

Cancer Research Technology

February 2012



Cancer Research
Technology

Advancing Discoveries to Beat Cancer



About Us



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Who we are

Cancer Research Technology (CRT)

- ▶ Technology development & commercialisation arm of CR-UK (140 staff)
- ▶ Exclusive rights to intellectual property from CR-UK funded research
- ▶ HQ in London, US subsidiary in Boston, partner in Australian consortium
- ▶ Provide technology transfer services, including access to CRT/CR-UK translational resources, to both CR-UK and non CR-UK affiliated institutions worldwide
- ▶ Internal drug discovery laboratories with major partnerships with AstraZeneca and Cephalon

Cancer Research UK (CR-UK)

- ▶ World's leading charity dedicated to saving lives through research
- ▶ Launched in 2002 following merger of two long-standing cancer charities – operational for more than 100 years
- ▶ Employs its own scientists and funds research in UK universities
- ▶ Entirely funded by donations from the public
- ▶ Scientific spend is > \$550 million annually
- ▶ Partnerships with more than 20 charities and academic institutes worldwide



What we offer

- ▶ We source and develop cancer discoveries – translating world-class research into industrial propositions
- ▶ We work with, and can identify top academics for collaborative interactions
- ▶ We can partner with industry to create commercial value and patient benefit from cancer discoveries
- ▶ We seek to identify innovative scientific and business solutions to meet unmet needs in oncology



Why CRT?

What makes CRT special

- ▶ Primary focus is Cancer
 - Specialist skills and experience
- ▶ Discovery & early clinical development capability
 - Discovery Laboratories, Discovery Committee, BIDD, NAC
 - Greater ability to match customer needs
- ▶ Global project sourcing, with multi-finder scope
 - CR-UK, other charities & institutes, CRT Inc, CTx
 - Critical mass of discoveries and intellectual property
- ▶ Focus on patient benefit

Standing out from the crowd

- ▶ Access to more than **\$550m** worth of publicly funded research
- ▶ Our funded Scientists are authors of over **20,000** publications
- ▶ Over **200** projects in development
- ▶ **85** drug discovery professionals in CRT-DL (>70% industrially trained)
- ▶ Over **30** partnered therapeutics
- ▶ **29** years experience and success in oncology commercialisation
- ▶ More than **20** spin out companies
- ▶ Partnerships with more than **20** charities and institutes worldwide
- ▶ **7** treatments in our Clinical Development Partnership initiative
- ▶ **2** drugs in Phase III clinical trial
- ▶ **2** major industry partnerships with CRT-DL
- ▶ Ranked No. **2** for oncology licensing
- ▶ **1** focus - cancer



Our Operational Model



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Routes to Commercialisation

Intellectual Property

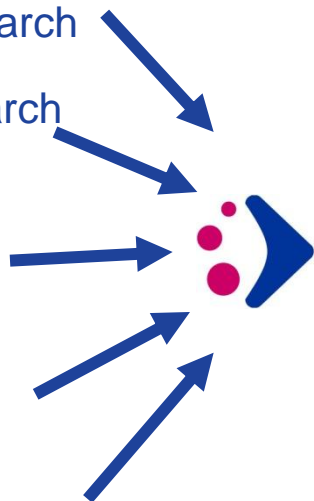
CR-UK funded drug discovery
and development research

CR-UK funded basic research

Other charities

Global institutes

CTx Ltd (Australia)



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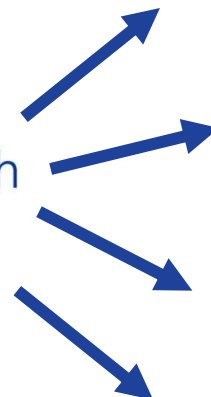
Commercial Environment

Licences

Consortia

Spin-outs

Collaborations



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Translational Research & Development with CRT

Company strategy focused on both discovery & clinical development

Discovery:

- ▶ Over 120 programmes under development through:
 - Collaborative development with industry
 - Support from CR-UK translational funds in universities or academic drug discovery centres
 - Development in CRT's Discovery Laboratories

Clinical Development

- ▶ In conjunction with CR-UK's Drug Development Office (DDO):
 - We work with academics and industry to progress promising clinic-ready cancer agents
 - Through our Clinical Development Partnerships initiative (CDP), pharma deprioritised agents are moved into clinic
 - 7 treatments have entered the CDP programme since 2006

Our Cancer Research Community



Small Molecule Drug Discovery

- ▶ CR-UK funded Small Molecule Drug Discovery programmes (SMDD) established in 2008 at the following:
 - Imperial College London
 - London School of Pharmacy
 - Strathclyde University
 - Oxford University

- ▶ CRT in conjunction with the University Project Leaders, is seeking collaboration with industry on the SMDD projects.



Drug Discovery at PICR, BICR & CTU

➤ CR-UK investment of £16m in 2 new Drug Discovery Programmes:

- Paterson: Donald Ogilvie
- Beatson: Martin Drysdale



➤ CR-UK Cancer Therapeutics unit (CTU) at the ICR

- Established in 2006, directed by Paul Workman
- Academic drug discovery and development group set up to discover and develop novel and effective therapeutics for the treatment of cancer



➤ CRT manages all IP related to these programmes



Our Discovery Laboratories



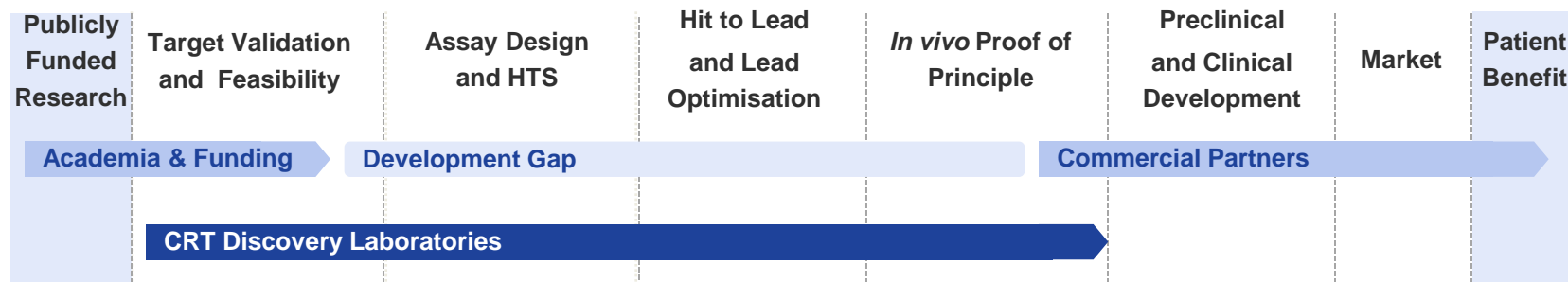
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Role of the CRT-DL

- To develop (and de-risk) to *in vivo* proof of principle stage
 - Partner at this stage
 - Maximise number of projects developed
- HTS, pharmacology, medicinal chemistry, crystallography; project validation function
 - Focus on industry experience and skills to prosecute a maturing portfolio
- Select “novel” targets as priority from CR-UK funded and other academic research
 - Collaborations worldwide with leading academic research groups
 - Discovery alliances with industry (AstraZeneca and Cephalon)
- Fully integrated part of CR-UK long-term Drug Discovery Strategy

CRT bridges the gap between academia and Industry







History & Growth of CRT-DL

- ▶ Operation commenced in July 2004 in London
 - Wolfson Institute UCL and Dominion House, St Bartholomew's Hospital
 - ~ 13 molecular biologists and biochemists
- ▶ By 2005 Wolfson Institute for Biomedical Research (WIBR) UCL, became primary DL site
 - 45 scientists based at WIBR by 2007
- ▶ CRT-DL became a multi-site operation by 2008 with facilities close to CR-UK institutes:
 - London (Wolfson/Birkbeck)
 - Cambridge
 - Glasgow (Beatson)
 - Manchester (Paterson)
 - Currently ~ 85 full time scientists across these sites



CRT-DL Portfolio

Target	Target Validation	Hit Identification	Hit Validation	Lead Identification	Lead Optimisation	Partner
PKC						 Cephalon
Autotaxin						
CDC7						
PAK4						
Undisclosed						AstraZeneca 
Undisclosed						AstraZeneca 
Undisclosed						 THE UNIVERSITY OF AUCKLAND
Undisclosed						



Our Track Record



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Selected Partnered Therapeutics in Development






CRT has >30 partnered agents in preclinical and clinical development and 4 partnered marketed drugs

Agent/Target	Company	Institute	Indications	Preclinical	Phase I	Phase II	Phase III	Market
Temodal®	Schering-Plough (now Merck)	Aston	Glioma					
Zytiga®	Cougar (now J&J); BTG	ICR	Prostate					
Erivedge™	Genentech/Roche; Curis	Harvard; CRT	BCC					
Stimuvax®	Merck KGaA; Oncocyteon	Guy's Hospital	NSCLC					
Anyara	Active Biotech	PICR	Renal					
PARP	Pfizer	Newcastle	Ovarian; Breast; Melanoma					
HSP90	Novartis; Vernalis	ICR; Exeter	Multiple myeloma ; Breast					
SG 2000	Spirogen	Imperial	Ovarian; Haematological tumours					
GSK1070916A	GSK		Advanced solid tumours	CDP*				
IMA950	immatics biotechnologies		Glioblastoma Multiforme	CDP*				
PI 3-kinase	Genentech; Plramed	LRI; ICR; Ludwig						
ONX-0801	Onyx Pharmaceuticals	ICR	Advanced solid tumours					
Akt/PKB	AstraZeneca; Astex	ICR						
AT 13148	Astex Therapeutics		Advanced solid tumours	CDP*				
AZD 3965	AstraZeneca			CDP*				
DI-B4	Merck KGaA		Leukaemia & Lymphoma	CDP*				
CEN-209	Centella Therapeutics		Advanced solid tumours	CDP*				
AZD 0424	AstraZeneca		Advanced solid tumours	CDP*				
Undisclosed	Genentech	Oxford						







* Clinical Development Partnerships

Our Start-up Companies

CRT has been involved in the formation and development of more than 22 start-ups

Company	Summary
	Cancer-focused preclinical and clinical development company. Entered 5-year collaboration agreement with Roche. Acquired Aptamera Inc. Partnered ASA404 with Novartis.
BLiNK Therapeutics	Founded in June 2011 by CRT and Paris based Kurma Life Sciences Partners to generate monoclonal antibodies using a novel platform.
	Discover and develop small molecule drugs based upon chromatin biology. Raised \$53m in series C financing.
	Develop agents that target key cell cycle regulators. Merged with Xcyte Therapeutics Inc. and subsequently raised \$45m.
	Develop drugs based upon DNA damage recognition, signalling and repair. Acquired by AstraZeneca for \$210m in 2006.
MISSION Therapeutics	Formed in August 2011, the company will translate cutting-edge cell biology research on DNA repair into drugs that will markedly improve the management of life-threatening diseases, particularly cancer. MISSION Therapeutics has secured £6M in Series-A funding.
	Develop anti-cancer signal transduction inhibitors. PI 3-kinase programme partnered with Genentech has potential milestones of \$230m plus royalties. Acquired by Roche for \$160m in 2008.

Competing in the Pharma/Biotech world

Company	Number of licensing deals in oncology (2000-2009)
 Bayer HealthCare Bayer Schering Pharma	32
 Cancer Research Technology	30
 Roche	29
 GlaxoSmithKline	28
 Genentech <small>IN BUSINESS FOR LIFE</small>	27
 genzyme	25
<small>THE UNIVERSITY OF TEXAS</small> MD ANDERSON CANCER CENTER <i>Making Cancer History*</i>	23
 HELSINN	19

Source: PharmaDeals® Agreements, PharmaVentures Ltd

CRT-DL team up with Industry

Strategic Alliance: Case study

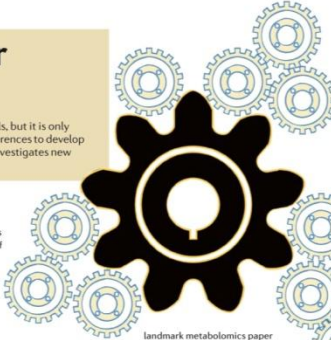
- ▶ 3-year, multi-project alliance with AstraZeneca to create “cancer metabolism drugs”
- ▶ Integrated joint development model
- ▶ Jointly resourced initiative with a combined team of 30 scientists
 - Focusing on relevant projects selected by CRT from CR-UK funded research programs
 - Research carried out at CRT-DL in London and Cambridge and AstraZeneca cancer centre near Manchester
- ▶ AstraZeneca responsible for taking the most promising projects into preclinical and clinical development
- ▶ 4 CR-UK funded projects have been committed to the alliance since signing the deal in December 2009

NEWS & ANALYSIS

NEWS FEATURE

Targeting tumour metabolism

Metabolism in cancer cells differs from that in normal cells, but it is only recently that opportunities to specifically target these differences to develop novel anticancer drugs are being revealed. Jim Schnabel investigates new collaborations to harness this potential.



Earlier this year, two R&D agreements were established to develop anticancer therapeutics that target the changes in metabolism observed in cancer cells. In February, Cancer Research Technology (CRT) — the commercialization and development arm of the world's largest cancer charity Cancer Research UK (CR-UK) — announced a 3-year alliance with AstraZeneca. And in April, the early-stage biotechnology company Agios Pharmaceuticals announced a strategic collaboration with Celgene.

Investigating the metabolic changes in cancers cells, such as their higher rates of glycolysis (the generation of energy through the metabolism of glucose to pyruvate), has been a basic research focus for decades. But efforts to translate this knowledge into therapies have been held back by the uncertainty of what is driving what, says Eyal Gottlieb, Head of the Apoptosis and Tumour Metabolism Group at the CR-UK-funded Beatson Institute for Cancer Research in Glasgow, UK. “Is the changing metabolism seen in cancer cells simply an adaptation to energy demand, or is it really important for driving cancer?”

Interest in this question has been fuelled by increasing evidence showing that cancer-linked proteins involved in signal transduction pathways are actually dysregulating metabolic enzymes. For example, mutations in proteins of the PI3K-mTOR (phosphoinositide 3-kinase—mammalian target of rapamycin) pathway — which is commonly activated in cancer — have been shown to drive altered cellular metabolism, says David Schenkein, Chief Executive Officer of Agios.

Moreover, “A big shift in perspective came when studies revealed that mutated forms of metabolic enzymes could promote cancer — in particular, the identification of fumarate hydratase and succinate dehydrogenase as tumour suppressors [whereby the loss of enzyme function contributes to cancer progression],” says Gottlieb.

More recently, scientists at Agios reported that a mutated form of isocitrate dehydrogenase 1 (IDH1) has a novel enzymatic activity that may contribute to the formation and progression of brain tumours (Nature 462, 739–744, 2009). This added to research reported by Lewis Cantley's laboratory in 2008 that showed that the fetal M2 isoform of pyruvate kinase (PKM2) — which catalyses the last step in glycolysis — is switched on by cancer cells to promote rapid growth and is critical for tumour formation (Nature 452, 181–186; 2008). Soon after this research was published, Cantley co-founded Agios with Tai Mak and Craig Thompson with US\$33 million in venture capital funding.

Novel technologies have contributed substantially to these recent advances in the understanding of cancer metabolism. “Large-scale cancer genome sequencing projects are revealing driver mutations in genes such as IDH1 that have not been previously associated with cancer,” says Almut Schulze, group leader of the Gene Expression Analysis Laboratory at CR-UK's London Research Institute, who is participating in the alliance with AstraZeneca. “Also, RNA interference technology has been used to uncover [previously unknown] processes that are essential for cancer cell survival,” she adds. “The third technological advance is the development of analytical tools to study metabolite levels with unprecedented resolution. For example, there was a landmark metabolomics paper in Nature in 2009, which was focused on prostate cancer [Nature 457, 910–914; 2009].”

Such advances are providing increasing support for the idea that there are tumour-specific changes in cell metabolism that could be targeted by novel drugs. “What is new is the ability to translate the science of cancer metabolism into a drug discovery programme that makes a difference in the clinic,” says Schenkein. “While there are some approved drugs that I would argue as having cancer metabolism targets — like asparaginase and the antifolates — we are entering into a whole new zone as we think about how to make these new metabolic targets druggable with a safe therapeutic index.”

Agios is already in the process of validating PKM2 and IDH1 as therapeutic targets, but their broader ambition is to identify as many druggable cancer metabolism targets as possible. “The next 3–5 years are the critical window of opportunity to really go after this space, because I think that the important targets are likely to be discovered in this time frame,” says Schenkein.

To achieve their goal, Agios is building up their cancer metabolism teams and research infrastructure with the \$130 million that the company received as an upfront payment from Celgene. “I can't tell you today which is absolutely the best target, and so we wanted to have enough resources and a partner that would allow us to broadly explore this

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Academic Consortia Models

Senectus Therapeutics Ltd

- ▶ A virtual drug discovery company focused on the development of novel therapeutics targeting cellular senescence
- ▶ Founded around a hand picked consortium of world-class scientists whose research expertise in telomere biology, autophagy and tumour suppression is being utilised to develop innovative drug development programs
- ▶ Unique approach is designed to deconvolute senescence signalling pathways and build a network of genes for target and biomarker discovery
- ▶ Secured \$1M of funding (through July 2010) and is currently seeking collaboration and/or investment partners to be part of our future
- ▶ In March 2011, Senectus and AstraZeneca signed a deal to collaborate to identify triggers to cell ageing

Our Clinical Partnerships Initiative

Clinical Development Partnerships (CDP)

Objectives

- ▶ Joint initiative between CRT and CR-UK, formed in 2006
- ▶ Aim is to increase the number of clinical trials being undertaken for the treatment of cancer
- ▶ Targeted at leading pharma and biotech companies
- ▶ Bring new life to de-prioritised cancer agents
- ▶ Early clinical development at no cost to the company
- ▶ Projects undertaken on a shared risk-reward basis

Treatments in CDP programme

- ▶ **AstraZeneca** - AZD3965 – targets the monocarboxylate transporter 1 (MCT1)
- ▶ **Immatics biotechnologies** - IMA950 treatment vaccine, for GMB
- ▶ **Merck KGaA** - DI-B4, an investigational anti-cancer drug to target leukaemia and lymphoma
- ▶ **GSK** - 1070916A, an aurora kinase inhibitor drug to target advanced solid tumours
- ▶ **Astex Therapeutics** - AT13148 - a protein kinase B inhibitor
- ▶ **AstraZeneca** - AZD0424 - a tyrosine kinase inhibitor
- ▶ **Centella** – CEN-209 – a radiotherapy-enhancing drug

Our Research Tools Business

- ▶ CRT has been commercialising research reagents created in academic institutes for more than 20 years
- ▶ Our portfolio exceeds 600 monoclonal and polyclonal antibodies as well as cell lines and transgenic mice models
- ▶ The majority of our antibody portfolio is marketed through major worldwide chemical suppliers:
 - Abcam, EMD Millipore, BD BioSciences etc
- ▶ Cell lines and transgenics are supplied directly to industry
- ▶ We maintain hundreds of licensing agreements with over 60 companies
- ▶ > £2m in revenues generate from Research Tools business for the 2010/11 financial year

CRT in the News

CRT spins out company to develop cancer surgery machine to melt tumours

26th January 2012 – CRT has launched Acublate Limited, a spin-out company which will develop a next-generation High Intensity Focused Ultrasound (HIFU) surgery device to treat a range of solid tumour types. HIFU is a highly precise non-invasive type of surgery which uses ultrasound energy to heat and destroy tumours while leaving surrounding healthy tissue intact.

CRT and Cancer Research UK establish Lipid Metabolism Research Team

29th September 2011 – CRT has established a group of scientists with expertise in lipid metabolism – getting energy from fats and making building blocks for cell growth – to develop targets for potential new cancer drugs. Five world-class research groups will collaborate on an initial two-year research project. The groups will receive a total of £600,000 over two years, jointly funded by Cancer Research UK and AstraZeneca.

MISSION Therapeutics, a new Cambridge based spin-out company, secures £6M in Series-A funding led by Sofinnova Partners

25th August 2011 – A team led by Professor Stephen Jackson together with CRT and the University of Cambridge has announced the launch of MISSION Therapeutics Ltd, with Series A funding from a top venture capital syndicate.

Thank You



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