Childhood Cancer: Accelerating drug development for children with neuroblastoma

Interim progress report for Abbie’s Fund
November 2013

Written in conjunction with Dr Louis Chesler

Over the last decade, advances in technology have triggered an explosion in our knowledge about the biology of adult cancers – but we know far less about what causes cancers in children.

Gaps in our understanding of how to target children’s cancers and less investment from the pharmaceutical industry due to the smaller numbers of cases, have too often left doctors reliant on use of old-style, non-specific chemotherapy drugs designed for adults. But the side-effects of these drugs can be devastating for children: growth abnormalities, cosmetic deformity, and secondary cancers and infertility in later life.

Here at The Institute of Cancer Research (ICR), we are helping lead the fight-back, by pioneering the design and testing of new molecularly targeted therapies specifically designed to combat childhood cancer.

Our goal is to accelerate the incorporation of new drugs into frontline treatment – a personalised approach to treating children with cancer who currently die from their disease.

Background - How we are using Abbie’s Fund support

In November 2012 Abbie’s Fund generously pledged to continue their support of our proposal to develop techniques which will allow us to assess new treatment options for patients whose current therapy is not working, as well as to analyse the effectiveness of new targeted therapeutic drugs.

This project seeks to combine the use of two cell-based detection techniques developed with previous Abbie’s Fund support (bone marrow isolation, and blood and bone-marrow testing) with the use of new equipment and technology in mass spectrometry in order to detect additional blood changes (detection of circulating proteins and metabolites) in neuroblastoma. This combined approach would be developed in both cancer models and in human patients.
Additionally, we have now added the capability to detect epigenetic signatures in blood to our list of tests (epigenetic markers are small chemical tags added to DNA by our cells to help control activity of our genes; epigenetic signatures represent the pattern of epigenetic markers in our cells). We have also introduced a combination of techniques to detect gene signatures (the specific combination of genes expressed in a given cell that is associated with a particular type disease or cancer) associated with single cells.

This represents a critical phase of our research, since we can now accelerate and expand the development of an existing clinical testing platform and use it to analyse purified bone-marrow derived neuroblastoma tumour cells. The ability to analyse tumour cells in the bone-marrow is critical for neuroblastoma patients because we cannot ethically obtain repeated tumour tissue samples from patients who have relapsed.


Through the support of Abbie’s Fund Dr Louis Chesler and his team are developing four tests which will speed up the process of bringing molecularly targeted drugs into the clinic. These drugs are made more effective through the 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.

In early clinical studies in adult oncology, measuring biological characteristics (biomarkers) is now routine and has allowed investigators to understand if drugs are hitting their target in the cancer cell, as well as which patients will benefit most from each drug. These tests will support the use of biomarkers in upcoming clinical studies of neuroblastoma.

One such test uses mass spectrometry, which identifies and distinguishes between distinct molecules based on differences in their mass. In collaboration with the ICR’s Dr Paul Huang at our laboratories in Chelsea, we are analysing the levels of MYCN oncoproteins in both blood and tumour samples. In pre-clinical studies we have successfully used two potential drugs to target cancerous neuroblastoma cells with the overactive gene MYCN. This gene has been known to scientists for some time as a potentially important cancer target but was widely considered to be undruggable. However, through our research programme we believe that therapeutic strategies for targeting the activities of MYCN will become a clinical reality.

As mentioned in the last report, we have also successfully shown that our gene signature tests sensitively detect the existence of circulating neuroblastoma tumour cells in both blood and bone marrow of neuroblastoma models. Working with the ICR’s Dr Michelle Garrett and Dr Jennifer Smith and using flow cytometry techniques (using laser technology to count, sort and isolate cells of interest), these signatures will be used as biomarkers to improve the quality of our pre-clinical drug development efforts. Research continues to gather proof-of-principle that circulating neuroblastoma cells do exist and are detectable in neuroblastoma models.
Additionally, we continue to refine a successful epigenetic signature test for neuroblastoma in blood using human blood and bone marrow samples.

Further preliminary data is needed for all four of these tests. Currently a grant application in conjunction with Professor Andy Pearson is being developed to present the pilot data to establish this panel of tests for clinical use. If successful, the next stage will be to get these written into clinical trial protocols, so that in the next year or two, children with neuroblastoma will start to benefit from targeted therapies not associated with the devastating side effects of current standard treatments.

### Expenditure

In November 2012, we received £25,000 from Abbie’s Fund towards developing clinical tests for neuroblastoma, as the first tranche of two from a pledge of £50,000. Here we provide details of the expenditure against this amount.

<table>
<thead>
<tr>
<th>Item</th>
<th>Expenditure 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass spectrometry and molecular biology</td>
<td>£10,935.51</td>
</tr>
<tr>
<td>Chemicals for Mass Spectrometry</td>
<td>£4,515.97</td>
</tr>
<tr>
<td>Laboratory consumables and supplies</td>
<td>£4,554.51</td>
</tr>
<tr>
<td>Total (actual spend)</td>
<td>£20,005.99</td>
</tr>
<tr>
<td>Committed expenditure</td>
<td>£4,994.01*</td>
</tr>
<tr>
<td>Total</td>
<td>£25,000</td>
</tr>
</tbody>
</table>

*Although this amount is unspent at this point in time, it (and more) has been committed to experiments currently running and directly related to the budget headings for this award, however charges have not been made to date.

We remain extremely grateful to Abbie’s Fund for their continued and generous support of the ICR’s research into neuroblastoma. It is through the support of organisations such as yourselves that we are able to make the discoveries that defeat cancer.