BioXyTran Inc.

# Galectin Antagonists in Long-COVID

# Forward Looking Statement

This Descriptive Presentation (the "Presentation") has been prepared by Bioxytran, Inc (the "Company") and recipients are not entitled to rely on the accuracy or completeness of the Presentation. Statistical information contained in this Presentation is based on information available to the Company that the Company believes is accurate. It is generally based on publications that are not produced for securities offerings or economic analysis. The Company has not reviewed or included data from all sources and cannot assure prospective parties of the accuracy or completeness of the data included in this Presentation. Forecasts and other forward-looking information obtained from these sources are subject to the same qualifications and the additional uncertainties accompanying any estimates of future market size, revenue, and market acceptance of products and services. The Company undertakes no obligation to update forward-looking information to reflect actual results or changes in assumptions or other factors that could affect those statements.

This Presentation has not been filed or reviewed by the Securities and Exchange Commission ("SEC") or any securities regulatory authority of any state, nor has the SEC or any such authority passed upon the accuracy or adequacy of this Presentation. This Presentation does not constitute an offer to sell or a solicitation of an offer to buy any securities. This Presentation does not purport to contain all information that may be material to a prospective party, and recipients of this Presentation should conduct their own independent evaluation and due diligence of the Company. Each recipient agrees, and the receipt of this Presentation serves as an acknowledgment thereof, that if such recipient determines to engage in a transaction with the Company, its determination will be based solely on the terms of the definitive agreement relating to such transaction and on the recipient's own investigation, analysis and assessment of the Company and the transaction. The Company does not intend to update or otherwise revise this Presentation following its distribution.

# What is “Long-COVID”?

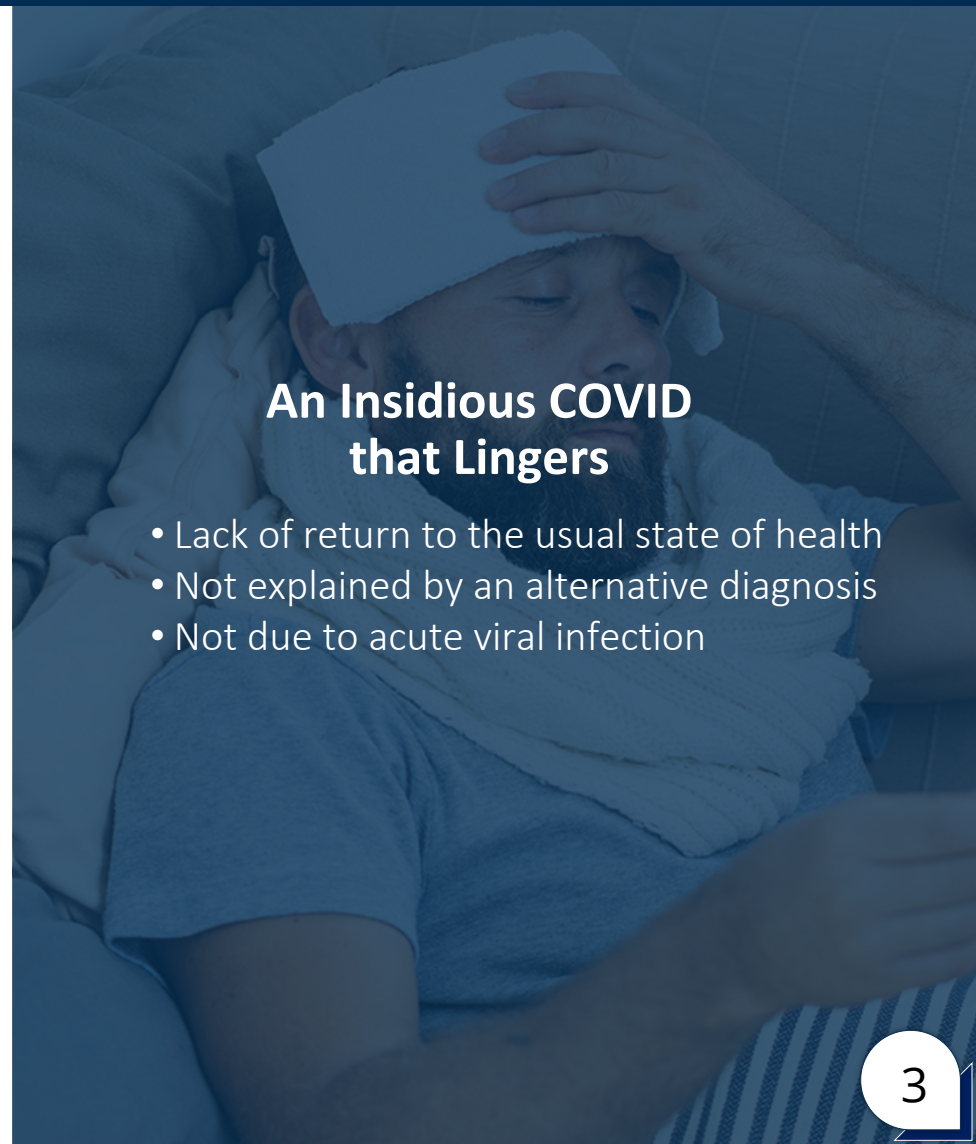
## Terminology

Long COVID, Long Haulers, Long-term COVID, Post-COVID conditions (PCC), Post-acute sequelae of SARS-CoV-2 infection (PASC), Post COVID-19 Syndrome (PCS)

CDC

Post-COVID conditions describe a range of new, returning, or ongoing health issues that persist four or more weeks after a person is first infected with the virus that causes COVID-19, sometimes after initial symptom recovery.

https://www.covid.gov/longcovid/definitions



## An Insidious COVID that Lingers

- Lack of return to the usual state of health
- Not explained by an alternative diagnosis
- Not due to acute viral infection

# Long Covid: Disabling America

- 65[1]-100[2] million estimated cases worldwide
- Lost work days: 1.6 million full-time equivalent workers
- $3.7 trillion[3] estimated economic burden
- 7.5%[4] of people report having long-COVID
- Quality of life decreases[5]
- CDC estimates that 6% of U.S. adults report currently having Long-COVID symptoms[6]
- No FDA-approved drugs for Long-COVID


[1]https://www.nature.com/articles/s41579-022-00846-2
[2]https://www.medrxiv.org/content/10.1101/2021.11.15.21266377v1
[3]https://www.brookings.edu/research/is-long-covid-worsening-the-labor-shortage/
[4]https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm
[5]https://www.frontiersin.org/articles/10.3389/fpubh.2022.975992/full
[6]https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

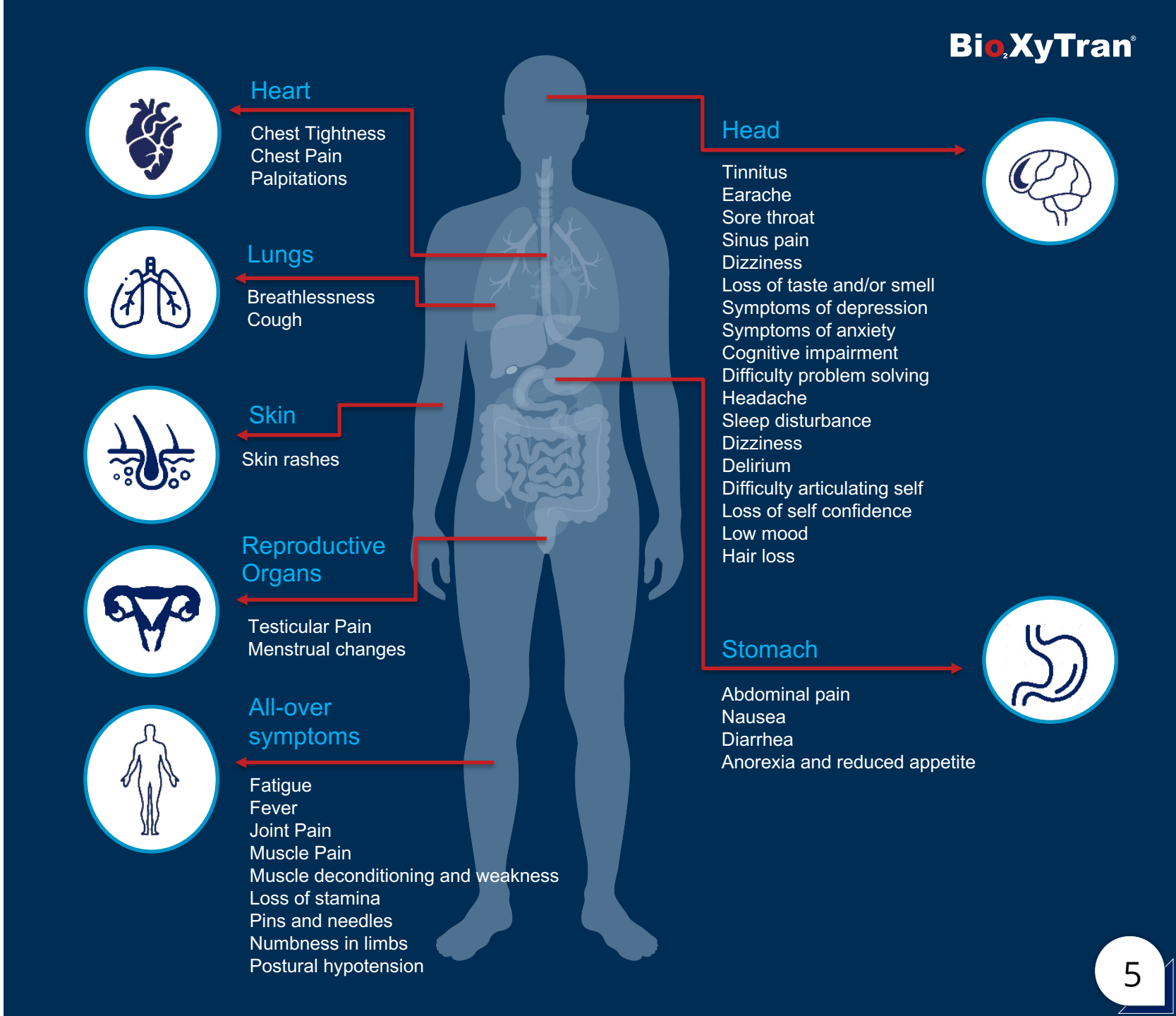
# Long Covid

## Symptoms

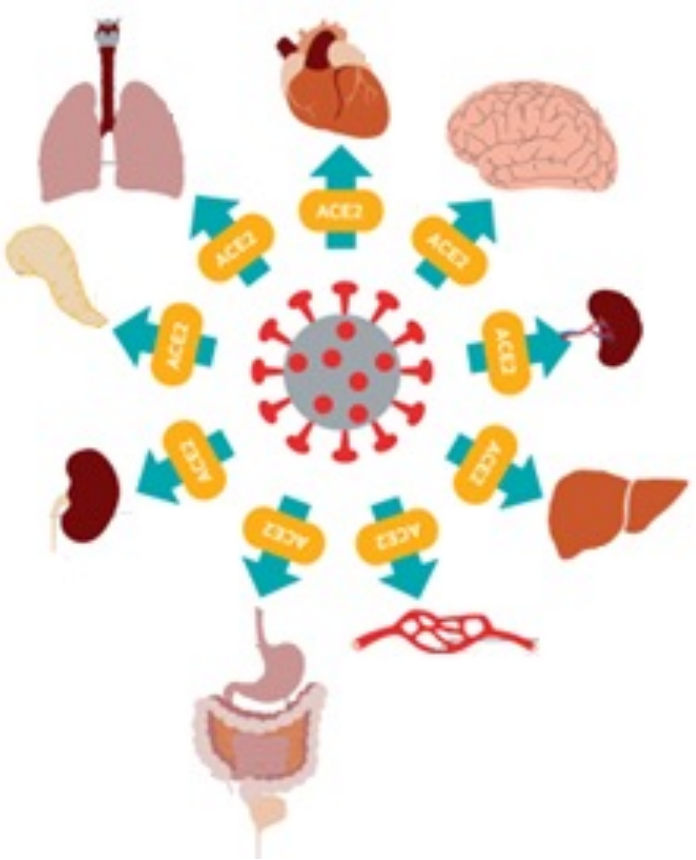
The Most commonly reported symptoms of ongoing symptomatic COVID-19 and post-COVID-19 Syndrome Include (but are not limited to) the following:

## Common Symptoms of Long Covid

- Brain Fog
- Fatigue
- Loss of Smell
- Difficulty Breathing
- Join Pain
- Digestive Issues

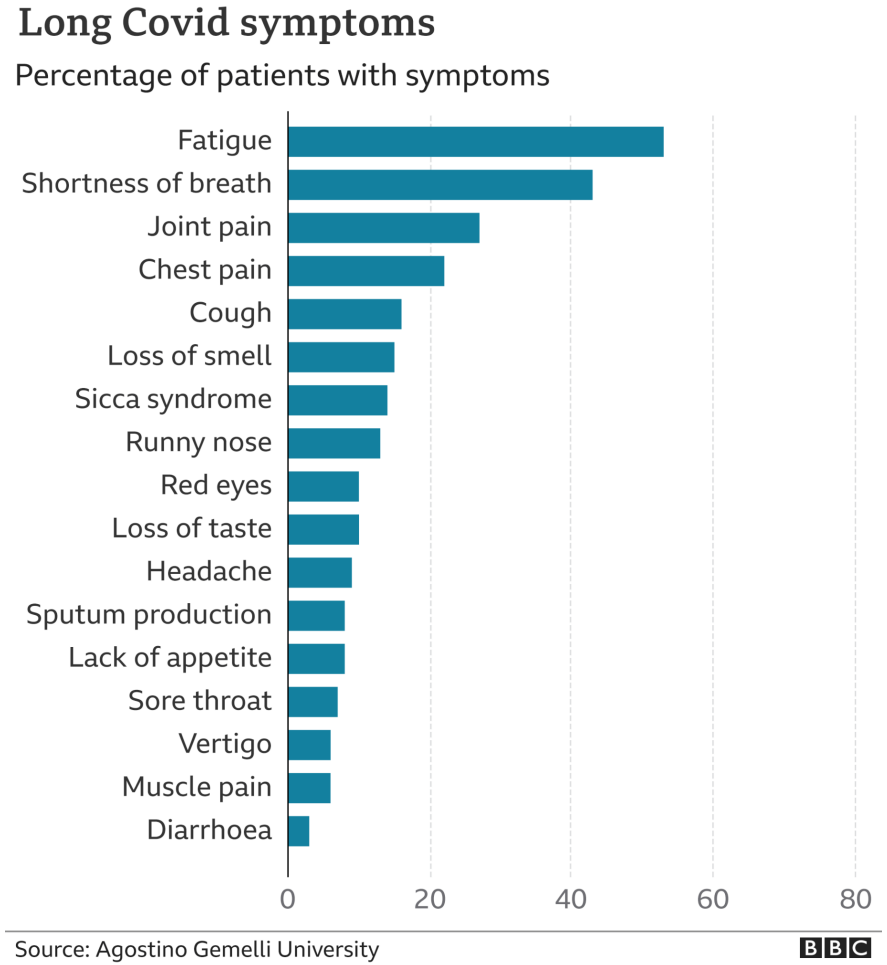


## Mapping ACE2[1] (72 Tissues)



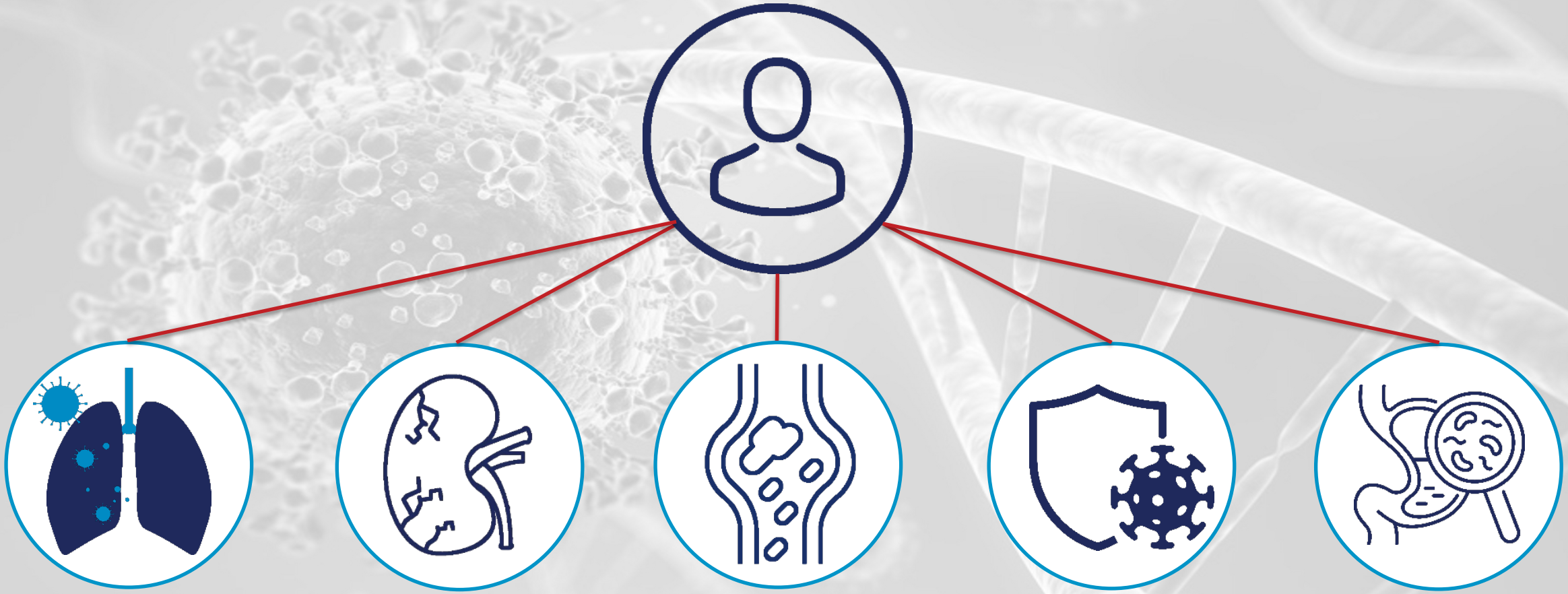

**ACE2 Facilitates Viral Spread to Organs**

**Residual infection in affected tissues lead to Long-COVID symptoms**



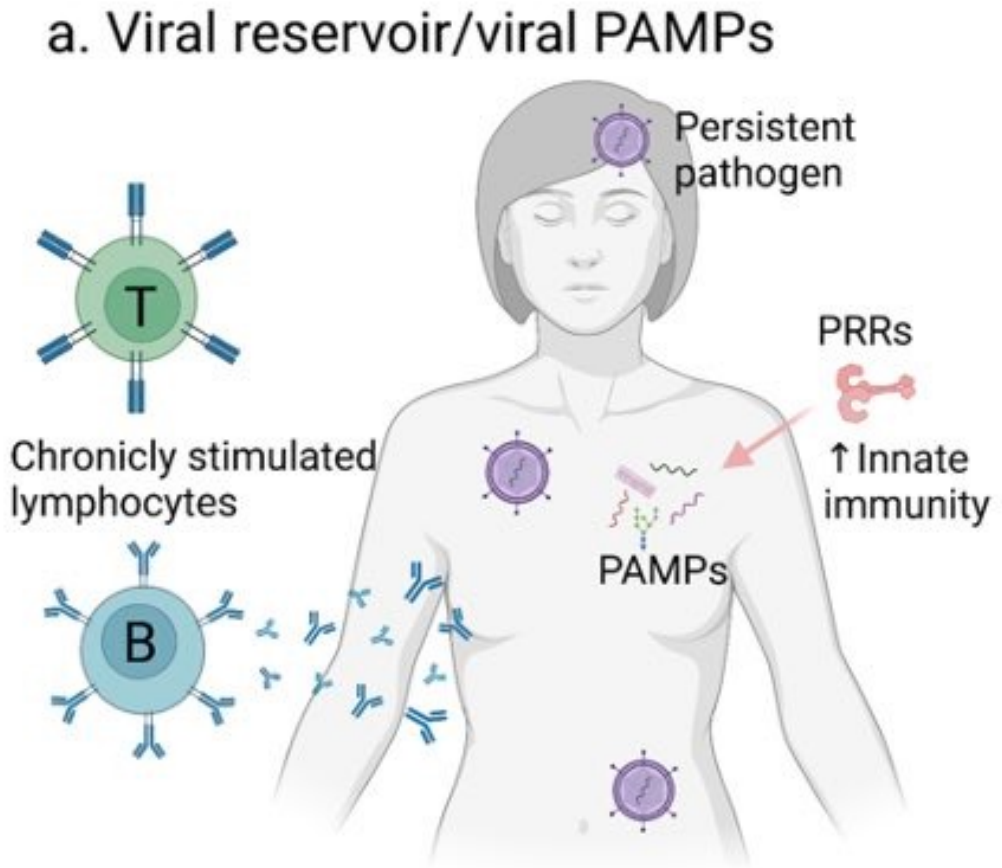

[1]https://www.frontiersin.org/articles/10.3389/fmed.2020.594495/full

# Long-COVID Theories



# Viral Persistence/Pathogen Remnants

- Evidence that there's active virus in tissues up to 9 months after infection[1]
- Paxlovid treatment lowers incidence of long-COVID[2]
  (9.43 lowered to 7.11 per 100)
- Ongoing viral replication/viral reservoirs might drive Long-COVID
- Persistence of viral remnants such as S1 subunit may drive pathology[3]
- ProLectin stops infection and binds to S1, potentially addressing both persistence theories

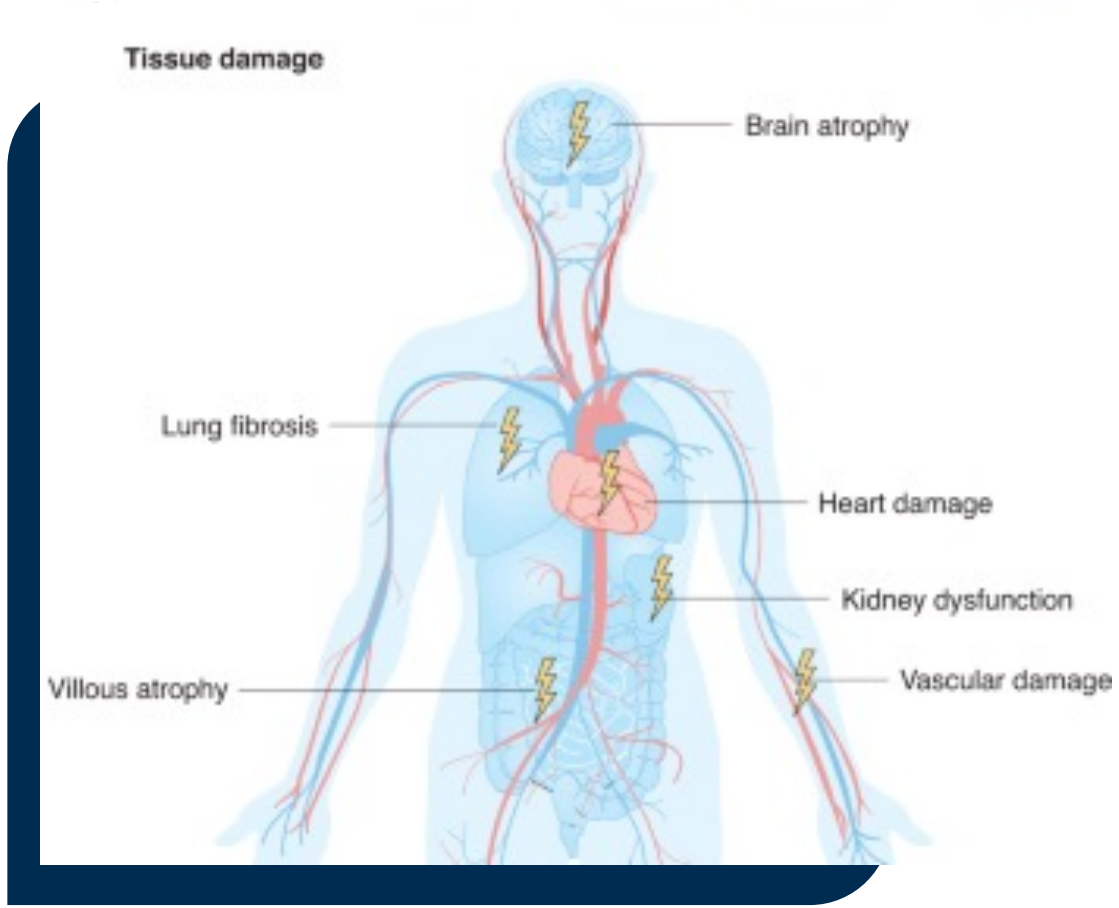



[1]https://academic.oup.com/cid/article/76/3/e487/6686531
[2]https://www.medrxiv.org/content/10.1101/2022.11.03.22281783v1
[3]https://www.frontiersin.org/articles/10.3389/fimmu.2021.746021/full

# Tissue Damage and Microclots

- Galectin-3 is a DAMP and promotes coagulation
- Galectins promote fibrosis/scarring and are being studied as antifibrotics
- ProLectin-I blocks various galectins including 1 and 3

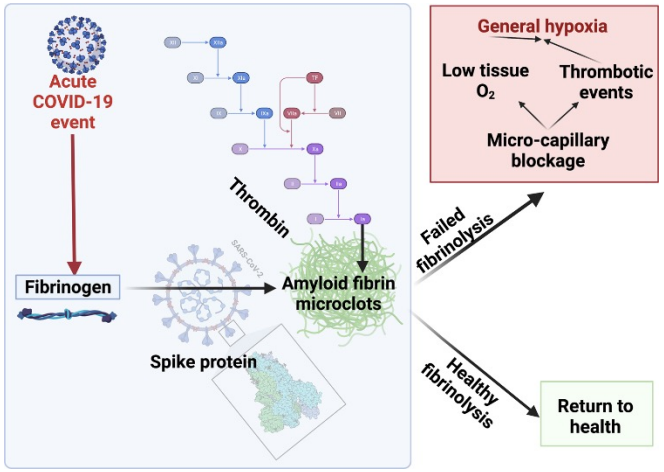
[1]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4357586/
[2]https://www.sciencedirect.com/science/article/pii/S1357272520301989

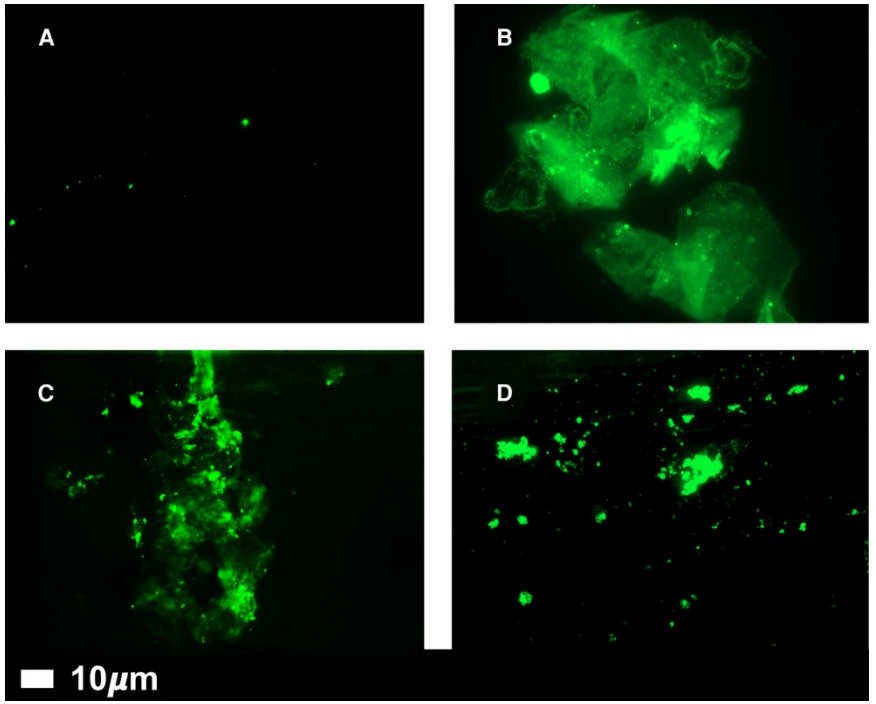


# Microclots

## A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications[1]

- Microclots formed by aberrant amyloid fibrin triggered by the spike protein.
- Microclots present novel antigens that lead to production of autoantibodies, exacerbating symptoms.



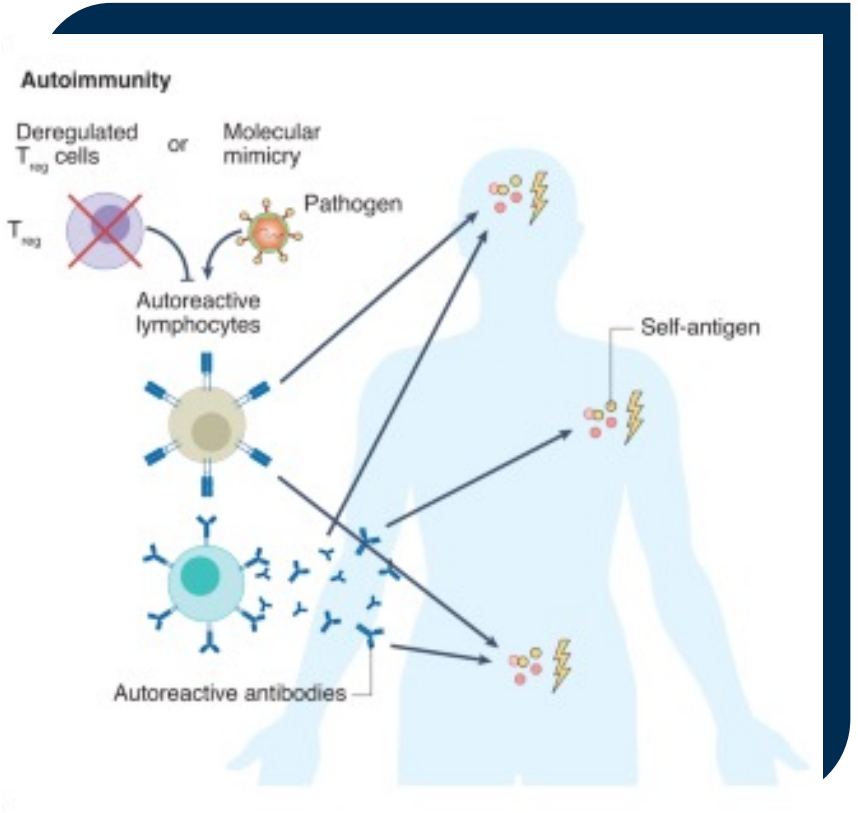




Fluorescence microscopy of sample micrographs showing microclots (green) in the circulation of controls (A) and in patients with Long COVID (B–D).

[1] https://portlandpress.com/biochemj/article/479/4/537/230829/A-central-role-for-amyloid-fibrin-microclots-in
[2] https://cardiab.biomedcentral.com/articles/10.1186/s12933-022-01579-5
[3] https://europepmc.org/article/ppr/ppr436609

# Autoimmunity

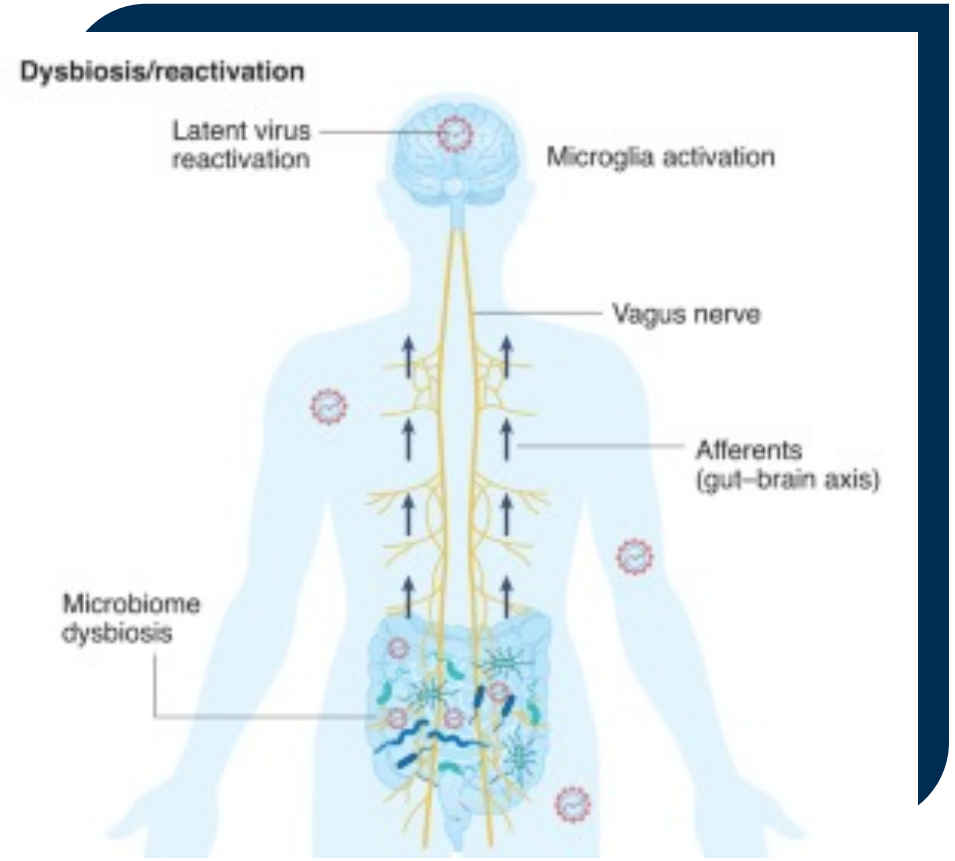
- Inflammation or autoimmunity might drive Long-COVID symptoms
- Galectins are drivers of inflammation and are implicated in autoimmunity
- Prolectin-I may have a beneficial effect in reducing autoimmune reactivity
- Iwasaki says galectin-1 is elevated in long-COVID[2]




https://www.medrxiv.org/content/10.1101/2022.08.09.22278592v1.full-text

# Dybiosis/Reactivation

- Disruption of flora and subsequent reactivation of latent viruses (EBV) may cause long-COVID symptoms
- ProLectin has not been tested against EBV yet, but has demonstrated broad-spectrum activity with other viruses



# Heterogeneous Disease = Clinical Trial Challenge

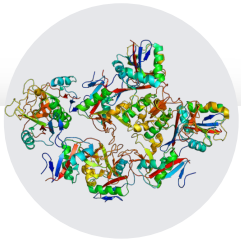
Short Long-Haulers:  9 months

Testing Long COVID & Determining Endpoints

- No validated tests/diagnostics
- No industry guidance on endpoints

Long Long-Haulers:  Over 9 months

# Inspiration For Glycovirology



## Adhesion Drug

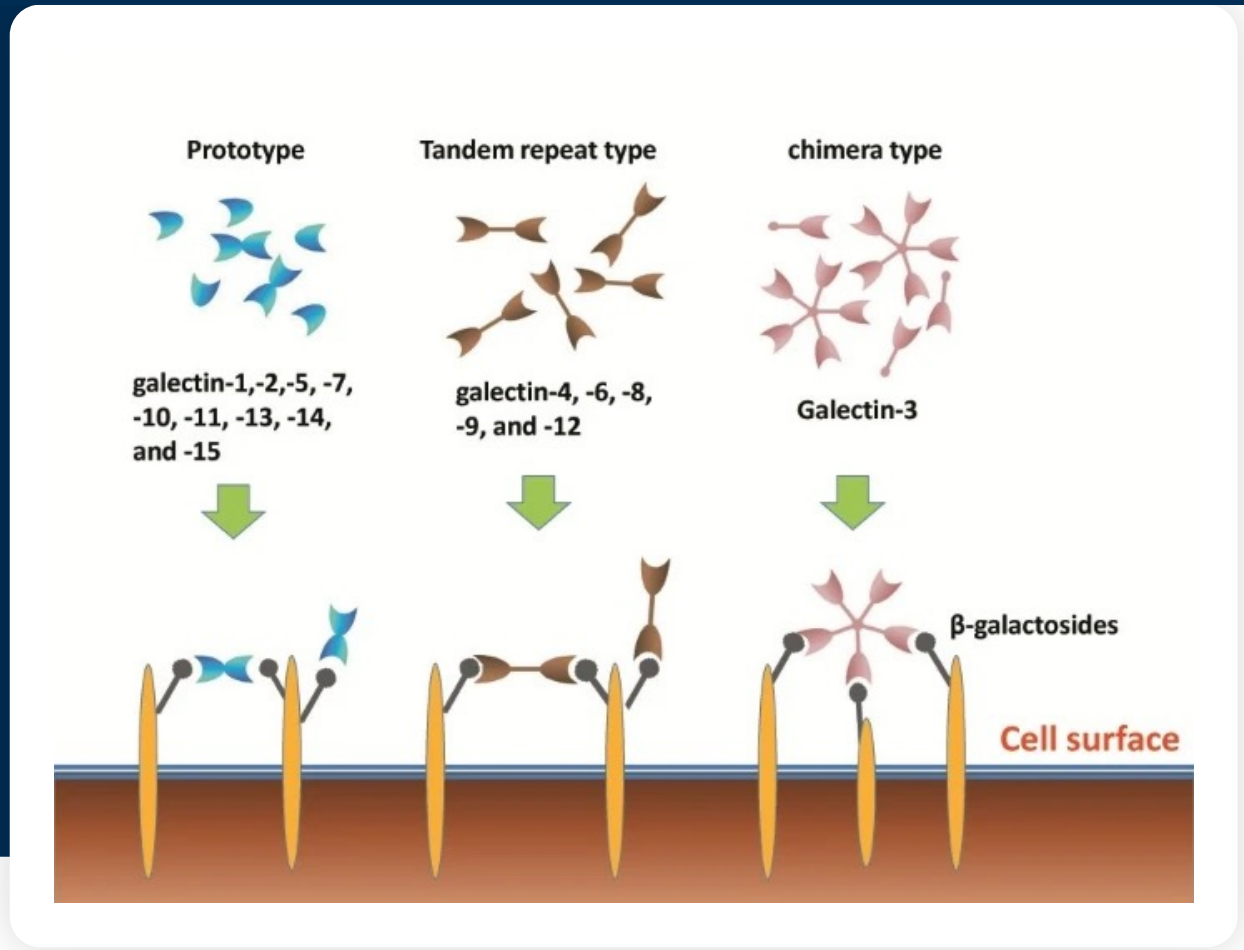
- Common means of viral adhesion: surface lectins combining with carbohydrates
- Carbohydrates can block surface lectins.
- Galectins are adhesion molecules (extracellular matrix)
- Galectins thought to aid in viral docking
- Galectins strongly implicated in viral diseases

## Entry Inhibitor

- Galectin Fold discovered on spike protein in a conserved region
- Interfere with spike protein activation
- Creation of a physical barrier

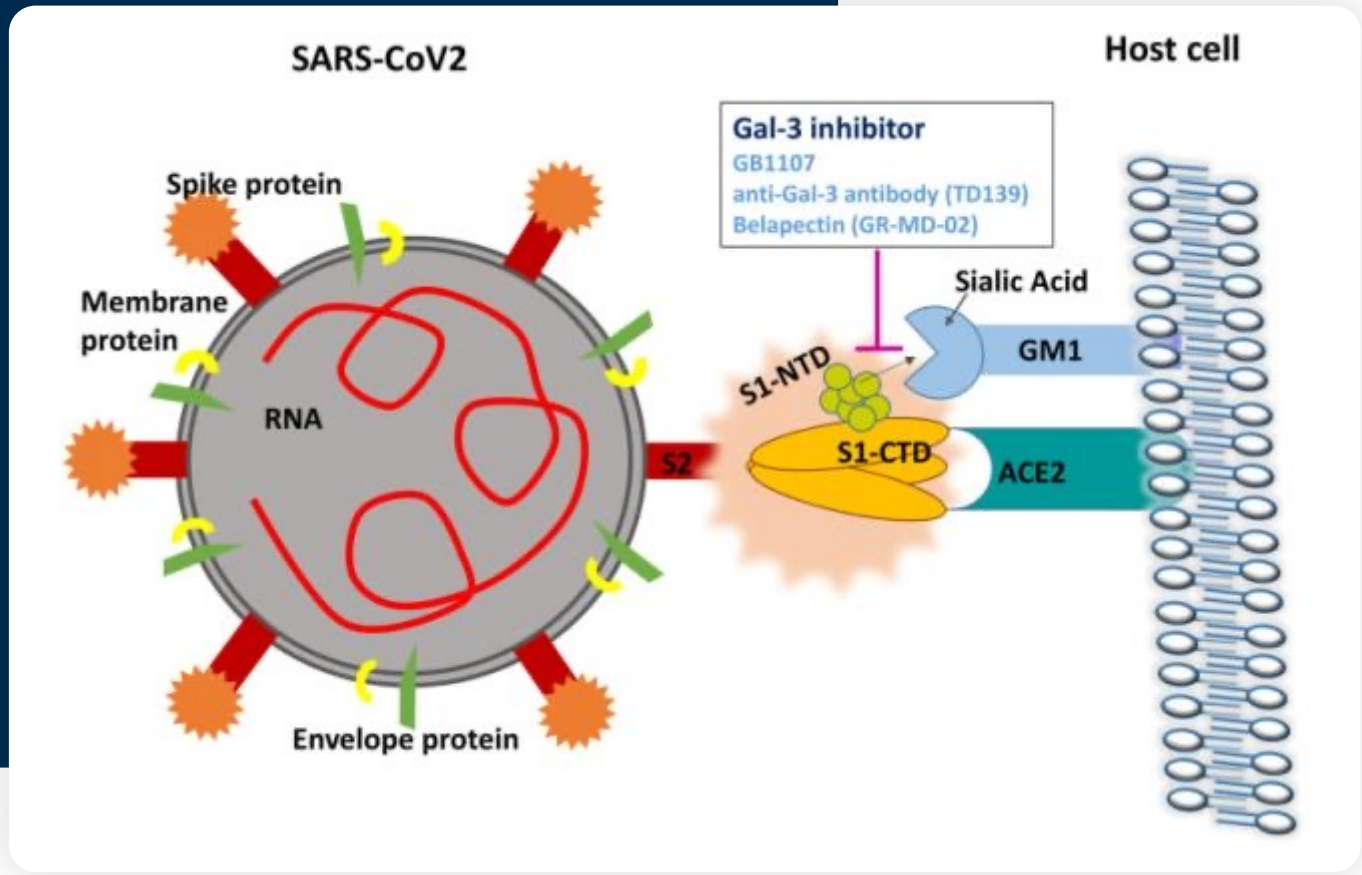
# Galectins Explained

A Galectin is a protein that recognizes carbohydrates and modulates intra cellular and extracellular interactions primarily related to the immune system. In some cases, Galectins act as a glue bringing molecules such as surface receptors together. The major focus of research is on extracellular interactions.




https://www.pharma-iq.com/pre-clinical-discovery-and-development/articles/why-galectin-3-has-emerged-as-a-focus-for-drug-research-and-development-1

# Galectin Inhibition MOA

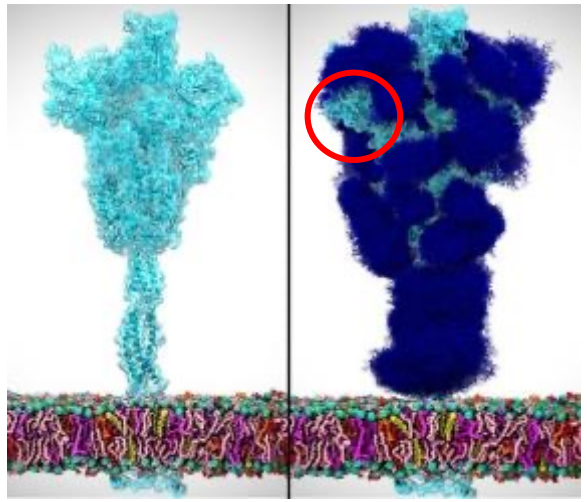



- Binding to the spike protein in Blood
- Liver removes carbohydrates drug and virus.
- Restoration of Adaptive immune system – peel off galectin plaque
- Adaptive immune system creates long term immunity

# Neutralizing the Spike Protein

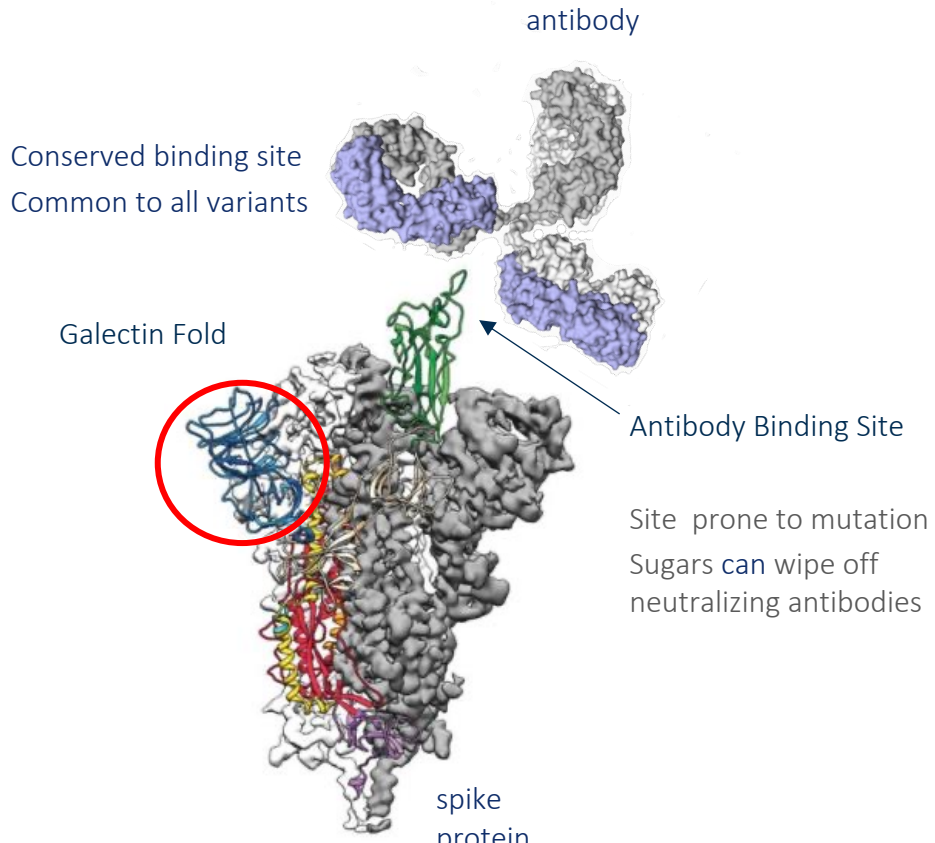
## How it Works

No Sugar Shield  Shielded in Sugar



Part of the Problem

Antibodies need a place to attach.  The sugar shield is not static, but rather a dynamic shape shifting like coating with windshield wipers on the surface that limit areas of attachment.




### Galectin Fold Ideal Binding Site

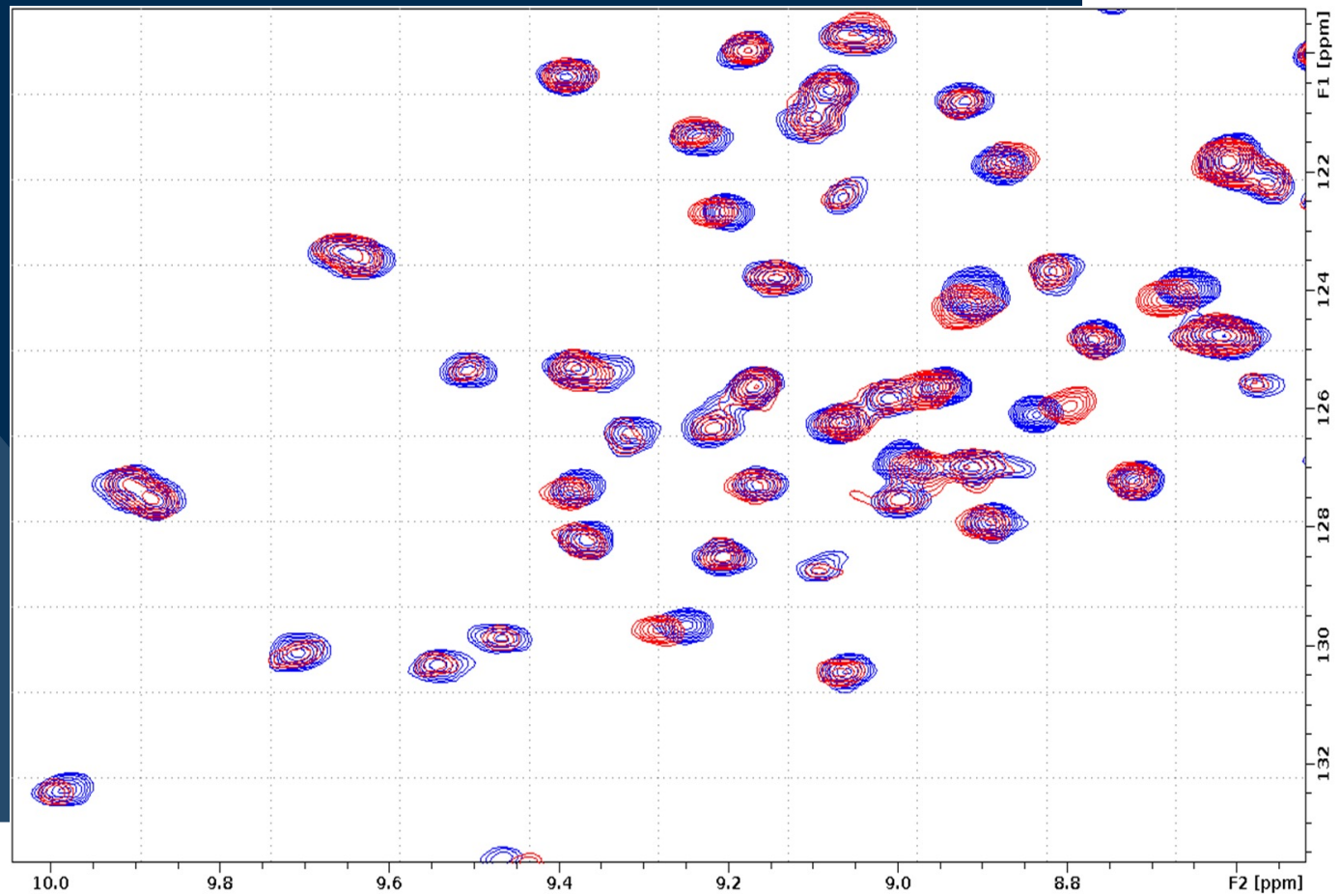
Binding to the spike protein prevents viral entry

Immensely tighter bond to galectin fold vs tip (Prolactin-RX 99% binding affinity)

Antibodies take time to be produced – slower response to infection

### Prolactin Neutralizes Like Antibodies

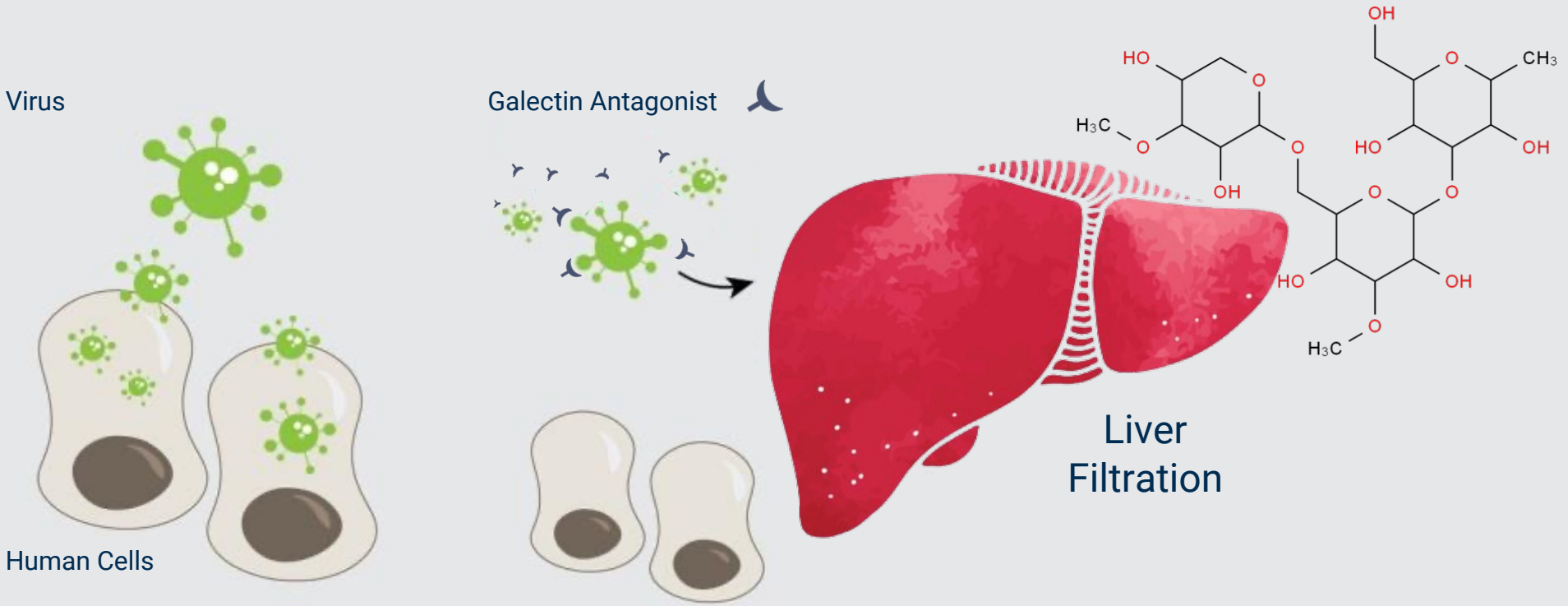
# Complex Carbohydrate Design Using Advanced NMR Spectroscopy Techniques




[1] Galectin approach to lower covid transmission - Drug Development for clinical use

# Galectin Antagonist Tags Virus For Elimination

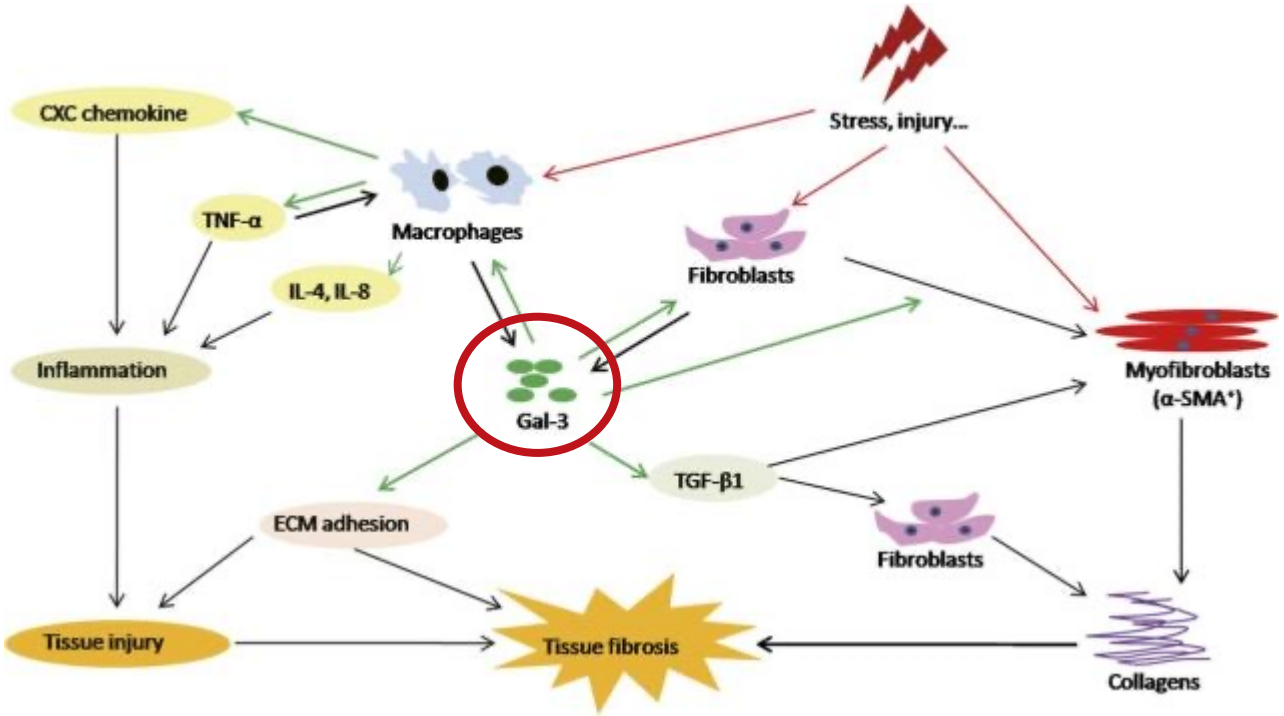
## Theoretical Mechanism of Action




Approach used for the 1st Time in History of Drug Development

# Galectin Trouble-Maker

## The Center of Inflammatory Feedback Loops

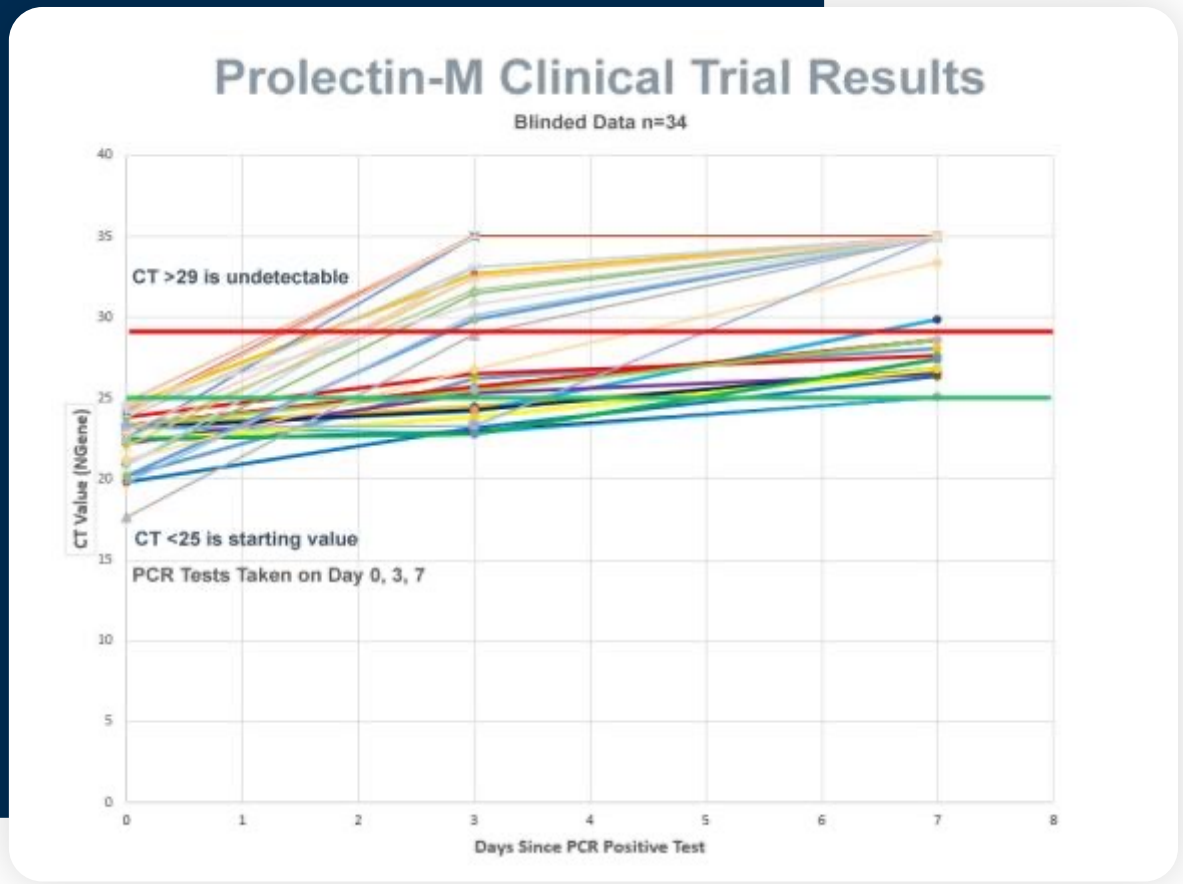



- Gal-3 is a Pro-inflammatory Molecule
- Inhibiting it blocks cycle of inflammation
- Galectin is the KEY modulator of inflammatory molecules

http://jpet.aspetjournals.org/content/351/2/336
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5752178/

There is little downside to blocking galectin-3 entirely from the body potentially ameliorating many chronic and deadly diseases

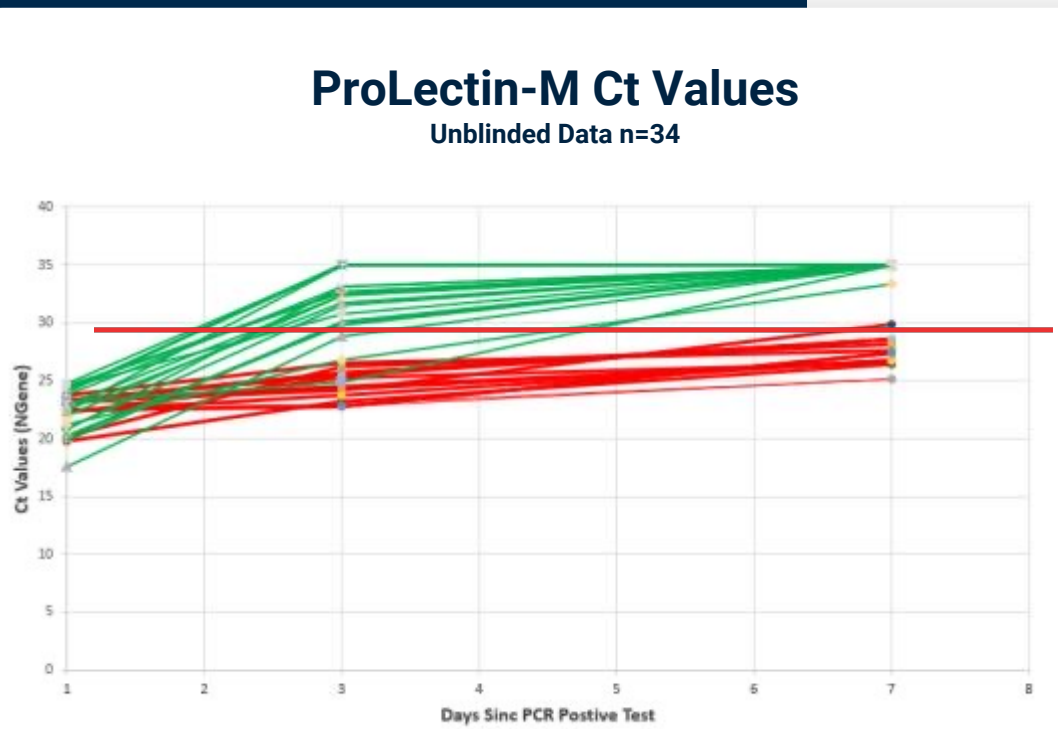
# PCR Test Data (Blinded Phase 2)



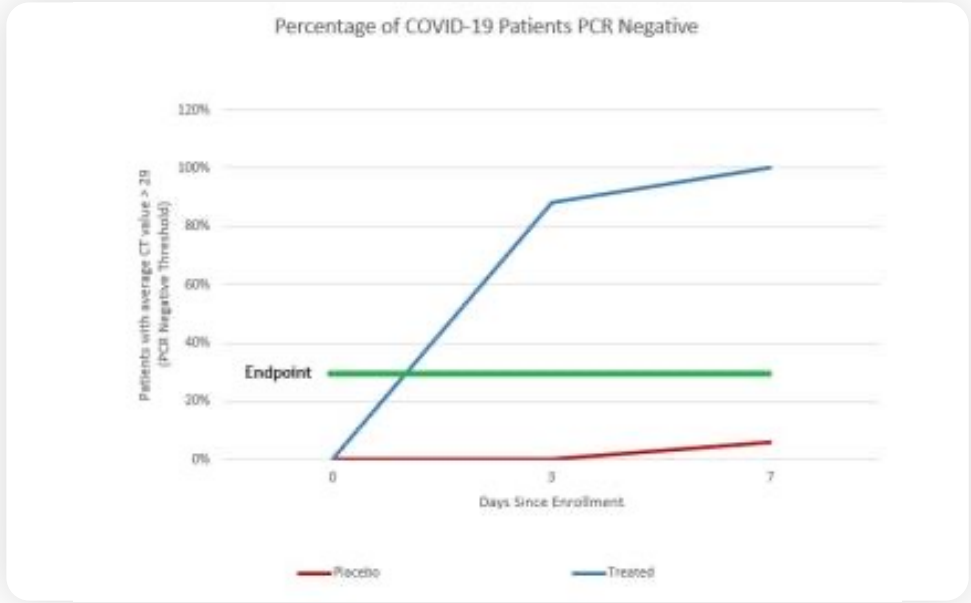

- Cycle Threshold (Ct) values are used to assess infectivity of the patient using a nasal pharyngeal test. Lower values are a proxy for higher viral loads and increased infectivity. Values over 29 are considered PCR negative. Starting Ct values of patients were under 25.
- Day 3 – 15 out of 34 were PCR negative (44.1%)
- Day 7 – 18 out of 34 were PCR negative (52.9%) n = 34
- No toxicity signals
- Randomized 1:1
- Double Blind Placebo Controlled
- Very Encouraging Data Grouping and indications of efficacy with no safety signals

[1] Galectin approach to lower covid transmission - Drug Development for clinical use (medRxiv.org)

# PCR Test Phase 2 Data




- Day 3 – 14 out of 17 were PCR negative (88%)
- Day 7 – 17 out of 17 were PCR negative (100%) n = 34
- No toxicity signals
- Randomized 1:1
- Double Blind Placebo Controlled Trial




Actual results show tight grouping btw treated arm and placebo arm

[1] Galectin approach to lower covid transmission - Drug Development for clinical use (medRxiv.org)

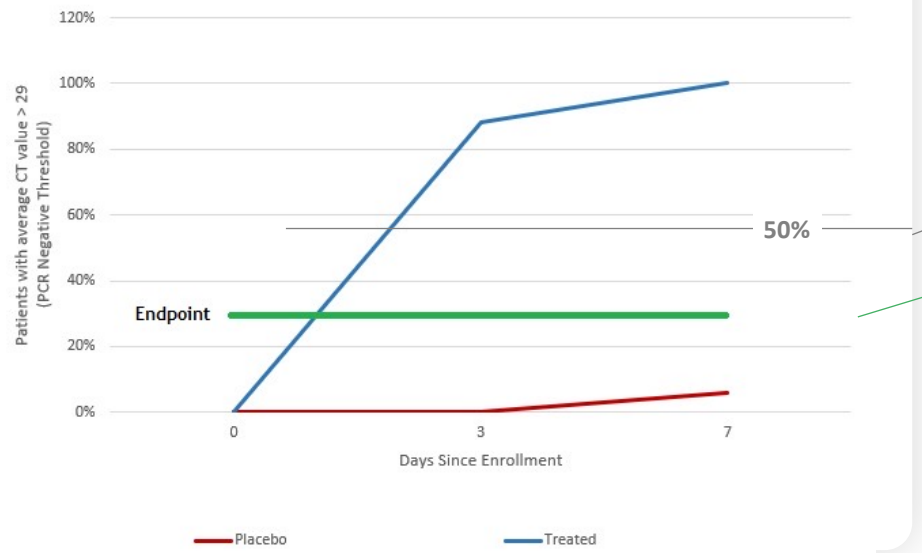
# ProLectin-M vs Pfizer's Paxlovid

- Day 3 – 14 out of 17 were PCR negative (88%)
- Day 7 – 17 out of 17 were PCR negative (100%) n = 34
- No toxicity signals
- Randomized 1:1
- Double Blind Placebo Controlled Trial

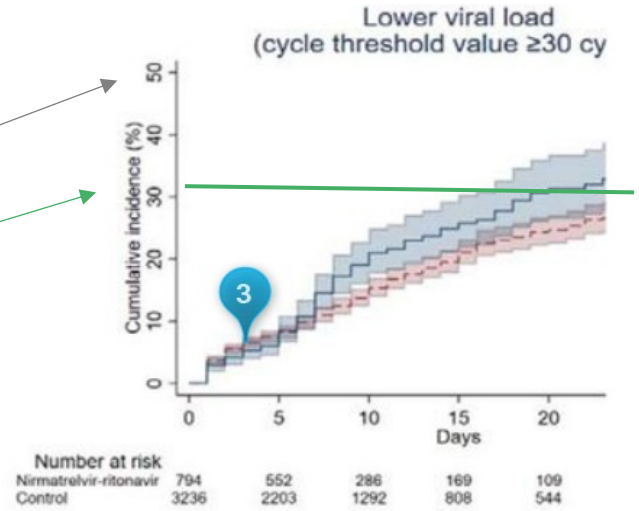
- Day 20 PCR negative (30%)
- Toxicity (Drug to Drug Interactions)
- Limited to Underlying Medical Conditions

**Bioxytran's** Phase 2 Data

Percentage of COVID-19 Patients PCR Negative (n=34)

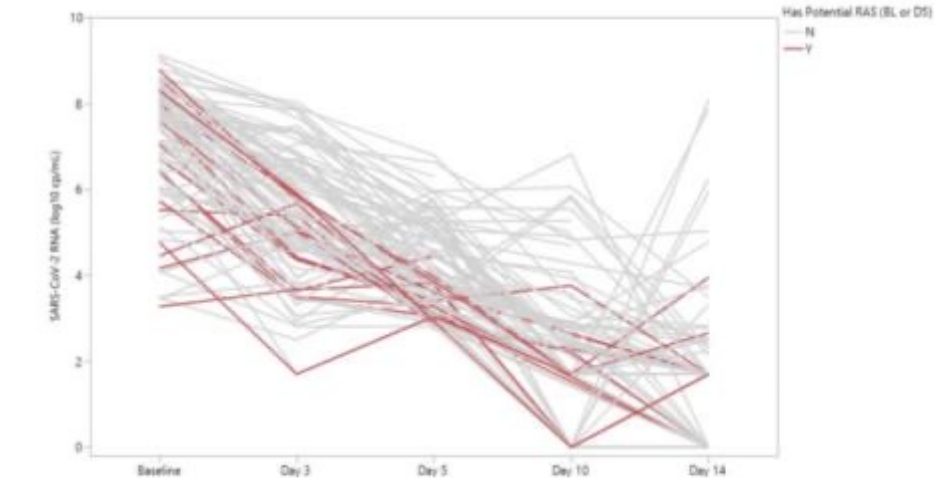



**Pfizer's** Paxlovid Real World Data[1]




[1] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00507-2/fulltext

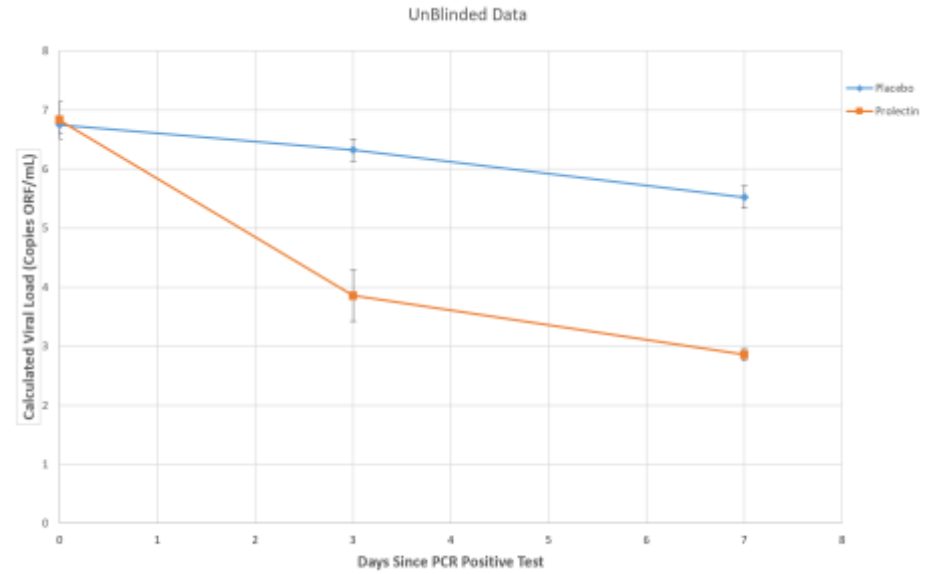
# Elimination of Viral Rebound




Source: FDA analysis.

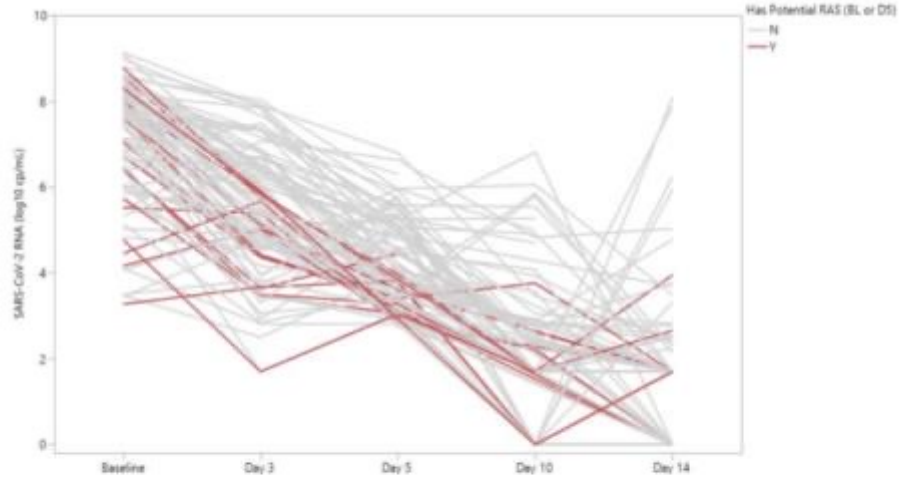
**Figure 2. SARS-CoV-2 RNA levels in NP swabs among Paxlovid treated subjects with or without SARS-CoV-2 amino acid substitutions detected in Mpro or cleavage site positions potentially associated with resistance.**

There were no rebounds within 14 days.




[1]Galectin approach to lower covid transmission - Drug Development for clinical use (medRxiv.org)

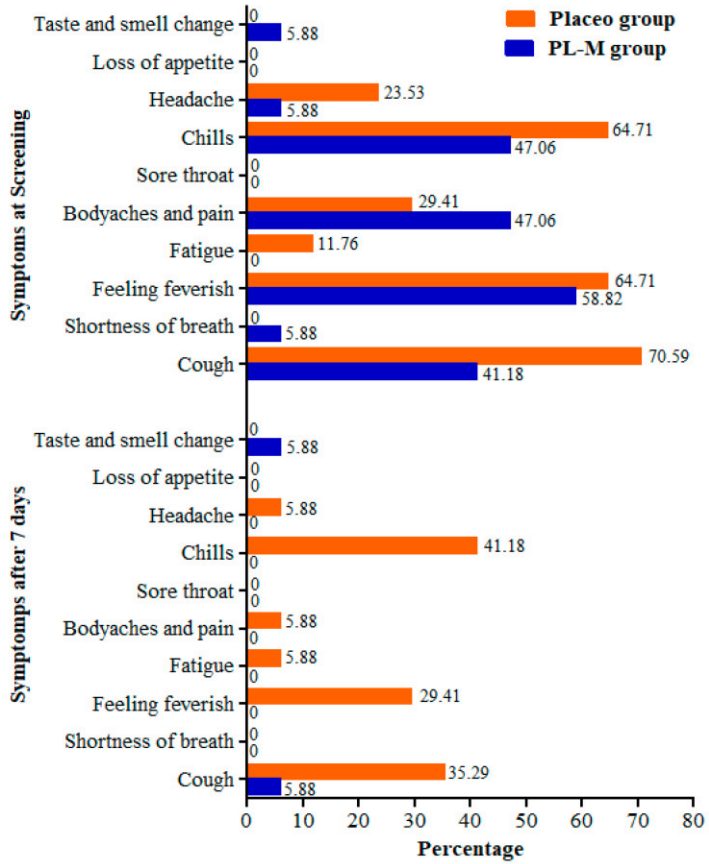
# Elimination of Viral Rebound




Source: FDA analysis.

**Figure 2. SARS-CoV-2 RNA levels in NP swabs among Paxlovid treated subjects with or without SARS-CoV-2 amino acid substitutions detected in Mpro or cleavage site positions potentially associated with resistance.**

## Frequency of COVID-19 symptoms in the study groups before and after treatment




[1]Galectin approach to lower covid transmission - Drug Development for clinical use (medRxiv.org)
[2]An Oral Galectin Inhibitor in COVID-19—A Phase II Randomized Controlled Trial

# Clinical Trial Results Summary

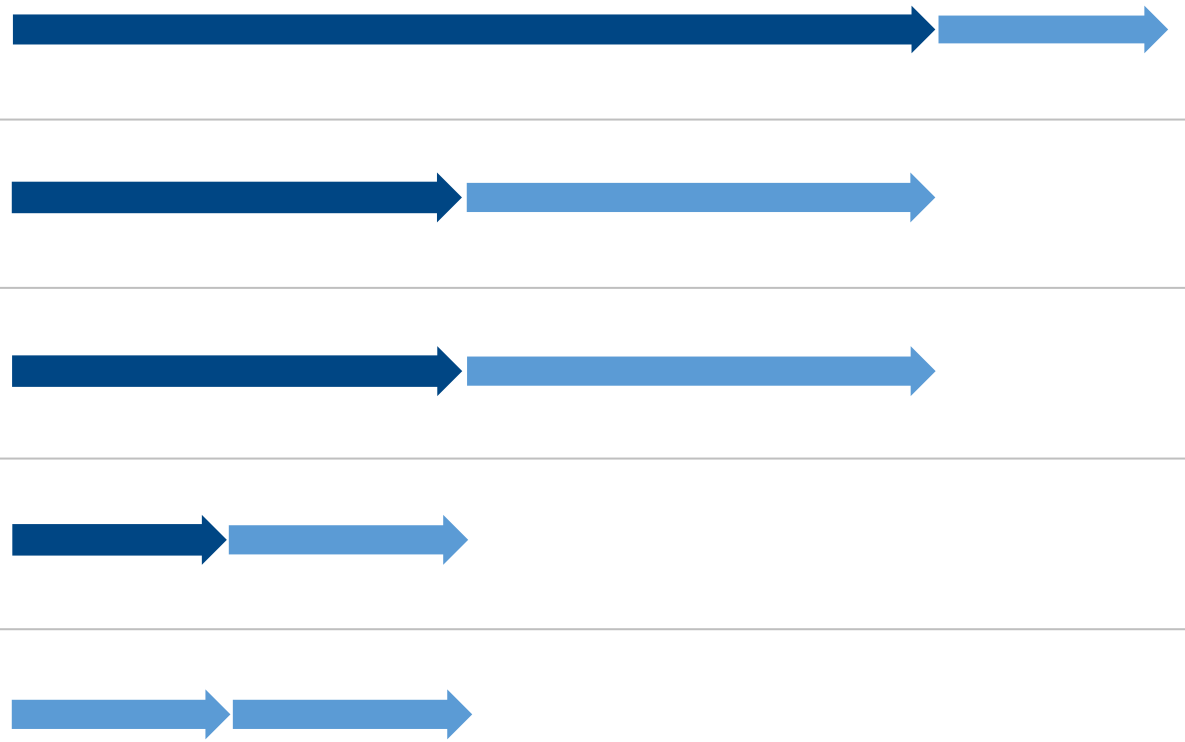
- Elimination of the viral load and symptoms within 5 days
- Reduction of infectivity
- Quieting the cytokine storm
- Robust antibody response (Post Infection Immunization

# Glycovirology Pipeline

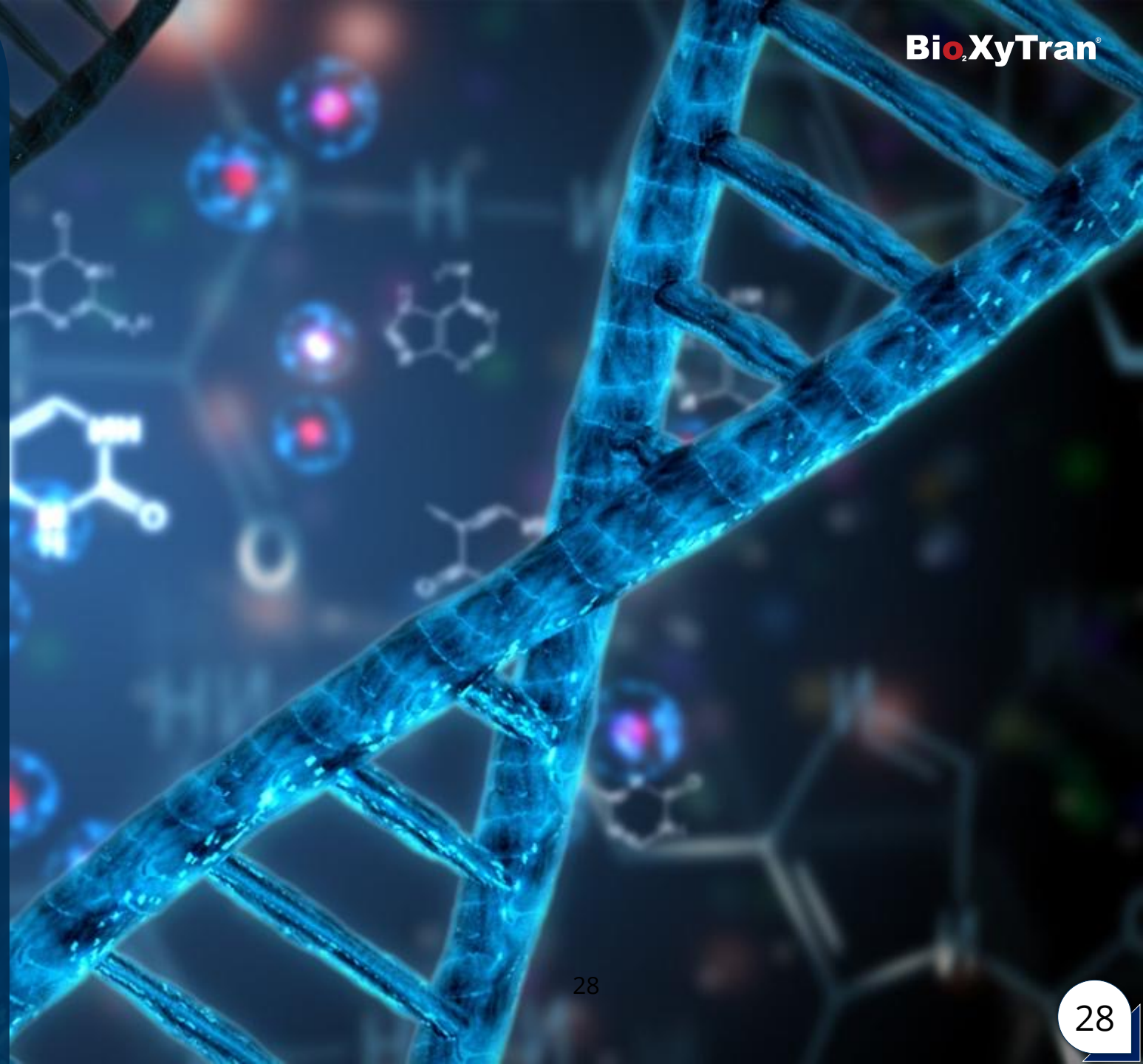
## Drug & Process Development Cleared

Completed  Planned

| Product | Indication | Preclinical | IND Submission | Phase I | Phase II | Phase III | Phase IV |
|---|---|---|---|---|---|---|---|
| **ProLectin-M** *Oral* | **Virology – Mild to Moderate** • Covid-19 | | | | | | |
| **ProLectin-I** *Intravenous* | **Virology – Severe cases** • Covid-19 • Long Covid | | | | | | |
| **ProLectin-F** *Intravenous* | **Fibrosis:** • Pulmonary Fibrosis • Other Fibrotic Conditions | | | | | | |
| **ProLectin-X** *Miscellaneous* | **Other Viral Indications:** • Conjunctivitis (in progress) • Influenza (evaluation) • RSV (evaluation) | | | | | | |
| **ProLectin-A + Oxysense*** | **ARDS** as result from viral infection | | | | | | |



* FDA 510(k) Clearance



BioXyTran Inc.

BioXyTran, Inc.

233 Needham St., Suite 300
Newton MA, 02464
(617)-454-1199
www.bioxytraninc.com
info@bioxytraninc.com

# Hypoxia Science Research Won the Nobel Prize in 2019

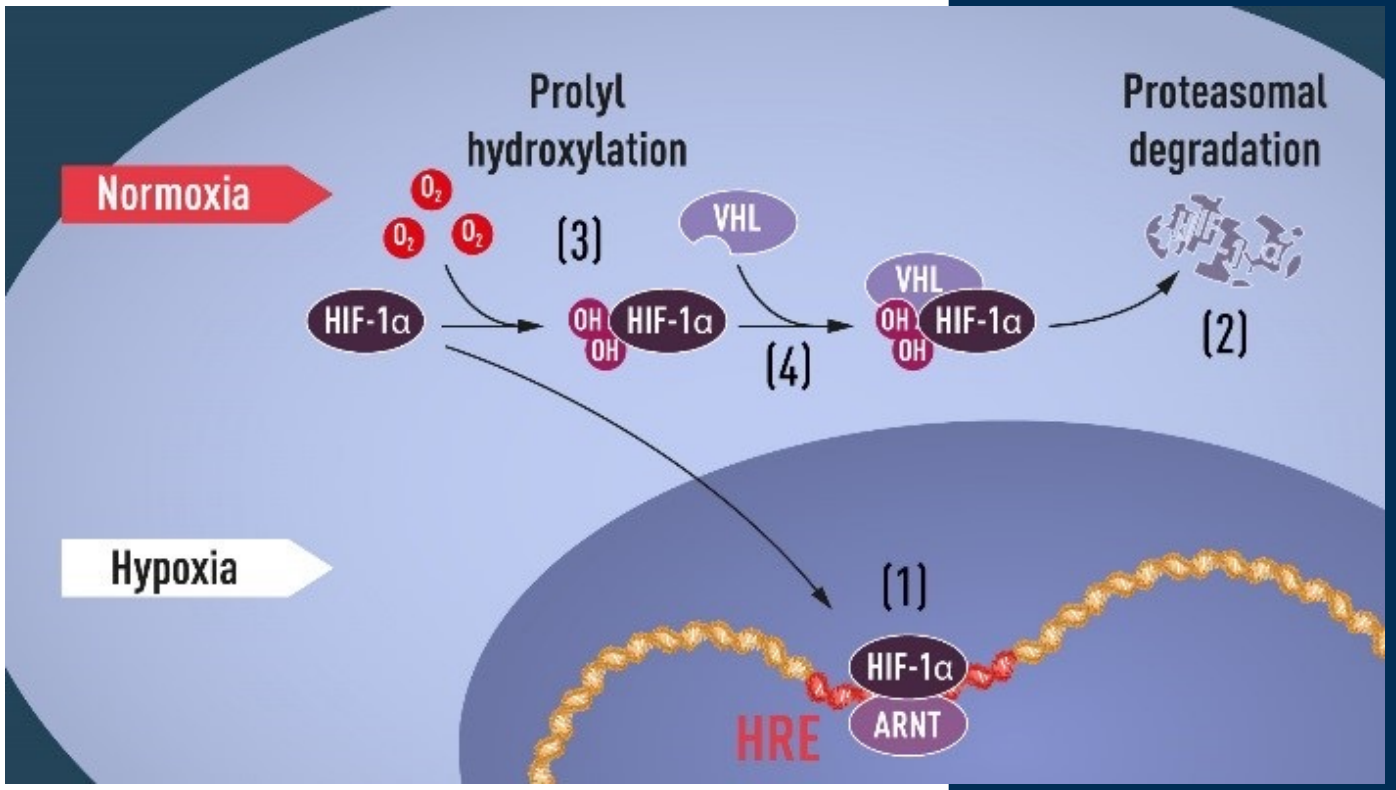

2019 NOBEL PRIZE WINNERS
William Kaelin Jr., Sir Peter Ratcliffe, and Gregg Semenza
Discovery: how cells adapt to changing oxygen levels

BIOXYTRAN
World **Leaders** in the Field of Hypoxia

- Bioxytran has the only FDA approved device to measure tissue oxygenation.
- Its MDX Viewer quantify hypoxia (measuring the efficacy of treatments).
- Bioxytran has a molecule (BXT-25) to deliver oxygen and reverse cell hypoxia.
- Increased research activity could generate demand for Bioxytran's tools in clinical research and medicine.

# Theory of the Cellular Universe
# This is the E=mc2 for cells

Delivering Oxygen to Tissues Reduces Hypoxia:
Reduced Hypoxia Improves the Condition of Tissues




https://www.nobelprize.org/prizes/medicine/2019/press-release/Nobel Prize Laureates

Theory Predicts Cellular Interaction
within the Tissue Micro-Environment

# Defeating the Outbreak – A Simple Plan

## Time a luxury we don't have.

- Containing the disease takes time
- Developing a vaccine take time
- Learning how it transmitted takes time
- Use of antiretrovirals


## Use of Virus Drugs

Only Viable Option to Treat Symptoms

Distribution of drugs a real challenge in uncontrolled settings. Measuring efficacy is impossible without a device to measure tissue health.

Primary Reason People Die From the Virus

↓

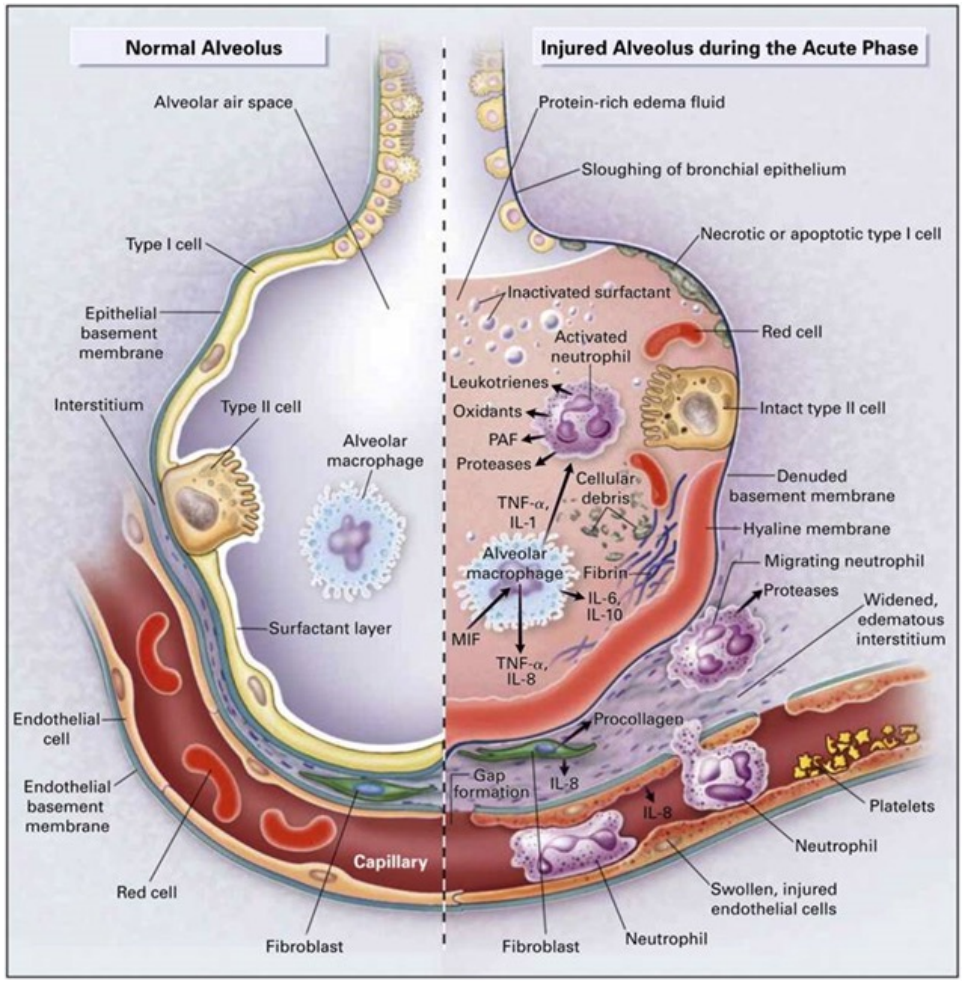
Fluid in the lungs.
Why does fluid in the lungs kill people?

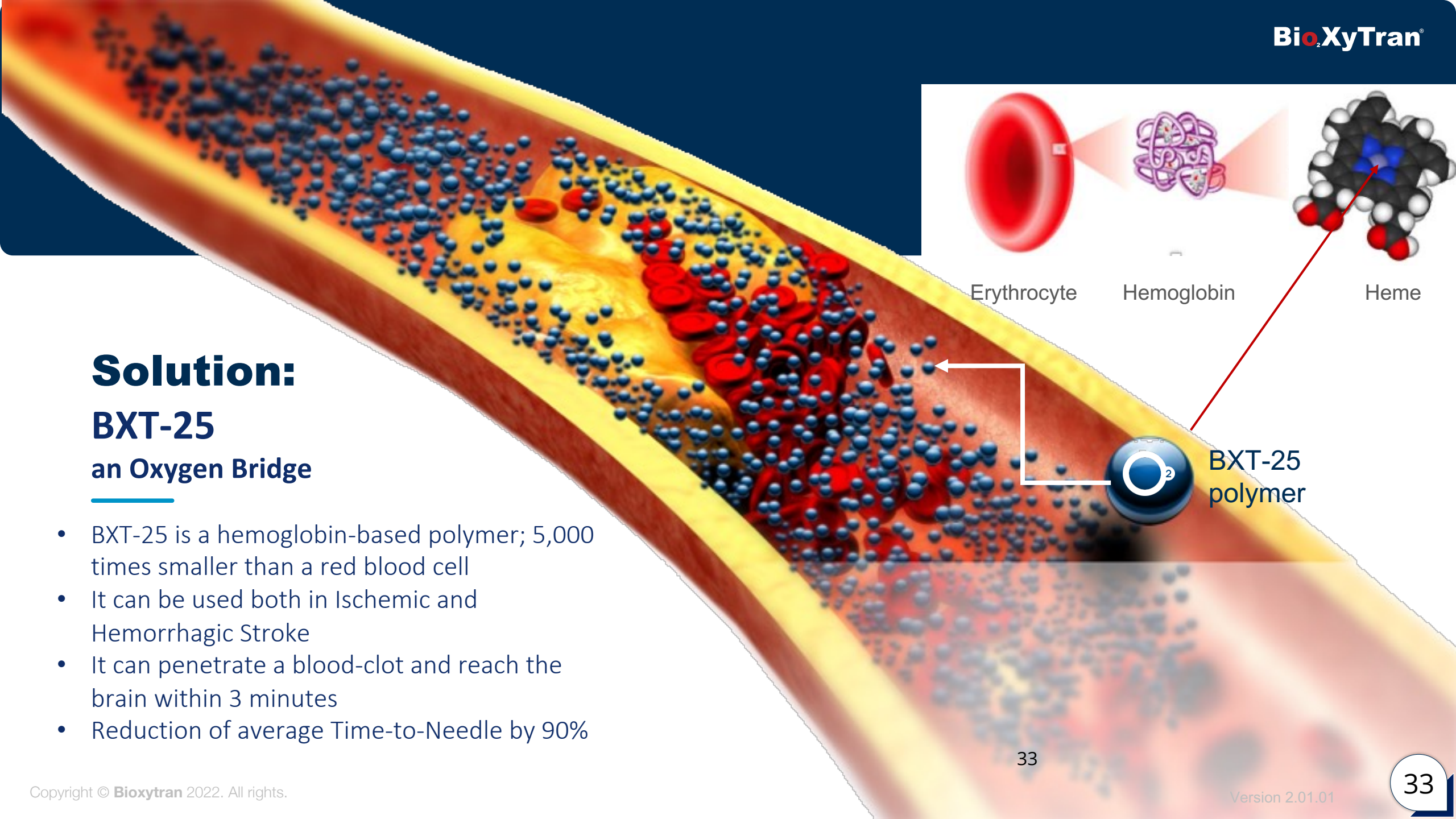
↓

They cannot get enough oxygen to sustain the organs and the lack of oxygen leads to organ failure and death.

# The Real Problem – Tissue Oxygenation & Real-time Monitoring

- Late-Stage Coronavirus Patients develop fluid in their lungs
- Respirators force liquid levels of alveoli sacks lower so blood can get closer to O2 (Not very effective)
- The blood is physically not close enough to the O2 to get oxygenated
- Organs start to shut down from lack of oxygen that leads to death
- Perfect environment for infection to take route






# Solution:

## BXT-25

### an Oxygen Bridge

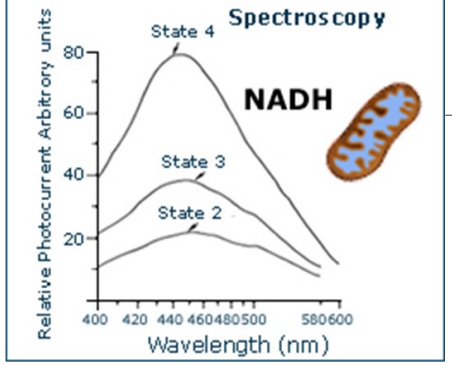
- BXT-25 is a hemoglobin-based polymer; 5,000 times smaller than a red blood cell
- It can be used both in Ischemic and Hemorrhagic Stroke
- It can penetrate a blood-clot and reach the brain within 3 minutes
- Reduction of average Time-to-Needle by 90%

BioXyTran

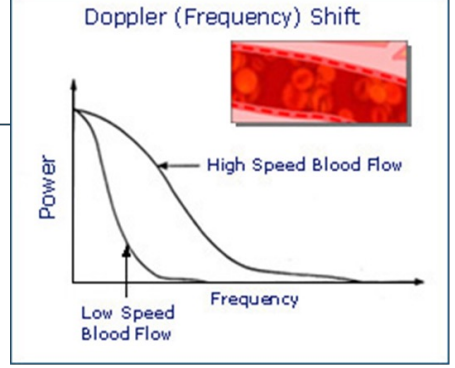
# Continuous Real-time In-vivo Tissue Spectroscopy

*When oxygen level in the cell is limited (i.e. Hypoxia) the NADH is accumulated in the mitochondria and the production of ATP will decrease.*

**Mitochondrial Function**

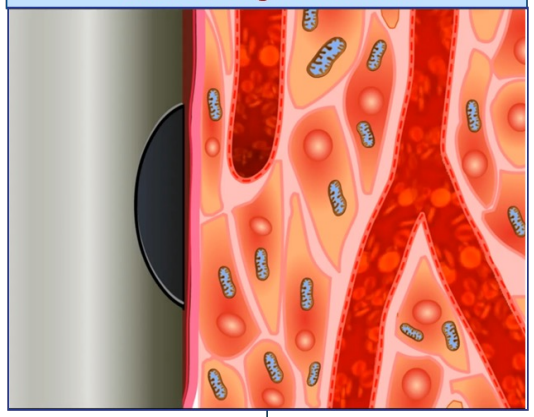



**Tissue Blood Flow**



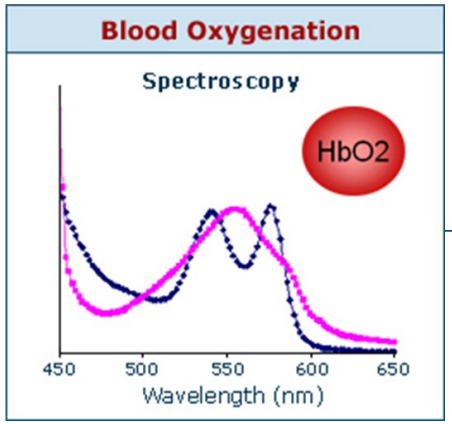

*When TBF will decrease to a very low-level production of ATP will stop.*

**Various Light Sources**

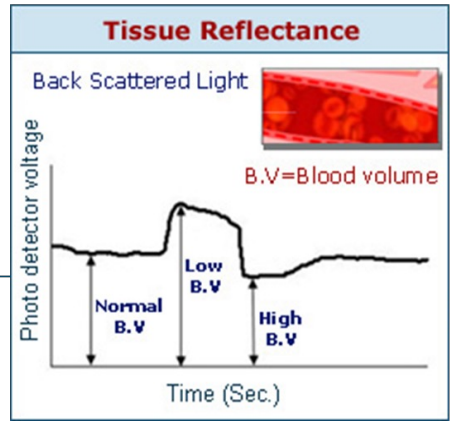


*The microcirculatory HbO2 level reflects the balance between the supply and demand of oxygen in the Tissue.*

**Blood Oxygenation**




**Tissue Reflectance**

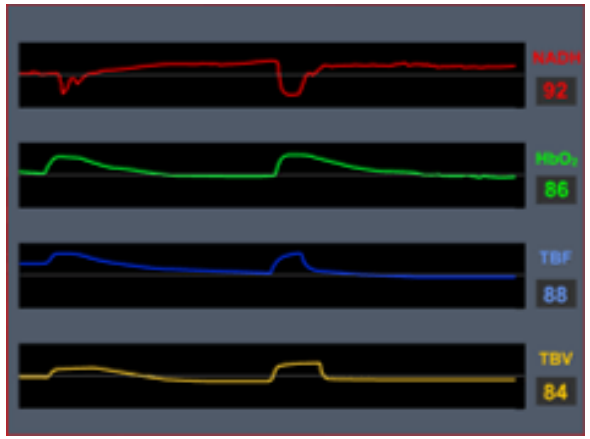



*This parameter is used in calculating the corrected NADH fluorescence.*

# FDA Approved Proprietary Companion Diagnostics

MDX Viewer - A clinical end-point for measuring oxygen delivery to the brain in real-time

Tissue/brain monitored parameters




Mitochondrial **NADH** (ATP)

Hb Saturation ($O_2$)

Cerebral Blood Flow

Tissue Reflectance

Brain metabolic score

90

Tissue metabolic score

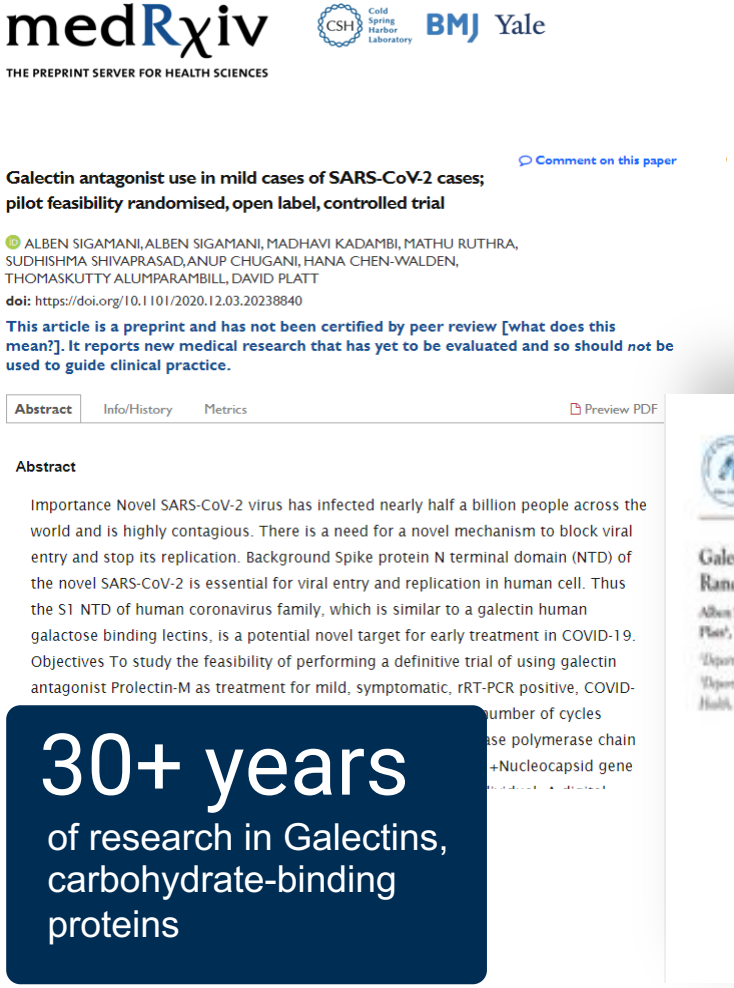
Measures real time tissue oxygenation levels

Assists in determining organ viability

# Science Behind Galectin Antagonists

## Clinical Research

- Proven Safety Profile in Drug Class
- Peer-reviewed clinical trial in COVID-19
- Galectin Inhibitors in phase 2 & 3 trials for IPF, NASH, Cancer, Atopic Dermatitis, Psoriasis, Covid-19




**4000+**
Journal Articles on Target Receptors

**30+ years**
of research in Galectins, carbohydrate-binding proteins

# Galectin Antagonist Treatment Results in SARS-CoV-2 Spike Protein Specific Antibody Immunity

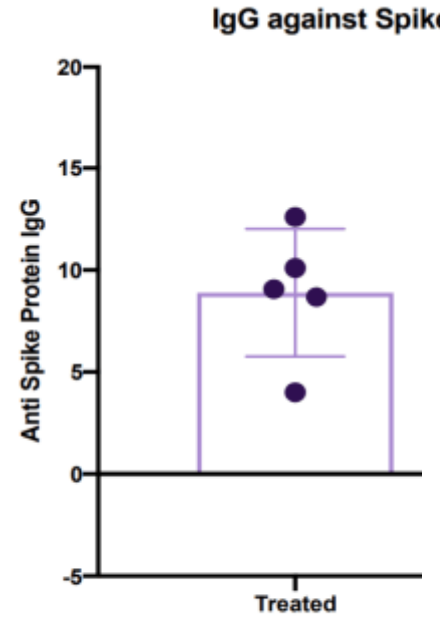



Figure 4 – difference in IgG on day 28

## Introducing Post Infection Immunization

Galectin antagonists clear the blood of viral load thereby reducing the strain on the Innate immune system so the Adaptive immune system can build a robust response toward future infection.

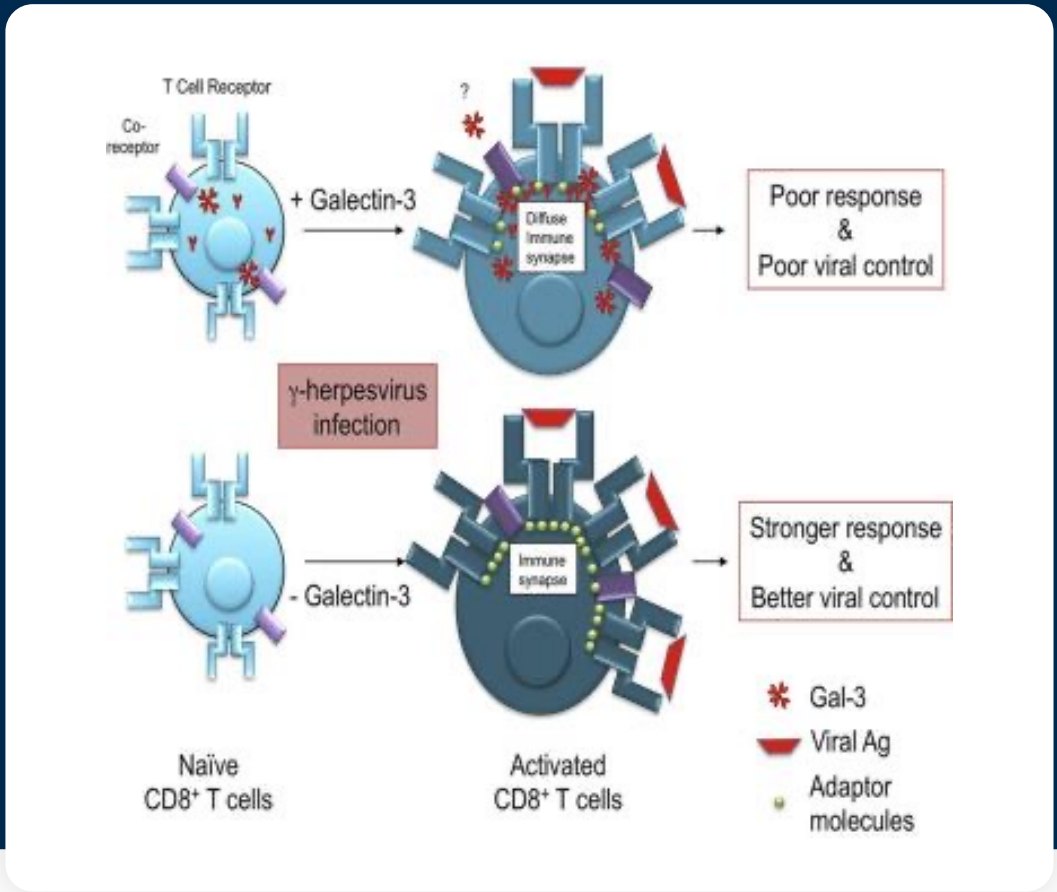
[1] Galectin Antagonist use in Mild Cases of SARS-CoV-2; Pilot Feasibility Randomised, Open Label, Controlled Trial (longdom.org)

## Galectin-3 Upregulated

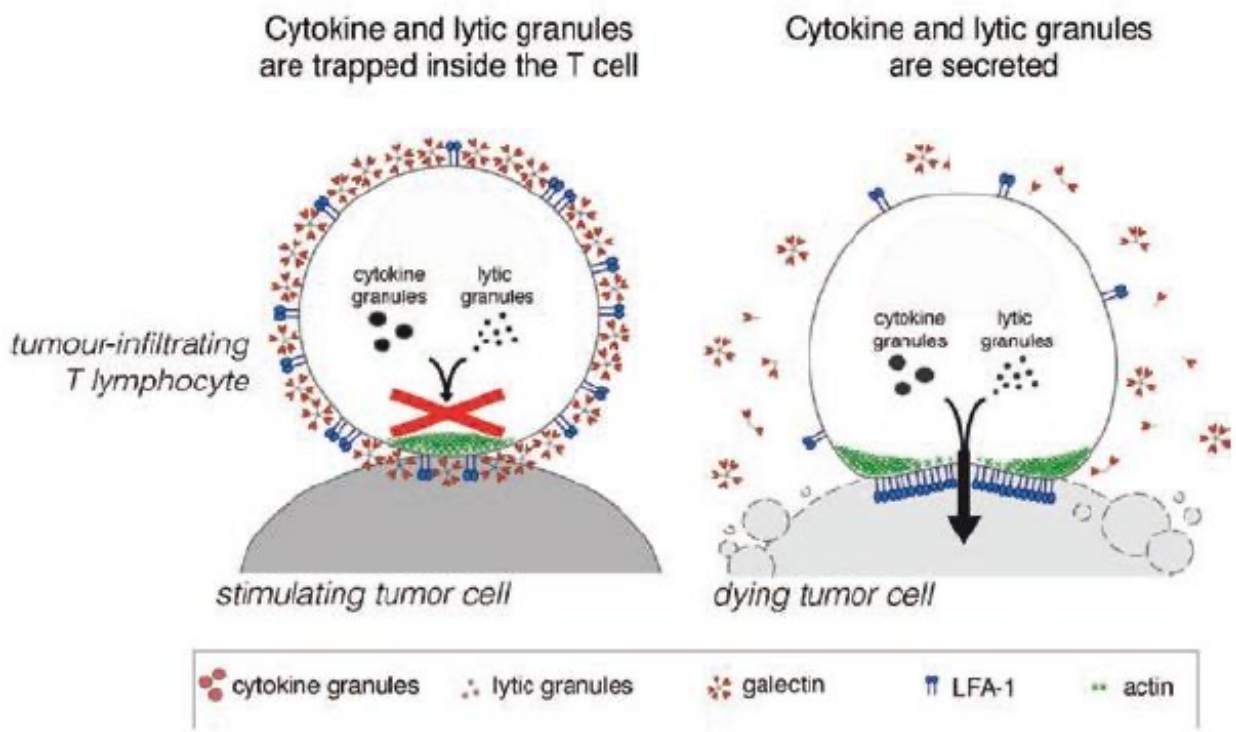
Virally infected cells upregulate Gal-3 which is used in the budding process of virion. When cells burst after the nuclear material is used up it goes into the inflammatory environment.

## Effect of Elevated - Galectin-3

Galectin-3 plaque creates CD8+ T-Cell Anergy. Gal-3 also promotes the trafficking of inflammatory macrophages via adhesion that allows invasion and extravasation into the vasculature. Gal-3 is also responsible for all types of organ fibrosis (brain, heart, lungs, kidney, GI tract).



# Galectin Effect (T-Cell Anergy)



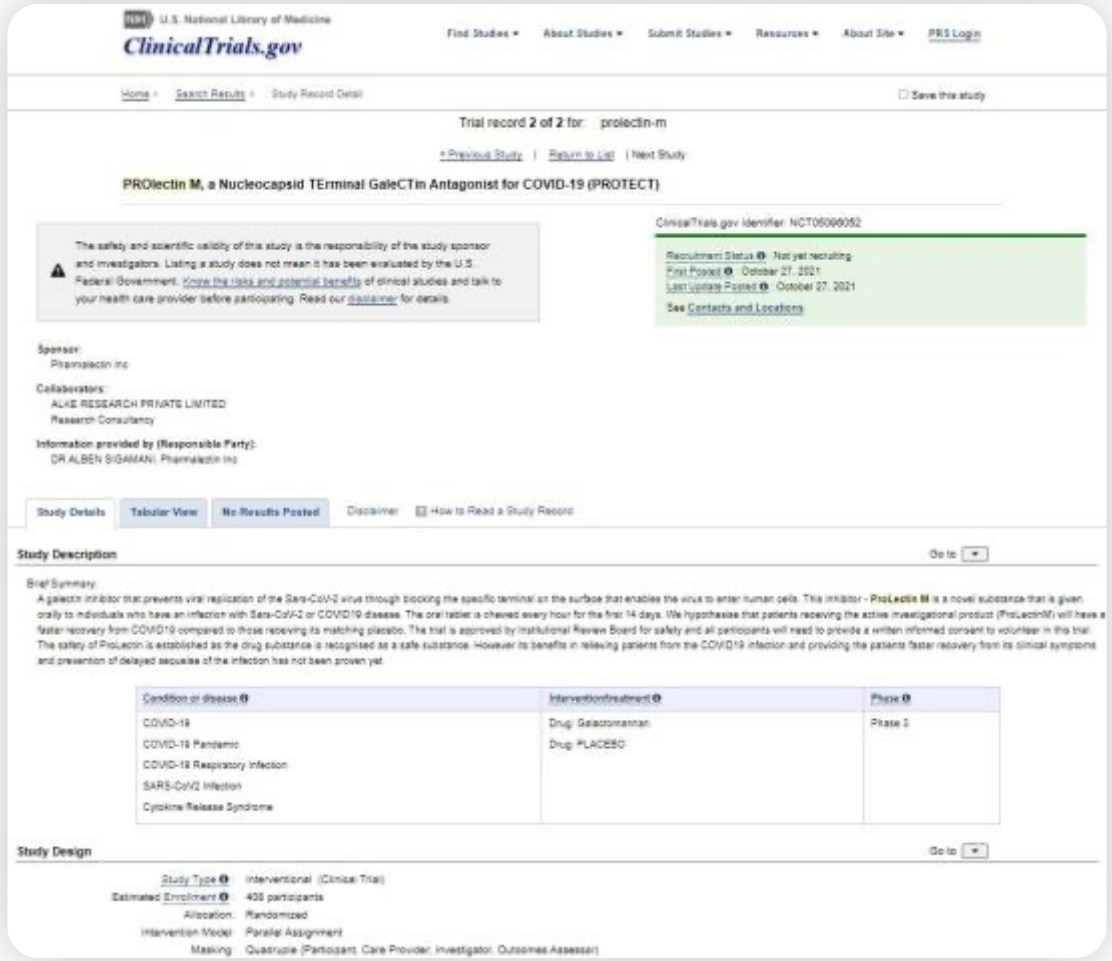

Cytokines and lytic enzymes are produced normally by human tumor-infiltrating T lymphocytes but remain trapped inside the cells.

https://www.deduveinstitute.be/sites/default/files/upload/%20Annual%20Report%20DDUV%202017.pdf
https://seekingalpha.com/instablog/47560554-vision-and-value/5210387-gr-mdminus-02-keytruda-s-partner

Galectins are responsible for T-Cell anergy and prevent the LFA-1 lectins (depicted in blue) from coalescing at the target cell and developing good adhesion in order to destroy it with cytotoxins.

SAME MOA IN VIRUSES

# Proposed Clinical Trial Design




## Clinical Trial

- 408 participants
- Double Blind Randomized Controlled Trial (DBRCT)
- Change in seropositivity at day 14
- Broad inclusion criteria

  (Vaccination status irrelevant)

# Galectins Linked to Chronic Disease

30 years of research

Over 4000 Journal articles on Galectins

Galectins are a key biomarker of chronic disease

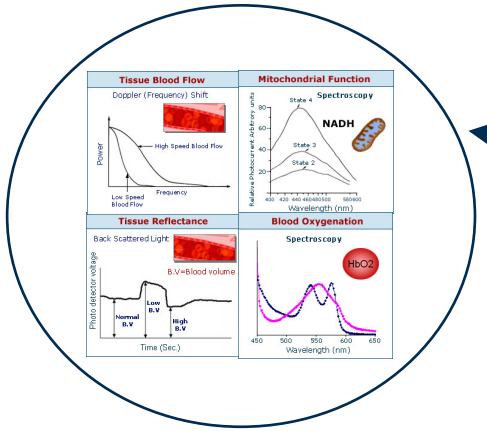
No approved Galectin inhibitor - YET

| Disease Indication | Journals | Areas of Focus |
|---|---|---|
| Cancer | 1500 | Cervical, Breast, Endometrial, Pancreatic, Thyroid, CRC, Biomarker |
| Cardiovascular Disease | 622 | Biomarker for heart failure, stroke, other cardiovascular disease |
| Brain | 350 | Predictive Biomarker stroke, TBI, Postpartum Depression |
| Kidney | 211 | Fibrosis, Biomarker in chronic kidney disease |
| Lung | 200 | Cancer, Fibrosis, Biomarker |
| Liver | 185 | NASH, NAFLD, Fibrosis, Biomarker |
| Skin | 127 | Wound Healing, infection, Lupus, Psoriasis, Cancer, Biomarker |
| Digestive System | 109 | Gastric & Colorectal Cancer, Metastasis, Inflammatory, Biomarker |

https://www.pharma-iq.com/pre-clinical-discovery-and-development/articles/why-galectin-3-has-emerged-as-a-focus-for-drug-research-and-development-1

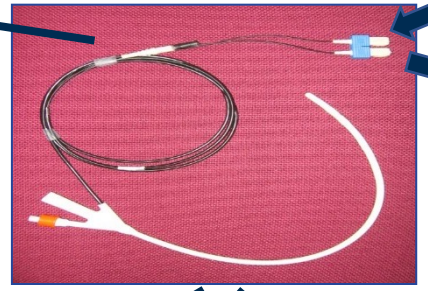
# MDX Monitoring for Acute Respiratory Distress Syndrome (ARDS)

## Systemic vital parameters (probe 3)




Systemic vital parameters (probe 2)

Photoplethysmography analysis



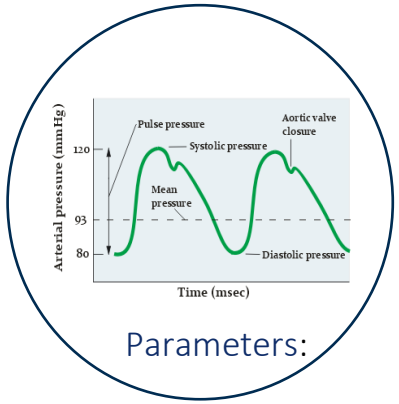
Light Source Unit

Detection Unit

Electronics & Embedded Computer System

Power Supply

Panel Computer




Parameters:

Core Temperature