AGING IS NOT PROGRAMMED.

Dr Xanya Sofra, Ph.D. Ph.D

HONORARIUM OR TRAVEL EXPENSES FOR:**THIS PRESENTATION:** [NONE]

SYMPOSIA OR OTHER PRESENTATIONS

AT THIS CONGRESS: [NONE]

OUTSIDE WORKSHOPS,

PRESENTATIONS, ADVISORY BOARDS

etc. [NONE]

AGING IS A BIOLOGICAL OVERSIGHT NOT OUR DESTINY

DR XANYA SOFRA

AGING IS NOT PROGRAMMED.

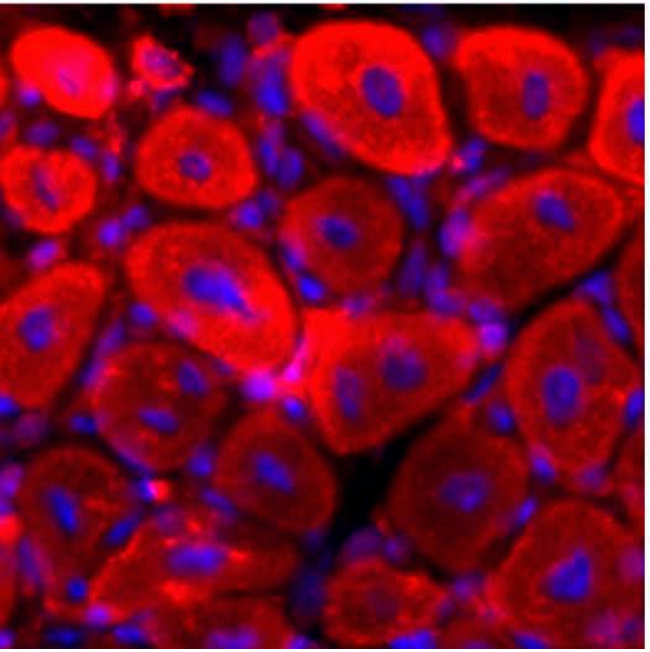
AGING IS A BIOLOGICAL OVERSIGHT NOT A DESTINY

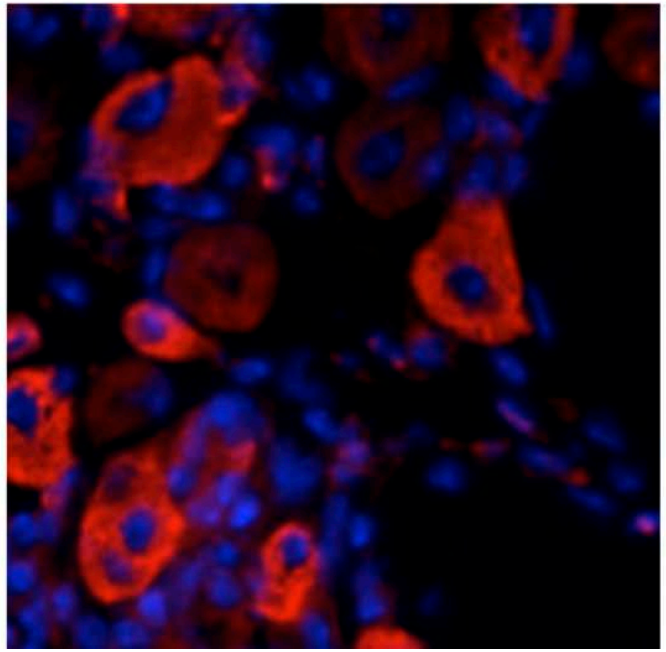
DR XANYA SOFRA

YOUNG VS OLD AGE IS BIOLOGICALLY GOVERNED BY DIFFERENT SETS OF RULES

The best most effective Signaling Pathways selected by Evolution to raise the brightest flame of the “fittest” -- when aimlessly continued after the developmental purpose is completed lead to aging, diseases and death.

YOUNG **OLD**





THE BRIGHTEST FLAME CASTS THE DARKEST SHADOW

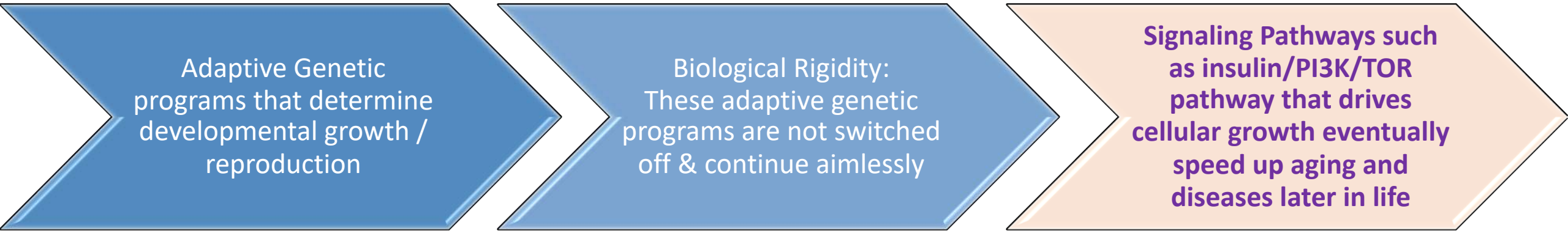
George Martin

Aging is the result of earlier programmed processes which were not switched off and aimlessly continued after the developmental purpose was completed (M. V. Blagosklonny 2013, Cell Cycle 2736-3742)

SEMI PROGRAMED THEORIES OF AGING

Biological Rigidity = Inertia = A measure of the body's ability to resist movement

or in general terms: The body's TENDENCY to RESIST CHANGE



STABILITY IS ADAPTIVE - GOOD

INERTIA AND PERSISTENT RIGIDITY ARE MALADAPTIVE - BAD

Biological Rigidity= Biological tendency to resist change = BIOLOGICAL STABILITY GOOD = AIMSLESSLY CONTINUES - BAD

Emotional Rigidity= Emotional tendency to resist change = EMOTIONAL STABILITY GOOD = LACKS FLEXIBILITY - BAD

Personality Rigidity= Personality tendency to resist change = PERSONALITY STABILITY GOOD = LACKS FLEXIBILITY - BAD

Interpersonal Relationships Rigidity= Tendency to resist change= STABILITY IN INTERPERSONAL RELATIONSHIPS GOOD

= AIMSLESSLY CONTINUES DESPITE OBVIOUS DISADVANTAGES -- BAD

Theories	Defining feature	Purposeful?	Programmed?	Caused by ROS?	Kills via age-related diseases?	Causes death directly?	Menopause in women is	Link between aging and diseases	Use of energetic resources
Programmed	functional decline	yes	yes	mostly	unspecified	yes	programmed	unspecified	unspecified
Stochastic	functional decline	sometimes*	in some cases*	mostly	sometimes#	yes	programmed	vulnerability to diseases#	slows aging (via repair)
Quasi-programmed	hyperfunction	no	no	no	always	no	prototypical disease	manifested by diseases	fuels aging (via TOR)

IS AGING A DESTINY?

CAN IT BE SLOWED DOWN OR AS SCIENCE PROGRESSES AVOIDED?

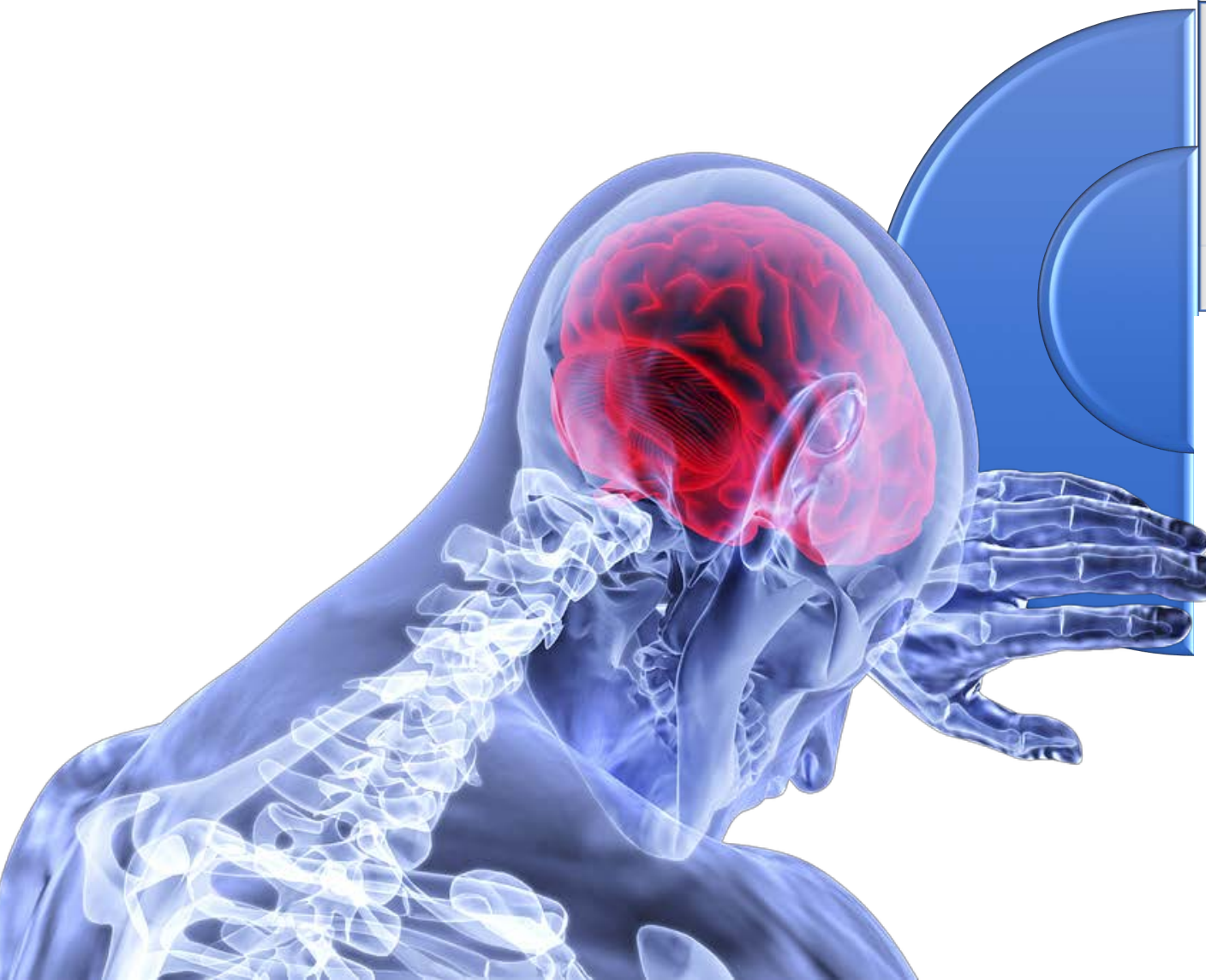
NO SOLUTION.

WE ARE DESTINED TO AGE AND DIE

YES. By reducing Functional Decline and Slowing Aging via Repair

YES. By Shutting Down Signaling Pathways which are Maladaptive later in Life

INFLAMMATION



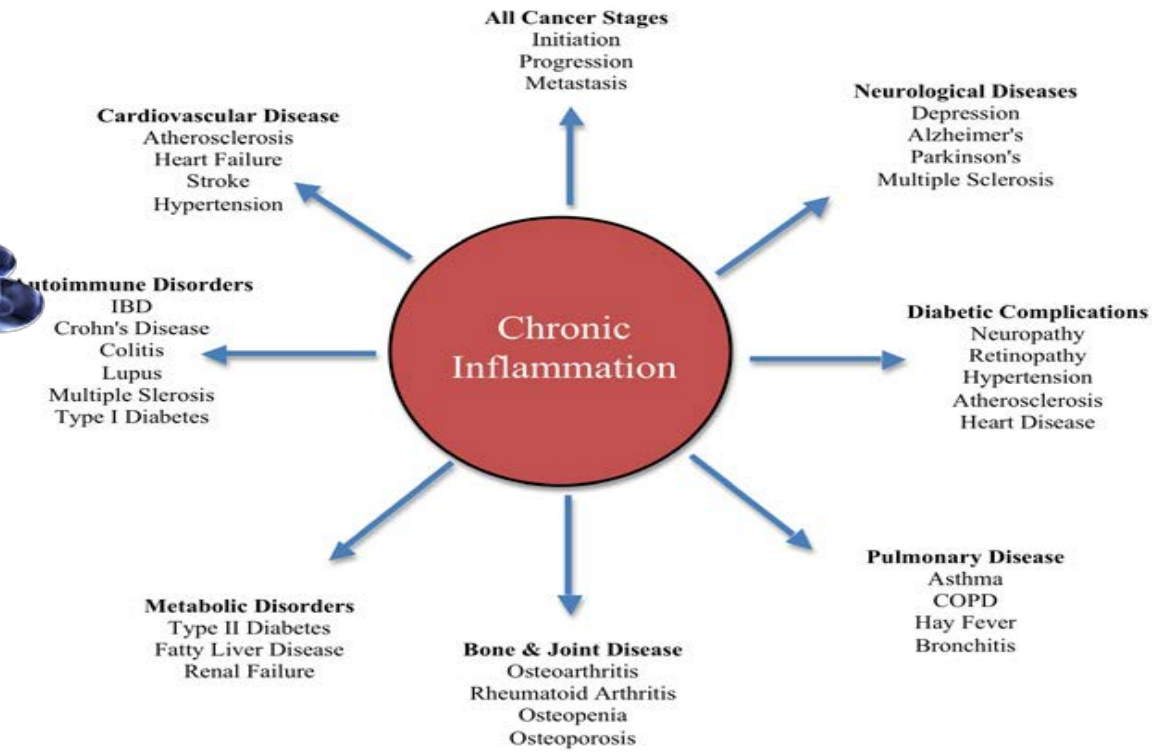
YOUNG

IFLAMMATION is vital in the Young

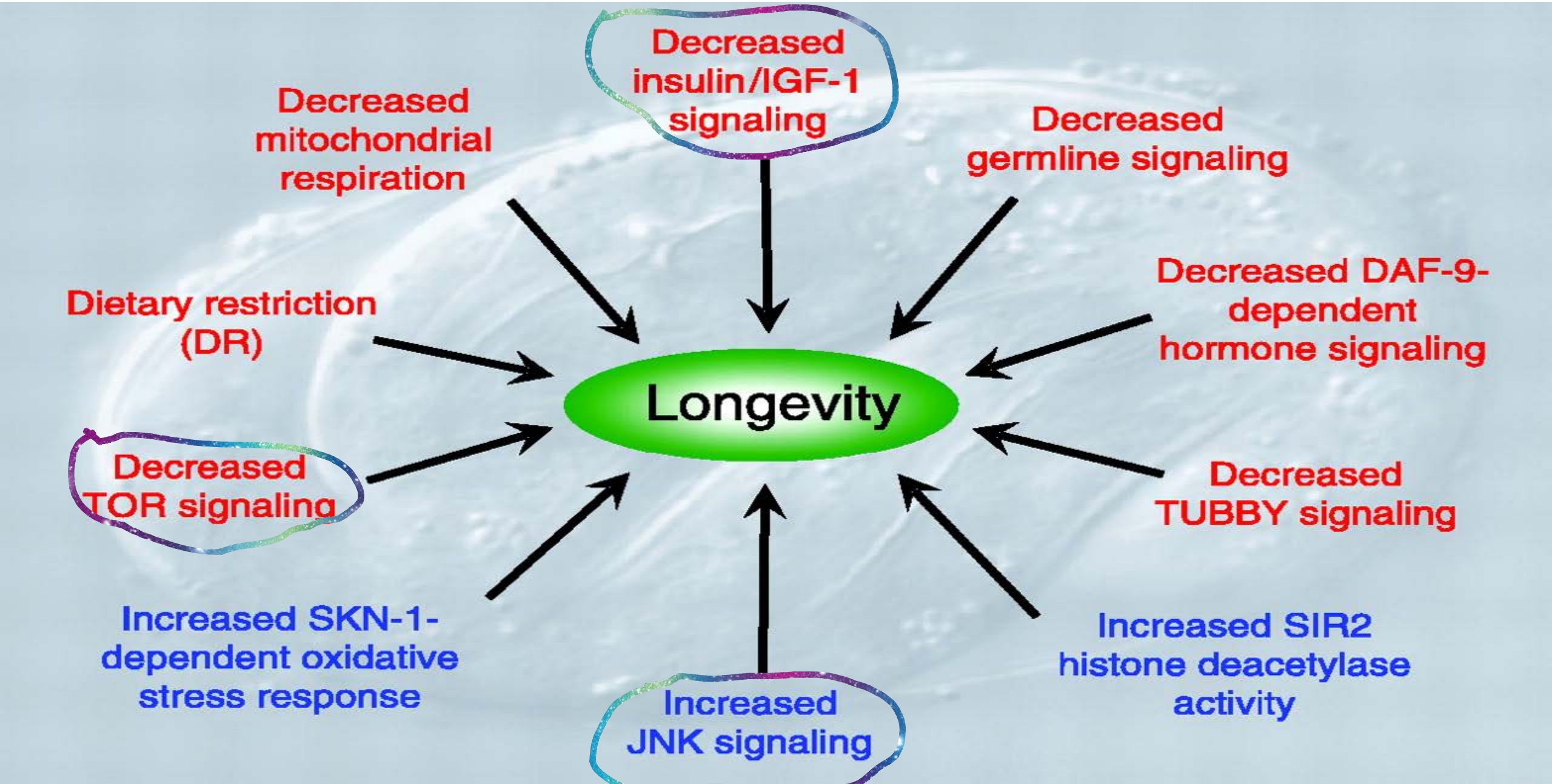
IN FIGHTING OFF DISEASE

OLD

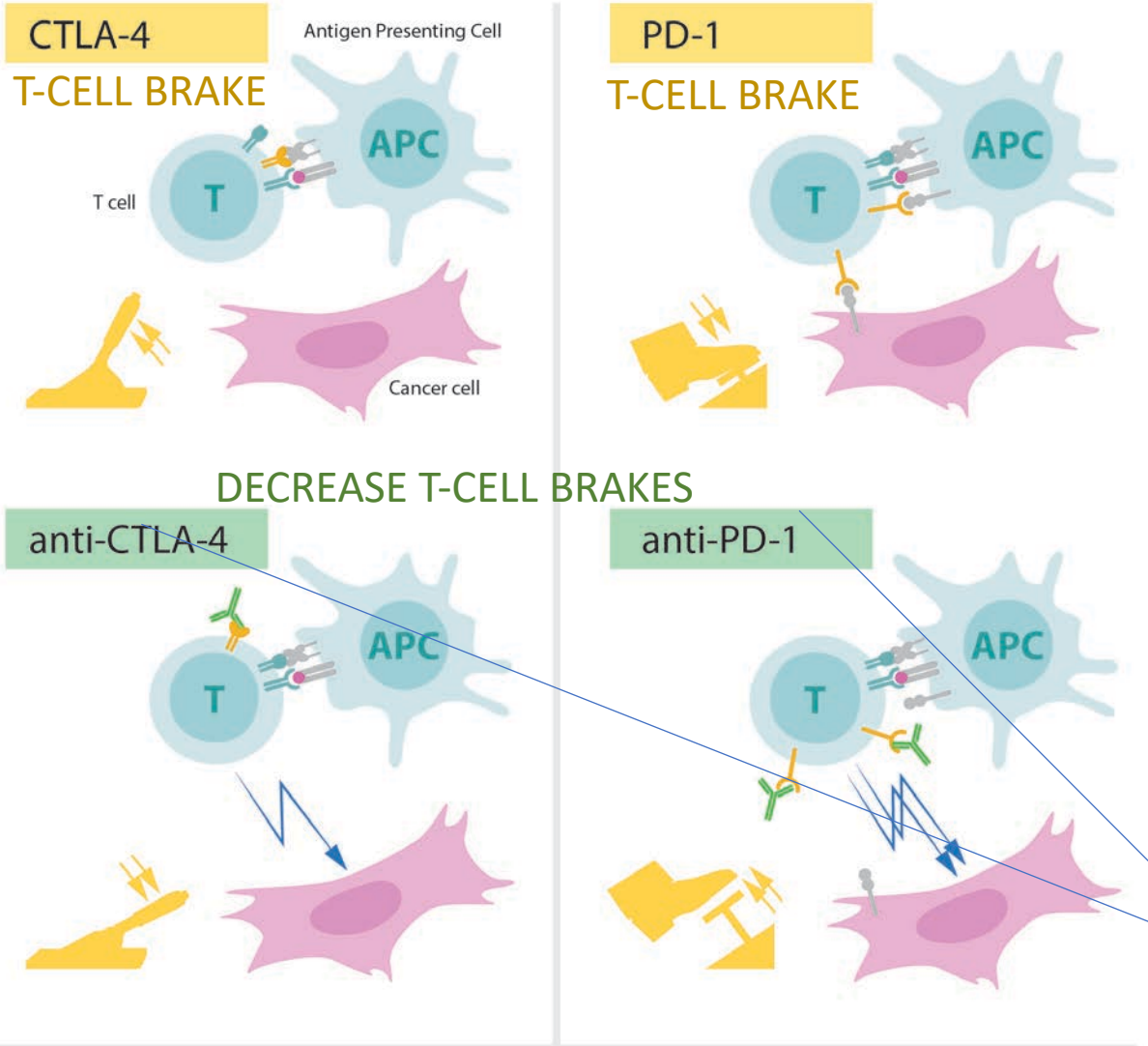
MILD CHRONIC INFLAMMATION LEADS TO DIABETES, HEART DISEASE ETC



CERTAIN MECHANISMS MUST INCREASE WHILE OTHERS MUST DECREASE TO ATTAIN LONGEVITY



CANCER THERAPY BY ELIMINATING IMMUNE SYSTEM SIGNALING RESPONSES



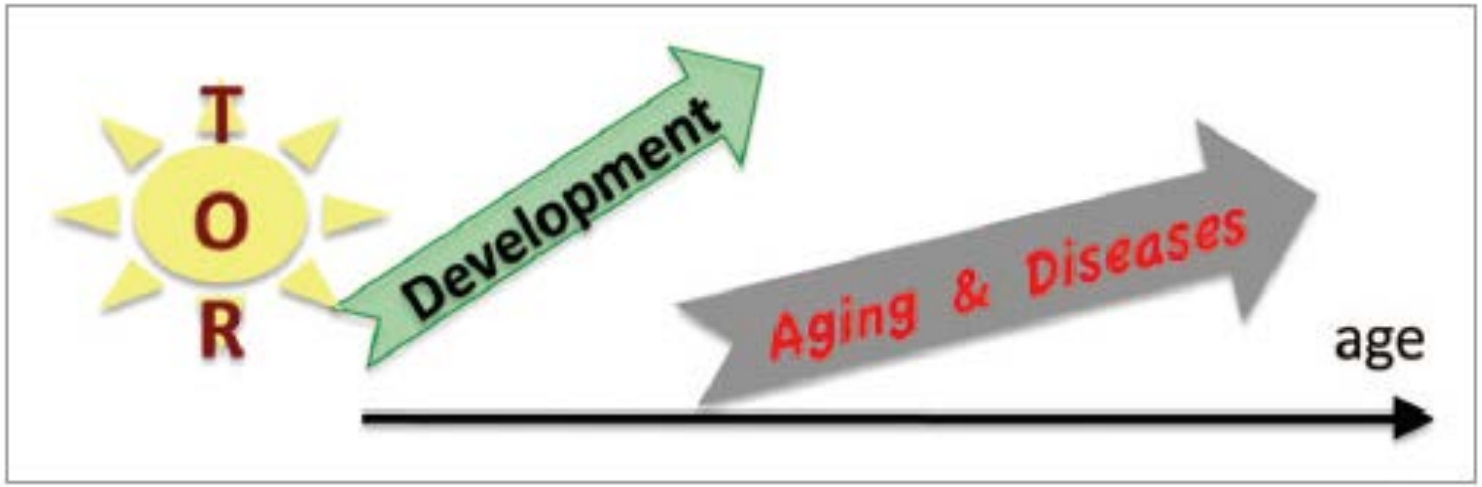
The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of

Cancer therapy by inhibition of negative immune regulation

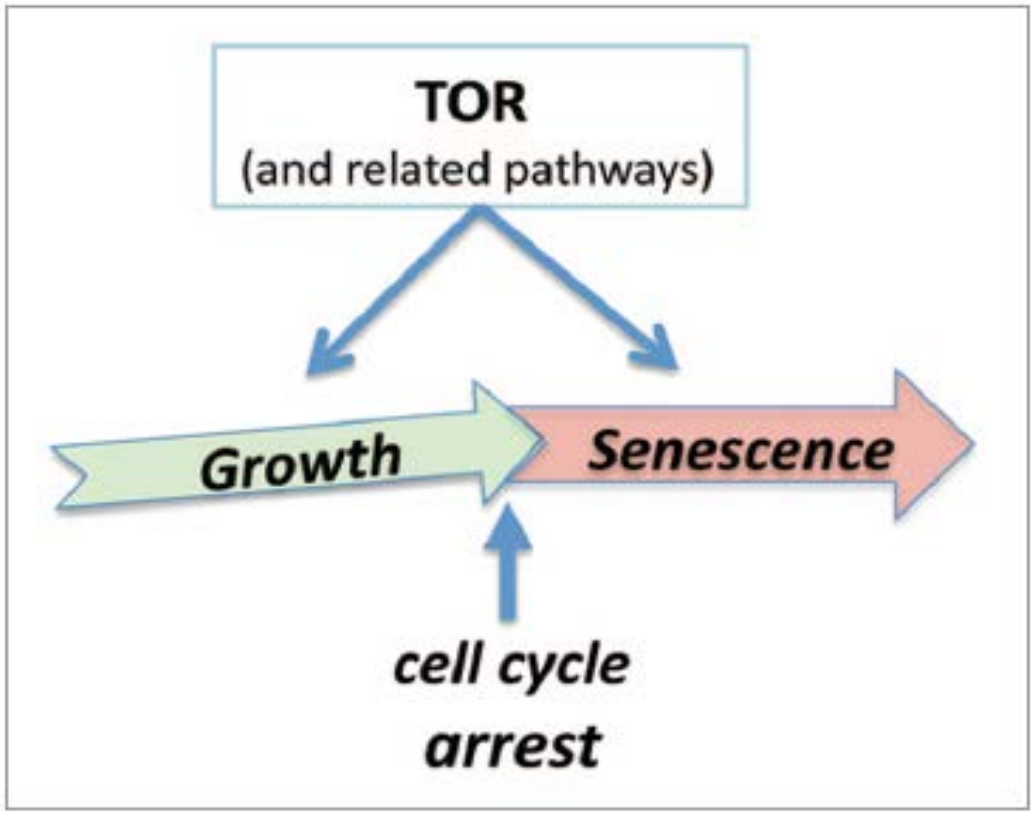
DECREASING THE IMMUNE SYSTEM SIGNALING RESPONSES CURES CANCER

CTLA- 4 functions as a brake on T cells
PD-1 is another T-cell brake that inhibits T-cell activation

SEMI PROGRAMED THEORIES OF AGING



MTOR
MAMMALIAN
TARGET
OF RAPAMYCIN

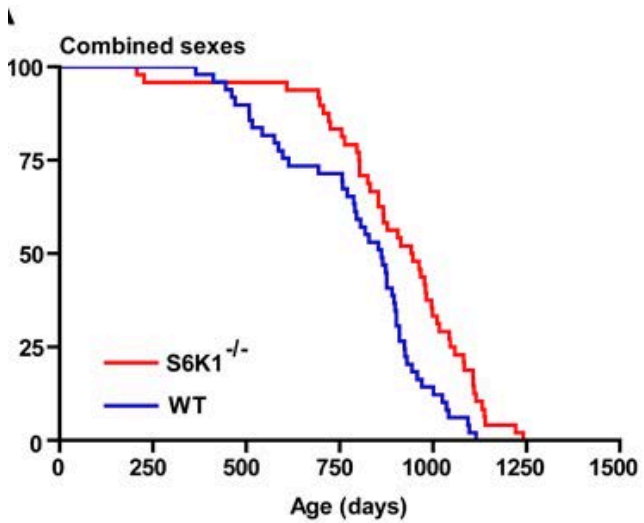


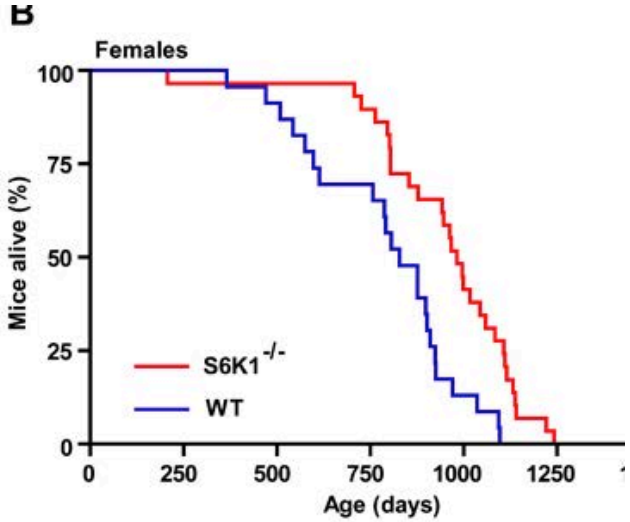
MTOR MAMMALIAN TARGET OF RAPAMYCIN IS A SIGNALING MECHANISM

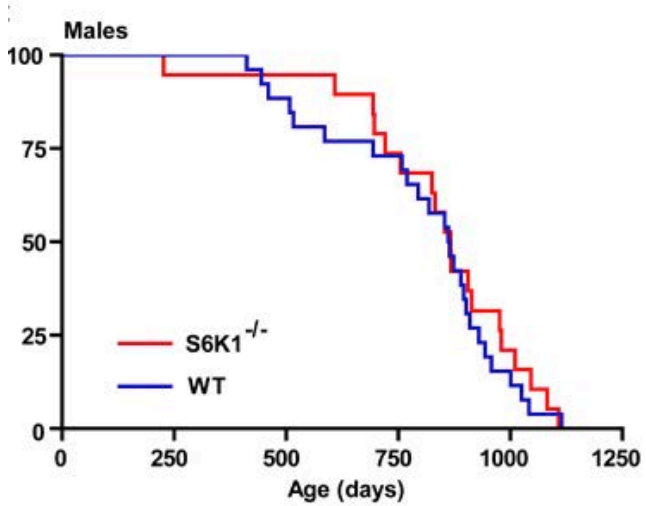
The same signalling pathways (such as TOR) that are involved in chronological senescence are also involved in organismal aging, and age-related diseases

Clinical and Experimental Findings: **SOLUTIONS**

- Inhibitors of the TOR pathway, including specific signals decelerate chronological aging.
- Inhibitors of the TOR pathway, including Rapamycin also decelerate chronological aging.

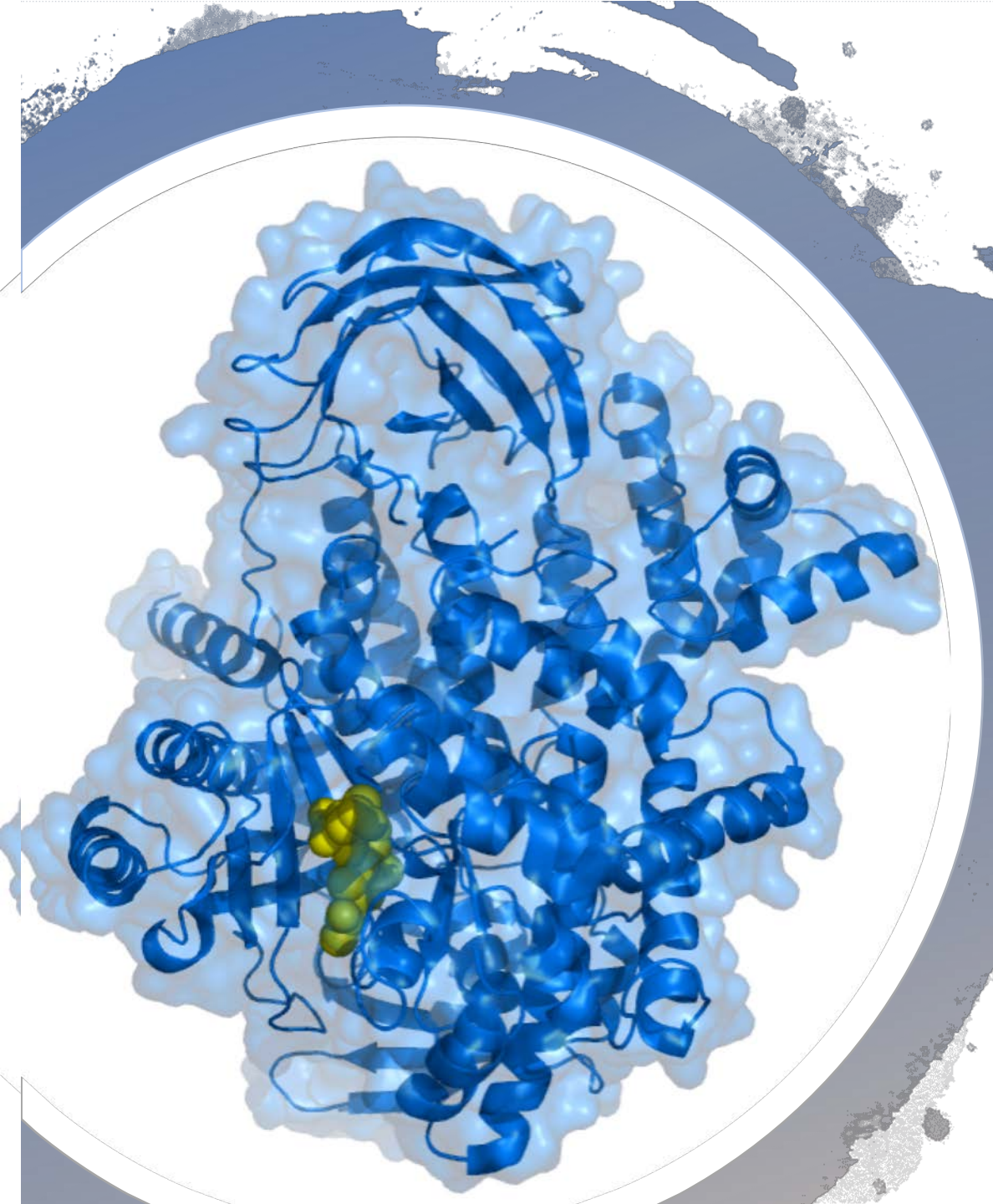






Clinical and Experimental Findings: **SOLUTIONS**

Selman et al (science 2009 Oct 2; 326) demonstrated that **deletion of ribosomal S6 protein kinase 1 (S6K1), a component of the nutrient-responsive mTOR** (mammalian target of rapamycin) signaling pathway, led to **increased life span and resistance to age-related pathologies, such as bone, immune, and motor dysfunction and loss of insulin sensitivity.**



SEMI PROGRAMED THEORIES OF AGING

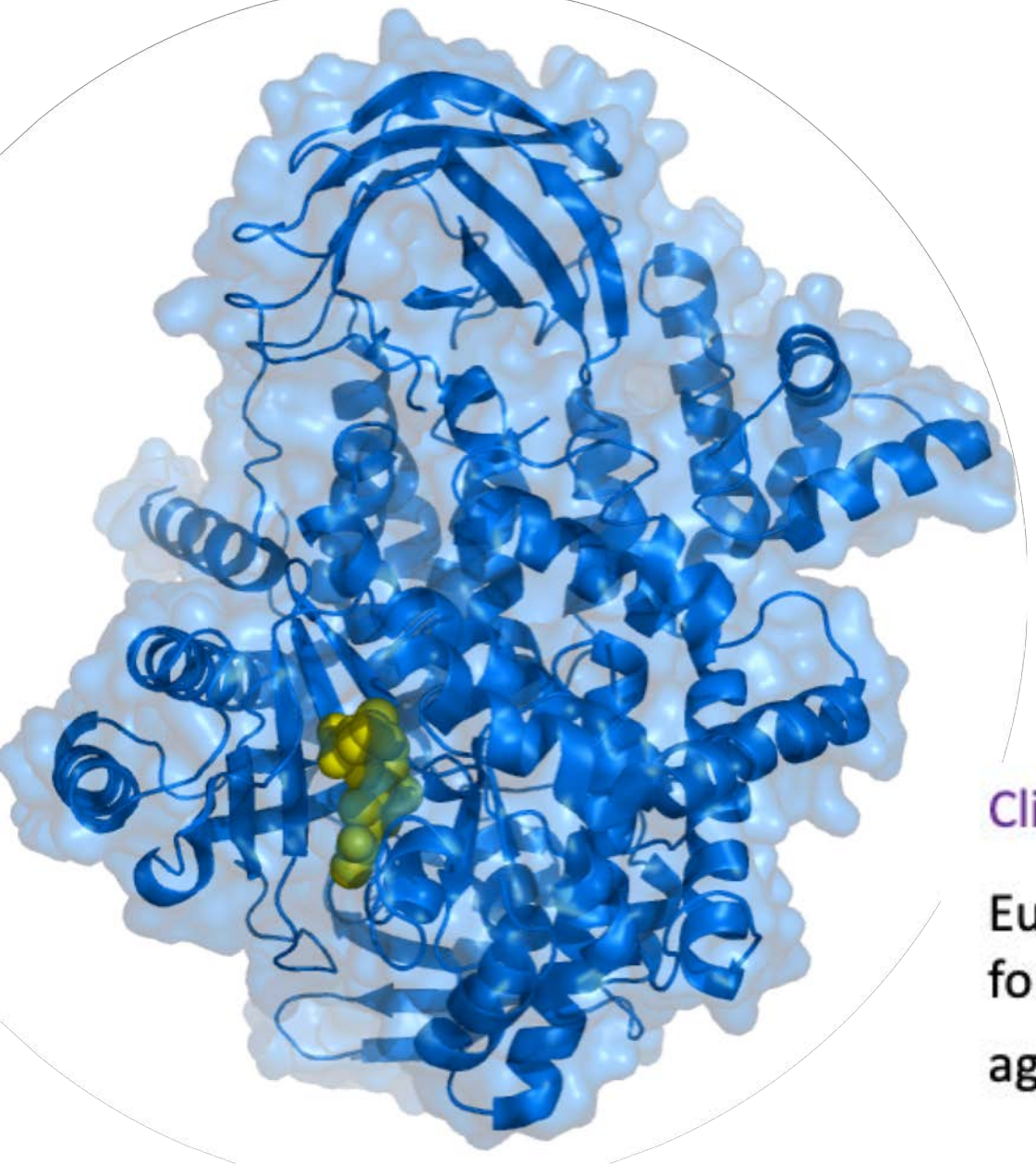
PI3K (Phosphoinositide 3-kinases)

PI3K are a family of enzymes involved in cellular functions

* cell growth
* cell proliferation
* cell differentiation
* cell motility
* cellular survival
* cell intracellular trafficking

THE GOOD

THE BAD

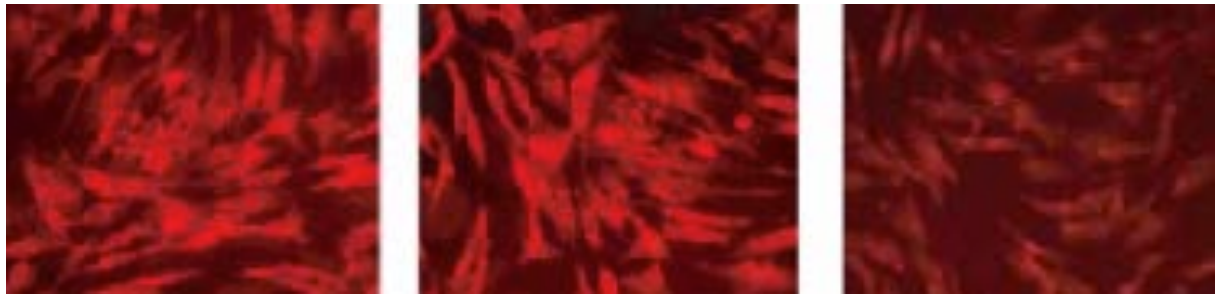


SEMI PROGRAMED THEORIES OF AGING

PI3K (Phosphoinositide 3-kinases)

PI3K signalling INDUCES ROS GENERATION

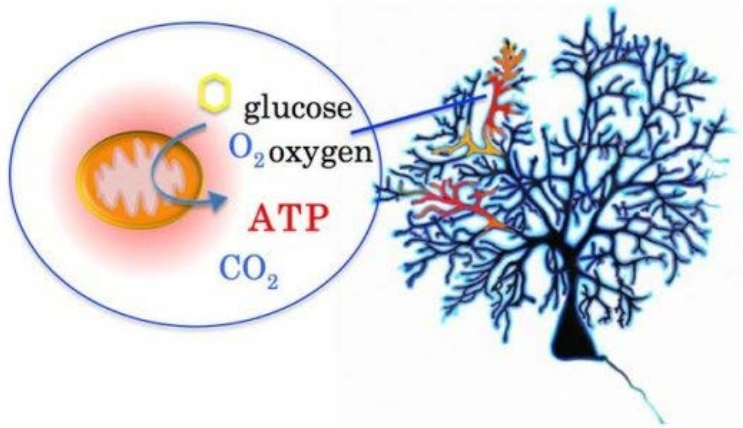
ROS GENERATION speeds up aging of skin cells.



Clinical and Experimental Findings: **SOLUTIONS**

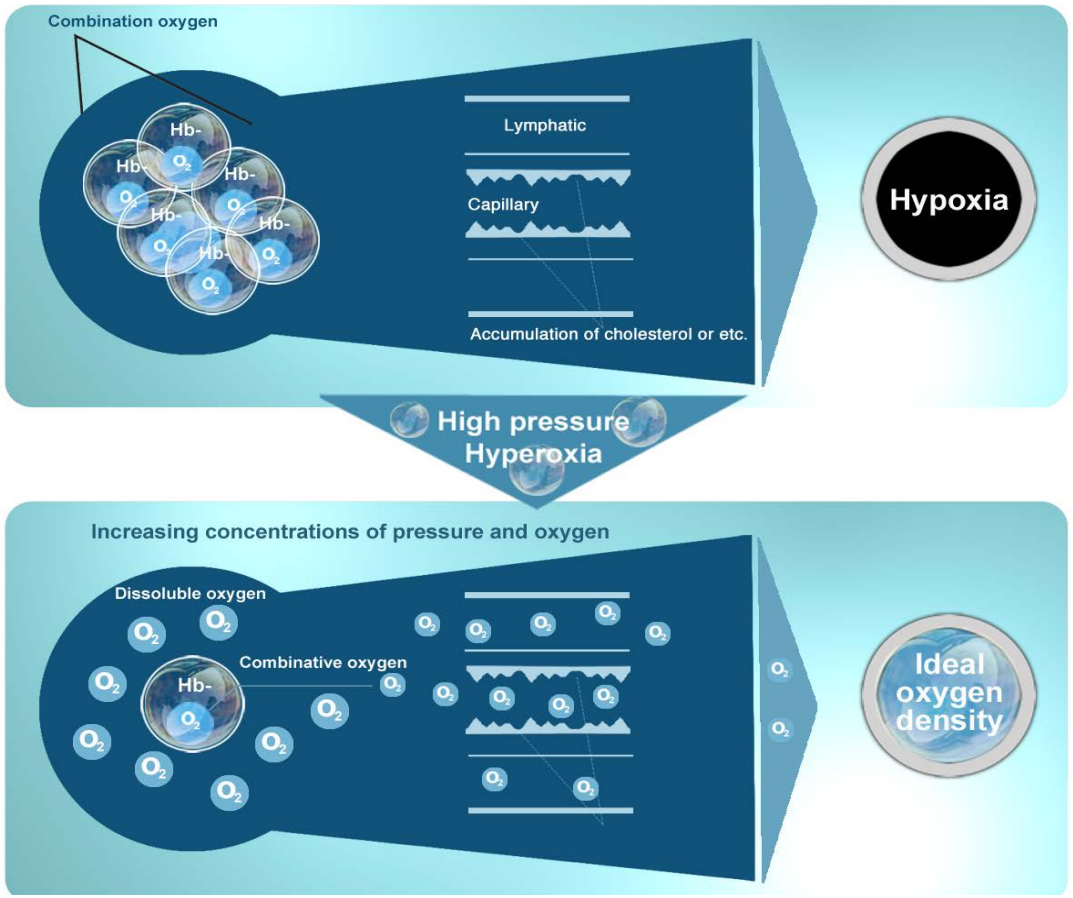
Eun-Mi Noh et al (Oxidative Med Cell Longev, Vol 27 2016) found that increased **ROS production** that speeds up skin aging **can be blocked by inhibition of PI3K**

OXYGEN IS NECESSARY FOR ENERGY PRODUCTION



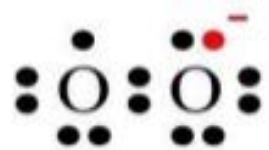
THE SAME PROCESSES THAT SUPPORT LIFE DESTROY LIFE

LIFE DEPENDS ON OXYGEN
but Oxygen can Harm Life



- During metabolism, the O_2 molecule splits and energy is released. To regain stability, the free single oxygen atom (oxygen free radical) seeks out or steals electrons from other available sources. This may result in a bond with dangerous properties:

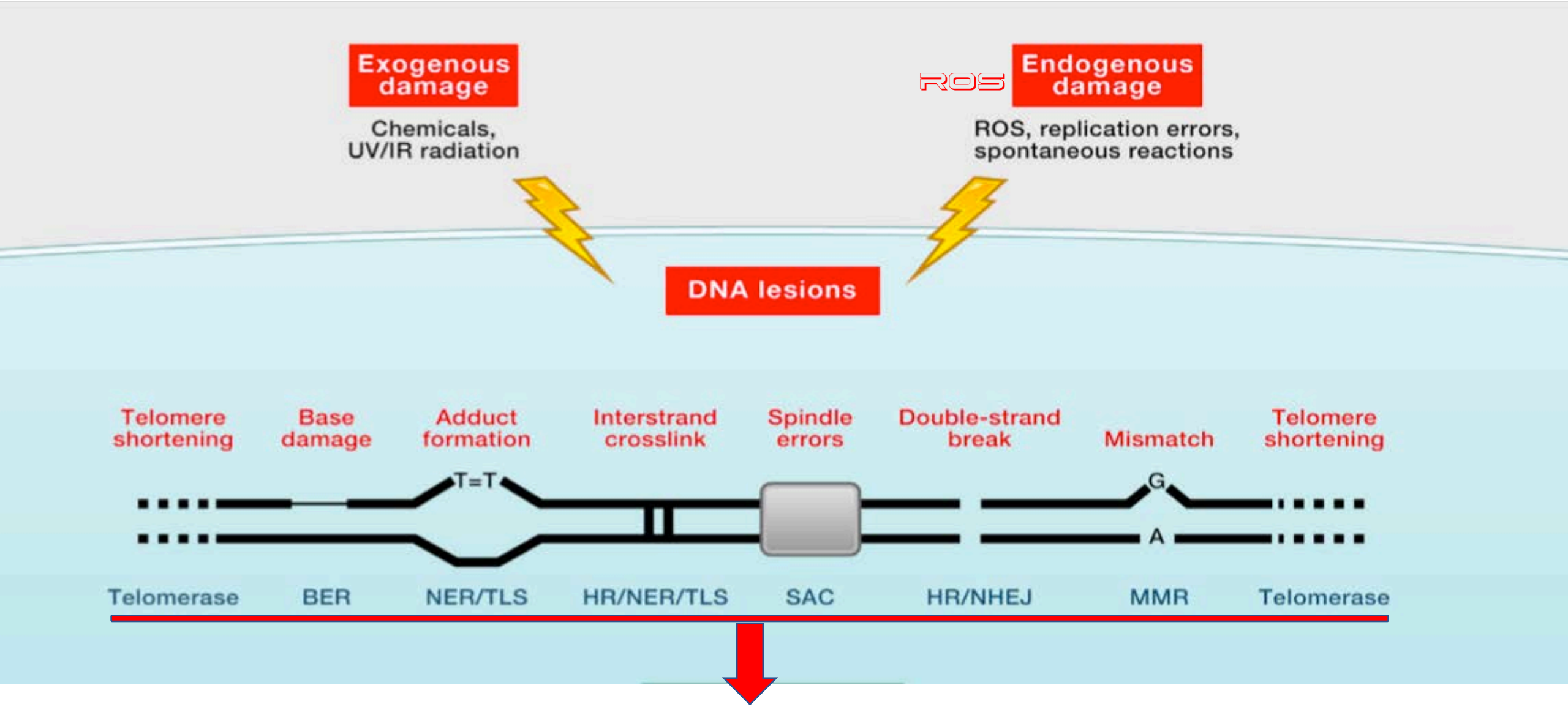
. If oxygen accepts one electron, it becomes *superoxide anion radical* ($O_2^{\bullet -}$)



. If oxygen accepts two electrons, it produces *peroxide*. O_2^{2-}

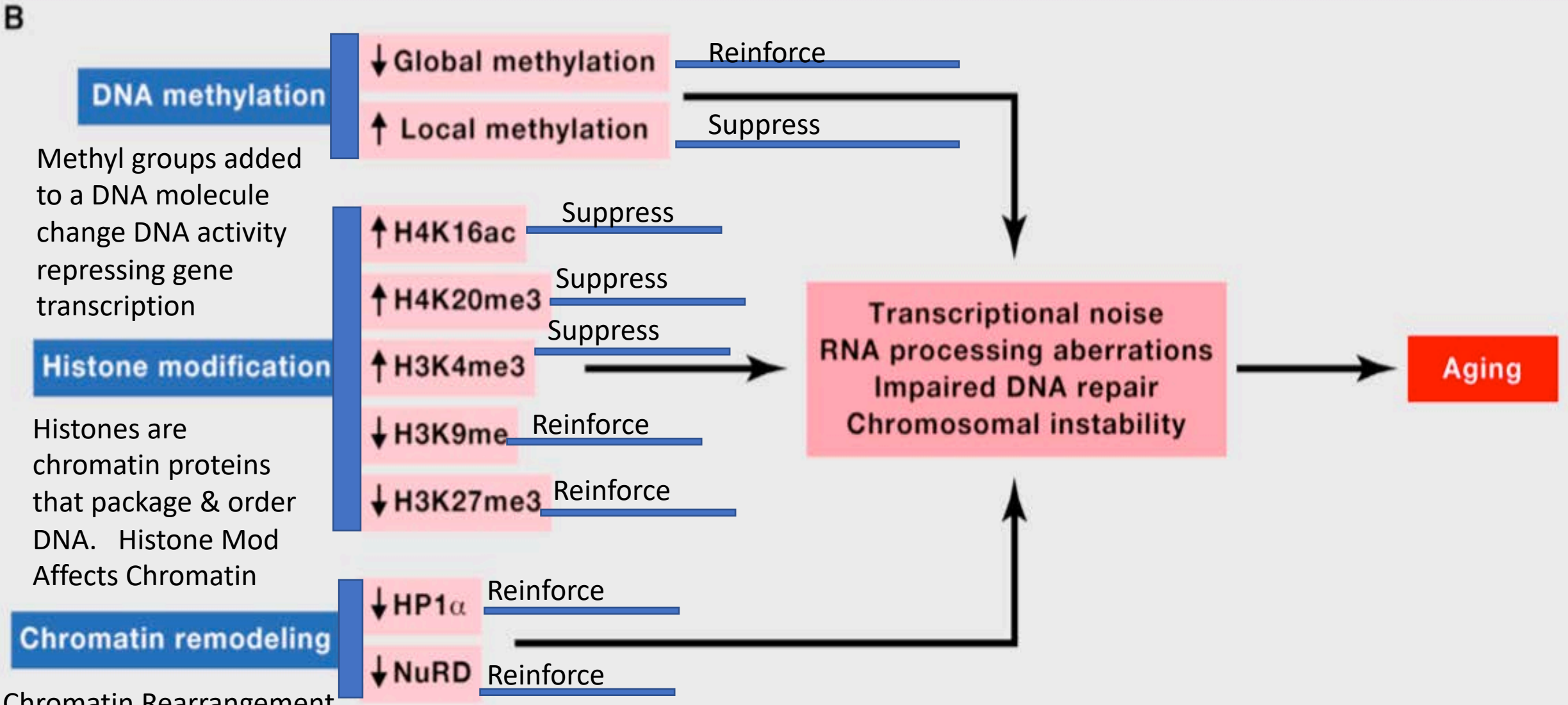
SEMI PROGRAMED THEORIES OF AGING

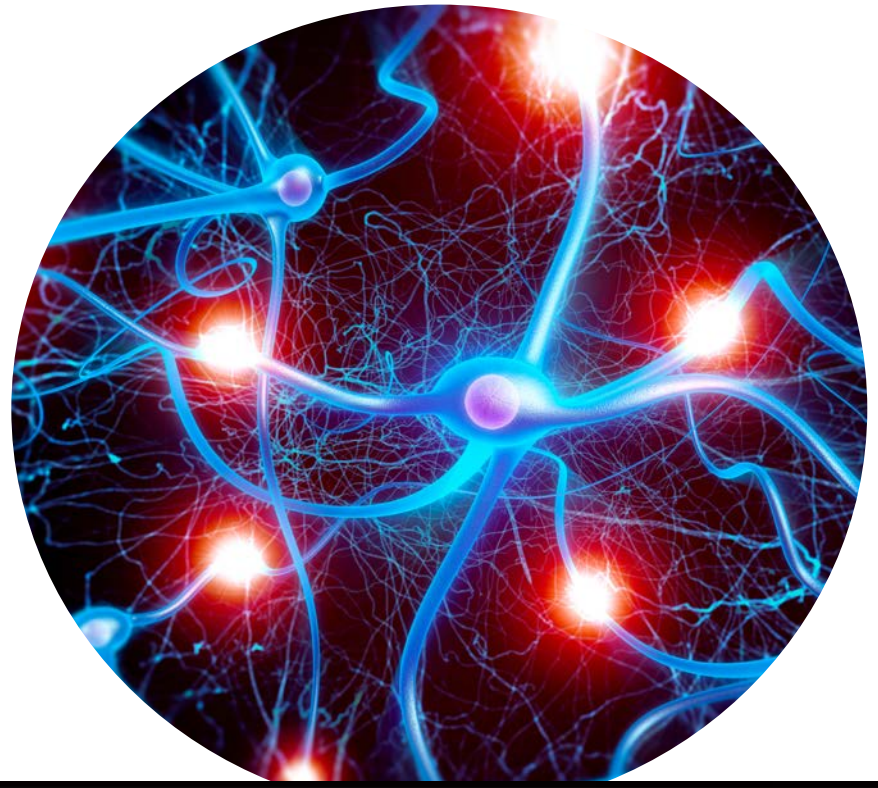
ROS: REACTIVE OXYGEN SPECIES

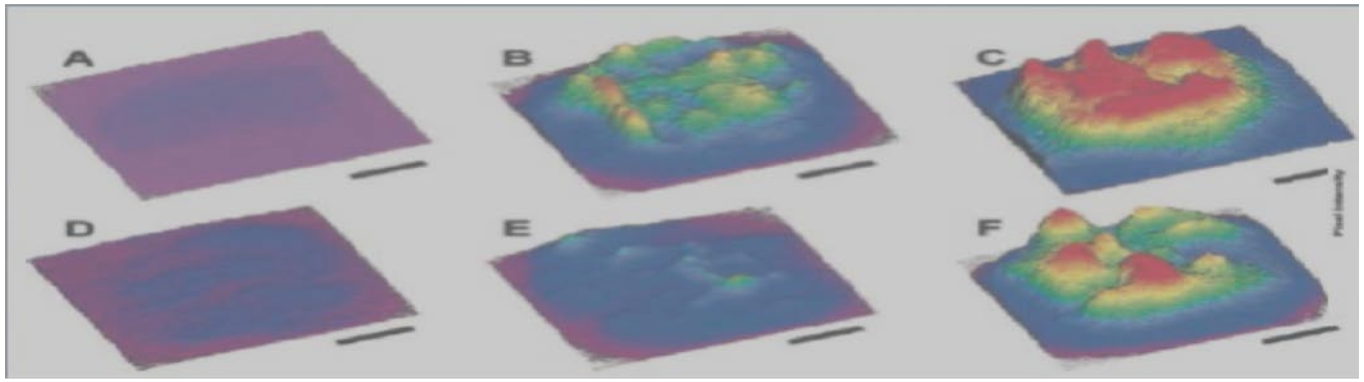


AGING / DISEASE / DEATH

The Deleterious Combination of the Aging Process and How to Reverse it

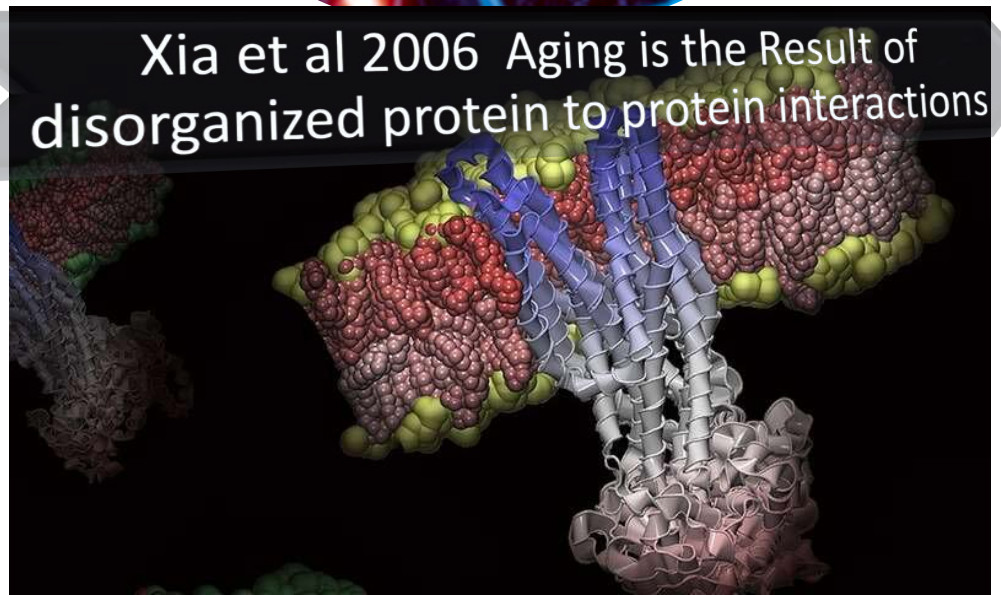


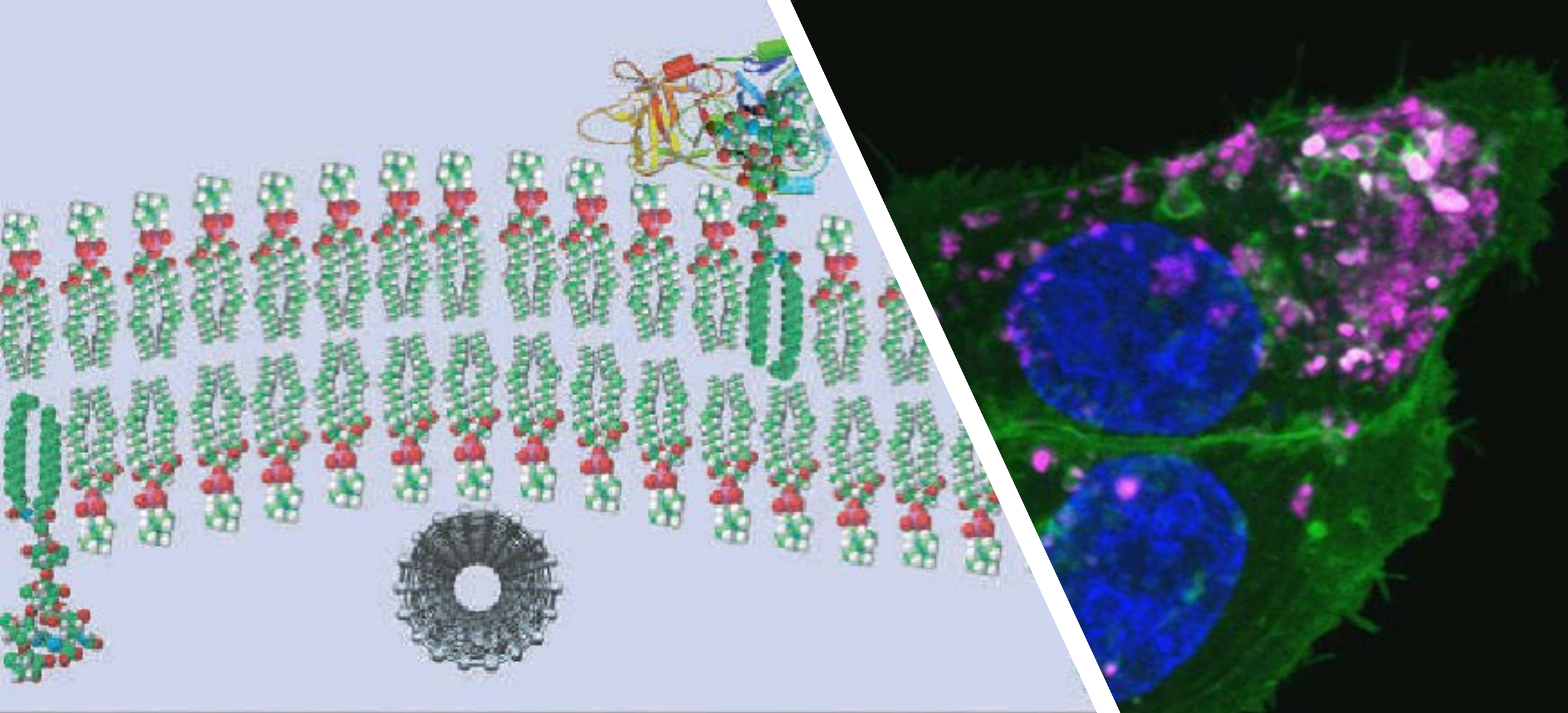




Interactions between the herein reviewed pathways are sensitive to even incremental changes in the cellular environment,

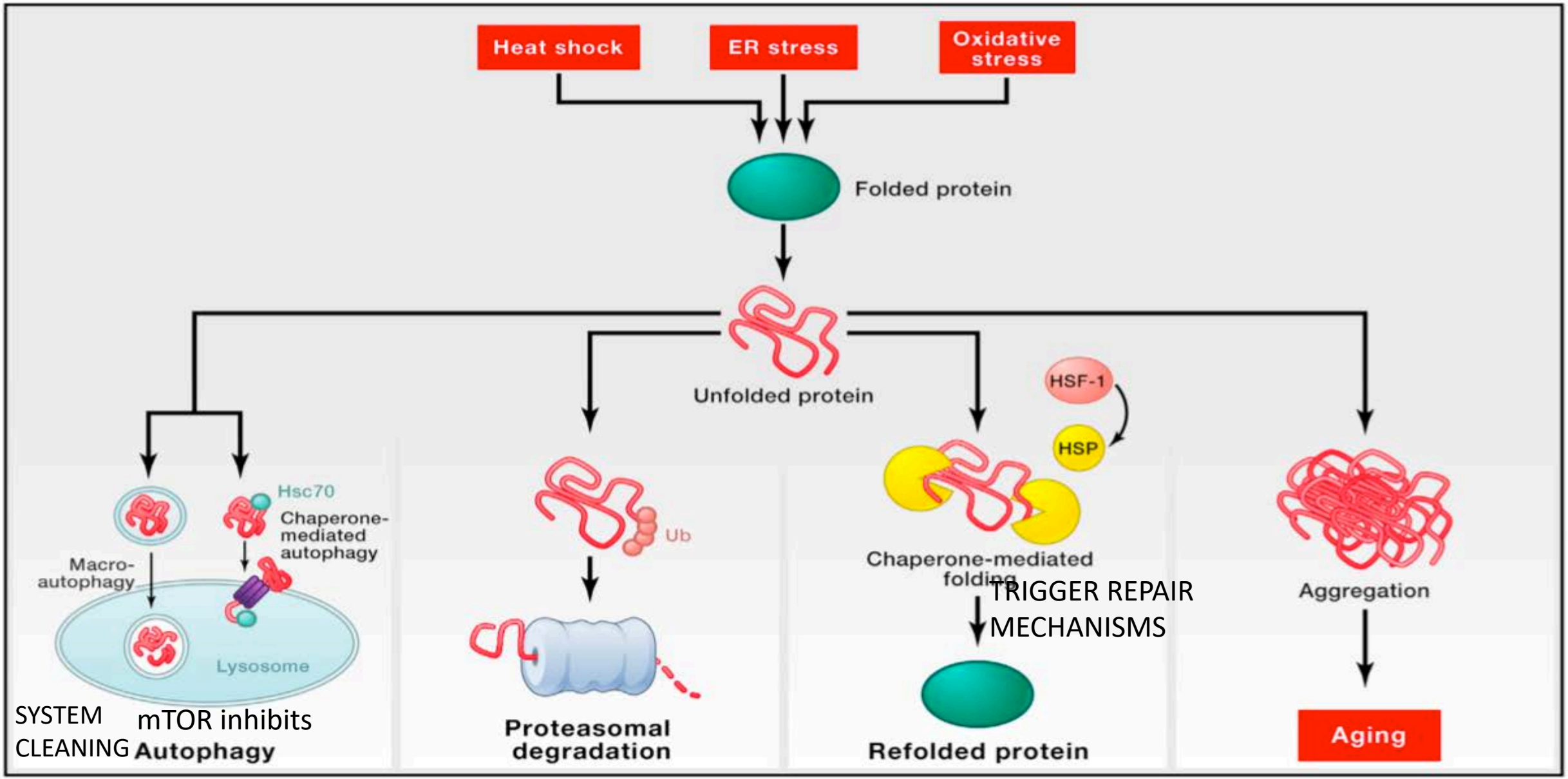
SIGNAL TRANSDUCTION DEFECTS





PROTEINS COMMUNICATE WITHIN THE CELL AND THEIR ENVIRONMENT

Aging Due to NONSENSE MISFOLDED PROTEINS



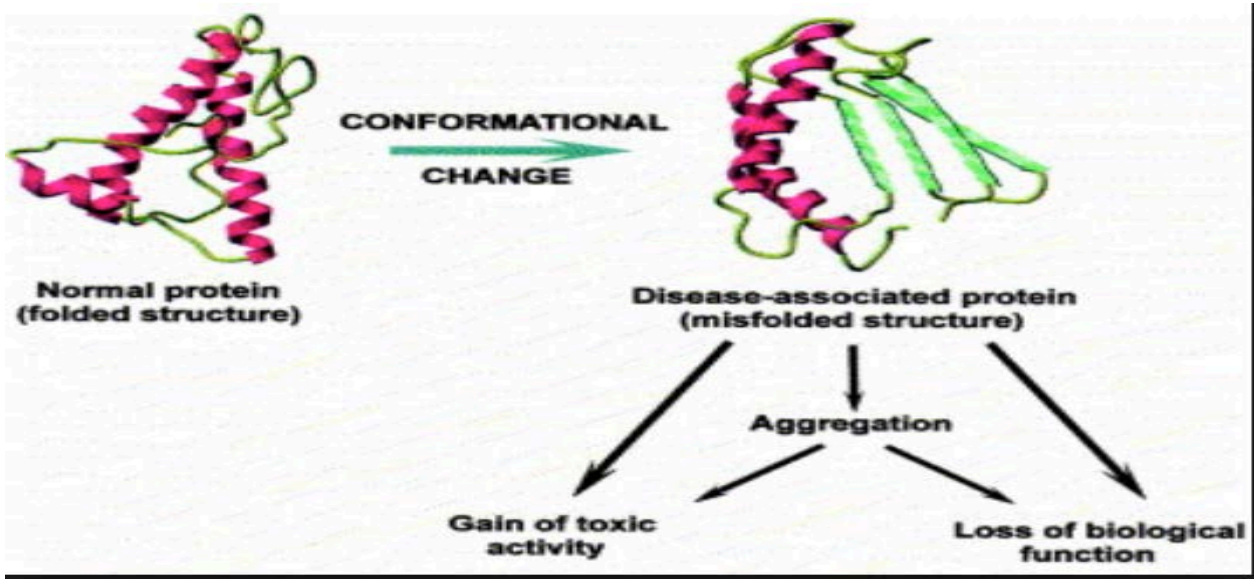
SYSTEM CLEANING

mTOR inhibits Autophagy

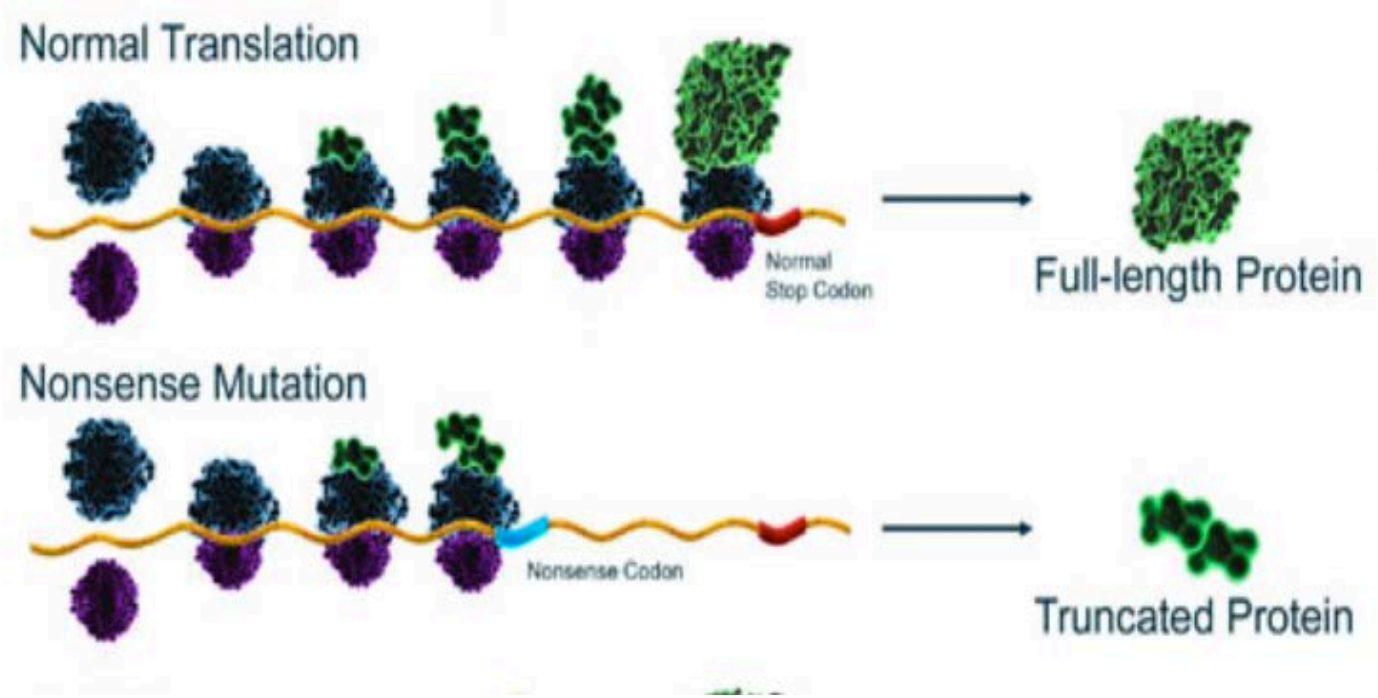
TRIGGER REPAIR MECHANISMS

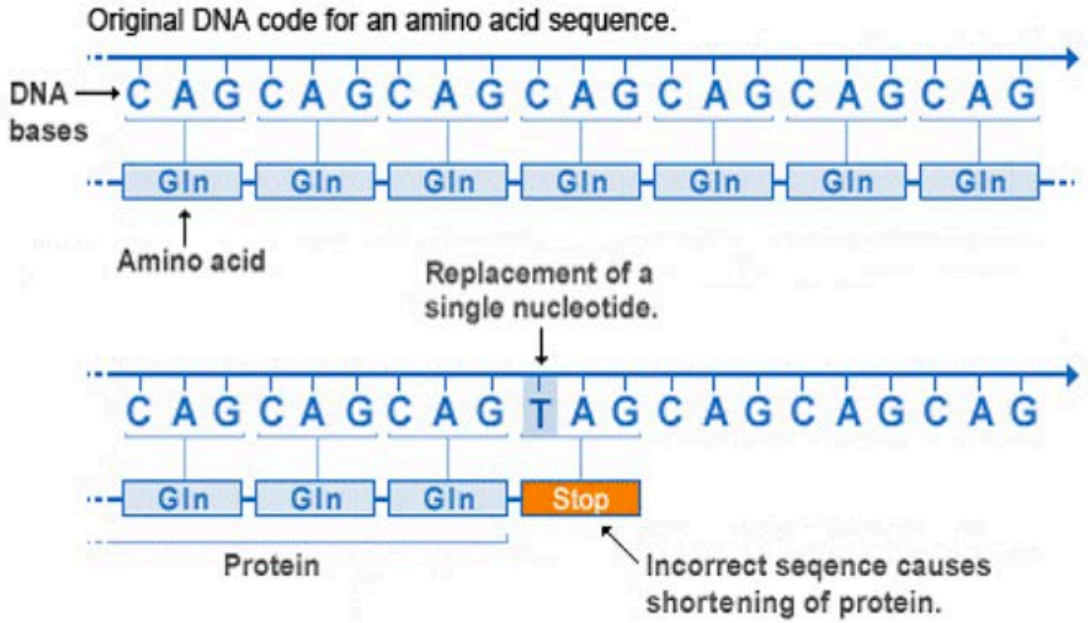
* Aging Due to NONSENSE MISFOLDED PROTEINS

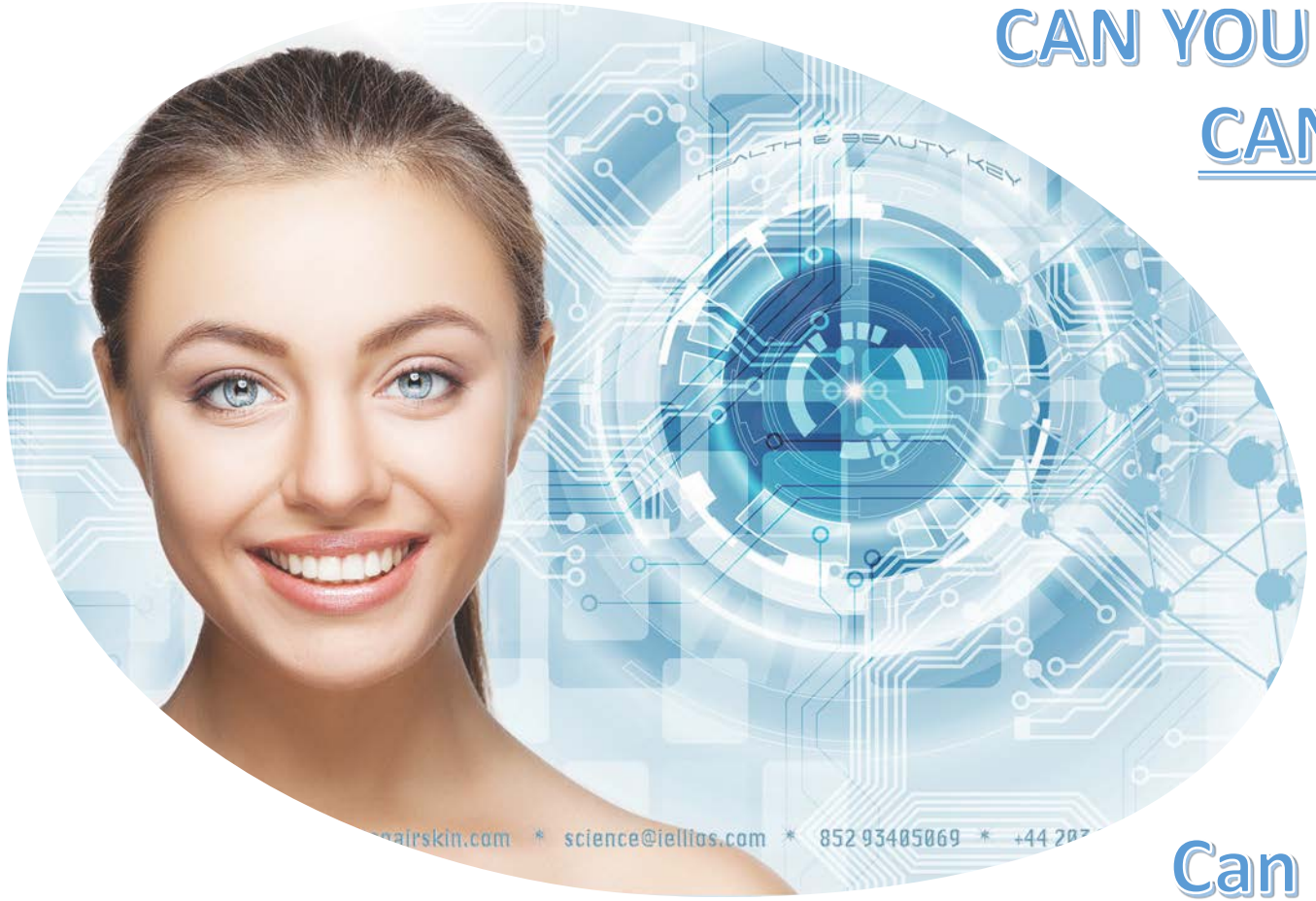
Misfolded Proteins cause Aging and Disease because they emit NONSENSE SIGNALS



Nonsense mutation







CAN YOU REFOLF UNFOLDEDPROTEINS?

CAN YOU UNBOIL AN EGG?

Can Aging be Reversed by Targeting Molecular Mechanisms Such as Cellular Proteins?

Is there a Technology than can Accomplish that?

Identify Zika virus RNA
in primary cells and tissues
Learn more >
affymetrix
eBioscience

YOU CAN UNBOIL AN EGG BY REFOLDING misfolded PROTEINS WITHIN THE CELL VIA RESONANT SIGNALING

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

Altmetric 1 0

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

Share this: 1.5K

KUNGL. VETENSKAPS-AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

English
English (pdf)

Swedish
Swedish (pdf)

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

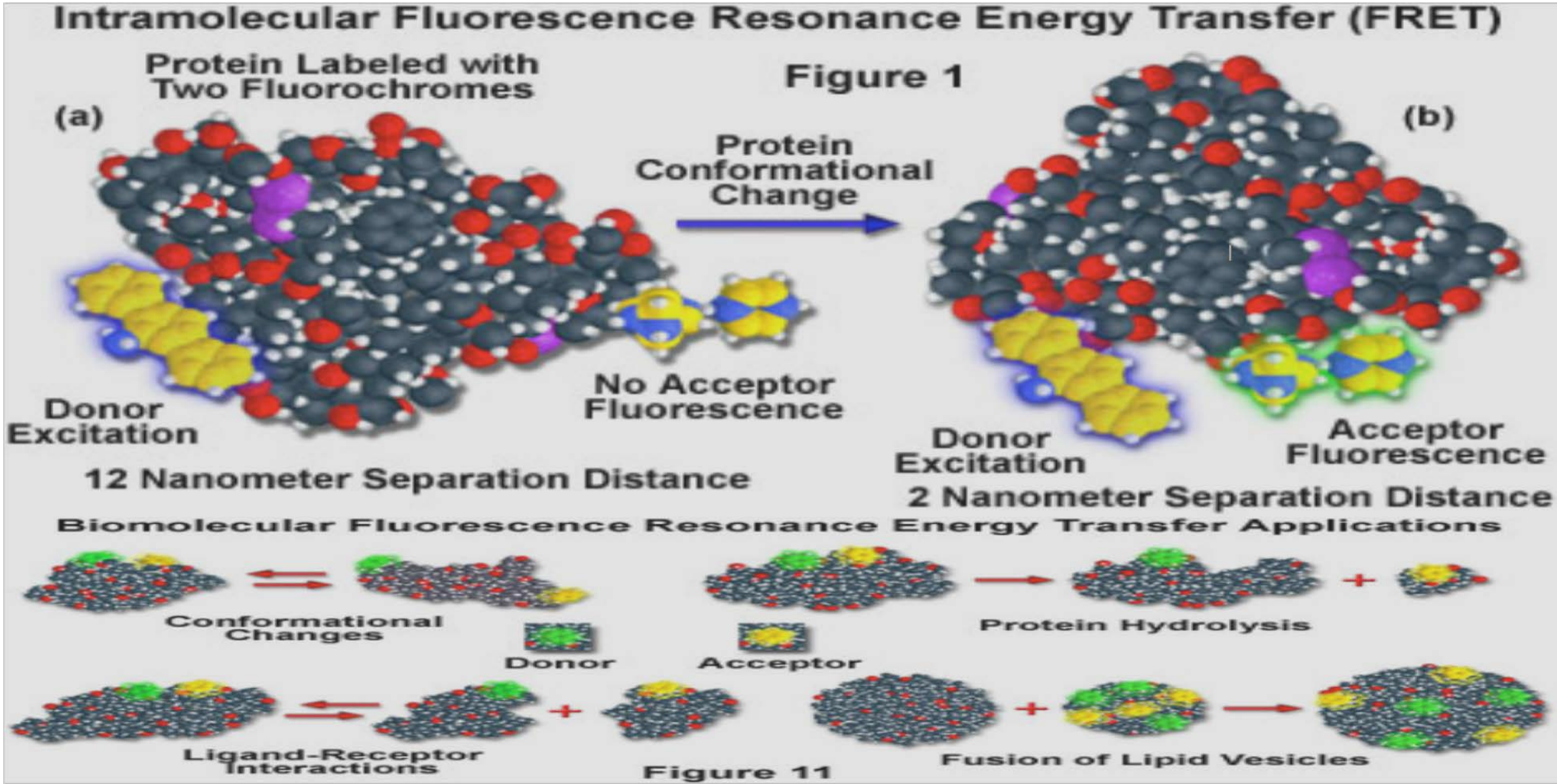
"for mechanistic studies of DNA repair"

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.

Q: IS RESONANCE ENERGY TRANSFER A THEORY OR A FACT?

A: IT IS A DOCUMENTED FACT



Q: Is it proven that cells use SIGNALS to communicate & fulfil functions ?
A: YES it is!

Summary

Press release

NOBELFÖRSAMLINGEN KAROLINSKA INSTITUTET
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

October 12, 1998

The Nobel Assembly at Karolinska Institutet has today decided to award the Nobel Prize in Physiology or Medicine for 1998 jointly to

Robert F. Furchgott, Louis J. Ignarro and **Ferid Murad**

for their discoveries concerning "nitric oxide as a signalling molecule in the cardiovascular system".

Nitric oxide (NO) is a gas that transmits signals in the organism. Signal transmission by a gas that is produced by one cell, penetrates through membranes and regulates the function of another cell represents an entirely new principle for signalling in biological systems. The discoverers of NO as a signal molecule are awarded this year's Nobel Prize.

Robert F. Furchgott, Louis J. Ignarro and Ferid Murad discovered that Signal transmission that is produced by one cell, penetrates through membranes and regulates the function of another cell represents an entirely new principle for signalling in biological systems.

Press release

German

English

French
Swedish

NOBELFÖRSAMLINGEN KAROLINSKA INSTITUTET
THE NOBEL ASSEMBLY AT THE KAROLINSKA INSTITUTE

11 October 1999

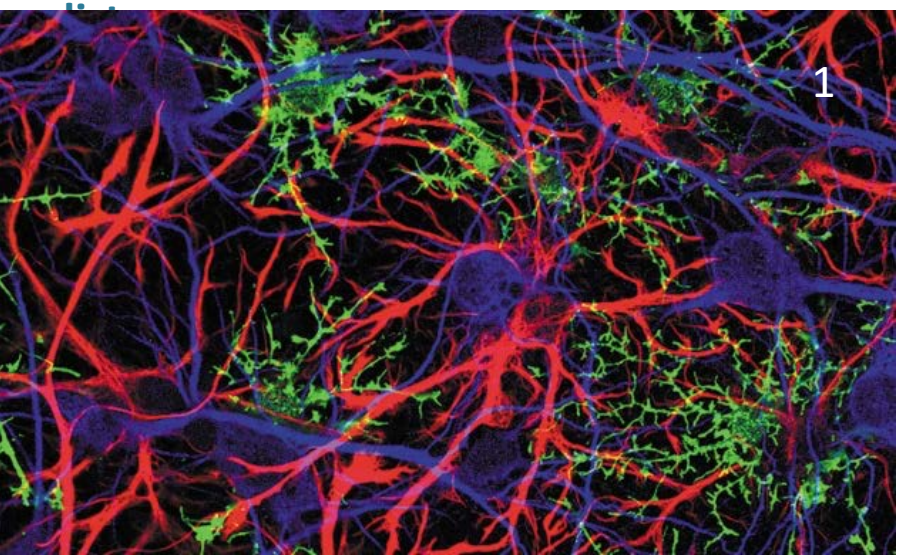
The Nobel Assembly at Karolinska Institutet has today decided to award the Nobel Prize in Physiology or Medicine for 1999 to

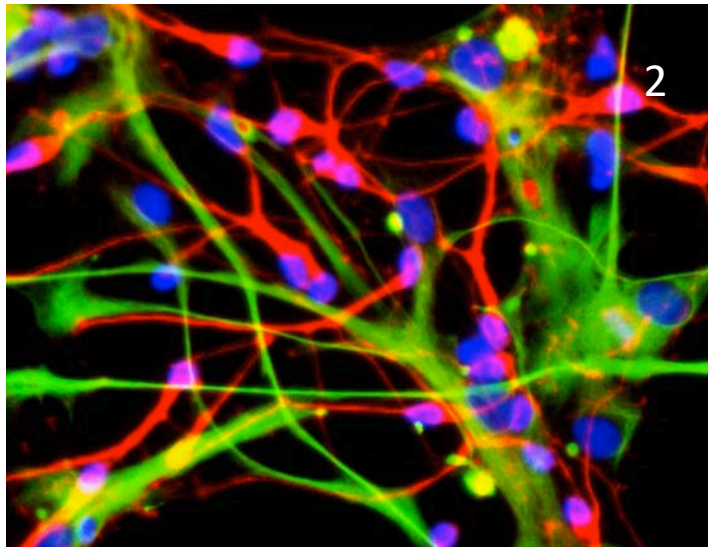
Günter Blobel

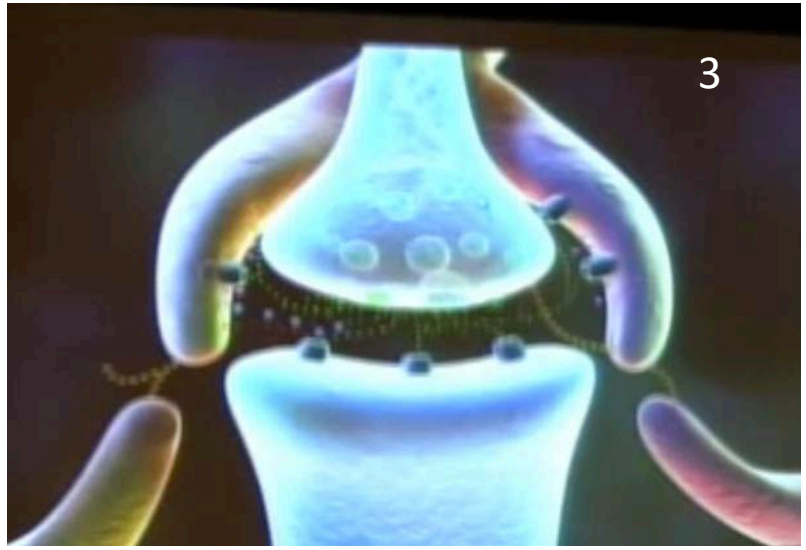
for the discovery that **"proteins have intrinsic signals that govern their transport and localization in the cell"**

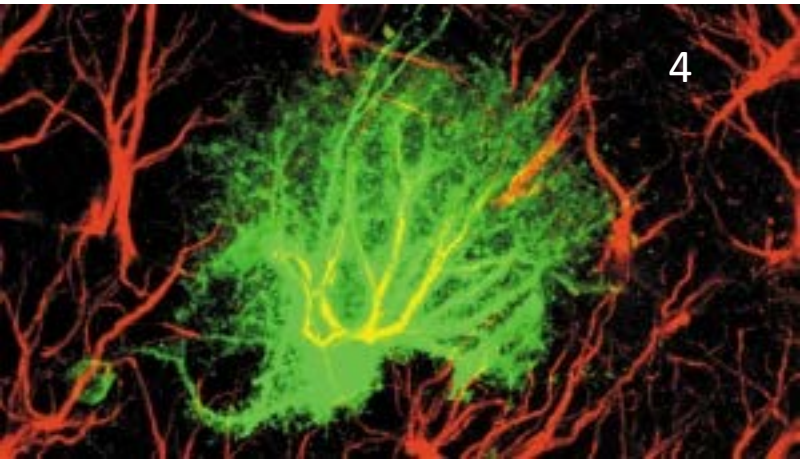
Günter Blobel's "signal hypothesis" is now proven and confirmed the around 1 billion protein molecules in the approximately 100,000 billion cells of the human body, are all carrying signals like "address tags" or "zip codes" to safely get them to their needed destination

Neurons Communicate 'Telepathically.' In Douglas Fields experiments the axons of neurons twitched releasing photons (2). Astrocytes (4) control neuronal signals in their proximity (1, 3) and can also spread these signals through their own non electrical non-neuronal astrocyte network to control distant neuronal synapse that are not even wired together (2, 3). ASTROCYTES COMMUNICATE BY BROADCASTING SIGNALS. NEURONS COMMUNICATE LIKE LANDLINE TELEPHONES SERIALLY across the synapses. GLIAL CELLS (1, 2, 3, 4, 5, 6) COMMUNICATE LIKE CELLPHONES broadcasting the signals across large

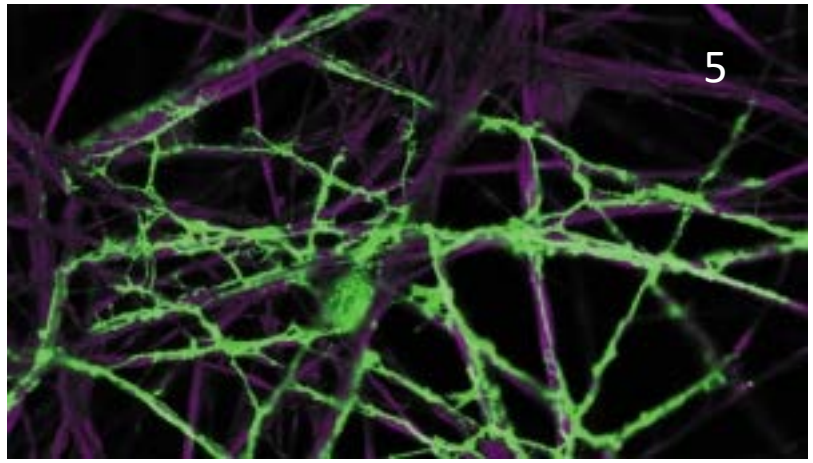




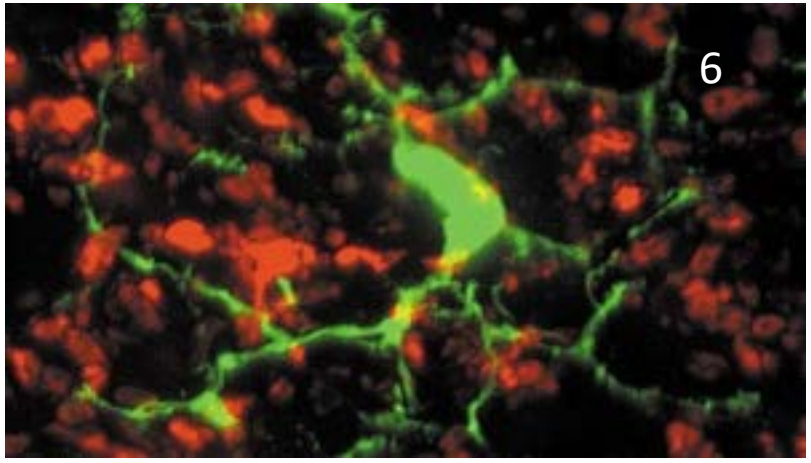




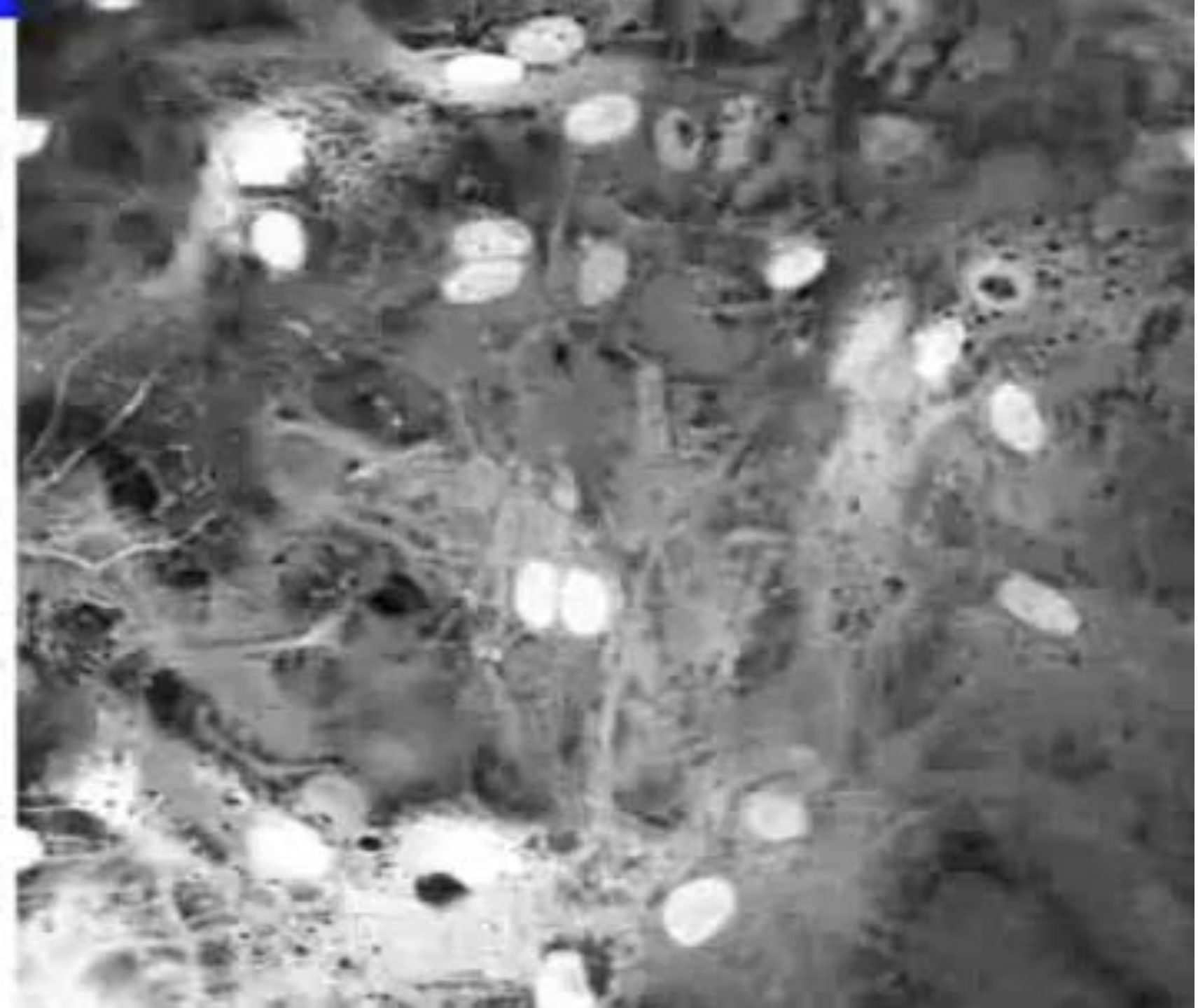
Red and Green: Astrocytes (regulate excitability)



Oligodendrocytes (green) – Increase Conduction Velocity by 50 times



Microglia (green) – responsive to NS injury and infection



This is LIVE UNDER THE MICROSCOPE RECORDING OF NON-ELECTRICAL NEURONAL COMMUNICATION BY GLIAL CELLS BROADCASTING SIGNALS ALONG LARGE DISTANCES. OBSERVE HOW SIGNALS JUMP AND SPREAD ALONG THESE SEVERAL THOUSANDS OF CELLS. Cell to body is equivalent to an ant compared to the entire continent of Asia

SCIENCE + TECHNOLOGY

'Psychic cells': Scientists discover cells can communicate through physical barriers

Kim Irwin | January 31, 2013

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Scientists at UCLA and Charles R. Drew University of Medicine and Science have discovered a possible method by which cancer cells and dying cells communicate with nearby normal nerve cells without being physically connected to them.

Dr. Keith Norris, senior author of the research and assistant dean for clinical and translational science at the David Geffen School of Medicine at UCLA, said the study contributes to the understanding of cell communication, which until now was known to take place only through direct contact or direct stimulation of receptors in the cells of molecules known as ligands or in hormones, signaling factors, nerves and other pathways.

It now appears, the researchers say, that cells may be able to effectively communicate through physical barriers. Their study appears in the January 2013 issue of the peer-reviewed American Journal of Translational Research.

For the study, Norris and his colleagues reported on how normal nerve cells isolated in an enclosed chamber behave during a function known calcium signal processing. The team found that when these isolated nerve cells were surrounded by other normal nerve cells outside the barrier, they had the same calcium signaling properties.

However, when the normal isolated nerve cells were surrounded by cancer cells or dying cells, they processed the calcium signals differently, suggesting there was communication from the surrounding cells. The physical barrier between the cells prevented hormonal, ligand-receptor and other traditional forms of cell-to-cell communication.

Co-authors Dr. Christopher Reid and Victor Chaban of the Life Sciences Institute at Drew University noted that this novel finding may represent a potentially higher form of cell communication. Discovering that cancer cells and dying cells may have a previously undiscovered communication method with other cells may lead to new treatments for cancer, aging and other diseases, they said. Further studies are needed to uncover how the non-physical communication occurs.

"Understanding the many ways in which cells communicate is an important step toward developing new approaches to treat disease," said Dr. Steven M. Dubinett, executive director of the UCLA Clinical and Translational Science Institute (UCLA CTSI).

The study was funded by the National Center for Advancing Translational Sciences through the UCLA CTSI and the National Institute on Minority Health and Health Disparities at the National Institutes of Health.

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Physically disconnected non-diffusible cell-to-cell communication between neuroblastoma SH-SY5Y and DRG primary sensory neurons

Victor V Chaban,[1,2] Taehoon Cho,[1] Christopher B Reid,[1] and Keith C Norris[1,2]

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Abstract

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Background: Cell-cell communication occurs via a variety of mechanisms, including long distances (hormonal), short distances (paracrine and synaptic) or direct coupling via gap junctions, antigen presentation, or ligand-receptor interactions. We evaluated the possibility of neuro-hormonal independent, non-diffusible, physically disconnected pathways for cell-cell communication using dorsal root ganglion (DRG) neurons. Methods: We assessed intracellular calcium ($[Ca^{2+}]$) in primary culture DRG neurons that express ATP-sensitive P2X3, capsaicinsensitive TRPV1 receptors modulated by estradiol. Physically disconnected (dish-in-dish system; inner chamber enclosed) mouse DRG were cultured for 12 hours near: a) media alone (control 1), b) mouse DRG (control 2), c) human neuroblastoma SHSY-5Y cells (cancer intervention), or d) mouse DRG treated with KCl (apoptosis intervention). Results: Chemosensitive receptors $[Ca^{2+}]_i$ signaling did not differ between control 1 and 2. ATP (10 μM) and capsaicin (100nM) increased $[Ca^{2+}]_i$ transients to 425.86 + 49.5 nM, and 399.21 ± 44.5 nM, respectively. 17β-estradiol (100 nM) exposure reduced ATP (171.17 ± 48.9 nM) and capsaicin (175.01±34.8 nM) $[Ca^{2+}]_i$ transients. The presence of cancer cells reduced ATP- and capsaicin-induced $[Ca^{2+}]_i$ by >50% ($p<0.05$) and abolished the 17β-estradiol effect. By contrast, apoptotic DRG cells increased initial ATP-induced $[Ca^{2+}]_i$, flux four fold and abolished subsequent $[Ca^{2+}]_i$, responses to ATP stimulation ($p<0.001$). Capsaicin (100nM) induced $[Ca^{2+}]_i$ responses were totally abolished. Conclusion: The local presence of apoptotic DRG or human neuroblastoma cells induced differing abnormal ATP and capsaicin-mediated $[Ca^{2+}]_i$ fluxes in normal DRG. These findings support physically disconnected, non-diffusible cell-to-cell signaling. Further studies are needed to delineate the mechanism(s) of and model(s) of communication.

Keywords: Cell-cell communication, TRPV1, P2X3, DRG, SH-SY5Y

Am J Transl Res
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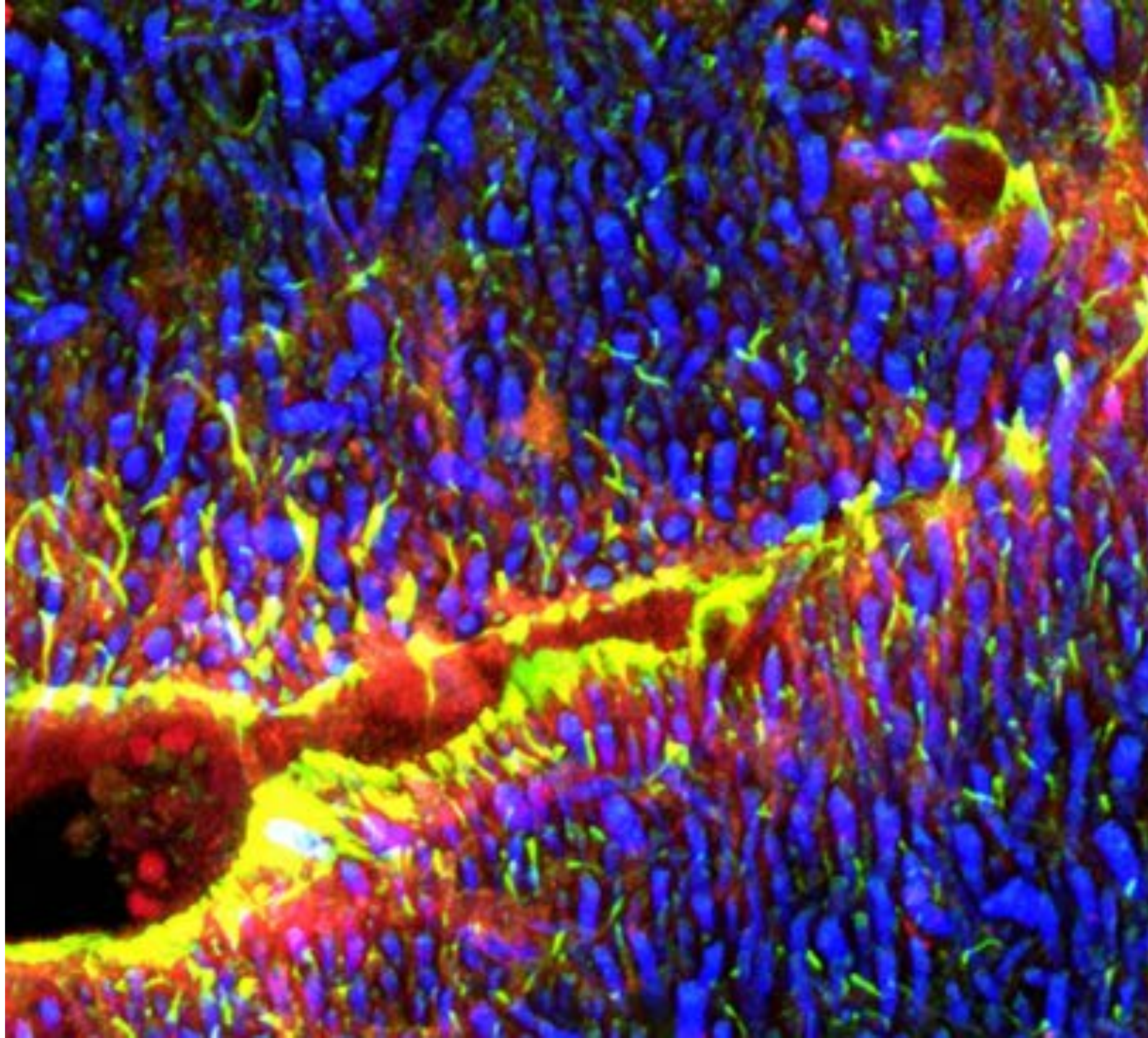
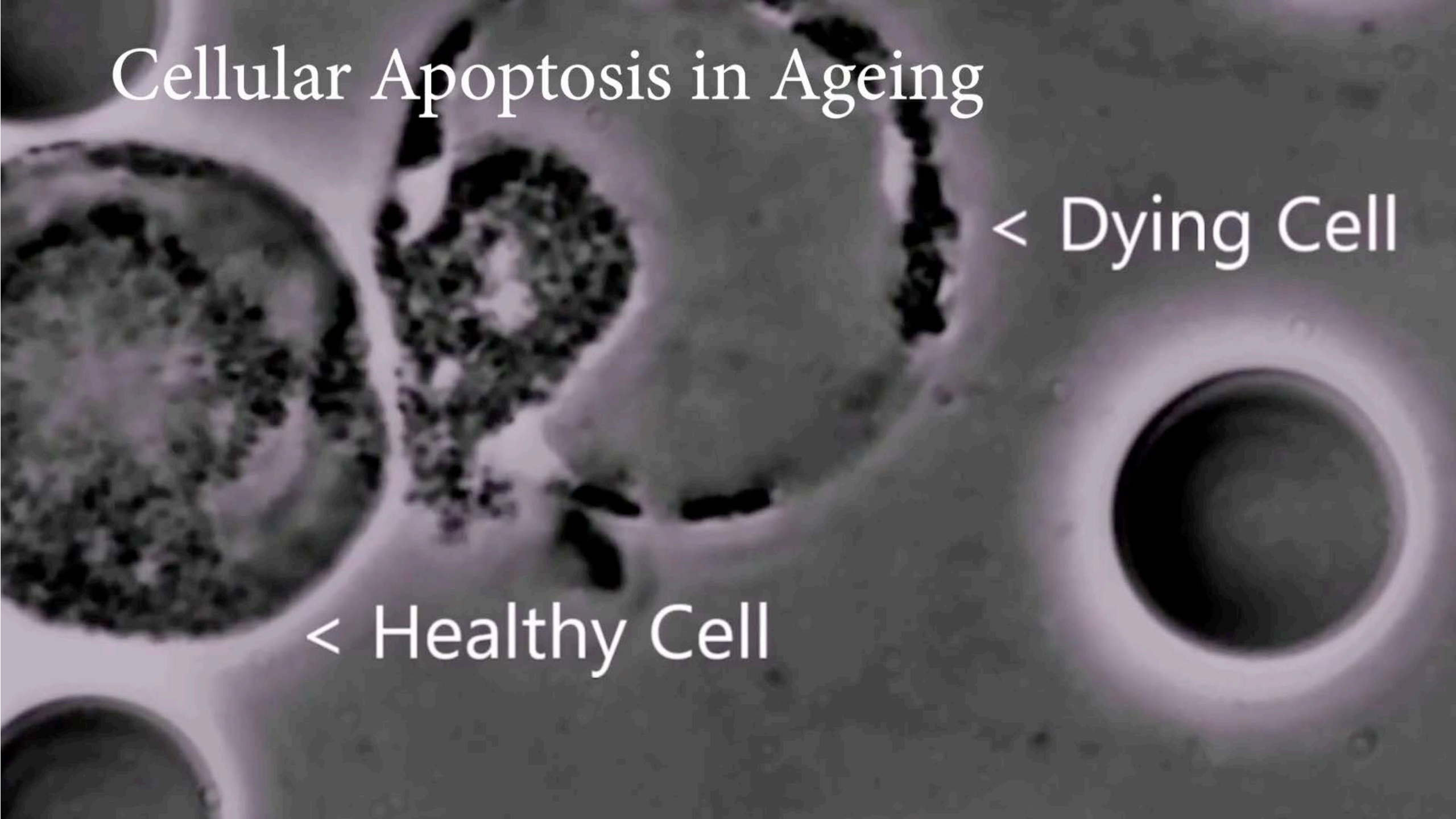
Recent Research (2013 – 2018) by Dr Keith Norris and others CONFIRMED that cells communicate through physical barriers without physical contact

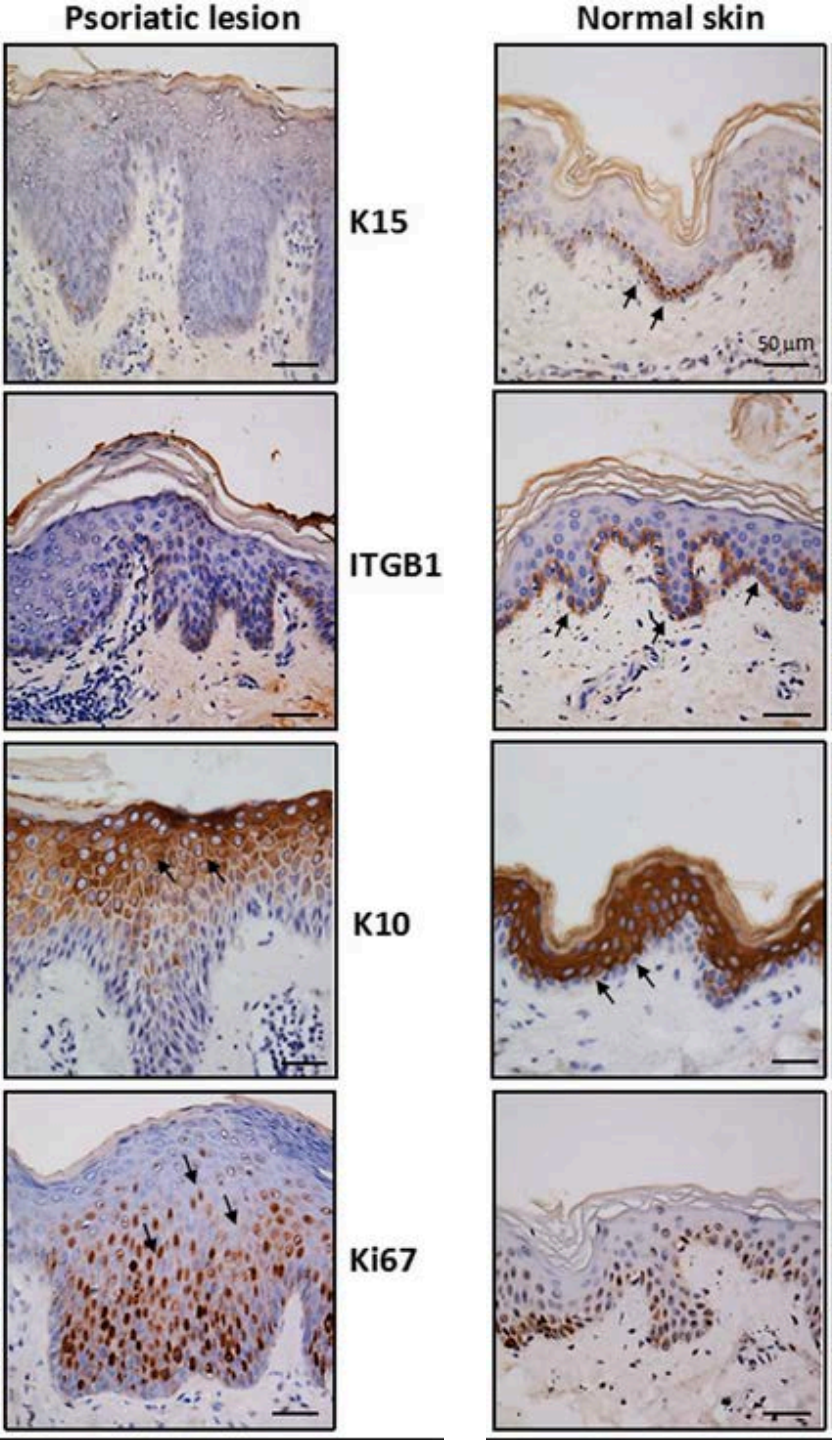
Norris and his colleagues observed cells isolated inside a barrier that did not allow for cell to cell communication via gap junctions, antigen presentation or ligand-receptor interaction (short distances) of hormonal mechanisms (long distances). These isolated cells had the same calcium signaling processes responding to normal cells outside the barrier. These isolated cells altered their signaling when cancer cells were outside the barrier suggesting that the isolated cells had adjusted their signals to specifically communicate with the cancer cells. In short the barrier contained isolated cells demonstrated different signaling responses when normal vs cancer cells were outside the barrier. Therefore the isolated cells altered communication depending on what type of cells were outside the barrier.

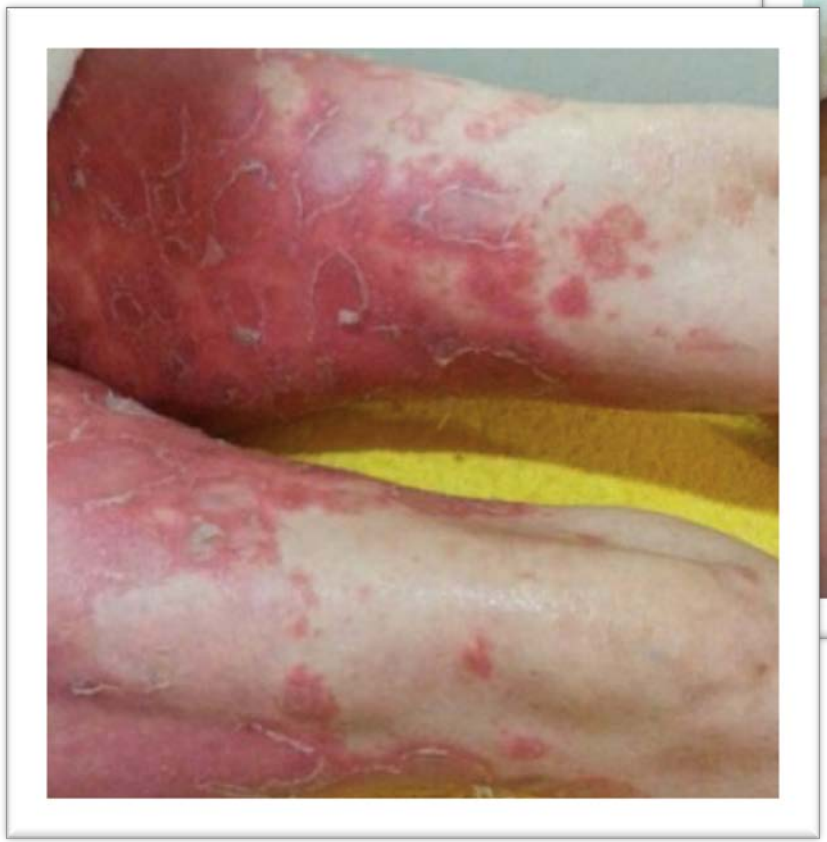


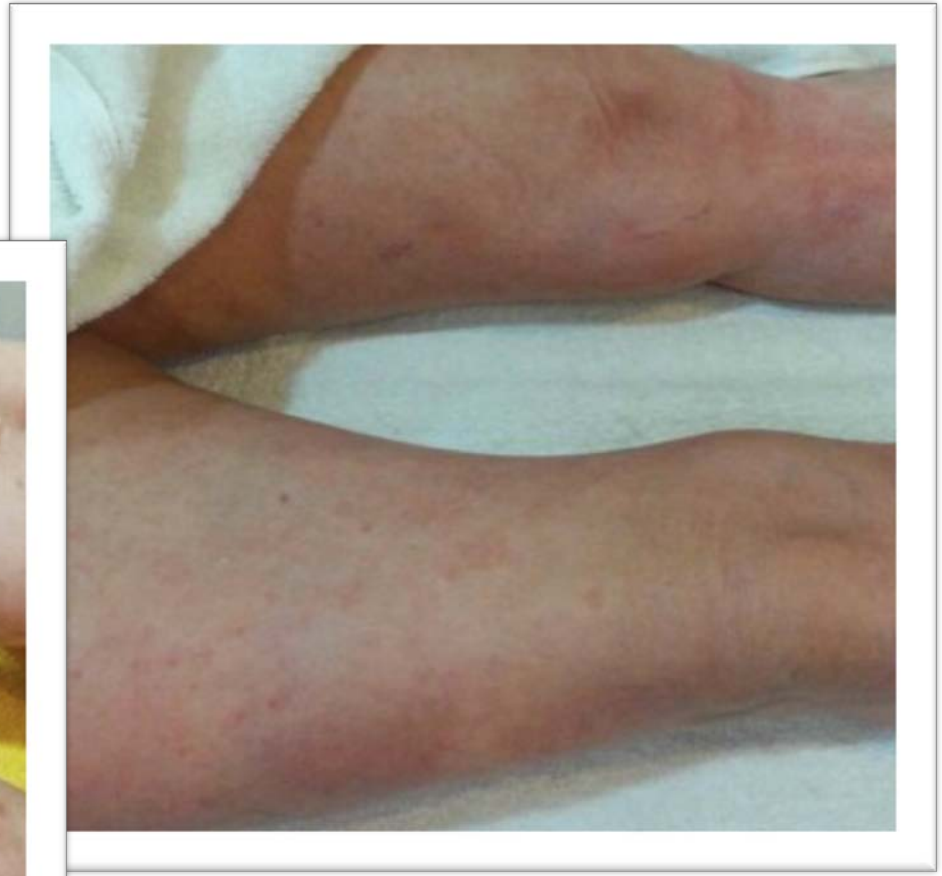
Cellular Apoptosis in Ageing



Clinical Evidence of Repaired Signaling Pathways

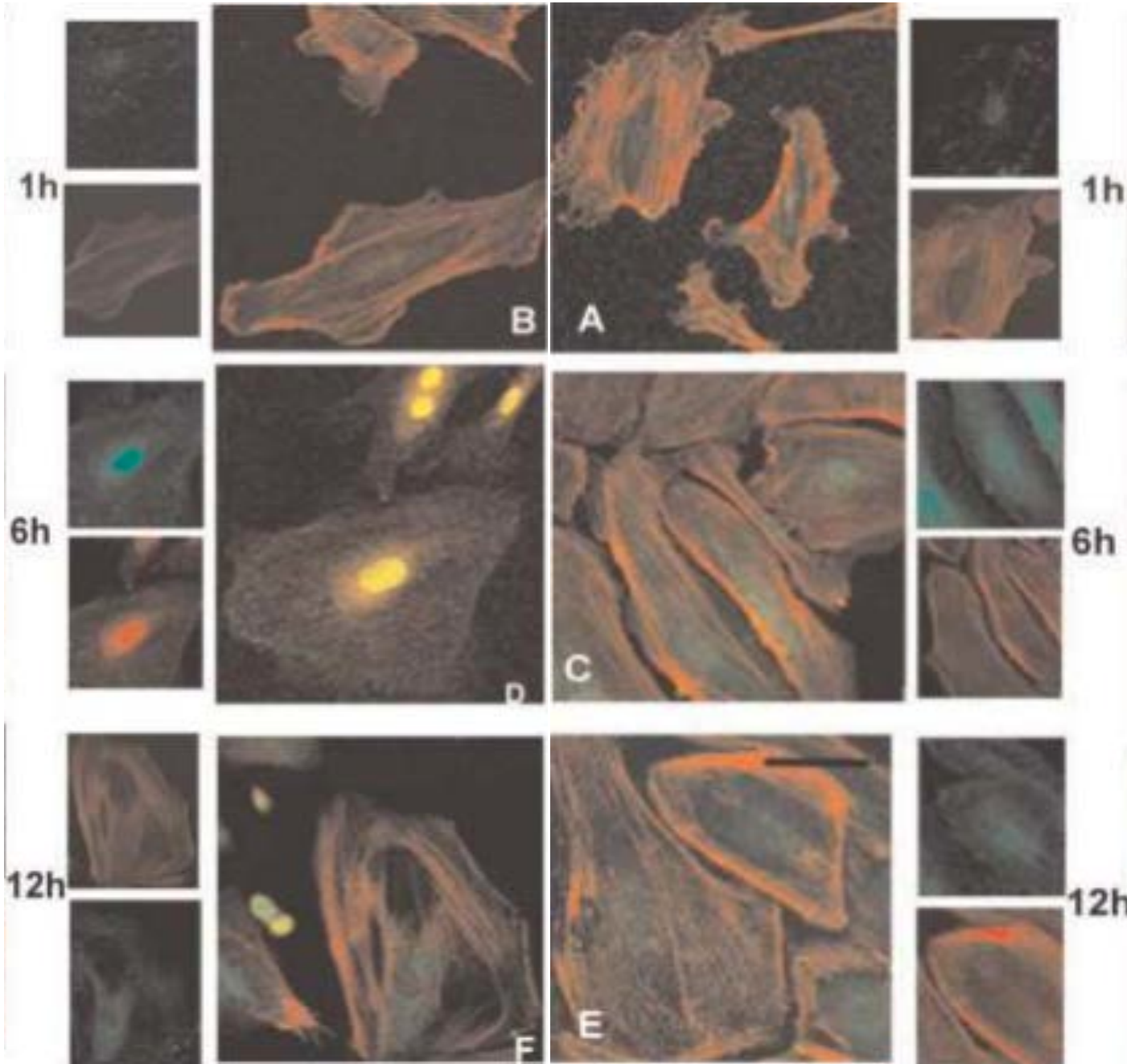


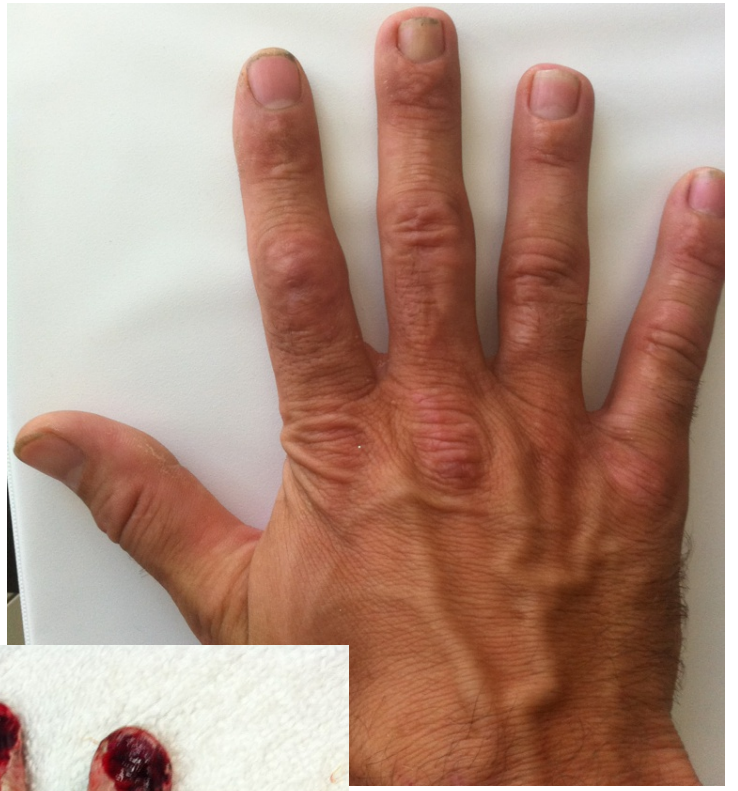


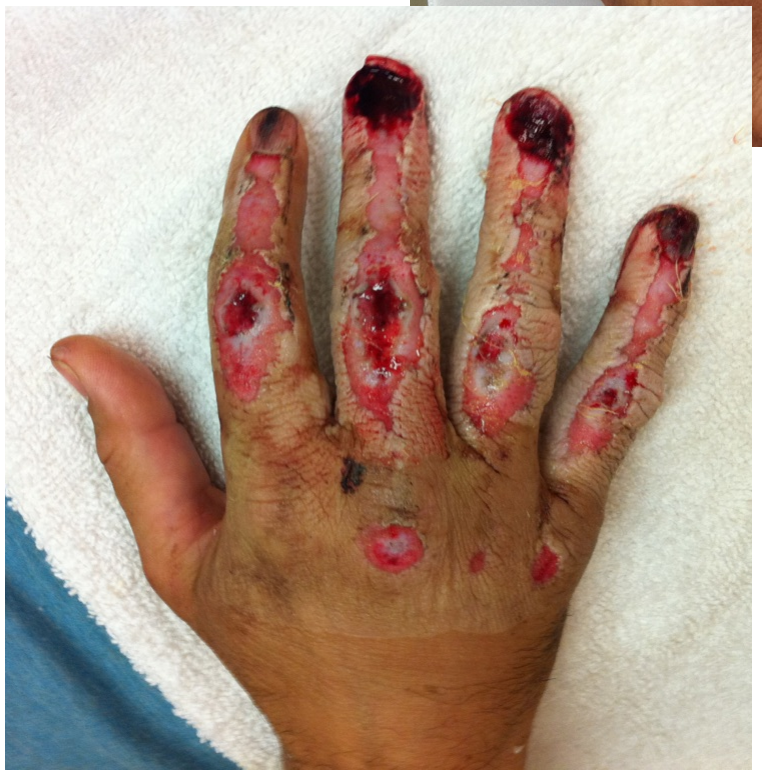


10 Treatments

UNTREATED TREATED





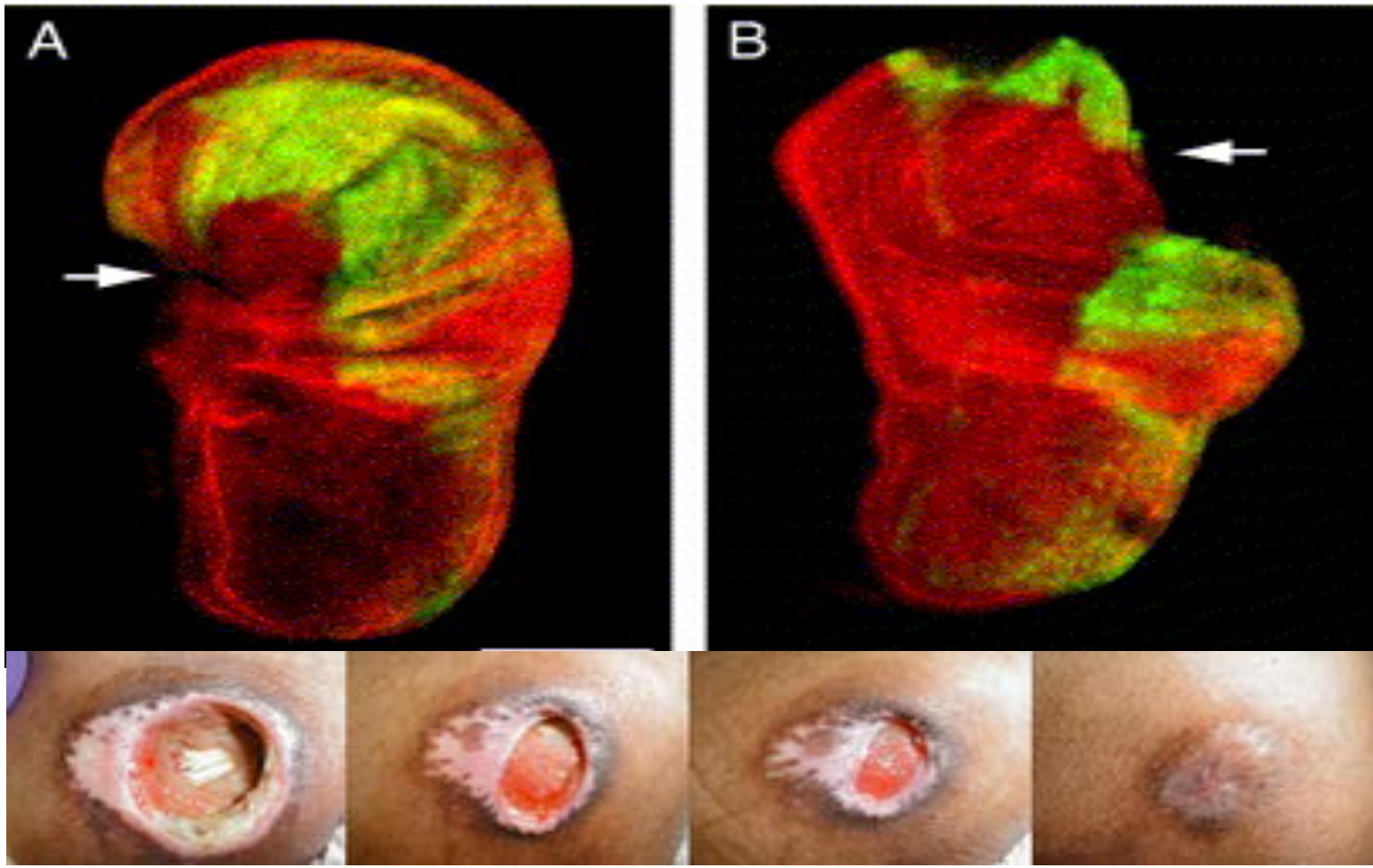


15 Treatments

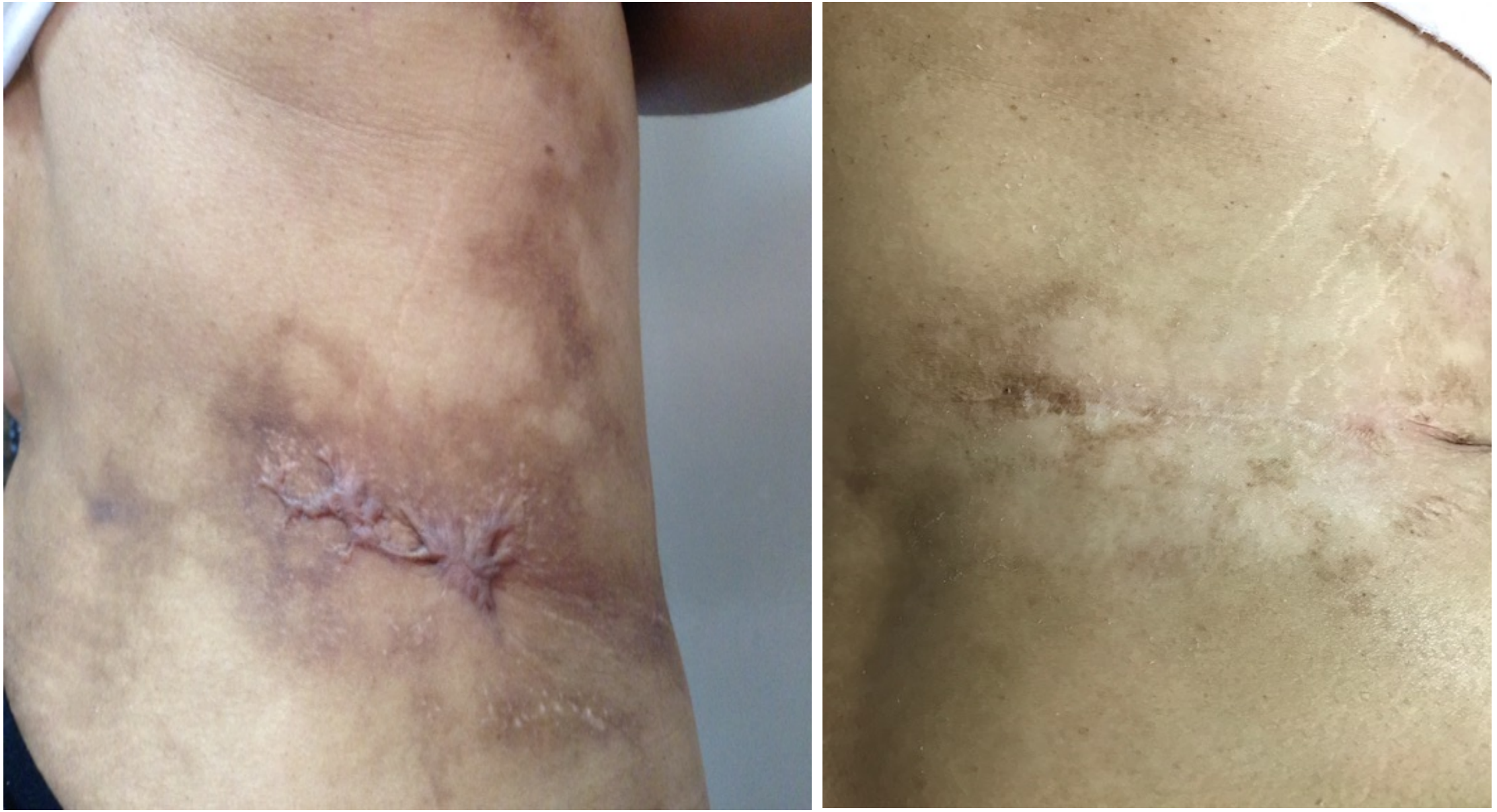
JNK Signaling Pathway Experimental Study

Signals that Up-regulate the JNK signaling pathway increase wound healing

Signals that down-regulate the JNK signaling pathway slow down wound healing

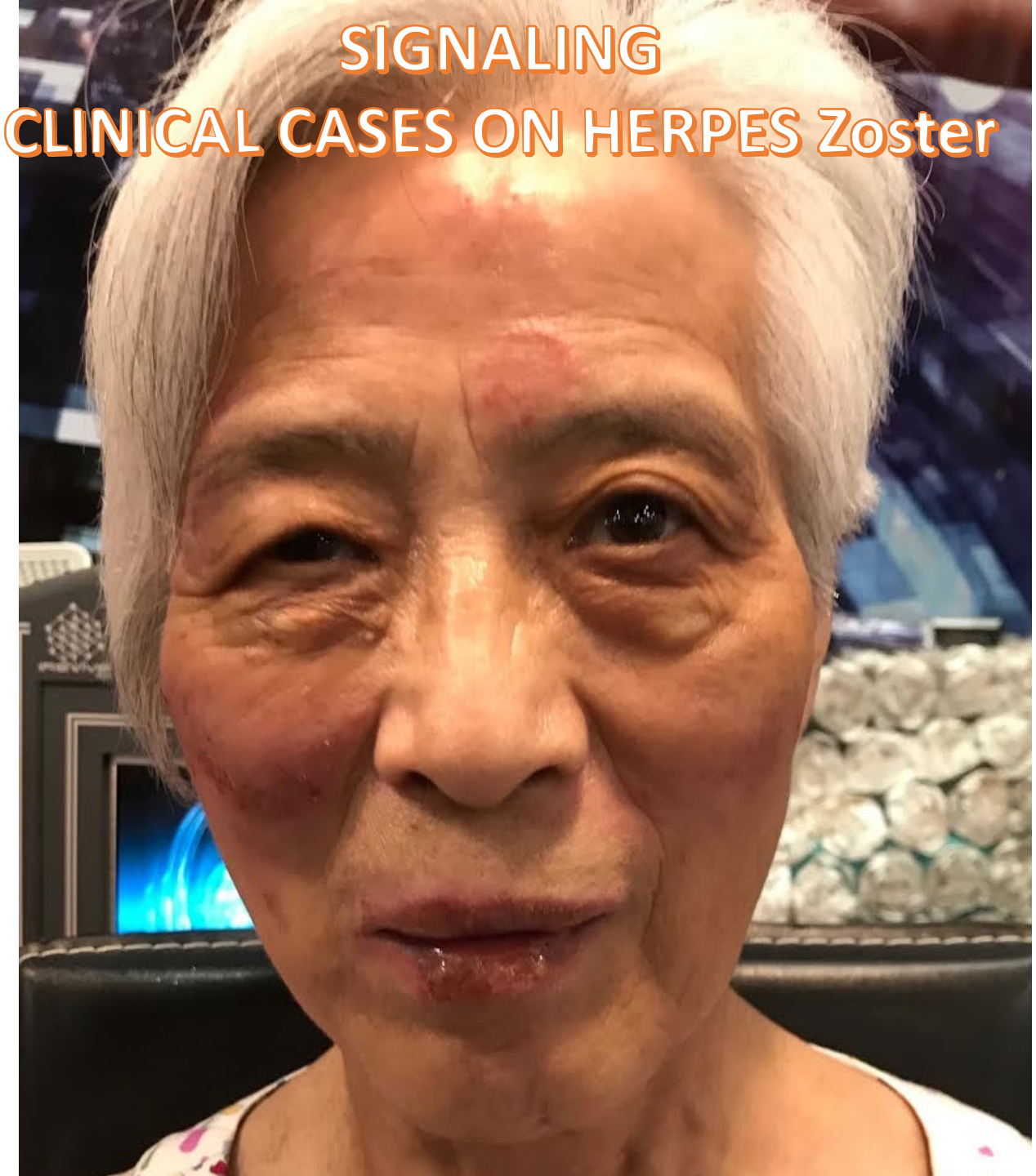


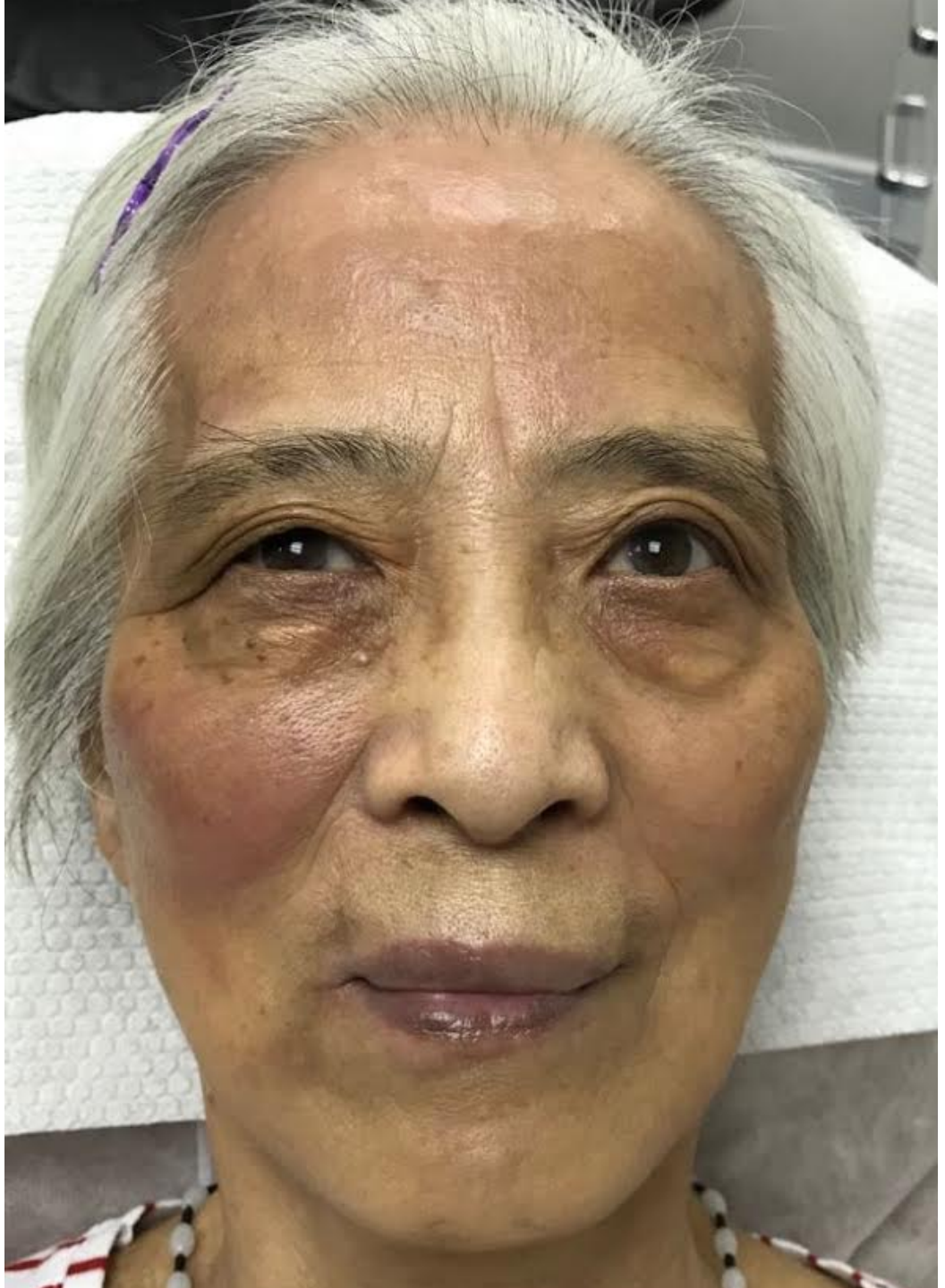
Statistical Analysis using the Fisher exact test showed that there was a significant difference ($p<0.05$) between controls and experimental subjects

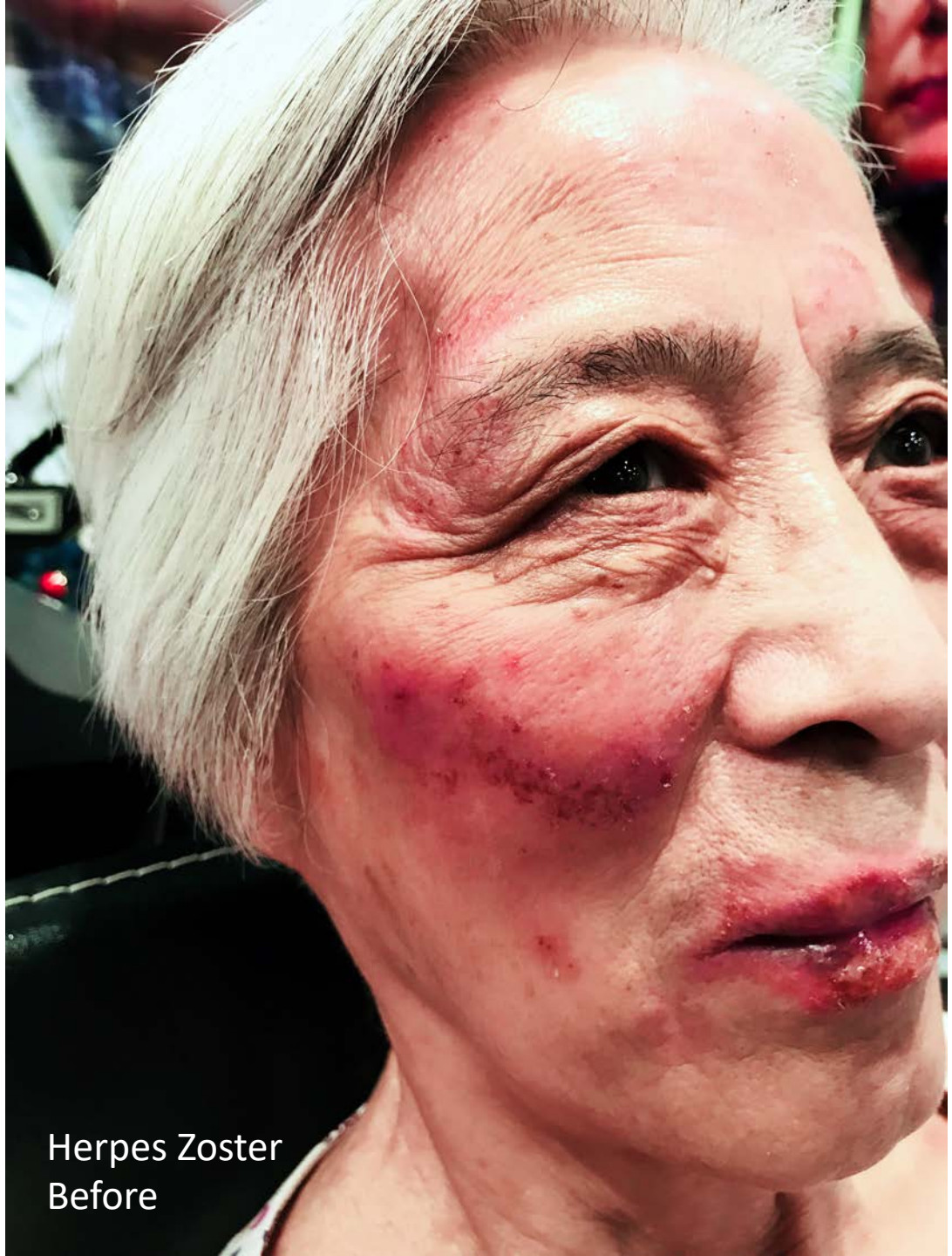


Liposuction scar two years old after 6 treatments; Nuris Lampe, M.D.

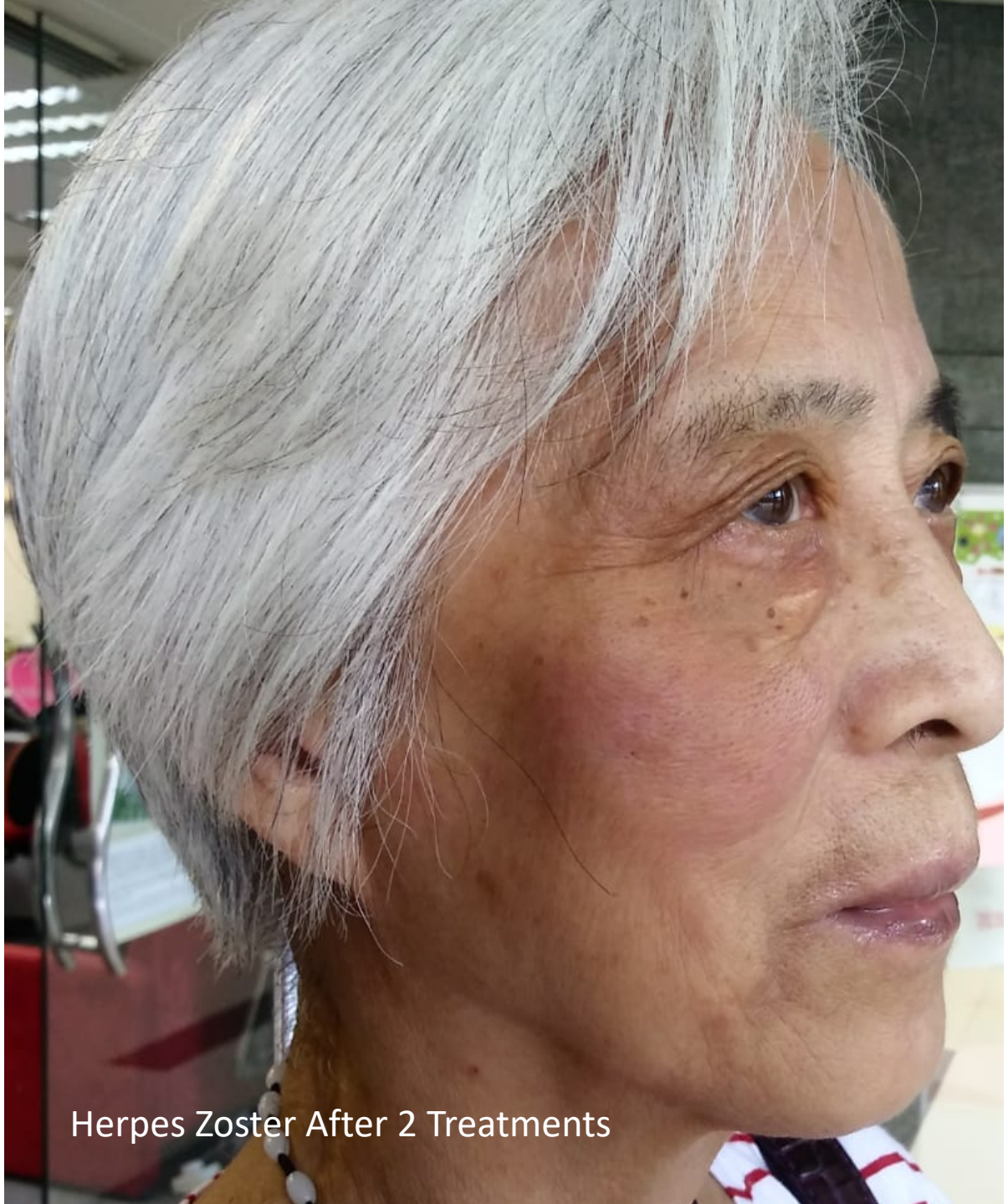
SIGNALING
CLINICAL CASES ON HERPES Zoster







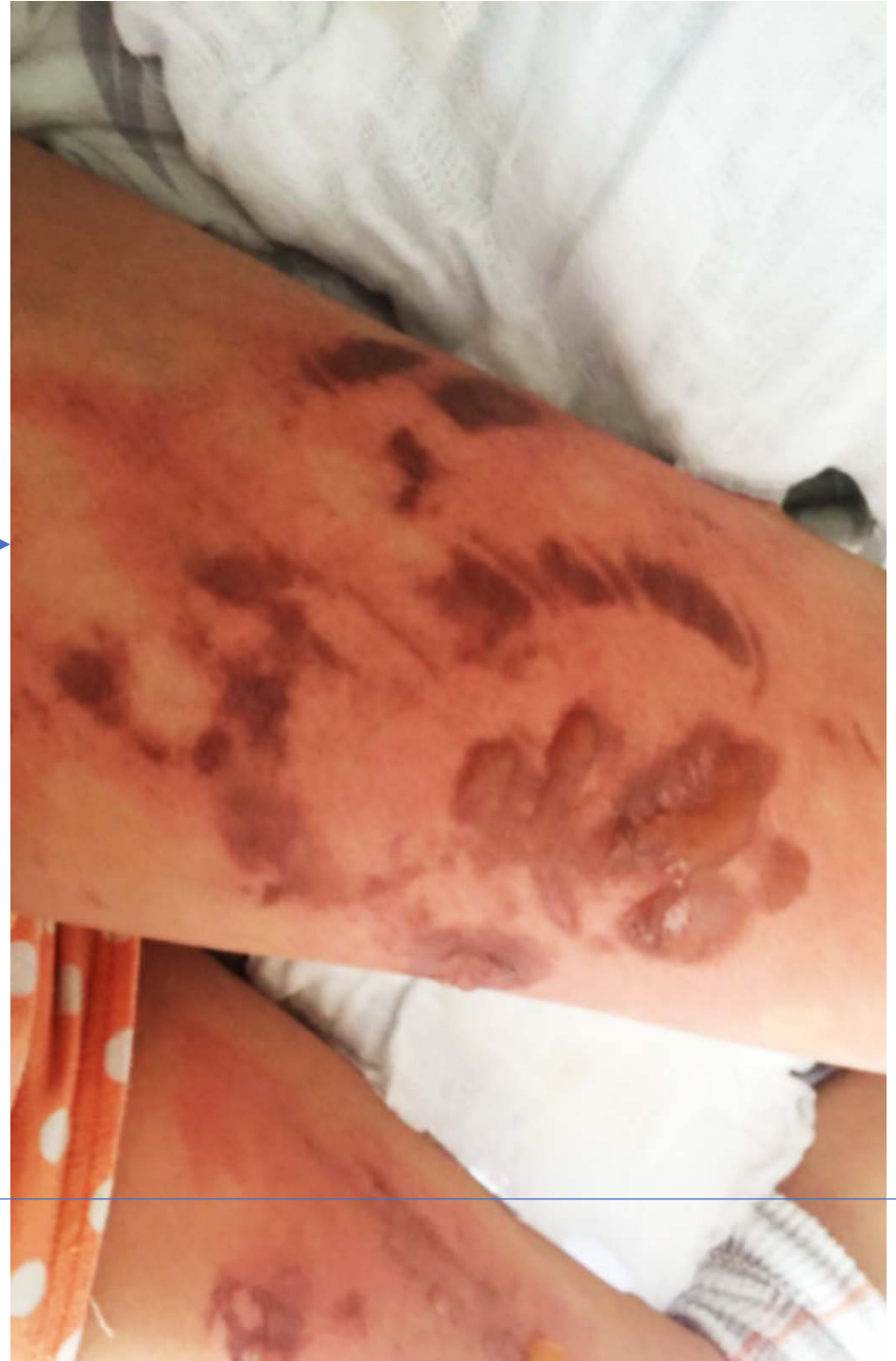
Herpes Zoster
Before



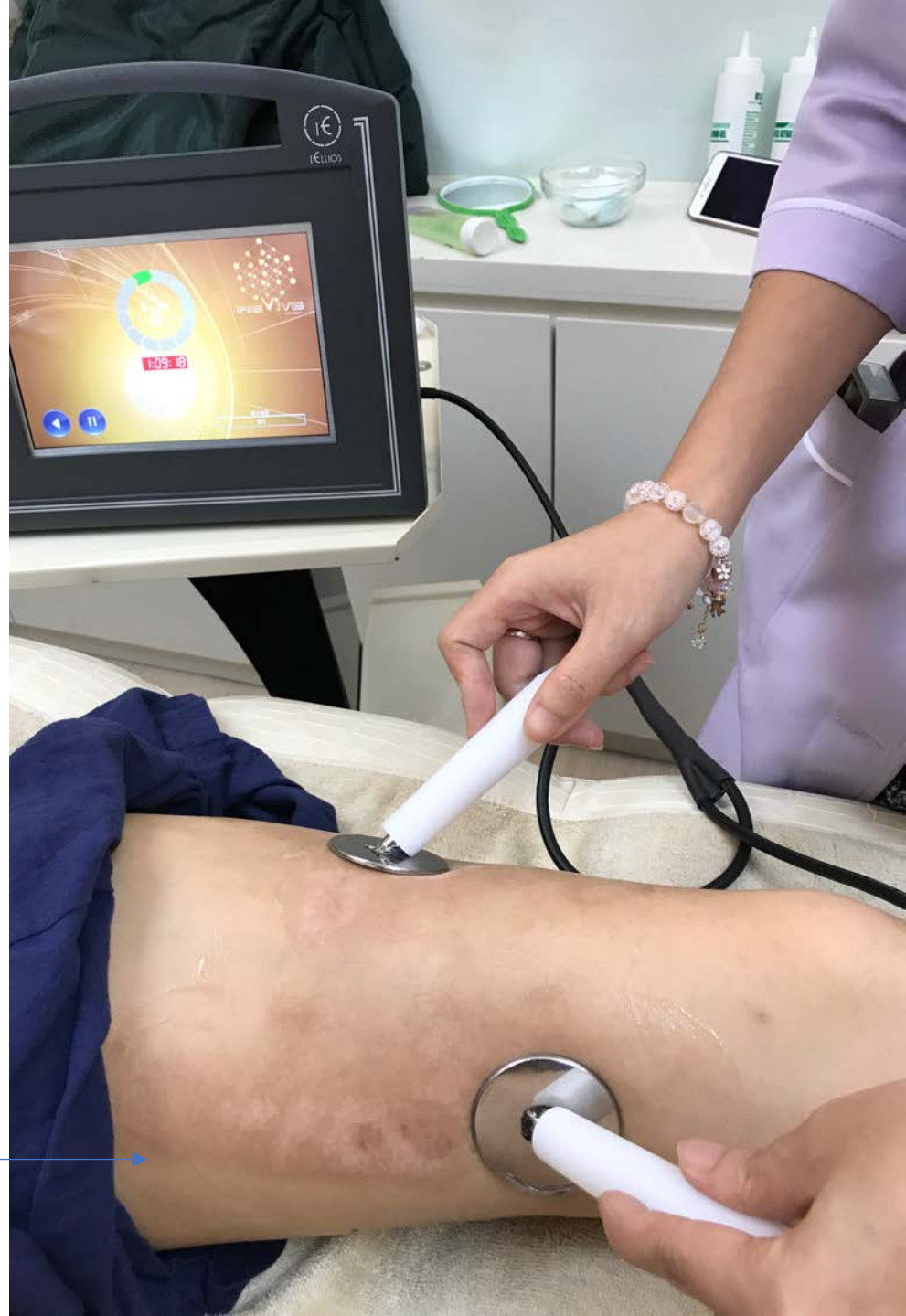
Herpes Zoster After 2 Treatments

CLINICAL CASES ON WOUNDS

IMMEDIATELY AFTER THE BURN

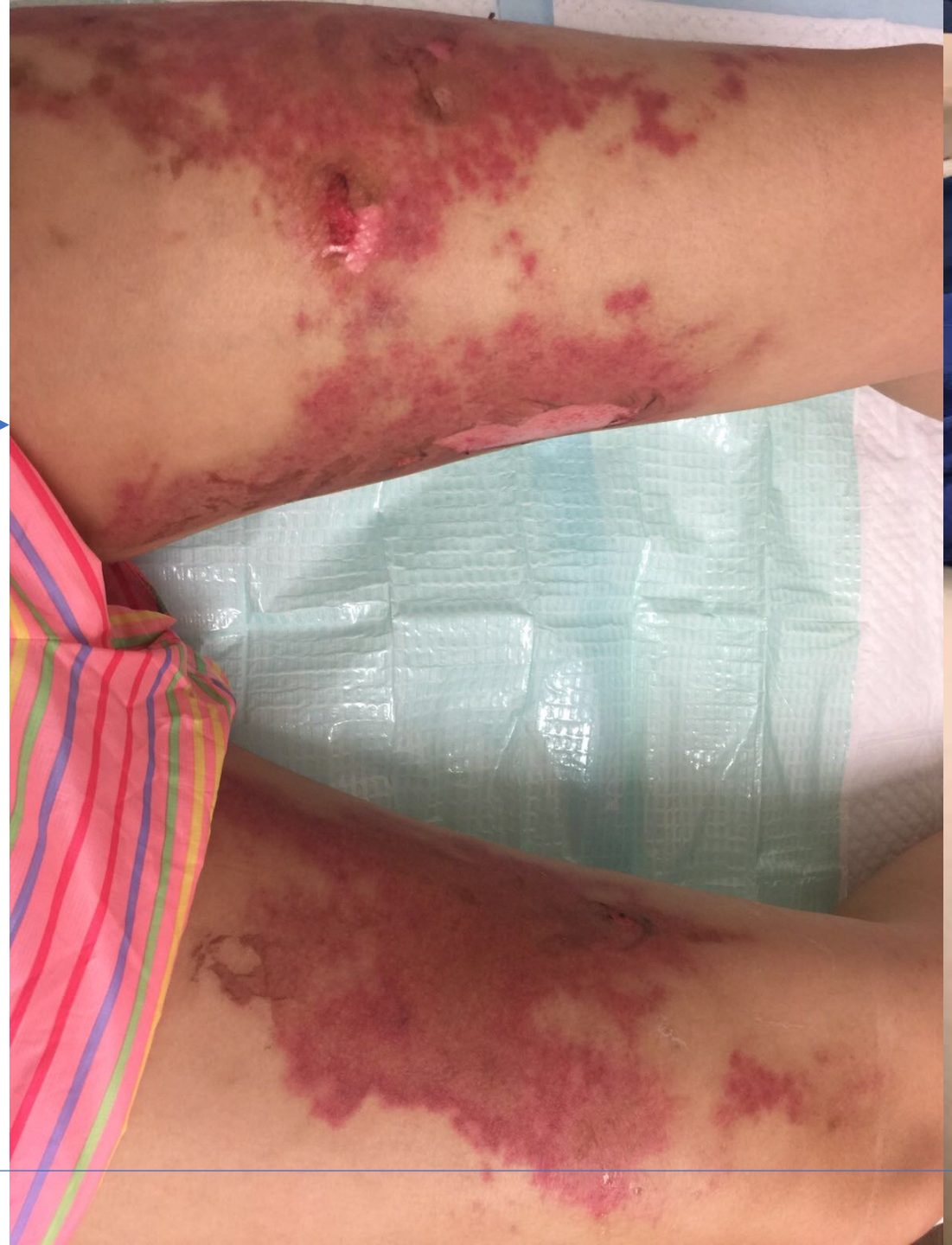


AFTER THE 3RD TREATMENT

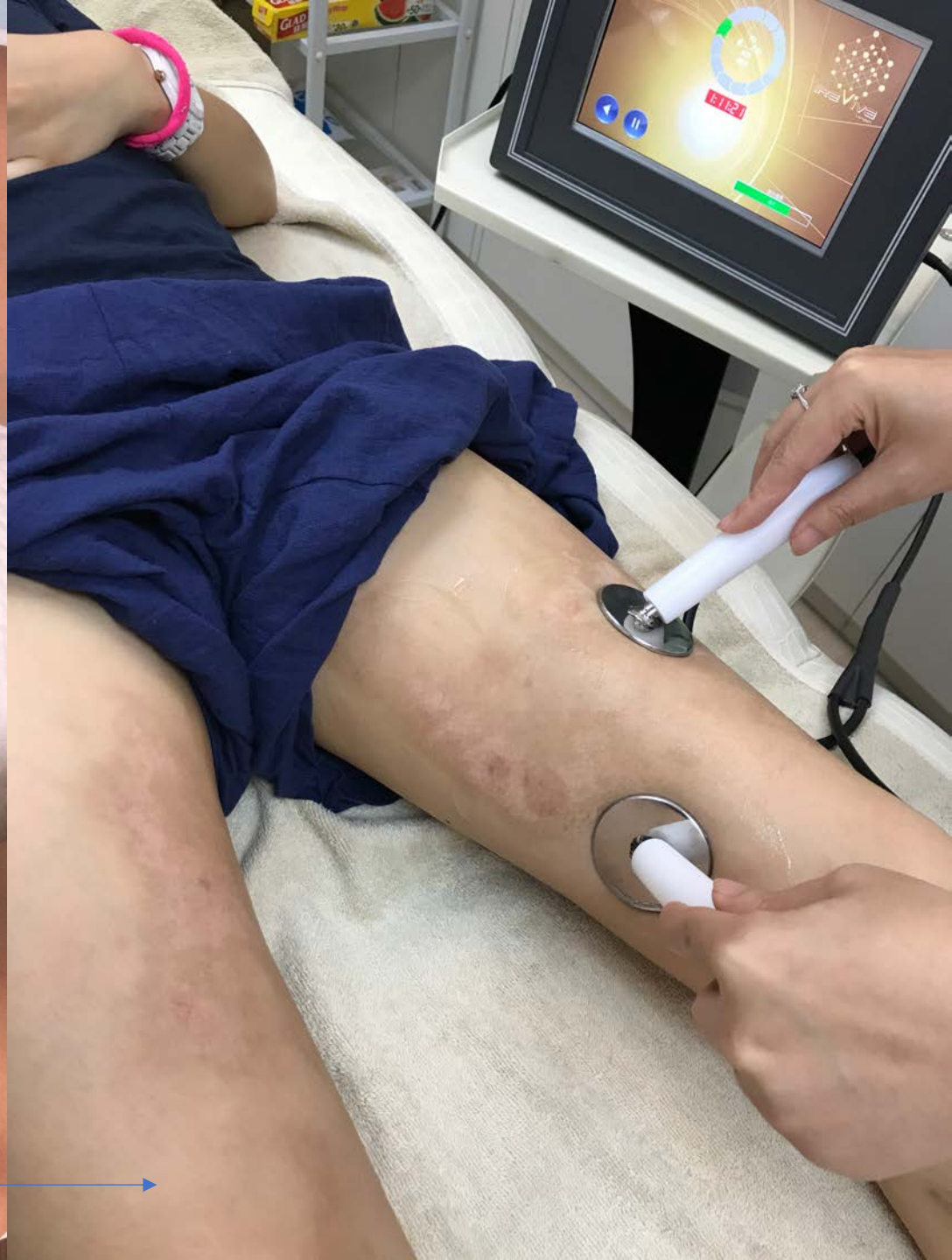


CLINICAL CASES ON WOUNDS

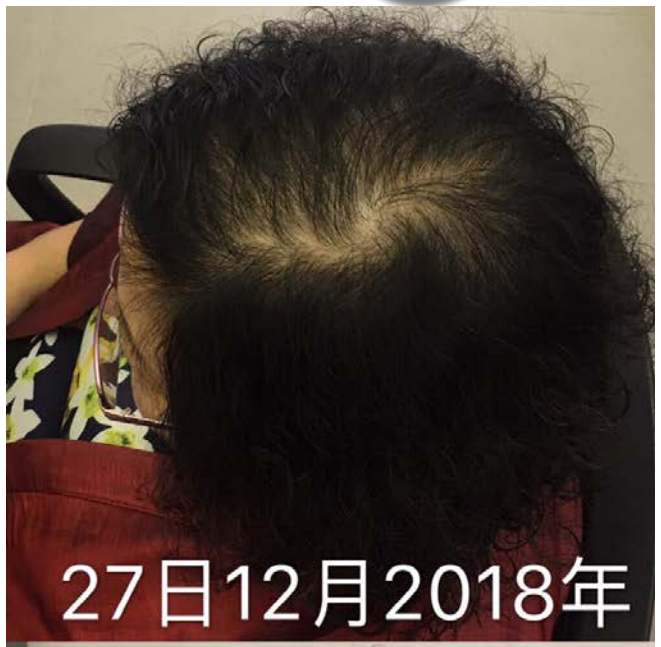
THE MORNING AFTER THE BURN

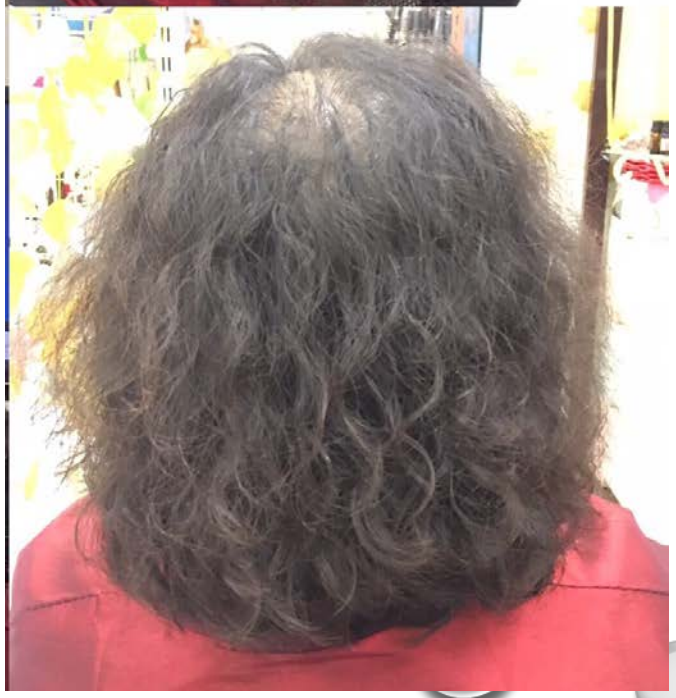


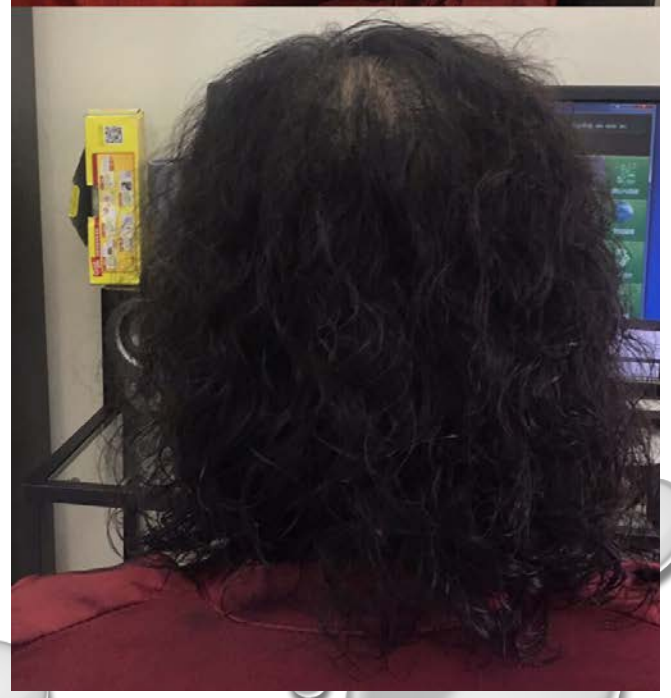
AFTER THE 4rth TREATMENT

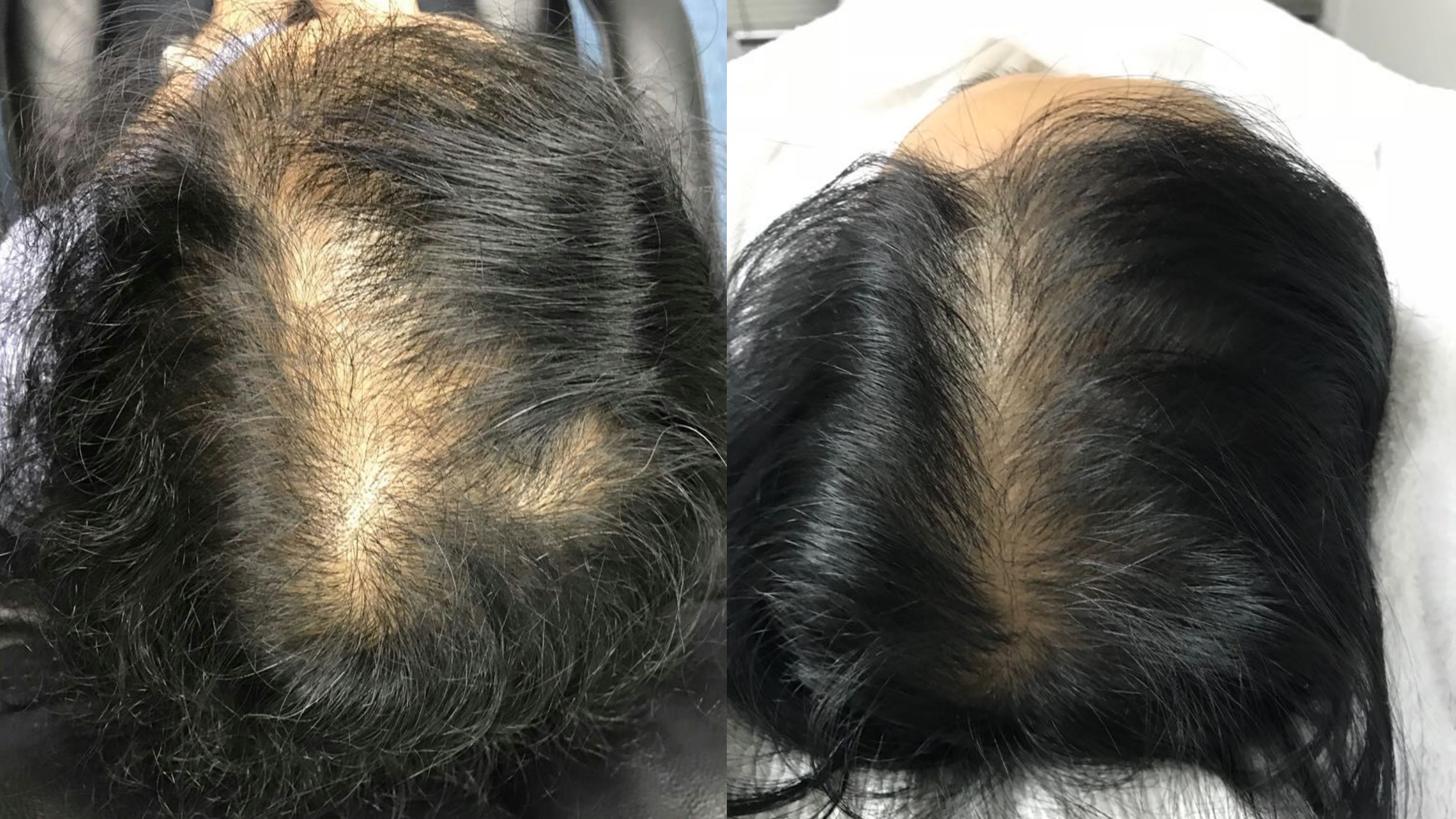


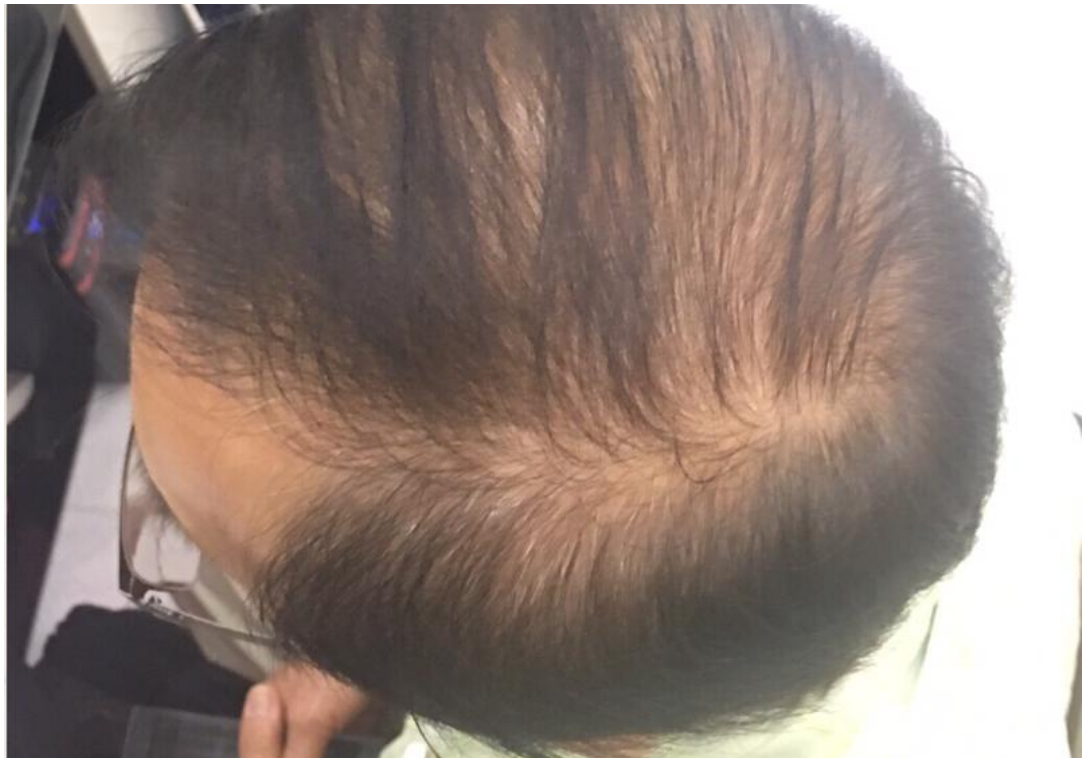
HAIR GROWTH

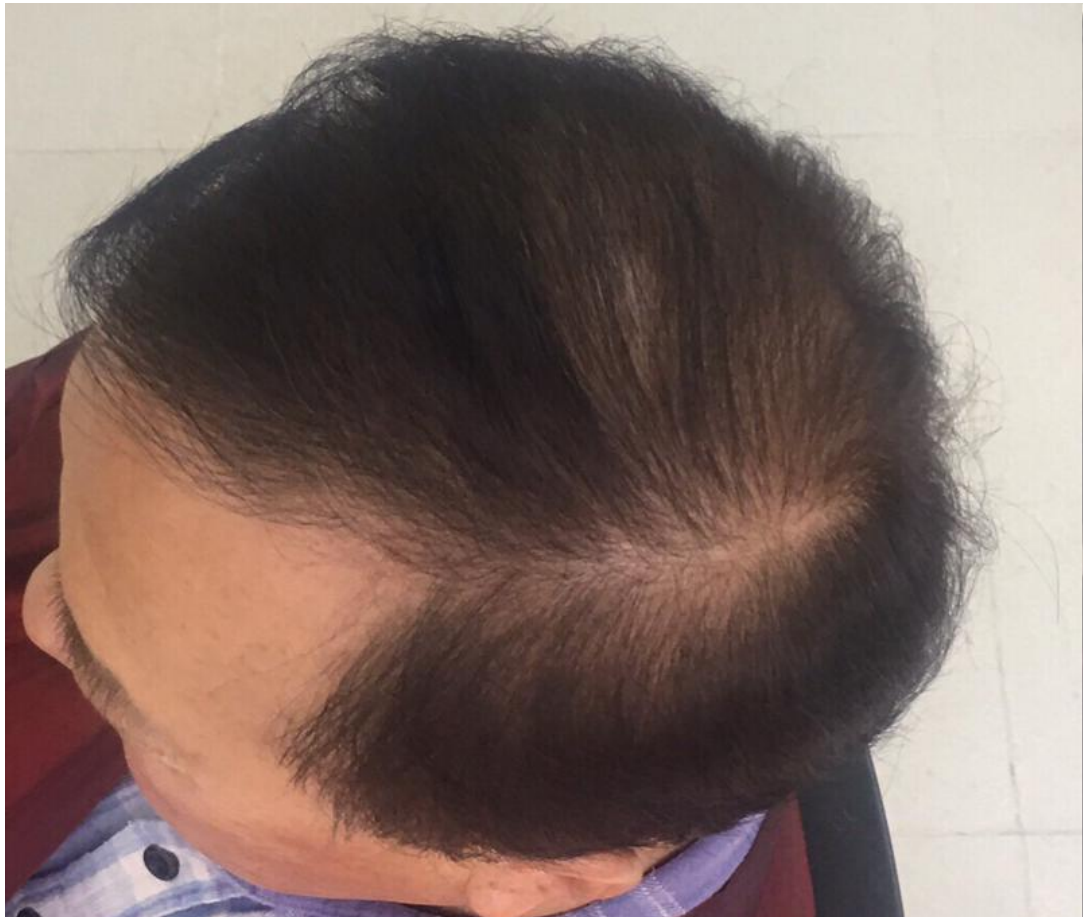




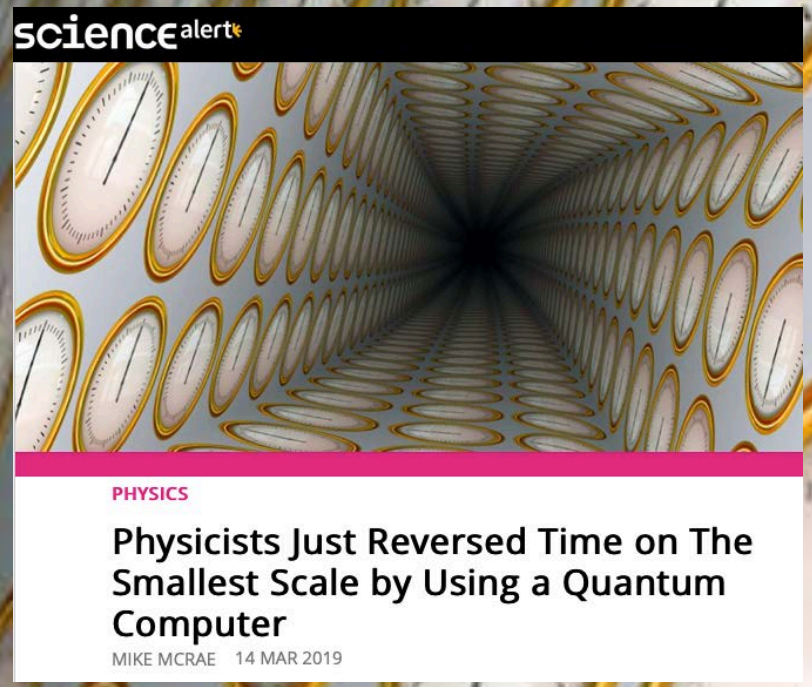


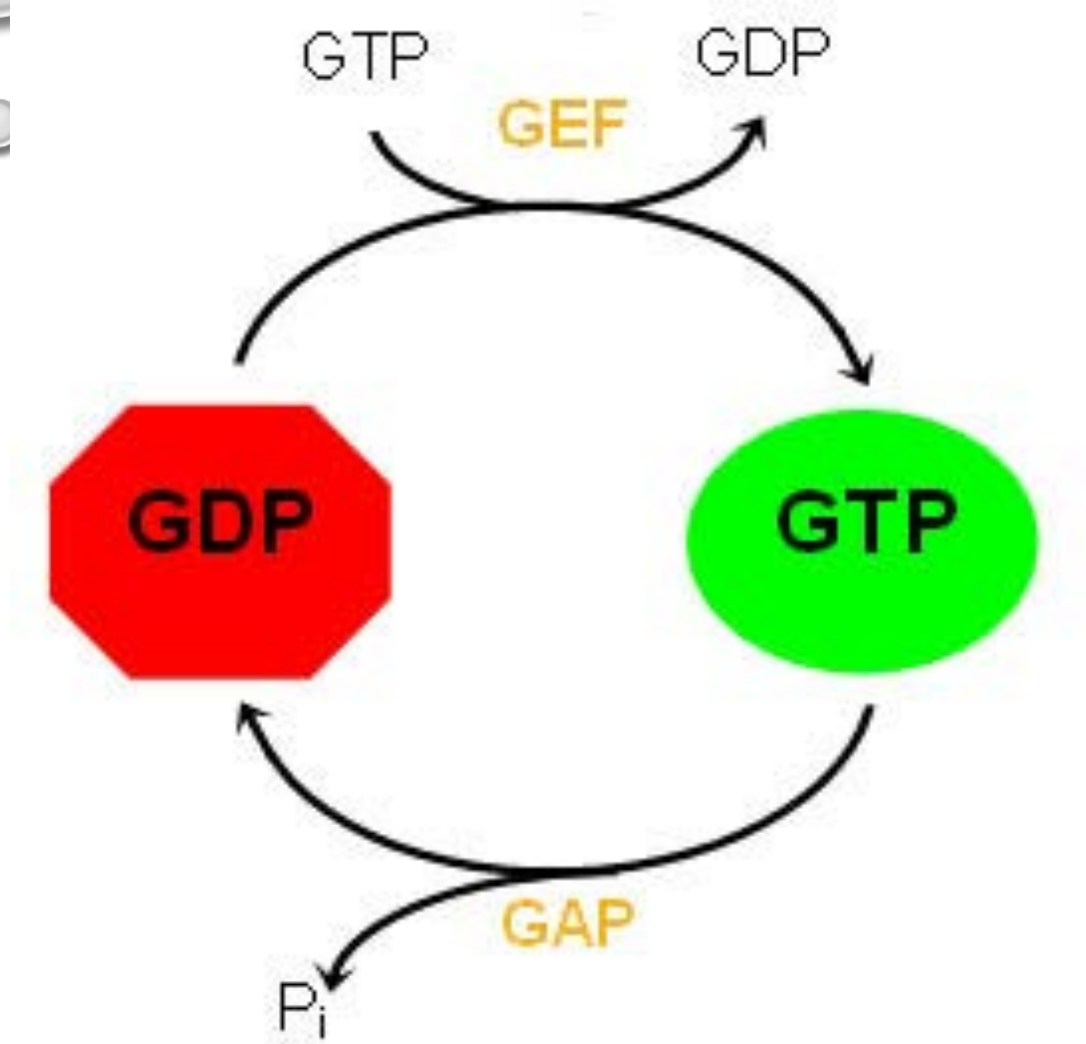


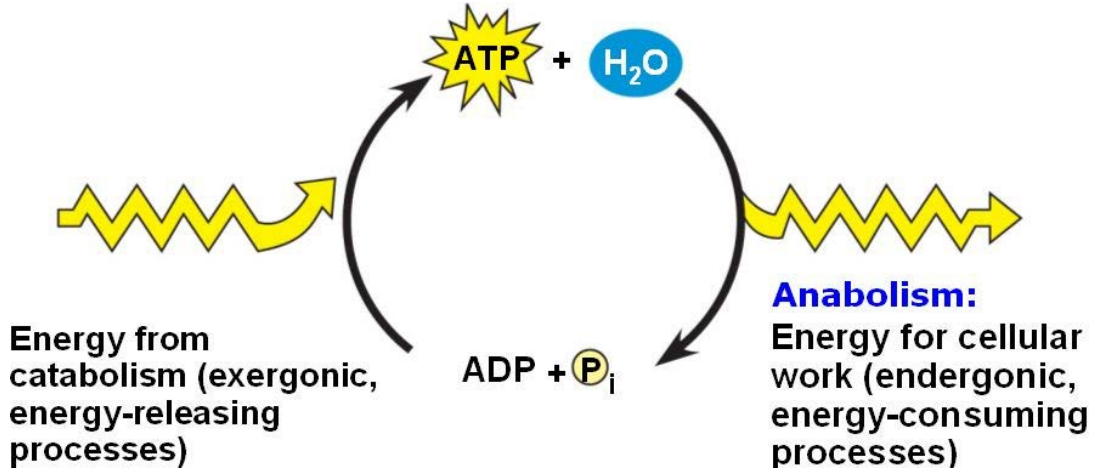




Time Reversal is only
possible
on The Smallest Scale

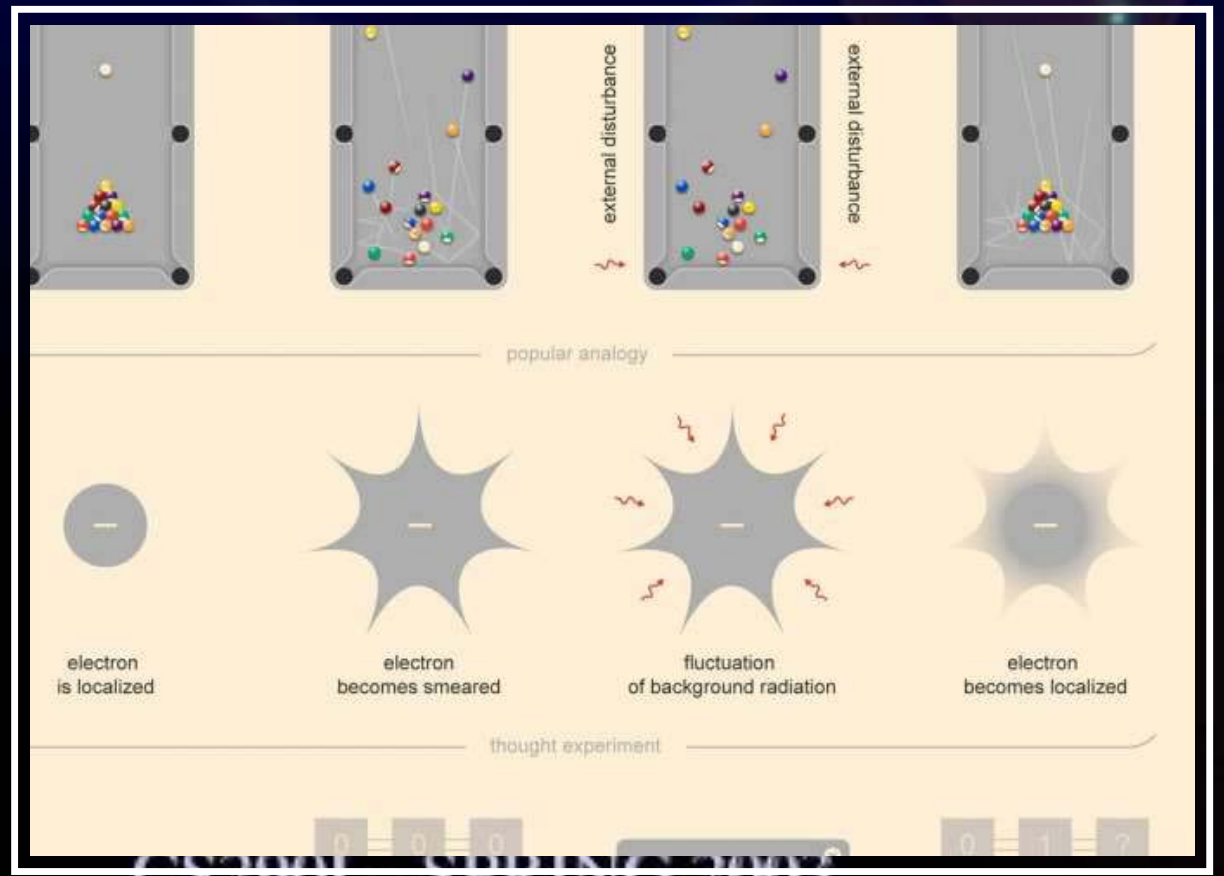


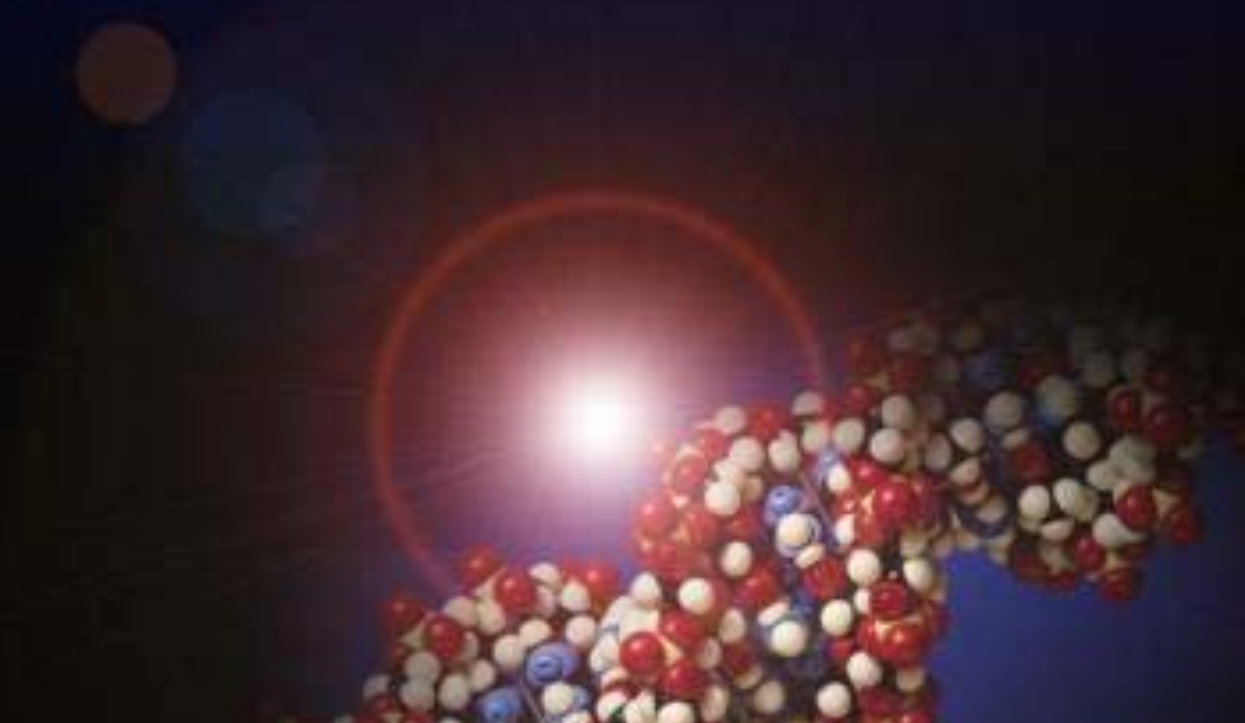

GTP
GDP
GEF
GDP
GTP
GAP
Pi


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

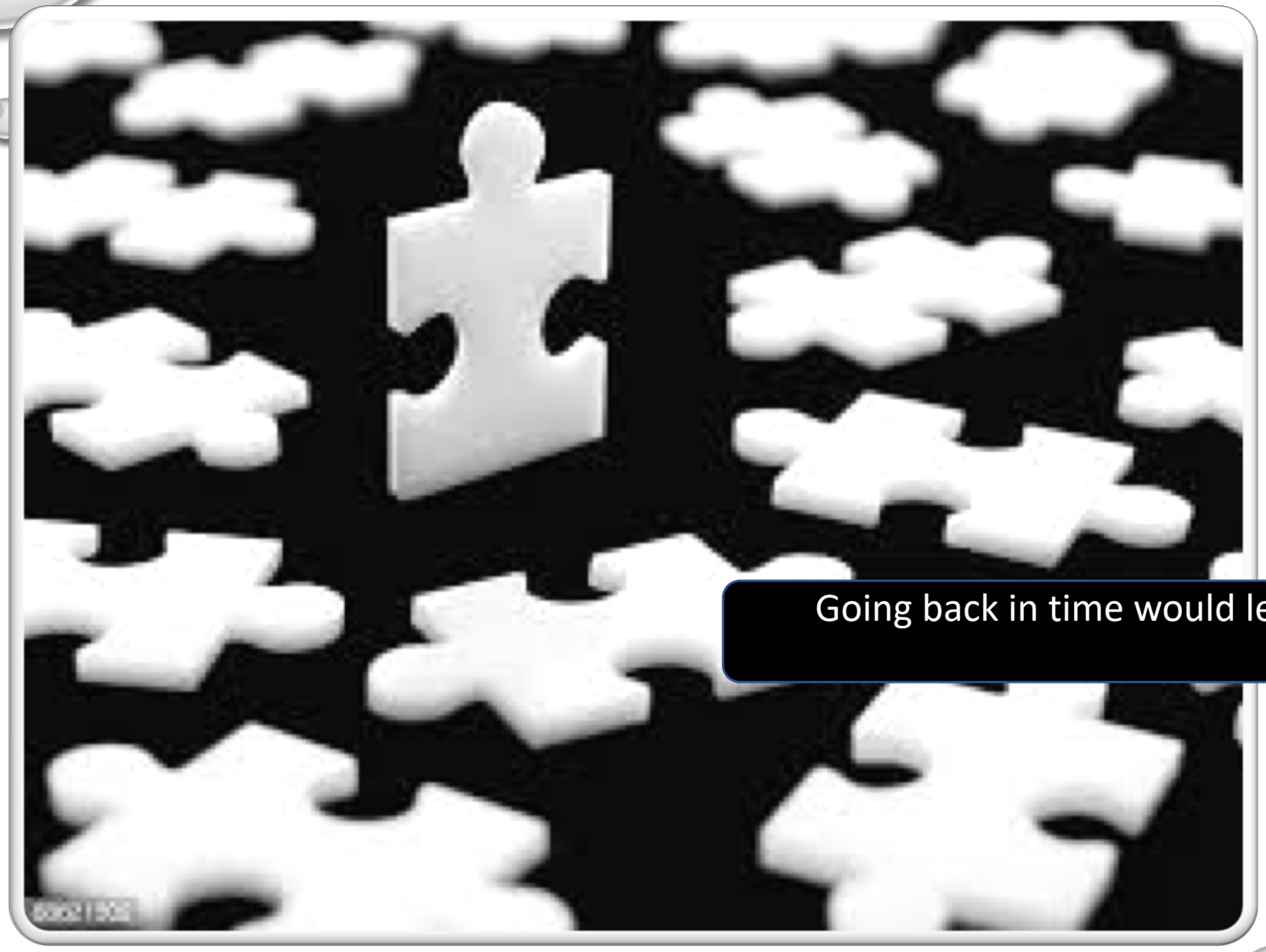
Genome Rearrangement

SORTING BY REVERSALS





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



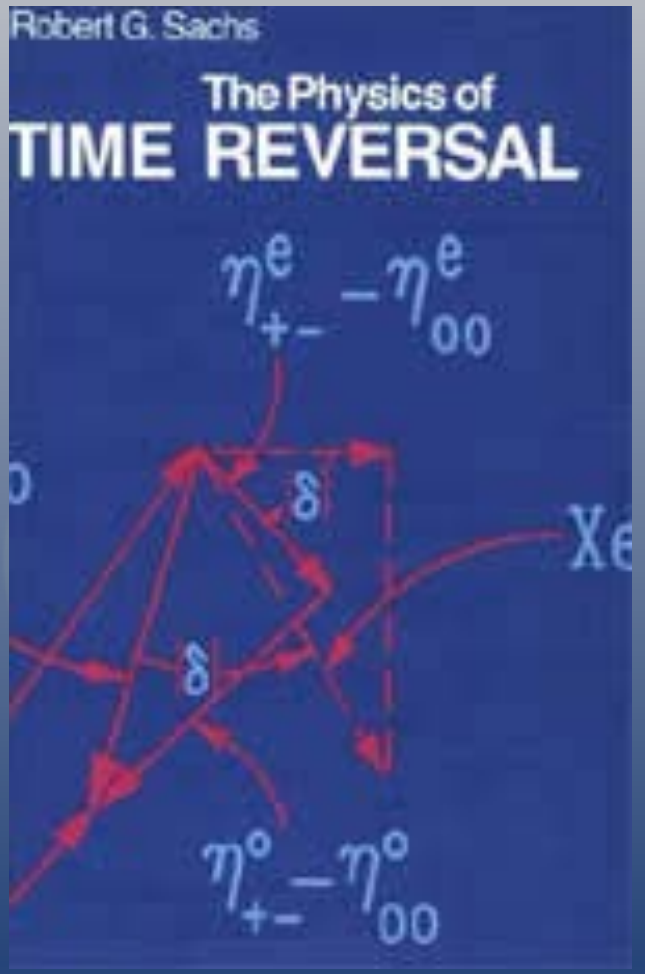
- THE GREATER THE AMOUNT OF COMPLEXITY THE GREATER THE DIFFICULTY OF GOING BACK IN TIME

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

CONCLUSION

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

- PERSON. = gestalt – no time reversal
- ORGANS (EG. SKIN which is the largest organ in our bodies) = gestalt – unlikely time reversal
- Layers of skin = gestalt – unlikely time reversal



WE CAN ONLY FOCUS ON MOLECULAR MECHANISMS (QUANTUM PHYSICS) THAT ARE CAPABLE OF REVERSING TIME RUTINELY

INTERNATIONAL ONGOING RESEARCH BY:

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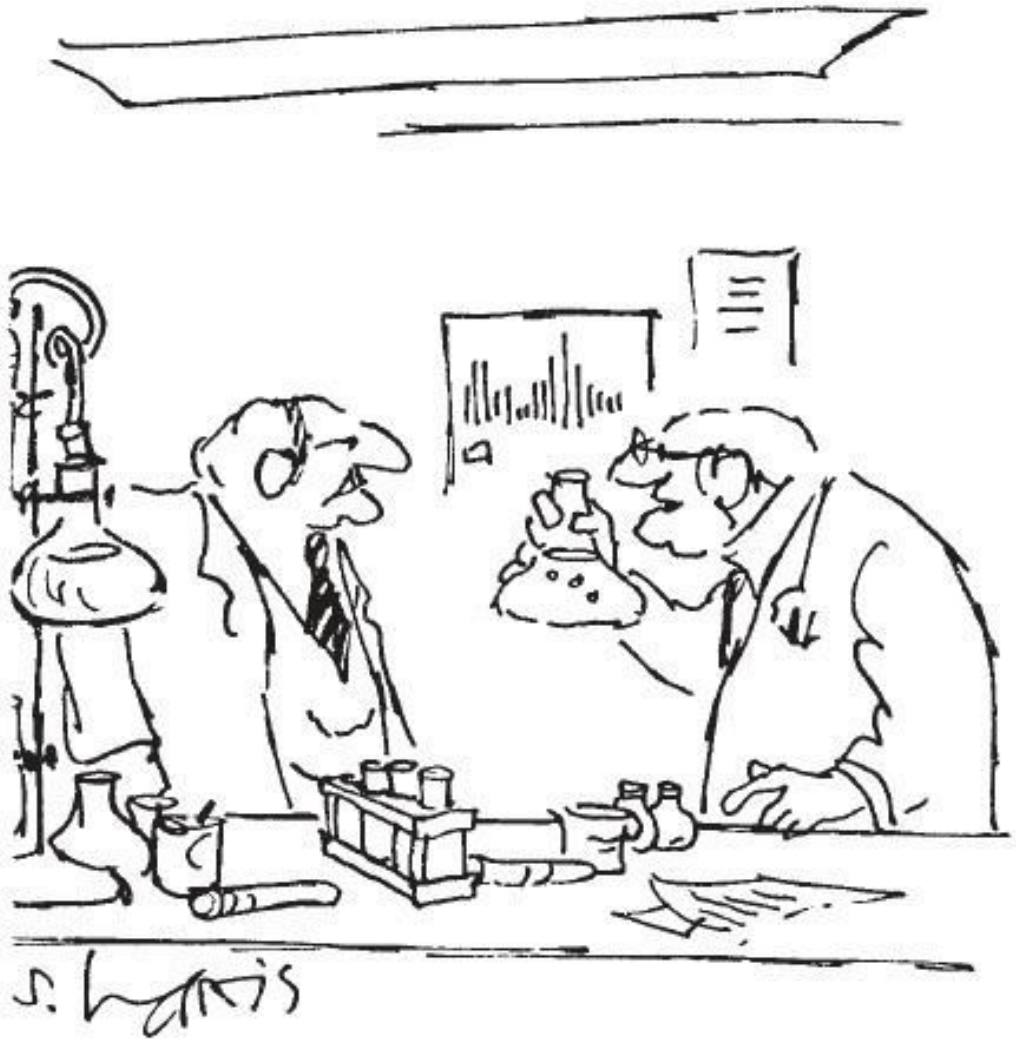

"IT MAY VERY WELL BRING ABOUT IMMORTALITY, BUT IT WILL TAKE FOREVER TO TEST IT."

thank you