WHY NOBEL WINNING STUDIES FOCUS ON MOLECULAR MECHANISMS?
The Time / Network Model of Anti-aging Medicine
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The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of Cancer therapy by inhibition of negative immune regulation. James P. Allison studied the T-cell protein CTLA-4 since 1990. He developed an antibody that could bind to CTLA-4 and block its function (see Figure). He now set out to investigate if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. In 1994 Mice with cancer had been cured by treatment with the antibodies that inhibit the brake and unlock antitumor T-cell activity. In 2010 an important clinical study showed striking effects in patients with advanced melanoma, a type of skin cancer. In several patients signs of remaining cancer disappeared by blocking CTLA-4 that disengages the T-cell brake allowing the immune system to attack cancer relentlessly. Such remarkable results had never been seen before in this patient group.

Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. PD-1, similar to CTLA-4, functions as a T-cell brake. PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer, renal cancer, lymphoma and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma.

The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm." These investigators found that when the period gene is active, periodmRNA is made. The mRNA is transported to the cell's cytoplasm and serves as template for the production of PER protein. A second clock gene, timeless, encoding the TIM protein that is also required for a normal circadian rhythm is bound to PER. The two proteins, TIM (timeliess) and PER (period) enter the cell nucleus where they block period genes activity to close the inhibitory feedback loop. What happens when these two proteins are compromised? Could such disturbance in molecular circadian rhythms cause a number of diseases? There have been several reports suggesting that the pathophysiology of psoriasis may be associated with aberrant circadian rhythms (Gelfant et al., 1982; Mozzanica et al., 1988; Bacaksiz et al., 2012)
. Psoriasis is a common chronic inflammatory skin disease characterized by increased proliferation, altered differentiation of the epidermis, and infiltration of inflammatory cells such as neutrophils into the dermis (Lowes et al., 2014)

A most recent study suggested an increased risk for psoriasis in night-shift workers who had aberrant circadian rhythms (Li et al., 2013). Ando et al (2015 found that circadian clocks may be a potent regulator of psoriasis by affecting IL-23R expression. Janich P et al (2013) found Human epidermal stem cell function is regulated by circadian oscillations. Izumi H et al (2014) discussed Circadian disruption and cancer risk. Yasuniwa Y, Izumi H, Wang KY, et al (2010) showed how circadian disruption accelerates tumor growth and angio/stromagenesis through a Wnt signaling pathway.

The Nobel Prize in Physiology or Medicine 2013 was awarded jointly to James E. Rothman, Randy W. Schekman and Thomas C. Südhof "for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells." Cells with defective transport machinery, give rise to a situation resembling a poorly planned public transport system. Rothman discovered that a protein complex enables vesicles to dock and fuse with their target membranes, binding to each other like the two sides of a zipper. The fact that there are many such proteins and that they bind only in specific combinations ensures that cargo is delivered to a precise location. Südhof discovered that vesicles are only allowed to release their contents when the cell signals to its neighbours. He identified a molecular machinery that responds to an influx of calcium ions and directs neighbour proteins rapidly to bind vesicles to the outer membrane of the nerve cell. The zipper opens up and signal substances are released. Südhof´s discovery explained how temporal precision is achieved and how vesicles´ contents can be released on command. The system is critical for a variety of physiological processes, ranging from signalling in the brain to release of hormones and immune cytokines. Defective vesicle transport occurs in a variety of diseases including a number of neurological and immunological disorders, as well as in diabetes. Without this wonderfully precise organization, the cell would lapse into chaos.

The plethora of new research focusing on molecular mechanisms compose a dynamic process of a matrix of signalling controls processes, delivered at specific times. It's an elegant, almost symphonic interaction of cellular circadian clocks, the time dimension and the multi-dimensional intra- and inter- cellular signalling network. Identifying and reproducing signalling processes necessary to sustain health and the discrete intervals in which they have to be delivered is the ultimate goal of Signalling technology that started with the Pacemaker research in London University and expanded to motor nerve signalling and new discoveries in Quantum Physics principles underlying cellular signalling. Compromised signals from denatured proteins can be deleterious to this very specific process, while signals enhancing protein refolding can reinstate systemic functioning, restoring the flow of previously disrupted signalling pathways. In other cases, as in the case of

CTLA-4 and PD-1 T-cell breaks, signalling that pauses certain mechanisms can be proven to be crucial both in Anti-aging Medicine and health status recovery.