The vascular NMDA receptor in Pulmonary Arterial Hypertension, an out-of-the-box academic scientific strategy towards therapeutic innovation

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Innovations to fight respiratory diseases

Prevention, research and treatments

December 3-4th 2024

Biocitech

Out of Breath?
Think of Pulmonary Arterial Hypertension (PAH)

Symptoms

- Shortness of breath
- Chest pain
- Dizziness and fainting
- Exertion fatigue

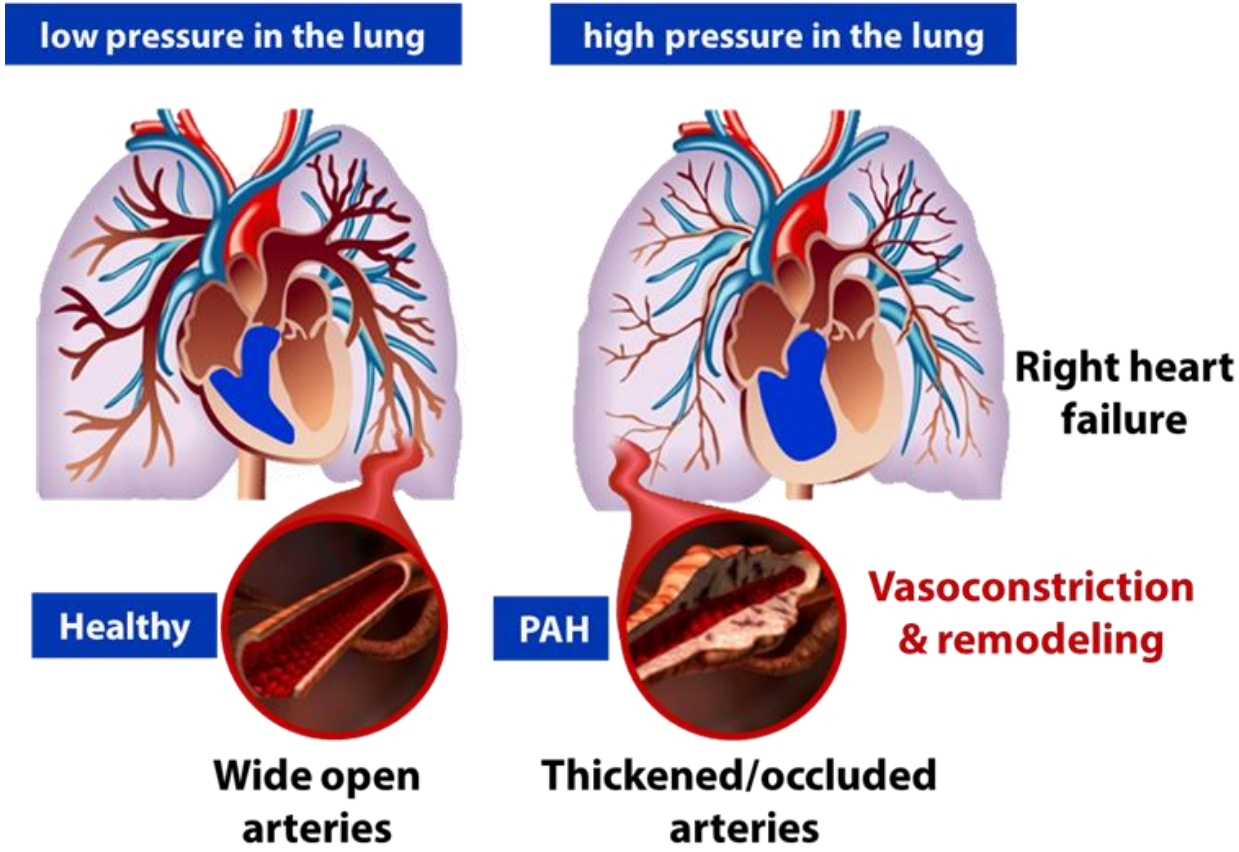
50 cases/million adults
Rare disease: ORPHA:182090

40 K
US+EU
PAH patients

6-7
Years
median survival

PAH Patients DO NOT have time

PAH, an unmet medical need with no cure



1 out of 10 patients dies every year

14
Drug approvals over the last 20 years

vasodilators

Improved survival and quality of life

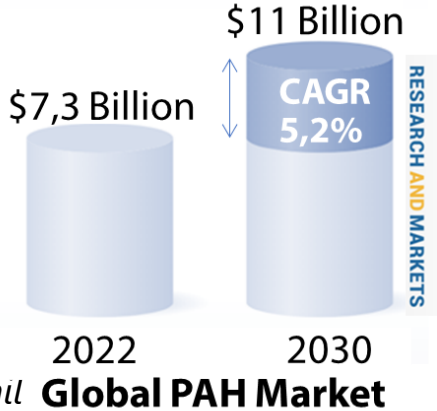
No cure
Hope in disease modifying therapies

High
Unmet medical need

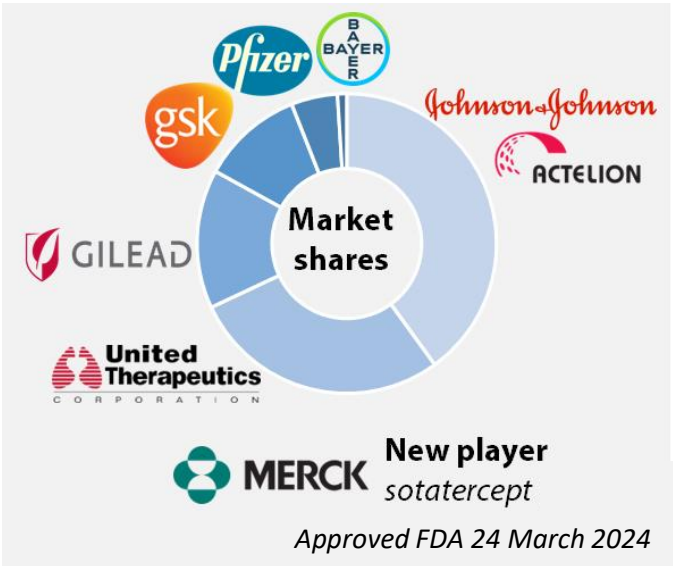
$7.3B
Global Market

6 Major companies

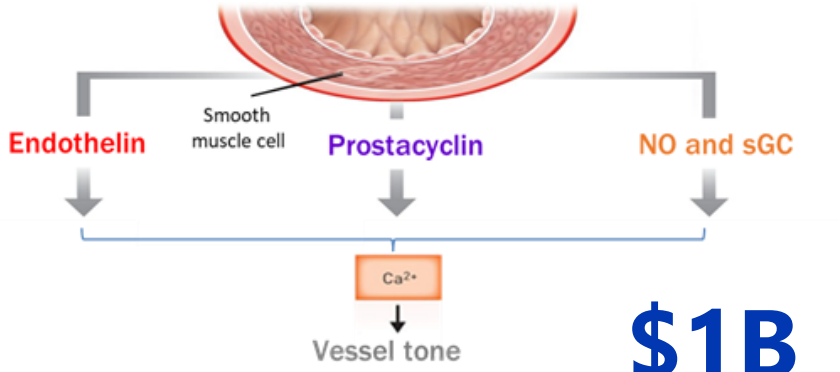
2 Blockbusters
bosentan, treprostinil



https://www.researchandmarkets.com/reports/3989875/



Since 1995, vasodilators, me-too non-healing drugs



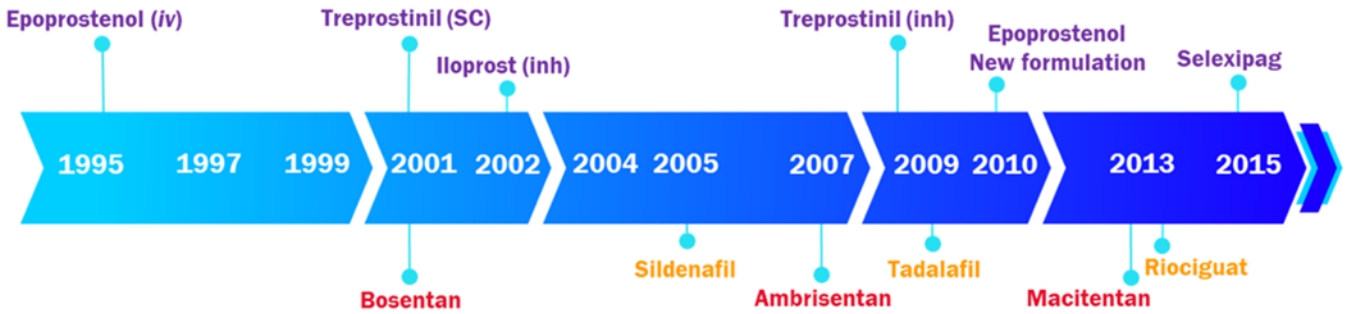
- Endothelin receptor antagonists
- Prostacyclin and analogs
- PDE5 inhibitors and sGC stimulators

Market $7 billions

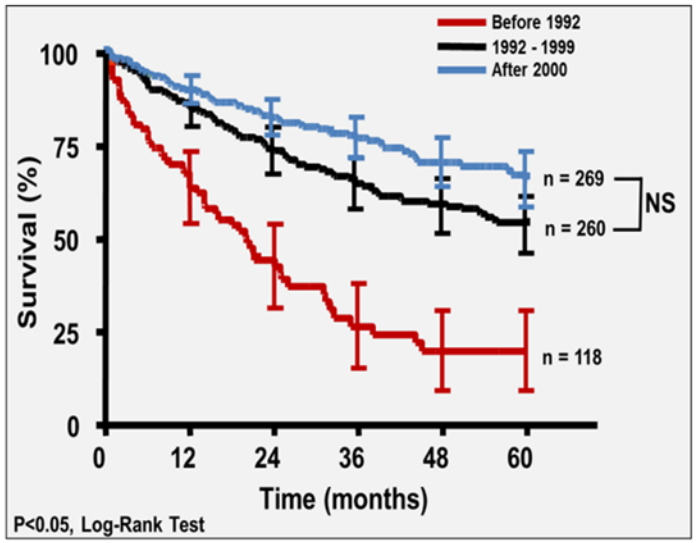
$1B

Epoprostenol (*iv*) — 1995
Treprostinil (SC) — 1997
Iloprost (inh) — 1999
Bosentan — 2001
$1.5B
Sildenafil — 2002
Ambrisentan — 2004
Tadalafil — 2005
Treprostinil (inh) — 2007
Macitentan — 2009
Epoprostenol New formulation — 2010
Riociguat — 2013
Selexipag — 2015

PAH, the clinical need to solve

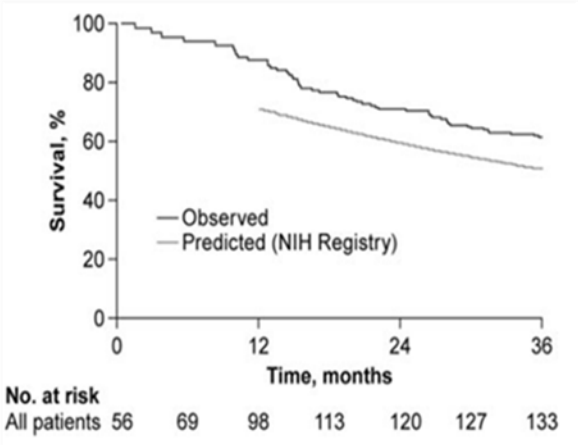


Current therapeutic approches



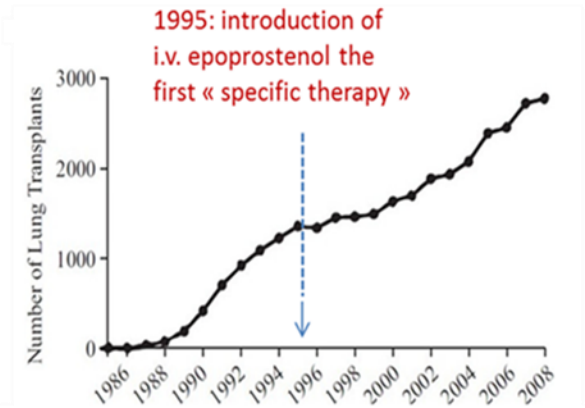
- Real technological/clinicalprogress with epoprostenol
- Combination therapy: Impact on survival ?

Meeting the challenge…



We still loose 10% patients/year, despite current PAH management strategies (combined therapies)

NIH, National Institutes of Health. Humbert M et al. 2010;



The number of transplantations continue to increase despite the so-called « specific therapies »

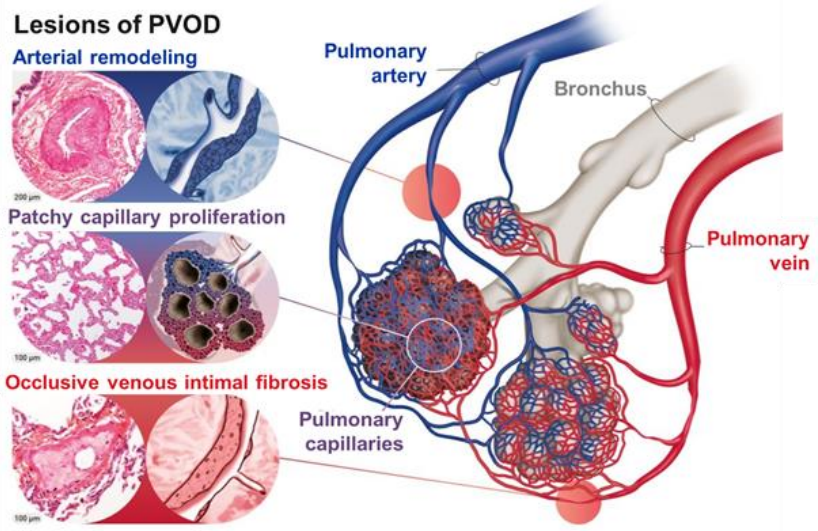
Georges P et al Pulmonary Circulation 2011

Pulmonary Veno-Occlusive Disease (PVOD): the most severe form of PAH, with no solution

10% of PAH patients

Low blood O_2 level

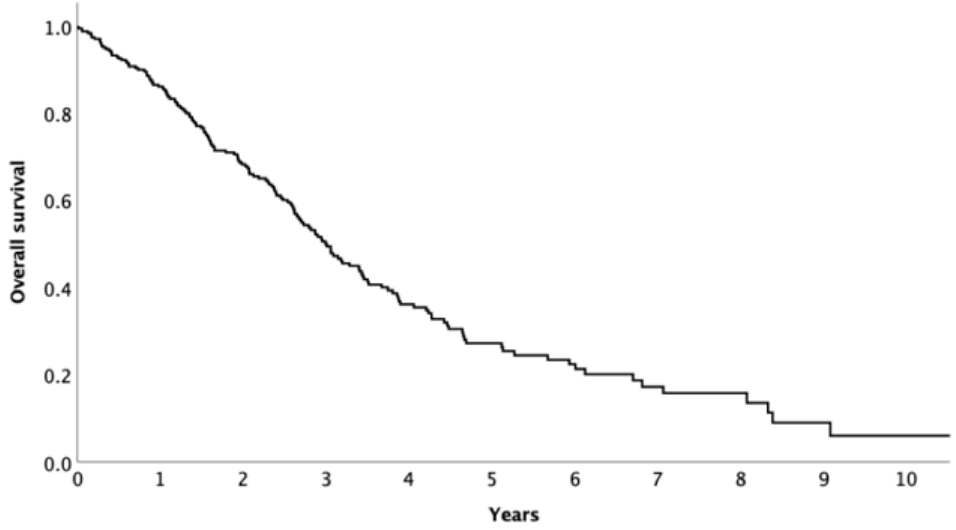
Non-responders
to existing PAH drugs



Adapted from Montani D, *Eur Respir J* 2016

Lung transplant
is the only option, if eligible

<3 yr median overall survival



Montani D. *et al.*, 2023, PVOD French registry [2006-2022], personal communication

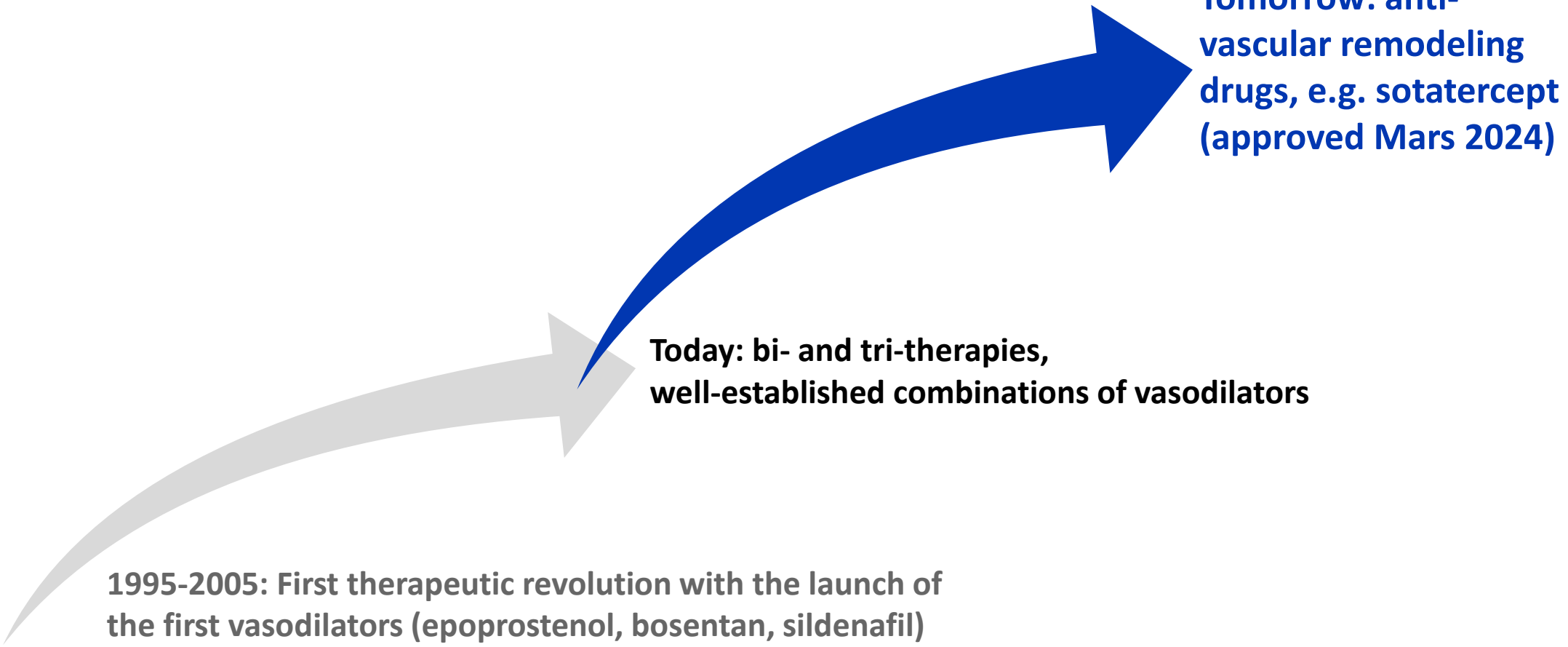
2 out of 3 patients dye within 2

It is urgent to change the game…
Which solution?

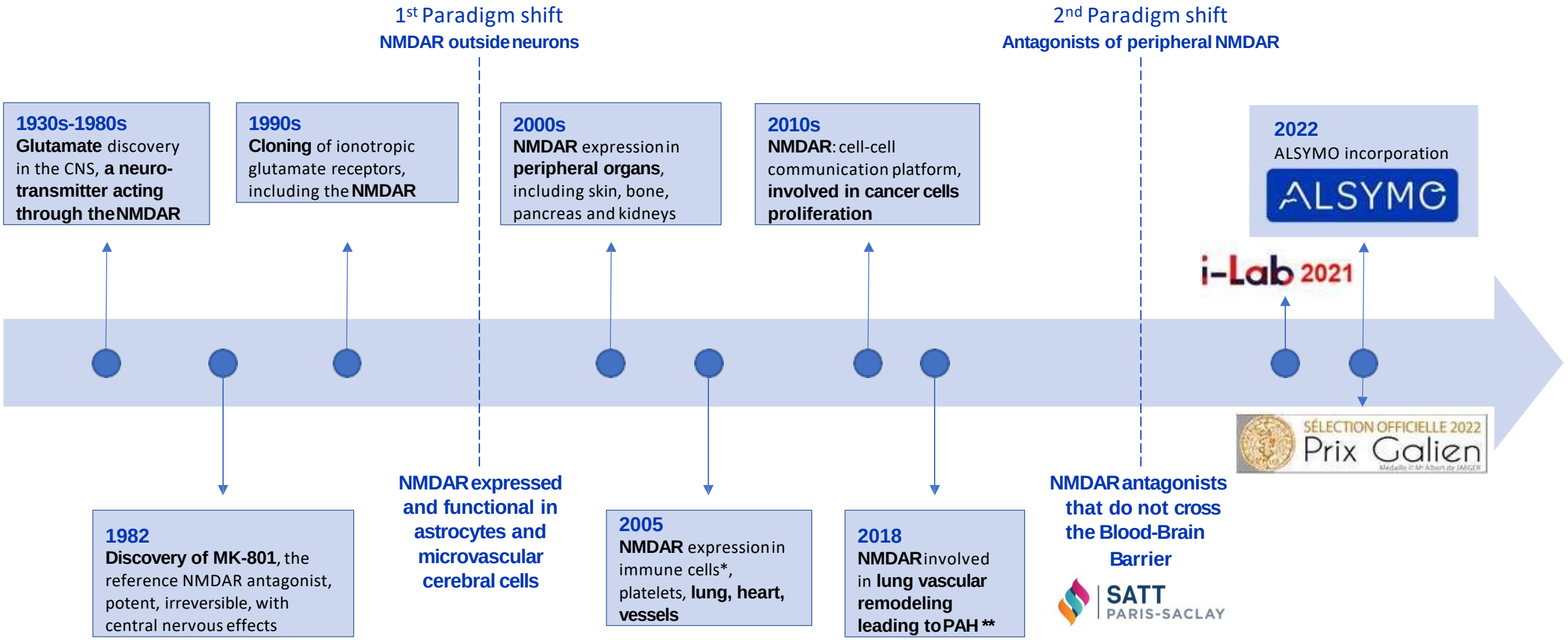
RIGHT TARGET
SMART DRUGS

ALSYMO

New drugs able to change the course of PAH are eagerly awaited



The NMDAR, a new therapeutic target in respiratory diseases



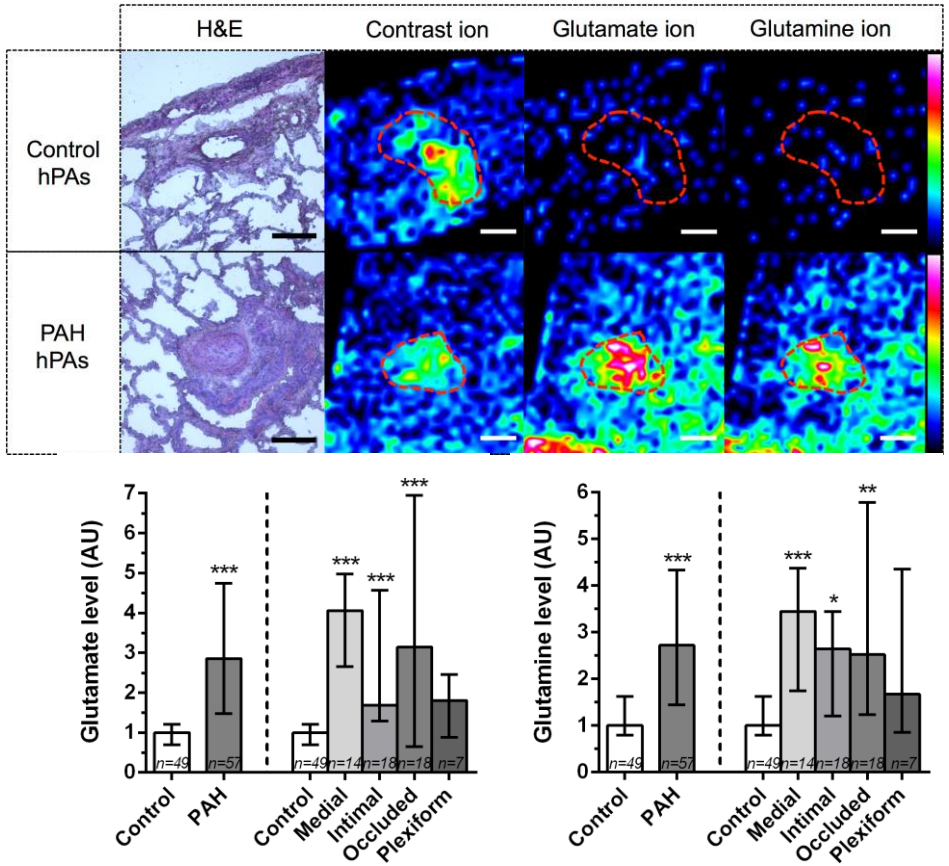
* Affaticati, et al Cell death differentiation 2011

** Dumas et al, Circulation 2018
Quatredeniers et al, AJP-Lung 2019

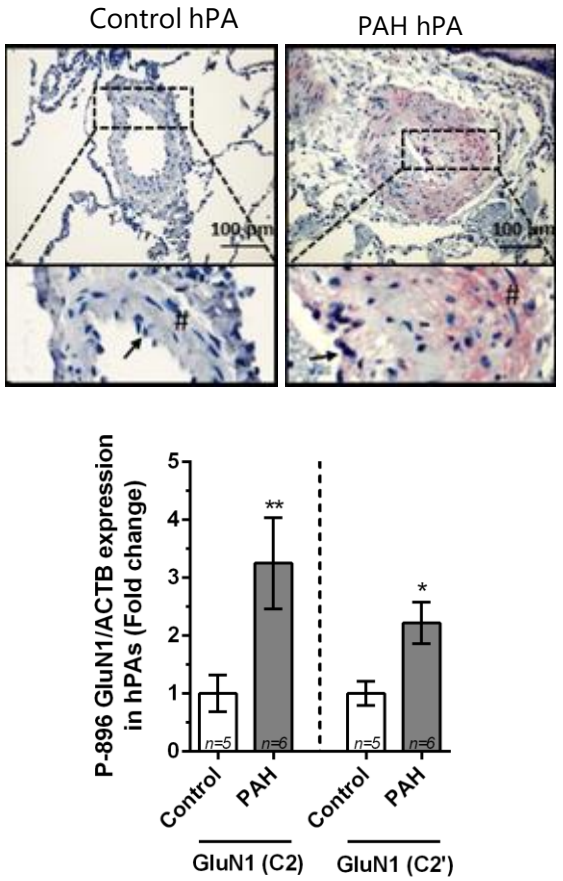
ALSYMO

The NMDA Receptor pathway is engaged in PAH patients

Mass spectrometry imaging on human lung sections



Immunohistochemistry on human lung sections



- The NMDAR is engaged, i.e. phosphorylated, **only** in remodeled PAH arteries
- Glutamate and its precursor glutamine accumulate **only** in remodeled PAH arteries

Working hypothesis

The NMDAR promotes lung vascular remodeling leading to PAH

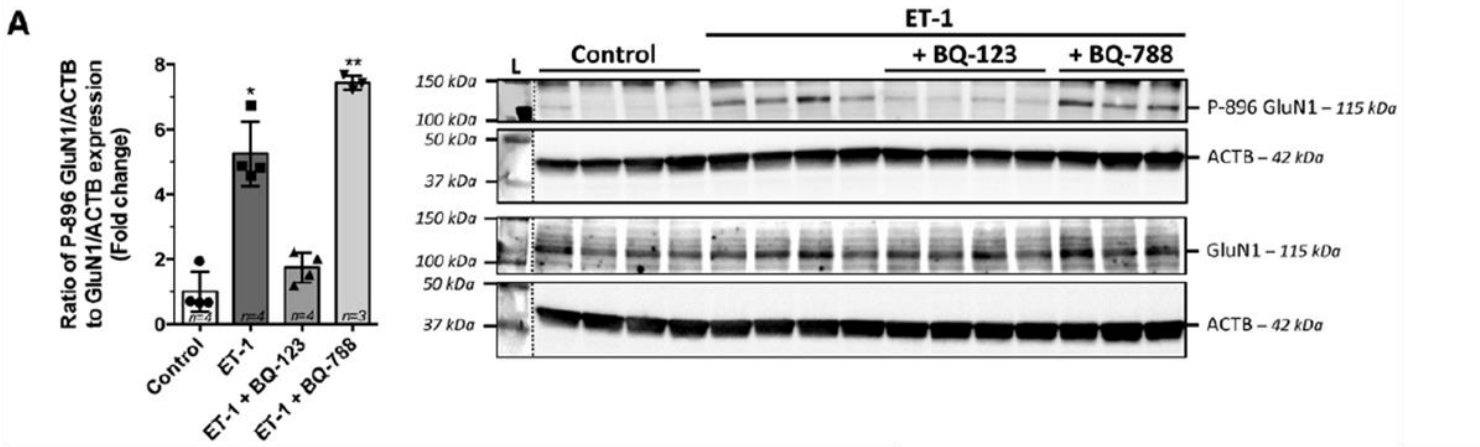
Dumas *et al.*, Circulation, 2018, 137(22):2371-2389

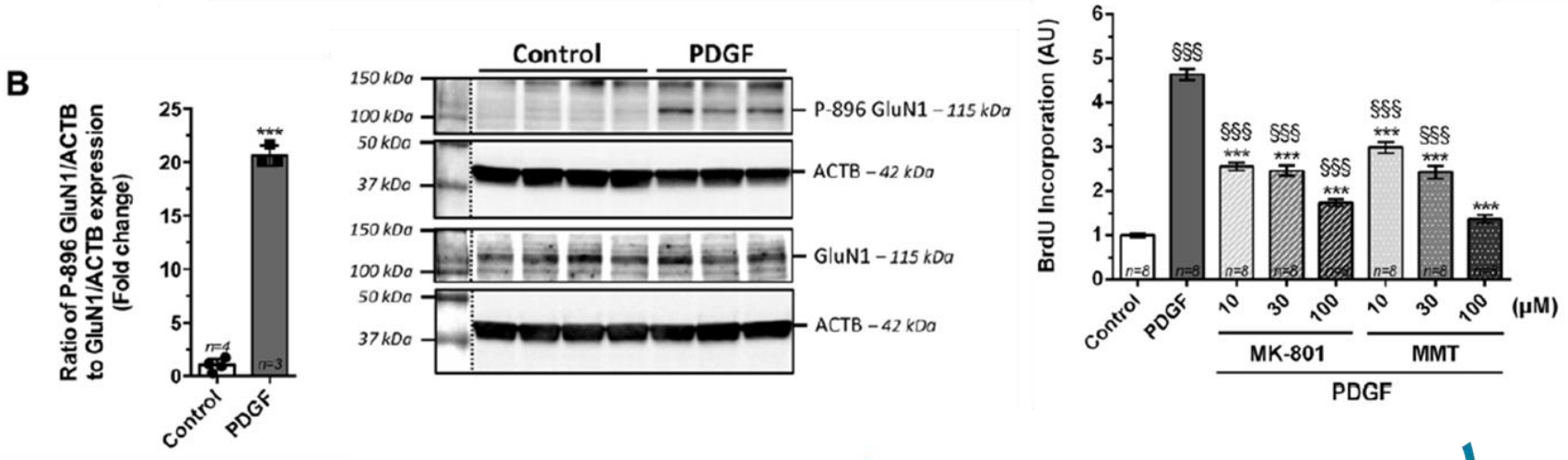
NMDAR an unexpected ion channel player in PAH in cross talk with the ET-1 and PDGF pathways

NMDA-Type Glutamate Receptor Activation Promotes Vascular Remodeling and Pulmonary Arterial Hypertension

Sébastien J. Dumas, Gilles Bru-Mercier, Audrey Courboulin, Marceau Quatredeniers, Catherine Rücker-Martin, Fabrice Antigny, Morad K. Nakhleh, Benoit Ranchoux, Elodie Gouadon, Maria-Candida Vinhas, Matthieu Vocelle, Nicolas Raymond, Peter Dorfmüller, Elie Fadel, Frédéric Perros, Marc Humbert, and Sylvia Cohen-Kaminsky

Dumas S et al. Circulation. 2018





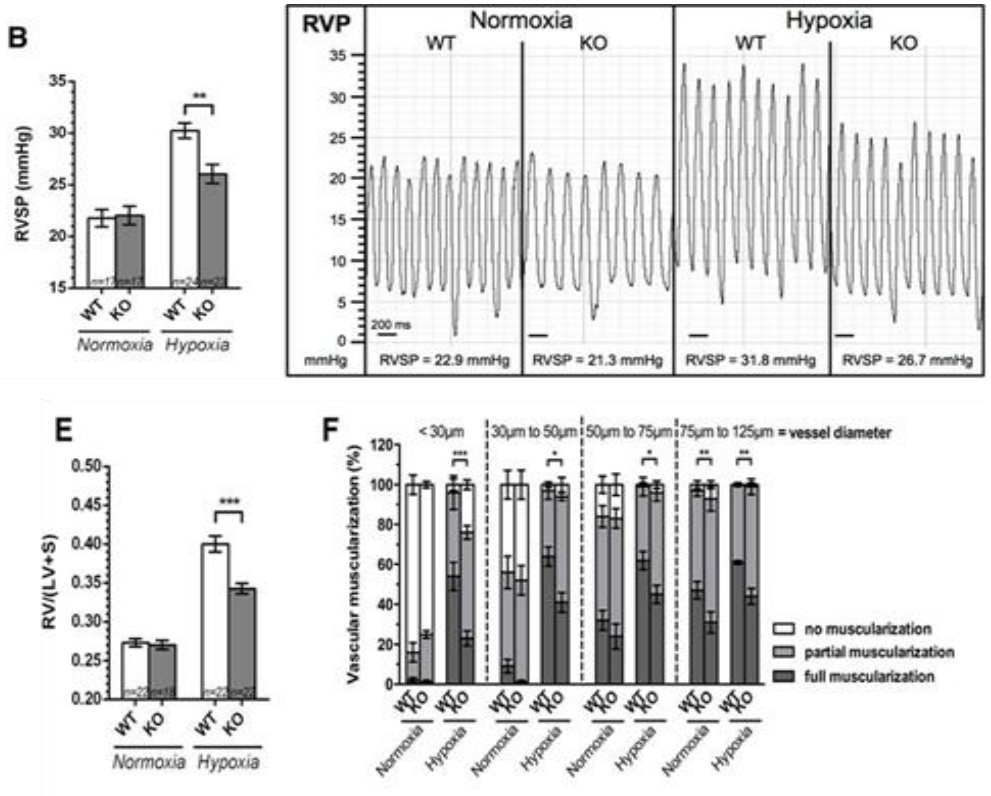
- **Endotelin1 and PDGF**, deregulated in PAH, are **NMDAR engagers**
- **NMDAR blockade inibits PDGF-dependent smooth muscle cell proliferation**

ANR NUTS-MAT
2014-2018

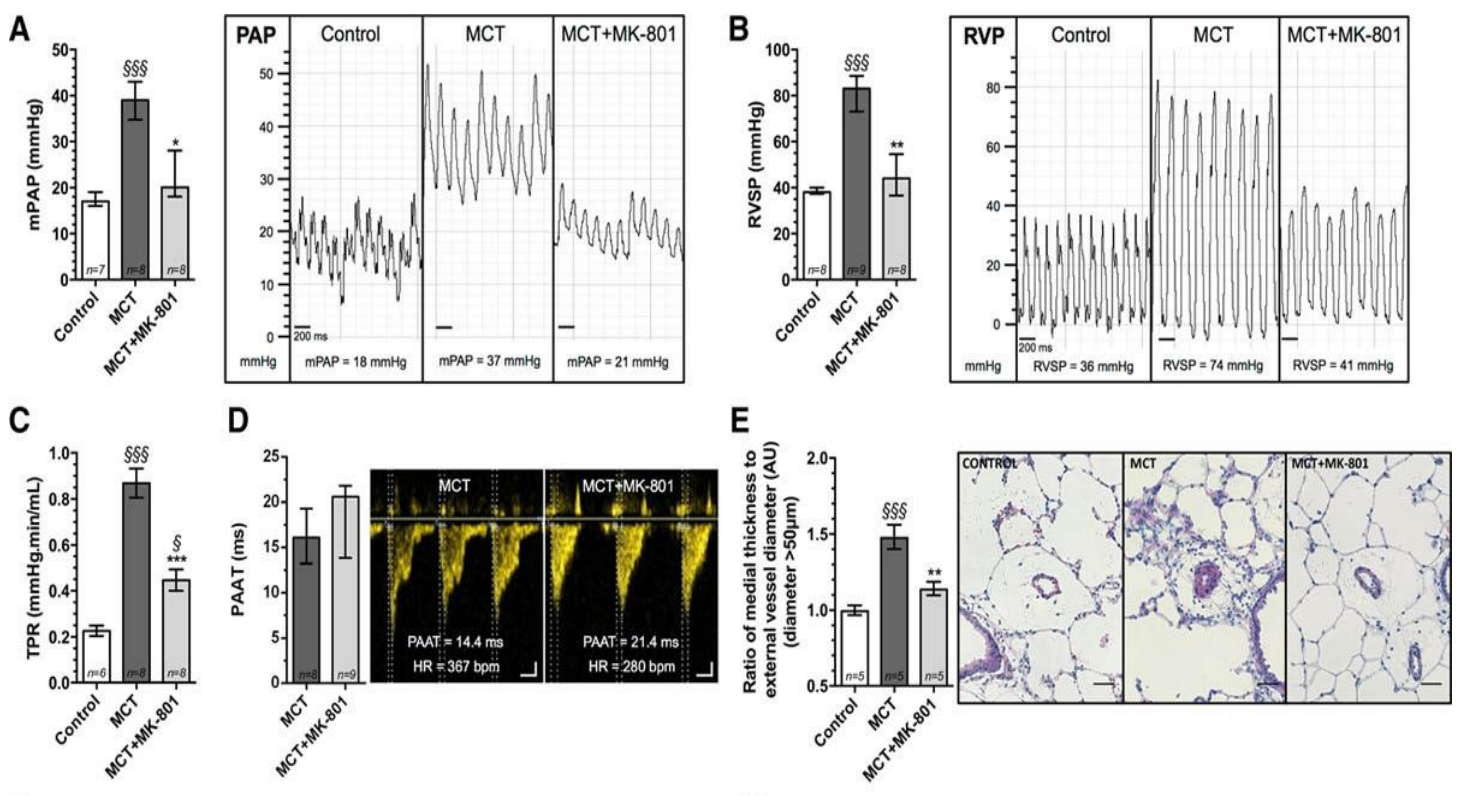
ANR-10-LabX-0033-LERMIT
2012-2018

Genetic inactivation or pharmacological inhibition of NMDAR reduces the development of PAH

Genetic inactivation of NMDAR in smooth muscle cells

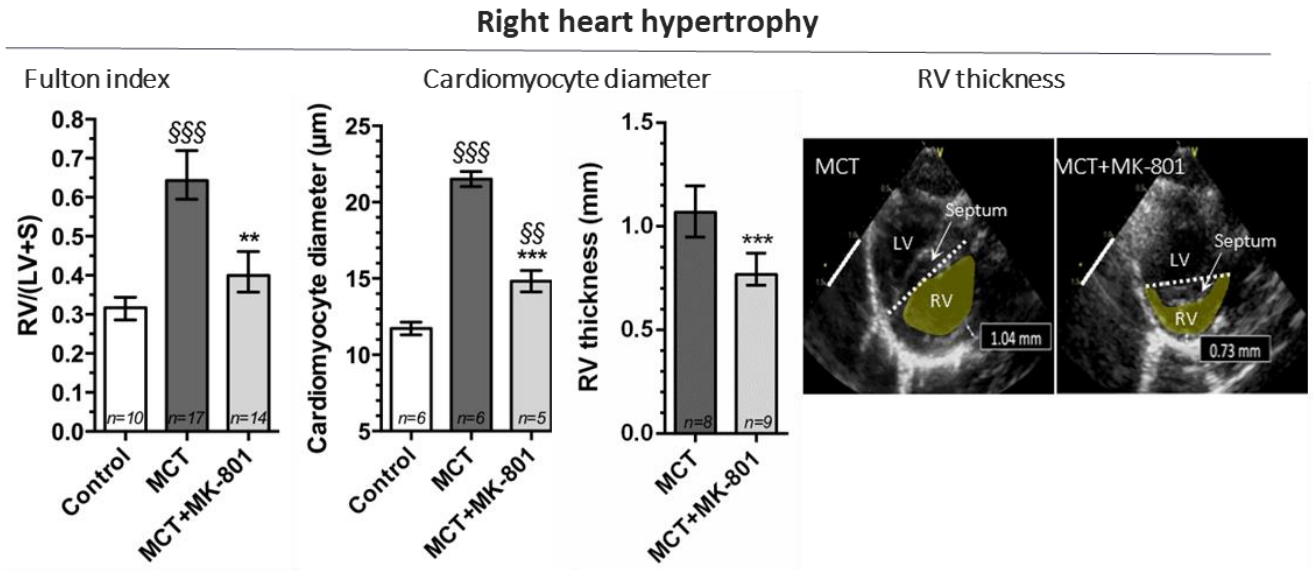


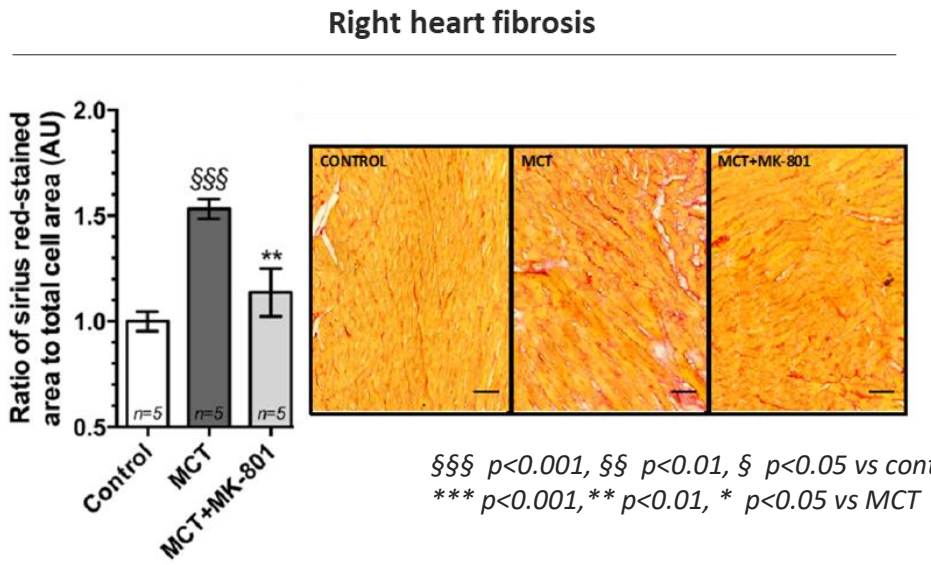
Pharmacological inhibition of NMDAR



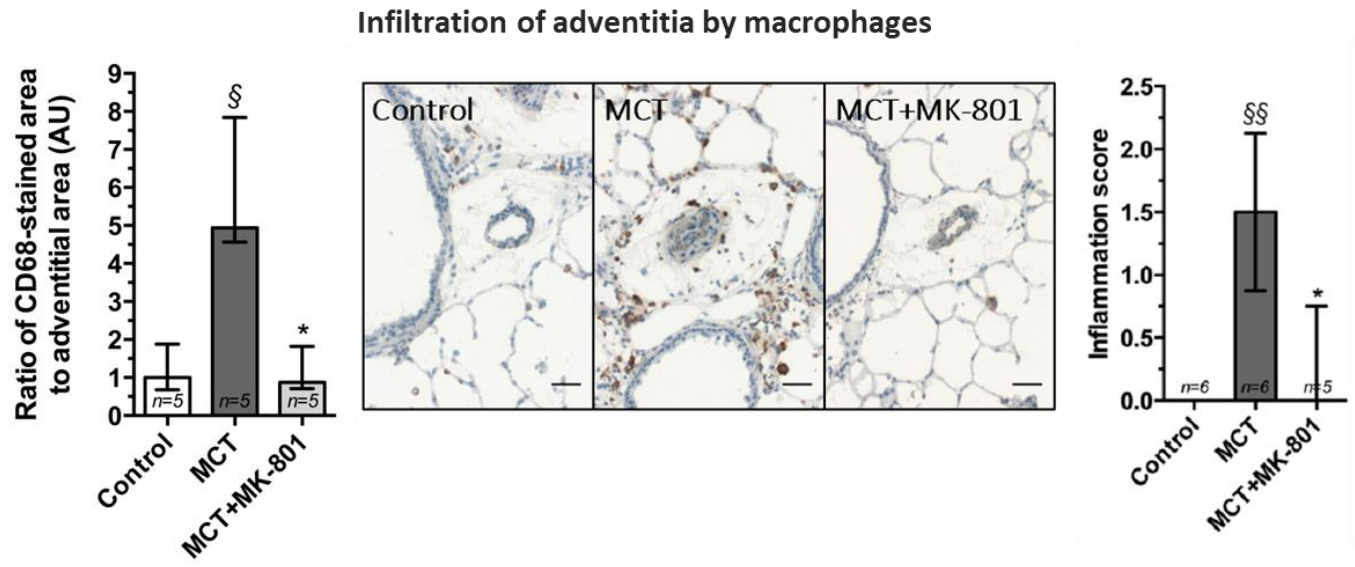
Dumas S et al. Circulation 2018; Quatredeniers M et al., Am J Physiol Lung Cell Mol Physiol. 2019

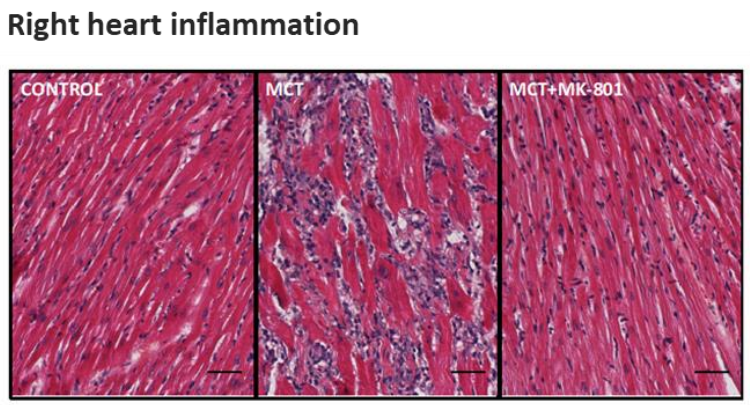
NMDAR blockade, decreases right heart hypertrophy and fibrosis, and resolves perivascular lung and right heart inflammation





§§§ p<0.001, §§ p<0.01, § p<0.05 vs control
**** p<0.001, ** p<0.01, * p<0.05 vs MCT*





§§ p <0.01, § p<0.05 vs control
** p<0.05 vs MCT*

Dumas *et al.*, Circulation, 2018, 137(22):2371-2389

In total, 19 disease-relevant parameters modulated *in vivo* by MK801, a reference NMDAR antagonist blocker

Hemodynamics

↓ mean pulmonary arterial pressure
↓ right ventricular systolic pressure
↓ total pulmonary resistance
↑ *Pulmonary Artery Acceleration Time*

…without effect on systemic pressure

Lung vascular remodeling

↓medial hypertrophy of large arteries
↓% of muscularized arterioles
↓% of occluded arterioles

Cardiac RV remodeling

↓RV thickeness
↓Fulton index
↑RVFS (myocardial contractility)
↓RV cardiomyocyte hypertrophy
↓RV fibrosis
↓RV inflammation

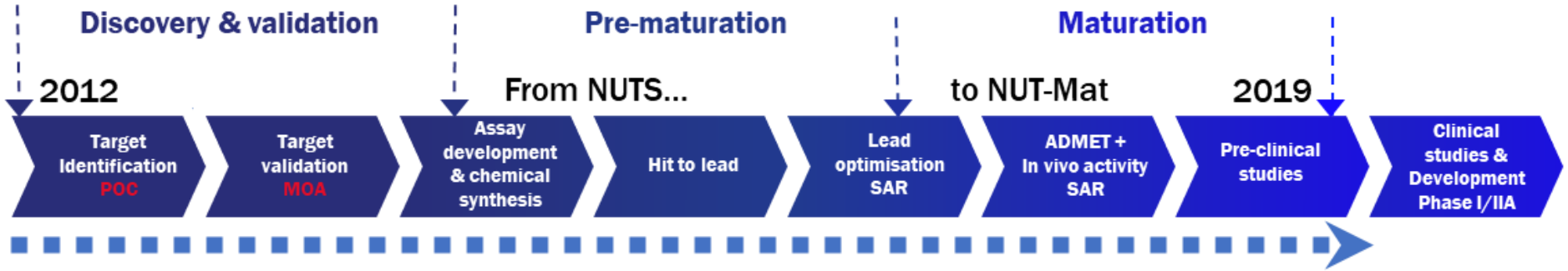
Cardiac output not significantly improved but ↑ Cardiac index

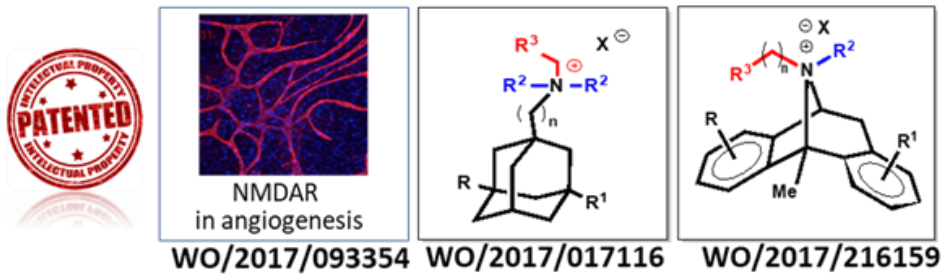
Disrupting NMDAR/glutamate axis

↓ NMDAR engagement in PAs
↓ GLS1 (Glutaminase) expression
↓ vascular cell proliferation
↓ vascular cell apoptosis resistance
↓ endothelial dysfunction (sE-selectin)
↓ perivascular adventitial inflammation

Dumas *et al.*, Circulation, 2018, 137(22):2371-2389

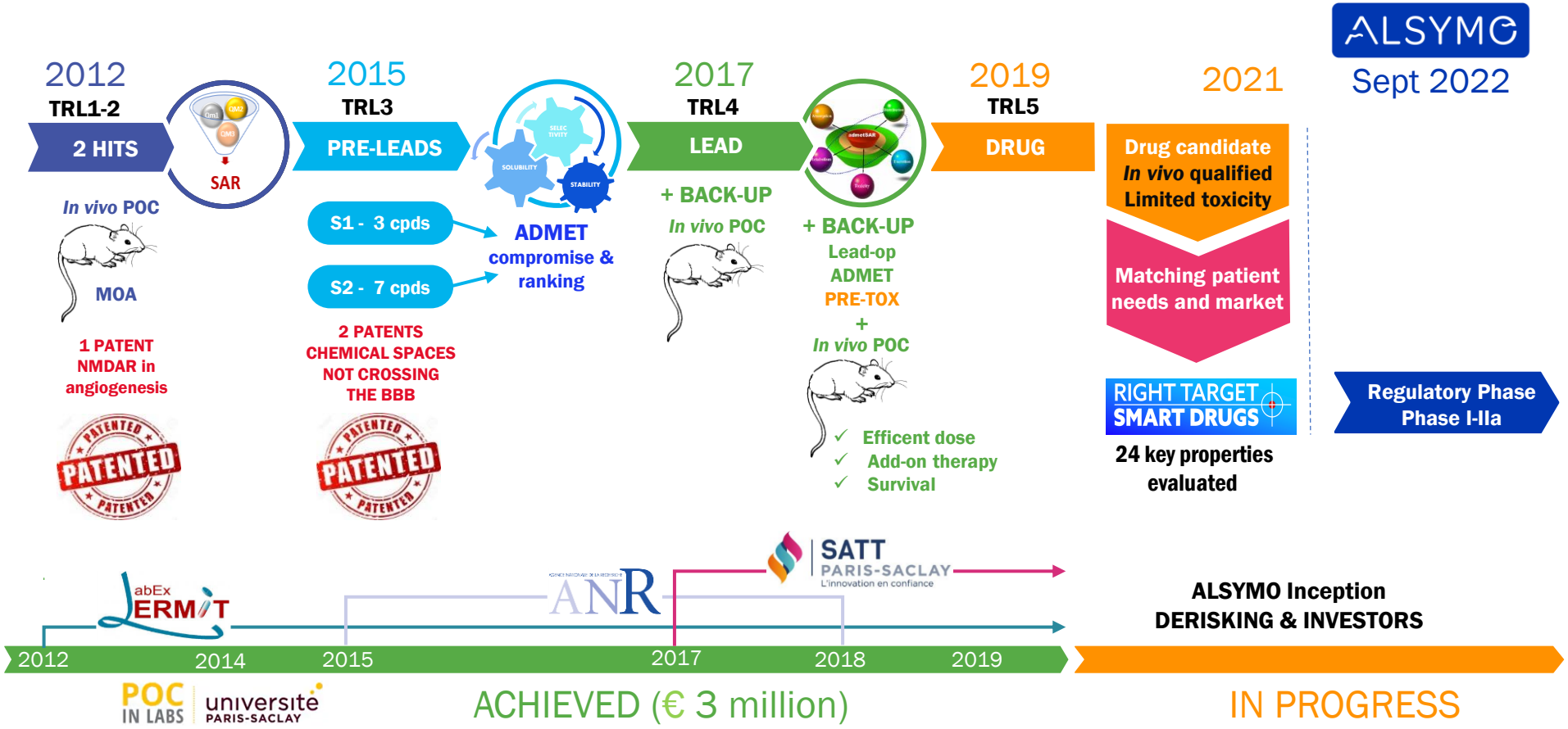
A long road from the target to the drug candidate





Smart drugs
that do not cross the BBB

Achievements and maturation program



SATT PARIS-SACLAY
L'innovation en confiance

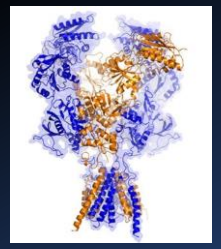
Maturation program

- Lead optimisation
- In vivo validation of the drug candidate
- Derisking
- CEO selection

https://satt-paris-saclay.fr/vitrine-technologique/nuts-mat/

ALSYMO solution based on breakthough innovations the target…and the drug candidate

NMDAR an innovative target



NMDA receptor

NMDAR, mainly known in the CNS, **is engaged in the lungs** and promotes vascular remodeling leading to PAH

ASM series first-in-class drugs

ASM 001 competitive advantage

Anti-remodeling drug candidate

In vivo POC
Efficacy & survival in an FDA-approved rat model of PAH

NMDAR
a **molecular hub** at the cross roads of PAH pathways

Competitive advantage

ASM 001 targets **multiple PAH pathways** at once

WO/2017/017116 WO/2017/216159
Patents granted worldwide and licensed-in

ALSYMO

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System biology approach: de-risking NMDAR as a therapeutic target

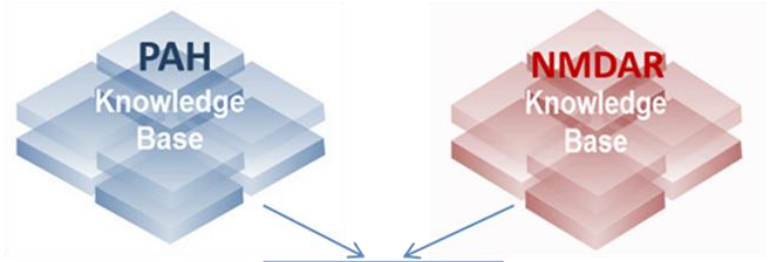
System biology & bioinformatics

A network involving NMDAR, at the crossroads of PAH pathways

Biological validation *(transcriptomics, proteomics, phospho-proteomics) lipidomics…*

NMDAR a molecular Hub

Systems biology strategy

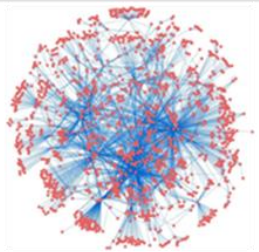


Common genes and proteins

Enrichment pathway analysis
Network building

344 entities
1000 pathways
8500 interactions

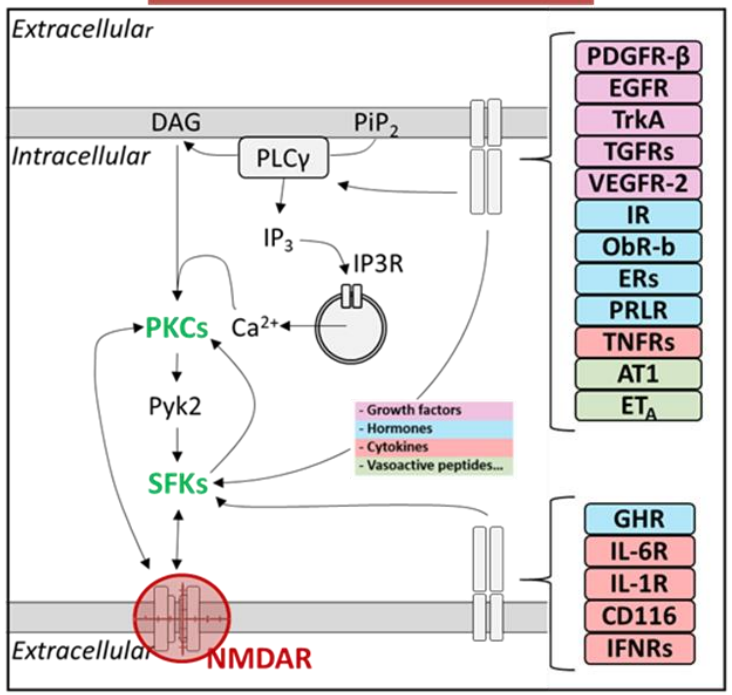
50 first pathways
31 entities



pathways falling In 7 categories

- Growth factors
- Hormones
- Cancer signaling
- Cytokines
- Chemokines
- Vasoactive peptides
- Others…

Added value



Targeting activated NMDAR may result in simultaneous targeting of multiple PAH pathways at a time…

Marceau **Quatredeniers**

Florent **Dumont**

Guillaume **Bernadat**

IPSIT SFR-UMS Institut Paris Saclay Innovation Thérapeutique

BioInfo

Quatredeniers,PhD Thesis Dec 2017, Quatredeniers et al, AJP-Lung 2019

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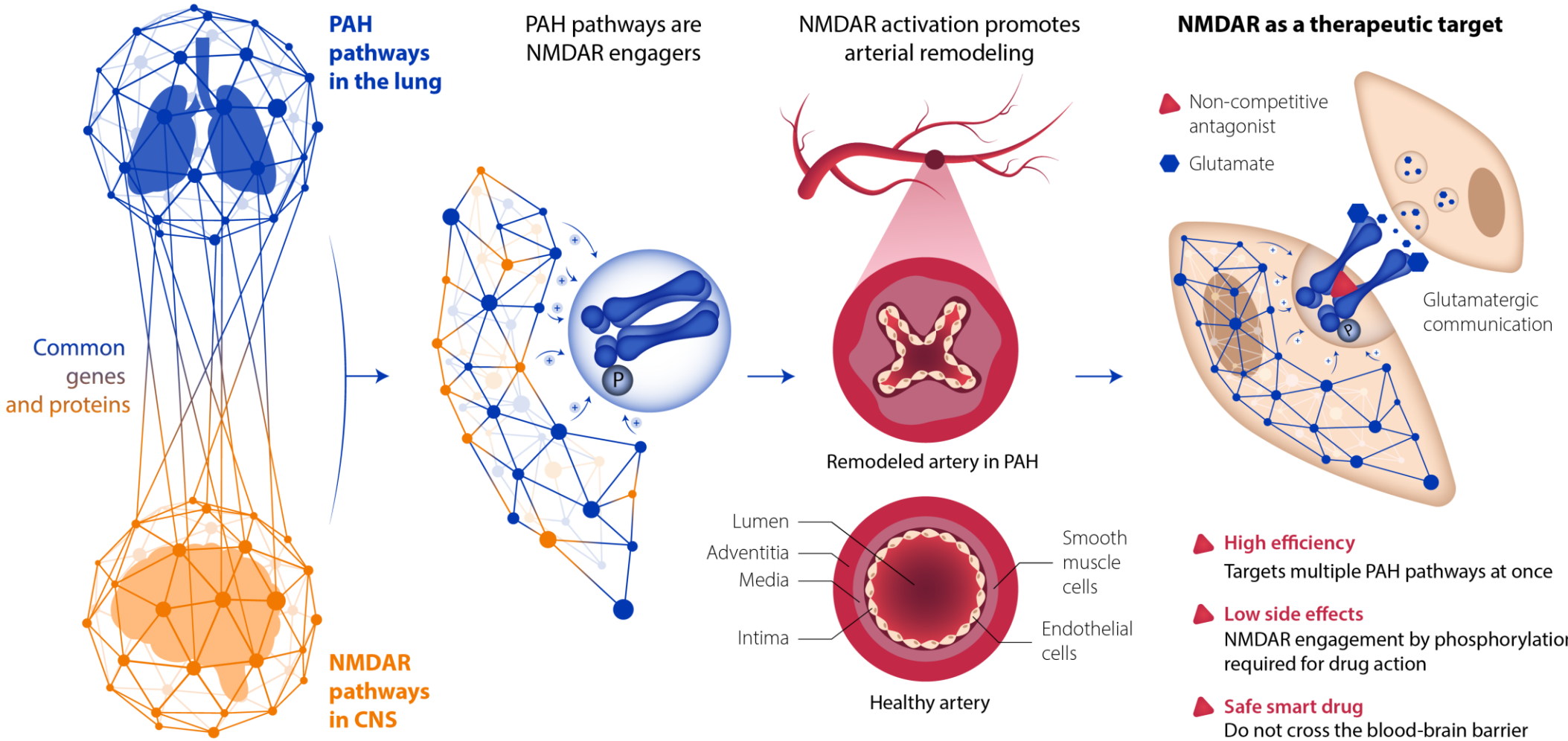
NMDAR, a molecular hub at the cross-roads of known PAH pathways



High efficiency
Targets multiple PAH pathways at once

Low side effects
NMDAR engagement by phosphorylation required for drug action

Safe smart drug
Do not cross the blood-brain barrier

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Biomarqueurs Innovants des Hypertensions Artérielles Pulmonaires par l'Imagerie

Rational BIHAPI

There are currently **no biomarker for pulmonary vascular remodeling.** Diagnosis based on remodeling could lead to earlier diagnosis and a better response to current and future treatments.

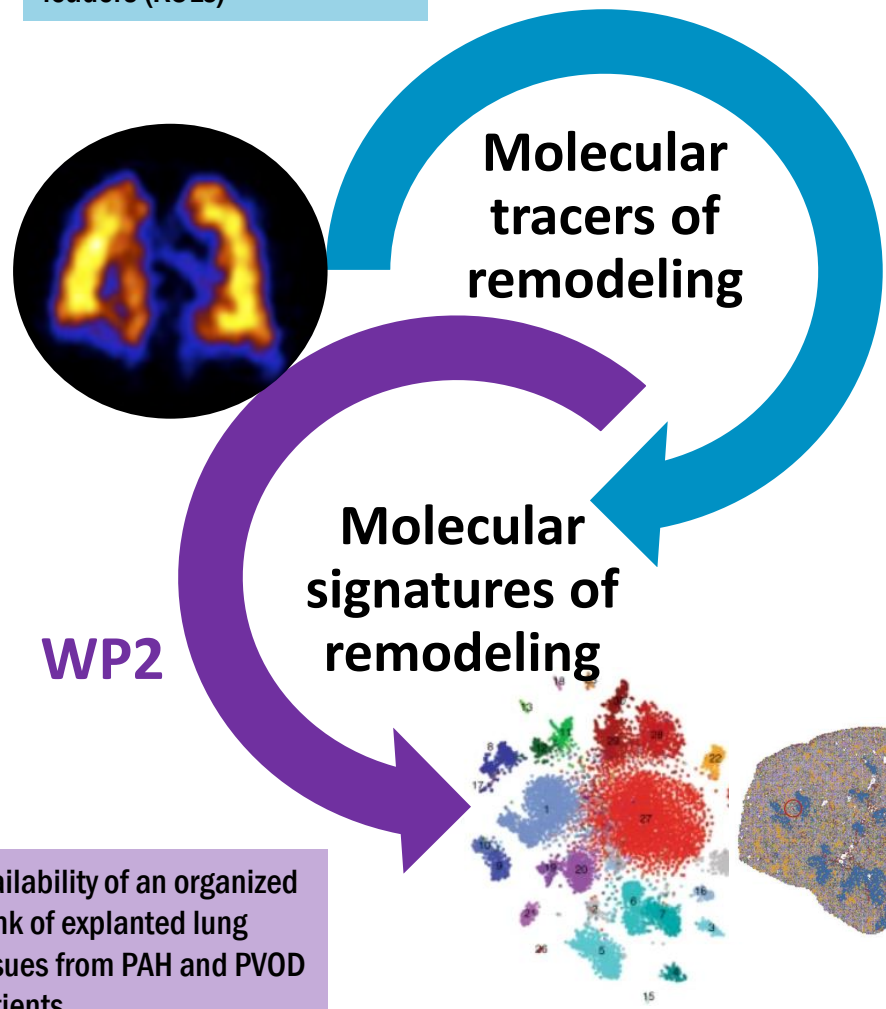
BIHAPI challenge

BIHAPI **combines multidisciplinary basic research and translational research to meet this challenge** and propose innovative biomarkers for PAH, including PVOD, using molecular imaging.

Objectives BIHAPI

1/to develop a **molecular tracer** for imaging pulmonary vascular remodeling in PAH, as a theranostic compagnon biomarker
2/to characterize the **spatial molecular signatures** of pulmonary vascular remodeling in PAH, including PVOD

A strategy endorsed by the reference center's opinion leaders (KOLs)



Availability of an organized bank of explanted lung tissues from PAH and PVOD patients

MSD AVENIR
méliorer la Vie ENsemble par l'Innovation et la Recherche

1,5 M€

InsermTransfert

A therapeutic innovation that has successfully mobilized the French ecosystem

PAH Ecosystem & KOLs

Financial Support

Institutions

Alsymo team and world-renowned KOLs working together on the Bicêtre Hospital campus

Co-founders

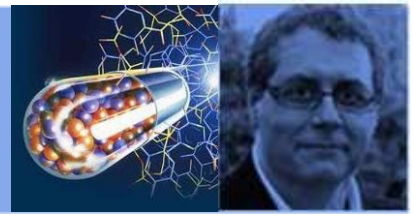
Biopharma R&D
Corporate strategy

Remi Delansorne
CEO

Biology
Medicine

Sylvia Cohen-Kaminsky
Head of Science

Medicinal
Chemistry



Mouad Alami
Head of Medicinal Chemistry

Analytical Chemistry
DMPK - Pharmacology

Alain Pruvost
Head of Pharmacology

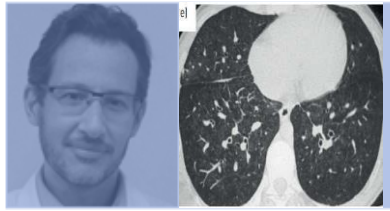
université PARIS-SACLAY

Clinical Advisory board

Pr Marc Humbert

Pulmonologist
Clinical trials
PAH

Pr David Montani



Pulmonologist
Clinical trials
PVOD

Pr Olivier Sitbon

Pulmonologist
Clinical trials
Patient registry

centre de référence maladies rares

HTAP France

HTAP Réseau Français

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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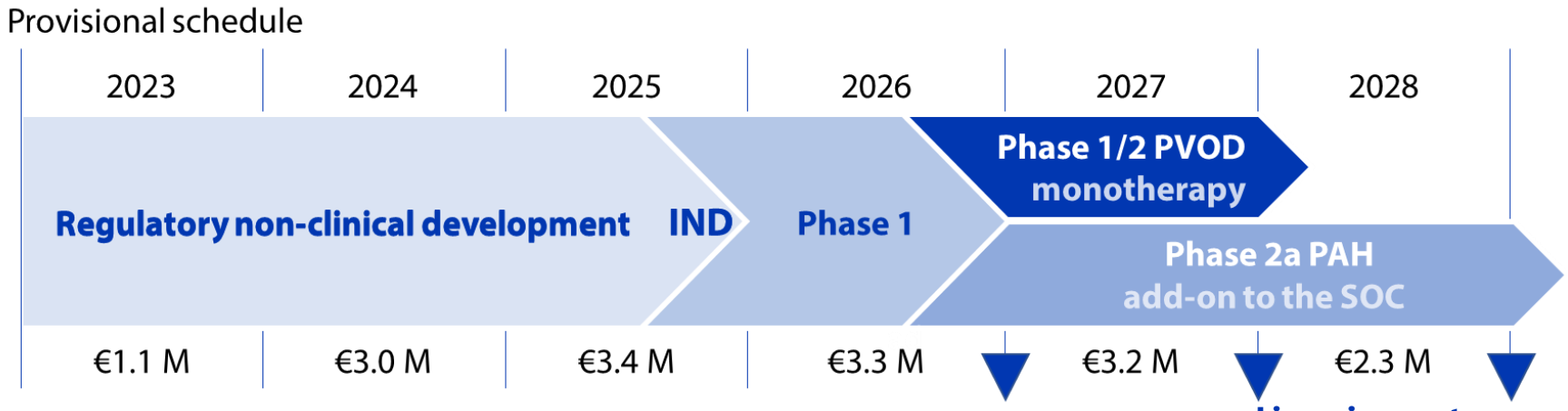
A clinical development plan conceived with KOLs … to make it happen within 5 years

Development steps towards clinical Proof-of-Concept



Cash needs

€7.5 M to IND

or

€10.8 M to end of Phase 1

Tech transfer to pharma is the bright future we want for ALSYMO

Clinical trial strategy

PVOD patients first

- The most severe form of PAH: **P**ulmonary **V**eno-**O**cclusive **D**isease
- 2 out of 3 die within 2 yrs

A niche opportunity

- To test the drug candidate as monotherapy in naive patients
- To penetrate the market

M&A activity in PAH

Pharma acquisition in PAH

- Actelion $30 billion to J&J
- Acceleron $11.5 billon to Merck & C°

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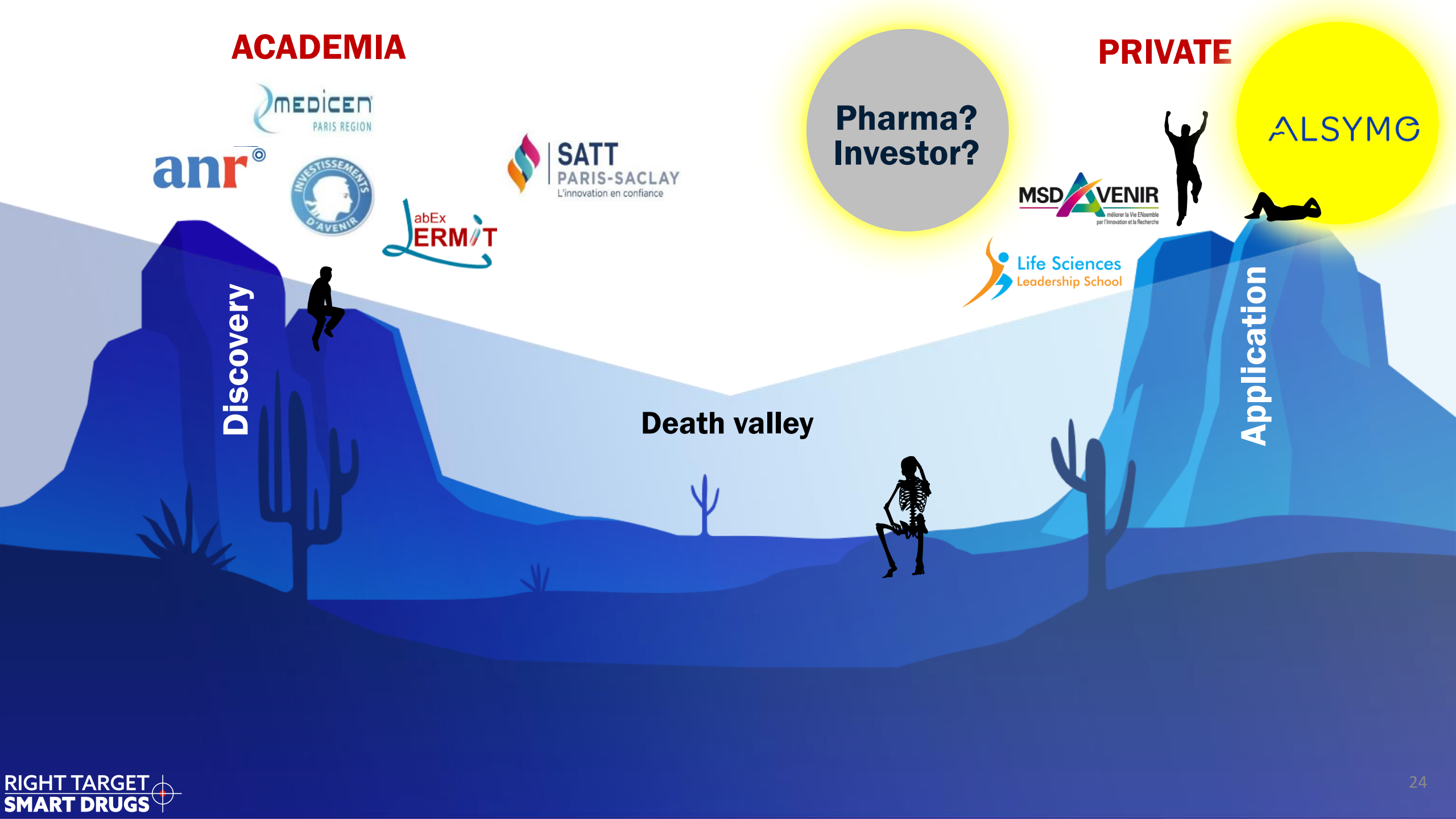

ACADEMIA
PRIVATE
Pharma?
Investor?
Discovery
Death valley
Application
ALSYMO
Life Sciences
Leadership School

Thanks for attention

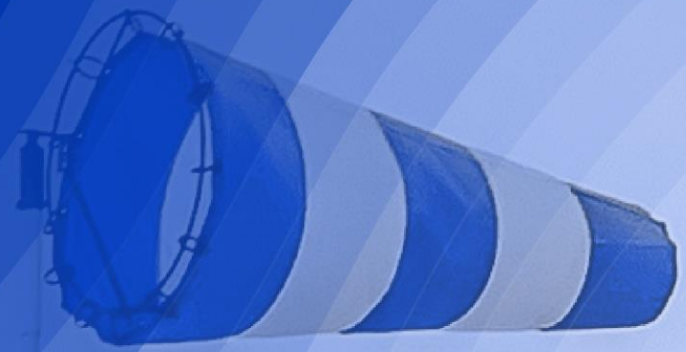
https://satt-paris-saclay.fr/2022/10/03/alsymo-faire-reculer-lhypertension-arterielle-pulmonaire/
https://www.satt.fr/alsymo/

If there is no way,
create one.
Banksy

ALSYMO

Missions and vision

- We innovate with commitment to patients RIGHT TARGET SMART DRUGS
- To tackle Pulmonary Arterial Hypertension
- And make it happen within 5 years



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Backup slides

LS-Lead : Life Science Leadership School

- Destinée aux créateurs de startup innovantes en sciences de la vie
- 40 journées interactives en distanciel sur 1 an
- 80 experts, 60 participants formés, 20 start up crées
- formation certifiée Qualiopi N°2023/103749.1

<u>Parcours 1 :</u> CONDUIRE UN PROJET DE CREATION D'ENTREPRISE EN SCIENCES DE LA VIE (voir programme détaillé slide suivante)

<u>Parcours 2</u> : CREATION et REPRISE D'ENTREPRISE EN SCIENCES DE LA VIE

- L'IDEATION « Analyser son marché & définir sa cible »
- LA CREATION « Choisir son statut juridique & financer son activité »
- LA STUCTURATION « Formaliser son business plan, commercialiser& piloter son projet »
- LA COMMUNICATION « Savoir communiquer sur son projet & asseoir sa posture d'entrepreneur »

Ecosysteme SDV Sante
DM, Médicament
Business plan
Juridique PI, pacte actionnaire, contrat
Négociation
Management
Droit social
Communication, Pitch
Market access
Financement, Levées de fond, comptabilité
Partage d'expérience
etc..

Ce que m'a apporté LS Lead

- culture entrepreneuriale très spécifique liée aux sciences de la vie et de la santé
- gain en assurance face à mes interlocuteurs, en particulier les investisseurs
- sentiment d'appartenance à une communauté, une grande familles solidaire et amicale
- accès à un réseau de mentors et d'experts sur qui je sais que je peux compter

LSLEAD est éligible aux financements publics de la formation continue : OPCO, Pôle emploi, BPI-PU

https://ls-lead.com/

Life Sciences Leadership School

PARCOURS DE FORMATION DE LIFE SCIENCES LEADERSHIP SCHOOL

- J1 Comment développer votre médicament
- J2 Comment piloter votre projet en Sciences de la Vie (project management)
- J3 Comprendre les passerelles public / privé
- J4 Quand et comment créer votre entreprise
- J 5 Comprendre les différentes formes de financement
- J6 Comment intégrer le réglementaire dans la stratégie de développement
- J7 Comment accéder au marché (market access) drug dans les Sciences de la Vie
- J8 Connaitre les modes d'hébergement des startups
- J9 Comment développer votre dispositif médical
- J10 Comment préparer votre Business Plan dans les Sciences de la Vie
- J11 Comment protéger au mieux ses innovations dans les Sciences de la Vie
- J12 Connaître l'écosystème des Sciences de la Vie
- J13 Comment protéger ses intérêts par le contrat
- J14 Comment réaliser les premières levées de fonds (seed et series A)
- J15 Comprendre la comptabilité et savoir gérer son cash
- J16 Comprendre le fonctionnement des sociétés
- J17 Comment gérer les relations avec les actionnaires investisseurs
- J18 Partage d'expériences de créateurs d'entreprises en Sciences de la Vie (Part I)
- J19 PREPARATION AU PITCH GAGNANT (PART I)
- J20 Comment préparer et maîtriser sa communication
- J21 Comment maîtriser les meilleures techniques de négociation
- J22 Comment négocier sa prise de licence (in licensing)
- J23 Motivation et performance
- J24 Questions ouvertes des stagiaires Part I
- J25 Comment négocier et gérer ses accords de développement
- J26 Comment négocier et maitriser la fabrication de ses produits de santé
- J27 Comment développer votre médicament en Oncologie
- J28 Comment Réaliser Les Levées De Fonds Série B Et Suivantes
- J29 Comprendre le pacte d'actionnaires
- J30 Comment éviter les ennuis en droit social
- J31 Partage d'expériences de créateurs d'entreprises en Sciences de la Vie (Part II)
- J32 Comment négocier sa concession de licence (out licensing)
- J33 Comment gérer ses alliances stratégiques dans les Sciences de la Vie
- J34 Questions ouvertes des stagiaires (Part II)
- J35 Préparation au pitch gagnant (Part II)
- J36 Découvrir les opportunités en Chine
- J37 Comment développer votre médicament de thérapie cellulaire
- J38 Comprendre les impératifs de qualité
- J39 Préparation au pitch gagnant (Part III)
- J40 PARTAGE D'EXPERIENCES PART III & JOURNEE DE SOUTENANCE DE PITCH DEVANT LE JURY LS LEAD

Single cell analysis in pulmonary hypertension reveals importance of treatment with NMDAR blockers

› Am J Respir Crit Care Med. 2020 Oct 6. doi: 10.1164/rccm.202006-2169OC. Online ahead of print.

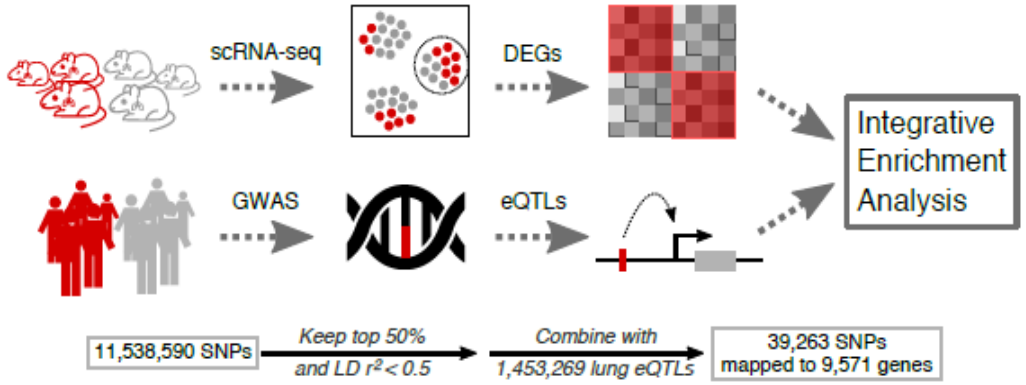
Single-cell Study of Two Rat Models of Pulmonary Arterial Hypertension Reveals Connections to Human Pathobiology and Drug Repositioning

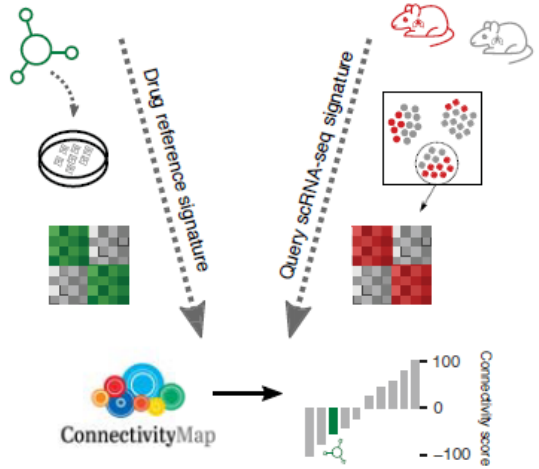
Jason Hong [1], Douglas Arneson [2], Soban Umar [3], Gregoire Ruffenach [3], Christine M Cunningham [3], In Sook Ahn [2], Graciel Diamante [2], May Bhetraratana [2], John F Park [3], Emma Said [2], Caroline Huynh [2], Trixie Le [2], Lejla Medzikovic [2], Marc Humbert [2], Florent Soubrier [4], David Montani [5], Barbara Girerd [6], David-Alexandre Trégouët [7], Richard Channick [2], Rajan Saggar [8], Mansoureh Eghbali [2], Xia Yang [2]

Affiliations + expand

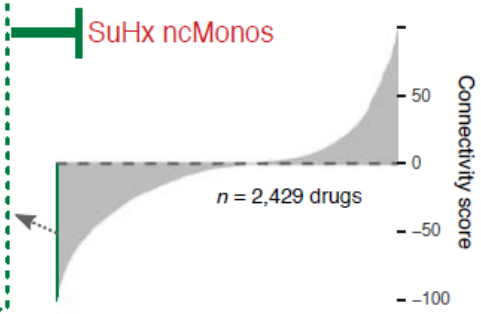
PMID: 33021809 DOI: 10.1164/rccm.202006-2169OC

Integrative analysis of rat scRNA-seq DEGs with **human PAH genetics** points to the relevance of the DEGs to human PAH





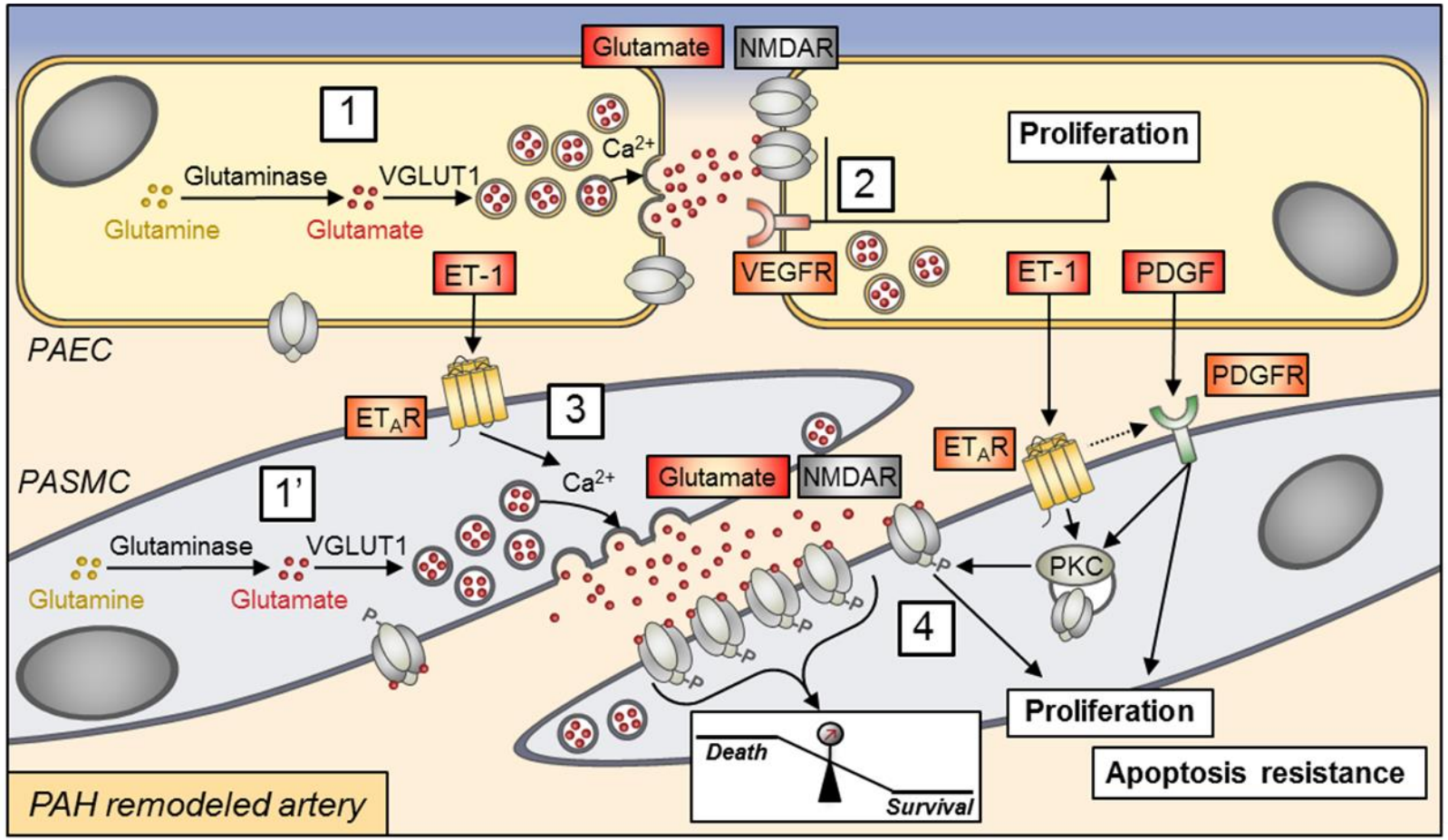
Rank	Score	Drug
1	-100	Treprostinil
2	-99	Tipifarnib
3	-98	Guaifenesin
4	-97	Phensuximide
5	-97	IWR-1-ENDO
6	-95	RITA
7	-95	Palonosetron
8	-95	Pindolol
9	-94	Temozolomide
10	-94	Memantine



- Integration of DEGs with Connectivity Map identifies potential candidate drugs for repositioning.
- Two NMDAR antagonists in the top 10 among 2429 drug tested

*Guaifenesin, a drug with expectorant properties, may also have NMDAR antagonist actions (half life 1 hour, kidney metabolisms)
* Memantine, a well known NMDAR blocker, authorized for the treatment of Alzheimer disease

NMDAR, a target linked to known PAH pathways



- Regulated calcium-dependent release of glutamate from vesicles equipped with VGLUT1

- ET-1 induces glutamate release through ET_AR

- ET1, PDGF and VEGF receptor activation induce NMDAR phosphorylation and mobilization at the cell membrane, thus inducing NMDAR-dependent vascular cell proliferation

A model of glutamatergic communication via NMDARs in vascular cells in cooperation with known PAH pathways

Dumas PhD Thesis (Nov 30, 2015)
Dumas et al Circulation 2028

Summary - Target identification and validation

Relevance to PAH

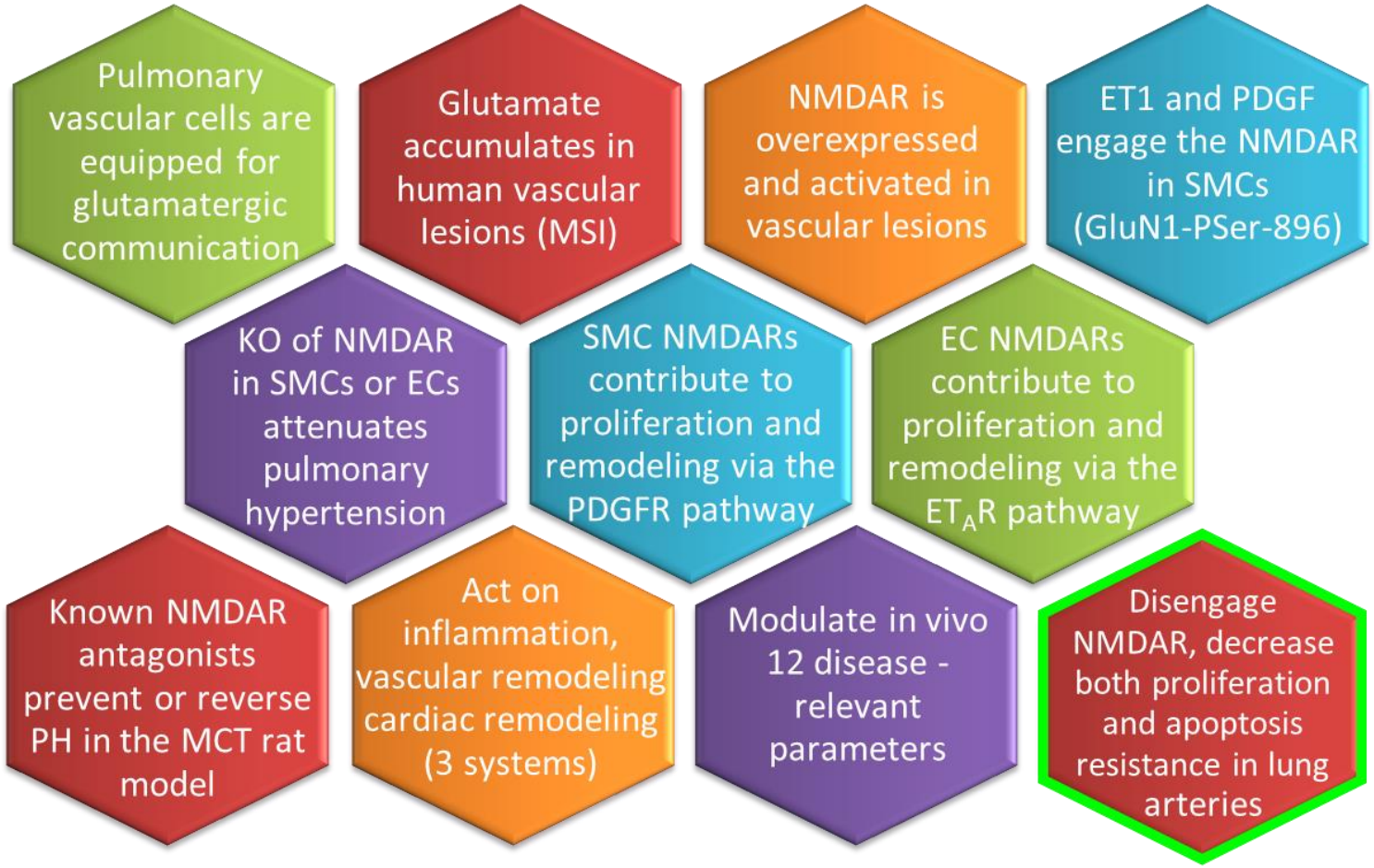
A disease relevant target and ligand deregulated in pulmonary arteries

Mechanisms

Target involved in PH development and activated by the ET1 and PDGF pathways

Therapeutic potency

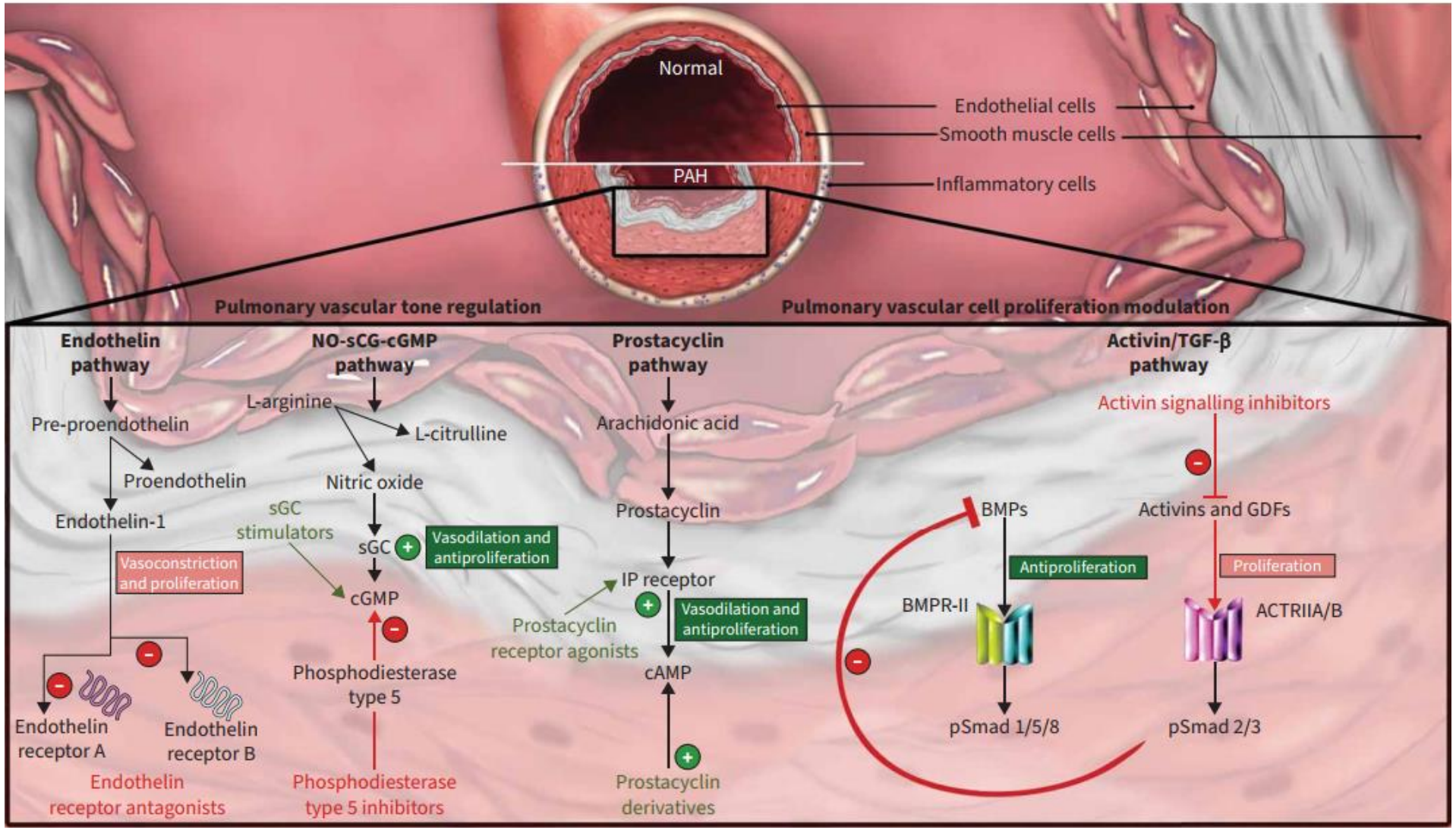
MK-801, NMDAR antagonist effective in vivo on the patho- phenotype



→ Activation of the NMDA-type glutamate receptor contributes to vascular remodeling and PAH

Dumas et al, Circulation 2018

Targets for established and emerging therapies in PAH

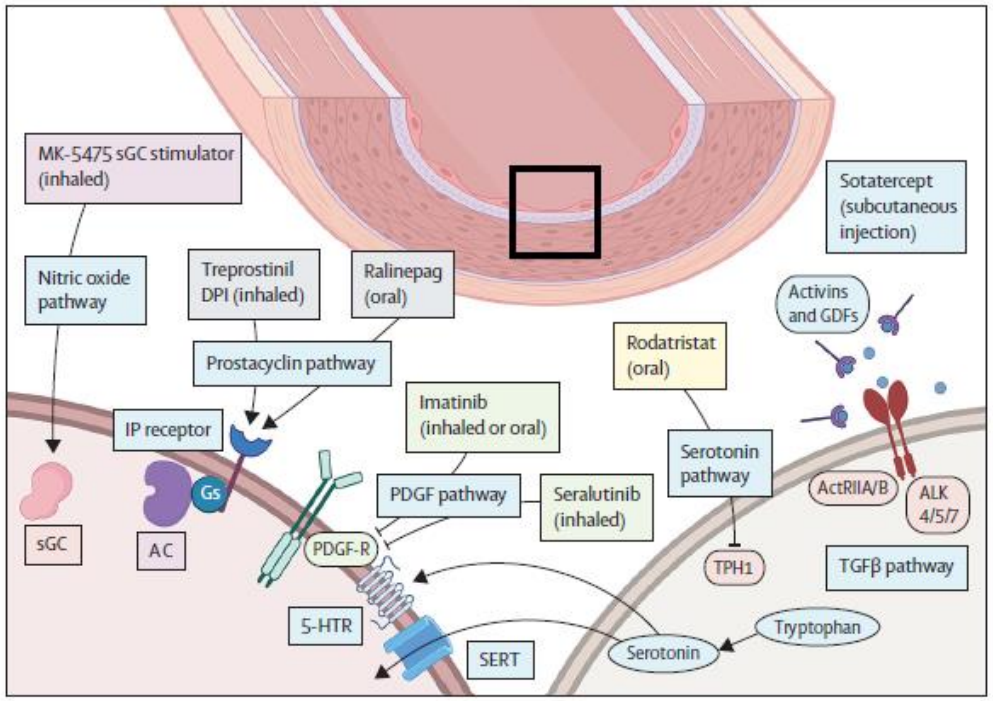


Sotatercept:
Fusion protein, ligand trap of activins and GDFs

Phase 3 Stellar trial
- Adults with PAH receiving stable background therapy
- Sotatercept s.c. every 21 days resulted in a greater improvement in exercise capacity over a period of 24 weeks than placebo.
- FDA approved and Lauched in March 2024

Hoepper MM et al New Englang J Medicine 2023
Humbert M, Eur Resp J 2023

Latest Phase 2 & 3 trials in PAH



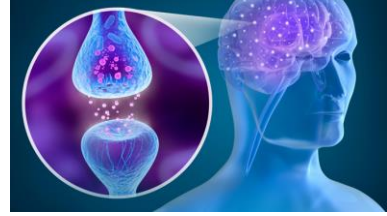
Weatherald et al., *Lancet* 2022, 400: 1884–98

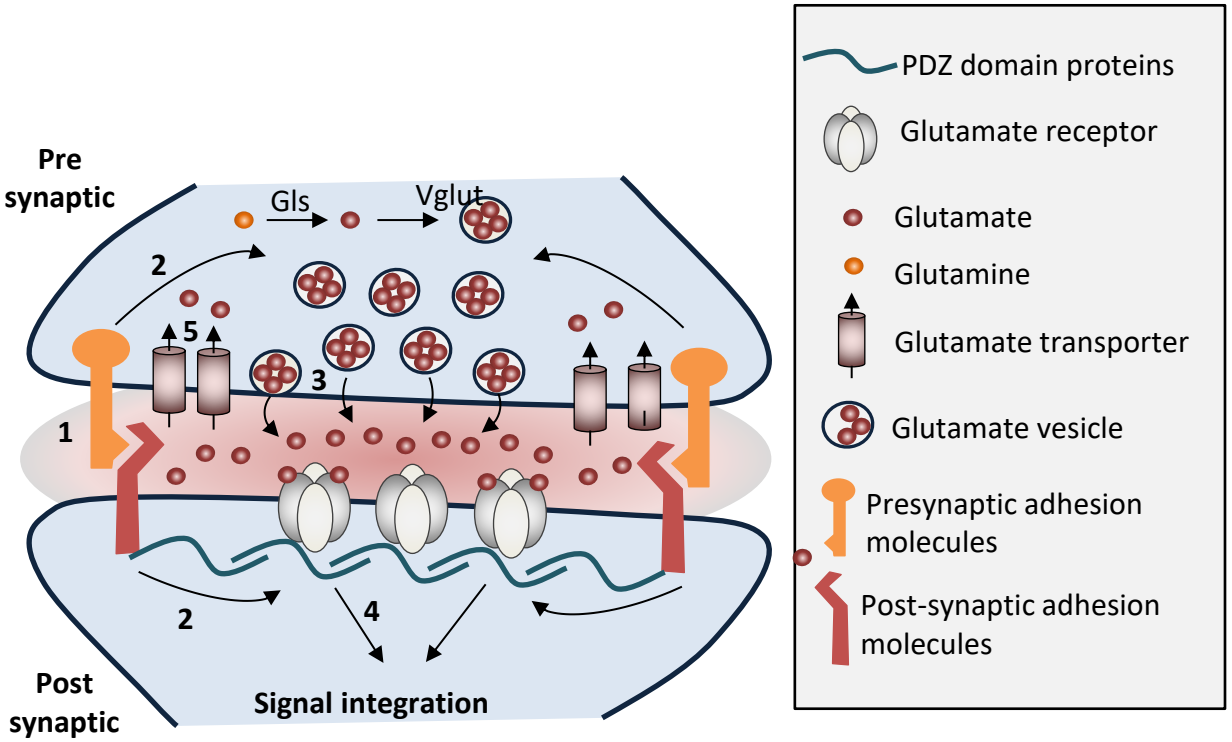
	Phase	Estimated size	Key eligibility criteria	Primary outcome
Ralinepag, prostacyclin receptor agonist				
ADVANCE (NCT03626688)	3	700	WHO/NYHA Class II–IV	Time to first clinical worsening event
ADVANCE CAPACITY (NCT04084678)	3	193	WHO/NYHA Class II or III, V_E/VCO_2 ≥38, VO_2 ≥10 to <18 mL/kg per min	Change in peak VO_2 at week 28
Vardenafil DPI (RT234), inhaled phosphodiesterase type-5 inhibitor				
VIPAH-PRN (NCT04266197)	2	86	WHO/NYHA Class II–IV	Treatment-emergent adverse events, change in blood pressure, change in peak VO_2
MK-5475, inhaled soluble guanylate cyclase stimulator				
INSIGNIA-PAH (NCT04732221)	2/3	450	WHO/NYHA Class II–IV	Phase 2, change in PVR at week 12; phase 3, change in 6MWD at week 12
Sotatercept, TGFβ superfamily modulator				
STELLAR (NCT04576988)	3	324	WHO/NYHA Class II or III, PVR ≥5 WU	Change in 6MWD at week 24
HYPERION (NCT04811092)	3	662	Newly diagnosed, intermediate and high risk	Time to clinical worsening, defined as the first confirmed morbidity event or death
ZENITH (NCT04896008)	3	200	WHO/NYHA Class III and IV at high risk	Time to first confirmed morbidity or mortality event, defined as all-cause death, lung transplantation, or pulmonary arterial hypertension-worsening-related hospitalisation of ≥24 h
Seralutinib, inhaled PDGF-R, CSF1R, and c-KIT inhibitor				
TORREY (NCT04456998)	2	86	WHO/NYHA Class II or III, PAWP or LVEDP ≤12 if PVR ≥5 and <6·25 WU, or PAWP or LVEDP ≤15 if PVR ≥6·25 WU	Change in PVR at week 24
Imatinib DPI (AV-101), inhaled tyrosine kinase inhibitor				
IMPAHCT (NCT05036135)	2b/3	462	WHO/NYHA Class II–IV	Phase 2b, change in PVR at week 24; phase 3, change in 6MWD at week 24
Rodatristat ethyl, tryptophan hydroxylase inhibitor				
ELEVATE-2 (NCT04712669)	2	90	WHO/NYHA Class II or III, PAWP or LVEDP ≤12 if PVR ≥4·4 and <6·25 WU, or PAWP or LVEDP ≤15 if PVR ≥6·25 WU	Change in PVR at week 24
Apabetalone, BRD4 inhibitor				
APPROACH-2 (NCT04915300)	2	72	WHO/NYHA Class II or III, mPAP >20 mm Hg, PVR >5 WU	Change in PVR at week 24

6MWD=6-minute walking distance. BRD4=bromodomain containing protein 4. c-KIT=stem-cell factor receptor. CSF1R=colony stimulating factor 1 receptor. DPI=dry powder inhaler. LVEDP=left ventricular end-diastolic pressure. PAWP=pulmonary artery wedge pressure. mPAP=mean pulmonary arterial pressure. PDGF-R=platelet-derived growth factor receptor. $PETCO_2$=partial pressure of expired carbon dioxide. PVR=pulmonary vascular resistance. TGFβ=transforming growth factor β. V_E/VCO_2=minute ventilation to carbon dioxide output ratio. VO_2=oxygen consumption. WHO/NYHA=WHO/New York Heart Association. WU=wood units.

Table: **Summary of investigational pulmonary arterial hypertension therapies and mechanisms currently in phase 2 and 3 trials**

Glutamatergic communication in the CNS

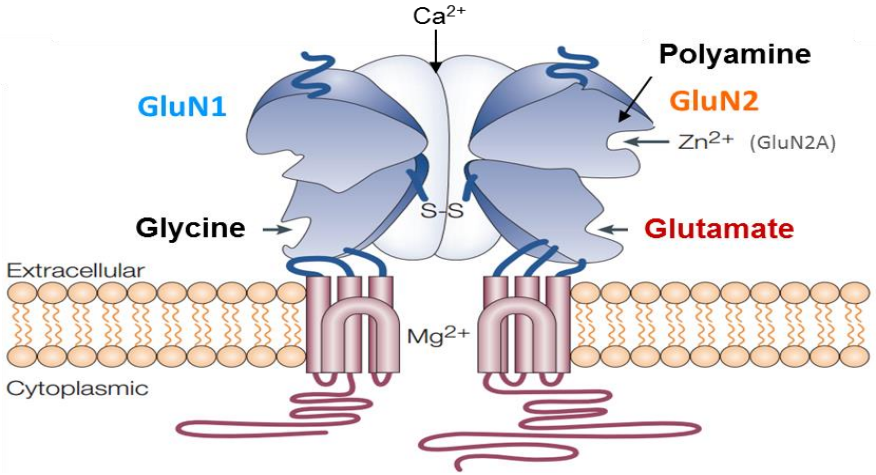




1. Interaction with synaptic adhesion molecules → Synaptogenesis
2. Recrutment of pre and postsynaptic elements
3. Calcium signal → vesicular secretion of glutamate in the synaptic cleft
4. Activation of postsynaptic receptors and signal integration
5. Glutamate recapture

*Gls : Glutaminase
*Vglut : Vesicular glutamate transporters

NMDA receptor



Ionotropic glutamate receptor, Voltage-dependent

- Calcium permeable channel, 4 subunits
- 2x**GluN1** : obligatory

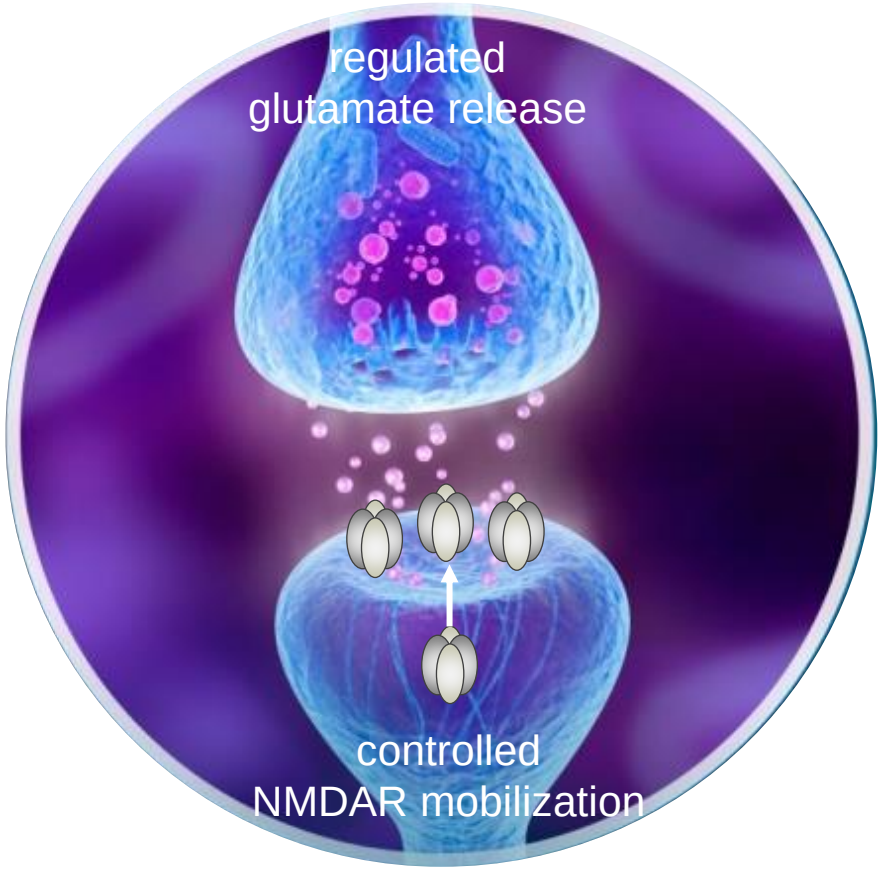
2x**GluN2 (A,B,C or D)** modulate channel properties

NMDAR activation: **glutamate, co-activator glycine**

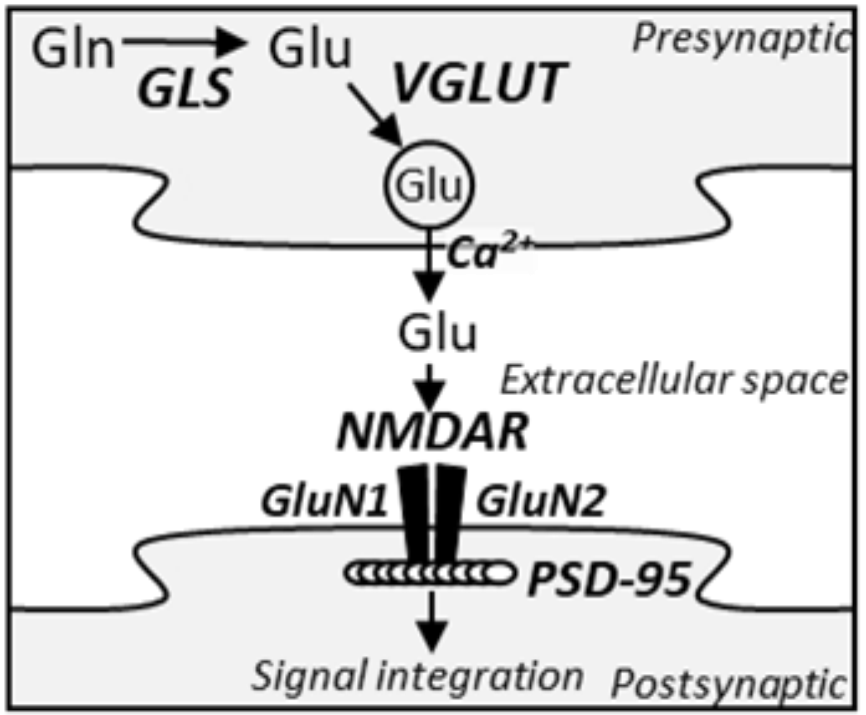
Widely expressed in the NCNS

- Neurons (synaptic communication), astrocytes
- **Microvascular endothelial cells in the brain**
- Neuronal plasticity...neurodegenerative diseases...

Coincident glutamate release and NMDAR activation



How the NMDA receptor is engaged at the cell membrane and activated ?



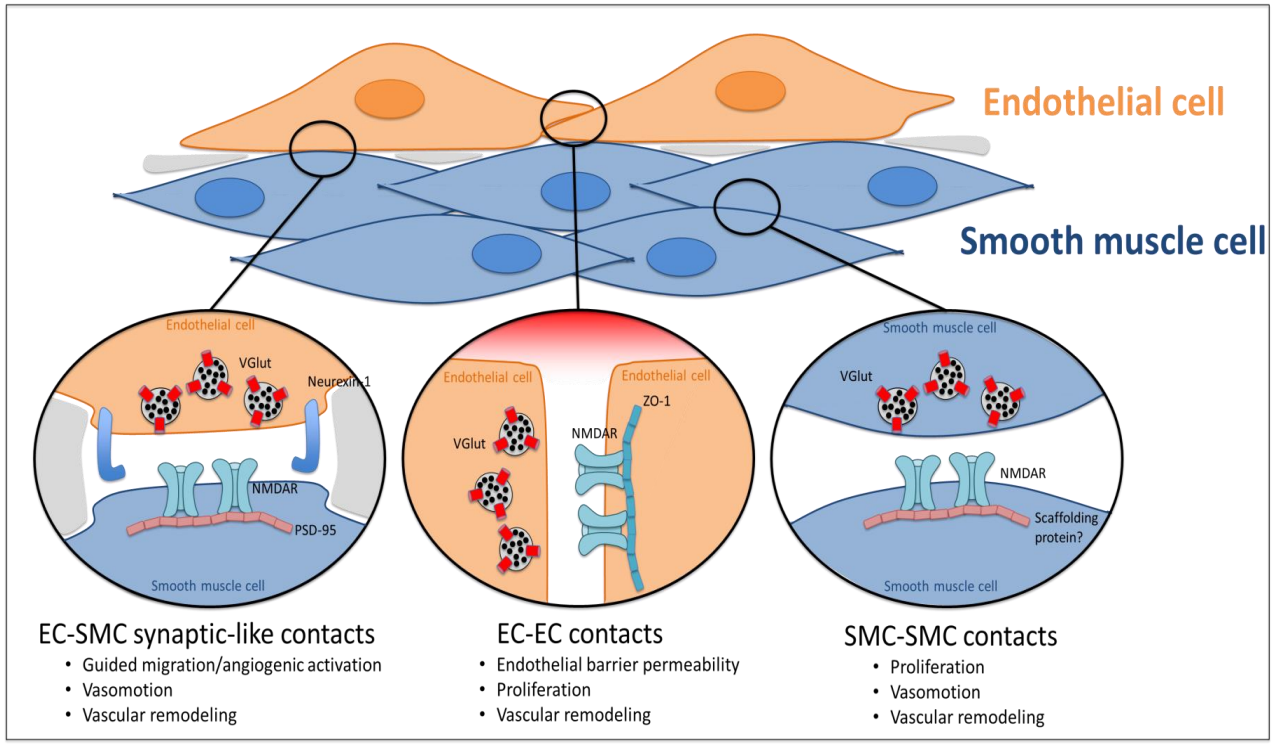
Vascular cell (and immune cells) are equipped for synaptic glutamatergic communication

Dumas et al Circulation 2018, Dumas PhD thesis 2015,
Affaticati et al PhD thesis, Affaticati et al Cell death differentiation 2011)

The NMDAR, a molecular hub at the crossroads of key pathways leading to PAH

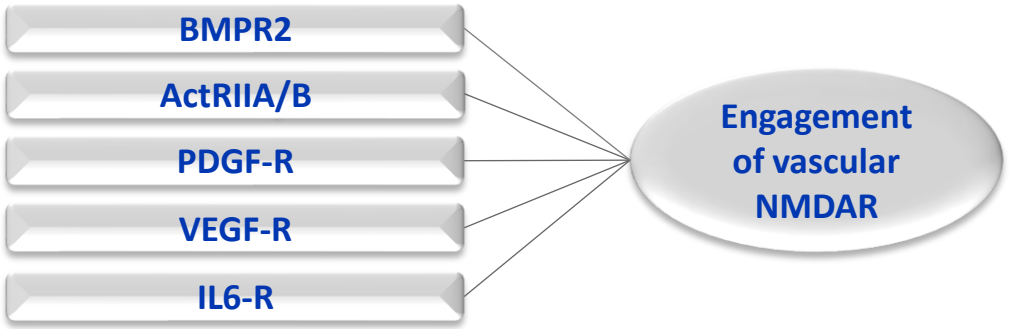
Glutamatergic communication in the vascular wall

NMDARs are present, quiescent or engaged, in both endothelial and smooth muscle cells, the two vascular cell types involved in PAH



NOTE: schematic representation on the basis of the the knowlege on NMDAR in vascular biology

Key PAH pathways are NMDAR engagers



Sébastien **Dumas**

Marceau **Quatredeniers**

Florent **Dumont**

Guillaume **Bernadat**

Key properties of ASM01