Novel therapy stimulates immune system to attack scaffolding surrounding pancreatic cancer tumors

Researchers at the Abramson Cancer Center, University of Pennsylvania (PA, USA) have discovered a novel way to treat pancreatic cancer utilizing the patient's own immune system to destroy the scaffolding surrounding the tumor.

The results were observed in an ongoing study that utilizes a unique research model designed to improve understanding of effective treatment options. The current clinical trial involved pancreatic cancer patients receiving standard gemcitabine chemotherapy with an experimental antibody manufactured by Pfizer that binds and stimulates the cell surface receptor CD40, a key regulator of T-cell activation.

> *"...we've used the CD40 receptor to re-educate those macrophages to attack – not promote – the tumor."*

The research team hypothesized that the experimental antibodies would turn on the T cells, allowing them to attack the tumor, and the treatment appeared effective, with some patients' tumors shrinking substantially, as well as the vast majority losing metabolic activity after treatment. However, all of the patients who responded to initial treatment did eventually relapse. On inspection of the tumor samples after treatment, obtained via biopsy or surgical removal, the researchers noted the absence of T cells and instead an abundance of macrophages.

This unusual observation prompted them to revert back to an earlier mouse model of pancreatic cancer developed several years previously at the University of Pennsylvania. Treating mice with the same gemcitabine and experimental antibody therapy resulted in similar effects in reducing tumor size and allowed the researchers to further investigate the macrophage abundance. The macrophages appeared to be attacking the tumor stroma, which surrounds the tumor to provide support. Pancreatic tumors secrete chemical signals to draw macrophages to the site, which would normally provide protection to the tumor. However, treatment with the CD40 antibodies appears to have the opposite effect. "It is something of a Trojan horse approach," commented Robert Vonderheide, Associate Professor of Medicine at the Abramson Family Cancer Research Institute. "The tumor is still calling in macrophages, but now we've used the CD40 receptor to re-educate those macrophages to attack – not promote – the tumor."

The researchers believe that the CD40 antibodies also activated T cells in the mice, but they were unable to reach the tumor or its surrounding tissue owing to the dense, fibrotic area surrounding pancreatic cancers. "We learned that T cells have a major problem with migration into tumors, and this may be a particular problem for pancreatic cancer. The area surrounding pancreatic cancers is very dense, fibrotic and hostile. This is one of the main reasons standard therapies for this disease often work so poorly," continued Vonderheide.

The researchers are looking at methods to capitalize on their novel discovery, testing ways to maximize the macrophage response and enabling the T cells to reach the tumor microenvironment. "Attacking the dense tissues surrounding the cancer is another approach, similar to attacking a brick wall by dissolving the mortar in the wall. Ultimately, the immune system was able to eat away at this tissue surrounding the cancer, and the tumors fell apart as a result of that assault. These results provide fresh insight to build new immune therapies for cancer," said Vonderheide.

"Beyond our specific findings, we think these findings point to a new approach for drug development in cancer – one where we use state-of-the-art mouse models for preclinical trials to guide which trials we should do next in patients. It should be faster, cheaper and give us a head start in the clinical trials," concluded Vonderheide.

Source: Penn Medicine News: www.uphs.upenn.edu/news/News_Releases/2011/03/pancreatic-cancer-immunotherapy/

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Medtonic's Consulta® and Syncra™ cardiac resynchronization therapy-pacemaker systems approved by the US FDA

Medtronic have announced the US FDA approval of its next-generation Consulta® and Syncra™ cardiac resynchronization therapy-pacemaker (CRT-P) systems. Both Consulta and Syncra provide fully automatic capabilities and adaptive therapies that help to ensure CRT, even during atrial fibrillation. These systems also allow physicians to monitor their heart failure patients in the office or remotely and include unique programming flexibility to help avoid phrenic nerve stimulation, consequently preventing the need for more invasive surgical approaches.

These stopwatch-sized devices are implanted in the upper chests of heart-failure patients to resynchronize the contractions of the ventricles by sending tiny electrical pacing impulses to the heart muscle allowing the heart to pump blood around the body more efficiently.

"Atrial arrhythmias are the number one cause of reduced cardiac resynchronization therapy; therefore, there is a real need for next-generation devices that can deliver lifesaving CRT in this patient population," enthused Robert Canby, Texas Cardiac Arrhythmia and Seton Medical Center, Austin, TX, USA.

While both Consulta and Syncra systems utilize the same technology, they have some distinguishing features. Consulta is the first CRT-P to include Medtronics exclusive OptiVol® Fluid Status Monitoring, as well as Complete Capture Management™, which monitors and adjusts to patient needs automatically and can positively impact device longevity and reduce in-office testing.

"These new innovative technologies allow physicians to proactively manage their heart failure patients, and offer cutting-edge features that contribute to patient safety and physician ease-of-use," concluded Canby.

Source: Medtronic Newsroom: http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1301008935694&lang=en_US

Landmark ipilimumab approval is good news for patients with inoperable or metastatic melanoma

Promising overall survival data on ipilimumab (Yrevoy™; Bristol Meyers Squibb, Princeton, NJ, USA) has paved the way for it to become the first unresectable or metastatic melanoma drug to be approved by the US FDA for over a decade. Ipilimumab manufacturer Bristol Myers Squibb announced the approval shortly after the publication of their pivotal data in the *New England Journal of Medicine* in March.

"Ipilimumab is the first in a new class of drugs that has been shown to offer a survival benefit for metastatic melanoma, which is often a fatal disease, and hopefully, this will lead to the development of related treatments for other cancers," said F Stephen Hodi, of the Dana-Farber Cancer Institute and a lead investigator of the US clinical study of ipilimumab.

Metastatic melanoma is an aggressive and deadly skin cancer, incidence of which has steadily increased over the past few years. Despite this, no treatments have shown significantly improved survival in a randomized controlled trial nor have any been approved in the past decade. As such this approval will be welcome news for those diagnosed with this disease in the USA.

"For the first time, oncologists have a treatment option for patients with unresectable or metastatic melanoma that has been proven in a randomized Phase III clinical trial to significantly extend the lives of patients," said Steven J O'Day, from The Angeles Clinic and Research Institute, an investigator of the pivotal trial. "In fact, the Kaplan-Meier curve from this study suggests a prolonged survival benefit for some patients."

The FDA based their decision primarily on a randomized, double-blind study in 676 patients with unresectable or metastatic melanoma who were previously treated with one or more of a selection of chemotherapeutic agents. The patients were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137 patients) or gp100 alone (136 patients). The Kaplan-Meier estimated survival rate at 1 year was 46% (95% CI: 37.0–54.1) in the ipilimumab arm versus 25% (95% CI: 18.1–32.9) in the gp100 peptide vaccine arm. The estimated survival rate at 2 years was 24% (95% CI: 16.0–31.5) in the ipilimumab arm versus 14% (95% CI: 8.0–20.0) in the gp100 arm. Median overall survival was 10 (95% CI: 8.0–13.8), 10 (95% CI: 8.5–11.5) and 6 (95% CI: 5.5–8.7) months for the ipilimumab alone, ipilimumab plus gp100 arm and gp100 alone arms, respectively.

The approval came alongside a boxed warning for immune-related adverse reactions, which occurred in both arms treated with ipilimumab. Despite this, the drug will be welcomed by the community. Postmarketing data is anticipated on the safety and efficacy of a higher dosage.

Sources: Bristol Myers Squibb press release: www.bms.com/news/press_releases/pages/default.aspx; Hodi FS, O'Day SJ, McDermott DF et al.: *Improved survival with ipilimumab in patients with metastatic melanoma.* N. Engl. J. Med. *363, 711–723 (2010).*

New research could lead to novel ways of controlling chronic pain

Recent research published in the *Proceedings of the National Academy of Sciences* has demonstrated cross-talk between two specific biological pathways could potentially lead to a better understanding of chronic pain.

Bora Inceoglu (University of California Davis Cancer Center, CA, USA) explains, "The interaction of many complex biological pathways is essential for the development of persistent pain, whether inflammatory or neuropathic." He goes on to say, "Pain is a major health concern and painkiller medications or analgesics do different things."

Authors of the study highlight the importance of research to better understand the pain mechanism, due to the "side effects and lack of wide-spectrum efficacy of current drugs". Pain is decreased as natural epoxy-fatty acids (EFAs) are stabilized via inhibition of the soluble epoxide hydrolase (sEH). When there is no underlying painful state, inhibition of this enzyme is not effective. Steven Jinks (University of California Davis School of Medicine) states, "This permits normal pain responses that serve to protect us from tissue damage to remain intact, while alleviating debilitating pain."

During the investigation, Inceoglu states, "To our surprise, we found that cAMP interacts with natural EFAs and regulates the analgesic or pain activity of sEH inhibitors." Researchers reported that acute pain in rodents was "dramatically reduced" by simultaneous inhibition of sEH and phosphodiesterase (PDE).

Investigators were able to demonstrate that inhibiting certain PDE isozymes, including PDE4, lead to "significant" increases in levels of EFA in a sEH-independent mechanism. Authors explain that this suggests "that the efficacy of commercial PDE inhibitors could result in part from increasing EFAs".

According to Bruce Hammock (University of California Davis Cancer Center) the research is "like something old, something new, something practical and something basic, too". It is 'old' as the research involves PDE inhibitors – an old class of drugs. It is thought that some of the action of PDE inhibitors is exerted by raising levels of epoxyeicosatrienoic acids (EETs). The research is 'new' as the Hammock laboratory has previously reported that EETs are increased and stabilized by sEH inhibitors (sEHIs) – a new class of experimental drugs.

Hammock explains, "A practical application of this work demonstrated by Bora Inceoglu is that the combination of this old and new class of drugs is highly effective in controlling pain. Of course, the basic aspects of the work include new insights in how EETs, cyclic nucleotides and the enzymes that degrade them interact to regulate a variety of biological functions."

According to Hammock, "We have all suffered pain and have friends with unrelenting chronic pain problems. The possibility of combining members of an old class of drugs with our new sEHI and actually providing relief for pain is very exciting."

Sources: Inceoglu B, Wagner K, Schebb NH et al.*: Analgesia mediated by soluble epoxide hydrolase inhibitors is dependent on cAMP.* Proc. Natl Acad. Sci. USA *108(12), 5093–5097 (2011); University of California, Newsroom: www.universityofcalifornia.edu/news/article/25100*

Chemoprophylaxis with tamoxifen: results suggest that benefits outweigh side effects

A study carried out at Archimedes Inc (San Francisco, CA, USA) have utilized a mathematical model of postmenopausal women under the age of 55 years to assess tamoxifen chemoprophylaxis versus no tamoxifen for the prevention of breast cancer. The model utilizes data from four randomized, placebo-controlled cancer prevention trials along with cancer incidence and survival data derived from surveillance, epidemiology and end results statistics.

Research has previously shown that tamoxifen is effective at protecting against breast cancer after cessation of treatment, but concerns over side effects, including pulmonary embolism, endometrial cancer, deep vein thrombosis and cataracts, means that identification of groups that are most likely to benefit from treatment is crucial. Peter Alperin and colleagues utilized their mathematical model to run a "virtual clinical trial" of tamoxifen treatment versus no treatment. The study showed that women of 55 years and younger at a 5-year risk of developing breast cancer of 1.66% or greater would benefit from tamoxifen chemoprophylaxis. "In this group of women, using tamoxifen to prevent breast cancer saves lives and has a low frequency of side effects," notes Alperin.

The group also included cost–effectiveness measures in their model utilizing non-cancer disease incidences, quality of life, and costs data taken from the medical literature. As Alperin notes, the group found that "chemoprevention with tamoxifen prevents 29 breast cancer cases and 9 breast cancer deaths per 1000 women treated, and it saves US$47,580 per 1000 women treated in the USA".

Results from this study could help inform personalized cancer prevention strategies in women.

Sources: ScienceDaily: www.sciencedaily.com/releases/2011/03/110314091636.htm; Noah-Vanhoucke J, Green LE, Dinh TA, Alperin P, Smith RA: Cost–effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer *DOI: 10.1002/cncr.25926 (2011) (Epub ahead of print).*

Drug Approvals February 2011 to April 2011.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Cardiology					
Edarbi	Azilsartan medoxomil	Hypertension	USA	Takeda	Feb 2011
Neurology					
Banzel®	Rufinamide	Seizures associated with Lennox–Gastaut syndrome in children 4 years and older and adults	USA	Eisai	March 2011
Gilenya®	Fingolimod	For patients with highly active relapsing–remitting multiple sclerosis despite treatment with IFN-β, or in patients with rapidly evolving severe relapsing–remitting multiple sclerosis	EU	Novartis	March 2011
Horizant™	Gabapentin enacarbil	Moderate-to-severe primary restless legs syndrome in adults	USA	GlaxoSmithKline	April 2011
Xeplion®	Paliperidone palmitate	Schizophrenia	EU	Janssen-Cilag	March 2011
Oncology					
Esbriet®	Pirfenidone	Mild-to-moderate idiopathic pulmonary fibrosis	EU	InterMune	March 2011
Halaven™	Eribulin	For patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease	EU	Eisai	March 2011
Jevtana®	Cabazitaxel	For use in combination with prednisone/prednisolone for the treatment of patients with metastatic hormone-refractory prostate cancer previously treated with a docetaxel-containing regimen	EU	Sanofi-aventis	March 2011
Sylatron™	Peginterferon alfa-2b	For the treatment of patients with melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy	USA	Schering	March 2011
Vandetanib	Vandetanib	For symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease	USA	AstraZeneca	April 2011
Yervoy™	Ipilimumab	Unresectable or metastatic melanoma	USA	Bristol-Myers Squibb	March 2011
Infectious disease					
Baraclude®	Entecavir	Chronic hepatitis B in adult patients with evidence of decompensated liver disease	EU	Bristol-Myers Squibb	Feb 2011
Viramune®XR™	Nevirapine extended-release	To be used once daily in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults	USA	BoehringerIngelheim	March 2011
Rheumatology					
Actemra™	Tocilizumab	For active systemic juvenile idiopathic arthritis in children aged 2 years and older	USA	Roche	April 2011
Benlysta®	Belimumab	For adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy	USA	Human Genome Sciences	March 2011
Other					
Daliresp™	Roflumilast	To reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations	USA	Forest	Feb 2011
Xiapex®	Collagenase clostridium histolyticum	For Dupuytren's contracture in adult patients with a palpable cord	EU	Pfizer	March 2011