The Neuroblastoma Society
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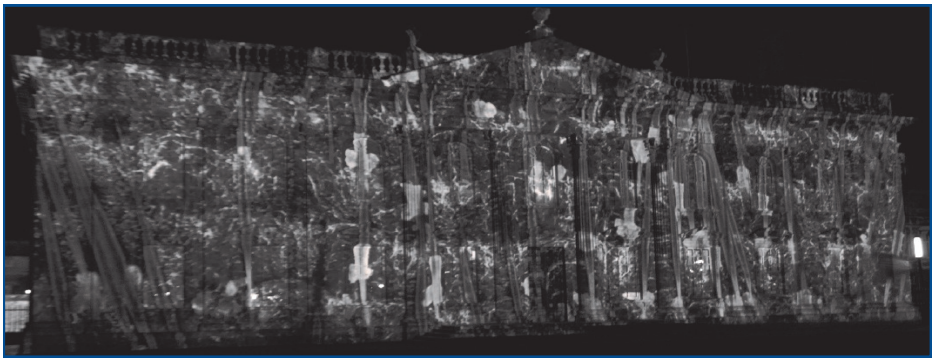
Report of the NEUROBLASTOMA RESEARCH SYMPOSIUM

Future Treatments for High Risk Neuroblastoma

Friday, 3rd December 2010
Cancer Research UK Cambridge Research Institute
Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE



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Neuroblastoma Research Symposium: Future Treatments for High Risk Neuroblastoma December 3rd 2010, Cambridge

On a cold Friday in December, researchers, clinicians and charities interested in understanding and improving treatments for neuroblastoma gathered for a Symposium in Cambridge, UK. The day was organized by the UK charity The Neuroblastoma Society, and the meeting benefited from generous support from Cancer Research UK and SPARKS charity.

The 3rd December was in the middle of the cold spell across the UK, and 4 of the original 16 speakers were unable to attend due to being snow-bound, along with some 30 delegates. Even so, it was very pleasing that about 100 delegates made it to Cambridge. The day included 12 talks, invited in topic areas that were thought to be key to current and future improvements in neuroblastoma treatment. While the presenters' backgrounds varied considerably, each provided new insight into how neuroblastoma arises and how patients can best be treated. The content from those presentations will be outlined in this report. We have attempted to make the science readable with as little jargon as possible, but some has been necessary. For topics we have failed to make clear, Wikipedia has useful related entries.

In addition to the talks, there were 21 posters presented by delegates. Professor Rob Mairs (Glasgow) and Dr John Anderson (UCL) selected two of these posters for cash prizes, donated by SPARKS charity. These were awarded to Owen Clark (UCL, Institute of Child Health) and to Jenny Gains (UCL Hospitals NHS Foundation Trust). A list of the titles of all posters is provided at the end of this report, along with digests of the two prize posters.

The Symposium deliberately brought together a mixture of practicing clinicians and research academics, in the hope that the interaction would be beneficial in both directions. Academics were exposed to the current standard of care and potential avenues for future treatments. Many clinicians went home with a greater understanding of not only the biology of neuroblastoma, but also of the treatments that they currently administer and the sorts of treatments that are likely to come on line in the future. It

was hoped that new contacts were made that will lead to collaborations in the future. Further Symposia will continue to facilitate links.

Whilst there are many other ways in which charities can help children with neuroblastoma, supporting the development of new treatments that will improve the survival of patients with high risk disease with minimal side-effects is of central importance, and it was good to see representatives from The Neuroblastoma Society, Cancer Research UK, SPARKS, Adam's Hats, The Neuroblastoma Alliance and Families Against Neuroblastoma take an active interest in proceedings. This meeting report is being sent to all charities for dissemination to interested parents.

Introduction

Neuroblastoma is the most common cancer diagnosed in the first year of life and accounts for around 15% of cancer deaths in children. Neuroblastoma is a tumor that originates in the sympathetic nervous system, which is responsible for, amongst other things, mobilizing our body's response to stress. Sites of primary tumours are most often within the adrenal medulla and otherwise in nerves alongside the spine from the base of the skull to the coccyx. Children are defined as having 'high risk' neuroblastoma if they have adverse combinations of disease stage, whether or not tumour cells have multiple copies of the MYCN gene, patient age, tumor cell chromosome number and the look of tumour cells under the microscope. High risk patients have 5 year survival of around 40%, and the survival rates in these patients have improved only modestly over the last 30 years, calling for continued and innovative research in the neuroblastoma field.

Professor Andrew Pearson (Institute of Cancer Research, Sutton) began the meeting with a comprehensive overview of high risk neuroblastoma treatment, past, present and future. Pearson praised SIOPEN (International Society of Paediatric Oncology - European Neuroblastoma) and its American counterpart COG (Children's Oncology Group), emphasizing how their collaborative efforts are vital for advancing the best standards of care for all children. Pearson also lauded the efforts of the neuroblastoma community in creating the International Neuroblastoma Risk Group (INRG) classification system, but also highlighted critical places requiring improvement. While the INRG classification system offers increased prognostic value compared to the previous International Neuroblastoma Staging System, it does not include a number of genetic and epigenetic abnormalities that are known to predict survival. Pearson also suggested that the dependency of the classification system on age should be removed as advances in the understanding of tumor biology are made. He called for improved treatment standards for patients with tumors containing MYCN amplification and activating mutations of the Anaplastic Lymphoma Kinase (Alk) gene, both of which are known to have unique treatment susceptibilities.

Neuroblastoma, a cancer of development

One theme that was evident across the meeting was the idea that neuroblastoma is fundamentally a tumor that arises from defects in embryonic development, necessitating a greater understanding of the basic mechanisms of sympathetic nervous system development and stem cell differentiation for successful disease treatment. The sympathetic nervous system is derived from a population of stem cells called the 'neural crest'. Professor Hermann Rohrer (Max Planck Institute for Brain Research, Frankfurt) described a network of master genes that control the turning-on and off of suites of other genes that correctly transform these neural crest stem cells into sympathetic neurons. One of these master genes, Phox2b, is known to be mutated in some inherited forms of neuroblastoma. Through elegant work using chick embryos, Rohrer was able to show that inducing mutations in the Phox2b gene makes cells that are becoming sympathetic neurons proliferate, that would otherwise not proliferate, and he proposed that neuroblastoma may result from this proliferation defect. Rohrer also showed that inhibition of the Alk gene (see above), another master gene that has recently been shown to be hyperactive in both inherited and non-inherited forms of neuroblastoma, results in decreased proliferation of sympathetic neurons. However, the role of Alk within development, and which other genes it controls, is only beginning to be understood.

It has been proposed that many tumours arise from a small population of tumor initiating cells (TICs, sometimes also referred to as cancer stem cells) and that these must be targeted to prevent tumor recurrence after treatment. TICs are thought to behave differently from bulk tumour cells and proliferate slowly, thereby evading many treatments that target rapidly dividing cells. Professor David Kaplan (SickKids, Toronto, Canada) is a pioneer of research into TICs found in the bone marrow of neuroblastoma patients with metastatic disease. Neuroblastoma TICs have many features in common with neural crest stem cells, though they are also thought to acquire attributes specific to the context in which they find themselves. Kaplan showed that TICs found in bone marrow metastases of neuroblastoma patients had a mixture of properties from two different cell types. They retain features of neural crest cells, such as high levels of the proteins Nestin and Tyrosine Hydroxylase, expected because this is their

tissue of origin. However, they also have high levels of proteins that are commonly found in blood cells, reflecting the bone marrow niche in which these TICs were found. In particular they have the signature of B-cell white blood cells. Furthermore, the TICs die if a protein involved in B-cell differentiation, Pax5, is therapeutically reduced. This potentially opens up new avenues for treatment in patients with disease that has spread to the bone marrow. Indeed, B-cell specific drugs used for treatment in lymphoma, such as Rituximab and Milatuzumab, have also been shown to be active in neuroblastoma TICs and may provide additional benefit to patients with metastatic neuroblastoma.

Since both neural crest cells and TICs display stem cell-like characteristics, understanding the fundamental behaviour of stem cells may lend novel insight into neuroblastoma. Professor Ben Simons (University of Cambridge) gave a broad overview of mechanisms of stem cell maintenance in normal developing tissues based on rigorous quantitation of patterns of stem cell division and differentiation. Stem cells were thought until recently only to divide asymmetrically, giving rise to one daughter cell that is identical to the mother stem cell, while the other daughter is a differentiated cell that has started down the route of becoming a particular cell type, for example a neuron. Tracking individual stem cells and their direct descendents over time allowed Simons and colleagues to demonstrate, in several different tissues, that in fact dividing stem cells produce either two daughter stem cells, two differentiated daughter cells, or one of each. Furthermore, the probability of the two types of symmetric division is identical and this results in the maintenance of resident stem cell populations. The likelihood that a stem cell will give rise to two differentiated cells, effectively removing the stem cell from the population, is balanced by an equal likelihood that a neighboring stem cell will undergo a symmetrical division yielding two stem cells. This has revolutionized our understanding of how stem cells behave, and allows us to start think of new ways of manipulating TIC behaviour, for example tipping the division balance towards differentiated cells in an attempt to eradicate the TIC population. Simons and collaborators are actively pursuing these possibilities.

MYCN

A strong focus on the basic science behind neuroblastoma was complemented by extensive discussion of new treatments for neuroblastoma. MYCN amplification, which means multiple copies of the MYCN gene in tumour cells, continues to be the factor most strongly correlated with poor prognosis in neuroblastoma. MYCN is part of a family of three Myc proteins in humans that also includes c-Myc and L-Myc. The Myc proteins act as master control genes that behave as a kind of cellular thermostat, single-handedly turning on a huge array of genes that increase the energy consumption of cells, leading to more rapid cell division and cell growth, and turns off genes with the opposite effect (such as Clusterin discussed below). It is no surprise therefore that the production of Myc proteins is elevated in most cancers. In neuroblastoma this is often achieved through multiple copies of the MYCN gene, but in neuroblastoma and other cancers, mutations in genes (or dysregulation of epigenetic mechanisms) that suppress Myc expression have a similar effect.

Professor Gerard Evan's group (Dept of Biochemistry, University of Cambridge) created a mouse line that allowed them to investigate the effect of reducing Myc protein production in tumours. They did this by introducing a gene into the DNA of a mouse that was an inhibitor of Myc production. Even better, they were able to control whether this Myc inhibitor was active or inactive through manipulating the diet of the mouse. Feeding it tetracycline induced Myc inhibition, and this could be reversed by removing tetracycline from the diet. When the Myc inhibitor was expressed in otherwise normal adult mice, this essentially halted all cell proliferation, including in the skin and gut walls, tissues that are known to have a high cell turnover rate. Remarkably, the animals remained in very good health and these cell proliferation defects were entirely reversed when tetracycline was removed from their diet. Most importantly, turning on the Myc inhibitor in mice carrying tumours lead to very impressive tumor regression. Moreover, in tumors that did not regress completely after the first period of tetracycline in their diet, several cycles of Myc inhibition were carried out resulting in increased tumor regression following each round. While it is clear that Myc is a challenging target for drug development, these results surely make it an attractive candidate for drug-mediated inhibition as a

treatment for a wide range of adult human tumours. For pediatric cancers the problem is more complicated, because the Myc proteins are essential for growth during development. However, the particular Myc protein that we are interested in, MYCN, is restricted to quite a limited role during development, and the side-effects of temporarily turning it off for periods during the first years of life after birth might not be too severe.

If MYCN is to be exploited as a therapeutic target, it is essential we have a better understanding of its role in the initiation and development of tumours. Dr Louis Chesler (Institute of Cancer Research, Sutton) is creating a series of genetically engineered models to evaluate MYCN protein over-production within various pediatric cancers. Currently the only successful model of neuroblastoma results from a genetically engineered model in which MYCN is expressed only in neural crest cells. Using models allows the thorough investigation of the efficiency of potential therapies. For instance, tumor growth and metastases can be observed non-invasively by introducing a fire-fly luciferase gene that only glows in tumour cells, making tumours easily visible, and tumor dependency on MYCN during different periods of tumour development can be evaluated by controlling the expression of MYCN through tetracycline in the diet, as used by Gerard Evan above. Evaluating differences across these models may yield further insight into whether neural crest cells show a critical period of susceptibility to becoming neuroblastoma tumours, as predicted by Rohrer above.

Avoiding relapse

Therapy aimed at reducing rates of relapse for high risk patients who have achieved remission currently includes treatment with 13-cis retinoic acid and immunotherapy to mop up minimal residual disease. Immunotherapy has been grabbing the headlines because of recent treatment successes, but progress is also being made in understanding how retinoic acid works. Recent evidence has shown that retinoic acid and celecoxib have a synergistic effect on neuroblastoma cell lines in the laboratory, but the mechanism of synergy has been unclear and celecoxib has no effect on its own. Drs Emma Bell, Chris Redfern and colleagues (Northern Institute of Cancer Research, Newcastle) have unraveled details of the mechanism of the synergistic effect of celecoxib. In doing so they have identified a gene (LOX-5) and a biochemical pathway (PPAR-delta) that are new potential therapeutic targets for reducing rates of relapse alongside retinoic acid (also see poster by Owen Clark below for a related approach).

A recent study in the USA lead by Dr Alice Yu has shown that immunotherapy reduces the rate of relapse in a certain group of neuroblastoma patients who achieve remission. The particular flavour of immunotherapy that has been shown to work involves giving patients particular types of antibodies against GD2, which forms part of the cell surface membrane of neuroblastoma cells. The human immune system is very complex and not fully understood. Indeed it is not yet known by what mechanism this proven anti-GD2 immunotherapy works. Nevertheless, immunotherapy is attractive as a therapy against many cancers because while treatment itself can be painful, fewer long-term side-effects are expected compared to most forms of chemotherapy. Immunotherapy is even being talked about as a potential front-line treatment, though many questions need to be answered before this can happen.

Neuroblastoma is an immunogenic tumor, meaning that the patient's natural immune system can attack tumour cells, and tumours can be found to have significant lymphocyte infiltration (evidence of an immune response) on biopsy at diagnosis or following chemotherapy, when surgically removed. Dr Juliet Gray (University of Southampton) is attempting to leverage this fact by utilizing the patient's own immune

system. Survivin is a protein expressed on the surface of cells from almost all neuroblastoma tumours, and has been shown to generate a strong T cell specific immune response in 8 out of 9 patients so far. By administering immune costimulatory molecules to amplify the natural anti-Survivin response, the Gray lab has seen some promising results in neuroblastoma models. Furthermore, these models had a long-term response to Survivin, suggesting this may be beneficial in patients with increased risk of recurrence.

In a related approach, Drs John Anderson and Martin Pule (UCL, London) are attempting to create designer white blood cells (T cell lymphocytes) that will mount an immune response against cancer cells that have unique antigens on their cell surfaces, such as GD2 in neuroblastoma. This technique is known as chimeric antigen receptor immunotherapy (CAR) and is already used to treat some adult cancers. This is an attractive technique because a range of features can potentially be engineered into the designed T cells to enhance, for example, the specificity of the T cells to neuroblastoma cells and the recruitment of other immune system cells. Anderson and Pule have also introduced a so-called "suicide" gene to the modified T cells, which is a safety switch doctors can use in case of a T-cell over-response. The suicide gene is activated by intravenous injection of a signal drug. This study is ready for Phase I trials to assess toxicity of the designer T-cells.

Epigenetic dysregulation in Neuroblastoma

The process through which a functional protein is produced in a cell from a gene of DNA involves many steps, some of which are regulated (enhanced or restricted) by so-called epigenetic mechanisms. These include the attachment of epigenetic markers onto or near a gene's DNA sequence itself, preventing the reading of the gene, and controlling how the DNA is coiled in the cell nucleus, determining whether genes are exposed for reading or hidden. Our understanding of the epigenetic regulation of gene expression is new and relatively poor, yet its control is vital for normal cell function, and is often awry in various cancers.

Two talks dealt with epigenetic dysregulation in neuroblastoma and both involved the role of the Polycomb Repressor Complex 2 (PRC2), which is a complex of proteins in the cell nucleus that binds to DNA and deposits epigenetic markers that can prevent the reading of genes. If this happens in error, and the gene in question is a tumour suppressor gene, this can lead to cancer. Dr Carol Thiele (National Cancer Institute, Bethesda, USA) presented work on one of these tumor suppressor genes, called CASZ1, found within the region of chromosome 1 that is commonly lost in high-risk neuroblastoma. CASZ1 was originally described as playing a role in the normal development of neurons from embryonic stem cells in the humble fruit-fly (Sarah Palin might be surprised to hear). Low production of CASZ1 protein is correlated with poor prognosis in neuroblastoma patients, and overproduction of CASZ1 in the laboratory causes slowing of tumor growth. Thiele found that CASZ1 is also regulated by the PRC2 complex, and that in neuroblastoma tumour cells, this regulation is enhanced and leads to suppression of CASZ1 expression. In neuroblastoma cell lines in the laboratory, drug inhibition of the effect of the PRC2 complex releases normal CASZ1 expression, and tumour cells differentiate into neurons.

Continuing on the theme, Dr Arturo Sala (UCL, London) presented a similar model of epigenetic repression. In neuroblastoma, overexpression of the MYCN protein is associated with low expression of the Clusterin gene, which like CASZ1 is thought to be a tumor suppressing gene. Sala's group found that MYCN protein binds directly to the DNA just next to the Clusterin gene. This stretch of DNA regulates the reading of the Clusterin

gene and can receive a variety of epigenetic markers, which can both enhance and interfere with reading. They hypothesized that MYCN was responsible for recruiting repressive PRC2 machinery to this Clusterin regulatory DNA. The Sala group then demonstrated that MYCN-mediated repression of Clusterin could be reversed by interfering with the functioning of the PCR2 complex. Further, administration of HDAC inhibitors, which inhibit PRC2 activity, caused increased expression of the Clusterin gene and subsequent inhibition of tumor growth. Importantly, the inhibition of tumor growth seen with HDAC inhibitors was reversed when Clusterin expression was independently suppressed. Thus, interfering with the docking of the PRC2 complex to the Clusterin regulatory DNA restored normal Clusterin expression, and hence its tumour suppressing function, even in the presence of amplified MYCN.

It should be noted though, that the PRC2 complex has a role in suppressing a large number of genes, and that broad inhibition of PRC2 therapeutically would cause other problems. The key would be to administer PRC2 inhibition specifically to tumour cells, or to find some unique signature of the action of the PRC2 complex on the Clusterin or CASZ1 genes that could be targeted. Nevertheless, the work of Thiele and Sala highlight epigenetic regulation as a potential therapeutic avenue for neuroblastoma. Tumour samples from individual patients could be screened for increased expression of tumor suppressor genes such as CASZ1 or Clusterin after HDAC inhibition. This might indicate therapeutic responsiveness, potentially providing a more personalized treatment approach for neuroblastoma patients.

Micro-RNAs

Another means of regulating gene expression is through micro-RNAs, which are very small lengths of RNA that interfere with protein production. There are now over a thousand known micro-RNA variants in human cells, somewhat less than the 30,000 genes in the human genome. Rather than being named with obscure and unhelpful names or acronyms, micro-RNAs have each been given an identification number. Professor Frank Speleman's group (Centre for Medical Genetics, Ghent, Belgium) has screened many of these, looking for micro-RNAs whose expression patterns in neuroblastoma cells correlated both with MYCN status and poor prognosis. One strongly correlated group were micro-RNAs from the 17-92 cluster, which coordinate the control of a number of processes including cell proliferation and cell death in neuroblastoma cells. Speleman and coworkers also compared micro-RNA expression patterns between normal neural crest cells and neuroblastoma tumour cells. One that differed significantly, being elevated in neuroblastoma cells, was micro-RNA 204. Intriguingly, this micro-RNA was shown to reduce Phox2b protein levels, which aligns well with Rohrer's results above, supporting the notion that the Phox2b gene has a tumor-suppressor role in neuroblastoma. Either when the Phox2b gene is mutated, or when micro-RNA 204 is over-expressed, too little Phox2b protein is produced, and this can result in neuroblastoma. Speleman also offered a tantalizing connection between Phox2b and MYCN, but this will require further work.

Approaches to chemoresistant disease

Most patients with high risk neuroblastoma initially respond to chemotherapy, but around 50% relapse with chemoresistant disease. Approaching treatment from a different angle, Professor Rob Mairs (Beatson Laboratories, Glasgow) presented a new therapeutic twist on an old technique (also see poster by Jennifer Gains below for a related study). Metaiodobenzylguanidine (mIBG) is a radiolabeled molecule that has been known for a long time to be ingested by cells of most neuroblastoma tumours because they possess a specific kind of cell surface transporter. Previously, mIBG uptake has been used to diagnose and stage patients with neuroblastoma as well as to monitor response to therapy. By using more potent radioactive concentrations of mIBG, mIBG administration can reach local radiation levels that are significant enough to cause DNA damage in neuroblastoma cells and cell death. By combining the more potent mIBG with other chemotherapeutic drugs (such as PARP inhibitors and topoisomerase inhibitors) the radiation induced DNA damage can synergize with inhibition of DNA repair. This treatment is soon to be incorporated into European high risk neuroblastoma trials for patients who respond poorly to chemotherapy or who relapse following chemotherapy.

Conclusion

The diverse presentation and variable natural history of neuroblastoma make this disease a particular challenge to scientists and clinicians alike. However, it is clear from this meeting that a deeper understanding of both the underlying normal development of the sympathetic nervous system, and changes in biology of neuroblastoma cells at different stages of this disease, will aid considerably in our understanding and treatment of neuroblastoma in the future.

This was a highly successful Symposium in many ways. Feedback forms were provided for delegates, and the response from these was extremely positive. All delegates were keen that The Neuroblastoma Society repeats such a Symposium every two years, alternating years with the world-wide Advances in Neuroblastoma Research conferences that many would expect to go to. The current plan is to hold the next Symposium in October 2011, attached to the SIOPEN AGM meeting in London. Details will appear on http://www.nsoc.co.uk. During the organization of this Symposium it became clear that the UK neuroblastoma community is in fact quite large, but also quite disparate. Hopefully this Symposium along with other initiatives such as the new CCLG Neuroblastoma Special Interest Group will galvanise the UK neuroblastoma community as a whole.

The printing and dissemination of this report on the Symposium was generously sponsored by Adam's Hats charity (http://www.adamshats.org).

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Alphabetic list of Poster Titles

Polysialyltransferase inhibition and tumour cell migration
Yousef Al-Saraireh & Robert Falconer, University of Bradford

Identification of micro-RNAs Contributing To Neuroblastoma Chemoresistance
Duncan Ayers & Jo Vandesompele, Center for Medical Genetics, Ghent University Hospital, Belgium.

Differentiation of human embryonic stem cells to sympathetic neurones: A model for understanding neuroblastoma pathogenesis
Jane Carr-Wilkinson & Deborah Tweddle, Northern Institute for Cancer Research, University of Newcastle-Upon-Tyne

Exploiting the embryonic environment to reprogram neuroblastoma cells
Rachel Carter & Diana Moss, Liverpool University

Epigenetic alterations in neuroblastoma and their effects on drug sensitivity
J. Charlet & Keith Brown, University of Bristol

Vanadium-Based Tyrosine Phosphatase Inhibitors Can Induce Apoptosis And Augment Retinoic Acid-Induced Neuritogenesis In Neuroblastoma Cells
Owen Clark & Andrew Stoker, UCL Institute of Child Health
Prize poster digest: This poster concerned the role a particular group of enzymes within cells, called the tyrosine-phosphatases, in the development and progression of neuroblastoma. The authors showed that chemicals that inhibit these enzymes could enhance the actions of retinoic acid – an important neuroblastoma drug - causing the maturation of malignant tumour cells to benign nerve cells, as well as activating signalling pathways vital for the survival of these nerve cells. Conversely, they showed that the same chemicals could selectively kill neuroblastoma cells when used alone. They are also examining whether specific members of this enzyme group are implicated in the initiation of neuroblastoma tumours.

Upregulated Angiogenin expression is associated with adverse clinicopathological and biological prognostic factors in neuroblastoma
Josiah Dungwa & Pramila Ramani, University of Bristol

Ca IX Is Significantly Upregulated In Mycn Amplified Neuroblastomas
Josiah Dungwa & Pramila Ramani, University of Bristol

The role of PML in the nervous system and in the pathogenesis of neuroblastoma
Maria Dvorkina & Paolo Salomoni, UCL Cancer Institute

^{177}Lutetium DOTATATE therapy for childhood neuroblastoma
Jennifer Gains & Mark Gaze, UCL Hospitals NHS Foundation Trust
Prize poster digest: The authors presented preliminary results of applying an established therapy for some adult cancers to neuroblastoma for the first time. The goal of the therapy is similar to that of mIBG therapy, in that radiolabeled molecules are introduced to the patient that it is hoped will home in on and kill neurobastoma cells only. In this case, the radioactive molecule is the peptide ^{177}Lutetium DOTATATE, and it homes in on and attaches to somatostatin receptors, present on the surface of cells from most neuroblastoma tumours. Prior to treatment, neuroblastoma tumours must be imaged with ^{68}Gallium DOTATATE in PET/CT scans to identify those suitable for therapy with ^{177}Lutetium DOTATATE. The authors summarised results for the first six children with relapsed or refractory high risk neuroblastopma. Therapy was found to be safe and feasible and this approach will now be taken forward in a Phase I/II clinical trial to look formally at toxicity and efficacy.

MYCN sensitises neuroblastoma to MDM2-p53 antagonists
Laura Gamble & John Lunec, Northern Institute for Cancer Research, Newcastle University

Chemical modulation of NF-kB dynamics in neuroblastoma cells affects gene expression
Catherine Heyward & Mike White, University of Liverpool

Up-regulation of autotaxin/LPA signaling alters cellular metabolism in advanced stage neuroblastoma
K Hodgetts & Carmel McConville, University of Birmingham

Targeting Bcl-2 family proteins to overcome hypoxia-induced resistance to chemotherapy in neuroblastoma
Tetanya Klymenko & Guy Makin, University of Manchester

Pain management tool for High-Risk Neuroblastoma patients having Anti-GD2 immunotherapy
Sophie Knight & Ramya Ramanujachar, Addenbrooke's Hospital, Cambridge

Identification and cloning of a new alternatively spliced isoform of Vascular Endothelial Growth Factor Receptor 2, Svegfr21-8
M Peiris-Pages & Pramila Ramani, University of Bristol

The effect of COX-2 expression on Celecoxib sensitivity and tumour growth in neuroblastoma
Frida Ponthan & Chris Redfern, Northern Institute for Cancer Research, University of Newcastle upon Tyne

Practical aspects of administration of Anti-GD2 immunotherapy in High-Risk neuroblastoma patients in the UK.
Ramya Ramanujachar, Addenbrookes Hospital, Cambridge & Peppy Brock, Great Ormond Street Hospital, London

A simple, highly visual in vivo screen for ALK inhibitors
Frederico Rodrigues & Robert Kelsh, University of Bath

The neuroblastoma ALK(I1250T) mutation is a kinase-dead RTK in vitro and in vivo.
Christina Schönherr & Bengt Hallberg, Umeå University, Sweden

MicroRNA-34 is a potent tumor suppressor molecule in vivo in neuroblastoma
Amanda Tivnan & Raymond Stallings, Royal College of Surgeons in Ireland, Dublin

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