Cereno Scientific Capital Markets Day

August 30, 2022

Cereno Scientific

Welcome and Introduction to Cereno CMD 2022

- Moderator today: Lars Frick, financial journalist at Börsveckan, specialist in Life Science
- Agenda – corporate and external speakers with commercial and scientific presentations
- Q&A and panel discussion – open for questions from audience in-situ and on the web
- Participants

Today’s program

Sten R. Sörensen
Chief Executive Officer

Dr. Björn Dahlöf
Chief Medical Officer

Dr. Raymond L. Benza
Professor of Medicine, Wexner Medical Center,
Ohio State University, SAB, Cereno and PI for CS1’s Phase II study

Dr. Phil Adamson
Divisional Vice President and Chief Medical Officer Heart Failure Division, Abbott

Dr. Michael Holinstat
Ass. Prof. at University of Michigan Medical School; and Director Translation Research, Cereno

Dr. Gunnar Olsson
MD, PhD; SAB member, Cereno

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Cereno’s Commitment to Transforming Cardiovascular Disease Management

Sten R. Sörensen
Chief Executive Officer (CEO), Cereno

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Most deaths worldwide are caused by cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels.

22.2 million people

are expected to die annually due to CVD by 2030.

80% of CVD deaths

are due to heart attacks and strokes.

WHY?

Most CVD complications happen because of thrombus formation – blood clots obstructing the cardiovascular system.

Existing treatment options are insufficient.

Sources: WHO Fact Sheet (link), European Heart Network (link), American Heart Association (link)

Cereno develops novel drugs to transform treatments for PAH and other cardiovascular diseases

Introducing epigenetic modulation through HDAC inhibition with disease modifying potential.

Lead program CS1 currently in US Phase II in PAH with strong rationale and supportive data – topline data expected end of 2022.

Pipeline portfolio:

CS1: Phase II HDACi, ODD in PAH

CS585: Preclinical Prostacyclin Receptor Agonist

CS014: Preclinical HDACi

Cereno's global presence

HQ: Gothenburg, Sweden

US subsidiary: Boston, MA

CS1 Clinical Phase II: 10 centers in the US in collaboration with Abbott

Preclinical R&D collaboration: University of Michigan, MI

Listed on Swedish Spotlight Stock Market since June 2016 (CRNO B)

Cereno's Scientific Advisory Board are top thought leaders in the field of CVD

Dr. Bertram Pitt
Chair of Board
Prof Em in Medicine, University of Michigan School of Medicine

Dr. Raymond L. Benza
Professor of Medicine, Wexner Medical Center,
Ohio State University

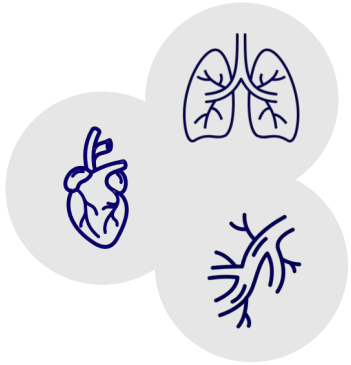
Dr. Deepak Bhatt
Prof of Medicine, Harvard Medical School

Dr. Gunnar Olsson
MD, PhD in Medical Sciences, Karolinska Institute

Dr. Gordon Williams
Prof of Medicine, Harvard Medical School

Dr. Faiez Zannad
Prof of Therapeutics and Cardiology, Université de Lorraine

Promising programs with potential to transform the CVD treatment landscape



Program	Indication	Discovery	Preclinical	Phase I	Phase II	Phase III	Next milestone
CS1	PAH	HDACi with epigenetic effects					Phase II top-line data: Q1, 2023
CS014	CVD	HDACi with epigenetic effects					Phase I IND submission: 2023
CS585	CVD	Prostacyclin receptor agonist					Phase I IND submission: 2023

HDACi = Histone deacetylase inhibitor

Growing and strengthening our management team with expertise for next stage

Sten R. Sörensen
Chief Executive Officer

Daniel Brodén
Chief Financial Officer

Björn Dahlöf
Chief Medical Officer

Nick Oakes
Head of Preclinical Development

Niklas Bergh
Chief Scientific Officer

Fredrik Frick
Head of Clinical Operations

Michael Holinstat
Director Translation Research

Jonas Faijerson Säljö
Chief Intellectual Property Officer

Merck $11.5 billion acquisition of Acceleron – highlights attractiveness of promising PAH pipeline drugs

- Merck acquired Acceleron Pharma Inc., with **sotatercept as the key asset, for approximately $11.5 billion** in November 2021
- Acceleron had just started Phase III in PAH, composition of matter patent expiring 2026, protected by extensions and ODDs.
- Shows the attractiveness of new drugs with promising characteristics such as Cereno's from big pharma companies' perspective.


MERCK

Media > News releases > News release

Merck Completes Acquisition of Acceleron Pharma Inc.

BARRON'S

Topics Stock Picks Magazine Data Advisor Penta 100 Years

BIOTECH AND PHARMA

Merck Closes Biggest Biotech Deal of the Year

By Josh Nathan-Kazis Follow Nov. 22, 2021 9:29 am ET Order Reprints Print Article

Leaving a mark in the medical community through abstracts accepted at top congresses

June 9-12, 2022

CS585 is a first-in-class compound targeting the IP receptor for prevention of thrombosis without increased risk of bleeding
S. Lambert, R. Adili, P. Yalavarthi, N. Rhoads, B. Dahlöf, A. White, N. Bergh, M. Holinstat

- Presented by M. Holinstat

June, 22-26 2022

Investigation of efficacy, safety and optimal dose of CS1 in subjects with pulmonary arterial hypertension: a prospective, randomized, multicenter, parallel-group phase II study
R. Benza, N. Bergh, P. Adamson, B. Dahlöf

- Presented by R. Benza

August 26-29, 2022

CS014 is a novel HDAC inhibitor regulating platelet activity, fibrinolysis and clot stability for prevention of thrombosis without increased risk of bleeding
M. Holinstat, R. Adili, L. Stanger, T. Hoang, S. Lambert, N. Rhoads, B. Dahlöf, N. Bergh

- Presented by M. Holinstat

Cereno Scientific

Overview of Cardiovascular Disease and Cereno's Focus Areas

Björn Dahlöf, MD, PhD, FESC, FACC
Chief Medical Officer (CMO) & Board member, Cereno

The cardiovascular (CV) epidemic has rapidly grown in recent years

It all started with a ”big bang”

13.8 billion years ago

Man appeared

200,000 years ago

Cardiovascular disease of epidemic proportions appeared

–100 years ago

Now no. 1 killer in the world

2020 ->

More than **200 million** people in the world today are at high risk of having a cardiovascular event

”Previously we used to work ourselves to death, today we rest ourselves to death while eating easily available food”

Inactivity = Smoking

Most deaths worldwide are caused by cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels.

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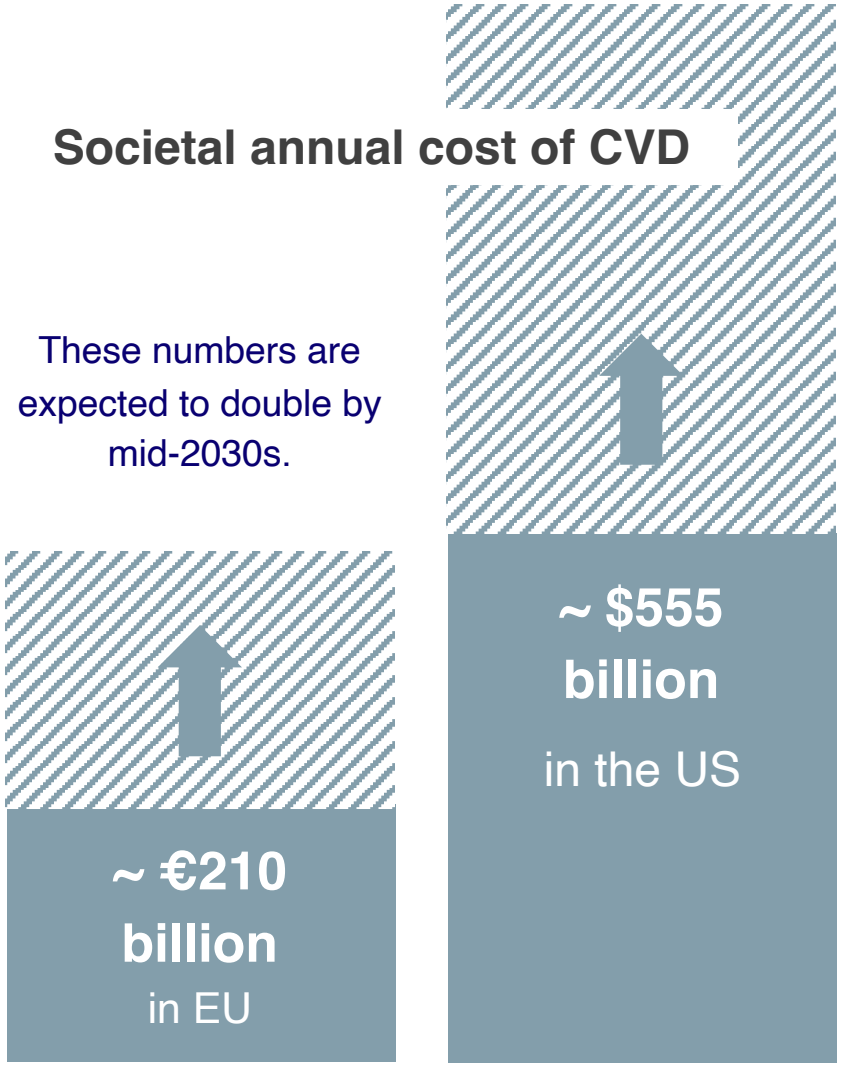
Sources: WHO Fact Sheet (link), European Heart Network (link), American Heart Association (link)

Cardiovascular disease equals exorbitant costs for patients, their families and society

- **Common and rare CVDs result in significant markets** due to their mortality threat and adverse effect on the quality of life of patients
- The **global anti-thrombotic drug market** is estimated to grow on average **7.5%** per year, resulting in a **$43.4 billion** market by **2025.**
- **$USD 11.7 billion** is the estimated global market size in 2027 for rare disease PAH – a Cereno target indication
  - **6.2%** is the estimated market increase for 2021–2027.
  - Growth is expected to be driven by increasing prevalence rates as well as government support for development of orphan drugs.



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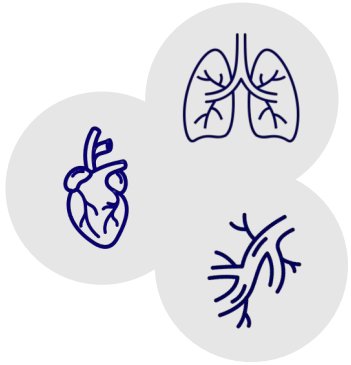
Sources: European Heart Network (link), American Heart Association (link) – 2017 data, Epigenetic Modulation for Cardiovascular Disease. Infogence Global Research (2021) “Global Pulmonary Arterial Hypertension (2021-2027)”, MSC Nordics analysis.

Cereno's promising programs has potential to transform the CVD treatment landscape



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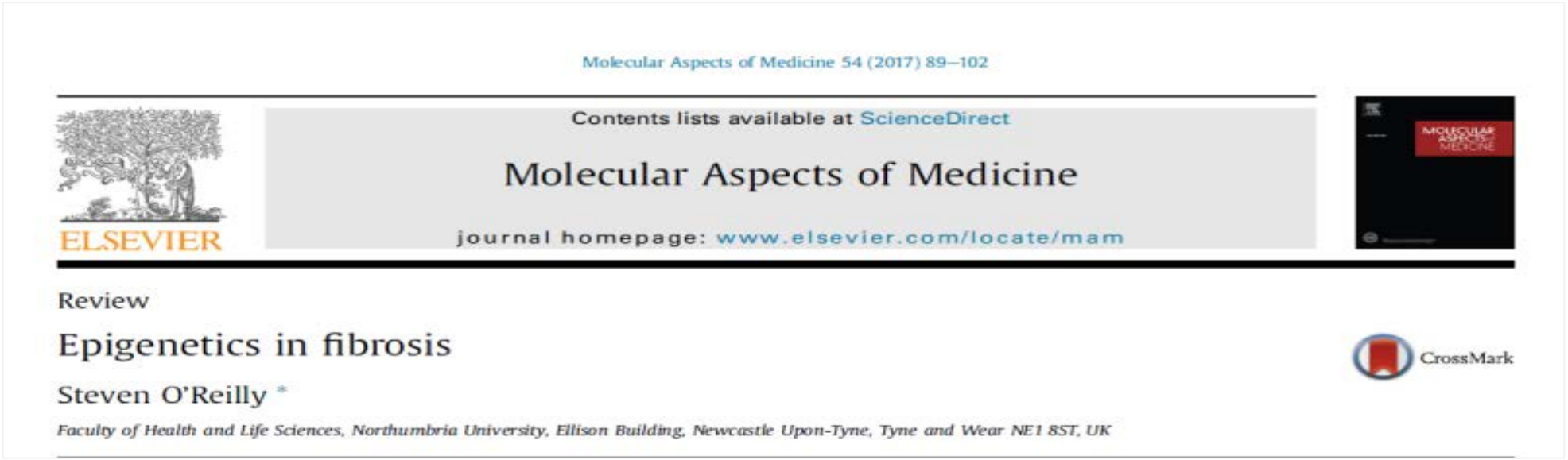


Molecular Aspects of Medicine 54 (2017) 89–102

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Epigenetics in fibrosis

Steven O'Reilly *

Faculty of Health and Life Sciences, Northumbria University, Ellison Building, Newcastle Upon-Tyne, Tyne and Wear NE1 8ST, UK

"Genetics clearly plays a role in disease, but **epigenetics may be the missing link** between the environment and the transcriptional responses and could explain why some individuals develop CV disease while others do not"

HHS Public Access
Author manuscript
J Am Coll Cardiol. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:
J Am Coll Cardiol. 2017 August 01; 70(5): 590–606. doi:10.1016/j.jacc.2017.05.067.

Translational Perspective on Epigenetics in Cardiovascular Disease

Pim van der Harst, MD, PhD[a,b,c], **Leon J. de Windt, PhD**[d], and **John C. Chambers, MD, PhD**[e,f]

[a]University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, The Netherlands [b]University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands [c]Durrer Center for Cardiovascular Research, Netherlands Heart Institute, Utrecht, The Netherlands [d]Department of Cardiology, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands [e]Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom [f]Ealing Hospital NHS Trust, Middlesex, United Kingdom

Abstract

A plethora of environmental and behavioral factors interact, resulting in changes in gene expression and providing a basis for the development and progression of cardiovascular diseases. Heterogeneity in gene expression responses among cells and individuals involves epigenetic mechanisms. Advancing technology allowing genome-scale interrogation of epigenetic marks provides a rapidly-expanding view of the complexity and diversity of the epigenome. In this review, we discuss the expanding landscape of epigenetic modifications and highlight their importance for our future understanding of disease. The epigenome provides a mechanistic link between environmental exposures and gene expression profiles ultimately leading to disease. We discuss the current evidence for transgenerational epigenetic inheritance and summarize the data linking epigenetics to cardiovascular disease. Furthermore, we review the potential targets provided by the epigenome for the development of future diagnostics, preventive strategies, and therapy for cardiovascular disease. Finally, we provide some suggestions for future directions.

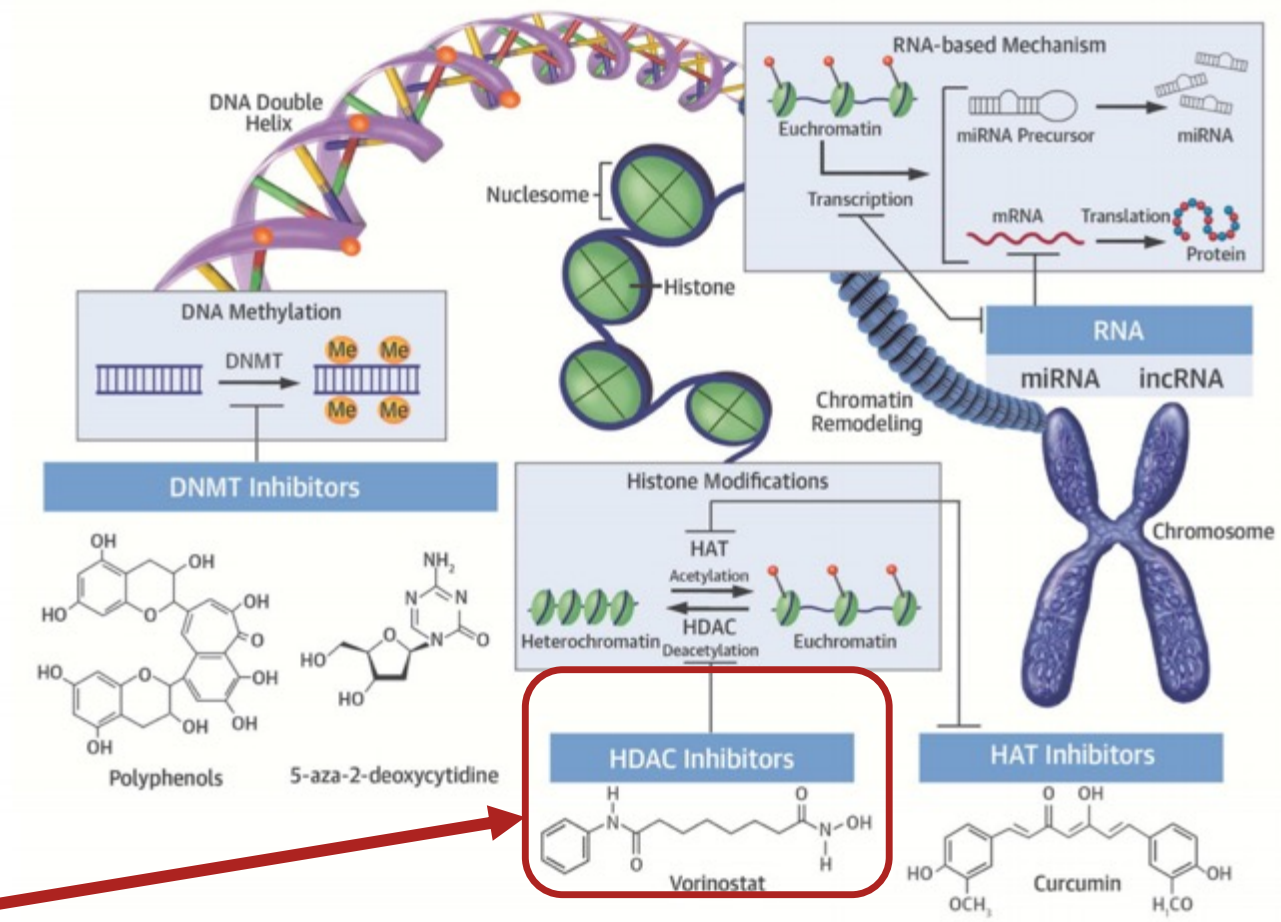


Figure. Potential Therapeutic Epigenetic Targets in Cardiovascular Disease Examples of targeting epigenetic mechanisms in CVD. *Possible targets include modifying DNA methylation, changing the acetylation or deacytylation of histones, and miRNA or lncRNA modificiations. DNMT = DNA methyltransferase; HAT = histone acetyltransferase; HDAC = histone deacetylase; lncRNA = long noncoding RNA; miRNA = microRNA.*

HDACi: Epigenetic modulation for cardiovascular disease

Review article in *The Lancet Healthy Longevity* supports the potential of epigenetic modulation via HDACi in CVD

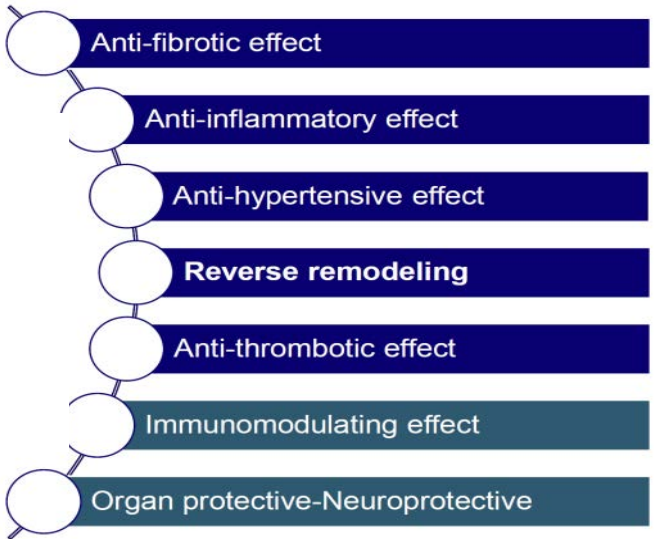
"Given the pleotropic properties of CS1's active substance being a HDACi with documented anti-thrombotic, anti-inflammatory, anti-fibrotic and pressure-reducing effects gives it a unique position to be developed for a variety of cardiovascular diseases with a disease-modifying potential."

Review article co-author and member of Cereno's SAB, Prof Faiez Zannad*

THE LANCET
Healthy Longevity

Histone deacetylase inhibitors for cardiovascular conditions and healthy longevity

João Pedro Ferreira, Bertram Pitt, Faiez Zannad



Strong potential in cardiovascular prevention

Myocardial infarction Heart failure

PAH Stroke PAD VTE

Atrial fibrillation Arterial hypertension

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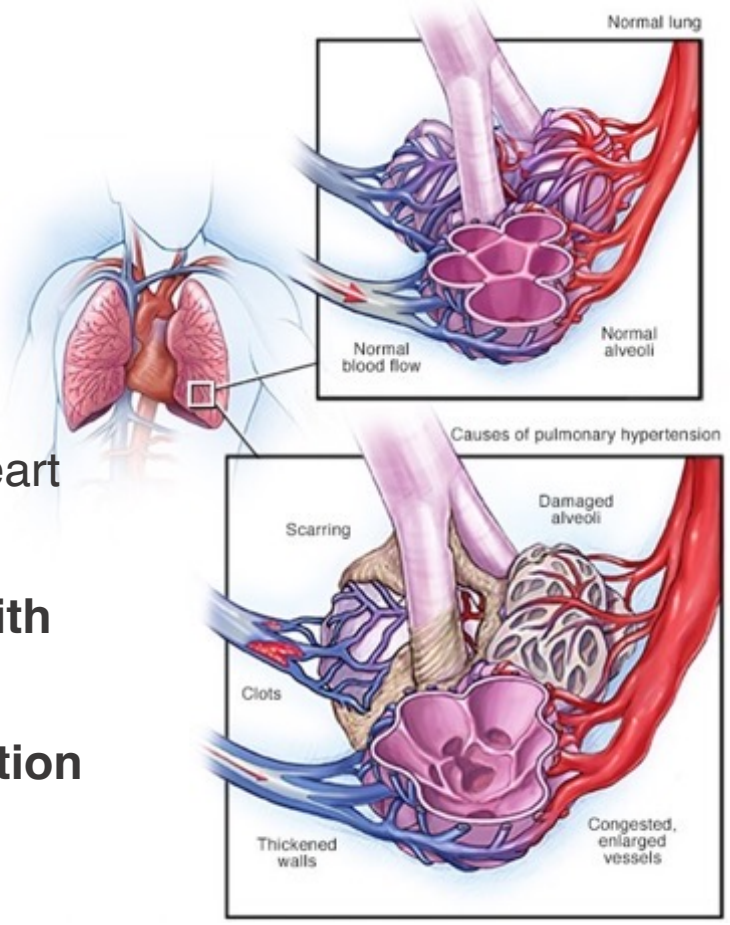
Source: Ferreira JP, Pitt B, and Zannad F, Lancet Healthy Longev 2021;2,e371-379 doi
*BioStock. Cereno Scientific drives a paradigm shift in CVD. June 11, 2021

Pulmonary arterial hypertension is a disease with poor prognosis and unsatisfactory treatment today

Pulmonary arterial hypertension (PAH) is a type of pulmonary hypertension, high blood pressure in the lungs

- A rare fatal **pulmonary vascular disease** with 5-15 / 100,000 people affected.
- **Patients experience** shortness of breath, fatigue, chest pain, edemas, fainting and heart palpitations.
- **Leads to problems** with oxygen supply and, ultimately, to fatal right heart failure.
- Today's therapy is insufficient, need for **disease-modifying therapy with reverse remodeling of the pulmonary vasculature and right heart**
- **HDACi has promise to disrupt therapy through epigenetic modulation**
- **Lung transplantation** is currently the only curative option, but many patients do not get it in time.



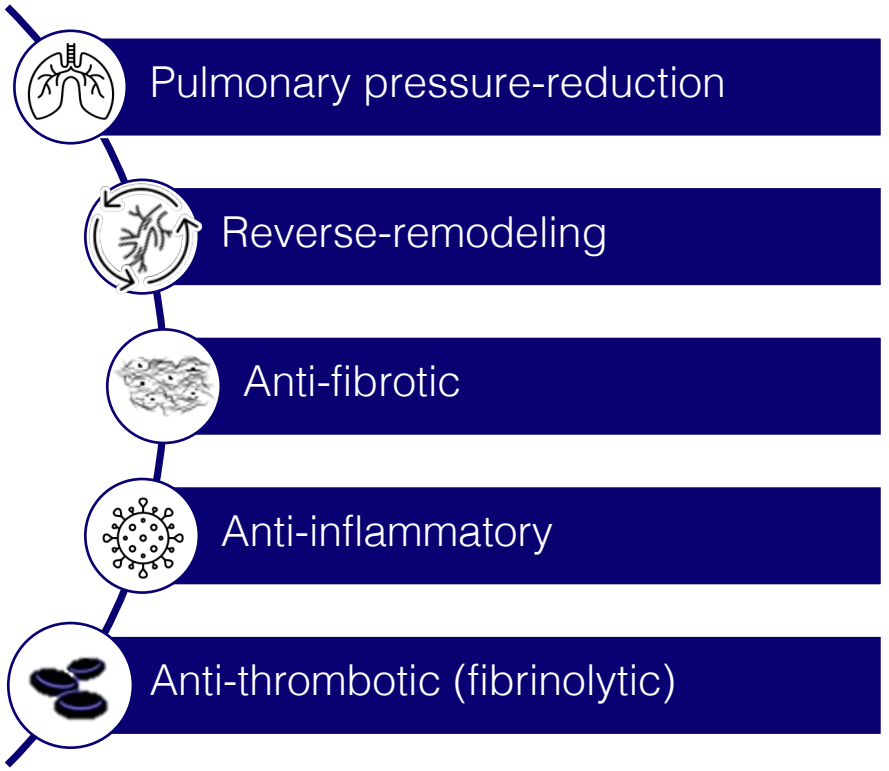
Sources: via Hibiscus BioVenture's analysis and image, MSC Nordics analysis

CS1 aims to offer an effective, safe and disease modifying treatment for PAH

CS1 is a new advanced reformulation and acts as an epigenetic modulator

- Proven good safety and tolerability in Phase I study.
- CS1's broad efficacy profile makes it a strong alternative to marketed and pipeline PAH drugs due to **reverse remodeling**.
- CS1 could fill the significant need for more efficacious and safer therapies with a **disease modifying potential** to improve survival and quality of life for PAH patients.*

CS1's multi-fold efficacy, all relevant for PAH



*Currently in Phase II development.

Towards personalized anti-thrombotic therapy

- There are many different potential uses of anti-thrombotic treatment as depicted A-L in the illustration to the right.

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 940–958
https://doi.org/10.1093/eurheartj/ehab642

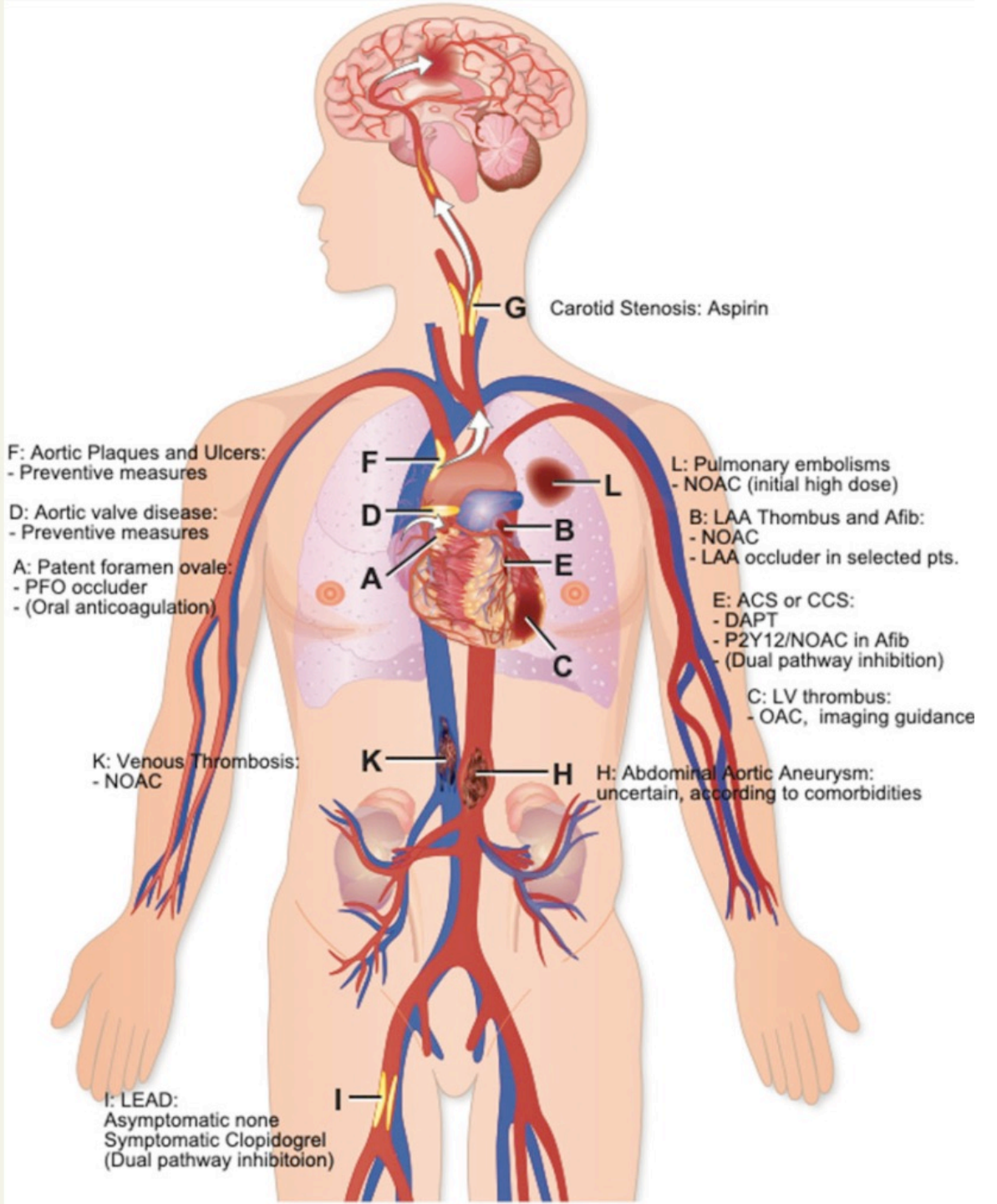
STATE OF THE ART REVIEW
Arrhythmias

Towards personalized antithrombotic management with drugs and devices across the cardiovascular spectrum

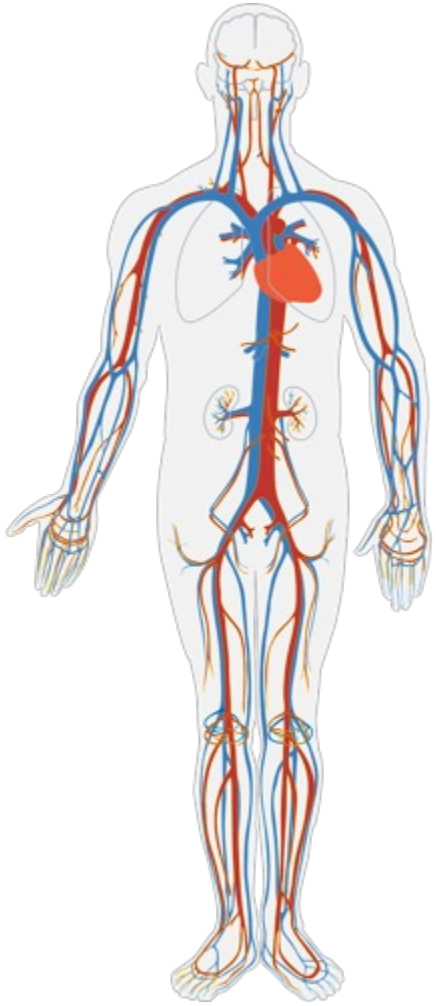
Thomas F. Lüscher [1,2]*, Allan Davies[1], Juerg H. Beer[2], Marco Valgimigli [3,4], Christoph A. Nienaber [1], John A. Camm[5], Iris Baumgartner[6], Hans-Christoph Diener [7], and Stavros V. Konstantinides [8]

[1]Royal Brompton & Harefield Hospitals, Heart Division, Guy Scadding Building, Dovehouse Street, Imperial College, London SW3 6LY, UK; [2]Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland; [3]CardioCentro, Lugano, Switzerland; [4]University of Bern, Bern, Switzerland; [5]St. Georges University and Imperial College, London, UK; [6]Angiology, Inselspital Bern, Bern, Switzerland; [7]Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty of the University Duisburg-Essen, Duisburg-Essen, Germany; and [8]Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany

Received 4 November 2020; revised 6 May 2021; editorial decision 24 August 2021; accepted 1 September 2021; online publish-ahead-of-print 8 October 2021



Current anti-thrombosis/blood thinning treatment involves the risk of serious bleedings



Waran
Xarelto
Bayer
Trombyl
Brilique
AstraZeneca
Eliquis
Bristol-Myers Squibb
Persantin Depot
Plavix
SANOFI
Pradaxa
Boehringer Ingelheim
Efient
Lilly

Systemic inhibition of coagulation/platelet function

↘

Increased risk of bleeding
Insufficient preventive effect

↘

Need for new preventive strategies

Cereno will enter one of the largest pharmaceutical markets with a profile which will impact thrombosis management

	Warfarin	NOACs/ Antiplatelets	CS585	CS1, CS014
Dose monitoring not required	Required	✓	✓	✓
Anti-thrombotic efficacy	✓	✓	✓	✓
Lower risk of bleeding	Increased bleeding	Increased bleeding	✓	✓
Organ protection	Not documented	Not documented	Not documented	✓¤

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¤ and anti-fibrotic,reverse remodeling, anti-inflammatory, CV protective e,g, in MI and stroke, neuroprotective, reduction pulmonary pressure shown for VPA

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Understanding PAH: Debilitating Rare Disease

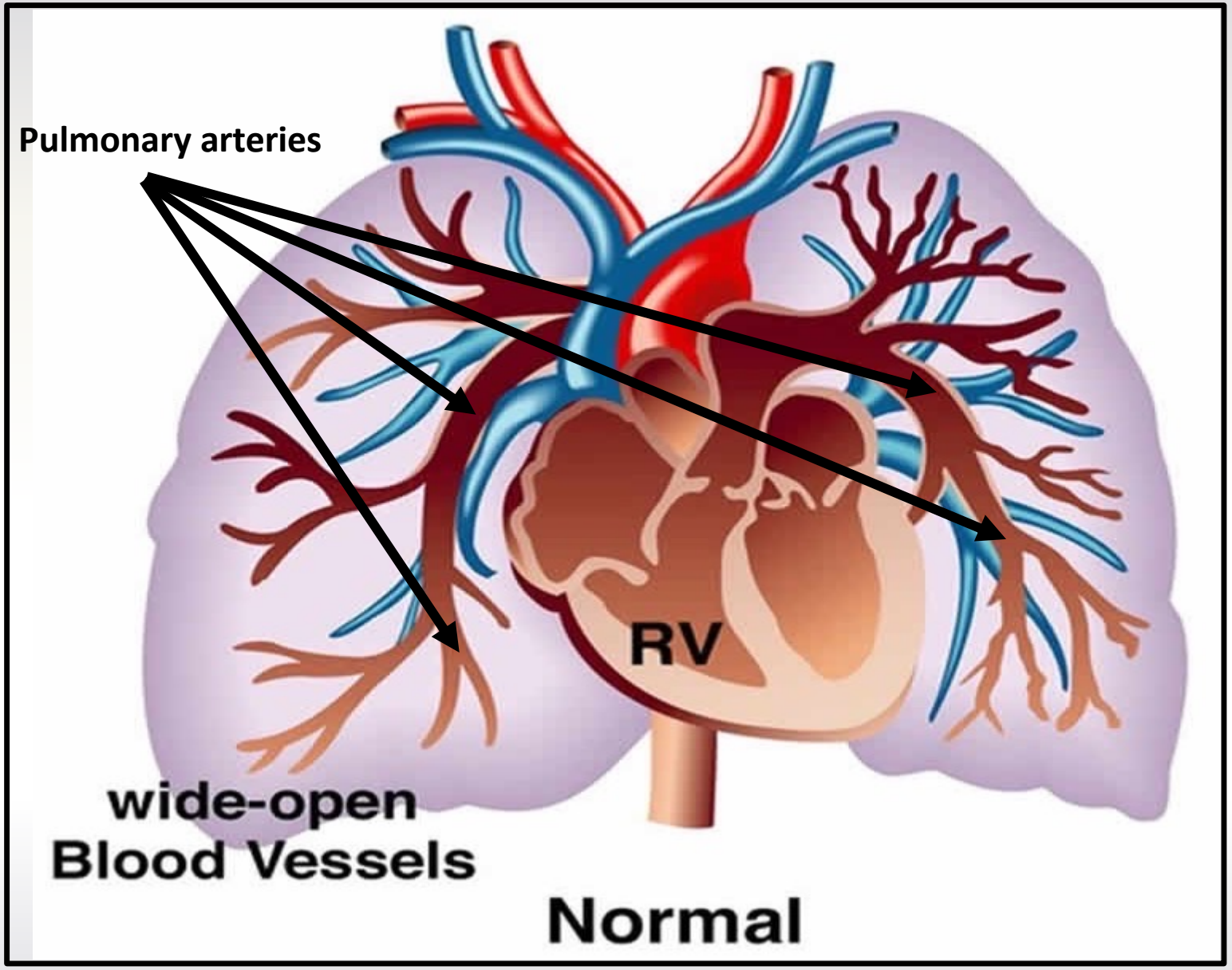
Dr. Raymond Benza
Prof. and Director at the Ohio State University Wexner Medical Center; PI of Phase II study with CS1

Pulmonary Hypertension; Focus on Pulmonary Arterial Hypertension

Raymond L. Benza, MD, FACC
Professor of Medicine
Division of Cardiovascular Diseases
Bob and Corrine Frick Endowed Chair of Heart Failure
Department of Medicine
The Ohio State University Wexner Medical Center

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Normal Human Circulation



Pulmonary Hypertension: High Pressure in the Pulmonary Arteries

Pulmonary hypertension= Mean PAP > 20 mmHg

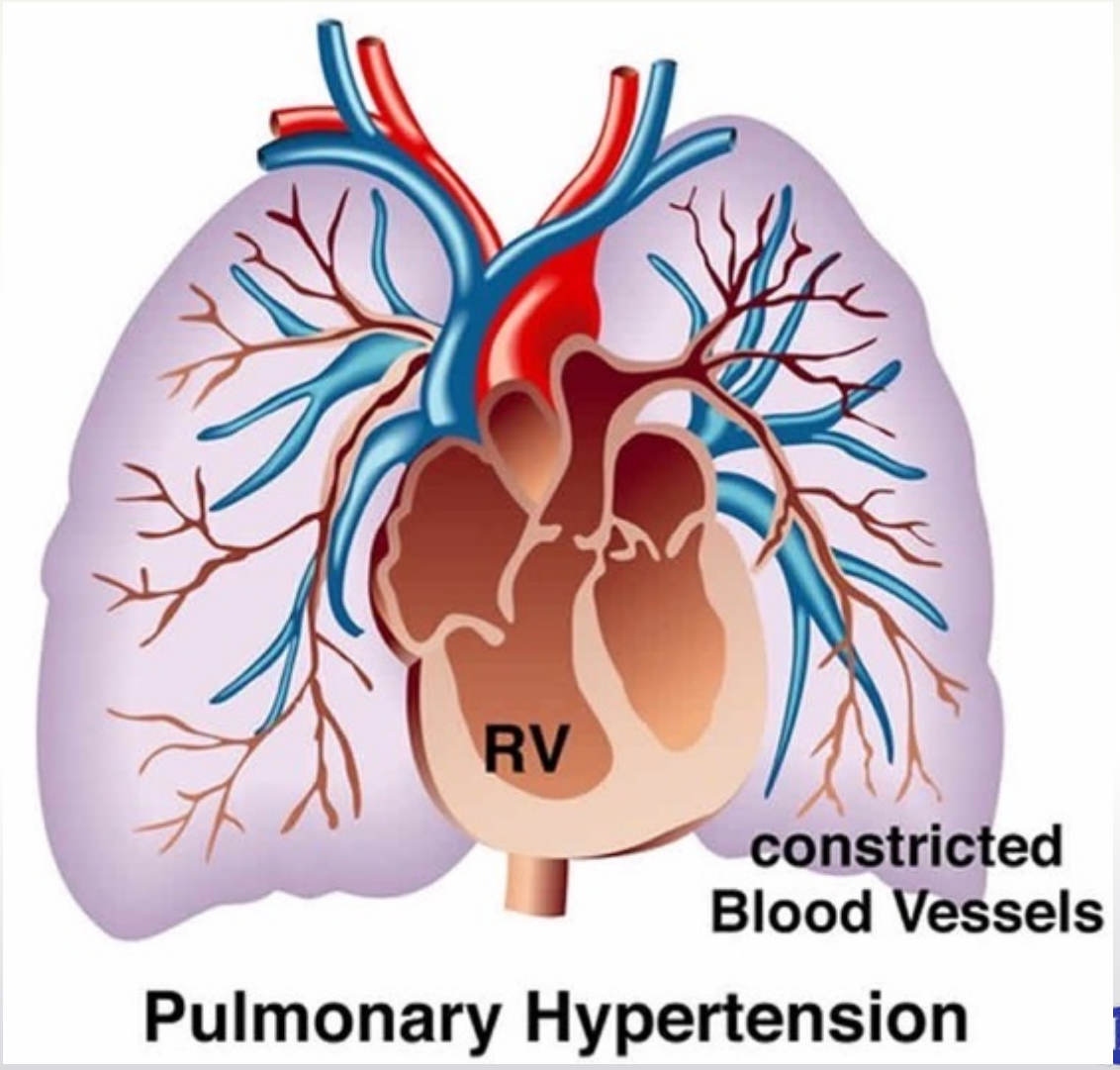
Normal mean pressure = 10-15 mmHg

- **Mild = Mean PAP 20-40 mmHg**
- **Mod = Mean PAP 41-55 mmHg**
- **Severe = Mean PAP > 55 mmHg**

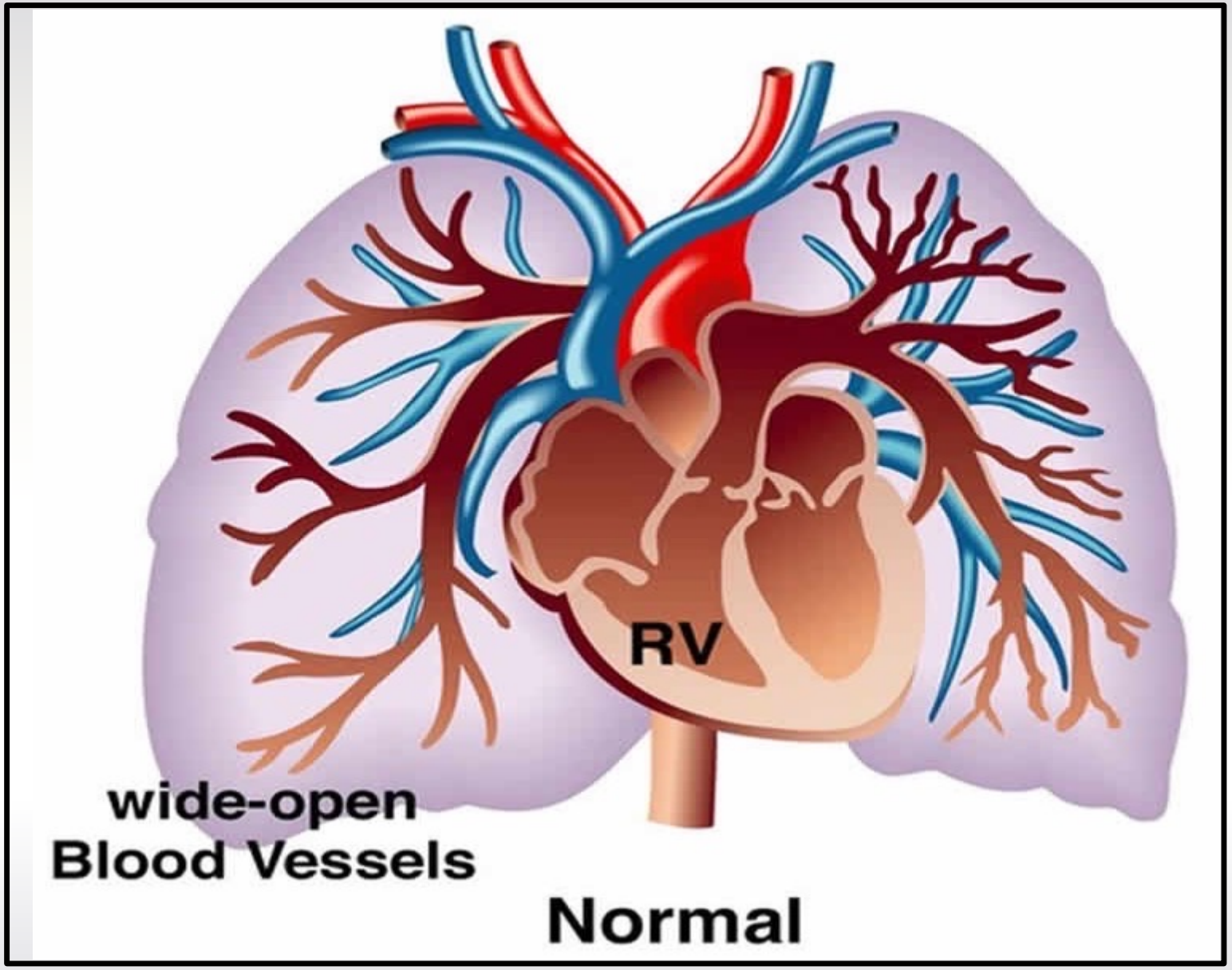
Galie N et al European Heart J 2004; 25:2243-78

Khan MG, Lynch JP III eds. Pulm. Dis. And Therapy. Baltimore: Williams and Wilkins 1997; 603-16

PHTN: A Disease of Lung Vessels and the Right Heart



Normal Human Circulation



Definition and Clinical Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension

2. Pulmonary hypertension due to left heart disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

4. Pulmonary hypertension due to pulmonary artery obstructions

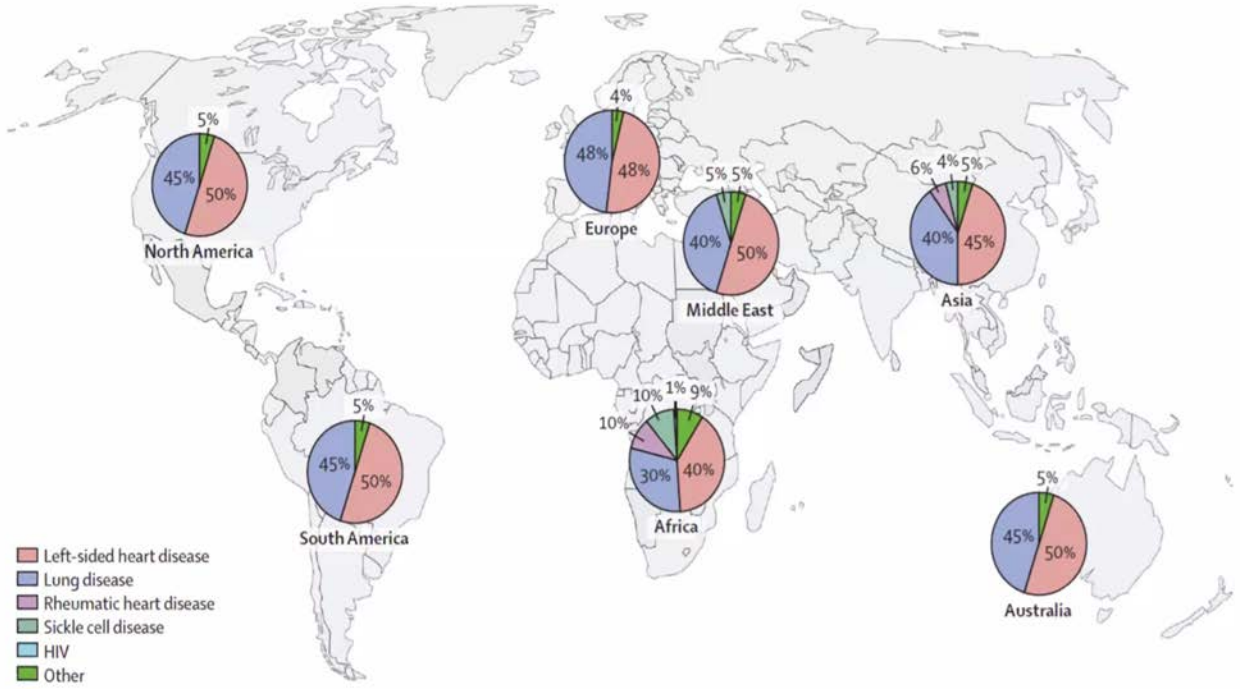
Simonneau, et al. *Eur Resp J 2019*
Hoeper MM et al. *J Am Coll Cardiol.* 2013;62:D42-D50.

PROBLEM

Global Burden of PHTN: It's a Pandemic!

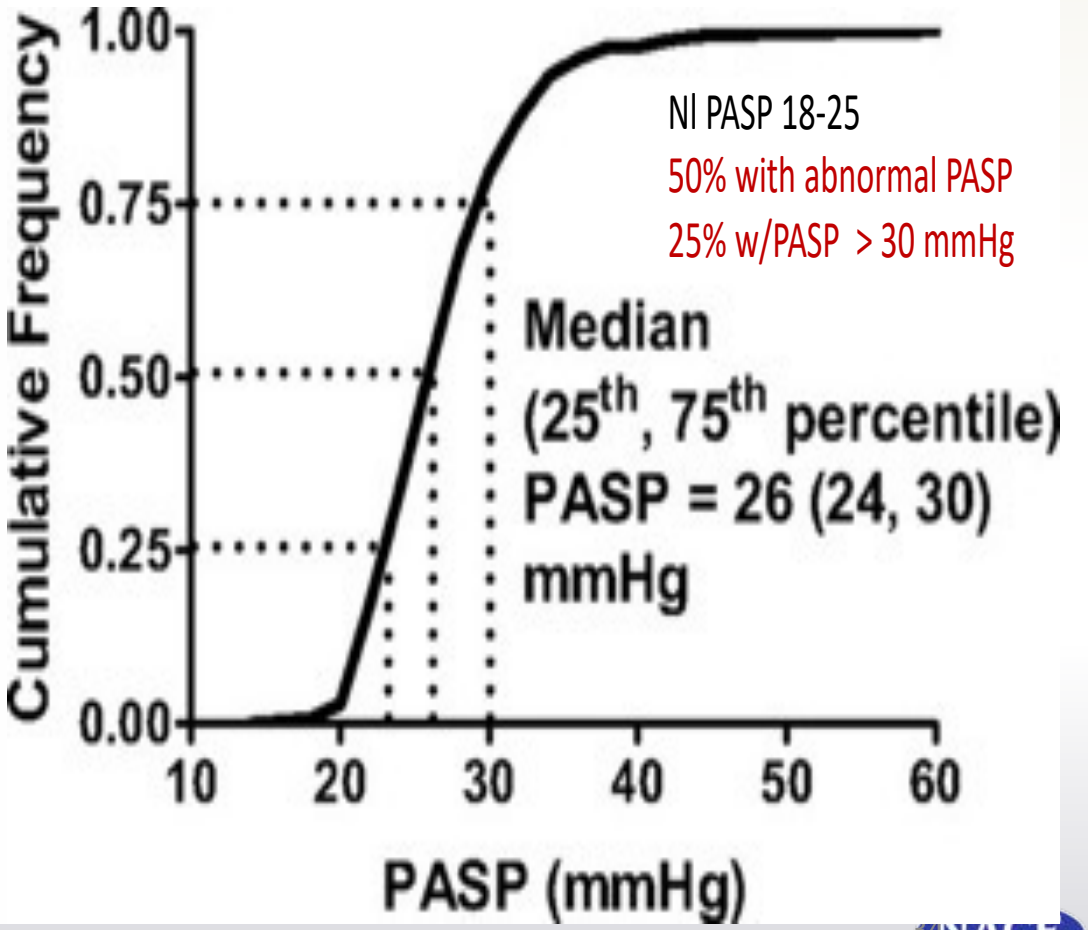
Estimated Global Distribution of Most Prevalent Forms of PH

- Estimated prevalence of PH: approximately 1% of the global population;78 million with some form of PH
- Increases up to 10% in individuals aged more than 65 years;780 million in those aged >650



Hoeper-MM et al. *Lancet Respir Med* 2016

PHTN in the Community



PROBLEM

- The Faces of Pulmonary Arterial hypertension: A progressive, chronic disease affecting primarily women (5:1) with a mean age of 50 y.o.

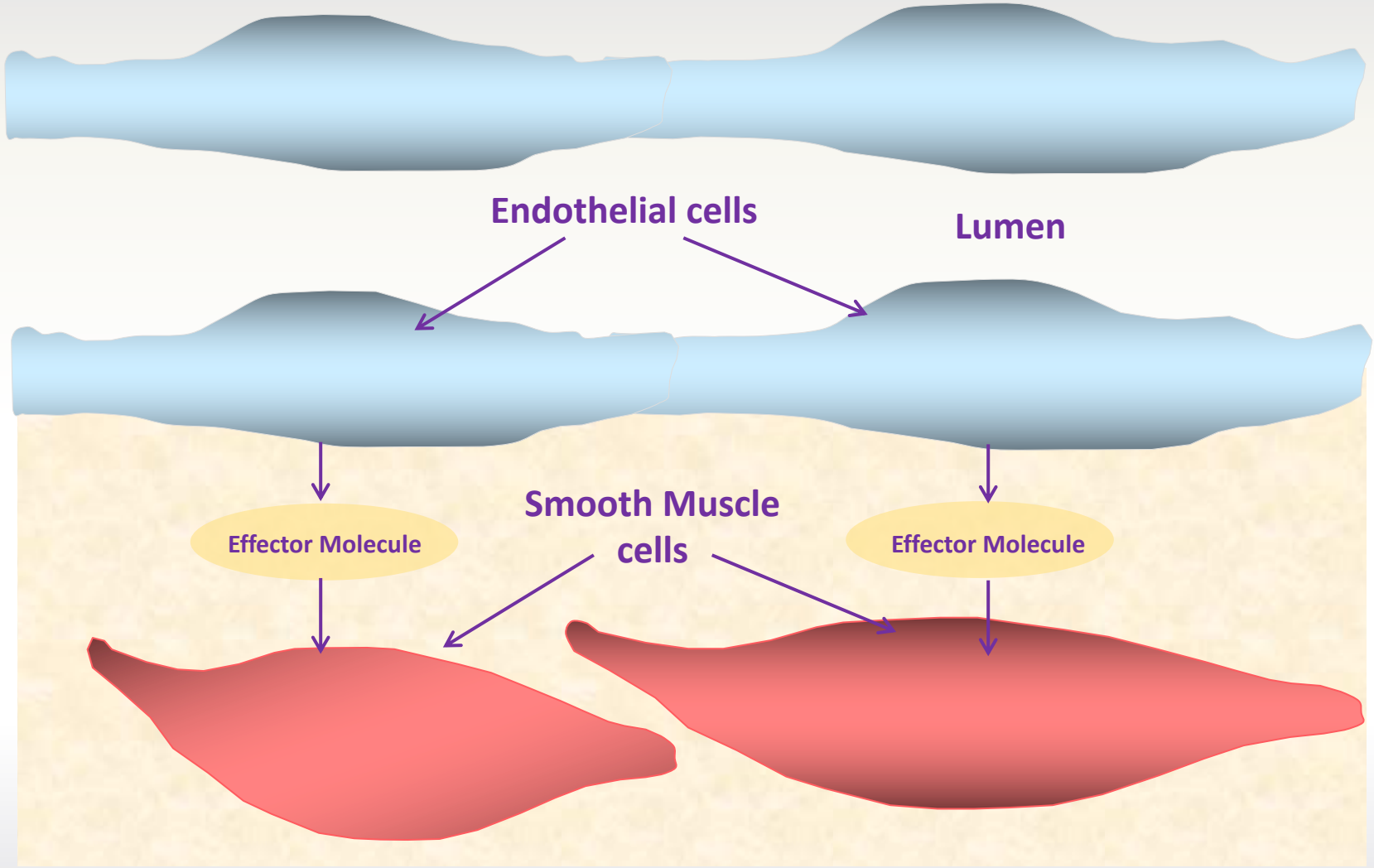
Five-Year Old Callie Inspires Parents to Fight for a PH Cure

How the Unknown Led to Certainty for PhD Student and PH Patient Raele Robison

Post-Transplant Life is Tough. But This Teen Feels Blessed

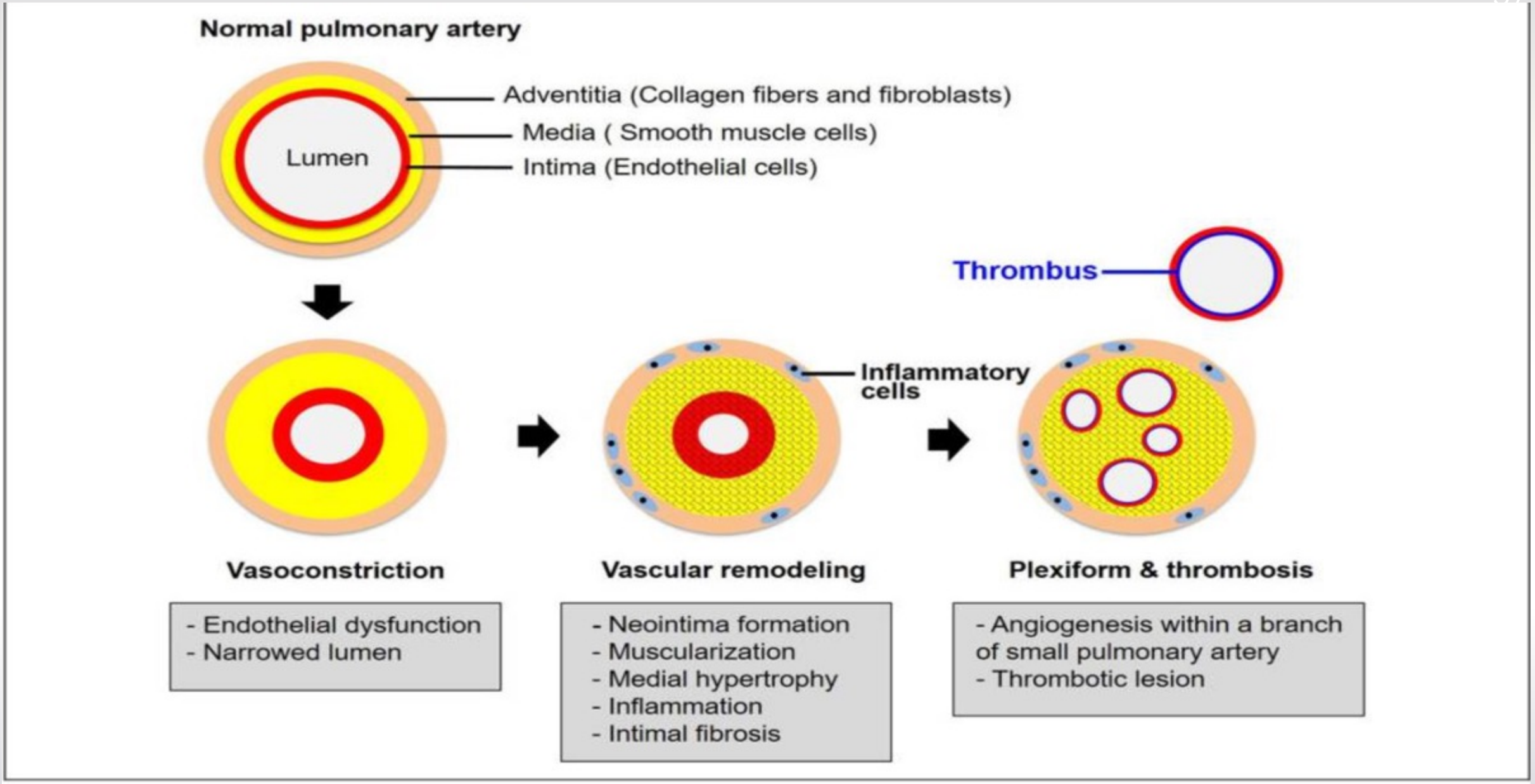
PH Changed Her Life. It Taught Her to Persevere

Pathology of Pulmonary Hypertension and PAH



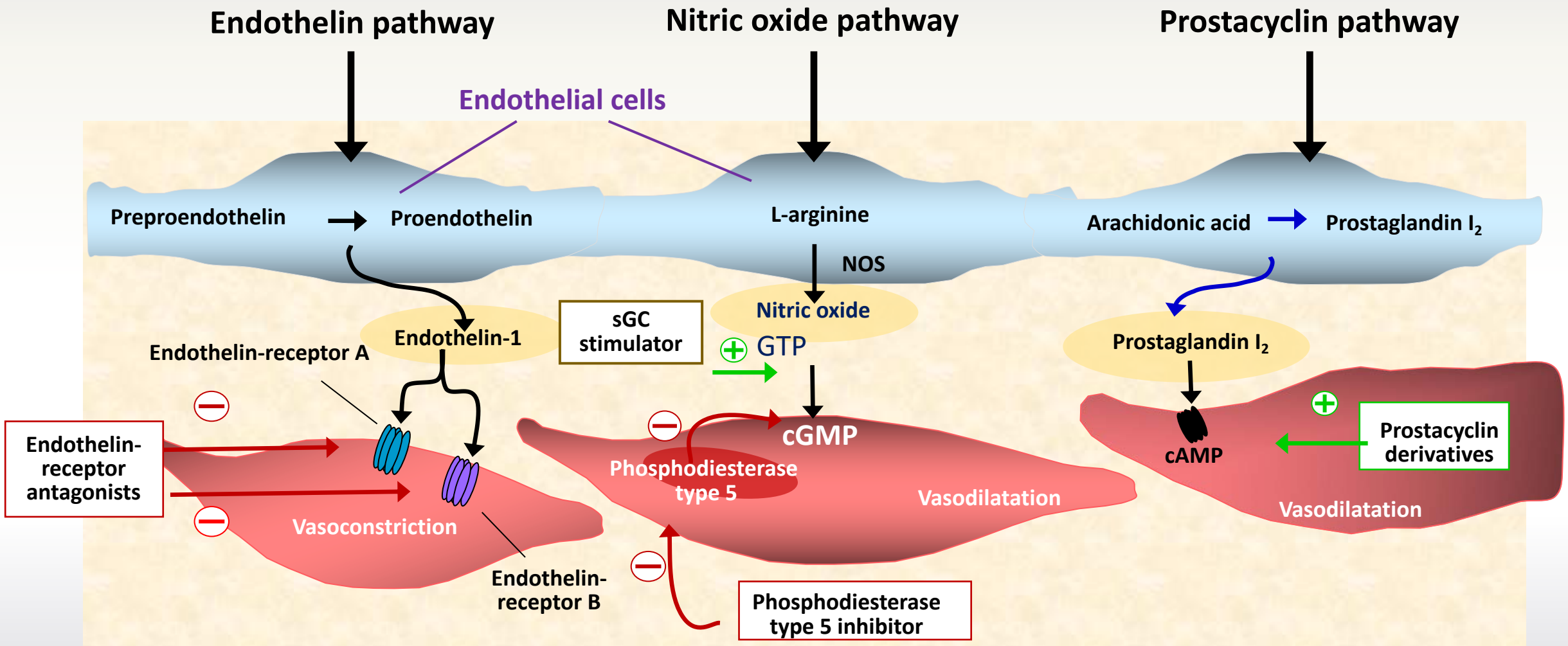
Adapted from: Humbert, et al. *N Engl J Med*. 2004;351:1425-1436.

Pathology of Pulmonary Hypertension and PAH



Woodcock ; J Cardiovasc Pharmacol Ther. 2019 Jul; 24(4): 334–354.

Three Most Cited Mechanisms of PAH

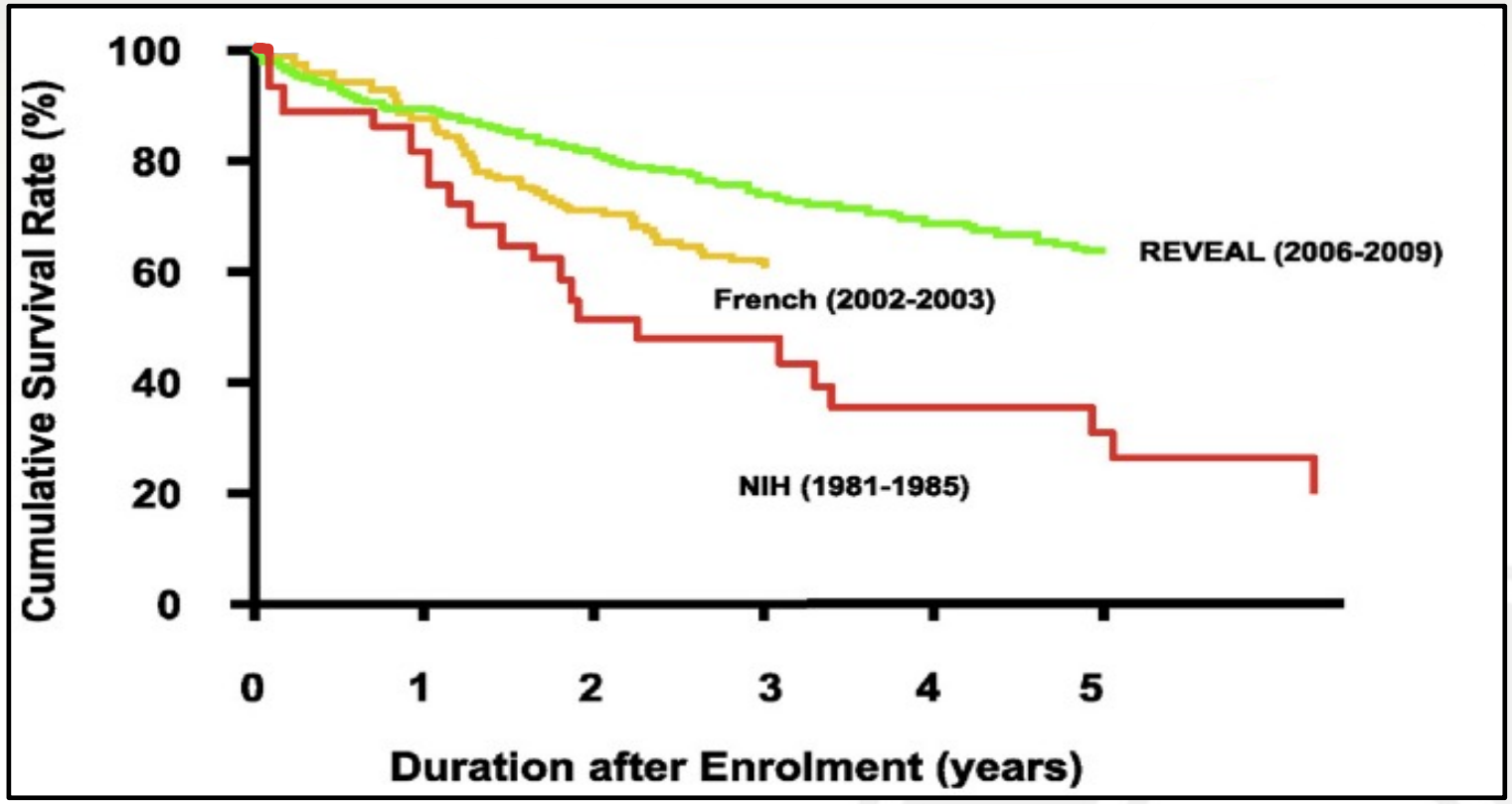


Adapted from: Humbert, et al. *N Engl J Med*. 2004;351:1425-1436.

Managing PAH

14 Pharmaceutical Therapies Implemented since 1991 yet Survival still Sub-Optimal

- Long-term data → observational registries
- Median survival has increased ~ 7 vs 3 years in the 80s
- Still, 7 year survival rate is unacceptable
- Morbid events now outrank mortal events and these predict future events (Mortal and Morbid)



Further changes in survival will be dependent on changes in management style (Risk based management), and new therapies that are “disease modifying”

How Does Risk Stratification Help us?

PAH – Deadly but unpredictable as to when and how

Short survival

- Sudden cardiac death
- Right heart failure

Who is the most vulnerable?

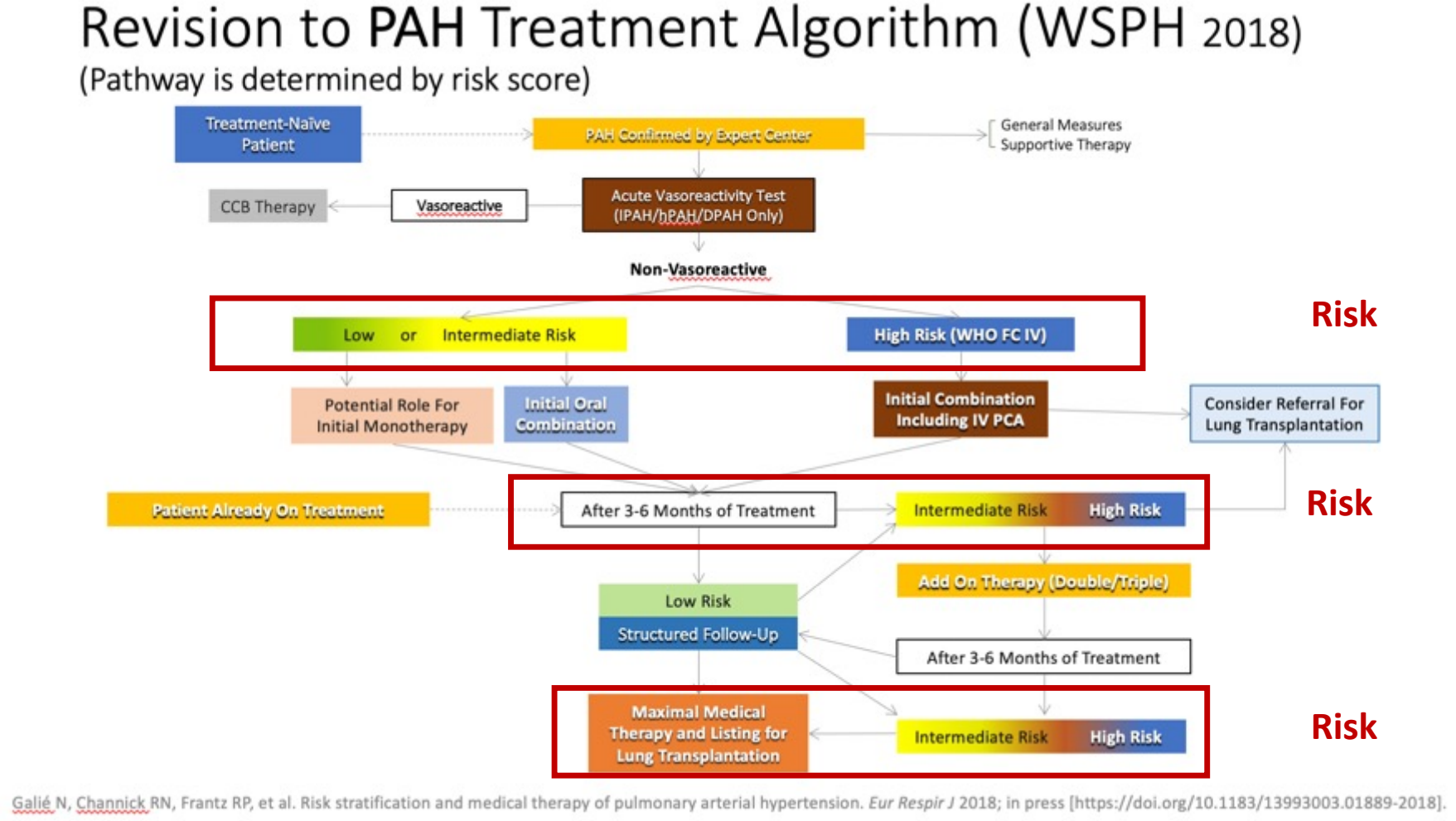
Acute exacerbation

- Sepsis
- Renal failure
- Arrythmia

Long survival, but chronic inadequate CO + venous congestion

- Systemic Organ Damage
- Systemic Inflammation
- Poor exercise capacity

Risk Stratification in PAH



Galié N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2018; in press [https://doi.org/10.1183/13993003.01889-2018].

We also Agree that “One test does not tell it all….We need the complete picture”

There is a need for a collective measurement tool to predict survival in the modern era of PAH therapy

Supplements Clinical Gestalt in experienced providers

Serves as a key decision tool for less experienced providers

REVEAL Risk Score Calculators

New risk calculator with better discrimination (CI 0.76)

Existing variables with revised weighting
- HR, POPH, NYHA

Existing variables with revised cut-off points
- PVR, DLCO

Existing variables with additional cut-off points
- BNP/NTproBNP, 6MWD

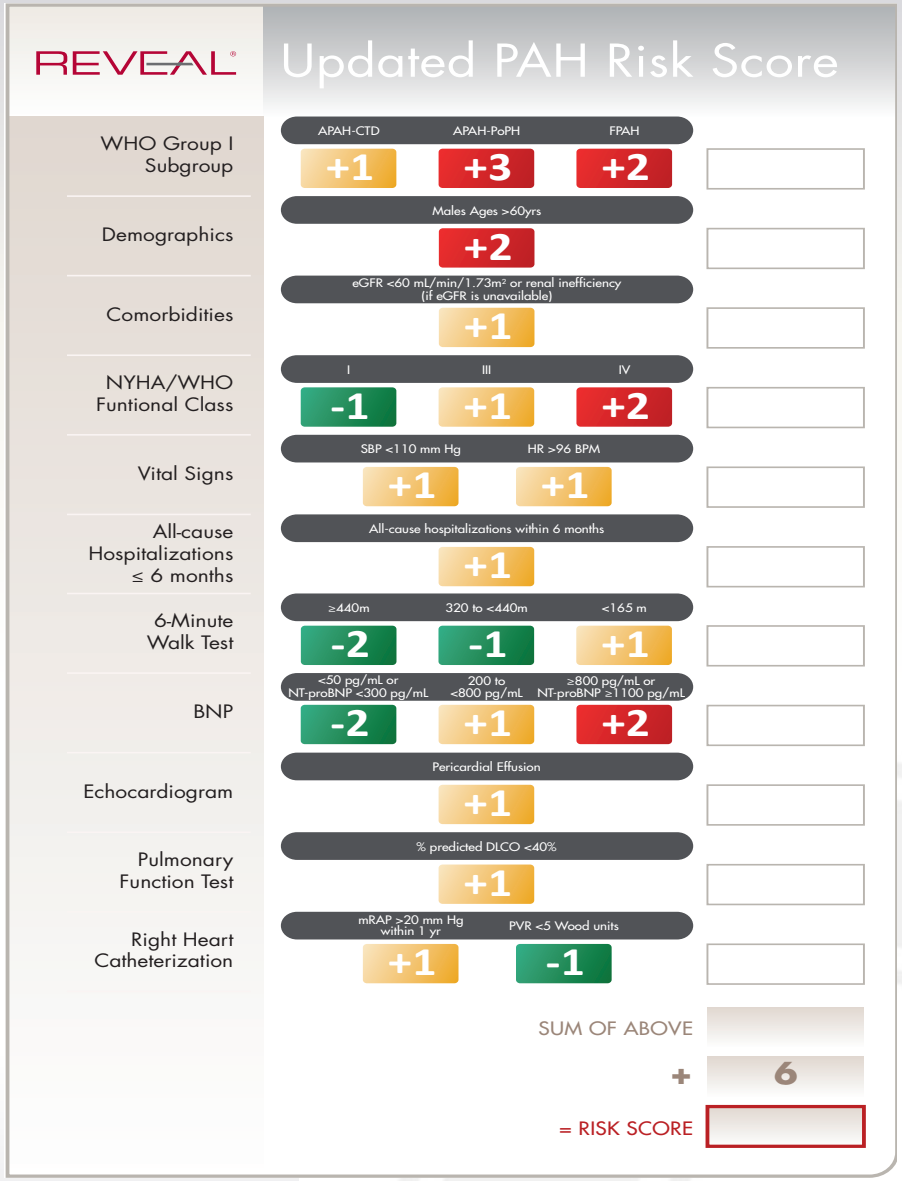
New variables based on current literature
- Hospitalizations within last 6 months, eGFR < 60 mL/min/1.73 m^2

More Versatile

More practical

Tighter Discrimination

Predicts Clinical Worsening in addition to Mortality



REVEAL is capable of offering three (categorial) or 8 (full score) lines of risk: better delineates level of intermediate and high risk

Benza R: Chest. 2019 Aug;156(2):323-337.

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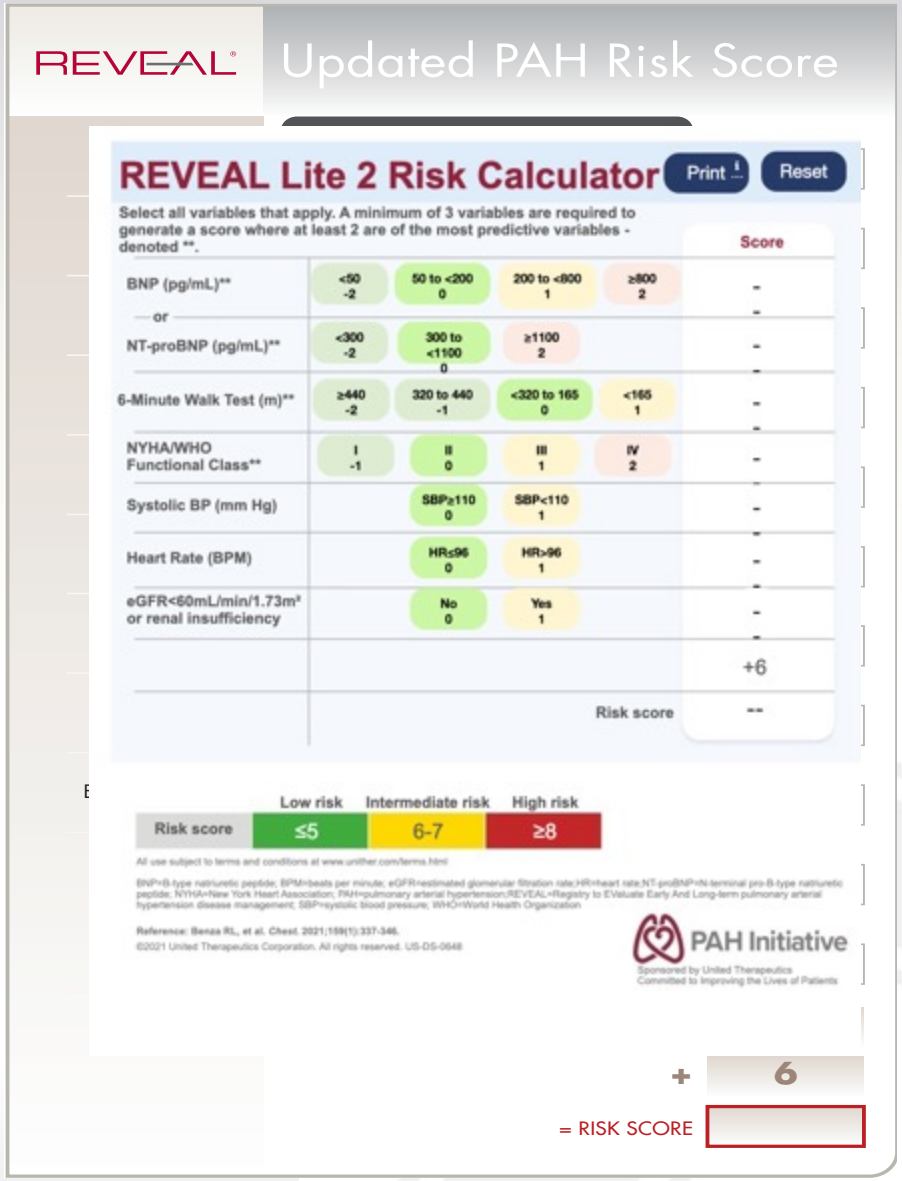

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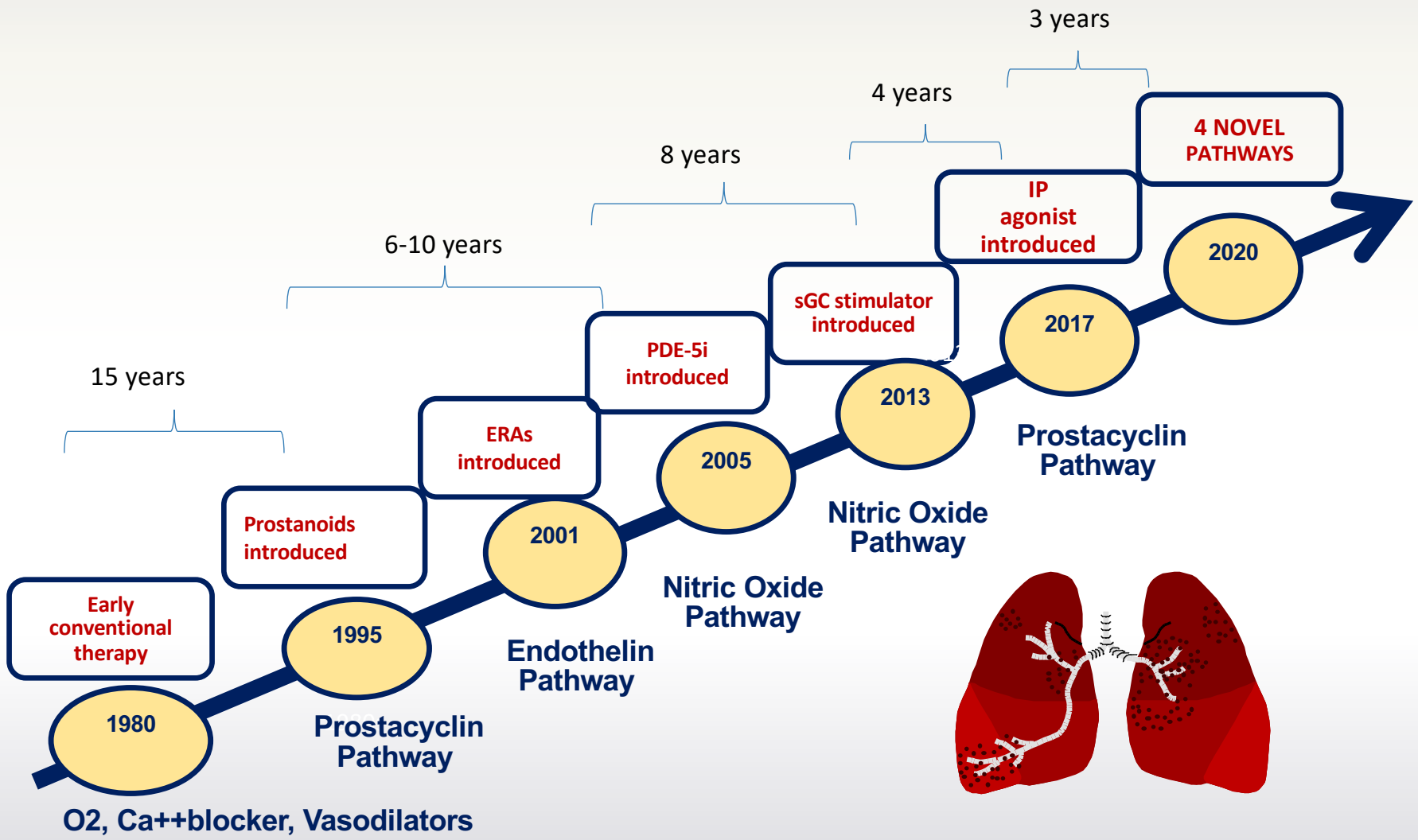
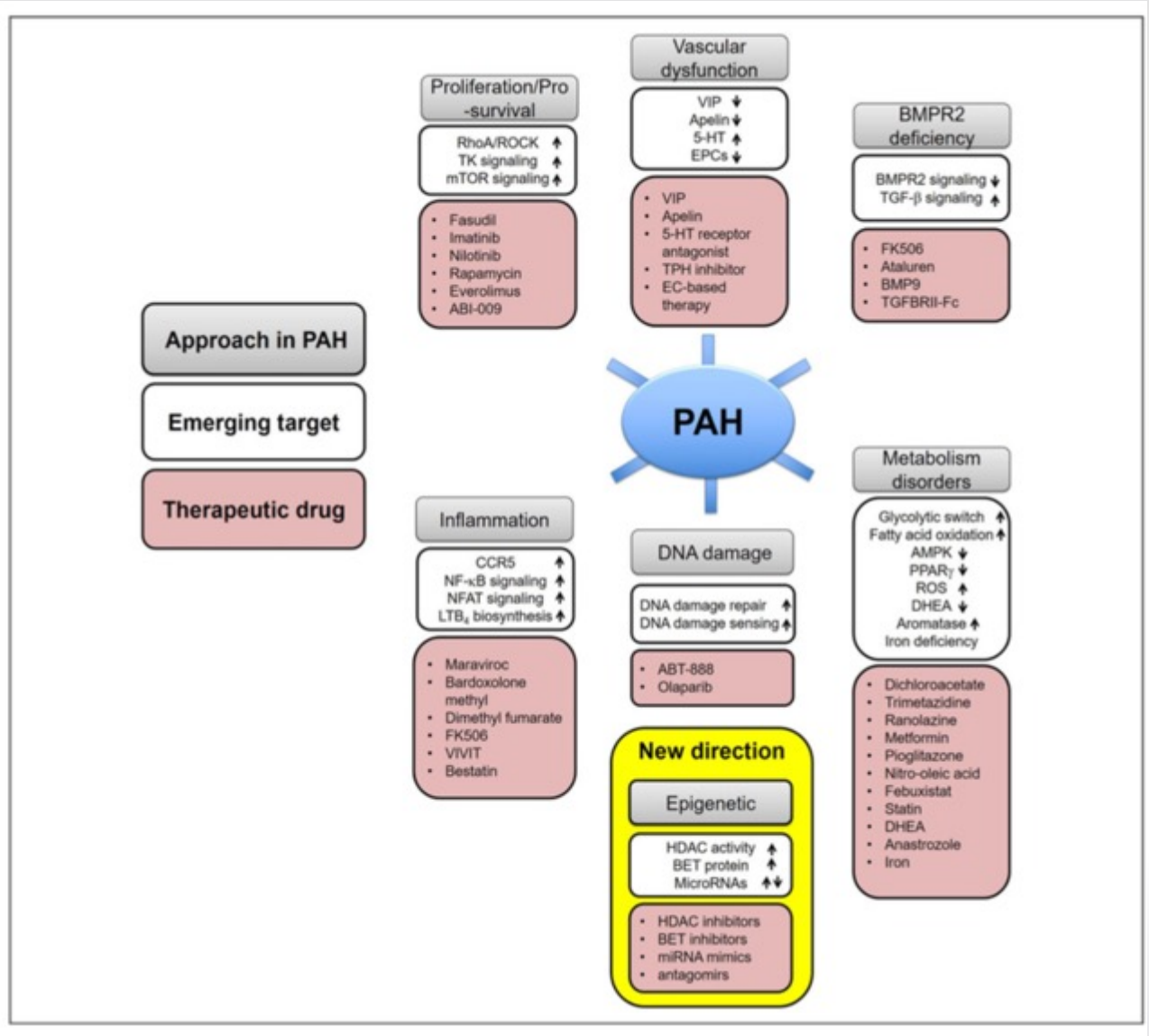
Benza R: Chest. 2019 Aug;156(2):323-337.

PAH Therapeutic Trials: We are Finally Catching up!



Agarwal R, Gomberg-Maitland M. *Am Heart J*. 2011;162(2):201-213. Galiè N. *J Am Coll Cardiol*. 2013;62(25 suppl D):D60-D72. Taichman D, et al. *Chest*. 2014;146(2):449-475.

New pathway Development and Clinical Trials



Clinical trials with drugs targeting metabolic dysfunction in pulmonary arterial hypertension

- **Metabolic syndrome: AMPK signalling and metformin**
- **Glycolysis: dichloroacetate**
- **Fatty acid oxidation: ranolazine and trimetazidine**

Clinical trials with drugs targeting inflammation in pulmonary arterial hypertension

- **Modulation of cytokines pathway: anakinra and tocilizumab**
- **Inflammation/Modulation of Nrf2 pathway/NF-κB pathway: bardoxolone methyl, ubenimex, CXA-10**

Clinical trials with drugs targeting other signalling pathways

- **Modulation of the estrogen pathway: anastrozole and fulvestrant**
- **Inhibiting PDGF signaling: Inhaled Iminitab, Seralutinib**
- **Augmenting BMR2 Signaling: Sotatercept**
- **Inhibiting peripheral Serotonin production: Rodatristat**
- **Improvement of oxygenation: acetazolamide**

Sitbon, O Eur Respir J. 2019 Jan; 53(1): 1801908.

Woodcock ; J Cardiovasc Pharmacol Ther. 2019 Jul; 24(4): 334–354.

New Pathway Development: Failed or Neutral Clinical Trials

Main recent clinical trials in pulmonary arterial hypertension with either negative result or tolerability/safety issues

Study/compound(s)	Phase	End-point: result	Formal presentation [ref.]	Published [ref.]
ASA-STAT: aspirin and simvastatin	2	6MWD: lack of efficacy	Yes	Yes [103]
ARROW: selonsertib (ASK-1 inhibitor)	2	6MWD: lack of efficacy	Yes [62]	No
Cicletanine (antihypertensive with vasorelaxant and diuretic properties)	2	PVR: lack of efficacy	Yes [104]	No
Aviptadil (vasoactive intestinal peptide)	2	PVR: lack of efficacy	Yes [105]	No
IMPRES: imatinib (tyrosine kinase inhibitor)	3	6MWD: positive tolerability and safety issues	Yes	Yes [45]
Terguride (partial dopamine agonist and serotonin receptor antagonist)	2	6MWD: lack of efficacy	Yes [68]	No
LIBERTY: ubenimex (leukotriene B4 inhibitor)	2	PVR: lack of efficacy	No	No

6MWD: 6-min walk distance; ASK1: apoptosis signal-regulating kinase 1; PVR: pulmonary vascular resistance.

Sitbon, O Eur Respir J. 2019 Jan; 53(1): 1801908.

New Pathways for Treating Pulmonary Arterial Hypertension

- Manipulating BMPR2
  - Sotatercept: PULSAR Study[1]
- Manipulating PDGF
  - Seralutinib: TORREY Study, a novel small molecule tyrosine kinase inhibitor for inhalation
  - Iminitab: AV-101-002 Study: Aerovate Therapeutics; Trials of AV-101, an inhaled, dry powder aerosol version of Novartis' cancer drug Gleevec (imatinib)
- Manipulating Serotonin: ELEVATE-2 Study: Altavant Sciences; rodatristat ethyl ("rodatristat") orally bioavailable, direct and reversible tryptophan hydroxylase (TPH) inhibitor designed to block peripheral serotonin production

[1]Humbert et al. N Engl J Med 2021

Role of CS1

- Anti-thrombotic activity (restoration of tissue-type plasminogen activator in pulmonary blood vessels and reduction of PAI-1)
- Anti-inflammatory activity
- Anti-fibrotic/remodeling activity
- Pulmonary pressure reduction

Role of CS1

- Anti-thrombotic activity (restoration of tissue-type plasminogen activator in pulmonary blood vessels and reduction of PAI-1)
- A Phase 2, **P**rospective, **R**andomized, **O**pen-label, **B**linded **E**ndpoint, Multicenter Study to Investigate Safety and Tolerability, PK and Exploratory Efficacy of 3 Doses of CS1 in Subjects with Pulmonary Arterial Hypertension
- Pulmonary pressure reduction

Cereno Scientific

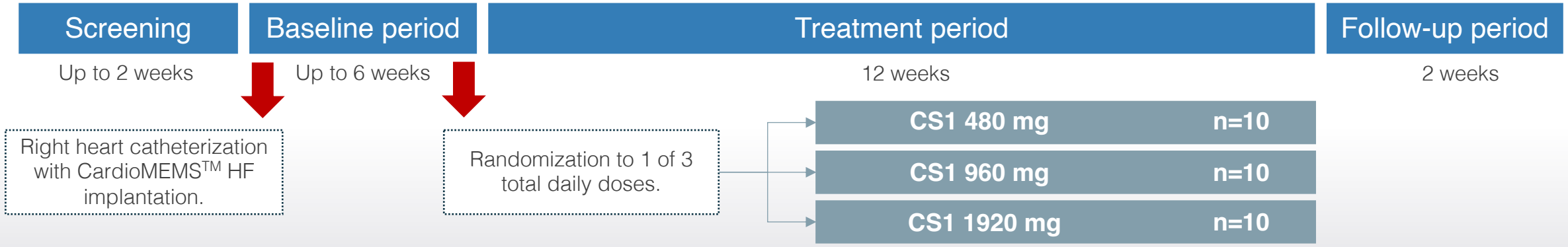
Clinical Phase II Study Design with CS1

Dr. Raymond Benza
Prof. and Director at the Ohio State University Wexner Medical Center; PI of Phase II study with CS1

CS1 Phase II study aims to evaluate safety, tolerability and exploratory efficacy

Phase II study of CS1 in patients with PAH

- Primary endpoint: Safety and tolerability.
- Other variables including all standard efficacy endpoints for this patient group (6MWT etc.), a calculated validated risk score, pharmacokinetics, and dose-finding based on mPAP changes.
- Abbott's CardioMEMS™ HF System technology for monitoring pulmonary pressure and pulmonary/RH hemodynamics.
- Includes 30 patients, at 10 different US clinical sites.
- Expected top-line results: Q1 2023.



The innovative Phase II study design was presented at top pulmonary congress

PVRI
Pulmonary Vascular Research Institute
June 22-26, 2022

Investigation of efficacy, safety and optimal dose of CS1 in subjects with pulmonary arterial hypertension: a prospective, randomized, multicenter, parallel-group phase II study

R. Benza, N. Bergh, P. Adamson, B. Dahlöf

- Presented by R. Benza

Phase II study: First patient has been randomized and entered the study's treatment period

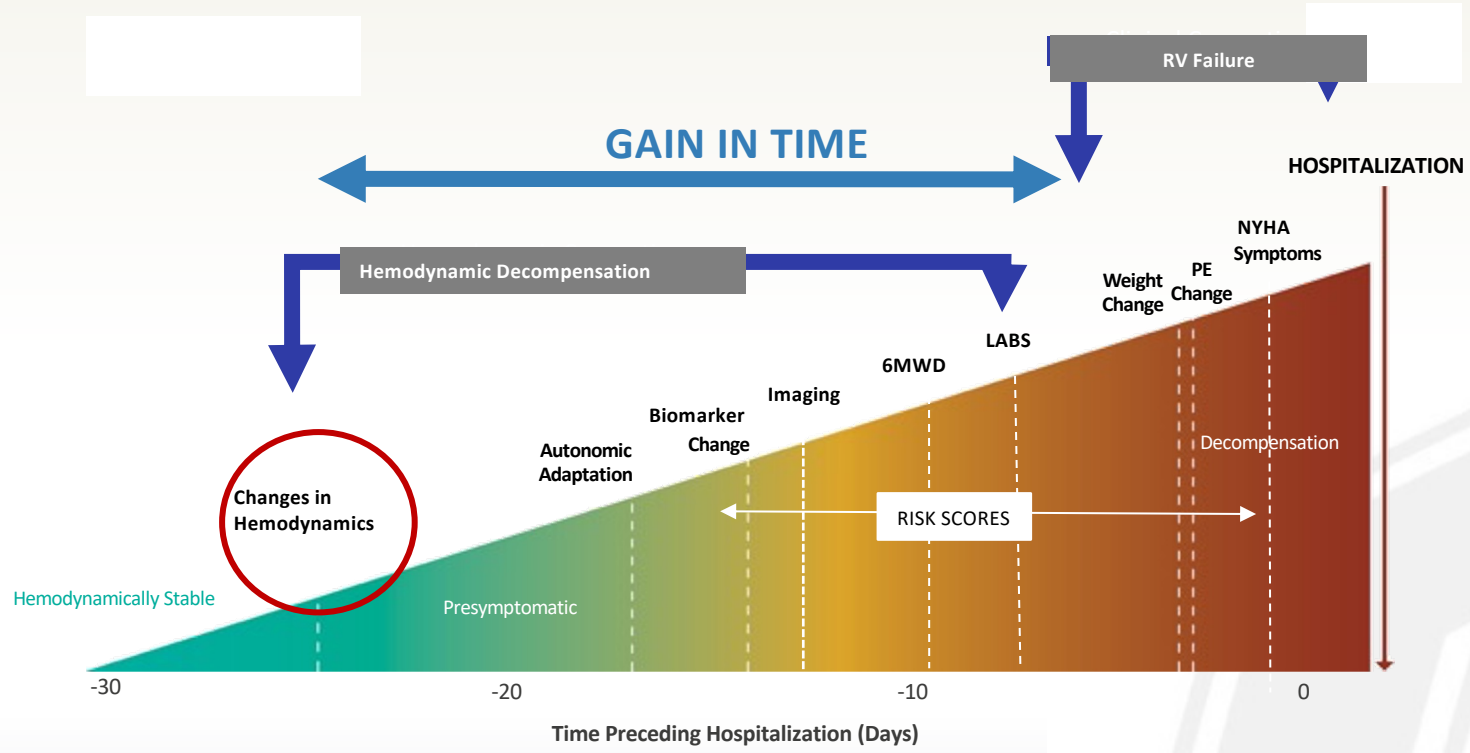
Update as of Aug 29

- First site activated: 14 Mar 2022
- First patient screened: 5 July 2022
- First patient randomized: 25 Aug 2022
- Activation of clinical sites is ongoing and will continue throughout early autumn
- Top-line results are expected Q1 2023

Phase 2 Study of CS1 in Subjects with Pulmonary Arterial Hypertension

- Novel Compound with Novel Actions
- Novel and Innovative Endpoints
  - REVEAL Risk Score
  - Cardiac MRI
  - CardioMEMs device
  - Novel biomarkers
- Traditional Endpoints (efficacy and safety)
  - 6MWD, hemodynamics, echo, biomarker

Archetypal Progression of Decompensation: Early and Remote Detection is Key



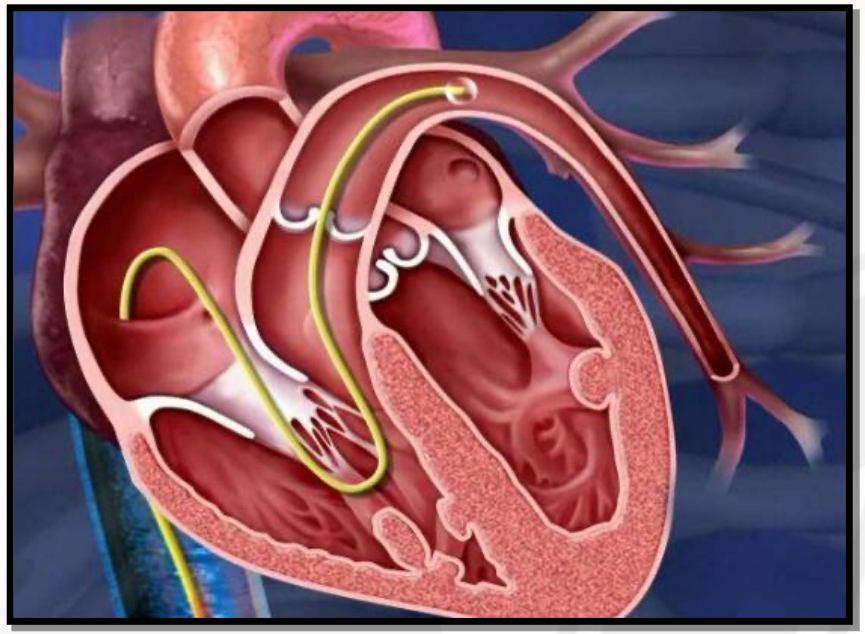
Adapted; Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Right Heart Catheterization: Contemporary Gold Standard for Evaluating PAH & RV Function

Hemodynamics are the Most Important Piece of HF Management but not Readily Obtainable

- Right Heart Cath (RHC) to Measure Pulmonary Artery Pressure Remains the Gold Standard for Cardiac Hemodynamics

- Shortcomings of RHC
  - Invasiveness
  - Risk
  - Cost
  - Single time point assessment
  - Supine and rest condition



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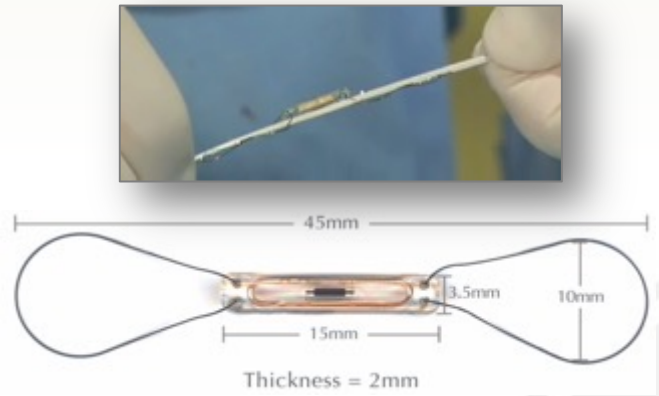
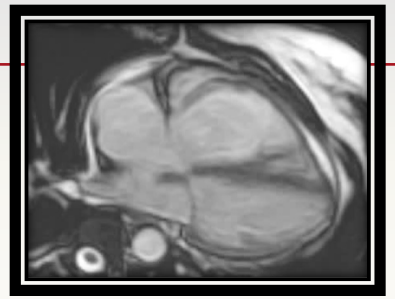
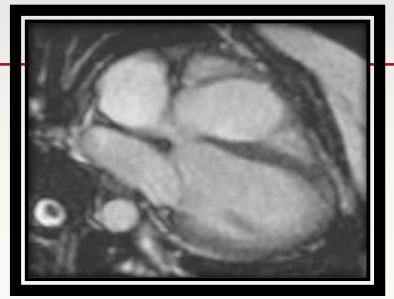
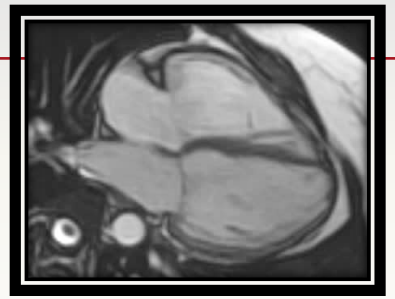
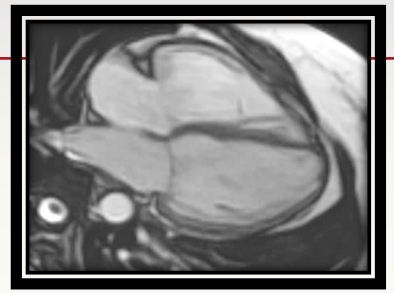
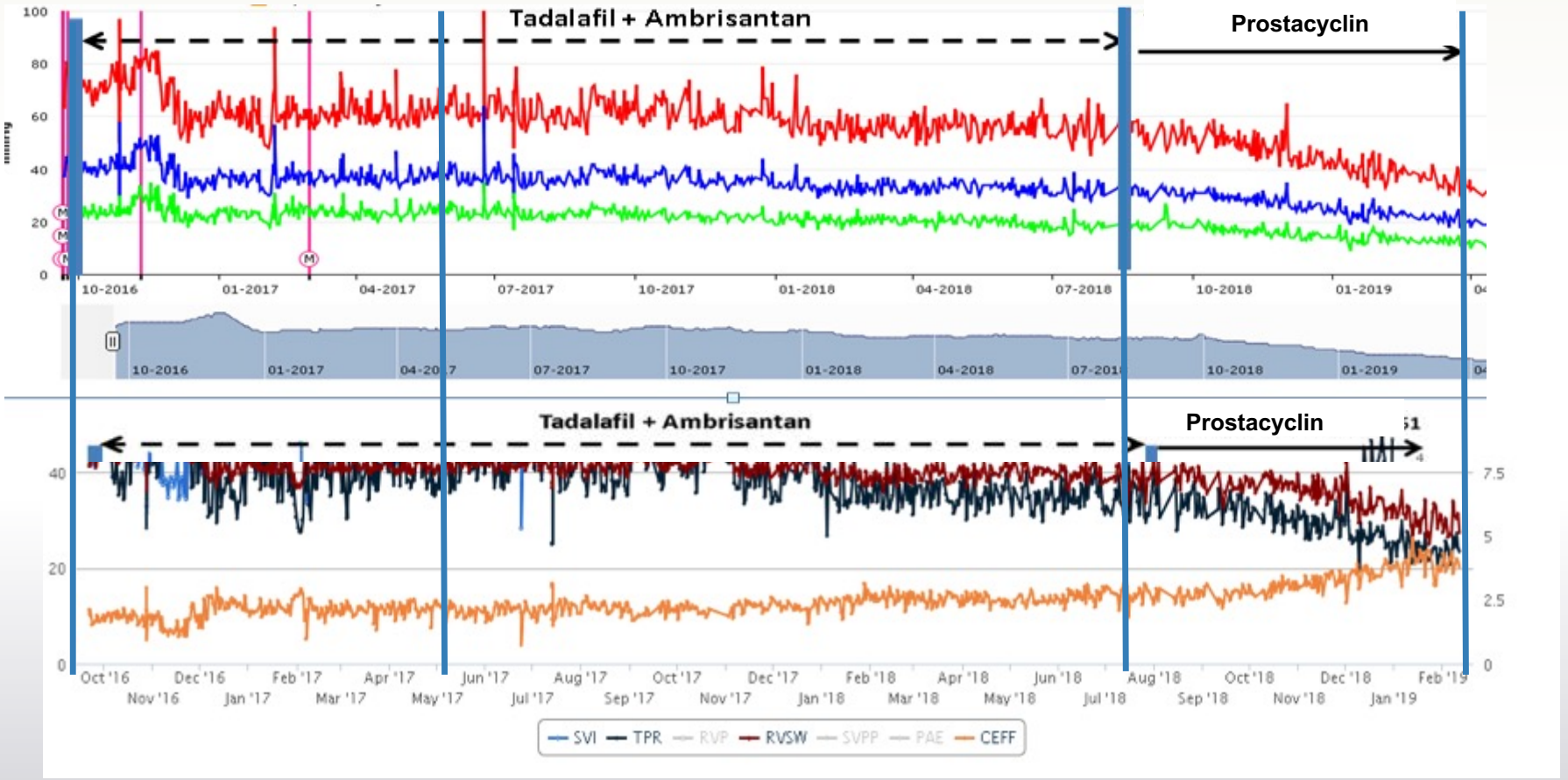


Changes in Right Ventricular Function with Management of mPAP



Cereno Scientific

CardioMEMS – Phase II Clinical Collaboration Between Abbott and Cereno

Dr. Phil Adamson
Divisional Vice President and Chief Medical Office Heart Failure Division, Abbott

CardioMEMS HF Monitoring System

PULMONARY ARTERY PRESSURE SENSOR

PATIENT ELECTRONICS SYSTEM

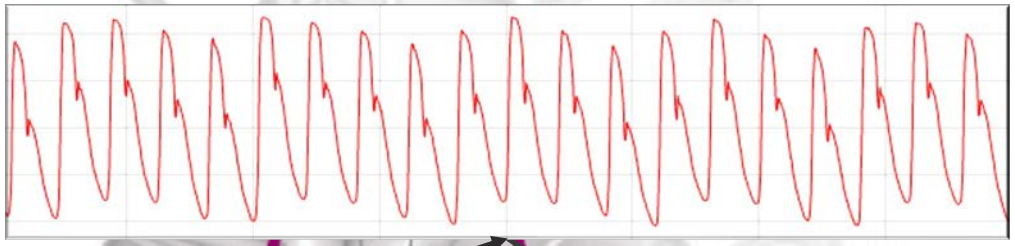
MERLIN.NET™ PATIENT CARE NETWORK (PCN)

Sensor inserted via right heart catheterization

Patients take daily sensor reading from the comfort of their home

Data wi transmi clinicia

TARGET LOCATION FOR PA PRESSURE SENSOR



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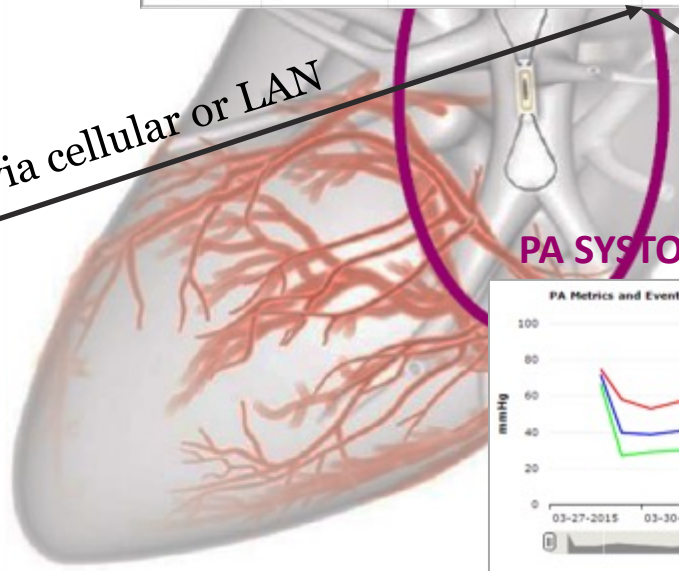
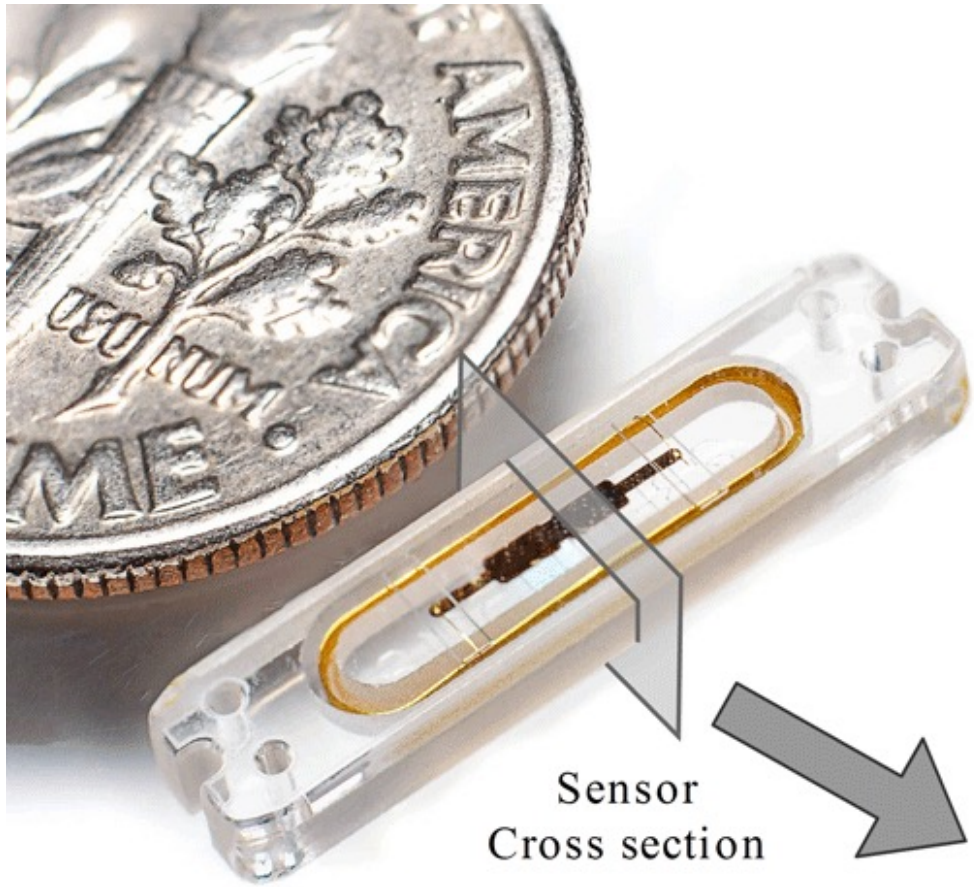
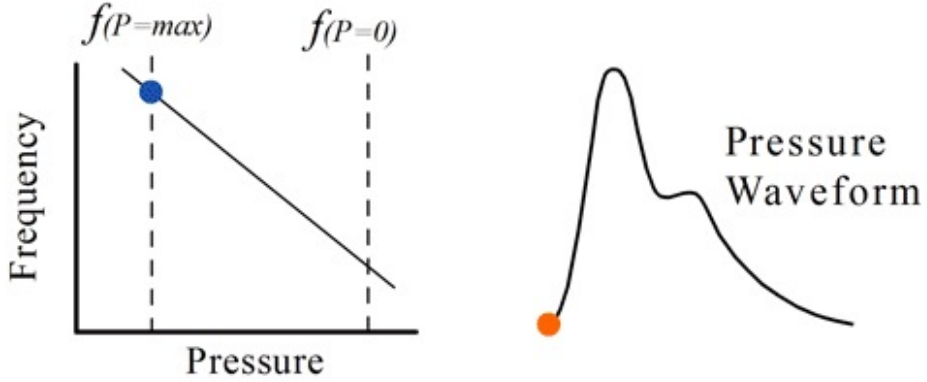
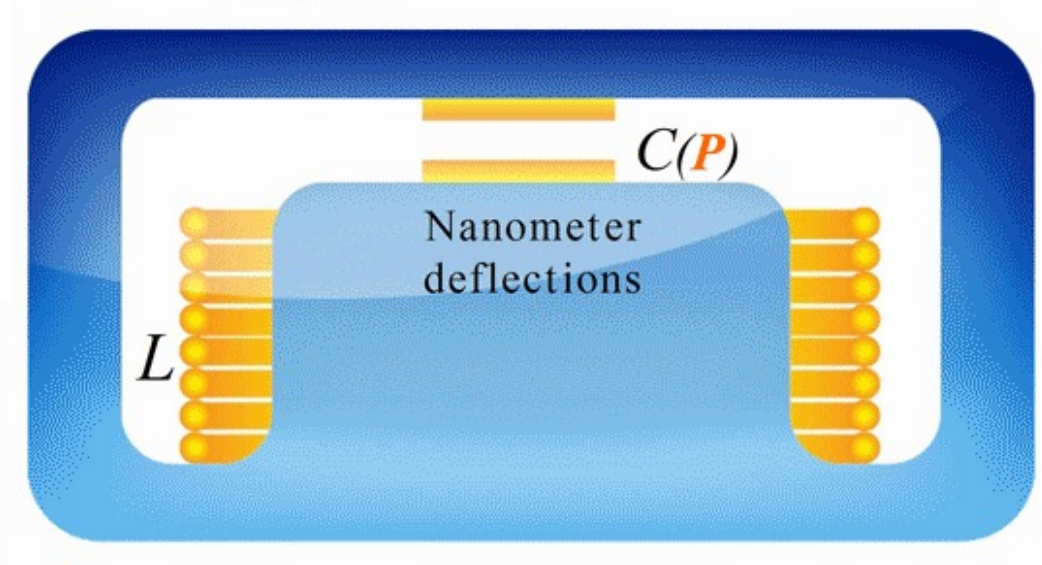


PA SYSTOLIC, DIASTOLIC AND MEAN. HEART RATE



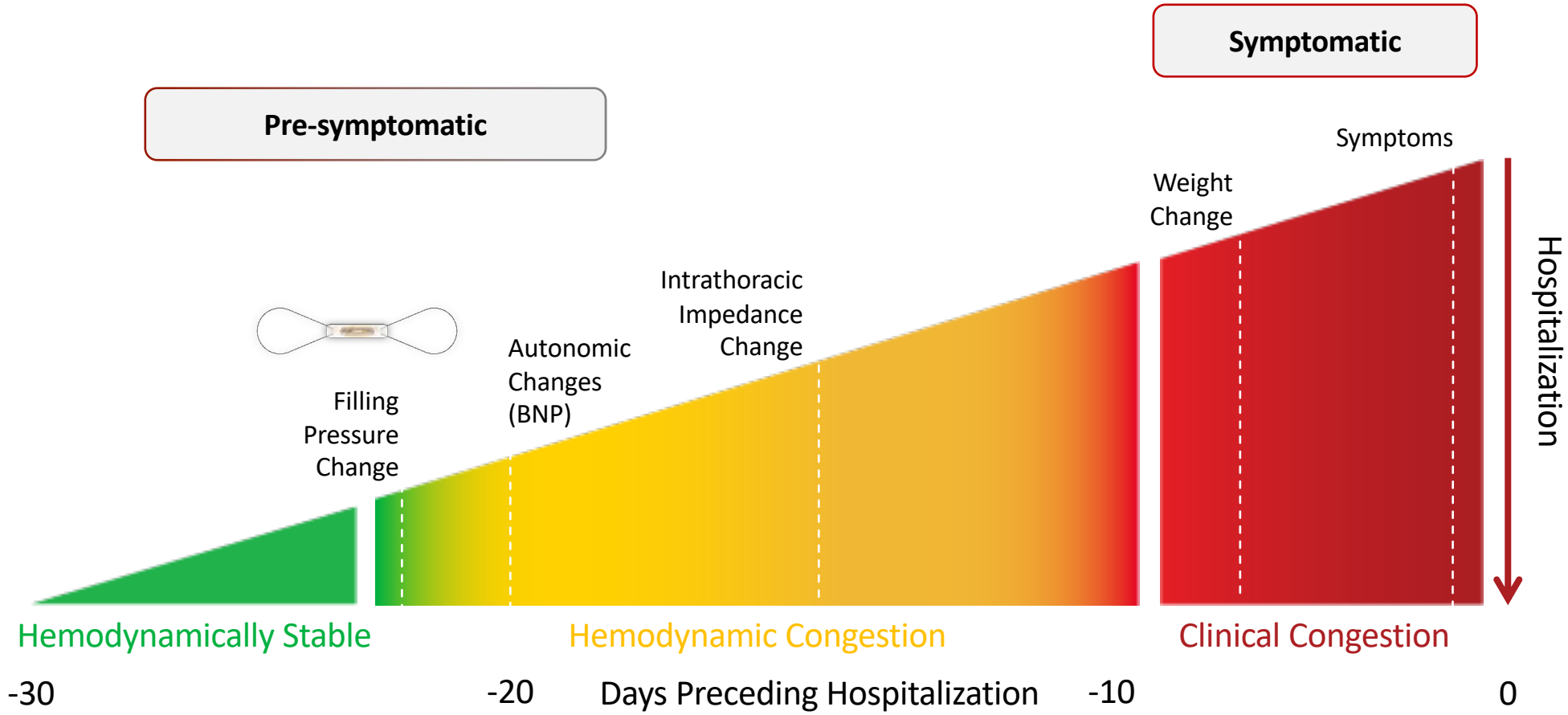
$$f = \frac{1}{2\pi\sqrt{L\ C(P)}}$$





Hemodynamic guided heart failure management

Insights into the mechanisms of acute decompensation



Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: new insights from continuous monitoring devices. *Current Heart Failure Reports*. 2009;6:287-292.

Totality of evidence - consistent benefit of CardioMEMS guided care

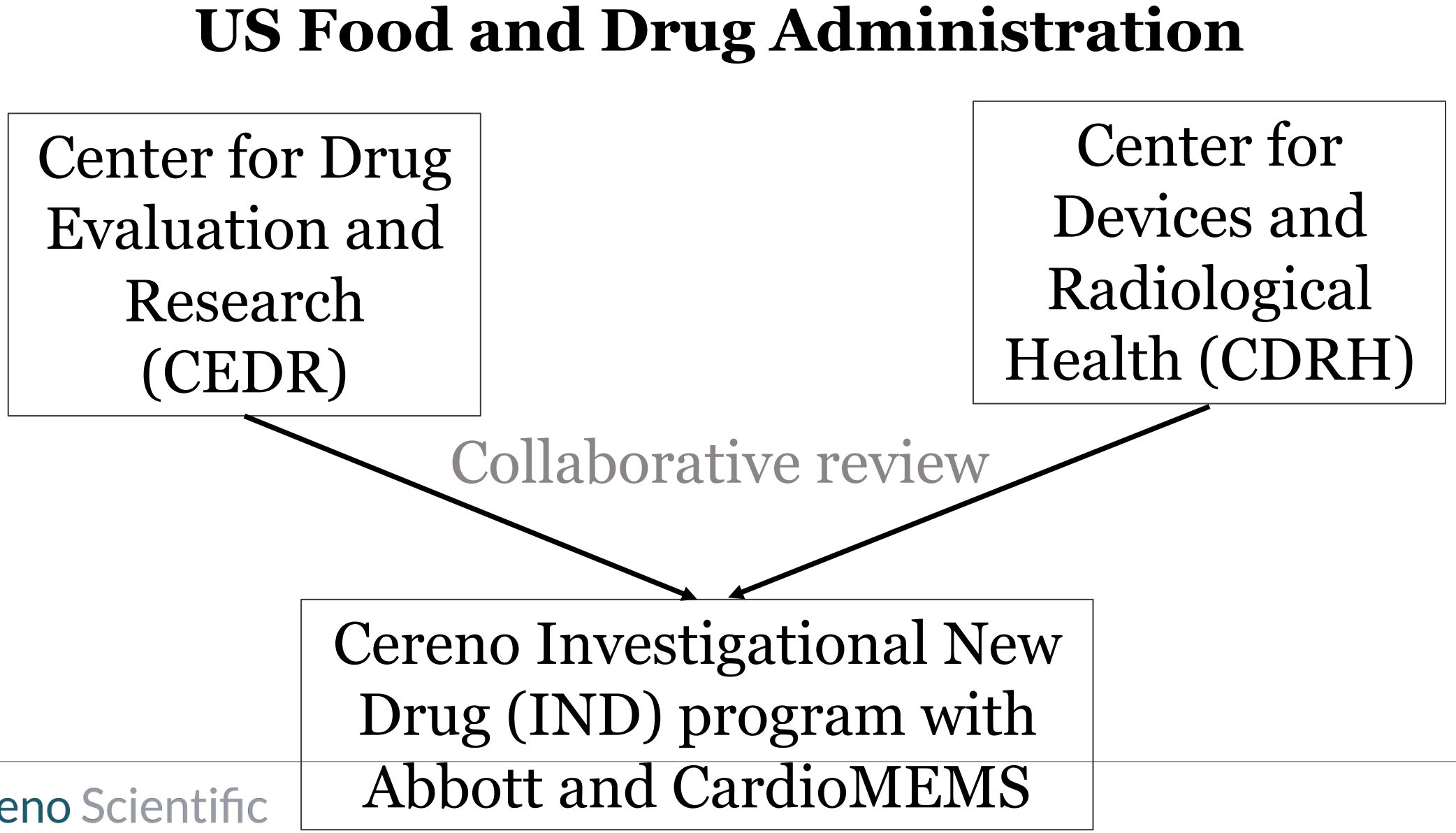
Study Type	Study	N	Follow up	Reduction in HFH	p-value
RCT	**GUIDE-HF IDE NYHA Class II-III** [1]	946	8.6 mo.	32%	$p < 0.01$
RCT	CHAMPION IDE [2]	550	18 mo.	33%	$p < 0.0001$
Retrospective	Propensity Matched Outcomes [3]	2,174	12 mo.	24%	$p < 0.001$
Single Arm	US Post-approval Study [4,5]	1,200	24 mo.	57%	$p < 0.0001$
Single Arm	MEMS-HF European Study [6]	234	12 mo.	62%	$p < 0.0001$
Single Arm	COAST-UK Registry [7] (NICE Guidance)	100	12 mo.	82%	$p < 0.0001$
Retrospective	Real World Clinical Practice: Claims Analysis [8]	1114 480	6 mo. 12 mo.	45% 34%	$p < 0.001$ $p < 0.001$
Retrospective	First 2,000 Commercial Implants [9]	2,000	Consistent reduction in PAP		

1. Lindenfeld, J., 2021, *Lancet* (NYHA Class II/III pre-COVID 19 follow-up cohort)
2. Abraham, W. , 2011 and 2016, *Lancet* (18mo. median follow-up)
3. Abraham, J., 2019, *JAMA*
4. Shavelle, D., 2020, *Circulation: HF*
5. PAS 2 year follow up completed. Manuscript pending
6. Angermann, C., 2020, *ESC*
7. Cowie, M., 2021, ESC HF
8. Desai, A., 2017, *JACC*
9. Heywood J., 2017, *Circulation*

Current USFDA and CE Mark approved CardioMEMS indications **February 21, 2022**

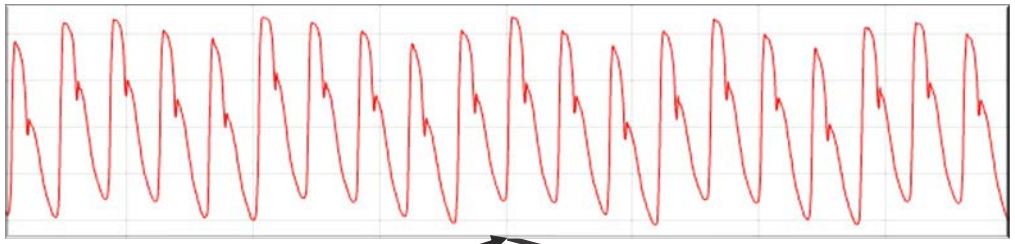
US	The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.
CE	The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class III heart failure patients with a hospitalization in the prior 12 months. Hemodynamic data are used with the goal of reducing heart failure hospitalizations

Cereno – Abbott Collaboration



CS1 Phase II study – CardioMEMS Monitoring

- All centers are experienced CardioMEMS users
- Patients upload hemodynamic information daily from home
- Investigators review pressures twice weekly during drug titration
- Effectiveness described using the targeted lesion – secondary endpoint



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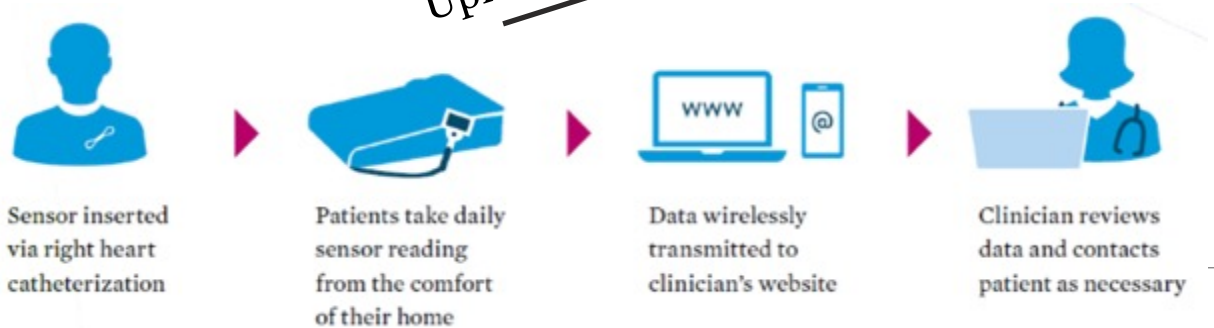


PA SYSTOLIC, DIASTOLIC AND MEAN. HEART RATE

Secondary pulmonary hypertension is almost always found in NYHA Class III patients

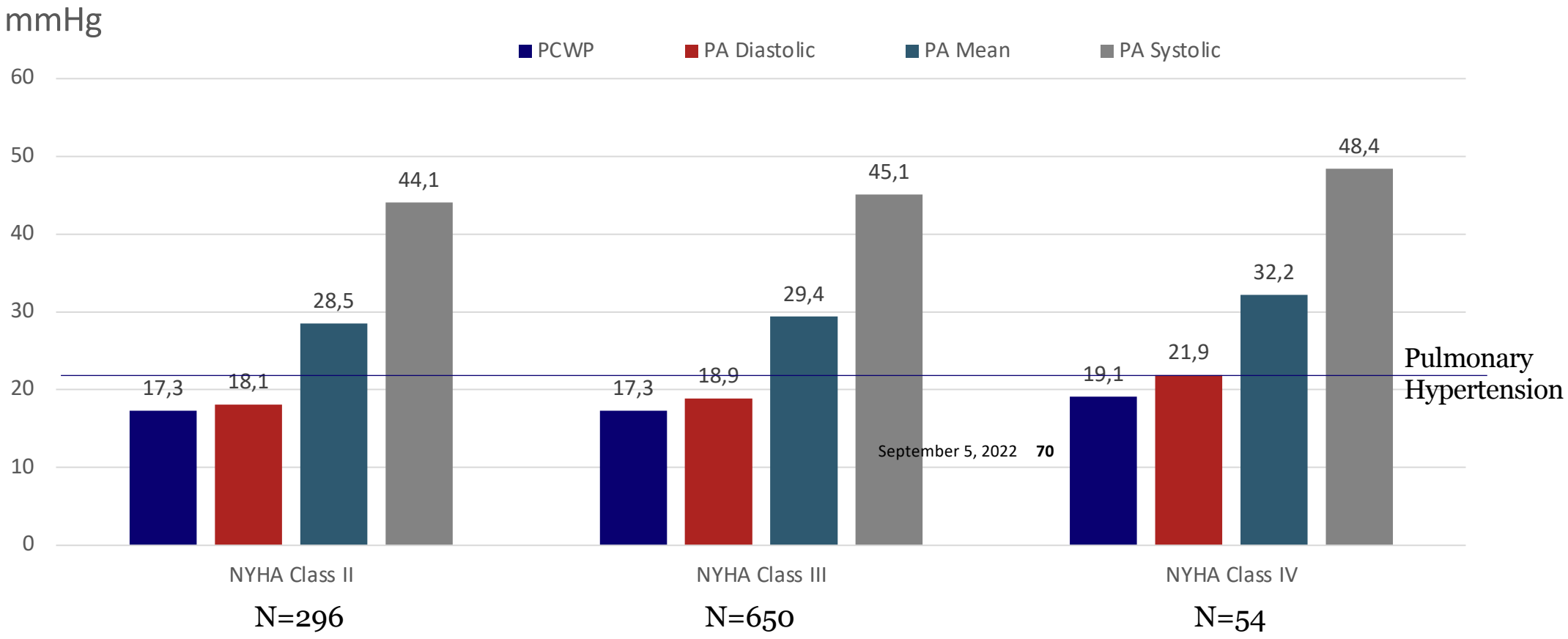
Trial	Total	≥ 35 mmHg	25-35 mmHg	<25 mmHg
CHAMPION	550 (545)*	201	192	152
Heywood	2,000	958	692	350
US PAS	1,200	550	434	211
MEMS-HF	234 (227)*	121	106	-
Totals	3,984 (3,967)*	1830	1424	713
%		46%	36%	18%

82%

* Number of patients with baseline readings

Angermann, et al. *Euro J Heart Fail*. 2020.
Shavelle, et al. *Circ HF*. 2020.
Abraham WT, et al. *Lancet*. 2016.
Heywood, et al. *Circulation*. 2017.

Clinical assessment and filling pressures - GUIDE-HF
- Does less symptomatic = less ill?

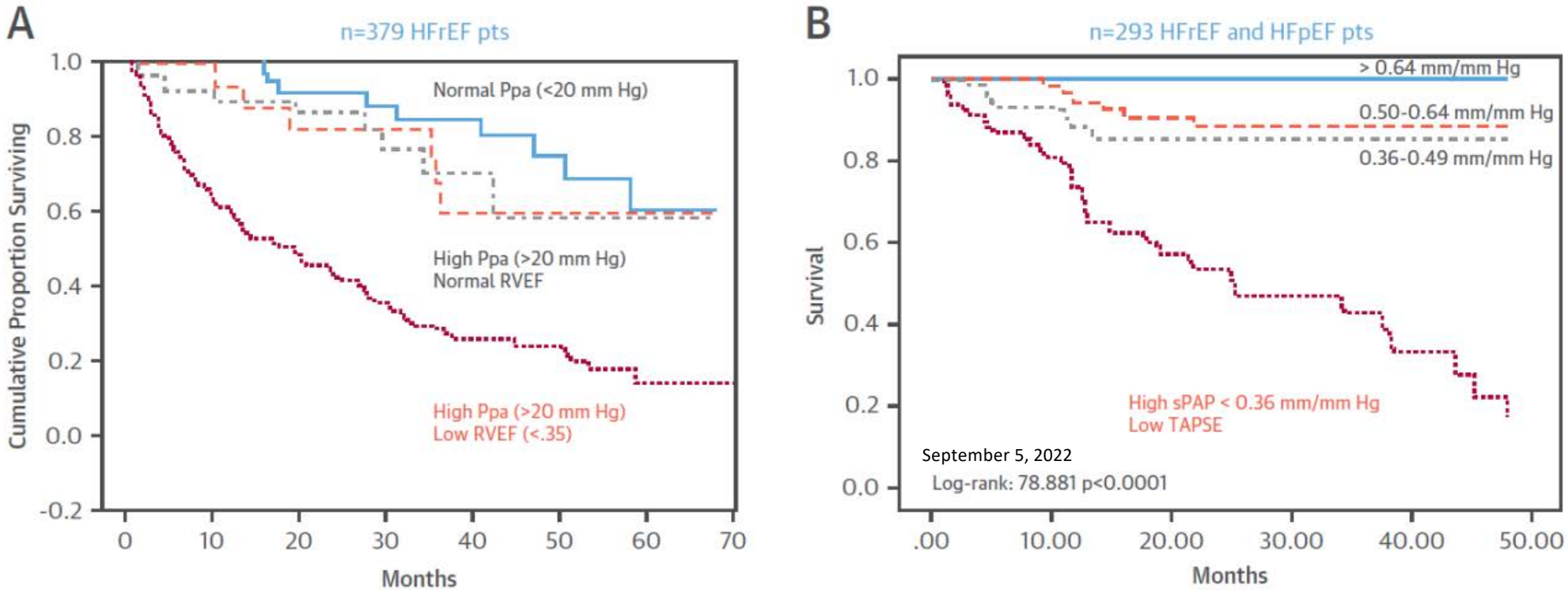


Lindenfeld, et al. *Am Heart J*. 2019.

Cereno Scientific

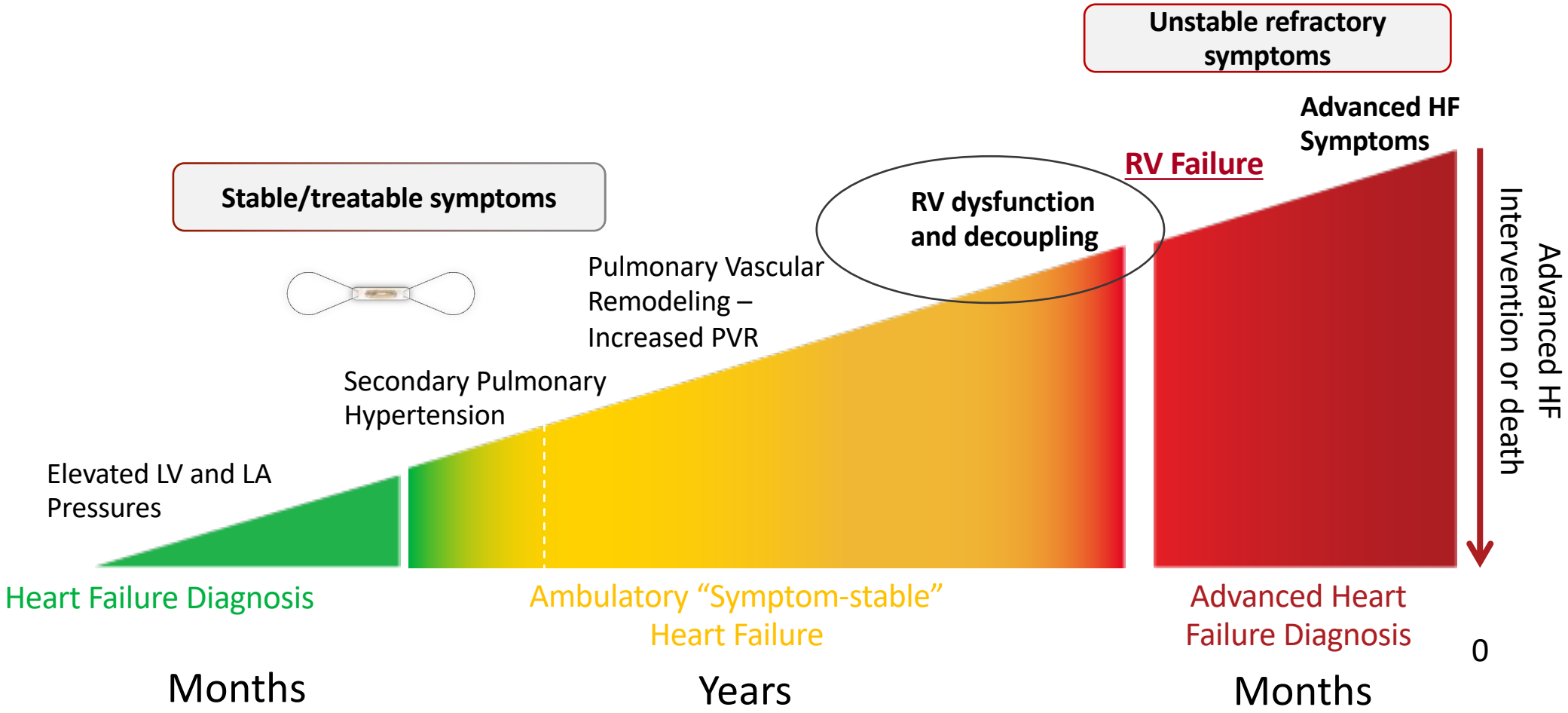
Prognosis in Group 2 pulmonary hypertension
Role of right ventricular dysfunction

FIGURE 6 Heart Failure Patient Survival by Systolic Pulmonary Artery Pressure and Right Ventricular Function Categorization



Marco Guazzi et al. *J Am Coll Cardiol* 2017; 69:1718-1734.

Unifying the impact of pulmonary hypertension



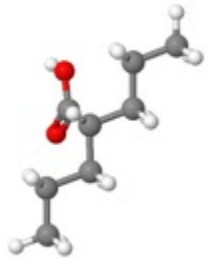
Cereno Scientific

Cereno's Drug Candidate CS1 to Treat PAH and Broader Potential

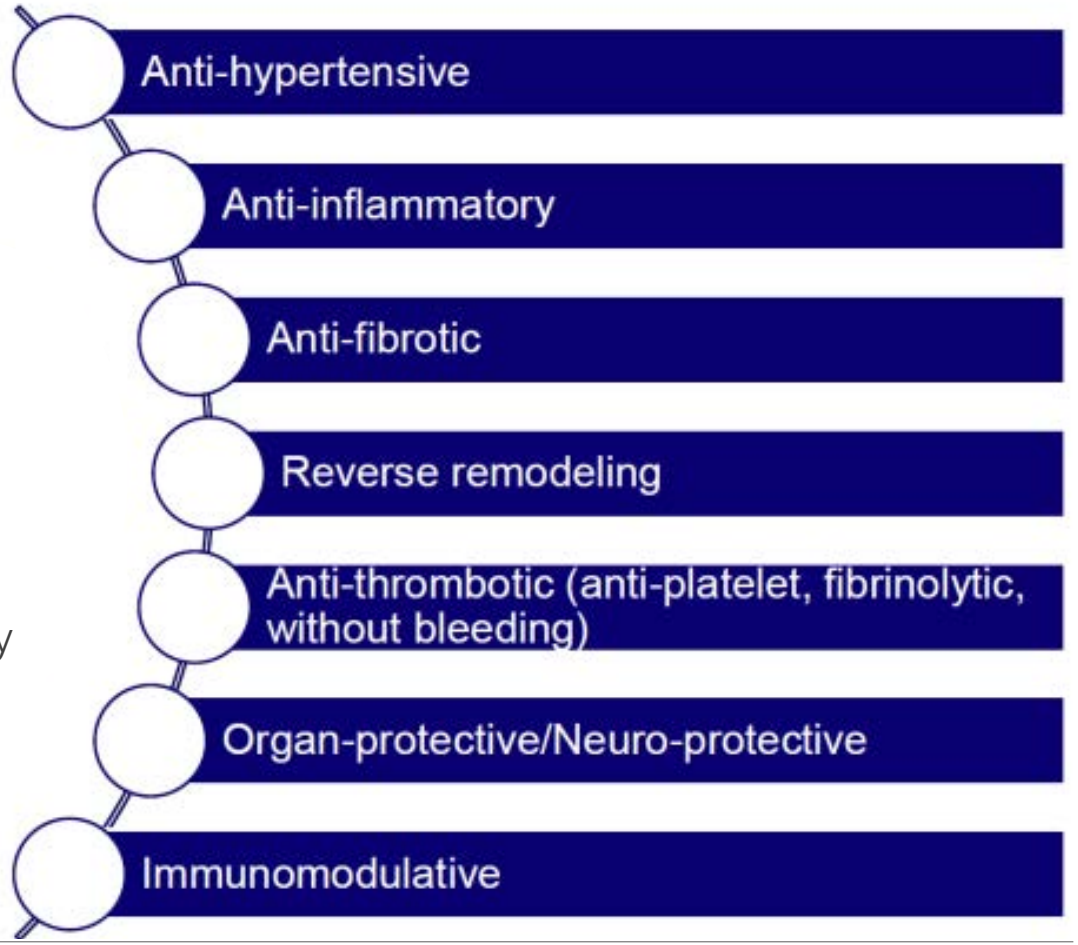
Björn Dahlöf, MD, PhD, FESC, FACC
Chief Medical Officer (CMO) & Board member, Cereno

ValProic Acid (VPA) an HDAC inhibitor

Epigenetic modulator for Cardiovascular Disease



- **First synthesized in 1882**
- Globally **established treatment for epilepsy** (and bipolar disease) **– used for the past 52 years**
  - The widest spectrum of all anti-epileptic drugs
  - Well tolerated in long-term in the majority (well-characterized hepatoxicity and teratogenicity)
- **HDAC I (II) inhibitory properties** discovered later
- Possesses the **longest clinical experience** compared to any other HDAC inhibitor
- **By far, the most widely researched HDAC inhibitor,** especially in non-cancer disease models
  - The only HDAC inhibitor registered for a non-oncologic disease
- **No QT-prolongation** (risk of fatal arrhythmias) unlike with many HDAC inhibitors
- **Broad epidemiological data in epileptic patients for MI and stroke reduction**
- **CS1 reformulated VPA (innovative delayed immediate release) has a strong patent protection and ODD in PAH**

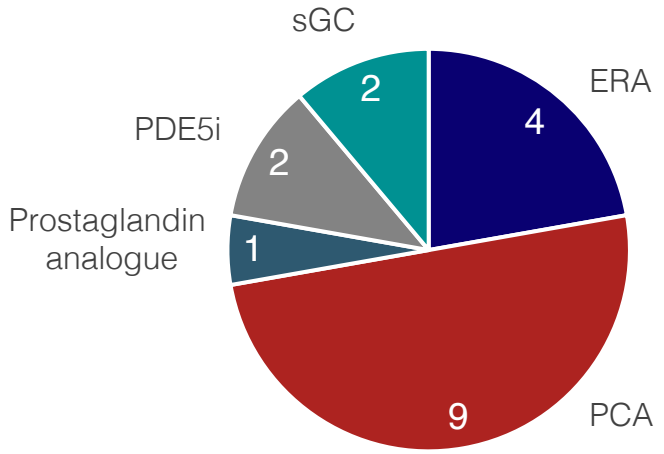


Existing treatment options are insufficient in PAH

Current therapies are vasodilators treating symptoms of PAH rather than the underlying pathophysiology

- Four main classes of current PAH therapies:
  - Endothelin receptor agonists (ERA)
  - Prostacyclin analogues (PCA)
  - PDE5 inhibitors (PDE5i)
  - sGC stimulators (sGC)
- Most marketed drugs today only provide an estimated 11% improvement of the patient's functional level and involve a moderate slowdown in the disease development.
- Need for therapies that treat the underlying pathophysiology with improved safety, tolerability and efficacy profiles **i.e. need for disease-modifying therapies**

No. of PAH drugs by class



Key unmet needs in PAH

- Therapies that treat the underlying pathophysiology
- Safer and more tolerable treatments
- Room for improvement in administration frequency

Source: Datamonitor Disease Analysis: Pulmonary hypertension, November 2021, MSC Nordics analysis.

The search for disease-modifying therapies in pulmonary hypertension: new direction in epigenetic modulation for PAH

Published in final edited form as:

J Cardiovasc Pharmacol Ther. 2019 July ; 24(4): 334–354. doi:10.1177/1074248419829172.

The Search for Disease-Modifying Therapies in Pulmonary Hypertension

Chen-Shan Chen Woodcock, PhD[1], **Stephen Y. Chan, MD, PhD**[1,2]

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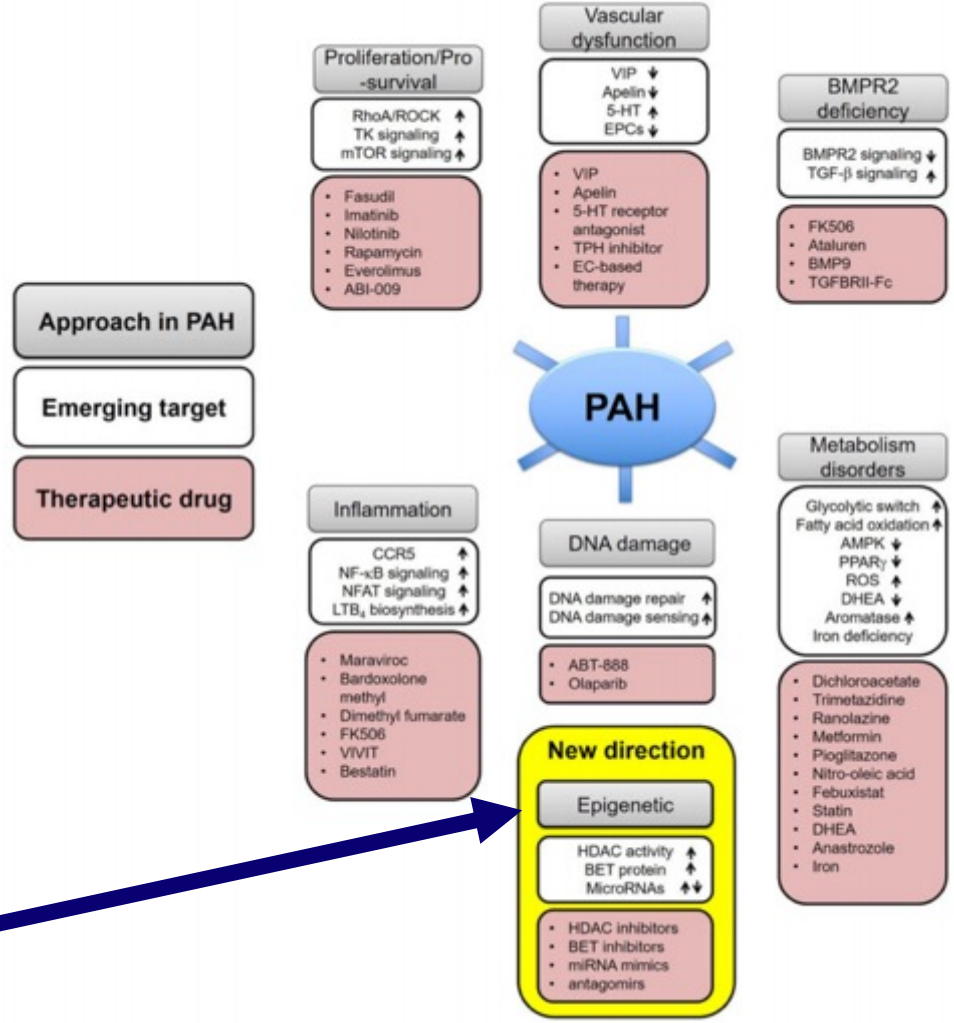
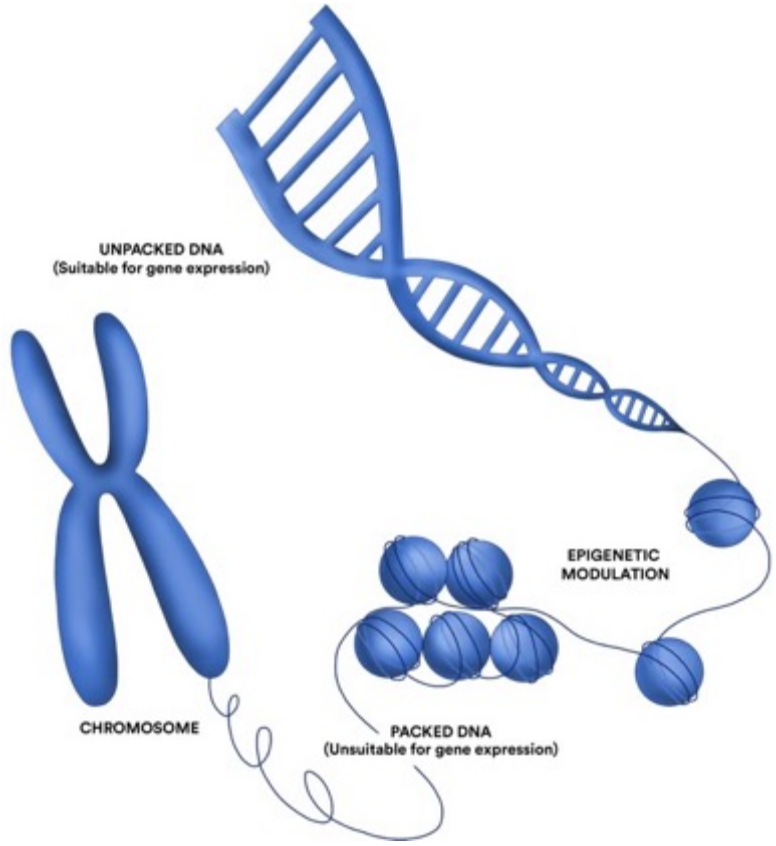


HDACi game-changing with epigenetic modulation of cardiovascular disease

CS1 and preclinical CS014 acts as epigenetic modulators

- Epigenetic modulation is the alteration of gene expression without altering genetic material.
- Epigenetic changes play a significant role in the pathogenesis of many CV diseases.
- Histone deacetylase (HDAC) inhibition plays an important role in epigenetic modulation.
- HDAC inhibition has played a critical role in new cancer therapies, but the use of epigenetic modulation in cardiovascular disease has just begun.
- Cereno's programs holds potential to bring safe, efficacious and **disease-modifying** therapies that will change future CV therapy in general and PAH in particular.



VascularBiology | M Bisserier *et al.* | Epigenetic mechanisms in PAH | 2:1 | R17–R34
2020

REVIEW

Targeting epigenetic mechanisms as an emerging therapeutic strategy in pulmonary hypertension disease

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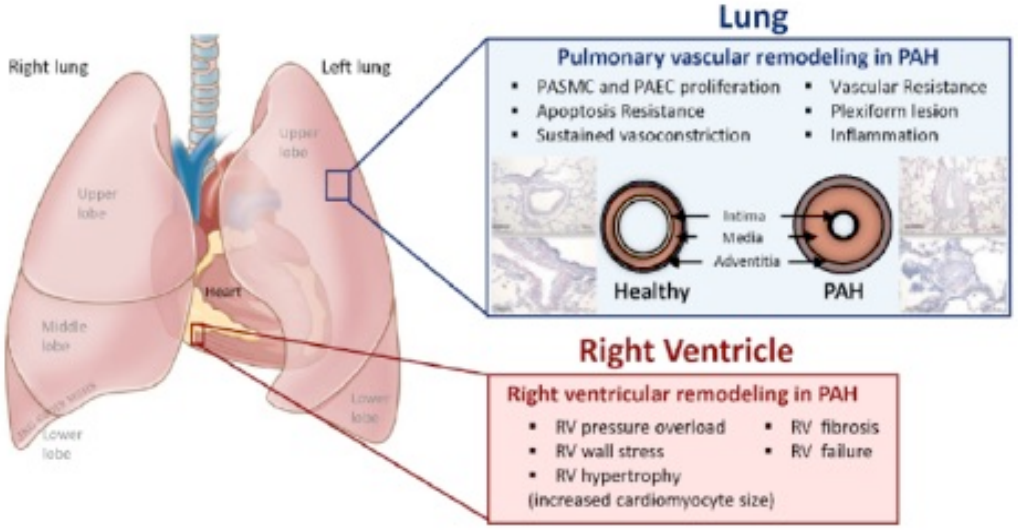
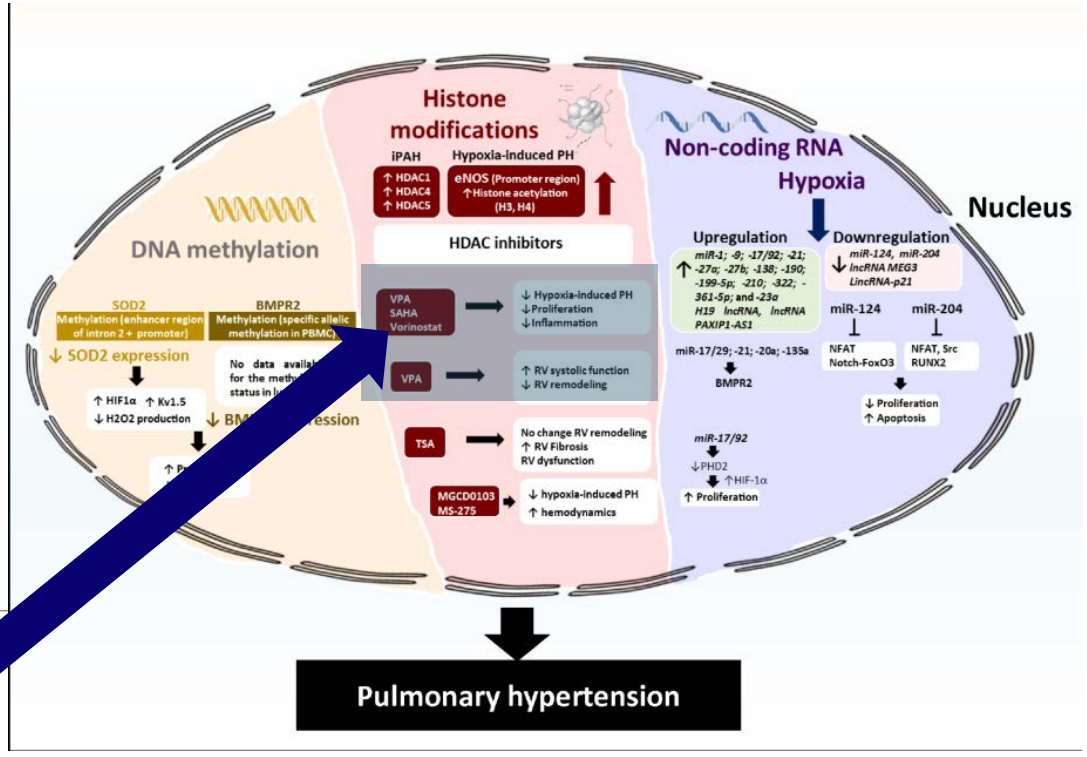
Abstract

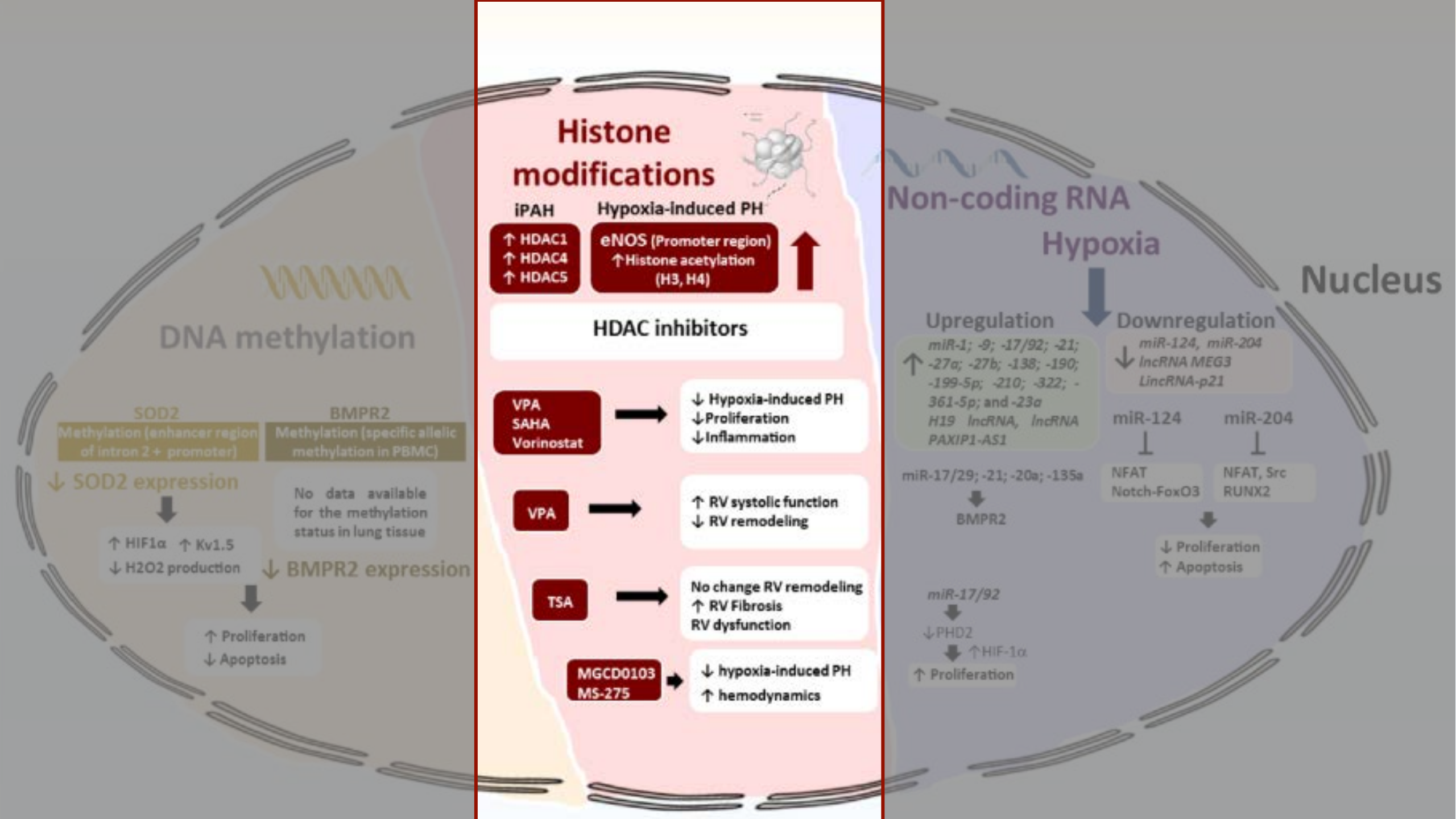
Pulmonary arterial hypertension (PAH) is a multifactorial cardiopulmonary disease characterized by an elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), which can lead to right ventricular (RV) failure, multi-organ dysfunction, and ultimately to premature death. Despite the advances in molecular biology, the mechanisms underlying pulmonary hypertension (PH) remain unclear. Nowadays, there is no curative treatment for treating PH. Therefore, it is crucial to identify novel, specific therapeutic targets and to offer more effective treatments against the progression of PH. Increasing amounts of evidence suggest that epigenetic modification may play a critical role in the pathogenesis of PAH. In the presented paper, we provide an overview of the epigenetic mechanisms specifically, DNA methylation, histone acetylation, histone methylation, and ncRNAs. As the recent identification of new pharmacological drugs targeting these epigenetic mechanisms has opened new therapeutic avenues, we also discuss the importance of epigenetic-based therapies in the context of PH.

Key Words

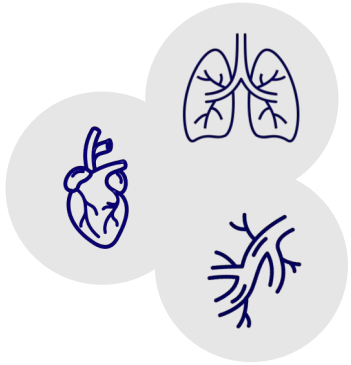
- PAH
- epigenetics
- vascular remodelling






DNA methylation
SOD2
Methylation (enhancer region of intron 2 + promoter)
BMPR2
Methylation (specific allelic methylation in PBMC)
↓ SOD2 expression
No data available for the methylation status in lung tissue
↑ HIF1α ↑ Kv1.5
↓ H2O2 production
↓ BMPR2 expression
↑ Proliferation
↓ Apoptosis
Histone modifications
iPAH
Hypoxia-induced PH
↑ HDAC1
↑ HDAC4
↑ HDAC5
eNOS (Promoter region)
↑ Histone acetylation (H3, H4)
HDAC inhibitors
VPA
SAHA
Vorinostat
↓ Hypoxia-induced PH
↓ Proliferation
↓ Inflammation
VPA
↑ RV systolic function
↓ RV remodeling
TSA
No change RV remodeling
↑ RV Fibrosis
RV dysfunction
MGCD0103
MS-275
↓ hypoxia-induced PH
↑ hemodynamics
Non-coding RNA
Hypoxia
Nucleus
Upregulation
↑ miR-1; -9; -17/92; -21; -27a; -27b; -138; -190; -199-5p; -210; -322; -361-5p; and -23a
H19 lncRNA, lncRNA PAXIP1-AS1
Downregulation
↓ miR-124, miR-204
lncRNA MEG3
LincRNA-p21
miR-124
miR-204
NFAT
Notch-FoxO3
NFAT, Src
RUNX2
↓ Proliferation
↑ Apoptosis
miR-17/29; -21; -20a; -135a
BMPR2
miR-17/92
↓PHD2
↑HIF-1α
↑ Proliferation

Cereno's portfolio includes HDAC inhibitors and a PCA with potential in CVD



Program	Indication	Discovery	Preclinical	Phase I	Phase II	Phase III	Next milestone
CS1	PAH	HDACi with epigenetic effects					Phase II top-line data: Q1, 2023
CS014	CVD	HDACi with epigenetic effects					Phase I IND submission: 2023
CS585	CVD	Prostacyclin receptor agonist					Phase I IND submission: 2023

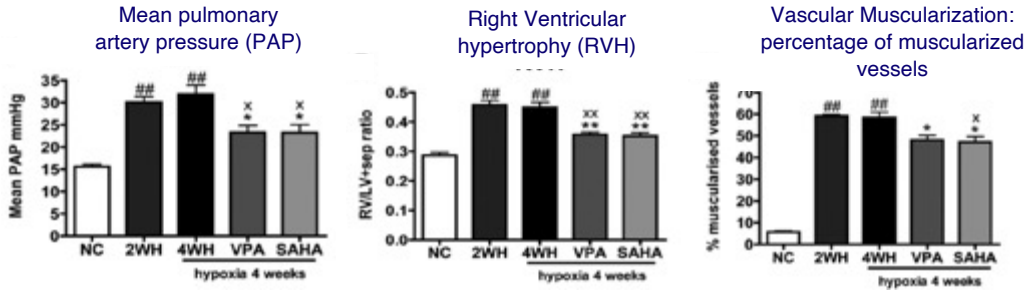
HDACi = Histone deacetylase inhibitor

CS1 vs Sotatercept
Important mechanisms for PAH - Selected preclinical data

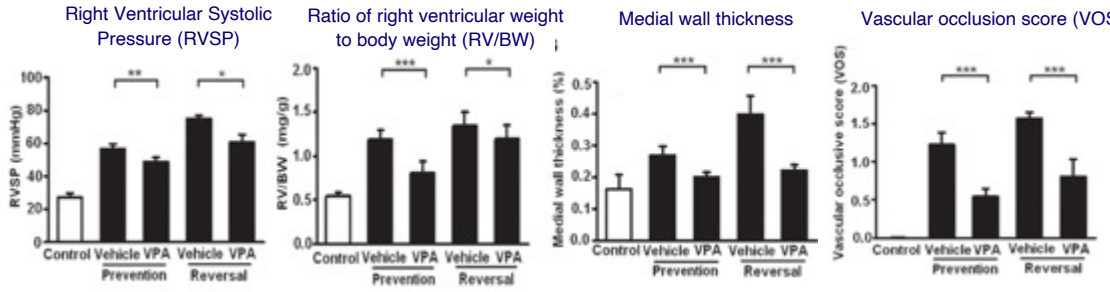
Comparison characteristics of CS1 vs Sotatercapt[1,2,3,4,5,6,7]

Generic name	Pulmonary pressure reduction	Reverse-remodeling	Anti-fibrotic	Anti-inflammatory	Anti-thrombotic	MoA	Phase
CS1	+ + +	+ + +	+ + +	+ +	+ + +	HDACi	II
Sotatercept	+ + +	+ + +	+ +	+ +	?	TGF-β ligand trap	III

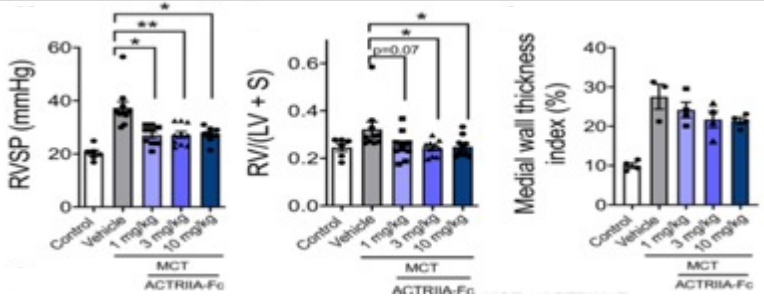
VPA: PAH model 4ws hypoxia, last 2ws treatment[8]



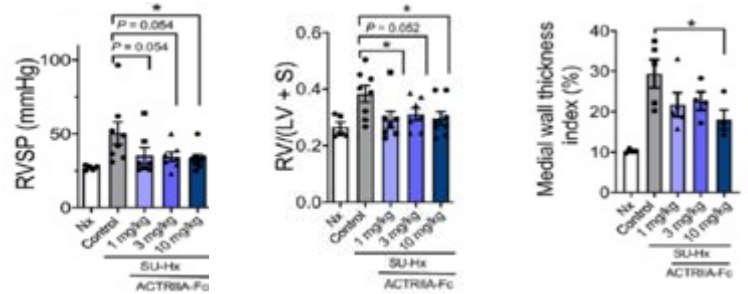
VPA: PAH model prevention 3ws MCT-Hx, treatment 2ws after 3ws with MCT-Hx[9]



Sotatercept: PAH model treatment for 2ws after MCT 4ws[10]



Sotatercept: PAH model Sugen-Hx 3ws, thereafter 3ws treatment[10]



MoA=Mode of Action, HDACi=Histone DeACetylase inhibitor, TGF-β =Transforming Growth Factor - Beta.

Cereno Scientific

Sources: 1. EMA, 2. FDA, 3. clinicaltrials.gov, 4. clinicaltrialsregister.eu, 5. MedTrack, 6. PubMed, 7. MSC Nordics analysis, 8. Therapeutic Potential of HDAC Inhibitors in PH, Zhao et al, CIRCULATIONAHA.112.103176; 9. Lan B, Hayama E, Kawaguchi N, Furutani, Y, Nakanishi T (2015) Therapeutic Efficacy of Valproic Acid in a Combined Monocrotaline and Chronic Hypoxia Rat Model of Severe Pulmonary Hypertension. PLoS ONE 10(1): e0117211; 10. ACTRIIA-Fc rebalances activin/GDF versus BMP signaling in pulmonary hypertension, Sci Transl Med. 2020 May 13; 12(543)

Disclaimer: The effects given should be seen as relative to other drugs and not as absolute effects, there are few direct comparative studies. There are no head-to-head comparisons between CS1 and Sotatercept, data has been selected where reasonable comparisons can be made.

Characteristics of CS1 vs Sotatercept

	CS1	Sotatercept
MoA	HDACi	TGF-β ligand trap (monoclonal antibody)
Administration	**Oral Innovative formulation,** delayed immediate release	**Subcutaneous**, every 3 weeks
Use patent	2038	2036
ODD	✓	✓
Potential disease modifying	✓	✓
Pulmonary pressure reduction	✓	✓
Reverse-remodeling	✓	✓
Anti-fibrotic	✓	✓
Anti-inflammatory	✓	✓
Anti-thrombotic	✓	?

MoA=Mode of Action, HDACi=Histone DeACetylase inhibitor, TGF-β =Transforming Growth Factor - Beta

CS1 stands strong vs established and pipeline PAH drugs based on preclinical data

	MoA	Company	Generic name	Pulmonary pressure reduction	Reverse-remodeling	Anti-fibrotic	Anti-inflammatory	Anti-thrombotic
Marketed	ERA	Misc	Ambrisentan,Bosentan, Macisentan	+ + +	+	+	+	0
	PDE5i	Misc	Sildanafil, Taldalafil	+ +	+?	+?	+?	0
	PGA	Misc	Epoprostenol, Ilioprost, Trepostinil	+ + +	+	+	+	+[1]
	sGC stim	Misc	Riociguat	+ +	++	+ +	+	0
	PCA	Misc	Selexipag	+ + +	+	+ +	+ +	+[1]
	HDACi	**Cereno**	**CS1(CS014)**	**+ + +**	**+ + +**	**+ + +**	**+ +**	**+ + +**
In development	TGF-β ligand trap	MSD (Acceleron Ph)	Sotatercept	+ + +	+ + +	+ +	+ +	?
	BET(BD2)i	Resverologics	Apabetalone	+ +	+ + +	++	+++	0
	PRA	United Ther	Ralinepag	+ + +	+	+ +	+ +	+[1]
	Inhibition ¤	Gossamer	Seralutinib inhal	+ + +	+ +	+	+	+[1]
	AT_2RA	Vicore Ph	C21	+ +	+ +	+ + +	+ +	0

1 Other candidates than CS1 with any anti-thrombotic effect curb only platelet aggregation which, unlike thrombofibrotic remodeling, plays a minor role in thrombus resolution (Bochenek et al Thomb Heamost 2017)

MoA=Mode of Action, HDACi=Histone DeACetylase inhibitor, BET(BD2)i=Bromodomain and Extra-Terminal inhibitor,TGF=Transforming Growth Factor, ERA=Endothelin Receptor Agonist, PDE5i= Phospho Di-Esterase5 inhibitor, sGC stim= soluble Guanylate cyclase inhibitor, PGA=ProstaGlandin Agonist, AT2RA=Angiotensin II Receptor type2 Agonist, ¤ = PDGFR α / β (Platelet derived growth receptor antagonist alpha/beta), CSF1R (colony stimulating factor 1), c-KIT (receptor tyrosine kinase).

Sources: EMA, FDA, clinicaltrials.gov, clinicaltrialsregister.eu, MedTrack, PubMed MSC Nordics analysis

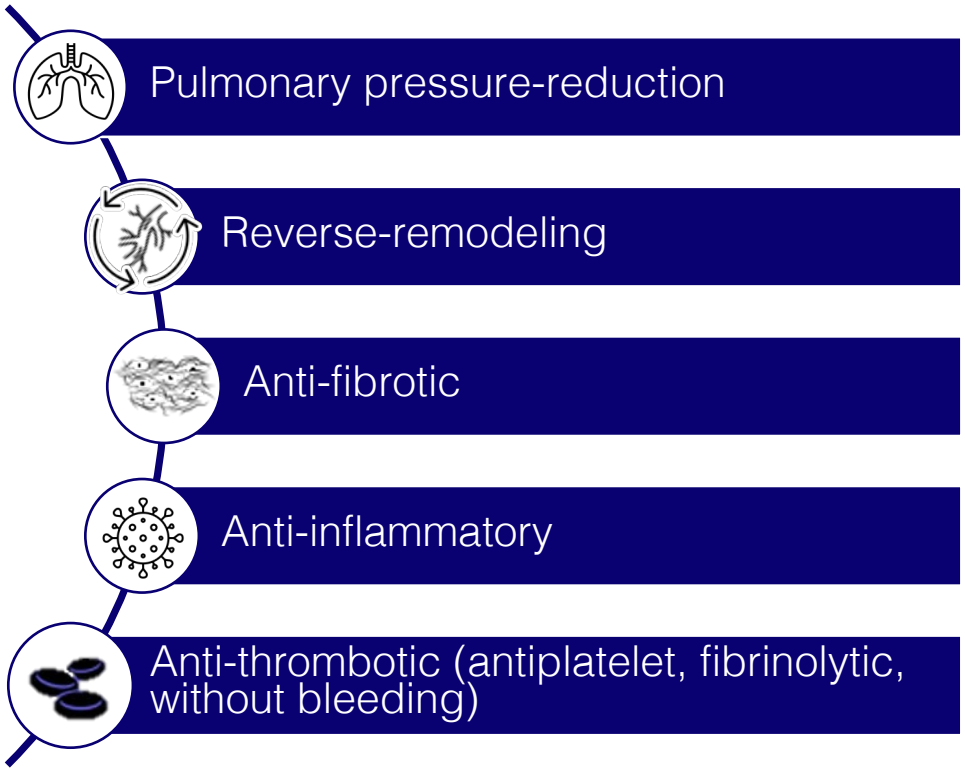
Disclaimer: The effects given should be seen as relative to other drugs and not as absolute effects, there are few direct comparative studies

HDAC inhibitor CS1 aims to offer an effective, safe and disease modifying treatment for PAH

CS1 is a new advanced reformulation and acts as an epigenetic modulator

- Proven good safety and tolerability in Phase I study.
- CS1's broad efficacy profile makes it a strong alternative to marketed and pipeline PAH drugs due to reverse remodeling.
- CS1 could fill the significant need for more efficacious and safer therapies with **a disease modifying potential** to improve survival and quality of life for PAH patients.*

CS1's multi-fold efficacy, all relevant for PAH



*Currently in Phase II development.

CS1 viewed as potential game-changer in PAH by global thought leader

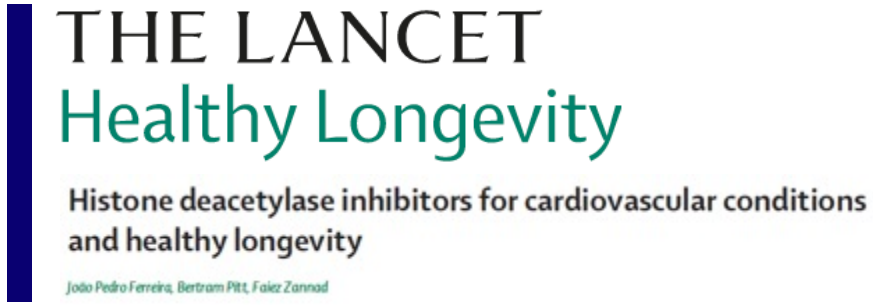
"CS1 has to definitely be tested in PAH, it could be game-changing for patients."

- CS1's Phase II study in PAH is ongoing with first patient dosed in August 2022.

– Dr Raymond Benza, global thought leader in PAH treatment and PI CS1-003, about Cereno's CS1.

Review article in *The Lancet Healthy Longevity* supports the potential of epigenetic modulation via HDACi in CVD

Accumulating evidence supports the role of epigenetic modulation through HDAC inhibition in the treatment of multiple medical conditions beyond the treatment of epilepsy, which has been documented as the first indication to be treated with the HDACi valproic acid (VPA).



"Given the pleotropic properties of CS1's active substance being a HDACi with documented anti-thrombotic, anti-inflammatory, anti-fibrotic and pressure-reducing effects gives it a unique position to be developed for a variety of cardiovascular diseases with a disease-modifying potential."

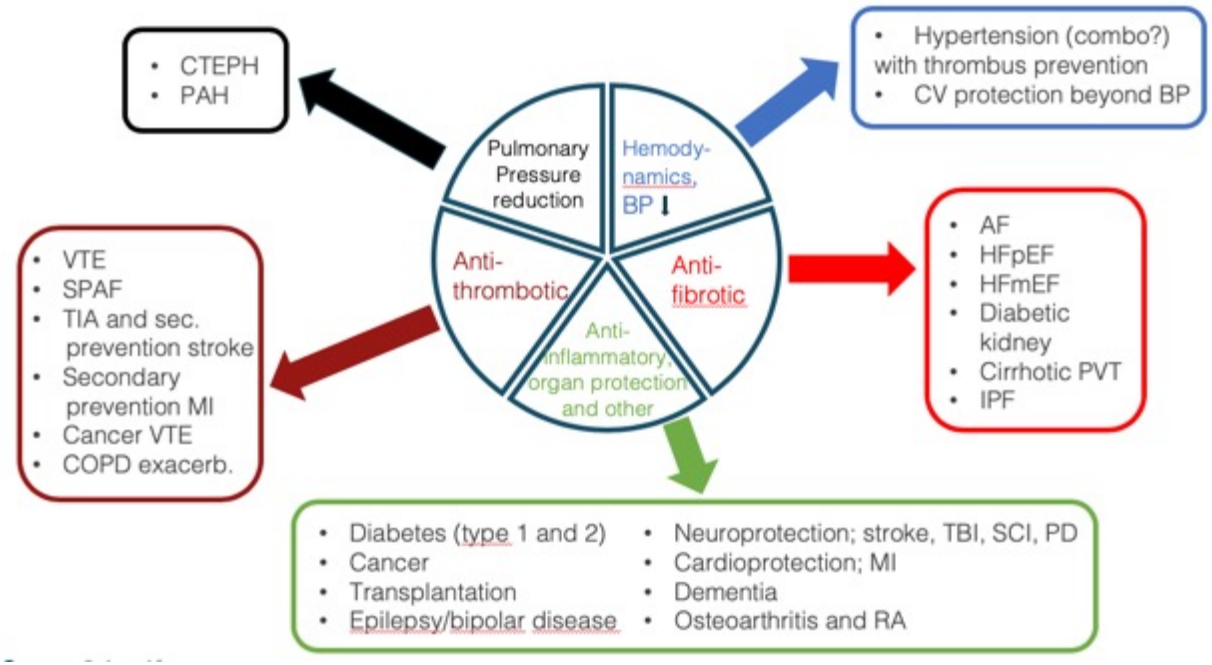
– Review article co-author and member of Cereno's SAB, Prof Faiez Zannad, MD.*

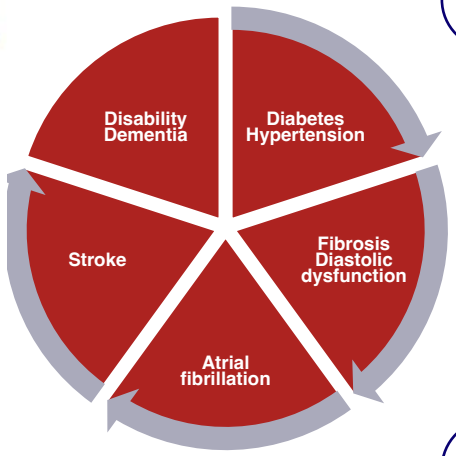
Strong potential in cardiovascular prevention

- Myocardial infarction
- Heart failure
- Pulmonary arterial hypertension
- Stroke
- Peripheral artery disease
- VTE
- Atrial fibrillation
- Arterial hypertension

Source: Ferreira JP, Pitt B, and Zannad F, Lancet Healthy Longev 2021;2,e371-379 doi
*BioStock. Cereno Scientific drives a paradigm shift in CVD. June 11, 2021

Beyond PAH: Cereno's robust strategy for cardiovascular disease management

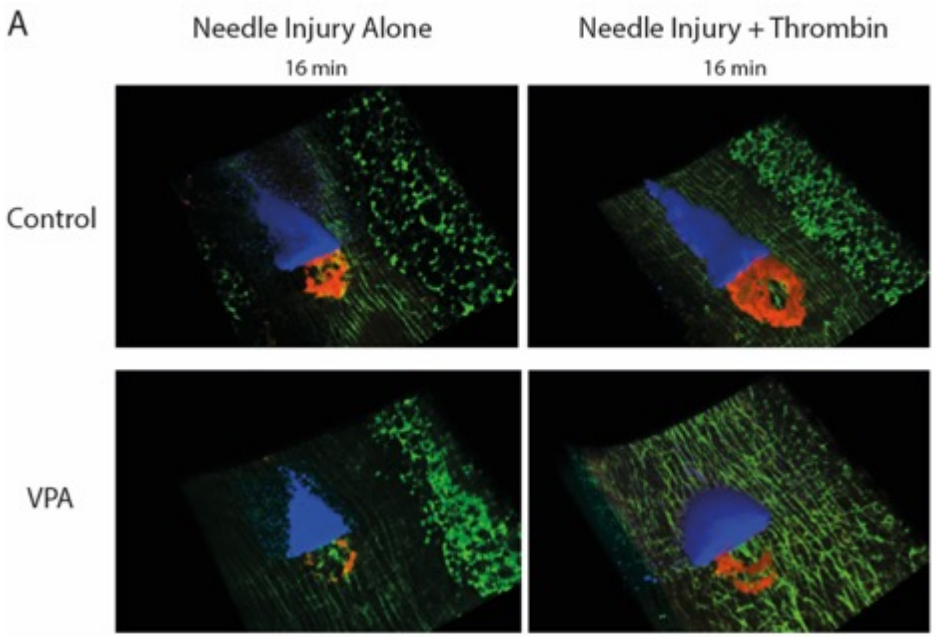




- Anti-hypertensive
- Anti-inflammatory
- Anti-fibrotic
- Reverse remodeling
- Anti-thrombotic (anti-platelet, fibrinolytic, without bleeding)
- Organ-protective/Neuro-protective
- Immunomodulative

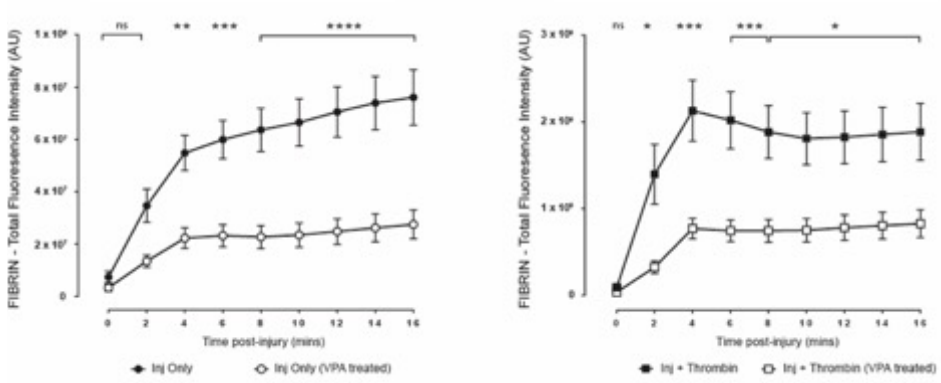
Treatment with the Cereno platform;
Epigenetic modulation with HDAC inhibition

CS1 active ingredient – pre-treatment reduces thrombus formation *in vivo* – without bleedings



Thrombus formation in mesenteric veins after mechanically-induced vessel injury (intra-vital confocal microscopy) and a **96h** pre-treatment with VPA in a mouse model

Fibrin (injury only) — Fibrin (injury + Thrombin)

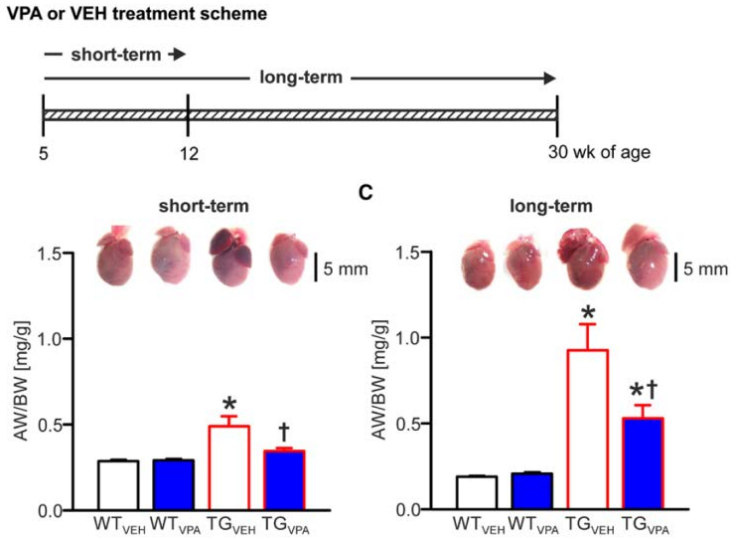


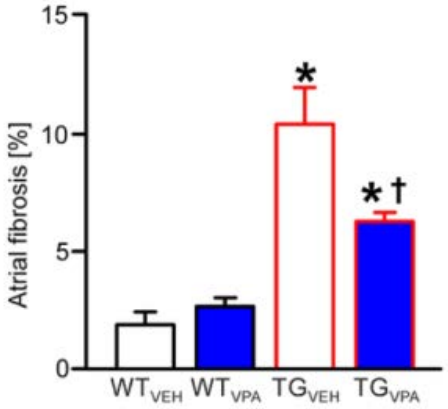
Thrombus volume (inj only) — Thrombus volume (inj + Thrombin)

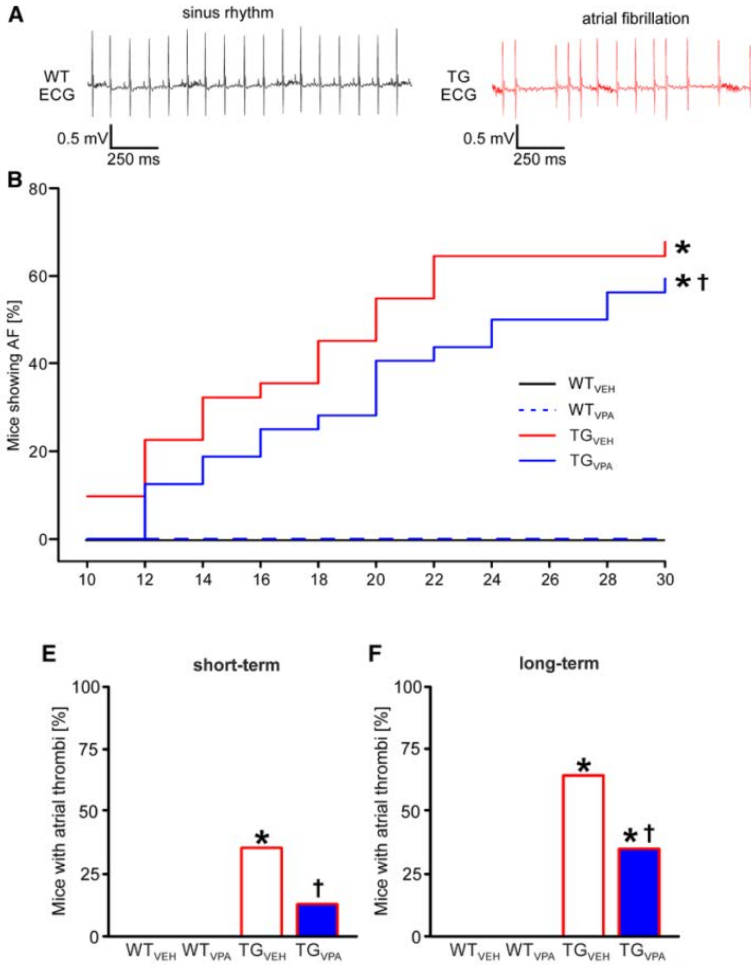
Source: Larsson et al JTH 2016

CS1 – prevention of fibrosis, atrial fibrillation and thrombosis

- Atrial fibrillation increases with age
- Associated with progressive (fibrotic) remodelling of the atrium
- The risk of thrombosis is linked to the size/fibrotic remodelling of the atrium







Findings show that CS1 has therapeutic potential to delay the development of atrial remodelling and the onset of atrial fibrillation (AF) in patients at risk.

Source: Scholz B et al Circ Arrhythm Electrophysiol 2019;12,e00707

CS1 is a novel delayed release formulation of VPA.

Potential of Cereno's pipeline of HDACi epigenetic modulators (CS1, CS014, CSXXX) based on unique efficacy profile

Cardiovascular disease	Efficacy profile of HDACi epigentic modulators: Systemic blood pressure reduction	Pulmonary pressure reduction	Anti-thrombotic	Anti-inflammatory/ Organ protection	Anti-fibrotic/ Reverse remodeling
PAH		✓	✓	✓	✓
VTE			✓	✓	✓
AF (SPAF)	✓		✓	✓	✓
Secondary prev MI/Stroke	✓		✓	✓	✓
HFpEF	✓			✓	✓
HFrEF (post-MI)			✓	✓	✓
Kidney failure	✓		✓	✓	✓
Cardiac transplantation			✓	✓	✓
Diabetes	✓		✓	✓	✓
IPF & other rare diseases with a strong cardiovascular link		✓	✓	✓	✓

EH: Essential Hypertension; AF: Atrial Fibrillation; SPAF: Stroke Prevention in Arterial Hypertension; HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; Post-MI: Post Myocardial Infarction; IPF: Idiopathic Pulmonary Fibrosis

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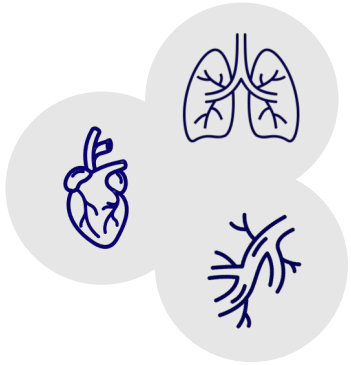
Cereno's Preclinical Candidates Potential to Break New Ground

Dr. Björn Dahlöf
Chief Medical Officer (CMO), Cereno

Cereno's portfolio of two pipeline drug candidates in preclinical development



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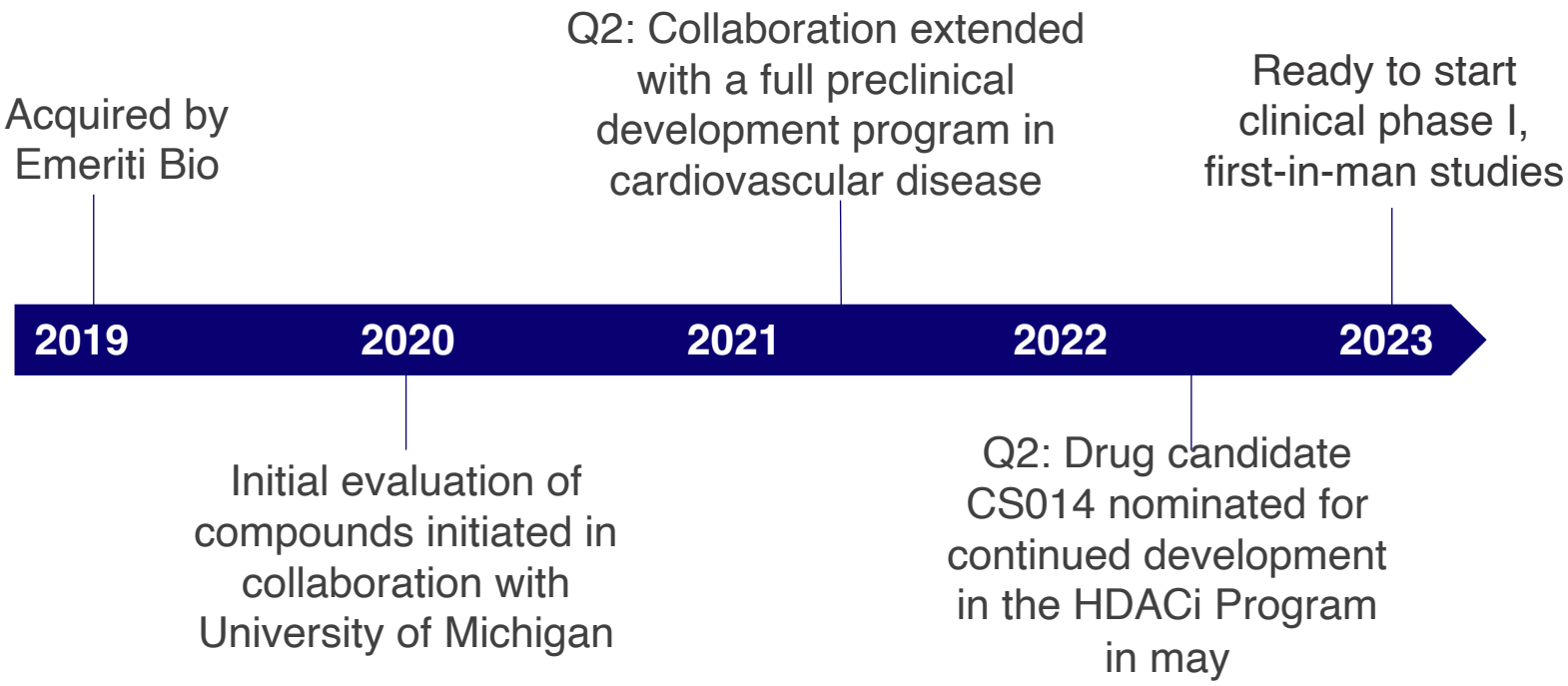
CS014	CVD*	HDACi with epigenetic effects					Phase I IND submission: 2023
CS585	CVD*	Prostacyclin receptor agonist					Phase I IND submission: 2023

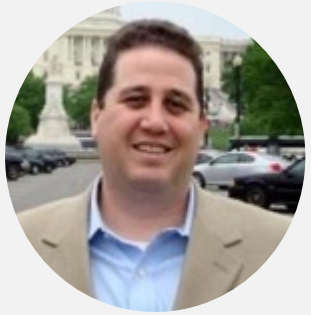
HDACi = Histone deacetylase inhibitor * Current focus areas; PAH, Thrombosis

CS014 is a novel HDACi with epigenetic modulation properties

Preclinical development program



Research collaboration



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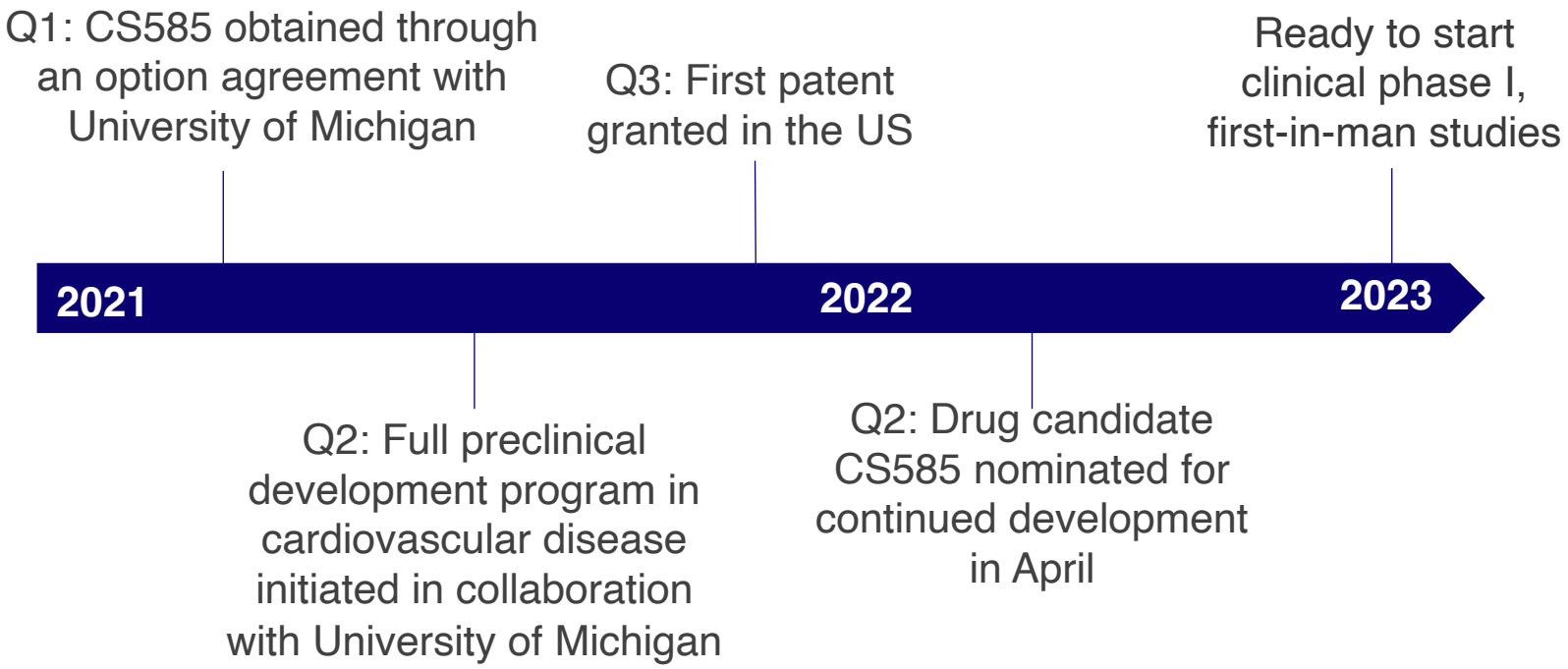
Dr. Michael Holinstat
Director Translational Research at Cereno and Associate professor of Internal Medicine, Division of CV Medicine at University of Michigan

CS585 is a prostacyclin receptor agonist utilizing a well-established drug class and regulatory pathway

Preclinical development program



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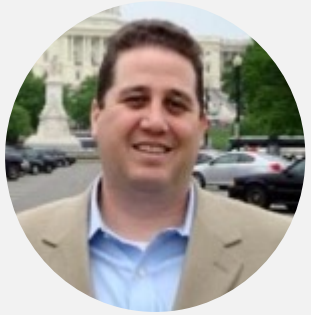

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Dr. Michael Holinstat
Director Translational Research at Cereno and Associate professor of Internal Medicine, Division of CV Medicine at University of Michigan

Leaving a mark in the medical community through abstracts accepted at top congresses

EHA 30 YEARS EUROPEAN HEMATOLOGY ASSOCIATION

June 9-12, 2022

CS585 is a first-in-class compound targeting the IP receptor for prevention of thrombosis without increased risk of bleeding
S. Lambert, R. Adili, P. Yalavarthi, N. Rhoads, B. Dahlöf, A. White, N. Bergh, M. Holinstat

- Presented by M. Holinstat

ESC European Society of Cardiology

August 26-29, 2022

CS014 is a novel HDAC inhibitor regulating platelet activity, fibrinolysis and clot stability for prevention of thrombosis without increased risk of bleeding
M. Holinstat, R. Adili, L. Stanger, T. Hoang, S. Lambert, N. Rhoads, B. Dahlöf, N. Bergh

- Presented by M. Holinstat

Cereno Scientific

CS585 – A First-In-Class Compound Targeting the IP Receptor for Prevention of Thrombosis Without Increased Risk of Bleeding

Dr. Michael Holinstat
Ass. Prof. at University of Michigan Medical School; and
Director Translation Research, Cereno

CS585 IS A FIRST-IN-CLASS COMPOUND TARGETING THE IP RECEPTOR FOR PREVENTION OF THROMBOSIS WITHOUT INCREASED RISK OF BLEEDING

Michael Holinstat, PhD, FAHA

Departments of Pharmacology, Internal Medicine (Division of Cardiovascular Medicine), and Vascular Surgery University of Michigan

Contributing authors: Sylviane Lambert, Livia Stanger, Reheman Adili, Pooja Yalavarthi, Nicole Rhoads, Bjorn Dahlof, Andrew White, Niklas Bergh

Scientific

Conflict of Interest Disclosure Slide:

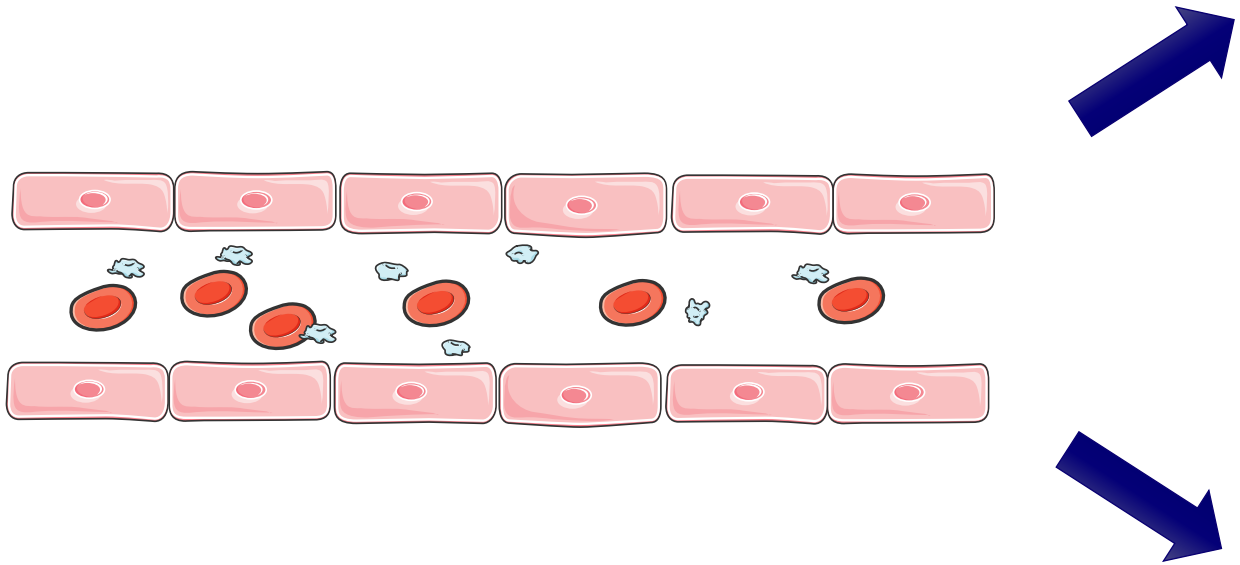
Consulting:

- I am a consultant and equity holder in Cereno Scientific and Veralox Therapeutics. I am also an inventor for the patents on CS585 and VLX-1005.

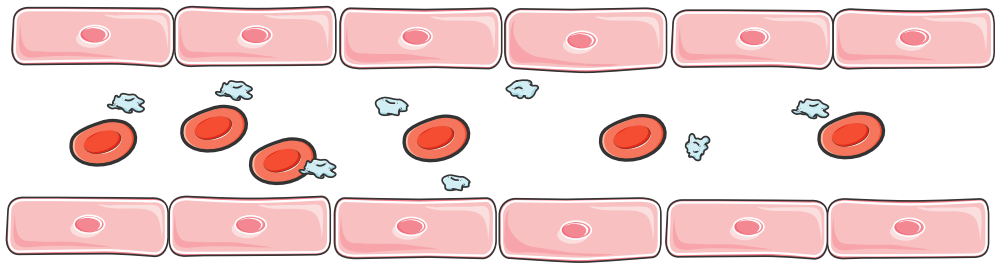
Grants:

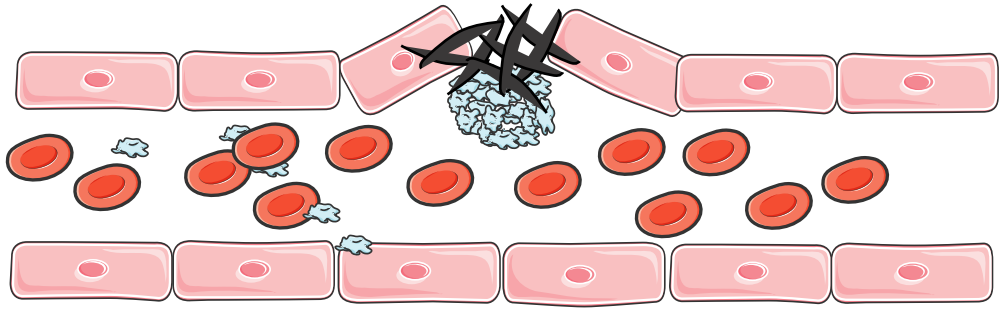
- I receive research grants from the NIH, Cayman Biomedical Research Institute (CaBRI), Cereno Scientific, and Veralox Therapeutics

Platelet physiology and pathophysiology



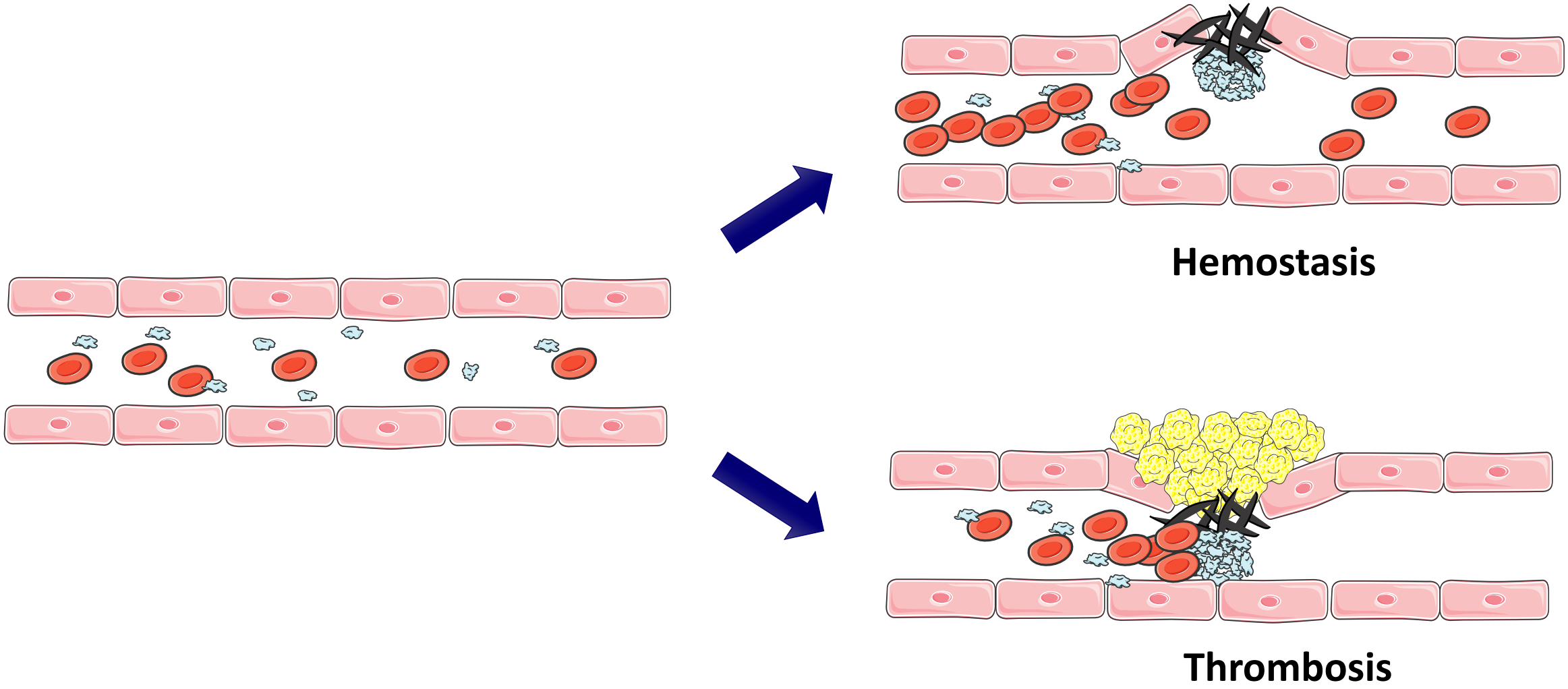
Platelet physiology and pathophysiology





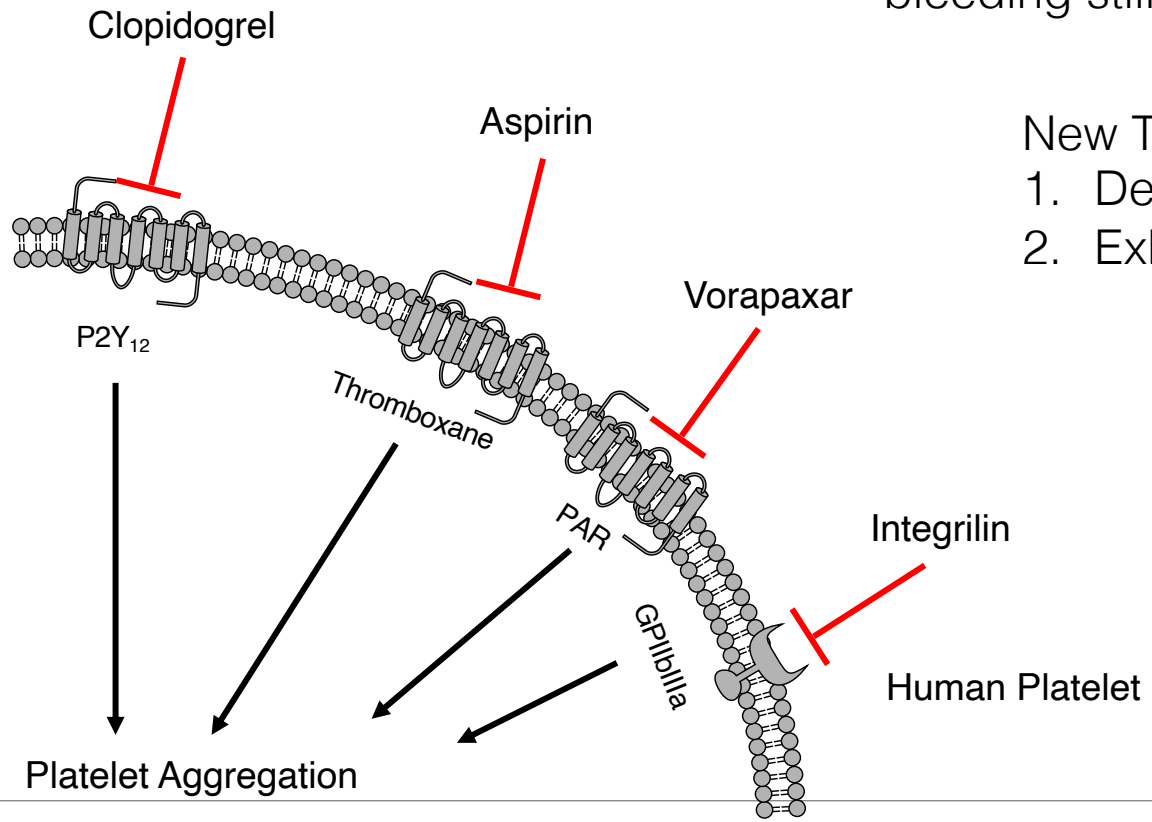
Hemostasis

Platelet physiology and pathophysiology



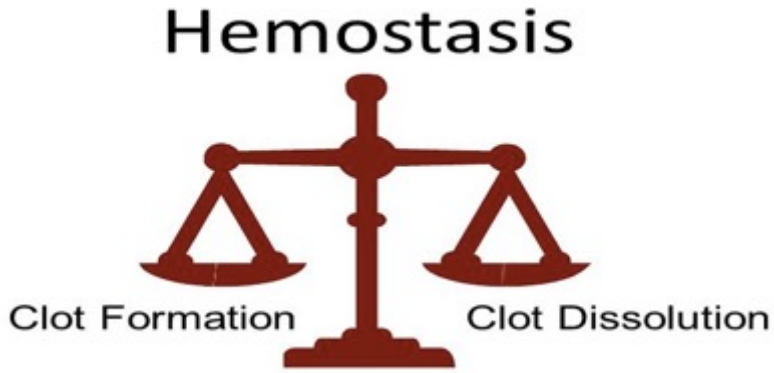
Regulation of human platelet function

- Currently approved Anti-platelet drug therapy has reduced the risk of morbidity and mortality by more than 26%.
- While current anti-platelet therapy has significant health benefits, morbidity and death due to thrombotic events and bleeding still remains a significant problem.



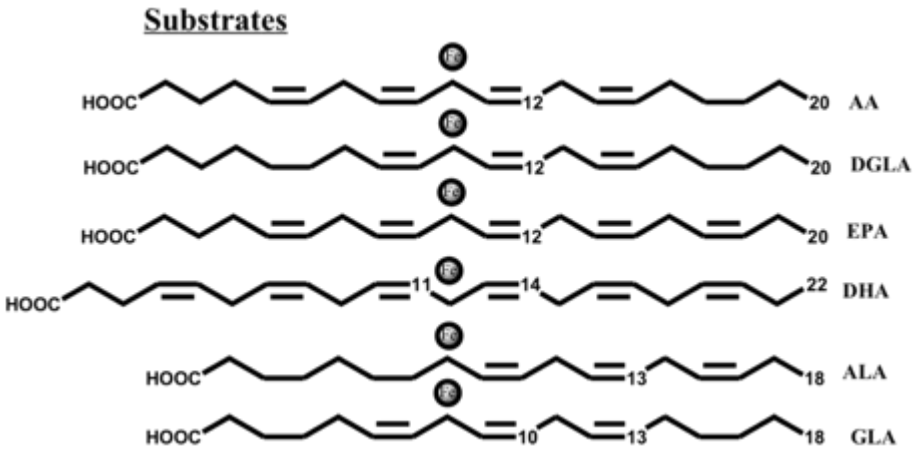
New Therapeutic Approaches are warranted that will:

1. Decrease platelet activation and thrombosis
2. Exhibit only limited risk of bleeding

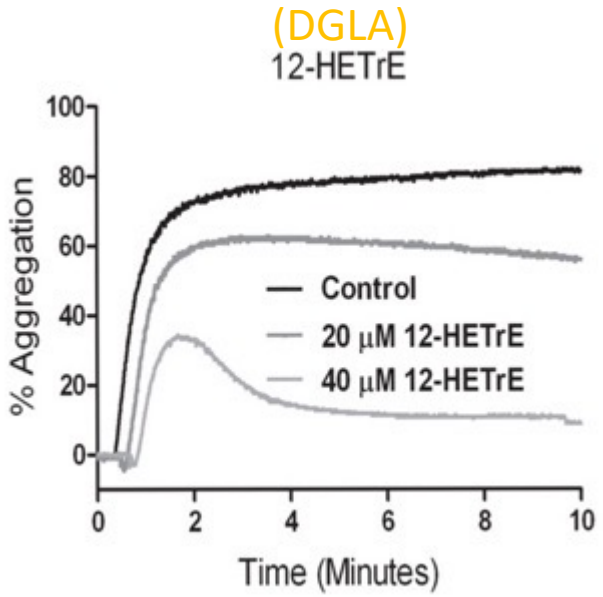


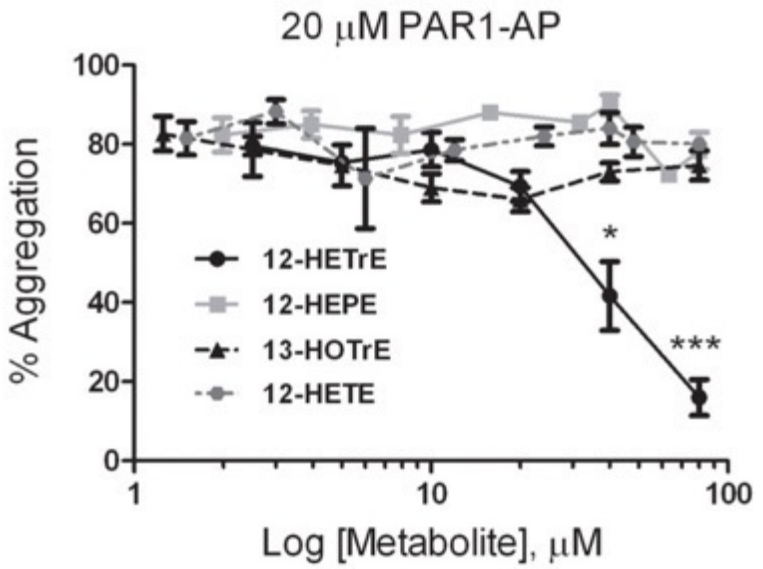
Eicosanoids function as negative regulators for platelet activation:

- 12-lipoxygenase oxidizes fatty acids to form bioactive lipids
- 12-LOX bioactive lipids represent novel targets for development of antiplatelet therapeutics
- Little is known about the mechanism by which 12-LOX bioactive lipids regulate platelet function, hemostasis, and thrombosis



Substrate	Product Name		Reduced Product
AA	12-HPETE (99.0%)		12-HETE
DGLA	12-HPETrE (99.0%)		12-HETrE
EPA	12-HPEPE (99.0%)		12-HEPE
DHA	14-HPDoHE (66%)	11-HPDoHE (33%)	14-HDoHE/11-HDoHE
ALA	13-HPOTrE (99.0%)		13-HOTrE
GLA	13-HPOTrE-γ (44.0%)	10-HPOTrE-γ (55.0%)	13-HOTrE-γ/10-HOTrE-γ
LA	No Product		
EDA	No Product		





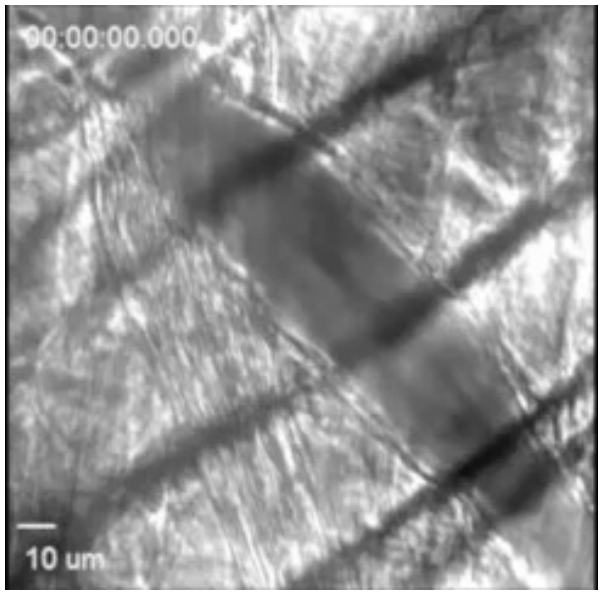
Ikei et al. J Lipid Res 2012; Tourdot et al. Front Pharmacol 2014

12(S)-HETrE protects vessel from Thrombosis

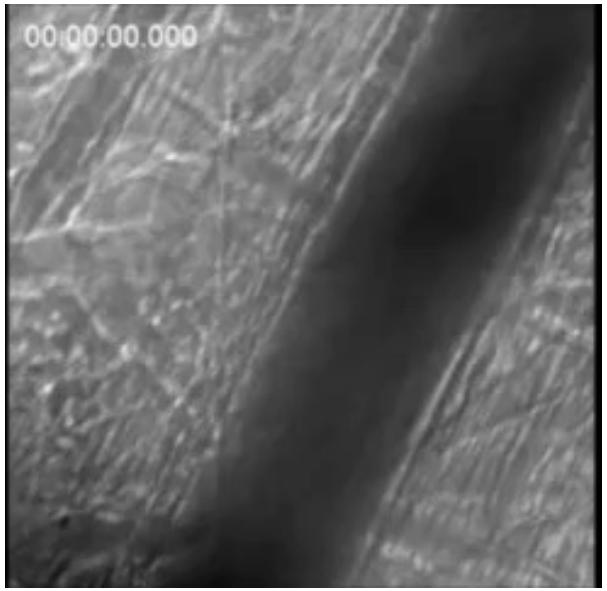
Control Vessel

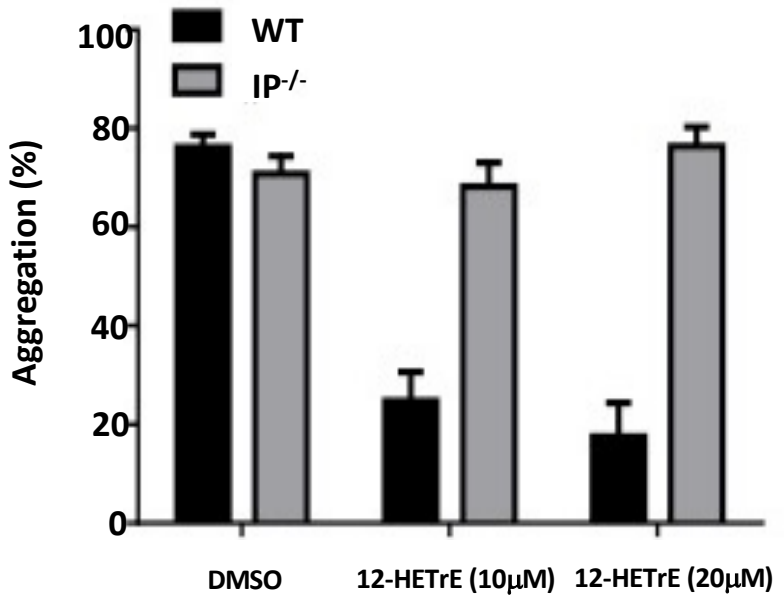
Platelets

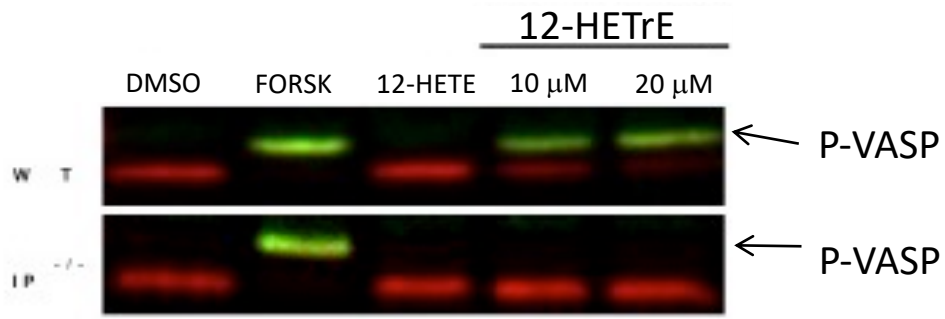
Fibrin

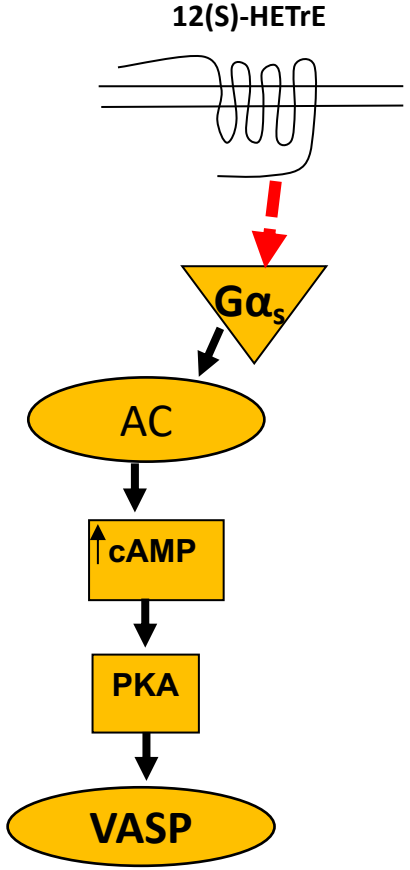


Vessel treated with **12(S)-HETrE**



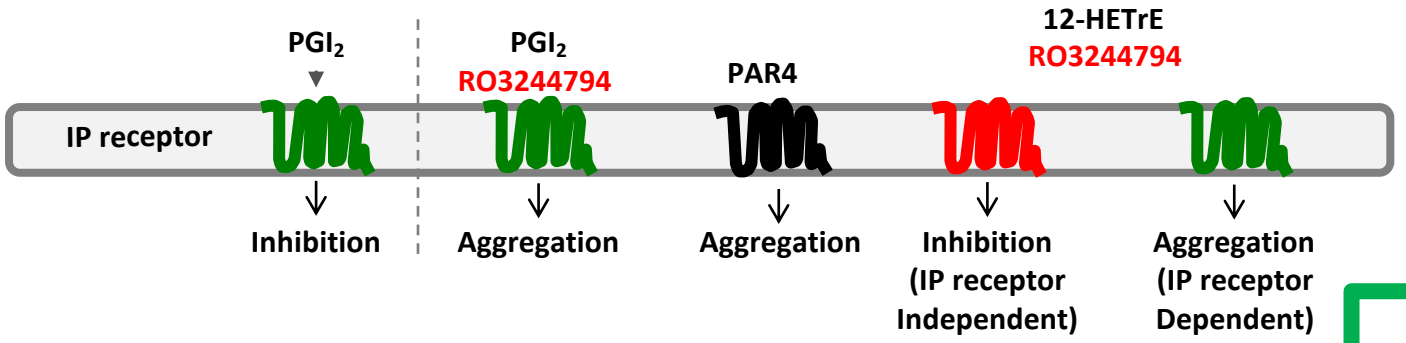






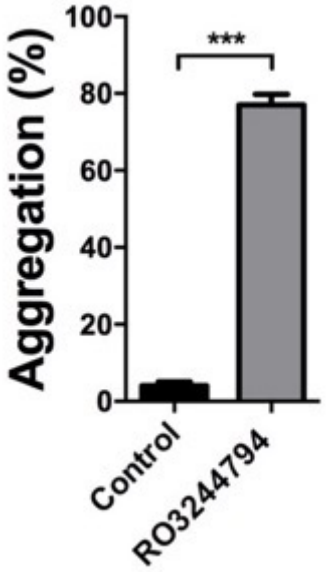
Yeung et al. ATVB 2016; Tourdot et al. Blood Adv 2017

12-HETrE signals through the IP receptor in human platelets

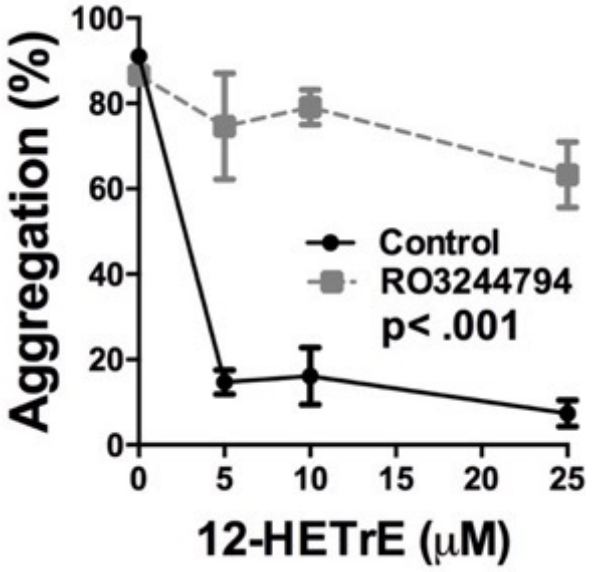


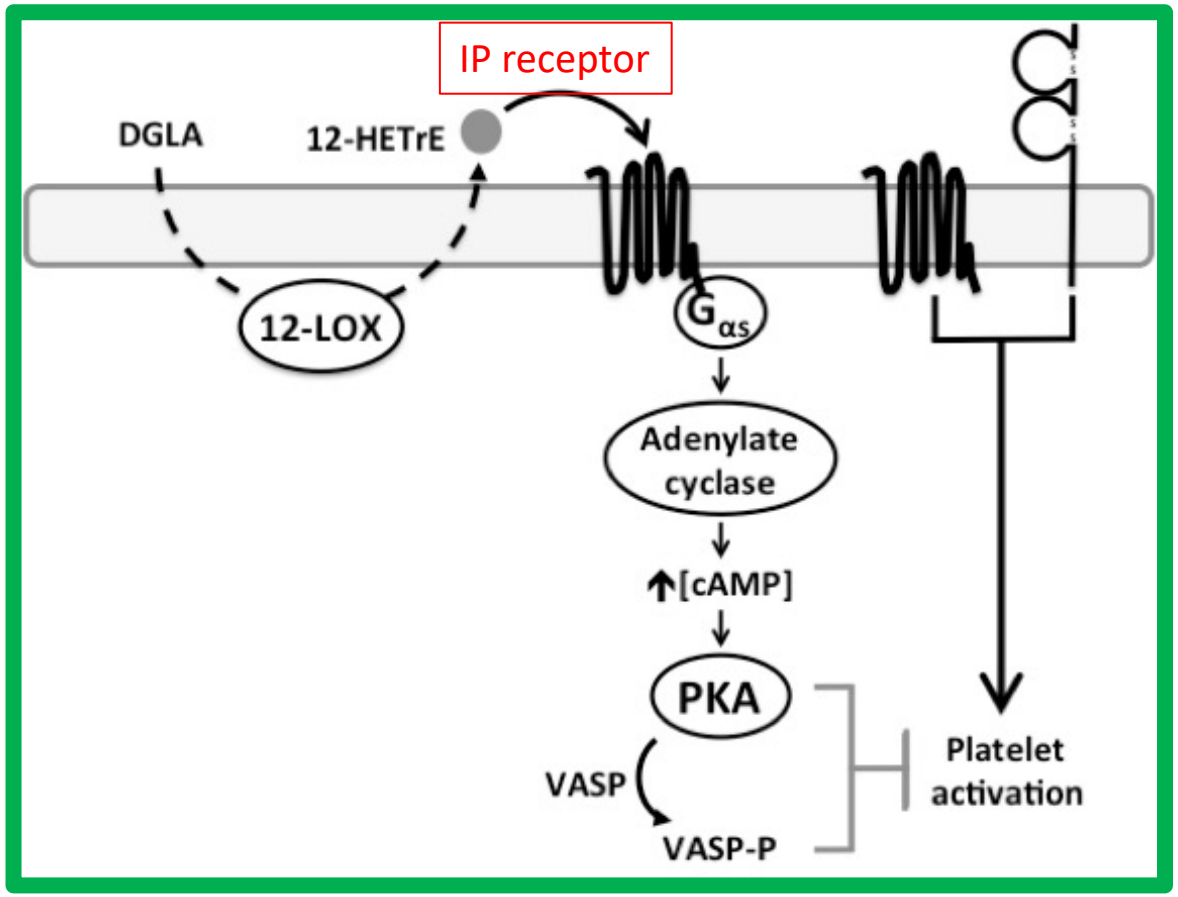
IP Receptor Antagonist

PGI_2



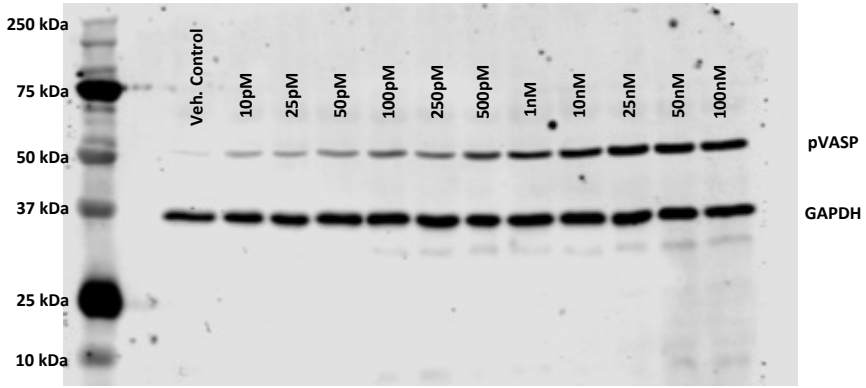
PAR4-AP

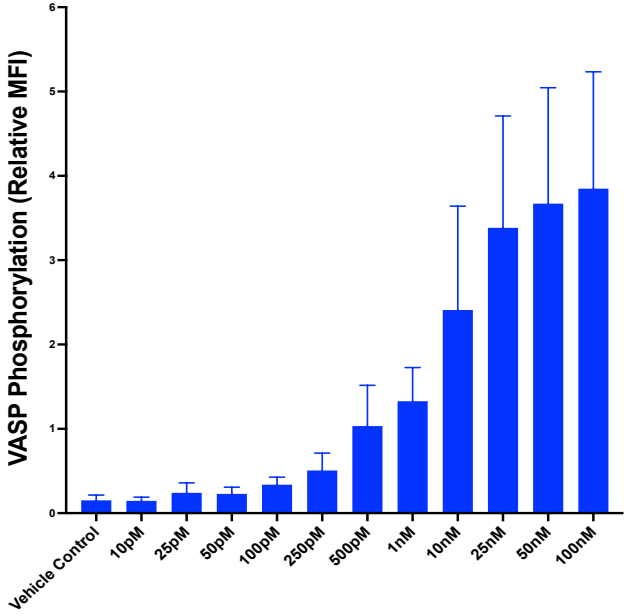




Tourdot et al. Blood Adv 2017

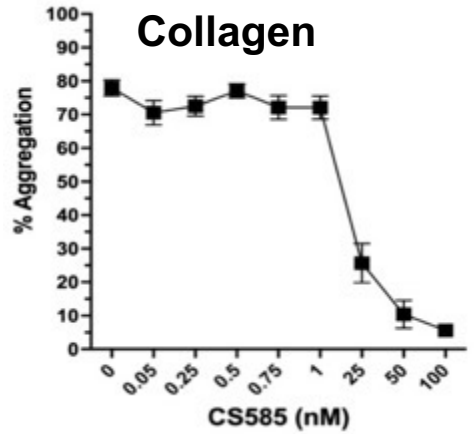
CS585 developed as a high potency analog of 12(S)-HETrE (human platelets)

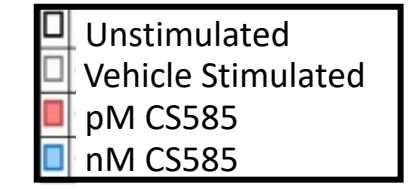


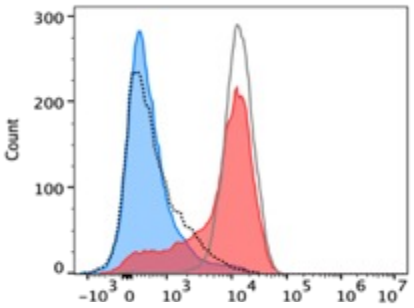


CS585 regulates Platelet function through:

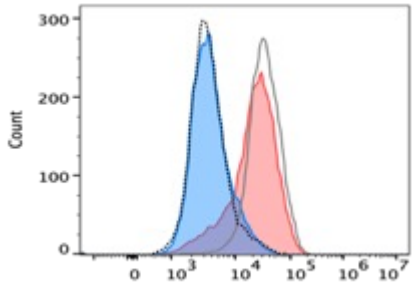
- VASP phosphorylation (IP receptor)
  - pM concentrations
- Integrin activation and granule secretion
  - aIIbb3
  - Alpha granule (CD62P; P-selectin)
  - Dense granule (CD63)
- Platelet aggregation



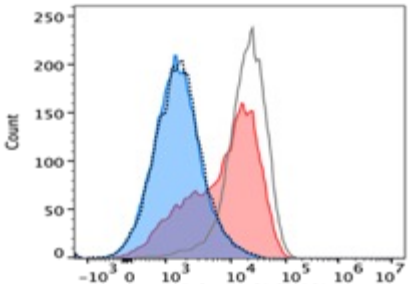




PAC1 FITC

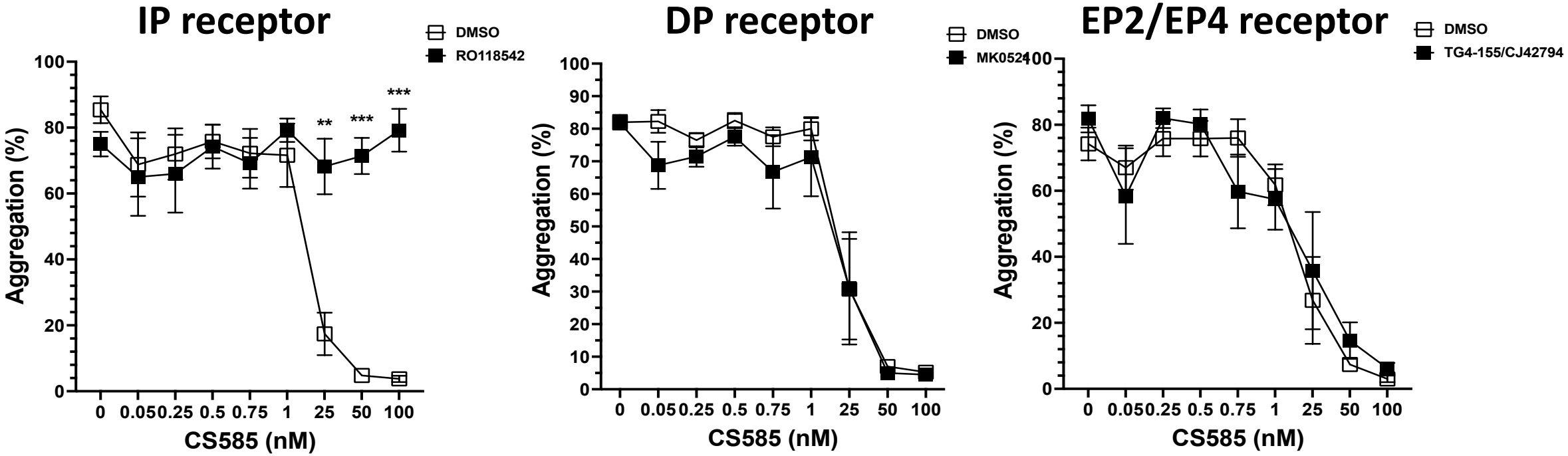


CD62P APC-Cy7



CD63 PE-Dazzle594

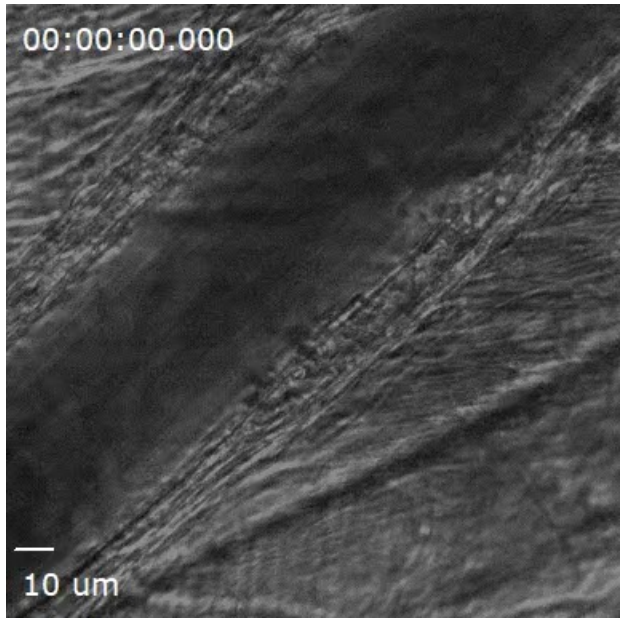
CS585 selectively signals through IP receptor



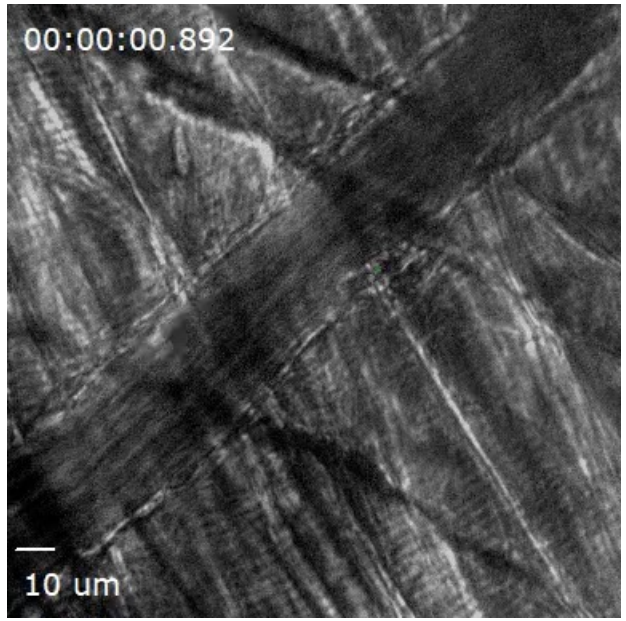
- CS585 inhibition of platelet aggregation is dependent on activation of the IP receptor
- CS585 inhibition is independent of the:
  - DP receptor
  - EP2 receptor
  - EP4 receptor

CS585 inhibits platelet clot formation following injury

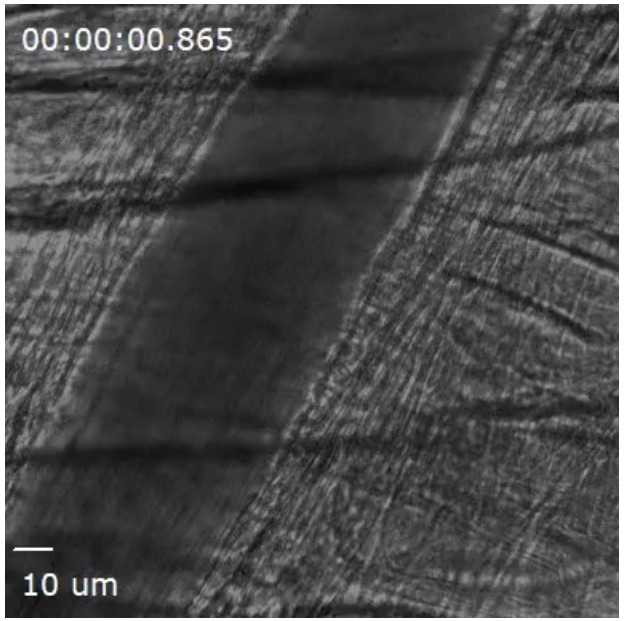
Vehicle control

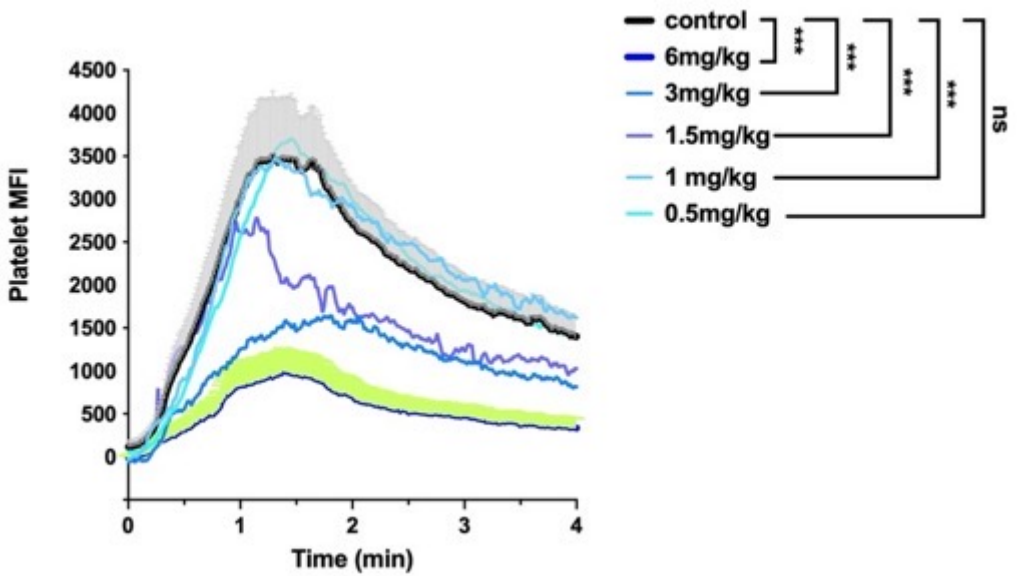


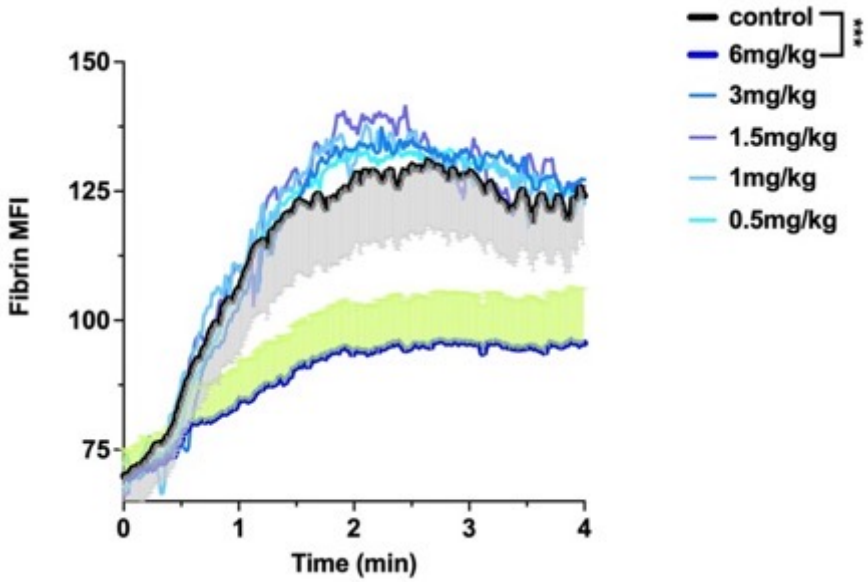
CS585 3mg/kg



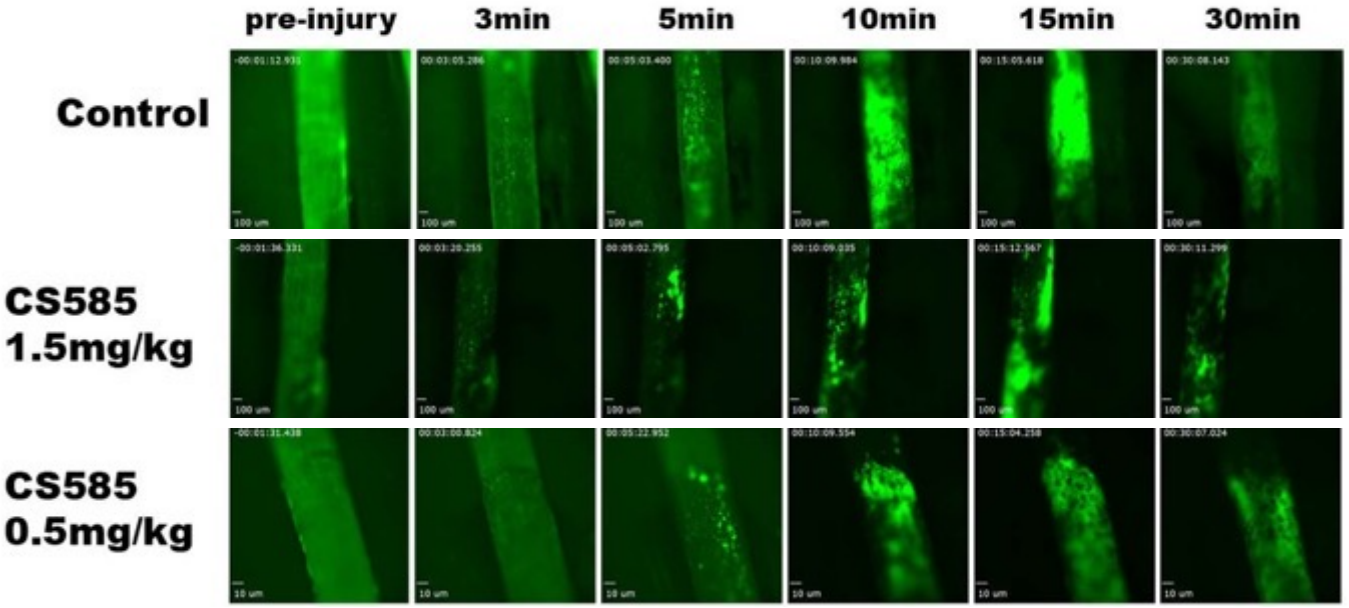
CS585 6mg/kg

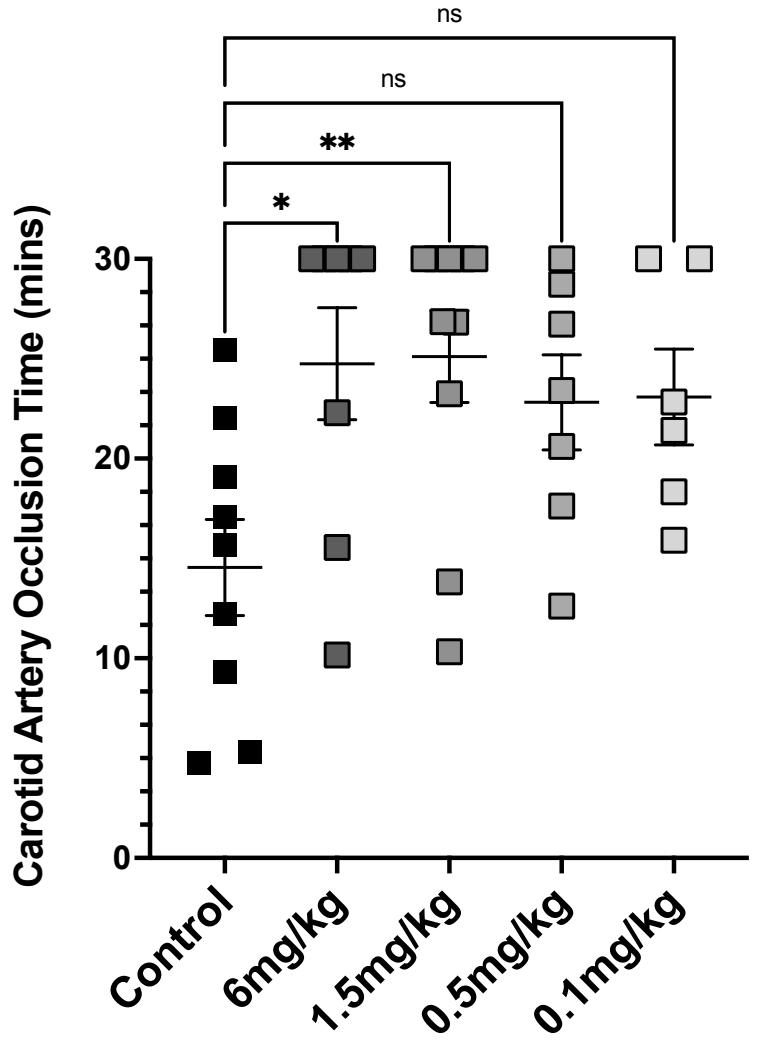




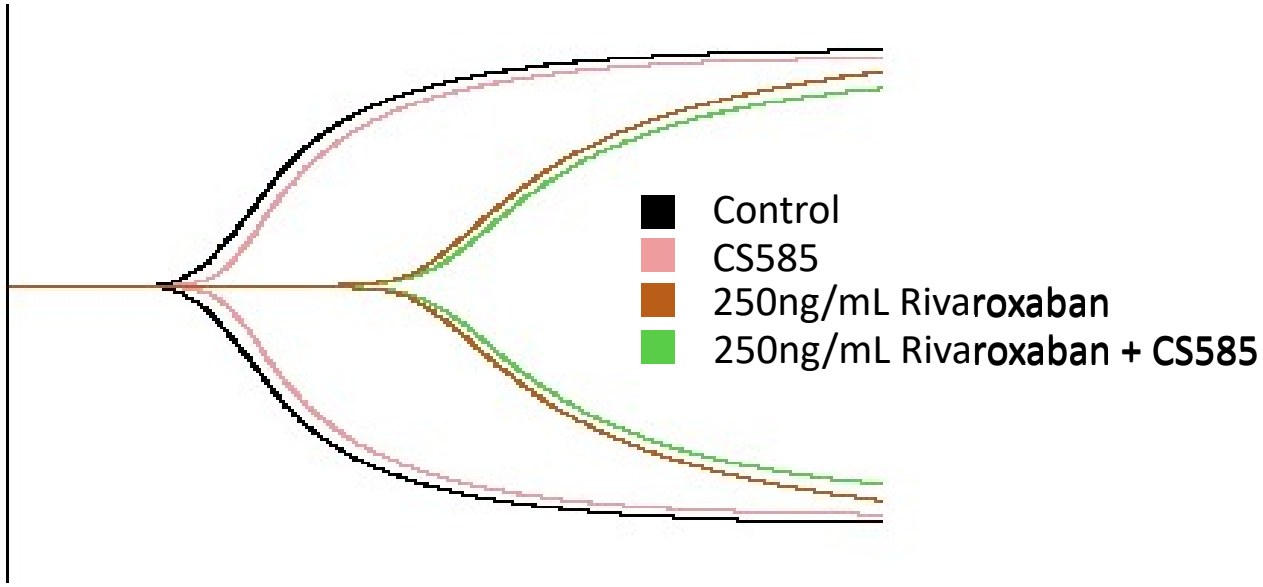


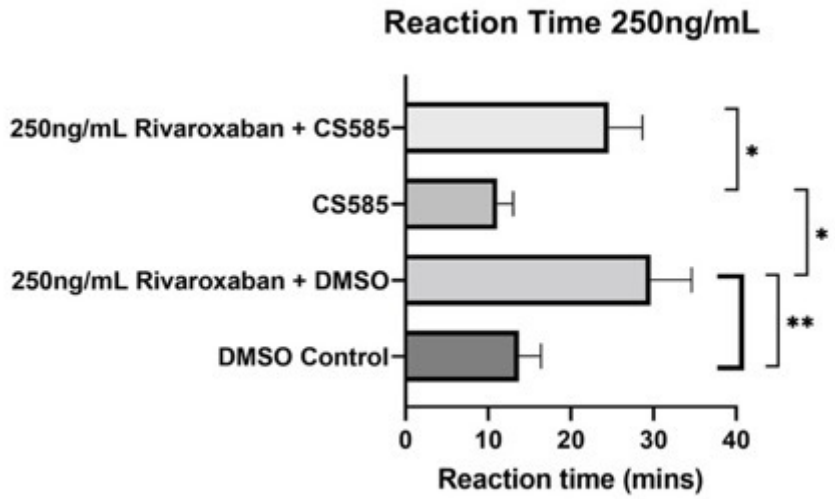
CS585 delays clotting and occlusion time in the carotid artery

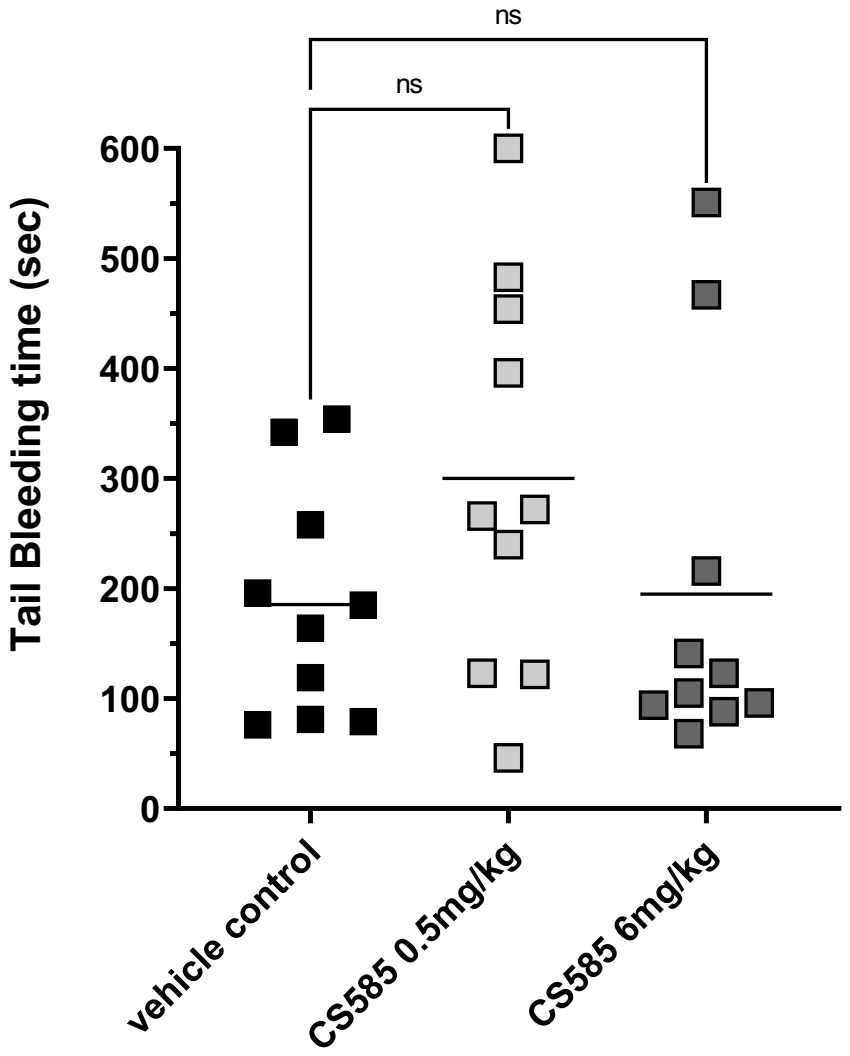




CS585 doesn't affect coagulation or bleeding

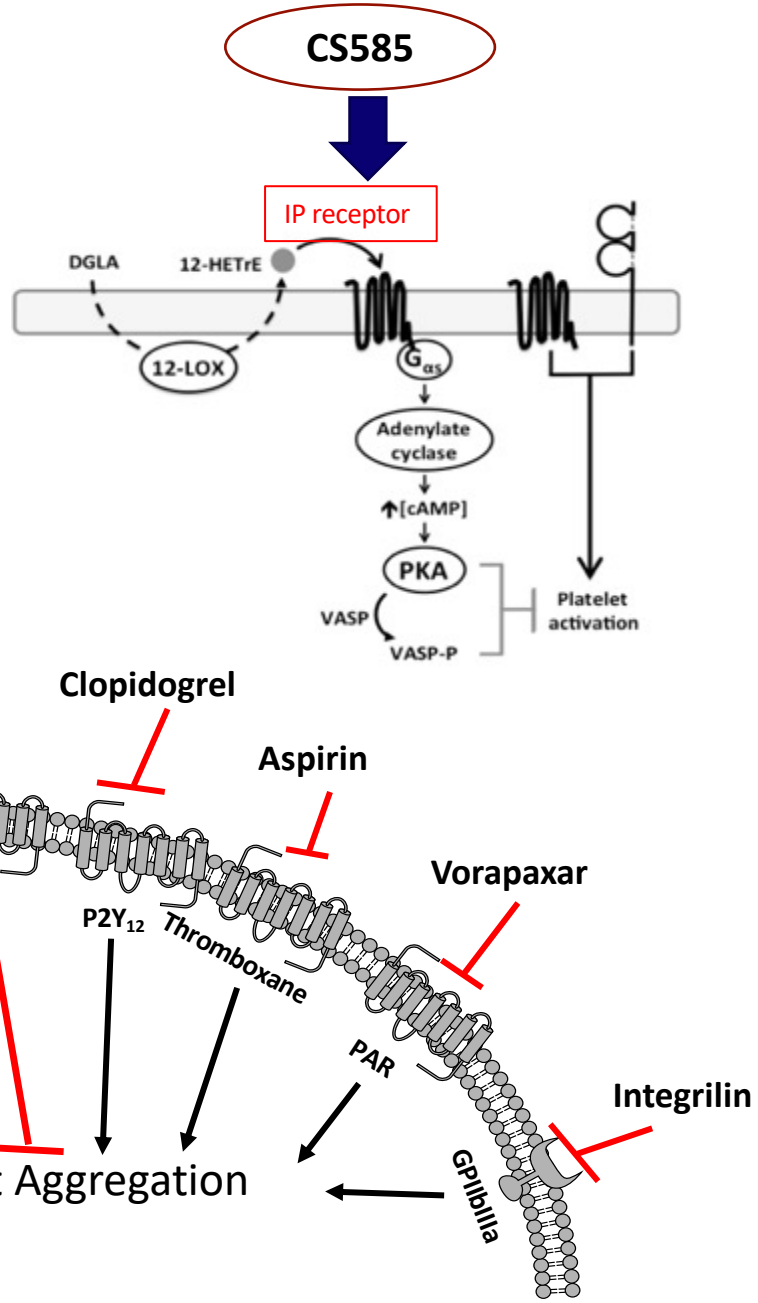






Summary:

- 12(S)-HETrE potently and selectively inhibits platelet activity and thrombosis through activation of the IP receptor
- CS585 is a novel IP agonist derived from 12(S)-HETrE
  - Stable in human plasma and blood
- CS585 selectively activates the IP receptor resulting in phosphorylation of VASP and inhibition of human platelet activation (Human blood)
  - Induces p-VASP
  - Inhibits activation of integrin aIIbb3
  - Inhibits granule secretion
- CS585 inhibits platelet activation in vivo (Mouse)
- CS585 potency is between 1000 to 100,000-fold more potent than 12(S)-HETrE at targeting IP receptor and regulating platelet function (Human).
- CS585 does not result in increased bleeding
  - No difference inTail Bleeding Time (Mouse)
  - No difference in coagulation time or amplitude by TEG (Human)



➢ **CS585 represents a new approach for prevention of thrombosis without increased bleeding**

Acknowledgements:

Current Holinstat Lab:

- Sylviane Lambert, PhD-Research Specialist
- Livia Stanger-PhD-Graduate Student
- Raymond Adili, MD-Associate Research Scientist
- Antonela Rodriguez, PhD-Graduate Studen
- Adriana Yamaguchi, PhD-Postdoctoral Fellow
- Eliana Botta, PhD-Postdoctoral Fellow
- Amanda Prieur, Phlebotomist
- Victoria Putzbach, BS-Technician
- Madison Caldwell, BS-Undergrad
- Andrew Rickenberg-Undergrad
- Pooja Yalavarthi-Undergrad
- Nicole Rhoads, BS-Technician

Accepting new Postdoctoral fellows

Collaborators:

- Cereno Scientific
  - Bjorn Dahlof
  - Niklas Bergh
- University of Gothenburg
  - Bjorn Dahlof
  - Niklas Bergh
- University of Michigan
  - Andrew White

National Institute of General Medical Sciences

Cereno Scientific

Support:

MTRAC

MEDC MICHIGAN ECONOMIC DEVELOPMENT CORPORATION

Mi-KICKSTART LIFE SCIENCES

NIH National Center for Advancing Translational Sciences

NIH National Institute on Aging

NIH National Heart, Lung, and Blood Institute

American Heart Association. | American Stroke Association.
Learn and Live.

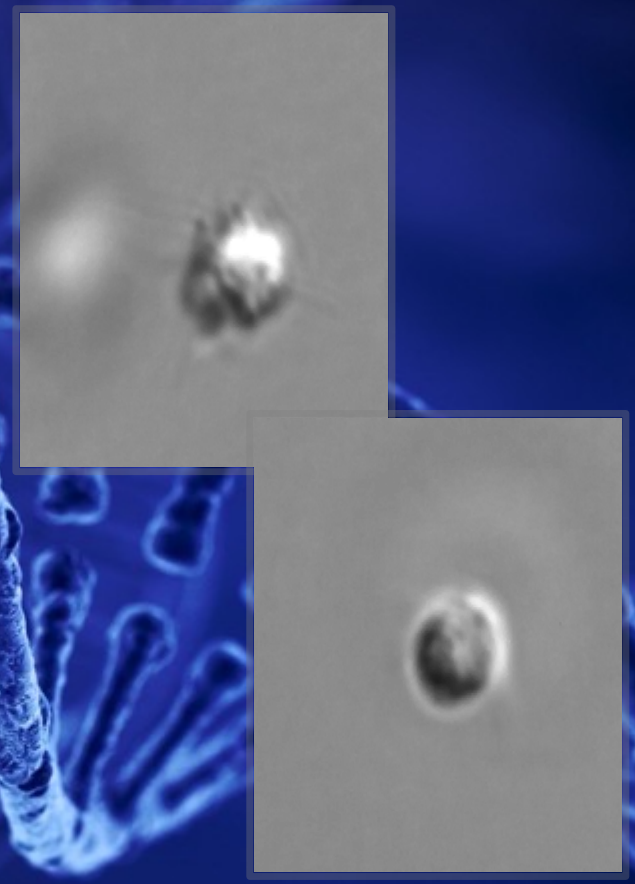
Cereno Scientific

CS014 – A Novel HDAC Inhibitor Regulating Platelet Activity, Fbrinolysis and Clot Stability for Prevention of Thrombosis Without Increased Risk of Bleeding

Dr. Michael Holinstat
Ass. Prof. at University of Michigan Medical School; and
Director Translation Research, Cereno

Cereno Scientific

CS014 is a novel HDAC inhibitor regulating platelet activity, fibrinolysis and clot stability for prevention of thrombosis without increased risk of bleeding

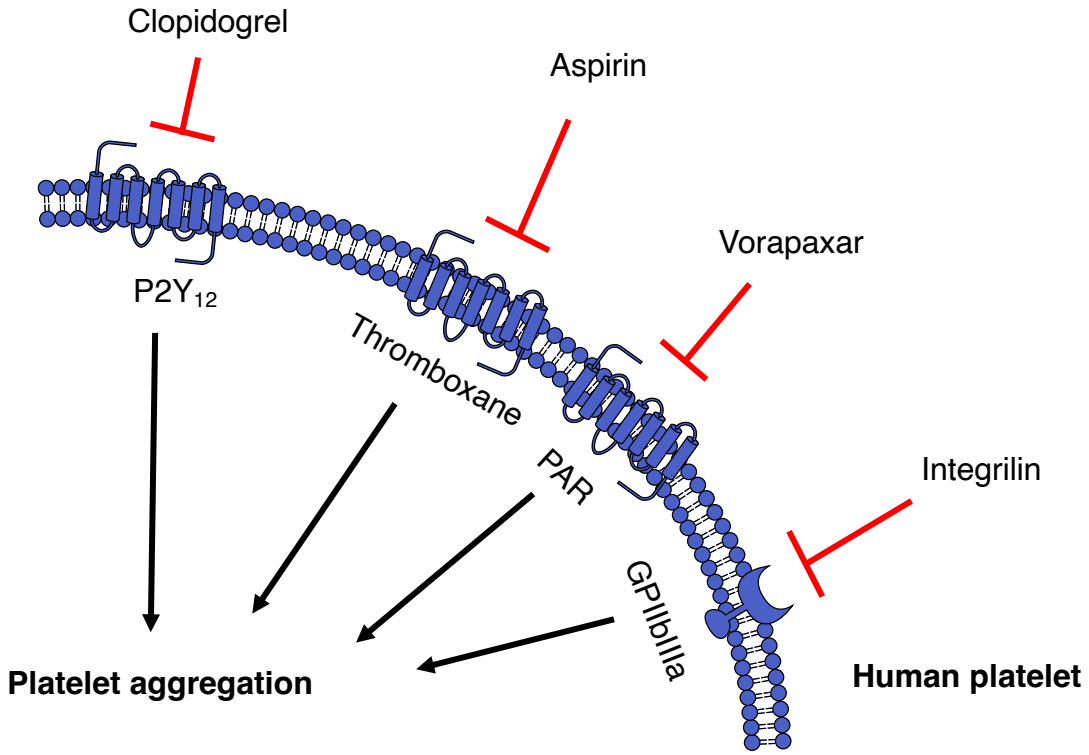


Michael Holinstat, PhD, FAHA

Departments of Pharmacology,
Internal Medicine (Division of Cardiovascular Medicine),
and Vascular Surgery, University of Michigan

Regulation of human platelet function

- Currently approved anti-platelet drug therapy has reduced the risk of morbidity and mortality by more than 26%.

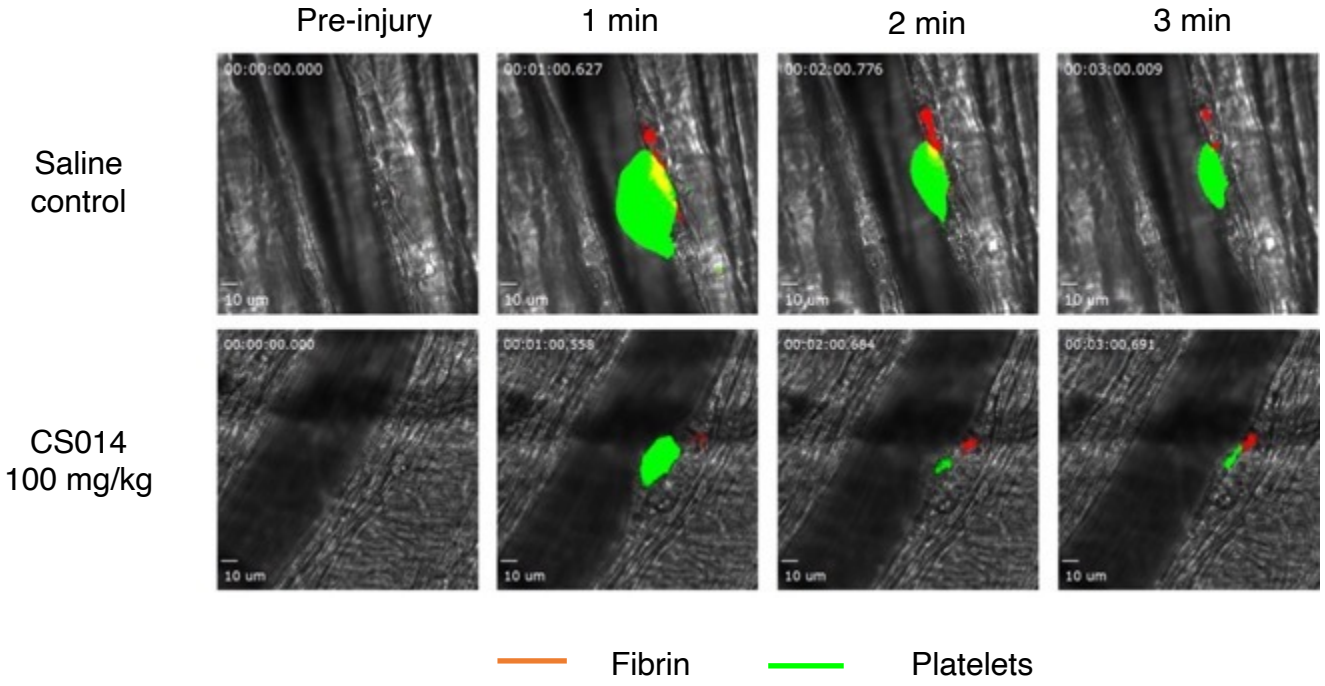


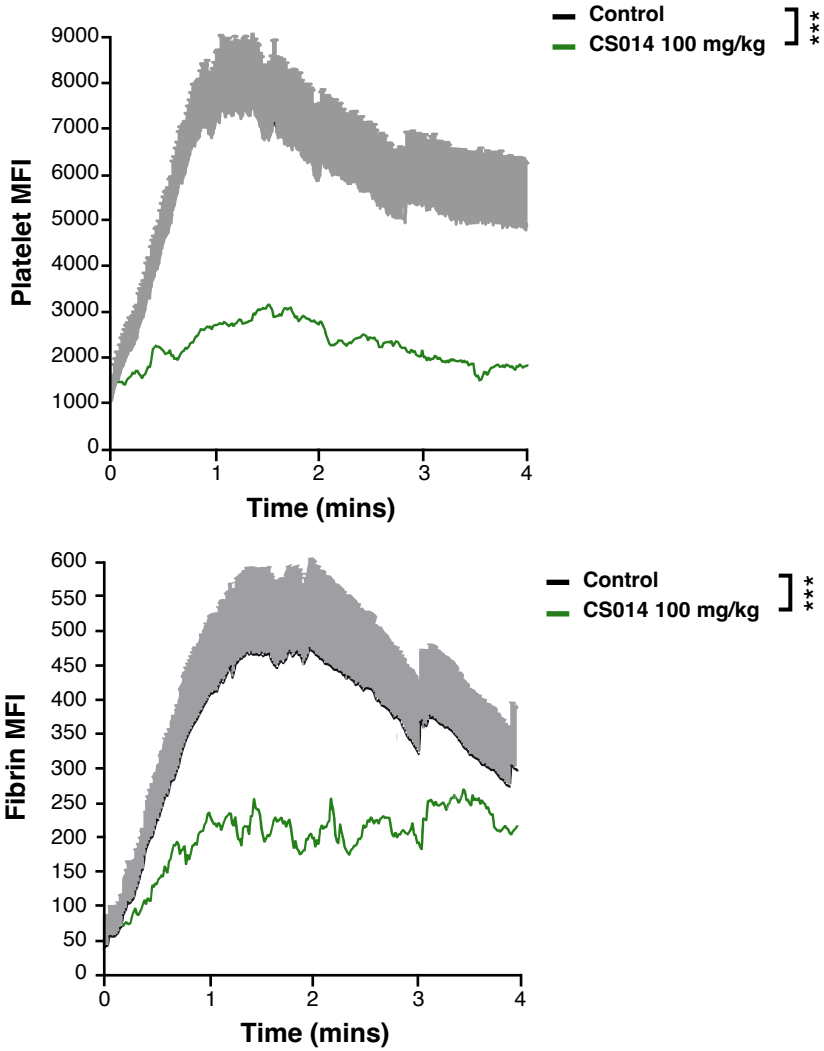
- While current anti-platelet therapy has significant health benefits, morbidity and death due to thrombotic events and bleeding still remains a significant problem.

New therapeutic approaches are warranted that will:

1. Decrease platelet activation and thrombosis
2. Exhibit only limited risk of bleeding

CS014 developed as an HDAC inhibitor with the ability to inhibit platelet clot formation following vascular injury



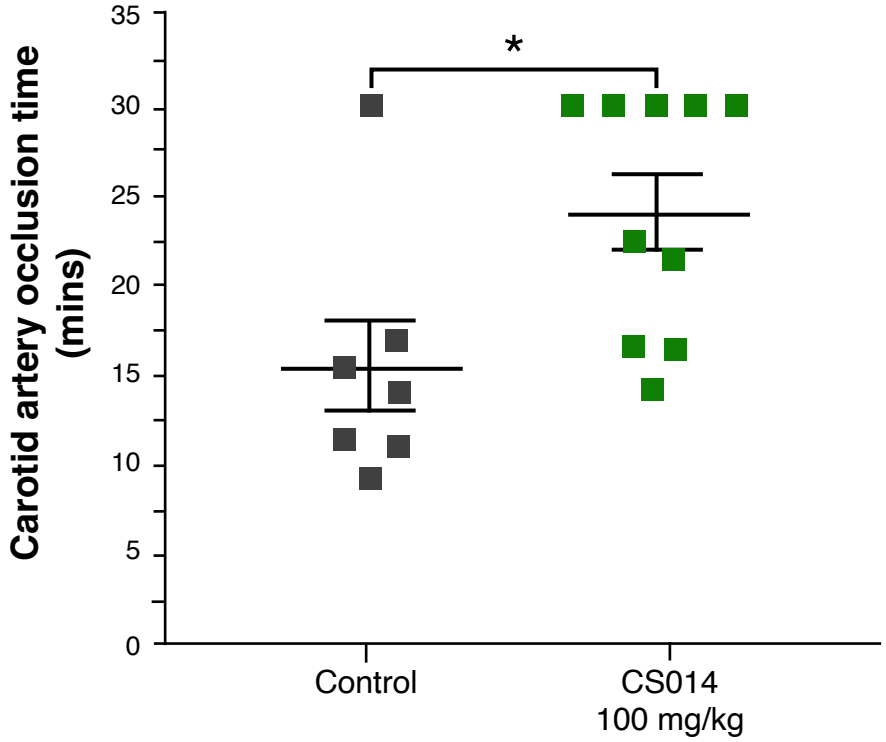


CS014 inhibits thrombosis by:

- **Attenuating platelet activation and clot formation at site of injury**
- **Significantly reducing fibrin formed at the site of injury**

***p<0.001 vs. control

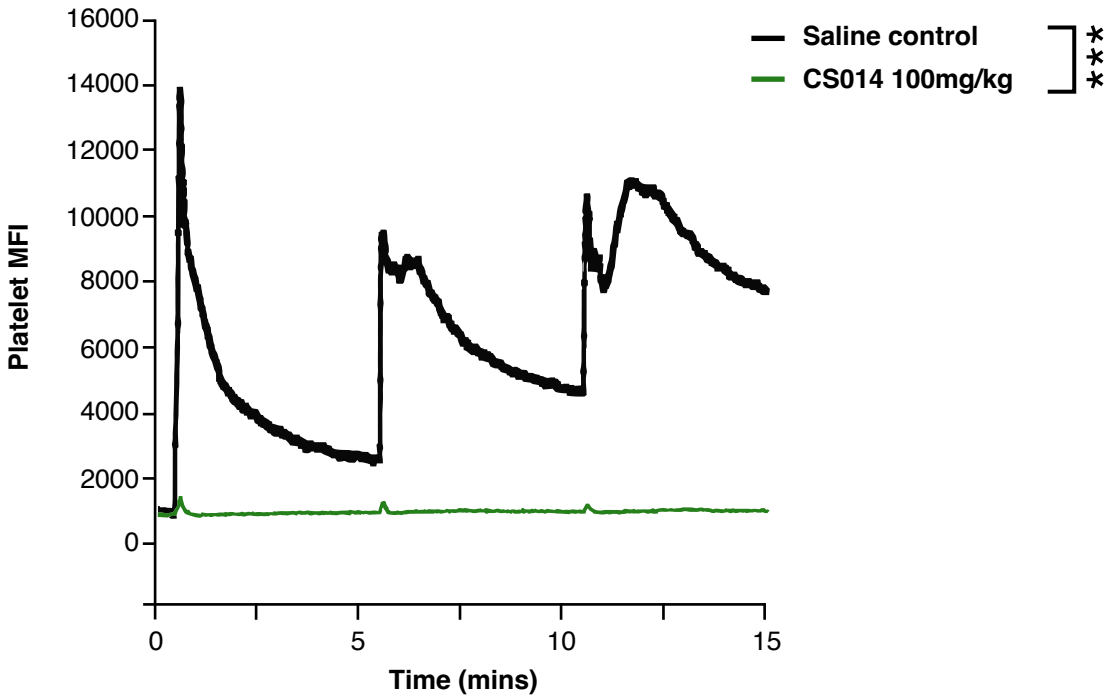
CS014 delays carotid artery occlusion time

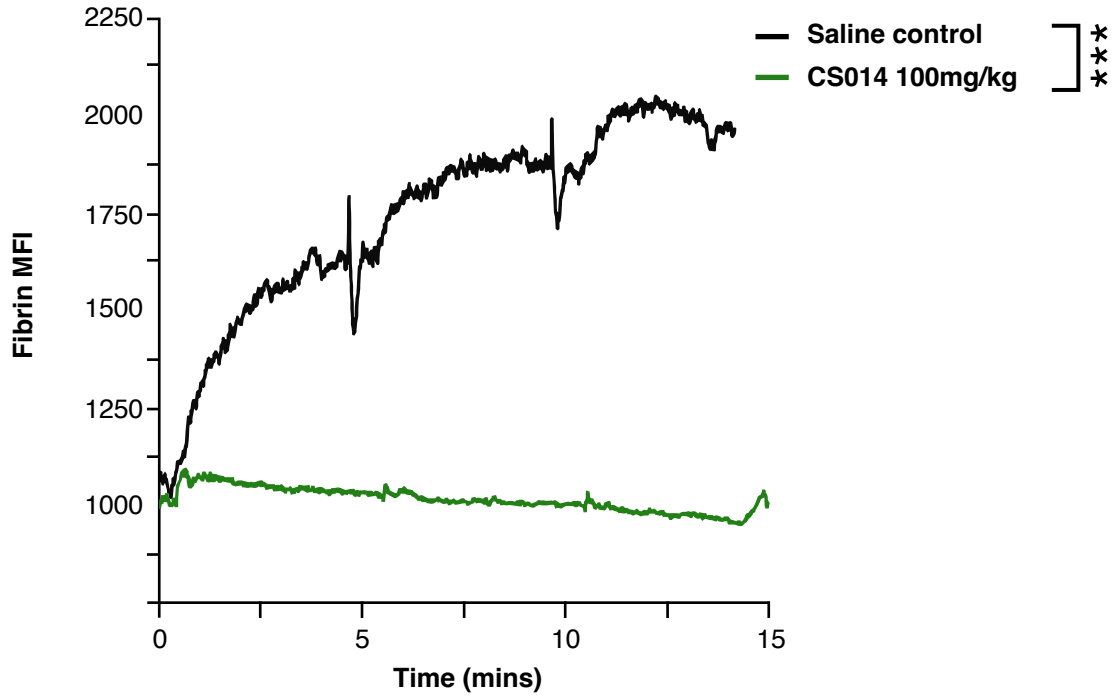


- CS014 significantly delays time to full occlusion of the carotid artery
- Destroying the vessel wall with 10% $FeCl_3$ results in full occlusion of the vessel in 15 minutes in control animals, but requires over 25 minutes in animals treated with CS014

*p<0.05 vs. control

CS014 prevents low shear clot formation and fibrin formation

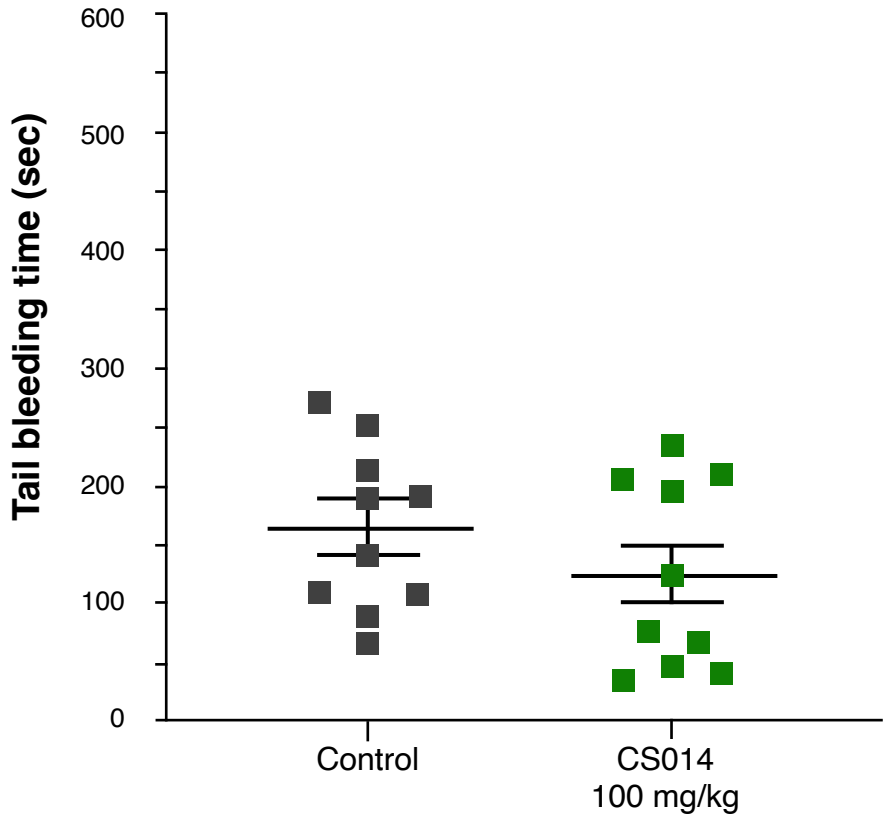




- CS014 prevents platelet clot formation following repeated vessel puncture in the saphenous vein (green)
- CS014 prevents fibrin formation following repeated vessel puncture in the saphenous vein (green) compared to control (black)

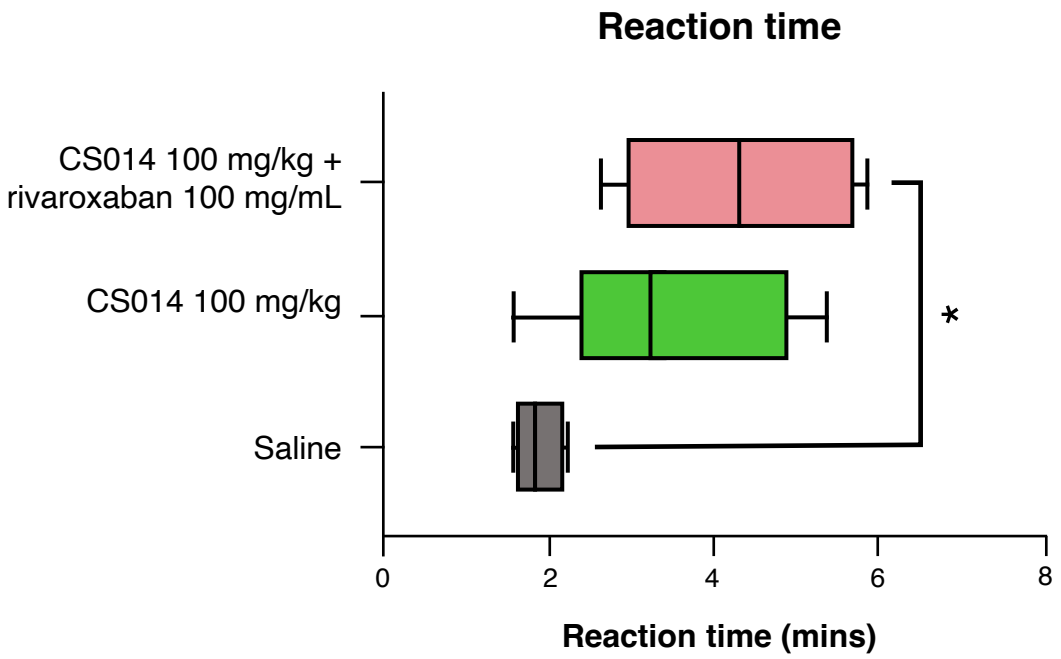
***p<0.001 vs. control

CS014 does not alter tail vein bleeding time



- CS014 has no increased time to cessation of bleeding compared to control mice following resection of tail
- CS014 does not demonstrate any increased risk for bleeding even at elevated levels of drug (tested on escalating concentration not shown)

CS014 does not alter coagulation activity in the blood



- CS014 did not alter reaction time in whole blood as assessed by TEG
- Rivaroxaban (an FXa inhibitor) significantly delays reaction time for clot formation in blood
- Reaction time for rivaroxaban plus CS014 was not significantly different from rivaroxaban alone, indicating no additional risk for bleeding with the combination of CS014 and an FXa inhibitor.

*p<0.05 vs. control

Conclusions:

- **HDACi CS014 inhibits both small and large vessel clotting and fibrin formation**
  - CS014 prevents high shear arterial platelet clot formation and fibrin formation following vascular injury
  - CS014 significantly delays vessel occlusion in high shear large vessels.
  - CS014 prevents platelet activation and fibrin formation in low shear conditions following injury
- **CS014 does not increase the risk for bleeding**
  - No difference in tail bleeding time
  - No difference in coagulation time by TEG
  - No additive effect of rivaroxaban with CS014 in bleeding risk assessment by TEG
- **CS014 represents a new class of inhibitors for prevention of platelet activation and thrombosis with potential protection from:**
  - Myocardial Infarction (MI)
  - Stroke
  - DVT
  - VTE

CS014 represents a potentially new drug class for prevention of thrombosis without increased bleeding

Cereno Scientific

Panel: The Need for True Innovation in CVD Management – Focus on PAH and Thrombosis

Dr. Björn Dahlöf
Chief Medical Officer, Cereno

Dr. Phil Adamson
Divisional Vice President and Chief Medical Officer
Heart Failure Division, Abbott

Dr. Michael Holinstat
Ass. Prof. at University of Michigan Medical School; and Director Translation Research, Cereno

Dr. Gunnar Olsson
MD, Prof, KI; SAB member, Cereno

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Questions from Audience

Cereno Scientific

Concluding Words

Sten R. Sörensen
Chief Executive Officer (CEO), Cereno

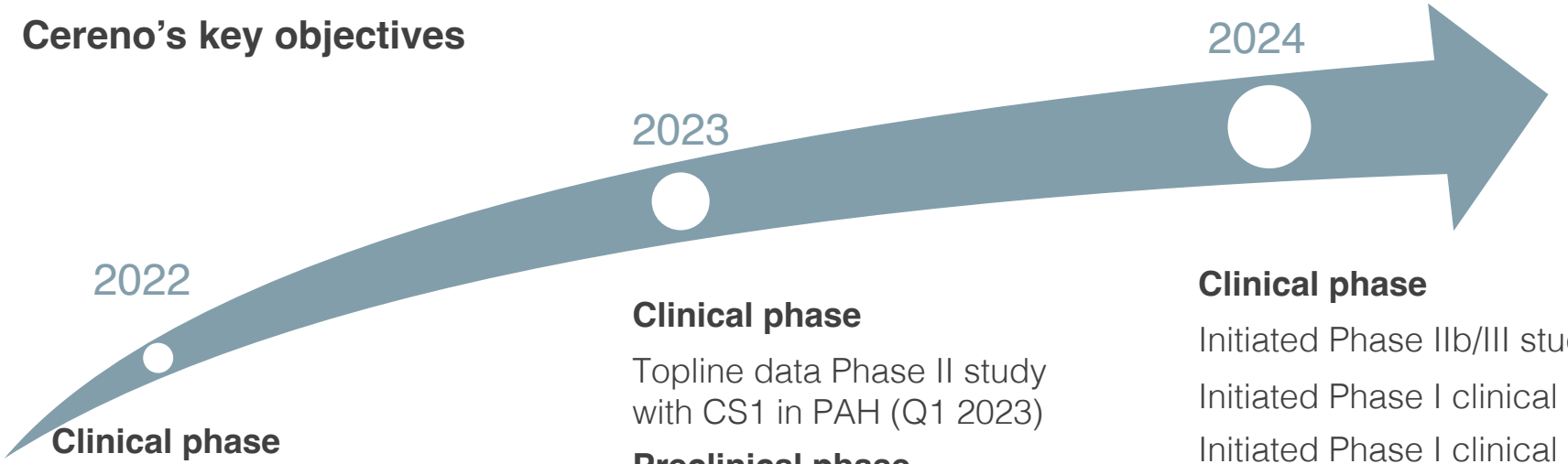
Full steam ahead in 2022

Key 2022 achievements and upcoming milestones

- ✓ CS585 and CS014 nominated in Q2 as CDs for further development towards IND submission for clinical programs
- ✓ CS585 thrombosis data (*prevention of thrombosis without increased risk of bleeding*) accepted for EHA June 2022
- ✓ CS014 thrombosis data (*prevention of thrombosis without increased risk of bleeding*) accepted for ESC Aug 2022
- ✓ First patient dosed in CS1's Phase II study in PAH in collaboration with Abbott
- ✓ Solidified IP position with two new patents across two of CS1's three patent families
- ✓ Executive management team strengthened with hiring of Head of Clinical Operations and Head of Preclinical Development
- New financing with up to 114 MSEK from exercise of warrants of series TO2 – Q3, 2022
- Topline data from CS1's Phase II study in PAH – Q1, 2023

Cereno's strategy to provide value for patients and stakeholders

Cereno's key objectives



2022

Clinical phase

Start Phase II study in PAH with CS1

Preclinical phase

Ongoing development programs for CS014

Ongoing development programs for CS585

2023

Clinical phase

Topline data Phase II study with CS1 in PAH (Q1 2023)

Preclinical phase

IND submission Phase I for CS014

IND submission Phase I for CS585

2024

Clinical phase

Initiated Phase IIb/III study in PAH with CS1

Initiated Phase I clinical studies with CS014

Initiated Phase I clinical studies with CS585

Utilizing the project portfolio's full potential on profitable markets within cardiovascular disease.

Warrants of series TO2

- The warrants of series TO2 were issued in Oct 2020 in connection to a directed share issue
- In total, 34.5 million warrants of series TO2 are outstanding and are trading on Spotlight Stock Market under the short name CRNO TO2B
- Upon full exercise, the company can receive a maximum of approximately SEK 114.8 million, based on the maximum subscription price.

Terms of the warrants:

- Each warrant give the holder the right to subscribe for one new share in Cereno during the period from 14 September 2022 to 28 September 2022.
- The subscription price will be 70% of the volume weighted share price during 29 August 2022 to 12 September 2022 (maximum subscription price is 3.33 SEK)

Cereno is well-positioned to become a leader in developing innovative treatments for cardiovascular disease

Global presence
Offices in biotech hot spots Gothenburg, Sweden and Boston, MA, US and significant R&D collaboration with University of Michigan, MI, US.

Inherently profitable market
Rare disease development has a high ROI, followed by larger and even more profitable CVD indications.

Extensive therapeutic potential of CV pipeline
Establishing Cereno in rare diseases creates an opportunity to expand into major cardiovascular indications.

Strong team with key competencies
Combining decades of commercial, medical, pharma development and IP experience.

External validation
Cereno's leadership and portfolio have attracted world-class scientific advisors and collaboration with one of the leading healthcare companies.

Cereno Scientific is a clinical stage biotech company within cardiovascular diseases. The lead drug candidate, CS1, is a Phase II candidate in development for the treatment of the rare disease pulmonary arterial hypertension (PAH). CS1 is an HDAC (histone deacetylase) inhibitor that acts as an epigenetic modulator with pressure-reducing, reverse-remodeling, anti-inflammatory, anti-fibrotic and anti-thrombotic properties, all relevant for PAH. A clinical Phase II study is ongoing to evaluate CS1's safety, tolerability, and efficacy in patients with PAH. A collaboration agreement with global healthcare company Abbott allows Cereno to use their cutting-edge technology CardioMEMS HF System in the study. Cereno also has two promising preclinical drug candidates in development for cardiovascular disease through research collaborations with the University of Michigan. Drug candidate CS585 is a stable, selective, and potent prostacyclin receptor agonist. In preclinical studies CS585 has been documented to target the IP receptor for prevention of thrombosis without increased risk of bleeding. Drug candidate CS014 is a novel HDAC inhibitor with epigenetic effects. In preclinical studies CS014 has been documented to regulate platelet activity, fibrinolysis and clot stability for prevention of thrombosis without increased risk of bleeding. Cereno Scientific is headquartered in Gothenburg, Sweden, and has a US subsidiary Cereno Scientific Inc. based in Kendall Square in Boston, Massachusetts, US. Cereno is listed on the Swedish Spotlight Stock Market (CRNO B).