

Ancient Informatics and a New Approach to Treating Inflammatory Diseases

Paul S Kayne, PhD



Ohrid North Macedonia

September 28, 2024

What is Informatics?

- Informatics studies the representation, processing, and communication of information in ***natural*** and engineered systems
- It has computational, cognitive and social aspects
- The central notion is the transformation of information - whether by computation or communication, whether by ***organisms*** or artifacts.



THE UNIVERSITY of EDINBURGH
informatics



Ancient Informatics: The Genome

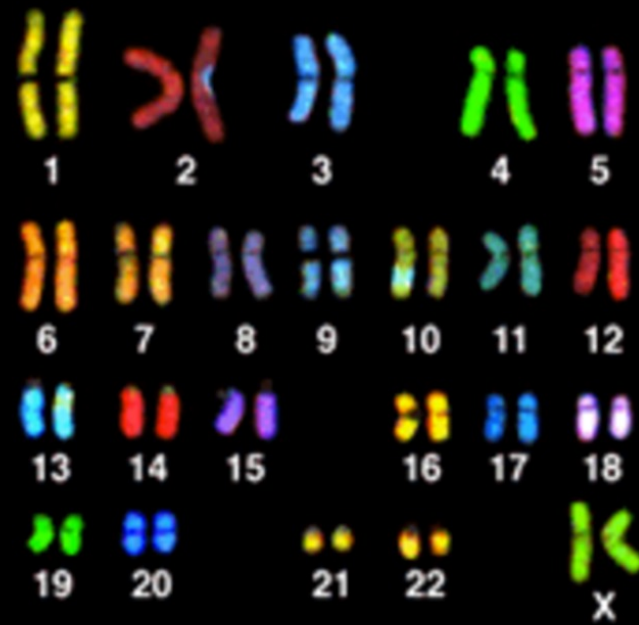
A New Approach to Treating Inflammatory Disease
The Melanocortin System

Incognito Escrow: A Modest Proposal

Ancient Informatics

The Genome

EVOLVED

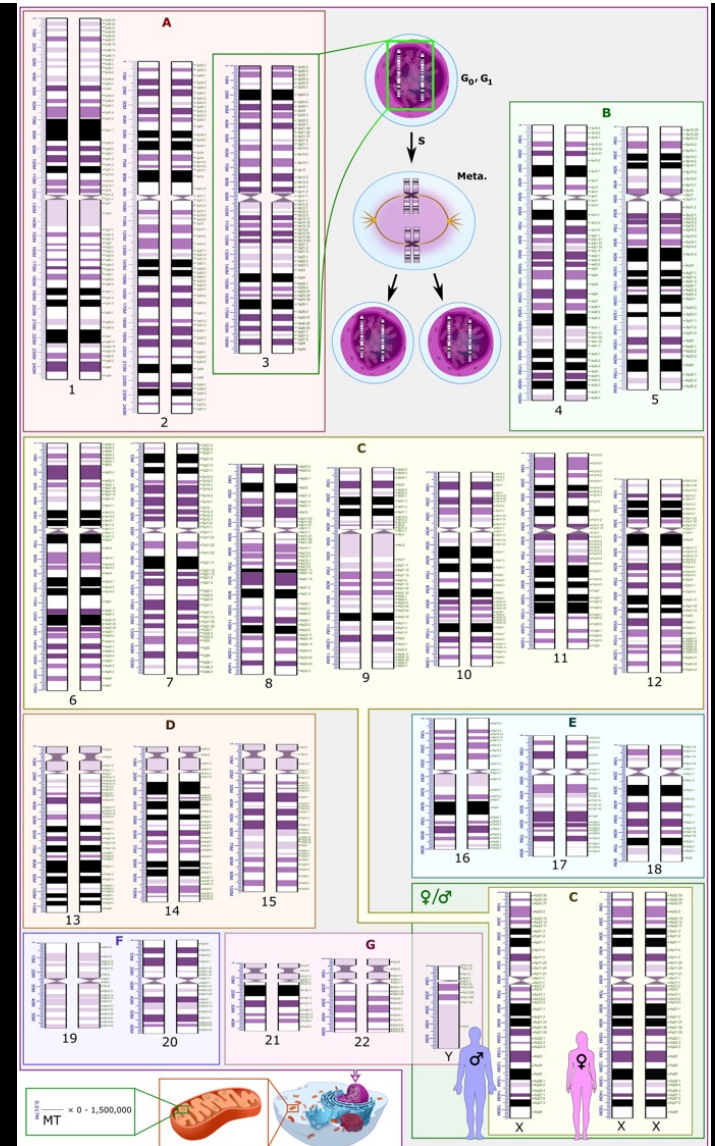


Human Genome

Ancient Informatics

The Genome

PHYSICAL STRUCTURE

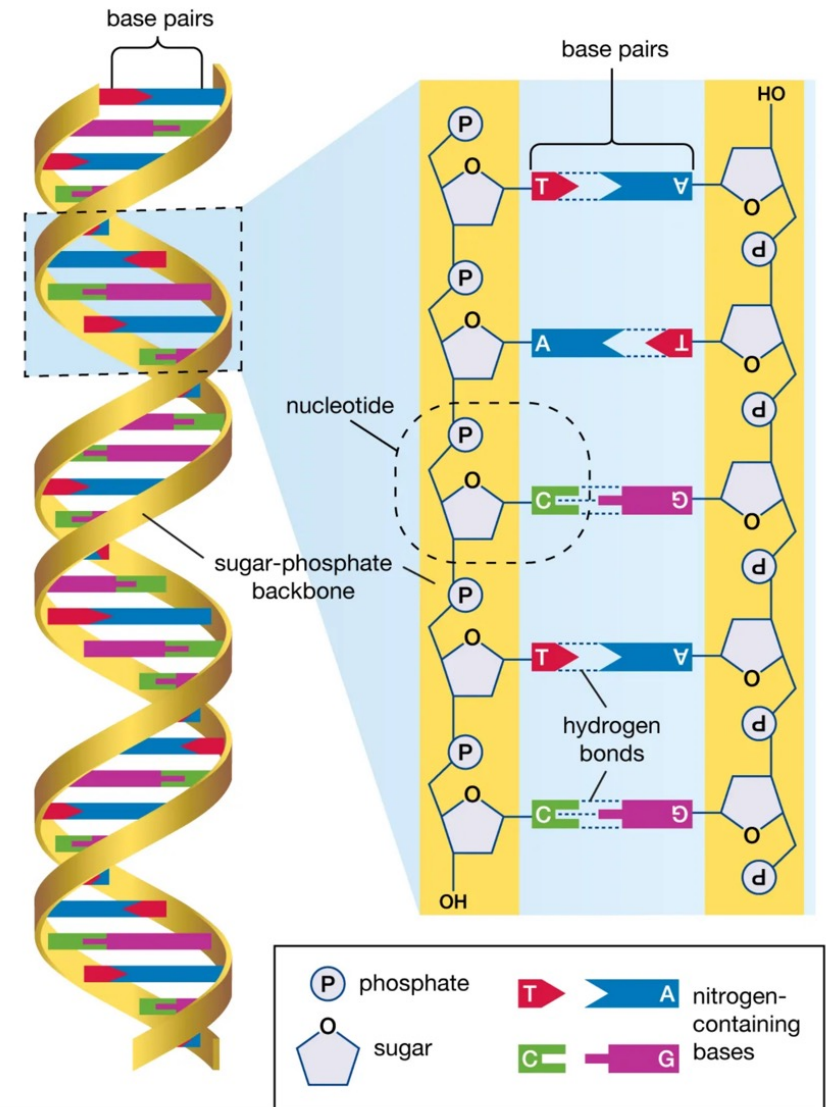


Ancient Informatics

Composition

ENCODING

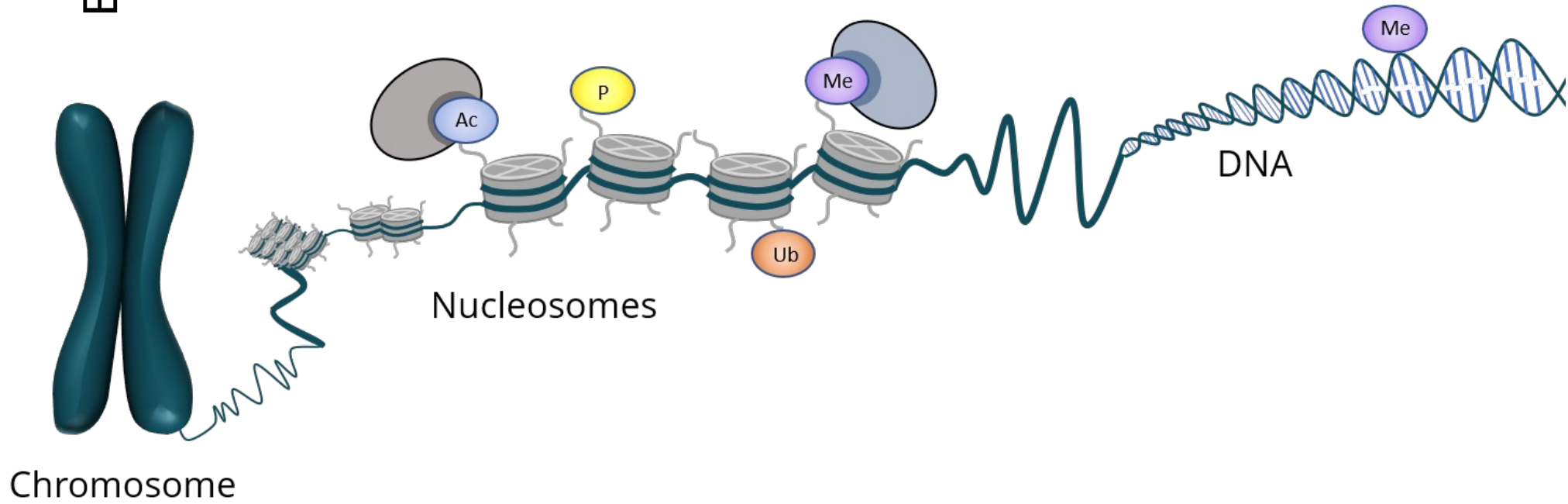
- A quaternary code
 - 4 nucleotides
 - A::T / T::A
 - G::C / C::G
 - Anti-parallel configuration
- 3 billion base pairs
 - ~1.5 GB equivalent



Ancient Informatics

Epigenetics

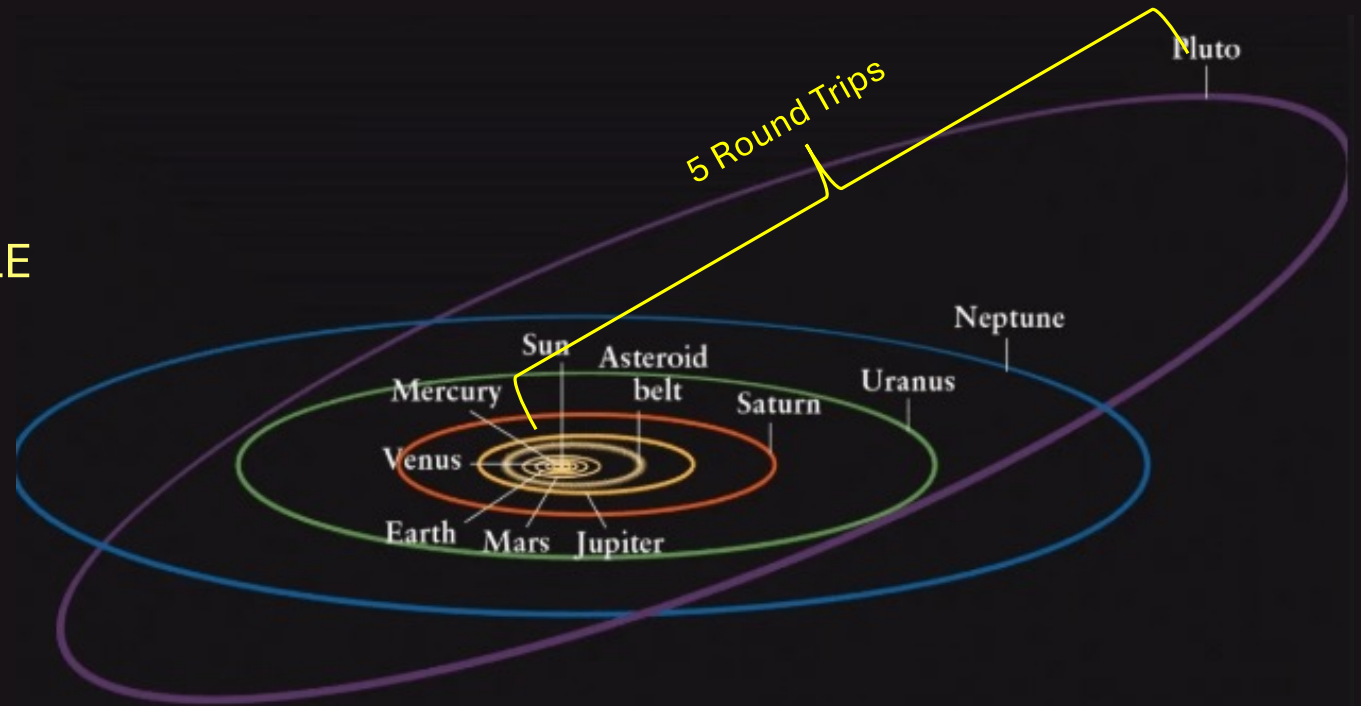
MODIFICATION



Ancient Informatics

Efficient Packaging

INCONCEIVABLE



~2 M/cell

~30 trillion cells/body

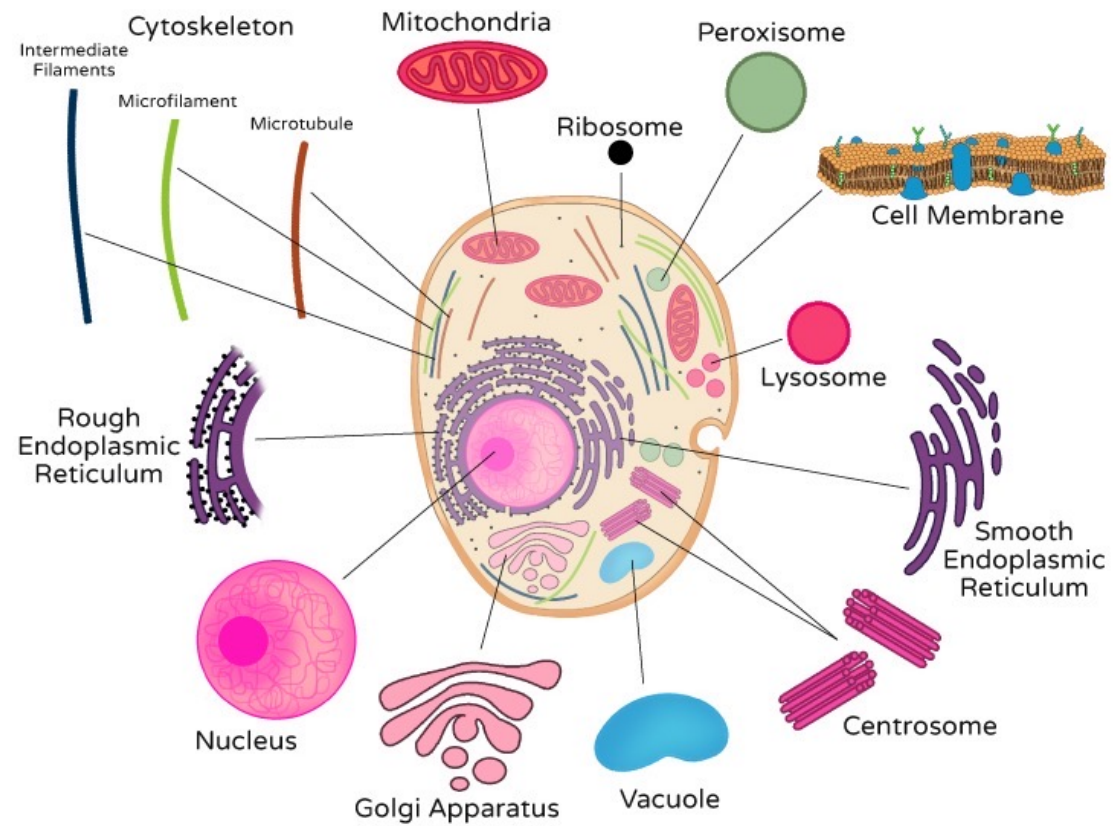
~60 billion KM/total

~6 billion KM/sun to Pluto

Ancient Informatics

Organelles

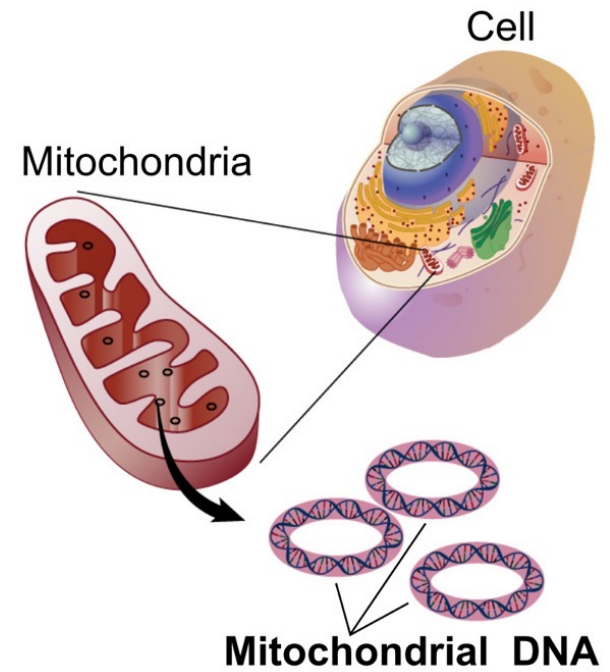
MODULES



Ancient Informatics

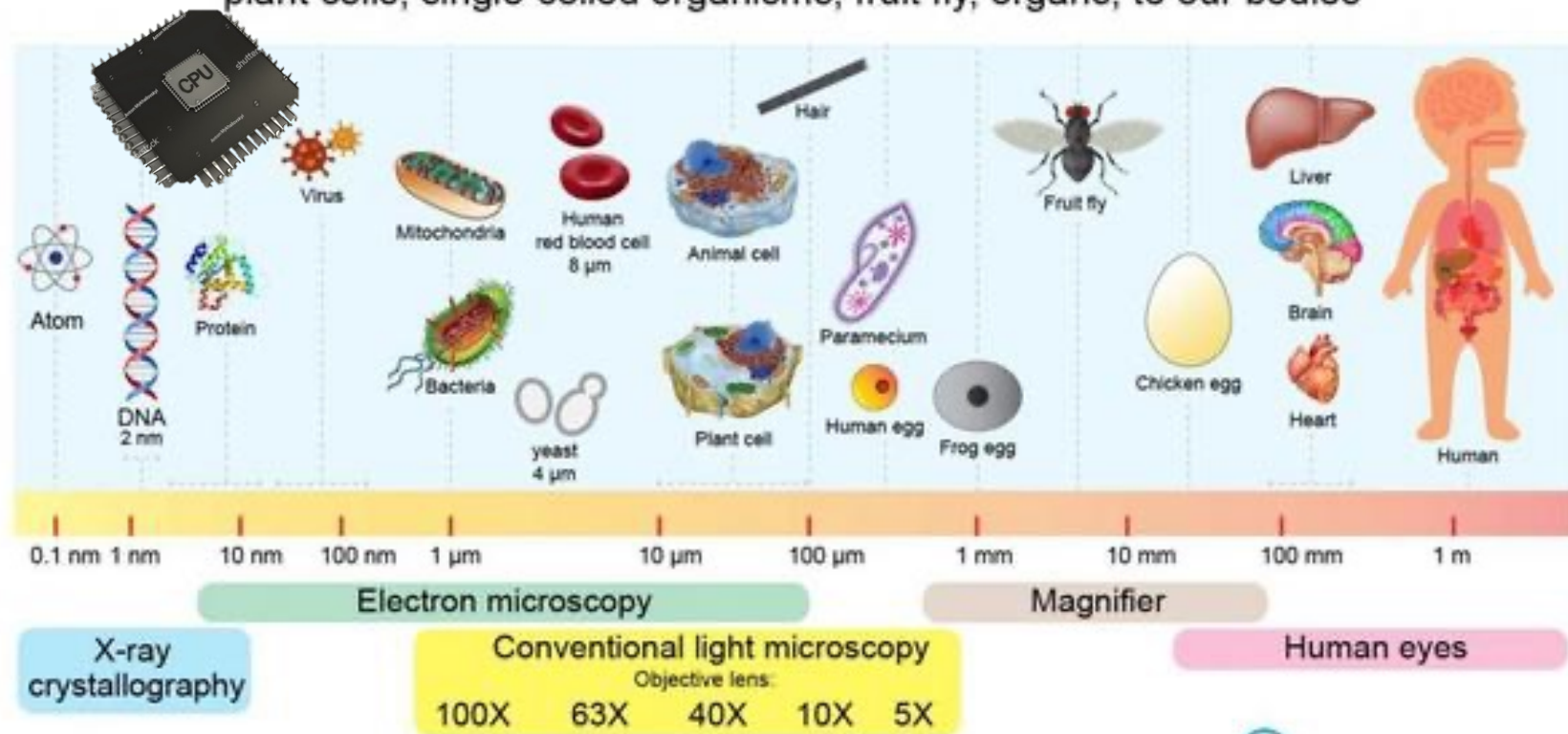
More Processors

ANOTHER GENOME



THE LENGTH SCALE OF BIOLOGY

from atoms, DNA, proteins, viruses, bacteria, mitochondria, animal and plant cells, single-celled organisms, fruit fly, organs, to our bodies

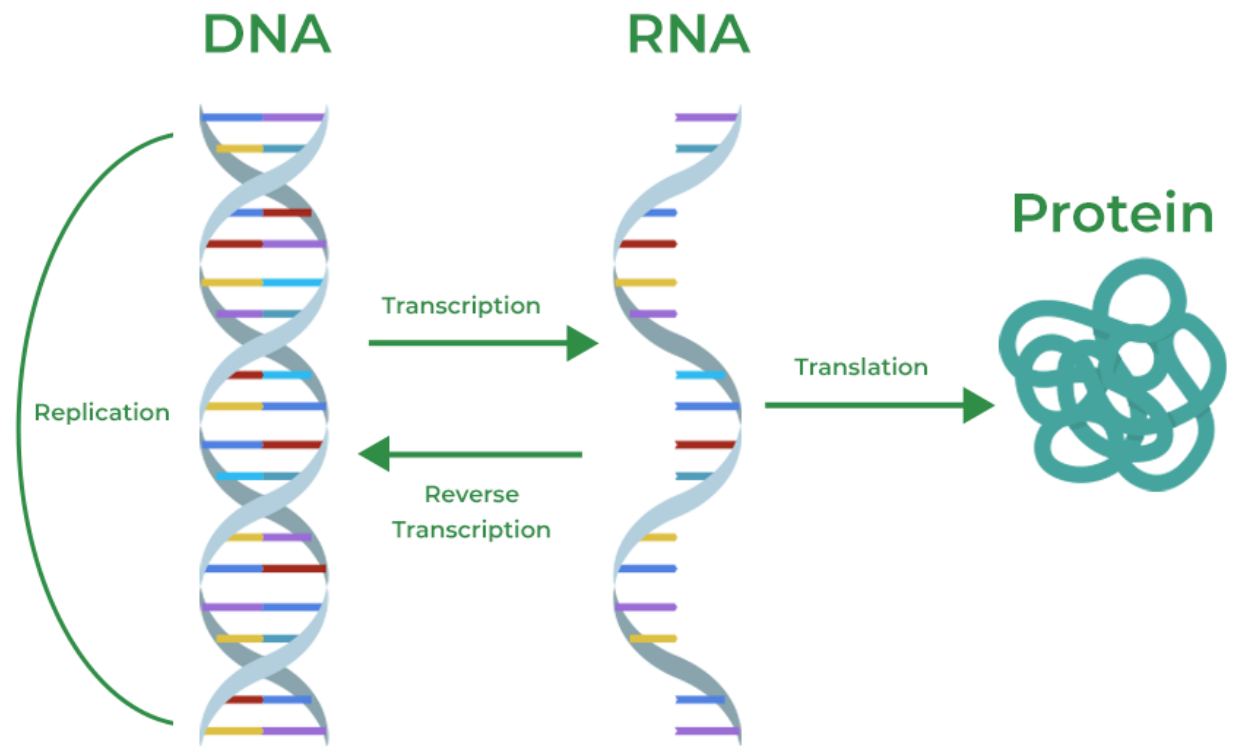


rsscience.com

Ancient Informatics

Central Dogma

TRANSCRIPTION
TRANSLATION

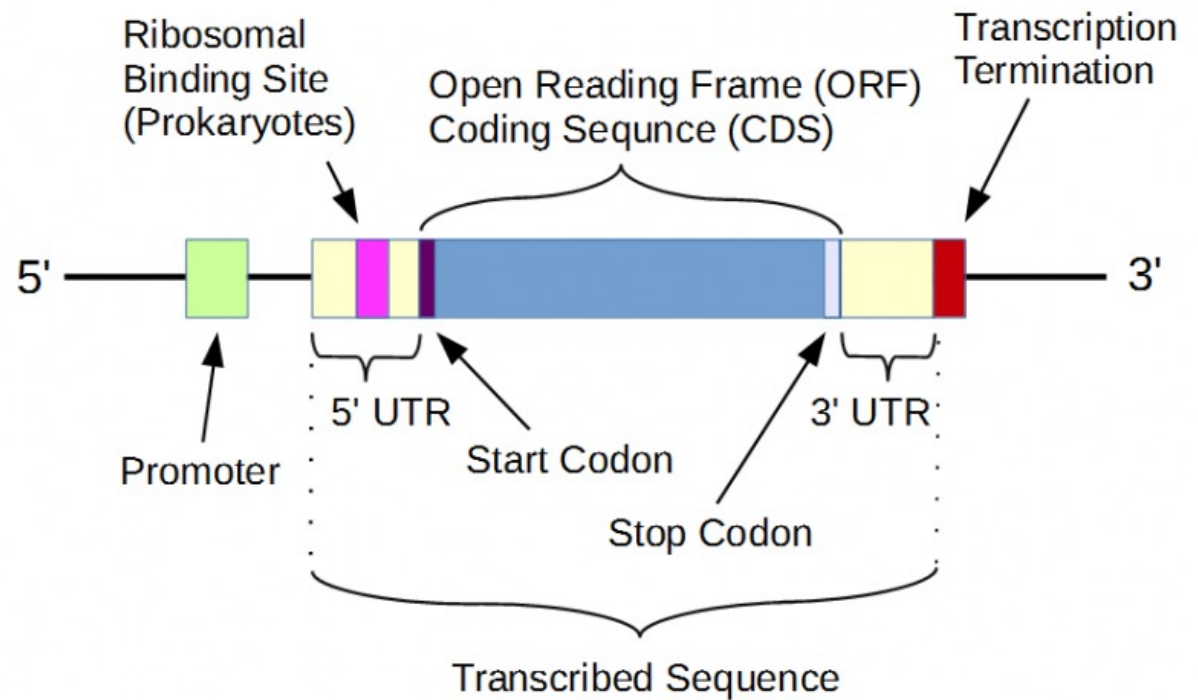


Ancient Informatics

Central Dogma

TRANSCRIPTION

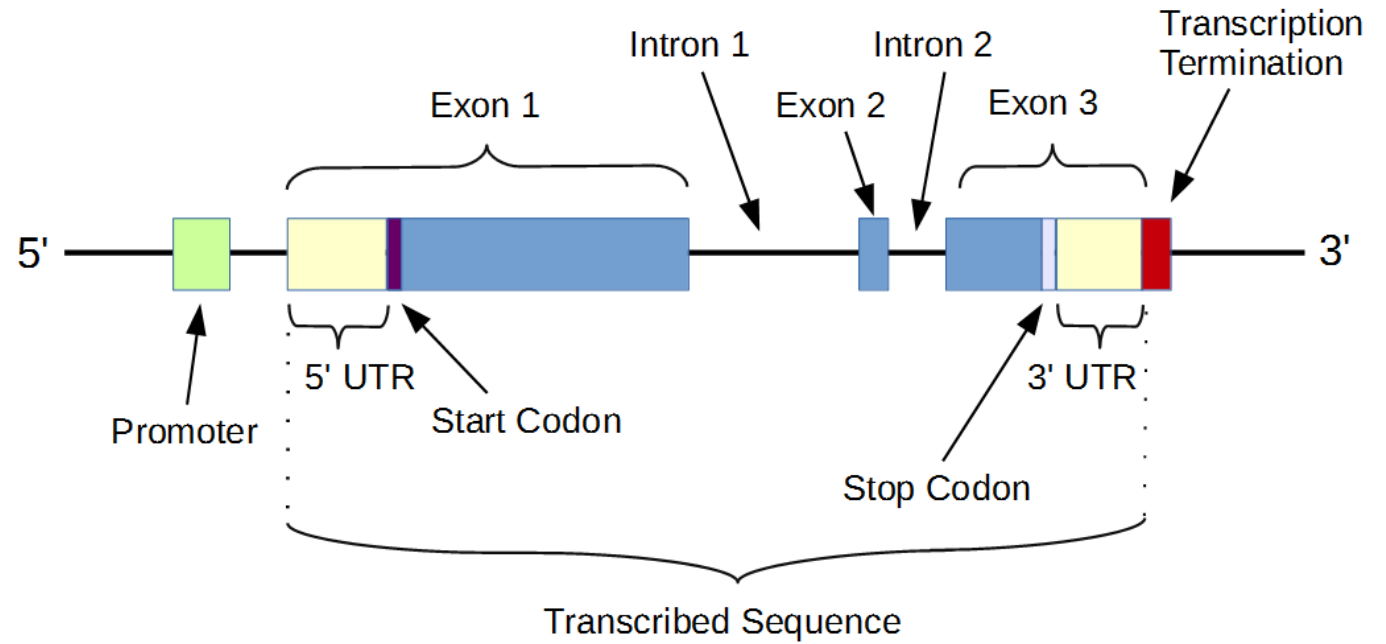
GENE



Ancient Informatics

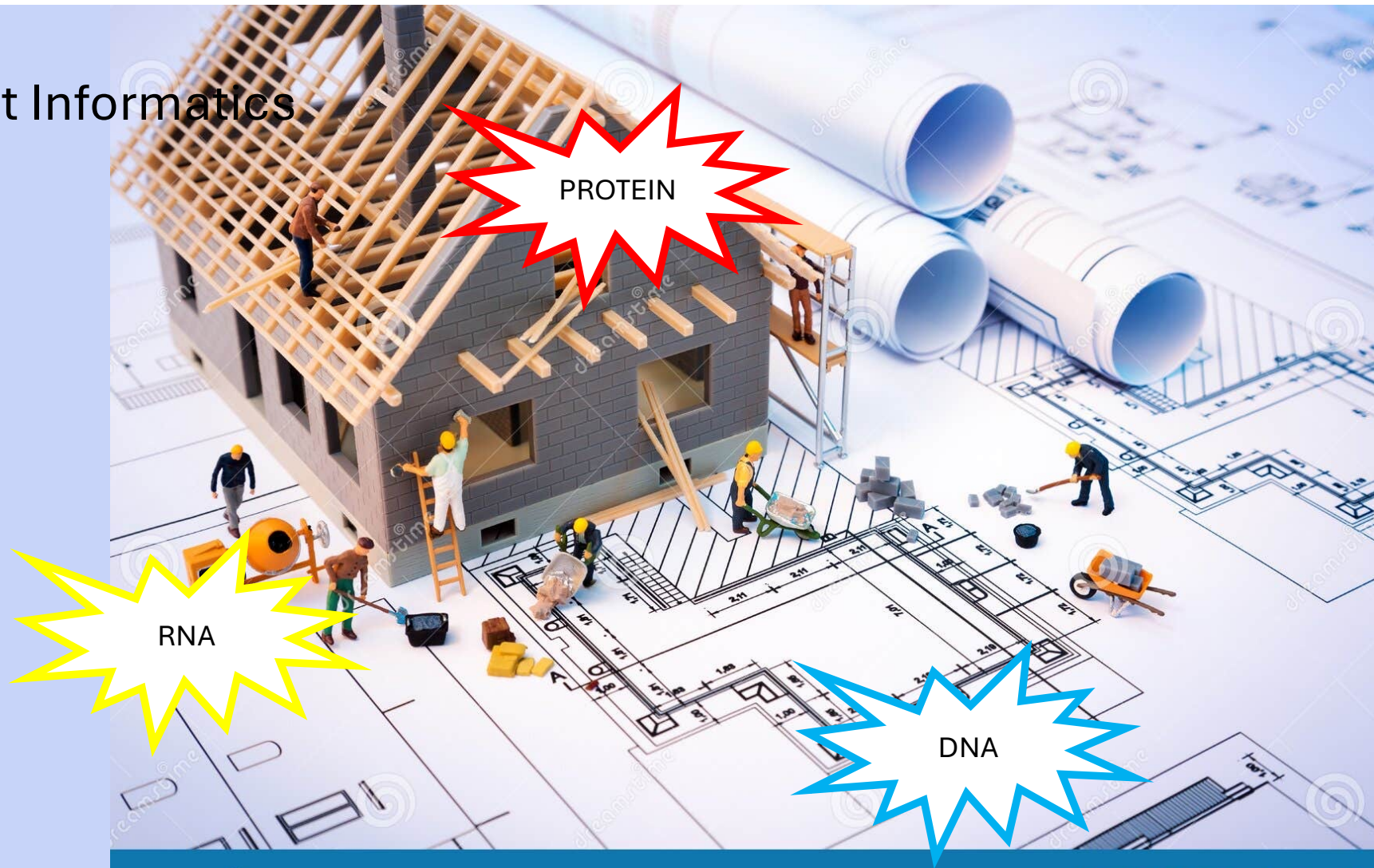
Expanded Dogma

SPLICING



Ancient Informatics

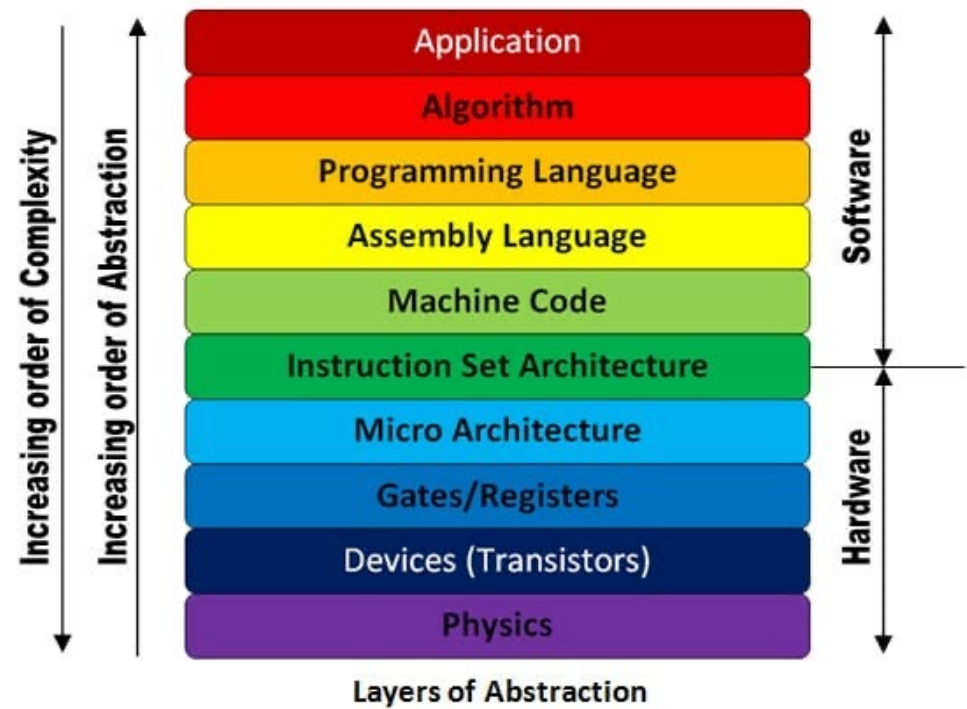
Design and Builder



Current Informatics

Hardware and Software

LEVELS OF COMPLEXITY



Ancient Informatics

Original Neural Net

ORGANIC INTELLIGENCE



Ancient Informatics

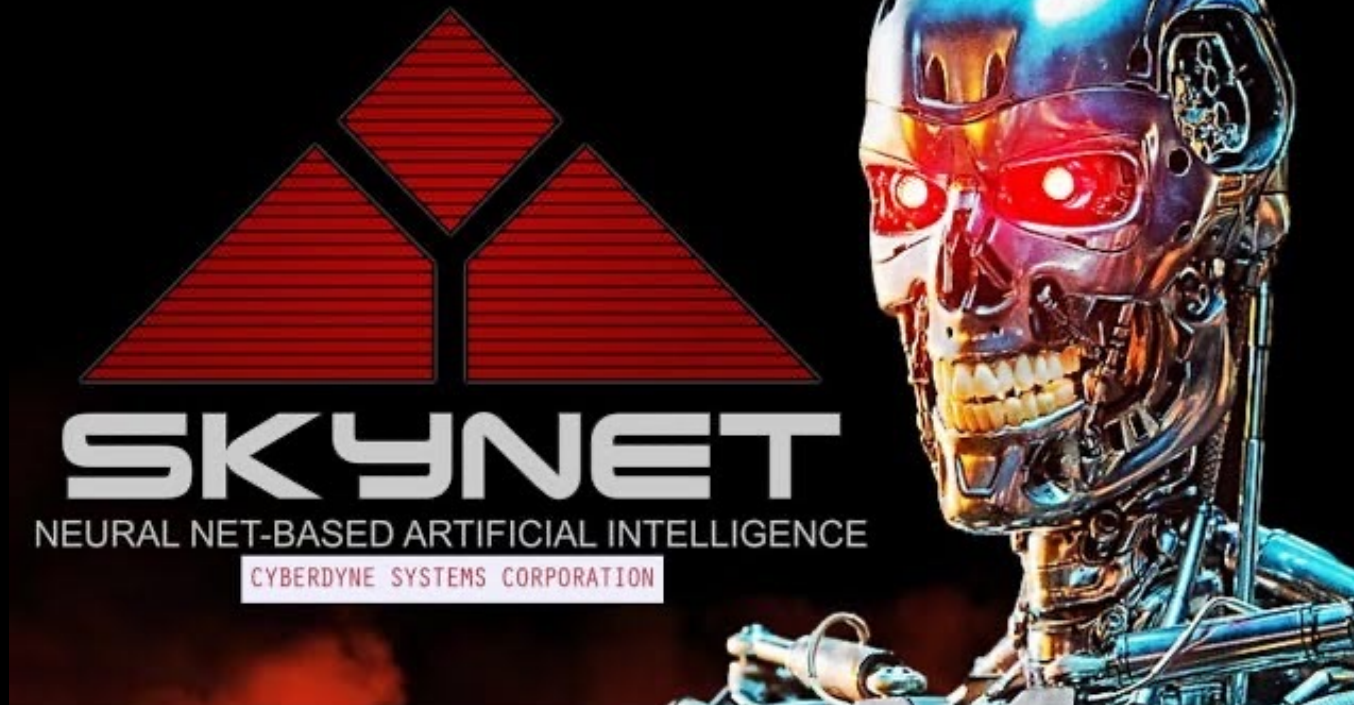
Self Aware

GENETIC MODIFICATION



Future Informatics

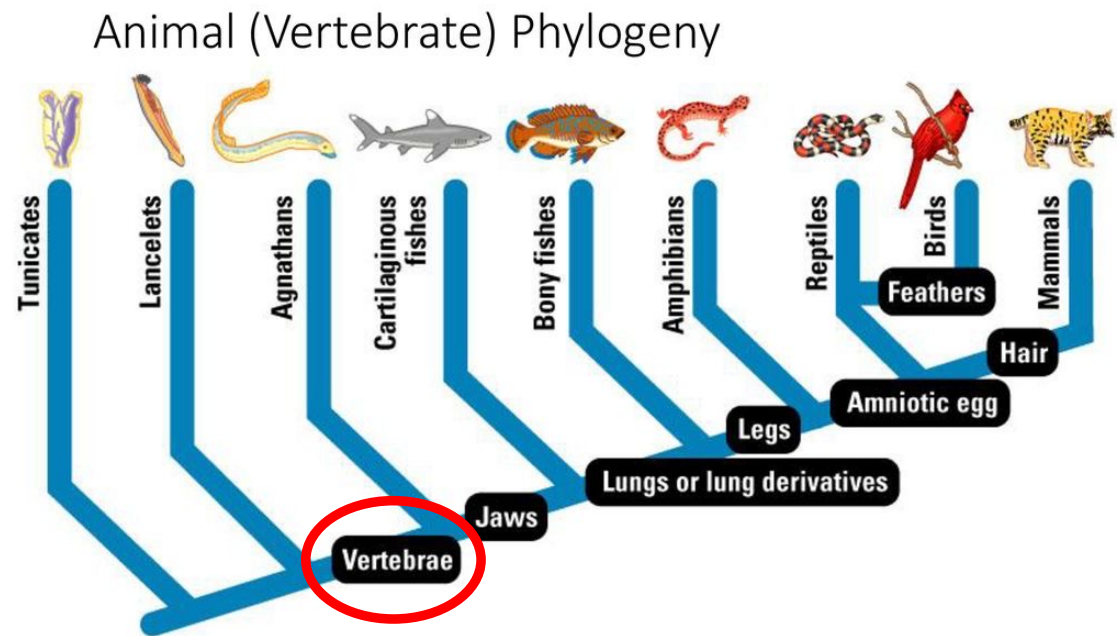
The End



The Melanocortin System

Ancient Functions

ANCIENT BIOLOGY

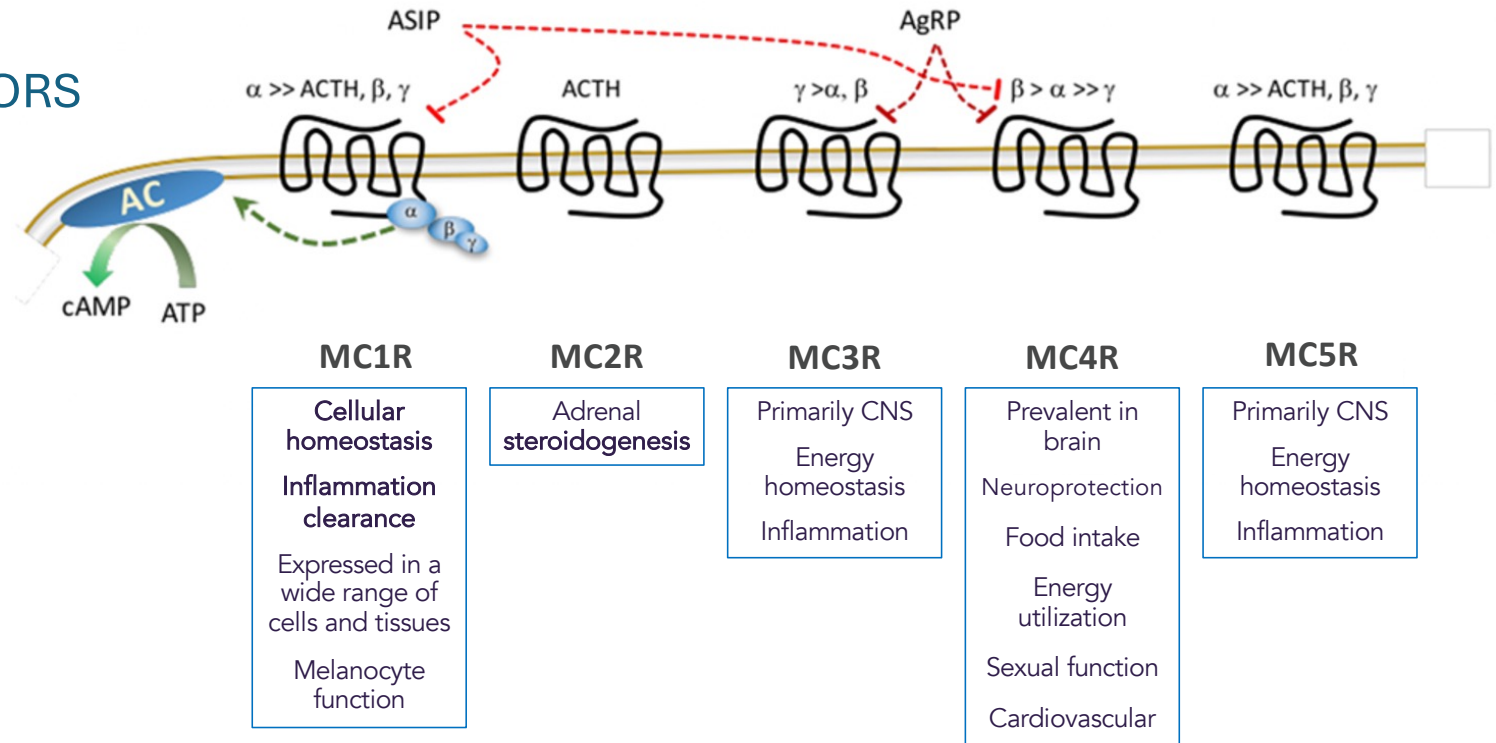


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The Melanocortin System

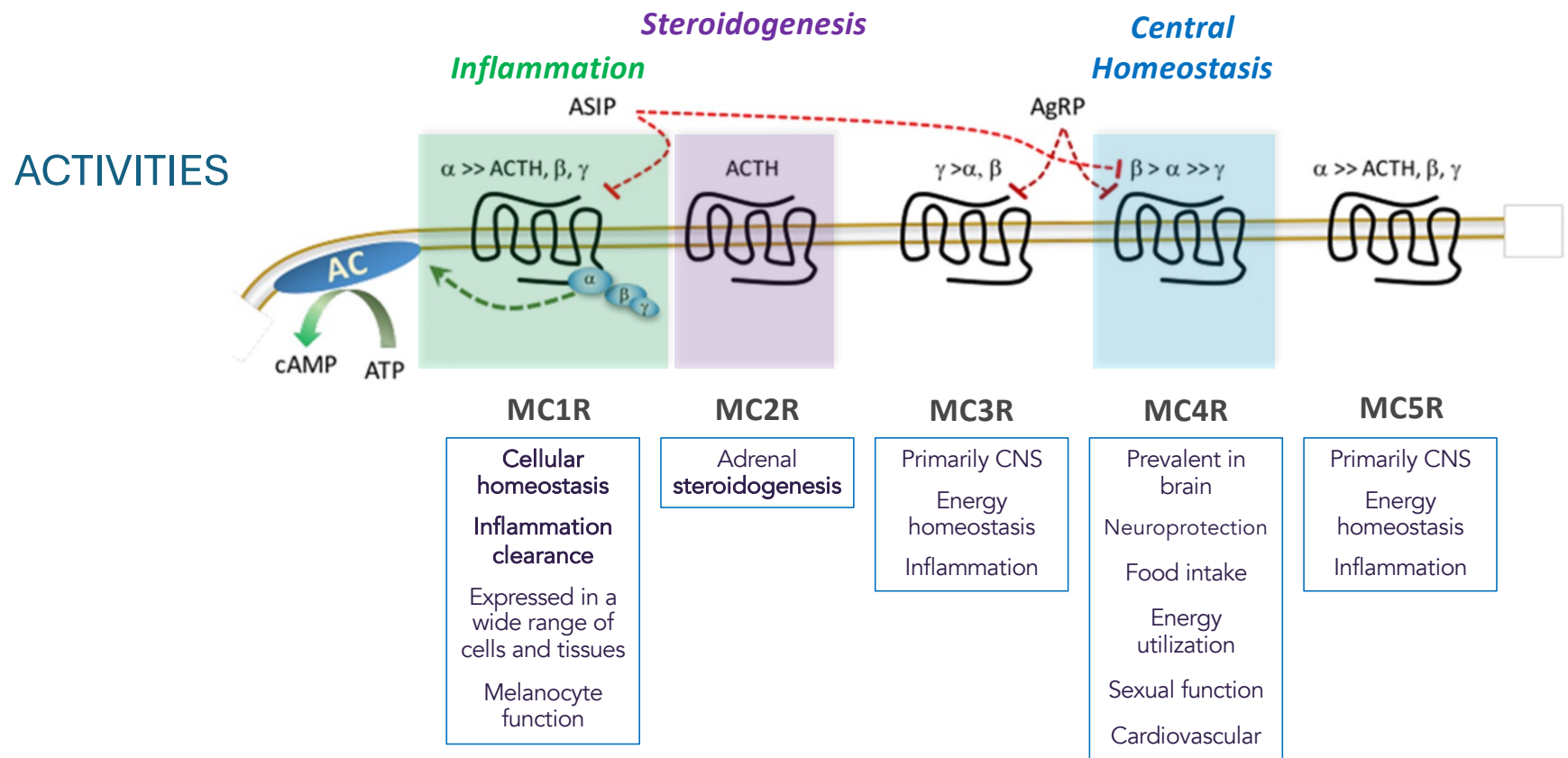
Composition

5 RECEPTORS



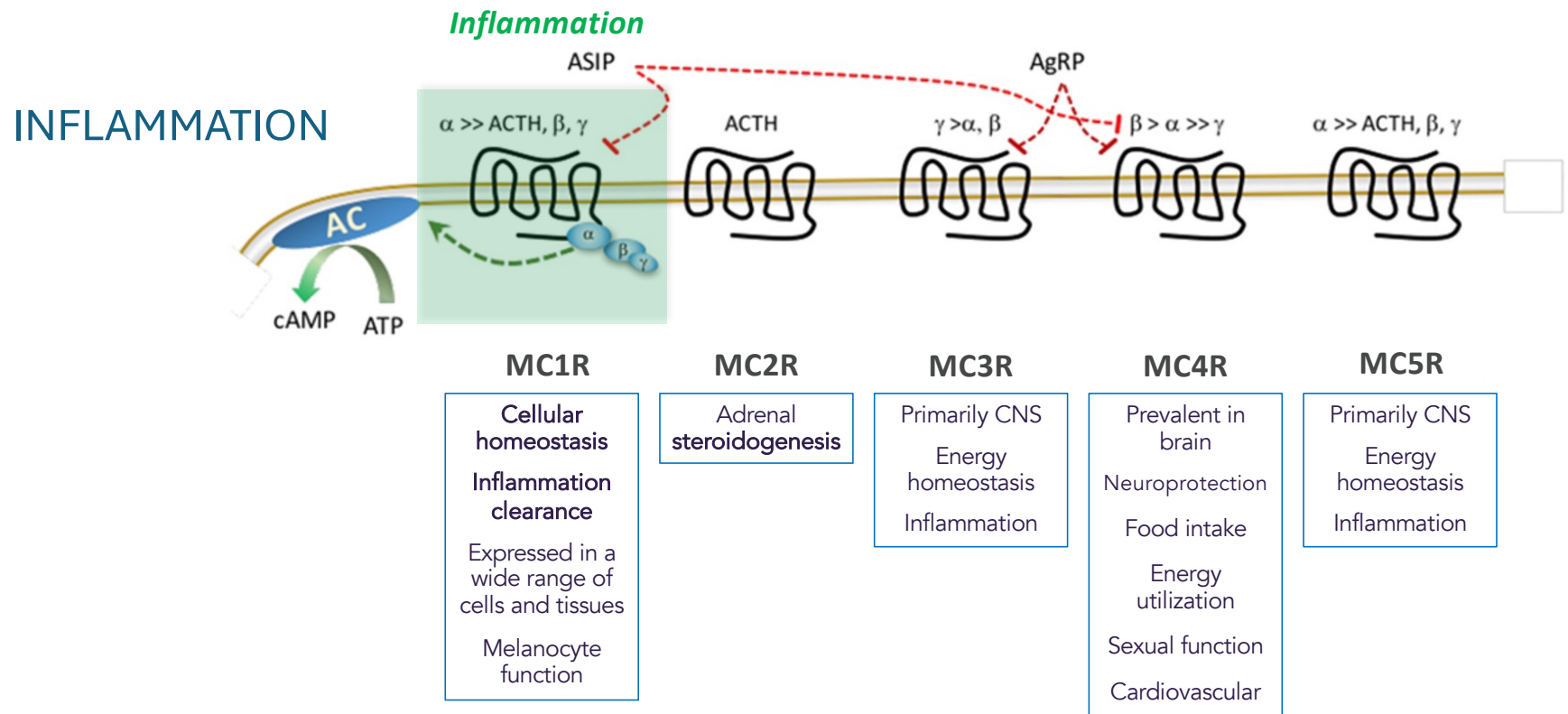
The Melanocortin System

Composition



The Melanocortin System

Composition



The Melanocortin System

Models of Inflammation

Inflammatory Ophthalmic Diseases			
Cataracts	Diabetic Retinopathy	Corneal Injury	Diabetic Macular Edema
Dry Eye	Glaucoma	Uveitis	

Inflammatory Diseases			
Acne	COPD	Multiple Sclerosis	Seborrhea
Ankylosing Spondylitis	Crohn's disease	NASH	Sepsis
Alzheimer's	Diabetic complications	Nephritis	Stroke
Asthma	Gout	Osteoarthritis	Traumatic shock
Atherosclerosis	Idiopathic lung fibrosis	Parkinson's	Ulcerative colitis
Burns	Interstitial Cystitis	Psoriasis	Vasculitis
Chemotherapeutic cytokine storm	Keloids	Rheumatoid Arthritis	Vitiligo
Contact Dermatitis	Lupus	Scleroderma	Wound Healing

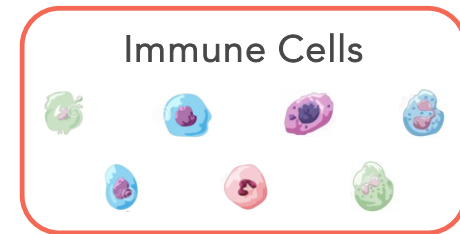
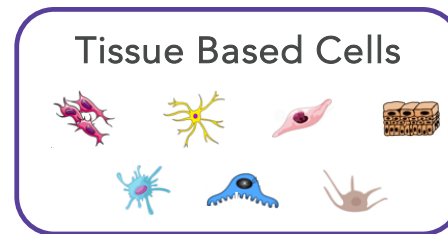
Inflammation models confirmed with Palatin compounds

EFFECTIVE IN A WIDE RANGE OF MODELS

The Melanocortin System

Immune System

MONITORS



Unstressed State

Insult Surveillance

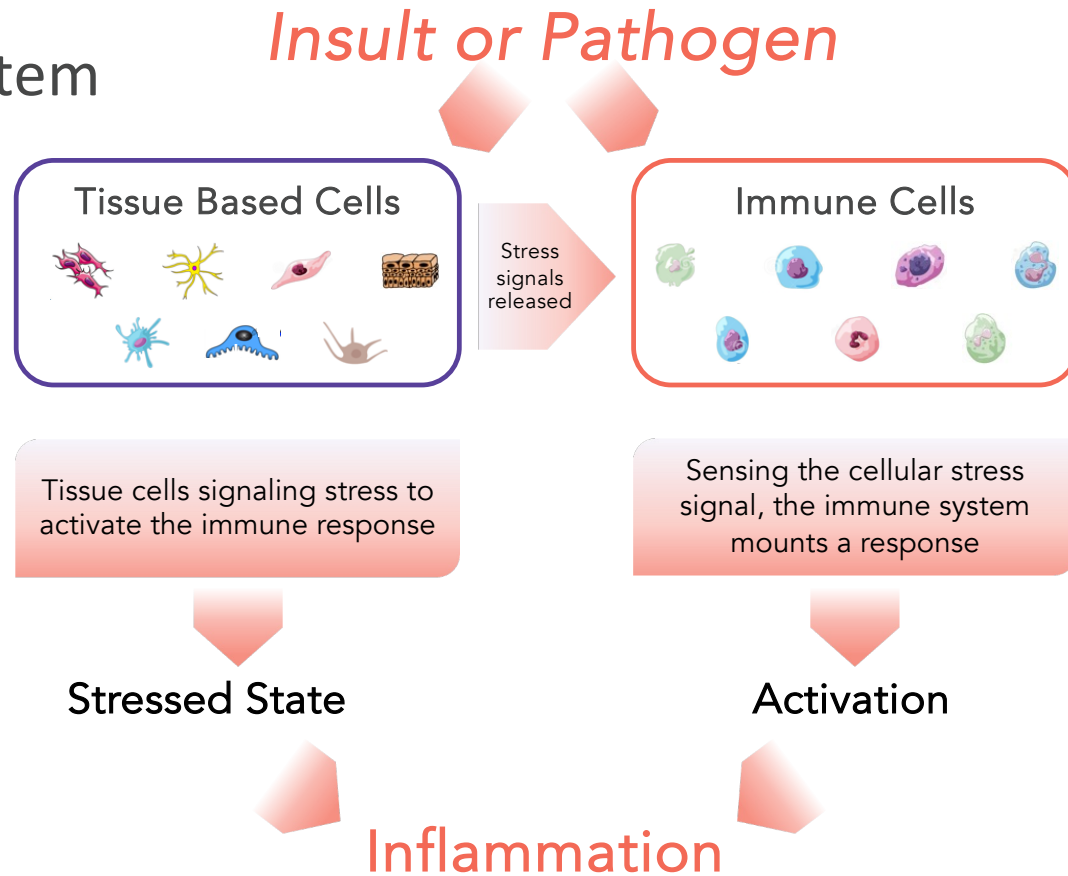
Homeostasis

- A complex network of organs, cells and proteins that defend the body against infection, injury, and oncogenic events, whilst protecting the body's own cells

The Melanocortin System

Immune System

RESPONDS

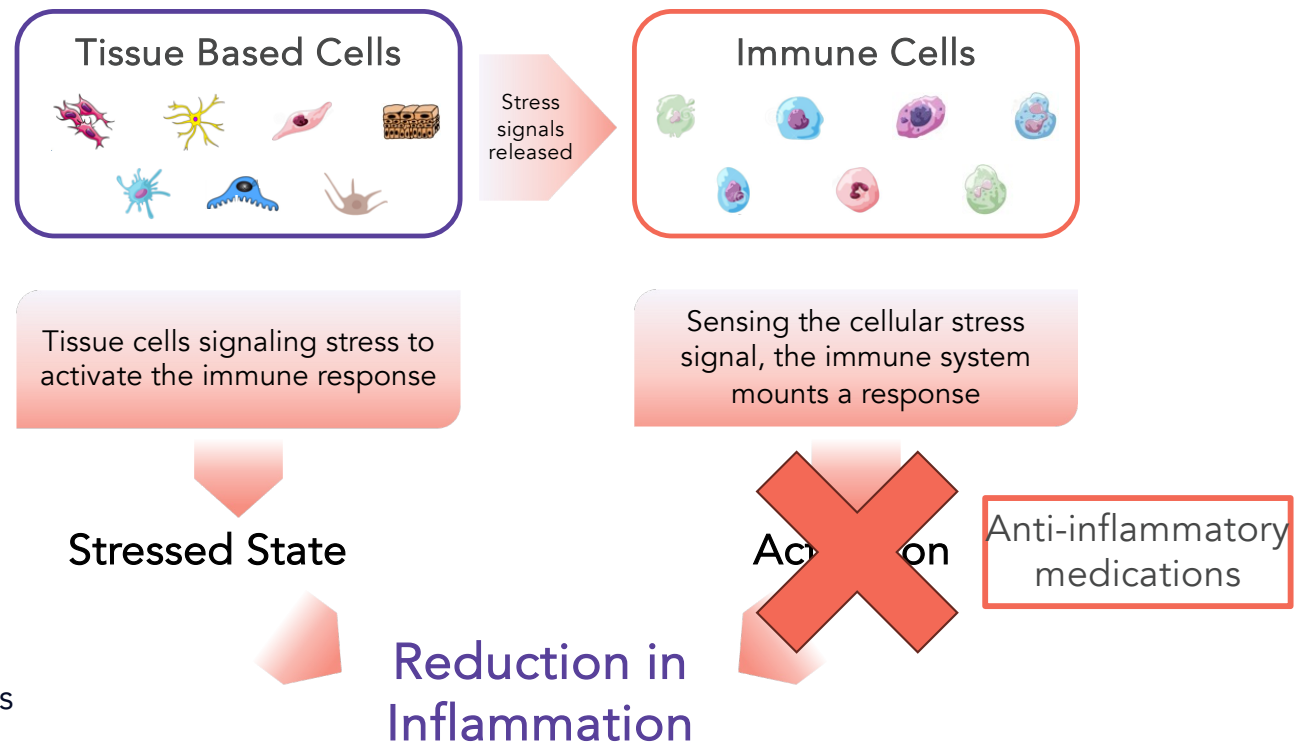


- Innate, adaptive acquired, and highly specific responses deployed
- Inflammation persists until *threat is neutralized*

The Melanocortin System

Immune System

DISEASE

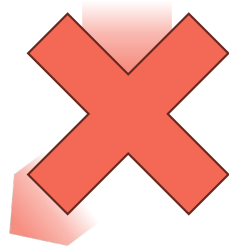


- The immune system attacking the body's own tissues, resulting in inflammation
- Anti-inflammatory medicines block aspects of the immune response reducing inflammatory disease

The Melanocortin System

Anti-Inflammatory Medicines

BLOCKING



Anti-inflammatory
medications



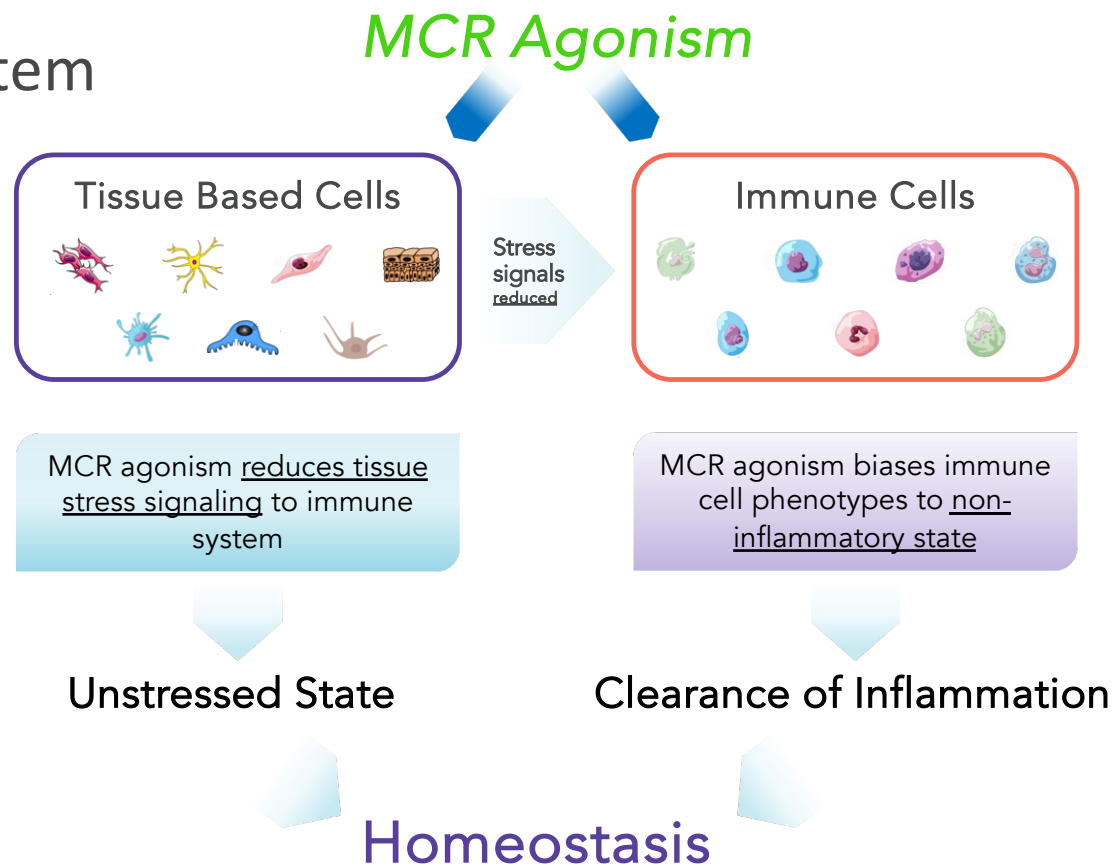
Anti-inflammatory medicines:

- Block aspects of the immune response
- May impede the immune response in uninvolved tissues
- Inhibiting this required system can lead to adverse events
- Long term use increases risk
- Efficacy must be balanced against safety

The Melanocortin System

Immune and Tissue Cells

RESOLUTION



- Palatin's compounds *harness* the Melanocortin System in diseased patients to return them to a *healthier state*

The Melanocortin System

Clinical

DRY EYE DISEASE



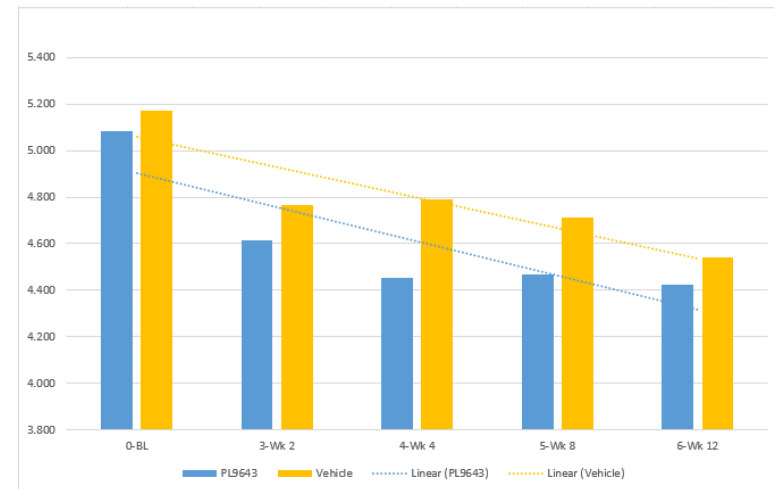


The Melanocortin System

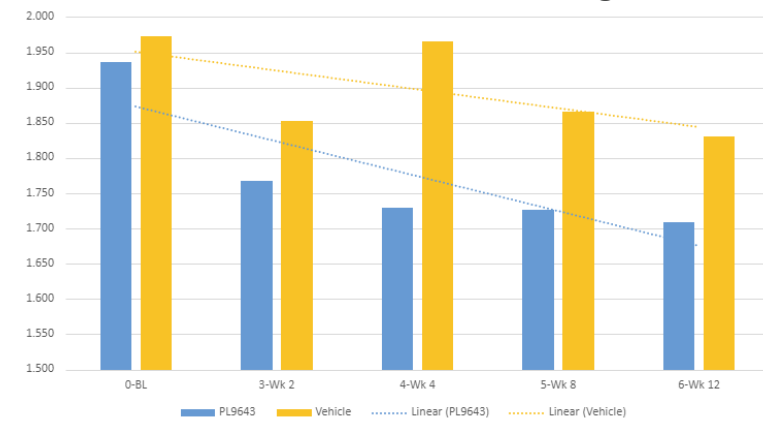
Dry Eye Disease

EFFICACY : SIGNS

Corneal Fluorescein Staining



Inferior Fluorescein Staining

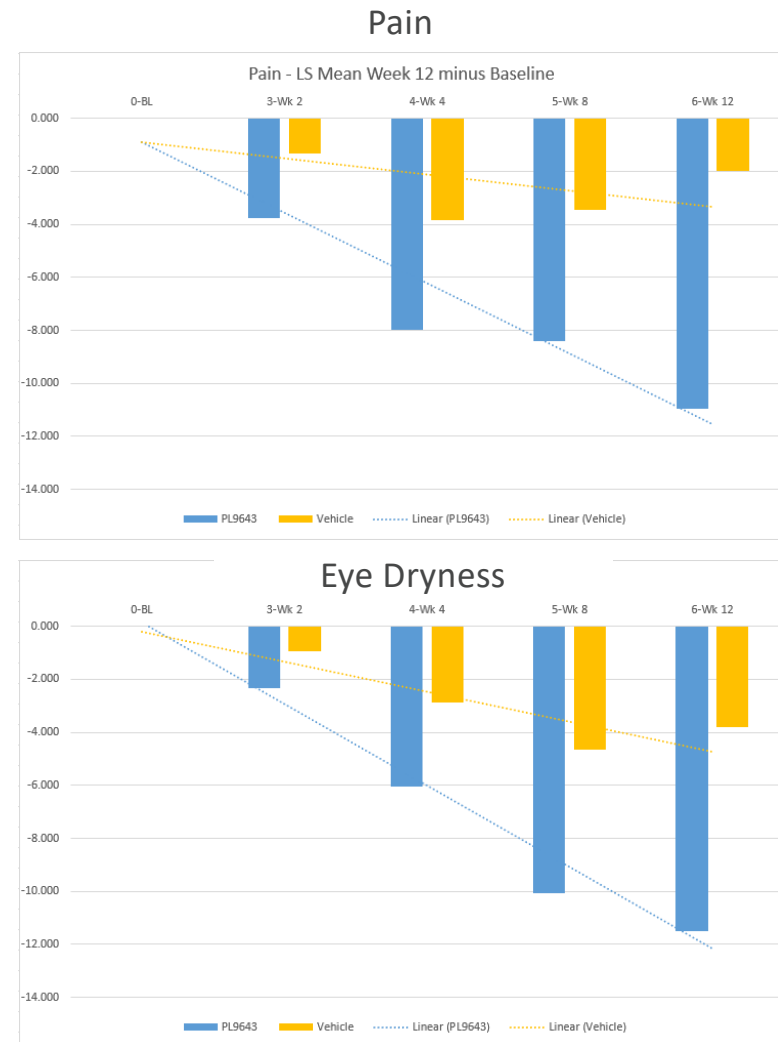




The Melanocortin System

Dry Eye Disease

EFFICACY : SYMPTOMS





Dry Eye Disease

The Melanocortin System

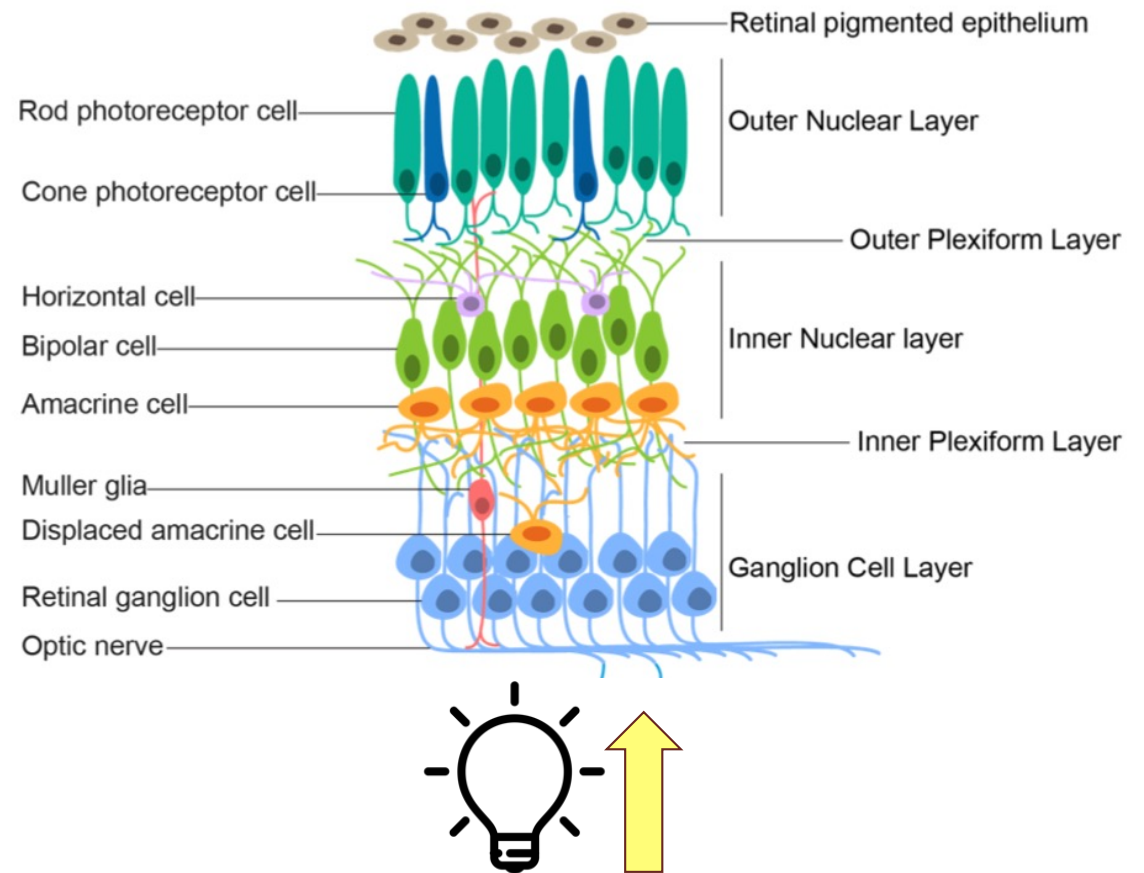
SAFETY AND TOLERABILITY

Approved Products		PL9643			
		Phase 2 Study (N=160)		Phase 3 Lead-In Cases (N=120)	
Restasis		PL9643 (N=80)	Vehicle (N=80)	PL9643 (N=60)	Vehicle (N=60)
Ocular Burning	17%	0%	0%	0%	3%
Xiidra					
Instillation Site Irritation	18%	0%	0%	0%	0%
Dysgeusia	13%	0%	0%	0%	0%
Reduced Visual Acuity	4.7%	0%	1%	0%	0%
Cequa					
Instillation Site Pain	22%	0%	9%	0%	0%
Conjunctival hyperemia	6%	0%	0%	0%	0%
Eysuvis					
Instillation Site Pain	5%	0%	9%	0%	0%
Tyrvaya					
Sneezing	82%	0%	0%	0%	0%
Cough	5-16%	0%	0%	0%	0%
Throat Irritation	5-16%	0%	0%	0%	0%
Site Instillation Irritation	5-16%	0%	0%	0%	0%
Miebo					
Blurry Vision	1-3%	0%	0%	0%	0%
Conjunctival Redness	1-3%	0%	0%	0%	0%

The Melanocortin System

Retinopathy

RETINA

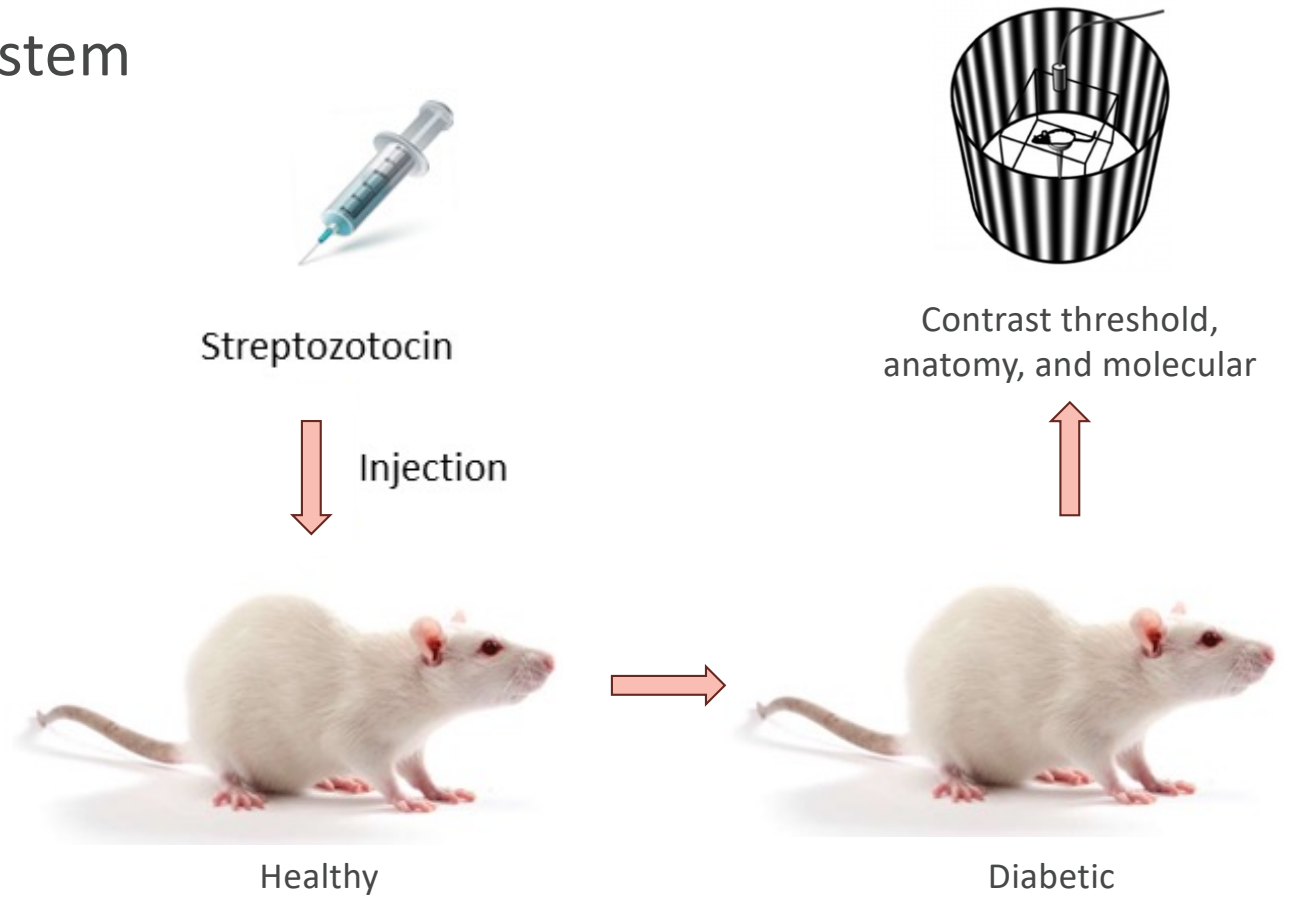




The Melanocortin System

Diabetic Retinopathy

MODEL



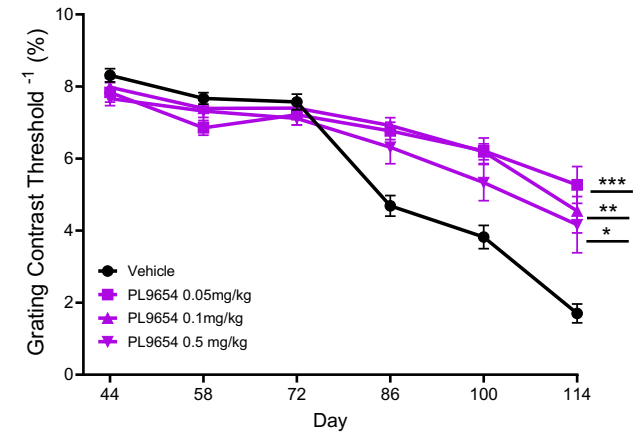
The Melanocortin System

Diabetic Retinopathy

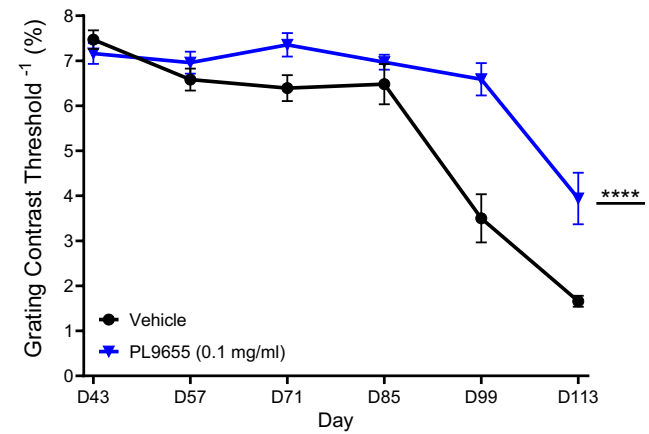
CONTRAST VISION

- Contrast vision preserved by MCR agonists
- Animals remain diabetic throughout the experiment

Subcutaneous



Topical

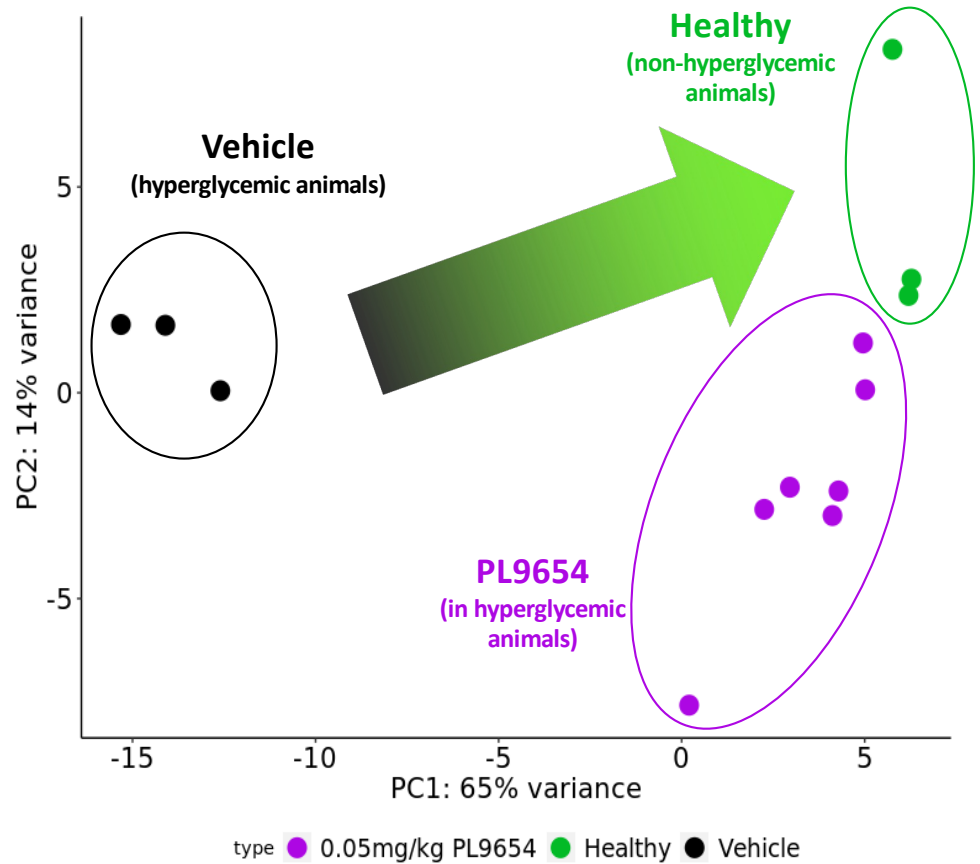


The Melanocortin System

Diabetic Retinopathy

RETINAL GENE EXPRESSION

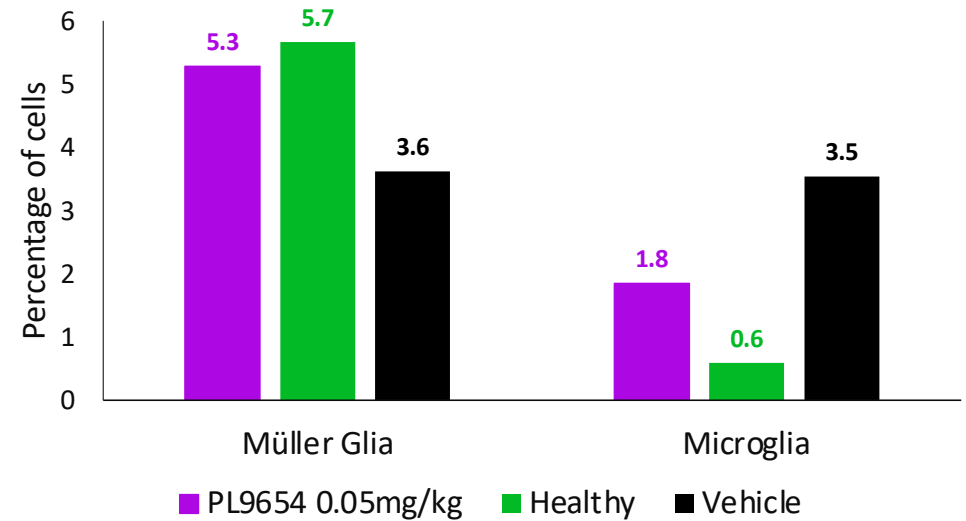
- PCA of combined snRNAseq data
- PL9654 dosed animals were still challenged by diabetic stress (HG)



The Melanocortin System

Diabetic Retinopathy

CELL POPULATIONS



Müller glia:

- Responsible for the homeostatic and metabolic support of retinal neurons
- Regulate the tightness of the blood-retinal barrier

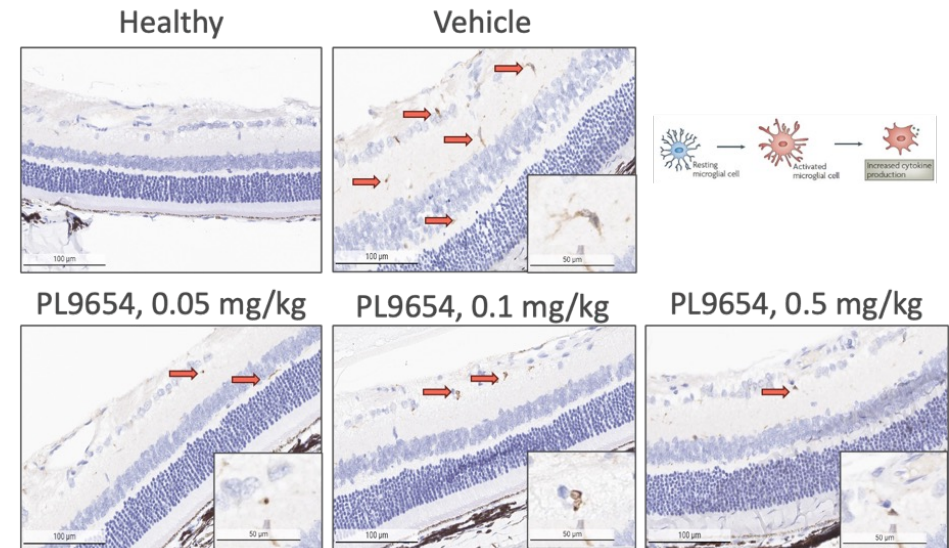
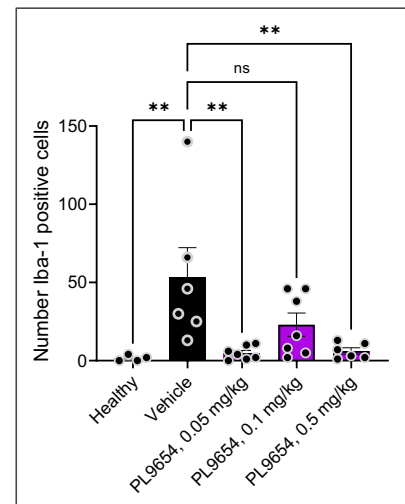
Microglia:

- Pro-resolution AND pro-inflammation
- State dependent

The Melanocortin System

Microglia

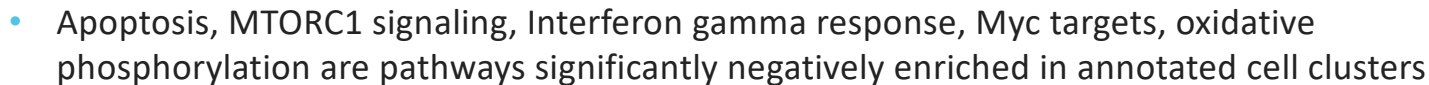
STATE CHANGE



- Activation of microglial cells leads to production of pro-resolving cytokines and mobility to reach inflamed tissues

Pathway Regulation

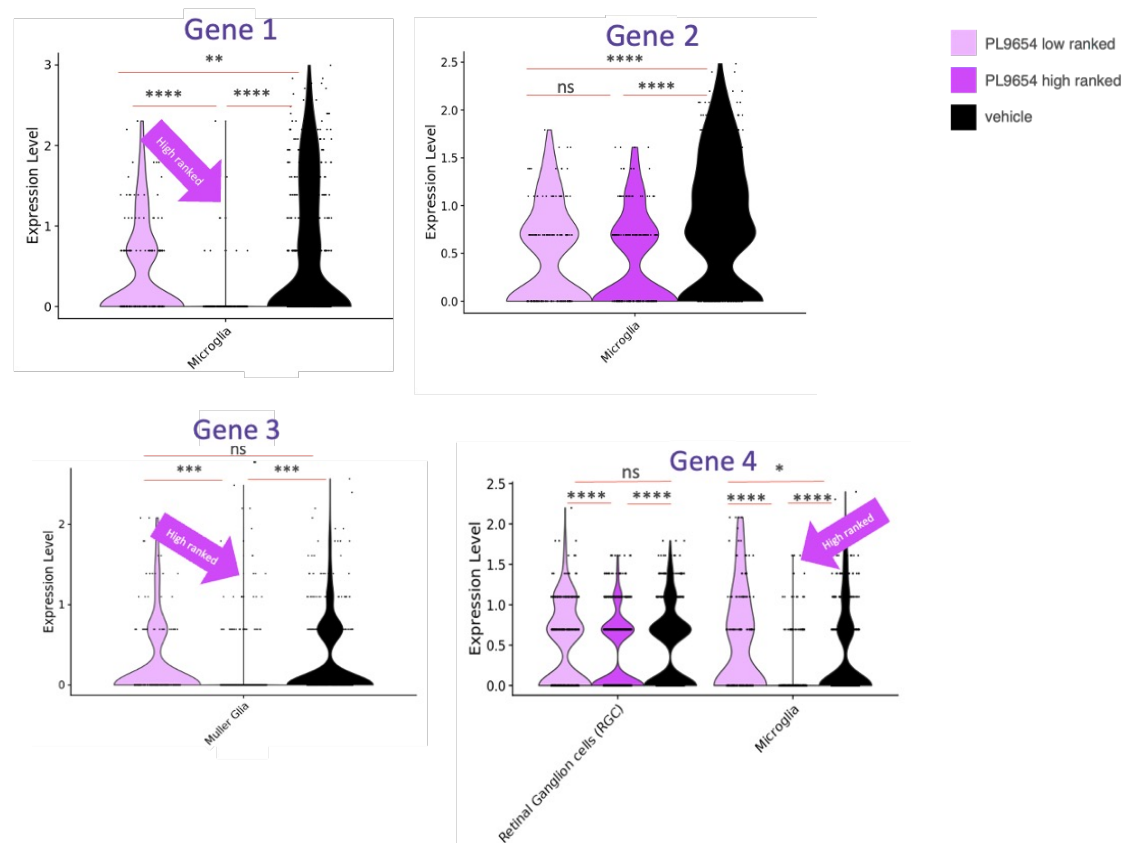
IMMUNE
DOWN
REGULATED



The Melanocortin System

Differentially Expressed Genes

IMMUNE SYSTEM



- PL9654 treatment causes key immune response gene expression to move away from diseased towards healthy

Used wilcox test for statistical analysis. *p<0.05, ** p<0.01, *** p<0.005, **** p<0.001 ns: not significant

The Melanocortin System

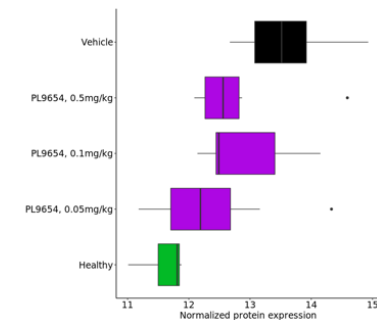
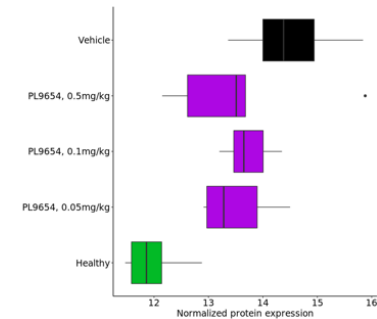
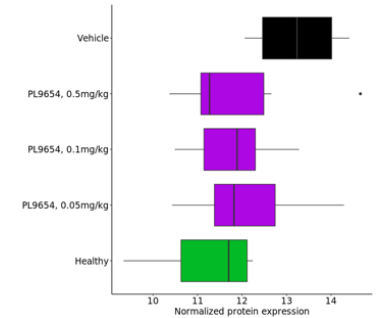
Differentially Expressed Proteins

IMMUNE SYSTEM

- PL9654 treatment causes key immune response proteins to move away from diseased towards healthy

Protein 1 plays a role in inflammation, apoptosis and angiogenesis

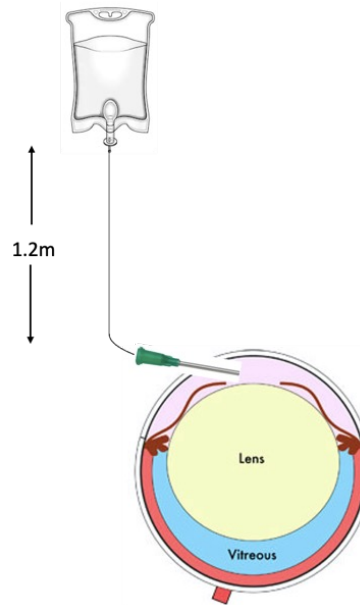
- Protein 2 is a well-established biomarker of astrocyte injury and considered one of the early signs of retinal metabolic stress
- Protein 3 upregulation reported in the vitreous and neovascular retina of patients with diabetic retinopathy



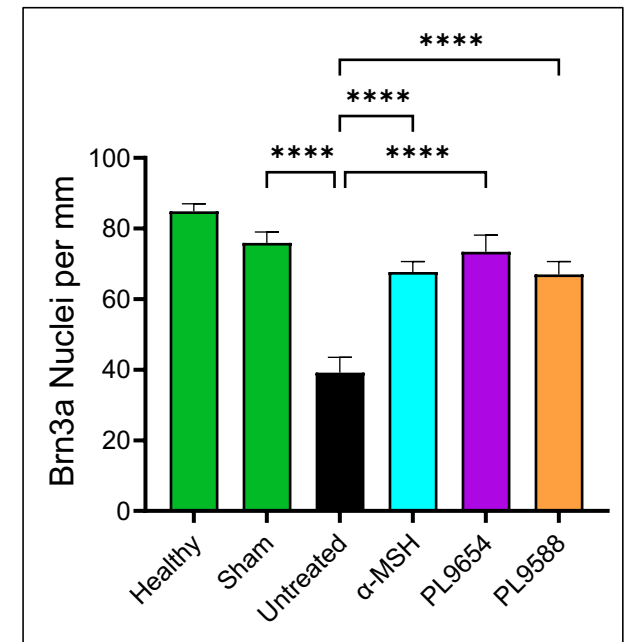
The Melanocortin System

Ischemia/Reperfusion

MODEL



Viable Retinal Ganglion Cells (brn3a Positive)



****P ≤ 0.001

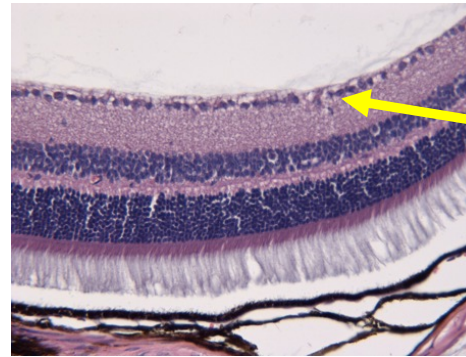
- Model Damages anatomical structure and cells
- PL9654 protects ganglia that form the optic nerve

The Melanocortin System

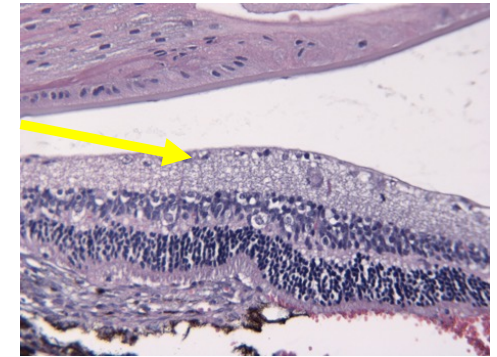
Ischemia/Reperfusion

NEUROPROTECTION

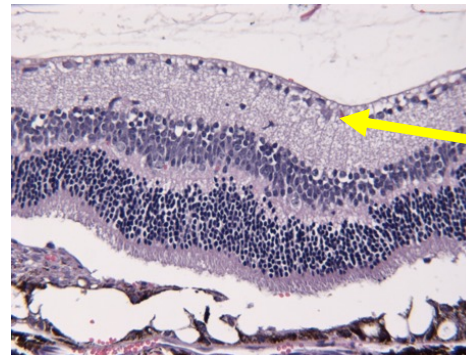
Naïve



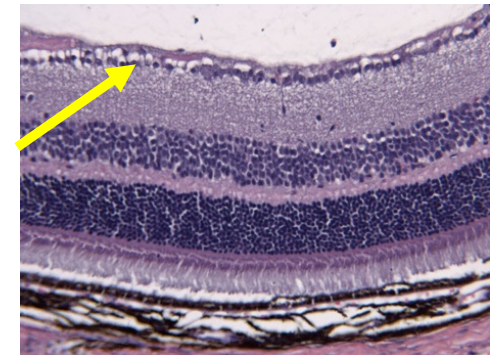
Vehicle



α -MSH



PL9654



GCL: Ganglion Cell Layer

The Melanocortin System

Future Indications

Inflammatory Ophthalmic Diseases			
Cataracts	Diabetic Retinopathy	Corneal Injury	Diabetic Macular Edema
Dry Eye	Glaucoma	Uveitis	

Inflammatory Diseases			
Acne	COPD	Multiple Sclerosis	Seborrhea
Ankylosing Spondylitis	Crohn's disease	NASH	Sepsis
Alzheimer's	Diabetic complications	Nephritis	Stroke
Asthma	Gout	Osteoarthritis	Traumatic shock
Atherosclerosis	Idiopathic lung fibrosis	Parkinson's	Ulcerative colitis
Burns	Interstitial Cystitis	Psoriasis	Vasculitis
Chemotherapeutic cytokine storm	Keloids	Rheumatoid Arthritis	Vitiligo
Contact Dermatitis	Lupus	Scleroderma	Wound Healing

Inflammation models confirmed with Palatin compounds

EFFECTIVE IN A WIDE RANGE OF MODELS

Incognito Escrow

A Modest Proposal

DATA LENDING



Incognito Escrow

Big Data

OPPORTUNITY

- Improved medicines
- Improved clinical outcomes
- Expanded biology insights
- New paradigm for research

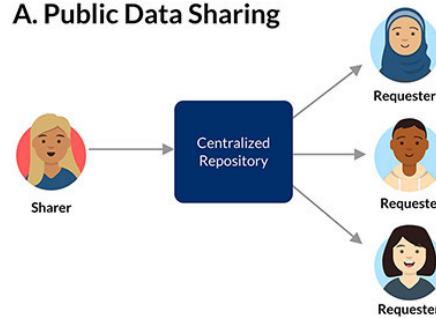


Incognito Escrow

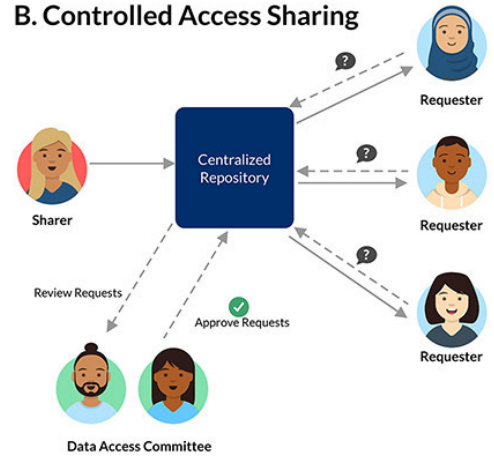
Big Data

SHARING MODES

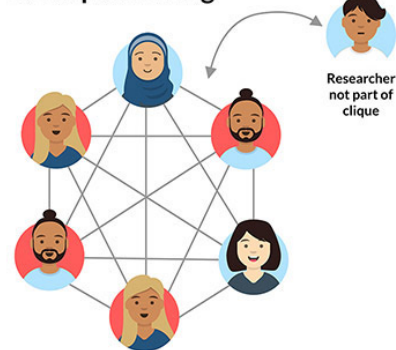
A. Public Data Sharing



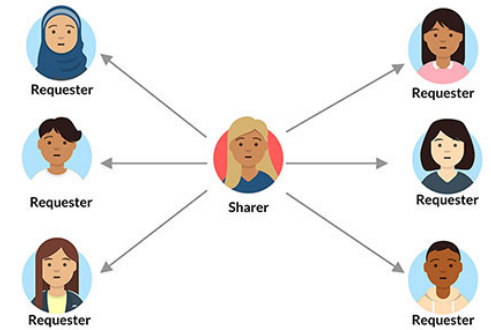
B. Controlled Access Sharing



C. Clique Sharing



D. Sharing Upon Request



Incognito Escrow

Big Data

CHALLENGES

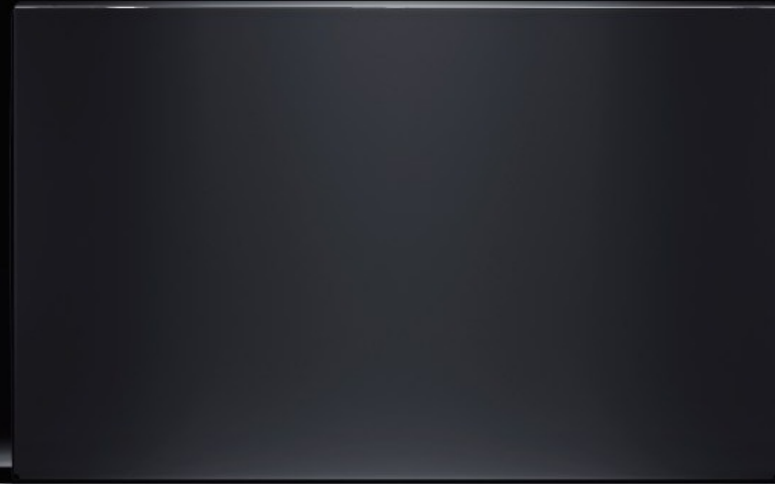
- Petabytes of data
- Most data never released
- Structure
- Annotation
- Privacy
- Security
- Intellectual Property
- Analysis



Incognito Escrow

Big Data

INCOGNITO POOL



- Participants provide complex omics data sets
- All relevant data queried regardless of ownership
- Summary results returned
- Original data never revealed

Incognito Escrow

Substantiation

OBSTACLES

- Recruiting initial partners
- Funding
- Designing the black box
- Defining data parameters
- Security model
- Legal model
- Adapting analysis code
- Creating actionable reports

Incognito Escrow

Big Data

OPPORTUNITIES



Benefits

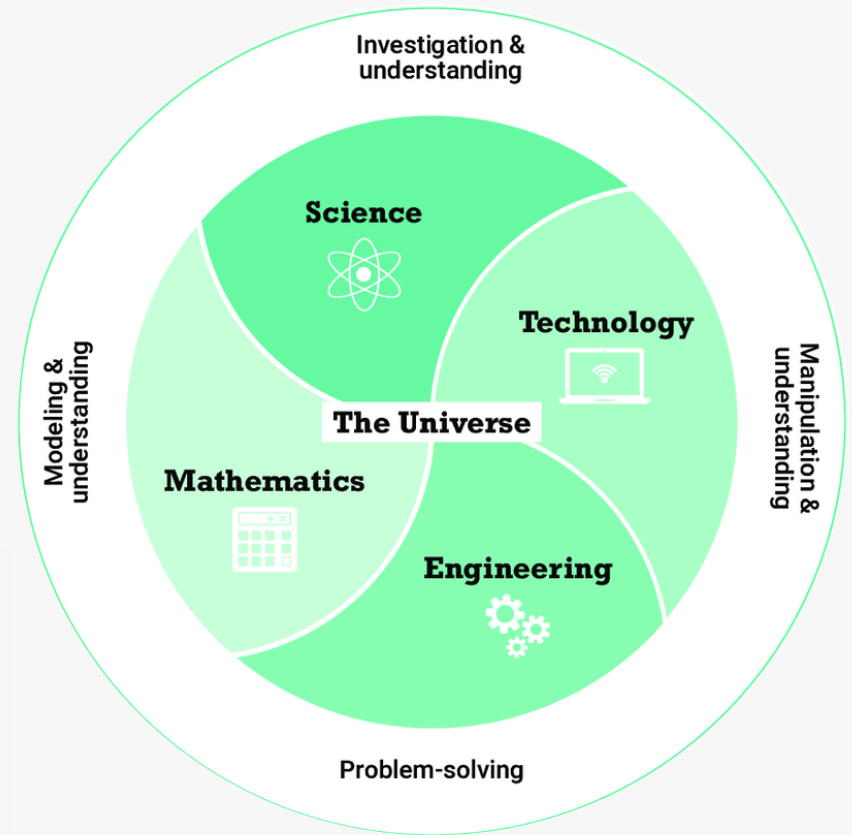
- Petabytes of data
- Available for analysis
- Unified structure
- Improved annotation
- Privacy maintained
- Security elevated
- Improved IP
- Improved analysis

Incognito Escrow

Big Data

OPPORTUNITIES


Benefits



Model for other disciplines

Ancient Informatics and a New Approach to Treating Inflammatory Diseases

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September 28, 2024