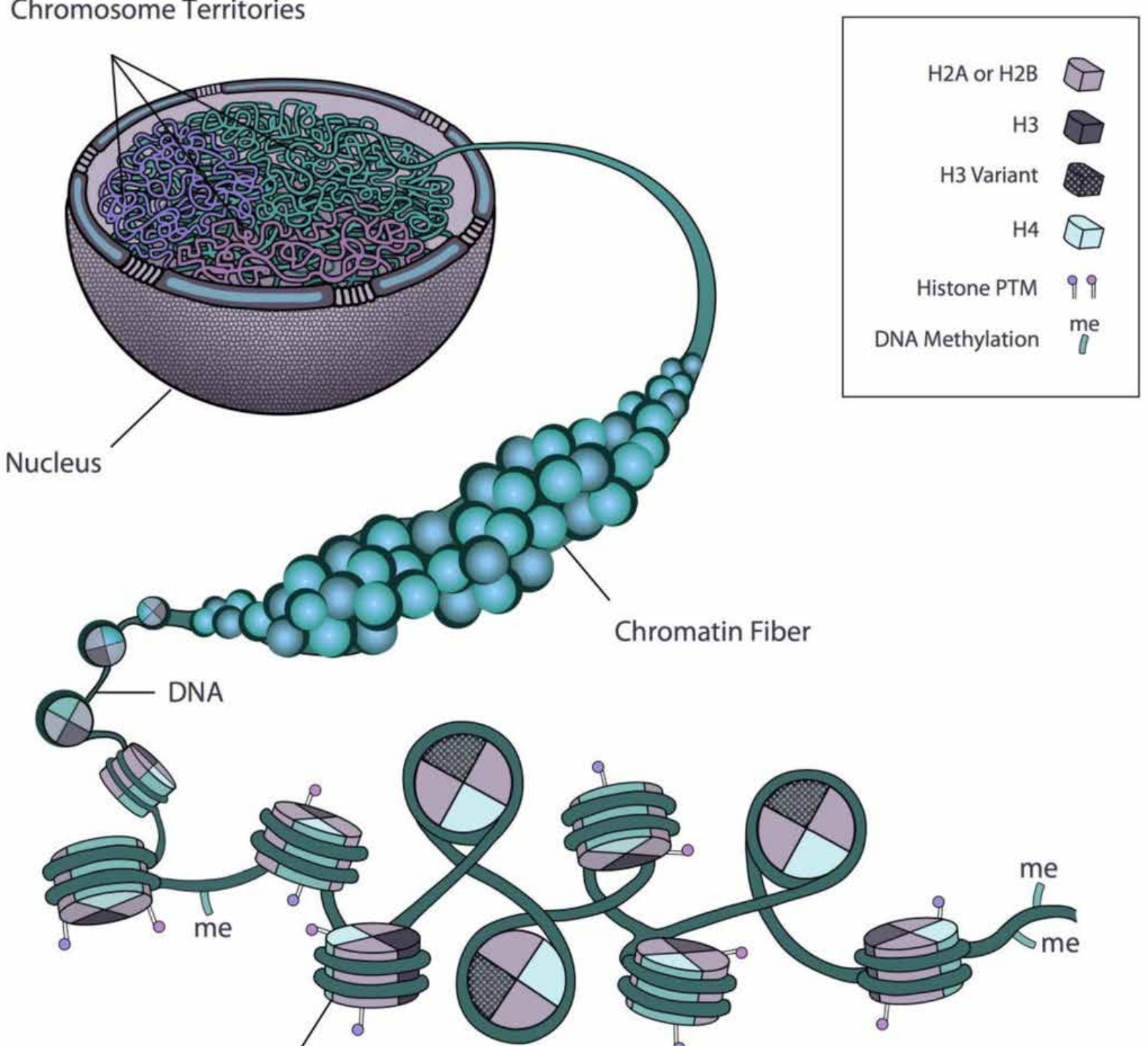
WHY NOBEL WINNING STUDIES FOCUS ON MOLECULAR MECHANISMS?

Dr Xanya Sofra, Ph.D, Ph.D

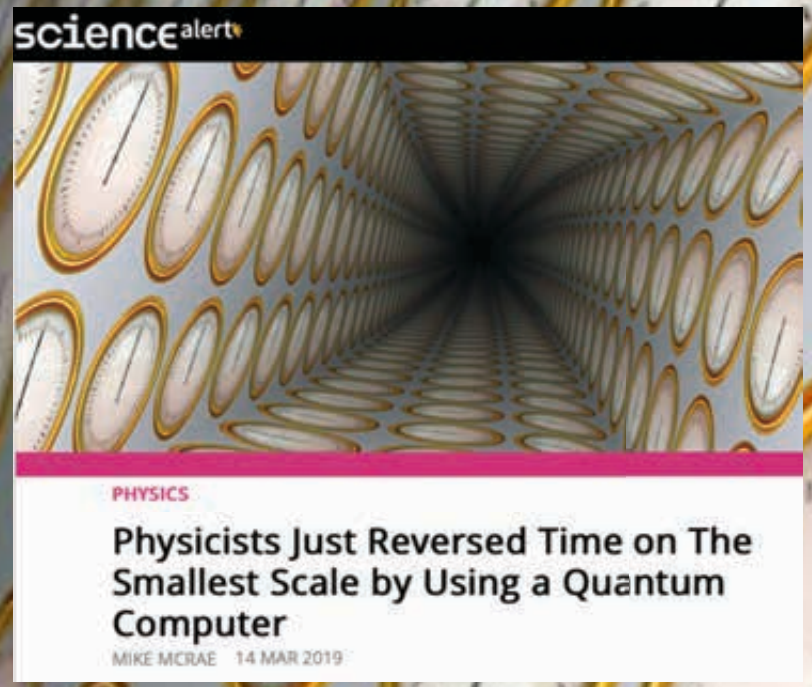
Because:

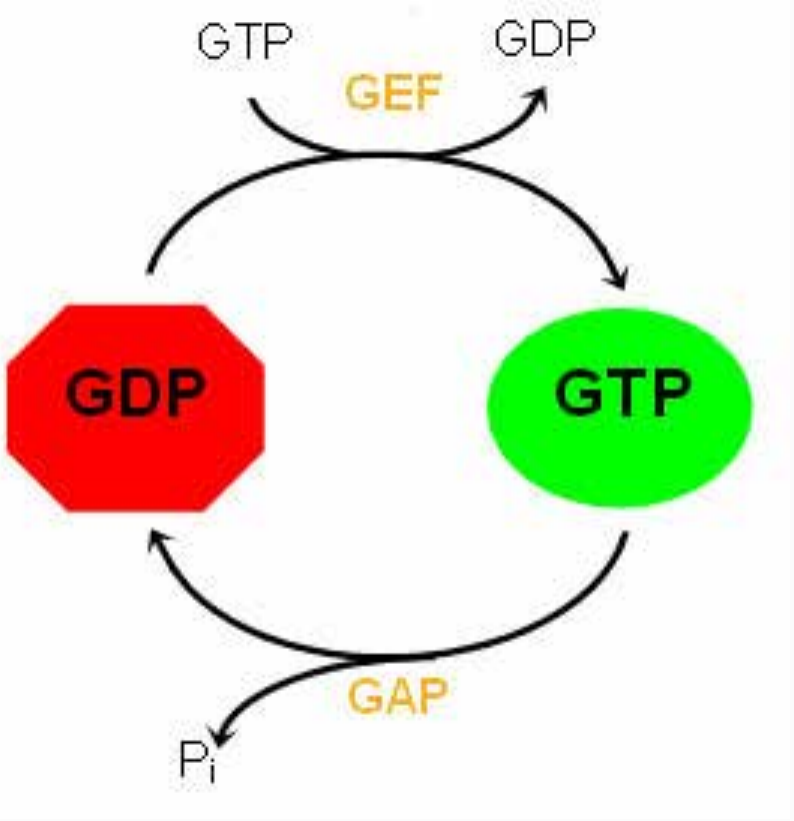
1. THE SMALLER THE MECHANISM
THE EASIER & FASTER THE REPAIR

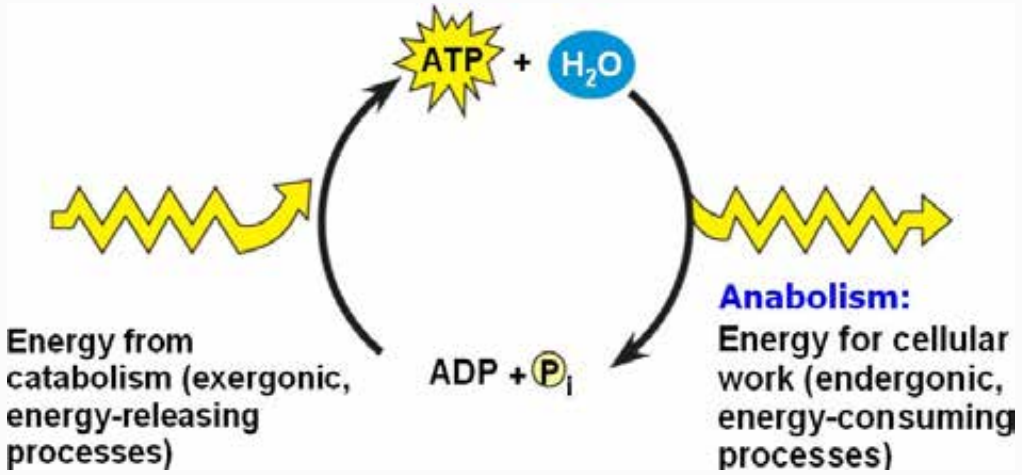
2. Time Reversal (GOING FROM PART TO THE WHOLE and BACK) is ROUTINELY ADOPTED by molecular mechanisms



Time Reversal is only
possible
on The Smallest Scale

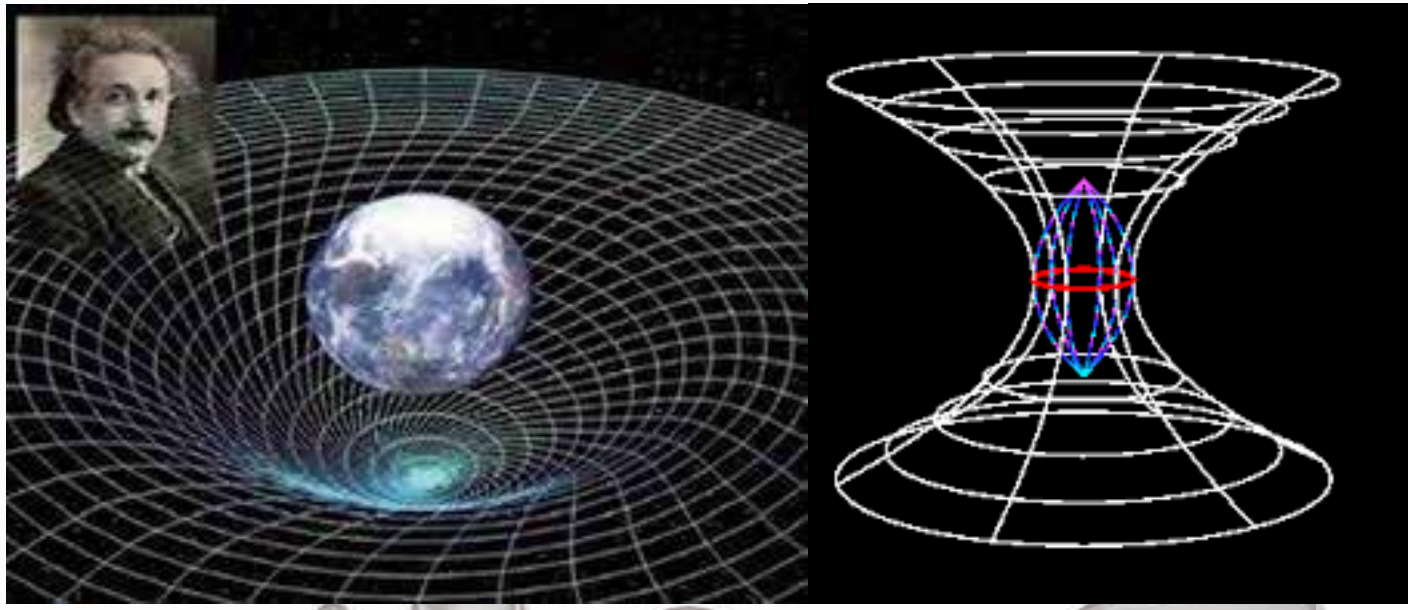




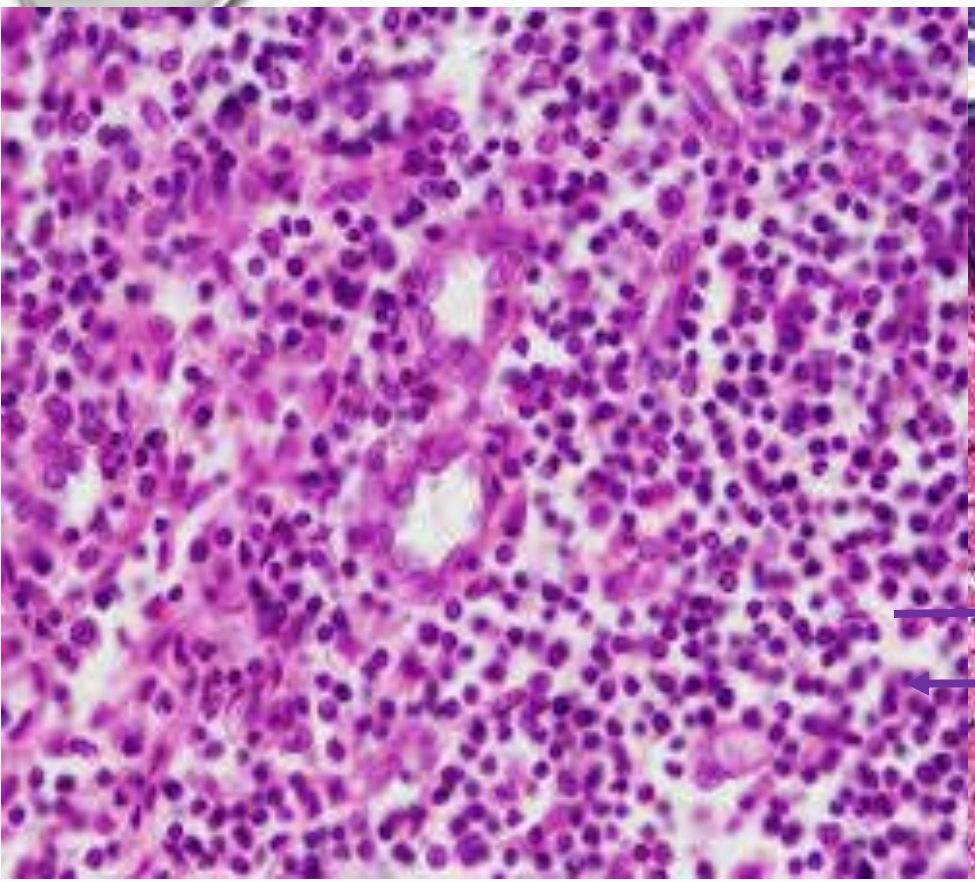


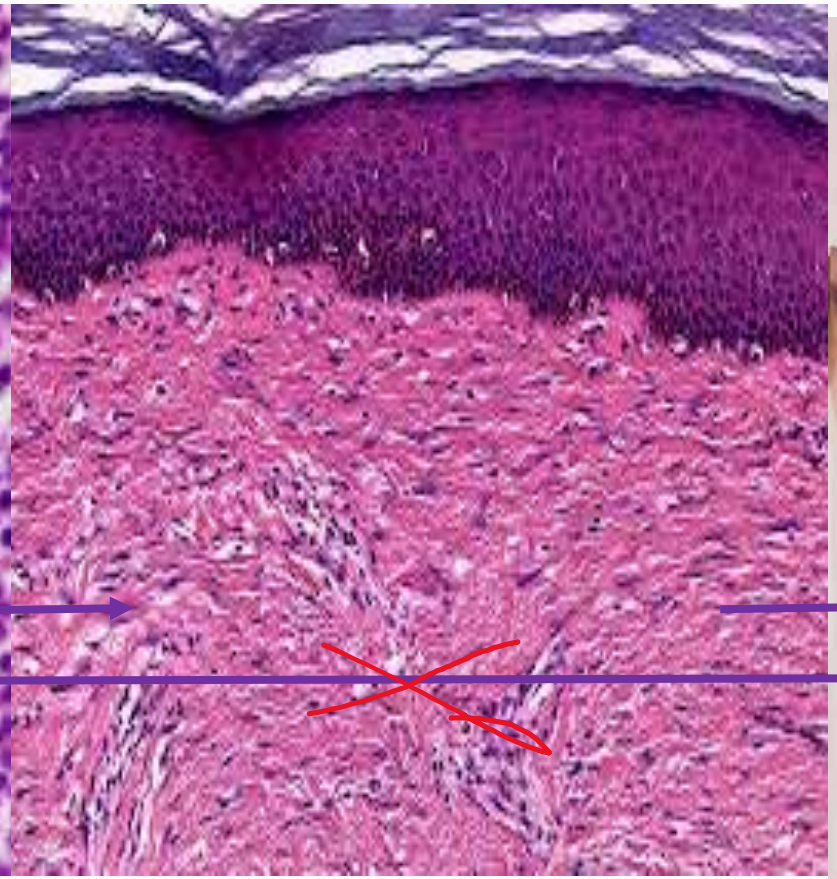
MECHANISMS OF THE SMALLEST SCALE
GO FORWARD AND BACKWARDS ON TIME ROUTINELY

The way very large objects like the earth sun go forward
and backward in the space / time fabric Einstein's fourth Dimension



WHY DO WE CONTINUE TO AGE AND CANNOT GO BACK IN TIME?



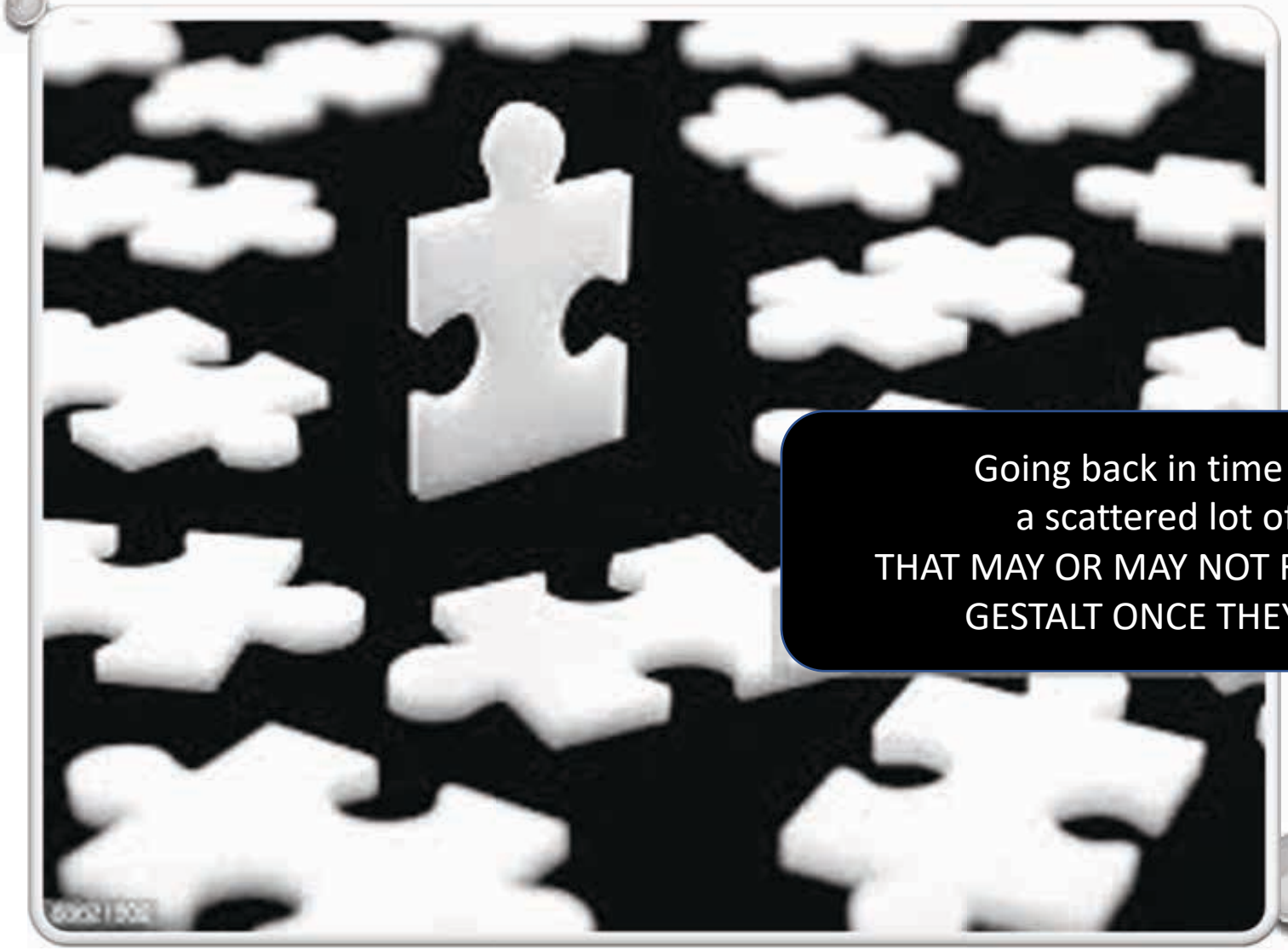


WHY DOES THE ARROW OF TIME ONLY GO ONE WAY? FROM YOUTH TO AGED?

BECAUSE with INCREASING COMPLEXITY THE PARTS MERGE INTO A NEW ENTITY
A **GESTALT** THAT IS MORE / DIFFERENT THAN THE SUM OF ITS PARTS

THE CHALLENGE IS NOT REVERSING TIME IN ALL OUR CELLS -- THAT MAY BE POSSIBLE

THE CHALLENGE IS RECOMPOSING OUR CELLS INTO THE EXACT SAME ENTITY THAT WE WERE AT AN EARLIER



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 CELLS
THAT MAY OR MAY NOT FORM THE SAME ENTITY /
GESTALT ONCE THEY ARE RECOMPOSED

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

TWO PRIMARY ANTIAGING THEORIES:

SCHOLASTIC THEORIES:

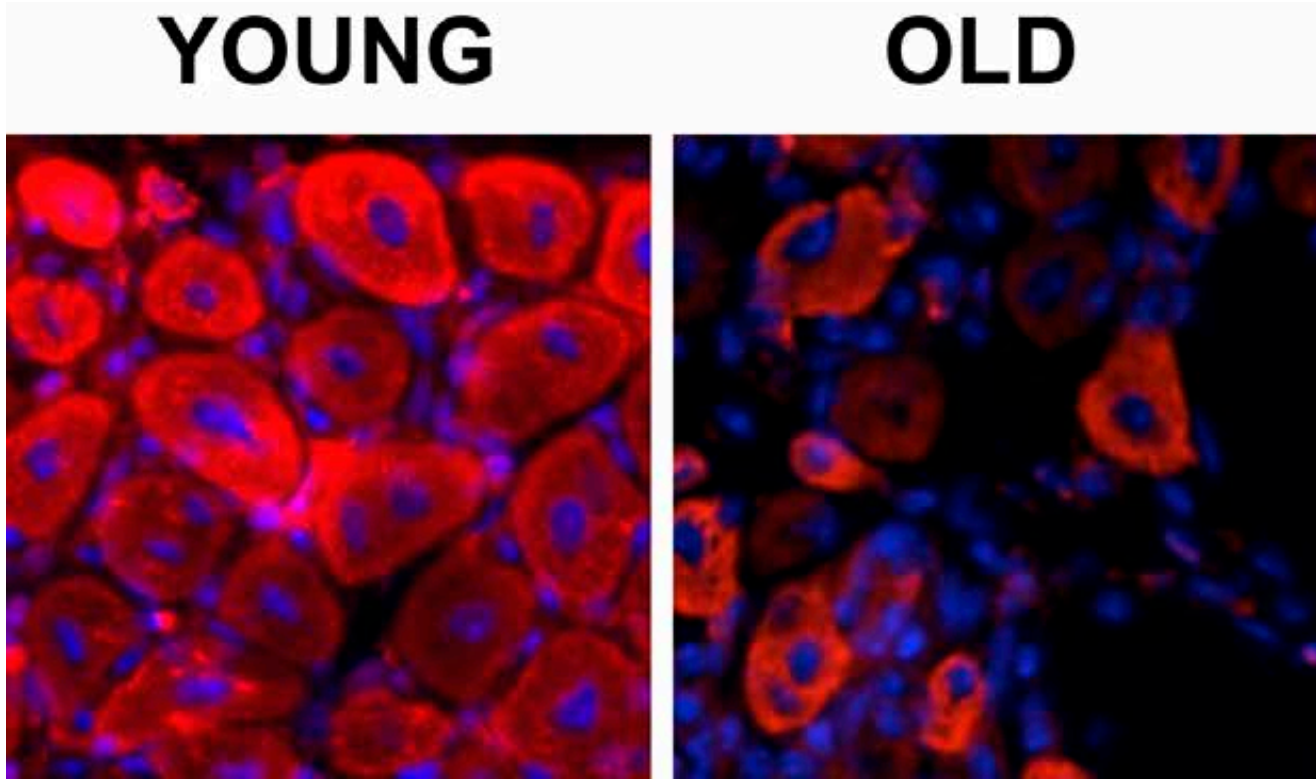
REPAIR DNA ERRORS - REFOROLD NONSENSE PROTEINS – REPAIR SIGNALLING PATHWAYS

SEMI-PROGRAMMED THEORIES:

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.

THE BRIGHTEST FLAME CASTS THE DARKEST SHADOW

George Martin



WE CAN REVERSE TIME ON MOLECULAR MECHANISMS

Mechanistic studies of DNA Repair

DNA REPAIR HAPPENS BY:

1. PROTEINS ACTIVELY REPAIRING DNA

2. EXCISION – ELIMINATING CERTAIN BIO-MECHANISMS

The Nobel Prize in Chemistry 2015

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Tomas Lindahl

Prize share: 1/3

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Paul Modrich

Prize share: 1/3

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Aziz Sancar

Prize share: 1/3

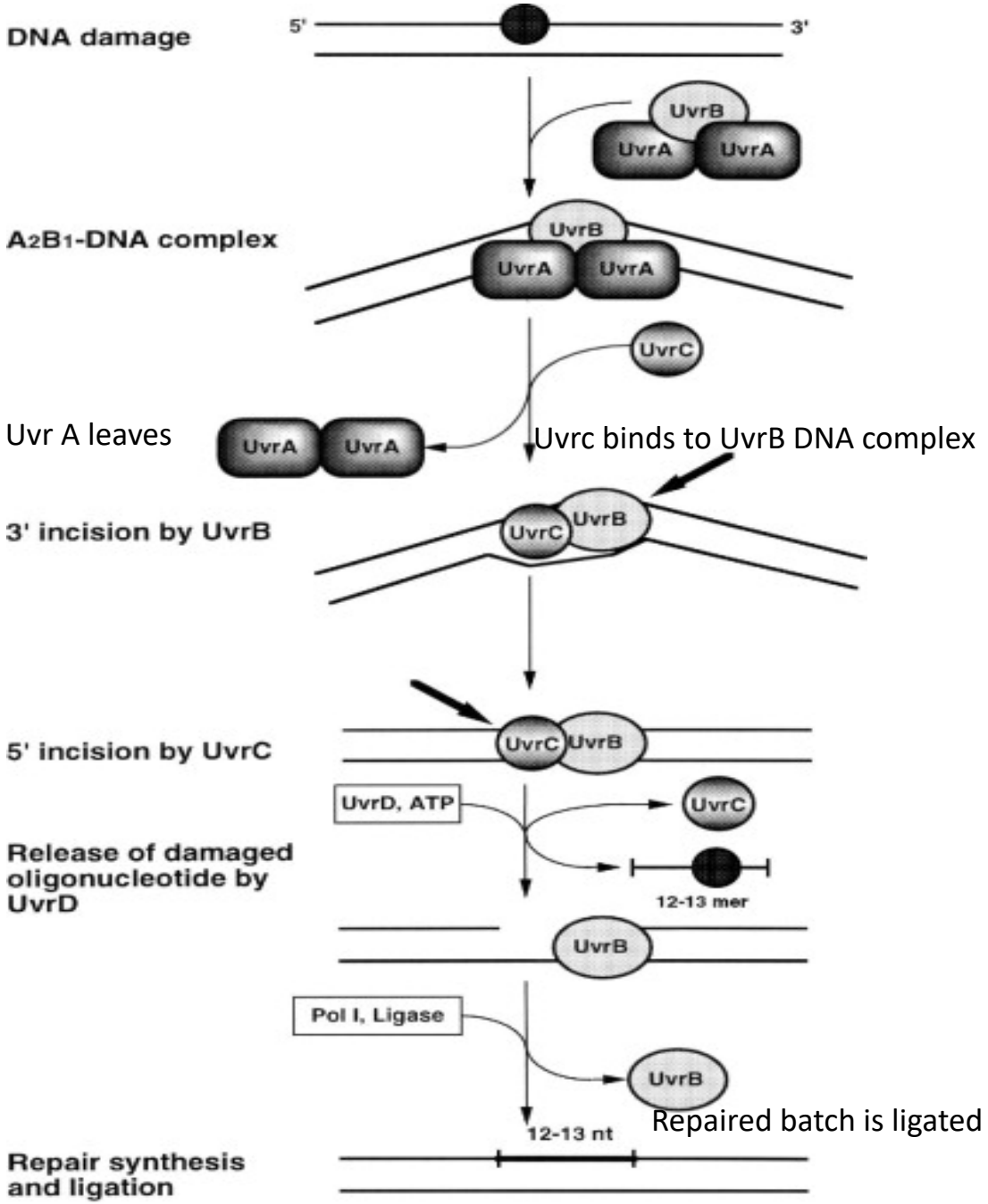
- Thymine dimers inhibit DNA synthesis

- NUCLEOTIDE EXCISION REPAIR OF DNA -- **NER**
  (by removal of thymine dimers)

- Sancar (83) used the purified UvrA, UvrB, and UvrC proteins to reconstitute essential steps in the NER pathway

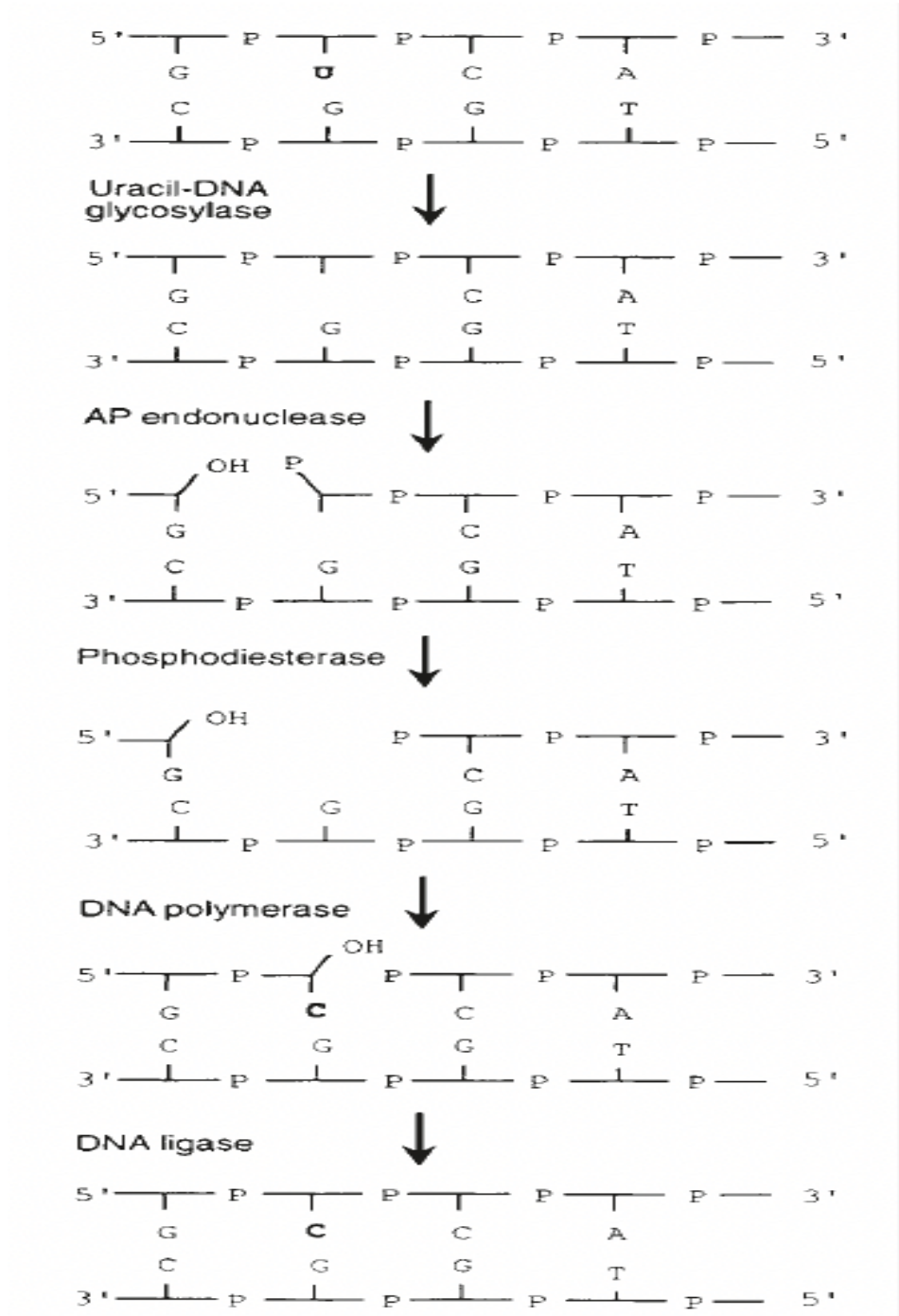
- Mutations in the NER system is linked to a number of human genetic disorders

- *e.g. Xeroderma pigmentosum* (XP), that has a very high risk for skin cancer



- **Uracil-DNA glycosylase (UNG)** is the founding member of a large family of proteins that orchestrate ***Base Excision repair*** **(BER)**

- ***Mismatch Repair***, reduces the error frequency during DNA replication by about a thousandfold

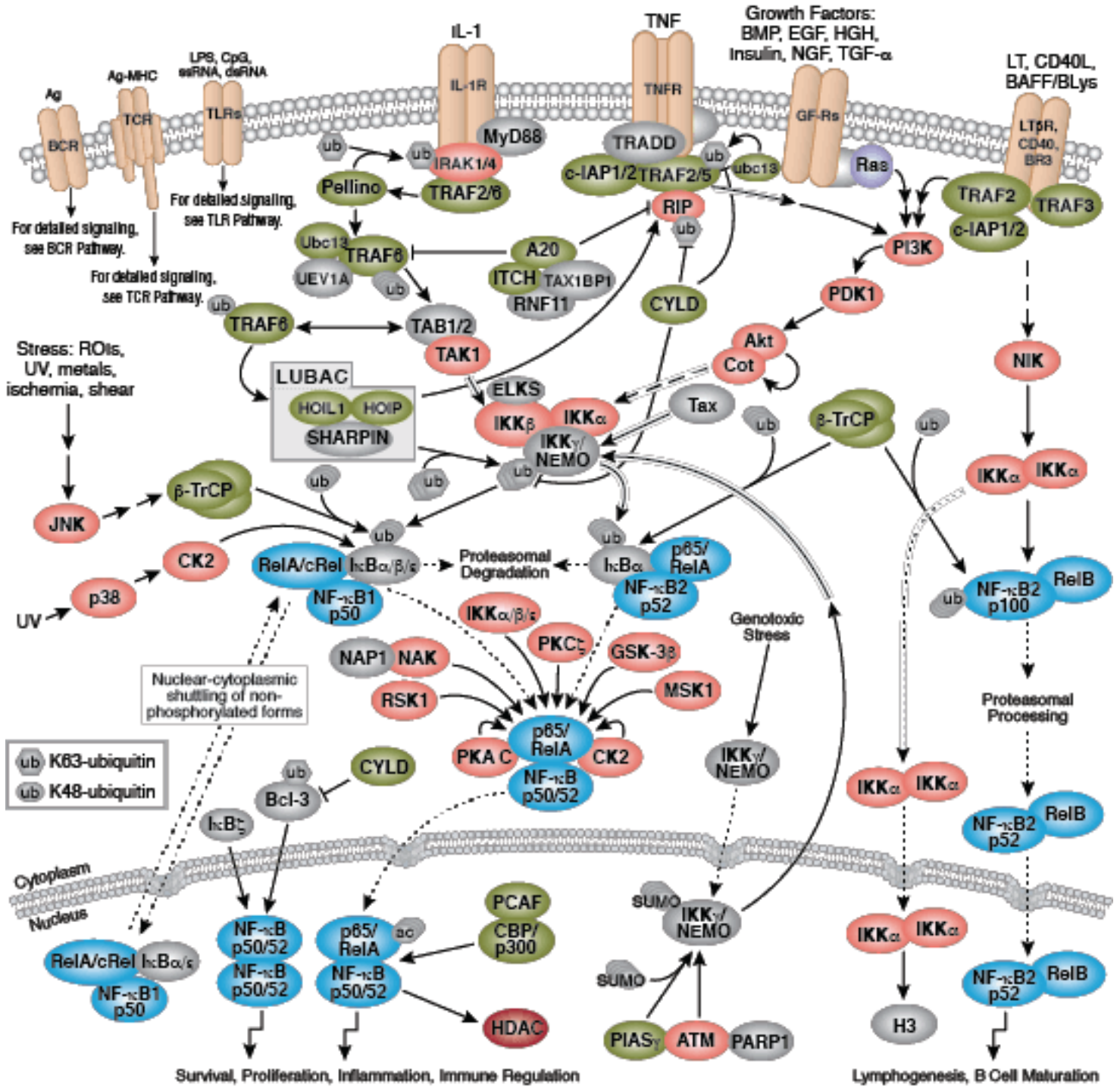


The base excision repair pathway for removal of endogenous damage from cellular DNA.


DNA MUTATION

BUT IT'S NOT ONLY ABOUT
REPAIRING THE DNA
OR REPAIRING THE CELL.

MOST IMPORTANTLY
WE HAVE TO REPAIR
THE NETWORK
INTERCOMMUNICATIONS
WITHIN THE CELL
AND BETWEEN CELLS



NOBEL RESEARECH ON CELLULAR NETWORK

REPAIR BY TRANSPORT & DELIVERY OF MOLECULAR CARGO REQUIRED FOR:

1. RELEASE OF NEUROTRANSMITTERS
2. EXPORT OF HORMONES TO CELL SURFACE
3. COMMUNICATION WITHIN THE CELL
4. COMMUNICATION BETWEEN CELLS

TRANSPORT OF MOLECULAR CARGO TO SPECIFIC DESTINATIONS INSIDE AND OUTSIDE THE CELL

The Nobel Prize in Physiology or Medicine 2013

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James E. Rothman

Prize share: 1/3

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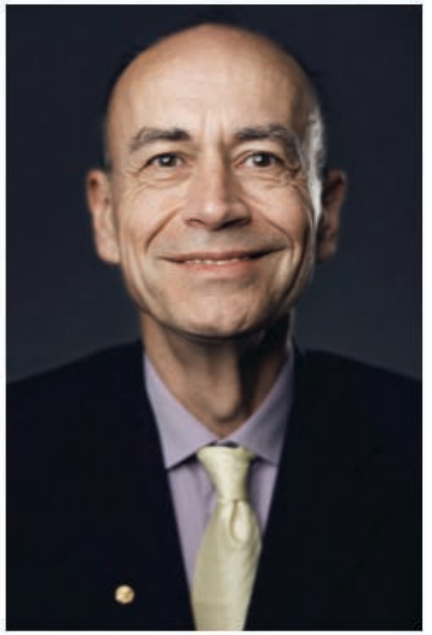
Randy W. Schekman

Prize share: 1/3



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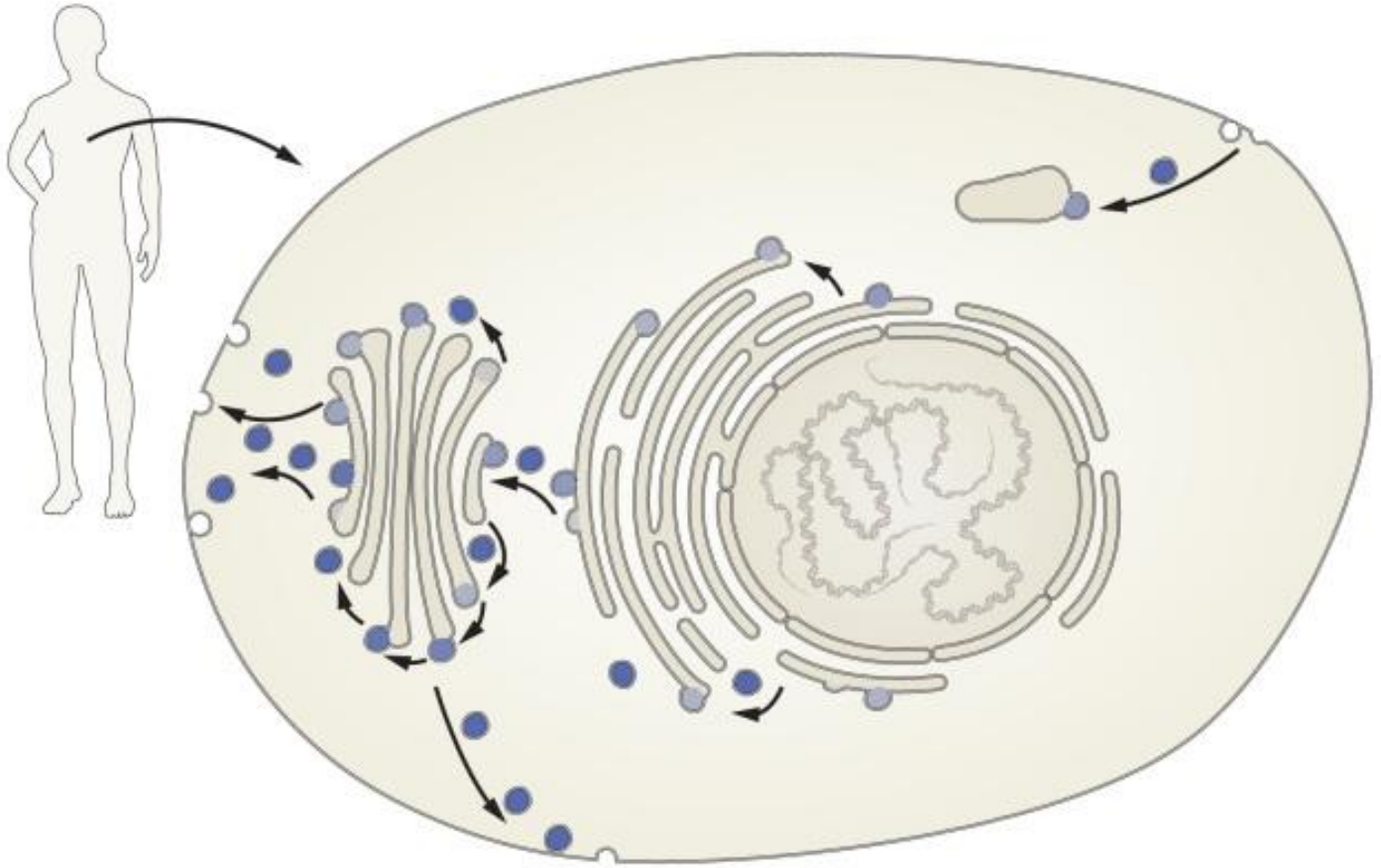
Thomas C. Südhof

Prize share: 1/3

Identified a set of Genes critical for vesicular trafficking. He showed that these genes were essential for life and could be classified into three categories regulating different aspects of vesicle transport.

Randy W. Schekman

Prize share: 1/3



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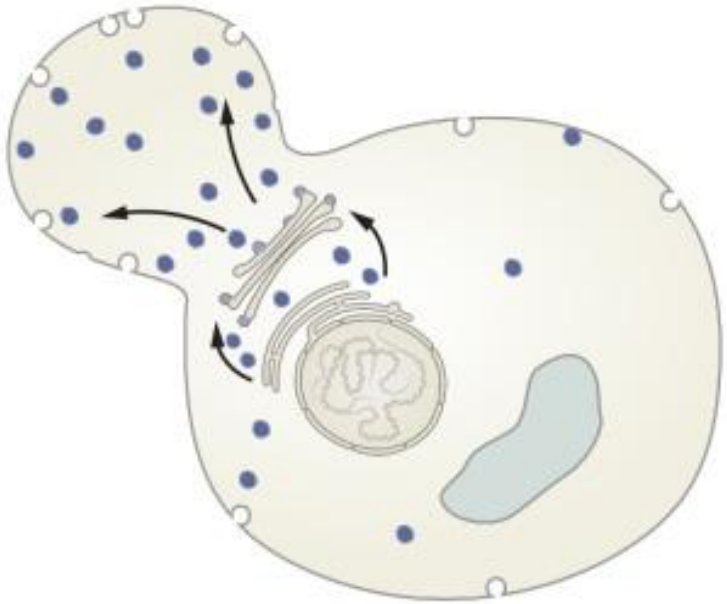
James E. Rothman

Prize share: 1/3

Identified Proteins on the vesicle and target membrane sides bind in specific combinations, ensuring precise delivery of molecular cargo to the right destination.



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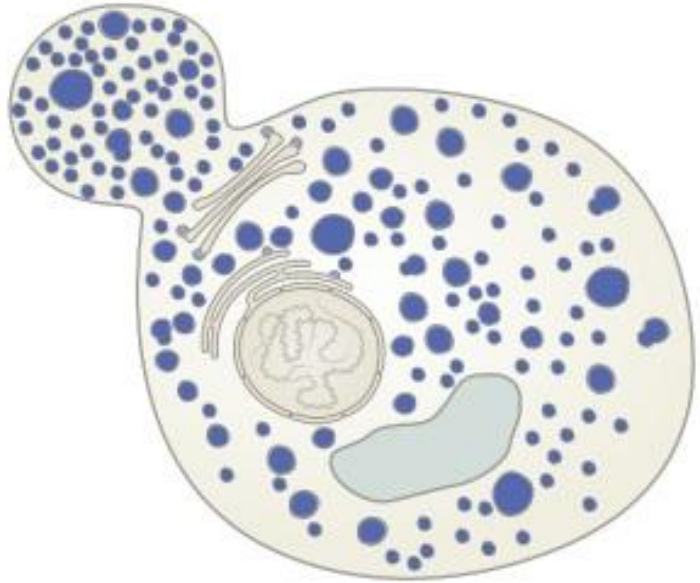

Mutant

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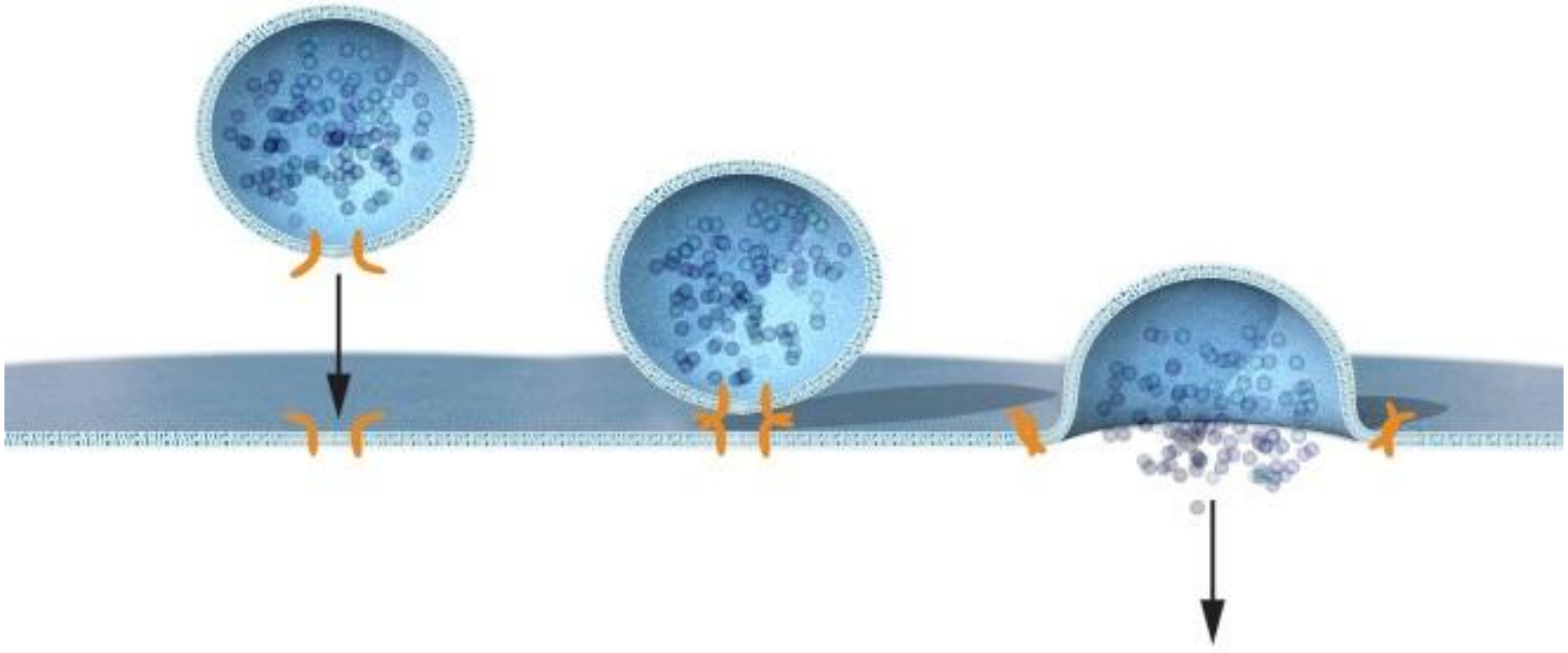
Thomas C. Südhof

Prize share: 1/3

Indentified the **molecular machinery that senses calcium ions** and converts this information to vesicle fusion, thereby explaining how temporal precision is achieved and how vesicles can be released on command.



The Nobel Prize in Physiology or Medicine 2018

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James P. Allison

Prize share: 1/2

© Nobel Media AB. Photo: A. Mahmoud

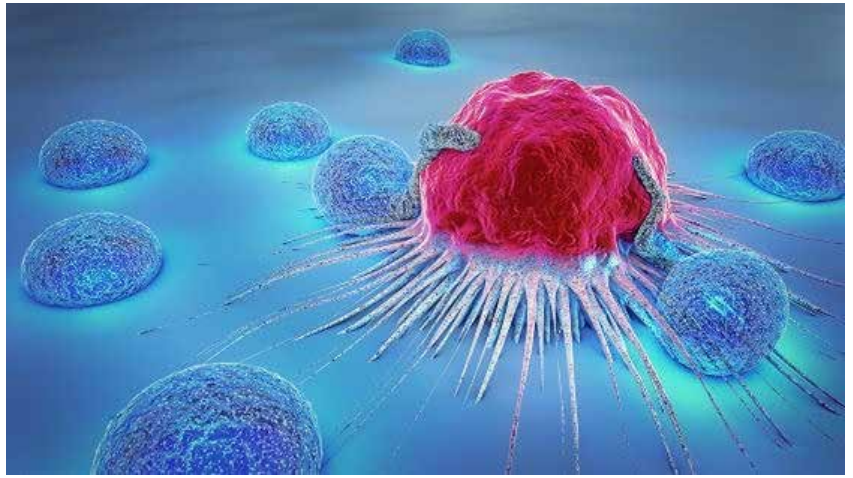
Tasuku Honjo

Prize share: 1/2

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."

REPAIR BY ELIMINATION

By **stimulating the inherent ability of our immune system to attack tumor cells** the 2018 Nobel Researchers have established an entirely new principle for cancer therapy.



CTLA-4

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James P. Allison

Prize share: 1/2

In 1994 Mice with cancer had been cured by treatment with the antibodies that **inhibit the CTLA-4 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 brake allowing the immune system to attack cancer relentlessly**.

Such remarkable results had never been seen before in this patient group.

PD-1

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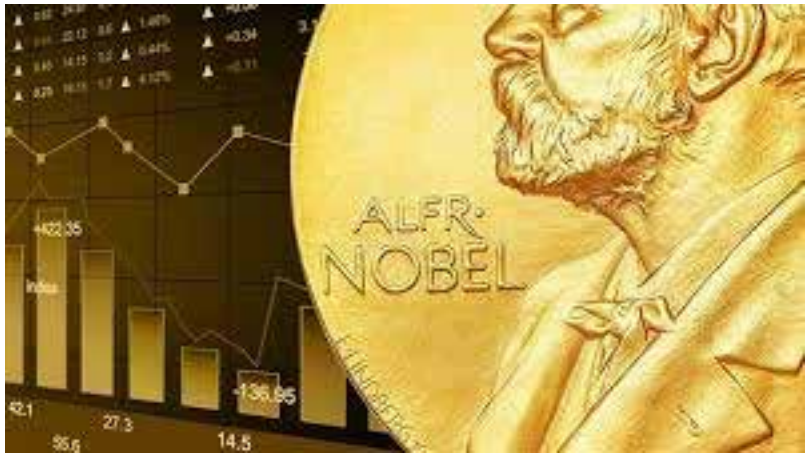
Tasuku Honjo

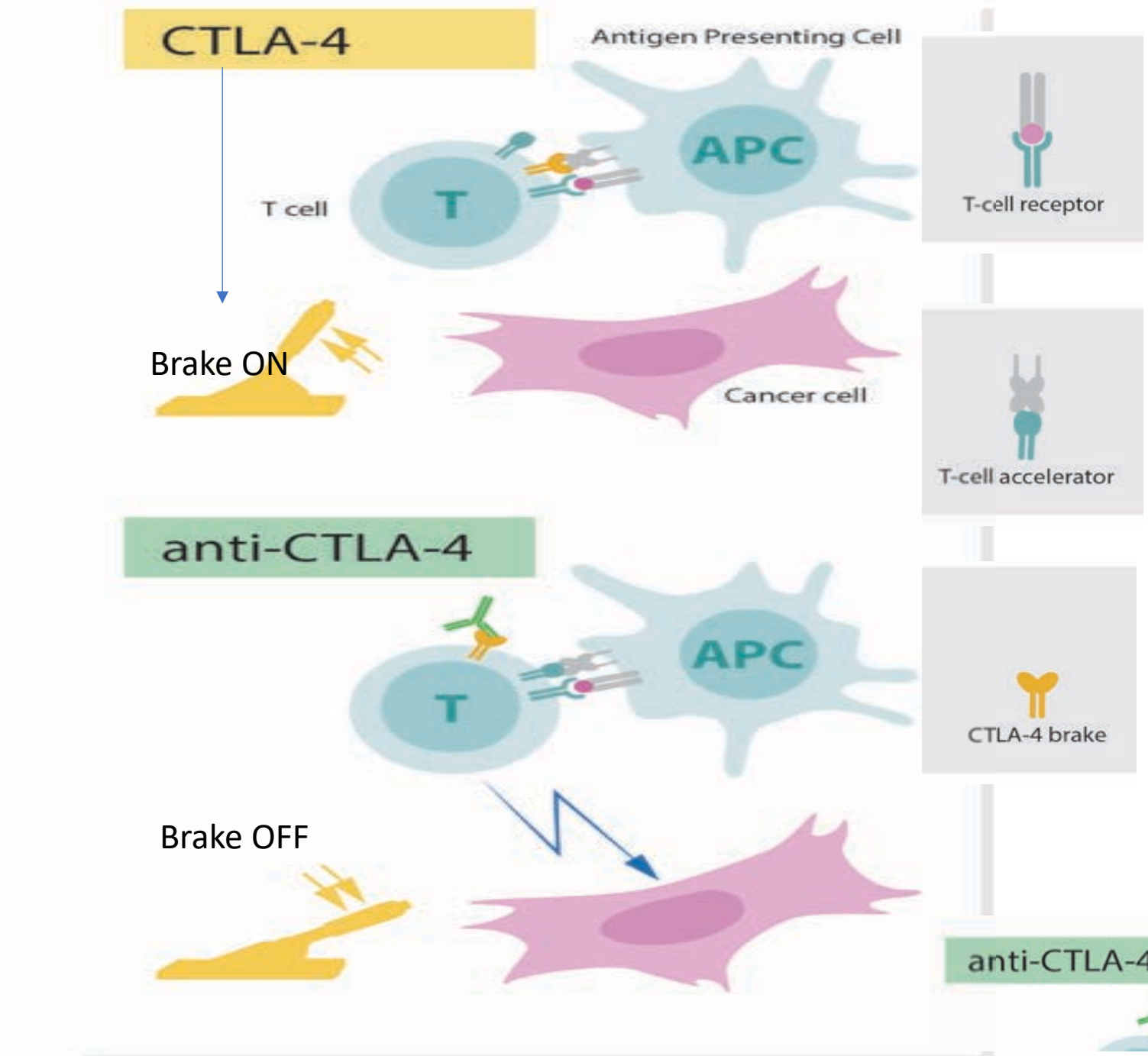
Prize share: 1/2

Tasuku Honjo discovered **PD-1**, another protein that functions as a **T-cell brake**.

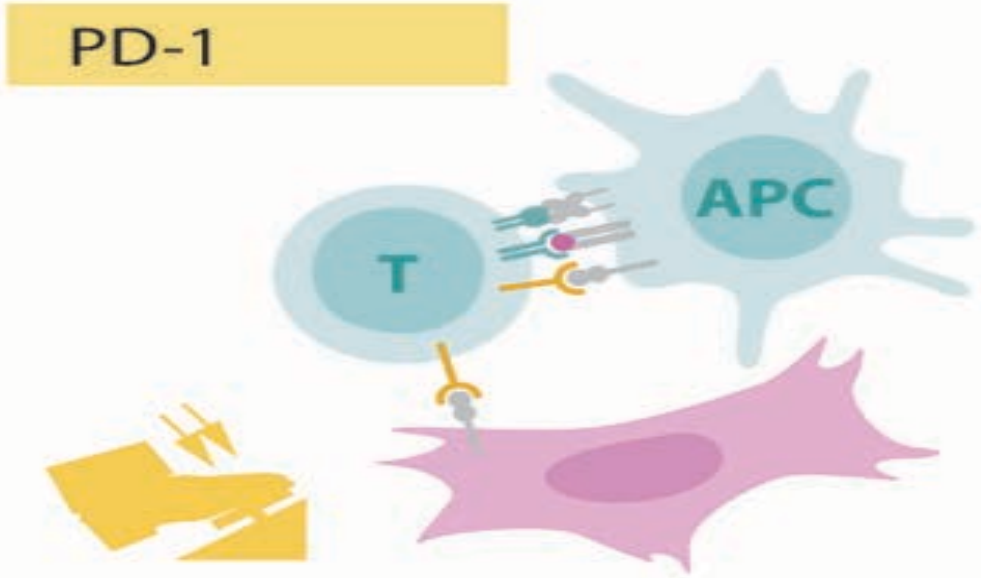
PD-1 has proven more effective and positive results are being observed in several types of cancer, including **lung cancer, renal cancer, lymphoma and melanoma**.

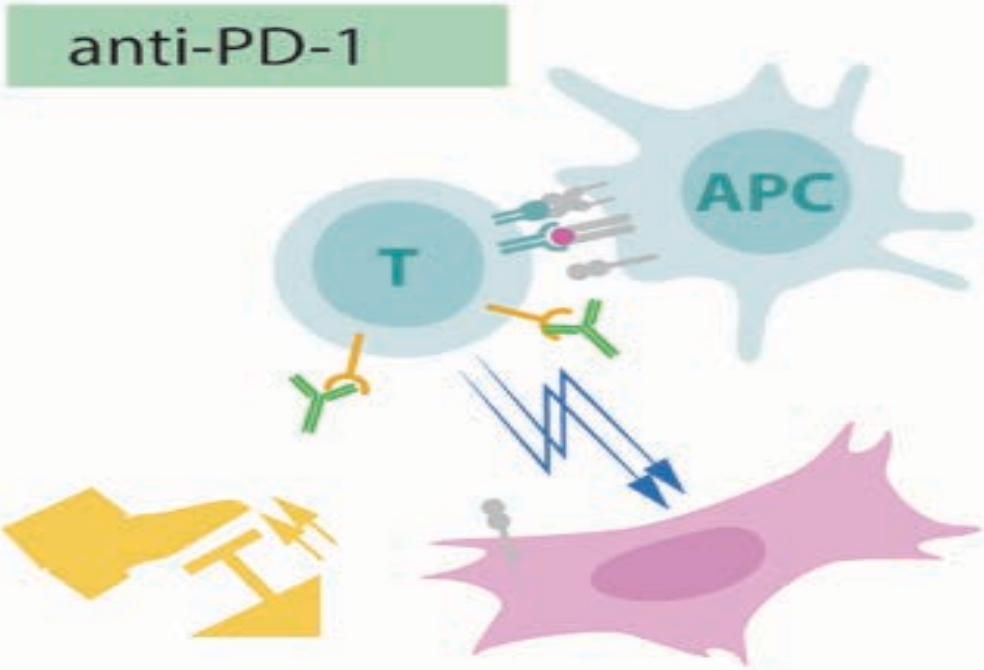
New clinical studies indicate that combination therapy, **targeting both CTLA-4 and PD-1**, can be even more effective, as demonstrated in patients with melanoma.





- **Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as ”non-self”.**
- A protein functioning as a T-cell accelerator is also required for T cell activation.
- CTLA- 4 functions as a brake on T cells that inhibits the function of the accelerator.
- **Antibodies (green) against CTLA-4 block the function of the brake** leading to activation of T cells and attack on cancer cells.





- **Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as ”non-self”.**

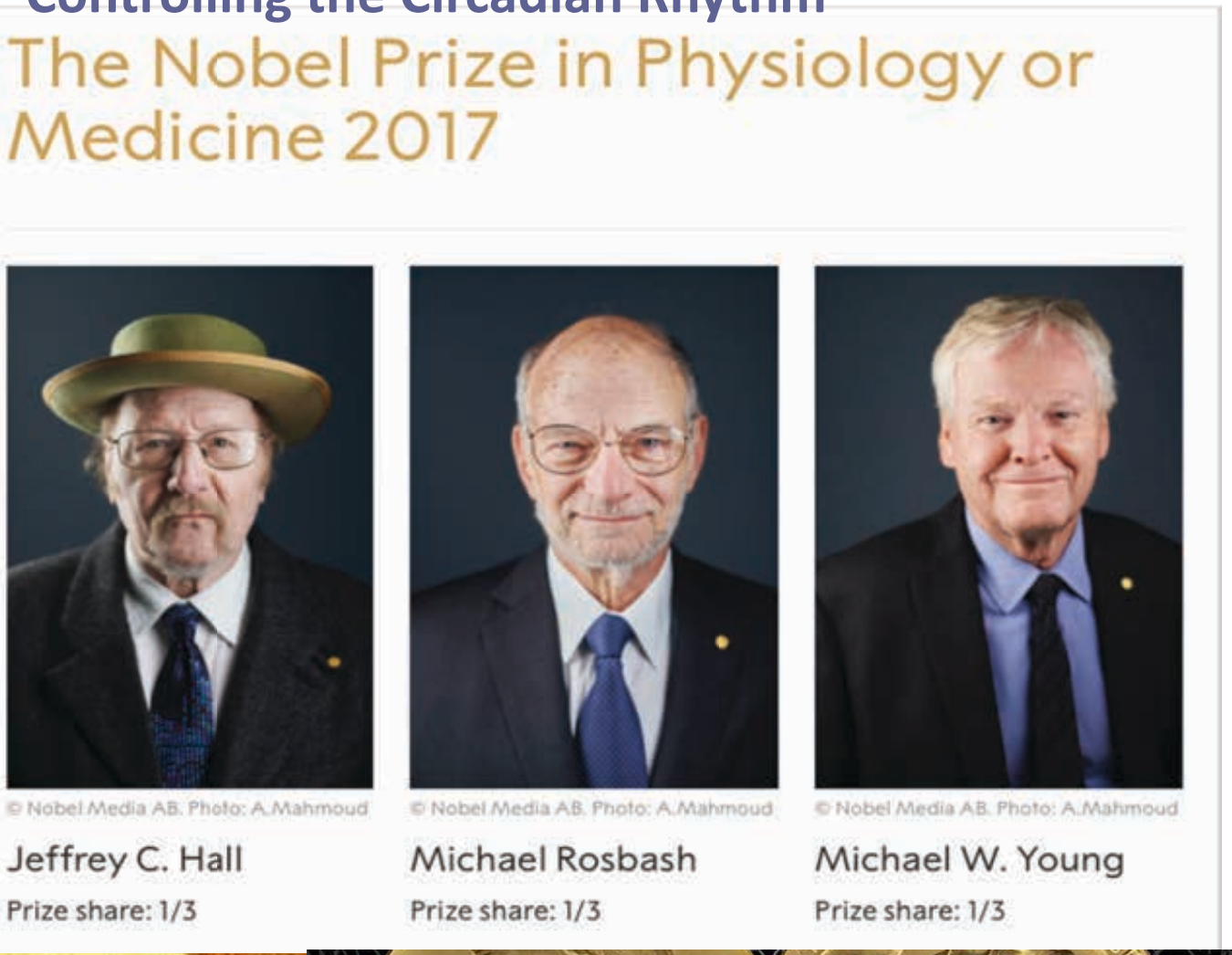
- A protein functioning as a T-cell accelerator is also required for T cell activation.

- PD-1 is another T-cell brake that inhibits T-cell activation.

- Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.

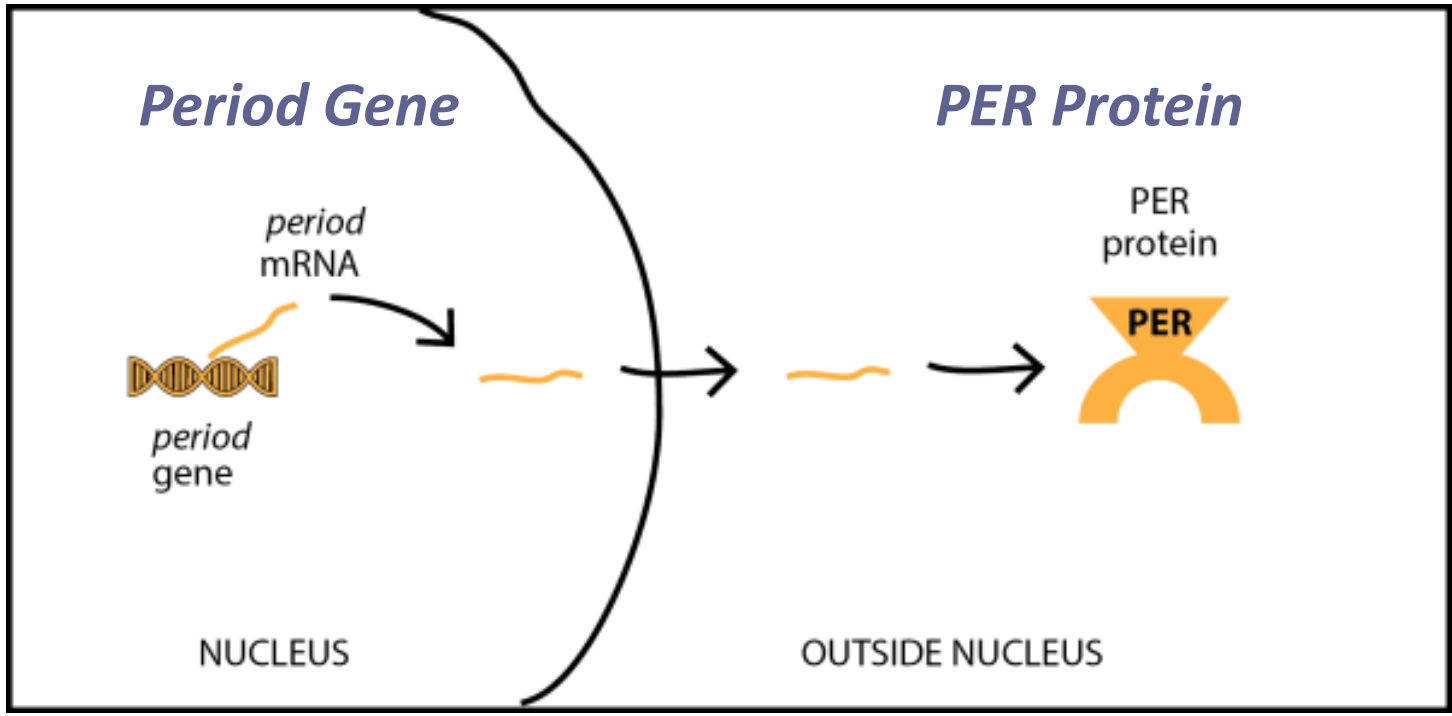
Discoveries of Molecular Mechanisms Controlling the Circadian Rhythm

BUT BOTH DIRECT REPAIR
AND REPAIR
BY ELIMINATION
INVOLVE A TIMING
COMPONENT



CIRCADIAN RHYTHMS ARE VERY WELL KNOWN…. BUT:

- Konopka and Benzer, 1971 found organisms with 3 mutations:
  - 1. Arrhythmic
    2. 19h Circadian Rhythm
    3. 28h Circadian Rhythm
- All three mutations involved the gene ***Period***.
- Subsequently the focus shifted onto ***the Period protein PER*** and how it may function to produce **circadian oscillations**.



PER Protein

A. Trascriptional Regulator
Hardin et al., 1990

B. Proteoglycan:
Brings cells together
Facilitates inter-cellular connections through gap junctions.

C. Negative autoregulatory feedback model
Accumulation of PER protein
GENE TIMELSS mRNA expression

PER Protein

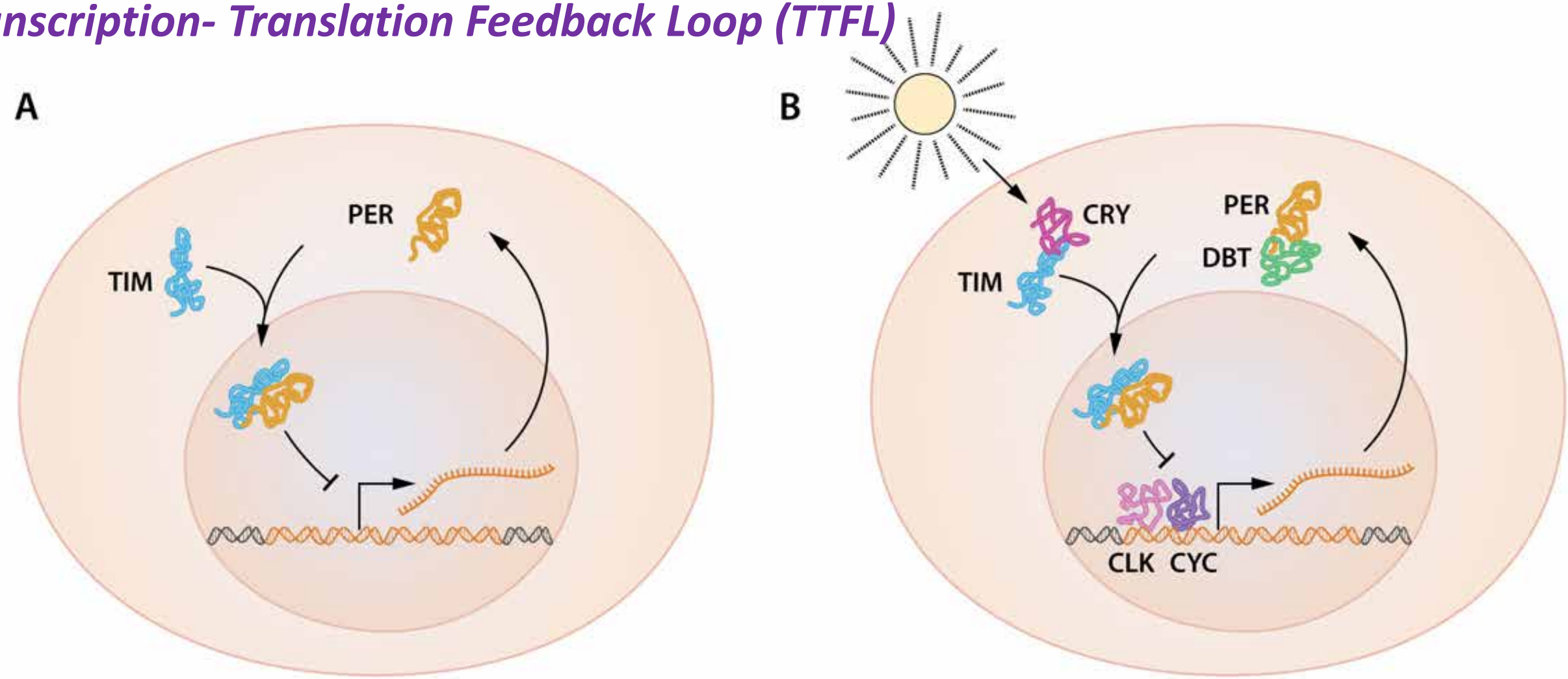
B. Gene **Timeless** **Influencing Circadian Clock** (Myers et al., 1995; Sehgal et al., 1995)

TIM Protein binds directly to PER Protein

Without Timeless Period Expression is ambolished

Without PERIOD Circadian Cycles were Lost

Transcription- Translation Feedback Loop (TTFL)

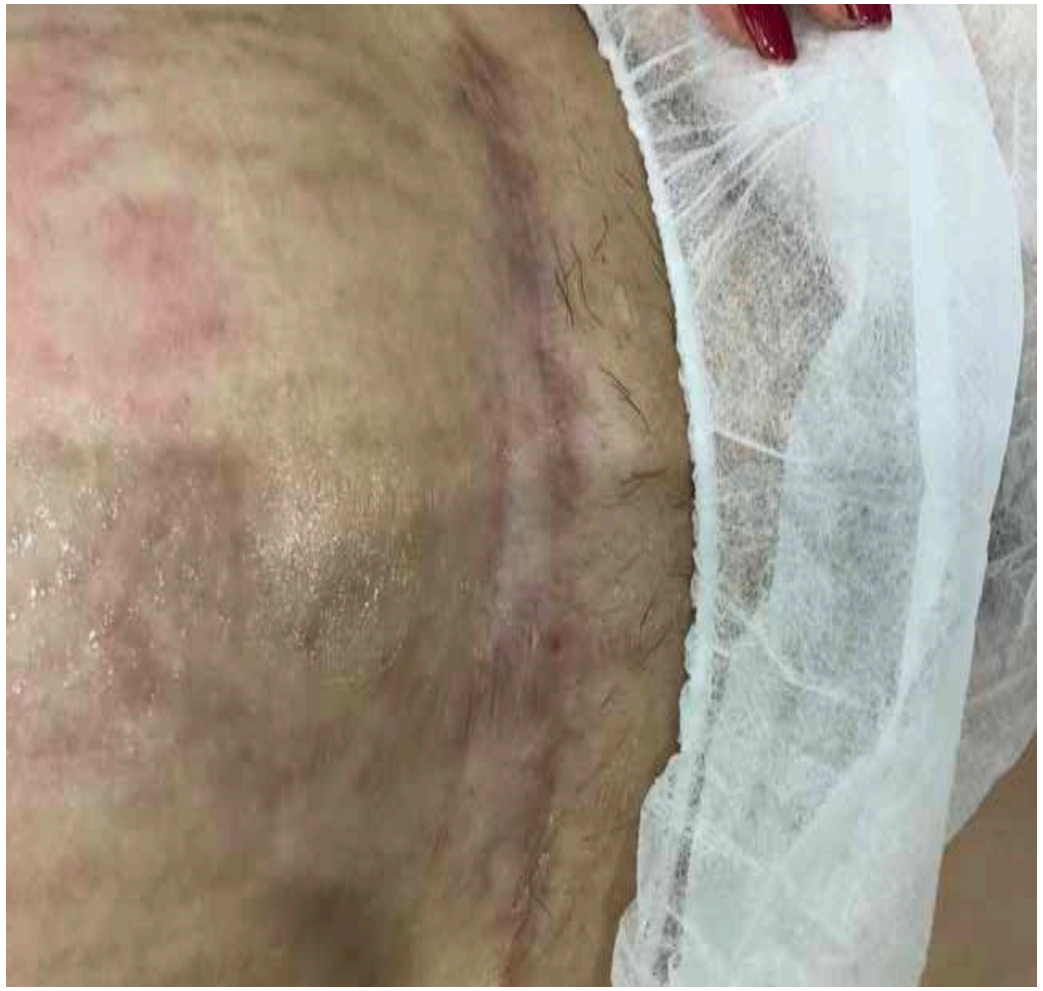


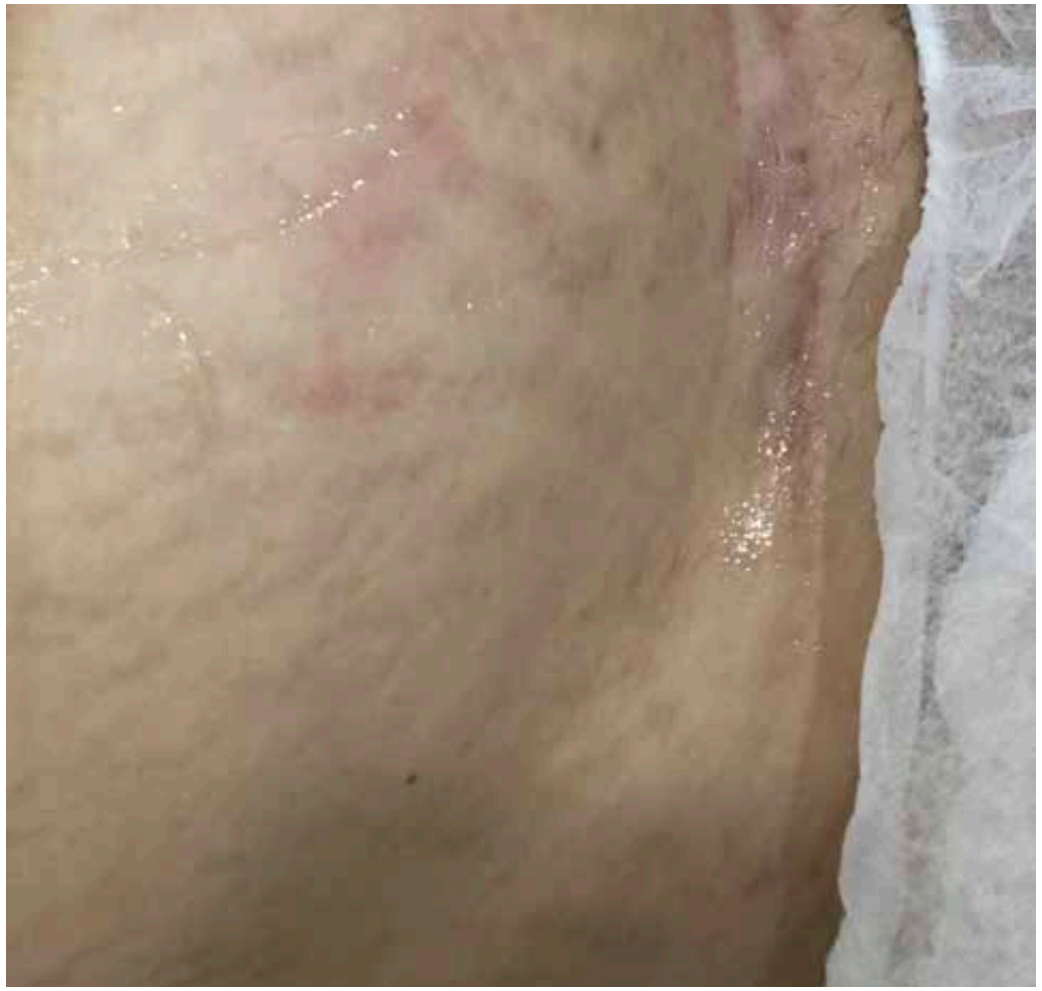
Both period mRNA and PER protein oscillate
TIM protein binds to PER protein

CLK and CYK proteins, encoded by the clock and cycle genes, are two transcription factors that activate the period gene

DBT protein leads to PER protein degradation

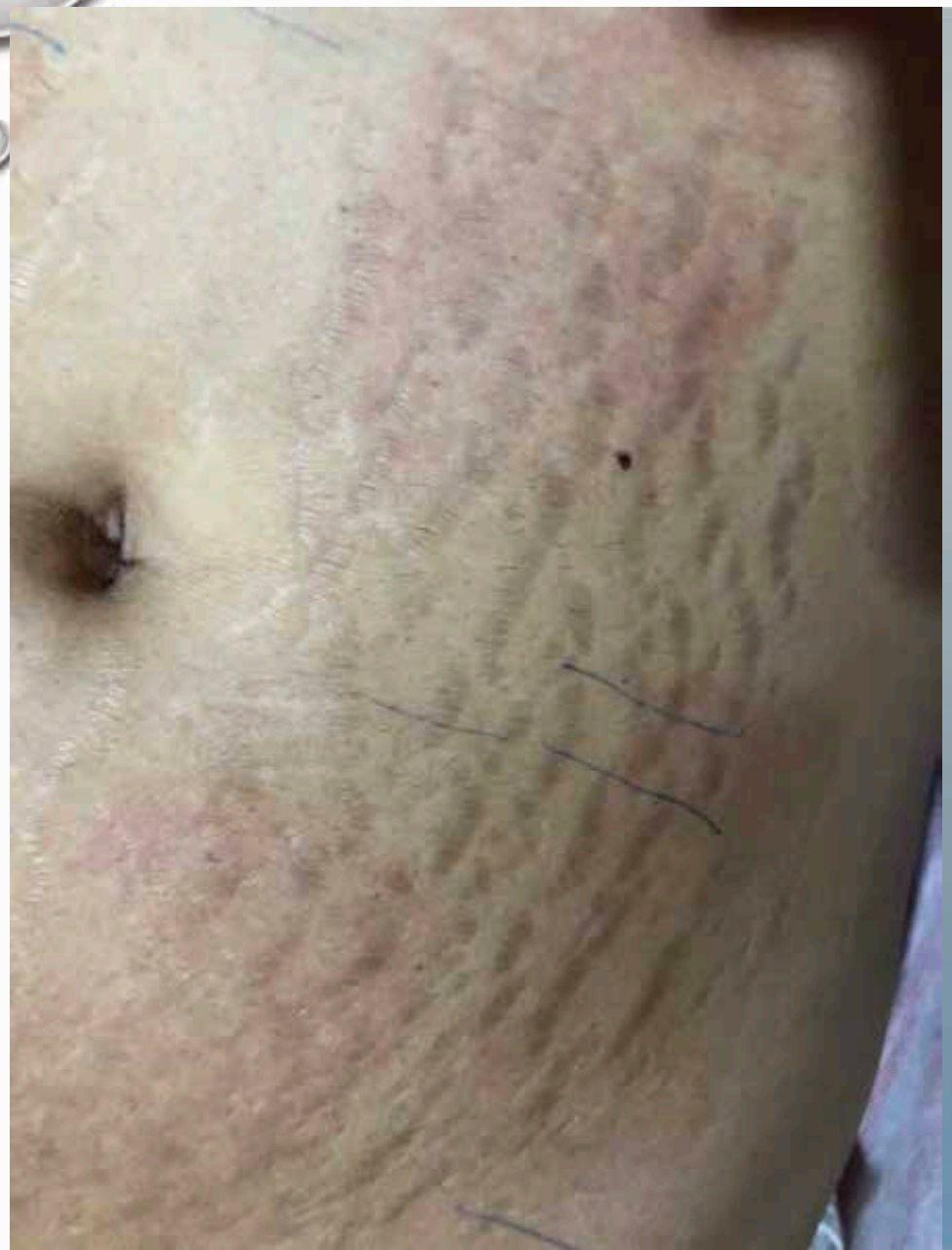
KELOID SCARS ARE THE RESULT OF DISREGULATION
IN GENE CLOCKS

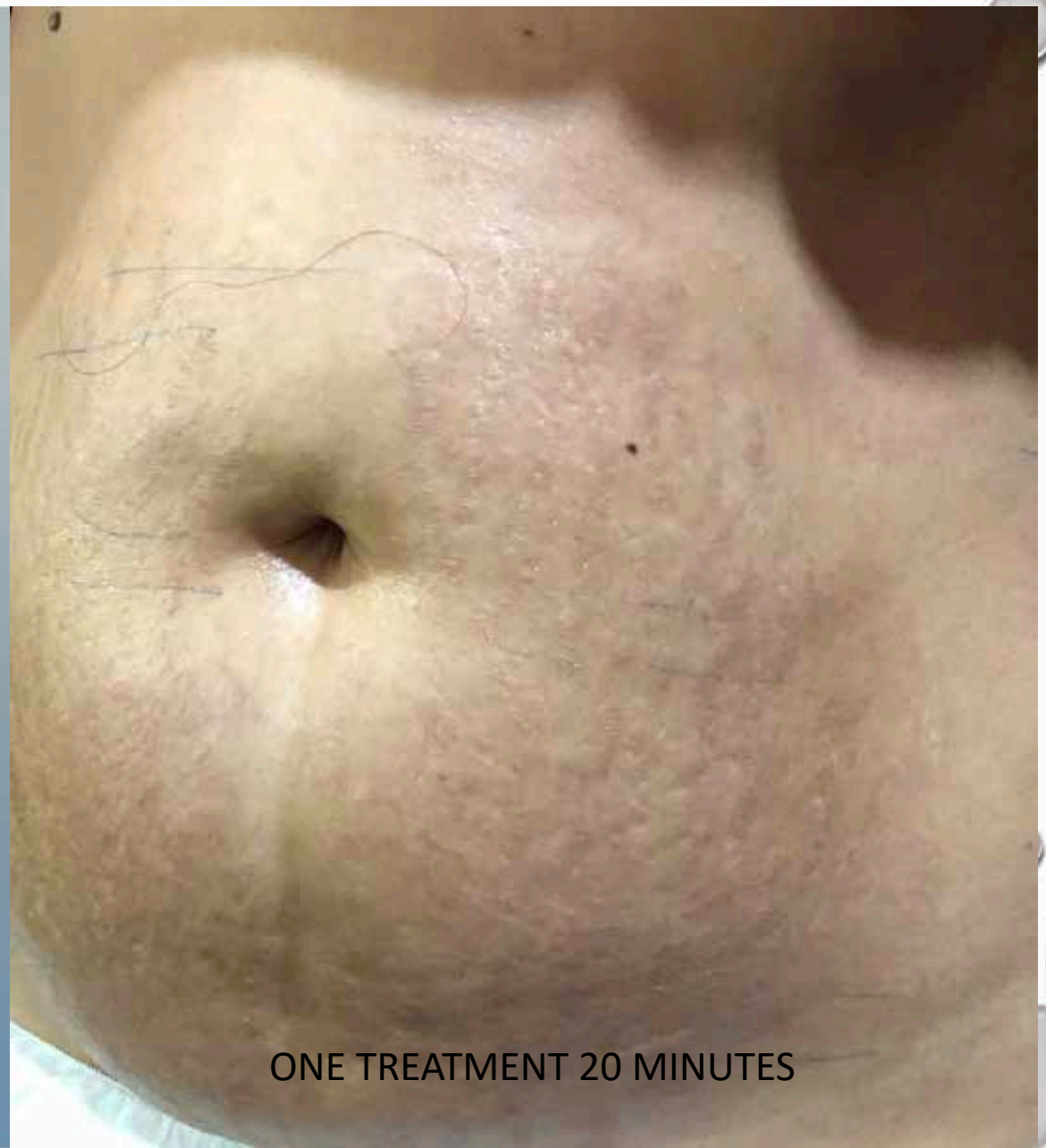




AGTER 20 MINUTES OF SIGNALING

THE SAME DISTURBANCE IN GENE CLOCKS IS INVOLVED IN STRETCHMARKS



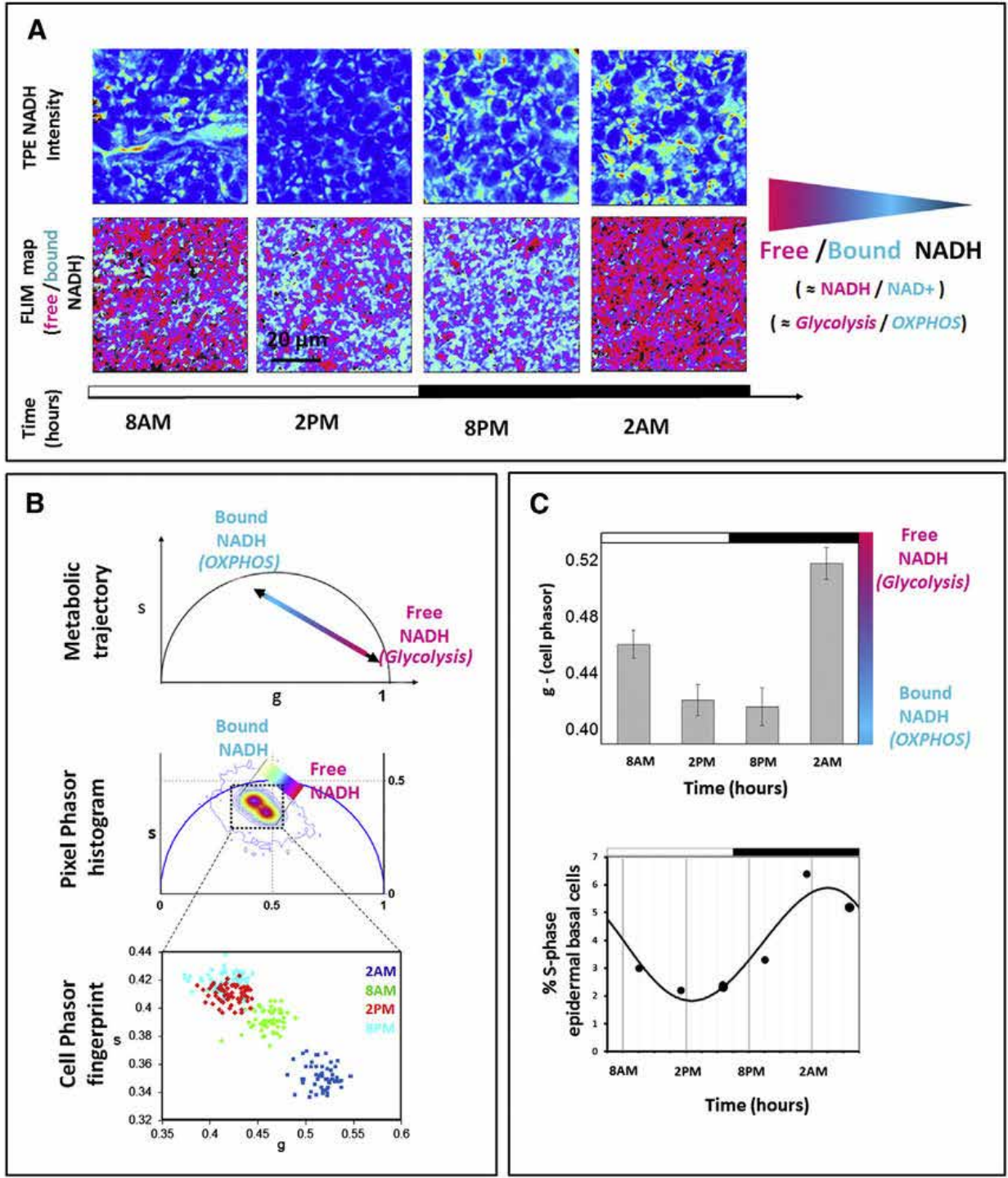


ONE TREATMENT 20 MINUTES

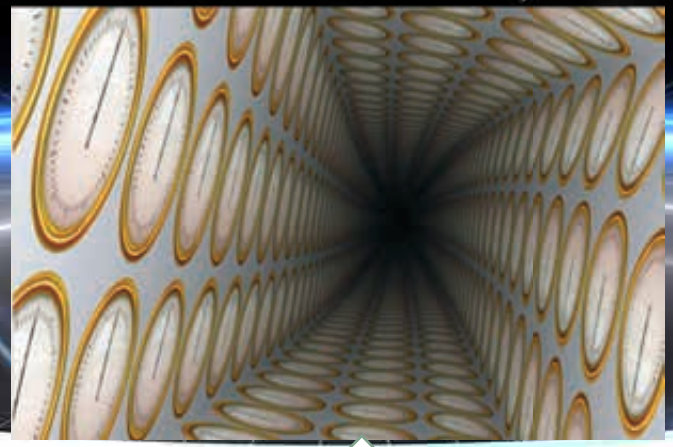
- Janich P et al (2013) found Human epidermal **stem cell function** is regulated by **circadian oscillations**.

- Izumi H et al (2014) discussed **Circadian disruption** and **cancer risk**.

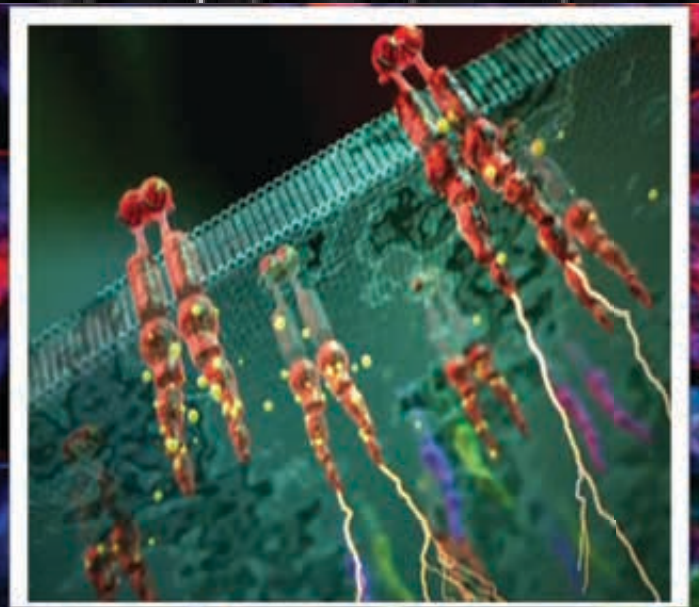
- Yasuniwa Y, Izumi H, Wang KY, et al (2010) showed how **circadian disruption** accelerates **tumor growth** and angio/stromagenesis through a ***Wnt Signaling Pathway.***

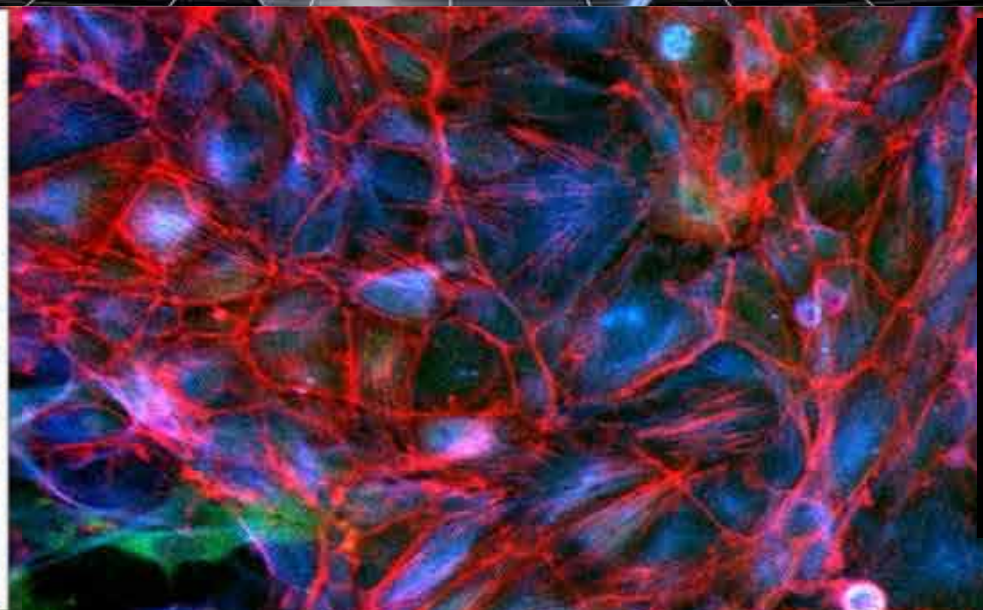


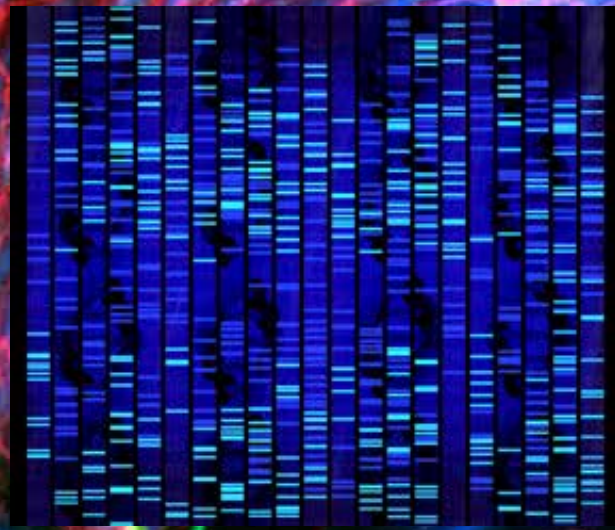
MOLECULAR MECHANISMS COMPOSE A DYNAMIC PROCESS LIKE A MUSICAL PIECE

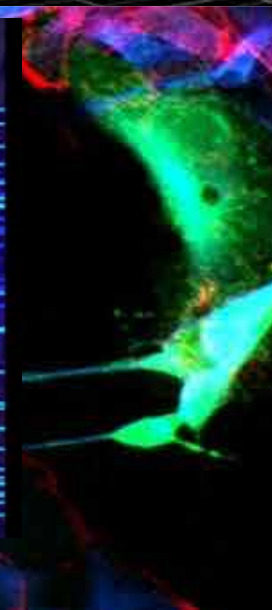


SIGNALING CONTROLLED PROCESSES → DELIVERED AT SPECIFIC TIMES → **PROMOTING GENE EXPRESSION**





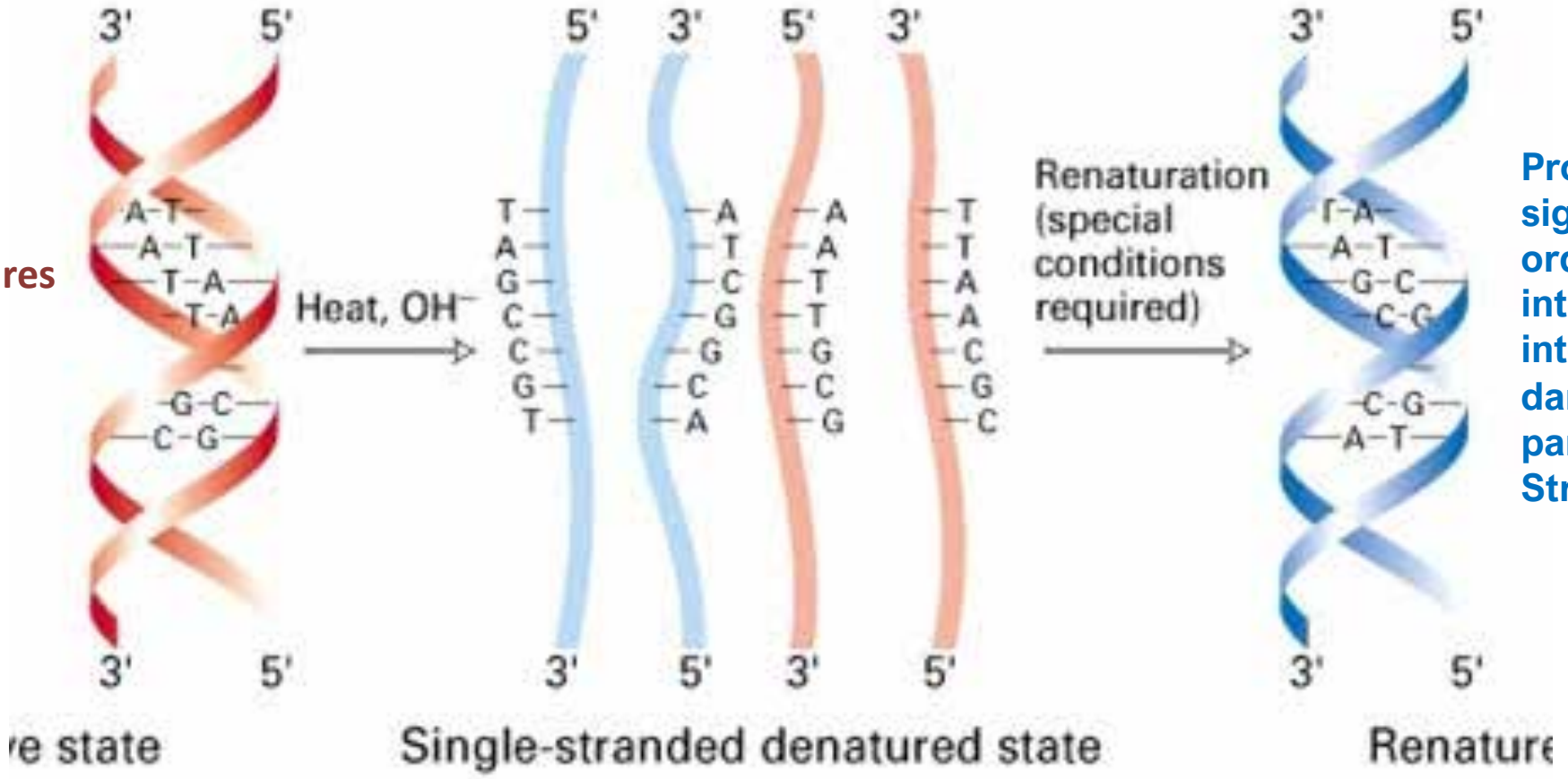




Compromised signals from denatured proteins can be deleterious to this very specific process, while signals enhancing protein refolding can reinstate systemic functioning, restoring the flow of previously disrupted signalling pathways.

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

Heat Denatures DNA



Protein command signals WILL order enzymes to intervene to intervene & repair damaged parts of DNA Strand

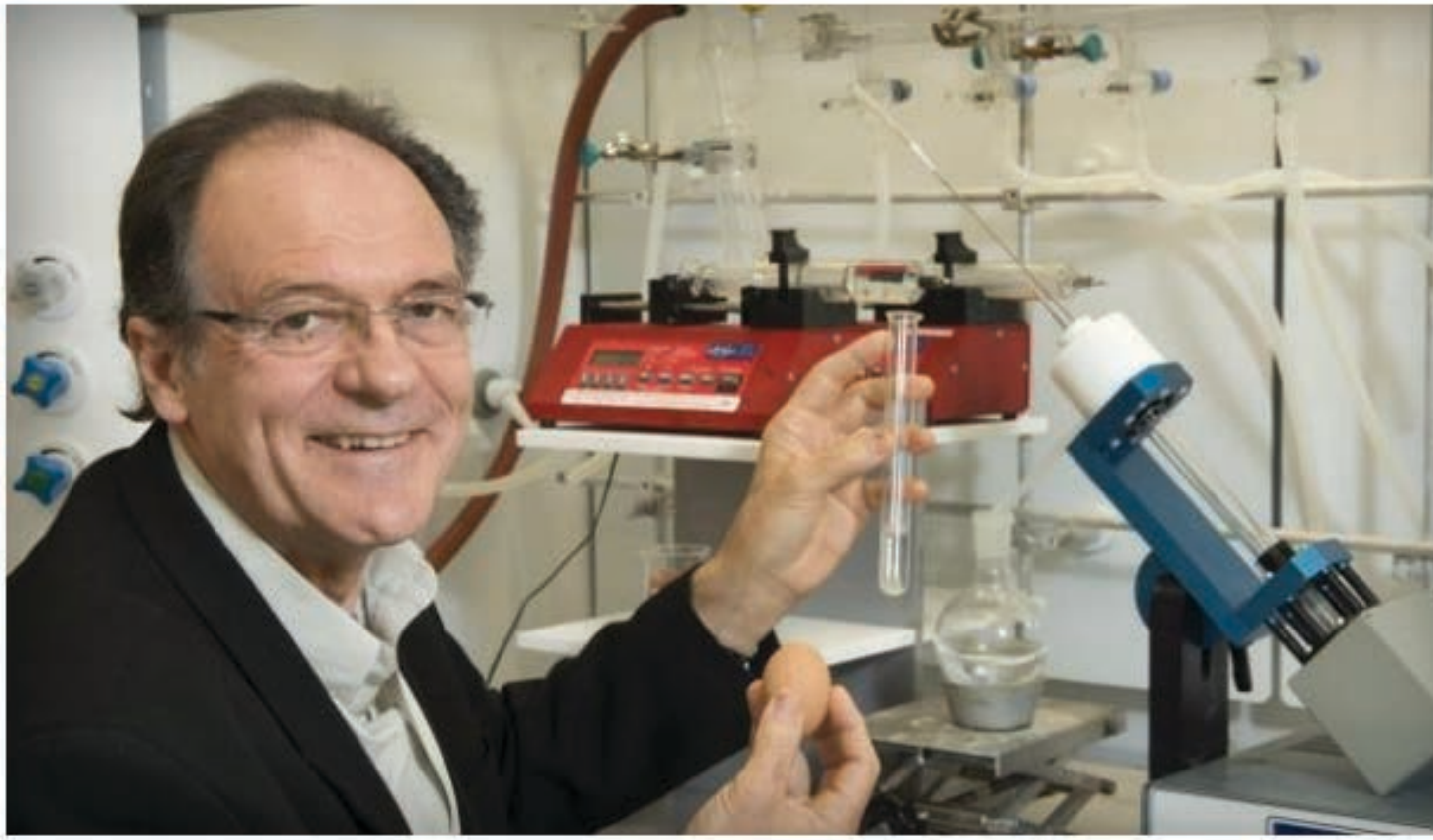
CAN YOU UNBOIL AN EGG?

YOU CAN REVERSE DESEASES
OR SKIN DAMAGE
BY PROTEIN REFOLDING

How ‘unboiling an egg’ leads to better cancer treatments

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

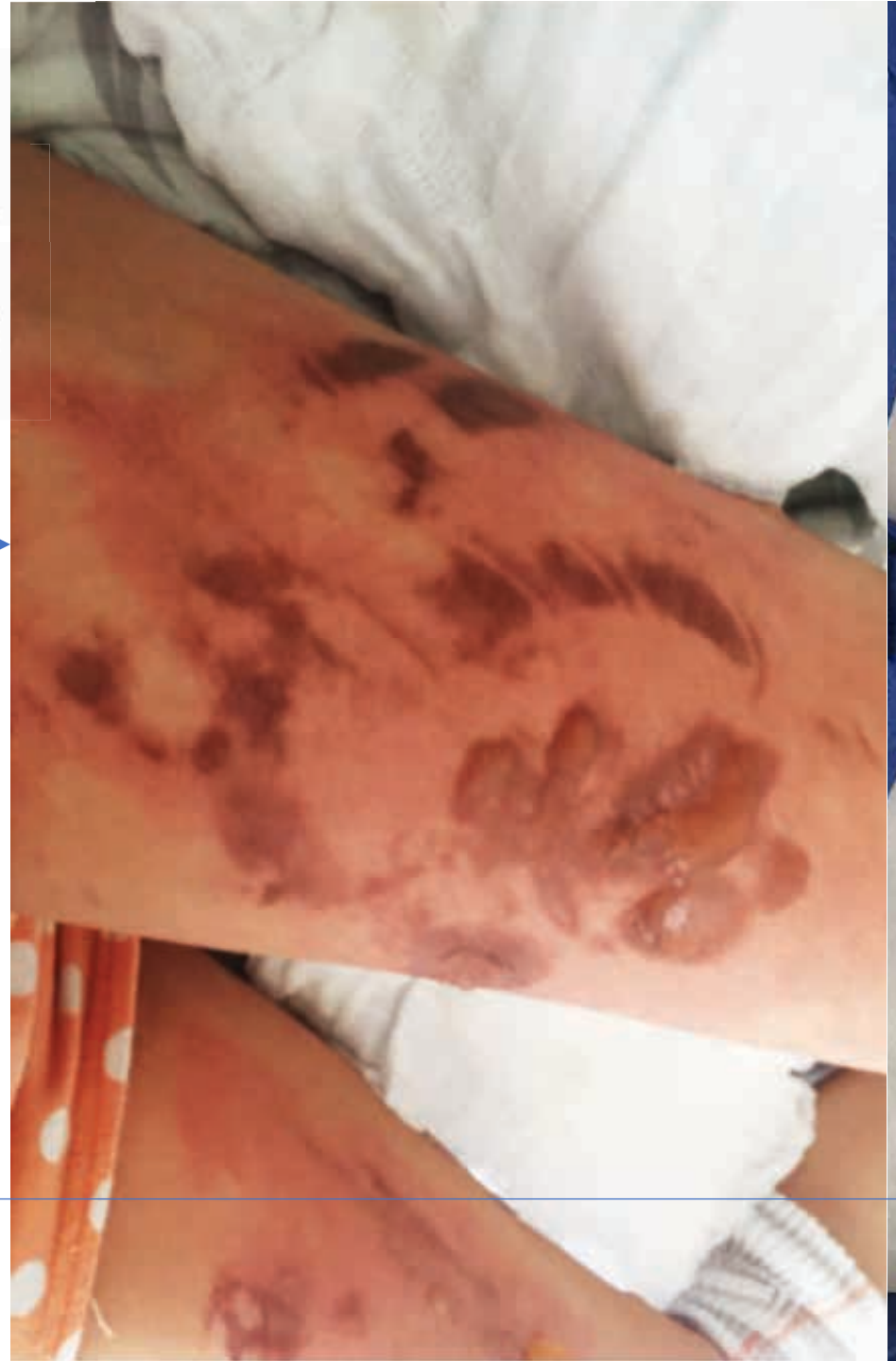
488 shares



SIGNALING CLINICAL CASES ON HERPES Zoster

CLINICAL CASES
Third burn Repair within two weeks

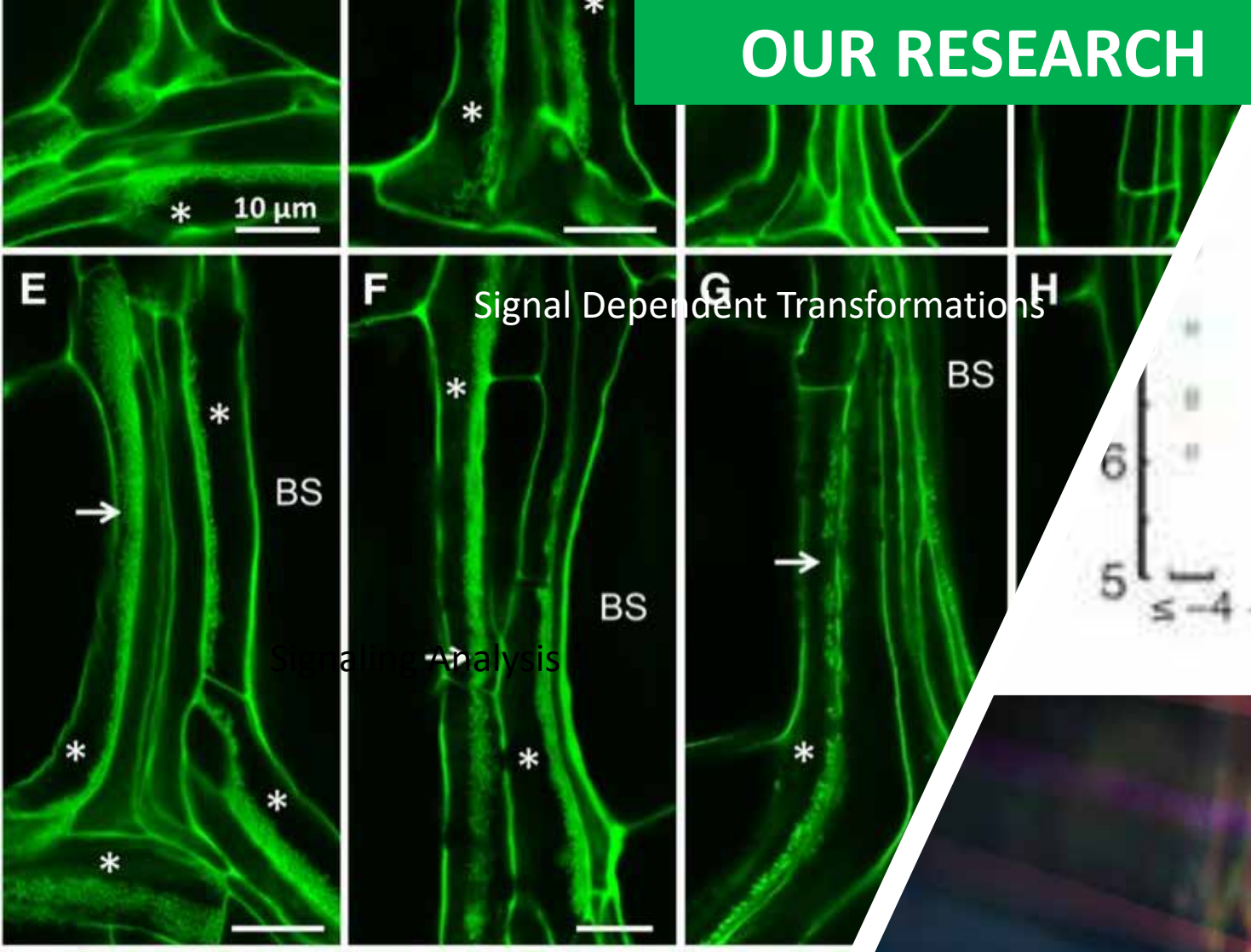
IMMEDIATELY AFTER
THE BURN →



AFTER
THE 3RD
TREATMENT →

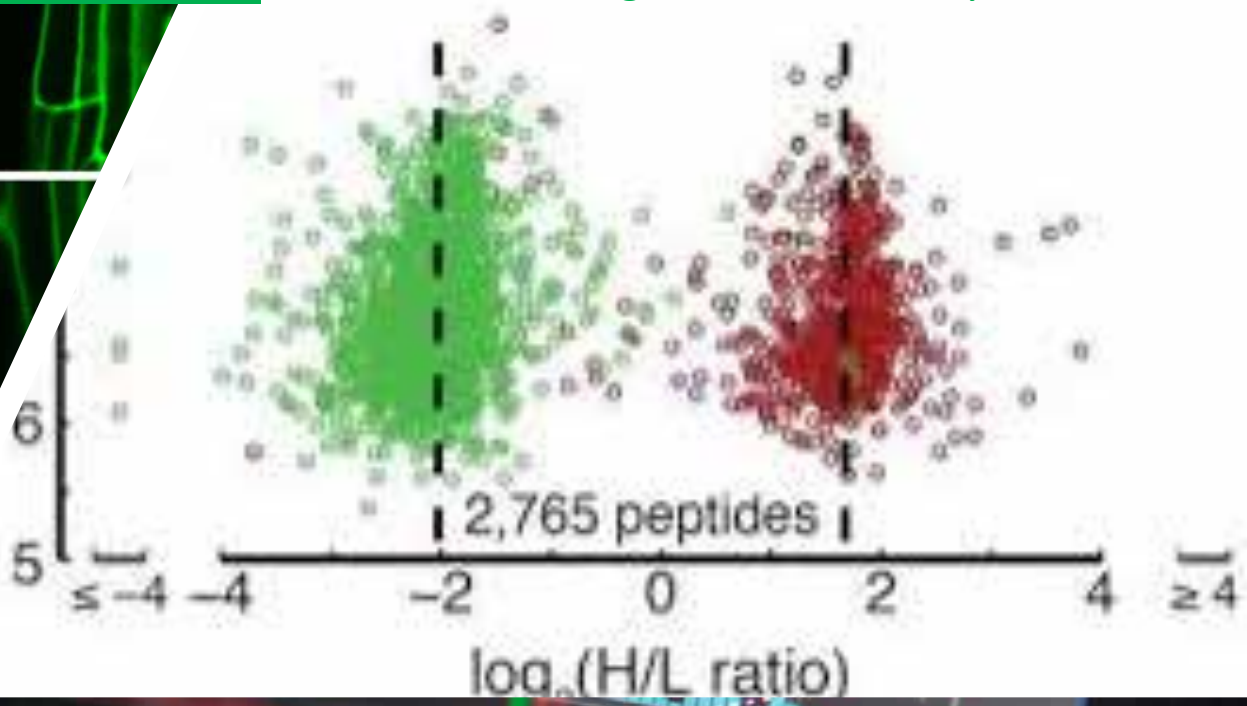
OUR RESEARCH

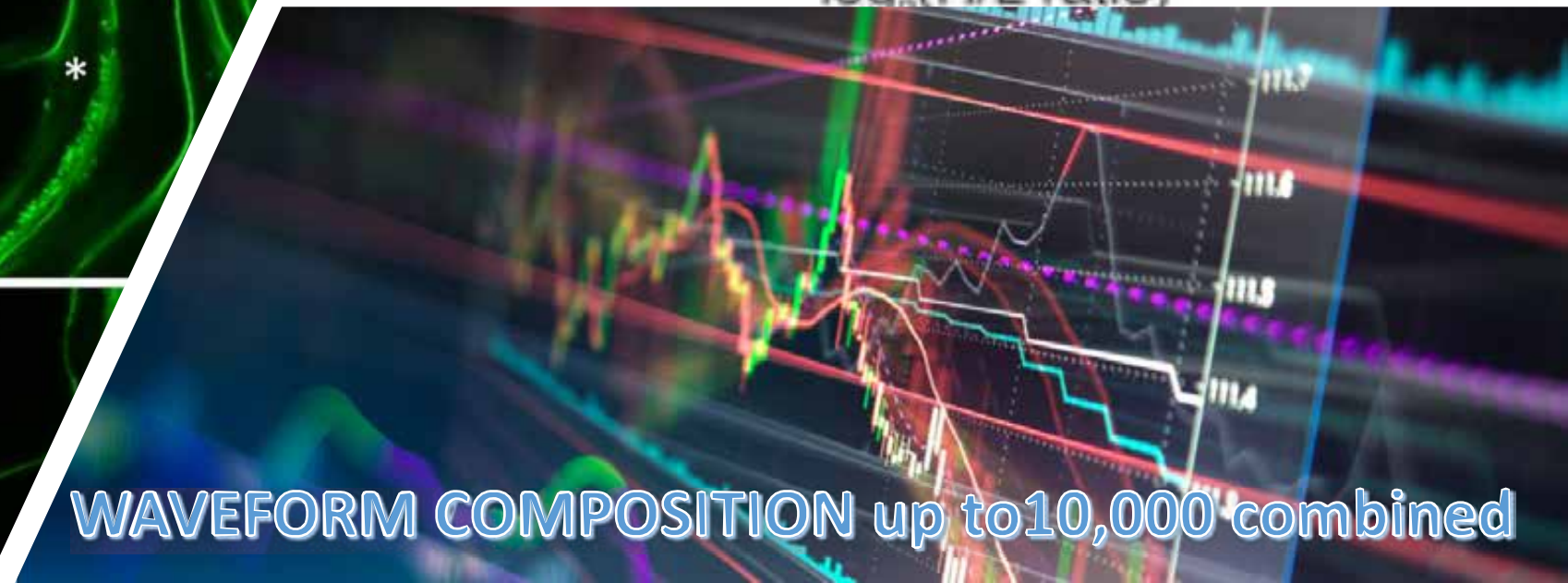
SIGNAL PROCESSING BLUEPRINTS
Signal Clusters Analysis



Signal Dependent Transformations

Signaling Analysis






At Proprietary Microenergies

Our Research Started in the 70s in London University

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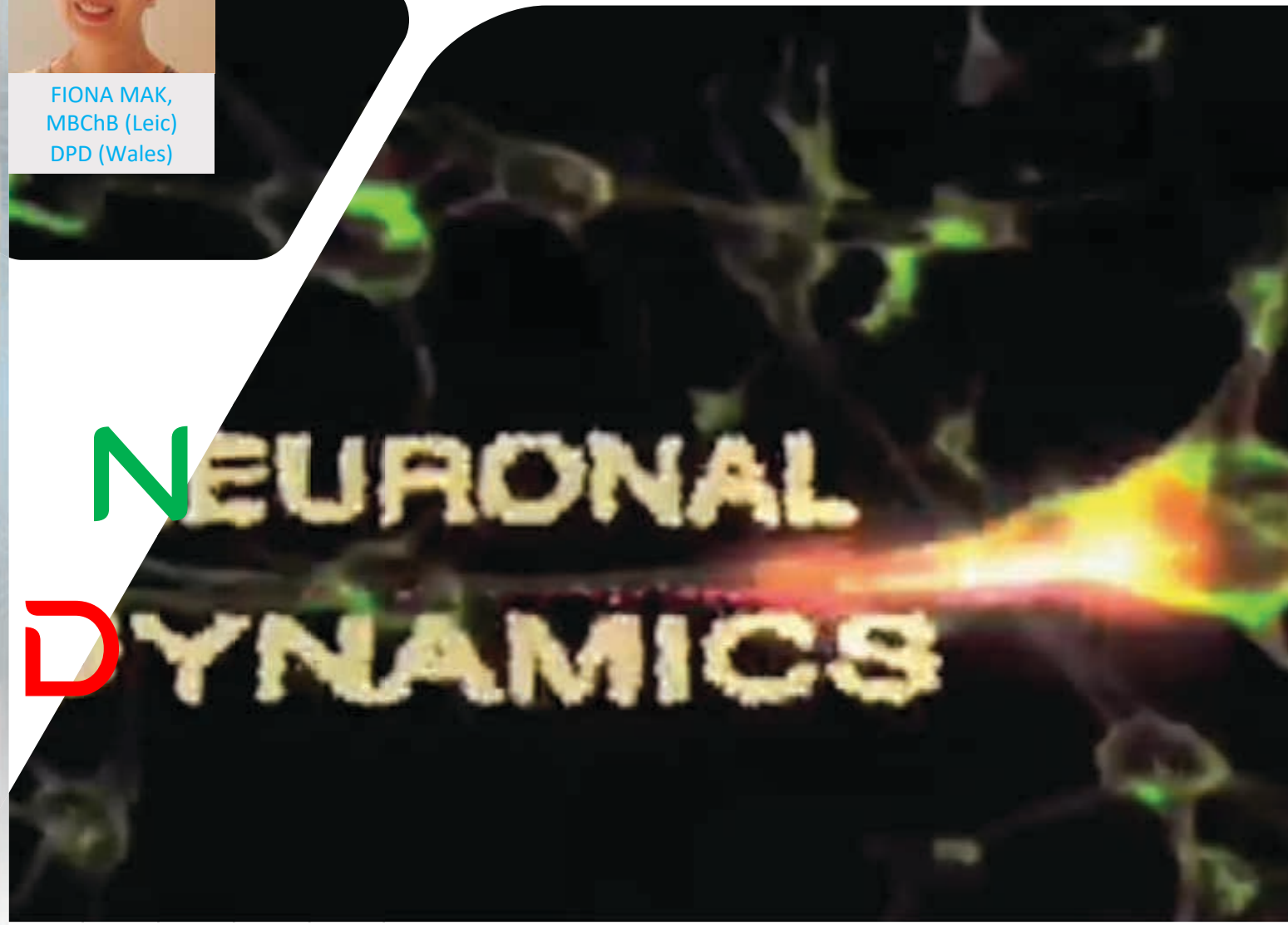


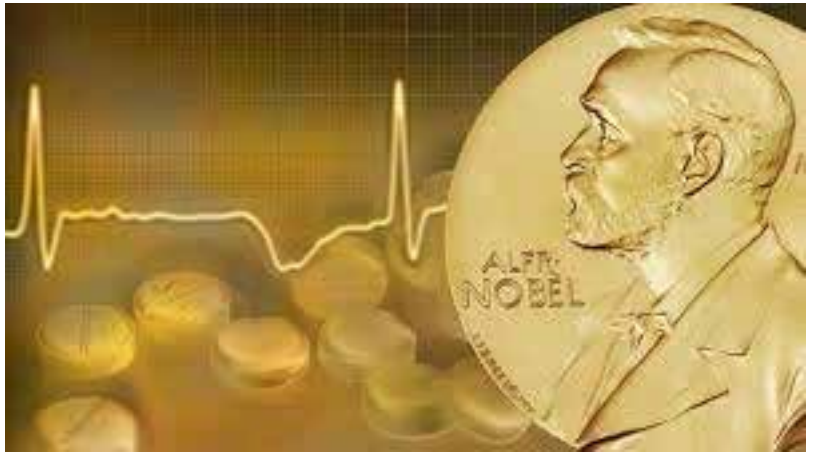
The Nobel Prize in Physiology or Medicine 1999

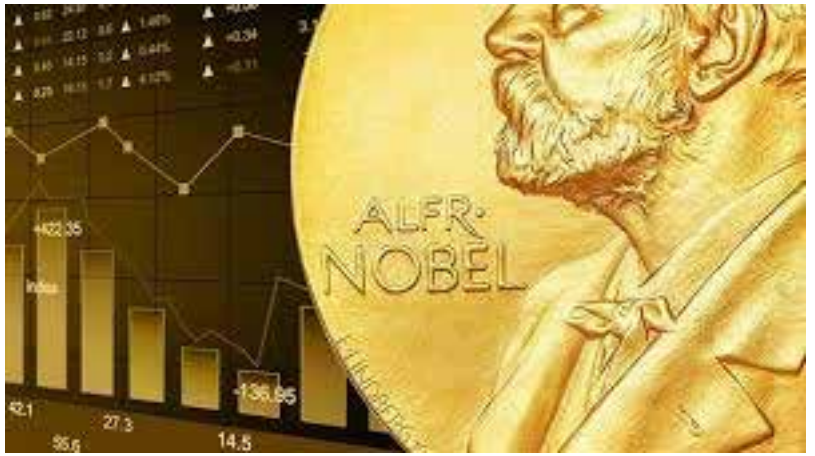
Photo from the Nobel Foundation archive.

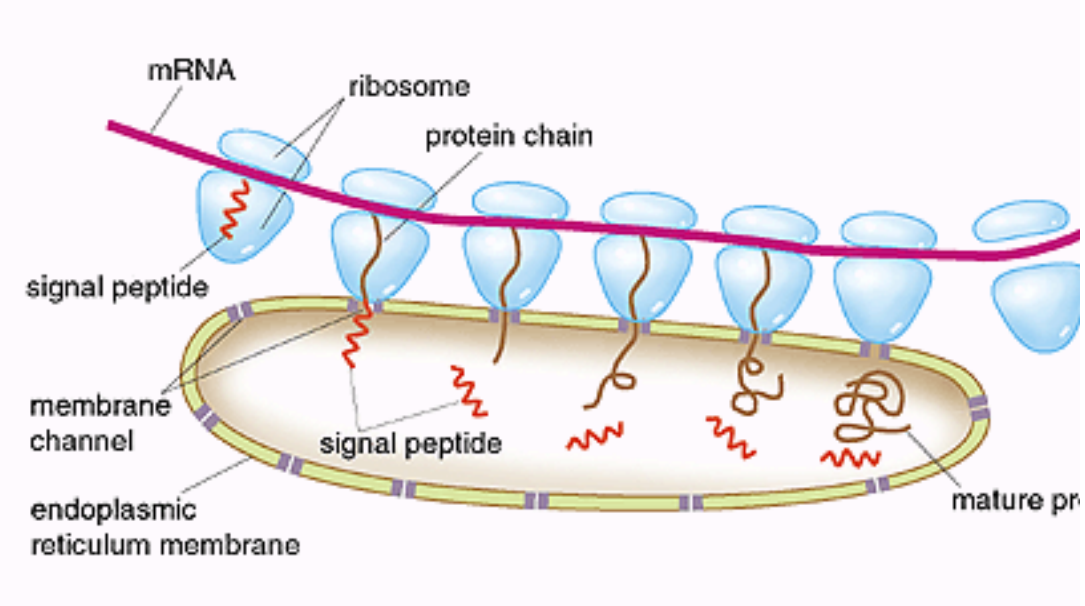
Günter Blobel

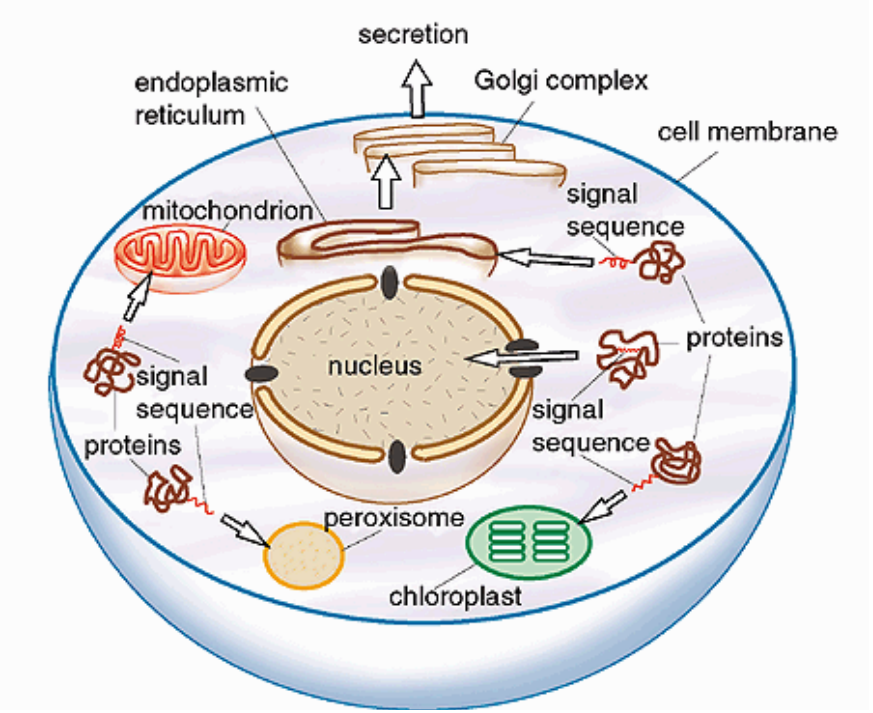
Prize share: 1/1

The Nobel Prize in Physiology or Medicine 1999 was awarded to Günter Blobel "for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell."









- "signal hypothesis". Proteins contain an intrinsic signal.

- Transport Signals can be compared to zip codes which ensure that a cell's signals arrive to another target cell

- These signal sequences are in fact a chain of different amino acids present either **as a short "tail" at one end of the protein**, or sometimes **located within the protein.**

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