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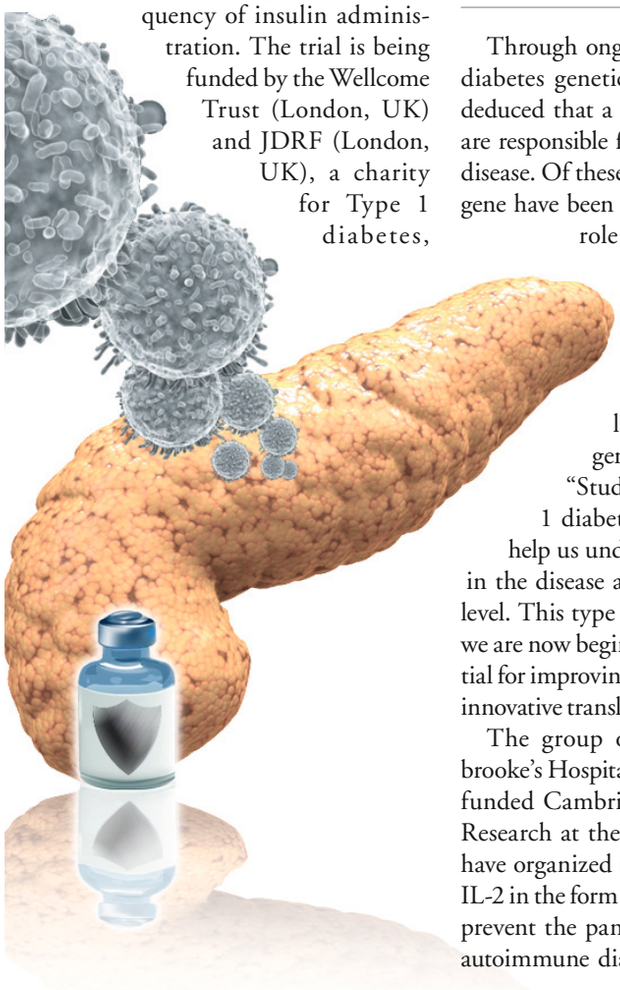
CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Clinical trial using a drug form of IL-2 hopes to improve management of Type 1 diabetes

A new clinical trial using a drug that regulates the immune system in sufferers of Type 1 diabetes is underway in the UK. The investigators, basing their research on recent findings relating to the genetics of the disease, believe that if effective, the tested drug could have important implications on the management of diabetes, particularly regarding the frequency of insulin administration. The trial is being funded by the Wellcome Trust (London, UK) and JDRF (London, UK), a charity for Type 1 diabetes, along with the National Institute of Health Research – a UK government body that coordinates research for the NHS.



"The group of researchers ... have organized this trial to assess whether IL-2 in the form of the drug aldesleukin can prevent pancreatic damage."

Through ongoing research into Type 1 diabetes genetics, scientists have already deduced that a number of different genes are responsible for the development of the disease. Of these genes, variants of the *IL-2* gene have been identified as playing a key role in diabetes. John Todd from the Wellcome Trust Diabetes and Inflammation Laboratory at University of Cambridge (Cambridge, UK) highlighted the importance of genetic research for the clinic: "Studying the genetics of Type 1 diabetes has proved essential to help us understand what is happening in the disease at a cellular and molecular level. This type of research takes time, but we are now beginning to test its true potential for improving the lives of patients in our innovative translational medicine program."

The group of researchers at Addenbrooke's Hospital and the Wellcome Trust-funded Cambridge Institute for Medical Research at the University of Cambridge have organized this trial to assess whether IL-2 in the form of the drug aldesleukin can prevent the pancreatic damage caused by autoimmune diabetes in newly diagnosed patients. An important objective of the trial was to find out what dosage of the drug is the most effective for achieving acceptable patient outcomes. Frank Waldron-Lynch, from the University of Cambridge, who is leading the trial, explained what they hope to achieve: "Type 1 diabetes is a potentially very serious disease that requires lifelong treatment and regular insulin injections throughout the day. Our aim is to use aldesleukin to rebalance the immune system so that patients can significantly reduce the number of insulin injections needed to just once or twice a week by slowing the progression of the disease."

Currently, the first two patients have been enrolled onto the trial and have received treatment. The treatment has been administered in very low amounts as the investigators assess what the necessary dose in adults is. It has been reported that, so far, the results appear to be very positive, with no detectable side effects. However, more participants will need to be recruited onto the DILT1D study to help determine whether the drug is effective and at what dose.

If successful, this trial could change the frequency of doses for insulin administration, having an important effect on the quality of life of patients. Michael Dunn, at the Wellcome Trust explained the importance of this kind of research and the bridge between genetics and immunotherapy: "We have invested heavily in genetics over the past few decades to understand the biological causes of diseases. At the same time as showing us how complex diseases are, it has also provided tantalizing clues as to how they may be

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treated. This is the first time that immunotherapy – in other words, trying to rebalance the immune system – has been trialed in the UK as a way of tackling Type 1 diabetes, and it would not have been possible without the strong foundation of genetics and immunology research that underpins it."

Written by Jonathan Wilkinson

Source: Wellcome Trust press release: www.wellcome.ac.uk/News/Media-office/Press-releases/2013/WTP052844.htm

Early results indicate safety of radiation–antibody combination in HER-2 positive cancers

The first results of a Phase I study on the safety of a radiation–antibody combination for the treatment of HER-2 positive cancers have been presented at the recent Society of Nuclear Medicine and Molecular Imaging annual meeting (Vancouver, Canada). The radiation–antibody combination was not shown to cause long-term toxicity in the patients 6 months after treatment. These early results are part of an ongoing Phase I trial conducted by researchers at the University of Alabama at Birmingham (AL, USA).

The study involves 18 patients with HER-2 positive cancer of the abdomen who have failed on previous treatments. At present, eight of these patients have received the combination of the antibody-based treatment herceptin (trastuzumab) and the radioactive material Pb-212, and results of the first three were presented: "So far we have only preliminary data in a few patients. Should further studies prove this combination treatment to be safe and effective, however, it could be useful against the 40% of HER-2-expressing ovarian and gastric cancers, while sparing normal tissues," explained Ruby Meredith (University of Alabama at Birmingham).

At present, there has been no build of radioactive material or negative effects on the patients' bone marrow. The scientists have also found that the radioactivity has remained in the abdomen.

The effectiveness of the radiation–antibody combination is due to the collective action of its components. The Herceptin antibody is able to attach itself to the HER-2-protein present on the cell surface of HER-2-positive cancers, which then allows the radioactive material to intercept the DNA in the HER-2-positive cancer cells, leading to the destruction of the cells.

It is hoped that this approach, which entails cells being killed individually, will help to combat cancers that have already spread: "By killing cancer cell by cell, our approach promises to be useful against metastases that have spread along the lining of the abdomen," explained Meredith.

Following these positive results, the next stage of the study will include an increase in the dose of this radiation–antibody combination.

Written by Natasha Galukande

Source: University of Alabama at Birmingham press release: Early data from first human study suggests radiation–antibody combination is safe: www.uab.edu/news/latest/item/3534-early-data-from-first-human-study-suggests-radiation–antibody-combination-is-safe

Genetically modified mesenchymal stem cells to be trialed in advanced cancer patients

The international biopharmaceutical company Apceth GmbH & Co. KG (Munich, Germany) has received approval to conduct a clinical trial using its genetically modified, adult mesenchymal stem cells in cancer patients. This is a novel approach to the treatment of advanced cancer, for which there is currently no effective treatment available.

The multicenter, open-label trial will recruit patients diagnosed with advanced adenocarcinomas of the gastrointestinal tract. The basis of this novel therapy is the harvesting of autologous stem cells from the patient's bone marrow. These cells are processed, genetically modified and subsequently reinfused into the patient. The modified stem cells specifically target the tumor and their cytotoxic gene product is selectively activated at the site of the tumor or its metastases. It is hoped that such a therapy would increase local efficiency while reducing systemic toxicity, a principle that would be applicable to other cancer types.

The clinical trial will commence at the University Hospital Grossharden (Munich, Germany) in collaboration with experts from the National Center of Tumor Diseases (Heidelberg, Germany) and the Karolinska Institute (Stockholm, Sweden). A number of leading international cancer centers have also expressed interest in taking part in the trials including the MD Anderson Cancer Center (Houston, TX, USA), the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) and the Lombardi Cancer Center of the Georgetown University (Washington, DC, USA).

The Director of the Lombardi Cancer Center John Marshall explained his institution's interest in the trial stating: "This is a very exciting new class of drugs based on adult stem cells delivering a true innovation for patients with advanced cancer. There is a clear unmet medical need for this and we are hopeful that we can begin testing in the USA soon."

Written by Hannah Wilson

Source: Apceth press release: www.apceth.com/newsroom/press-releases/2013

Nivolumab undergoing Phase I testing on metastatic renal cell carcinoma

Research on the clinical Phase I trial of nivolumab (Bristol-Myers Squibb, NY, USA) has been presented at the American Society of Clinical Oncology annual meeting (IL, USA). The team from Dartmouth-Hitchcock Norris Cotton Cancer Center (NH, USA) presented a poster of the PD-1 receptor blocking antibody nivolumab, which is being evaluated in conjunction with other drugs in patients diagnosed with kidney cancer.

Metastatic renal cell carcinoma (mRCC) is the seventh most common global cancer, resulting in an estimated 116,000 deaths. Approximately 25% of those diagnosed with mRCC, are metastatic at diagnosis.

Nivolumab is currently being tested in various cancers, such as non-small-cell lung cancer and advanced melanoma. Nivolumab carries out its mechanism of action by restoring T-cell antitumor function and suppressing an immune checkpoint modulator.

In the Phase I study, nivolumab is to be used in combination with existing treatments such as pazopanib and sunitinib or with ipilmumab. Although the existing treatments have demonstrated a reduction in disease progression, they do not display lasting responses. In addition to this, many patients also develop a resistance to these existing therapies. In other Phase I and II clinical trials, nivolumab has demonstrated a durable response in patients with kidney cancer.

The poster presented at the American Society of Clinical Oncology's annual meeting, described a Phase I four-arm study in which combinations of nivolumab with existing therapies and ipilmumab were administered to patients with mRCC.

The objective for the study is to primarily assess tolerability and safety of the drug, as well as to determine the recommended dose to carry through to Phase II studies. The second aim of the study is to review antitumor activity. As well as this, researchers will be evaluating the pharmacodynamics, pharmacokinetics, immunogenicity and overall survival of nivolumab, as well as the predictive biomarkers for the combinations used with nivolumab.

Written by Priti Nagda

Source: Dartmouth-Hitchcock Norris Cotton Cancer Center press release: www.cancer.dartmouth.edu/about_us/newsdetail/63819

Creation of an educational tool to boost Hispanic participation in clinical trials

Cancer patients from a Hispanic background have extremely low participation rates in clinical trials. Researchers from the Moffitt Cancer Center (Tampa, FL, USA) looked into why this was the case, and why awareness of cancer trials was also low in this population.

There are approximately 45.5 million Hispanics residing within the USA, and taking into account that this is the nation's fastest growing ethnic group, a need exists for the creation of educational materials that are aimed at this particular culture and language. Instead of merely translating educational materials from English, the material should be adapted to specially meet a groups cultural needs.

To find out, focus groups consisting of 36 cancer survivors who spoke Spanish from Puerto Rico and Tampa were set up. From these groups, researchers were able to ascertain that low participation rates could be due to a multitude of factors, from a language barrier to the cultural belief that it is only doctors and not patients that can guide treatment decisions.

Using feedback received at the focus groups, the researchers set out to develop a video and booklet tailored for a Spanish-speaking audience in order to both empower and educate patients to be able to take part in treatment decisions.

Gwendolyn Quinn (Moffitt Cancer Center, FL, USA), the lead author on the study, explained their findings further, "We found that Hispanic patients who prefer information in Spanish had different informational needs and concerns than non-Hispanic patients." Quinn also explains why tailoring to their needs may work, "Keeping that in mind, we developed educational materials using a social marketing approach, which targets a specific audience instead of creating a generic product for everyone. This approach increases the chances a patient may relate to the material, making their behavior change more likely."

The focus groups also revealed culturally biased ideology that may explain the rare participation of Hispanics in clinical trials. For instance, there was uncertainty and confusion as to why a doctor would ask a patient to be involved in trial participation and Hispanic patients' core belief is that a doctor will provide all the guidance. As well as this, within Hispanic culture the patient relies on their family to make decisions related to health care.

The researchers will be using their specially tailored Spanish booklet and video in a randomized clinical trial to evaluate how effective these educational aides are in improving the perceptions that Spanish speaking cancer patients have of clinical trials.

The hope for the outcome of the trial is explained by Quinn, "They may say no, but they will be prepared with knowledge about the purpose of clinical trials and will not be making an uninformed decision."

Written by Priti Nagda

Sources: Quinn GP, McIntyre J, Gonzalez LE, Antonia TM, Antolino P, Wells KJ. Improving awareness of cancer clinical trials among hispanic patients and families: audience segmentation decisions for a media intervention. *J. Health Commun.* doi: 10.1080/10810730.2013.768723 (2013) (Epub ahead of print); Moffitt Cancer Center press releases: www.moffitt.org/home/moffitt-in-the-news/press-releases/2013/quinn-hispanic-clinical-trials