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Gene Expression in Alzheimer's Disease Patients

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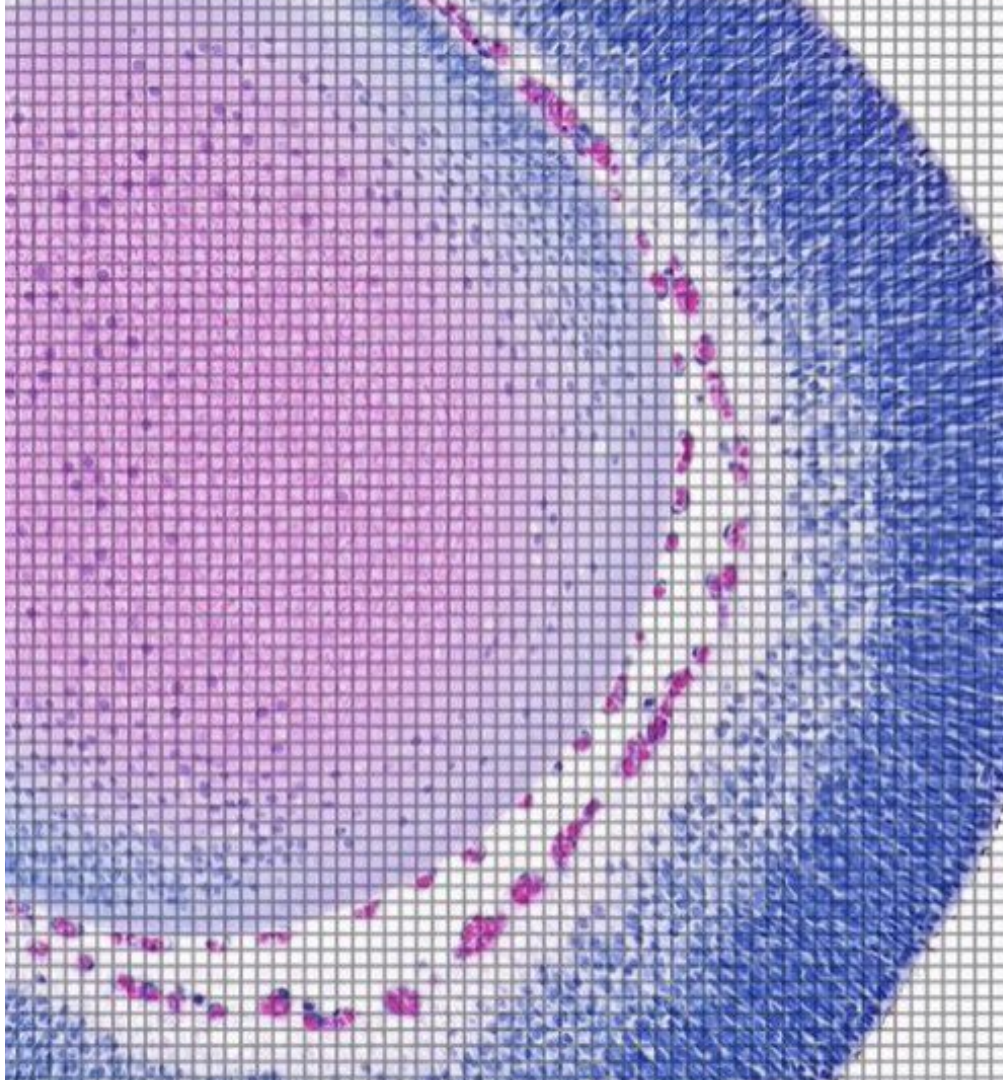
Groups of Interest:

- Moderate vs Incipient
- Severe vs Moderate



Agenda

1. Introduction to Alzheimer's Disease
2. **Moderate vs Incipient** Group Analysis
    a. 4 pathways of interest
3. **Severe vs. Moderate** Group Analysis
    a. Observations against the same 4 pathways of interest
4. Questions

Introduction to Alzheimer's Disease (AD)

Common Symptoms

- Memory loss
- Cognitive difficulties
- Mood swings

Biological Changes

- Current knowledge suggests tau proteins accumulate in memory-centers of the brain
- Beta-amyloid proteins clump between neurons
- Eventually the neurons begin to die

Need for Research

- There is no known cause or treatment for AD
- The use of genetic data could help determine a cause or treatment

Moderate vs. Incipient

Estrogen Receptor Pathway

- **How does it function normally?**
  - Estrogen receptors bind to estrogen, a female sex hormone, and initiate a multitude of physiological responses.
    - This includes protein synthesis that affects the cardiovascular system, liver, brain, and more.
  - Estrogen has a **"protective effect"** on neurons, emotion, and inflammation in the brain
- **How does it relate to Alzheimer's Disease?**
  - Post-menopausal women have a significantly higher chance of developing AD due to the sharp decline in estrogen in their bodies
    - Almost ⅔ of diagnosed AD patients are women
    - Research shows estrogen can reduce the release of beta amyloid proteins
  - Moderate Alzheimer's patients had 2 genes significantly less expressed in this pathway compared to incipient patients
    - JUN (transcription factor) and PPARA (regulates an enzyme that produces beta-amyloid)
      - Both have a negative fold change and $p < 0.001$

Enrichment Analysis Findings for Insulin Resistance

Let's focus on this first

Comparing Moderate vs Incipient Groups

Insulin resistance is a significant pathway with

- **0.01 p-value**
- **4/108 overlap**

Linked Genes:
SLC27A6 | PPARA | PRKAG3 | MTOR

Comparing Severe vs Moderate Groups

We see **17 occurrences** of different pathways that regulate insulin production, secretion and resistance

- **3** of those with **p-values < 0.05**
- Most highlight the insulin release controlled by **glucagon-like peptide-1** in intestines

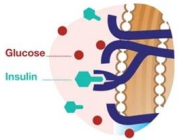
Linked Genes:
PRKAR2A | RAPGEF4 | DOK1

Lets understand the function of Insulin

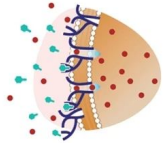
A healthy process

1. When you eat food, your body converts it into dietary sugar

2. Your Pancreas secretes a hormone called “Insulin”



3. Insulin instructs your cells to convert that sugar into energy



4. Your cells convert the sugar into energy and you feel energized

Insulin Resistance / Pre-Diabetes

1. When you eat food, your body converts it into dietary sugar

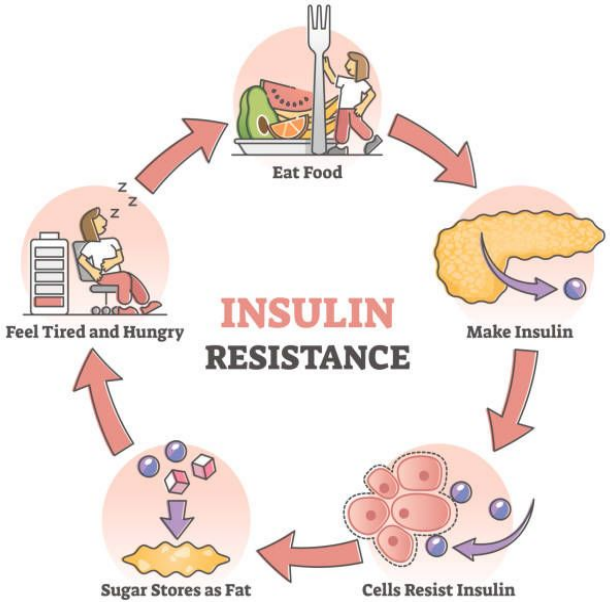
2. Your Pancreas secretes a hormone called “Insulin”

3. Your cells don’t convert sugar into energy, and instead you store it as fat

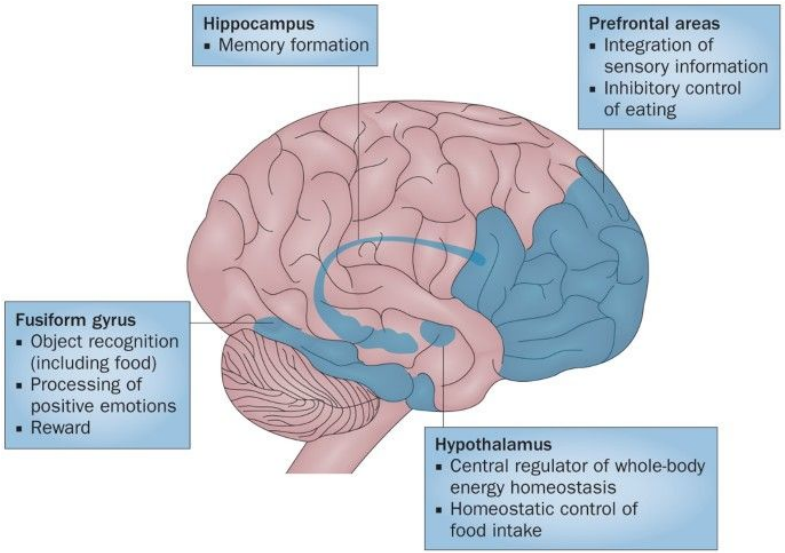
4. You end up feeling tired and hungrier

Insulin Resistance in the Body vs Brain

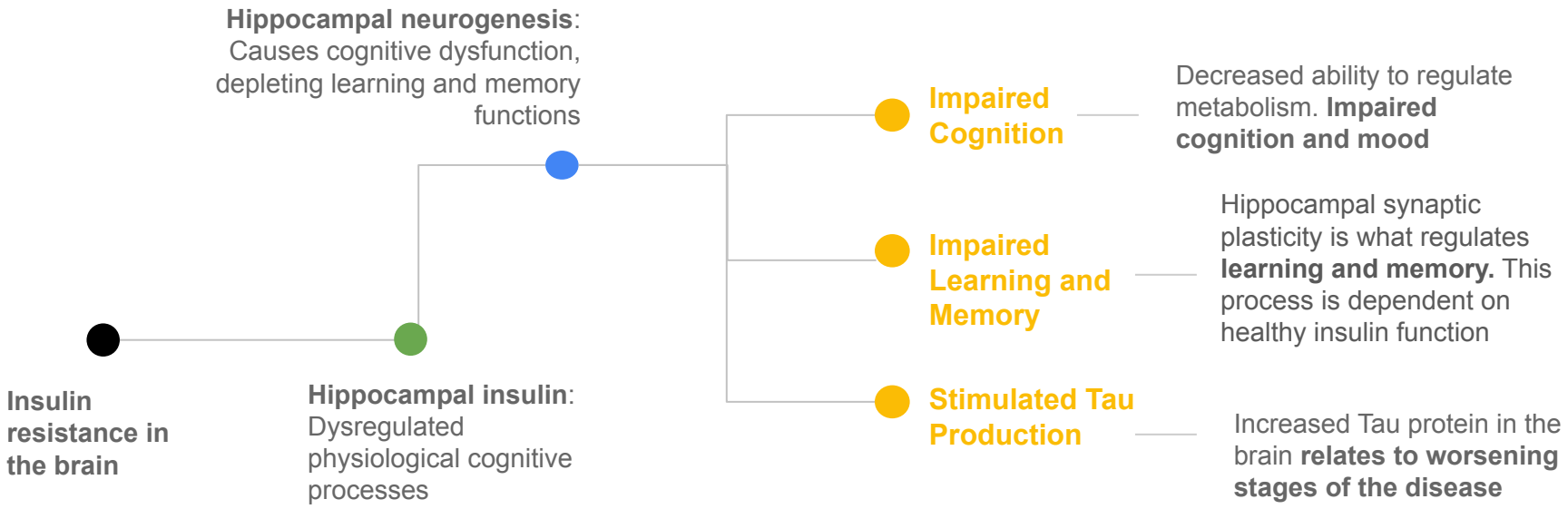
Insulin Resistance in the body:
A vicious cycle



Insulin Resistance in the brain:
Disrupts various functions



Research: How Insulin Resistance Shows Up in Early Alzheimer's Disease



- **Definition:** Insulin resistance may be defined as the failure of brain cells to respond to insulin. AD is regarded as diabetes mellitus of the brain.
- **Reason:** Lack of response to insulin may be due to various causes, including downregulation of insulin receptors, the inability of IR to bind insulin or an impairment of the insulin cascade
- **Anti Diabetic and Hormonal Therapies have a known progressive effect on patients with AD**

Neuroinflammation WP-4919

Impacts the Brain: Involves immune activation within the CNS due to injury, infection, toxins, or diseases.

Chronic Neuroinflammation: Linked to conditions like Alzheimer's, Parkinson's, and Multiple Sclerosis.

Key Immune Cells Involved:

- **Microglia Activation**
  - **Dual Role**: Defend against pathogens and clear debris but can become harmful when chronically activated.
  - **In Disease**: Release proinflammatory molecules, leading to neuronal damage, synaptic disruption, and protein accumulation (e.g., amyloid-beta in Alzheimer's).

- **Astrocytes in Neuroinflammation**
  - **Reactive Astrogliosis**: Structural and functional changes in response to neuroinflammatory signals.
  - **Impact**: Contributes to neuronal injury and worsens the inflammatory environment.

Consequences of Chronic Neuroinflammation

- **Pro-inflammatory Cytokines**: Released by activated microglia and astrocytes.
- **Neurotoxic Environment**: Accelerates neuronal death and disease progression.
- Moderate Alzheimer's patients had 2 differentially expressed genes in this pathway (p-value: 0.0044)
  - JUN and MTOR - play crucial roles in exacerbating inflammation in the brain

Mitochondrial Protein Import Pathway (R-HSA-1268020)

Normal Function:

- Transports essential proteins from cytosol into mitochondria to maintain cellular energy
- Key functions:
    - **ATP Production:** Provides proteins necessary for the electron transport chain, enabling efficient ATP generation.
    - **Oxidative Phosphorylation:** Essential for coupling ATP production with oxygen consumption, a key process for high-energy organs like the brain.
    - **Regulation of Apoptosis:** Ensures cell survival by regulating proteins involved in programmed cell death.

Gene Alterations: (0.014 p-value, 3/65 overlap)

CHCHD10

- Supports mitochondrial structure and cristae stability, indirectly influencing protein import efficiency.

ACO2

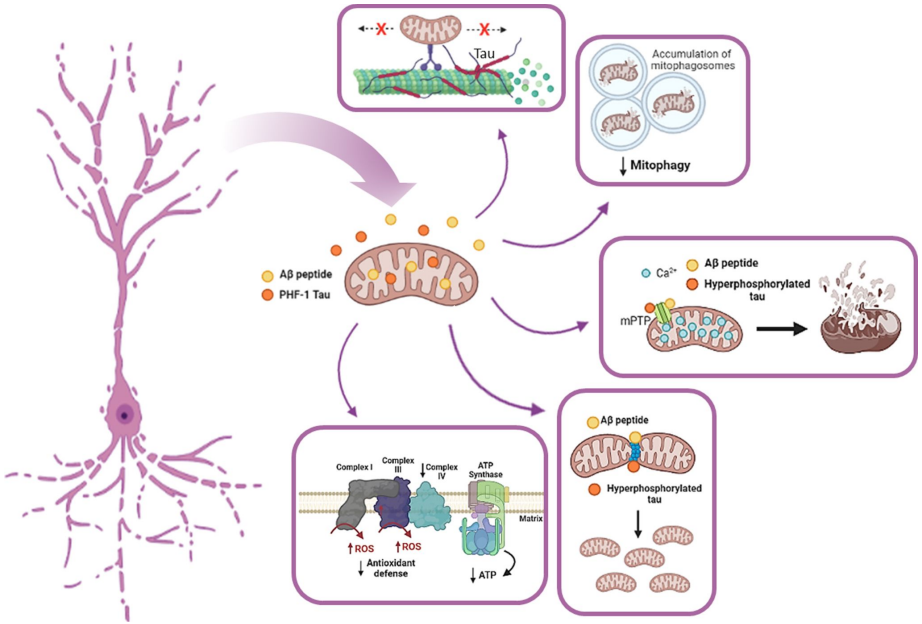
- encodes aconitase 2
- Crucial in the TCA cycle to produce cellular energy, essential for sustaining mitochondrial processes.

HSPD1 (Hsp60)

- Acts as a mitochondrial chaperone, fold into their correct three-dimensional shapes, ensuring they are functional stability

Mitochondrial Protein Import Pathway (R-HSA-1268020)

- **Energy Deficits**:
  - Disrupted import reduces ATP production
  - neuron energy shortages
- **Oxidative Stress**:
  - inefficient import raises free radical levels
- **Mitochondrial Instability**:
  - Dysfunction weakens mitochondria
  - neurodegeneration
- **Neuron Loss**:
  - Impaired import triggers apoptosis
  - Associated with loss of grey matter in AD
- **Biomarker Potential**:
  - Mitochondrial genes may help in AD detection and treatment



Severe vs. Moderate

Estrogen Receptor Pathway

- **This pathway was already discussed and significant results were found in both comparison analyses.**
  - Both p values were less than 0.001
  - Meaning as AD progresses, estrogen receptor pathways continually decline in function.
  - 2 differentially expressed genes in this pathway: ACOX1 (breaks down fatty acids in brain) and CYP1B1 (regulates homeostasis in brain)
    - Both have a negative fold change
- **Could this be pertinent to treatment options?**
  - Estrogen therapy has been proposed as a potential treatment for AD, but is still in the early stages of research
  - Effectiveness has been shown to vary greatly across patient groups
    - Factors that influence effectiveness could be age, smoking status, and history of breast cancer
    - The overall conclusion is estrogen may have an important preventative effect against AD but is less effective as a treatment once the disease has progressed

Insulin Resistance in Patients with Severe AD - Let's revisit

So IR manifests in more complex ways here

Comparing Moderate vs Incipient Groups

Insulin resistance is a significant pathway with

- **0.01 p-value**
- **4/108 overlap**

Linked Genes:
SLC27A6 | PPARA | PRKAG3 | MTOR

Comparing Severe vs Moderate Groups

We see **17 occurrences** of different pathways that regulate insulin production, secretion and resistance

- **3** of those with **p-values < 0.05**
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Linked Genes:
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Insulin Behaviour in Patients with Severe AD

Not enough research: Insulin Resistance is a risk factor typically associated with early stages of Alzheimers

Reduced Brain Glucose Metabolism

Glucose Metabolism Dysregulation gradually intensifies the severity of AD

- Insulin resistance disrupts glucose metabolism in AD.
- Creates an “energy crisis” in neurons.
- Accelerates cognitive decline.

Increased Tau production

Insulin Resistance Stimulates Tau Protein Production

- Decreased insulin signaling in the brain leads to tau hyperphosphorylation.
- Contributes to worsening AD pathology.

Neuroinflammation

Chronic insulin resistance promotes inflammation

- Brain inflammation disrupts cellular communication.
- Weakens the blood-brain barrier.
- Accelerates neuronal loss and cognitive decline in advanced AD stages.

Oxidative Stress

Insulin resistance can exacerbate oxidative stress

- Insulin resistance raises oxidative stress in the brain.
- Increases neuron vulnerability to damage.
- Speeds up progression of AD symptoms.

Regulation Of I-kappaB kinase/NF-kappaB Signaling

- Related to the neuroinflammation pathway
- Significant results found in both comparison analyses (p-value: 0.00043)

Key Genes Involved

PER1, TRAF4, CLEC7A, LPAR1, REL, MUL1, CFLAR, TMEM106A, LTF

Significance in Alzheimer's Progression:

Chronic Inflammation: Linked to cognitive decline and worsening of symptoms.

Therapeutic Strategy

- **Anti-Inflammatory Drugs**: Reduce inflammation to protect neurons.
- **Cytokine Inhibition**: Inhibit specific pro-inflammatory cytokines to slow down disease progression.
- **Modulating Immune Response**: Adjust microglial and astrocytic activity to limit neurotoxicity.

Goal

To slow Alzheimer's progression by reducing neuroinflammation and protecting neurons from further damage.

Mitochondrial Protein Import Pathway (R-HSA-1268020)

Gene Alterations: (0.024 p-value, 3/65 overlap)

COQ2

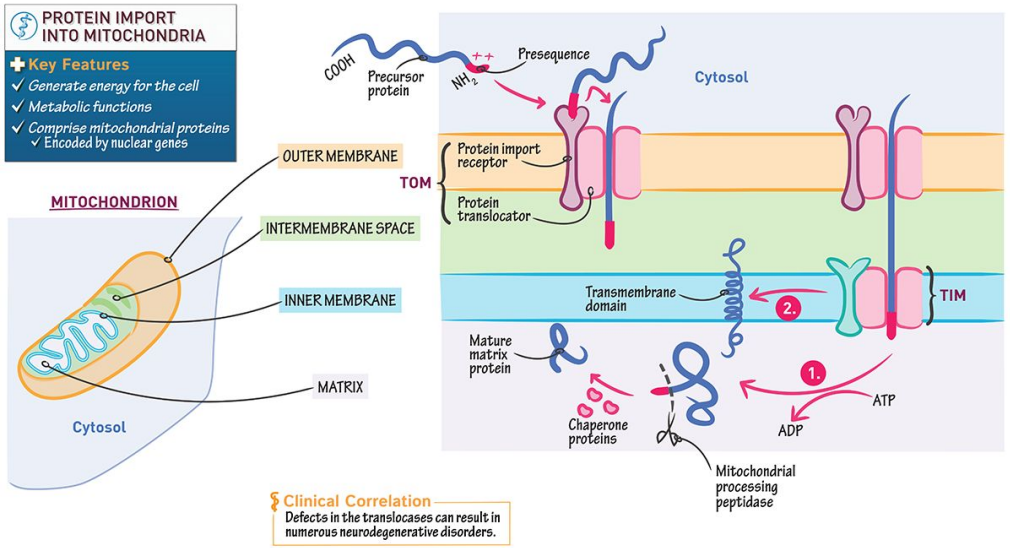
- Involved in coenzyme Q10 biosynthesis, essential for mitochondrial electron transport and ATP production.

TIMM17A

- Part of the TIM complex, facilitates protein import into the mitochondrial matrix, supporting energy metabolism.

TOMM22

- A core component of the TOM complex, responsible for recognizing and translocating proteins into mitochondria.



Questions?

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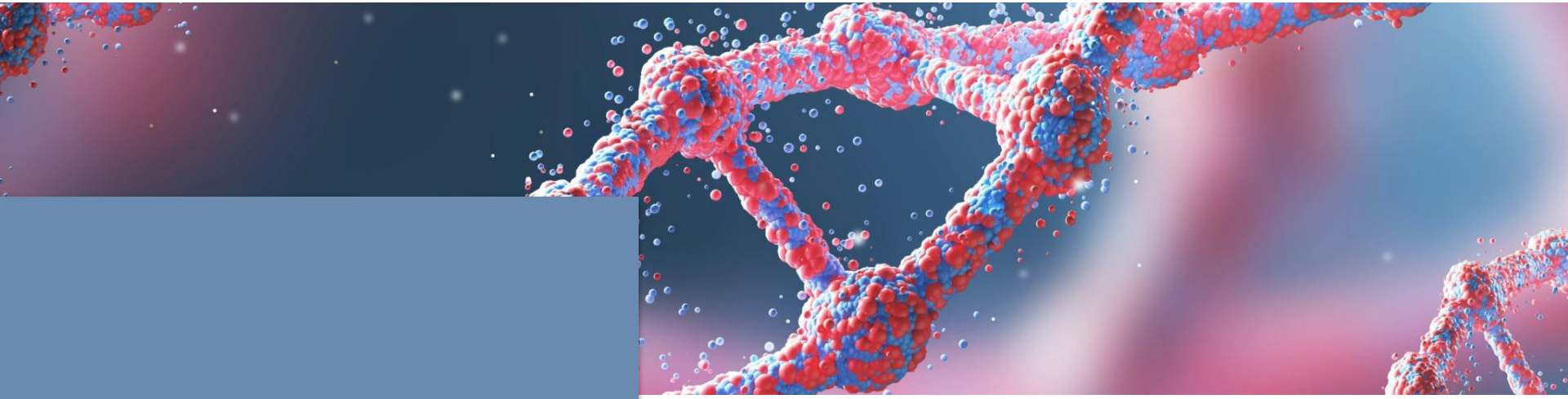

Thank you. We look forward to your feedback and comments.

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