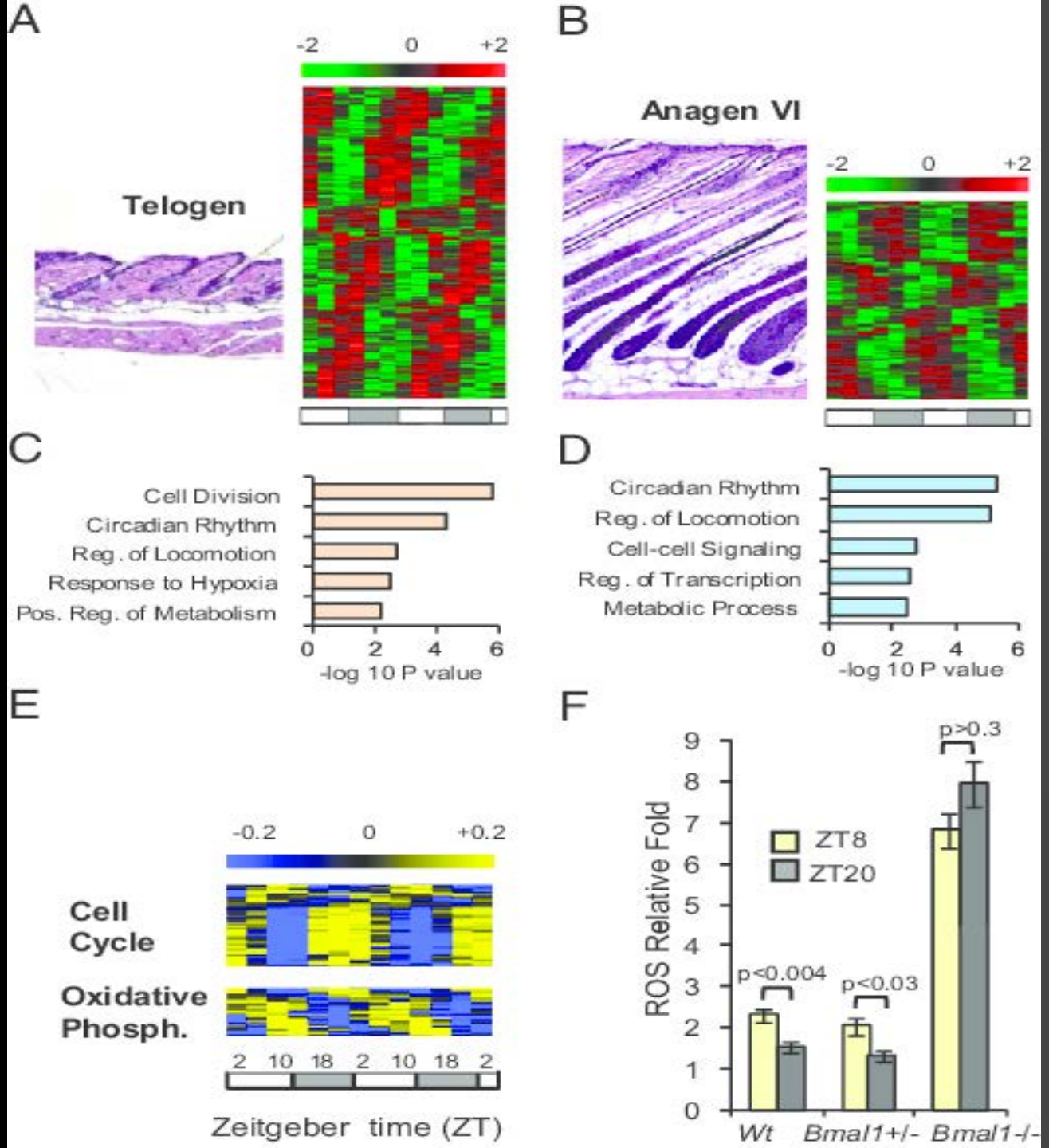
CIRCADIAN SKIN IS A REALITY

BY XANYA SOFRA PH.D, NEUROPHYSIOLOGY

ANTI-AGING = HEALTH

- HEALTH / ANTI-AGING IS A COMPLEX SYSTEMIC PROCESS WITH MANY PARTS
- WE WILL FOCUS ON:
  +1. PROPER FUNCTIONING OF **BIOLOGICAL CIRCADIAN CLOCKS**

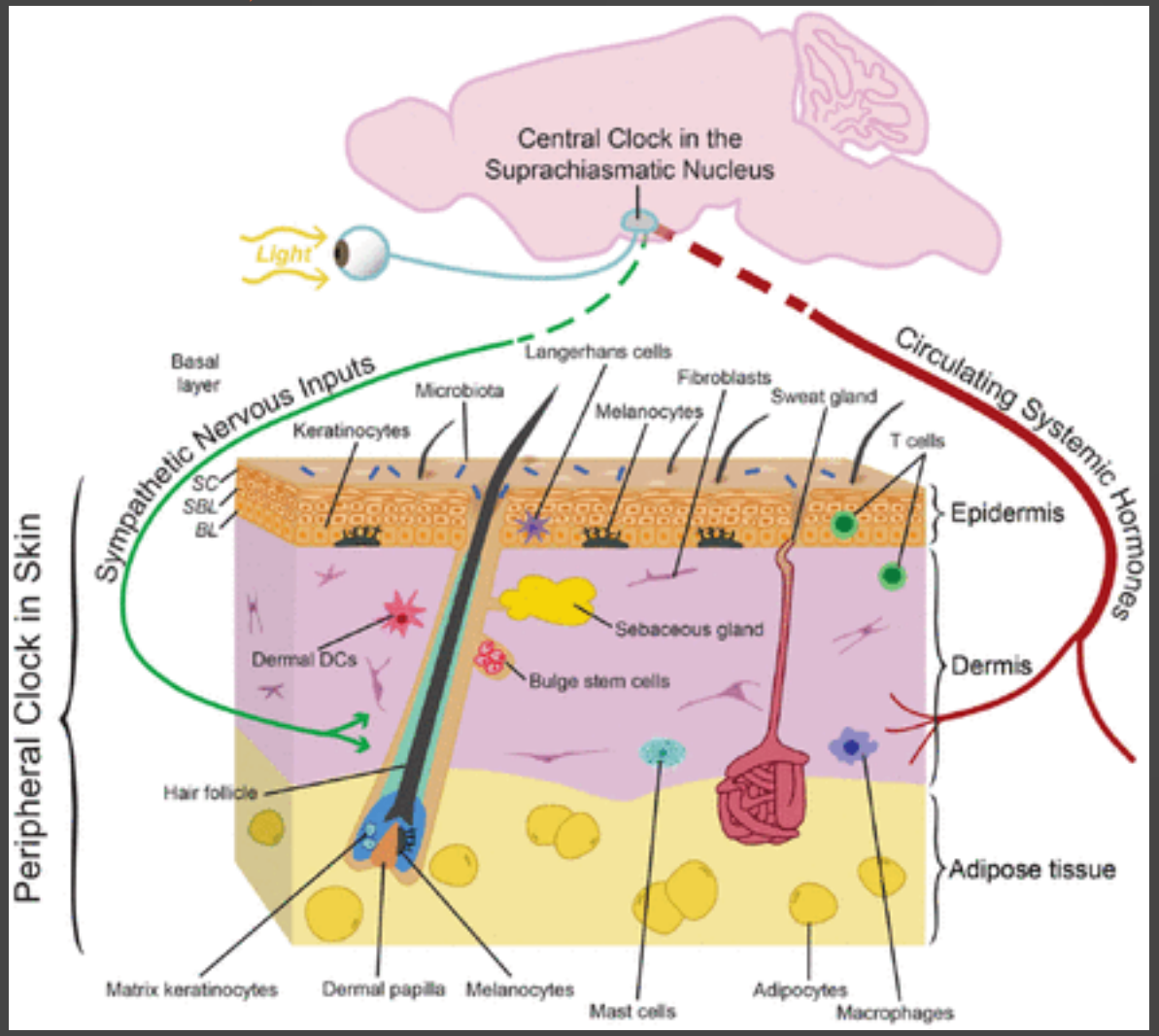
  +2. MEANINGFUL **SIGNALING:** RELEVANT CELLULAR COMMUNICATIONS DELIVERED IN A SPECIFIC ORDER DEFINED BY TIME



The circadian transcriptome of skin

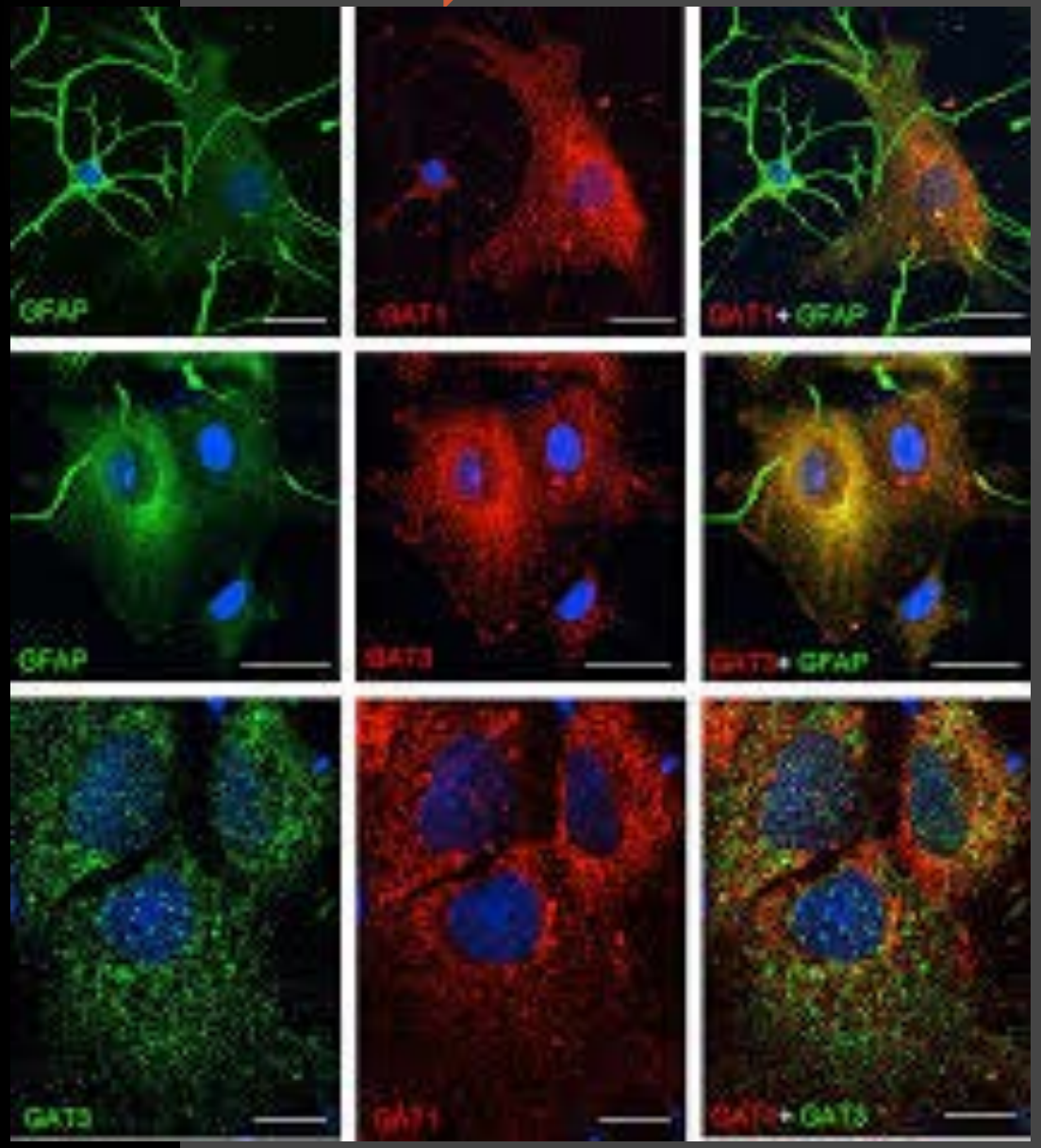
In recent years, skin has emerged as a model for studying circadian clock regulation of

1. cell proliferation
2. stem cell functions
3. tissue regeneration
4. aging
5. carcinogenesis



Cellular circadian clocks are located in the suprachiasmatic nucleus (SCN), the brain's primary circadian pacemaker, but also throughout the brain and peripheral tissues. However we have now identified other non-SCN systemic clocks

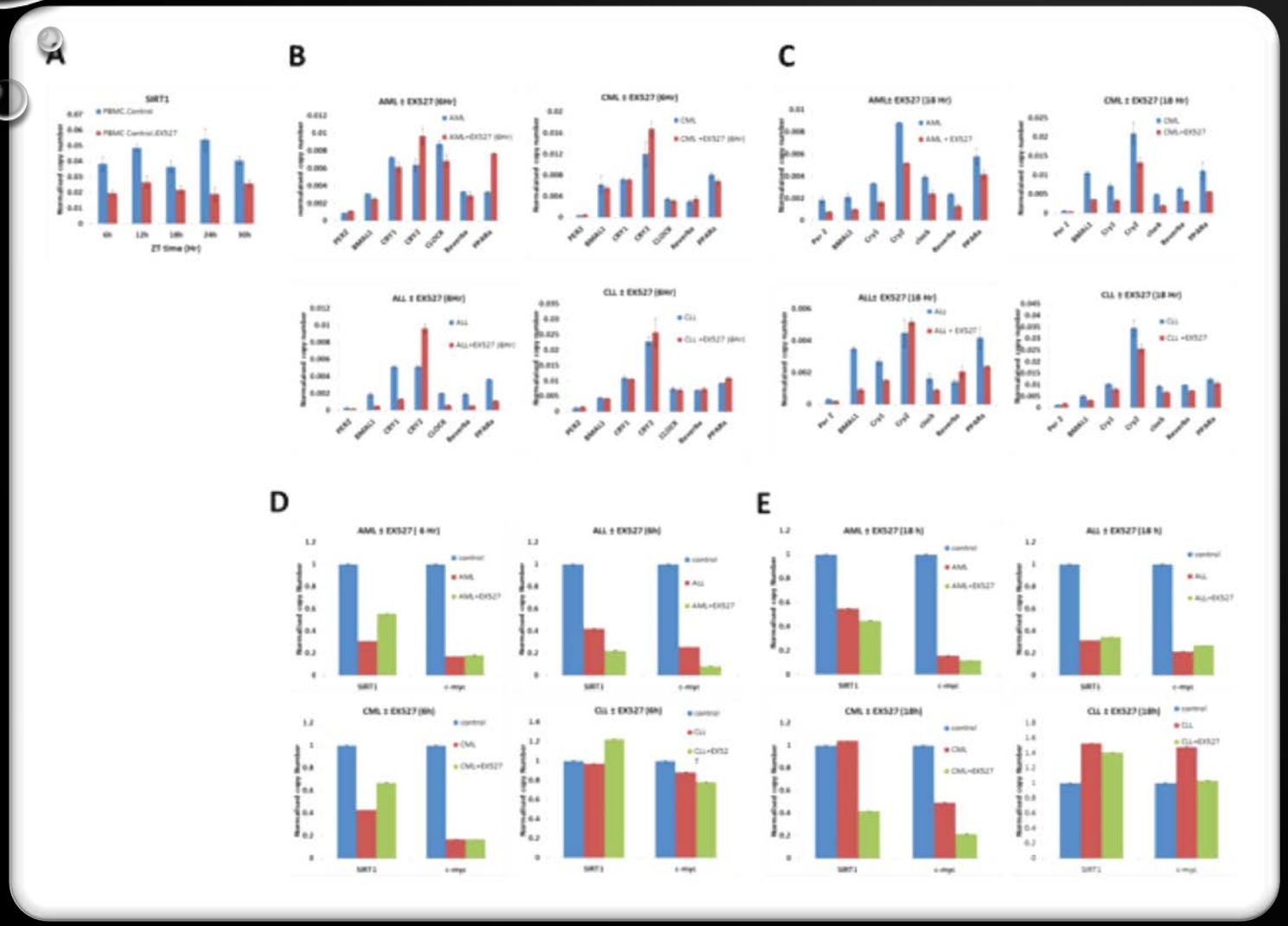
Localization and Expression of
GABA Transporters in the Suprachiasmatic Nucleus



TIMING WITHIN THE CELL

- "EVERY SINGLE CELL IN YOUR BODY IS CONTROLLED BY ITS OWN CIRCADIAN CLOCK. IT HELPS EVERY CELL FIGURE OUT WHEN TO USE ENERGY, WHEN TO REST, WHEN TO REPAIR DNA, OR TO REPLICATE DNA." *SALK INSTITUTE CIRCADIAN RESEARCHER SATCHIN PANDA*

CLOCK GENES

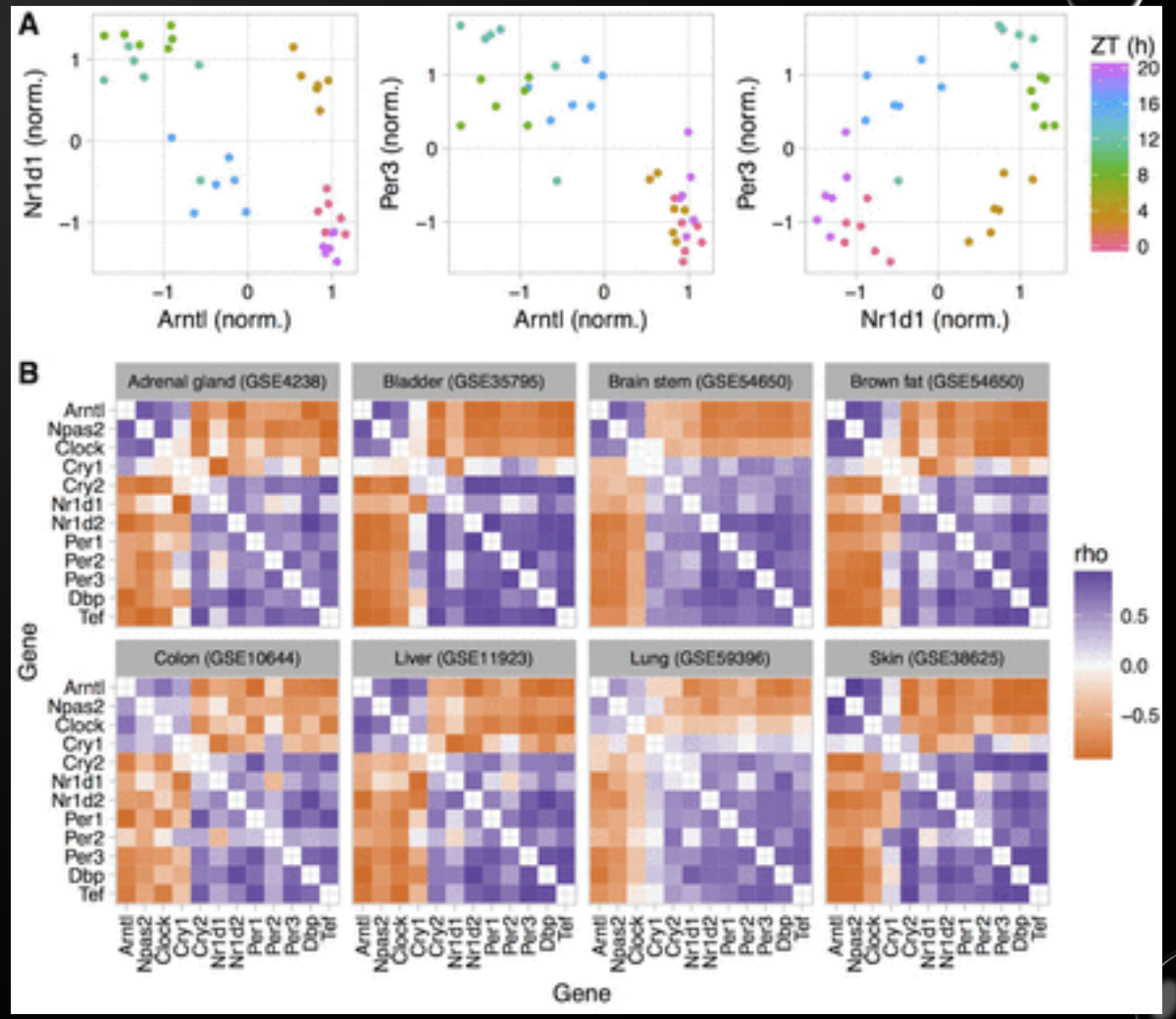


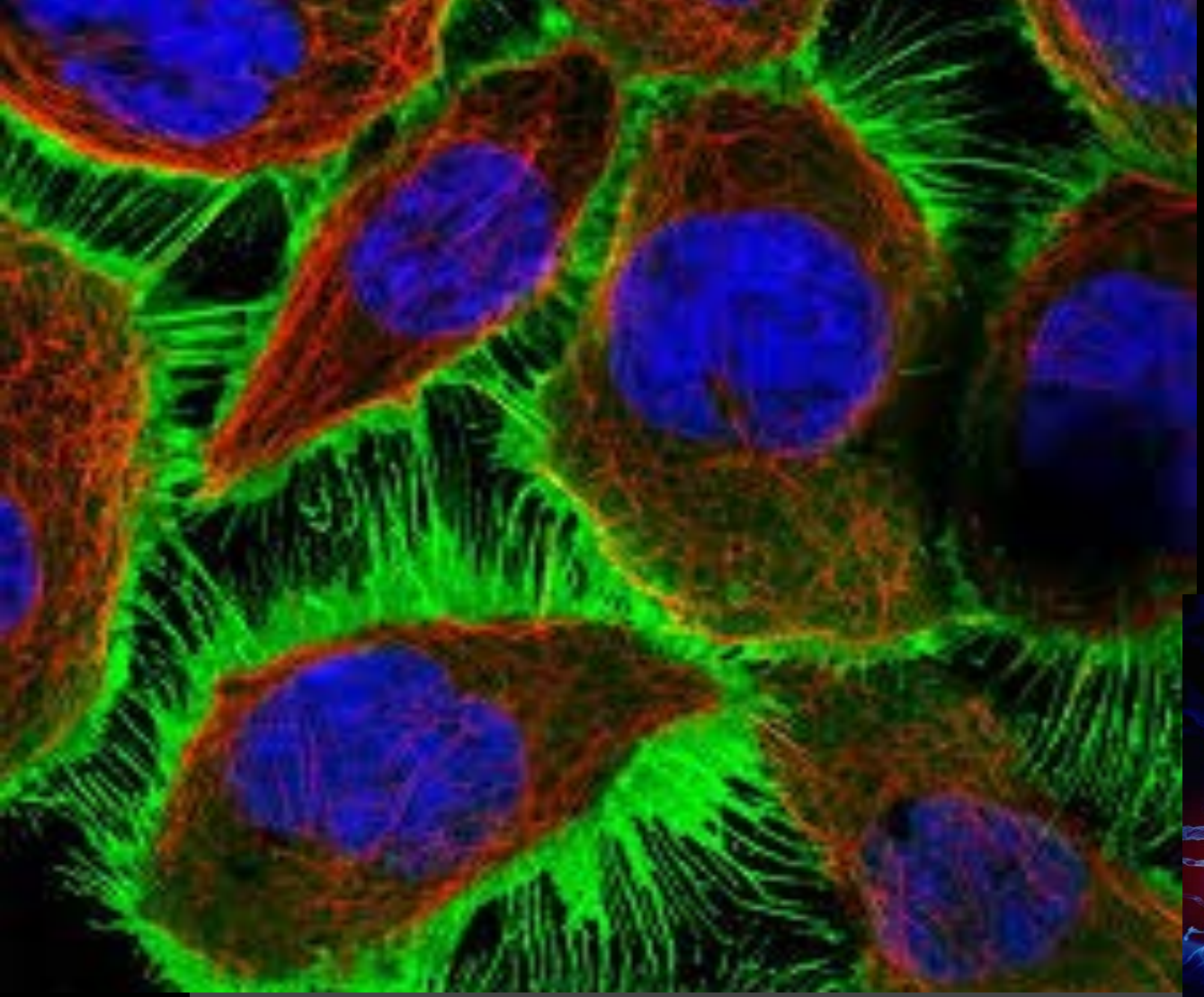
Circadian Genes in Leukemia

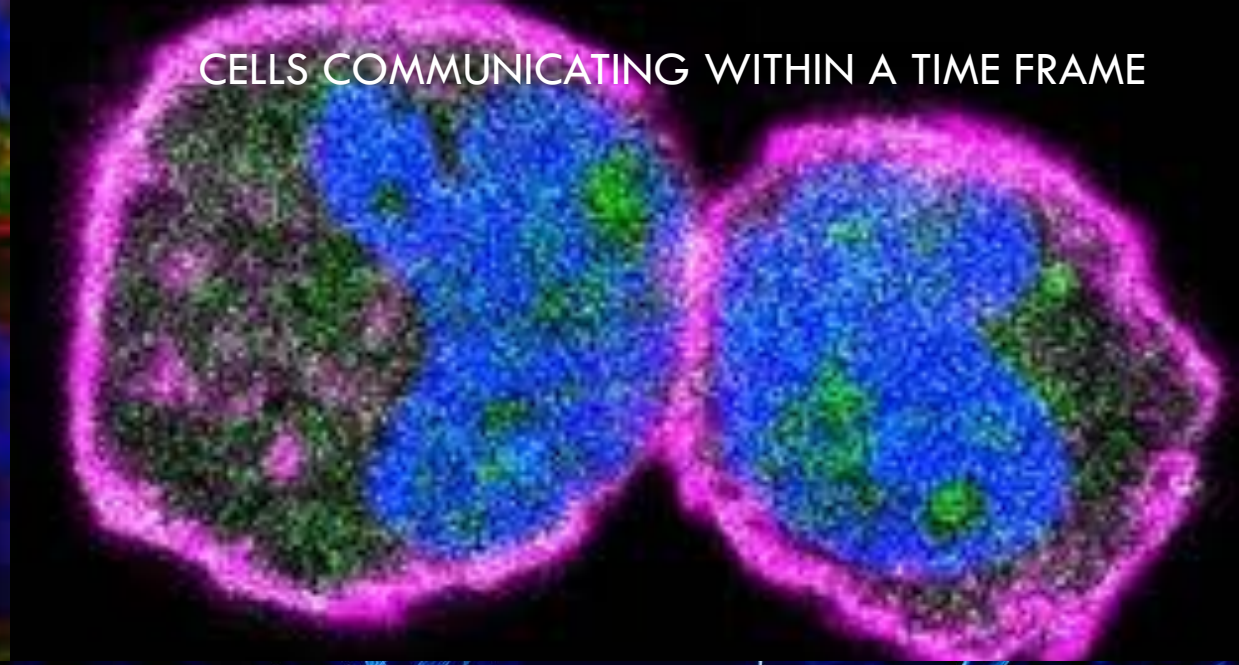
- AT A CELLULAR LEVEL WE HAVE A RANGE OF 'CLOCK GENES'
- CLOCK GENES INFLUENCE CELL ACTIVITY.
- CLOCK GENES PREPROGRAM PROTEINS TO GUIDE CELLS WHEN TO USE ENERGY, WHEN TO REST, WHEN TO REPAIR DNA, OR TO REPLICATE DNA.

The circadian genes on the positive arm of the clock that peak in expression on sunrise ZT0, tend to be positively correlated with each other and negatively correlated with genes in the negative arms of the clock, that peak near ZT10 and ZT18

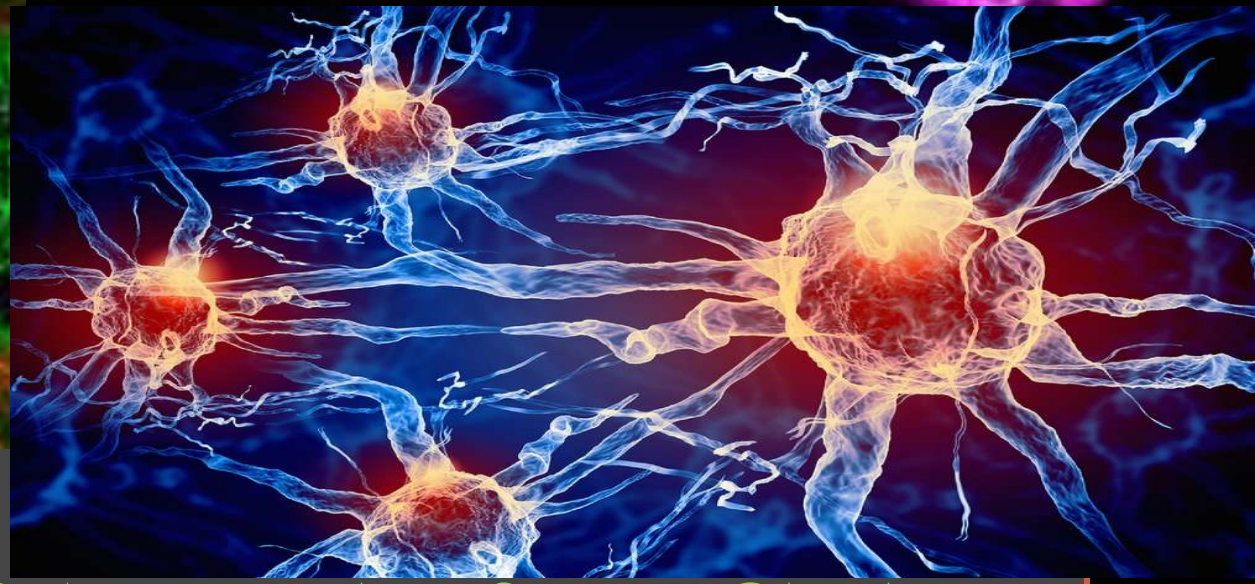
Jacob J. Hughey
doi: https://doi.org/10.1101/130765



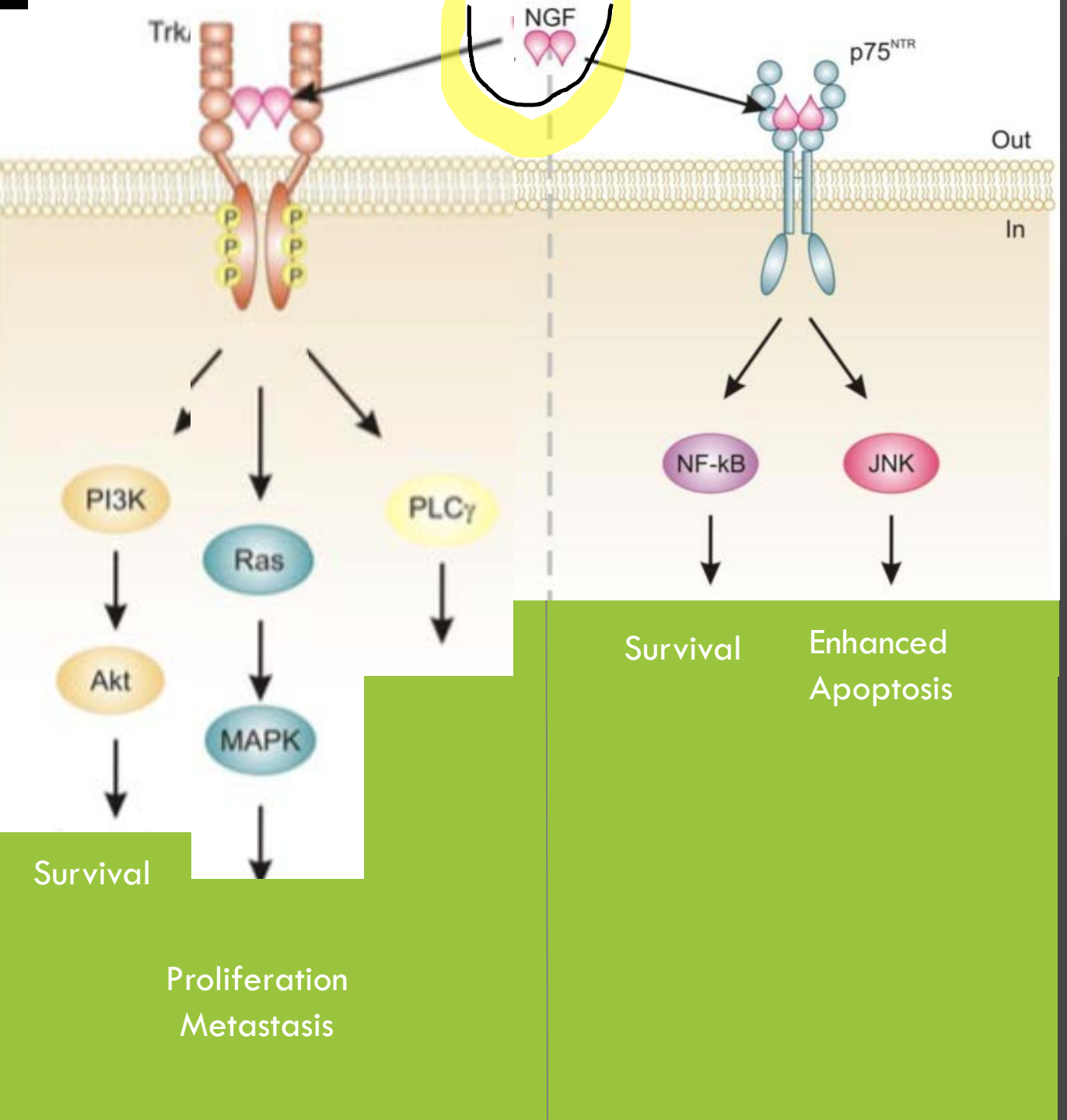




CELLS COMMUNICATING WITHIN A TIME FRAME

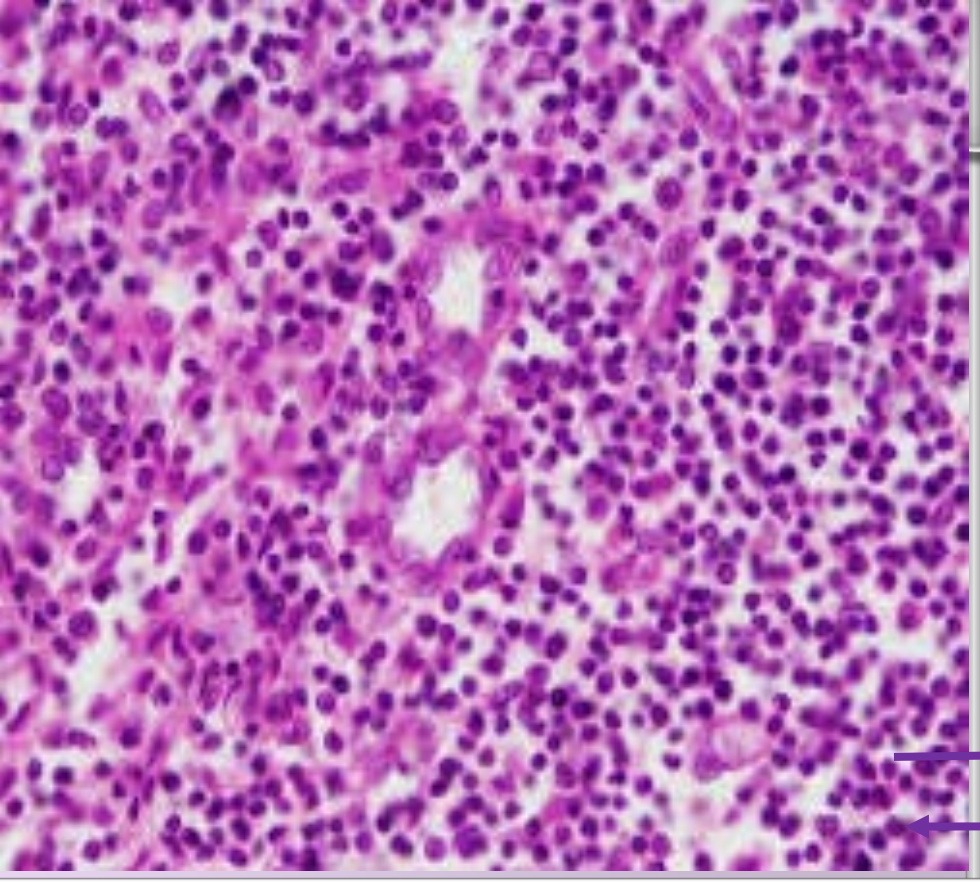


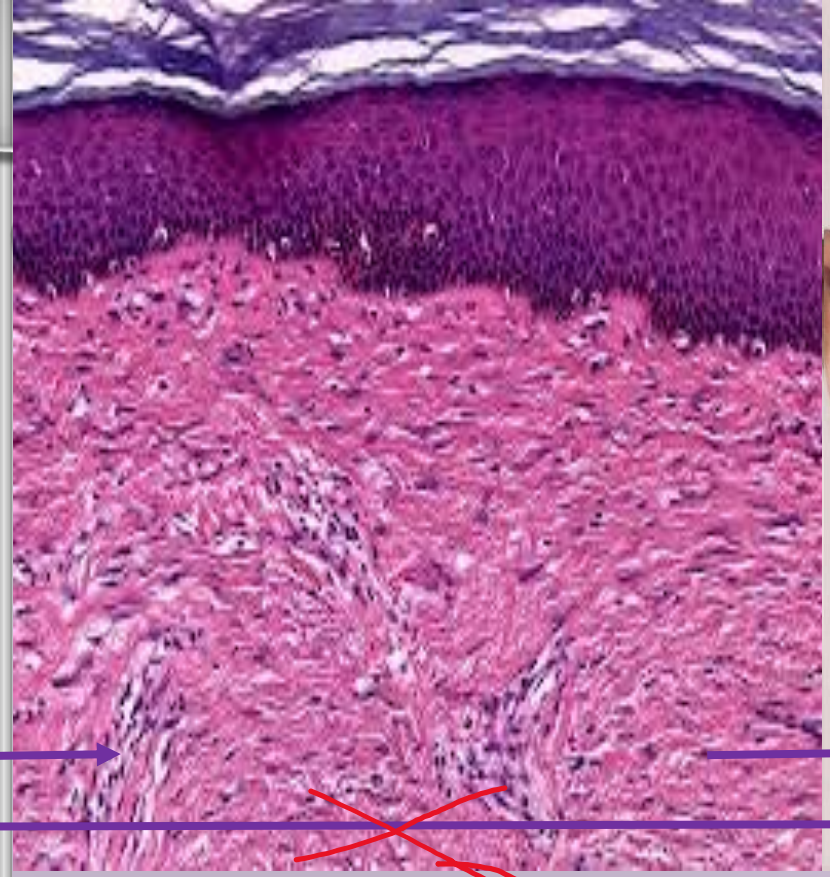
DISRUPTION OF CELLULAR CIRCADIAN RHYTHMS IS FOLLOWED BY A DISRUPTION IN CELLULAR COMMUNICATIONS

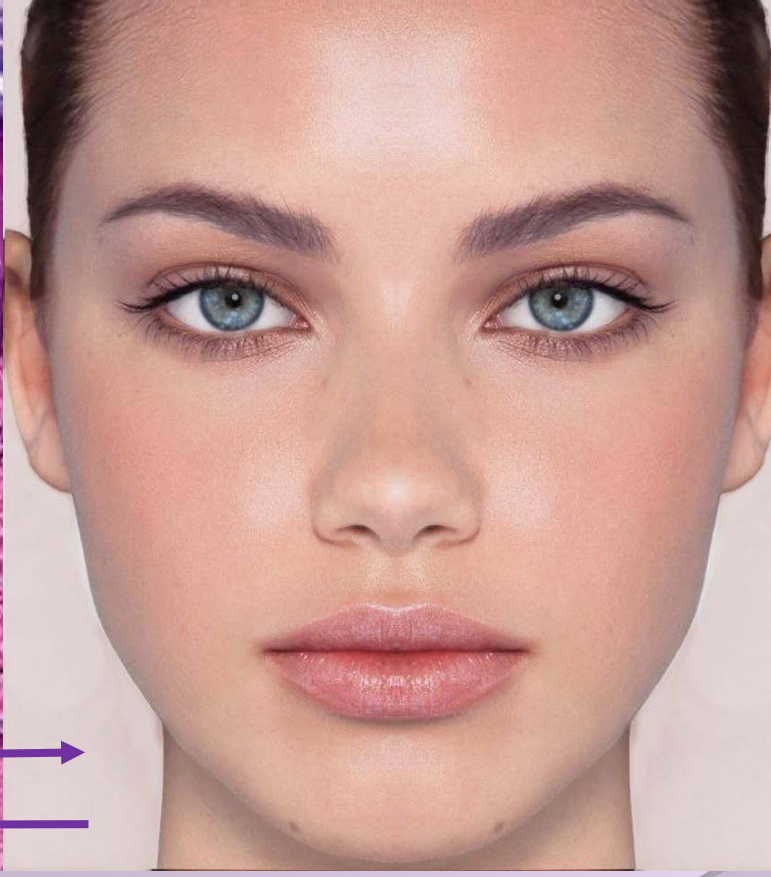


THE SAME SIGNAL EMITTED AT DIFFERENT TIMES CAN ENHANCE OR SUPPRESS CANCER

The same signal of NGF can cause opposite effects depending on TIMING that determines what other signals are reinforced







CELLULAR CIRCADIAN CLOCKS IN HUMAN DEVELOPMENT

CELLS MULTIPLY AND DIE WITHIN SPECIFIC TIMES

CLUSTER OF RESONANT CELLS MAKE ORGANS

ORGANS DEVELOP AND INTERACT MAKING AN INDIVIDUAL

THE ARROW OF COMPLEXITY GOES ONLY ONE WAY

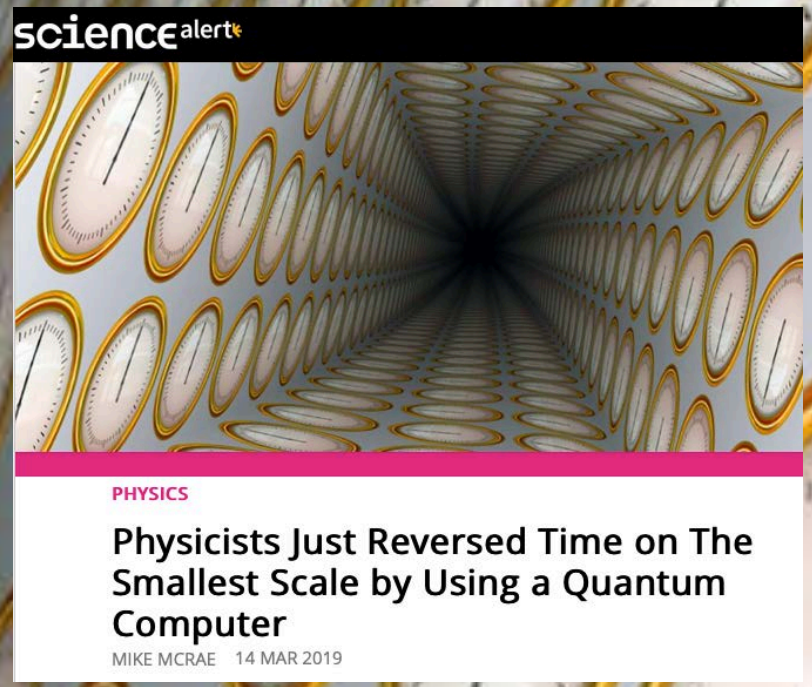
Ben Tippett from British Columbia and David Tsang from University of Maryland developed a mathematical formula for time travel (TARDIS – 2017).

Although Einstein's TIME dimension goes both forward and backward, we cannot go back in time because Gestalt formation proceeds exclusively in the FORWARD dimension

THE SMALLER THE MECHANISM
THE EASIER & FASTER IT IS PUT IT
TOGETHER THE WAY IT WAS BEFORE
TO GO BACK IN TIME
YET A BROKEN CUP CANNOT GO BACK
TO BEING WHOLE

AN ENZYME HAS BEEN INSTRUCTED
TO ENCIRCLES THE DOUBLE HELIX
TO REPAIR A BROKEN STRAND
OF DNA

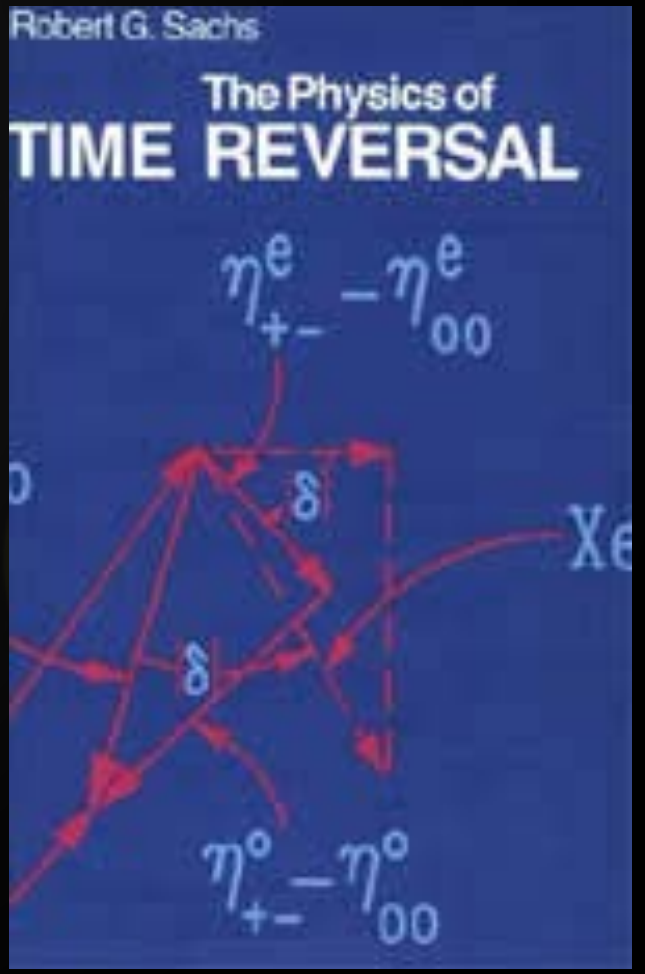
Time Reversal is only
possible
on The Smallest Scale



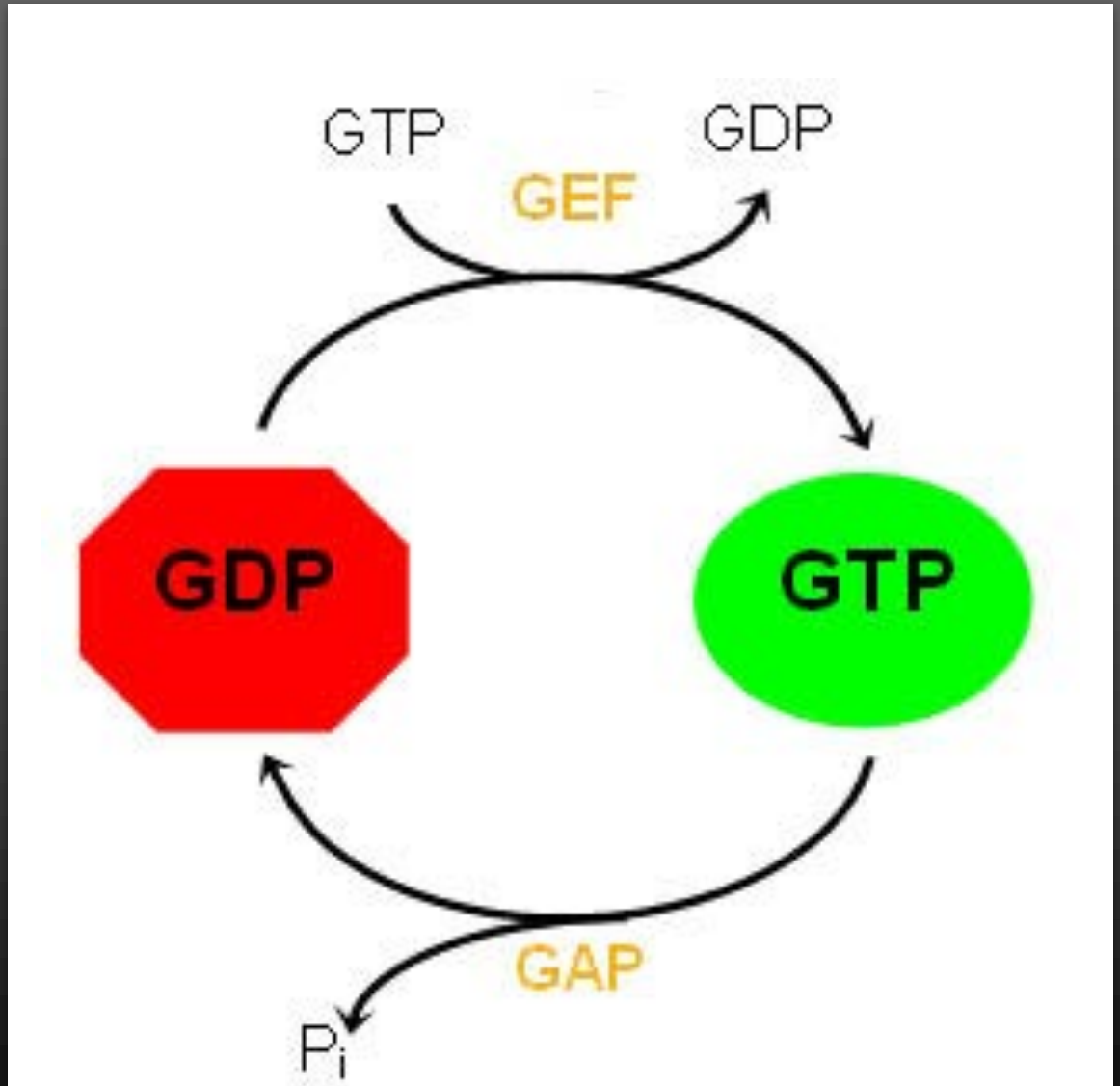
CONCLUSION

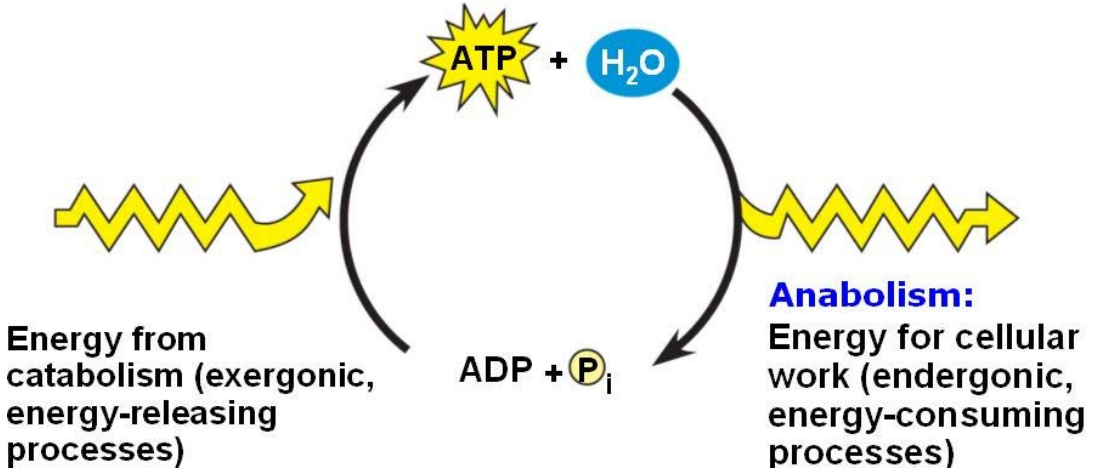
IN ORDER TO SUCEED IN ANTI-AGING MEDICINE WE CANNOT FOCUS ON THE

- INDIVIDUAL
- ORGANS (EG. SKIN WHICH IS THE LARGEST ORGAN IN OUR BODIES
- LAYERS OF SKIN



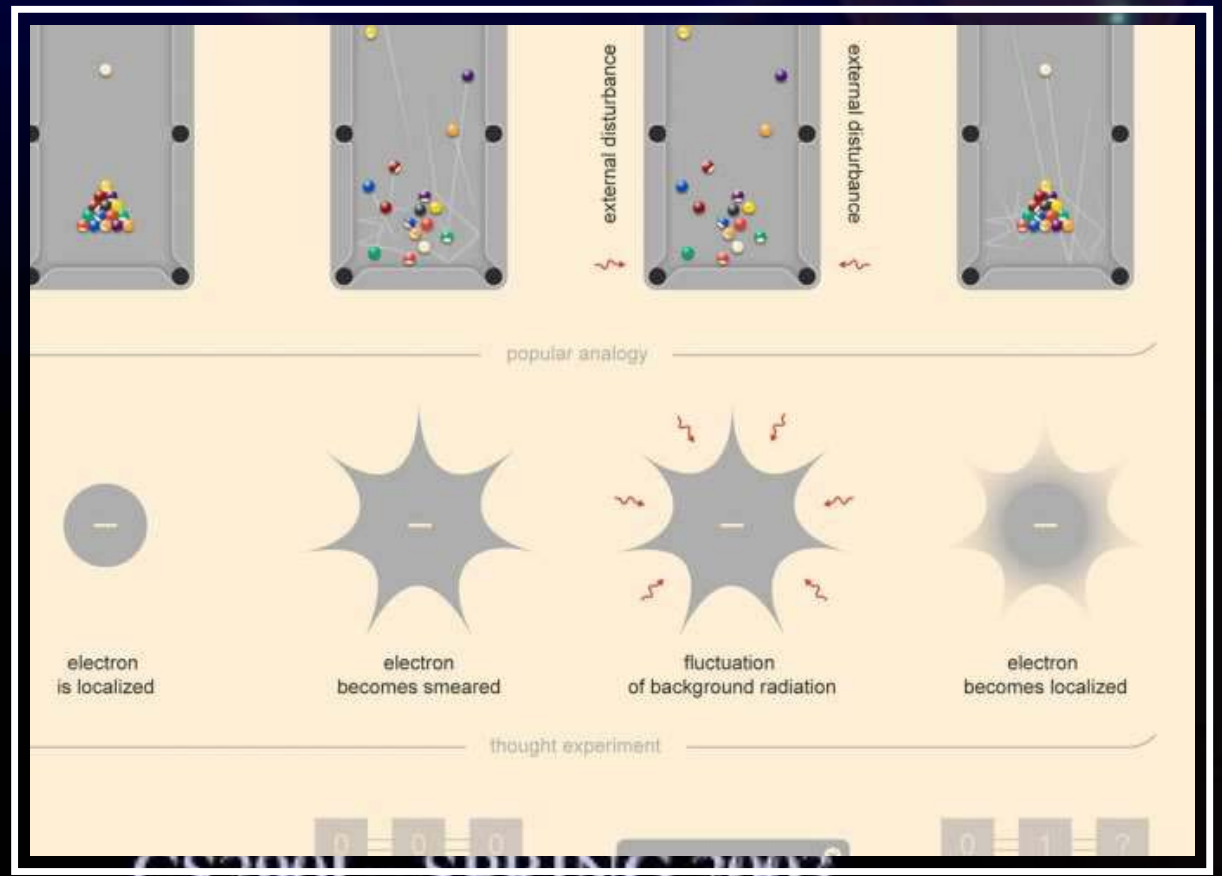
THE HIGHER THE LEVEL OF COMPLEXITY THE MORE UNLIKELY THE TIME REVERSAL PROCESS
WE CAN ONLY FOCUS ON MOLECULAR MECHANISMS (QUANTUM PHYSICS)
THAT ARE CAPABLE OF REVERSING TIME RUTINELY

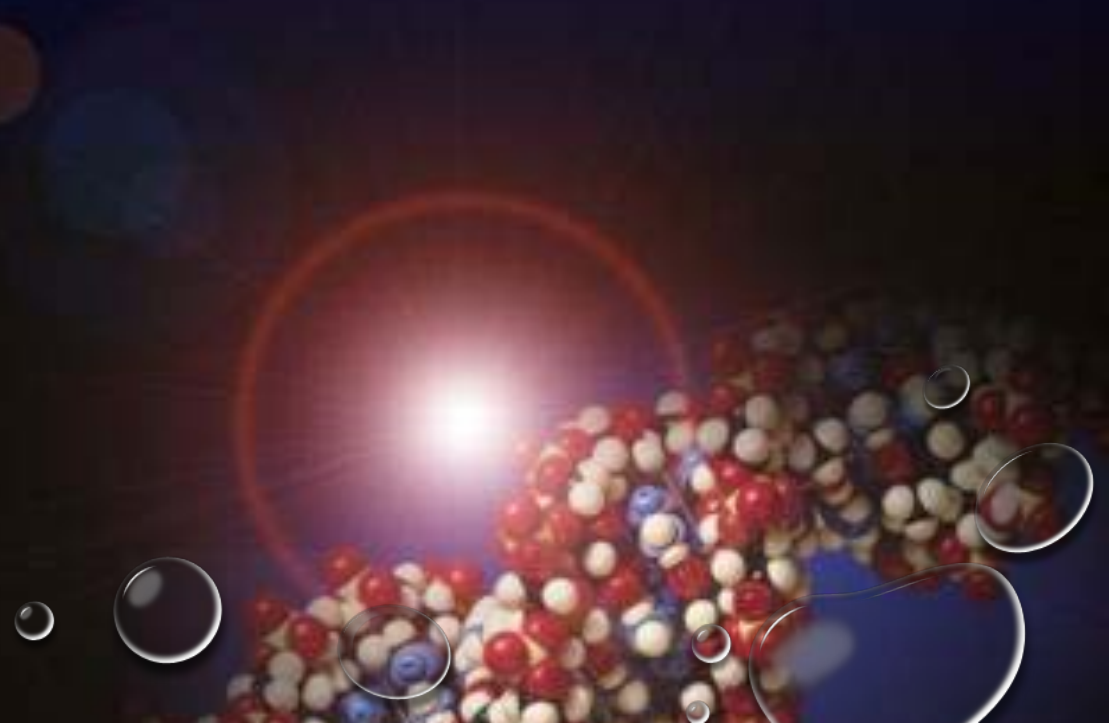

GTP
GDP
GEF
GDP
GTP
GAP
Pi


ATP
+
H2O
ADP + Pi
Energy from catabolism (exergonic, energy-releasing processes)
Anabolism:
Energy for cellular work (endergonic, energy-consuming processes)

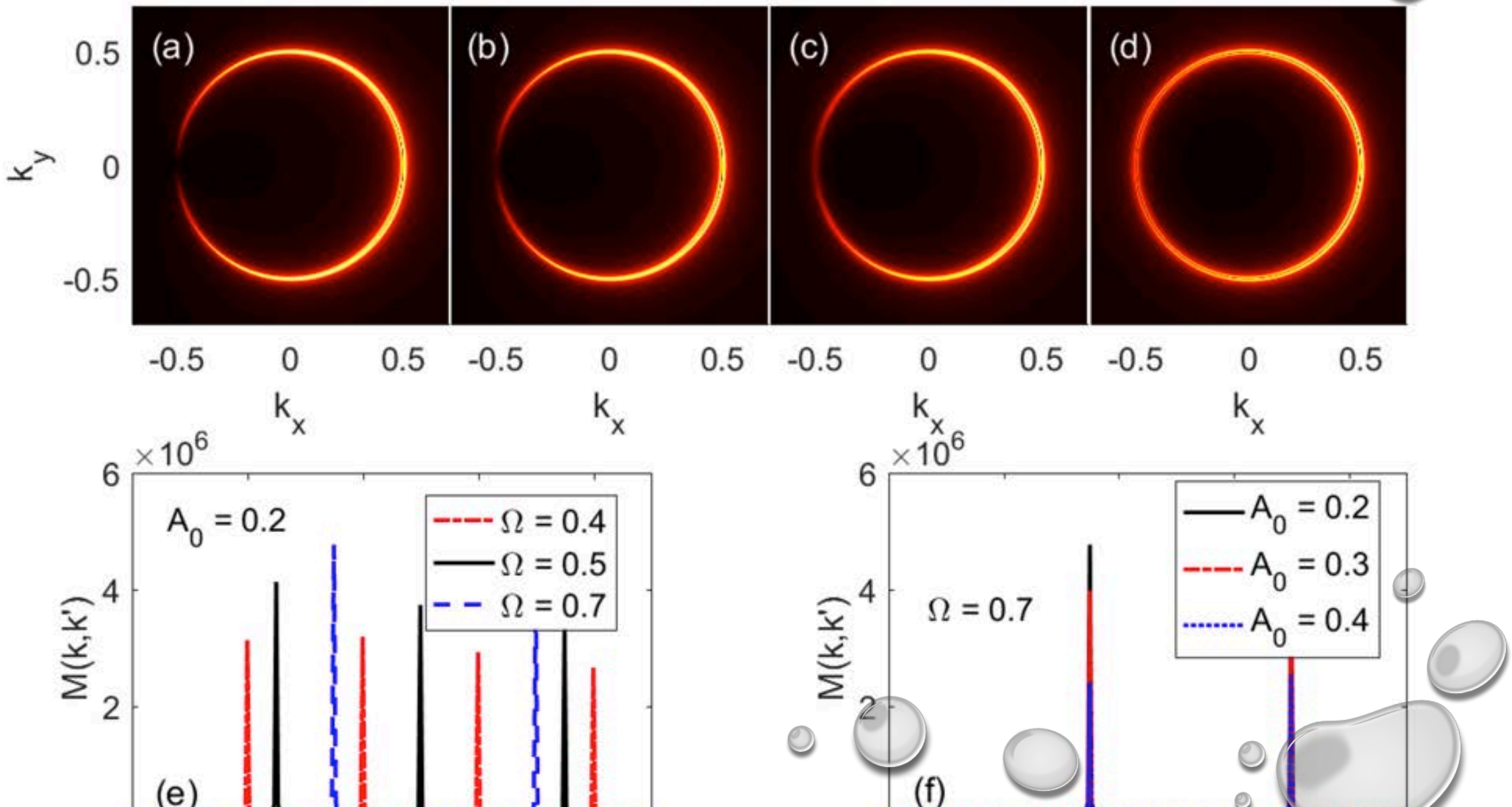
Genome Rearrangement

SORTING BY REVERSALS

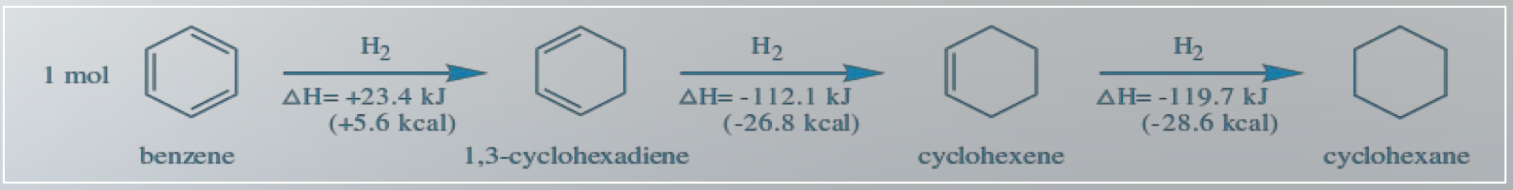




From: Time-reversal invariant resonant backscattering on a topological insulator surface driven by a time-periodic gate voltage



WHAT IS RESONANCE?



RESONANCE is a way of describing bonding in certain molecules or ions by the combination of several **contributing structures** (*resonance structures* or *canonical structures*) into a **Resonance Hybrid**

Mitochrondrial Protein-Protein Association with FRET

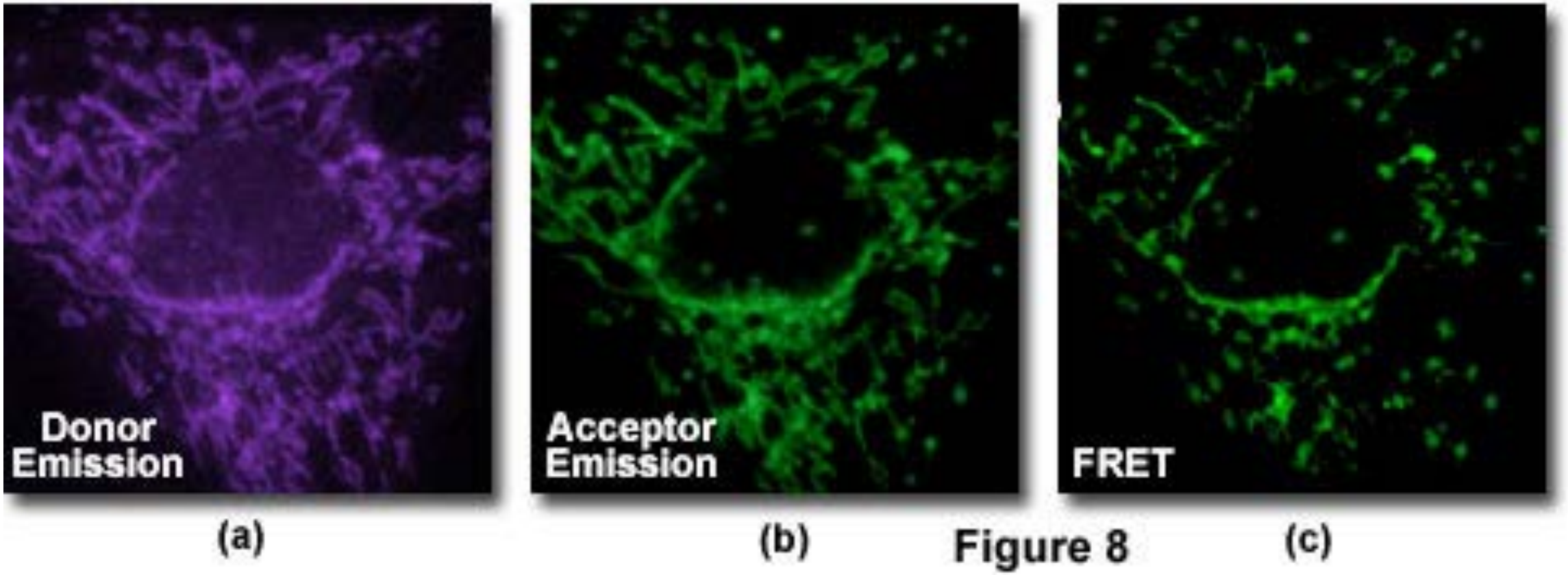


Figure 8

Figure 8(a)) contains only fluorescence from the BFP-labeled proteins, while the corresponding acceptor emission profile (Figure 9(b)) illustrates signals due to proteins labeled with GFP (and some contribution from donor emission). A FRET filter (Figure 8(c)), as described below, reveals fluorescence derived from resonance energy transfer between the two proteins

Contributing Authors

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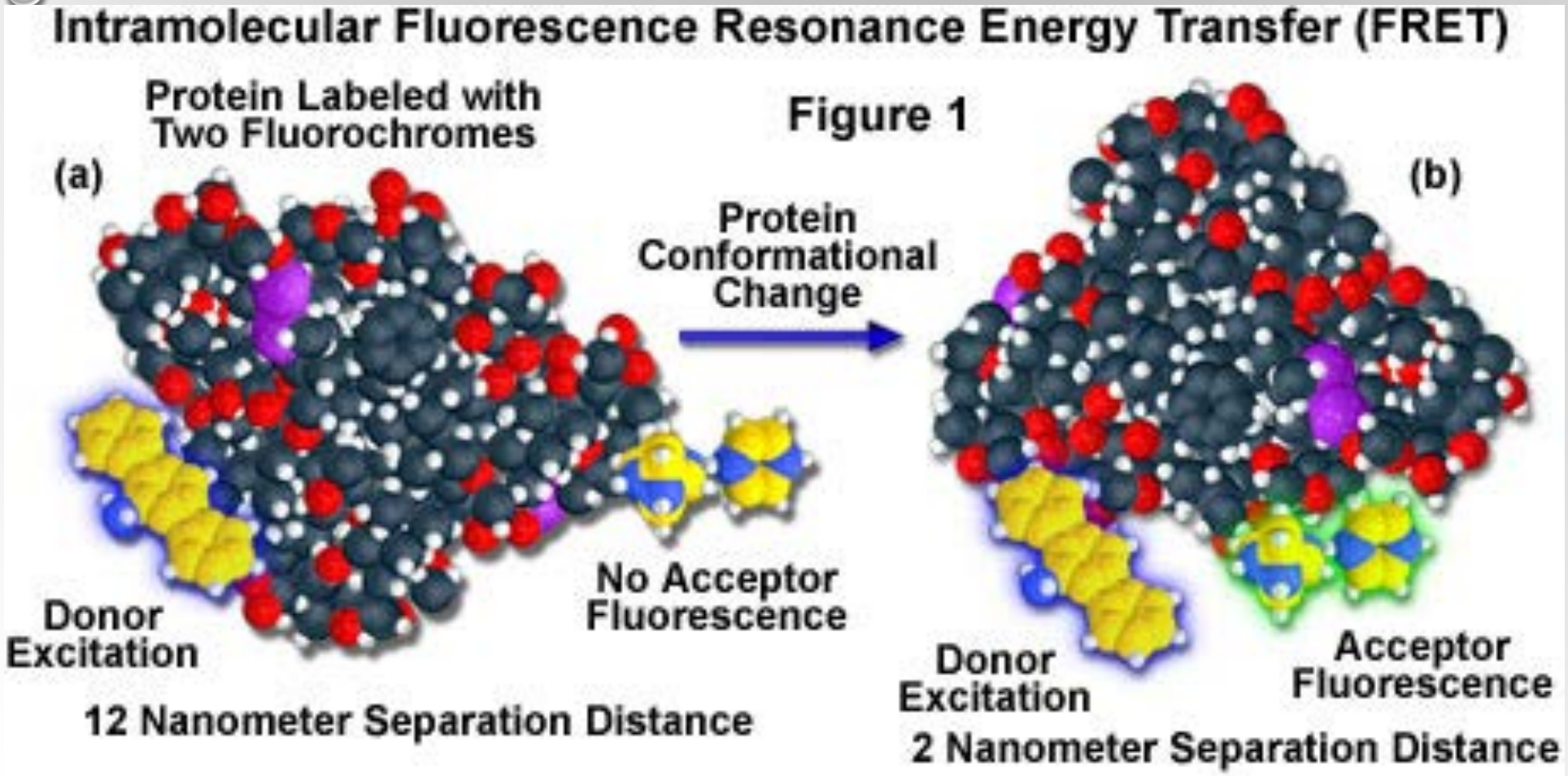
RESONANCE ENERGY TRANSFER BETWEEN PROTEINS FOR REPAIR AND COMMUNICATION



Resonance energy transfer is a non-radiative quantum mechanical process that does not require a collision and does not involve production of heat.

Resonance Energy Transfer Jablonski Diagram

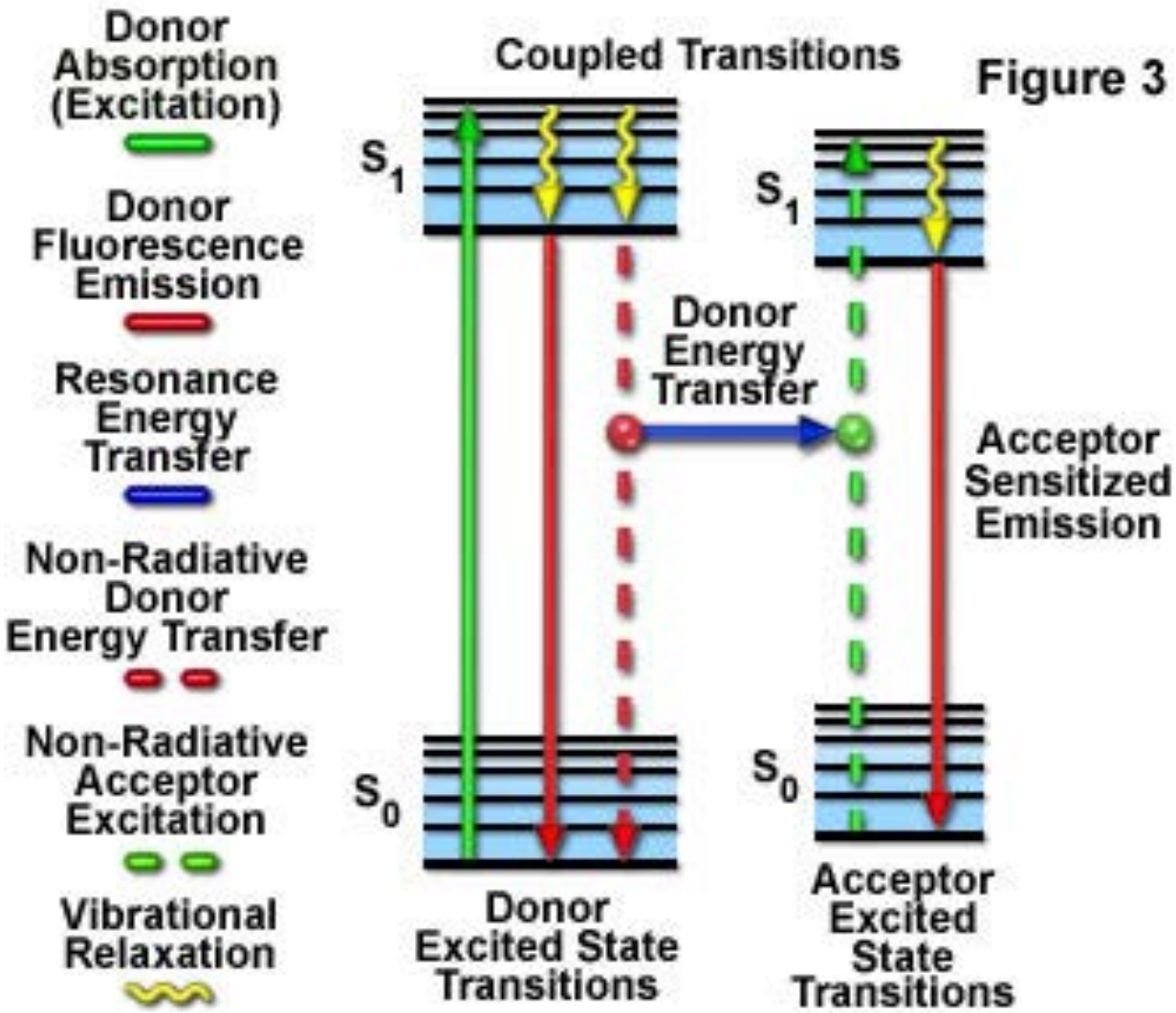
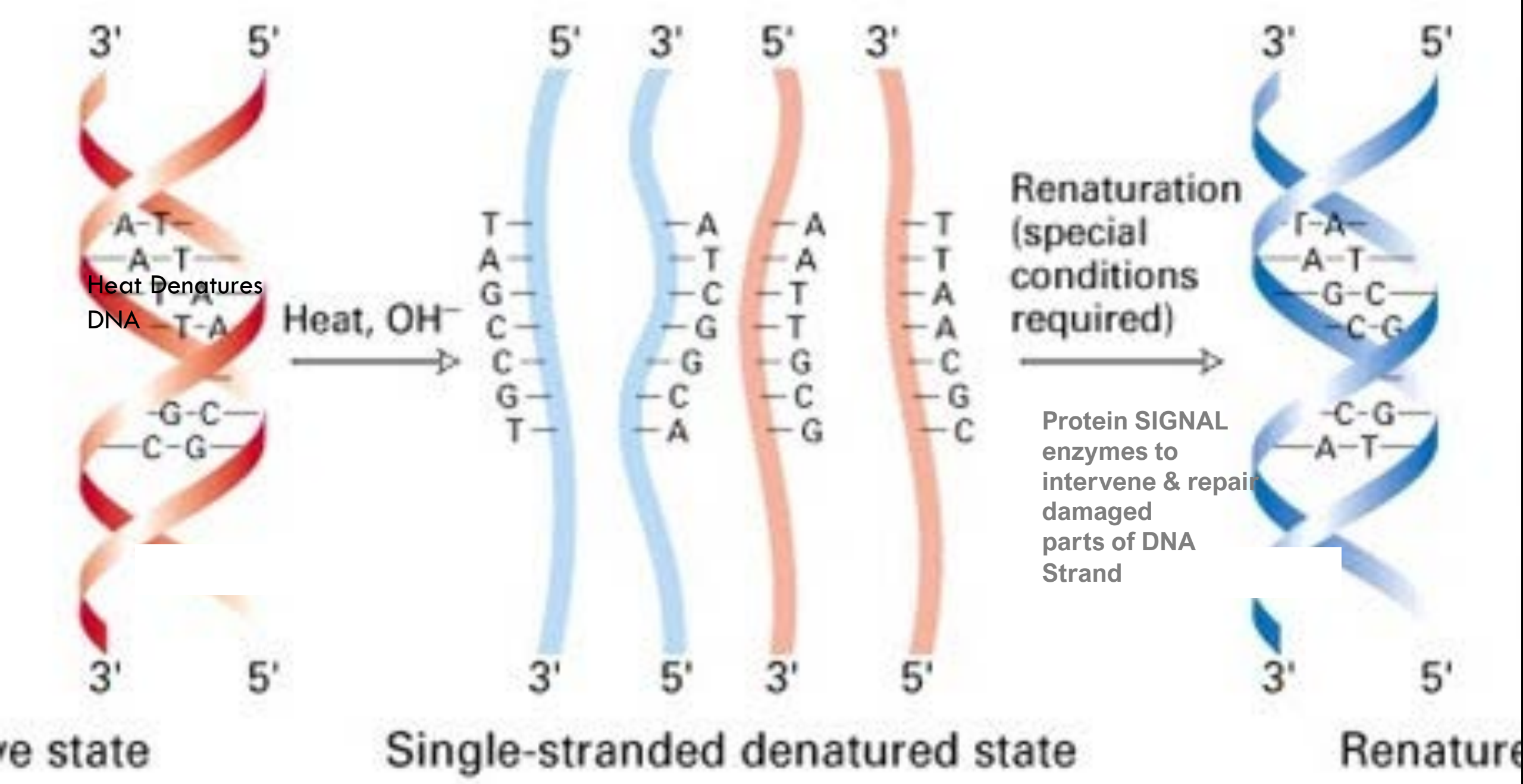


Figure 3

Figure 7

Radiofrequency (10 MHz–300 GHz) Radiation leads to DNA denaturation = DNA damage



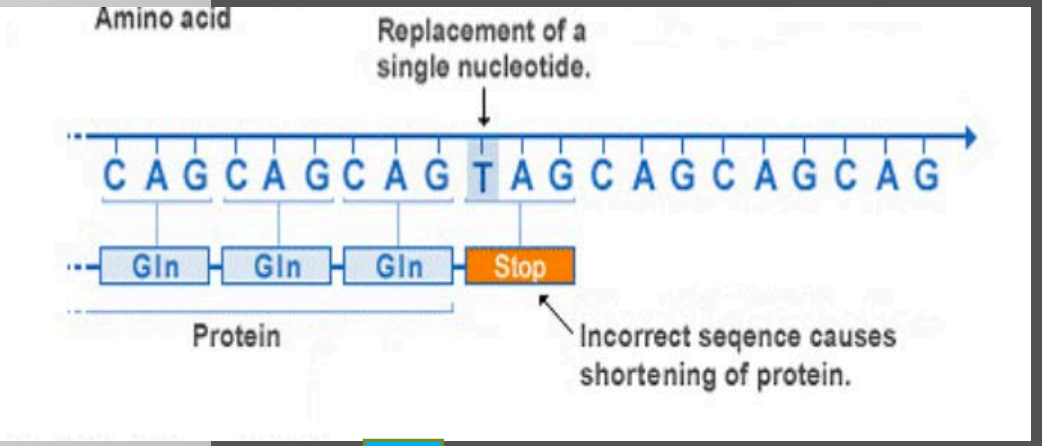
SIGNALING TO REPAIR DNA

- OUR RESEARCH FOCUSES ON THE INVESTIGATION OF BIOSIGNALS AND HOW TIMING AFFECTS THEIR MEANING WITHIN THE BIOLOGICAL NETWORK

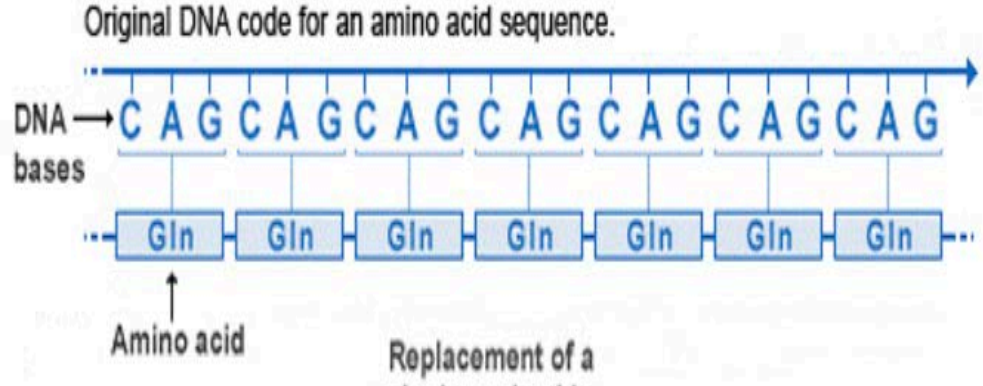
SIGNALING CAN REINSTATE FADED OR BROKEN BIO-SIGNALS BY EMITING HIGHLY BIORESONANT SIGNALS THAT CAN FUSE WITH BIOLOGICAL SIGNALS TO AMPLIFY FADED BIOLOGICAL SIGNALS

SIGNALING CAN REINSTATE FADED OR BROKEN BIO-SIGNALS BY EMITING HIGHLY BIORESONANT SIGNALS THAT CAN FUSE WITH BIOLOGICAL SIGNALS TO FILL IN THE GAPS OF BROKEN BIOLOGICAL SIGNALS THUS REINSTATING THEIR ORIGINAL MEANING

BIO RESONANT SIGNALS DELIVERED AT SPECIFIC TIMES CAN "FILL IN THE GAPS" IN DETERIORATED NONSENSE SIGNALS TURNING THEM INTO MEANINGFUL SIGNALS.



A er at n F e en
F in a b o-la a e



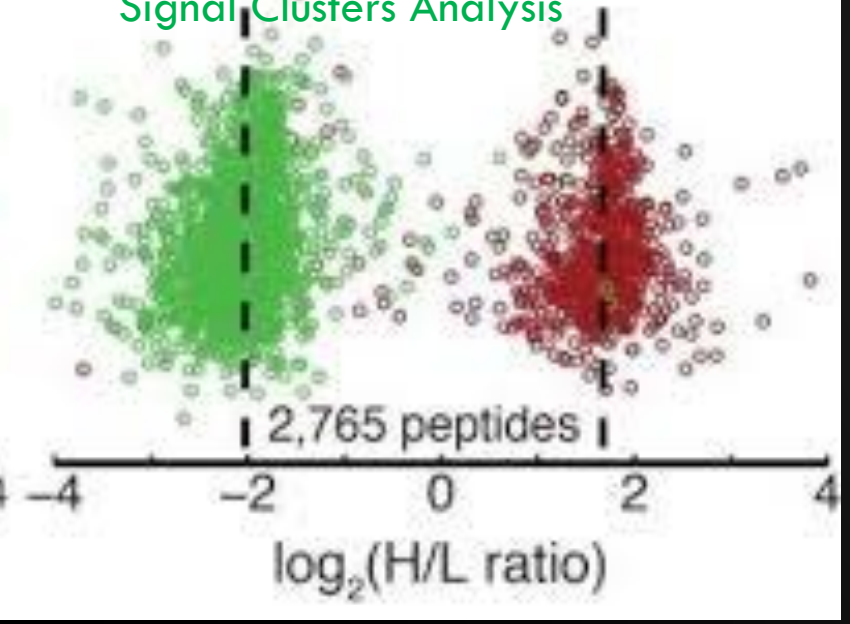
Alternating Frequencies forming a bio-language

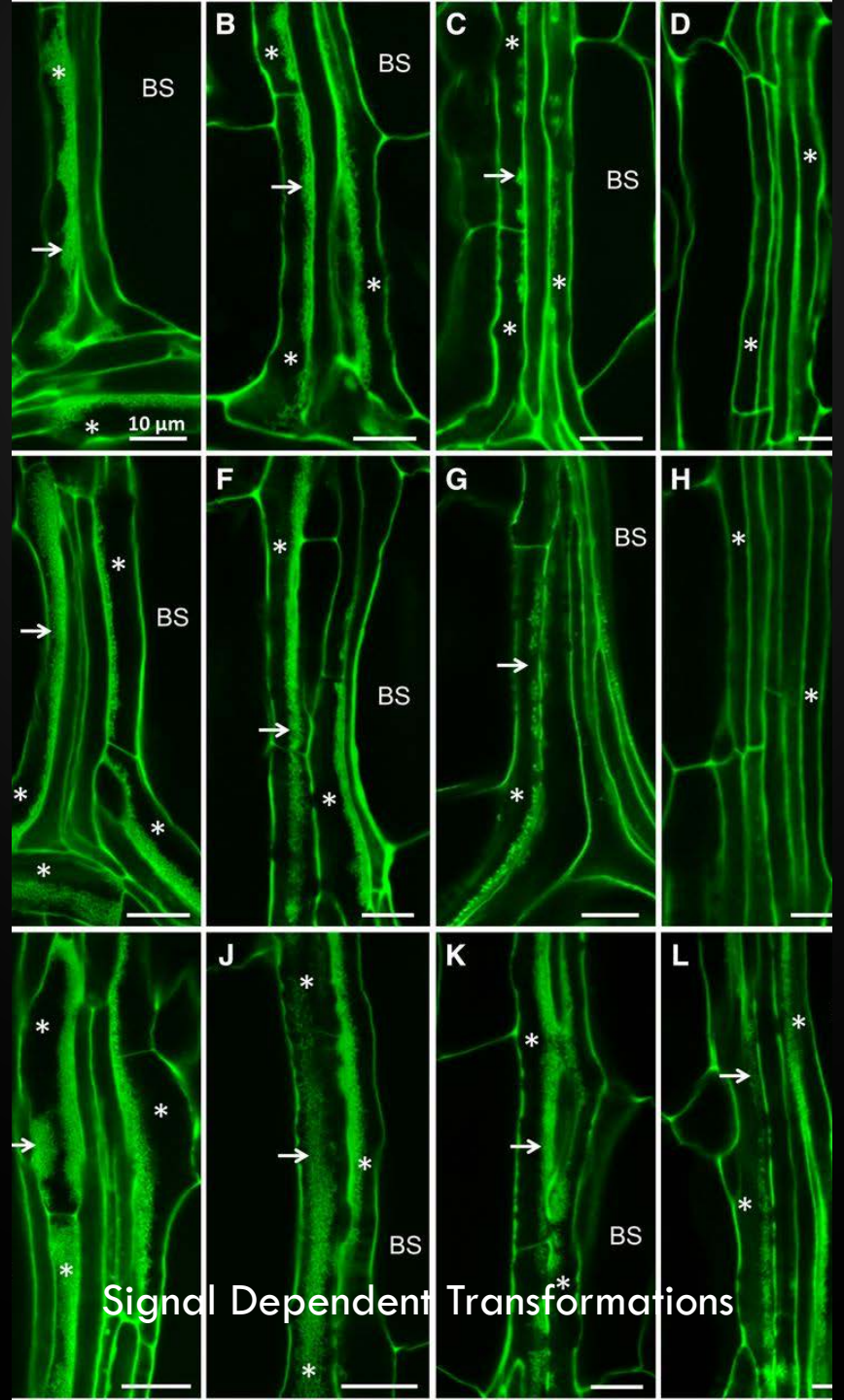
FIVE BASIC MECHANISMS OF SIGNALING

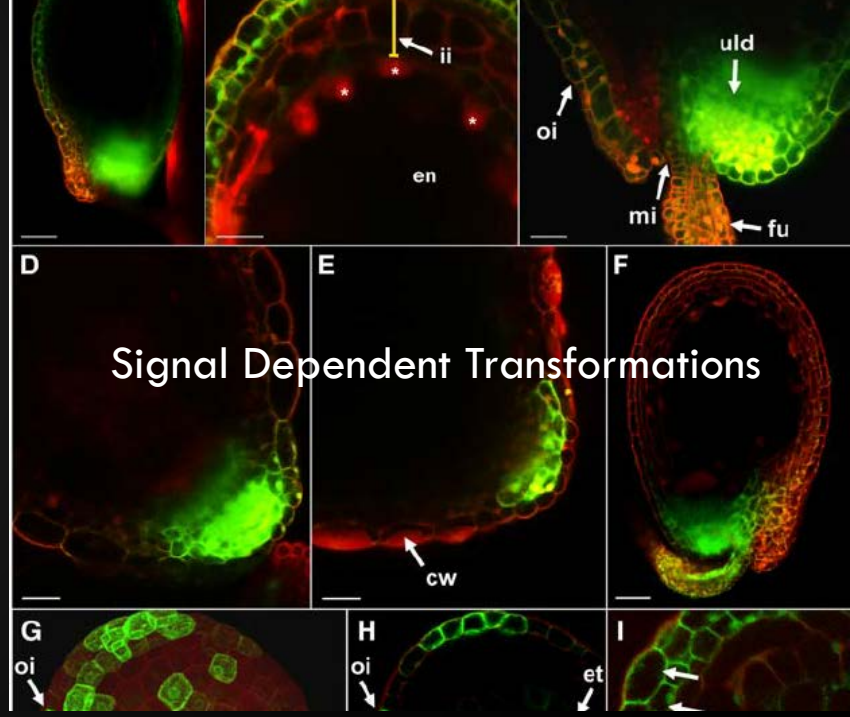
- BLUEPRINT SIGNALS RESONANT ON “IN SYNCH” WITH BIOLOGICAL SIGNALS
- ULTRA LOW ROPRIETARY ENERGIES (BASED ON MATHEMATICAL PROOF (ELECTRON GATED ION CHANNELS 2008) WHERE ELECTRONS CONTROL AND AMPLIFY ION CHANNELS (POINTS OF ENTRY)
- SIGNALS ARE EMITTED IN VARIABLE DISCRETE TIMES (CIRCADIAN RHYTHM TIMETABLE)
- MULTIPLE RESONANT SIGNALS EMITTED SIMULTANEOUSLY
- MEGA ANTI-OXIDANT EFFECT BY THE ELECTRONS CARRYING THE SIGNALS INTO THE SYSTEM

SIGNAL PROCESSING BLUEPRINTS

Signal Clusters Analysis



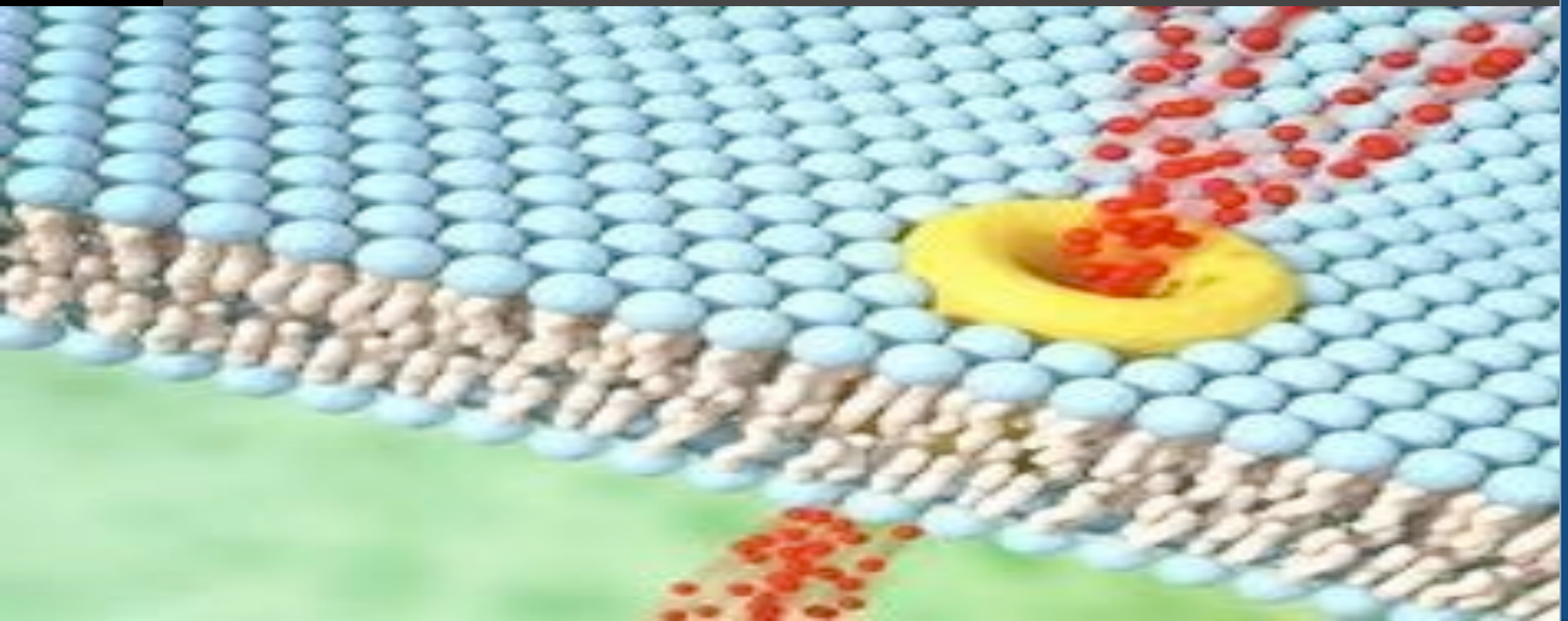


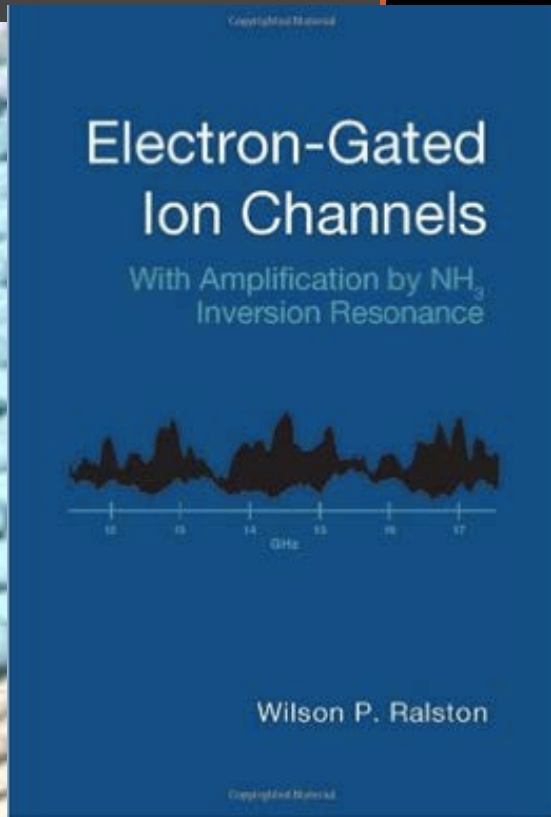


SIGNALS ARE COMPOSED BY COMPLEX WAVEFORM CONSTRUCTS

SIGNALS MUST BE DELIVERED AT ULTRA LOW ENERGIES (BELOW THERMAL NOISE)

At very low energies in the nanorange electrons RESONATE & *amplify* the energy of Ion Channels by increasing or decreasing the height of the energy at the gating cavity in this Ion Channel

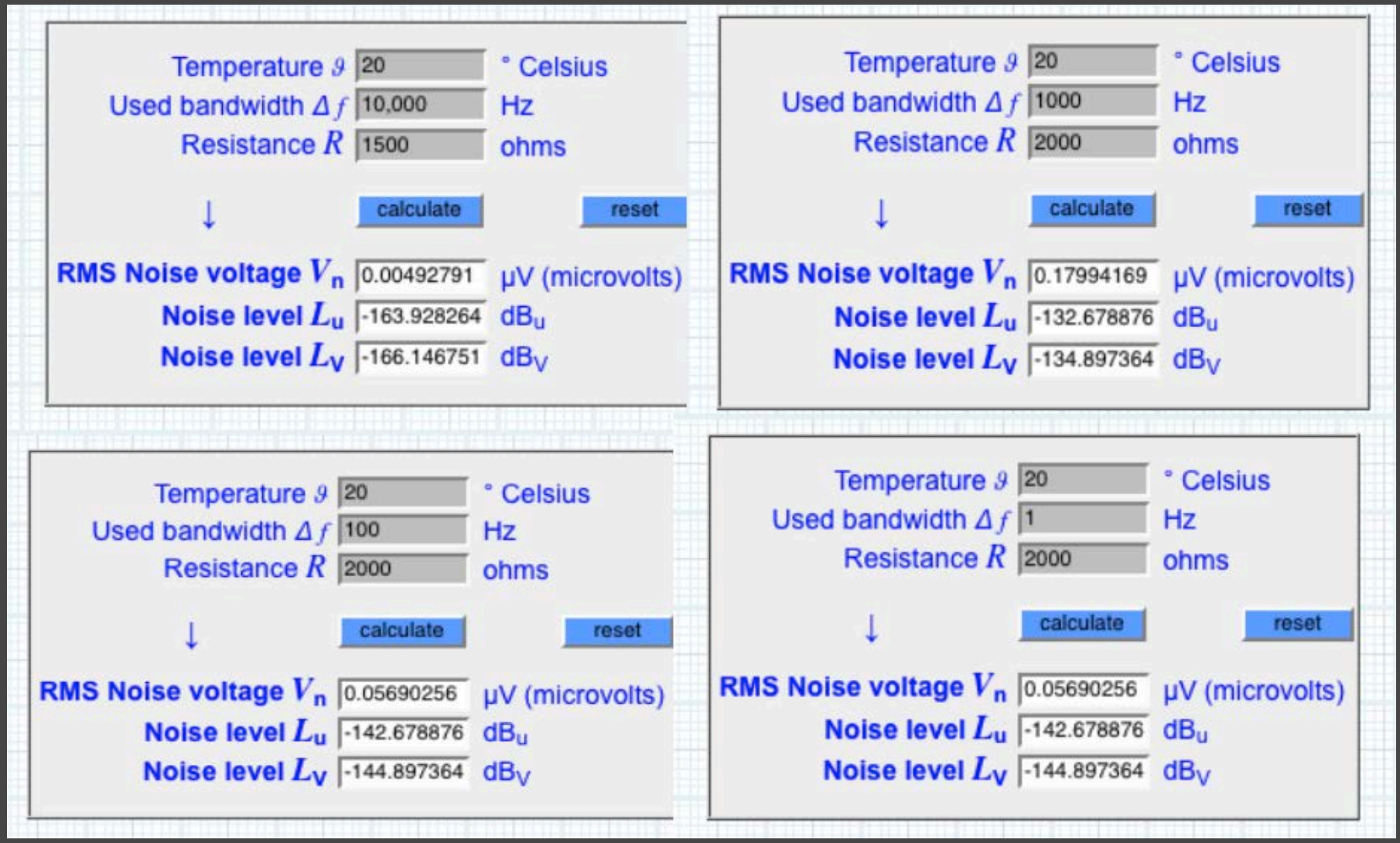




THERMAL NOISE IS A MEASURABLE FACT

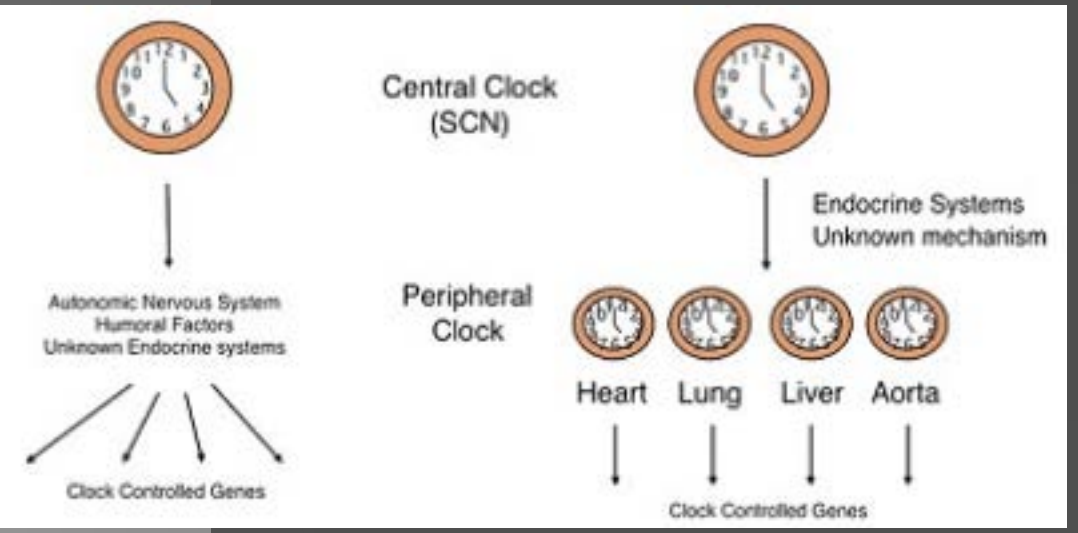
SOME EXAMPLES OF THERMAL NOISE SPECS

NOTE: 0.0049 MICROVOLTS IS 0.000049 VOLTS

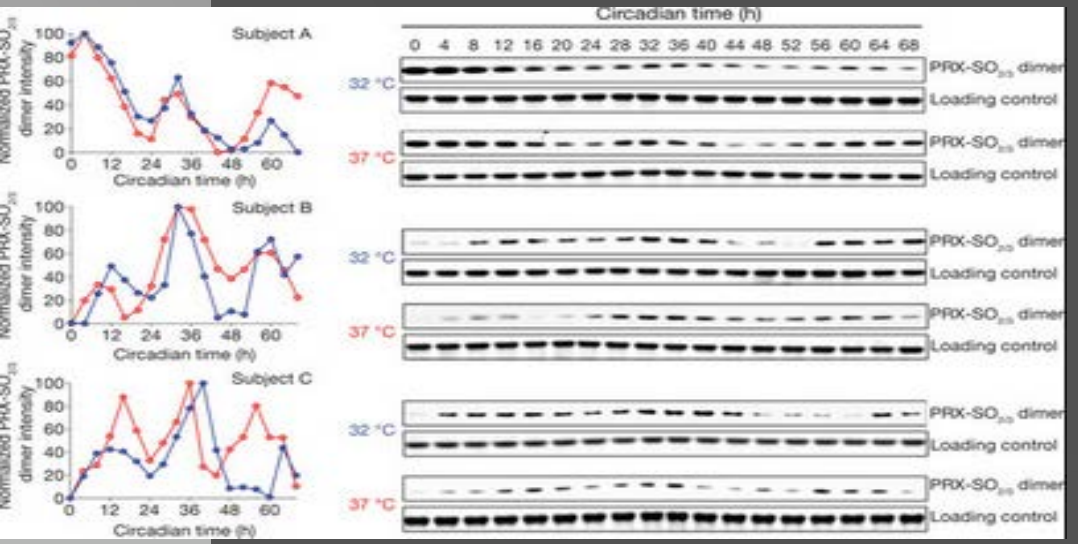


THE TIME DIMENSION

OUR CELLS HAVE A CIRCADIAN CLOCK



CLOCK-DEPENDENT REGULATION OF THE CELL CYCLE IS AN ESSENTIAL IMMUNE CONTROL MECHANISM.



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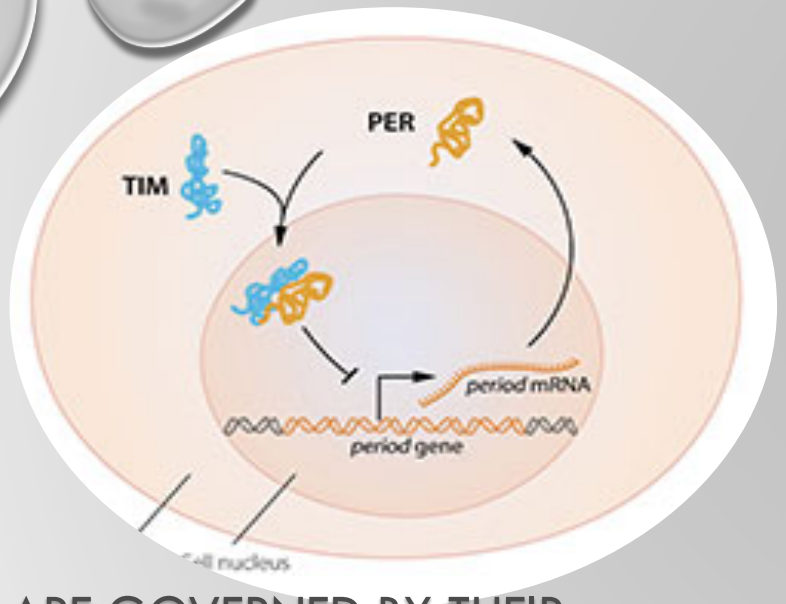


CELLS ARE GOVERNED BY THEIR BIOLOGICAL CLOCKS IN ORDER FOR OPTIMUM COMMUNICATION TO TAKE PLACE BETWEEN ARTIFICIAL INTELLIGENCE (AI) BLUEPRINT SIGNALS AND NATURALLY OCCURING BIOLOGICAL SIGNALS, THE AI SIGNALS MUST BE DELIVERED WITHIN PRE-DEFINED VARIABLE TIMES THAT MAPS THE TIME SCHEDULE OF BIOLOGICAL SIGNALS. THEREFORE THE IREVIVE IS DESIGNED ON THE BASIS OF A MATRIX OF SIGNALS DELIVERED WITHIN A TIME MATRIX

The Nobel Prize in Physiology or Medicine 2017

© Nobel Media AB. Photo: A.Mahmoud

Jeffrey C. Hall

Prize share: 1/3

© Nobel Media AB. Photo: A.Mahmoud

Michael Rosbash

Prize share: 1/3

© Nobel Media AB. Photo: A.Mahmoud

Michael W. Young

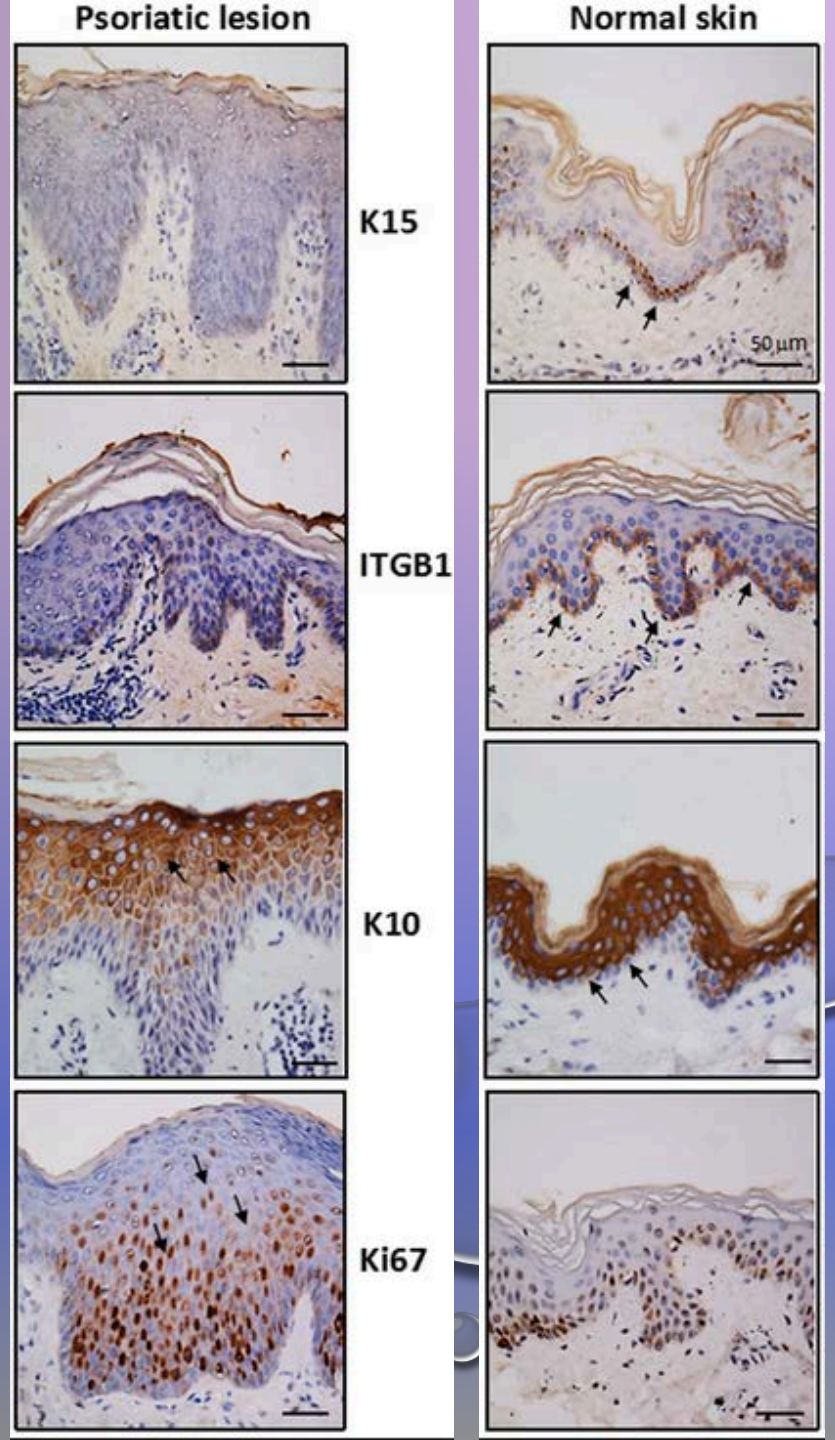
Prize share: 1/3

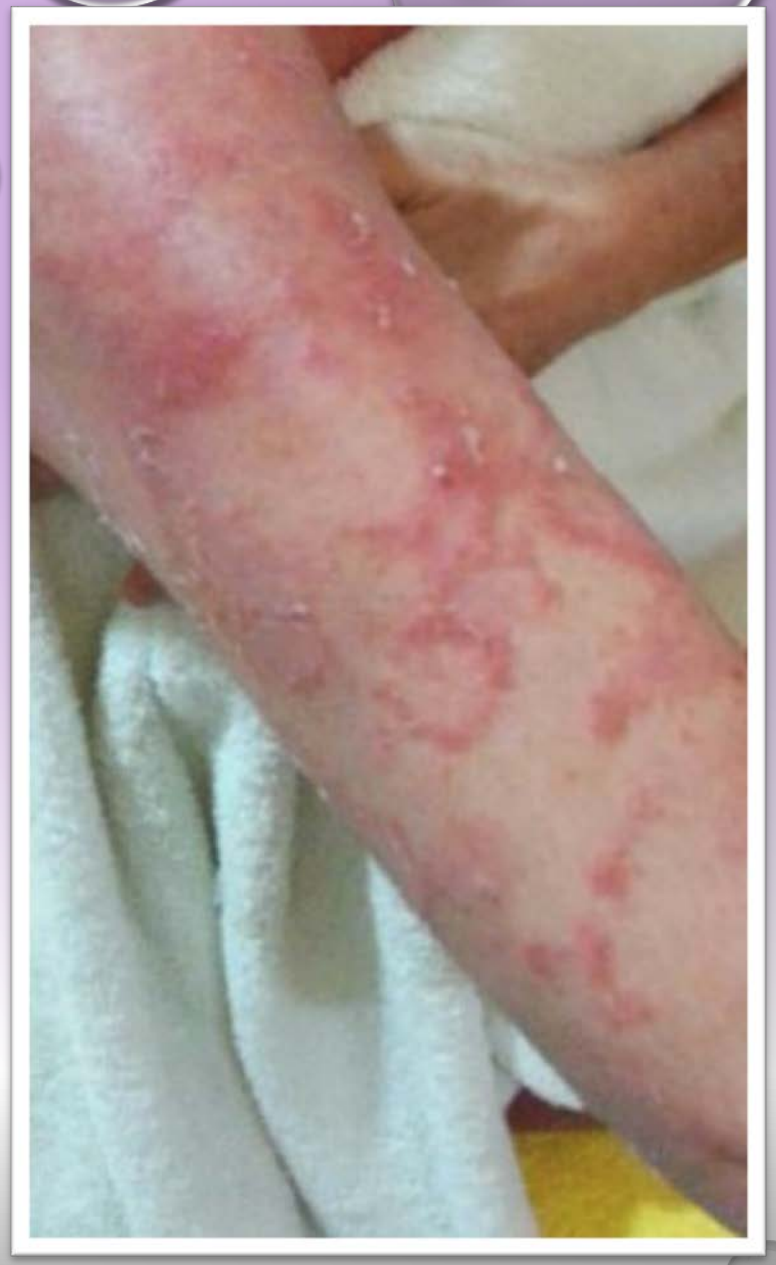
The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm."

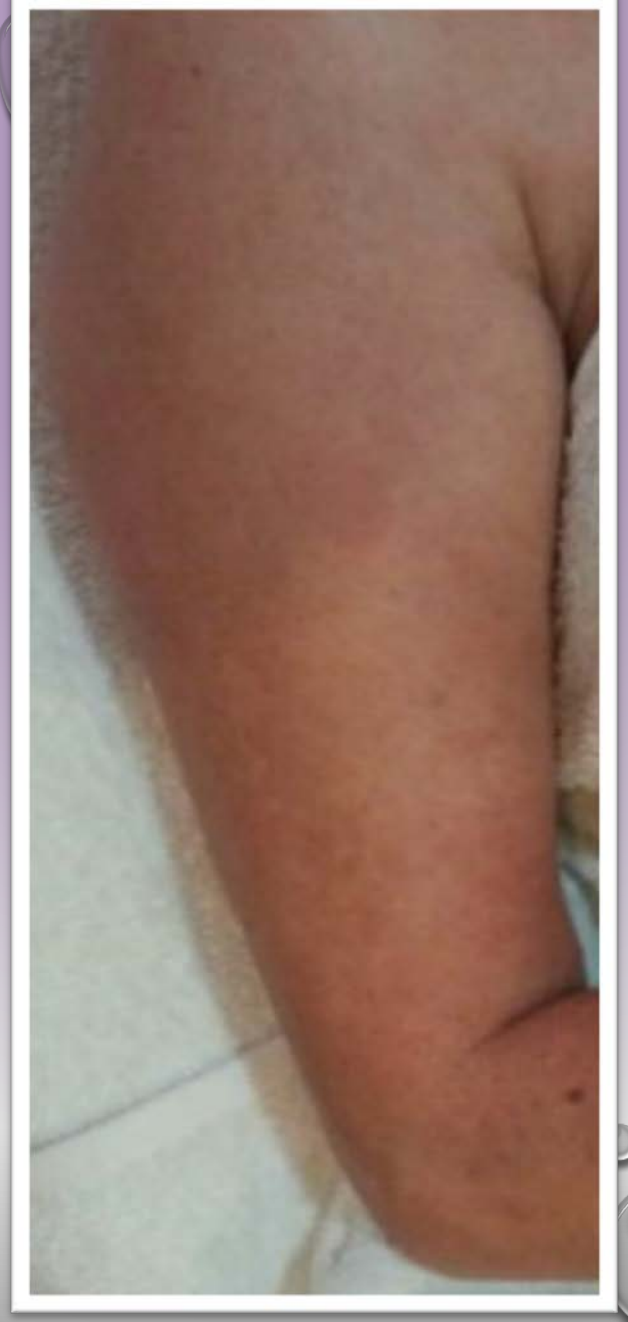
Recent studies have already linked the skin's circadian clock to Psoriasis

Psoriasis is one of the most common immune--mediated skin disorders.

PSORIASIS : INLAMMATION due to the DISRUPTION of signals delivered at a time schedule outside the required range of cellular circadian clocks

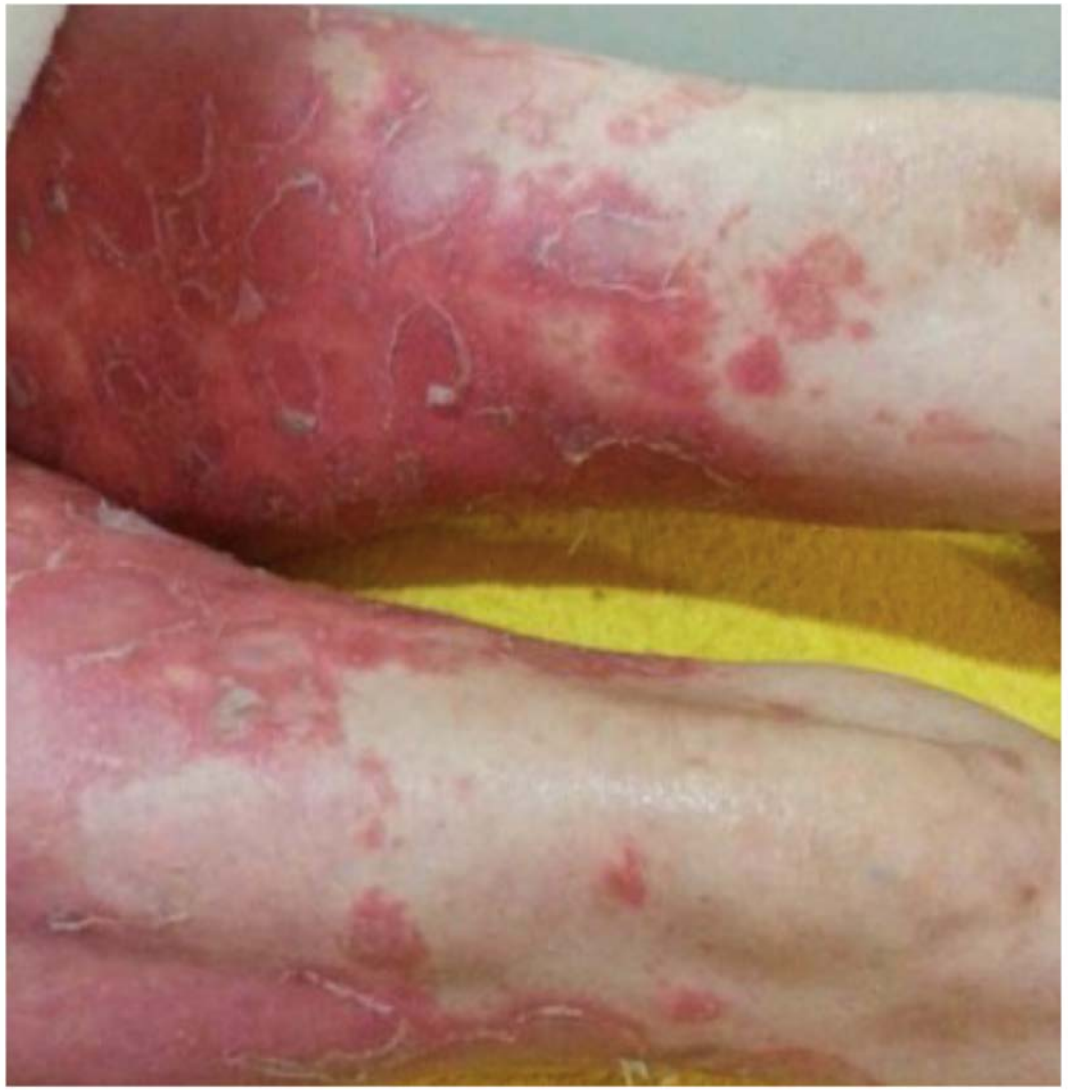


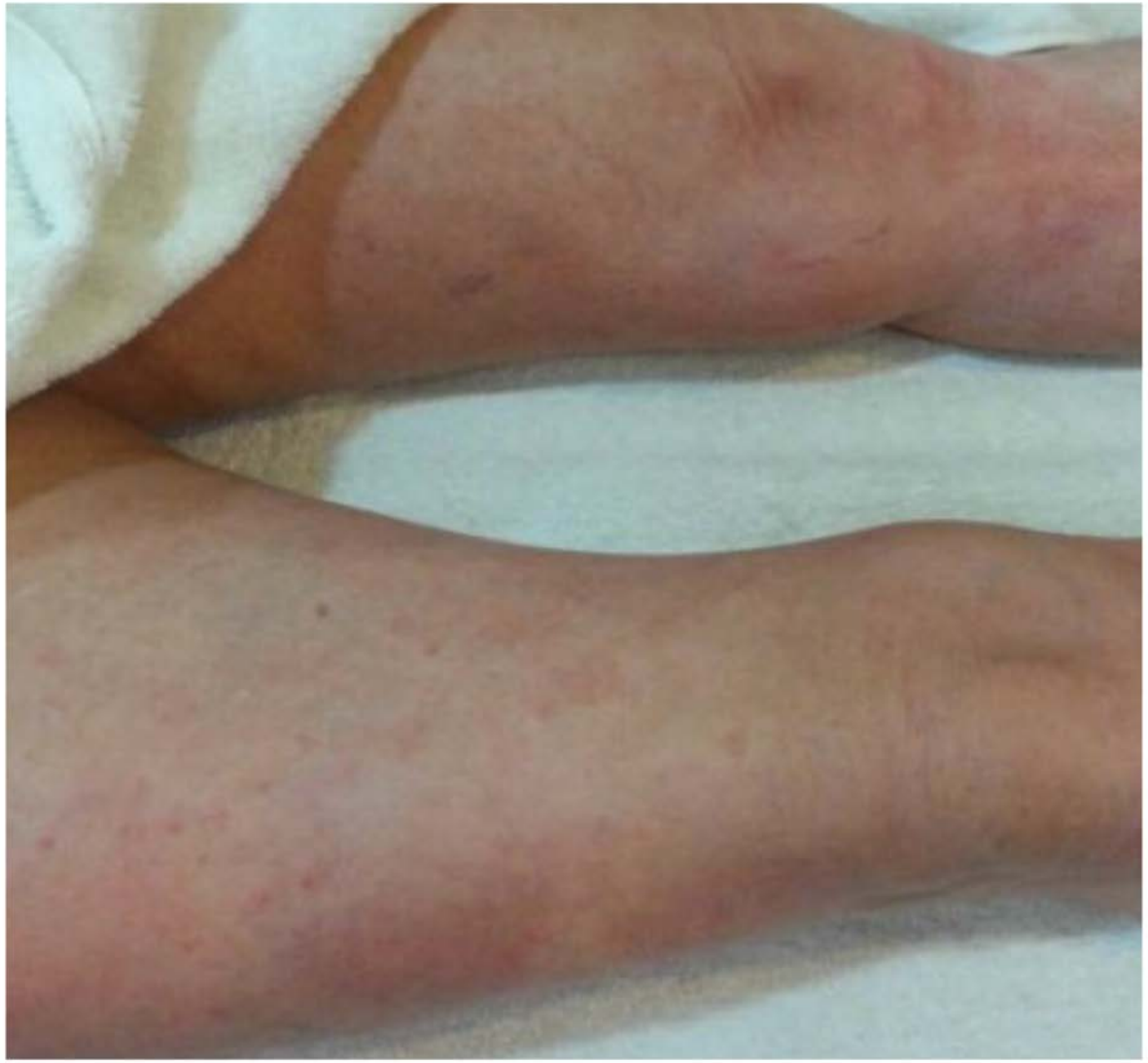




PSORIASIS
BEFORE AND AFTER
10 SIGNALING TREATMENTS

Veronica Yap, Singapore





PSORIASIS

BEFORE AND AFTER 10 SIGNALING TREATMENTS

Veronica Yap, Singapore

Effects of varicella-zoster virus on cell cycle regulatory pathways

The normal cell cycle of human foreskin fibroblasts is dysregulated

Activates transcription factors through protein kinase pathways extracellular-regulated kinase (ERK)

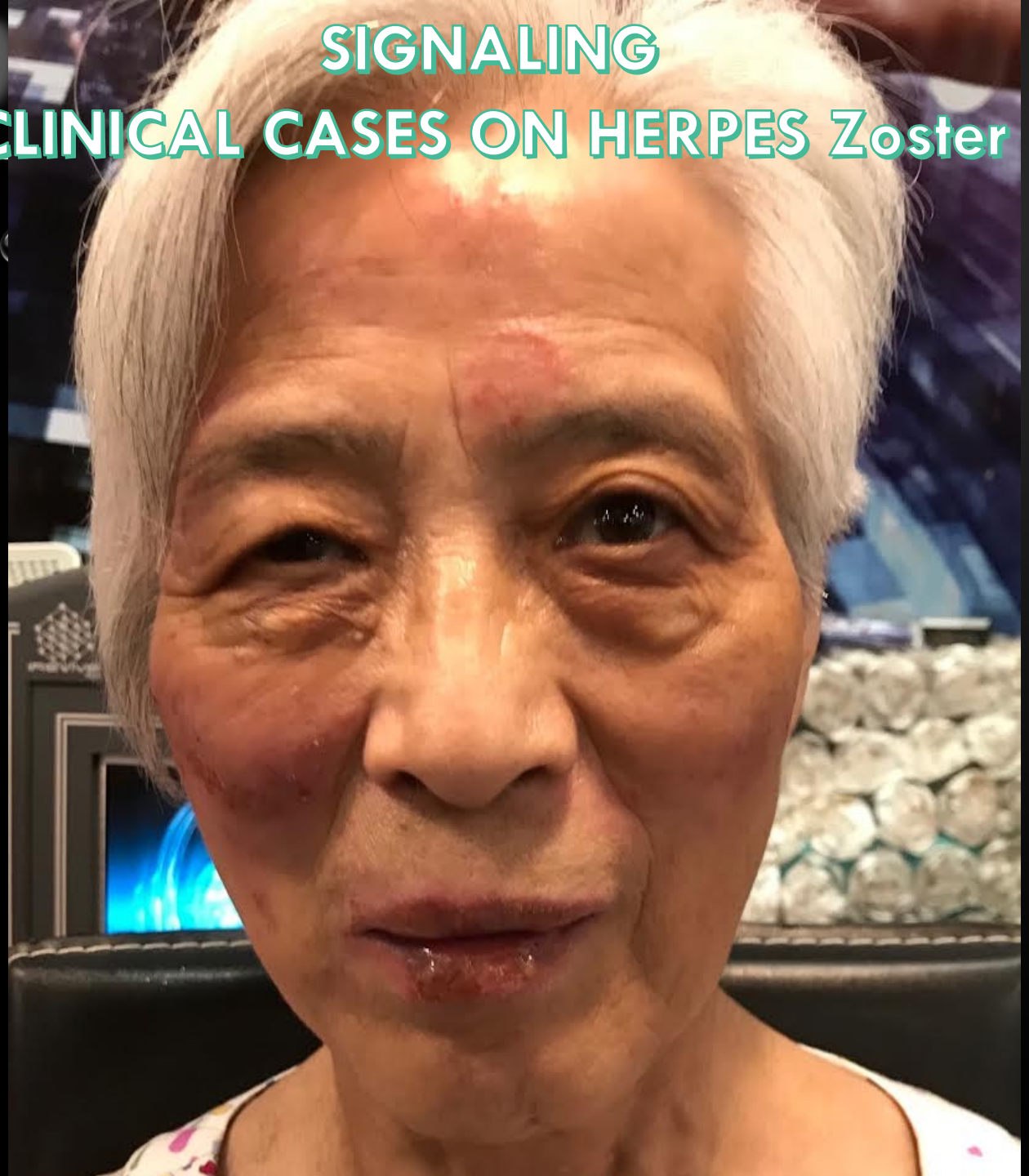
Activates transcription factors through c-Jun N-terminal kinase (JNK pathway).

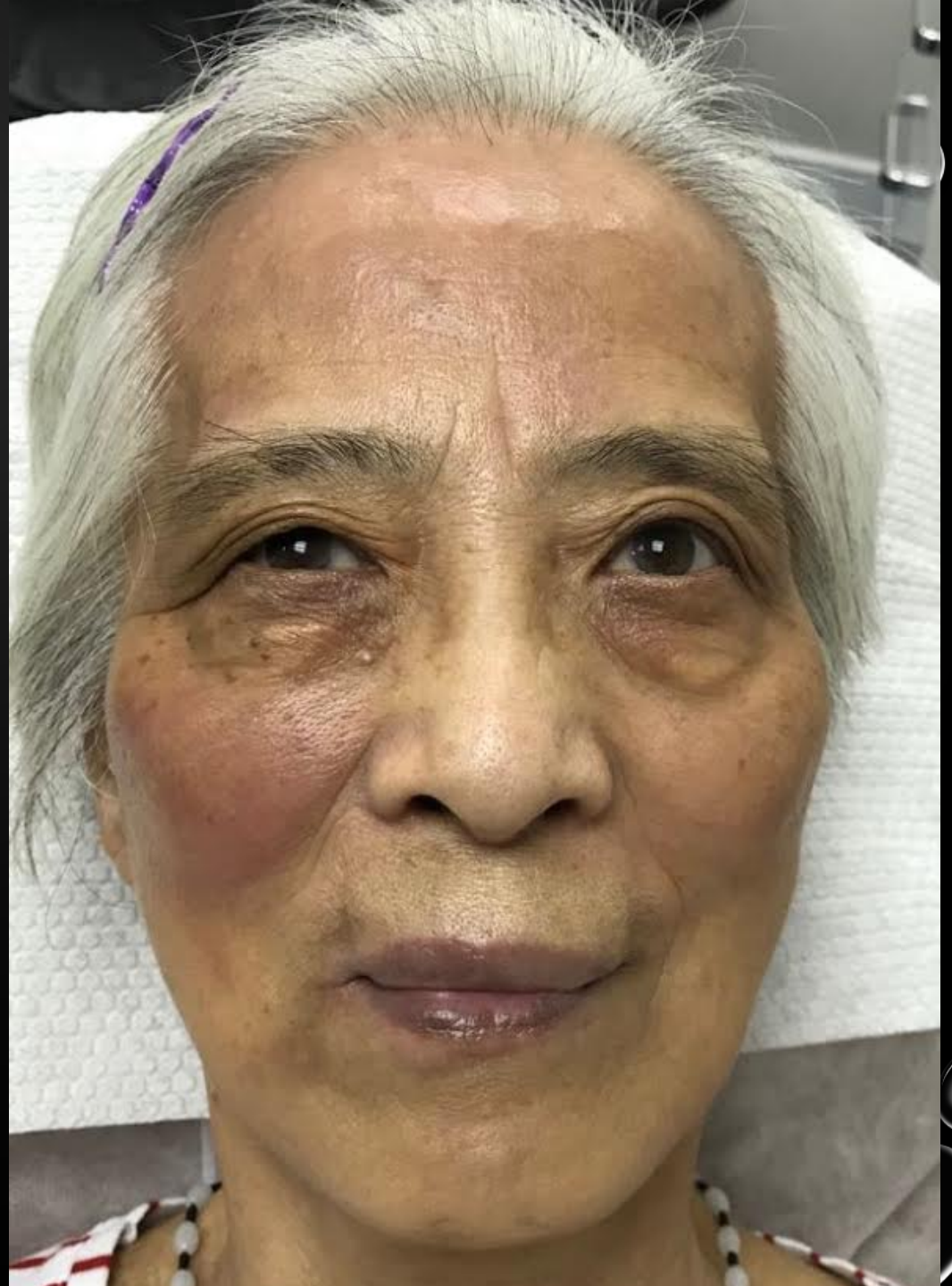
JNK pathway increase cyclin levels (A, B1, and D3 cyclins)

Moffat JF[1], Greenblatt RJ. Curr Top Microbiol Immunol. 2010;342:67-77. doi: 10.1007/82_2010_28.

Treatment by targeted Signaling to enhance cell cycle Regulatory Signaling Pathways

SIGNALING
CLINICAL CASES ON HERPES Zoster





SIGNALING
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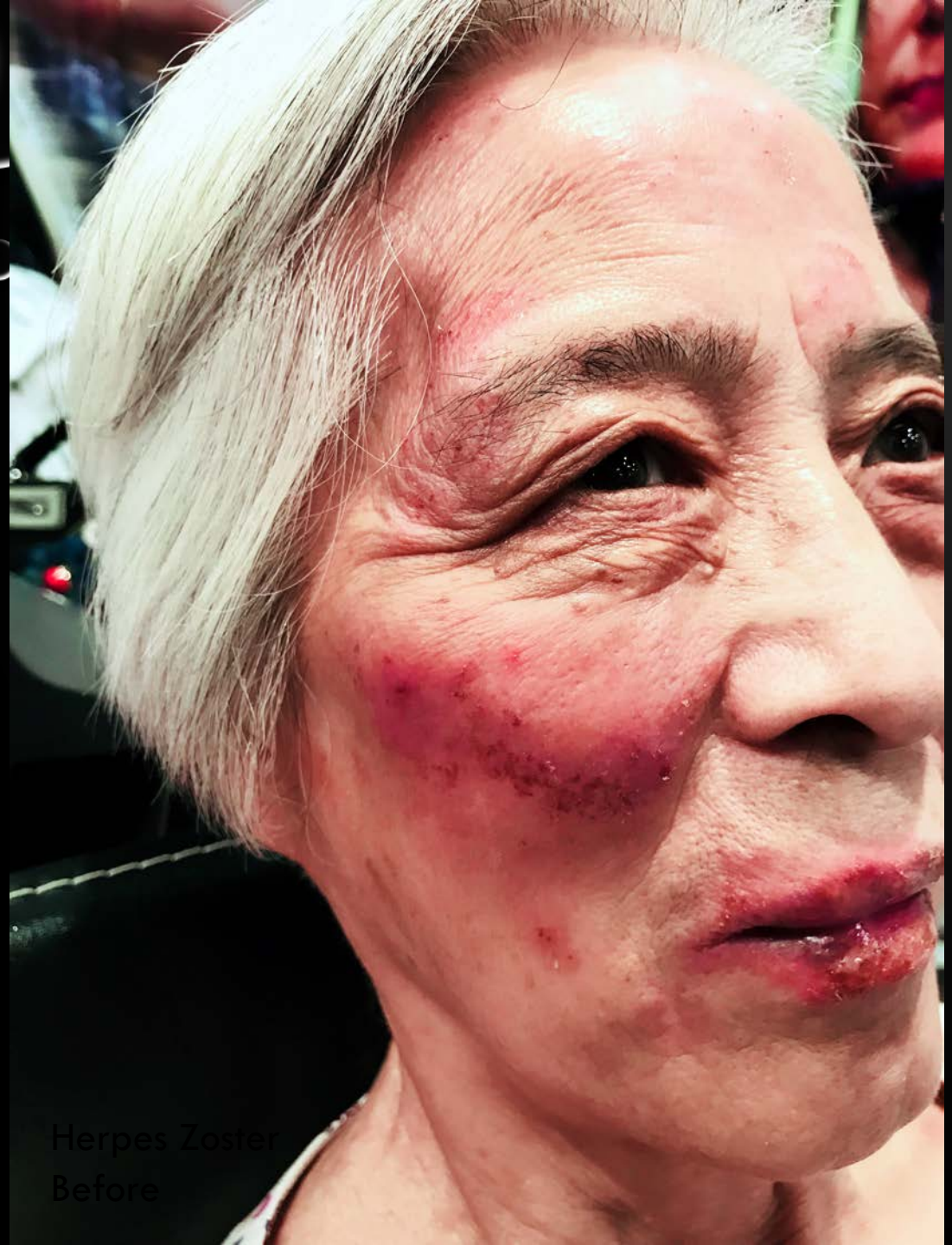

Herpes Zoster
Before

SKIN DISORDERS CAN BE REVERSED BY REVERSING PROTEIN DAMAGE AT THE CELLULAR LEVEL

BUT CAN WE GO BACK IN TIME?

CAN YOU UNBOIL AN EGG?

YOU CAN UNBOIL AN EGG BY REFOLDING misfolded PROTEINS WITHIN THE CELL. IELLIOS does that VIA RESONANT SIGNALING

< Previous Article

Volume 79, Issue 7, p1129–1132, 30 December 1994

Minireview

Protein folding and the regulation of signaling pathways

Suzanne L. Rutherford, Charles S. Zuker

DOI: http://dx.doi.org/10.1016/0092-8674(94)90003-5

Summary References Comments

Abstract

A growing number of intracellular signaling molecules are found associated with components of the cellular protein folding machinery. In this minireview we suggest that the same ancient cellular process that promotes the folding and assembly of nascent proteins plays a pivotal role in signal transduction by promoting the regulated folding or assembly and disassembly of mature signaling molecules between active and inactive states. Members of the protein folding machinery mediate the activity of various kinases, receptors, and transcription factors. These may be poised in late stages of folding or assembly until upstream signaling events trigger their biogenesis into activated molecules.

How ‘unboiling an egg’ leads to better cancer treatments

By John Hewitt on October 8, 2015 at 7:30 am | 5 Comments

488 shares

The Nobel Prize in Chemistry 2015
Tomas Lindahl, Paul Modrich, Aziz Sancar

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THE ROYAL SWEDISH ACADEMY OF SCIENCES

English
English (pdf)

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Press Release

7 October 2015

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry for 2015 to

Tomas Lindahl
Francis Crick Institute and Clare Hall Laboratory, Hertfordshire, UK

Paul Modrich
Howard Hughes Medical Institute and Duke University School of Medicine, Durham, NC, USA

and

Aziz Sancar
University of North Carolina, Chapel Hill, NC, USA

"for mechanistic studies of DNA repair"

The cells' toolbox for DNA repair

The Nobel Prize in Chemistry 2015 is awarded to **Tomas Lindahl**, **Paul Modrich** and **Aziz Sancar** for having mapped, at a molecular level, how cells repair damaged DNA and safeguard the genetic information. Their work has provided fundamental knowledge of how a living cell functions and is, for instance, used for the development of new cancer treatments.

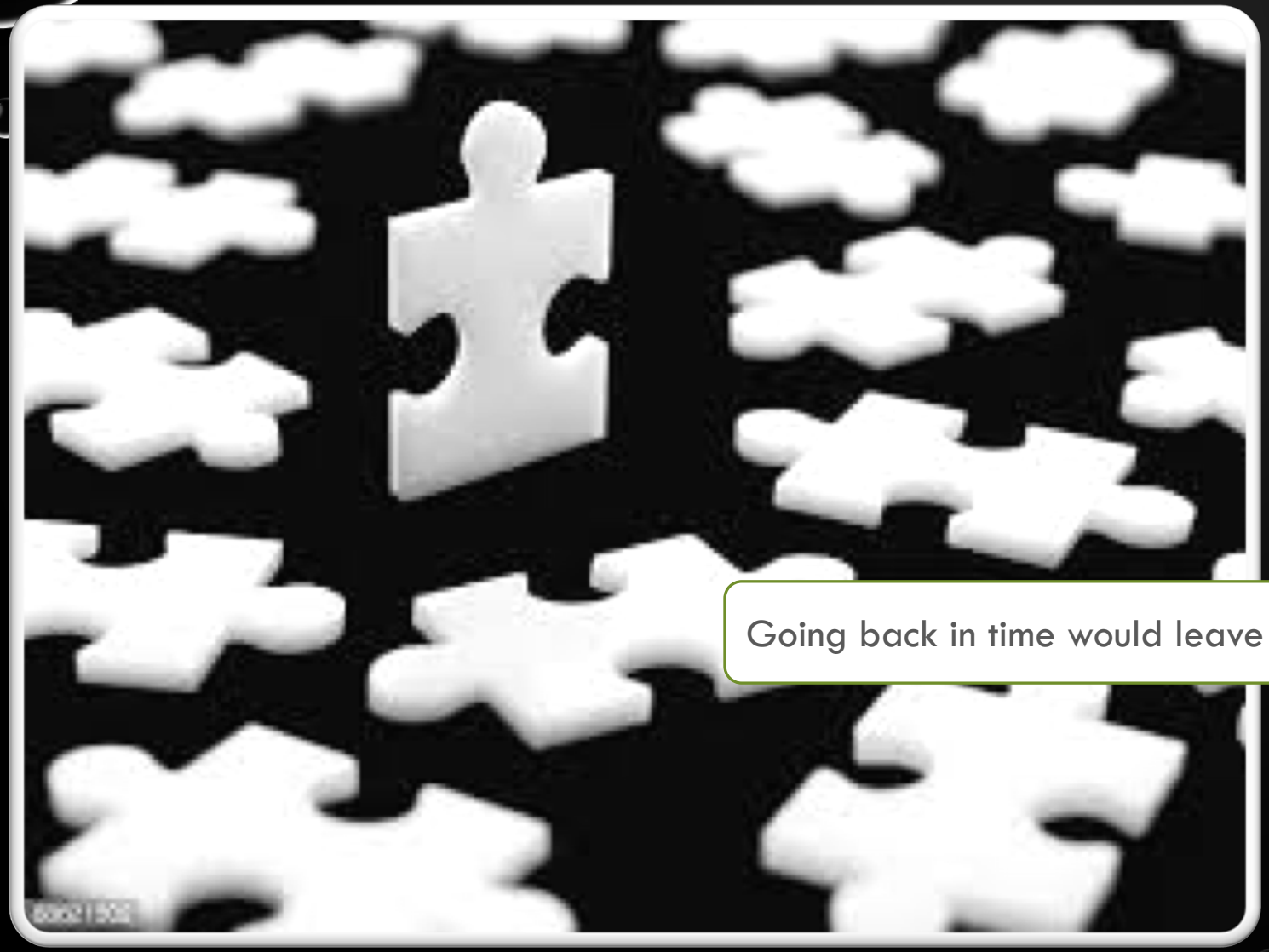
WHY FOCUS ON THE THE TIMING AND SIGNALING OF CELLS RATHER THAN WHOLE ORGANS OR ORGANISMS?

Molecular mechanisms hold the secret of time reversal.

What is routine for molecular mechanisms is impossible for whole organisms.

a broken cup can never go back in time and be what it was before it broke

ANTI-AGING IS ABOUT GOING BACK IN TIME. WHY CAN'T WE GO BACK IN TIME???



- THE GREATER THE AMOUNT OF COMPLEXITY THE GREATER THE DIFFICULTY OF GOING BACK IN TIME

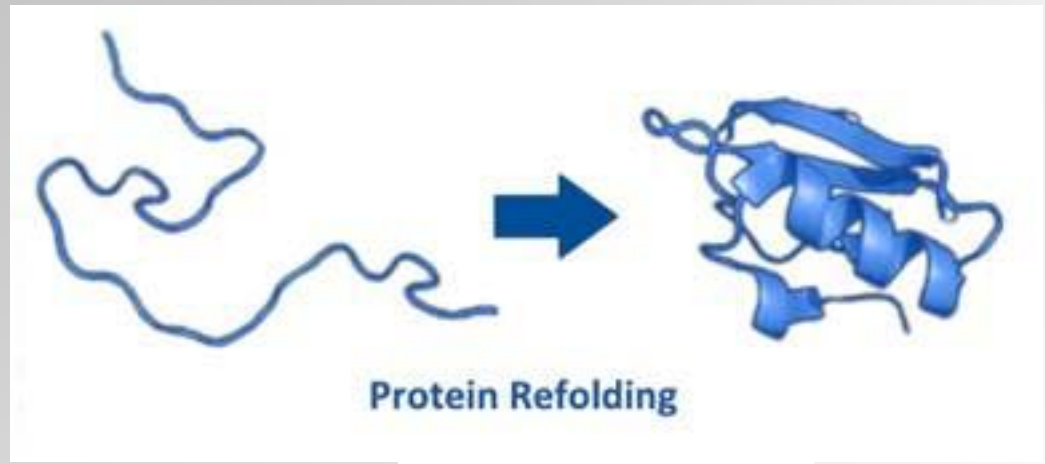
Going back in time would leave us into a scattered lot of billions of particles

PROTEIN REFOLDING OCCURS ROUTINELY INSIDE THE BODY UNDER THE SUPERVISION OF CHAPARONE PROTEINS. HOWEVER IT BE ALSO ACCOMPLISHED BY TECHNOLOGY

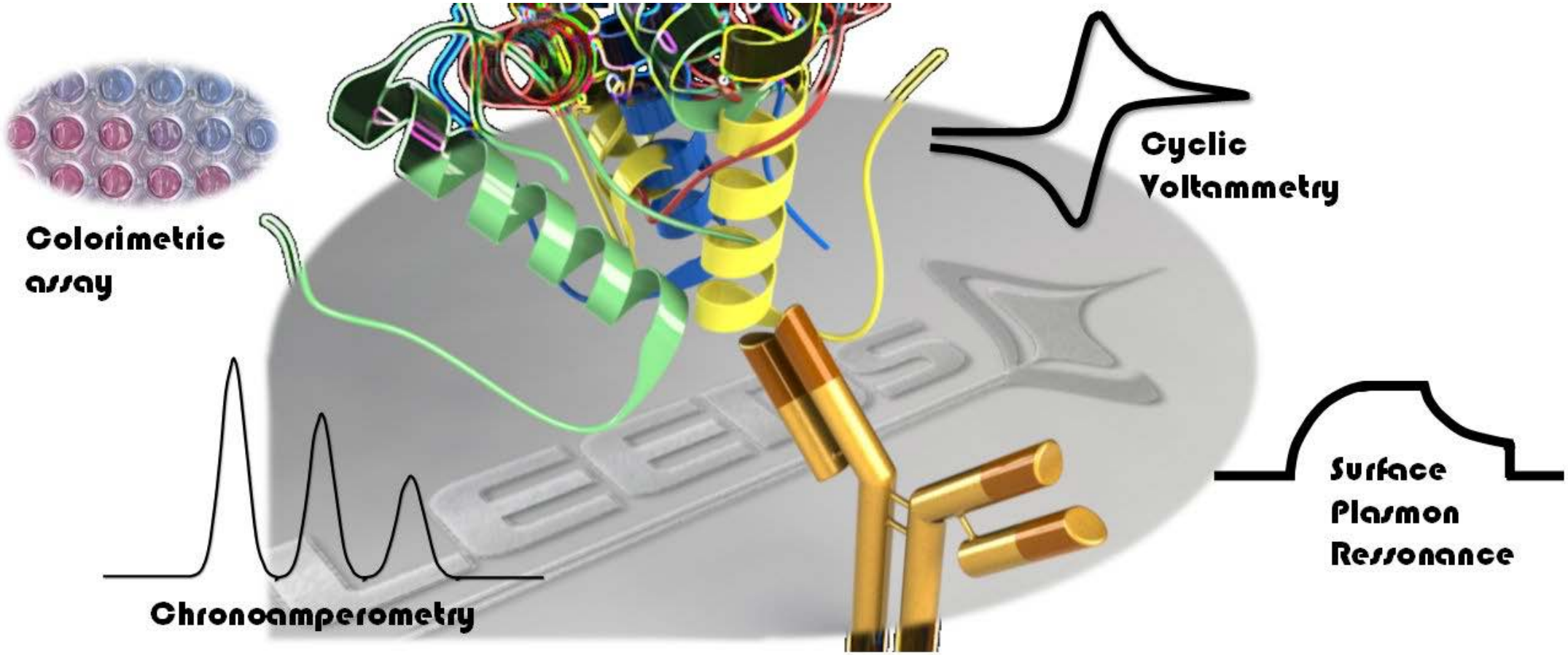
Singh et al (Journal of Bioscience and Bioengineering Volume 99, Issue 4, April 2005 pages 303-310)

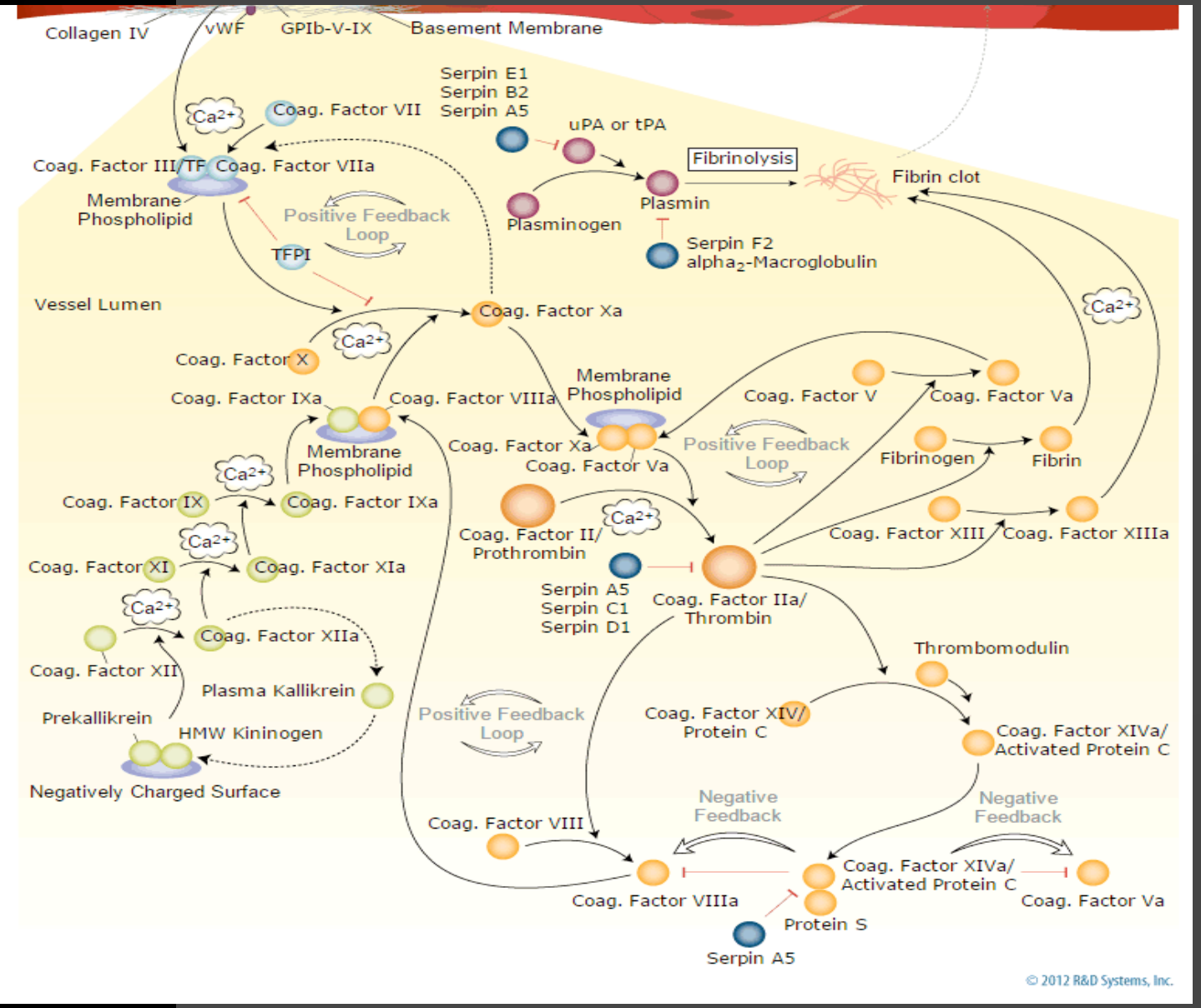
Recent improvements in renaturation procedures have included the inhibition of aggregation during refolding (Satoru Misawa Izumi Kumagai, 12 January 2004)

Other investigators succeeded in folding proteins by using surface plasmon resonance



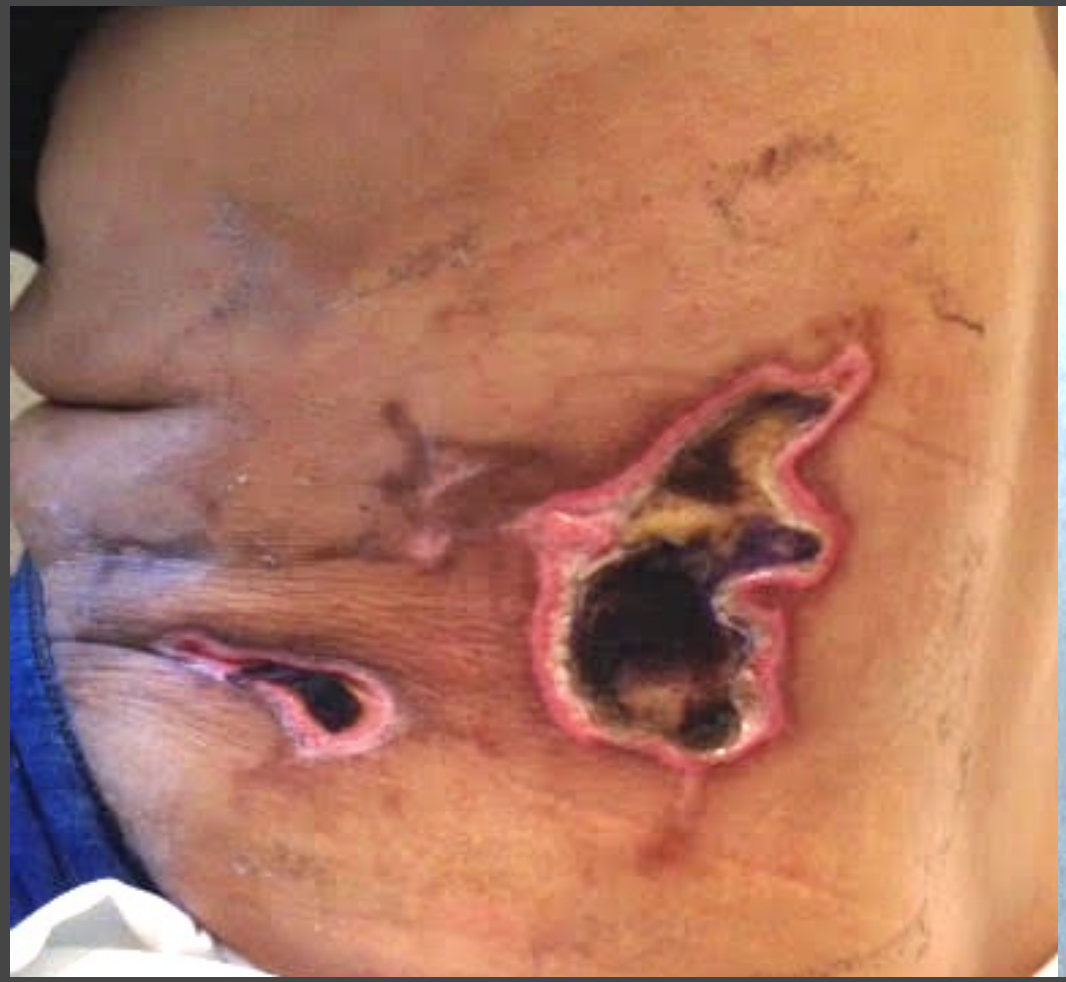
DIFFERENT METHODS OF PROTEIN REFOLDING

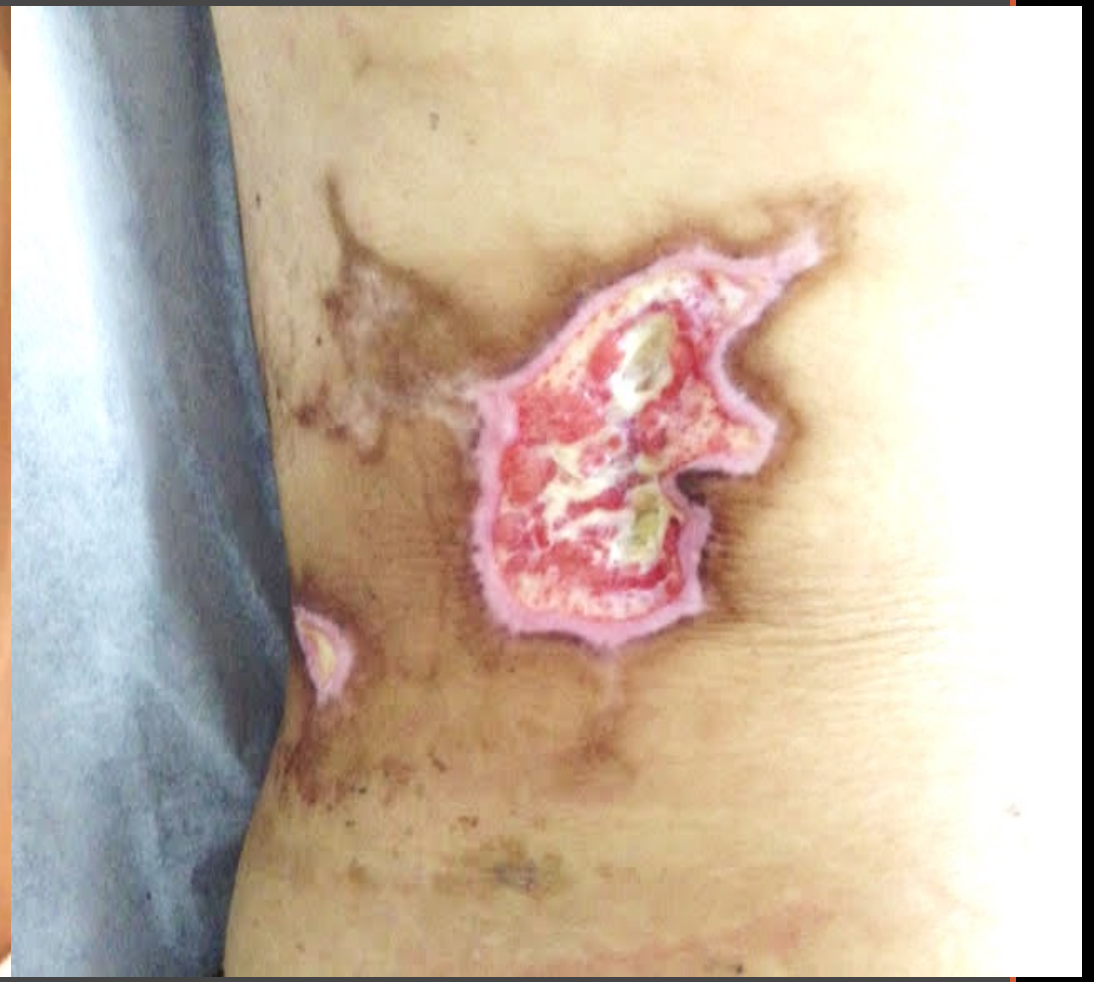




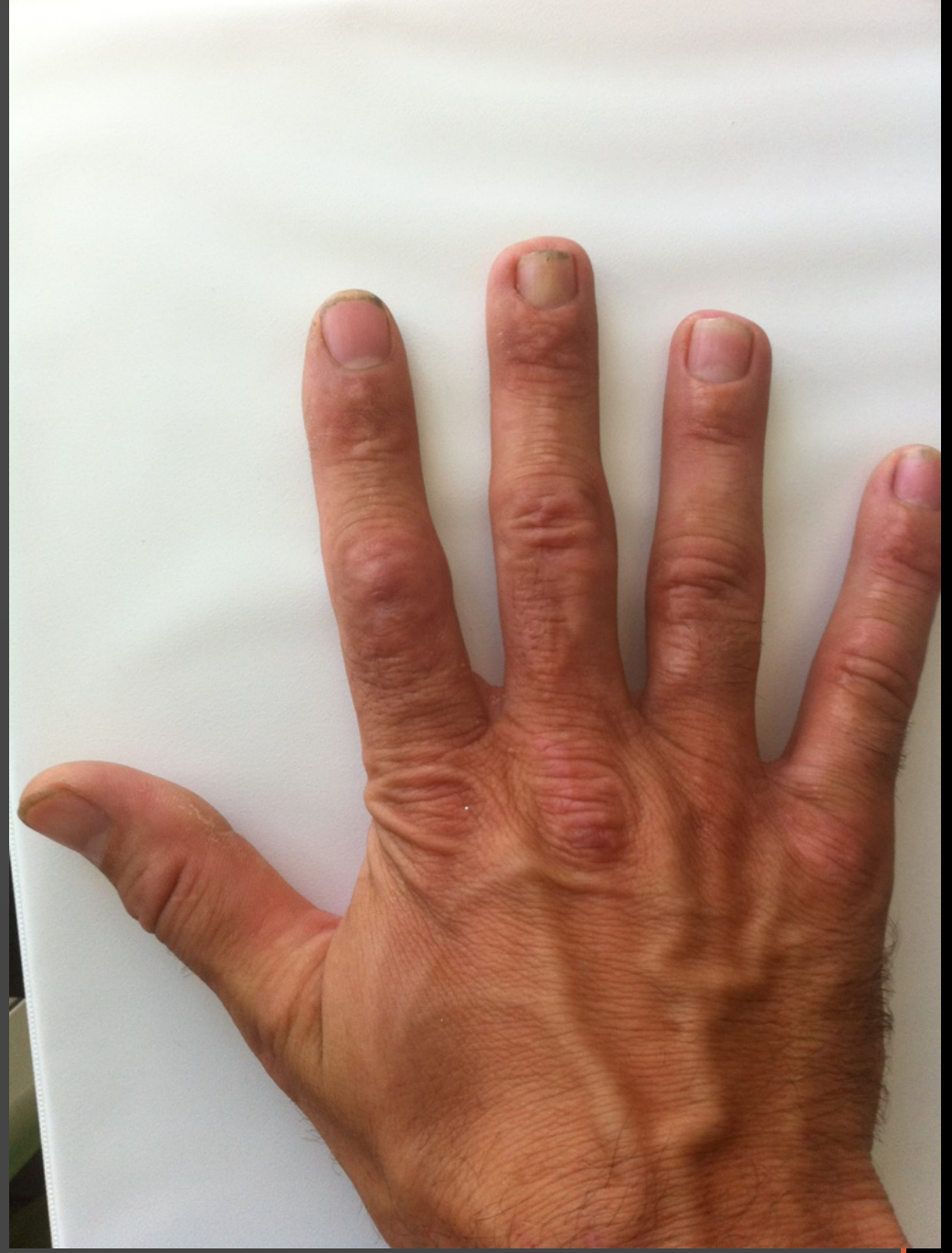
WOUND AND SCAR HEALING INVOLVES A MATRIX OF SIGNALS WITHIN A MATRIX OF SPECIFIC TIMINGS

RESEARCH ON WOUND HEALING

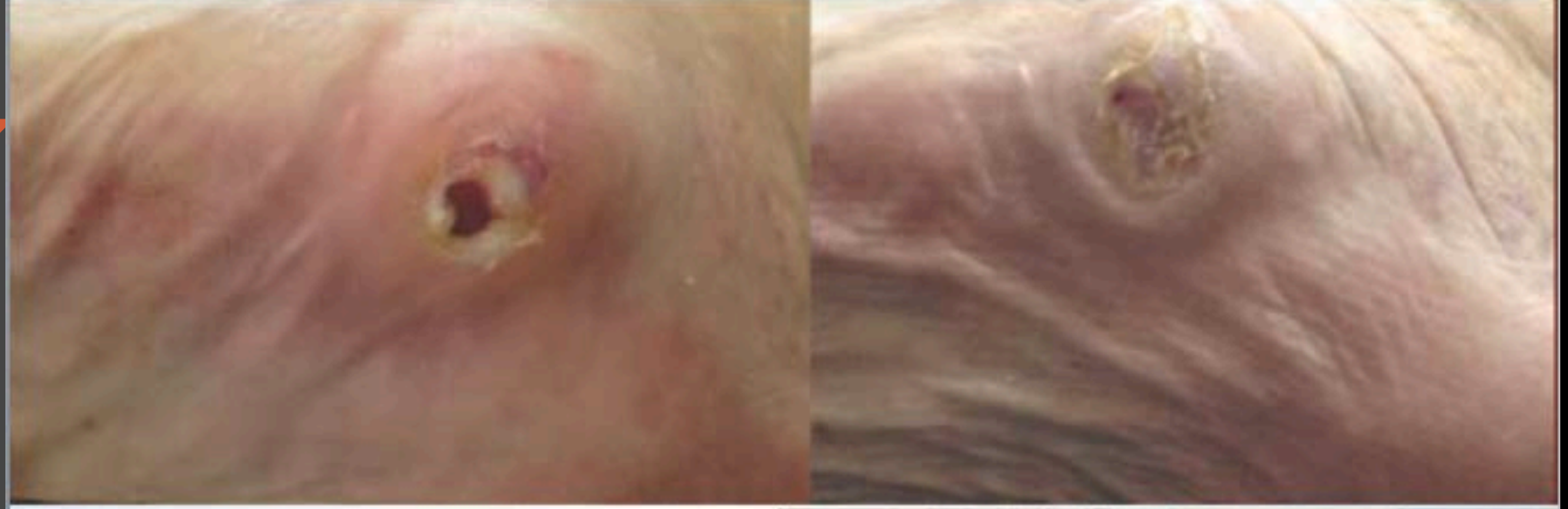




NURIS LAMPE, MD, ARUBA

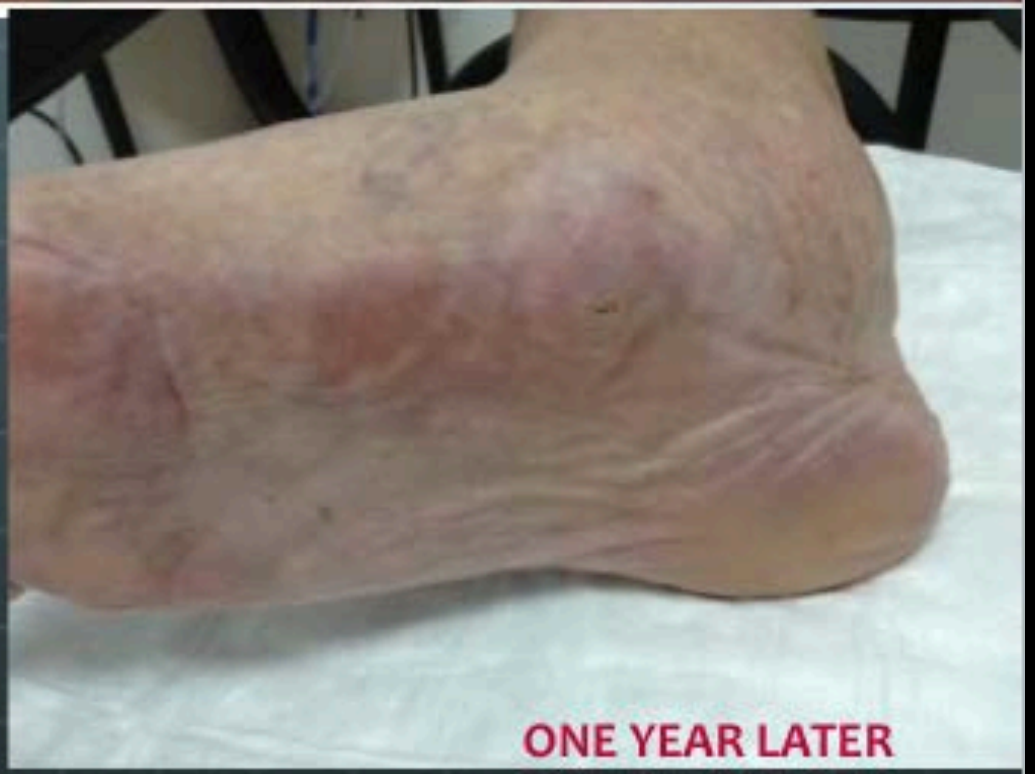


DR XANYA SOFRA USA,



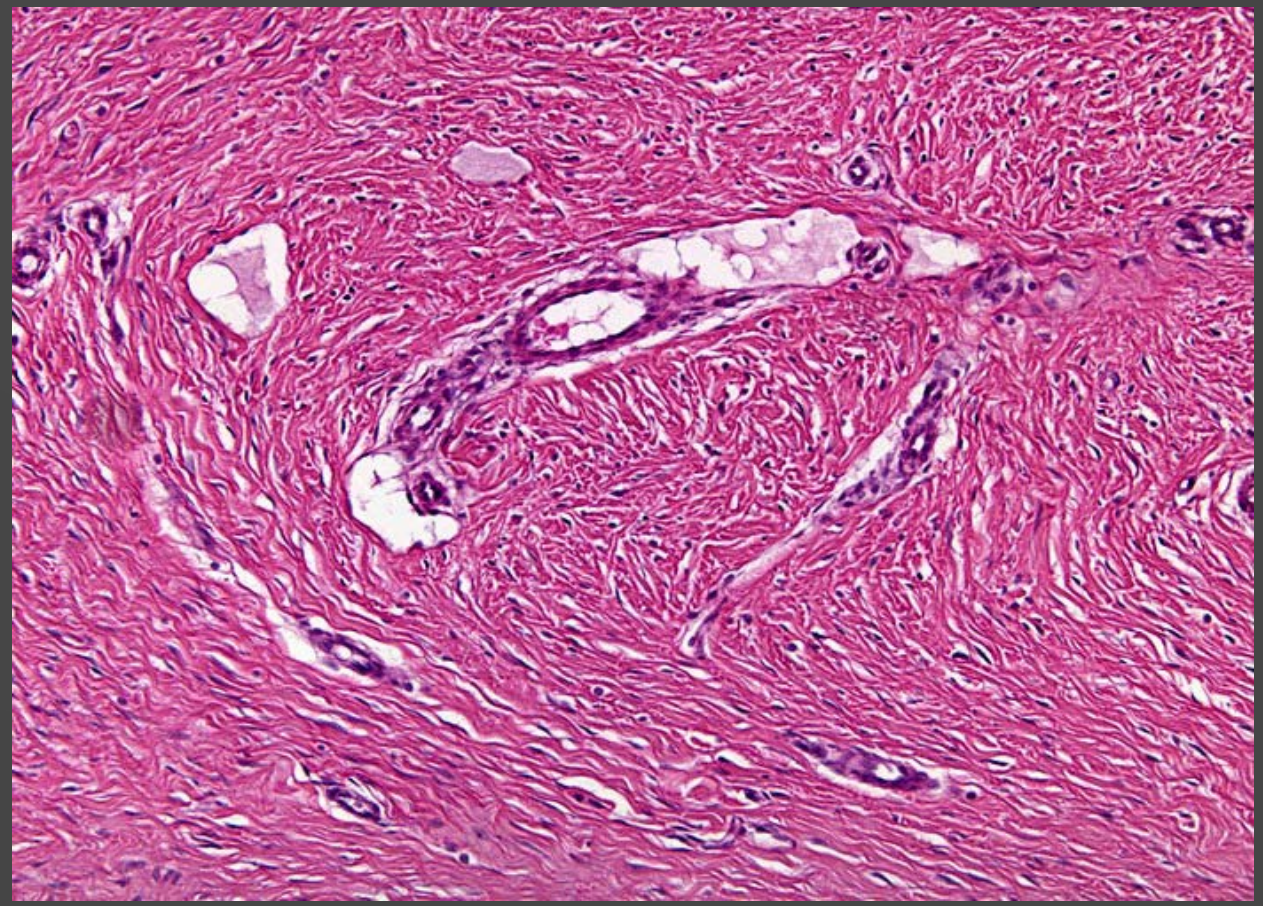
Diabetic Wound 6 Treatments during one year

NURIS LAMPE, MD
ARUBA

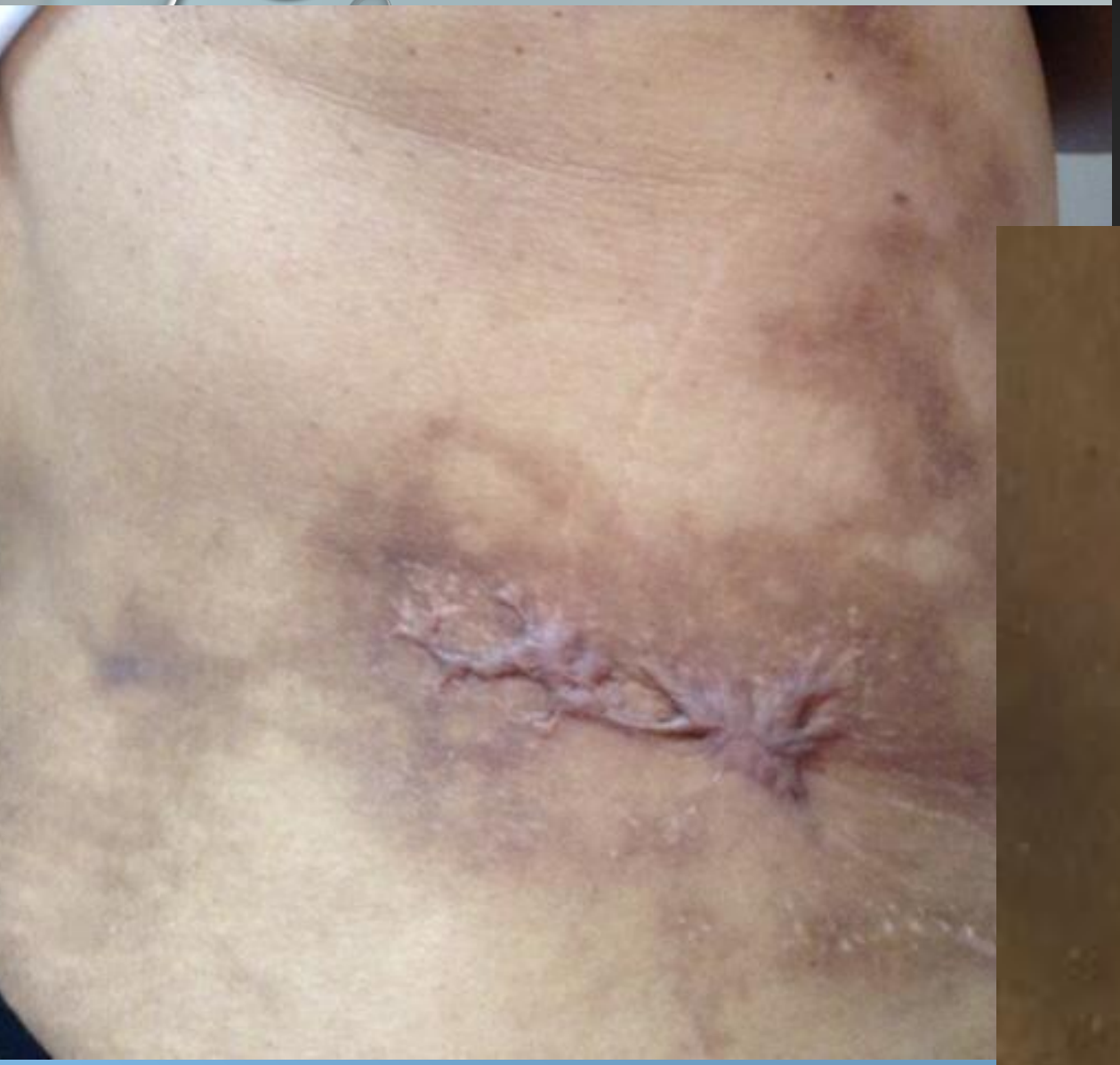


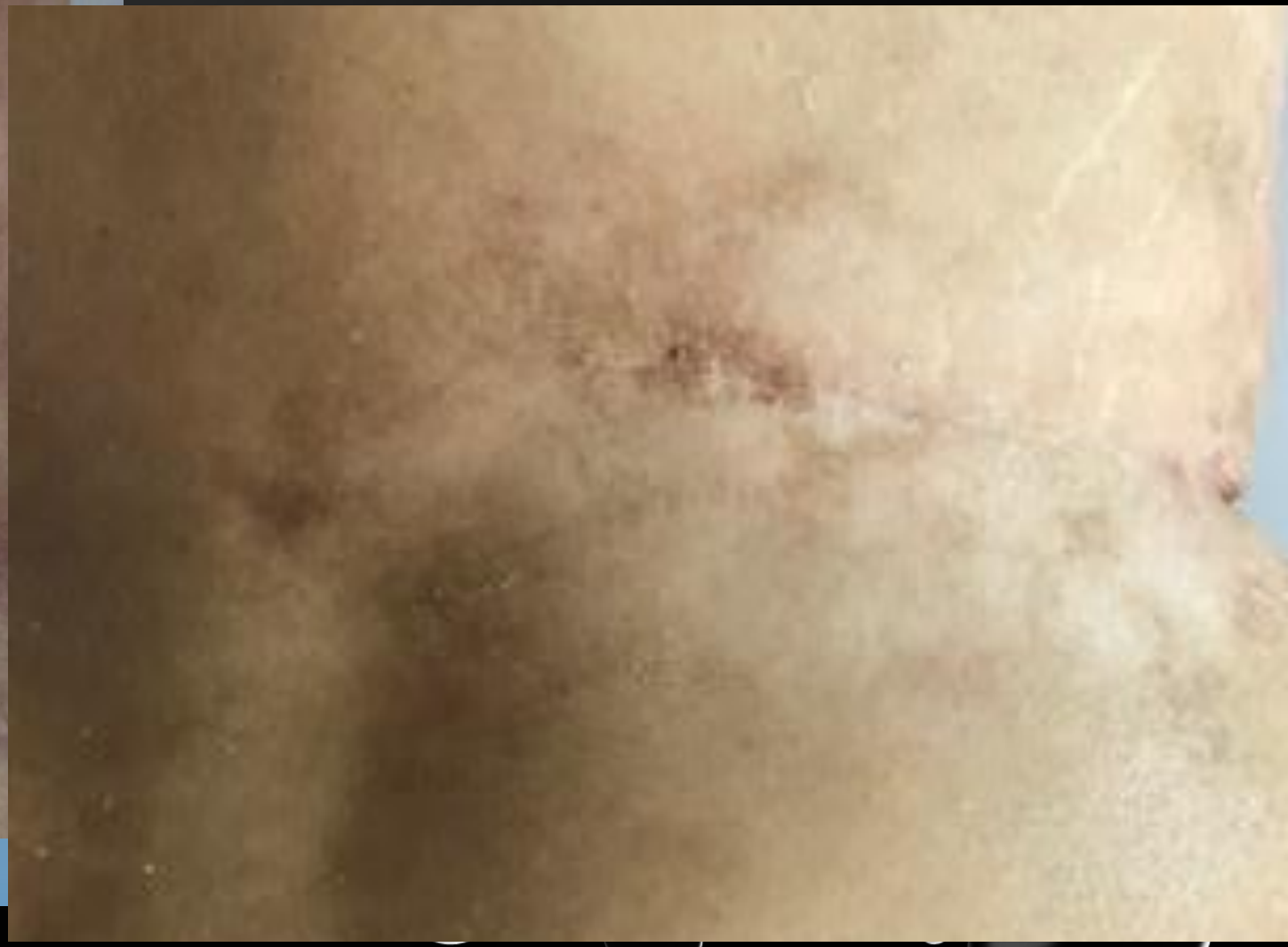
KELOIDS SCARS AND STRETCHMARKS ARE THE RESULTS OF UNTIMELY UNBALANCED PROCESSES

- IT HAS BEEN SHOWS THAT KELOIDS INVOLVE INCREASED UNTIMELY ACTIVITY OF FIBROGENIC CYTOKINES SUCH AS TGF B1, IGF01 AND INTERLEUKIN--1 AND MUTATIONS IN REGULATORY GENES SUCH AS P53.
- THE SAME UNBALANCED **UNTIMELY** PROCESSES ARE OBSERVED IN AGING.

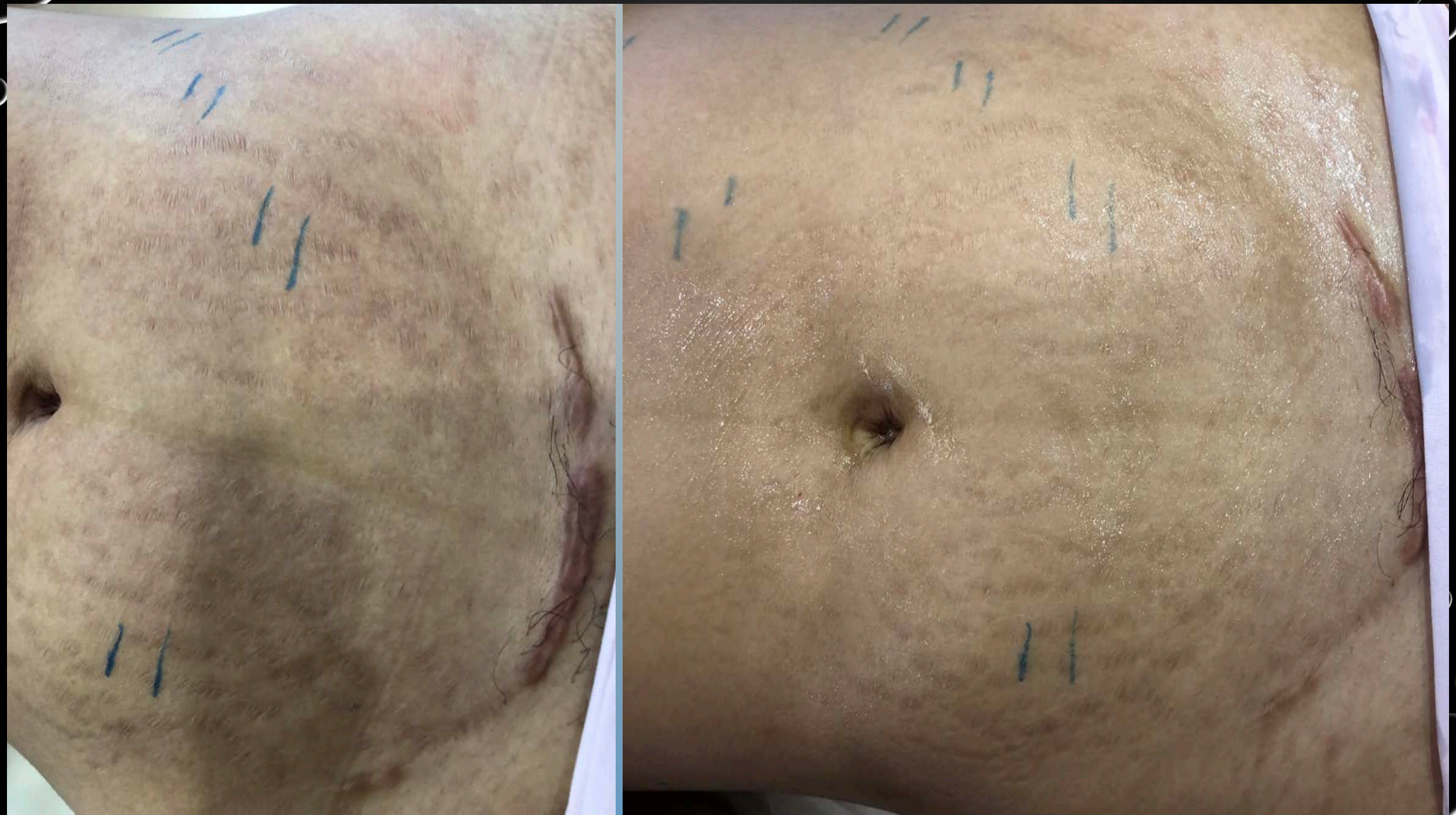


KELOID SCAR AFTER LIPOSUCTION WOUND TREATED WITH SIGNALING – 6 TREATMENTS

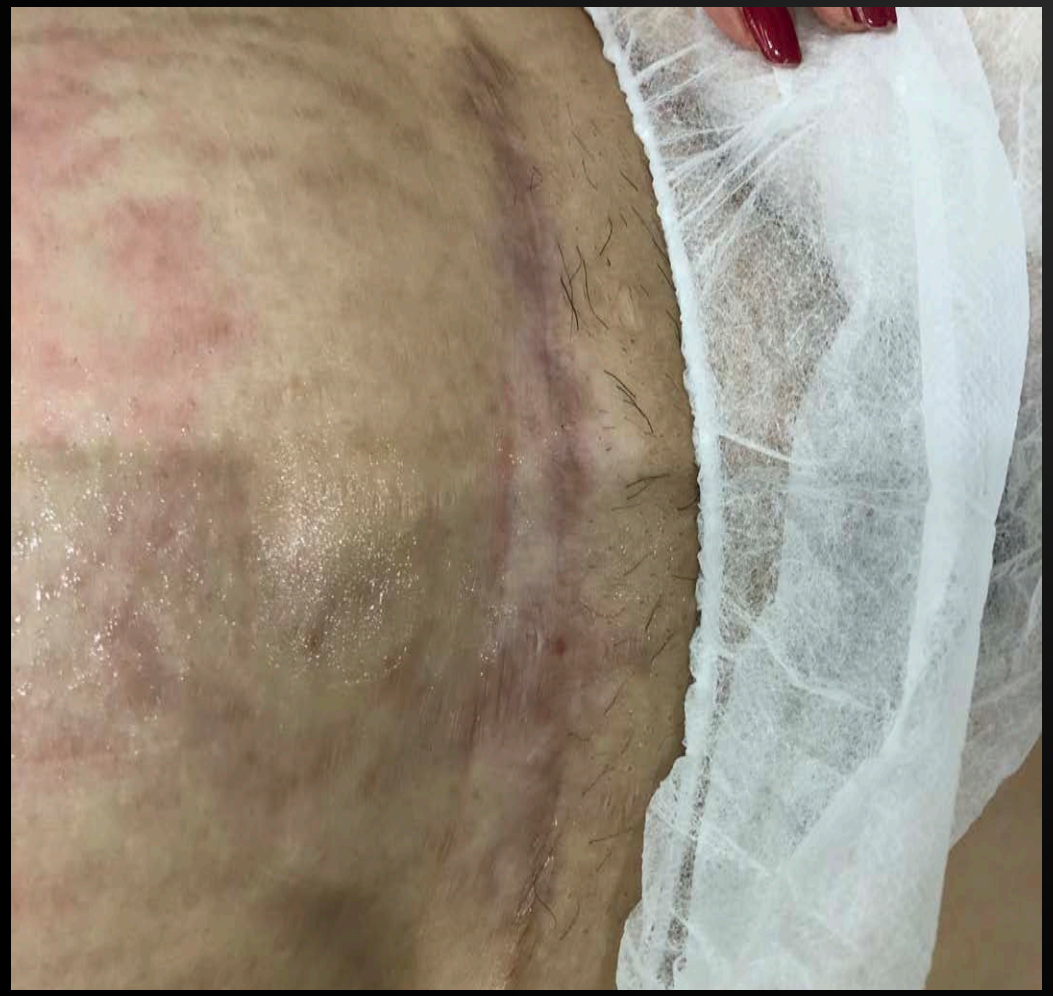


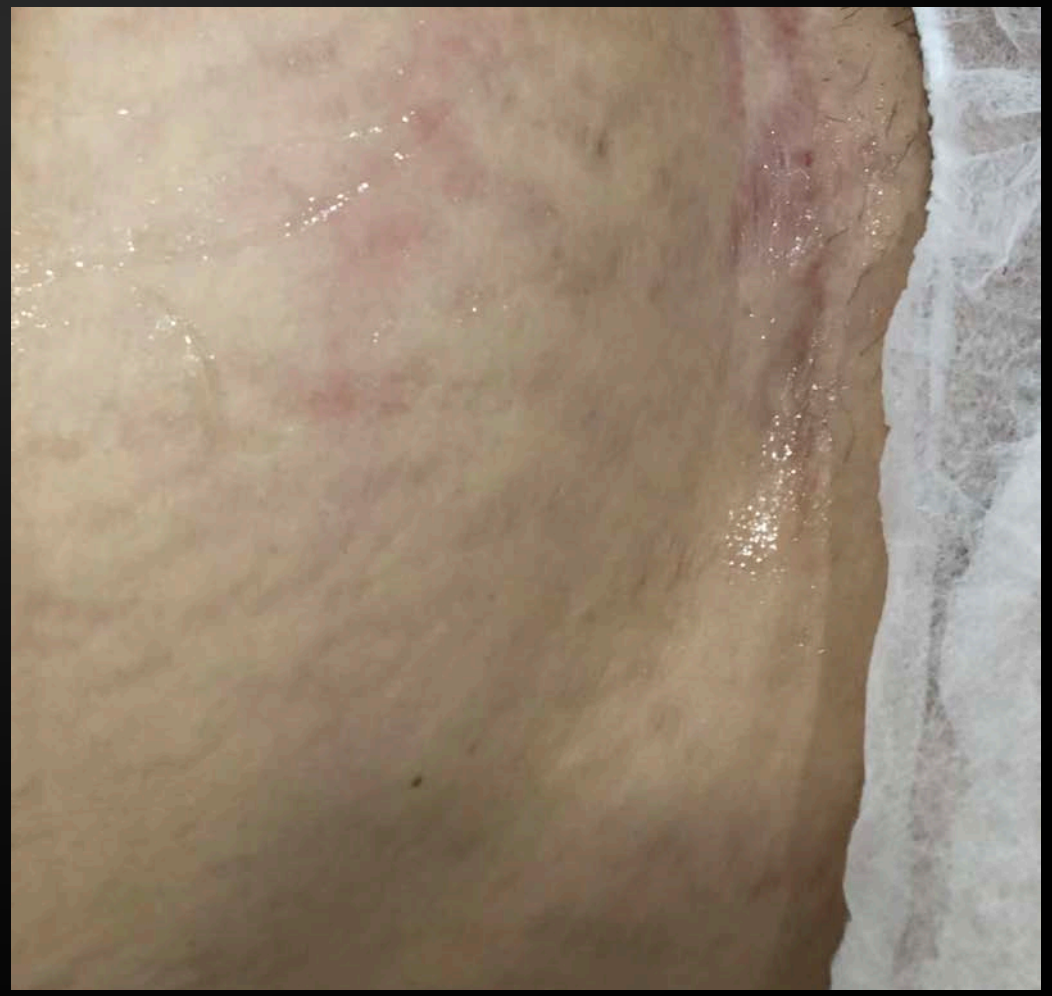


ONE TREATMENT 20 MINUTES

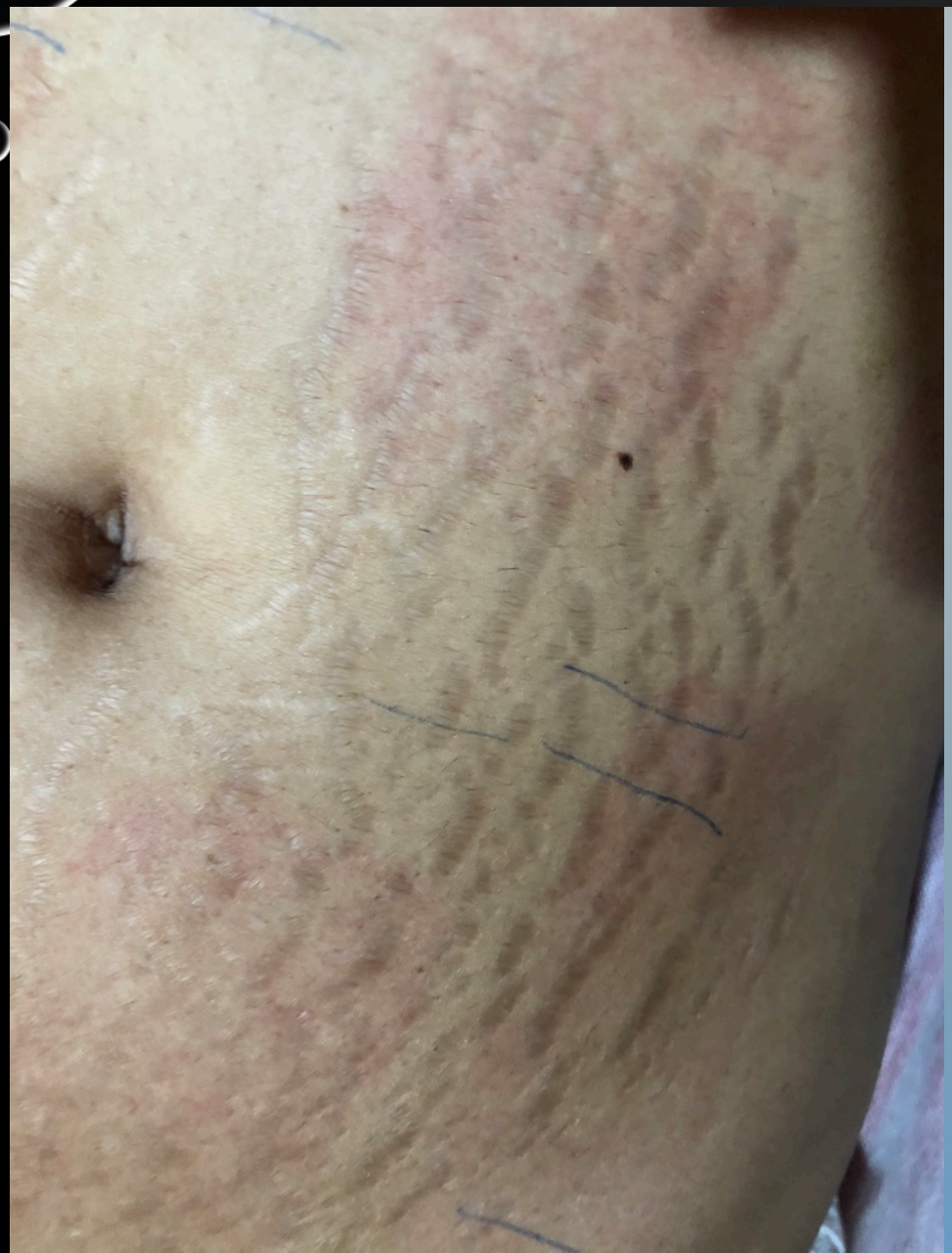


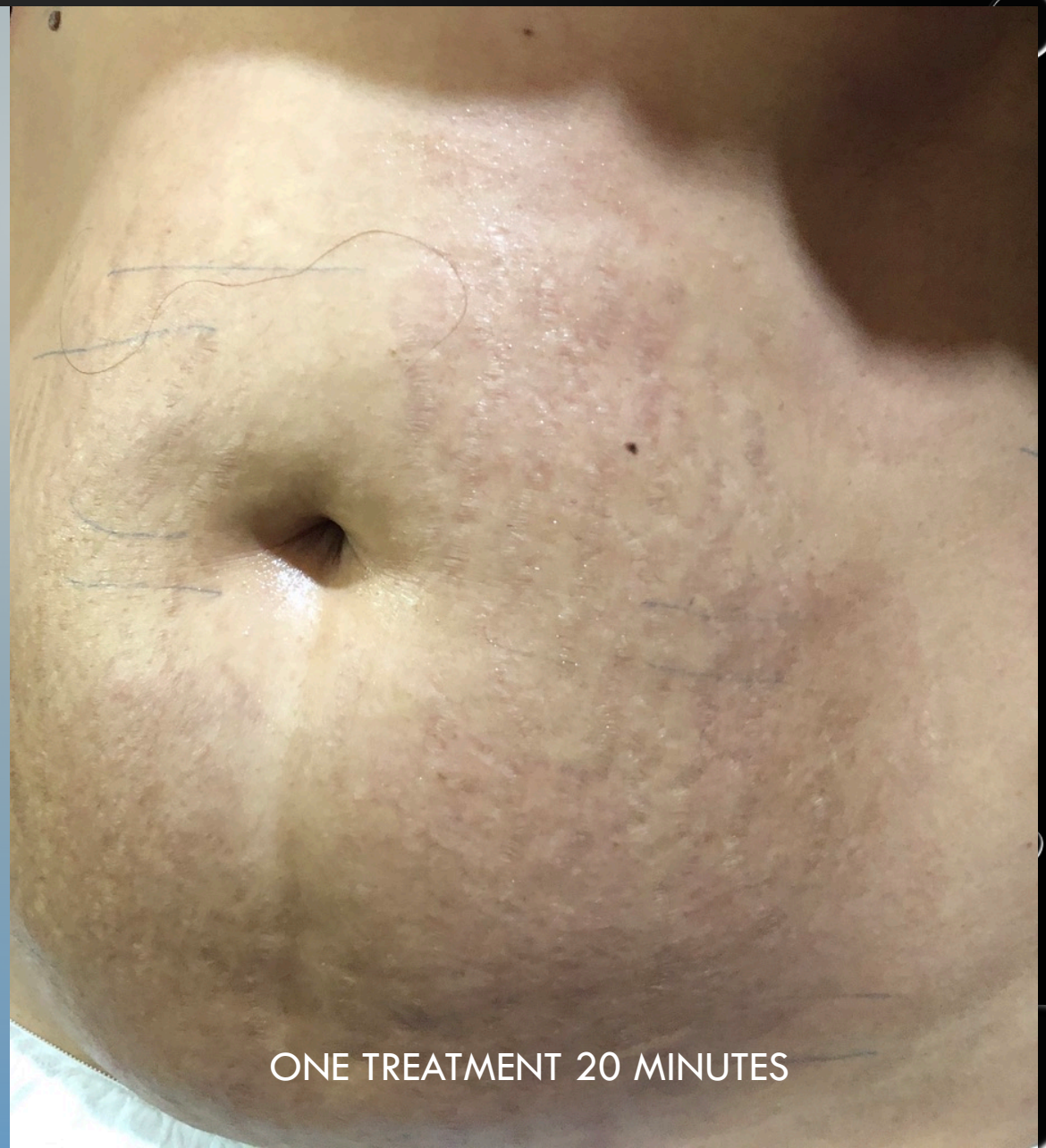
ONE TREATMENT 20 MINUTES





THE SAME UNTIMELY PROCESS IS INVOLVED IN STRETCHMARKS





ONE TREATMENT 20 MINUTES

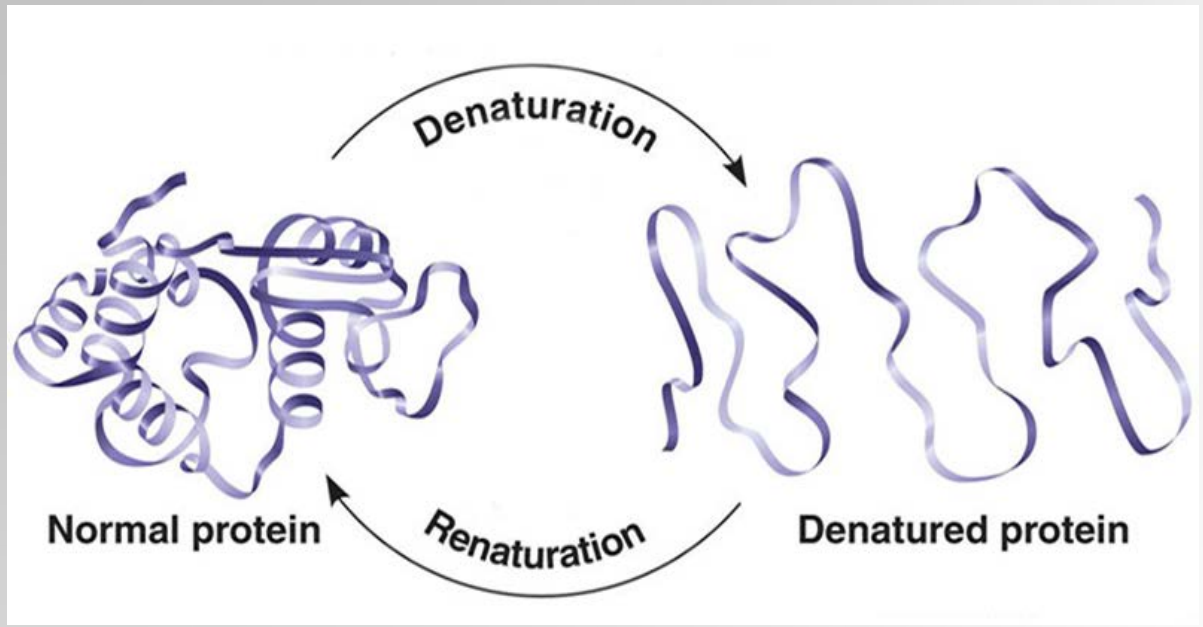
ANTI-AGING VIA PROTEIN RENATURATION / Protein Folding
WITHIN THE PARAMETERS OF TIME WITH RESPECT TO CIRCADIAN CLOCKS

HOW TO TEST RESULTS ARE DUE TO PROTEIN FOLDING?

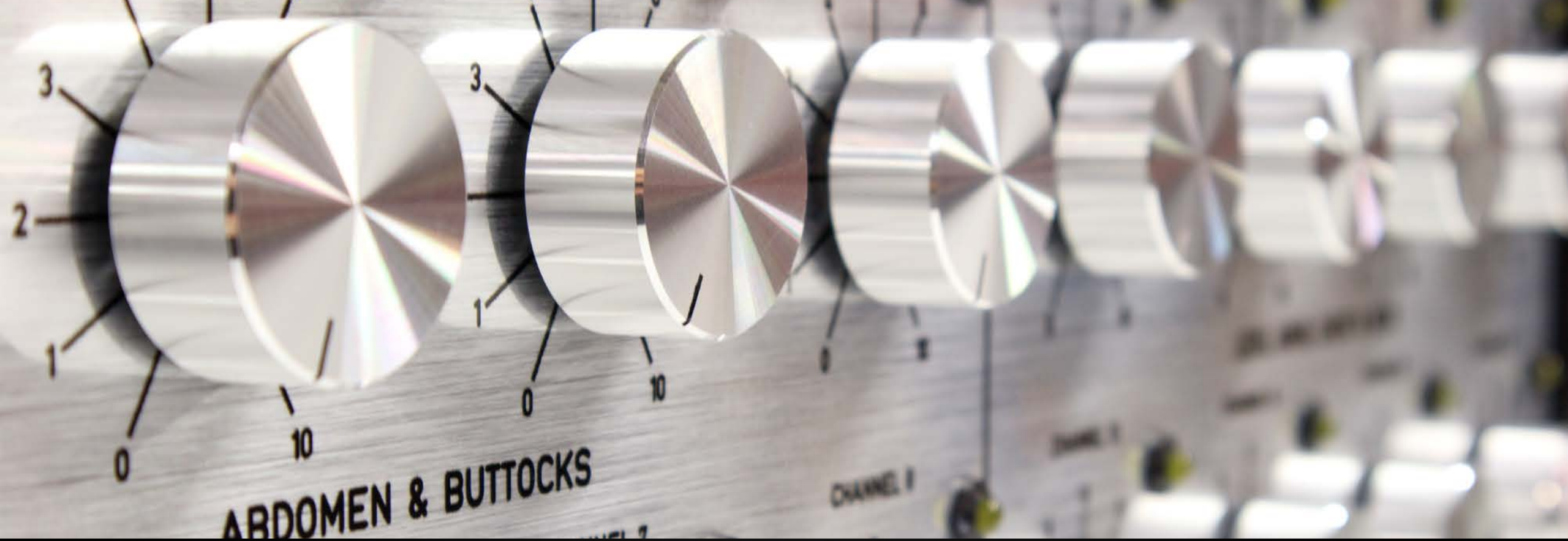
Second virial coefficient (SVC) measurements

* -VE SVC is indicative of -VE protein–protein interactions.
- **Protein aggregation INCREASES** during refolding
  Protein Refolding compromised

* +VE SVC indicates +VE protein–protein interactions -
Protein aggregation DECREASES
  Protein Refolding Successful



Jason G.S. Ho,[1] Anton P.J. Middelberg,[1] Paul Ramage,[2]Hans P. Kocher[2]Protein Sci.10.1110/ps.0233703



THANK YOU
FOR YOUR KIND ATTENTION