Cancer-imaging nanoparticles progress to clinical trials in landmark approval

The US FDA has granted regulatory approval to a nanoparticulate cancer imaging technology, in the first regulatory approval of an inorganic treatment modality. This will be a welcome affirmation for the many groups working on nanoparticle-based treatment strategies.

The approval was granted to so-called 'Cornell dots' or C dots, a technology developed by researchers at Cornell University (NY, USA). The C dots consist of dye particles enclosed in an inert silica shell. For human trials, the silica particles will be coated in polyethylene glycol to avoid a foreign body response in the patient. They can also be labeled with organic molecules that can direct the dot directly to the relevant tumor mass. The dye can then be activated by infrared-spectrum energy, providing a much brighter luminescence and much clearer picture of the tumor characteristics than with regular uncoated dyes. Pharmacokinetic and pharmacodynamic studies in mice have proven very little interaction with bodily functions and safe, effective clearance via the urine.

The C dots have a number of interesting features, one of which being they can be tailored to any particle size. Current studies have shown that even ultrasmall particles to a size of 5–7 nm in diameter can be retained for a finite amount of time and then safely excreted in mouse models. Thanks to the recent Investigational New Drug Application approval from the US FDA, these C dots will be used in their first clinical trial at Memorial Sloan Kettering Cancer Center (MSKCC; NY, USA) on five healthy patients. The silica particles will be attached to radiolabeled iodine to make them visible to PET scans. This technique will then be used to study basic pharmacokinetic and pharmacodynamic properties in humans, in an attempt to verify findings from mouse studies.

If successful, researchers say there could be further applications for this technology, such as using it to specifically target treatments to very specific cancer cells. "This is a very exciting and important first step for this new particle technology that we hope will ultimately lead to significant improvements in patient outcomes and prognoses for a number of different cancers," said Michelle Bradbury, radiologist at MSKCC and lead investigator on the first-in-man clinical trial.

This regulatory approval is pivotal in creating tangible clinical applications for a technology many groups are developing. It is hoped that this will pave the way for realization of other nanoparticle-based treatment development programs.

Source: Memorial Sloan Kettering Cancer Center Press Release: www.mskcc.org/mskcc/html/102185.cfm

in the news...

Phase III clinical study results offer new hope for improved survival rates in patients with advanced metastatic melanoma

Genentech, a member of the Roche Group, recently announced that the BRIM3 clinical study of RG7204 (PLX4032), has successfully demonstrated a marked survival benefit in patients with previously untreated BRAF V600 mutation-positive metastatic melanoma, the most aggressive and deadliest form of skin cancer. Participants treated with RG7204 exhibited a greater overall survival and progression-free survival compared with participants who received dacarbazine, the current standard of care.

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James Larkin from The Royal Marsden cancer centre in London, UK, terms this "an incredibly exciting breakthrough", going onto speculate: "Malignant melanoma is a very difficult disease to treat, and with a growing incidence in younger people the results of this Phase III trial are very encouraging."

Hal Barron, chief medical officer and head of Global Product Development remarked: "For the first time, a personalized investigational medicine, RG7204, has shown a significant survival benefit in metastatic melanoma. This is an important advance for people with the BRAF V600 mutation-positive form of the disease who have had extremely limited treatment options."

The drug in question, RG7204, is a potential first-in-class molecule whose mode of action centers on selectively inhibiting the mutated BRAF protein, which is present in approximately 50% of all cases of metastatic melanoma. It is one of 800 drugs currently in trial for the treatment of cancer and presents a clear example of the personalized healthcare approach to identifying the right medicine for the right patient undertaken by the biotechnology company.

Frequent adverse events linked to the drug are often skin-related, but some mild and reversible increases in liver enzymes are sometimes also observable in patients. Researchers studying the safety profile of the drug found it to be generally consistent with previous studies.

Cancer Research UK's Doctor Leslie Walker remarked: "The drug is not yet licensed and is unavailable to patients not on a clinical trial, but we hope that these results will change this situation very rapidly."

The complete data from this trial is to be presented at a conference later this year.

Source: Press Release Genentech: www.gene.com/gene/news/press-releases/display.do?method=detail&id=13187

Powerful immune stimulant, Hiltonol®, receives funding to enter production

Production of the immunological stimulant Hiltonol® (Poly-ICLC) has been given the green light thanks to an investment agreement between Oncovir Inc (Washington, DC, USA) and the Cancer Vaccine Acceleration Fund (New York, NY, USA).

Oncovir will be provided with US$450,000 to fund the manufacture of clinical grade Hiltonol. In return, 10,000 doses of Hiltonol will be dedicated for use in 10–15 early- and mid-phase clinical trials that will be conducted within the Cancer Vaccine Collaborative (CVC; NY, USA), a global network of academic clinical trial sites and advanced immunological monitoring laboratories.

Hiltonol, a pathogen-associated molecular pattern, provides a 'danger signal' that prompts the generation, targeting and maintenance of effective high-quality, long-lasting immune responses against multiple pathogens and tumors. Hiltonol has at least four known interrelated clinical actions, any of which could be responsible for its antitumor and antiviral activity: induction of interferons; broad immune enhancing effect; activation of specific enzymes, especially oligoadenylate synthetase and the p68 protein kinase; and broad gene regulatory actions.

Lloyd Old, Director of the CVC commented on the agreement, "Providing funding that will enable a large quantity of clinical grade Hiltonol to be manufactured is essential to furthering both Oncovir's and our program's clinical research objectives. Specifically, having a supply of Hiltonol under CVC control will make it possible for our investigators to identify its optimal use within the context of cancer vaccines, particularly in combination with other critical agents, such as antibodies that have the capacity to neutralize cancer-induced immunosuppression. The partnership with Oncovir brings us one step closer to an optimally effective therapeutic cancer vaccine for patients."

Source: Cancer Research Institute press release: www.cancerresearch.org/press-room/2011/01/21/cancer-research-institute-and-oncovir-partner-to-produce-clinical-grade-poly-ICLC-hiltonol-for-trials-of-cancer-vaccines-and-other-immunotherapies

Allogenic stem cell injection for the treatment of critical limb ischemia to be evaluated in a Phase II/III clinical trial

European and US regulators have granted approval to biotherapuetics company Pluristem Therapeutics, Inc. (Haifa, Israel) to proceed with the clinical trial program for their lead product, PLX-PAD, an allogenic stem cell therapy designed to treat critical limb ischemia related to peripheral artery disease.

The Pluristem PLacental eXpanded (PLX) cells are placenta-derived cells that are incubated in Pluristem's specialist bioreactor, where they are exposed to an artificial environment of stromal cells and substrates and allowed to develop into treatment-specific adherent stromal cells. The lead product in this line has been developed to treat critical limb ischemia related to peripheral artery disease. In developed countries,

sedentary lifestyles have led to recent increases in the number of cases of this disease, so novel therapies are warranted.

Preclinical data on this product suggested promising efficacy in animal models. PLX-PAD cells were intramuscularly administered to mice whose hind legs were rendered ischemic. Post-treatment evaluation using Doppler technology indicated revascularization of the limb treated with PLX-PAD cells but not in those that were not treated with PLX-PAD. "PLX-PAD has shown an early read-out of efficacy throughout its clinical development and I am pleased that PLX-PAD has made the necessary progress, from a regulatory perspective, to move forward with advanced trials," commented Edwin Horwitz, President of the International Society for Cell Therapy, and the head of Pluristem's scientific advisory board.

Following successful Phase I studies in healthy patients, Pluristem plan to initiate Phase II/III studies in the EU and the USA, involving primary study end points of major amputation-free survival rates (amputations and death) at 12 months from the initial treatment with PLX-PAD or placebo. Patients with severe critical limb ischemia will be enrolled and treated with two PLX-PAD treatments or with two placebo treatments, a few months apart. PLX-PAD or placebo will be administered via multi-intramuscular injections delivered to the affected leg.

Pluristem will be hoping for success in these trials, which may pave the way for further allogenic stem cell treatments under investigation to progress. Pluristem have already planned development programs for stem cell therapies for inflammatory bowel disease, ischemic stroke and multiple sclerosis based on the same PLX technology.

Source: Pluristem press release: www.pluristem.com/18_01_2011.asp

New multistage TB vaccine shown to produce stronger, longer-lasting response against *Mycobacterium tuberculosis*

In a recent National Institute of Allergy and Infectious Diseases (NIAID) and the Bill and Melinda Gates Foundation funded study, researchers from the USA and Europe have found a new vaccine strategy that produces stronger, longer-lasting protection from TB infection than the currently used Bacille Calmette–Guérin (BCG) vaccine.

Tuberculosis is caused by the bacterium *Mycobaterium tuberculosis* and was estimated to be responsible for 1.7 million deaths in 2009. Furthermore, despite the widespread availability of the BCG vaccine, a resurgence of TB cases has been seen in Western European countries and the infection poses a particular problem in prisons. Furthermore, drug-resistant strains are increasingly being seen and are contributing to the problem. The BCG vaccine provides protection against initial TB infection, but does not prevent latent infection, which may consequently develop into active infection in later years.

In their recent study coordinated by the NIAID-funded TB Vaccine Testing and Research Material Program at Colorado State University (CO, USA) the team of researchers, including Peter Andersen of the Statens Serum Institut (Copenhagen, Denmark), developed a multistage vaccination strategy combining early and latency-associated *M. tuberculosis* antigens. The early antigens Ag85B and 6-kDa early secretory antigenic target (ESAT-6) have previously been shown to improve the effectiveness of the BCG vaccine. These proteins were combined with Rv2660c, a latency-associated protein that is stably expressed in the late stages of *M. tuberculosis* infection, to produce the H56 vaccine. This novel vaccine was administered to uninfected CB6F1 mice prior to and after BCG vaccination; 6 weeks later the vaccinated mice were exposed to *M. tuberculosis*. The group found that, not only did this multistage strategy protect against initial illness, but it also controlled reactivation of latent infection and reduced pulmonary levels of the mycobacterium more effectively than vaccination with BCG alone.

Andersen commented on these findings, "Preventing latent TB from relapse is the most efficient way of controlling transmission and thereby the global spread of TB."

The H56 vaccine was able to promote a T-lymphocyte-mediated response against the three protein components of the vaccine, as characterized by a high proportion of polyfunctional $CD4^+$ T cells. Owing to its ability to elicit cell-mediated responses against the latency-associated protein, the H56 vaccine may be able to compensate for the shortcomings of the BCG vaccine, as Andersen explains, "The BCG vaccine is efficient in children but cannot be used to boost already infected individuals. Furthermore, BCG does not prevent the establishment of latent persistent infection or reactivation of clinical disease – a major need for both infected patients and for reducing further transmission. The H56 vaccine contains antigens that are expressed in the early and late stages of TB and combated late-stage infection in both pre- and post-exposure mouse models."

The team hope to expand on this finding and consider its clinical application.

"If successful in clinical trials we hope that the vaccine can be integrated into the vaccination program to boost adolescents before they leave school and thereby prevent pulmonary TB in adults. One potential application may also be, together with preventive chemotherapy, to shorten the treatment period and prevent the steady increase in multidrug-resistant strains of *M. tuberculosis*."

Sources: EurekAlert: NIH, Gates Foundation and Colorado State team up to find new approach to a TB vaccine: www.eurekalert.org/pub_releases/2011-01/nioa-ngf012511.php; Aagaard C, Hoang T, Dietrich J et al.*: A multistage tuberculosis vaccine that confers efficient protection before and after exposure.* Nat. Med. *17(2), 189–194 (2011).*

Drug Approvals December 2010 to February 2011					
Trade name	**Generic name**	**Indication**	**Region**	**Manufacturer**	**Date approved**
Cardiology					
Amturnide™	Aliskiren, amlodipine and hydrochlorothiazide	High blood pressure	USA	Novartis	December 2010
Prazaxa®	Dabigatran etexilate	Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation	Japan	Boehringer Ingelheim	January 2011
Neurology					
Viibryd™	Vilazodone HCl	Major depressive disorder	USA	Trovis Pharmaceuticals	January 2011
Invega®	Paliperidone ER	Treatment of psychotic or manic symptoms of schizoaffective disorder	EU	Janssen-Cilag International NV	January 2011
Oncology					
Abstral®	Fentanyl	For the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain	USA	ProStrakan Inc.	January 2011
Gardasil®	Human papillomavirus quadrivalent (types 6, 11, 16 and 18) vaccine, recombinant	Prevention of anal cancer and associated precancerous lesions due to human papillomavirus types 6, 11, 16 and 18, in males and females from 9 to 26 years of age	USA	Merck and Co. Inc.	December 2010
Rituxan®	Rituximab	A maintenance treatment for patients with advanced follicular lymphoma who responded to initial treatment with rituximab plus chemotherapy (induction treatment)	USA	Roche	January 2011
Sprycel®	Dasatinib	Treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph^+) chronic myelogenous leukemia in chronic phase	USA	Bristol-Myers Squibb	December 2010
Sutent®	Sunitinib malate	Treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults	EU	Pfizer	December 2010
Other					
Fortesta™	Testosterone	Hypogonadism	USA	Endo Pharmaceuticals	January 2011
Gralise™	Gabapentin	For the management of postherpetic neuralgia	USA	Abbott Products Inc.	January 2011
Makena™	Hydroxyprogesterone caproate	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth	USA	Hologic Inc.	February 2011