Cancer Therapeutics CRC

ANNUAL REPORT

2015-16

Australian Government
Department of Industry, Innovation and Science

Business Cooperative Research Centres Programme

CEO Statement

2015-16 has been a pivotal year for CTx and it is with great pleasure that I can detail its development and achievements in the second year of the current CRC Programme support.

Australia Day, 26 January, was the day CTx hit the heights in its drug discovery and development history. The inhibitors of PRMT5 Project was licensed to MSD (known as Merck & Co, Inc. in USA and Canada) in an exclusive worldwide licensing deal that involved CTx, along with the Wellcome Trust and CRT UK. Financially it can be classified as one of the biggest novel drug, preclinical licensing deals in Australia. A signature payment of USD$15 million (~$21 million) carries downstream potential milestones and royalties with the potential milestones alone being more than $750 million. Between 70% and 75% of all revenue comes back to the CTx partnership. The Chief Scientist, Alan Finkel and the President of Universities Australia, Barney Glover, both used this as an example of successful translation and commercialisation in separate addresses to the National Press Club.

We had the pleasure of sharing the CTx portion of the signature payment across the partnership, with Participants from both the first and the current CRC partnerships receiving a distribution. This event occurred late in the financial year with payments going to 20 past and current Participants. The majority of our current partners showed strong support for CTx's future performance by reinvesting a significant share of their distribution back into the partnership. As a result CTx retained more than $8 million to invest back into its drug development pipeline.

In addition to the licence deal MSD agreed to fund a research collaboration of more than $3 million to advance the haemoglobinopathy arm of the project. This is to continue the work previously funded under the Wellcome Trust award. We are optimistic that this collaboration may be significantly extended next year to fund additional oncology research within the CTx partnership network.

The CTx Board has endorsed a framework and plan for the future of CTx after the anticipated end of CRC Programme support in June 2020. The strategic intent to position CTx as a self-sustaining drug discovery organisation required underpinning with some significant commercial success and the MSD licence has provided the confidence required. That transition is now less than 4 years away and by end of next year there will be a detailed plan in place for the future of CTx. The additional investment in the CTx pipeline detailed above provides an increased probability of further commercial success over the next four years providing even more support for a successful future.

Thanks to the generosity of the Victorian Comprehensive Cancer Centre (VCCC) and the Victorian State Government we will be moving CTx headquarters into the new VCCC building in Parkville. CSIRO has made us very welcome over the past 15 months as the landlord for our current office space in Royal Parade. We will miss the warm collegiality we have enjoyed within CSIRO when we move in early 2017 but the move will place us in the centre of the Parkville Precinct.

As a semi-virtual organisation we are heavily reliant on our IT platforms to support the collaborative-networked nature of the business. Under the leadership of Paul Reeve, CTx has had a major reconfiguration of its IT infrastructure, positioning us to be independent of Participants and with state-of-the-art systems as we move forward. The final step is the configuration of a new suite of tools for our scientists, which is nearing completion. In parallel we have been building improved project management skills across the organization through targeted training for groups of our scientists.

Measurement of CTx's performance shows that we are ahead of many key milestones in all three of our Research Programs. Led by our partner, the Children's Cancer Institute, the development and delivery of a national Tailored Treatment Service for children has received additional funding and has been branded Zero Childhood Cancer. This initiative is already changing the lives of children with cancer. CTx's engagement with the FDA on novel clinical trial design for drugs directed at early metastasis was strengthened with a very well attended round-table at the FDA sponsored AAADV

meeting in Bethesda USA. Publication plans for the outputs of a collaborative meeting with CRT UK are well advanced.

Our education activities result in strong involvement from within and outside our immediate network. We have a range of initiatives that meet different needs and they always attract strong interest. The redevelopment of the Molecules to Medicine Program has resulted in a strategic partnership with Biomedical Research Victoria and continues to receive strong support from the Victorian Government. The program is being re-launched in the 2016-17 year with a number of new corporate and professional partners.

Our collaborative culture and network is stronger than ever and our drug discovery project teams are key examples of this culture at work. Guided by the CTx Board and scientific advisors our projects are scientifically exciting with great promise to deliver benefits in the future for patients with cancer. Our Industry Growth Centre, MTPConnect, is headquartered in Victoria and we are pleased to have the opportunity to work closely with them to accelerate progress in our sector.

We can look back with much pride on our achievements of the past year but remain fully aware that, given the long timeframes of drug development, our successes owe recognition to the platform established and developed over the past eight years. CTx is dependent on the excellence and dedication of its scientists and management team. My thanks go to them and our Board and advisors for all their contributions to another successful year for CTx, which has been highlighted by the successful translation and commercialisation of Australian research.

Warwick Tong

October 2016

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1 Executive Summary

1.1 Achievements

Research and Collaboration

- Two projects promoted to Lead Generation
- One new Hit Discovery Project
- Research agreement with MSD for PRMT5i in haemoglobinopathies

Commercialisation and Utilisation

Merck Deal

CTx and Cancer Research Technology UK (CRT) have entered into a license agreement with MSD (known as Merck & Co, Inc. in the US and Canada), to develop inhibitors of protein arginine methyltransferase 5 (PRMT5). The licence provides for a signature payment, milestone payments and royalties on sales. All payments will be shared between CRT, CTx and the Wellcome Trust with the majority being returned to CTx and its Australian research partners. As part of the research and development activities, MSD has also agreed to fund a research collaboration with CTx focusing on blood disorders.

Education and Training

- Eight undergraduate students received Summer Vacation scholarships to conduct research at Peter MacCallum Cancer Centre and MIPS.
- Seven students who had completed Honours in 2015 were supported by CTx to attend and present their work at the 28th Lorne Cancer Conference in February 2016.
- 20 PhD students were awarded CTx Top Up scholarships for projects relevant to Research Program 1
- 2 PhD students were awarded CTx Top Up scholarships for their project relevant to Research Program 3
- 2 HDR Symposia were held, as well as student involvement and a leadership workshop during the annual CTx Retreat.
- Six International Travel scholarships were awarded to CTx Affiliate PhD students
- Financial support has been provided to Student-led Higher Degree Research Symposia at Peter Mac and Monash
- After the successful completion of the Molecules to Medicine program, CTx collaborated with Biomedical Research Victoria, BioMelbourne, Women in Science Australia and the Industry Mentoring Network In STEM to be awarded a continuation grant from the Victorian Government to support development of an online platform to provide biomedical early to mid-career researchers with new skills and connections in research commercialisation and drug discovery to help address our greatest health challenges. The program – STEMM Bootcamp – was officially launched by Victorian Minister for Small Business, Innovation and Trade Philip Dalidakis on 30 June 2016.

- CTx and INC Research Australia enabled three Clinician and Translational Researchers to attend the Oncology Drug Development in Practice Training Course held from 26 – 28 November 2015 in Amsterdam, The Netherlands.
- 30 staff members were supported to attend and present CTx work at several Australian and International meetings and workshops.
- 10 CTx staff undertook Project Management Training
- 4 CTx staff undertook Change Management Training

1.2 Risks and impediments

CTx has established a Risk Management Plan (RMP) and Risk Register, endorsed and reviewed by the Audit & Risk committee and the CTx2 Board.

The RMP was most recently reviewed by the Audit & Risk committee in April 2016 and is monitored by CTx management and updated as changes in risk are identified.

Global Markets

CTx is active in the international pharmaceutical and biomedical industry, and as such is exposed to global market conditions.

Competition and fluctuation in currency exchange are two major influencers on potential licensing and profitability from offshore clients. To offset these impacts, CTx is investigating changes to its overseas contracts and hedging strategies.

Loss of Participant

The loss of a Commercial End User Participant would have significant impact on CTx business. Continual relationship management with End User Participants and ongoing plans to attract new commercial Partners/Participants are ongoing to mitigate against this risk.

Resourcing

CTx operates lean, leveraging the capabilities and capacity of its partners. There is an indirect implication that resourcing changes within our partner organisations may have a detrimental impact on project progress. CTx mitigates against this through regular operational and project meetings, comprising scientific leads who in addition to driving best practices and capability development, also have the ability to manage resourcing.

Intellectual Property

The loss, disclosure or security breach of sensitive IP is understandably a high impact risk. CTx has implemented a range of process, policy, protocols and disaster recovery steps to limit the opportunity and impact of exposure. Routine inductions, security testing and policy reviews are undertaken throughout the year to keep CTx up to date with best practice and standards.

Commercial Relevance

Central to the success of CTx is the commercial relevance of its discovery pipeline. We are commercially led through the input from our commercial end-user Participants who also have representation at the regular Pipeline Review Meetings to ensure that CTx drug discovery projects have sound commercial input in addition to scientific rigour. Though CTx has a track record of having commercialised 4 compounds since inception in 2007, there is a risk that new products may fail to be commercialised. The CRC remains focussed on maintaining a pipeline addressing a range of relevant

targets. The oversight by the independent SAB and Board ensures that hard decisions are taken with respect to inclusion and removal of projects in the pipeline.

1.3 End-user environment

The end-user environment for new cancer drugs is dynamic. New science can quickly drive the global focus into new areas and immuno-oncology has become a major focus over the last five years. Like most cancer therapy the approach is requiring combination regimens to provide the best clinical results. The field has been significantly driven by biologics but relevant small molecule targets are increasingly being recognised as important augmenters of immune responses.

Our commercial end-user partners recognise the importance of this trend and their input has helped shape the direction of the entry of new projects to the CTx pipeline in addition to the input from management and the SAB.

In addition to our commercial end-user partners, CTx management has interactions with major pharmaceutical companies and with a wide range of biotech companies. By engaging with potential end-user partners outside of existing Participants CTx ensure that it receives additional input into its research direction to shape target product profiles and that opportunities for research and commercial collaborations are fully explored. The commercial potential for novel small molecules directed at novel targets is currently very strong especially if the scope encompasses areas such as immuno-oncology and epigenetics. Deals are being signed for pre-clinical molecules with upfront payments in double-digit millions of dollars with total potential downstream payments in the hundreds of millions range. For Research Program 2 (RP2), the end-user environment is broad but key at the early stage is the engagement of major regulatory authorities. There is a strong drive to improve cancer therapy outcomes but these authorities need to accept that the focus needs to move significantly from the treatment of late stage metastatic cancer to the treatment / prevention of the progression of very early metastatic spread. Early buy-in to this major change in strategic direction will only be facilitated by the full involvement of such authorities in at the beginning of this change. The cancer drug development paradigm is resistant to change.

1.4 Impacts

Analysis of the CRC's Impact has been updated to provide an estimate of risk-adjusted valuation of the Outputs from each of the three CTx research programs at 30th June 2016.

This update has encompassed only project progress and achievement of milestones, changes to timing of future milestones and probabilities of Output generation, Utilisation or Impact (where reasonably assessable). It did not encompass changes to assumptions and variables associated with the broader industry-operating environment, thus enabling a like-for-like comparison of CRC performance.

Overall Benefit

The risk-adjusted benefit ascribed to all three research programs in 2013 at the time of the Extension Bid, was $510,127,300, with a benefit:cost ratio of 3.27:1.

After the updates indicated above, the risk adjusted benefit currently ascribed to all three research programs has increased to $641,646,549.

2 Research

2.1 Performance against activities

Research Program 1: New Drugs for Preventing Cancer Recurrence and Progression and Research Program 3: New Drugs for Treating Paediatric Cancer

Program Leader: Dr Ian Street (CSO, CTx)

Licensing of CTx PRMT5 Inhibitors

In May 2014 CRT (UK), a Participant in CTx until June 30th 2014, chose to exercise their commercialisation option on the PRMT5 inhibitors project developed by CTx. However, in June 2014, Epizyme (Boston) disclosed a series of potent and selective PRMT5 inhibitors that had significant structural similarity to the lead chemical series in the CRT UK licence. A new generation PRMT5 project was started in August 2014 after consideration by the Scientific Advisory Board and CTx CRC Ltd Board of Directors. An intensive effort through 2014 and 2015 delivered new chemical series and lead candidate molecules. There was heightened commercial interest in this target from early 2015 and by June 2015, in conjunction with CRT UK, advanced negotiations were proceeding with five companies. MSD (known as Merck & Co, Inc. in the USA and Canada) were chosen as the lead party and the resulting worldwide exclusive licensing deal was executed in January 2016.

In addition to the licensing deal, a $3 million research collaboration agreement to progress a stream of development work covering potential haemoglobinopathy (sickle cell and thalassemia) indications was also agreed between CTx and MSD.

The transfer of control of the PRMT5 program to MSD is now complete, and the inaugural meetings of the Joint Alliance Committee and the Joint Steering Committee were held on 19 March 2016. Merck now has a team of over 30 scientists working on the project and Ian Street (CSO) visited the MSD research group in Boston to meet the project team and facilitate technology transfer. Discussions around an additional oncology collaboration are now well advanced and specific proposals regarding the continued investigation of AML, myelodysplastic neoplasms, mantle cell lymphoma and the development of acquired resistance have been submitted to MSD. We anticipate that this additional collaboration agreement will be finalised early in the 2016-17 year, and this agreement will not only bring a further $2.7 million dollars in research funding to the CTx network but the research will make a significant contribution toward the rapid advancement of CTx PRMT5 inhibitors towards clinical studies.

As foreshadowed in the licensing negotiations, CTx filed six additional provisional composition of matter patent applications. These include 3 selection patents covering specific compounds in Series 3 and 4, and an additional 3 provisional applications covering new chemical series. The PCT applications on Series 3, 4 and 5 were published in late March.

Development of CTx Pipeline

The key recommendation from the May Pipeline Review meeting was to focus 90% of CTx resources on progressing 4 projects to lead optimization as fast as possible. Resources and key objectives have been set for each of the selected projects and progress will be reviewed at the annual retreat in December 2016. The four selected projects are below:

i) Tip60 (Hit Identification, MYST Family KAT, epigenetic and immune therapy target).

ii) MELK (Lead Generation, kinase, cancer stem cell target).

iii) WDR5 (Lead Generation, RP3 Target).

iv) STING (Hit Identification, immune therapy target).

Hit Identification

Again, the majority of CTx projects are in the Hit Identification or Discovery phase, to insure against the inevitable failure of some to progress. Current Hit Identification projects are summarised in the table below.

It should be noted that the projects MYCN, MLL, WDR5 and GCS are formally RP3 projects (New Drugs for Treating Paediatric Cancer), however, since all paediatric targets also have potential adult cancer indications, all Hit Discovery projects are listed together in the same table.

Table 1: Hit ID Projects (RP1 and RP3) 2015-16

Project	Target Biology	Target Cancers	End User	Project Status
PRMT1	Protein methylation, epigenetic regulation	Paediatric neuroblastoma,	Bionomics until Dec 2015 SYNthesis Research from Dec 2015	High Throughput screens of CTx, fragment and one additional library all complete. No novel chemical matter identified. On Hold as of May 2016.
PRMT4	Protein methylation	Colorectal cancer epigenetic regulation	SYNthesis Research	Tool compound supplied to a number of research groups to validate target, clearly define the biological rationale and determine most relevant clinical indication. Ongoing
MELK	Cancer stem cells	Triple Negative Breast Cancer (TNBC), Glioblastoma Multiforme	Bionomics	Benchmarking tool compound developed, novel series of inhibitors generated. Additional HTS commissioned to identify back-up series. Promoted to Lead Generation in May 2016.
MYCN	Tumour initiation, Maintenance of malignant phenotype	MYCN-amplified tumours, including Paediatric neuroblastoma, Small cell lung cancer	TBD	Primary screen in progress. Ongoing
MLL	Oncogenic MLL-fusion proteins	Mixed Lineage Leukaemias (paediatric and adult)	TBD	Primary screen completed. Hit validation in progress. Ongoing.
WDR5	Binding and activation of oncogenic MLL and MYCN proteins	Paediatric neuroblastoma, Mixed lineage leukaemias	TBD	Fragment and virtual screen completed, with identification of two independent chemical series suitable for further development. Promoted to Lead Generation, May 2016.

Project	Target Biology	Target Cancers	End User	Project Status
GCS	Overcoming glucocorticoid resistance	Glucocorticoid- resistant acute lymphoblastic leukaemia (ALL)	TBD	Investigating viability of prosecuting HTS campaign using patient derived cell line. Ongoing.
STING agonists	Stimulate type 1 interferon secretion in tumour microenvironment thereby promoting more robust response to approved checkpoint inhibitor therapies	Smoking-related lung cancer, UV exposure-associated melanoma Stomach cancer, Oesophageal cancer	TBD	Accepted as Hit Discovery Project, September 2015. Currently prosecuting both cell-based high throughput and SPR-based fragment screens to enable a chemistry program and promotion to Lead Generation. Ongoing
Tip60	Treatment of malignancies where tumour-associated T-reg suppression of the host immune system is evident	Lung, Breast, Ovarian & Pancreatic cancers	TBD	Accepted as Hit Discovery project, May 2016. HTS scheduled for Q3 2016. Limited medicinal chemistry to develop tool compounds and progress existing leads. Optimising in vitro proof of concept assay in T-reg cells. Ongoing.

Lead Generation

With the advent of checkpoint inhibitors and the increasing interest in immunological approaches to cancer treatment, the development and function of regulatory T cells (Tregs) has become of great interest. In cancer, Tregs can facilitate tumour progression by suppressing adaptive immunity against tumours and infiltration of Treg cells in many tumour types correlates with poor patient prognoses. Conversely, Treg cell depletion in tumour models demonstrates enhanced anti-tumour immune responses. It has been shown that acetylation of certain regulator proteins by the MYST family member, TIP60, is essential for Treg activity. Therefore, inhibition of TIP60 is proposed to lead to depletion in suppressive Treg cells, promoting increased anti-tumour immune responses. Consequently, the general MYST inhibitor program has been placed on hold, while efforts are focused on developing selective inhibitors of Tip60.

Two Hit Discovery projects, MELK and WDR5, were promoted to Lead Generation at the Pipeline Review Meeting in May 2016.

Table 2: Lead Generation Projects 2015-16

Project	Target Biology	Target Cancers	End user	Project Status
917ADC	Antibody drug conjugate using 917 as warhead	Multiple	TBD	Proof of concept studies *in vitro* with CTx917-Herceptin ADC were inconclusive. Project terminated December 2015.
MYST inhibitors	Epigenetic regulation	Haemopoietic (AML, infant ALL), multiple solid tumours	TBD	Identification of proliferation dependent myeloma and MLL cell lines. Potential biomarker strategy. On track for progression to Candidate Generation by 2016.

Project	Target Biology	Target Cancers	End user	Project Status
				General program terminated May 2016 to allow focus on Tip60 project.
MELK	Cancer stem cells	Triple Negative Breast Cancer (TNBC), Glioblastoma Multiforme	Bionomics	Promoted to Lead Generation in May 2016. Clinical development plan for TNBC being planned. Medicinal Chemistry ongoing.
WDR5	Binding and activation of oncogenic MLL and MYCN proteins	Paediatric neuroblastoma, Mixed lineage leukaemias	TBD	Accepted as Lead Generation project, May 2016. Two chemical series identified, additional HTS being conducted for back-up series. Pharmacological validation of biological rationale a high priority. Ongoing.

Candidate Generation (Lead Optimisation)

Our second Candidate Generation Project CTx-917 is a potent anti-mitotic molecule with a novel mechanism of action.

As such, we anticipate that this compound would not be susceptible to the alterations in tubulin that can render taxanes ineffective in the clinic, and work is ongoing to develop CTx-917 as an intravenous cytotoxic agent for treatment of taxane-resistant cancers (breast, lung, colorectal, ovarian and prostate). Very promising data has been shown in experiments with CTx-917 in treatment-resistant patient derived xenograft (PDX) models of lung and ovarian cancer. The Project team has been consolidated around late preclinical and clinical expertise, and the major challenge now is to find capital to enable IND-enabling studies and a Phase 1 trial in taxane-refractory patients to go ahead. An application has been submitted to the NCI Experimental Therapeutics (NExT) Program in the USA as a potential collaborative funder of the next phase of this project with an alternative funding route planned via the CRC-P funding mechanism.

Table 3: Candidate Generation Projects 2015-16

Project	Target Biology	Target Cancers	End User	Project Status
PRMT5 Next Generation Inhibitors	Epigenetic regulation	Mantle Cell Lymphoma Acute myeloid leukaemia (AML) Foetal Globin Regulation (non-cancer)	Wellcome Trust (Hb) CRT UK MSD (Merck in the USA and Canada)	Commercial discussions with several big Pharma, resulting in deal with MSD signed on 26 January. Research collaboration for haemoglobinopathy indication also signed in January, and discussions underway for Research collaboration in oncology indication.
CTx-917	LaminB1 binding	Taxane resistant cancers Breast/Prostate/ Colorectal/Ovarian/Lung	CTx1	Good results have been observed in a number of patient derived xenograft models, including a taxane-resistant models.

Project	Target Biology	Target Cancers	End User	Project Status
				Seeking funding and partnerships to support progression to the clinic. Ongoing.

Research Program 2: New Clinical Trial Designs for the Rapid Advancement of New Oncology Drugs

Program Leader: Mr Mark Sullivan (Medicines Development Ltd)

The objective of RP2 is to establish new, evidence-based preclinical and clinical models that enable efficient evaluation of treatments (alone and in novel combinations) to prevent metastatic spread and disease progression in both adults and children. The models will constitute a new regulatory framework (for example, as Food and Drug Administration (FDA) "Guidance for Industry") for product development, and will be constructed to enable prospective data collection for formal assessment of the clinical and economic benefits that arise from addressing these major gaps in cancer therapy. These trial models will allow more efficient development of new oncology treatments in two areas: screening and evaluation of treatments with the potential to affect metastatic spread; and paediatric development. This will enhance the early stage cancer clinical trial environment in Australia for local and international drug development.

The strategic approach of PR2 is to focus on two areas of drug development where new compounds are not efficiently developed or used:

- Drugs to prevent or limit the spread of metastatic cancers, and
- Paediatric dosing guidance for new, targeted molecular drugs.

Development of new drugs to prevent or limit the spread of metastatic cancers is hampered by the high cost and complexity of conducting clinical trials based on endpoints involving patient survival. Unlike cytotoxic drugs or immunotherapies where reduction of tumour burden may be evident within months, prevention of new metastases may not impact patient survival for many years. These long time frames are unattractive to drug developers, and this is evident in the lack of drugs being developed or registered to prevent or limit the spread of metastatic disease. The RP2 team have identified that the FDA Accelerated Access and Breakthrough Designation programs may provide faster and cheaper routes to registration for anti-metastatic drugs based on regulatory approval using surrogate endpoints. The RP2 program is now enacting a pre-competitive strategy of engaging with clinicians and scientists from academia, industry and regulatory agencies to identify and validate biomarkers and preclinical models as surrogate endpoints appropriate for approval of anti-metastatic agents.

In October 2015, Mark Sullivan (RP2 Leader- Medicines Development), Sally Kinrade (Medicines Development), and Warwick Tong (CTx) attended a metastasis workshop coordinated by Cancer Research Technology, UK (CRUK). This workshop included key stakeholders from CRUK, the United States National Cancer Institute (NCI), and academic institutions from across Europe. The workshop focussed on recent discoveries in metastasis biology that may provide targets for anti-metastatic agents. A summary of this meeting has been synthesised into a paper that has been accepted for publication in Nature Reviews Clinical Oncology.

In May 2015, the RP2 team presented a satellite symposium at the FDA-sponsored Accelerating Anticancer Drug Development and Validation (AAADV) conference. The group discussed the different regulatory and clinical hurdles for developing anti-metastatic drugs, and the discussions during this symposium were synthesised into a white paper where Accelerated and Breakthrough Designations were proposed as appropriate pathways for developing anti-metastatic agents.

At this year's AAADV 2016 conference, Mark Sullivan and Warwick Tong led a follow-up workshop entitled "Accelerating the Development of Drugs to Prevent Metastatic Progression". The FDAs Accelerated Approval and Breakthrough Designation programs were provided as an example of existing regulatory frameworks that could be utilised to increase the focus of drug developers on anti-metastatic agents. The workshop drew a broad range of participants, including cancer researchers and physicians, drug developers and regulatory agency representatives. Outcomes of this meeting included engagement and awareness raising with approximately 50 participants, including key

opinion leaders and a significant number of FDA officers, and informal feedback that the use of alternative regulatory pathways are an appropriate regulatory strategy for the development of anti-metastatic compounds.

Discussions during this workshop are being synthesised into an academic paper that reviews different routes to registration, factors missing to allow efficient clinical development of these agents, and ways to accelerate investment in anti-metastatic drug development.

Improving paediatric access to new molecular-targeted therapies is the second strategic focus of RP2. Despite contributing to significantly improved cure rates in the preceding decades, many conventional chemotherapies used to treat paediatric cancers have now reached a therapeutic plateau and new drugs are needed. The development of modern, targeted therapeutics specifically for children is hampered by limited commercial funds, time, patient numbers, and low levels of public and philanthropic funding. Many of the molecularly targeted drugs developed for adult cancers target similar molecular pathways as children's cancers, but the use of these drugs to treat childhood malignancies is often limited by the lack of safety and dosing guidance for paediatric populations. Dosing guidance for paediatrics is often not reliably generated during adult clinical development of new drugs. This neglect is largely driven by the small commercial rewards from the paediatric market in comparison to the high costs of expanding development and conducting paediatric trials.

The RP2 leaders have recently assembled a multi-disciplinary consortium including Monash University, Medicines Development, CTx and d3 Medicine to develop new *in silico* clinical pharmacology models of molecularly targeted cancer drugs based on the pharmacokinetic, safety and pharmacodynamic data acquired during clinical trials in adults. These models will be used to inform paediatric-dosing guidance of drugs already approved for adult cancers.

A white paper has been developed detailing the issues of paediatric drug dosing and the use of *in silico* modelling and allometric scaling to inform paediatric dosing guidance.

The consortium steering committee is scheduled to first meet in October 2016 to discuss the program scope, pilot project work plan, student involvement and resourcing.

Upcoming milestones for the RP2 project in 2017 include:

- Engagement with regulatory, industrial and clinical stakeholders at the AAADV2017 meeting in May 2017, and the formation of a pre-competitive working group to establish and promote the development anti-metastatic agents. The edict of this group is to develop and promote an FDA "Guidance for Industry" document that highlights 'approvable' clinical trial designs for anti-metastatic agents.
- Publication of review papers in the academic literature providing detailed case studies and frameworks for surrogate endpoints appropriate for registering anti-metastatic agents using Accelerated Approval pathways.
- Development and publication of a whitepaper highlighting the need for targeted molecular therapies in paediatric oncology and the use of in silico modelling and allometric scaling to inform paediatric dosing.
- Initiation of a pilot project by the paediatric dosing consortium to develop and validate a clinical pharmacology model of an already approved drug where improved paediatric dosing guidance could improve clinical practice.
- Enrolment of PhD students for 'industry ready' training in support of the anti-metastatic drug development and clinical pharmacology modelling and simulation programs.

Further activities aimed at building momentum for this change, through facilitating engagement with a broad range of stakeholders nationally and internationally, continue to be identified.

Research Program 3: New Drugs for Treating Paediatric Cancer & Tailored Treatment for Children with Cancer

Development of the Tailored Treatment Program remains on track for RP3 milestones, leveraging collaborative relationships at the Garvan Institute of Medical Research, the Murdoch Children's Research Institute (MCRI), the Peter MacCallum Cancer Centre, the NIH National Cancer Institute (USA), and more recently the German Cancer Research Centre (DKFZ), Heidelberg.

There were 27 patients enrolled in the TARGET study to develop the program platforms and pipelines (more than double the initial target for the feasibility study). The majority of these have undergone some degree of molecular profiling, *in vitro* screening, and patient derived xenografting (PDX). Notably, all acute lymphoblastic leukaemias (ALL) PDX have successfully engrafted, and completed drug efficacy studies, one of which resulted in recommendation of drug for alternative treatment to the treating clinician (work performed by CTx funded *in vivo* RA, Angela Xie).

The funding committed through the Lion's Kid's Cancer Genome Project (a partnership with the Garvan Institute of Medical Research) is allowing for a greater number of patients to undergo whole genome sequencing (WGS), with test cases being submitted to inform the build and optimisation of the WGS analysis and reporting pipeline.

The bioinformatic and curation pipeline development continues to progress. The CCI's CTx funded bioinformatician, embedded within Prof Papenfuss' WEHI/Peter Mac informatics lab continues to progress with work to integrate the multiple "'omic" data sets into the Path-OS analysis and curation software to allow for more streamlined reporting. The Cloud Instance of Path-OS has been opened up to the CCI molecular team, and regular curation meetings are taking place as required when TARGET patient analyses are completed and in need of review and sign off. We continue to work on fulfilling the critical need of highly skilled curation scientists and upskilling our existing workforce.

The *in vitro* single agent screening platform has been implemented with a standard customised personalised medicine library available for use on patient samples enrolled in the TARGET feasibility study. Optimisation of culturing conditions for tumour types is continuing, and an opportunity to collaborate on optimisation of culturing conditions for ALL has been identified in Europe and is being pursued.

Now that single agent *in vitro* drug screening has been established, work to develop high content imaging assays and In vitro screening for combination therapies is being initiated within the limitations of the technologies available.

The *in vivo* platforms, while challenging for solid tumours, are progressing well. We have successful models for ALL's and we have had early successes with engraftment across all tumour types.

Technical and logistical challenges including optimal sample size, sample collection, maintenance of sample integrity, shipping, receipt, and coordination of outsourced services have been studied, and learning outcomes are informing the development of site lab manuals in preparation for national roll out in 2017.

A review of the results obtained In mid-2016 from work undertaken on TARGET patients has shown that we have a 40% rate of detection of targetable genetic mutations, a high rate of engraftment success (~60%) for the patient derived xenografts (PDX), and successful *in vitro* drug screens in ~40%.

2.2 Education and Training

CTx continues its strong support of careers in drug discovery and translation at undergraduate, PhD, staff and end-user levels. CTx Medicinal Chemistry and Cancer Biology Project Leaders continue to provide on-the-job training for staff involved in drug discovery and development projects. Industry relevance and partnering opportunities are regularly tested at project reviews attended by highly respected national and international biotechnology industry experts.

The Education program, which expanded in 2012/13 to include the postdoctoral M2M on-the-job business intern program, is focussed on four groups essential to fostering the cancer drug development industry in Australia.

Undergraduates

CTx aims to attract top undergraduates to cancer related laboratory research, drug discovery and development by supporting students with scholarships to partake in a research project during their summer vacation. In 2015-16, CTx awarded eight summer vacation scholarships: four to students at the Peter MacCallum Cancer Centre and four to students at MIPS. Each scholarship of $1,000 generally goes to support the laboratory sponsoring the research, but can go directly to the student at the discretion of the supervisor.

In 2016, all eight of the summer scholarship students commenced Honours studies.

Honours Students

CTx supported 7 students who had completed Honours in 2015 to attend the 28th Lorne Cancer Conference from 11 – 13 February 2016. The students, who came from Queensland (Griffith University), NSW (Children's Cancer Institute), and Victoria (Monash Institute of Pharmaceutical Sciences and the Peter MacCallum Cancer Centre) presented posters of their research, and met with the CTx CEO, CSO, and Scientific Directors. In addition, the students attended a Mentoring Breakfast with several conference speakers to learn about and discuss their fields of interest, tips for developing their careers and future opportunities.

Masters Program

In collaboration with the Victorian Comprehensive Cancer Centre, CTx has formed a working group to design a module for a new Masters of Cancer Sciences course being proposed by University of Melbourne. The University has delayed development of the course, however, the scope of the module had been determined already and planning continues.

PhD students

CTx postgraduates are supported in their PhD training as either CTx Top up Scholarship or CTx Affiliate Students. Both postgraduate schemes support students to complete research related to cancer drug discovery and development and equip them with additional non-research skills to facilitate their employment in cancer-related fields.

CTx PhD Top Up scholarship are awarded to existing students for up to three years, with the bulk of the funding going directly to the student and an additional amount of $3,000 going to supervisor(s) as a grant to support the student in travel to conferences or to help defray costs of the student's project.

In addition, CTx is committed to providing opportunities for clinicians to develop and sustain a career in cancer research, and have a instituted a new award for Clinician Researcher PhD students. This scholarship is awarded for a maximum of three years, with a total value of $20,000 per annum. Of this, $17,000 will be awarded to the student and $3,000 will be awarded to the supervisor(s) as a grant to support the student in conference travel or to defray costs of the student's project.

During 2015-16:

13 scientific and 7 clinician scientist PhD students were awarded CTx Top Up scholarships for projects relevant to Research Program 1.

2 clinician scientist PhD students were awarded CTx Top Up scholarships for projects relevant to Research Program 3.

To date, CTx has supported 40 students conducting research projects in all areas of drug discovery from early target validation through to translational clinical research. By 30 June 2016, five of these students had completed their PhD theses, although as yet none have graduated.

The choice and direction of student projects are carefully considered and monitored to avoid any potential conflicts with third parties, and students are not directly involved in commercially-sensitive projects since this could compromise their ability to present and publish their work. Projects are closely aligned with CTx research and in many cases add vital information to the science underlying CTx projects or tackle universal problems in translational research.

A full list of Top Up PhD students can be found in Appendix 2. Supervisors of these students include 23 University staff members and 9 non-University staff members. Five CTx2 Top-up Scholarship holders have submitted their thesis, however none have graduated as yet.

In addition, CTx mentors 53 Affiliate PhD students, who are enrolled with our Participants and are eligible for skills development programs and competitive travel scholarships to allow presentation of their research at overseas conferences and laboratories. Affiliates are also able to participate in the annual CTx Higher Degree Research Symposium. In 2015-16, six travel scholarships were awarded to Affiliate students to support their attendance at prestigious overseas conferences and visits to laboratories of key leaders in their field.

Finally, CTx provided financial support to the Student-led 10th Annual Postgraduate Research Symposium at the Monash Institute of Pharmaceutical Sciences, Parkville, in November 2015.

Postdoctoral fellows

CTx uses a number of approaches to build commercial awareness for early career researchers through on-the-job training and mentoring in translation and commercialisation of biomedical advances.

Three post-doctoral fellows from Participant Organisations were selected, in a competitive process, to attend the Oncology Drug Design in Practice course in Amsterdam from 25 – 27 November 2015. This 3-day educational program teaches knowledge and skills needed by professionals in oncology drug development working in the corporate or the academic setting. Oncology drug development is different from drug development in other therapeutic areas and the specific features of the preclinical and clinical development of new therapeutic agents for the treatment of cancer were addressed during the course. In addition to the complete development process, from preclinical development, through early-phase and late-phase clinical development, to post-registration clinical studies, the course also addressed the essentials of tumour biology, medical oncology, haemoncology, tumour immunology and immunotherapy as well as biostatical and regulatory issues in the development of cancer therapeutics.

A former CTx Top Up PhD student and now a postdoctoral fellow at MIPS, Dr Caroline Le, was nominated by CTx and FAL Lawyers for the Australian American Leadership Dialogue (AALD). This prestigious two-year program brings promising young leaders together to engage on issues that concern today's youth and future generations. The program includes attendance at discussion forums and events held in Australia and the US. Caroline was accepted into the program, and will represent Australia at the Young Leadership Dialogue (YLD) in Washington DC in July this year.

Professional Development

CTx continues to support the development of its staff by providing in-house tailored training, or by supporting staff attendance at relevant workshops, courses, programs, and conferences nationally and internationally.

A postdoctoral member of the CTx medicinal chemistry team at MIPS was supported to attend the Merck Women in Chemistry Symposium in Boston, MA and the SciFinder Future Leaders in Chemistry Program, Columbus, OH, USA, both in August 2015.

To support the expansion of Project Management capabilities within CTx, eight staff members from CTx Participants attended a two-day tailored Project Management Course on 8-9 April 2016 in Melbourne. Providing they submit their follow up assessment work, due Q3 2016, these staff will be accredited as Australian Institute of Project Management Certified Practising Project Practitioners.

Four members of CTx management attended the APMG Change Management Foundation Course in Melbourne from 7–9 June 2016, with all four successfully passing the Change Management Foundation Exam.

In addition, 30 CTx staff attended the following national and international conferences:

- Australian High Content Screening and RNAi Meeting, July 2015, Melbourne, Victoria
- Queensland EMT Symposium, 16 Oct 2015, Brisbane, Queensland
- TEMTIA-VII conference, October 2015, Melbourne, Victoria
- Brisbane Breast Cancer Research Workshop, November 2015, Brisbane, Queensland
- VCCC-TransBCR Breast Cancer Symposium, November 2015, Melbourne, Victoria
- Tow Research Day, November 2015, Prince of Wales Hospital, Sydney, NSW
- 28th Lorne Cancer Conference, February 2016, Lorne, Victoria
- Advances in Neuroblastoma Research Congress, June 2016, Cairns, Queensland.
- RICT 2015 - Drug Discovery and Selection: Understanding Targets and Mechanisms, 1 – 3 July 2015, Avignon, France
- 18th SCI/RSC Medicinal Chemistry Symposium, 13-16 September 2015, Cambridge, United Kingdom
- European Cancer Congress 2015, 25–29 September 2015, Vienna, Austria
- Cancer Research Technology & CRUK CDD Metastasis Workshop, 19 October 2015, London, UK
- ARMS 2015, Research Management in a Global Context, 1-2 October 2015, Singapore
- JP Morgan 34th Annual Healthcare Conference, 11-14 January 2016, San Francisco, CA, USA
- AACR Annual Meeting, 16–20 April 2016, New Orleans, USA
- FDA's AAADV Workshop, 4-6 May 2016, Bethesda, Maryland, USA
- 3D Models & Drug Screening Conference, 11-12 May 2016, Berlin, Germany
- 2016 BIO International Convention, 6-9 June 2016, San Fancisco, CA, USA

Finally, CTx sponsored training and interactions with industry at the following conferences:

- Australian High Content Screening and RNAi Meeting, July 2015, Melbourne, Victoria
- Cancer Research Technology & CRUK CDD Metastasis Workshop, 19 October 2015, London, UK
- Advances in Neuroblastoma Research Congress (ANR 2016), 19 – 23 June 2016, at the Cairns Convention Centre.

3 Results

3.1 Utilisation and commercialisation

Status/current performance of existing spin off companies

CTx1 is the current spin off / commercialisation company for the Cancer Therapeutics CRC. Under the current Participants agreement, CTx1 is already appointed as a nominated commercialisation agent for the CRC and discussions with potential funding bodies and investors have already commenced. CTx1 holds the rights to the PRMT5 technology that was ultimately licensed to MSD. Significant up-front fees have been received by the CRC as a result of this transaction and these funds have been made available and/or distributed to the relevant CRC Participants. Pleasingly, the majority of the current CRC Participants have chosen to re-invest this financial return back into core CTx Activities.

3.2 Intellectual Property Management

Due to the long and risky development path of any human therapeutic medicine, particularly new cancer drugs, extensive and expert intellectual property (IP) protection is essential to successful commercialisation and development to the human healthcare market.

At the CRC, a framework of legal agreements covering IP gives the Cancer Therapeutics CRC the required rights for commercialisation.

The terms of the Background IP License agreements have been pre-approved via inclusion in the Participants agreement as Schedule 4 and this ensures that any additional Background Licenses that may be required are easily obtained.

The CRC also prepares and executes Commercialisation License Agreements as required once Projects mature to a commercially relevant stage. These grant the CRC's commercialisation partners the rights to commercialise project IP and associated background IP rights.

The substantive terms of the above two agreements were included in the Participants Agreement and this lowers the administrative effort required to ensure that the CRC can access the rights it requires in order allow for the commercialisation of CRC Projects.

The CRC owns the rights to the relevant Project IP generated from each approved Project, and has the authority to file and prosecute patent applications emerging from these projects and to assign each application from the inventor/employee, through their employers (the Project Participants) to the CRC confirming ownership, either through CTxT Pty Ltd, the trustee for both trusts, or CTx1 as the case may be, as the owner of the IP.

3.3 Communications

CTx's main stakeholders are the pharmaceutical and biotechnology industry, our research partners and workforce, and the Australian Federal and State governments.

External Communications

CTx's external communication strategy, though modest, has been devised to enlist partnering and licensing opportunities, attract promising small-molecule drug targets, and to promote Australia's innovative research, capabilities and facilities.

Conferences, Publications and Presentations

CTx is at the forefront of driving greater awareness of new approaches to finding cures for cancers. Key Presentations and submissions, backed by robust cience, in national and international arenas such as AAADV and AACR are elevating CTx's profile as a centre of excellence and leader in Metastasis and novel cancer drug development. In 2015/16, these included the following

- Cancer Research Technology and the CRUK Centre for Drug Development Metastasis Workshop, 19 October 2015, London, UK

- "Accelerating the Development of Drugs to Prevent Metastatic Progression". Satellite symposium as part of the US FDA's Accelerating Anti-Cancer Agent Development and Validation (AAADV) Workshop in Bethesda, Maryland, USA, May 2016
- AACR Annual Meeting, 16 – 20 April 2016, New Orleans, USA

A full list of publications and presentations is available in Appendix 1.

Sponsorship

The 2015/16 sponsorship program included support for the following conferences:

- Australian High Content Screening and RNAi Meeting, July 2015, Melbourne, Victoria
- Cancer Research Technology and the CRUK Centre for Drug Development Metastasis Workshop, 19 October 2015, London, UK
- Advances in Neuroblastoma Research Congress (ANR 2016), 19-23 June 2016, Cairns Convention Centre, Cairns, Australia.

Internal Communications

CTx Participants are kept up to date through various means including face-to-face interaction, emailed newsletters, tweets, regular research updates and event and industry information.

During 2015/16, CTx produced newsletters and regular email updates to keep staff, Participant representatives and students informed about events and CTx progress.

In support of its education programs, CTx reported on its training options to Participant undergraduates, PhD students, postdoctoral fellows, Participants and staff.

CTx continues to help PhD students develop their skills in oral and written communication, poster presentations, articulation of research capability and job readiness.

CTx continues to hold regular meetings for Research Projects, Staff, the CTx Operational Group, Project Management Group and Participants as well as two six-monthly Full Project Reviews, one of which coincides with the annual retreat.

4 Resources

4.1 Governance

CTx is governed by an independent skill-based Board and led by a highly experienced management team. This collaborative research and business model allows innovative approaches to drug discovery as well as commercialisation of the research pipeline.

Management Structure

A new company, CTx CRC Ltd (CTx2) was constituted in in April 2014 to be the managing entity for the CRC from 1 July 2014 (CRC2). CTx2 is limited by guarantee and was granted Not For Profit and Charitable Status in March 2015.

The managing company for the previous funding period (up to 30 June 2014, CRC1) was Cancer Therapeutics CRC Pty Ltd (CTx1). This company was maintained as a commercialising entity for future CRC assets and subsequently became an Essential Participant in the CRC.

In addition, CTxT Pty Ltd was created as the legal owner and trustee for intellectual property and two trusts were created to hold the intellectual property from the two partnerships associated with the two funding periods.

In addition to the Participants Agreement and Commonwealth Agreement the following agreements have been executed:

- Deed of Transition and Ratification of Trust 2007 (July 2014)
- Trust Deed – Trust 2014 (July 2014)
- Management Deed between CTx2 and CTx1 (July 2014)
- CRC Programme Deed of Variation (DoV), June 2015)
- CRC Programme DoV (May 2016)

The Transition Deed ensures protection for the beneficial interest in IP for Participants in the original partnership with the Trust Deed ensuring similar protection for the new partnership.

The Management Deed allows CTx1 to commercialise intellectual property under direction of the CTx2 Board.

The June 2015 DoV recognised changes in both the Commonwealth Funding and the CRC budget in addition to a change in the Participant list.

The May 2016 DoV recognised the renaming of the Department as well as changes in both the Commonwealth Funding and the CRC budget.

Board

Board Members

Dr Tony Evans *PhD, MAICD* - Board Chair (Independent)

Key skills: Specialist in managing collaborative research and industry drug development.

Dr Evans has also been a director of Biolayer Corporation, Neurodiscovery, Coridon, Dendright, Promics, Q-Pharm and Spinifex. From 1988 to 1997 he worked in California, USA at Genentech then Onyx Pharmaceuticals. On returning to Australia, he was appointed CEO and director of the CRC for Diagnostic Technologies and later, CEO and director of Xenome. From 2008 to October 2011, he was CEO of Cancer Therapeutics CRC. Dr Evans holds a BSc from the University of Sheffield, UK, a PhD from the Australian National University, and was Queen Elizabeth II Research Fellow in the Heidelberg Department of Medicine, Victoria, Alberta Heritage Post Doctoral Research Fellow at the University of Calgary and a Post Doctoral Research Fellow at The University of North Carolina.

Dr Warwick Tong MB, ChB, MPP, GAICD - CEO

Key skills: Senior leadership in medical, clinical, commercial and business development in the pharmaceutical and biotechnology sectors

From 2005 to 2011, Dr Tong was SVP, Development, for Surface Logix Inc, Boston USA. Previously he held positions of increasing seniority at GlaxoSmithKline (GSK), including country, regional and global roles as Medical Director, Business Development Director and VP Commercial Strategy for Infectious Disease. Before his pharmaceutical industry career, Dr Tong worked in primary care medicine for 14 years, founding two medical clinics in New Zealand. He graduated as Senior Scholar in Medicine from Auckland University, New Zealand and has a postgraduate qualification in Public Policy from Victoria University, Wellington New Zealand.

Dr George Morstyn MB, BS, BMedSci, PhD, FRACP, MAICD - Director (Independent)

Key skills: Specialist in translational and clinical oncology

Dr Morstyn has extensive experience in drug development and biotechnology. He was head of the clinical program at the Ludwig Institute for Cancer Research in Melbourne and Principal Investigator on the earliest clinical studies of haemopoietic growth factors. He is Chair of the Investment Advisory Committee of GBS Bioventures, Chair of BioMedVic, board member and chair of the scientific advisory board of Symbio (Japan), board member of ANZBCTG. He is a member of the commercialisation committee at the Walter and Eliza Hall Institute and Deputy Chair of the Health Forum of the ATSE.

Dr Deborah Rathjen PhD, FTSE, MAICD - Director (Participant)

CEO - Bionomics

Key skills: End user and specialist in research, business development and licensing.

A seasoned biotech executive for almost 20 years, Dr Rathjen joined Bionomics in June 2000 from Peptech Limited, where she was Manager of Business Development and Licensing. Dr Rathjen was a co-inventor of Peptech's TNF technology and leader of the company's successful defence of its key TNF patents against a legal challenge by BASF, providing Peptech with a strong commercial basis for licensing negotiations with BASF, Centocor and other companies with anti-TNF products. Dr Rathjen has significant experience in research, business development and licensing. In 2004 Dr Rathjen was awarded the AusBiotech President's Medal for her significant contribution to the Australian biotechnology industry, in 2006 she received a Distinguished Alumni Award from Flinders University, in 2009 the BioSingapore Asia Pacific Woman Entrepreneur of the Year, and in 2010 the Bio Innovation SA Industry Leader Award.

A/Professor Nicholas Gough PhD, FTSE, MAICD - Director (Independent)

Key Skills: Biomedical research, cancer biology, biotechnology industry, CRC Programme

Dr Gough is the inventor of technologies underpinning a number of biopharmaceuticals and biotechnology products, including GM-CSF (sargramostim), one of the first pharmaceuticals based on Australian science and IP, Mavrilimumab, under development by AstraZeneca for rheumatoid arthritis, and ESGRO™ used for the maintenance of embryonic stem cells. Nick is Associate Professor (Honorary) in the Department of Medicine, University of Melbourne and Chair of the Research Advisory Committee Wound Management Innovation CRC. Key past appointments include: Head, Molecular Haematology Laboratory The Walter and Eliza Hall Institute of Medical Research; Research Director AMRAD Corporation Limited; CEO Cerylid Biosciences Limited; CEO Cooperative Research Centre for Genes for Common Human Diseases; Director, Molecular and Genomic Discovery ES Cell International Pte Ltd (Singapore); Chair, Scientific Advisory Board Innovative Dairy Products CRC; Chair, Scientific Advisory Board LactoPharma (New Zealand).

Dr Ian McDonald PhD - Director (Independent)

Medicinal chemistry consultant

Key skills: Medicinal chemist, specialist in managing drug discovery and design teams

Ian has more than 25 years international experience in managing drug discovery and design teams in Europe and USA. He was most recently Chief Scientific Officer at Pharmaxis Ltd. Prior positions held include Vice President of Drug Discovery at Structural GenomiX, USA, Vice President of Chemistry at Structural Bioinformatics, with responsibilities for medicinal and biochemistry at SIBIA Neuroscience (now part of Merck Research Laboratories) and Merrell Dow (now part of Sanofi-Aventis). Under his leadership, six compounds have been developed and evaluated in clinical trials. Dr McDonald has BSc and PhD degrees in chemistry from the University of Western Australia, has co-authored 78 peer-reviewed manuscripts and book chapters, and is an inventor on 43 issued US patents.

Dr McDonald resigned from the CTx2 Board effective 30 November 2015.

Dr Katherine Woodthorpe - Director (Independent)

Key Skills: Specialist in private equity, innovation, media and government relations

Dr Katherine Woodthorpe is an experienced non-exec Director, serving on boards ranging from ASX listed companies to research institutions and government entities for over 17 years. She currently serves on six boards as well as an adviser to others and as a Council member of the AICD. She was the Chief Executive of AVCAL, the Australian Private Equity and Venture Capital Association for seven years. Prior to AVCAL, she held a broad range of management and board positions, in Australia and overseas. Katherine has a long experience, expertise and track record in public affairs including media and government relations. Katherine has deep knowledge of the private equity industry and the superannuation industry in the financial sector and a strong track record in a broad range of technology orientated industries including mining and healthcare. She has been cited in various media as one of Australia's most influential people in innovation and has a track record for commercialisation.

Dr Woodthorpe resigned from the CTx Board, effective 30 June 2016

Table 4: Board Attendance 2015-16

	2015			2016	
Board Member	**August**	**October**	**December**	**February**	**April**
Dr Tony Evans	✖	✔	✔	✔	✔
Dr Warwick Tong	✔	✔	✔	✔	✔
Dr Ian McDonald	✔	✔	Resigned 30 November 2015		
Dr George Morstyn	✔	✔	✔	✔	✔
Dr Deborah Rathjen	✔	✔	✔	✖	✔
A/Prof Nicholas Gough	✔	✔	✔	✔	✔
Dr Katherine Woodthorpe	✖	✔	✔	✔	✔

Committees

Audit and Risk Committee

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

The Audit and Risk Committee met three times during the reporting period.

Table 5: CTx Audit and Risk Committee 2015-16

Name	**Role**	**Key skills**	**Organisation**
Dr Deborah Rathjen	Chair	Expertise in research, business development and licensing	Bionomics
Dr Tony Evans	Board Chair	Expertise in managing collaborative research and industry drug development	Independent
A/Prof Nicholas Gough	To represent the Board	Expertise in research, business development and licensing	Independent
Ms Verity McDonald	Company Secretary / Finance Manager (Invitee)	Ensuring the Company's compliance in respect of all corporate governance matters. Day to day and long term financial management of the Company	CTx
Dr Warwick Tong	To represent Management (Invitee)	CEO. Expertise in managing collaborative research and industry drug development	CTx

Scientific Advisory Board

The CTx Scientific Advisory Board (SAB) oversees, consults and reviews all project activities.

The SAB meets face to face twice yearly, at the mid-year Pipeline Review and at the December Retreat.

Table 6: CTx Scientific Advisory Board 2015-16

Name	**Role**	**Key skills**	**Organisation**
Professor Grant McArthur (Chair)	Head, Translational Research & Head, Molecular Oncology	Translational and clinical oncology	PMCC
Professor Sue Charman	Professor, Pharmaceutics & Director, Centre for Drug Candidate Optimisation	Drug Metabolism and Pharmacokinetics	MIPS

Dr Ashley Dunn	Consultant	Specialist in cancer biology	Independent
Sir Simon Campbell	Ex SVP, Drug Discovery, Pfizer	Medicinal chemistry, drug discovery	Independent
Dr Bill Denny	Director, Auckland Cancer Society R&D Laboratories	Medicinal chemistry, drug discovery	Independent
Dr Donald Ogilvie	Head of Cancer Research UK Drug Discovery Unit, Paterson Institute	Biochemistry, cancer drug discovery and early clinical development	Independent

CTx Operational Group

The CTx Operational Group (COG) includes CTx management, Project Leaders, and key leaders of the platforms required for all phases of drug discovery, from hit discovery through lead generation to candidate generation.

The COG met 8 times during the reporting period.

Table 7: CTx Operational Group 2015-16

Name	Role	Organisation
Mr Paul Reeve (Chair)	Director, Operations	CTx
Dr Warwick Tong	CEO	CTx
Dr Ian Street	CSO	CTx
Dr Cathy Drinkwater	Director, Research and Education	CTx
Ms Verity McDonald	Company Secretary / Finance Manager	CTx
Mr Michael Vovos	Contracts and IP Manager	CTx
Ms Rebecca Moss (from 18 Jan 2016)	Manager, Research Technologies	CTx
Dr Rhiannon Jones (from 24 April 2016)	Manager, Operations	CTx
Dr Gabriel Kremmidiotis (until Sep 2015)	VP, Cancer Biology	Bionomics
Dr Tina Lavranos (from Sep 2015)	Director of Cancer Research	Bionomics
Dr Andrew Harvey (until Feb 2016)	VP, Medicinal Chemistry	Bionomics
Dr Tom Peat	Protein Production & Structural Biology	CSIRO
Dr Brendon Monahan	Director, Discovery Biology	WEHI
Dr Vicky Avery	High Throughput Screening	GU
Dr Graeme Stevenson	Director, Computational Chemistry	GU / CTx
Prof Sue Charman	Drug Metabolism and Pharmacokinetics (DMPK)	MIPS
Dr Robin Anderson	Translational Biology	PMCC
Dr Mark Devlin	Director, Translational Biology	PMCC
Dr Paul Stupple	Director, Medicinal Chemistry	MIPS
Dr Hendrik Falk	Director, Discovery Technologies	WEHI

Education Advisory Committee

Representatives from the majority of CTx Research and University Participants are on the CTx Education Advisory Committee.

The committee aids in coordination of the CTx Education Program and provides valuable advice on career development strategies and activities for undergraduate and post-graduate students, post-doctoral researchers, staff and end users.

The Education Committee met 6 times in 2015-16 (Aug, Oct, Dec, Jan, Apr, Jun) plus one meeting where quorum was not achieved (March 2016).

Table 8: CTx Education Advisory Committee 2015-16

Name	Org	Role
Dr Cathy Drinkwater (Chair)	CTx	Director, Research and Education
Dr Ian Street	CTx	CSO and advisor to the committee
Dr Graeme Stevenson (until Sep 2015)	GU	Medicinal Chemistry Group Leader
Ms Angela Hillsdon (from Sep 2015)	GU	Administrative Assistant
Dr Sumone Chakravarti (until 16 October 2015)	VCCC	Project Manager Education
Dr Andrew Harvey (until Feb 2016)	Bionomics	Vice President Drug Discovery
Dr Annabell Leske (Feb – Apr 2016)	Bionomics	Research Associate Drug Development
Dr Amanda Philp	CCI	Careers and Strategy Manager
Dr Timothy Adams	CSIRO	Research Program Leader (Biosciences)
Dr Colin Pouton	MIPS	Head of Pharmaceutical Biology, Co-theme leader, Medicinal Chemistry and Drug Action
Dr Karen McConalogue	MIPS	Manager, Research Programs
Dr Caroline Owen	PMCC	Education & Communication Coordinator (Research)
Dr Keely Bumsted-O'Brien	WEHI	Scientific Education Officer

Key Staff

Changes to CTx Management:

- Dr Graeme Stevenson left Griffith University on 31 August 2015, and was appointed directly to CTx in his role as Director, Computational Chemistry from 1 September 2015.
- Ms Rebecca Moss was appointed by CTx as Manager, Research Technologies, on 18 January 2016.
- Dr Rhiannon Jones was appointed by CTx as Manager, Operations on 24 April 2016.

Table 9: CTx Management 2015-16

Name	Org	CRC Position / Role	Time
Dr Warwick Tong	CTx	CEO	100%
Dr Ian Street	CTx	CSO	80%
Ms Verity McDonald	CTx	Company Secretary / Finance Manager	100%
Mr Michael Vovos	CTx	Contracts and IP Manager	40%
Dr Cathy Drinkwater	CTx	Director, Research and Education	100%

Name	Org	CRC Position / Role	Time
Mr Paul Reeve	CTx	Director, Operations	100%
Dr Paul Stupple	WEHI	Director, Medicinal Chemistry	100%
Dr Hendrik Falk	WEHI	Director, Discovery Technologies	100%
Dr Brendon Monahan	WEHI	Director, Discovery Biology	100%
Dr Mark Devlin	PMCC	Director, Translational Biology	100%
Dr Graeme Stevenson	GU CTx	Director, Computational Chemistry	100%
Ms Rebecca Moss	CTx	Manager, Research Technologies	80%
Dr Rhiannon Jones	CTx	Manager, Operations	40%

4.2 Participants

All CTx Participants are Essential. There were no changes during the reporting period.

Table 10: Essential Participants in CTx

Participant Name	ABN or ACN	Organisation Type	Role
Bionomics Limited	53 075 582 740	Industry/ Private Sector/ SME	End User & Research Provider
Cancer Council Victoria	61 426 486 715	Other	Research Provider
CTx1 (Cancer Therapeutics CRC Pty Ltd)	69 125 693 003	Other	End User
Cancer Trials Australia	21 105 748 605	Other	Research Provider
Children's Cancer Institute	41 072 279 559	Other	Research Provider
Clinical Genomics Pty Ltd	88 119 063 222	Industry/ Private Sector/ SME	End User & Research Provider
CSIRO	41 687 119 230	Australian Government	Research Provider
Griffith University	78 106 094 461	University	Research Provider
INCResearch Australia Pty Ltd	67 080 425 387	Other	Research Provider
Medicines Development Limited	79 116 977 523	Other	Research Provider
Melbourne Health	73 802 706 972	State Government (Victoria)	Research Provider
Monash University	12 377 614 012	University	Research Provider
National Cancer Centre Singapore	N/A	International Research Institute	Research Provider
Peter MacCallum Cancer Centre	42 100 504 883	Other/Research Institute	Research Provider
SYNthesis Research Ltd	28 159 666 314	Industry/ Private Sector/ SME	End User & Research Provider
Victorian Comprehensive Cancer Centre Limited	84 140 233 790	Other/ Research Institute	Research Provider
Walter & Eliza Hall Institute of Medical Research	12 004 251 423	Other/ Research Institute	Research Provider

4.3 Collaboration

Collaborations between Participants

CTx depends heavily on collaboration between its Participants, with all projects involving collaborations of five or more organisations. Each CTx cancer drug discovery and development project requires a number of Participants to work together in every phase - Hit Generation, Lead

Generation and Candidate Generation. The nature of these projects necessitates broad ranging and varied skills and expertise. They include high throughput screening, protein production, X-ray crystallography, animal modelling, DMPK, medicinal chemistry and clinical translational expertise. To move any project forward, individual CTx Participants come together to provide the many different scientific skills required.

The Education Program is also organised and executed by a group of Participant representatives.

Collaborations between Researcher and End User Participants

CTx works extensively with its end user Participants to guide drug discovery projects since they ultimately determine the success to market of all projects. SYNthesis Research and Bionomics Ltd. are both extensively involved in project selection and management as well as project commercialisation. Each has a representative on CTx's Pipeline Review Committee, which is critical in portfolio review, project selection and project management.

In 2015/16 examples of specific collaborations included:

- Joint research between CTx and Bionomics on the MELK project.
- Collaboration between CTx and CRT UK on PRMT5 haemoglobinopathy project supported by Wellcome Trust Seeding Drug Discovery Grant.

Collaborations between End User Participants and the Market

CTx's end user Participants are networked into the wider biotechnology and pharmaceutical community. Bionomics' arrangements include collaborations with major pharmaceutical companies and licenses to large biotechnology companies.

External Linkages

In 2015/16 examples of specific collaborations between CTx and non-CTx research groups included:

- Joint research between CTx and groups led by Professor Stephen Jane and Dr David Curtis at the Australian Centre for Blood Diseases & the Alfred Hospital (Monash Health) and Professor Annemarie Hennessy (University of Western Sydney) and Dr Suzanne Pears (Sydney Local Health District) on various aspects of PRMT5 biology.
- Joint research between CTx and groups led by Professor Tony Burgess, Dr Guillaume Lessene, Dr Marie-Liesse Asselin-Labat and Dr Clare Scott at WEHI on the effects of CTx-917 in animal models of colorectal, lung and taxane-resistant cancers.
- Joint research between CTx and Drs David Segal, Tim Thomas and Anne Voss at WEHI, Drs Ygal Haupt, Lloyd Pereira and Amardeep Dhillon at Peter MacCallum Cancer Centre, Professor Jonathan Baell at MIPS and Dr Mark Guthridge at the Alfred Hospital (Monash Health) on the effects of MOZ family inhibitors in cancer stem cells and cell lines.
- Joint research between CTx and Dr Jack Ryan at CSIRO on the selection and supply of fragments and analogues from the CSIRO library for the WDR5 and MOZ projects.
- Joint research between CTx and Professor Ricky Johnstone at the Peter MacCallum Cancer Centre on biological assays of the WDR5 benchmark molecule
- Joint research between CTx and Dr Tao Liu at the Children's Cancer Institute, Sydney on biological discovery for the WDR5 project
- Joint research between CTx and Dr Martin Scanlon at Monash Institute of Pharmaceutical Sciences on the development and execution of fragment library screens for multiple CTx projects, including WDR5, PRMT1 and PRMT4

Cancer Research Technologies (CRT)

CTx still maintains strong links with CRT, over and above the existing commercial ties. In October 2015, CTx worked closely with CRT and the CRUK Centre for Drug Development to hold a workshop to discuss the complexities and opportunities within anti-metastatic drug development. The workshop was chaired by Dr Pat Steeg (US National Cancer Institute) and Dr Rob Jones (Glasgow University), and included national and international experts from industry, academia and regulatory sectors. Discussions covered topics ranging from discovery science, preclinical model systems and biomarker development, through to clinical trial and regulatory strategies, and potential pathways to market.

MSD (known as Merck & Co, Inc. in the USA and Canada)

In addition to the Licensing deal mentioned earlier in this Report, two research collaboration agreements covering work on

- Potential haemoglobinopathy indications (worth approximately $3 million)
- Biomarker analysis of PRMT5i treated cells (worth approximately $200,000)

were agreed between CTx and MSD.

The transfer of the PRMT5 program to MSD is now complete, and the inaugural meetings of the Joint Alliance Committee and the Joint Steering Committee were held on 19 March 2016. Merck now has a team of over 30 scientists working on the project and the CTx CSO, Ian Street, has visited the MSD laboratories in Boston to meet the project team and facilitate technology transfer.

Moreover, discussions around an adjunct oncology collaboration are now well advanced and specific proposals covering the continued investigation of AML, myelodysplastic neoplasms, mantle cell lymphoma and the development of acquired resistance have been submitted to MSD. We anticipate that this collaboration agreement will be finalised in the near future, bringing not only a further $2.7 million dollars in research funding to CTx, but also contributing towards the rapid translation of CTx PRMT5 inhibitors into the clinic.

EMPathy BCN

The EMPathy Breast Cancer Network (EMPathy BCN) is a national collaboration of scientists, surgeons, medical oncologists and a consumer advocate investigating the role of epithelial mesenchymal plasticity (EMP) in breast cancer.

EMPathy is funded by the National Breast Cancer Foundation and involves personnel from the following research institutes

- St. Vincent's Institute of Medical Research (Lead Institute)
- Baker IDI Heart and Diabetes Institute
- Centre for Cancer Biology, University of Adelaide
- Griffith University
- Institute of Molecular Bioscience & Diamantina Institute, University of Queensland
- Monash University
- Murdoch Children's Research Institute
- Peter MacCallum Cancer Centre
- St. Vincent's Hospital
- University of Melbourne

- University of Newcastle
- University of Sydney
- University of Western Australia
- Walter & Eliza Hall Institute of Medical Research

The primary goal of EMPathy BCN is to develop therapeutics targeting breast cancer recurrence; in particular agents targeting EMP. Important secondary goals are the development of improved diagnostics that predict response to therapy and likelihood of recurrence.

CTx is the preferred commercialisation partner for the EMPathy Collaboration and as such has been granted a first option to review and license any new discoveries/cancer targets for the purpose of discovering and developing new treatments for breast cancer.

5 Glossary of terms

AAADV	Accelerating Anti-Cancer Agent Development and Validation
AACR	American Association for Cancer Research
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
BCN	Breast Cancer Network
BIP	Background Intellectual Property
CCI	Children's Cancer Institute
CCV	Cancer Council Victoria
CDCO	Centre for Drug Candidate Optimisation
CLA	Commercialisation Licence Agreement
COG	CTx Operational Group
CRC	Cooperative Research Centre
CRC1	2007 – 2014 Participant Membership
CRC2	2014 – 2020 Participant Membership
CRT	Cancer Research Technology Ltd
CRUK	Cancer Research UK
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CSO	Chief Scientific Officer
CTx	Cancer Therapeutics CRC
CTx1	Cancer Therapeutics CRC Pty Ltd (Commercialisation Company)
CTx2	CTx CRC Ltd (Management Company and signatory to new Commonwealth Agreement)
CTxT	CTxT Pty Ltd (legal owner and trustee for intellectual property)
DKFZ	German Cancer Research Centre
DMPK	Drug Metabolism and Pharmacokinetics
DoV	Deed of Variation
ELN	Electronic Laboratory Notebook
EMP	Epithelial Mesenchymal Plasticity
FAK	Focal Adhesion Kinase
FDA	Food and Drug Administration (USA)
FTE	Full time equivalent
GSK	GlaxoSmithKline
GU	Griffith University
Hb	Haemoglobin
HTS	High Throughput Screening
IP	Intellectual Property
IT	Information Technology
LIMK	LIM Kinase

M2M	Molecules to Medicine
MCRI	Murdoch Children's Research Institute
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIPS	Monash Institute of Pharmaceutical Sciences
MLL	Mixed Lineage Leukaemia
MOZ	Monocytic leukaemia zinc finger protein
MRP	Multidrug resistant protein
MSD	Merck, Sharp & Dohme (known as Merck & Co., Inc. in the USA and Canada)
MTPConnect	The Medical Technologies and Pharmaceuticals Industry Growth Centre
MU	Monash University
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
NIH	National Institute of Health (USA)
PCT	Patent Cooperation Treaty
PMCC	Peter MacCallum Cancer Centre
PRMT	Protein arginine methyltransferase
RET	Receptor for members of glial cell line-derived neurotrophic factor family
RMP	Risk Management Plan
SAB	Scientific Advisory Board
SME	Small to Medium Enterprise
STEMM	Science, Technology, Engineering, Maths and Medicine
STING	Stimulator of interferon genes
TGA	Therapeutic Goods Australia
UoM	University of Melbourne
VCCC	Victorian Comprehensive Cancer Centre
VEGFR3	Vascular Endothelial Growth Factor Receptor 3
WDR5	WD Repeat Domain 5
WECC	WEHI's chemical library
WEHI	Walter and Eliza Hall Institute of Medical Research