Pfizer's rare heart disease drug succeeds in late-stage study

Experts create ImmunoMap to test patients' response to immunotherapy

WASHINGTON, April 2, (Agencies): Johns Hopkins scientists have used a form of artificial intelligence to create a map that compares types of cellular receptors, the chemical "antennas" on the surface of immune system T-cells. Their experiments with lab-grown mouse and human T-cells suggest that people with cancer who have a greater variety of such receptors may respond better to immunotherapy drugs and vaccines.

A report on how the scientists created and tested what they call "ImmunoMap" appeared Dec. 20 in Cancer Immunology Research.

"ImmunoMap gives scientists a picture of the wide diversity of the immune system's responses to cellular antigens," says Jonathan Schneck, MD, PhD, professor of pathology, medicine and oncology at the Johns Hopkins University School of Medicine, and a member of the Johns Hopkins Kimmel Cancer Center.

Receptors on T-cells recognize antigens, or pieces of other cells that trigger an immune response, particularly antibodies. If the antigens are foreign, T-cells raise the alarm within the immune system, which can distribute an "all-points bulletin" to be on the lookout for the unfamiliar antigens.

Because diseases such as cancer tend to evade detection by T-cells' receptors, allowing a tumor to grow unchecked, scientists have long sought "intel" on this process as a means of developing therapies that target malignant cells, but leave healthy cells alone.

"Much of immunotherapy today is built on the premise that we know these antigens," says Johns Hopkins biomedical engineering MD/PhD student John-William Sidhom. "But we actually don't know as much as we need to about them and the T-cells that recognize them."

To address that need, Sidhom used high-powered computing to create a mathematical model-essentially a digital map-of genomic sequence data of receptors from human T-cells that were exposed to a virus in the laboratory. "Our goal was to cluster T-cell receptors that are similar and may target the same antigen," says Sidhom.

Using an unsupervised learning algorithm, the team was able to convert the T-cell receptor sequencing data into numeric distances based on similarities in the receptor sequences and cluster them by functional specificity. For example, if two receptor sequences were similar, the computer assigned a short distance rank between the two sequences. If the sequences were different, they received a longer distance rank.

Once the thousands of sequences were converted into these "distance" metrics, the computer system's artificial intelligence algorithms looked for patterns among the receptors.

"That's how we got ImmunoMap, by characterizing receptor sequences as they relate to each other," says Schneck. "T-cell receptors that are very similar, with slight differences in their sequences, may be recognizing the same antigen."

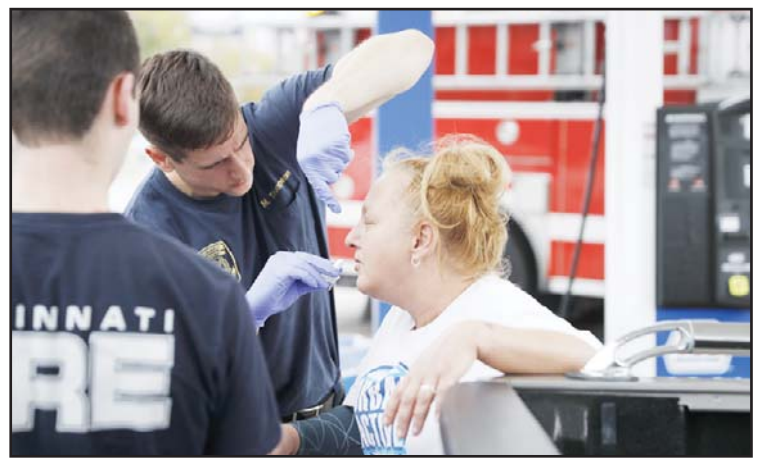
The Johns Hopkins team tested ImmunoMap's ability to correlate immune responses on receptor sequencing data from T-cells in the tumors of 34 patients with cancer enrolled in a nationwide clinical trial of the immunotherapy drug nivolumab.

Of the 34, three patients with melanoma responded to nivolumab, and the rest did not respond. In the responders, the scientists found more-an average of 15-different T-cell receptor clusters compared with eight to nine in the non-responders.

The scientists also found that the diversity of T-cell receptors decreased among the responders by 10-15 percent four weeks after nivolumab treatment.

"Those patients had a broad array of receptor weaponry before their treatment, which may have allowed the right receptor to kill their cancer cells," says Schneck. "Once their immune system found the correct receptor, T-cells expressing those receptors multiplied, leading to an overall reduction in the structural diversity of their T-cell receptors."

Schneck says some scientists have emphasized that response to immunotherapy is largely dependent on whether T-cells are infiltrating the tumor site, but his research suggests that while, "infiltration is important, it's not enough to explain patients' variable responses to immunotherapy drugs."



In this Nov 2, 2017, file photo, Cincinnati Fire Department medics nasally administer naloxone to a woman while responding to a possible overdose report at a gas station in downtown Cincinnati. New surges in the use of methamphetamine and cocaine, often in mixtures with synthetic opioids, are fueling rocketing overdose death tolls in states such as Ohio, one of the nation's hardest hit during the opioid crisis. (AP)

Also:

WASHINGTON: Pfizer Inc's experimental drug to treat a rare and fatal disease linked to heart failure reduced deaths and need for hospitalizations in a late-stage study.

The company's clinical study investigated the efficacy, safety and tolerability of an oral dose of tafamidis capsules compared with a placebo in 441 patients.

Pfizer said tafamidis met the main goal of statistically significant reduction in deaths and frequency of cardiovascular-related hospitalizations compared with a placebo at 30 months. The data also showed that tafamidis was generally well tolerated by the enrolled patients.

Tafamidis was being tested for the treatment of transthyretin cardiomyopathy, a condition that results from deposits of transthyretin protein in the heart, which leads to eventual heart failure.

Brokerage SunTrust Robinson Humphrey said it expects tafamidis global sales of $130 million in 2022.

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ARKANSAS: Arkansas' attorney general has joined the widening mass of litigation against opioid manufacturers, accusing three drugmakers of promoting addictive painkillers in ways that falsely denied or trivialized their risks.

Arkansas Attorney General **Leslie Rutledge** filed a lawsuit in state court in **Little Rock** accusing Purdue Pharma LP, Johnson & Johnson and Endo International Plc of engaging in misleading marketing practices.

The case made Arkansas at least the 17th **US** state to sue manufacturers of prescription opiods amid a nationwide epidemic of addiction to the painkillers.

The lawsuit contended the drugmakers spent millions of dollars on promotional activities that downplayed the risks of addiction associated with opioids while falsely touting the benefits of using the drugs to treat chronic pain.