NEWS IN BRIEF

NOBEL PRIZE IN MEDICINE 2019

The Nobel Prize this year has gone to 3 physician-scientists who discovered the mechanisms by which cells sense oxygen. Physician-scientists are a new breed. They have a degree in both medicine and science. They spend a small time on clinical work and a significant amount of time on basic science research. They are now playing a critical role in translational research.

Greg Semenza is a pediatrician in John Hopkins Institute, who during his post-doctoral work found that when subjected to hypoxia, cells activated genes that produced certain factors. Similar work done by Dr Ratcliffe from Oxford helped clarify how hypoxia regulates the production of erythropoietin. Meanwhile William Kaelin at the Danan Farber Cancer Research Institute in Boston was studying patients with Von Hippel Lindau (VHL) Disease who harbor a mutation in the *VHL* gene, and are predisposed to certain cancers. He found that the *VHL* gene was important for the way the cell responds to oxygen levels. Then Ratcliffe and Kaelin together worked out that the VHL protein interacts with the hypoxia-inducible factors (HIF) to regulate the cell response to oxygen.

The clinical importance of this work is now unfolding. Drugs called prolyl hydroxylase inhibitors interfere with the attachment of VHL proteins to HIF, and may help to treat patients with anemia and renal failure. More importantly, the three scientists are being applauded for their scientific rigor. Kaelin has often said "the most dangerous result in science is the one you were hoping for, because you declare victory and get lazy." (*Nature News 7 October 2019*)

PATIENT CUSTOMIZED GENE THERAPY

In December 2016, a 6-year-old child from Colorado (USA) was diagnosed with the fatal neurodegenerative disorder – neuronal ceroid lipofuschinosis. However, genetic testing found only one mutation in the *CLN* gene. Further testing revealed that she had a 2000 base pair long transposon in an intron of the *CLN* gene, which caused an error during transcription into mRNA.

Timothy Yu, a neurogeneticist in Harvard, then developed an oligosense nucleotide that would block the translation of the abnormal segment of mRNA, resulting in a normal protein. This drug, named Milasen, was loosely based on the structure of nusirensin that has been previously cleared for treatment for Spino-muscular Atrophy. Yu and colleagues raced through Institutional Review Boards and FDA timelines to be able to clear the drug within a year. After initial dose escalation every 2-weekly, it was continued in maintenance dose every 3-monthly. Patient's seizures declined remarkably and her rapidly declining milestones somewhat stabilized.

This innovation has generated much discussion in academic circles because of the high cost entailed for a drug designed for just one individual. In this case, the child's parents managed to raise millions of dollars, which most people would consider a pipe dream. However, the FDA is anticipating an increase in such individualized drug requests. How should regulatory bodies like the FDA approach these requests? What should the level of evidence be, before clearing a drug for a single individual? Should the urgency of the patient's illness color the decisions? Can the cost be brought down with time? Who should benefit? Who should pay? There are many questions that need to be addressed in this unique 21st century problem. (*N Engl J Med. 2019;doi: 10.1056/NEJMoa1813279. [Epub ahead of print*])

COMPASSIONOMICS

Stephen Trzeciak is an intensivist and physician-scientist in New Jersey. One day, his 12-year-old son asked him to help out with his school assignment. The assignment was an essay on "What is the most pressing problem of our time?" His son's assignment got done that day, but it started him pondering on what was the most pressing problem in medicine today.

Though he was working on cutting edge work, he realized the deepest problem in medicine today is the compassion crisis. He carried out a systematic review of how the practice of compassion affects patients and doctors. He found enough rigorous data showing that compassionate, patient-centered care is associated with lower unnecessary resource use – less diagnostic testing, fewer referrals to specialists, fewer hospitalizations and lower total health care charges. Interestingly, it also reduced physician's burnout and stress. He found 20 distinct mechanisms by which compassion for patients can have beneficial effects, including less medical errors, modulation of pain perception by the patient and effects on the neuroendocrine and immune system. A randomized controlled trial showed that just 40 seconds of complete attention and empathy by the doctor to the patient had significant reduction in anxiety levels in patients.

His book Compassionomics written along with Antony Mazarrelli details the data, which suggest that compassion could be the new wonder drug we have incidentally overlooked. (*https://www.medscape.com/viewarticle/911250_4*)

GOURI RAO PASSI
gouripassi@gmail.com