-SM6** is a fully human monoclonal antibody (mAb) of the IgM type which targets a variant of human GRP78 and human apolipoprotein B100 (apoB100) found in low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). It has been successfully utilized in both melanoma and multiple myeloma clinical trials. Further clinical trials for this product candidate have been deferred due to manufacturing issues.

- **PAT-LM1** is a fully human IgM mAb that targets a variant of the human NONO protein (also named nmt55 and p54nrb), which is described to be a multi-functional nuclear protein. PAT-LM1 has shown promise in a range of preclinical cancer models.

- **Deoxymab 3E10** is a lupus autoantibody that penetrates live cell nuclei by binding to DNA or its precursors outside of cells and then following it into cell nuclei through a nucleoside transporter. Once in the nucleus, Deoxymab 3E10 interferes with DNA repair processes. To prepare Deoxymab 3E10 for clinical development Patrys humanised and optimised the antibody. The lead candidate, PAT-DX1, was selected from a large number of humanised 3E10 variants that Patrys designed to optimise for efficacy, manufacturability and novelty. The selection of PAT-DX1 was based on its performance in a suite *of in vitro* assays where it surpassed other variants in its ability to penetrate into cells' nuclei, and also subsequently kill cancers cells. PAT-DX1 has been shown to kill a wide range of DNA repair-deficient cancer cells, and has reduced tumor size and increased survival in an animal model of glioblastoma . Patrys acquired the rights to technology conjugating nanoparticles to Deoxymab 3E10 in 2017. The Company will further develop PAT-DX1 conjugated to nanoparticles, designated PAT-DX1-NP.

- **Deoxymab 5C6** is another lupus autoantibody that penetrates live cell nuclei. Similar to Deoxymab 3E10, 5C6 penetrates cells' nuclei and is highly toxic to cancer cells and has similar potential to be used in cancer therapy. Deoxymab 5C6 is currently in preclinical development.

# Pipeline


Product
(Target)
Discovery
Preclinical
Phase I
Phase 2a
PAT-SC1
(CD55)
PAT-SM6
(GRP78)
PAT-LM1
(NONO)
PAT-DX1
(DNA)
PAT-DX1-NP
(DNA)
Deoxymab 5C6
(DNA)
Chinese rights out-licensed
M. Myeloma Trial Deferred
Licensing candidate
Licensed from Yale University
Licensed from Yale University
Licensed from Yale University

# Letter from Chairman and CEO

Dear Shareholders,

Welcome to Patrys' 2018 Annual Report.

Patrys has had a successful 12 months with the reporting of a number of advances with its Deoxymab platform and substantial strengthening of its financial position with both an underwritten rights issue and a follow on capital raise. The Board and management team are pleased with progress to date and the continued opportunities in the cancer oncology space. We believe Patrys' technology provides a unique approach to treating cancer, especially those cancers with reduced overall survival.

As mentioned previously, during this phase of development there may be long periods between announcements which is reflective of the nature of the work being undertaken. The Board appreciates your patience throughout these times as we focus Patrys' programs and clinical strategy. In the coming months we will be reporting on the use of PAT-DX1 in a range of animal models, and initiating the first stages of cell line development which is essential as we progress PAT-DX1 towards the clinic.

The planned phase 1b/2a combination clinical trial of PAT-SM6 in patients with relapsed and refractory multiple myeloma is still on hold due to previously described manufacturing issues. The Company is focusing its efforts on the licensed novel nucleus-penetrating antibody technology platform ("Deoxymab") from Yale University, until non-dilutive capital can be sourced to progress the PAT-SM6 program.

## Deoxymab

Deoxymab 3E10 is the name assigned by Patrys to 3E10, a lupus derived autoantibody. Unlike normal antibodies that the body produces to bind to foreign cells (eg. pathogens) or aberrant cells (eg cancer cells) and trigger an immune response, autoantibodies bind to normal cells. While most antibodies bind to markers on the surface of cells, Deoxymab 3E10 penetrates cells' nuclei and binds directly to DNA. Having bound to the DNA, Deoxymab 3E10 inhibits DNA repair and damages DNA. Normal cells repair DNA damage utilizing intact DNA repair processes, however, Deoxymab 3E10 can kill cells that have mutations or deficiencies in DNA repair mechanisms as found in various cancer cells. As well as showing single agent therapeutic potential, Deoxymab 3E10 has been shown to significantly enhance the efficacy of both chemo- and radiotherapies.

Since acquiring the rights to develop and commercialize Deoxymab 3E10 Patrys has completed detailed in silico biology to optimize Deoxymab 3E10 and selected a lead candidate PAT-DX1, a di-scFv antibody. The Company reported on a number of pre-clinical studies in both 2H 2017 and 1H 2018. Additional pre-clinical studies are still ongoing and we are expecting to make further announcements on the following research topics:

- Initiate stable cell line development of PAT-DX1 (H2 2018)
- PAT-DX1 - Solid cancer animal data (H2 2018)
- Select target indication for PAT-DX1 clinical development (H2 2018)
- PAT-DX1 – Further solid cancer animal data (Q4 2018)
- PAT-DX1 in combination with Temozolomide and radiation, brain cancer animal model (Q4 2018)

PAT-DX1 has potential as a therapy for cancers that remain difficult to treat including glioblastoma, endometrial, ovarian, pancreatic, colon and some breast cancers. To date, PAT-DX1 has performed particularly well in animal models of glioblastoma.

PAT-DX1 is a very exciting development stage asset with a number of patents filed around the technology to create a barrier to entry for competitors. We have filed further patents to protect the humanized form, PAT-DX1. There is the possibility to pair this technology with other existing treatments and create combination therapies, enhancing the attractiveness of this asset to potential partners. Two further provisional patent applications have been filed and we look forward to reporting those to our shareholders once they are published.

## IgM assets

During the past year the Company has continued to put on hold any further research into PAT-SM6 and other IgM assets. The Company has determined what resources would be needed to restart manufacturing, but given the significant cost and time involved with these programs Patrys will only consider reactivation on a partnered, risk sharing basis or if non-dilutive funds can be accessed. Discussions with a number of potential partners are ongoing.

The IgM patent portfolio has reached maturity and all of patents have now been granted. A research collaboration with Macquarie University is ongoing, and will be extended to the end of 2018.

Patrys has been pleased to report in the period progress of its asset PAT-SC1, which was licensed in 2015 to Hefei Co-source Biomedical, an integrated Chinese drug development company. Our Chinese partners have been working diligently to progress the development of PAT-SC1, and the first annual Joint Development Committee meeting was held in China in October 2016. This license deal covers the exclusive development and commercialization rights for all oncology indications in China (excluding Hong Kong and Taiwan) for PAT-SC1. Patrys received an up-front licensing fee, and may, pending the achievement of prescribed milestones, receive multiple milestone payments and royalties on eventual product sales.

## Looking ahead

The Patrys team is focused on progressing its Deoxymab platform with lead candidate PAT-DX1 and PAT-DX1 conjugated to nanoparticles (PAT-DX1-NP) in a consolidated pre-clinical program both in the U.S. and Australia. Whilst the company has the resources to progress its PAT-DX1 asset towards the clinic it will consider appropriate valued co-development opportunities from reputable partner organisations. We are also focused on finding a suitable path forward for our existing IgM assets. With prudent financial controls in place and a well credentialed Scientific Advisory Board the Company believes it's in an excellent position to build value from its existing base of capital and assets and looks forward to sharing this journey with its shareholders over the coming year.

John Read
Chairman

Dr James Campbell
Managing Director and CEO

# The Board of Directors

## John Read, BSc (Hons), MBA, FAICD
### Chairman

Mr. Read is an experienced Chairman and Director in public, private and government organisations. Through his extensive career in venture capital, private equity and commercialization he has gained a depth of experience in the formation and growth of emerging companies with an emphasis on commercial entities that provide broad societal benefits. He is currently the Chairman of CVC Limited (ASX: CVC) and previously Chairman of Eildon Capital Limited (ASX:EDC) from 2013 to 2016, Pro-Pac Packaging Limited (ASX:PPG) from 2005 to 2010, The Environmental Group Limited (ASX:EGL) from 2001 to 2012 and The Central Coast Water Corporation from 2011 to 2014.

## James Campbell, BSc(Hons), PhD, MBA, GAICD
### Managing Director & Chief Executive Officer

Dr. Campbell has more than 25 years of international biotechnology research, management and leadership experience and has been involved in the creation and/or transformation of multiple successful Australian and international biotechnology companies. Dr. Campbell was previously the CFO and COO of ChemGenex Pharmaceuticals Limited (ASX:CXS), where, as a member of the executive team he helped transform a research-based company with a market capitalization of $10M to a company with completed clinical trials and regulatory dossiers submitted to the FDA and EMA. In 2011 ChemGenex was sold to Cephalon for $230M. Dr. Campbell was a foundation executive of Evolve Biosystems, and has assisted private biotechnology companies in Australia, New Zealand and the USA with successful capital raising and partnering negotiations. Dr. Campbell sits on the IP and Commercialization Advisory Committee of the CRC for Mental Health, and sits on the Advisory Board of Deakin University's Centre for Innovation in Mental and Physical Health and Clinical Treatment (IMPACT). Dr. Campbell is a Non-Executive Director of both Invion Limited (ASX:IVX) and Prescient Therapeutics Limited (ASX:PTX).

## Michael Stork, BBA
### Non-Executive Director

Mr. Stork is the Managing Director of Stork Holdings Ltd, an Investment Holding company active in the Canadian technology startup sector. Mr. Stork was until early this year active on the Board of Governors of the University of Waterloo and is the Chairman of the Waterloo Accelerator Centre, a technology company incubator affiliated with the University. He is currently the Chairman of Spartan Biosciences Inc., an Ottawa based DNA analytics company, the Chairman of Dejero Labs Inc., a Waterloo based broadcast technology company, and active on the Boards of a number of other leading Canadian technology startup companies.

## Suzy Jones
### Non-Executive Director

Ms. Jones is Founder and Managing Partner of DNA Ink LLC, a life sciences advisory firm in San Francisco with clients in the United States and Europe. DNA Ink provides corporate strategic guidance to its clients that support corporate growth. Prior to starting her own firm, Ms. Jones spent 20 years at Genentech where she served in many roles including Interim Head of Partnering, Head of Business Development, Senior Project Manager and Research Associate. She managed several products teams during this time including Rituxan, the first monoclonal antibody launched to treat cancer. Ms. Jones has very extensive networks within the pharmaceutical and biotech companies and VC community in North America. Ms. Jones is a Non-Executive Director of Calithera Biosciences, Inc. (Nasdaq:CALA), a clinical-stage pharmaceutical company focused on discovering and developing novel small molecule drugs directed against tumor metabolism and tumor immunology targets for the treatment of cancer.

# Management

### Melanie Leydin, BBus (Acc Corp Law)
### Company Secretary

Melanie Leydin holds a Bachelor of Business majoring in Accounting and Corporate Law. She is a member of the Institute of Chartered Accountants and is a Registered Company Auditor. She graduated from Swinburne University in 1997, became a Chartered Accountant in 1999 and since February 2000 has been the principal of chartered accounting firm, Leydin Freyer. The practice provides outsourced company secretarial and accounting services to public and private companies specialising in the resources, technology, bioscience and biotechnology sector. Melanie has over 25 years' experience in the accounting profession and has extensive experience in relation to public company responsibilities, including ASX and ASIC compliance, control and implementation of corporate governance, statutory financial reporting, reorganisation of companies and shareholder relations.

### Deanne Greenwood, BSc (Hons), PhD, MBA, GAICD
### Vice President, Business Development & Intellectual Property

Dr. Greenwood joined Patrys in 2008 and has held various roles in the company. Dr. Greenwood's efforts are focused on commercialization of the IgM and Deoxymab assets and management of the intellectual property portfolio. Dr. Greenwood has extensive experience in drug development, relationship management, contracts and grants. Dr. Greenwood led the negotiations with Hefei Co-source Biomedical Co. LTD, a Chinese based company which has taken an exclusive license to PAT-SC1. Prior to joining Patrys, Dr. Greenwood spent 10-years in academia conducting immunology research in the areas of vaccine development and autoimmunity, with the last four years at the Centre for Animal Biotechnology, The University of Melbourne. Dr. Greenwood has a PhD degree in Immunology from the Monash University, Masters of Business Administration (Technology) from La Trobe University and is a graduate of the Australian Institute of Company Directors. Dr. Greenwood is a co-author on 11 publications on immunological related topics.

### Valentina Dubljevic, BSc, MBB, GAICD
### Vice President, Scientific & Clinical Development

Ms. Dubljevic joined Patrys in June 2012 and is responsible for the pre-clinical and clinical development of Patrys' products. Ms. Dubljevic brings more than 20 years of scientific and commercial experience in the areas of anti- cancer therapies, vaccine development, and diagnostics. Prior to joining Patrys, she worked at the Monash University conducting research on malaria vaccine development; at Cytopia Limited developing small molecule anti-cancer drugs and at Monash Institute of Medical Research (MIMR) developing antibody therapies for cancer. She has extensive experience related to the drug development, management of pre-clinical studies, manufacturing, regulatory and clinical operations, contracts and project management and has co-authored multiple scientific papers and grants. Ms. Dubljevic holds a Bachelor of Biomedical Science degree from Griffith University, Brisbane, a Masters in Biotechnology and Business degree from RMIT and is a graduate of the Australian Institute of Company Directors (GAICD).

# Scientific Advisory Board

### Pamela M. Klein, BA, MD

Dr. Pamela M. Klein completed her medical training at Stritch School of Medicine, Loyola University in Chicago, followed by internal medicine training at Cedars-Sinai, Los Angeles, prior to spending 7 years working at the U.S. National Cancer Institute. Dr. Klein then moved to Genentech where, as Vice President, Development she led the development of a large portfolio of drugs including all the HER (Herceptin, Tarceva, Perjeta), Apoptosis (antibodies and small molecules) and Hematology compounds. After Genentech Dr. Klein was appointed to the position of Chief Medical Officer of Intellikine where she built the clinical development capability and brought multiple early compounds from laboratory to clinic prior to Intellikine being acquired by Millennium/Takeda. Currently, Dr. Klein currently serves as an advisor to a range of different biotech and investment companies, with roles on Scientific Advisory Boards and Corporate Boards as well as broader advisory roles.

### Allen Ebens, BSc, PhD

Dr. Allen Ebens completed a PhD at UCLA and Post-doctoral training at UCSF before joining Exelixis as a scientist in the Discovery Biology group. After 6 years with Exelixis, Dr. Ebens moved to Genentech where he worked in Research Oncology for 11 years developing therapeutics from concept to clinic across multiple therapeutic platforms including antibodies, small molecule drugs, and antibody-drug conjugates. Dr. Ebens was recruited from Genentech to establish Research Oncology at Juno Therapeutics, and has served more recently as Senior Director of Immune Oncology at NGM Biopharmaceuticals. Dr. Ebens is currently Chief Scientific Officer of Trucode Gene Repair. Over a twenty year career Dr. Ebens' contributions include significant contributions to the scientific literature as well as advancement of five discovery projects to clinical development.

# About Anti-DNA Autoantibodies

The study of the generation of autoantibodies has helped shape our understanding of the basic mechanisms of immune regulation. It is a complex and growing field of research. Normally, the immune system is able to recognize and ignore the body's own healthy proteins, cells, and tissues, and to not overreact to non-threatening substances in the environment. On occasion, the immune system ceases to recognize one or more of the body's normal constituents as "self", leading to the production of pathological autoantibodies, and emergence of autoimmune diseases. Quantitative changes in the profiles of particular autoantibodies can be indictors of disease status. Many autoimmune diseases (notably systemic lupus erythematosus; SLE) are distinguished by the production of autoantibodies that specifically bind to DNA (known as anti-DNA autoantibodies). The development of anti-DNA autoantibodies has not been fully elucidated.

It was originally thought that because the vast majority of DNA is housed within the nucleus, an area where antibodies were considered unable to gain access, production of anti-DNA autoantibodies was unlikely to occur. It was believed that these anti-DNA autoantibodies could only bind to the small amounts of free DNA present outside of cells (so-called extracellular DNA, or xDNA). However, in recent years, a large body of evidence has accumulated demonstrating that a select group of lupus anti-DNA autoantibodies can traverse into the nuclei of living cells where they can bind to their target DNA.

This finding raised the possibility that such autoantibodies could be used in molecular therapy techniques, in particular for the treatment of cancer. Among the many antibodies that have been considered, two stand out as having great potential for use against cancer, Deoxymabs 3E10 and 5C6.

# About Deoxymab 3E10

Deoxymab 3E10 is a lupus autoantibody that penetrates live cell nuclei by binding to DNA or its precursors outside of cells and then following it into cell nuclei through a nucleoside transporter. Once in the nucleus Deoxymab 3E10 interferes with DNA repair processes, but with modest inhibition insufficient to kill a normal cells that have the ability to repair DNA damage. In contrast cancer cells, that are exquisitely sensitive to DNA damage because their DNA repair machinery is already impaired, accumulate more DNA damage than they can tolerate when they encounter Deoxymab 3E10, and ultimately die.

Deoxymab 3E10 is therefore selectively toxic to cancer cells that have deficiencies in DNA repair, including a wide range of malignancies such as glioblastomas, endometrial, pancreatic, colon, prostate, breast and ovarian cancers. When combined with DNA-damaging agents such as chemotherapy or radiation, Deoxymab 3E10 has an even greater effect.

- Generation of Humanized Form PAT-DX1

Since acquiring the rights to develop and commercialize Deoxymab 3E10 Patrys has completed detailed *in silico* analysis in order to prepare Deoxymab 3E10 for clinical development. The Deoxymab 3E10 parental murine sequence was humanized and de-immunized to remove any components that might cause lupus-like side effects and de-risked for manufacturing. In addition, the new Deoxymab 3E10 variants generated were optimized to enhance their binding to DNA and increase their effect on DNA repair-deficient cancer cells. Sixteen different sequence variants of di-scFv Deoxymab 3E10 fragments were synthesized, cloned, expressed and tested in functional assays. The rationale behind creating di-scFv antibody format is to allow more than one binding site to DNA (ie. di-scFv has two binding sites). The scientific article regarding the humanization of Deoxymab 3E10 was published in leading scientific journal Biochemical and Biophysical Research Communications in early 2018 (Z Rattray, V Dubljevic, NJW Rattray, DL Greenwood, CH Johnson, JA Campbell, JE Hansen. Re-engineering and evaluation of anti-DNA autoantibody 3E10 for therapeutic applications. Biochem Biophys Res Commun. 2018, 496(3): 858-864).

Patrys has selected its lead candidate PAT-DX1, a di-scFv from the collection of 3E10 variants based on its physicochemical attributes and ability to penetrate nuclei and selectively cause DNA damage and cell death in cancer cells with DNA repair defects.

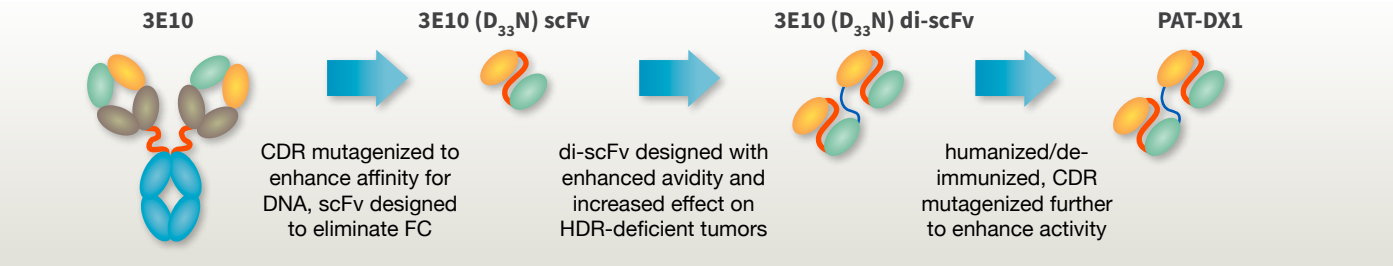



*Figure: Evolution of Deoxymab 3E10 into humanized PAT-DX1*

The selection of PAT-DX1 allows Patrys to progress its pre-clinical program in a consistent manner. The same antibody format and expression system is used to make multiple batches of material for pre-clinical testing.

# PAT-DX1

## Colon Cancer

In the period the Company announced that working with contract research organizations and collaborators at Yale School of Medicine, Patrys has shown that PAT-DX1 outperformed the non-humanized 3E10 antibody in cell penetration and cancer cell death assays. These pre-clinical studies confirmed that PAT-DX1 has the ability to kill colon cancer cells that lack key DNA repair enzymes such as BRCA2, a modality consistent with the understanding that PAT-DX1 binds to nuclear DNA and blocks DNA repair.

## Glioblastoma

Glioblastoma is a particularly aggressive, highly malignant form of brain cancer characterized by very fast cellular reproduction. Glioblastomas constitute approximately 17% of all primary brain cancers, with almost 12,000 new cases diagnosed in the U.S. each year. The current standard of care for glioblastoma is surgical resection followed by radiation and chemotherapy (temozolomide), with a median survival period of 15 months, depending on disease severity. One of the key prognostic markers in glioblastoma is the methylation status of the promoter for DNA repair gene MGMT. Methylated MGMT is predictive of better response to temozolomide and improved survival, while MGMT-unmethylated glioblastoma has a worse prognosis and is more difficult to treat.

Initial experiments in the laboratory of Dr James Hansen at Yale School of Medicine showed that PAT-DX1 was active against primary human glioblastoma tumor cells from patients.

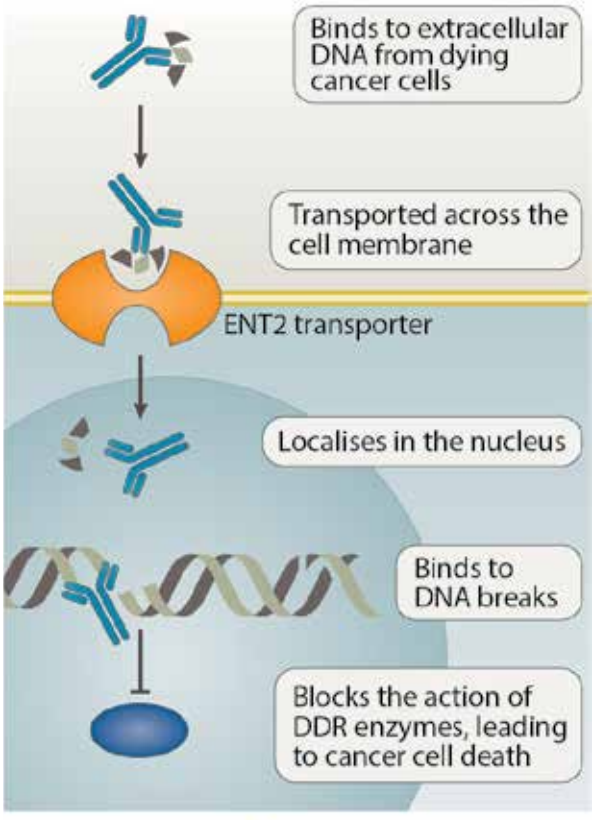
Further work by Drs James Hansen and Jiangbing Zhou of Yale University then shared that PAT-DX1 administered by tail vein injection significantly reduced tumour size and improved survival in an orthotopic animal model of MGMT-unmethylated glioblastoma derived from human tumour explants. Mice treated with PAT-DX1 showed a statistically significant median survival 20% longer than control animals with no observable toxicity.

## Combination with PARP Inhibitor olaparib

The Hansen laboratory at Yale School of Medicine also found that both PAT-DX1 and the approved PARP inhibitor olaparib killed a range of different cancer cells as single agents, and when used simultaneously their combined action was synergistic rather than additive, supporting the understanding that they act through different but complementary pathways.

Olaparib is a targeted therapy for cancer, approved by both the FDA and EMA. Olaparib interferes with DNA repair and acts against cancers with defects in homologous recombination due to BRCA1 or BRCA2 mutations, including some ovarian, breast, and prostate cancers. Olaparib was the first PARP inhibitor approved for use in humans, and numerous other PARP inhibitors are in clinical trials. PARP inhibitors are particularly interesting in the clinical setting because of their toxicity against cancer cells with impaired DNA repair mechanisms.

Combinations of PAT-DX1 and olaparib were tested on both brain and colon cancer cells with defective DNA repair pathways. In both cancers PAT-DX1 and olaparib by themselves were toxic to the cells in a dose responsive manner, and when used in combination they synergized to significantly increase cancer cell death compared to use of either agent singly. Furthermore, cells with intact DNA repair were not killed by PAT-DX1, olaparib, or the combination. Taken together, these findings indicate the potential for combinations of PAT-DX1 and PARP inhibitors to have an increased impact on DNA repair-deficient tumors while still sparing normal tissues.




## Crossing the Blood Brain Barrier

In February 2018 the Company announced that PAT-DX1 administered by tail vein injection crossed the blood brain barrier to significantly reduce tumour size in an orthotopic animal model of glioblastoma based on human tumor explants. Evaluation of brain sections showed that the glioblastoma tumors in mice treated with PAT-DX1 were more than 40% smaller than the comparable tumors in control mice. The blood brain barrier is a protective layer of endotheial cells that only allows certain molecules to transit from the blood into the cerebrospinal fluid that surrounds the brain. The blood brain barrier is a significant challenge to drug development and that observation that PAT-DX1 is able to cross and penetrate shows promise for its utility in

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this space.

### New Collaborations Established Utilising PAT-DX1

- Garvan Institute of Medical Research

An Australian Federal Government Innovation Connections grant has been awarded to support research aimed at determining the efficacy of Patrys' PAT-DX1 in *in vitro* studies of pancreatic cancer cell lines, and Garvan's unique, genetically well-characterised pancreatic cancer animal models, both as a single agent and in combination with therapies commonly used in this indication. The collaboration should provide data regarding the potential effectiveness of PAT-DX1 as a treatment for pancreatic cancer, which has the highest mortality rate of all major cancers.

- The Walter and Eliza Hall Institute of Medical Research

The collaboration will be used to couple Patrys' PAT-DX1 with a proprietary antibody from the WEHI (7D10) to generate a bi-specific antibody with the potential to kill cancer cells via a novel pathway. Previous studies have shown that once inside cells 7D10 interacts with the Bak protein to cause cell death, however a technology to reliably deliver 7D10 into cells has not previously been identified. Combining the two complementary technologies by the generation of a bi-specific 7D10-PAT-DX1 antibody will result in a novel antibody that should be able to enter a cell, bind to its target and act to help circumvent survival pathways typically employed by cancer. Patrys and WEHI were recently awarded a $100,000 State Government Victorian Medical Research Acceleration Fund grant to support research within the PAT-DX1 program that aims to develop new treatments for cancer.

- Beth Israel Deaconess Medical Center (BIDMC)

This collaboration will bring together experts from Yale School of Medicine in New Haven, Connecticut and Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts. A pilot study has shown that PAT-DX1 has antitumor activity in an orthotopic, immune-competent mouse model of triple negative breast cancer (TNBC), a particularly aggressive form of breast cancer. The expanded research program will further investigate PAT-DX1 in this model.

## PAT-DX1-NP

### Glioblastoma

Glioblastoma is an aggressive form of brain cancer. Based on successful studies with PAT-DX1 alone further work was performed with PAT-DX1 linked to nanoparticles (PAT-DX1-NP). The conjugated molecule was shown to be preferentially attracted to tumor tissues and, as a result, delivered its payload specifically to tumors. Previous studies with murine 3E10 have shown that similar conjugations significantly increased the efficacy of drug therapy.

The Company announced that when compared to unconjugated nanoparticles, experiments in mice with orthotopic glioblastoma brain tumors showed significantly higher localization of PAT-DX1-NP at the tumor sites. Further, PAT-DX1-NP localization was not elevated over background in other organs, including the heart, lungs, liver, spleen and kidneys, confirming the tumor-specificity of the conjugate. To enable visual quantification and localization of PAT-DX1-NP, the nanoparticles used in the study were loaded with staining reagent; however, future studies will use nanoparticles loaded with chemotherapeutic agents.

In addition, both PAT-DX1 alone and conjugated to nanoparticles have shown promise with preliminary studies on human glioblastoma cancer stem cells. PAT-DX1-NPs showed significant increased localisation to tumor spheres and targeted cells inside the spheres. These spheres are derived from human tumor explants and are grown in culture and resemble more closely the heterogeneity of the tumor compared with other preclinical methodologies.

### Triple Negative Breast Cancer

The Company announced studies performed in the laboratories of Dr James Hansen and Dr Jiangbing Zhou at Yale School of Medicine in a xenograft triple negative breast cancer animal model. Mice with breast cancer tumors were treated with free NPs or PAT-DX1-NPs, with both sets of nanocarriers loaded with a staining reagent to allow them to be directly tracked in the mice by an imaging system. The PAT-DX1-NPs showed improved targeting of the primary tumors, which is consistent with previous studies with murine 3E10 and PAT-DX1 in breast and glioblastoma tumor models. Significantly, it was observed that PAT-DX1-NPs appeared not only to localise to primary tumors, but also to axillary lymph node metastases. This finding supports the hypothesis that PAT-DX1 targets the cloud of extracellular DNA released by dying cancer cells. it is therefore not surprising that PAT-DX1-NPs have a potential to target not only primary tumors but cancerous cells elsewhere in the body including lymph nodes and distant metastases.

### About Deoxymab 5C6

Deoxymab 5C6 is another lupus autoantibody that penetrates live cells nuclei. Similar to Deoxymab 3E10, 5C6 penetrates cells' nuclei and is highly toxic to cancer cells and has similar potential to be used in cancer therapy. Yale University has also found that 5C6 has a toxic effect on BRCA2-deficient cells in colon cancer.

# IgM Assets

Patrys' IgM natural human antibody assets have shown anti-tumor activity in mice and in humans, and have shown a very good safety profile and signals of clinical efficacy. These antibodies can theoretically be combined with existing chemotherapeutic treatments potentially without any cumulative toxicology effects. Patrys is one of only a few companies worldwide with expertise in development of the IgM class of antibody. We continue with business development efforts for all IgM assets in our portfolio.

## PAT-SC1 License Update:

In 2015, the Chinese rights for PAT-SC1 were licensed to Hefei Co-source Biomedical Co. LTD, which is progressing well with its development plans. The Joint Development Committee met in October 2017, and Patrys' VP, Scientific and Clinical Development Ms. Valentina Dubljevic was pleased to be hosted by our partner at its site in China. The pre-clinical development of PAT-SC1 program including manufacturing utilising a CHO cell expression system is progressing well, and a further Joint Development Meeting is planned to be held in October 2018. This alliance provides possible future milestone payments and royalties. Patrys has retained the right to develop and commercialize PAT-SC1 outside of China (including Hong Kong and Taiwan).

*Hefei Co-source Bio-medical Co. Ltd building Shushan District, Hefei, Anhui, P.R China.*

## PAT-SM6 update

Patrys in conjunction with its partners completed a review focussed on the fundamental issues that arose with manufacturing of PAT-SM6 antibody. Further clinical studies of PAT-SM6 in multiple myeloma will remain on hold until non-dilutive capital can be sourced.

*From left to right: Dr Shu Gao, Founder and CEO of Hefei Co-source, Ms. Valentina Dubljevic, Patrys VP, Scientific & Clinical Development, Dr. Shanchun Zhang, CEO of Hefei Bio-Medicine at a meeting of the Joint Development Committee*

## Intellectual Property

Patrys' patent portfolio undergoes a constant process of expansion and consolidation.

The six patents underlying Deoxymab 3E10, PAT-DX1, Deoxymab Nanoparticles and 5C6 are licensed from Yale University and include:

- Cell-penetrating anti-DNA antibodies and uses thereof to inhibit DNA repair
- Multivalent fragments of antibody 3E10 and methods of use thereof
- Cell penetrating nucleolytic antibody based cancer therapy
- Antibody-mediated autocatalytic, targeted delivery of nanocarriers to tumors
- Binding proteins 1
- Binding proteins 2

The first patent in the Deoxymab family "Cell-penetrating anti-DNA antibodies and uses thereof to inhibit DNA repair" for cancer treatment has been granted in the U.S, Japan and China with pending applications in Europe and further U.S. continuation filed. The predicted expiry date for the first filed patent is May 2032. A further two provisional applications have been filed which are currently undisclosed.

The six patents that encompass the current IgM portfolio covering products PAT-SM6 and PAT-LM1 include:

- Adenocarcinoma specific antibody SAM-6, and uses thereof
- Human monoclonal antibody having fat-reducing effect
- Novel glycosylated peptide target in neoplastic cells
- Neoplasm specific antibodies and uses thereof
- LM-antibodies, functional fragments, LM-1 target antigen, and methods for making and using same
- PAT-LM1 epitopes and methods for using same

There are 25 granted applications in these families combined, and all cases have been granted. The first of these patents will expire in 2024 and protection extended to 2032 for some families. Patrys is seeking to partner the IgM assets.

# Recent Publications

## Deoxymab 3E10

Rattray Z, Dubljevic V, Rattray NJW, Greenwood DL, Johnson CH, Campbell JA, Jansen JE. Re-engineering and evaluation of anti-DNA autoantibody 3E10 for therapeutic applications. Biochem Biophys Res Commun, 2018, 496(3): 858-864.

Chen Z, Patel JM, Noble PW, Garcia C, Hong Z, Hansen JE and Zhou J. A lupus anti-DNA autoantibody mediates autocatalytic, targeted delivery of nanoparticles to tumors. Oncotarget, 2016, 7(37): 59965-59975.

Noble PW, Bernatsky S, Clarke AE, Isenberg DA, Ramsey-Goldman R and Hansen JE. DNA-damaging autoantibodies and cancer: the lupus butterfly theory. Nat Rev Rheumatol., 2016, 12(7): 429-34.

Weisbart RH, Chan G, Jordaan G, Noble PW, Liu Y, Glazer PM, Nishimura RN and Hansen JE. DNA-dependent targeting of cell nuclei by a lupus autoantibody. Sci Rep., 2015, 5: 12022.

Noble PW, Chan G, Young MR, Weisbart RH and Hansen JE. Optimizing a lupus autoantibody for targeted cancer therapy. Cancer Res., 2015, 75(11): 2285-91.

## Deoxymab 5C6

Noble PW, Young MR, Weisbart RH and Hansen JE. A nucleolytic lupus autoantibody is toxic to BRCA2-deficient cancer cells. Sci Rep., 2014, 4: 5958.

## PAT-SC1

Hensel F, Timmermann W, Von Rahden B, Brändlein S, Rosenwald A, Illert B. Ten year follow up of a prospective trial for the targeted therapy of gastric cancer with the human monoclonal antibody PAT-SC1, Oncol Rep., 2014, 31(3): 1059-66.

## PAT-SM6

Rasche L, Menoret E, Dubljevic V, Menu E, Vanderkerken K, Lapa C, Steinbrunn T, Chatterjee M, Knop S, Düll J, Greenwood DL, Hensel F, Rosenwald A, Einsele H, Brändlein S. A GRP78-directed monoclonal antibody recaptures response in refractory multiple myeloma with extramedullary involvement, Clin. Cancer Res., 2016, 22: 4341–4349.

Rache L, Duell L, Castro I, Dubljevic V, Chatterjee M, Knop S, Hensel F, Rosenwald A, Einsele H, Topp M and Brändlein S. GRP78-directed immunotherapy in relapsed or refractory multiple myeloma – results from a Phase I trial with monoclonal antibody PAT-SM6, Haematologica, 2015, 100(3): 377-84.

Loos A, Gruber C, Altmann F, Mehofer U, Hensel F, Grandits M, Oostenbrink C, Stadlmayr G, Furtmuller PG and Steinkellner H, Expression and glycoengineering of functionally active heteromultimeric IgM in plants, PNAS, 2014, 111(17): 6263-8.

# Corporate Directory

## DIRECTORS

Mr John Read, Chairman

Dr James Campbell, Managing Director & CEO

Mr Michael Stork, Non-Executive Director

Ms Suzy Jones, Non-Executive Director

## COMPANY SECRETARY

Ms Melanie Leydin

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