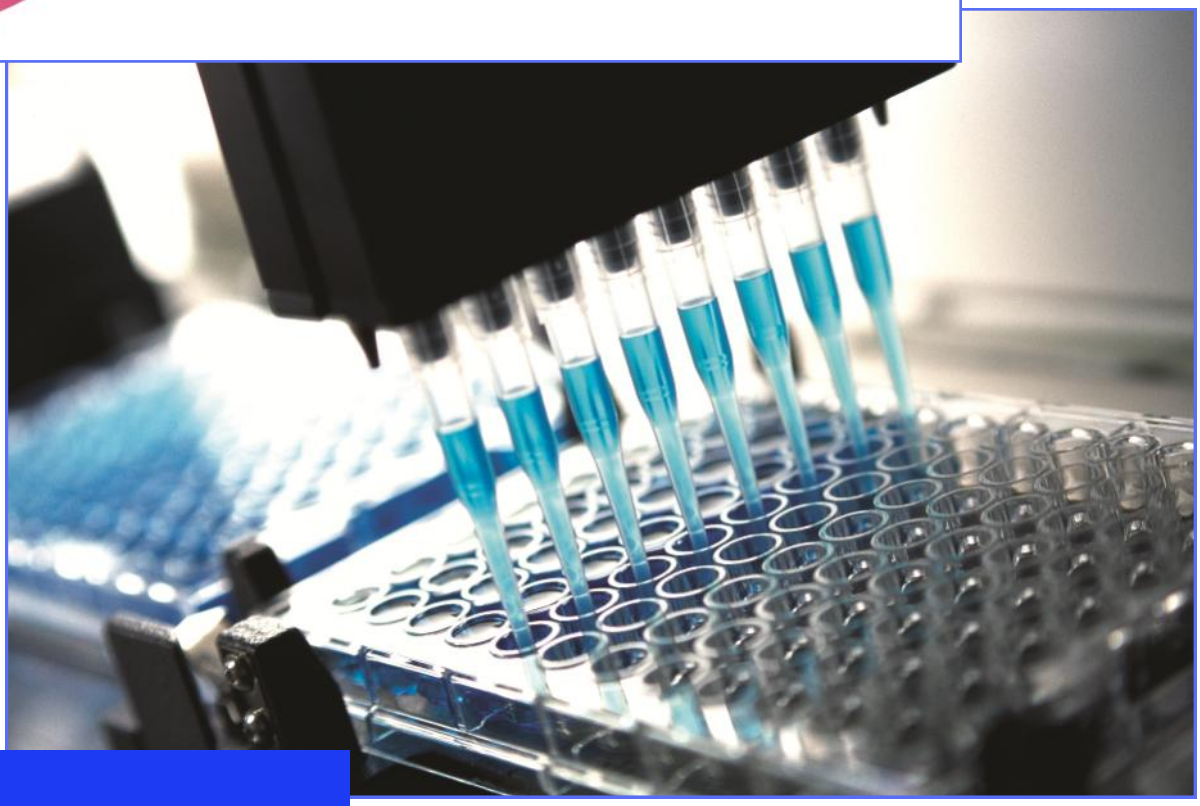
Cancer Therapeutics CRC



Annual Report 2012/13

Highlights

An Australian Government Initiative

CRC AUSTRALIA

Message from the CEO

This has been the year that the plans laid out when CTx was founded, and reiterated at the third-year review, have started to deliver the outputs that we had confidently promised. The high risk of drug discovery is well documented and we had no reason to believe that we would be significantly more successful than established benchmarks. In fact, because we had deliberately chosen targets that were more novel and demanding, there was good reason to accept that we may have set ourselves stretched goals.

Our goal, as agreed at the third year review, was to deliver four compounds with established preclinical proof-of-concept to commercial partners by 30 June 2014. We can now be confident of delivering that promise with two compounds formally licensed to our partner CRT UK in September 2012. In April 2013 our other commercial partner, Bionomics, announced that they were exercising their option on another program and that licence agreement was signed in June 2013, moving us ahead of our milestone schedule. In addition we successfully licensed a molecule that arose out of our drug discovery program, for use as a commercially available research tool. We are well on track to deliver the fourth and final output in the year to come with two more projects in the last stage of their development and already generating discussions with commercial partners.

These achievements are the result of intense collaborative project-focused efforts from all of our research partners. Each project team has a different combination of partners with some scientists contributing across many projects. The drive to deliver new cancer drugs for patients provides the core motivation for these teams and unites and integrates the teams on each project. The ownership of project champions is balanced by the overview and advice from senior scientific management and our independent advisory groups. This ensures that we remain hard-headed about projects and know when to cull and move on.

"We are well on track to deliver [our] fourth and final output in the year to come, with two more projects in the last stage of their development and already generating discussions with commercial partners."

Our education initiatives have been boosted by the new Molecules to Medicines Program initiated as a three-year pilot program with significant support from the Victorian State Government. After the first year the program has had uptake well in excess of plan and has received very positive feedback from interns, their employers and the State.

The other major activity of the year has been preparing for our funding extension application to the CRC Program. This was submitted in early June 2013 and we were shortlisted for interview in November. Starting with a strategic review in October 2012 the plans and the application have been refined with input from current and future partners. Underpinning the application is our success over the first six years of operation and the resulting licensing achievements detailed above. Our application is driven by two key aims; to be independent of direct Government support after six years and to focus our drug discovery on blocking the metastatic process early in its development. We want to bring the expertise of all our partners to bear on this outstanding challenge of metastatic spread as it is the major cause of cancer death. With CRC funding being competitive, even submitting a compelling application is not a guarantee of funding. In parallel to our application we have developed other plans to ensure that we maximise the benefit to Australia and our partners of all the intellectual property that has been generated over the first seven years of CTx.

I want to thank all our Partner shareholders for their ongoing commitment to CTx and, even more importantly, all the dedicated scientists that through their intellect and effort are directly responsible for our achievements.

Warwick Tong

October 2013

Board & Management Team

Tony Evans PhD MAICD
Independent Chair

The CTx Board comprises six directors and an Independent Chair, adheres to the Governance Principles outlined by the ASX and CRC, and provides strategic oversight to CTx Management.

Warwick Tong MBChB MPP MAICD
CEO

Keith Blundy PhD MBA
Director (CRT UK)

Deborah Rathjen PhD FTSE MAICD
Director (Bionomics Ltd)

George Morstyn FRACP FTSE MAICD
Independent Director

Ian McDonald PhD FRACI
Independent Director

Stephen Thompson PhD MBA GAICD
Independent Director

Committees supporting the Board

Audit & Risk Committee
- reviews and oversees the operation of risk management systems and internal compliance and control, codes of ethics and conduct, and legal and regulatory compliance

Portfolio Management Group (PMG)
- includes independent scientific and clinical experts and plays a critical role in defining and managing the CTx Project Portfolio

Education Advisory Group
- coordinates educational and career development activities for undergraduates, postgraduates, staff and end users

Operations Management (COG)
- includes CTx Management, Group Leaders and Key Project Leaders

Management Team

Chief Executive Officer
Dr Warwick Tong

Chief Scientific Officer
Dr Ian Street

Commercial Manager
Dr Guy Heathers

Business Manager & Company Secretary
Ms Verity McDonald

Research Manager & Communications Officer
Dr Cathy Drinkwater

R&D Operations Manager
Ms Samantha Smith

Education Officer
Ms Cathy Sage

Group Leaders

Dr Andrew Harvey
Dr Gabriel Kremmidiotis
Dr Graeme Stevenson
Dr Ian Holmes (resigned Oct 2012)

Dr Kurt Lackovic
Dr Mark Devlin
Dr Michael Parker
Dr Paul Stupple (from Nov 2012)

Dr Robin Anderson
Prof Susan Charman
Dr Tom Peat
Dr Vicky Avery

Cancer Therapeutics CRC

Translating cancer b

The Cancer Therapeutics CRC (CTx) is translating Australia's highly regarded cancer biology research into new cancer treatments

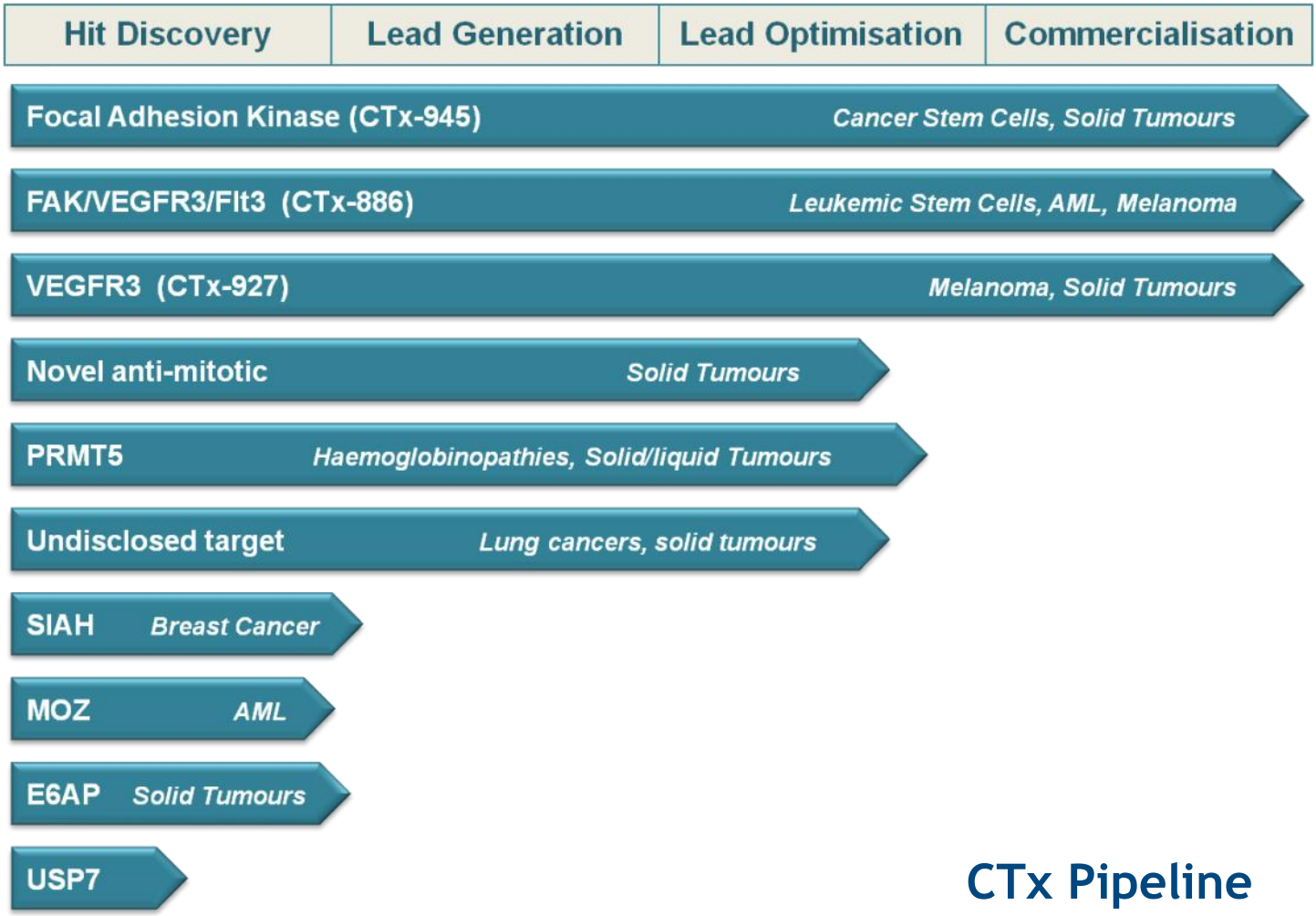
Through its Participants, CTx has assembled the capabilities needed to discover and develop novel small molecule cancer drugs

CTx is working closely with its two commercial Participants and other pharmaceutical and bio-technology companies to build the partnerships that will move these new drugs into early clinical evaluation, pharmaceutical development and global marketing

CTx has a pipeline of exciting new Drug Discovery projects that, with further development, have the potential to greatly improve the lives of cancer patients

To date, CTx has licensed three novel cancer drug development candidates to biotech partners for further development and marketing

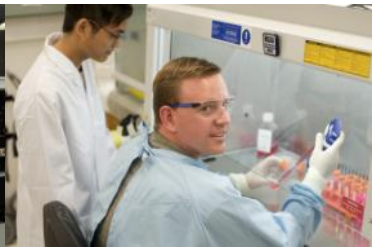
iology research into novel oncology treatments



CTx Pipeline

Target	Description
FAK	A highly selective small molecule inhibitor of focal adhesion kinase (FAK) for combination therapy in a range of cancers. **LICENSED to CRT UK for further development and marketing**
FAK/FLT3/ VEGFR3	Triple kinase inhibitor, targeting FAK, FMS-like Tyrosine kinase-3 (FLT3) and vascular endothelial growth factor receptor 3 (VEGFR3) to treat solid tumour metastasis and acute myeloid leukaemia (AML). **LICENSED to CRT UK for further development and marketing**
VEGFR3	Inhibition of VEGFR3 promises to prevent peritumoural lymphangiogenesis, lymph node metastasis and, possibly, proliferation of lymphatic vessels. **LICENSED to Bionomics Ltd for further development and marketing**
Novel anti-mitotic	A potent inhibitor of cellular mitosis with potential therapeutic benefit in colorectal and taxane-resistant cancers.
PRMT5	Inhibition of protein arginine methyltransferase 5 (PRMT5) activates the tumour suppressor protein, p53 and will also .
MOZ	Moz, an epigenetic modulator, is implicated as one cause of acute myeloid leukaemia (AML), therefore its inhibition should aid treatment of this disease.
SIAH & E6AP	E3 ubiquitin ligases that target tumour suppressors for destruction.
USP7	Inhibition of the deubiquitination enzyme, USP7, would lead to an increase in the tumour suppressor protein, p53.

Highlights 2013-14



Research

The focus of our research over the past year has been on moving our most advanced projects forward ensuring that we achieve all milestones and outputs. We have also undertaken a significant consolidation of projects in the earlier stages of our pipeline (RP1 and RP2) to again focus resources on bringing our most promising projects to completion over the next year.

RP1—Bioactive ("Hit") Discovery

Two series of compounds identified by the screening campaign against PRMT5 progressed to Lead Generation in the latter half of 2012, and this project is now entering a very exciting stage. Armed with excellent tool compounds, project biologists are now well positioned to address critical questions and move towards proof of concept in both cancer and haemoglobinopathy indications.

Progress on other Bioactive Discovery projects has been slowed by the reassignment of the majority of CTx resources onto Lead Optimisation projects, to drive the realisation of late stage and commercialisation outputs. Nonetheless, significant advances have been made in the development of a biochemical assay protocol suitable for high throughput screening (HTS) against Usp7 (which may contribute to prostate, bladder and liver cancer) and the HTS campaign is expected to commence in the second half of 2013. A new HTS assay targeting the histone acetyltransferase protein, MOZ (implicated in acute myeloid leukaemia), has also been developed and optimised, and is expected to be completed before the end of 2013.

Additional screening against the E3 ligase targets, E6AP and Siah, was performed against a number of external libraries. A total of ~40,000 additional compounds were screened for both targets, plus a further 23,000 compounds screened against Siah. Confirmation studies of the "hits" identified during these screens have identified around 36 compounds that warrant further investigation.

RP2—Lead Generation

After significant medicinal chemistry efforts on the PRMT5 inhibitor project, efforts progressed rapidly through the lead generation phase, and compound series was promoted to RP3, Lead Optimisation in December 2012

RP3—Lead Optimisation

In May 2013, the VEGFR3 program reached its Proof of Concept milestone, with the potent and selective compound, CTx-0357927. This compound effectively suppressed both tumour growth and reduced the number of lymph node metastases in a pre-clinical model of melanoma and, on the basis of this result, Bionomics exercised their commercialisation option on this project.

Good progress is also being made in the optimisation of compounds specifically inhibiting PRMT5. Studies are underway to investigate the effects of these compounds on the haemopoietic system of mice. In addition, studies have been initiated to assess the effects of PRMT5 inhibition on tumour growth in mouse xenograft models for a number of cancer types. Work is also ongoing to establish a pharmacodynamic biomarker for PRMT5 inhibition that will provide a quick and accurate screening method to determine efficacious compound dose in pre-clinical studies, and later, in clinical trials.

Two new Lead Optimisation projects were licensed from CTx Participants in 2012/13, and work on both projects is proceeding satisfactorily. A new, safe, scale-up process for the synthesis of an antimitotic compound has been developed and, if successful, this project will deliver a new class of therapies benefitting patients with tumours that have become resistant to standard of care chemotherapies such as taxanes.

The second new Lead Optimisation project is developing inhibitors against a protein family recently identified as oncogenic drivers in specific sub types of lung cancers. Optimisation of the series of inhibitors in-licensed by CTx is progressing well with the identification of potent and selective compounds which have an improved physicochemical profile. We expect to test the first project compounds in pre-clinical models of lung cancer in Q2 2013-14.

Education

Postgraduate Researchers

CTx postgraduates are supported in their PhD training as either Top Up Scholarship or Affiliate Students. Both schemes support student research related to cancer drug discovery and equip students with additional non-research skills to facilitate their future employment.

CTx Affiliate PhD students are eligible for skills development programs, competitive travel scholarships, and participation in the annual CTx student symposium. By 30 June 2013, a total of **39** CTx Affiliates had graduated and been awarded postdoctoral research positions, 16 of these in prestigious overseas laboratories. **21** CTx Affiliate graduates now hold positions in the biotechnology industry.

Two new CTx Top up Scholarship PhD students were enrolled during 2012/13, bringing the total number for CTx to **22**, three of whom have graduated and obtained postdoctoral placements in Australia or overseas.

This year 10 Affiliate PhD students were awarded CTx travel scholarships, taking the total awarded over the life of the CRC to **63**.

In October 2012, the annual CTx student symposium was held at the Walter & Eliza Hall Institute, and **55** CTx Affiliated or Top Up students from eight Institutions attended. **13** students gave oral presentations and **31** presented posters.

Students also attended a presentation skills workshop in October 2012.

12 PhD Top up students attended the annual CTx retreat where they joined a one day workshop on writing skills and

articulating research skills capabilities for career readiness. About 80% of students rated the workshop as beneficial and thought-provoking. At the retreat, students presented posters to senior researchers and industry advisors, providing them with invaluable networking opportunities.

Two of our PhD Top Up students were finalists in the CRCA Showcasing Early Career Researchers competition for 2013. Entry to the competition was via a 30 second video, with the six best entrants invited to give a 5 minute presentation at the Collaborate|Innovate|2013 Conference held in Melbourne in May 2013. Monique Topp (WEHI) presented her work on personalised models to change the way we treat ovarian cancer. Not all ovarian cancers are the same and by tailoring treatment to the individual we will likely improve their outcome. Her aim is to match patients to the treatment best predicted to control their ovarian cancer.

Caroline Le (Monash University) presented her research into the links between stress and cancer. She showed how stress weakens the immune system and actually helps cancer cells spread throughout the body and went on to demonstrate that the use of some existing drugs may be able to block these stress signals from having their effect.

Caroline was declared overall winner.

Professional Development

CTx uses a number of approaches to build commercial awareness for postdoctoral and early career researchers.

A key addition to existing training in 2012/13 has been the Molecules to Medicine (M2M) program. M2M is a knowledge and skills based training and mentoring pilot program to help early-career research scientists become familiar with the essential elements of managing the translation of biomedical research from basic science to clinical results. The program provides a year-long series of commercialisation seminars that support researchers in on-the-job training with their Business Development Managers. Foundation participants in the program are CSIRO, CTx, Baker IDI, Florey Neurosciences, Murdoch Children's Research Institute, MIPS, Burnet, SVI and WEHI. CTx and Biomentoring Australia attracted a $500K Victorian government grant to operate M2M as a three-year pilot program, administered by CTx. The first review of M2M by the Victorian Government's Department of Business Innovation in December 2012 applauded the set up, governance, online systems, management and evidence-based assessment of the program, which attracted double the number of organisations (nine not five) and research interns (30 not 15) as anticipated in its first year.

The M2M program was shortlisted for the 2013 CRCA Education Innovation Award and the concept and operation of M2M was presented to several interested parties at the 2013 CRCA conference in May. Interest in the program was high, and in 2013/14 enrolments are expected to increase by another third.

Following on from the successful Drug Discovery Workshops held in previous years, a third CTx Drug Discovery Workshop was held in April in conjunction with the University of South Australia (UniSA) International Drug Discovery Symposium. The workshop, which attracted 30-40 end-user delegates from local and international biotechnology organisations, was a forum for investigating collaborative opportunities, especially with China, UK and New Zealand. CTx sponsored eight CTx staff to the event and arranged separate end user meetings with Bionomics Ltd senior staff.

CTx Education also supported one of our Key Researchers to complete a Graduate Diploma in Drug Discovery from the UNSW in December 2012, and sponsored training and interactions with industry at the following meetings:

- 6th Australian High Content Screening Conference, 13 July 2012, Melbourne, Australia
- 14th International Biennial Congress of the Metastasis Research Society, 2-5 September 2012, Brisbane, Aust
- 7th Annual Collaborative Crystallisation Centre User Meeting, 22 March 2013, Melbourne, Australia

Commercialisation

CTx has now licensed a total of three drug candidates to development partners for formal pharmaceutical development.

- A highly potent and selective focal adhesion kinase (FAK) inhibitor has been licensed to Cancer Research Technology, UK (CRT UK).
- CRT UK has also licensed unique triple-kinase inhibitor that shows efficacy in preclinical models of acute myeloid leukaemia (AML).
- Bionomics Ltd. has licensed a CTx-derived inhibitor specific for the vascular endothelial growth factor receptor 3 (VEGFR3), which has achieved proof of concept as a potential treatment for melanoma and breast cancers.

In addition, SYNkinase Pty Ltd. has licensed a pan-kinase affinity molecule for development and sale as a research and diagnostic agent. The compound was jointly discovered and developed by CTx and the Garvan Institute of Medical Research and is capable of capturing over 200 kinases from a single cell line, making it one of the most powerful kinase capture tools identified to date. This unique ability to

detect most protein kinases within a biological sample gives the pan-kinase binding molecule significant potential to become a remarkable research tool for life scientists around the globe and in particular, will be valuable in the development of a 'kinome profile' of normal vs diseased cells, which will prove useful in identifying potential drug markers. It also has the potential to be developed into a diagnostic agent to determine cancer status in patients.

The CTx project to develop selective inhibitors of PRMT5 moved into the Lead Optimisation phase during the year with significant progress on chemical novelty and selectivity. The project is attracting significant interest from potential external partners and a number of confidential discussions have been initiated.

Five patent applications were filed in 2012/13.

Participants

Bionomics

CSIRO

Cancer Council Victoria

FIAT LUX Walter+Eliza Hall Institute of Medical Research

CANCER RESEARCH TECHNOLOGY

Griffith UNIVERSITY

SVI ST VINCENT'S INSTITUTE MEDICAL RESEARCH

Peter Mac

MONASH University

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