Because enzymes are such efficient catalysts, researchers in the 1990s tried to develop new enzyme variants to drive the chemical reactions needed by humanity. List decided to try and find out what happens when biocatalysts are stripped down to their most basic chemical form. In 2000, List and his team found out that one of them – proline – can on its own catalyse asymmetric aldol reactions with enantiomeric ratios up to 98:2.

List described proline as a micro-aldolase, an enzyme mimic that combines a nucleophilic centre (the amino group) and an acid–base co-catalyst (the carboxylic acid group). In the aldol reaction, proline binds to the ketone, forming an enamine intermediate that is more reactive than the ketone itself, as its highest occupied molecular orbital (HOMO) is higher in energy. Proline's handedness then infuses the reaction with asymmetry by only allowing the aldehyde to approach in one position.

MacMillan wanted to develop a catalyst for the Diels–Alder reaction, which could alleviate the shortcomings of the highly air- and moisture-sensitive metal catalysts. He discovered that a modified phenylalanine could catalyse asymmetric reactions between α,β-unsaturated aldehydes and dienes with enantiomeric ratios up to 98:2.

L-phenylalanine works as an asymmetric organocatalysis in Diels-Alder reaction.

The phenylalanine derivative reacts with the unsaturated aldehyde to form an iminium ion, whose lowest unoccupied molecular orbital energy is lower than that of the aldehyde – making it more reactive. As in the case of List's enamine catalysis, iminium attaches itself to the substrate with a reversible covalent bond, which allows it to transfer its chirality onto the reagents.

Since then, the process they evolved has led to a “gold rush” in the catalysis field. The multitudes of new organocatalysts developed have helped drive a variety of chemical reactions, in turn accelerating pharmaceutical drug research. The asymmetric organocatalysts have allowed researchers to efficiently produce new molecules with complete certainty of the 3-D orientation.

When strychnine was first synthesized in 1952, it required 29 different chemical reactions and only 0.0009 per cent of the initial material formed strychnine and rest was wasted. In 2011, with organocatalysis, strychnine was build in just 12 steps with 7,000 times more production efficiency. Today, organocatalysis is recognized as the third pillar of asymmetric catalysis. List, MacMillan and a host of chemists inspired by their work, are discovering more and more organocatalytic reactions, including organocatalysed versions of classic asymmetric reactions, such as Mannich reactions, Michael additions and Friedel–Crafts reactions. Organocatalysis has even been merged with another green corner of chemistry: photocatalysis. The real revolution of this discovery is only surfacing now with extremely reactive catalysts that can do wonders that which cannot be achieved with enzymes or even with the most sophisticated metal complexes.

Given the huge growth and impact of organocatalysis in its present form, it will certainly be exciting to observe the development of the field upon heterogenization. In the coming years, various approaches for immobilization will be considered, with a focus on whether a novel methodology for the immobilization of organocatalysts could be discovered. It would be also interesting to see the explorations of noncovalent interactions and entrapment in nanosized materials in developing supported organocatalysts.

Making sense out of senses

Dr. Birija Sankar Patro

How we sense

our surroundings remained most enigmatic for ages in human minds. Our ability to sense heat, cold and touch is essential for survival and underpins our interaction with the world around us. However, the science behind the sense of touch and pain remained unknown for long. Several breakthrough discoveries in the field of sensory systems had already recognised many Nobel prizes: (1) Sherrington and Adrian, awarded 1932 Nobel prize in Physiology or Medicine "for their discoveries regarding the functions of neurons". (2) Erlanger and Gasser were awarded the Nobel prize in 1944 "for their discoveries relating to the highly differentiated functions of single nerve fibres. (3) Georg von Békésy, awarded the 1961 Nobel prize in Physiology or Medicine "for his discoveries of the physical mechanism of stimulation within the cochlea." (4) Ragnar Granit, Haldan Keffer Hartline and George Wald were awarded the 1967 Nobel prize in Physiology or Medicine "for their discoveries concerning the primary physiological and chemical visual processes in the eye. (5) Richard Axel and Linda B. Buck were awarded the 2004 Nobel prize in Physiology or Medicine "for their discoveries of odorant receptors and the organization of the olfactory system.

After a year and a half of devastating pandemic and extraordinary feats of developing multiple lifesaving vaccines, this year's Nobel prize in Physiology or Medicine was something of a surprise. It was awarded for discoveries related to a series of pioneering studies clarified how our neurons with thermosensors and mechanosensors works. The prize went to David Julius and Ardem Patapoutian.

In the 1990s, David Julius and colleagues at the University of California, San Francisco (San Francisco, CA, USA) asked most sought-after question to answer – as how do we perceive heat or temperature? In this regard, they have exploited unique characteristics of some of the spice derived molecules, e.g. Capsaicin from chilly, which triggers hot sensation. In their one of the most seminal paper (Caterina et al., 1997), Julias and colleagues conducted a series of experiments to isolate mRNAs from dorsal root ganglia, converted them into a library of complementary cDNAs and expressed them heterologously in heat insensitive embryonic kidney cells. These genetically transformed cells were challenged with capsaicin to evoke intracellular calcium. This led to discovery of mammalian homologue of the transient receptor potential (Trp) ion channel, later named as TRPV1, which uniquely responds to capsaicin and temperature in neurons. This seminal discovery further begets several other astounding findings by Julias and colleagues. In another 5 years, Julius and colleagues discovered cold and menthol-sensitive receptor (CMR1), a member of the TRP family of excitatory ion channels, and proposed that it functions as a transducer of cold stimuli in the somatosensory system (McKemy et al., 2002).

Interestingly, Patapoutian (Genomics Institutes of Novartis Research Foundation, San Diego and The Scripps Research Institutes, La Jolla, CA) independently began to answer his curiosity to understand the thermosensory properties of additional TRP family proteins. In their seminal discoveries, Patapoutian and colleagues have shown that TRPM8 responds to cold and cooling sensation of menthol and icillin (Peier et al., 2002) while TRPA1 responds to cold and garlic, wasabi and mustsard (Story et al., 2003). This discovery of Patapoutian led to understanding that TRP1 variants are associated with diverged sensory functions in the living world. The variants of TRPV1 help camels and squirrels to resist high temperature while TRPA1 is used as infrared detector by some snakes.

A decade after the discovery of TRPV1 by Julius, Patapoutian and colleagues started tweezing to understand the enigmatic science behind the mechanical touch. Employing high risk brute force but systematic approach, Patapoutian team embarked upon identifying a mouse neuroblastoma cell and zeroed in 72 putative ion channels with hitherto unknown functions. In their years of research, they have knocked down these channels one by one by small interfering RNA

(siRNA) but failed miserably to identify the change in electrophysical parameters in response to pressure stimulation in knockdown cells. However, the eureka moment experienced when they finally knocked down one of the proteins, which showed dynamic changes in the inward current in response to pressure (Figure 1). They named these mechanically-activated channels as Piezo1 and Piezo2, after the Greek term for pressure, in their seminal discovery, published in "Science" in 2010 (Coste et al., 2010). Piezos are transmembrane proteins and expressed in several tissues in vertebrates. Its homologues are also found in invertebrates and plants.

Patapoutian with Sanjeev S Ranade, one of the key Indian researchers in his team, showed that Piezo1 knockout mice are embryonically lethal due to defects in vascular remodeling and inability of responding to shear stress of blood flow by endothelial cells, due to lack of Piezo1 (Ranade et al., 2014a). Intriguingly, they discovered that Piezo2 knockout mice are viable. They showed that mice lacking Piezo2 exhibit a profound loss of touch sensation. In their seminal discovery, they reveal that "We find that touch and pain sensation are separable, suggesting that as-yet-unknown mechanically activated ion channel(s) must account for noxious (painful) mechanosensation." (Ranade et al., 2014b). More recently, Patapoutian extended the science behind the function of Piezo in baroreflx and blood pressure and advocated its critical sensory function in other species too (Drosophila, Cenorhabditis and Arabidopsis).

The discoveries of Julius and Patapoutian have immense translation opportunities. TRP channels are considered as attractive druggable targets for managing pain. Both agonists and antagonists of TRP channels have therapeutic potentials for relieving muscle and bone joints. For example, resiniferatoxin, an analogue of capsaicin, show excellent effect in relieving pain in dogs with bone cancer. Mavatrep, a second-generation drug, has recently found to be effective against osteoarthritic pain. Although pharmacological targeting of TRP channels was focussed on pain but its potential hitherto extended to many new clinical conditions like respiratory disorders, neurological and psychiatric diseases, diabetes and cancer. The discoveries of Julius and Patapoutian undoubtedly opened up whole new era of our understanding the sensory function behind pain, touch, pressure and other internal homeostatic process.

".....The challenge is to develop drugs that don't have side effects outside of pain and to develop drugs that diminish chronic pain but don't interfere with the pain system doing its job as an acute warning system," .....David Julius.

Albeit discoveries are sometime accidental and serendipitous, the seminal discoveries of sensory channels by Julius and Patapoutian was based on "curiosity driven research" and "research driven curiosity" for decades. Experimental failures, long lonely hours in the labs, clueless real science than expected, sometime too good to believe the results are the ways forward to great science – In short, there is no shortcut for achieving the best.

Patapoutian tweeted once ".....But there is hope! My first grant after cloning PIEZOs was triaged. But @NIH did ultimately fund the work that showed PIEZO2 is the principal mechanosensor for touch and proprioception. Message: stay positive, don't doubt yourself, and keep trying.".

When Dr Juilus was asked what did he learn from his Nobel Laureate mentors (Randy Schekman and Richard Axel), he said

".....I worked with them long before they got their Nobel Prizes but, you know, they're all unbelievably curious, that's the main thing. But you know they have an intensity and a curiosity that's just really special."

The Nobel Prize is wonderful recognition of these discoveries," Congratulations to Dr Julius and Dr. Patapoutian for the Nobel Prize in Physiology or Medicine; your success is great motivation for all the researchers to excel in science while answering fundamental questions.

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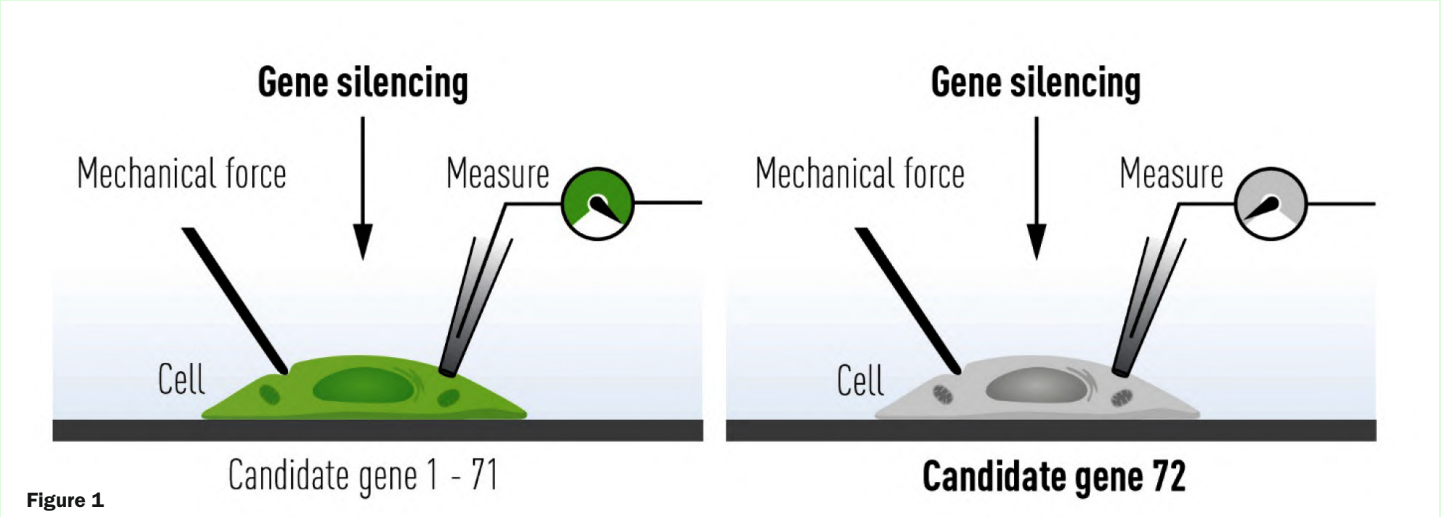

Figure 1

Piezo and Piezo2 mechanoreceptors were discovered in neuroblastoma cells through gene silencing of candidate 72 genes expressions. Adapted from https://www.nobelprize.org/prizes/medicine/2021/press-release/