Cellastra

Encoded Gene Vectors:

Prevention & Treatment
of Acute & Chronic Complications
of COVID-19, Surgery, & Burn Injuries

Cellastra Key Success Factors

- **Proven** Executives
- **Profoundly** unmet medical needs in tissue injuries after COVID-19, Surgery & Burns
- **Proprietary** Gene Vectors / Peptides
- **Proven Effects** of Peptide on Root Causes of Tissue Damage and Scarring
- **Proven** Concept: Vector expresses the Peptide in vivo for months
- **Proven** safety of Lactoferrin Peptides
- **Promising** Prospects Near & Long Term

Pharmacia · Novartis · BIOTECanada · astellas Leading Light for Life · University of Guelph · UCSF University of California San Francisco · Mayo Clinic · Linköping University · Karolinska Institutet

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Scar Prevention: Global Unmet Needs

- Long COVID: Multi-organ inflammation, diffuse clotting, & scarring (fibrosis) can lead to chronic complications (heterogenous symptoms: fatigue, memory loss, breathing difficulties, arrhythmias, etc.) lasting for >12 weeks –>12 months
- Hypertrophic dermal scarring after surgery & burns
- Potentially impacting Quality of Life or even debilitating
- Severe socio-economic impact – Long COVID alone $3.5 Trillion in US

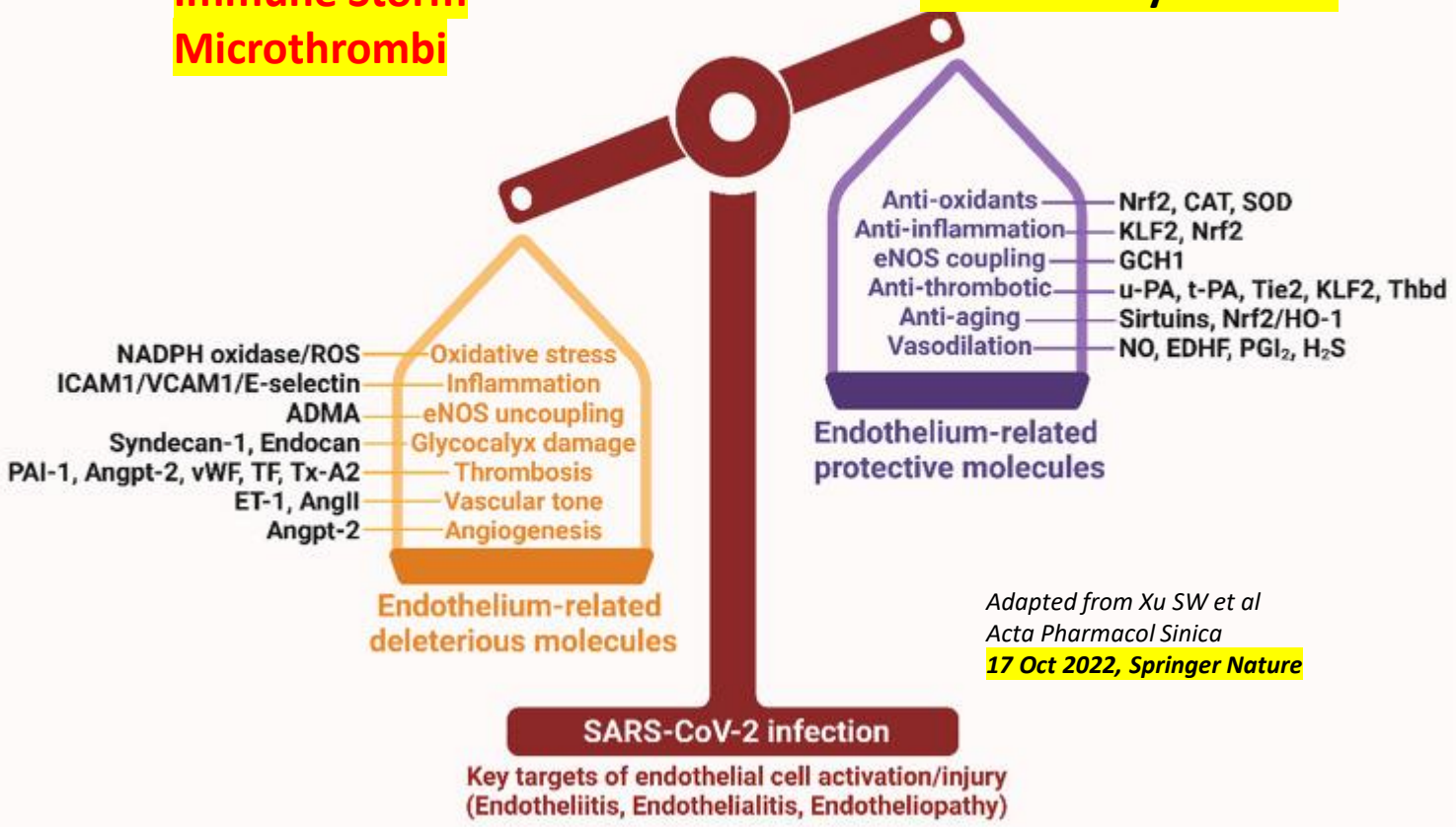
David Cutler, Prof. Economics, Harvard

NO EFFECTIVE DRUGS ON THE MARKET

Imbalanced Immuno/Hemostasis Axis

Imbalance by:
Immune Storm
Microthrombi

Ensereptide helps rebalance:
- **Down regulates Cytokines**
- **Pro-fibrinolytic effect**



Adapted from Xu SW et al
Acta Pharmacol Sinica
17 Oct 2022, Springer Nature

Virlexa in COVID-19

Turning the Lungs Into Temporary Bioreactors

- Total lung epithelial surface area = 100 sqm – The size of a racquet ball court
- One inhalation enables expression of peptides for the 30-day life cycle of the lung epithelial cells
- Vector may bind to the ACE-2 receptors for COVID, enabling targeted transfction to infected tissues potentially blocking further infection

+ One intramuscular Injection

May enable systemic levels of peptide for several months – for long-term protection

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Studies of Triple Mutant AAV6.2FF Gene Vector

Associate Prof Sarah Wotton, University of Guelph

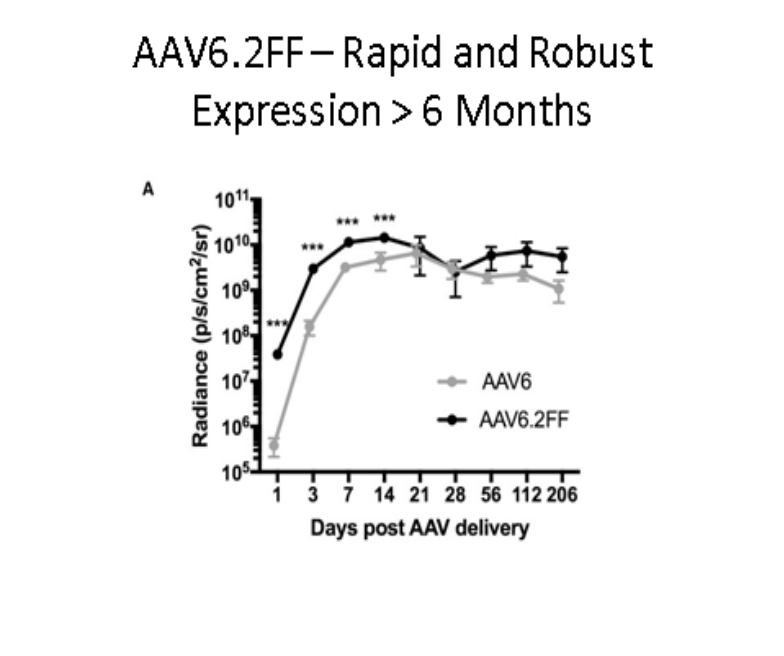
Chair of Cellastra SAB

Gene Vector:* Robust Expression for 6 Months

Triple Mutant AAV6.2.FF Administered intramuscular or Intra-pulmonary

Compared to natural AAV6:

- Lower immunogenicity
- Higher transgenic expression in muscle (>100-fold) and lung (49-fold) at 24 hours
- 10-fold greater expression in the lung at 21 days and significantly increased expression on Days 1, 7, and 14 in muscle
- Robust expression maintained at high levels throughout the 6-month study period



** Intramuscular injection of triple mutant AAV6.2FF vector in mice has:*

- *Rapid and superior early expression*
- *Maintained at high level >6 months*

van Lieshout et al Clin Dev. 2018 Jun 15; 9: 323–329.pdf

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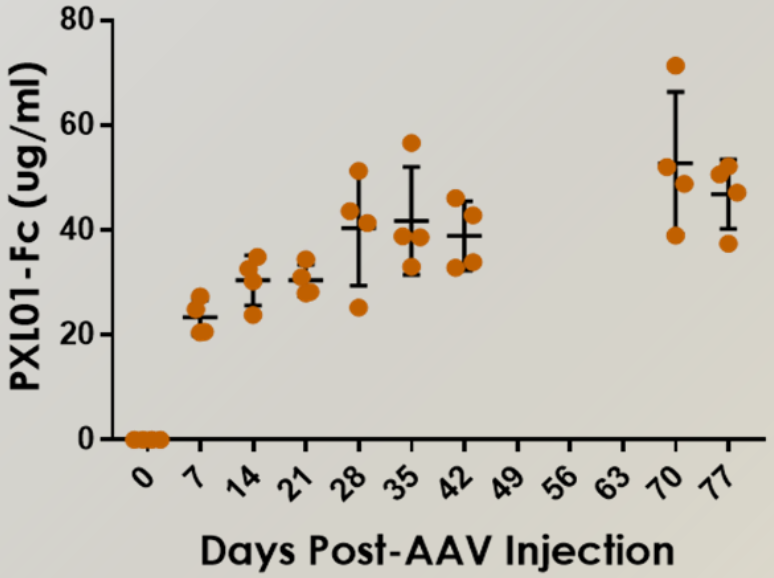
AAV6.2FF: Expression of Ensereptide in Mice

- Robust expression in mice until sacrificed on Day 77
- Intramuscular admin. of encoded vector
- ***Fc tag was added to gene construct to:***
  - ***enable quantification expression &***
  - ***possibly prolong half-life ("Next Generation Analogue")***



Balb/c mice were intramuscularly administered $1x10^{10}$ vector genomes of AAV6.2FF expressing PXL01 fused to the Fc domain of human IgG1 (PXL01-Fc). Plasma levels of PXL01-Fc were measured over time until ***the experiment was terminated at 77 days post AAV-administration***

PXL01 = Anti-scarring peptide Ensereptide
Fc= human IgG constant domain

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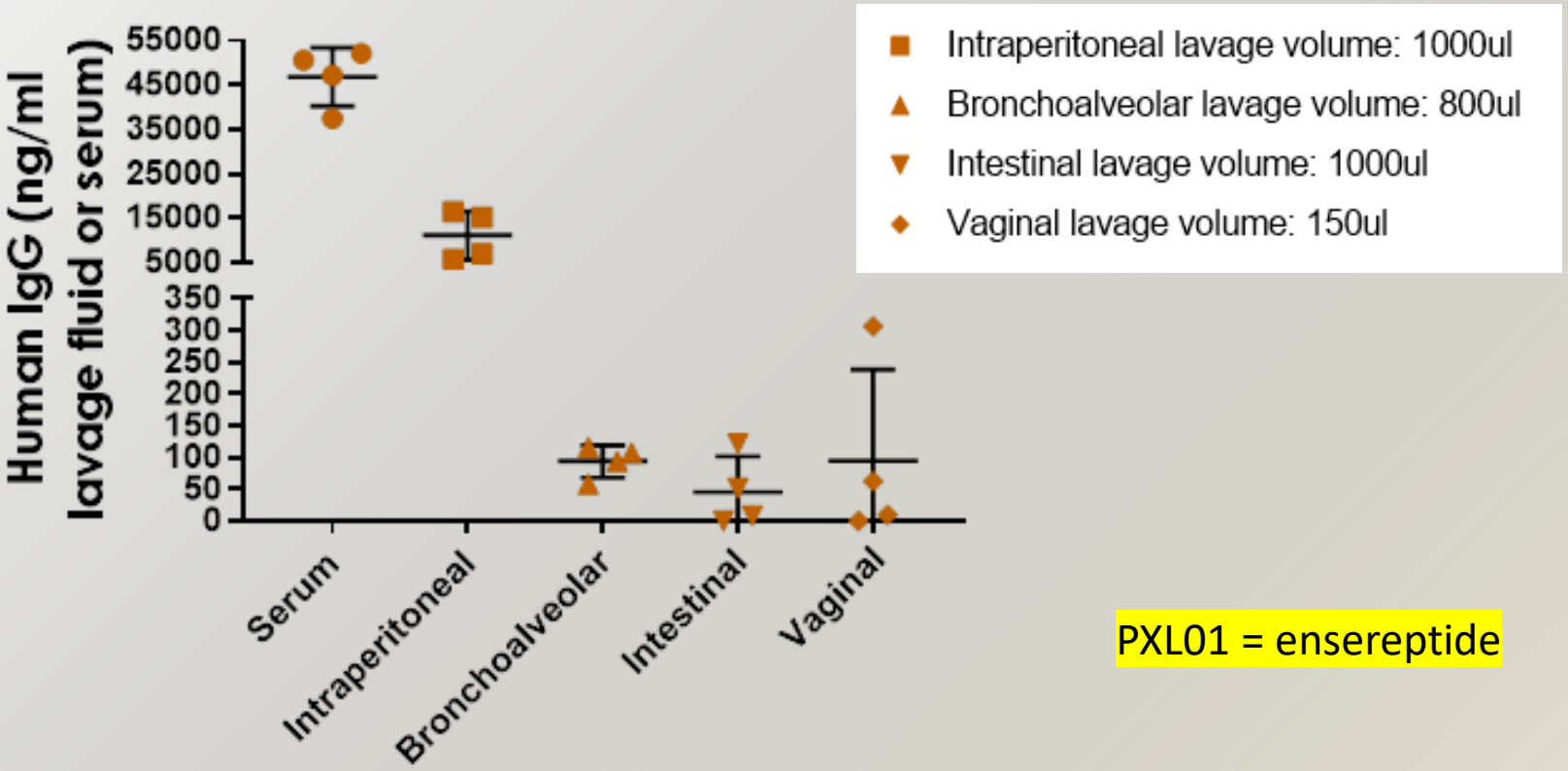
PXL01-Fc expression levels at mucosal surfaces



PXL01 = ensereptide

Balb/c mice administered $1x10^{10}$ vector genomes of AAV6.2FF expressing PXL01 fused to the Fc domain of human IgG1 (PXL01-Fc) **were terminated on day 77** and lung, peritoneal cavity, intestinal and vaginal lavages were performed. Concentration of PXL01-Fc is reported as ng/mL of lavage fluid. Volume of lavage fluid is reported above.

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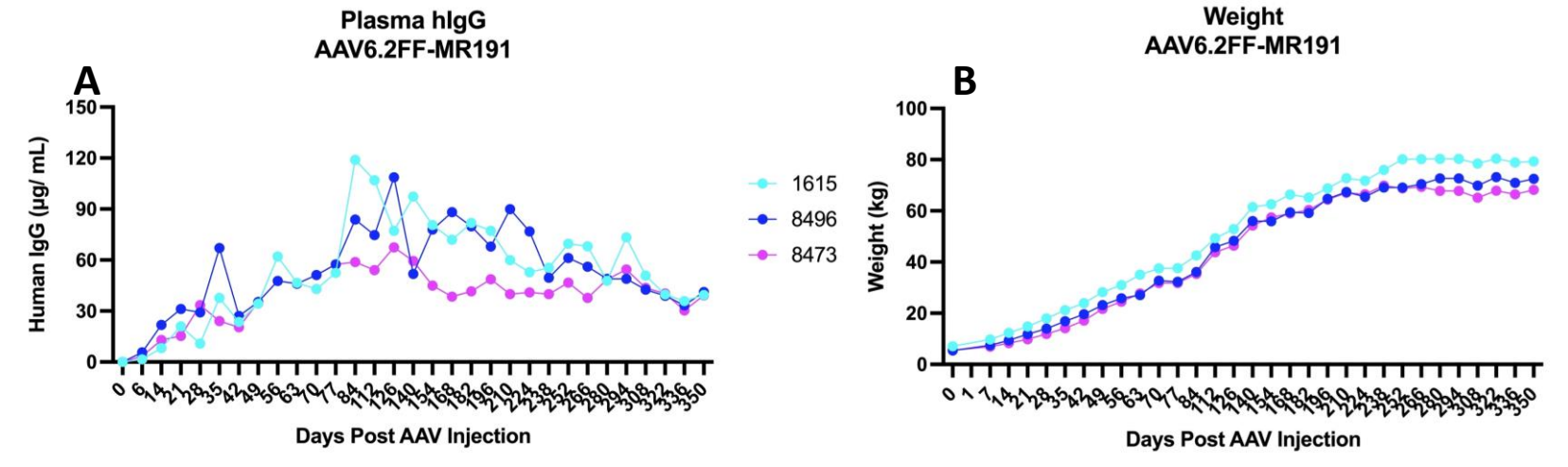
AAV6.2FF: Preclinical Toxicology Studies

- Acute toxicology study in mice – DOI:10.3390/biomedicines9091186
- Acute toxicology study in sheep - DOI: 10.3390/biomedicines9091186
- Chronic pharmacology study in sheep - Ongoing

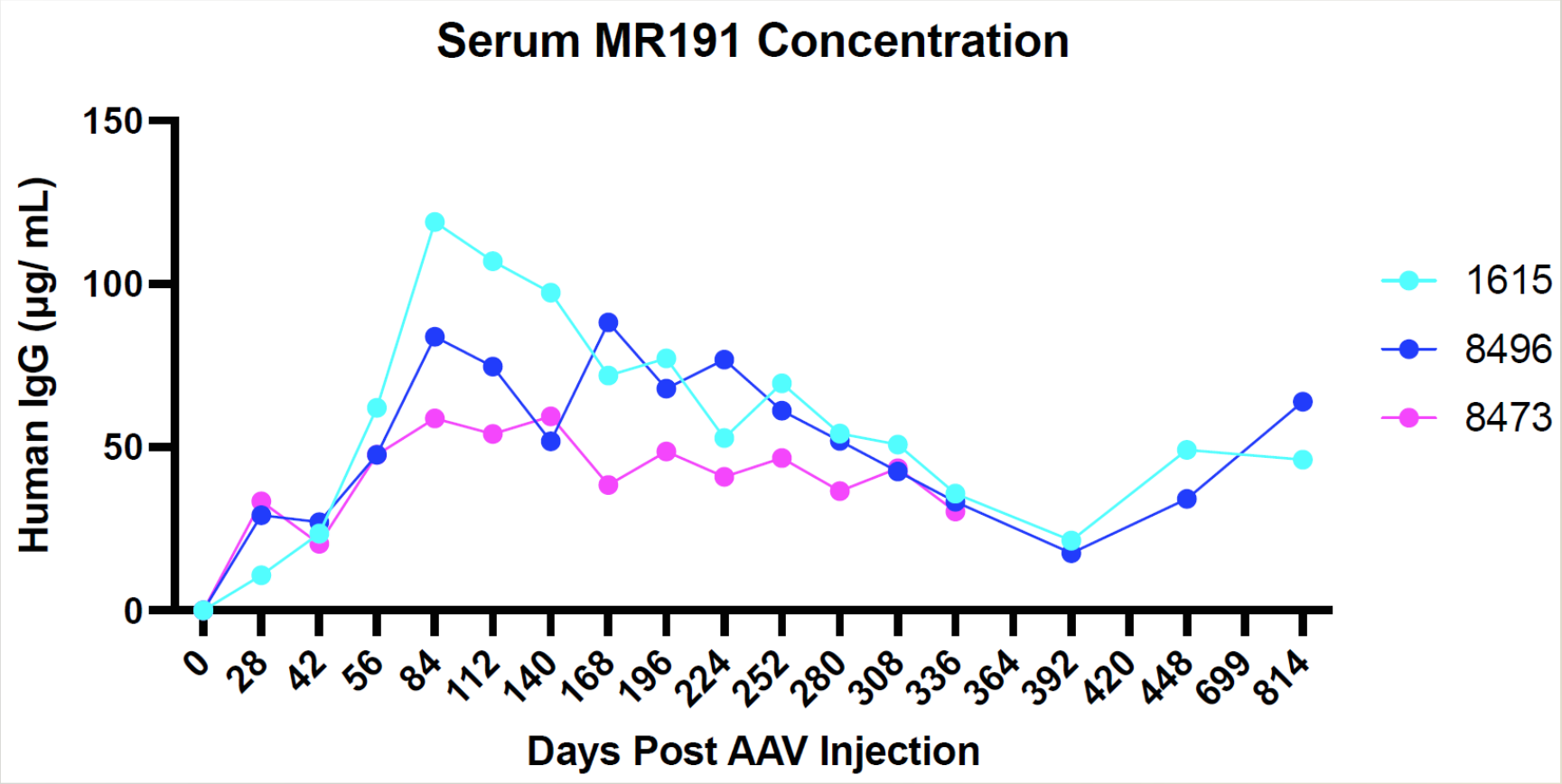


(A) Two-week-old Dorset sheep were intramuscularly administered 5e12 vg/kg of **AAV6.2FF expressing a human IgG mAb and plasma concentrations of hIgG were monitored for 1 year.**

(B) hIgG expression was stable over the 1-year monitoring period despite an increase in animal weight from 5 to 80 kg.

Long-Term Expression in Sheep

hIgG expression was stable over the monitoring period out to 814 days.



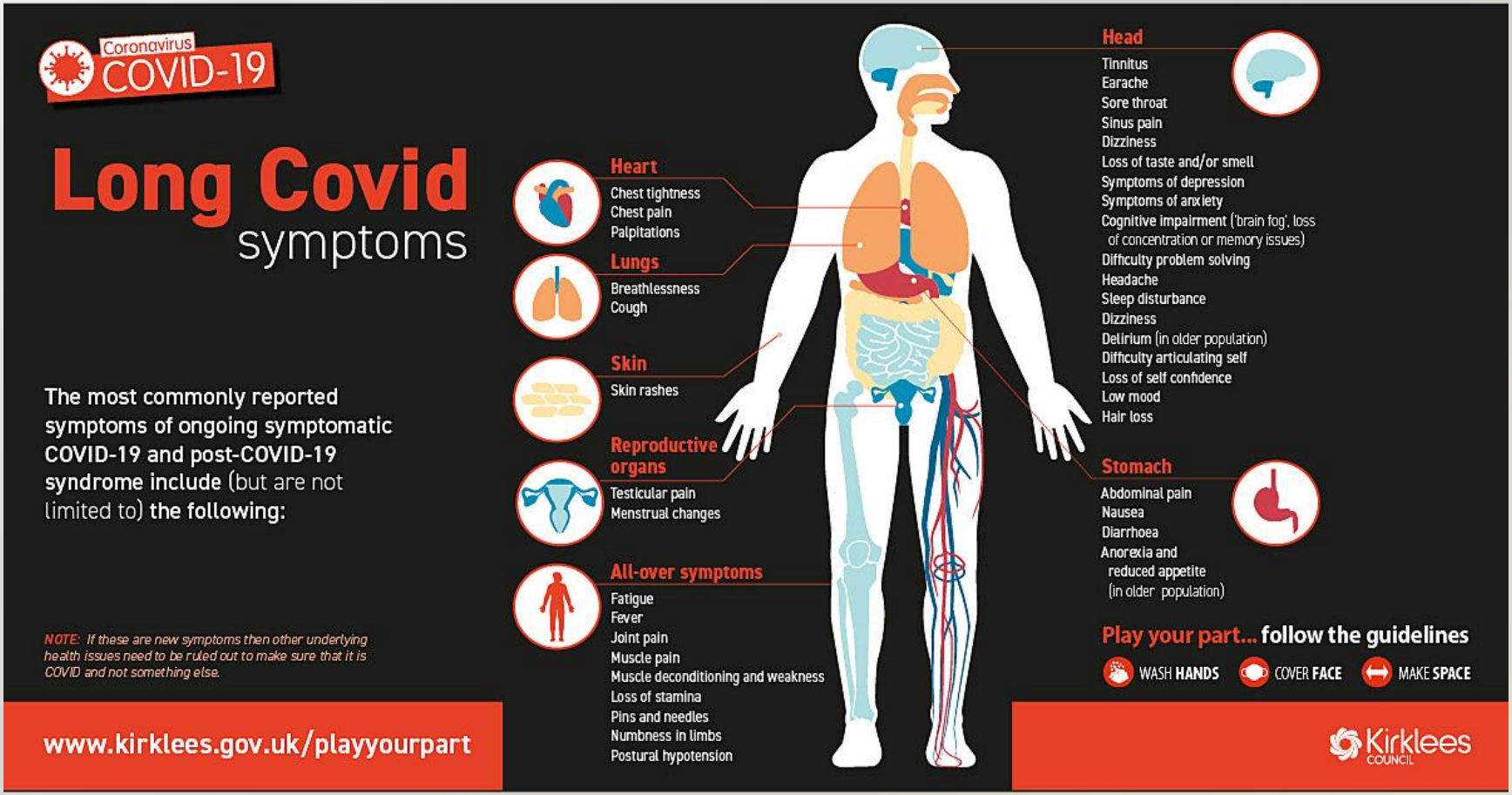
Long Covid Pathophysiology

Hank Kulmala, PhD,
EVP Regulatory & Product Development

Long-COVID

- A rather mysterious illness following COVID-19 of any severity, but especially after severe infection
- A similar syndrome is seen after other viral infections, but not in these numbers.
- Majority of patients do not test positive for virus after initial acute infection, in contrast to chronic COVID-19 among immunosuppressed patients.
- Over 200 symptoms were described affecting all body systems. Most prominent symptoms are respiratory, where most infections started. Some are new, some continuing, some worsening
- Terminology is confusing as is timing:
  - Long-COVID (long Covid), PASC (direct viral), long haulers
  - At least 30 days after infection, perhaps 90 days, but lasting a year or more (>2 years) in many patients
- Incidence and prevalence are variable; may depend on the variant and subvariant (less with Omicron, which also caused less severe disease cases).
  - Reports of >20% to >5% incidence; often reports of substantial numbers of patients not totally recovered at 1 year or longer
  - Could be 18 million subjects in the US alone, and est. 120 million globally

Long COVID: Pathophysiology and Symptoms



Pathophysiology of COVID-19

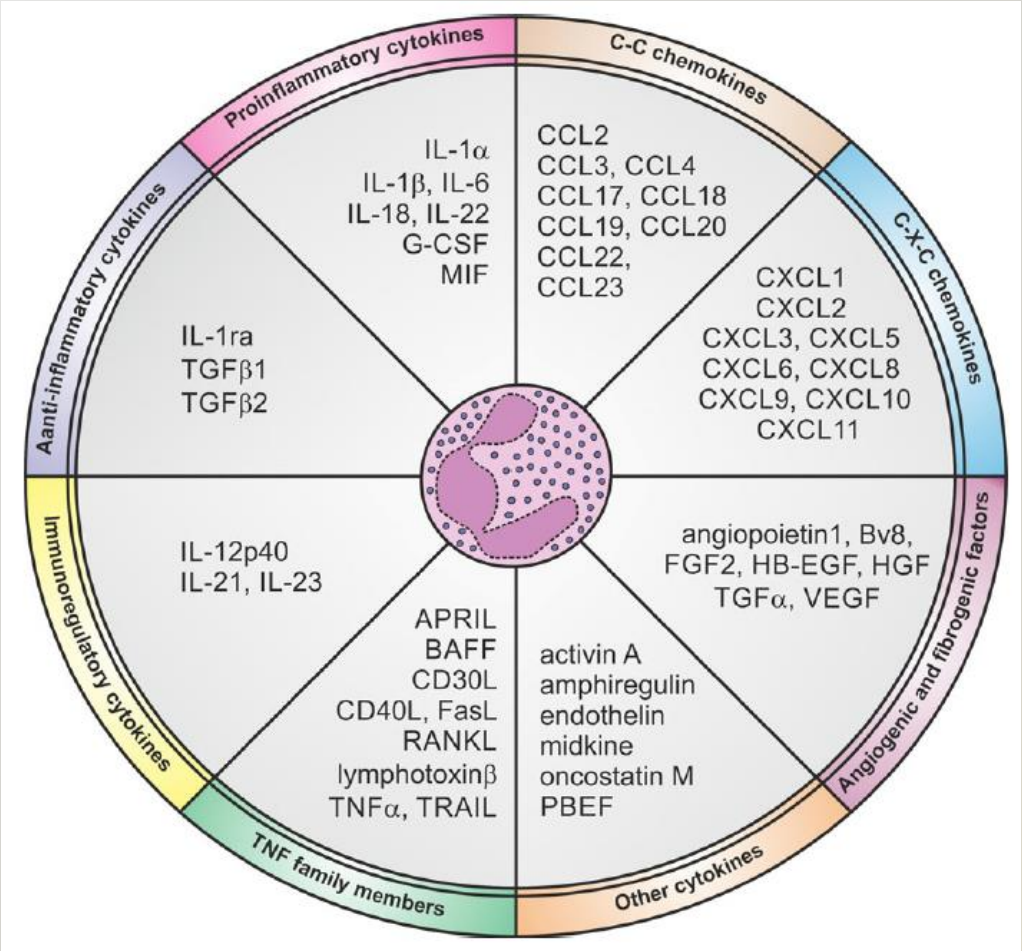
- The lungs are generally attacked first by SARS-CoV-2, leading to defining COVID-19 as a type of pneumonia. It is much more, as we now know.
- Deep lungs were affected by Wuhan-1 variant (original) and most subsequent variants (Alpha, Beta, Gamma, Delta).
- Omicron appears to attack more superficial lungs tissues, resulting in differing symptoms.
- SARS-CoV-2 also is swallowed and often results in GI symptoms (and virus or viral RNA in feces).
- All recent subvariants are from Omicron, which evolved and became dominant because it has advantages over other variants (more virulent, shorter incubation time, more contagious).
- COVID-19 is unlikely to disappear but could become seasonal.
  - According to a recent study, most respiratory infections occur in the winter because cold weather "kills off" a large percentage of the innate immune system in nasal tissues.
  - In cold weather, people gather in warm places where viruses are easily spread.

The Trilogy in the Pathophysiology

Inflammation – Immune Response – Vasculature

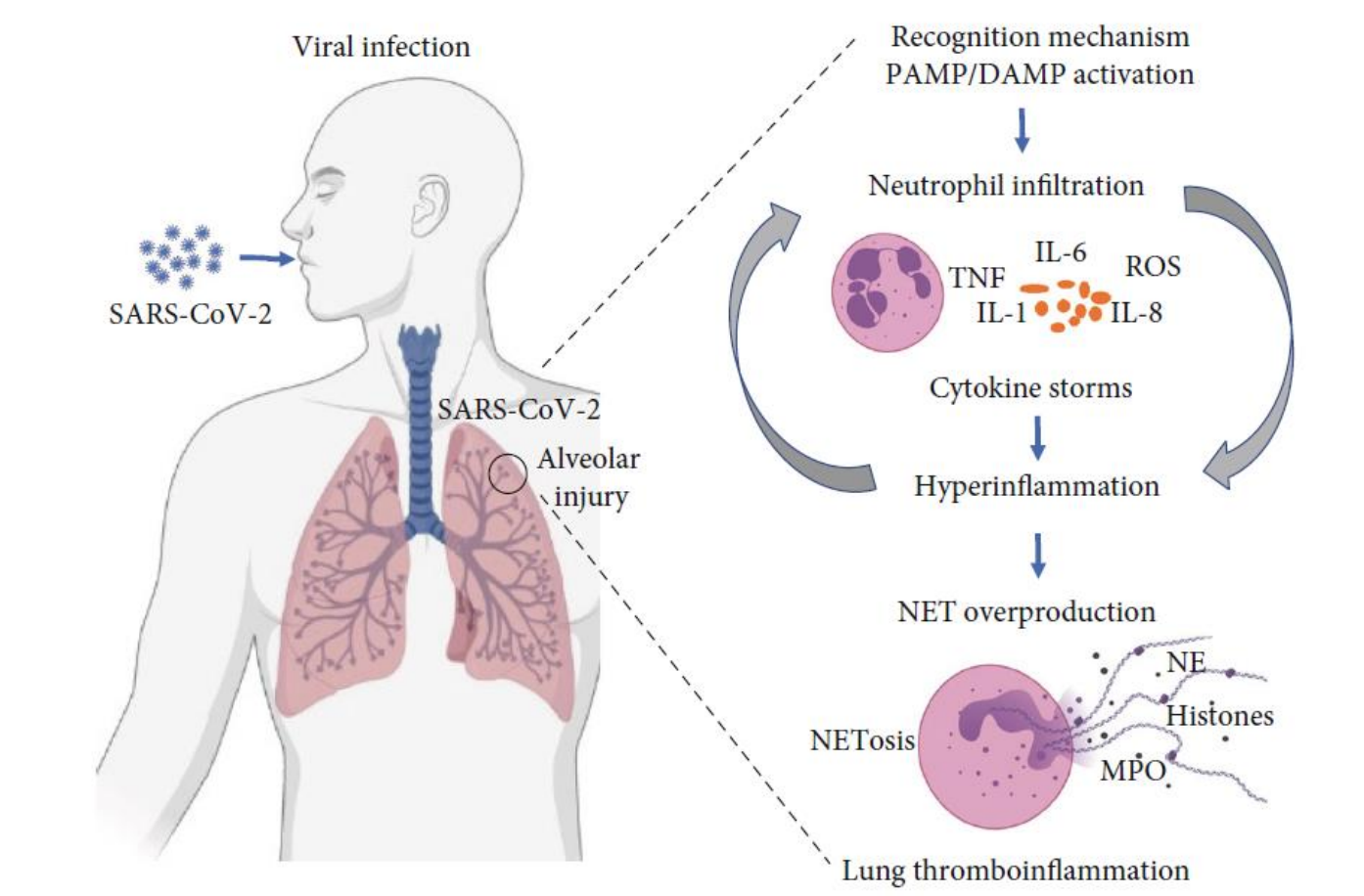
- Inflammation is a common response to viral infection in all body areas. Chronic inflammation can lead to exaggerated immune response and tissue fibrosis. Hyperinflammation is pathological.
- Common factor in all cases is an immune response to the virus:
  - Asymptomatic cases result when the subject's immune system fights off the virus.
  - Vaccination aims to induce immune system to produce antibodies to the Spike protein of the virus.
  - In some cases, a hyperimmune or deranged immune response is seen, resulting in a cytokine storm.
- Vasculature is a common link for affected body areas: carry the virus and immune cells. Excessive clotting and microthrombi can induce further tissue damage (inflammation, ischemia), including that in blood vessels.
- Neutrophils, an integral early part of the immune system response, may participate in the pathology of COVID-19 and Long-COVID.

Cytokines Produced by Human Neutrophils



Tamassia et al., 2018

Neutrophils and Lung Hyperinflammation



Borges et al., 2020

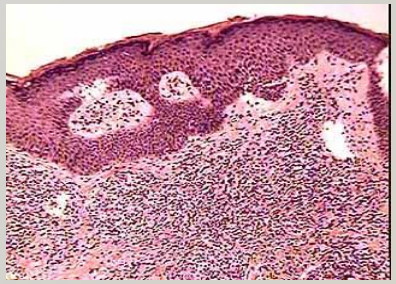
Ensereptide – Mechanisms of Action Non-Clinical & Clinical Proof of Concept

Hank Kulmala PhD

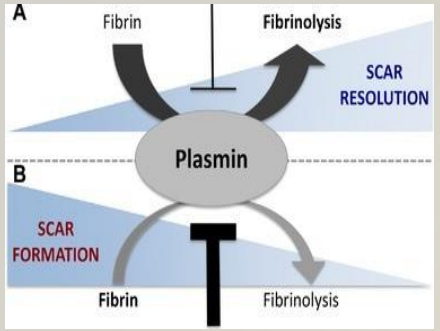
Ensereptide: Targets Root Causes of Vasc. Damage

Ensereptide

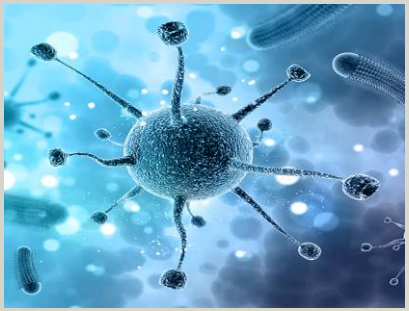
Prevents cytokine storm



Prevents micro-thrombi



Anti-microbial



Ensereptide = PXL01

Nilsson E et al, Ann Surg . 2009,250(6):1021-8.

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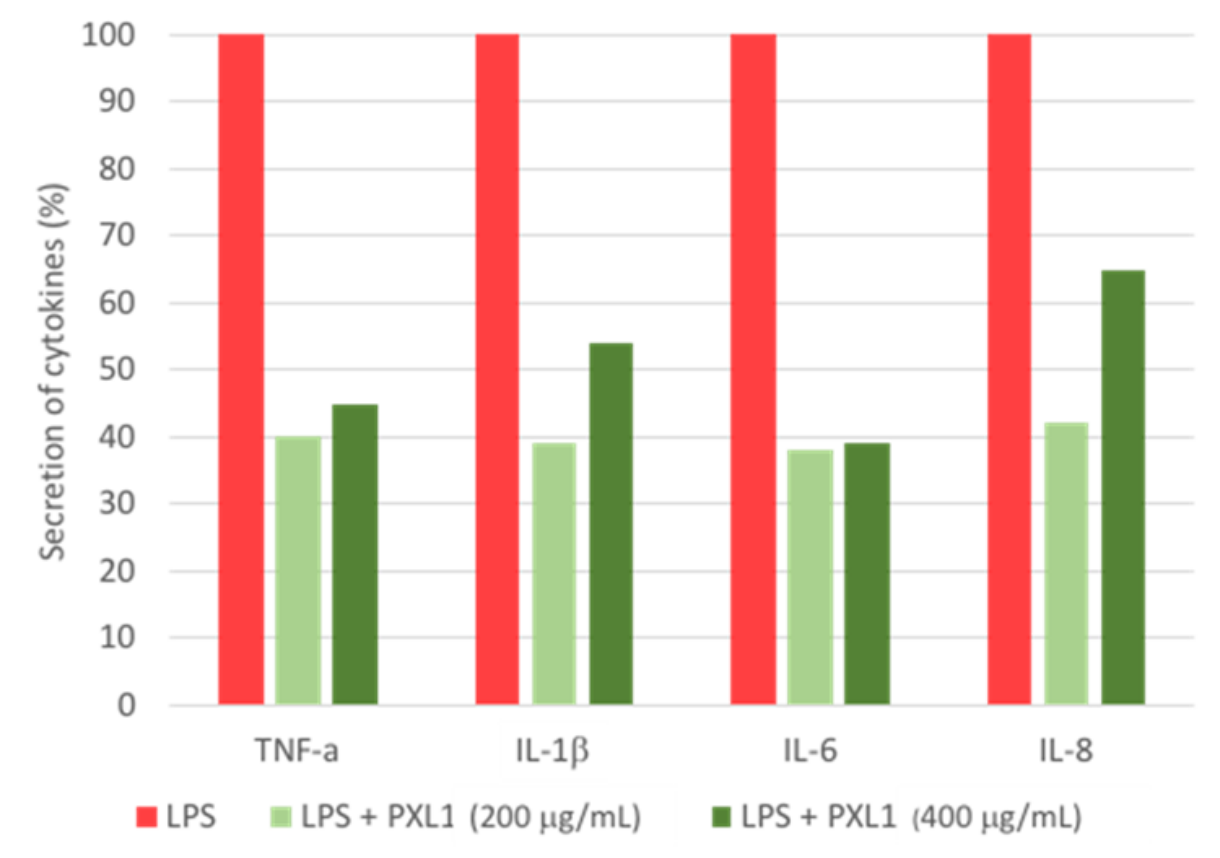
Ensereptide Mitigates Inflammation in vitro

40-60% reduction of cytokines



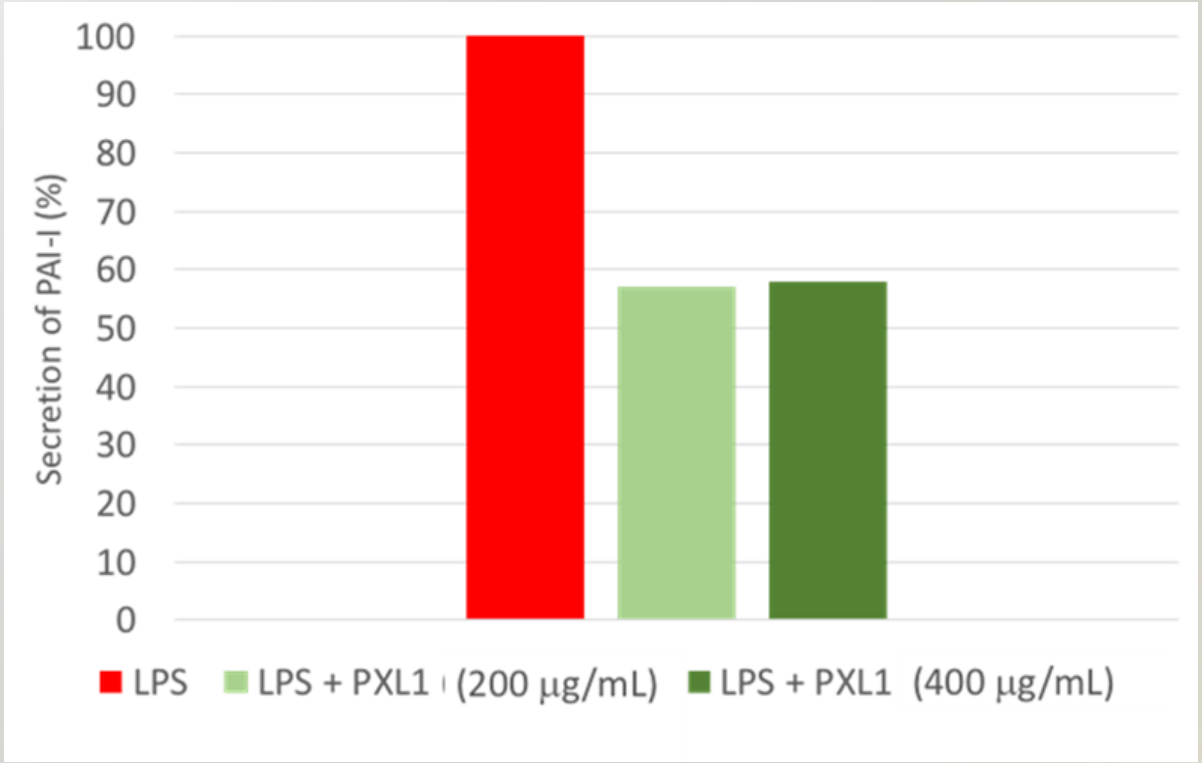
Nilsson E et al, Ann Surg. 2009,250(6):1021-8.

Ensereptide = PXL01

Ensereptide Mitigates Fibrin Formation in vitro

40% Reduction of PAI

(Plasminogen Activator Inhibitor)



Nilsson E et al, Ann Surg. 2009,250(6):1021-8.

Ensereptide = PXL01
LPS = lipopolysaccharide

Enseretpde Antimicrobial Effects in vitro

Ensereptide (PXL01) is 40-80 X more potent than Lactoferrin

	Escherichia coli MMC 99%; µg/mL	Staphylococcus aureus MMC 99%; µg/mL	Pseudomonas aeruginosa MMC 99%; µg/mL
PXL01	12.5	12.5	25
Lactoferrin	>1000	>1000	>1000

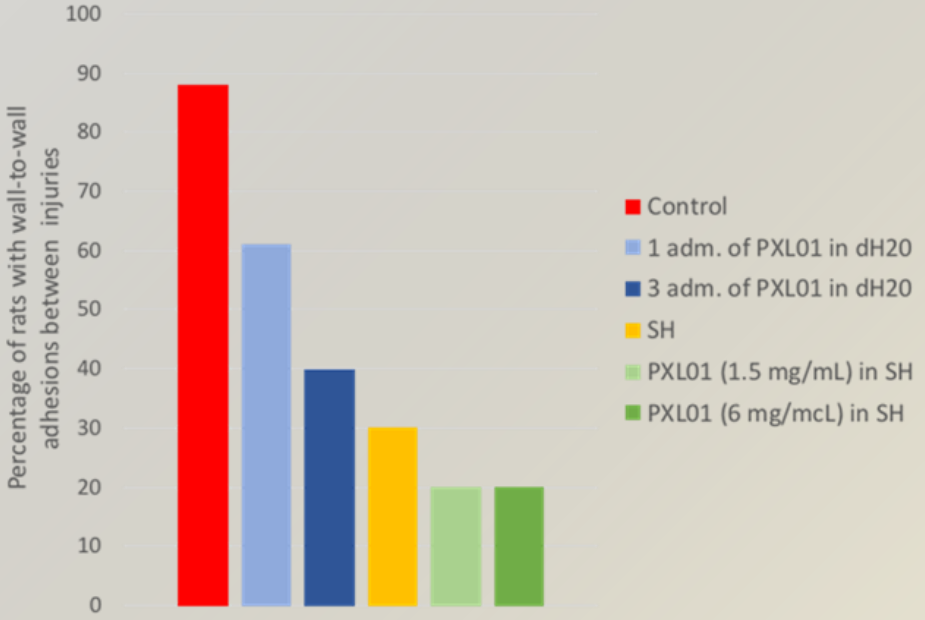
Nilsson E et al, Ann Surg. 2009,250(6):1021-8.

Ensereptide Anti-Scar/Adhesion Effect (Rat)

>75% reduction of # rats with extensive adhesions

- Sustained peptide levels for 48 hrs. with SH (= Sodium Hyaluronate formulation)
- No safety concerns

Gold Standard Rat multiple abrasion model
Nilsson Ann Surg. 2009;250(6):1021-8



Non-Clinical Proof Of Concept Studies

Wish List to be discussed with Agencies

- Toxicology studies including immunotoxicology
- Effects of the peptide and vector in wound healing or infection models:
  - Protection of animals from SARS-CoV-2 (efficacy and safety)
  - Cell culture studies of effects on neutrophils, cytokine production, clotting, other factors
  - Models of chronic or acute inflammation, in vitro or in vivo
  - Studies of antimicrobial (antiviral) effects of vector and peptide
  - Studies of immune system response: cell mobilization, cytokine formation, others
  - Transfection of different cell types by the vector and peptide expression
  - Characterization of vector (full, partial, empty capsids)

Ensereptide Scarring Clinical Proof of Concept

- Phase 1 completed in healthy volunteers – good safety profile, low systemic concentrations reported only after high dose (Promore annual report)
- Phase 2 study completed and published [1]
  - **Randomized, double-blind study in 138 patients**
  - **40 mg PXL01 vs. placebo (saline) injected locally around repaired tendon at surgery**
  - ***Safe through 12 months' observation period***
  - ***Achieved four of five scarring efficacy endpoints, good safety profile***

1. Wiig M, et al., PLOS One 2014;9(10):1-11.

Clinical Studies of Virlexa and Scarlexa

Vinod Kumar, MD, CMO EVP and
Hank Kulmala, PhD, EVP
Regulatory & Product Development

Clinical Studies

Administration:

- ***COVID-19:*** Inhale gene vector Day 1 - Potential IM. booster Days 1 and 30
- ***After surgery:*** Apply by injection immediately as solution under skin in wound area ***before wound closure***
- ***After Burn Injury:*** ***in vitro Transfected keratinocytes 0r*** Spray suspension mixed with skin cells on top of burn wound

Vinod Kumar, MD
CMO, EVP

- **Prev. Prof. of Neurology/**
- **Psychiatry U of Illinois & Miami**

- **Section Head, Neuroscience and Executive Global Program, Medical Director, Novartis**

Virlexa Proposed Clinical Developm. Strategy

Start Inhalational or Combined Treatment within 5 Days after testing positive

One Inhalation Day 1

To Treat COVID-19 and Prevent Long COVID

ry Distress Syndrome (ARDS)

- Hospitalization
- Death
- Severe disease

One IM Day 1 (+ possibly Day 30)

To Prevent or Treat Long COVID:

- Adverse event reporting
- Symptom Questionnaire
- Cognitive testing
- Disability/ Quality of Life assessment

Proposed Clinical Studies

- **Virlexa is the initial focus (Scarlexa may be out licensed)**
- **Administered by single inhalation or by single inhalation and intramuscular injection(s) immediately after positive COVID test**
- **Acute phase assessments of COVID-19 and Incidence of Long-COVID**
  - Phase 1-2 Dose Ranging, Safety, PK/PD; N = 30 – 60 (Blinded)
  - Phase 2-3 Study; N = 120-240 or more; Randomized, Blinded, Placebo-Controlled. May be used as the first pivotal study.
  - Potential for Emergency Use Authorization in COVID-19 after Phase 2 study, depending on results in acute COVID-19
  - Phase 3, Double-Blind, Placebo-Controlled Study (N = 400 or more).
  - Efficacy in acute phase of infection will determine number of subjects, as will background incidence of Long-COVID (lower incidence requires larger study)

**FDA discussion pending*

Clinical Studies Virlexa –Long Covid

- **Phase 1-2:** Biodistribution, Pharmacokinetics, Safety, and Efficacy
- **Phase 3:** Prevention of Long-COVID
  - Enroll large number of patients with 3 days of testing positive for COVID-19
  - Randomize 1:2 or 1:3 to vector or placebo, both inhaled
  - Subgroup also could receive IM injection of vector at days 1 and 30
  - Follow for the incidence of acute disease, by grade, and for Long-COVID after 30, 60, and 90 days.
  - Follow for safety for 5 years

Clinical Studies Virlexa Long Covid

- **Phase 3:** Treatment of Long-COVID
  - Randomize patients with Long-COVID to treatment with vector (inh +\- IM) or placebo
  - Select primary symptoms to follow (up to 3; one must be respiratory if present) and secondary symptoms (up to 10) for each subject
  - Assess patients for symptoms at 30 days (primary assessment) and at 7, 14, 21, 60, and 90 days (secondary assessments)
  - Score patients for each symptom using VAS scale (numerical score comparison for statistics)
  - Follow for safety for 5 years

Swedish Study in Burn Injuries
Center for Advanced Medical Product (CAMP)

Prof Folke Sjoberg, Linkoping University

President Elect International Society for Burn Injuries

Cellastra Invited to join Vinnova funded burn study

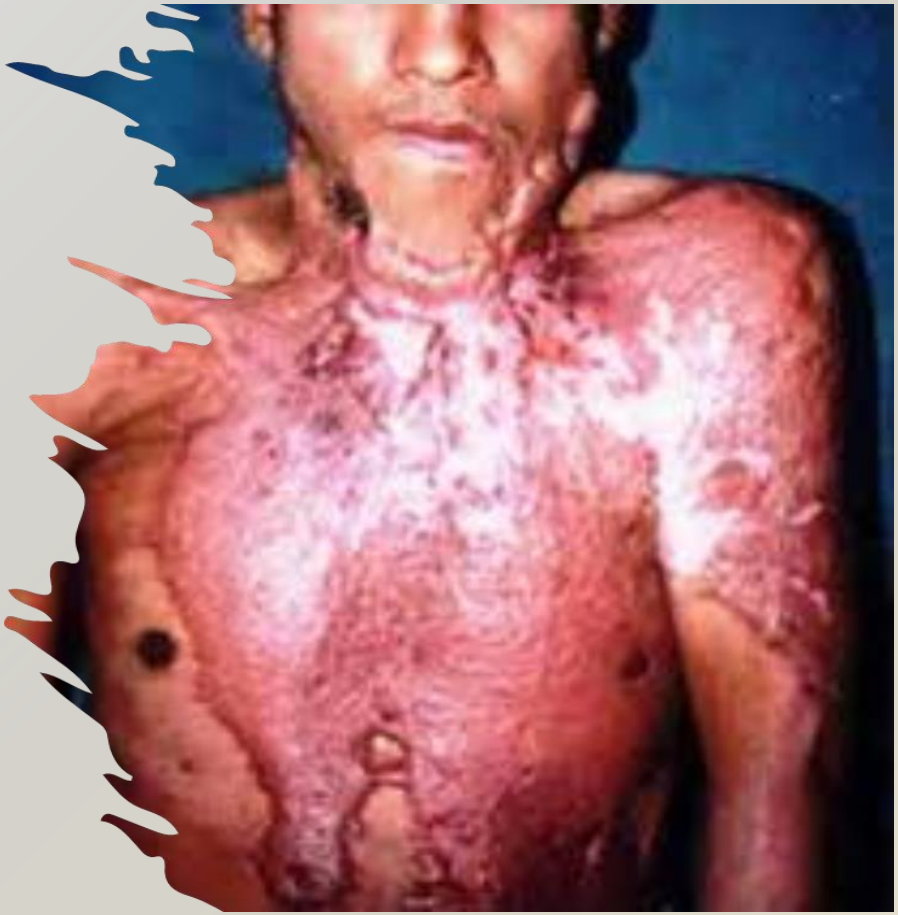
San Francisco, CA, June 22, 2021. Cellastra announces joining Centre for Advanced Medical Products (CAMP) to explore Cellexa gene vector in burn injuries

- Consortium funded with a 48M SEK grant from Swedish Government Innovation Agency Vinnova
- Cellastra to retain proprietary and commercialization rights

- Professor Folke Sjoberg, U. Linkoping
- Founder of CAMP
- Member of Cellastra SAB
- President Elect, (International Society (world association) for Burn Injuries

Cellexa Future Indication: Burn Injuries

- Burns are a worse global epidemic than polio at its peak
- In US, 400,000 ER visits/yr. and 28 specialized burn centers
- Annual cost in US >$10B



American Burn Association, 2021

Cellastra Pipeline (incl. potential partnering)

Tech-nology	Product	Indica-tion	Preclinical	Phase 1-2	Phase 3	Comment
AAV Vector for Inhalation	***Virlexa*** CLX-004	Respiratory		***EUA Q2 Year 3***		**BLA Q2, Year 4**
AAV Vector for Injection	***Scarlexa*** CLX-001	Dermal scar Breast Implant				**BLA Q4, Year 4**
		Dermal Scar C-Section* Burn injuries**				**BLA Q4, Year 4**

*May include other surgical indications if Agencies agree
**External explorative study funded by Swedish government

BLA = Biological License Application
EUA= Emergency Use Authorization

COVID-19: Is the pandemic becoming endemic?

- Globally 622 million total Cases and >6.5 million deaths (9/22) – cases currently decreasing (322k/day), 68% vaccinated globally (≥1 dose); <23% in low income
- US 96 million cases and >1 million deaths, 225M fully vaccinated (9/2022)
- Europe 223 million cases, 1.9 million deaths, 72% fully vaccinated
- S. America 66.4 million cases, 1.6 million deaths, vaccinations lagging
- China 777,624 cases, 9768 deaths, 1.2 B fully vaccinated
- India 43 million cases, 515,974 deaths, 792.4 million fully vaccinated
- Africa < 13 % vaccinated, no wide testing
- Antivirals: Ritonavir – Pfizer and Molnupiravir – Merck

Delta variant is no longer a global threat, replaced by Omicron Nov 2021 to March 2022, Omicron subvariants are now primary (BQ1, BQ.1.1, XBB, and others)

CELLASTRA Preliminary Budget ($1,000)

Product	Year 1	Year 2	Year 3	Year 4	Total
Virlexa (CLX-004)	4,984	10,787	4,700 (9,999)	1,200 (5000)	21,671
Scarlexa (CLX-001)	3,900	5,500	9,900	18,700	38,000
Operations	2,132	3,911	3,604	4,776	14,323
Total Cost	**11,016**	**20,208**	**18,104**	**24,776**	**73,994**
Rev Virlexa*	Low est.	100,000 pts		80,000	80,000
Rev Virlexa	High est.	400,000 pts		320,000	320,000
Total Revenue			***80,000-320,000***	**320,000 – 1,280,000**	

*Assuming price tag of USD 800 for the one-time treatment. Low estimate 2 million pts in Q4, Year 3, 20% severe, 25% capture rate, Full Year 4 = 4 x higher

Nonhospitalized Patients with COVID-19

- VIRLEXA inhaled once (potentially combined with one intramuscular injection) is initially intended for use in newly positive, high-risk COVID-19 patients to prevent:

  - Acute lung damage, ARDS and pulmonary fibrosis

  - Chronic multi organ Long Covid

- Can be combined with other treatments if indicated (antivirals & monoclonals)
- Can be used for new variants of SARS CoV-2 to reduce risk of tissue damage by inflammation, clots, secondary infections .Therapy for nonhospitalized patients with COVID-19 is limited
- Antivirals (Paxlovid and Lagevrio)and Monoclonal antibodies have limited efficacy with Omicron subvariants currently predominant

Dermal Scarring

No Previous Drug Candidates Approved

Company	Product	Status	Comment
Excaliard Pfizer	EXC001 antisense (ISIS) targeting CTGF (connective tissue growth factor)	Not moving beyond Phase 2 Hypertrophic scarring	Further development appears on hold
RXI	RXI 109 Anti-sense; prevents over-expression of CTGF	Not moving beyond Phase 2 Hypertrophic scarring	Phase 2 "Significant improvement" but non-conclusive (not randomized
Renovo	Justiva (evotermin) (Recombinant TGF beta 3)	Failed in Phase 3 Hypertrophic scarring	Phase 2 studies in healthy volunteers did not predict outcome in Phase 3
Capstone	AZX Peptide Smooth Muscle relax	Failed in Phase 2	Dosed Day 7, 9 and 21 12-month endpoint

*All 3 programs used s.c. dosing only first few days after surgery – May be too short treatment exposure

Why Did Competition Fail?

1. None of the 4 programs was discontinued due to safety issues, the drugs were reported to be well tolerated
2. All 4 programs used 1-2 or multiple small doses for the first week or first 3 weeks = Likely too short treatment exposure
3. 2 programs used within patient control and were equivocal
4. Results in healthy volunteers may not predict Phase 3 outcome in patients with scar revision

Cellastra Executive Team

- Karl Mettinger, MD, PhD, President & CEO, 35+ yrs.', incl. Karolinska Institute, Co-Founder/President Swedish Stroke Society (10,000 members, Queen Silvia Patroness) Kabi/Pharmacia, Supergen, Oncolytics, Pharmacyclics, 3Three Multi B USD Exits
- Vinod Kumar, MD, CMO, EVP, 30 years exp from U. Illinois, U Miami, Lilly, and Novartis (section Head/Global Program Medical Director)
- Henrik (Hank) Kulmala, PhD, EVP Product Development /Regulatory, 35+ years prev. exp incl Marion Merrell Dow, Fujisawa, Genix, 75 drugs (INDs, NDAs, BLAs)
- Brad Thompson, PhD, Chair, CTO, 35+ years , incl BIOTECanada, CEO Oncolytics, Avomed, Kickshaw Ventures, Inventor of several gene therapy patents
- Daniel Quintero, Esq, General Counsel, Secretary, 20+ years, incl Founding Partner Prometheus Partners LLP, Sony Optiarch / Electronics
- Bruce Phillips, CPA, SFO, 30+years exp incl Arthur Young, HPC, Xero, Aprio
- Kent Persson, PhD, Cofounder, 20+ years, incl UCSF, Bio-Rad, Octapharma

Board & Scientific Advisory Board

Board of Directors

- **Brad Thompson, PhD**, Cnair, CTO 35+ yrs.'. exp, incl BIOTECanada, Oncolytics, Avomed
- **Sven Andreasson, Vice-Chair, 35+ yrs.',** Kabi, Pharmacia, Active Biotech, NovaVax
- **Karl Mettinger MD, PhD,** 30+ yrs.' exp., President & CEO of Cellastra
- **Dan Quintero., Esq,** 20+ yrs.'
- **Kent Persson, PhD**, 20+ yrs.'. exp
- **Bruce Phillips, CPA**, CFO

Scientific Advisory Board (SAB)

- **Sarah Wootton, PhD**, Associate Professor, Dept. Pathophysiology, Ontario Veterinary College and University of Guelph, Ontario
- **Folke Sjoberg, MD, PhD,** Professor Burn Center LIU, Sweden, International KoL
- **Christopher Evans, PhD,** Professor Harvard, Mayo Clinic
- **Magda Forsberg, PhD,** Karolinska Institute, CEO Device company DVL-Op

Cellastra Value Proposition

- Proven management team
- Potentially revolutionizing new treatment paradigm:
  - Encoding scarless healing of wounds and tissue injuries
- First-in-class proprietary gene vectors:
  - Virlexa: respiratory infections
  - Scarlexa: post-surgery scarring, burn injuries
- Proof of Concept:
  - Anti-scarring peptide (Ensereptide) already established in root causes of tissue damage and scarring and safe and effective in preclinical and Phase 1-2 clinical studies
  - One application of gene vector – Robust expression for months
- Near-term exit opportunity and valuation in 1-4 years
- VIRLEXA Long COVID: up to $9B Year 5 - Dermal scar OTC market is projected to reach 46 B USD by 2028; SCARLEXA: up to 4.5B Year 5

Offer

- Series A
  - $27M in year 1
  - Manufacturing, Formulation, Preclinical Studies
- Series B
  - $27 M in year 2
  - Phase 1-2 clinical trials, Manufacturing
- Series C
  - $27M in year 3
  - Phase 3 clinical trials, Manufacturing

Forward Looking Statement

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