HOW GENE EXPRESSION AFFECTS THE ANTIAGING PROCESS

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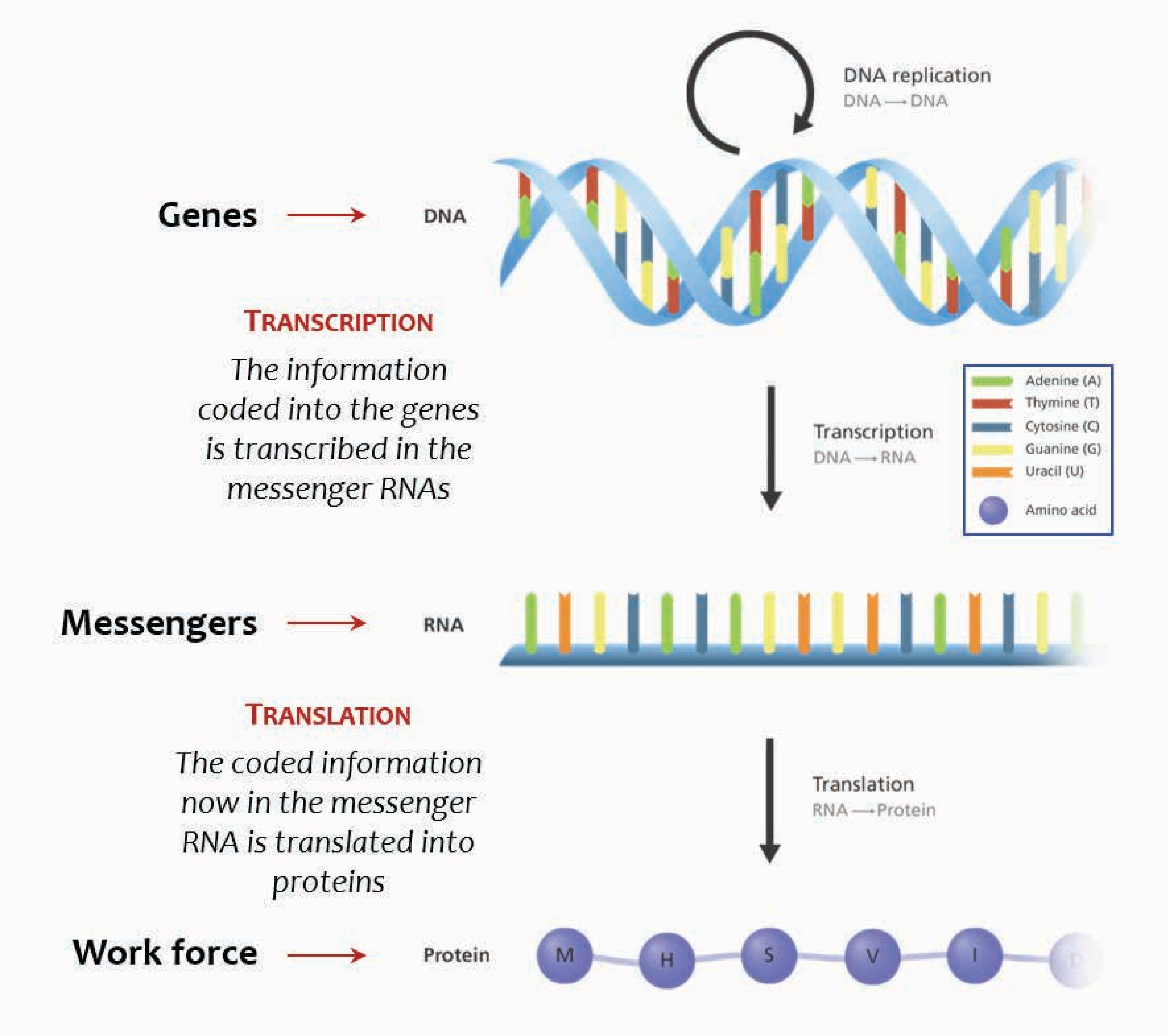
PH.D CLINICAL PSY

WHAT IS GENE EXPRESSION?

Gene expression is the process by which the **GENE INFO** OF THE DNA SEQUENCE is made into a FUNCTIONAL GENE product, such as **PROTEINS** or RNA.



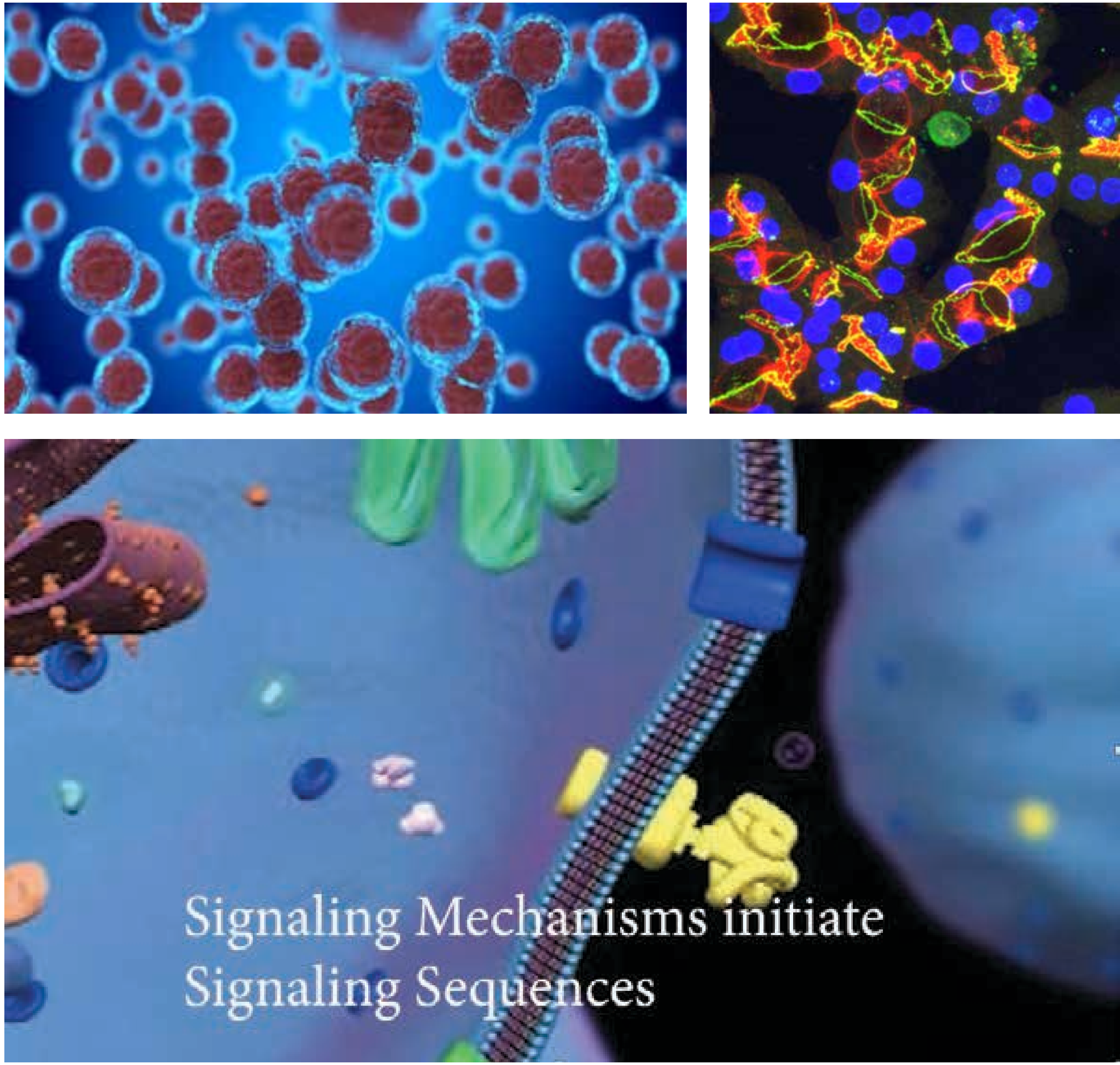
TRANSCRIPTION

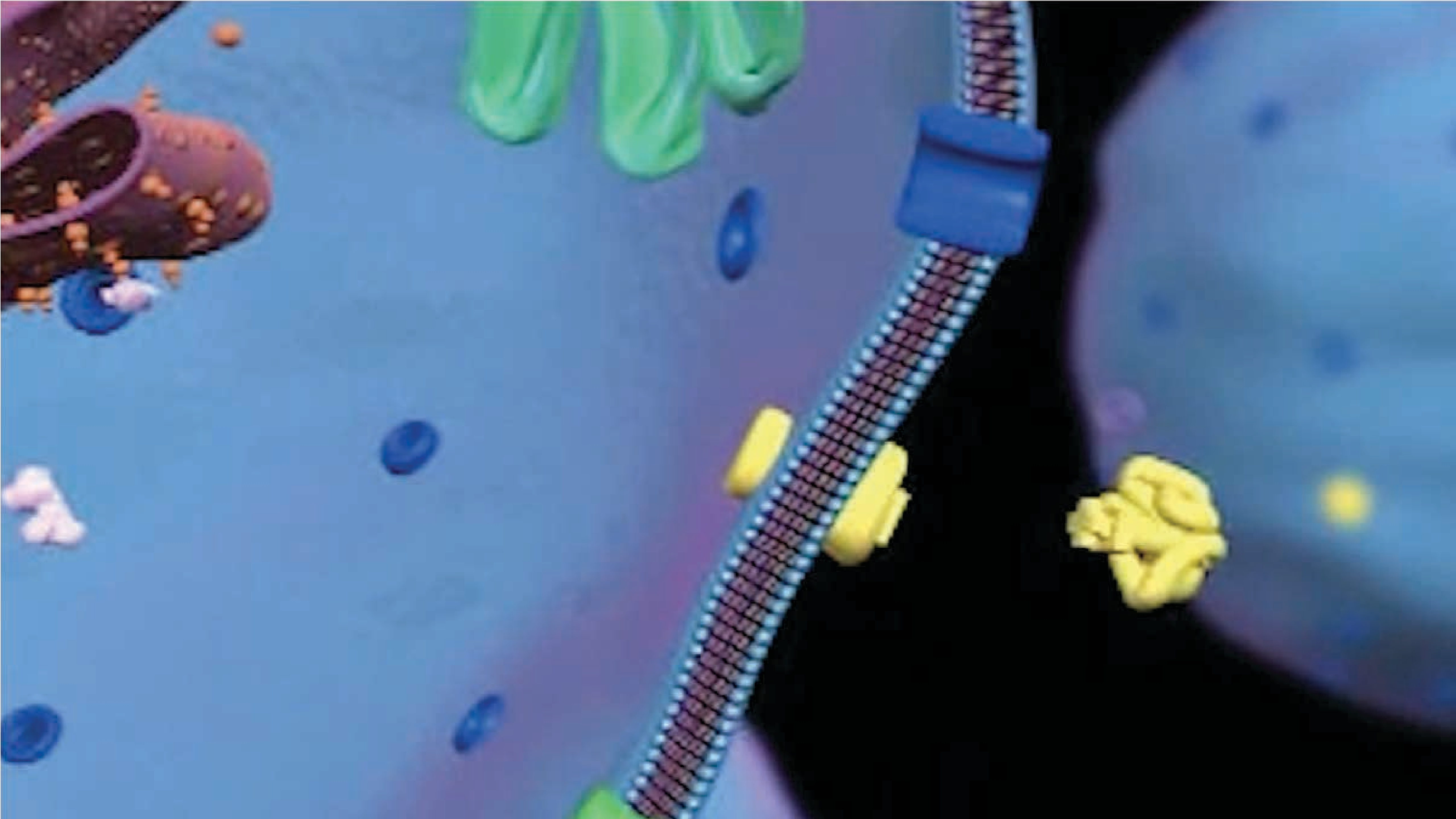
The information coded into the genes is transcribed in the messenger RNAs

TRANSLATION

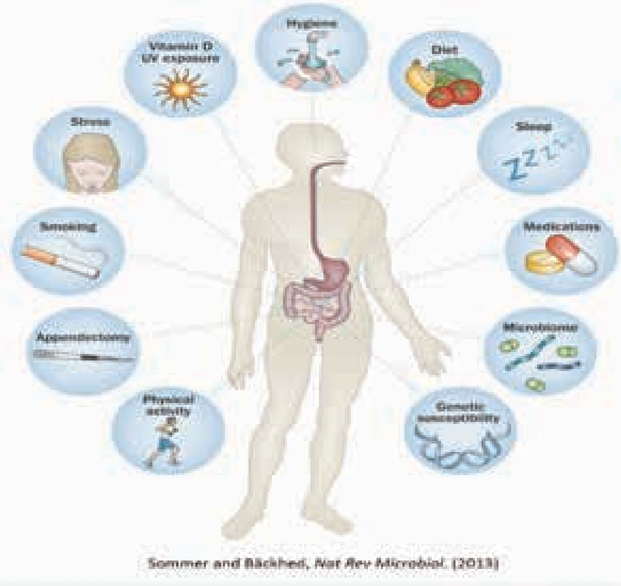
The coded information now in the messenger RNA is translated into proteins

- Signalling pathways are the key biological mechanisms that transduce extracellular signals to affect transcription factor mediated gene regulation within cells.
- Cell signalling plays a key role within biological systems
  -- i.e. to relay extracellular signals in order to regulate intracellular gene expression.

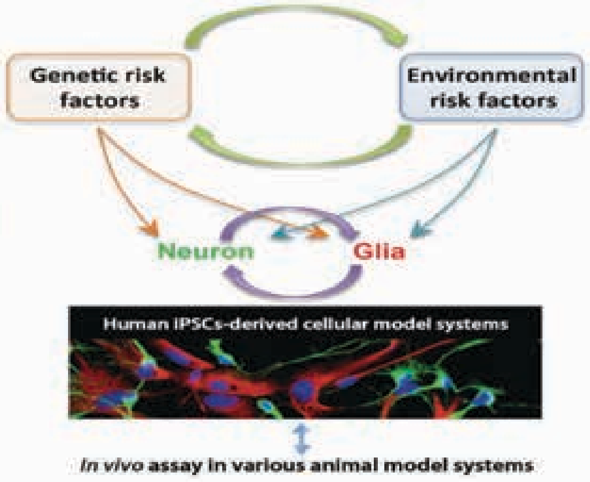




Virginie Orgogozo[1*], Baptiste Morizot[2] and Arnaud Martin[3]

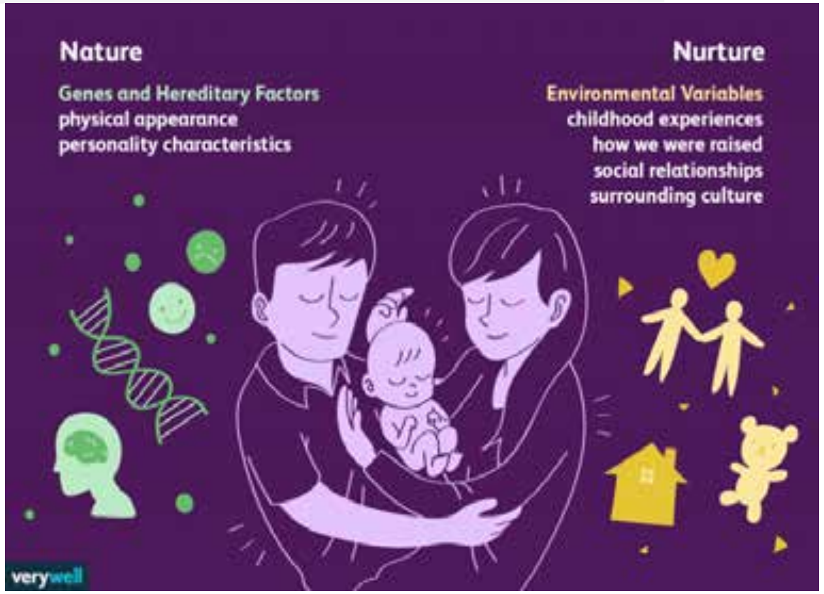


Sommer and Bäckhed, *Nat Rev Microbiol.* (2013)



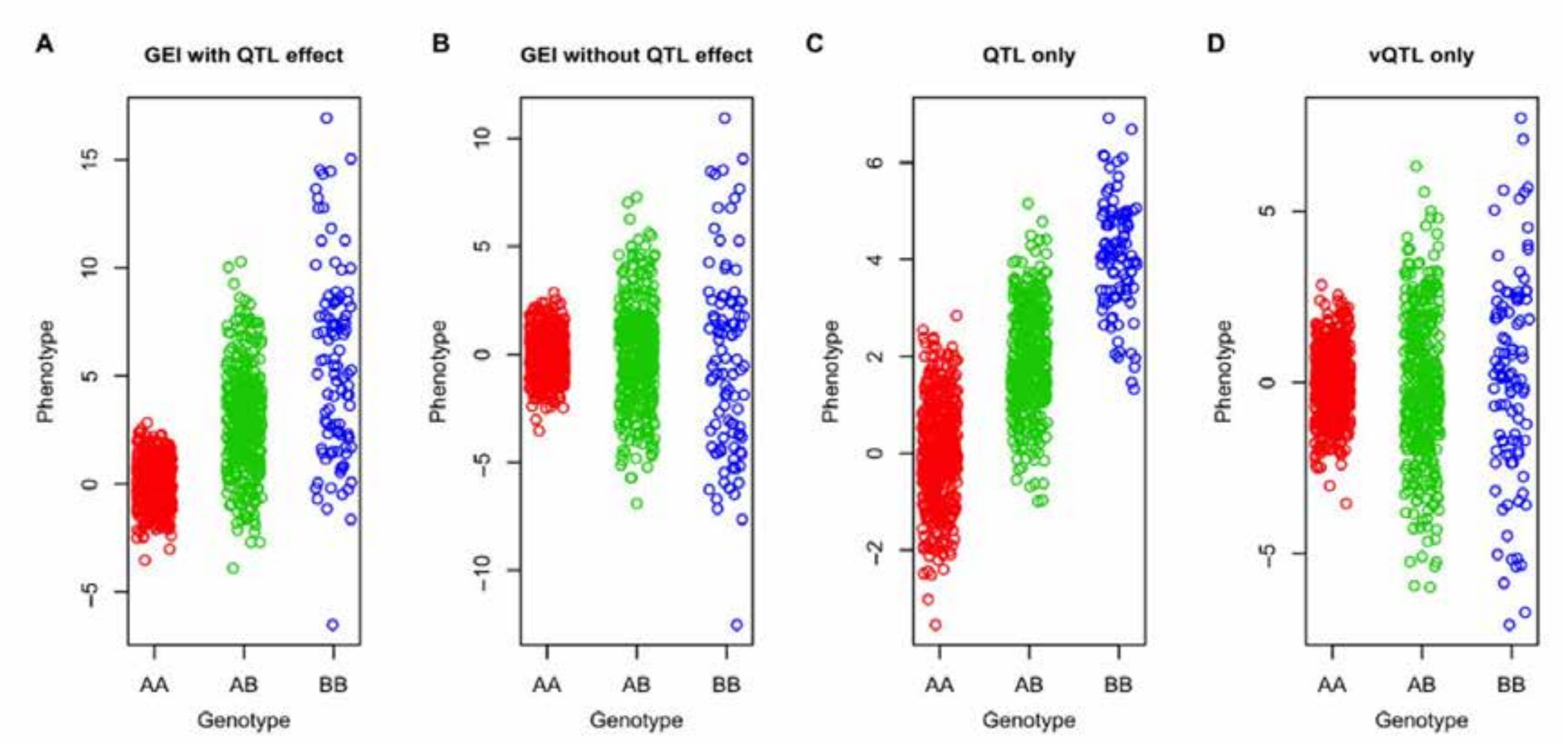
SIGNALING COMPLEXES WITHIN THE ORGANISM INTERACTING WITH SIGNALING COMPLEXES FROM THE ORGANISM'S ENVIRONMENT

SO WE CAN MAKE CHANGES IN THE ORGANISM BY CHANGING ITS ENVIRONMENT



- Gene expression is regulated by genetic effects and environmental factors (Brem et al. 2002; Cheung et al. 2003; Morley et al. 2004; Grundberg et al. 2012).
- Multiple genes interact with multiple environmental variables to produce the phenotype. (Orgogozo et al, 2015)

EFFECTS OF SMOKING, SUN AND STRESS ON THE SKIN OF TWINS



Wang et al (2019) analyzed data from more than 300,000 individuals with a known height and BMI.

ENVIRONMENT TRIGGERS GENETIC EXPRESSION FOR BMI AND OTHER OBESITY RELATED TRAITS.

HEIGHT IS AFFECTED BY BOTH ENVIRONMENT AND GENES BUT ENVIRONMENT DOES NOT AFFECT GENE EXPRESSION FOR HEIGHT

INDIVIDUALS WITH YOUTHFUL SKIN BODY &/OR FACE

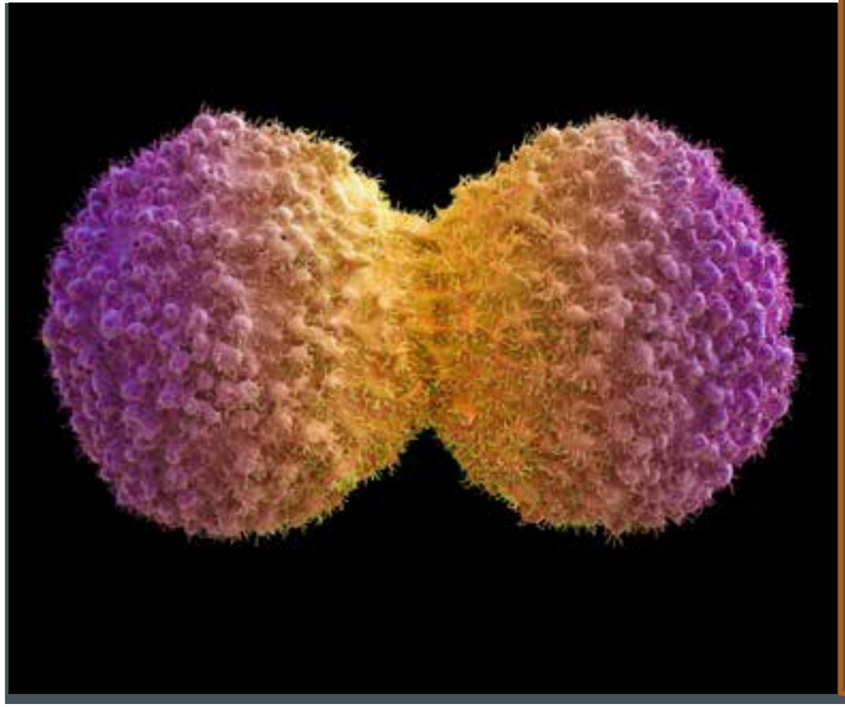
(WITHOUT BOTOX, FILLERS, LASERS, RADIOFREQUENCY, ETC)

Presented a specific gene expression profile mimicking the biology of much younger skin, as if their skin looked younger because it behaved younger

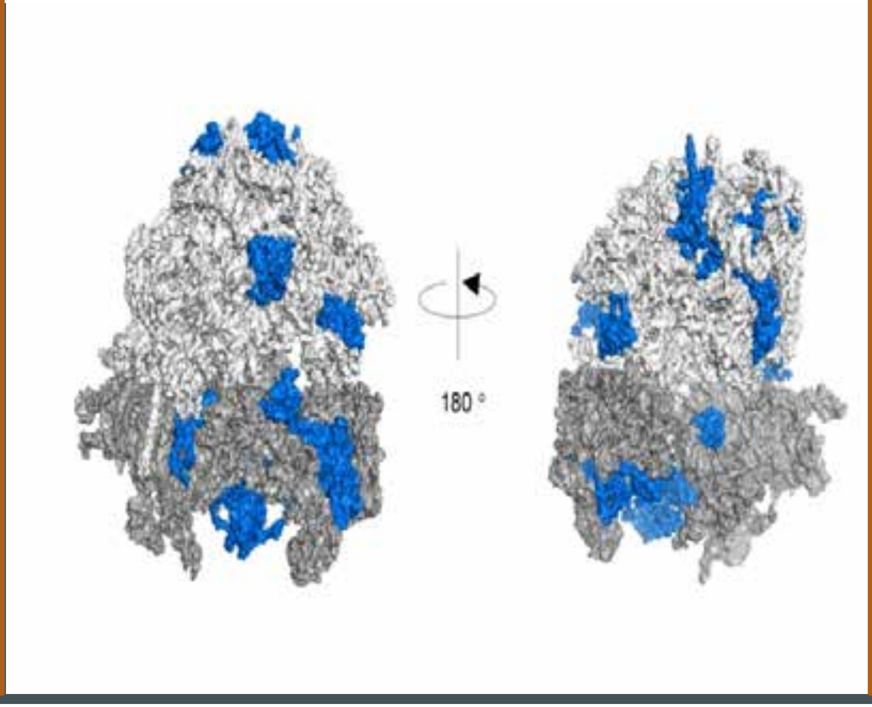
American Academy of Dermatology 2017

THE YOUNGER LOOKING OLDER WOMEN HAD INCREASED ACTIVITY IN GENES ASSOCIATED WITH OTHER BASIC BIOLOGIC PROCESSES SUCH AS:

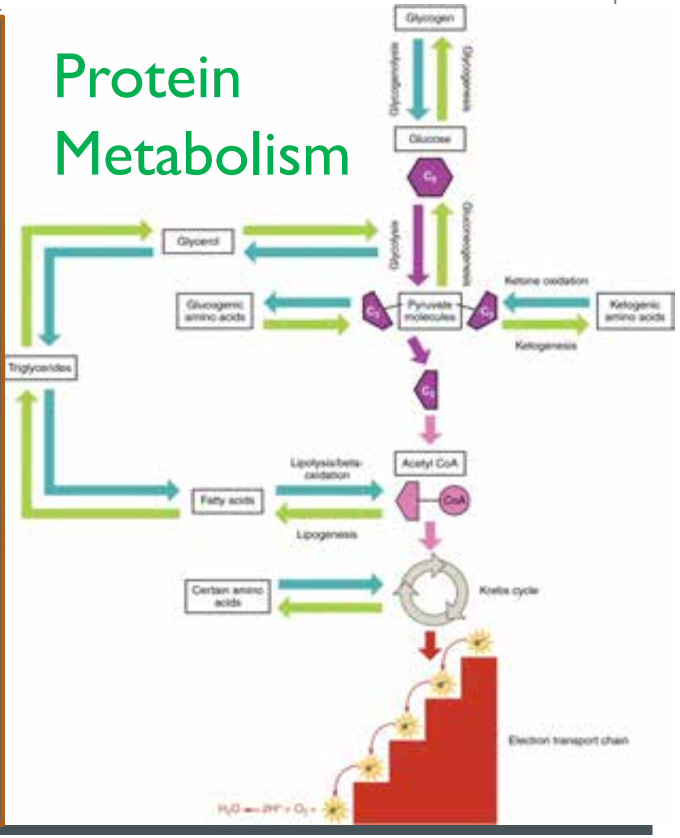
cell replication



response to oxidative stress

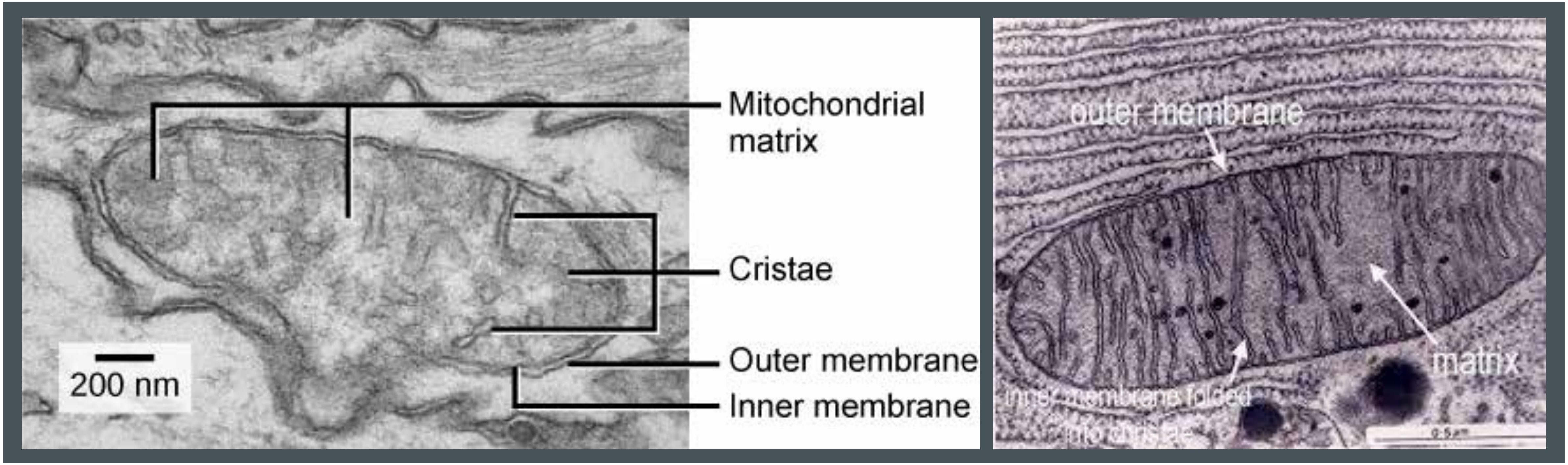


Protein Metabolism



WOMEN WITH EXCEPTIONALLY YOUTHFUL-APPEARING FACIAL SKIN IN OLDER AGE GROUPS ALSO HAD HIGHER EXPRESSION GENES ASSOCIATED WITH:

- Mitochondrial structure
- Metabolism



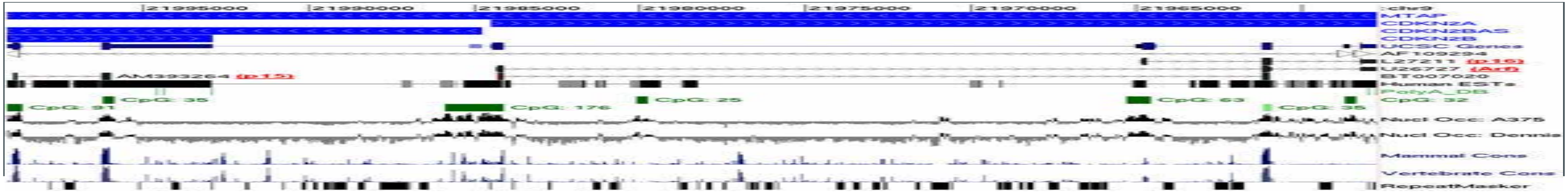
RATE OF EXPRESSION OF A GENE IS BASED ON SIGNALING

THE RATE OF EXPRESSION OF A PARTICULAR GENE IS CONTROLLED BY

1. ITS LOCATION WITHIN NUCLEOSOMES

2. NUCLEOSOME DYNAMICS INVOLVE AN INTERPLAY OF:

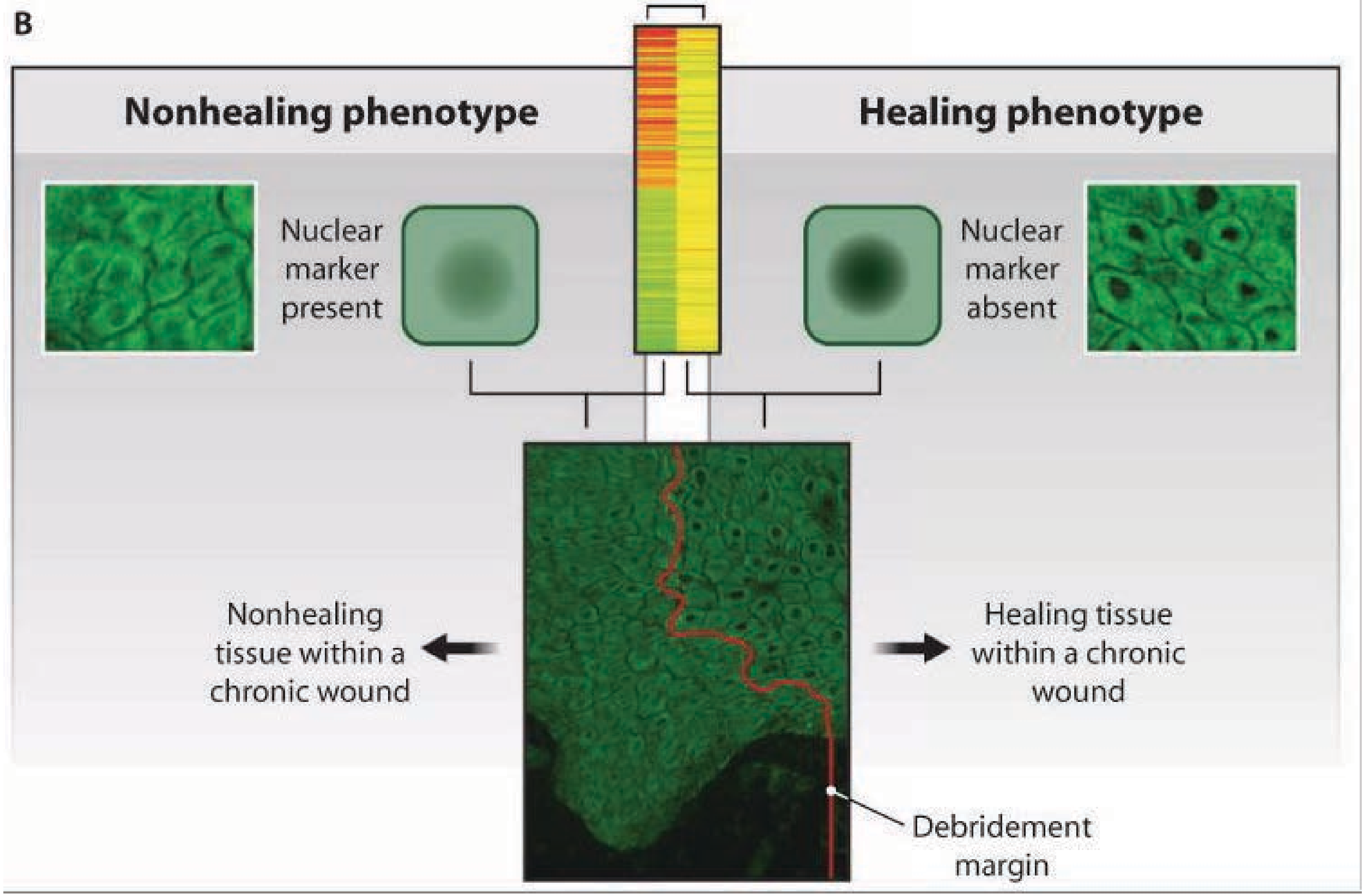
- ➢ HISTONE COMPOSITION
- ➢ HISTONE POST-TRANSLATIONAL MODIFICATION
- ➢ NUCLEOSOME OCCUPANCY AND POSITIONING WITHIN CHROMATIN
- ➢ CHROMATIN REMODELLERS
- ➢ CHAPERONES
- ➢ POLYMERASES



FUNCTIONS UNVELING COMPLEX CELL SIGNALING INTERACTIONS : SKIN

Women with exceptionally youthful-appearing facial skin in older age groups also had higher expression genes associated with:

- Overall epidermal structure
- Barrier function in their facial epidermal samples
- Dermal matrix production

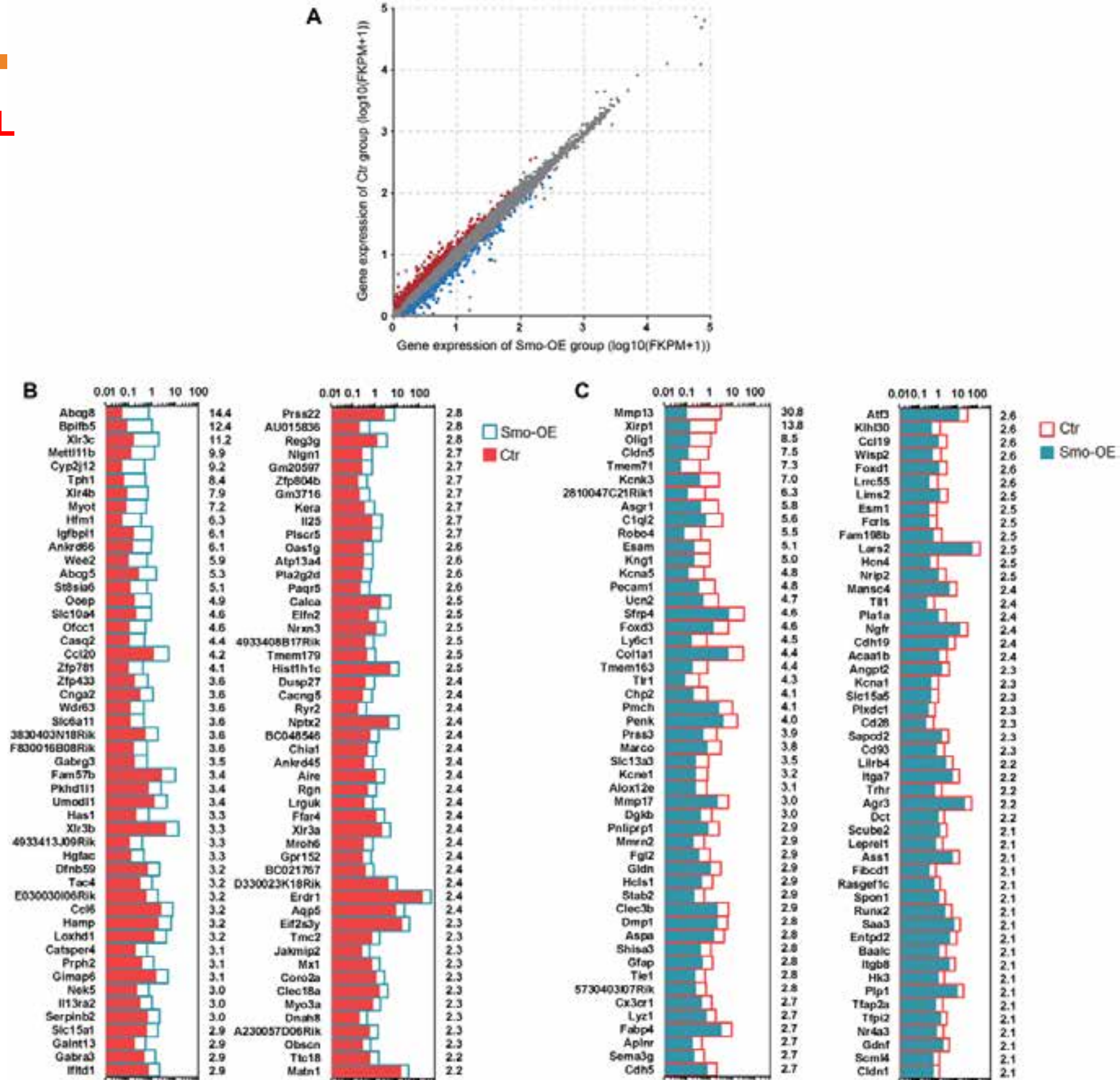


Signaling affecting wound healing – Sabine et al (2014)

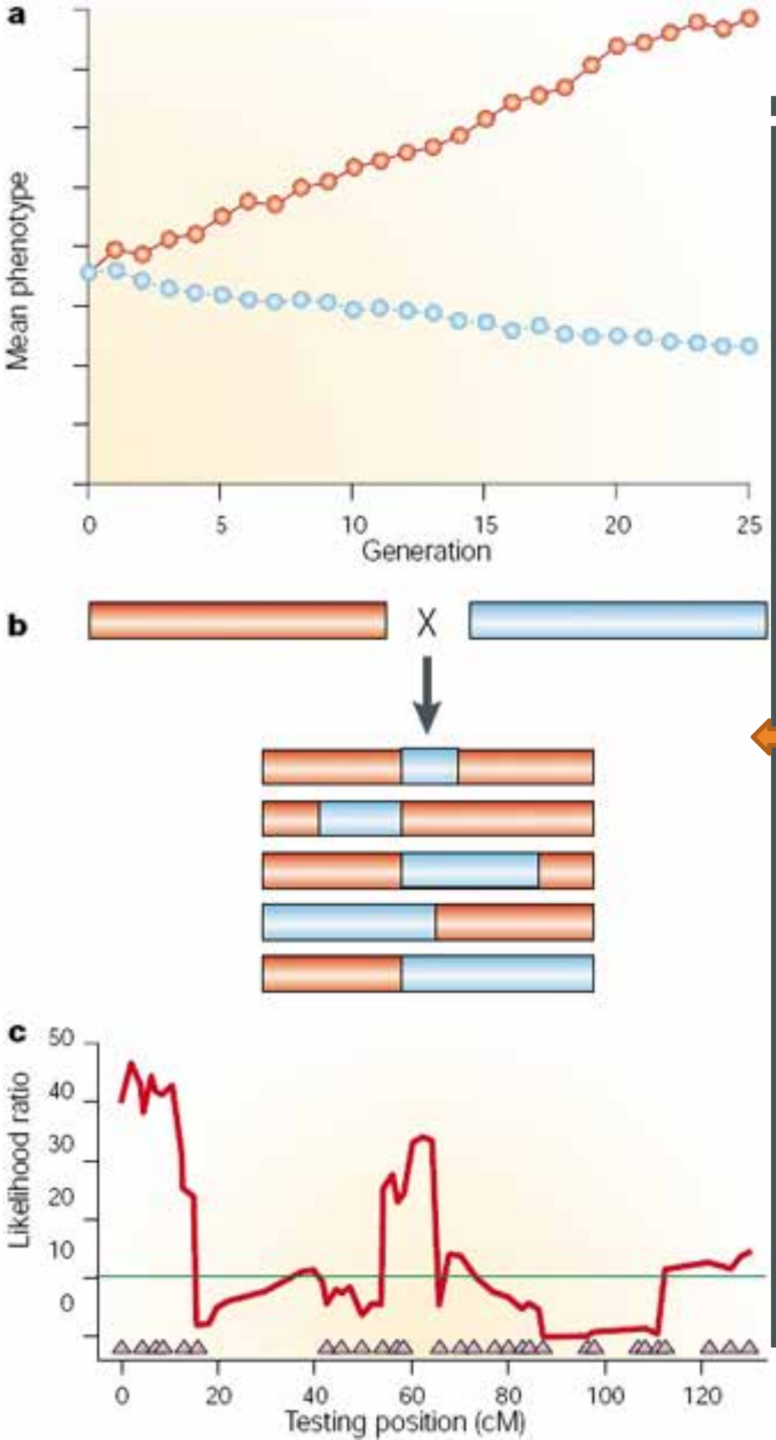
FUNCTIONS UNVELING COMPLEX CELL SIGNALING INTERACTIONS : HAIR

Women with exceptionally youthful-appearing facial skin in older age groups also had higher expression genes associated with:

- ➢Hair matrix production.



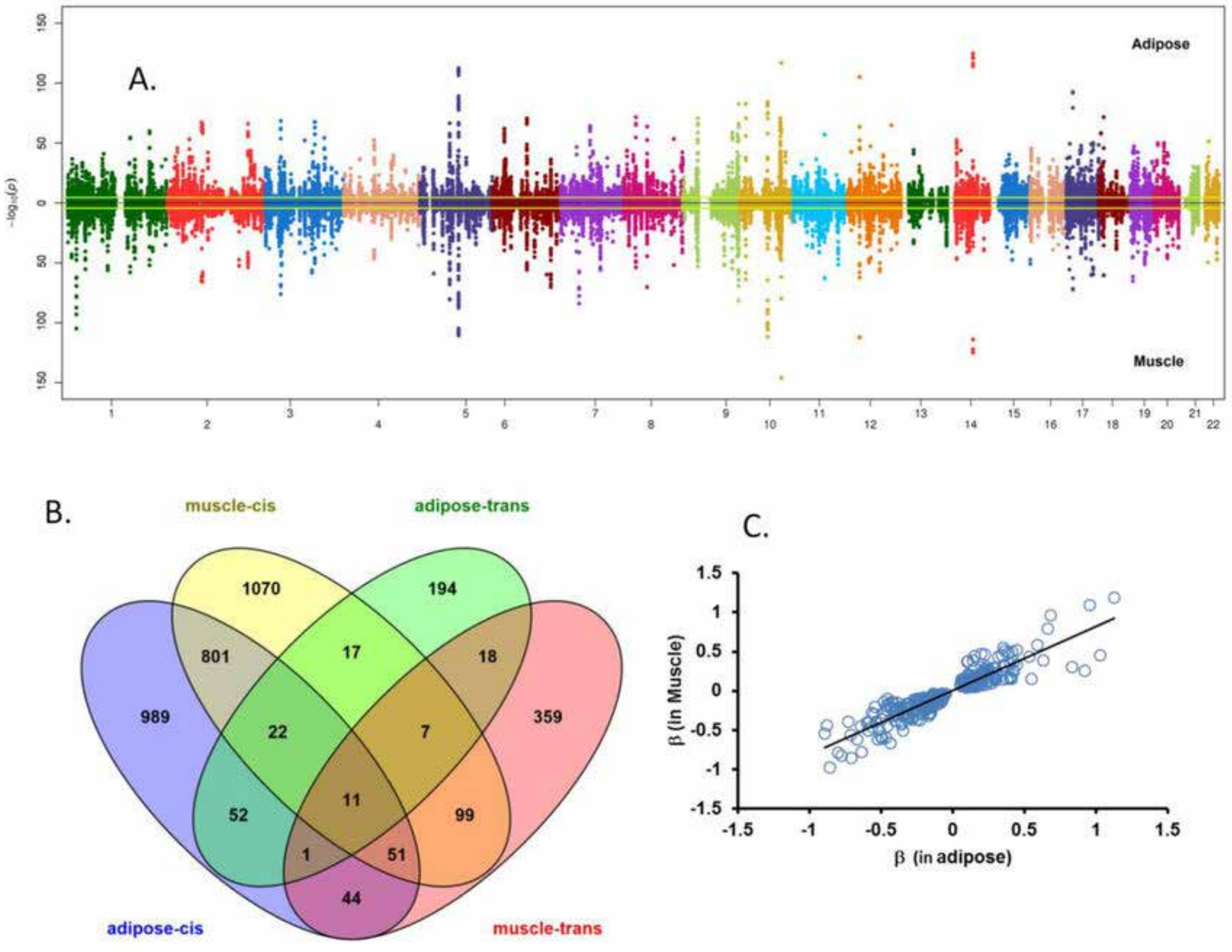
Hedgehog signaling on hair cell proliferation
Chuen et al. 2017



HOW DO WE MEASURE THESE SIGNALING INTERACTIONS?

- **A large number of studies have investigated the expression of quantitative trait loci, (eQTLs) and discovered that most genes are affected by at least one eQTL in at least one tissue (Albert and Kruglyak 2015)**
- **Quantitative trait locus** (QTL) **analysis** is a statistical method which links the phenotypic data (**trait** measurements) to genotypic data (usually molecular markers) to explain the genetic basis of variation underlying complex **traits** (Miles and Wayne, 2008).

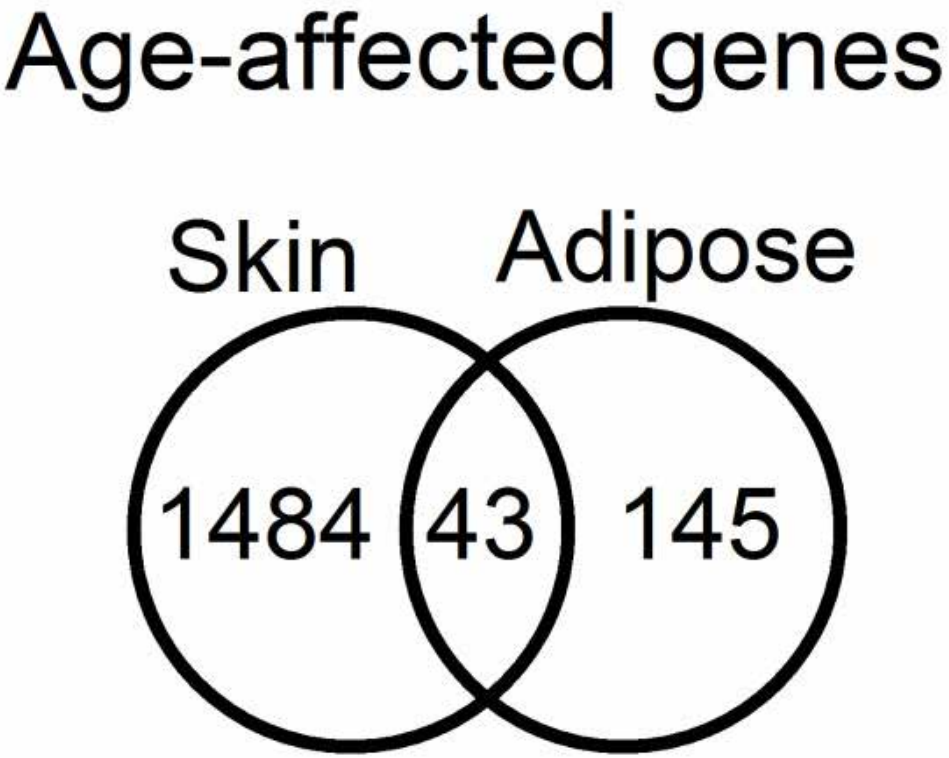
- A **quantitative trait locus** (**QTL**) is a region of DNA associated with a particular trait
- This trait is ultimately determined by genes and their environment.
- QTLs may be on different chromosomes.
- The number of QTLs indicates the genetic architecture of a trait.



SKIN SHOWS THE MOST AGE-RELATED GENE EXPRESSION CHANGES OF ALL THE TISSUES INVESTIGATED

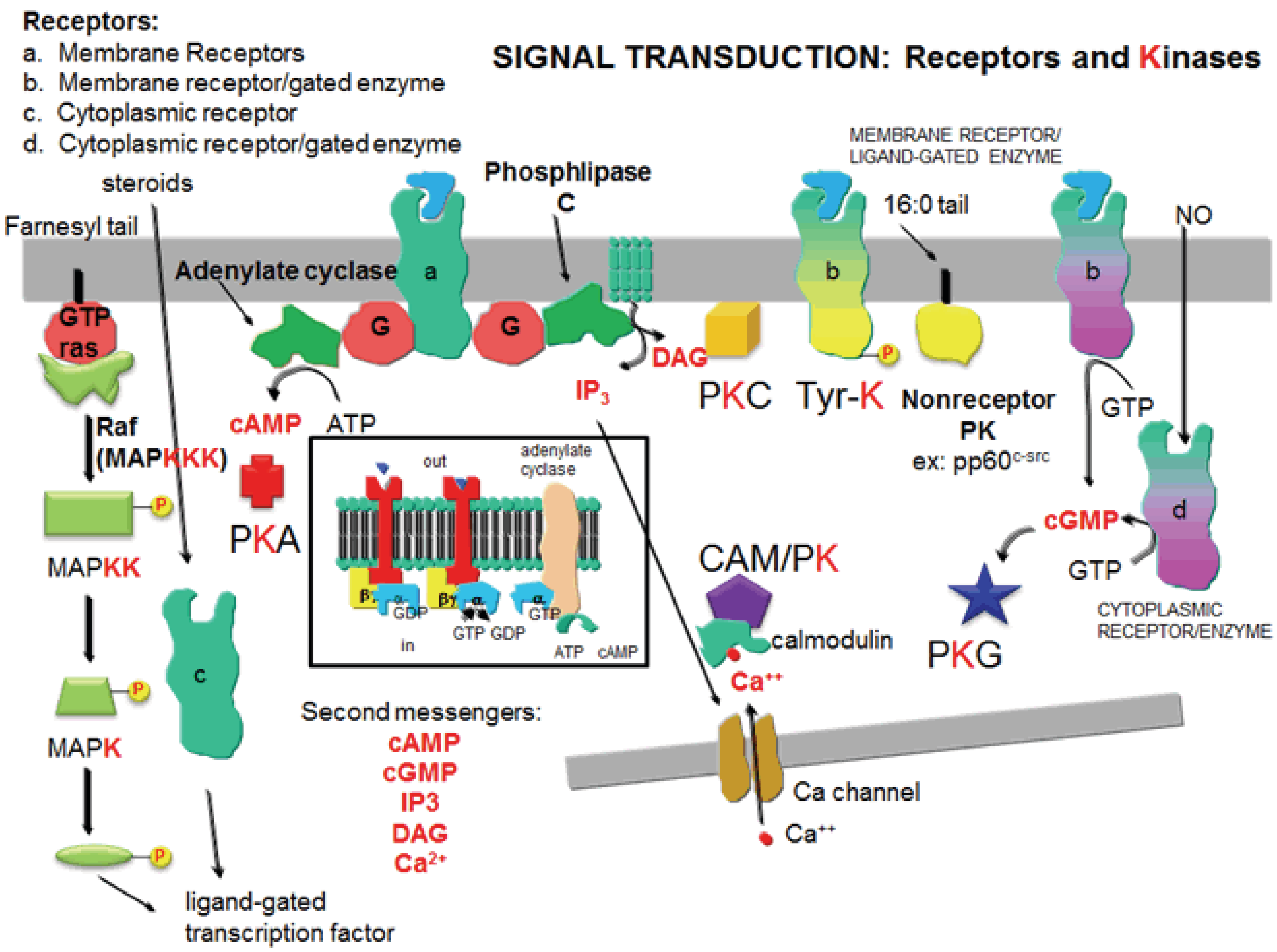
- Glass et al (2013) demonstrated that gene expression **changes with age in skin, adipose tissue, blood and brain**

- Skin shows most age-related gene expression with genes involved in
  1. Fatty acid Metabolism
  2. Mitochondrial Activity
  3. Cancer
  4. DNA / RNA Splicing
- A significant proportion of age-related changes in gene expression appear to be tissue-specific with only a few genes sharing an age effect in expression across tissues.



The 43 shared genes in skin and adipose tissue showed a single common identifiable pathway related to the stress response.

- SIGNAL TRANSDUCTION MAY BE INITIATED BY THE BINDING OF A LIGAND TO A MEMBRANE-BOUND RECEPTOR
- THIS TRIGGERS A CASCADE OF INTERCELLULAR SIGNALLING ACTIVITIES THROUGH MULTIPLE KINASES
- AND IMPACTS ON HOW TRANSCRIPTION FACTORS REGULATE DOWNSTREAM GENE EXPRESSION.



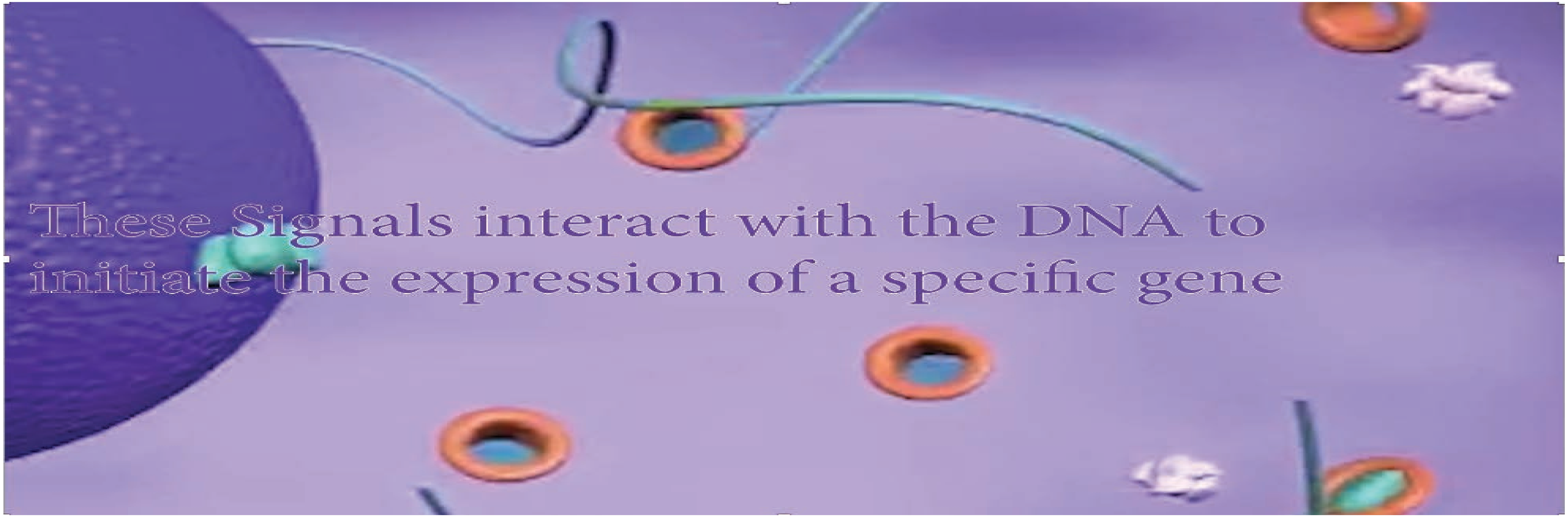
SIGNAL TRANSDUCTION: Receptors and Kinases

Receptors:

a. Membrane Receptors
b. Membrane receptor/gated enzyme
c. Cytoplasmic receptor
d. Cytoplasmic receptor/gated enzyme

Second messengers:
cAMP
cGMP
IP3
DAG
Ca^{2+}

CELLS DETECT INPUT SIGNALLING MOLECULES USING RECEPTORS, PROTEINS USUALLY LOCATED ON THE CELL SURFACE WHICH TRANSMIT THE SIGNAL TO THE INTERIOR OF THE CELL THROUGH A SERIES OF DOWNSTREAM PROCESSES THAT TYPICALLY LEAD TO CHANGES IN GENE EXPRESSION, RESULTING IN AN APPROPRIATE OUTPUT RESPONSE TO THE INPUT.

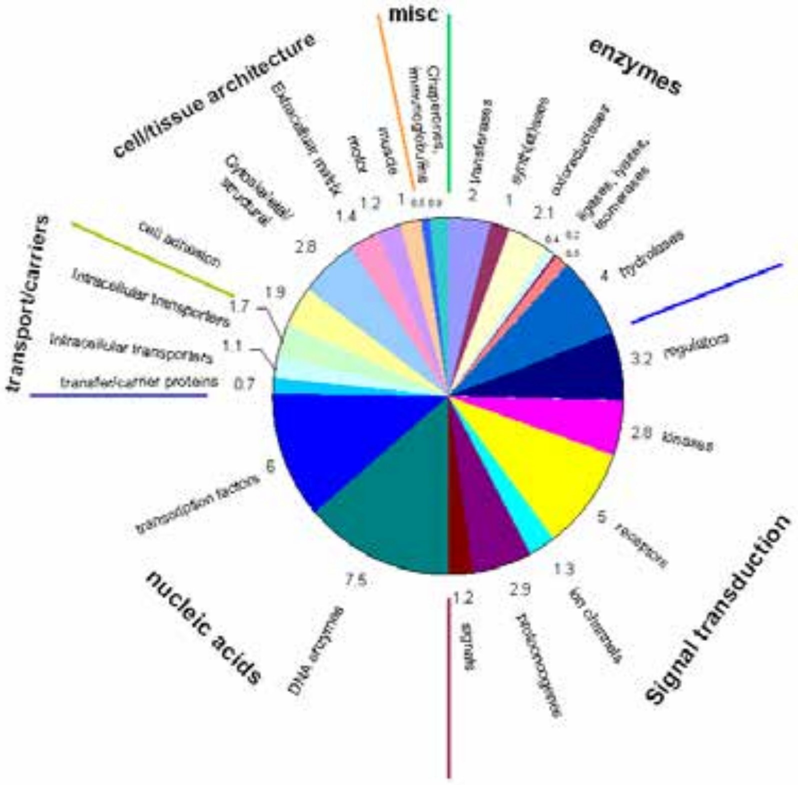


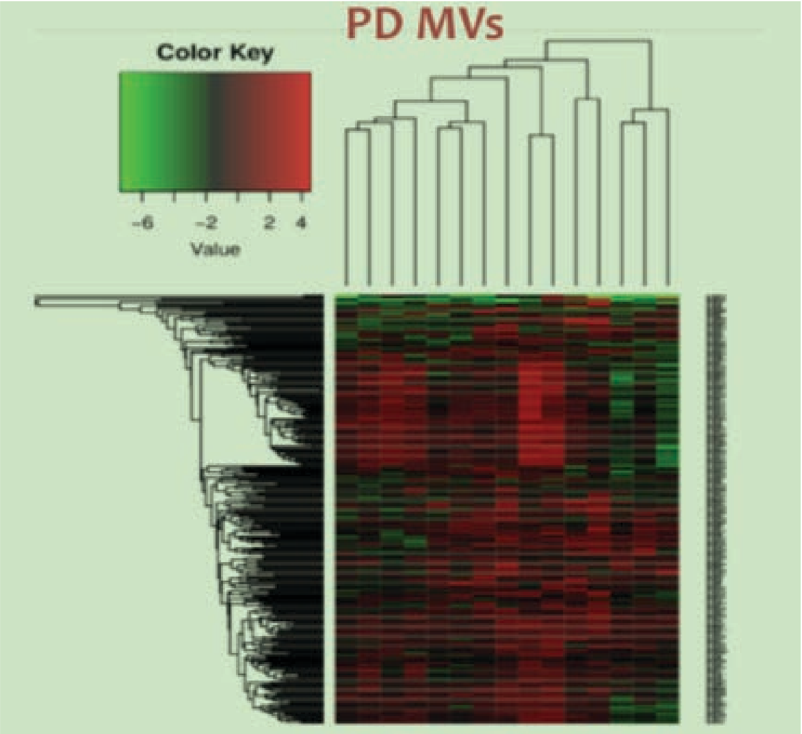
These Signals interact with the DNA to initiate the expression of a specific gene

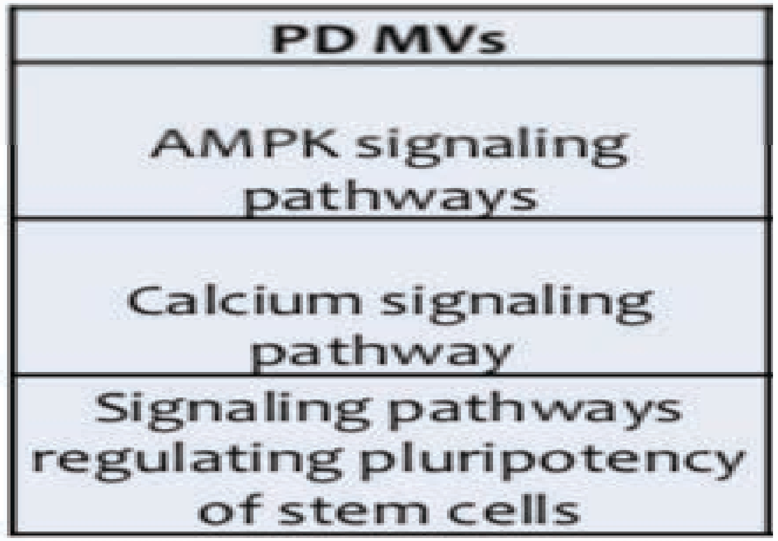
The coordinated activity of different signalling pathways within and between multiple cell types is the basis of many important biological processes, such as gene expression involved in human development, tissue repair and immunity.

DISTRIBUTION OF MOLECULAR FUNCTIONS OF 26,383 HUMAN GENES. % OF TOTAL GENE NUMBER. 42% UNKNOWN FUNCTION

Adapted from Science, 291, 1335 (2001)

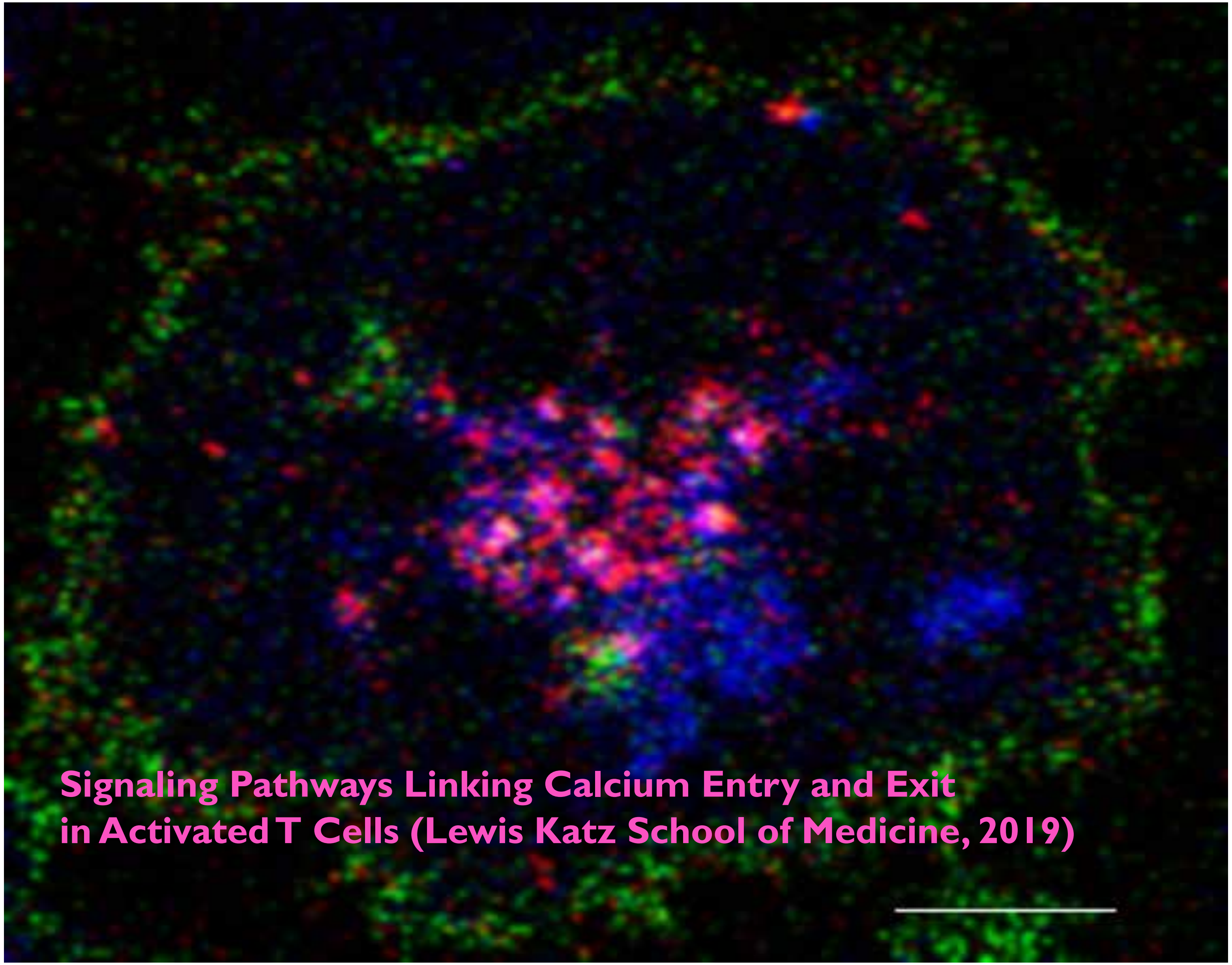






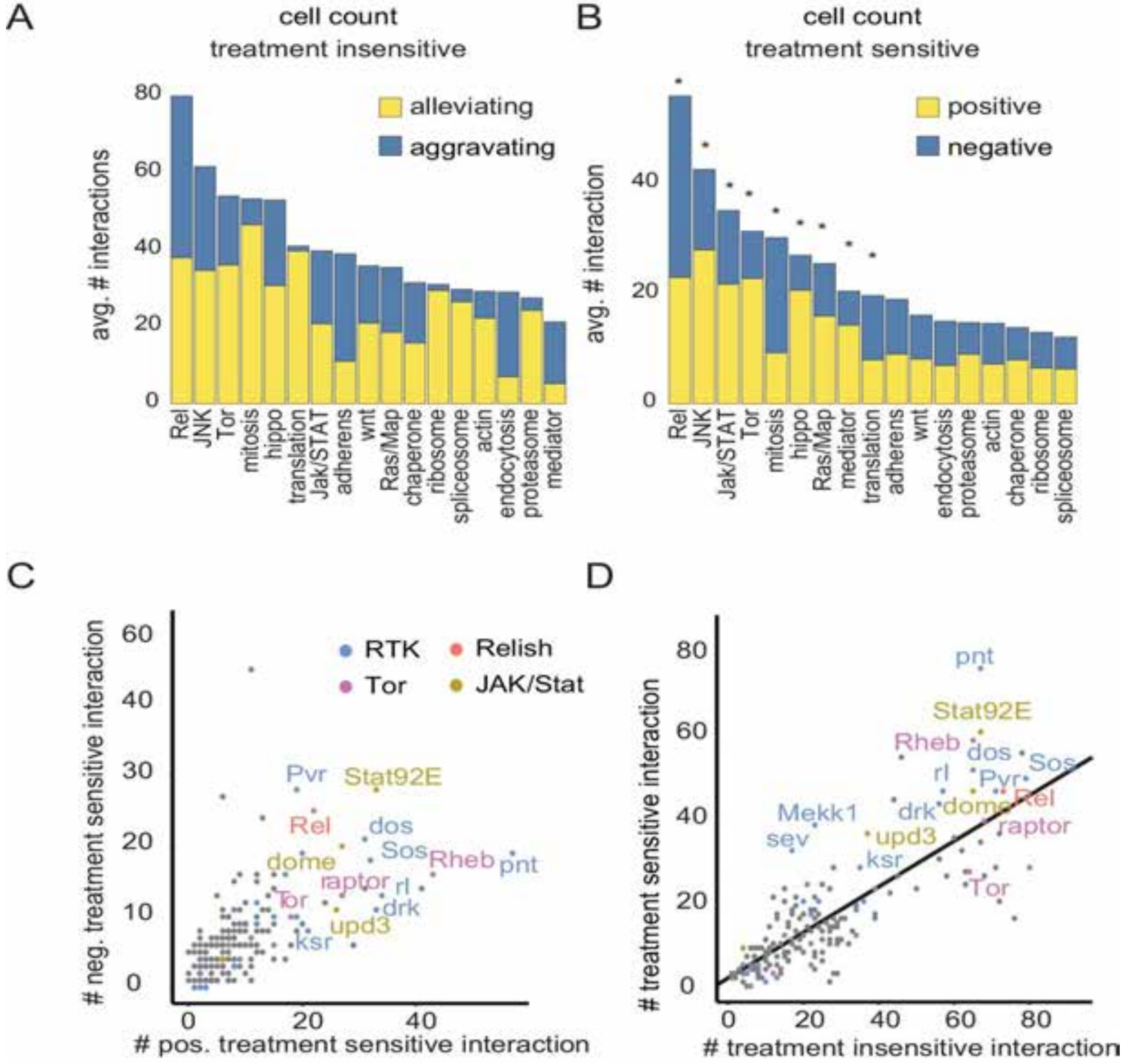
PD MVs
AMPK signaling pathways
Calcium signaling pathway
Signaling pathways regulating pluripotency of stem cells

- The response of biological systems to changing environmental conditions and aging factors is a dynamic process.
- Activation of different signalling pathways can lead to numerous physiological or cellular responses, such as:
  * cell proliferation
  * cell death
  * cell differentiation
  * cell metabolism
- Signalling determines the aging process



Signaling Pathways Linking Calcium Entry and Exit in Activated T Cells (Lewis Katz School of Medicine, 2019)

- A clear understanding of the activity / interaction between signalling pathways can help to design rational disease treatment &
- Tissue regeneration strategies for Anti-aging Medicine.



- We can identify the important signalling pathways of a cell by using gene expression and protein-protein interaction (PPI) data sets.
- Extensive, publicly available PPI data provide an opportunity to establish a general signalling pathway blueprint, to which cell type-specific gene expression data can be mapped
- We can then refine the general signalling pathway blueprint into a cell-type specific blueprint.

GENE EXPRESSION

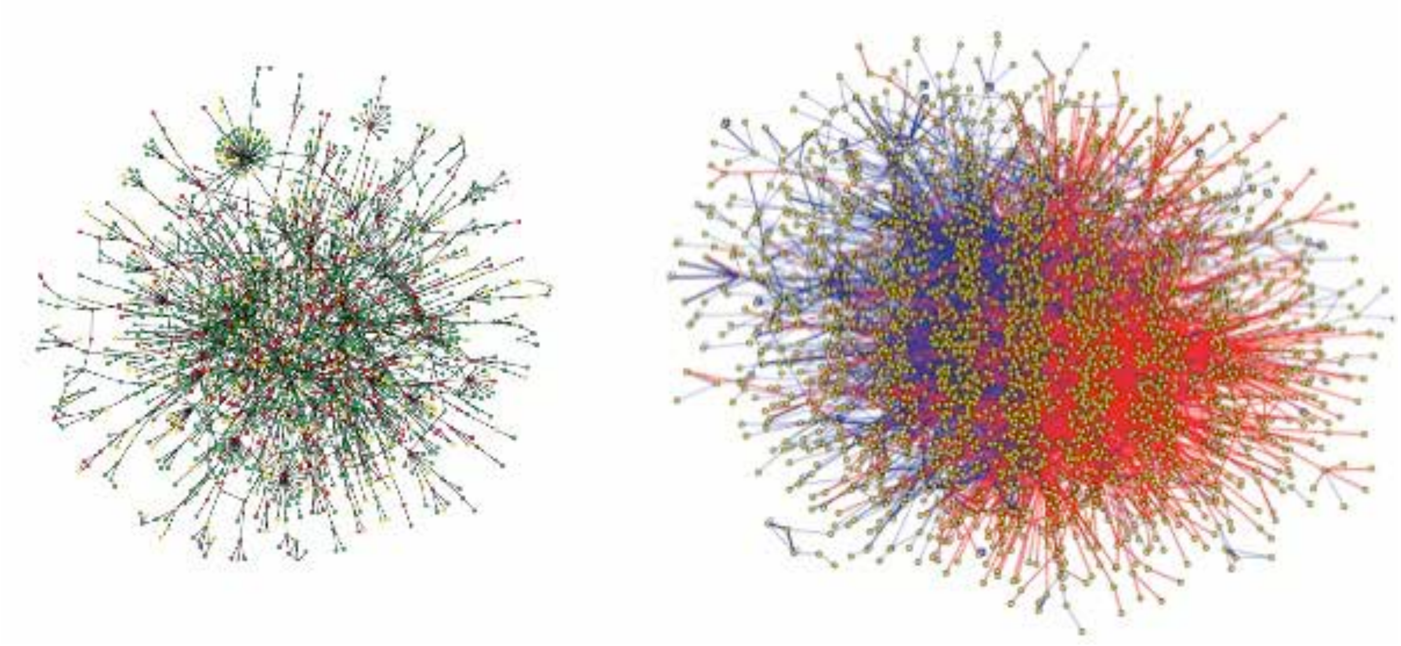
PROTEIN TO PROTEIN INTERACTIONS (PPI)

GENERAL SIGNALING PATHWAY BLUEPRINT

MAP CELL TYPE-SPECIFIC GENE EXPRESSION

REFINE GENERAL SIGNALING PATHWAY BLUEPRINT TO A SIGNALING PATHWAY BLUEPRINT

- A number of computational methods utilize PPI data along with gene expression data to uncover known signalling pathways.



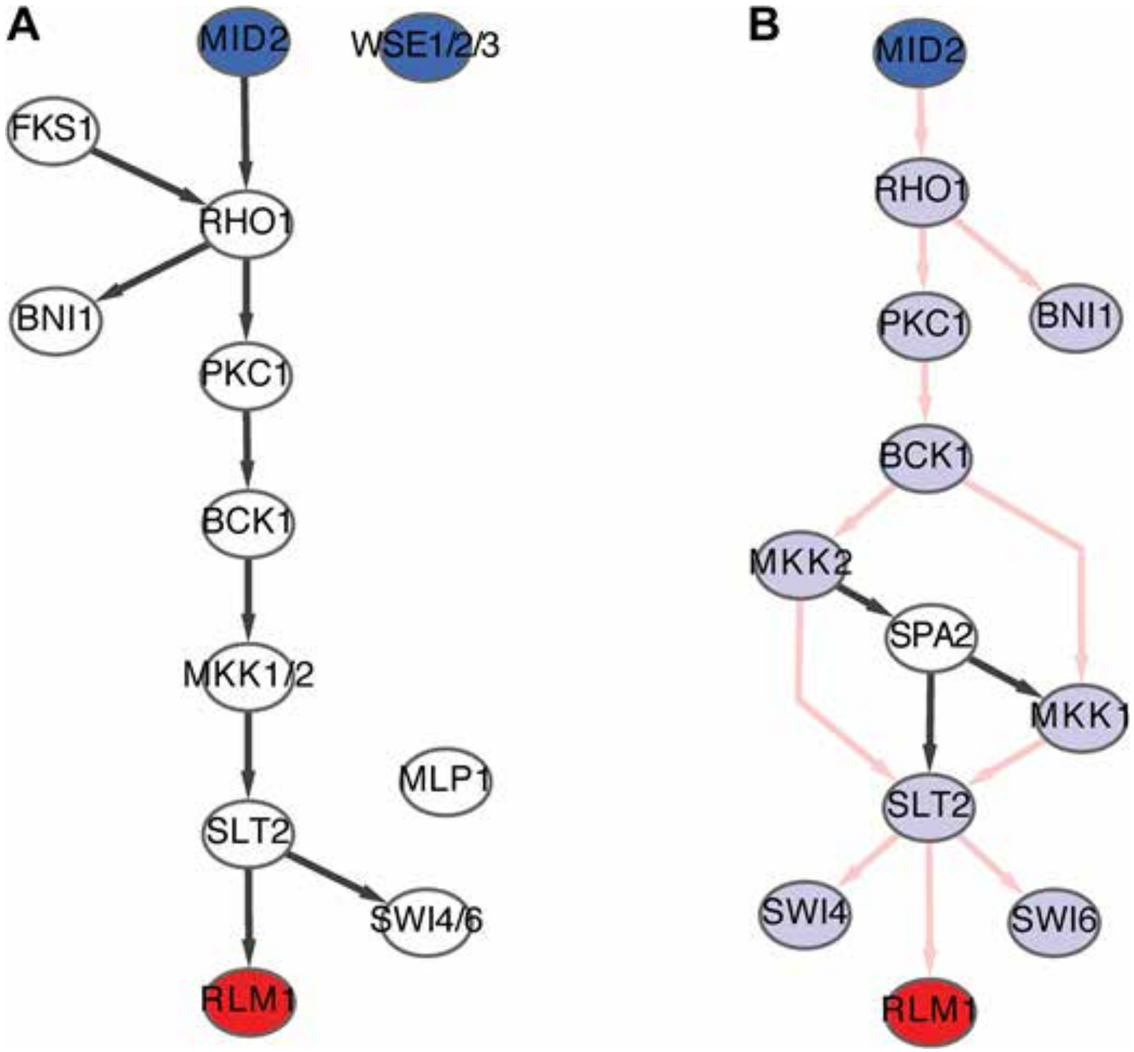
The **interactome** is the totality of PPIs that happen in a cell, an organism or a specific biological context.

Protein-protein interaction networks (PPIN) are mathematical representations of the physical contacts between proteins in the cell.

HYBRID INTELLIGENT APPROACH FOR IDENTIFYING DIRECTED SIGNALING PATHWAYS (HISP)

- A recently published method is called *HISP*
- It applies genetic algorithms relevant to:
  - selection
  - crossover
  - mutation
- It selects the topologies of resultant signalling pathways
- It uses gene knockout data to get directionality of the signalling pathways.

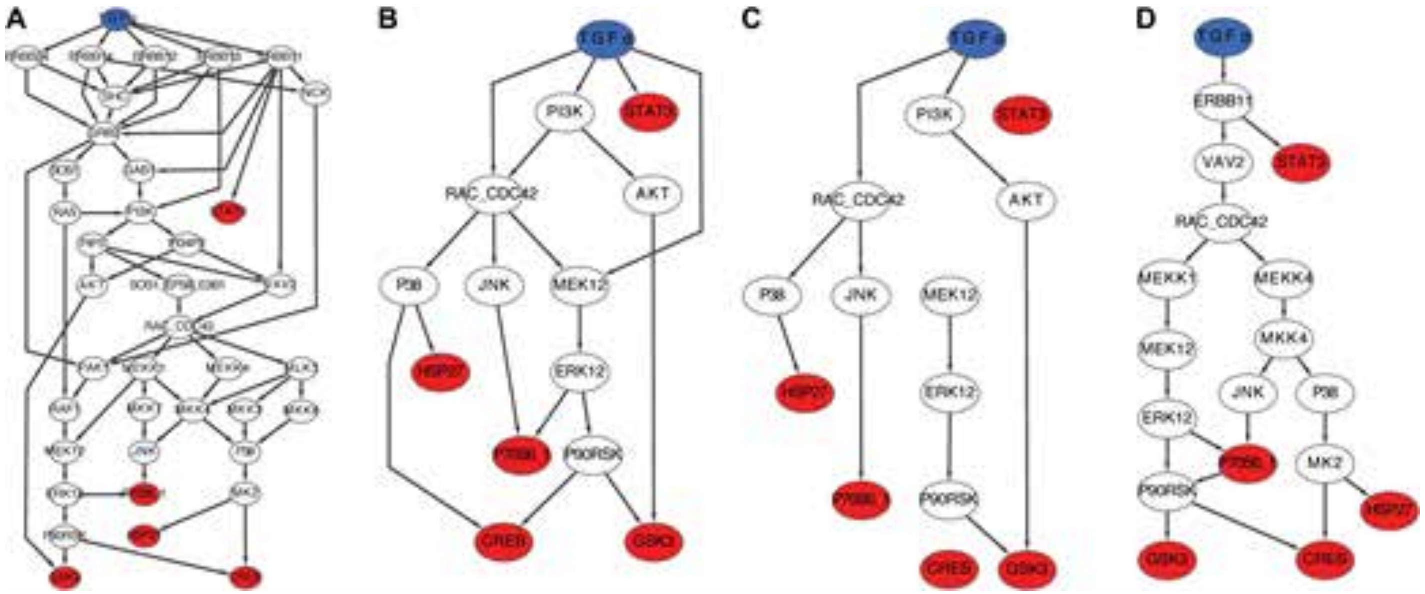
The signaling network of cell wall integrity



Dark blue points are starting points and the red ones are ending points.

INCREASING LEVELS OF COMPLEXITY

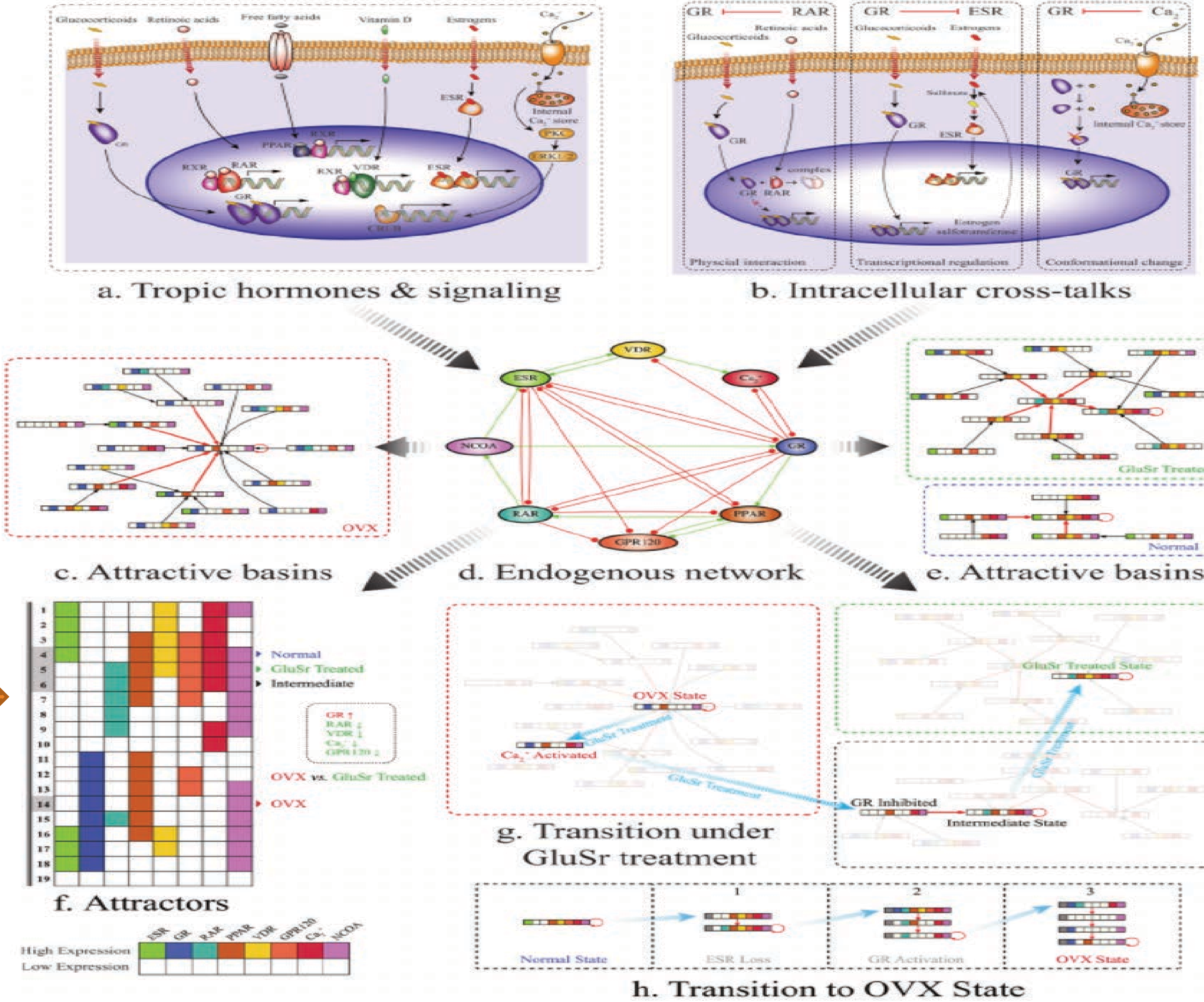
- EGFR/ErbB signaling pathway in human hepatocytes, HISP unveils a high-resolution signaling pathway, where many signaling interactions were missing by existing computational approaches.



EGFR/ErbB signaling pathway in human hepatocytes.

Signalling technology offers the most direct and comprehensive method in both understanding gene expression and in utilizing interactions between specific signalling pathways and gene expression as a successful interventions in several diseases as well as in Anti-aging Medicine.

Schematic diagrams of the proposed molecular mechanism for osteoporosis due to osteoblast function loss



GENE EXPRESSION YOUNG = OLD / YOUTHFUL APPEARANCE

The gene expression patterns from the women in the study who were younger appearing were similar to those in women who were actually younger in age.

Older women with Youthful Appearance had increased gene activity related to DNA Repair

American Academy of Dermatology 2017

ATGGGCACTGCTGGAAAAGTTATTAAATGCAAAGCAGCTGTGCTTTGGGAGCAGAAGCAACCCTTCTCCATTGAGGAAATAGA
AGTTGCCCCACCAAAGACTAAAGAAGTTCGCATTAAGATTTTGGCCACAGGAATCTGTCGCACAGATGACCATGTGATAAAAG
GAACAATGGTGTCCAAGTTTCCAGTGATTGTGGGACATGAGGCAACTGGGATTGTAGAGAGCATTGGAGAAGGAGTGACTACA
GTGAAACCAGGTGACAAAGTCATCCCTCTCTTTCTGCCACAATGTAGAGAATGCAATGCTTGTCGCAACCCAGATGGCAACCT
TTGCATTAGGAGCGATATTACTGGTCGTGGAGTACTGGCTGATGGCACCACCAGATTTACATGCAAGGGCAAACCAGTCCACC
ACTTCATGAACACCAGTACATTTACCGAGTACACAGTGGTGGATGAATCTTCTGTTGCTAAGATTGATGATGCAGCTCCTCCT
GAGAAAGTCTGTTTAATTGGCTGTGGGTTTTCCACTGGATATGGCGCTGCTGTTAAAACTGGCAAGGTCAAACCTGGTTCCAC
TTGCGTCGTCTTTGGCCTGGGAGGAGTTGGCCTGTCAGTCATCATGGGCTGTAAGTCAGCTGGTGCATCTAGGATCATTGGGA
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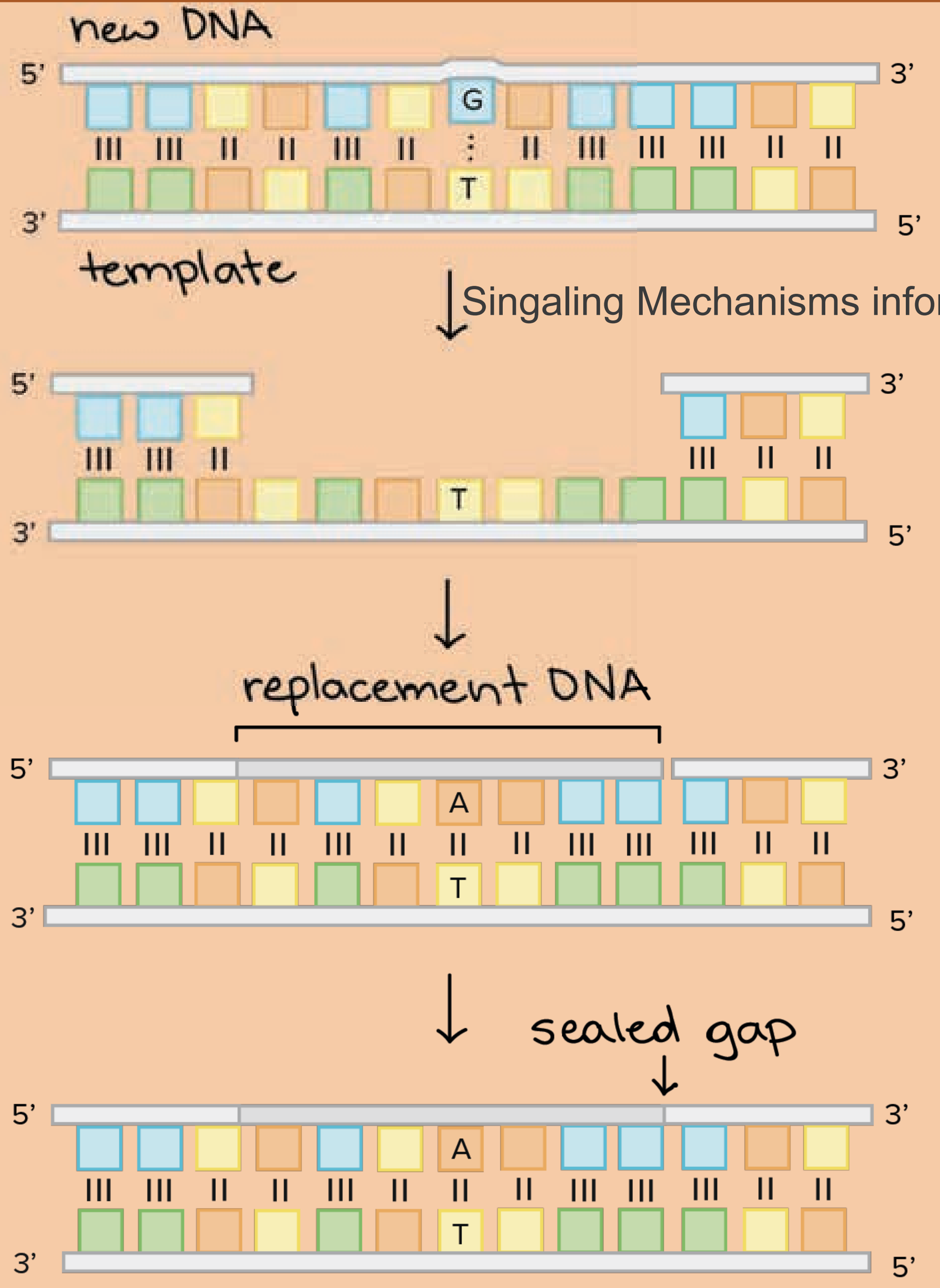
TGCCCTGGCATCCTGCCACATGAACTATGGGACCAGCGTGGTTGTAGGAGTTCCTCCATCAGCCAAGATGCTCACCTATGACC
CGATGTTGCTCTTCACTGGACGCACATGGAAGGGATGTGTCTTTGGAGGTTTGAAAAGCAGAGATGATGTCCCAAAACTAGTG
ACTGAGTTCCTGGCAAAGAAATTTGACCTGGACCAGTTGATAACTCATGTTTTACCATTTAAAAAAATCAGTGAAGGATTTGA
GCTGCTCAATTCAGGACAAAGCATTCGAACGGTCCTGACGTTT**TGA**

DNA REPAIR VIA SIGNALING CORRECTION



A mismatch is detected in newly synthesized DNA.

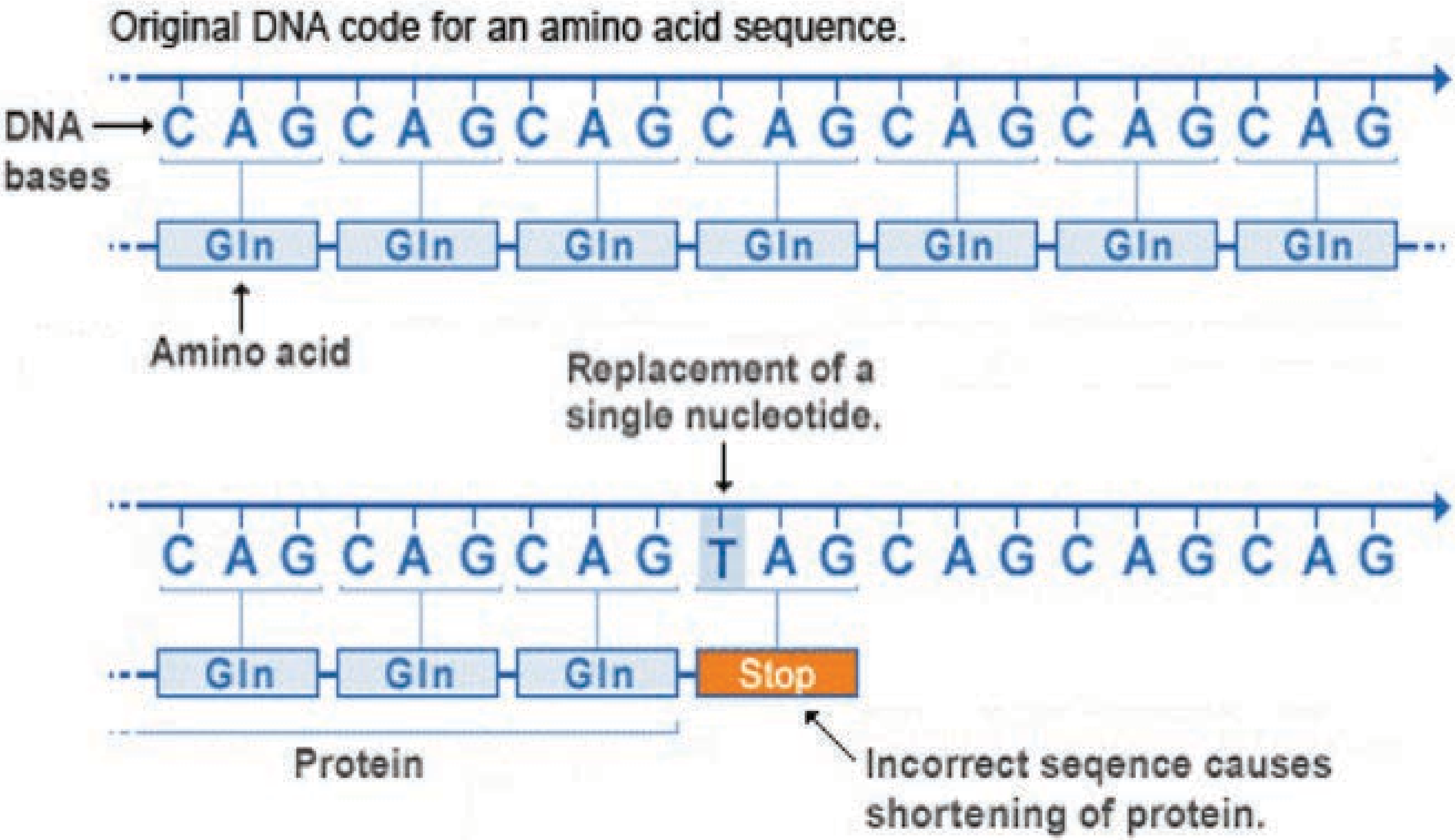
Singaling Mechanisms inform the network of the mismatch

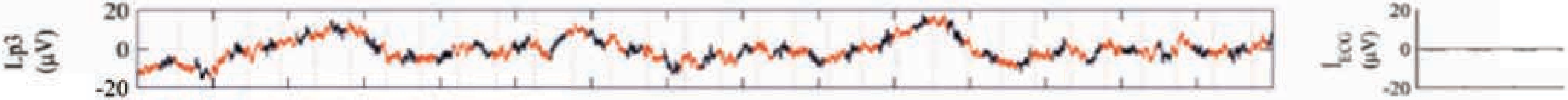
The new DNA strand is cut, and the mispaired nucleotide and its neighbors are removed.

The missing patch is replaced with correct nucleotides by a DNA polymerase.

A DNA ligase seals the gap in the DNA backbone.

Nonsense mutation





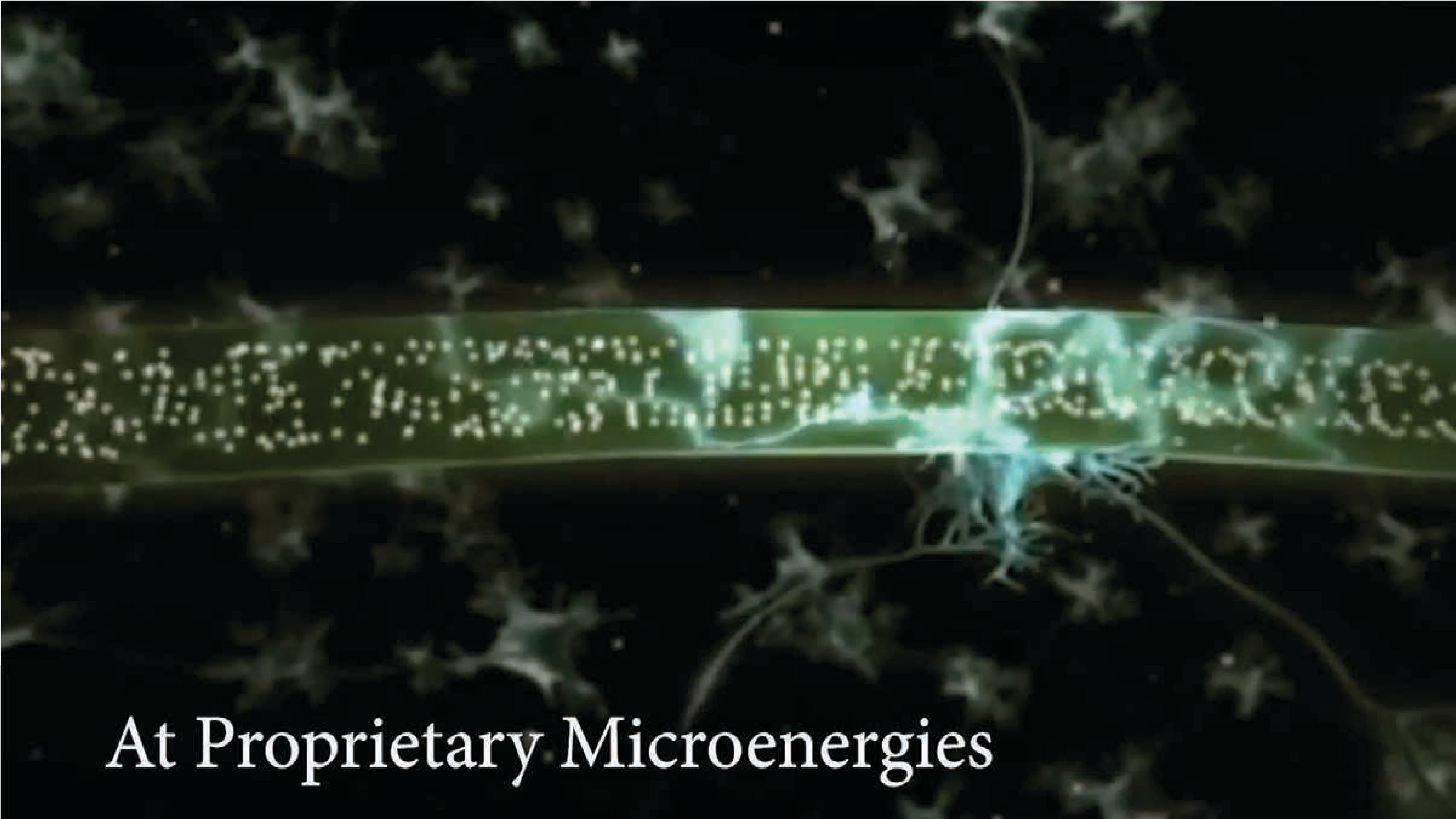
SIGNALING TO REPAIR DNA

- Our Current Research focuses on the Investigation and Replications of ever changing Bioresonant blueprint Signals that match the signals within and between cells

  Signals are emitted in a bioresonant dynamic sequence that matches the dynamic process of the biological network

FUSE WITH AND AMPRLIFY FADED BIOLOGICAL SIGNALS

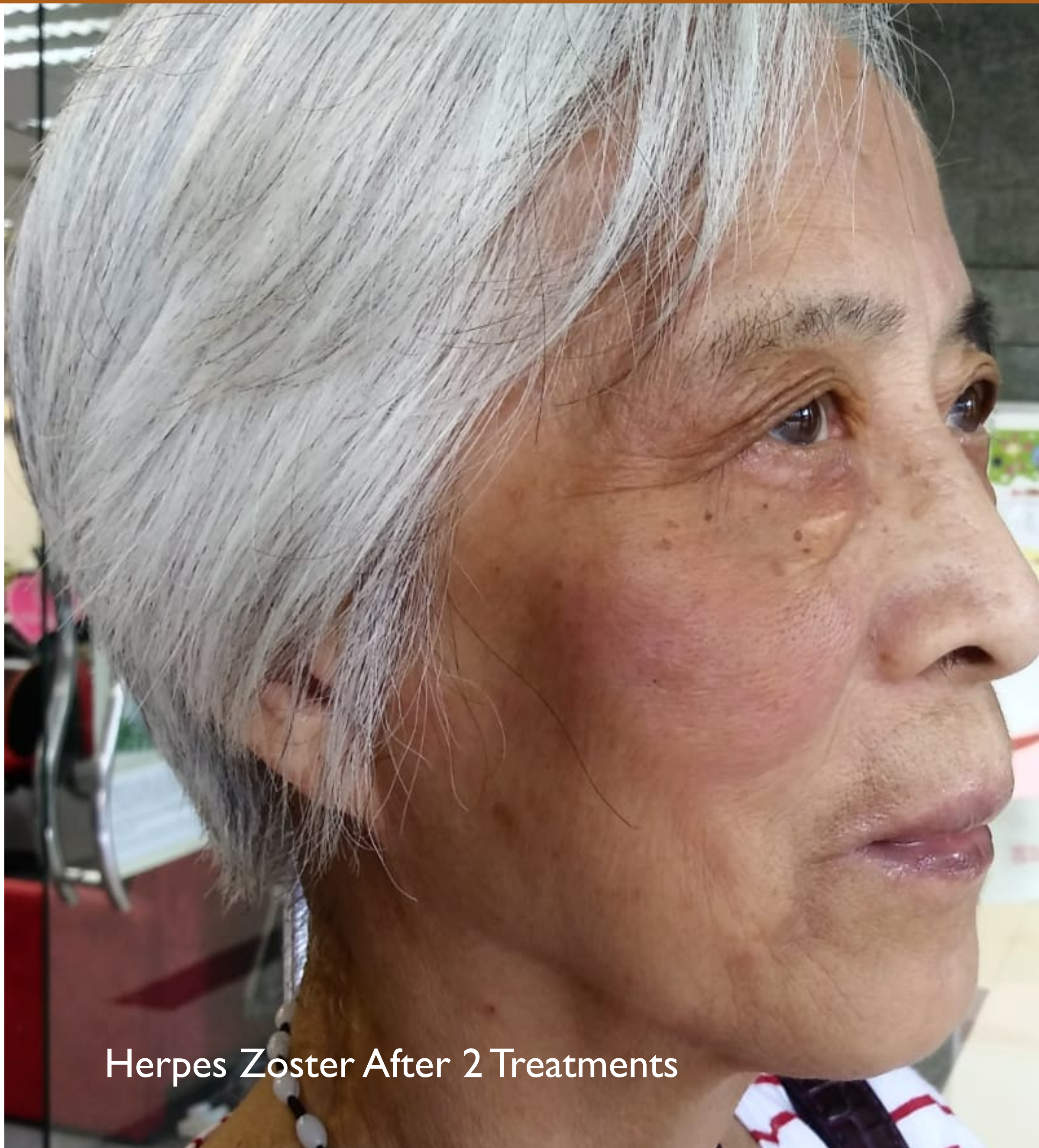
FILL IN / CORRECT MISMATCHED BIOLOGICAL SEQUENCES TO REINSTATING ORIGINAL MESSAGE



At Proprietary Microenergies

Signaling Effects on Skin and Wound Repair – Clinical studies today

Herpes Zoster
Before



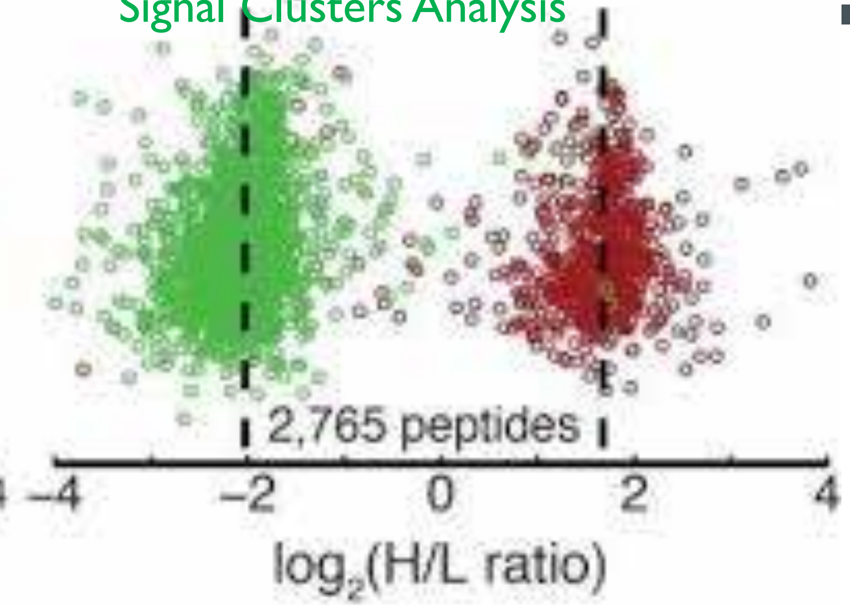
Herpes Zoster After 2 Treatments

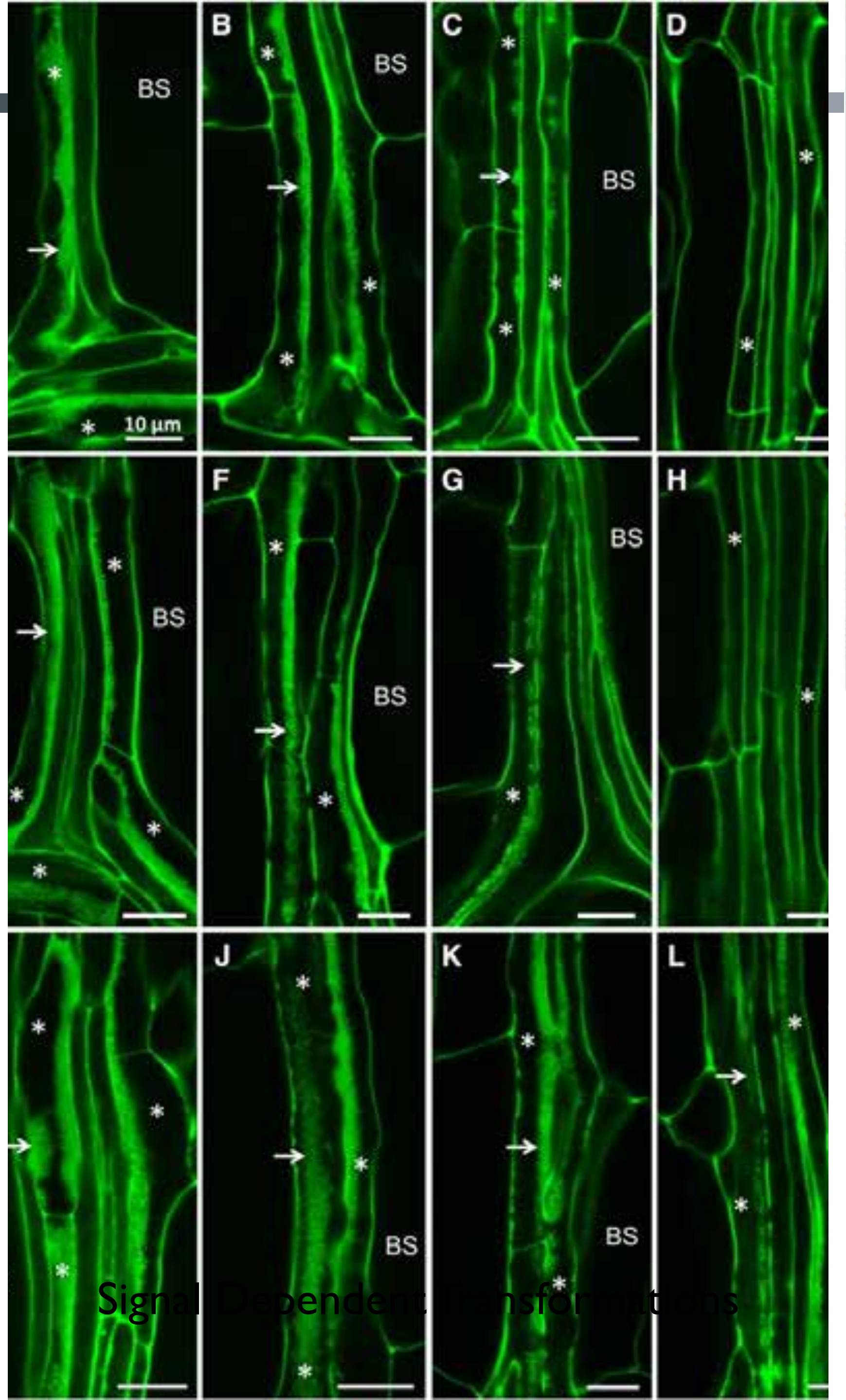
SIGNALING EFFECTS ON VISIBLE HAIR GROWTH (IN THE ABSENCE OF OTHER HAIR GROWING METHODS)

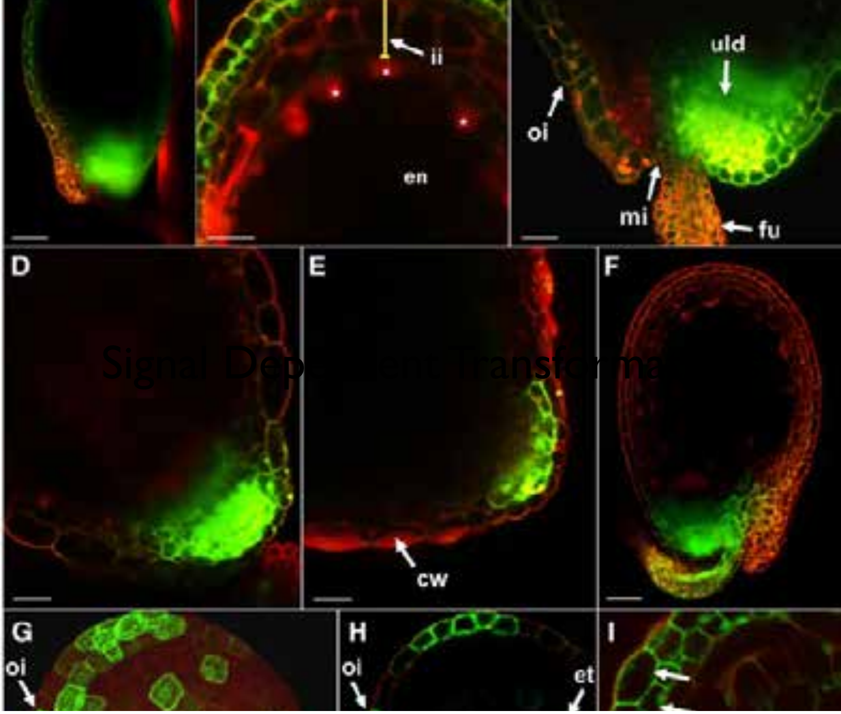
CLINICAL STUDIES TODAY

SIGNAL PROCESSING BLUEPRINTS

Signal Clusters Analysis







Signal Dependent Transformations

Signal Dependent Transformations

SIGNALS ARE COMPOSED BY COMPLEX WAVEFORM CONSTRUCTS

Section Time (Mins:Secs) : 00:01

Channel 1

	100	10	1	0.1	0.01
Frequency in Hertz x	0	0	1	1	8

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	1

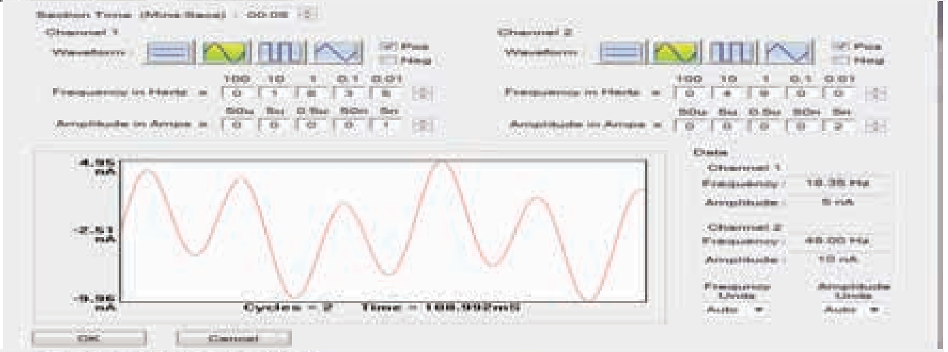
Channel 2

	100	10	1	0.1	0.01
Frequency in Hertz x	0	0	0	5	9

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	1

Cycles = 2 Time = 3.38983s

Data
Channel 1
Frequency : 1.18 Hz
Amplitude : 5 nA
Channel 2
Frequency : 590 mHz
Amplitude : 5 nA



Section Time (Mins:Secs) : 00:05

Channel 1

	100	10	1	0.1	0.01
Frequency in Hertz x	0	1	8	3	5

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	1

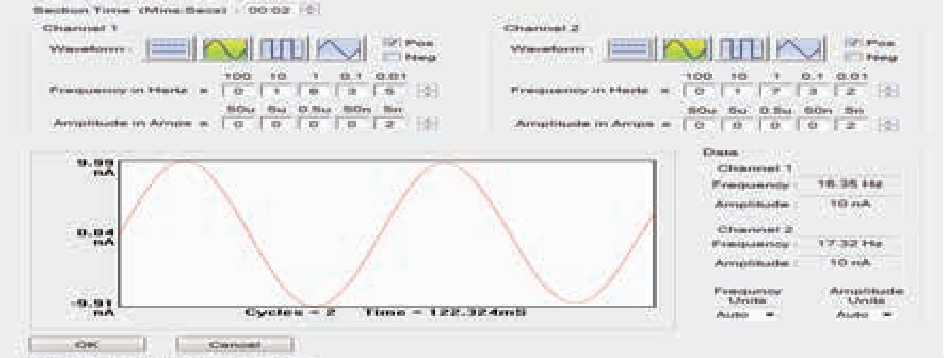
Channel 2

	100	10	1	0.1	0.01
Frequency in Hertz x	0	4	9	0	0

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	2

Cycles = 2 Time = 108.992mS

Data
Channel 1
Frequency : 18.35 Hz
Amplitude : 5 nA
Channel 2
Frequency : 49.00 Hz
Amplitude : 10 nA



Section Time (Mins:Secs) : 00:02

Channel 1

	100	10	1	0.1	0.01
Frequency in Hertz x	0	1	8	3	5

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	2

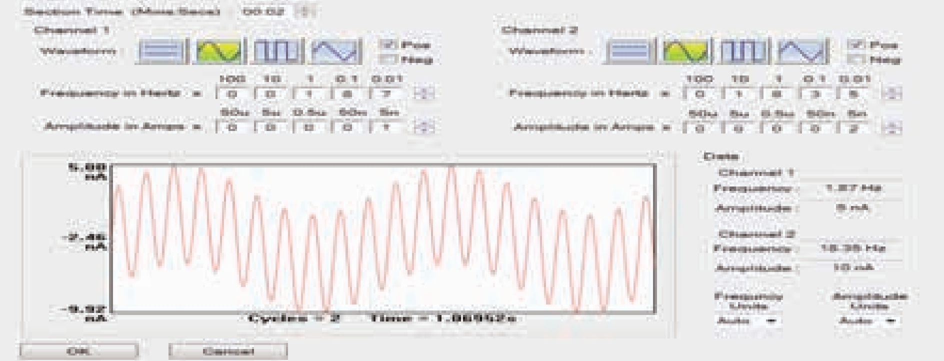
Channel 2

	100	10	1	0.1	0.01
Frequency in Hertz x	0	1	7	3	2

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	2

Cycles = 2 Time = 122.324mS

Data
Channel 1
Frequency : 18.35 Hz
Amplitude : 10 nA
Channel 2
Frequency : 17.32 Hz
Amplitude : 10 nA



Section Time (Mins:Secs) : 00:02

Channel 1

	100	10	1	0.1	0.01
Frequency in Hertz x	0	0	1	8	7

	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	1

Channel 2

	100	10	1	0.1	0.01
Frequency in Hertz x	0	1	8	3	5

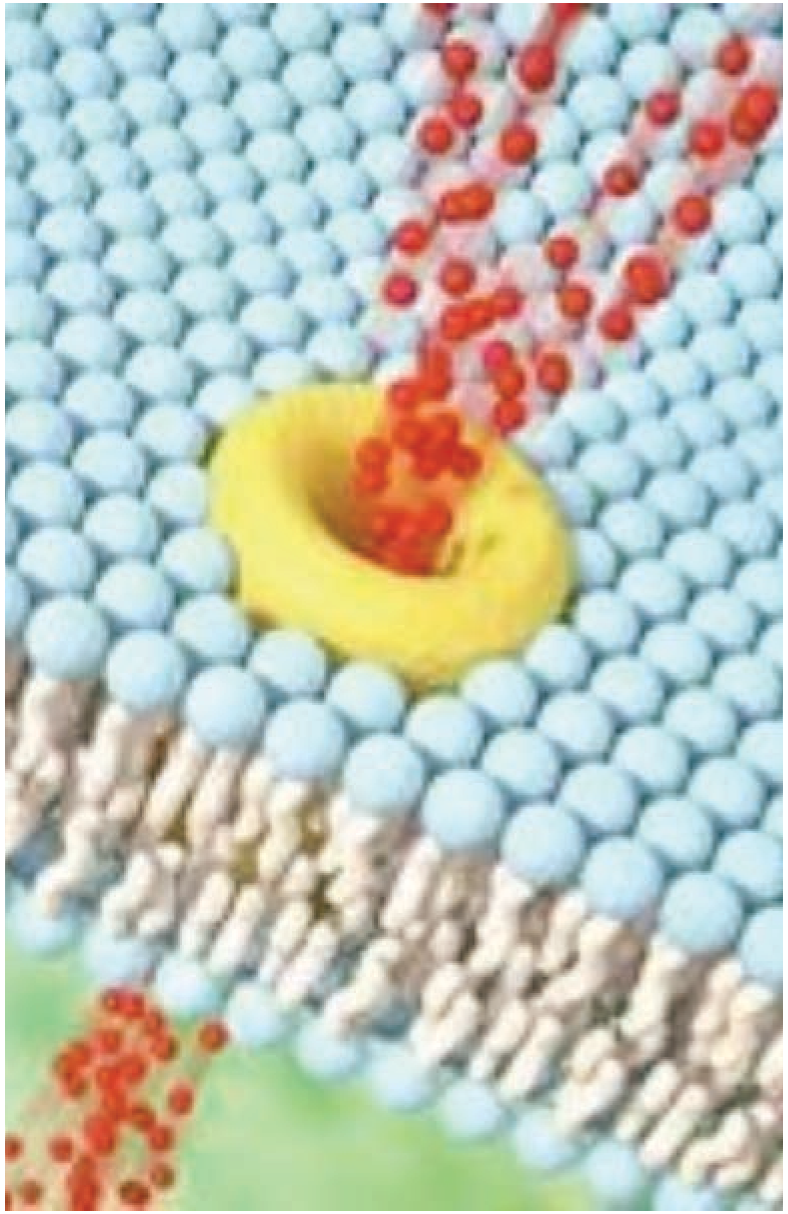
	50u	5u	0.5u	50n	5n
Amplitude in Amps x	0	0	0	0	2

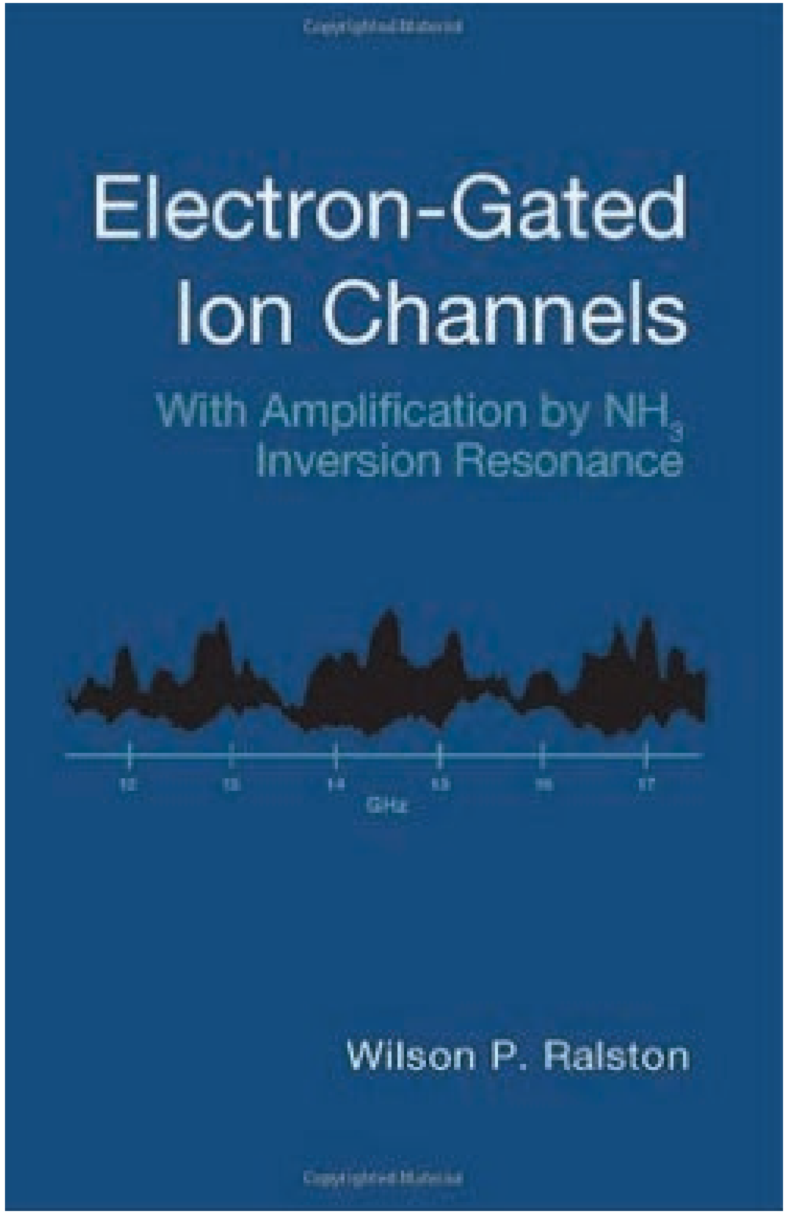
Cycles = 2 Time = 1.06952s

Data
Channel 1
Frequency : 1.87 Hz
Amplitude : 5 nA
Channel 2
Frequency : 18.35 Hz
Amplitude : 10 nA

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**

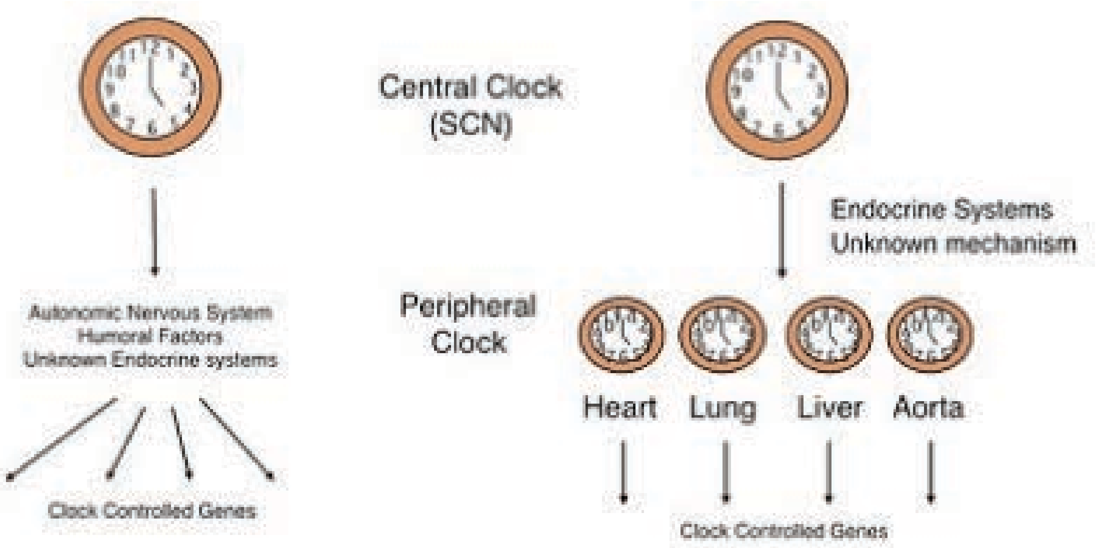


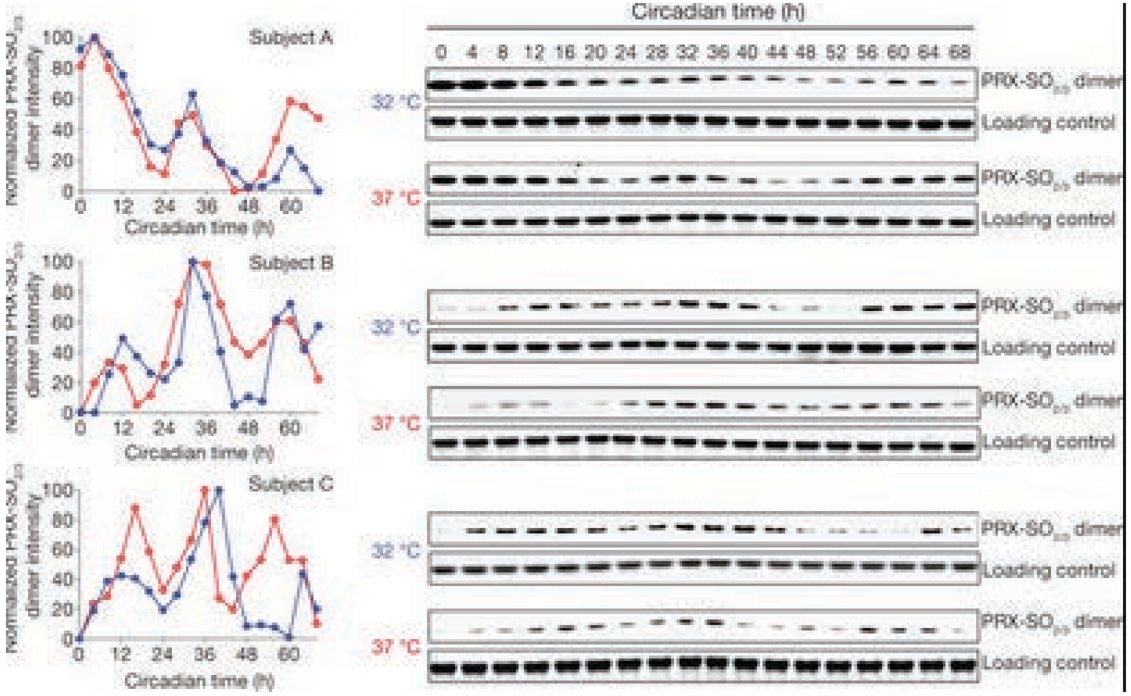


Electron-Gated
Ion Channels

With Amplification by NH_3
Inversion Resonance

Wilson P. Ralston

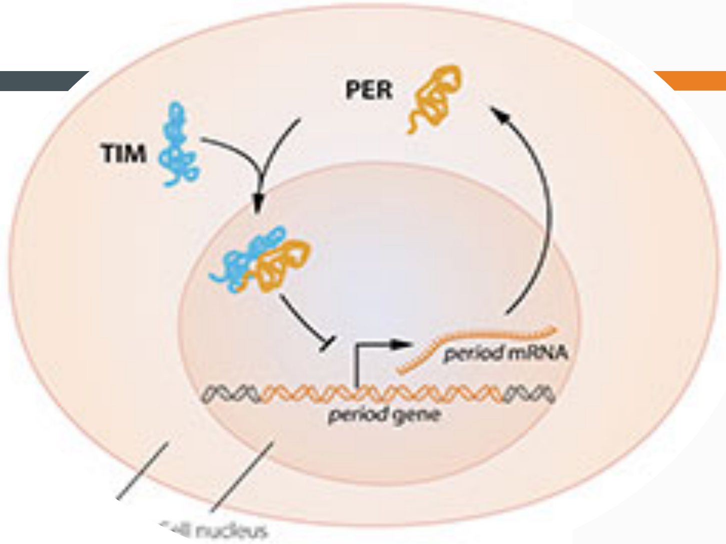




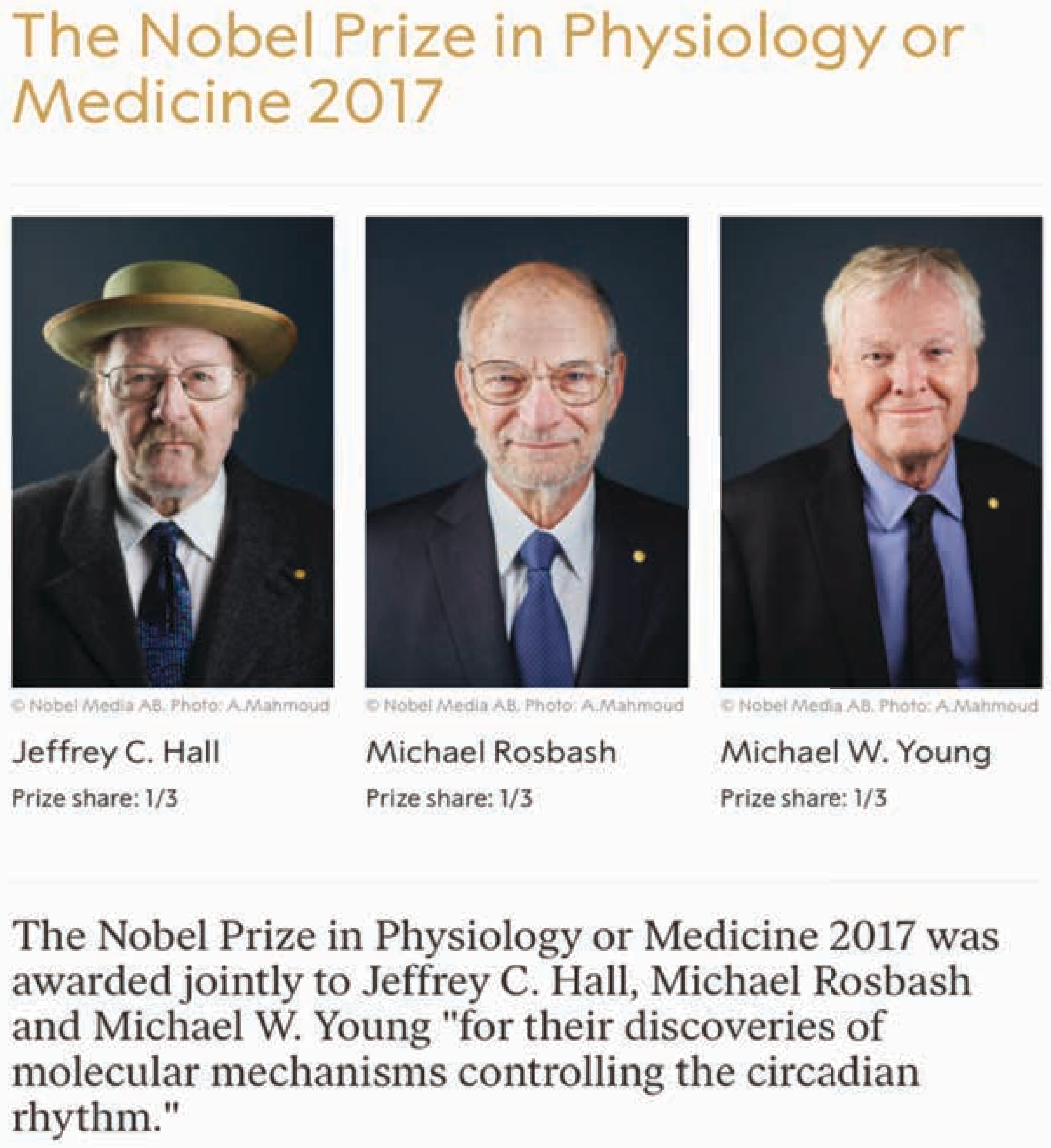
OUR CELLS HAVE A CIRCADIAN CLOCK

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

- "**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*



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

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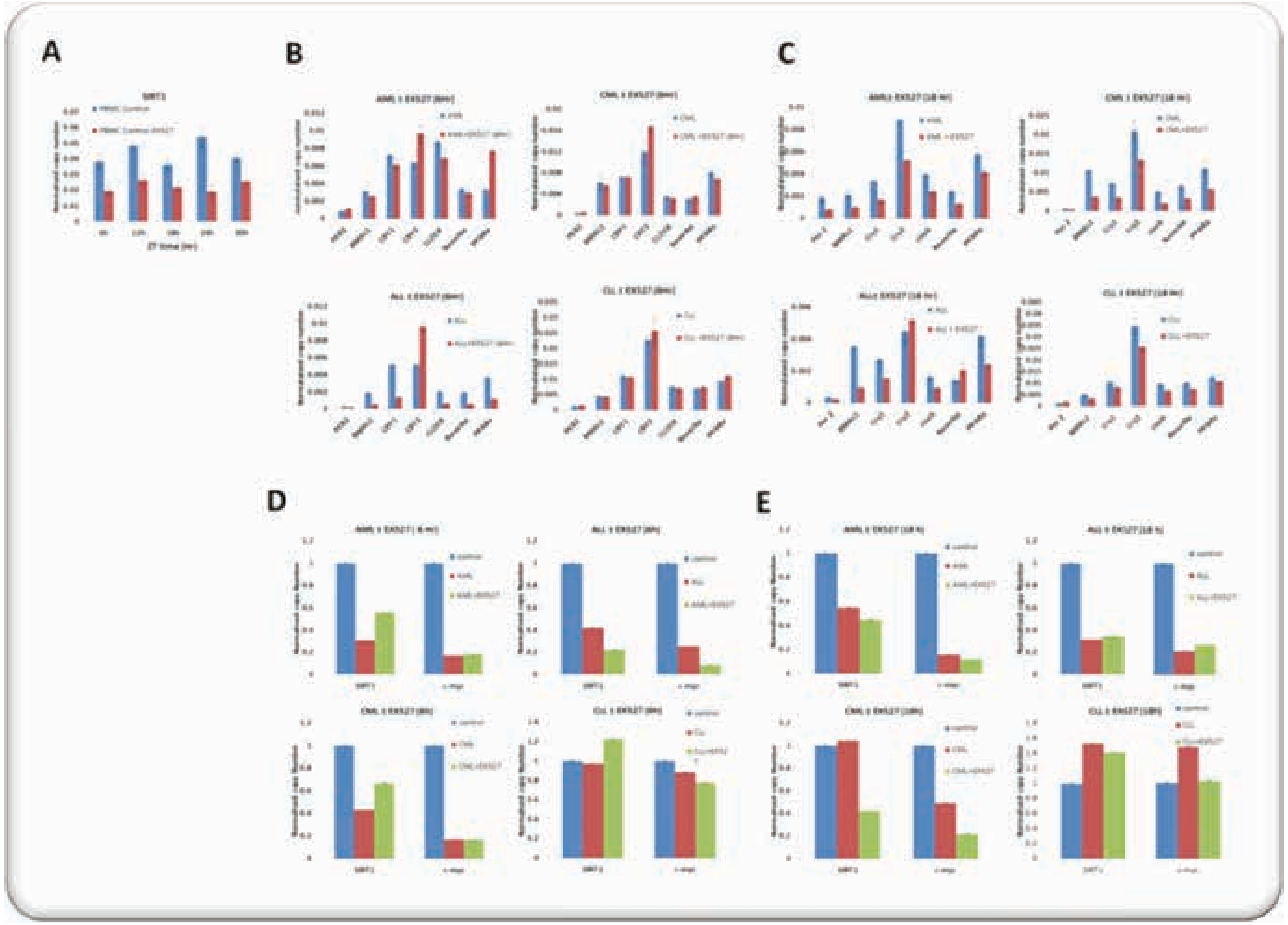
Jeffrey C. Hall	Michael Rosbash	Michael W. Young
Prize share: 1/3	Prize share: 1/3	Prize share: 1/3

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."



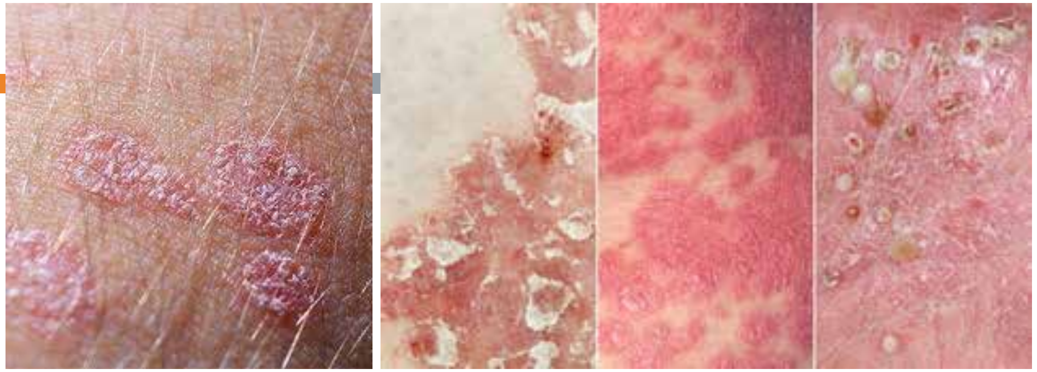
Circadian Genes in Leukemia

CLOCK GENES CAN DETERMINE SKIN DISORDERS, AGING AND DESEASE

- 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.

Psoriasis

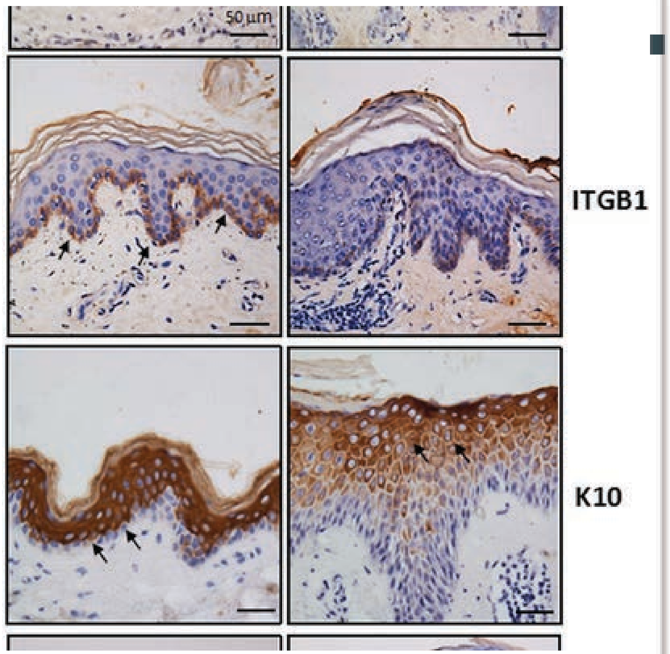
1. inflammatory skin disease
2. increased proliferation / altered differentiation of the epidermis
3. infiltration of inflammatory cells such as neutrophils into the dermis

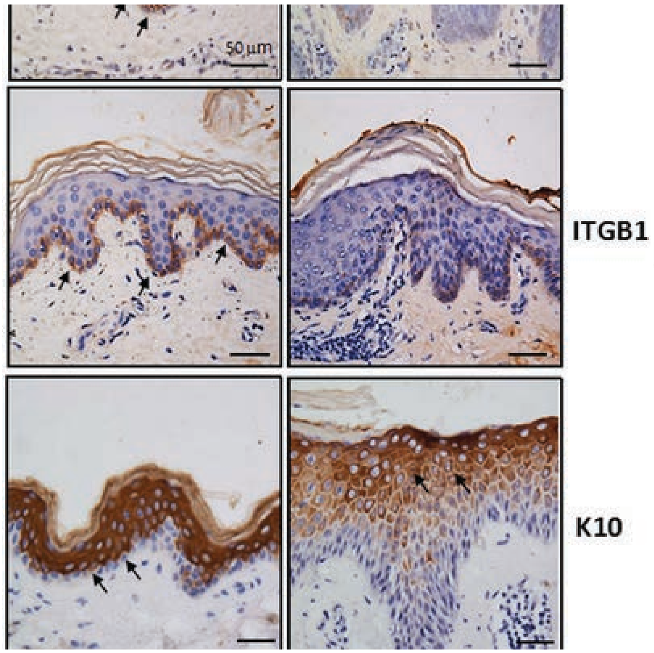


Pathophysiology of psoriasis is associated with Aberrant Circadian rhythms (Gelfant et al., 1982; Mozzanica et al., 1988; Bacaksiz et al., 2012)

Ando et al (2015) found that circadian clocks may be a potent regulator of psoriasis by affecting IL-23R expression.

Psoriasis Treatment by Repair of Signaling Interactions





KELOID SCARS ARE THE RESULT OF DISREGULATION IN GENE CLOCKS

KELOID AFTER LIPOSUCTION WOUND TREATED WITH SIGNALING – 6 TREATMENTS

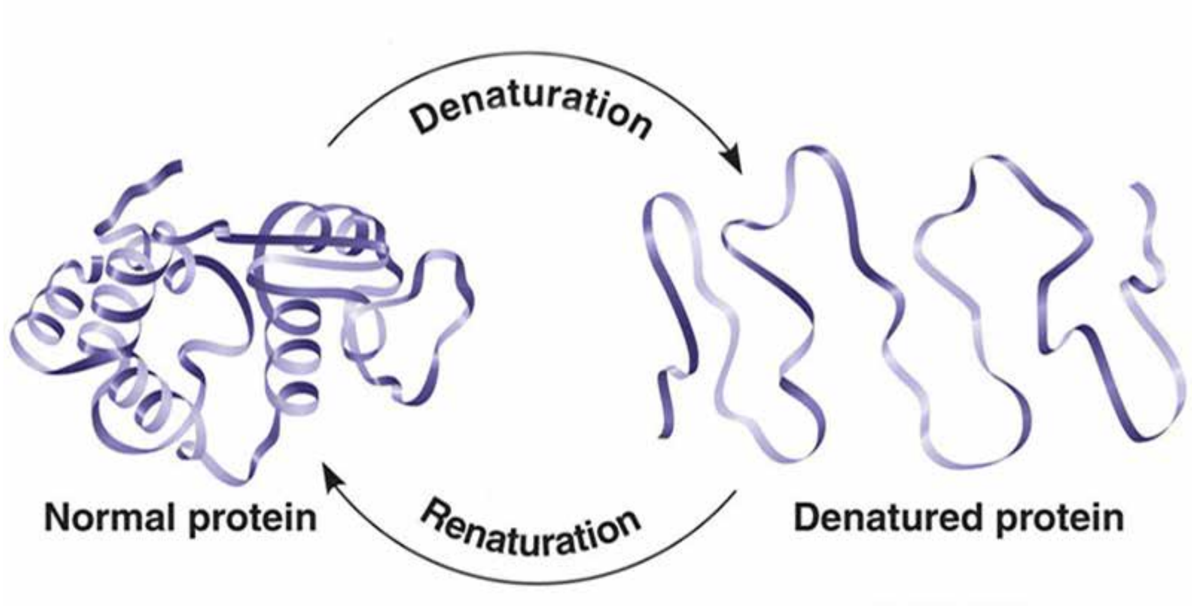
ANTI-AGING VIA PROTEIN RENATURATION / Protein Folding
WITHIN THE PARAMETERS OF TIME WITH RESPECT TO CIRCADIAN CLOCKS

HOW TO TEST RESULTS ARE DUE TO PROTEIN FOLDING?

Second virial coefficient (SVC) measurements

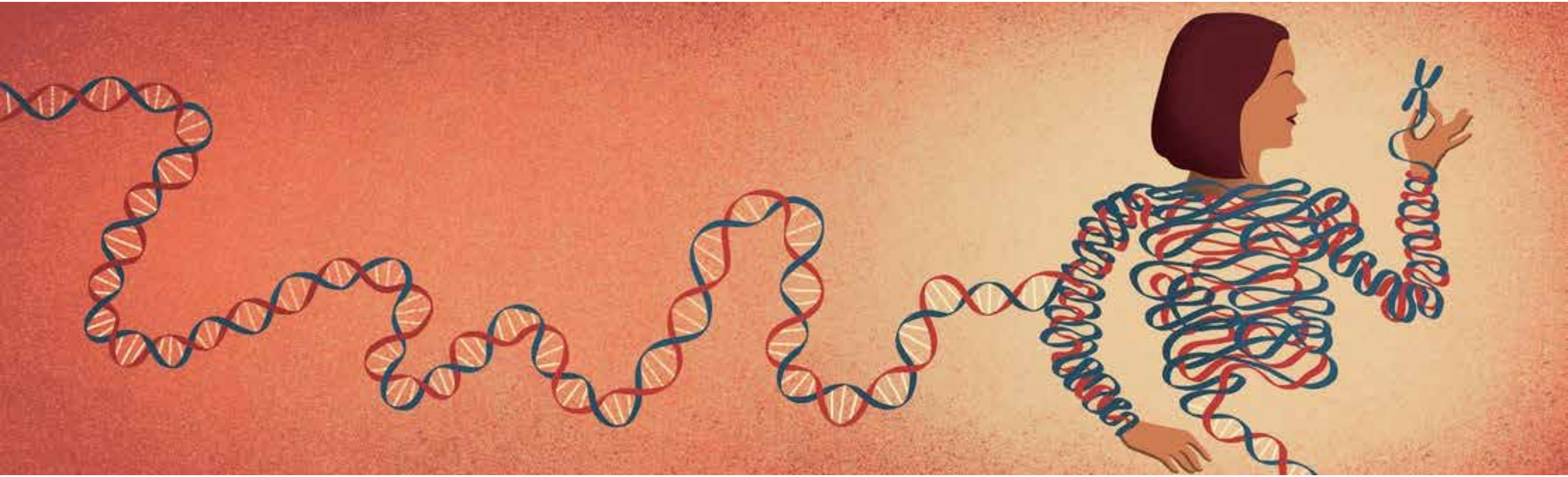
* -VE SVC is indicative of -VE protein–protein interactions. - **Protein aggregation INCREASES** during refolding Protein Refolding compromised

* +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



Any questions please e-mail: science@iellios.com