End of Grant Report

Report at the end of the grant by Christopher's Smile for the 2 year position of Scientific Officer in the Paediatric Drug Development Team at the Institute of Cancer Research

Christopher's Smile

coz kids get cancer too

ICR

The Institute of Cancer Research

Registered Charity 1129906

Contents

1. Position

Title	Scientific Officer in the Paediatric Drug Development Team
Details	
Start of Grant	January 2010
Period of Grant	2 Years
Name(s) of person in position	Hannah Webber (left May 2011, research carried on by Mark Williams and supervised by Albert Hallsworth)
Grant funding over period of grant	£85,314 (includes gift aid in year one)
Matched funding over period of grant	£28,435

Overview of role during grant period

The focus of children's cancer research at the ICR is the discovery, development and clinical introduction of molecularly targeted therapeutics into the clinic. This new generation of cancer drugs is more effective through specific targeting and elimination of cancer-associated proteins. Using this theory, the role of the Scientific Officer within the Paediatric Drug Development Team has been to co-ordinate pre-clinical trials in order to identify novel targeted therapeutics suitable to be taken forward for paediatric trials.

2. Objectives

Year 1

Set up and co-ordination of pre-clinical testing facilities for paediatrics.
Development of cancer models focussed on the MYCN gene (for neuroblastoma, medulloblastoma and rhabdomyosarcoma).
Identification of new drug candidates suitable for paediatric trials.

Year 2

Development of cancer models focussed on the ALK gene (for neuroblastoma and medulloblastoma).
Identification of new drug candidates suitable for paediatric trials.

3. Work Undertaken

Year 1

To improve the cure rate for children diagnosed with solid tumours, it is mandatory that new drugs which target the molecular drivers for cancer are used rather than conventional

chemotherapy. These new drugs need to be studied and tested before entering clinical use. Hannah was coordinating all our pre-clinical studies and during year one, specifically investigating three major types of agents (PI3 kinase-mTOR inhibitors, aurora kinase inhibitors and TORC1 and 2 inhibitors).
All three of these types – focusing on the *MYCN* gene implicated in paediatric solid tumours – still have significant possibilities of going into clinical trials in the clinic. In total nine agents were tested. Very detailed investigations carried out utilising models which closely mimic the relevant childhood tumours. The research Hannah carried out identified in the laboratory which anti-cancer agents have the greatest chance of these being effective in children with cancer.

Hannah carried out trials in the transgenic *MYCN* cancer model that closely mimics childhood neuroblastoma and is very similar to medulloblastoma. She carefully compared in total nine agents - three PI3 kinase-mTOR inhibitors, four aurora kinase inhibitors and two TORC1 and 2 inhibitors. The efficacy of these agents in terms of reducing the size of the tumours, various detailed imaging characteristics of the tumour and effects on the mechanism of the tumour cells have been determined. The three most effective agents, as mentioned above, were selected to be taken forward to be evaluated in children. The imaging characteristics were ones which it is intended to use in early clinical trials of these agents in children.

Year 2

Hannah, and then Mark and Albert after she left, continued to investigate several types of targeted therapeutic agents, focussed on the MYCN and now also the ALK gene. The total number of agents tested rose to fifteen, two of which will be critical in this field and have a significant possibility of entering paediatric trials in the very near future.

Albert, with support from Mark, is now specifically looking to improve our agents aimed at the ALK gene, looking at their resistance in ALK models.

This approach to drug development is based on scientific understanding and we believe this will have the best chance of curing children with solid tumours. We have evaluated a number of drugs mentioned above that target MYCN and ALK. In addition, we have six other paediatric cancer research themes.

4. Key Achievements

Year 1

Initially Hannah was instrumental in setting up and the refinement of processes and the structure of work carried out in the pre-clinical testing facilities. This is now being carried on by Mark and Albert.

Year 2

Currently, nine out of ten cancer drugs under development fail to reach the cancer clinic, because of difficulties in the pre-clinical validation and testing phases. This relates in large part to a deficiency of accurate cancer models that are vital in order to understand the biology of each cancer type and to develop novel therapeutic agents. Thanks to funding from Christopher's Smile, the Scientific Officer role has contributed to our development of an extensive pre-clinical testing capacity, using genetically engineered cancer models that recapitulate children's cancer much more accurately than other models. We believe this will allow us to identify more accurately in the laboratory which drugs will be successful in the clinic, accelerating the cycle of invention to clinical use of a new cancer therapy.

We have also developed methods to measure biological characteristics (biomarkers) that are indicators of measuring the progress of disease in children. By studying biomarkers we can also understand the way a drug is working and develop predictive biomarkers to select patients for therapy. There is now a very strong clinical team, new building and we are investigating an increasing number of new anti-cancer drugs in children - for example, the number of new drugs studied has increased from two in 2006 to the fifteen this year, mentioned above.

We are now poised to build on this basis and identify more drugs in the laboratory and rationally evaluate them in children with solid tumours using these approaches. With this strategy we believe that there will be a higher chance of new drugs reaching the clinic and helping children with cancer. We are increasingly working closely with three other centres internationally which provide complementary expertise to our research and an international network is being formed.

Our goal remains to rapidly introduce new drugs into the clinic by an internationally forefront* scientific approach and thereby cure more children with solid tumours.

* A rating of 'Forefront' implies that the research is of international importance and will have substantial impact (Cancer Research UK definitions) and awarded to the paediatric drug development team in October 2011

5. Objectives not met during grant period

One of the key areas which haven't been explored as hoped by this role/within the team is the testing of drug candidates in combination. However, as generously funded by Christopher's Smile, Dr Evon Poon has been recruited to advance this area and future reports will be provided on progress in this field.

We haven't yet adequately studied the long-term effect of some of the drug candidates identified by the Scientific Officer. We have shown they work in the short-term. Further studies are planned to look at their longer term endurance and to identify if they work best as a single agent or in combination.

An unforeseen 'issue' was of course Hannah leaving the ICR to join the Children's Cancer

Research Institute in Sydney, Australia. Due to alternative measures taken (and previously outlined) this didn't interrupt the original research plan. Indeed, we hope Hannah's new role will further our work in pre-clinical models and drug discovery by strengthening our collaboration with Professors Michelle Haber, Murray Norris and Glenn Marshall in Sydney. We have identified the research group in Sydney as having very significant potential for long term productive collaboration.

6. Contribution to published, peer reviewed scientific paper(s)

This list includes all publications related to pre-clinical work as funding from Christopher's Smile is associated with, every aspect of our pre-clinical work.

Faisal A, Vaughan L, Bavetsias V, Sun C, Atrash B, Avery S, Jamin Y, Robinson SP, Workman P, Blagg J, Raynaud FI, Eccles SA, Chesler L, Linardopoulos S. *The Aurora kinase inhibitor CCT137690 downregulates MYCN and sensitizes MYCN-amplified neuroblastoma in-vivo*. Mol Cancer Ther. 2011 Sep 1. PubMed PMID: 21885865.

Chesler L, Weiss WA. *GEMM - Contribution to our understanding of the genetics, molecular pathology and therapeutic targeting of neuroblastoma*. Semin Cancer Biol. 2011 Sep 21. PubMed PMID: 21958944.

Terrile M, Bryan K, Vaughan L, Hallsworth A, Webber H, , Stallings RL, Chesler L. miRNA Expression Profiling of the TH-MYCN Neuroblastoma Model Reveals Similarities with Human Tumors and Identifies Novel Candidate MiRNAs. PLoS One 2011;6(12):e28356. Epub Dec 2 2011. PMID: 22164278 (2011).

Vaughan L, Clarke PA, Cullis E, Barker K, Renshaw J, Raynaud F, Li X, Robinson SP, Pearson A, Maira M, Garcia-Echeverria C, Workman P, Chesler L. *Inhibition of mTOR-kinase destabilizes MYCN and is a potential therapy for MYCN-dependent tumors.* In review, Cancer Cell, Dec 2011

Berry T, Luther W, Jamin Y, Robinson S, Barker, K, Gray N, Eccles SA, George RE, Chesler L. *The ALKF1174L mutation potentiates the oncogenicity of MYCN in a model of neuroblastoma.* Submitted, Nature Medicine, Jan 2012.

Jamin Y, Cullis E, Vaughan L, Webber H, Boult J, Baker L, Burrell J, Koh D, Chesler L, and Robinson S. *Characterisation of a transgenic model of neuroblastoma by magnetic resonance imaging. In review*, Radiology, Jan 2012.

Brockmann, M, Vaughan, L, Cullis, L, Eilers, M and Chesler, L. *Aurora A kinase inhibitors effectively destabilise Mycn oncoprotein and selectively target MYCN-driven neuroblastom*a. In preparation, Cancer Cell, Jan 2012.

Ahmad, Z, Moore, A, Barker, K, Vaughan, L, Sergey, P, Pearson, A, Chesler, L. *MYCN drives the expansion of a CD133 positive tumour-initiating-cell in medulloblastoma.* In preparation, Cell Stem Cell, Mar 2012.

7. Overview by Team Leader of achievements during grant period

We have had several major benefits relating to funding through Christopher's Smile. Our core area of focus is in pre-clinical validation of novel therapeutics that target MYCN and ALK two major oncogenic drivers of high-risk pediatric cancers (medulloblastoma, neuroblastoma and rhabdomyosarcoma). We successfully designed and conducted a chemical-genetic screen identifying clinically usable MYCN destabilising compounds (small-molecules). Among these, PI3K/mTOR inhibitors were highly effective at eliminating MYCN oncoprotein in vivo, primarily in neuroblastoma models. We established the mechanism of MYCN inhibition, showing that this primarily relates to potency of mTORC2 in addition to mTORC1 inhibition. This provided a roadmap for the serial characterisation of mTOR inhibitors that are likely to be effective in the clinic, against MYCN driven cancers The first agent identified in these trials is being prepared to entrer clinical trials. We have gone on to validate another drug as a potent and selective mTOR complex inhibitor that is effective in both short and long-term preclinical studies against MYCN-driven neuroblastoma. We are working to take this drug into clinical trials in children as well. Additionally our screen identified multiple compounds also capable of antagonising MYCN (Aurora, CDK, CHK1, and PARP) and our funded postdoctoral fellow (E.P.) is characterising CDK and Aurora-A kinase inhibitors alone and in combination with chemotherapeutics and mTOR inhibitors for pre-clinical treatment of MYCN driven cancers.

Additionally we developed and characterised the first ALK-driven model of neuroblastoma and used it to establish that the ALK^{F1174L} mutation (common in neuroblastoma) is resistant to inhibition using the current clinical therapeutic ALK inhibitor (crizotinib). We have established a roadmap for the introduction of additional clinical treatment strategies for ALK-driven neuroblastoma. Negotiations are on-going to determine the scope and target agent for internationally collaborative neuroblastoma trials.

In summary the funding provided has been instrumental in the design, conceptualisation and implementation of our pre-clinical therapeutic testing initiative at the ICR. We hope to secure a substantial a core-funded programme grant to underpin continued activities in this setting.

8. Overview by Department Head of achievements during grant period

Our mission is to develop and bring to the clinic new therapies to cure children with cancer who currently die. At present the introduction of new drugs is a very slow process; our aim is to accelerate drug development in children with cancer.

We can bring to the international research community four strengths in the development of molecularly targeted therapeutics: - drug discovery, pre-clinical models, early clinical trials with biomarkers and cancer imaging.

Our central hypothesis is that the optimal development of molecularly targeted drugs is by selection based on molecular pathology and efficacy in pre-clinical models; evaluation in hypothesis-driven early clinical trials employing predictive *(*for patient enrichment*)* and pharmacodynamic biomarkers; novel trial design and introduction into frontline trials through a personalised molecular medicine approach.

The theme is a bench-to-bedside and back again approach: within the same institution drugs are discovered, tested in pre-clinical models and moved forward to clinical trials in children. We work in parallel to develop the tests that will identify which individuals will benefit from specific treatments, and to what extent these novel treatments are effective. This approach reflects the concept that one individual cancer drug is not appropriate for all patients with a particular cancer i.e. 'One size does not fit all' – and a more personalised approach is required (personalised medicine).

Funding from Christopher's Smile has been pivotal in the following achievements:-

1. **Pre-clinical testing facility** - The development of an extensive pre-clinical testing capacity, using our engineered models that recapitulate children's cancer much more accurately than other models. This is one of the world's first pre-clinical drug testing facilities that is totally focused on paediatric drug development. The facility combines state-of-the-art cancer models with advanced multimodality imaging techniques (MRI, CT scan, PET imaging and bioluminescence) increasing our power to accurately detect and describe drug response. Imaging modalities are developed in the adjacent; Cancer Research UK - ESPRC Cancer Imaging Centre, concurrently validated within our pre-clinical trials of novel drugs, and therefore is available for clinical use in children when a study drug reaches the hospital. We believe this will allow us to identify more accurately in the laboratory which drugs will be successful in the clinic.
2. **Development of Therapeutic Themes in Neuroblastoma** - Eight Therapeutic Themes in neuroblastoma have been established:- Targeting MYCN oncoprotein stability; Targeting MYCN through synthetic lethal interactions by drugging genes that modulate critical functions of MYCN; Anaplastic lymphoma kinase (ALK); Angiogenesis; MDM2-p53 antagonists; Checkpoint Kinase 1 (Chk1) inhibitors; MEK inhibition and radio nucleotide therapy. Drug development in neuroblastoma will be a paradigm for other childhood cancers. Therapeutic themes in sarcoma, medulloblastoma and glioma will be subsequently established.
3. **Rationale evaluation of the role of Engineered Models** – Our goal is to test the underlying hypothesis that engineered models more accurately replicate the biology of spontaneous tumours and will be a more predictive and cost effective approach to introducing novel targeted agents into clinical use in paediatric cancer.
4. **Selection of agents for early clinical studies** – The initial focus has been on targeting MYCN oncoprotein stability. Drugs have been selected to be taken forward for potential evaluation in the clinic. The next major focus is ALK inhibition.
5. **Targeting MYCN oncoprotein stability -** We have demonstrated that of the agents evaluated to date mTOR kinase inhibition is the most effective approach to reduce MYCN stability
6. **International Resource** - We can now bring to the international research community four strengths in the development of molecularly targeted therapeutics: - drug discovery, pre-clinical models (i.e. testing drugs in models and cells in the lab), early clinical trials with biomarkers and cancer imaging.
7. **Reducing the attrition of compounds reaching the clinic** – Funding from Christopher's Smile will facilitate the more accurate selection of agents to be evaluated clinically, so that a higher proportion of therapeutics tested pre-clinically enter the clinic.
8. **Clinical goal** - The funding has underpinned our clinical goal of opening two to three biological hypothesis-driven first-in-child early phase studies of molecular targeted anti-cancer agents with embedded predictive and pharmacodynamic biomarkers initiated and led by the RMH/ ICR Children and Young People's Drug Development Unit each year.
9. **Cancer Research UK Chair in Paediatric Oncology Programme** - The funding has been

absolutely critical to the overall success of the Cancer Research UK Chair in Paediatric Oncology Programme which was awarded 'International Forefront' implying that the research is of international importance and had substantial impact at an International Site Visit in October 2011.

10. **Strengthening our research base** - The funding from Christopher's Smile allows our research base and publication record to be strengthened to enable us to apply for additional programmatic funding from other organisations.