

Combination Epigenetic-Immunotherapy Shows Promise in Treating Cancer in Pre-clinical Animal Studies

Cell surface molecules that enhance recognition of cancer cells by the immune system are often down-regulated by epigenetic changes such as aberrant promoter DNA hypermethylation in cancer cells. Because DNA methyl transferase 1 (DNMT1) mediates methylation of promoter DNA, DNMT inhibitors (DNMTi) such as 5-aza-2-deoxycytidine and guadecitabine have been developed to re-express silenced genes in cancer cells. In a separate approach, immunomodulating antibodies that target immune-checkpoint proteins have been used to promote immune response against cancer cells. For example, ipilimumab, an anti-CTLA4 monoclonal antibody, has successfully been used to boost immune response against cancer cells. CTLA4, when expressed on the surface of T cells, binds to CD80/CD86 on antigen presenting cells (APCs) and serves as an immune checkpoint to inhibit activation of T cells that can act against cancer cells. An Italian research team has successfully tested a combination epigenetic-immunotherapeutic strategy in a mouse model. When they combined 5-aza-2-deoxycytidine and guadecitabine with antibodies against immune checkpoint proteins, the combination therapy had much better outcomes than those of each drug administered alone. These results encouraged them to design a phase Ib clinical trial in which they will administer guadecitabine and ipilimumab in sequence to metastatic melanoma patients. Notwithstanding the side-effects of epigenetic therapy, if this trial is successful, that will be a huge milestone in the treatment of metastatic melanoma which continues to have very poor prognosis.

—Dr. M. Zulfiqur Hossain

www.sciencedaily.com/releases/2015/09/150915090415.htm

FDA Approves First Drug to Treat a Rare Enzyme Disorder in Pediatric and Adult Patients

The U.S. Food and Drug Administration has approved Kanuma (sebelipasealfa) as the first treatment for patients with a rare disease known as lysosomal acid lipase (LAL) deficiency. Patients with LAL deficiency (also known as Wolman disease and cholesteryl ester storage disease [CESD]) have no or little LAL enzyme activity. This results in a build-up of fats within the cells of various tissues that can lead to liver and cardiovascular disease and other complications. Wolman disease often presents during infancy (around 2 to 4 months of age) and is a rapidly progressive disease. Patients with Wolman disease rarely survive beyond the first year of life. CESD is a milder, later-onset form of LAL deficiency and presents in early childhood or later. Life

expectancy of patients with CESD depends on the severity of the disease and associated complications. Wolman disease affects one to two infants per million births, and CESD affects 25 individuals per million births. Kanuma is approved for use in patients with LAL deficiency. Treatment is provided via intravenous infusion once weekly in patients with rapidly progressive LAL deficiency presenting in the first six months of life, and once every other week in all other patients. The most common side effects observed in patients treated with Kanuma are diarrhea, vomiting, fever, rhinitis, anemia, cough, headache, constipation, and nausea.

—Fabiha Tasnim

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476013.htm>

FDA Approves New Oral Therapy to Treat ALK-positive Lung Cancer

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new diagnoses and 158,040 deaths in 2015, according to the National Cancer Institute. An ALK (anaplastic lymphoma kinase) gene mutation can occur in several different types of cancer cells, including lung cancer cells. ALK gene mutations are present in about 5 percent of patients with NSCLC. In metastatic cancer, the disease spreads to new parts of the body. In ALK-positive NSCLC metastatic patients, the brain is a common place for the disease to spread. The U.S. Food and Drug Administration has recently approved Alecensa

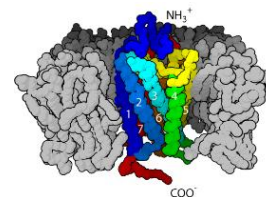
(alectinib) to treat people with advanced (metastatic) ALK-positive non-small cell lung cancer (NSCLC) whose disease has worsened after, or who could not tolerate treatment with, another therapy called Xalkori (crizotinib). The most common side effects of Alecensa are fatigue, constipation, swelling (edema) and muscle pain (myalgia). Alecensa may cause serious side effects, including liver problems, severe or life-threatening inflammation of the lungs, very slow heartbeats and severe muscle problems. Treatment with Alecensa may cause sunburn when patients are exposed to sunlight.

[U.S. FDA's Division of Drug Information]

TSRI Team Finds Unique Anti-diabetes Compound Using Powerful New Drug Discovery Method

Diabetes is a widely prevalent ailment worldwide which occurs either due to insulin deficiency or insulin insensitivity. Scientists from The Scripps Research Institute (TSRI), an American medical research institution have recently employed a strong new drug discovery technique to identify an anti-diabetes compound with a novel mechanism of action. The uniqueness of this finding lies in the fact that the scientists have put their effort into looking for a medication that selectively binds with the GLP-1 receptor present in the beta cells responsible for producing insulin. A known GLP-1 receptor agonist called Exendin-4, a small protein usually activates both the G protein and the beta arrest

in pathways, but the aim was to selectively activate only the G-protein pathway. Consequently, P5 could be isolated by altering the terminal peptide sequences of Exendin-4 which successfully activated only the GLP-1 receptor's G protein pathway and required lower dose in boosting glucose tolerance than its precursor. However, a drawback from the experiment on mouse models of diabetes demonstrated that P5 stimulates insulin production very weakly compared to Exendin-4. This limitation of the study was taken positively because less reliance on stimulating



insulin could mean less stress on beta cells. Moreover, P5 lead to the growth of new fat cells which surprisingly instead of contributing to insulin resistance was accompanied by signs of insulin sensitivity suggesting that the peptide works in part by alleviating insulin resistance. This was indeed an important observation as fat cells typically possess less number of insulin receptors thus leading to insulin resistance. Therefore,

Green Fluorescent Protein – An Important Biomolecular Research Tool in the Recent Years

Green fluorescent protein (commonly referred to as GFP) is the bioluminescent protein that has captured huge attention from the entire bioscience research arena immediately after its discovery due to its fluorescence properties. GFP is isolated from the jelly fish, *Aequorea victoria*. It has a remarkable capacity to produce a well visible, efficiently emitting internal fluorophore that is not only attractive but has introduced a new line of research in biological science, especially after this protein was cloned and expressed in the bacteria *Escherichia coli*.

GFP is a 27 kDa protein consisting of 238 amino acids where residues 65-67 in the GFP sequence spontaneously form the chromophore in an autolytic cyclization and without the need



after discovering the potential of P5 through the study scientists are looking forward to soon developing it into a new diabetes drug.

–**Tanisha Khan**

<http://labroots.com/trending/id/2046/tsri-team-finds-unique-anti-diabetes-compound-using-powerful-new-drug-discovery-method/clinical-and-molecular-dx>

for a cofactor for its luminescence unlike other light-emitting proteins. It is highly stable and resistant to many biological denaturants. The protein has absorbance maxima at 395 nm and 475 nm, and releases green light when placed under blue or long UV light.

GFP has transformed from an unknown protein to the most commonly used tool for cell and molecular biology, medicine, drug discovery, plants and most importantly as a marker for gene expression and protein targeting in tracer studies. Application that use GFP as a reporter molecule include protein localization and interaction studies, development of cell and tissue specific markers, monitoring of promoter activity, DNA immunization and gene therapy and others. Recently the field of nanotechnology is making use of GFP as well.

–**Nishat Jahan**

http://www.kva.se/Documents/Priser/Nobel/2008/sciback_ke_en_08.pdf

No Drill for Tooth Decay and Fewer Filling

Going to the dentist is a major fear factor for most people and for good reason too. There is always the thought of the drill used to scrape off the tooth decay. In the absence of effective caries preventive methods, drill based operative care became established as the means for caries control in general practice. Many preventative methods are usually suggested when dealing with caries. Water fluoridation results in a declining caries incidence which decreased further following the advent of fluoridated toothpaste. The challenge today is to develop a non-invasive model of practice that will provide a low level of primary caries experience in the younger generation and reduce risk of caries in the older generations. The Caries Management System (CMS) is a ten step non-invasive strategy to arrest and re-mineralize early lesions. The governing principle of this system is that caries management must include consideration of the patient at risk, the status of each lesion, patient management, clinical management and monitoring. Both dental caries risk and treatment are managed according to a set of protocols that are applied at various steps throughout

patient consultation and treatment. The anticipated outcome of implementing CMS in general dental practice is reduction in



caries incidence and increased patient satisfaction. Since the attainment and maintenance of oral health is determined mainly by controlling both caries and periodontal (gum) disease, the implementation of the CMS in general practice will yield both of these outcomes.

Results were positive in a 4-year post-trial study result (years 4–7) where at the end of the post-trial follow-up period, the CMS and control increments were 6.13 and 8.66, respectively, a difference of 29%. The new approach included the following: application by dentists of high concentration fluoride varnish on teeth showing signs of early decay, advice on how to brush teeth better, restriction of between-meal snacks and beverages containing added sugar, and lastly monitoring according to the level of risk. "Prevention is always better than cure."

–**Labiba Mahmud**

<http://www.smh.com.au/national/health/nodril-dentistry-stops-decay-reducing-fillings-says-sydney-uni-study-20151204-glfpkn.html>

Uridine Triacetate- A New Approval FDA

In order to provide emergency treatment to adult and pediatric patients who receive an overdose of the cancer treatment fluorouracil or capecitabine, or who develop certain severe or life-threatening toxicities within four days of receiving these cancer treatments, U.S. Food and Drug Administration granted approval to uridine triacetate on 11th December, 2015. Due to the adverse effect of this drug it is not recommended for the non-emergent treatment of adverse reactions related to fluorouracil or capecitabine as uridine triacetate may lessen the efficacy of these drugs. Additionally uridine triacetate got authorization based on two single-arm, open-label expanded access studies of patients who either received a fluorouracil or capecitabine overdose or presented

with severe or life-threatening toxicities within 96 hours of receiving fluorouracil or capecitabine. In these studies 130 (96%) patients survived and five (4%) died out of 135 patients. After evaluating the safety data it was found that the most common adverse reactions associated with this drug were vomiting (10%), nausea (5%) and diarrhea (3%). For adult the recommended dose and schedule is 10g orally every 6hr for 20 doses whereas for pediatric patient it is 6.2g/m² of body surface area orally every 6 hours for 20 doses. It can be expected that more research will be done on uridine triacetate to improve its therapeutic effect and reduce the related adverse reactions.

–**Tanisha Momtaz**

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476919.htm>