Immunotherapy pioneer honored by Saudi Arabian Royalty

Ronald Levy, chief of the oncology division at Stanford University has been presented with the prestigious King Faisal International Prize in Medicine for his revolutionary work in targeted anticancer therapy.

Levy developed the concept of using antibodies to deliver drugs directly to tumor cells. Rituxan, the drug that resulted from Levy's work, was approved by the US FDA in 1997, making it the first commercial antibody to treat cancer.

Rituxan has had a huge impact, proving successful at reducing tumor size in most patients when combined with other drugs and radiotherapy. Originally developed for the treatment of lymphoma, this class of drug is now part of the standard treatment for a wide range of cancers, including cancer of the breast, colon and lungs. "Now it's recommended for treating almost every lymphoma patient, and over 1 million people have been treated with it so far," Levy enthused. "Monoclonal antibodies have transformed the way cancer is treated."

"Dr. Ron Levy is one of the most remarkable and accomplished physician-scientists in the world," eulogized Philip Pizzo, dean of Stanford medical school. "With nearly laser-like focus he has dedicated his illustrious career to unraveling innovative ways of treating malignant lymphomas. He and his colleagues have virtually transformed our knowledge about tumor immunology and cancer biology, and his research has resulted in dramatic improvements in the treatment and survival of patients with lymphoma."

Rituxan targets CD20, a protein found on the surface of B cells and present in many lymphoma tumors. It is not necessary to concoct a custom-made antibody for each patient. Although Rituxan targets normal B lymphocytes in addition to the tumor cells, it causes fewer side effects than conventional cancer treatments and, surprisingly, results in no permanent damage to the immune system.

Levy was quick to realize the therapeutic potential of so-called "hybridomas", the creation of Georges Koehler and Cesar Milstein, of the University of Cambridge, UK in 1975, for which the pair were awarded the Nobel prize for physiology and medicine in 1984.

"They glued antibody-making cells together with cancer cells to produce hybridomas, which lived forever and provided a permanent supply of monoclonal antibody," explained Levy. "With this discovery, I realized there was a potential for therapeutic uses. I decided to use this approach against cancer cells, and it actually worked."

In this way, very specific antibodies targeting a particular marker, such as a protein that is present only on cancer cells, could be mass produced for the first time.

Together with Richard Miller and David Maloney, Levy injected monoclonal antibodies made from mouse hybridoma cells into humans, and those monoclonal antibodies eliminated the cancer cells but not normal cells.

Initially the team planned to make custom antibodies for each patient, but they soon realized that this would be too technically challenging, slow and expensive. Therefore, they began work on a drug that could work across different patients. This work would eventually lead to Rituxan.

Levy was presented with a certificate written in Arabic calligraphy describing his work, a commemorative 24-carat, 200-gram gold medallion and $200,000 in Riyadh by King Abdullah on March 29th.

"Our studies, our efforts and our treatment are for all humanity irrespective of color and religion. [*The Faisal prize*] transcends beyond science and medicine alone.

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It has a cross-cultural aspect, and it offers a special opportunity to make an impact beyond science." Levy acknowledged.

Levy emphasized the need for more work, with his own current research focusing on developing vaccines to treat cancer. "The problem of cancer has not been solved. That will require a lot more hard work involving international collaborations. The advantage of the vaccine is that you'd only have to administer it once, and it includes a complex mixture that will trigger a multifaceted response all at once," he said.

"We have not come as far as we would like; we have a lot further to go. The immune system is very powerful, and I would like to harness even more power from it. But that's only one approach. I would like to combine it with other approaches, some yet to be discovered-that's the exciting part."

Sources: http://med.stanford.edu/news_releases/2009/march/levy.html; http://www.medicalnewstoday.com/articles/143508.php

Testing on colon cancer vaccine is now underway

A new vaccine is being tested in the hope that it will prevent colon cancer in individuals at high-risk of developing the disease. Such a vaccine could, potentially, help patients avoid the invasive and inconvenient surveillance tests, including colonoscopy, that are routinely carried out to check at-risk populations for evidence of precancerous polyps.

Colorectal cancer is the third leading cause of cancer death in the U.S. and in 2008, the American Cancer Society estimated that there were more than 108,000 new cases of colon cancer and nearly 41,000 cases of rectal cancer. Cancer of the colon takes years to develop, commencing with the presence of a polyp, a benign growth in the intestine. Dangerous polyps that have the potential to become cancerous are known as adenomas.

At present, vaccines preventing cancer specifically block infection of viruses that are linked with cancer. Gardasil, for example, protects against human papilloma virus which is associated with cervical cancer. The Pitt vaccine, being tested by Robert E. Schoen and his team of researchers at the University of Pittsburgh, draws on a novel approach to cancer prevention. It is directed against an abnormal version of a protein called MUC1 which is produced in excess in advanced adenomas.

"By stimulating an immune response against the MUC1 protein in these precancerous growths, we may be able to draw the immune system's fire to attack and destroy the abnormal cells," explains Schoen. "That might not only prevent progression to cancer, but even polyp recurrence."

Thus far, approximately a dozen individuals have been given the Pitt vaccine, with the researchers planning to enroll a further 50 or so into the study. The participants, aged between 40 and 70 years old, must have a history of developing advanced adenomas (greater than or equal to 1cm in size, typed as villous or tubulovillous, or contain severely dysplastic, or abnormal, cells). After being dosed for the first time with the vaccine, the participants will receive shots after two weeks and then again after ten weeks. Blood samples will be taken in order to measure immune response at these time points, as well as at 12 weeks, 28 weeks, and one year later.

"Patients were able to generate an immune response despite their cancer-weakened immune systems," noted Olivera Finn, professor and chair at the department of immunology at the university. "Patients with advanced adenomas are otherwise healthy and so they would be expected to generate a stronger immune response. That may be able to stop precancerous lesions from transforming into malignant tumors."

Another advantage to this vaccine is that people who are at-risk of developing adenomas undergo regular colonoscopy so that any polyps that have developed can be removed before they get worse.

"Immunotherapy might be a good alternative to colonoscopy because it is noninvasive and nontoxic," suggested Schoen. "And, it could provide long-term protection."

Source: University of Pittsburgh Schools of the Health Sciences

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine.
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Adjuvant imatinib mesylate reduces risk of gastrointestinal stromal tumor recurrence

Data from a Phase III study published in the Lancet, suggest that adjuvant imatinib mesylate (Glivec®) taken after surgical resection of localized primary gastrointestinal stromal tumor (GIST) is safe and seems to improve recurrence-free survival compared with placebo.

The trial, led by the American College of Surgeons Oncology Group (ACOSOG), examined post-surgery treatment of more than 700 GIST patients. Researchers found that 98% of patients receiving 400 mg of imatinib daily remained tumor-free one year after surgery compared with 83% of the patients receiving placebo (P<0.0001). In addition, at median follow-up of 19.7 months, 8% of patients in the imatinib group had had tumor recurrence or had died compared with 20% in the placebo group. The treatment was well tolerated with a low rate of serious adverse events.

Imatinib was the first molecular targeted cancer therapy, and has revolutionized the treatment of GIST. It targets cancer growth by blocking specific aberrant tyrosine kinases that control pathways to proliferation.

Gastrointestinal stromal tumors are the most common soft tissue sarcomas, and can be found most often in the stomach and small bowel. In the EU, the incidence of GIST is estimated to be more than 5,000 cases per year, of which approximately 95% are Kit-positive. Kit (also known as CD117), in a mutated form has been identified as one of the major causes of GIST and is one of several proteins whose activity is inhibited by imatinib.

"The standard of care after surgical removal of primary GIST has been clinical and radiologic observation, since standard chemotherapeutic agents have been ineffective in this disease. This frequently resulted in tumor recurrence," explained Ronald DeMatteo, 1st author of the study. "Now, as The Lancet reports, by treating patients with Glivec after removal of their initial tumor, we can proactively impact the course of this disease by delaying, and in some patients possibly preventing, the return of the cancer."

Imatinib was recently approved in the US, Switzerland and several other countries for the treatment of GIST in the adjuvant setting, based on the ACOSOG data. This approval represented the tenth indication for imatinib in the US.

Sources: DeMatteo R, Ballman KV, Antonescu CR et al. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumor: a randomised, double-blind, placebo-controlled trial. Lancet. Published online March 19, 2009; http://www.medicalnewstoday.com/articles/142830.php

Approval of MEPACT offers new treatment option for osteosarcoma sufferers

The European commission has formally granted marketing authorization for MEPACT® (mifamurtide, L-MTP-PE) for the treatment of patients with non-metastatic, resectable osteosarcoma. Osteosarcoma is the most common type of malignant bone cancer, and the sixth most common type of cancer in children. A similar incidence rate is seen among boys and girls until adolescence, when boys are more commonly affected. Tumors usually appear in the bone around the knee causing pain. As the tumor grows, movement becomes limited and swelling can also occur.

The approval of MEPACT is an important one as it is the first new agent to be approved for the treatment of osteosarcoma in more than 20 years. The approval will allow MEPACT to be marketed in the 27 Member States of the European Union, as well as in Iceland, Liechtenstein and Norway.

"Today's approval of MEPACT is a significant milestone for physicians and patients in Europe, giving them access to the first new osteosarcoma treatment option in 20 years," said Timothy P. Walbert, president and chief executive officer of IDM Pharma. "As our lead product candidate and first to receive approval, this is also a major milestone for IDM Pharma. We look forward to amending the New Drug Application (NDA) for mifamurtide in the United States and continuing to work toward bringing this important treatment to market in the U.S."

The approval of MEPACT was based on the Phase III data which was conducted by the Children's Oncology Group and funded by the National Cancer Institute. The trial was the largest study ever completed in osteosarcoma. A total of 678 patients with newly diagnosed non-metastatic resectable high-grade osteosarcoma were treated with MEPACT in combination with chemotherapy. A 6-year follow-up showed that the probability of survival when MEPACT is combined with adjuvant chemotherapy is 77% in comparison to 66% without MEPACT. In addition, MEPACT was generally well-tolerated.

Eugenie Kleinerman, MD, professor and head of the Division of Pediatrics and professor of Cancer Biology at The University of Texas M.D. Anderson Cancer Center said: "As an investigator who has been involved in the development of MEPACT, I am thrilled that years of hard work and commitment by researchers around the world has resulted in this positive outcome,". She continued: "This is a remarkable advance for treatment of young patients with osteosarcoma and should give physicians and their patients hope in treating this rare disease."

Source: http://www.leaddiscovery.co.uk/news/4414

Arthritis and cholesterol drugs as potential treatments for prostate cancer

Celebrex® and Lipitor®, two FDA-approved drugs used to treat arthritis and high cholesterol, respectively, are the focus of a new clinical trial at The Cancer Institute of New Jersey (NJ, USA) that aims to determine whether the combination of these pharmacotherapies will be effective in reducing tumor growth in early-stage prostate cancer.

Previous research has indicated that Celebrex® and Lipitor® individually demonstrate a blocking effect against nuclear factor (NF)- B, a transcription factor with a known role in tumorigenesis. The trial, led by Susan Goodin, aims to combine the actions of these drugs in the hope that they will slow the growth of prostate tumors and sensitize tumor cells to other anticancer drugs. "Understanding the mechanism for tumor activation and growth may allow for targeting more specific tumor pathways for prostate cancer," Goodin states.

Participants of the trial will be at or above 18 years of age with a diagnosis of prostate cancer with increasing prostate specific antigen (PSA) levels but no other evidence of the disease. The trial will involve several tests for prostate cancer before and during treatment, including blood tests for PSA, CT and bone scans. Patients will take both drugs orally every day for 6 months, and after this time, will have their PSA levels assessed every 3 months for the next 2 years. The investigators at the The Cancer Institute of New Jersey hope that their approach of testing pre-approved drugs will speed up the transfer of new therapies from laboratory to clinic. Goodin summarizes, " by focusing on drugs that already have FDA approval, we can potentially bring targeted therapies to patients faster than if we were testing a brand new compound or drug".

Source: The Cancer Institute of New Jersey: www.cinj.org

Nitric oxide-coupled vitamin B12 produces 'miracle' results in dogs

Scientists from the Cleveland Clinic have tested a novel drug, nitrosylcobalamin (NO-Cbl) in pet dogs suffering from tumors that would normally have no hope of survival, with extremely promising results. So far only four dogs have been treated with the drugs but in case there have been significant improvements with no negative side effects.

"In all four dogs, there has been a significant reduction in tumor size without any toxic side effects or discomfort," Stated Joseph A. Bauer, one of the researchers who presented their findings at the 237th National Meeting of the American Chemical Society.

One of the dogs, Oscar, a Bichon Frise diagnosed with an extremely aggressive form of anal sac adenocarcinoma, had been unresponsive to chemotherapy and radiation and was thought unlikely to survive three months. After treatment with NO-Cbl, the cancer receded and Oscar was walking again within two weeks. Oscar is still alive and well.

Cancer cells express up to 100 times more vitamin B12 receptors on their surface than noncancerous cells. In order to exploit this, Bauer and his colleagues attached nitric oxide (NO) molecules to vitamin B12. The B12 is easily taken up by cancer cells and the subsequent release of toxic NO kills the cells from within.

The team aim to treat ten dogs with the drug and then slingshot the drug into human and dog Phase I trials.

"I'm committed to the animals, and my goal would be to do a dual clinical trial, Phase I human and Phase I dog," says Bauer. "This is one of the most rewarding things I've ever done in my life. It gets boring working in the lab, but to see the fruits of your labor in a positive outcome like this and to know you're responsible in some small way, that's pretty cool."

Source: http://www.medicalnewstoday.com/articles/143424.php

Bioengineered protein causes tumor regression in mouse model

Scientists from the University of Toronto have demonstrated that a bioengineered version of the von Hippel-Lindau (VHL) protein is capable of suppressing tumor growth in mice in a study published in the first issue of EMBO Molecular Medicine.

In the body VHL degrades hypoxia-inducible factor (HIF), a protein produced by tumor cells to allow them to continue to grow in hypoxic regions, such as the center of a tumor where poor blood flow often leads to a low-oxygen environment. However, VHL requires oxygen to work efficiently and so is ineffective in the very regions that it is most needed.

Therefore, the researchers, led by Michael Ohh of the Faculty of Medicine, engineered a novel version of VHL that can work efficiently in hypoxic regions. They tested the engineered VHL in a mouse model of kidney cancer, known to produce high levels of HIF, and observed dramatically reduced levels of HIF, tumor regression and limited formation of new blood vessels within the tumors.

"We used kidney cancer as a model because it is one of the most resistant tumors to conventional radiation and chemotherapy, but our findings provide a novel concept that could potentially serve as a foundation for smarter anticancer strategy for a wide variety of cancers," explained Ohh.

Sources: Sufan RI, Moriyama EH, Mariampillai A et al.: Oxygen-independent degradation of Hif via bioengineered Vhl tumor suppressor complex. EMBO Mol. Med. 1(1), DOI: emmm.200900004 (2009); http://www.medicalnewstoday.com/articles/143644.php