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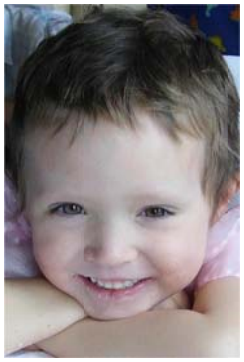
Abbie's Fund

Accelerating Drug Development for Children with Neuroblastoma

Lay report, February 2012



We remain extremely grateful to Abbie's Fund for your generous support of our Neuroblastoma research programme. It is through the support of organisations such as yourselves that we are able to continue to make the discoveries that defeat cancer.

The Institute of Cancer Research (ICR) is one of the world's most influential cancer research organisations. With our clinical partner The Royal Marsden Hospital we are engaged in a wide range of research across many cancer types to develop new treatments for cancer patients. These treatments are based on an understanding of the genes that cause the disease and then designing and developing drugs that counteract the effects of the faulty genes.

The focus of children's cancer research at the ICR is the discovery, development and clinical introduction of molecularly targeted therapeutics for neuroblastoma into the clinic. This new generation of cancer drugs is more effective through specific targeting and elimination of cancer-associated proteins. This is unlike conventional chemotherapeutic drugs, which target normal cells as well as cancer cells, and are therefore toxic and less effective. **Unlike adult cancer, where this new generation of molecularly targeted cancer drugs are already in clinical use, the vast majority of children are still treated with conventional chemotherapy drugs. Our aim is to change this.**

Using the theory above we are identifying the most appropriate drugs that target the faulty genes associated with neuroblastoma and hand-in-hand with this, we are developing scientific, integrated clinical studies to evaluate these drugs in children. In order to learn from a clinical study, it is necessary to incorporate clinical testing which confirms whether the new drug in fact behaves as expected, and targets the cancer gene or molecule of interest. We therefore 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 neuroblastoma i.e. 'One size does not fit all' – and a more personalised approach is required.

The ICR houses a world-leading cancer drug development programme. Working with our partner hospital, The Royal Marsden, for the first time anywhere in the world, new drugs specifically designed to combat childhood cancers will be tested on site.

The Drug Development Unit at the Children's and Young People's Centre was opened in September 2011 by the Duke and Duchess of Cambridge

Neuroblastoma is the commonest childhood solid tumour and fifty percent of children present with high-risk disease, i.e. the tumour has spread or there is genetic evidence (abnormalities in the MYCN neuroblastoma associated cancer causing gene) that the tumour will behave aggressively. At present, the majority of patients with high-risk neuroblastoma relapse following treatment and die. Our mission is to develop new therapy to cure patients who currently die.

Current treatments for high risk neuroblastoma include chemotherapy, surgery, high-dose chemotherapy, radiation therapy and antibody (or immune-based) therapy. The new drugs will help young patients to avoid the toxic side-effects that can result from these current treatment methods.

The ICR has the largest academic drug discovery unit in the world, the Cancer Therapeutics Unit, which on average discovers two new clinical candidate drugs each year: a feat unmatched anywhere else in the world. Unique to academic centres worldwide, the ICR has an on-site medicinal chemistry unit, with the capability to invent and chemically synthesise (produce) cancer drugs, in collaboration with biological scientists and medical doctors. It is very uncommon that a single centre possesses all the combined expertise to move from concept through the laboratory and into the cancer clinic. The ICR has discovered many drugs that are now used worldwide, for example, melphalan, busulfan and carboplatin. Most recently abiraterone has been discovered, which has been a major landmark drug for prostate cancer. We are now working to discover new drugs for neuroblastoma.

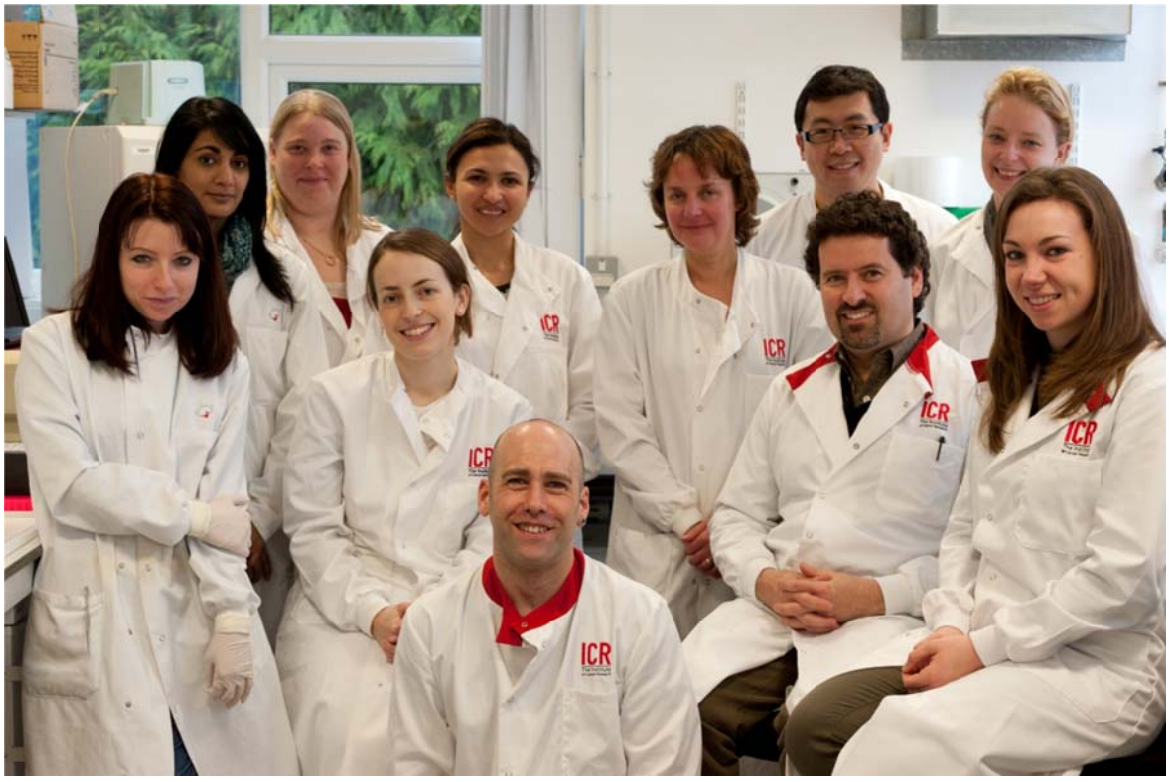
Dr Chesler in the lab

However it is also vitally important we work with the international neuroblastoma research community to link our centre of excellence to the complementary strengths of others. To this end we have established key collaborations with The Children's Cancer Research Institute (Sydney, Australia), The Children's Hospital of Philadelphia in the US and The Centro Nacional de Investigaciones Oncologicas (The Spanish National Cancer Research Centre), as well as others both in the UK and globally.

With the support of Abbie's Fund over the last two years we have been able to conduct experiments to successfully develop the isolation of neuroblastoma cells from the bone marrow of patients. Parallel to this, a study developed in collaboration with the University Of Leeds, is allowing us to test neuroblastoma models for tumour cells that circulate in the blood. This is a crucial step forward which will allow us to assess new treatment options for patients, if their current therapy isn't working, as well as analyse the effectiveness of new targeted therapeutic drugs.

Our approach to drug development is based on scientific understanding and we believe this will have the best chance of curing children with neuroblastoma. 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. We have developed 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 evaluated a number of drugs that target MYCN, a key gene that produces a cancer causing protein associated with very poor survival in neuroblastoma. In addition, we have five other paediatric cancer research themes aimed at improving treatments for children with neuroblastoma, including a new ALK gene model, which we believe is the first in the world. 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 are now very strong research and clinical teams, new hospital 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 2 in 2006 to 15 in 2011.



The Neuroblastoma Drug Development Team at the ICR

We are now poised to build on this basis and identify more drugs in the laboratory and rationally evaluate them in children with neuroblastoma 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 neuroblastoma.

With further funding we would propose to combine the two techniques developed with the support of Abbie's Fund, of isolating neuroblastoma cells in the bone marrow with the blood and bone marrow test to detect circulating tumour cells. This would accelerate and expand the development of our existing clinical testing platform. The ability to analyse tumour cells in the bone marrow is critical for neuroblastoma patients because ethically we cannot take repeated tumour tissue samples from children who have relapsed. These tests will form the basis of assessing our 'personalised medicine' approach of developing safer and targeted drugs for children with neuroblastoma.

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

"We thank Abbie's Fund for providing the support necessary to underpin these crucial studies in neuroblastoma. We are confident that this work will lead to improved testing for this disease, and to the deployment of targeted drugs that are safer and more effective for the treatment of MYCN-amplified neuroblastoma. We appreciate your continued support and interest in our work".
Dr Louis Chesler, Team Leader of the Neuroblastoma Drug Development Team

* A rating of 'Forefront' implies that the research is of international importance and will have substantial impact (Cancer Research UK definitions

Annual accounts:
http://www.icr.ac.uk/about_us/annual_accounts/annual_accounts_2011/22085.pdf

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