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Childhood Cancer Survivor

**CHILDREN'S CANCER
INSTITUTE AUSTRALIA**

**STEWARDSHIP REPORT 2006/2007 TO
THE APEX FOUNDATION**



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“Research is always collaborative...without the support of funding bodies, organisations, individuals and the community we would not have the ability to undertake our vital programs. As researchers we are grateful for the immense support we receive but like those who support us, our unwavering focus is on the children and families who we hope one day soon need never suffer again.”

Professor Michelle Haber AM, CCIA Executive Director

1. SUMMARY

Over the last year, The Apex Foundation has generously provided vital funding of \$51,000 to The Leukaemia Biology Program enabling our researchers to direct efforts to the evaluation of new drugs in the treatment of childhood leukaemia for fast-tracking to clinical trials in children.

The Apex Foundation (together with other grants) has assisted in funding the Pre-clinical Evaluation of New Therapies for Childhood Leukaemia Study. The ultimate goal is to develop therapies that have no toxic side effects or long-term consequences, and to find therapies that are effective in those children who relapse with aggressive and drug-resistant disease, giving more children a better chance of survival.

To date, the results of this study have shown great promise which we hope will substantially improve the treatment outcomes and quality of life for children with this disease.

2. ABOUT THE RESEARCH

The long-term goal of CCIA’s Leukaemia Biology Program is to improve the treatment of children with leukaemia through the development of new therapies and their preclinical testing in established experimental models. Over the past two years, the Program has made significant and exciting progress towards this goal.

The Leukaemia Biology Program includes four key areas of research:

- Identifying new targets for drug development;
- New therapies for Acute Myeloid Leukaemia (AML);
- Reversing drug resistance in leukaemia; and
- Preclinical testing of new anticancer treatments for ALL.

2.1 THE PROBLEM

In children the most common form of cancer that develops is leukaemia, a cancer of the white blood cells. Leukaemias cause the greatest number of cancer-related deaths in children than any other cancer. There are a number of different types of leukaemia, but the most common type found in children is Acute Lymphoblastic Leukaemia (ALL). The cure rate for ALL has risen dramatically over the last 50 years due to advances in

medical research and now stands at close to 80 per cent, however, at least two out of ten children with ALL relapse with aggressive, chemotherapy-resistant disease. The consequences of relapse are often grim and there is a great need to develop new treatment options for these children.

2.2 THE SOLUTION

To develop and test new treatments for leukaemia, we are using a living model of ALL that we developed in the laboratory. The laboratory model, which took several years to develop, closely mimics ALL in children. Critically, it allows us to carry out clinically relevant experimental work, such as testing the efficacy of a range of anticancer drugs, without directly involving children.

2.3 TESTING NEW CHILDHOOD CANCER DRUGS

Our model of ALL is recognised among the very best in the world. As a result, our scientists are taking part in a number of international collaborations to test new childhood cancer drugs as they are developed to identify which of these should be fast-tracked to clinical trials in children.

In 2005, CCIA was invited to join a new international consortium established by the USA's National Institutes of Health to test potential new drugs for the treatment of childhood cancer – the Pediatric Preclinical Testing Program (PPTP). The consortium involves five testing institutions in the USA together with CCIA. The main goal is to rank new drugs for childhood cancer clinical trials.

During the first year of the project several new drugs were successfully tested. A number of these looked to be promising and were moved on to the next phase of testing. We have since tested one new drug per month in our model of ALL and will continue to do so over the next four years. Over the last year we have identified more drugs which warrant further testing and/or consideration for clinical trials. The results of our research have been published in a number of prestigious scientific journals.

We are also involved in a second collaboration, the Therapeutic Advances for Childhood Leukemia (TACL) consortium, directed by the Children's Hospital Los Angeles (CHLA) Institute for Pediatric Clinical Research (IPCR).

Using our laboratory model of ALL, we are testing new anti-leukaemic drugs in combination with already established treatments. The aim of this work is to find out how these new drugs might best be used to treat children whose leukaemia is resistant to conventional treatment. As with the PPTP collaboration, the aim of this testing is to identify the most promising drugs and combination therapies, so that these can be accelerated into clinical trials for children with leukaemia.

We have recently demonstrated that a new drug which has been found to inhibit the family of proteins that block mechanisms responsible for destroying leukaemia cells in ALL patients, acts to enhance the effects of drugs commonly used to treat ALL. This result suggests that this drug has the potential to improve future treatment of ALL patients.

This work was published last month in the prestigious haematology journal *Blood*. This exciting result will enable the TACL consortium to put forward this drug for clinical trials in ALL affected children who relapse after conventional treatment.

In parallel with this testing, we are working on expanding our range of laboratory models of childhood ALL. There are several different sub-types of ALL, each of which have unique properties. We are working to create a laboratory model of each to help develop and test treatments that are specific to each sub-type. This will provide an essential resource for preclinical drug testing and future projects.

2.4 SIGNIFICANCE OF THIS RESEARCH

Over 400 new drugs are currently being trialed for the treatment of adult cancers, but until recently, there has been no systematic approach to prioritising which of these drugs should enter clinical trials in children. As a result, new drugs have been slow to reach the clinic. In addition to this, some children with cancer develop resistance to conventional drugs used to treat them. With no other treatment options to turn to, they face a bleak future.

The work that Dr Richard Lock and his team are conducting has real potential to speed up the availability of new drugs for children with cancer, and to find alternative drug combinations which will destroy drug-resistant cancer cells, helping to improve the chances of survival for these children.

2.5 THE FUTURE

The translation of research from bench to bedside is essential in driving advancement in treatment options for sufferers of childhood cancer. The development of drug resistance in certain cancers and the limited assortment of drugs available for current treatment protocols is of great concern to doctors and presents a grim outlook for families of children suffering from cancer.

The development of our experimental model of childhood ALL enables us to study various aspects of the biology of this disease, giving us a unique advantage in the ability to enhance our understanding of the mechanisms of ALL. This, in turn, will potentially allow us to identify new targets for therapy.

In addition, our involvement in the testing of new drugs, and our appointment as the international testing site in the PPTP study, have positioned us to make substantial contributions to the design of clinical trials for children with ALL in the immediate future. It is our aim to extend this testing in another form of childhood cancer, neuroblastoma, a cancer of specialised nerve cells.

3. KEY RESEARCHERS

DR RICHARD LOCK, PROGRAM HEAD, LEUKAEMIA BIOLOGY PROGRAM

Dr Richard Lock heads this major research program, which is focused on developing our knowledge and understanding of leukaemia, the most common cancer in children.

Dr Richard Lock joined CCIA in 1998, relocating from Kentucky, USA where he held an

appointment of Associate Professor in the Department of Medicine and Department of Biochemistry and Molecular Biology at the University of Louisville. He had already gained an international reputation in the cancer-related fields of cell cycle control, drug resistance, and mechanisms of programmed cell death (apoptosis).

As Head of the Leukaemia Biology Program, Dr Lock has built an internationally competitive research program focusing on the development of new experimental models of paediatric leukaemia to study the biology and treatment of the disease. The originality and impact of this research has been validated by a strong record of publications in high impact peer-reviewed journals, numerous invitations to give presentations on his areas of expertise, and strong national and international collaborations.

4. PAPERS AND CONFERENCES 2006-2007

4.1 PUBLICATIONS

Bachmann PS, Gorman R, Papa RA, Bardell JE, Ford J, Kees UR, Marshall GM, Lock RB (2007). Divergent mechanisms of glucocorticoid resistance in experimental models of pediatric acute lymphoblastic leukemia. *Cancer Research*, 67(9), 4482-4490.

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Choo A, Palladinetti P, Passioura P, Shen S, Lock R, Symonds G, Dolnikov A (2006). The Role of IRF1 and IRF2 Transcription Factors in Leukaemogenesis. *Current Gene Therapy* 6, 543-551.

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Kolb E, Gorlick R, Houghton P, Morton C, Lock R, Tajbakhsh M, Reynolds CP, Maris J, Keir S, Billups C, Smith M (2007). Initial Testing of Dasatinib by the Pediatric Preclinical Testing Program. *Pediatric Blood and Cancer* (*in press*).

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Verrills NM, Liem NL, Liaw TYE, Hood BD, Lock RB, Kavallaris M (2006). Proteomic analysis reveals a novel role for the actin cytoskeleton in vincristine resistant childhood leukemia - an in vivo study. *Proteomics*, 6(5), 1681-1694.

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4.2 CONFERENCES

Bachmann PS, Gorman RC, Lock RB (2006) Mechanisms of glucocorticoid action in childhood acute lymphoblastic leukaemia. Hunter Medical Research Institute Conference on Translational Cancer Research, Newcastle, NSW.

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Hsu AKW, Kerr BM, Jones K, Lock RB, Hart DN, Rice, AM (2006) Effects on leukaemic engraftment in mice injected with anti-leukaemic CTL. 8th MMRI DC Symposium, Brisbane, QLD.

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Hsu AKW, Kerr BM, Lock RB, Hart DN, Rice AM (2006) RNA transfected cord blood-derived dendritic cells generate anti-leukemic cytotoxic T lymphocytes. 9th International Conference on Dendritic Cells, Edinburgh, Scotland.

Kang YH, Szymanska B, Yen N, Wilczynska-Kalak U, Reynolds CP, Lock RB, Kang MH (2007) Activity of vincristine, L-asparaginase, and dexamethasone against acute lymphoblastic leukemia was enhanced by the Bcl-2 inhibitor ABT-737 *in vitro* and *in vivo*. American Association for Cancer Research Annual Meeting, Los Angeles, CA, USA.

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Yuan J, Yan BMP, Zhong ZH, Shats I, Milyavsky M, Lock RB, Rotter V, Reddel RR, MacKenzie KL (2006) Upregulation of survivin and the acquisition of anti-apoptotic potential in telomerase immortalized human fetal lung fibroblasts. Australian Telomere Workshop, Sydney, NSW.

4.3 INVITED PRESENTATIONS

- 19th Lorne Cancer Conference, Lorne, VIC.
- Enzon Pharmaceuticals Inc, Bridgewater, NJ, USA.
- Haematology Society of Australia & NZ, Annual Scientific Meeting, Hobart, TAS.
- Hunter Medical Research Institute Conference on Translational Cancer Research, Newcastle, NSW.
- Hanson Institute, Adelaide, SA.
- Oncology Research Centre, Prince of Wales Hospital, Randwick, NSW.
- Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC.

5. FINANCIALS & CORPORATE GOVERNANCE

At CCIA we adhere to a strong principle of stewardship of all funds and ensure financial resources are used carefully and wisely. In 2006, fundraising income represented 29.1 percent of CCIA's total revenue, almost \$7 million. Fundraising expenses totalled almost \$2.6 million with a net return in the order of \$4.4 million. Administration expenses were kept to a minimum, representing 3.8 percent of the organisation's total expenses¹. Recently CCIA implemented a very extensive business improvement program with a strong focus on compliance and risk management to further assist us in being good stewards of the funds we receive. CCIA's fundraising activities are subject to an annual independent audit undertaken by Deloitte.

¹ See CCIA's Annual Review 2006 for more financial information

6. THANK YOU

The Board and Executive of CCIA would like to thank you for your very important contribution to helping us achieve our vision, 'to save the lives of all children with cancer and eliminate their suffering'.

Without the support of organisations and individuals including The Apex Foundation, we would have been unable to continue our vital work into the testing of new drugs for childhood cancer and identification of potential candidates for clinical trials, developing our understanding of childhood leukaemia and working towards new and effective ways to clinically manage children suffering from ALL, improving their chances for a better second chance.