PNEUMOMEDICINA 2022

Milano, 26 - 28 maggio 2022 · Centro Congressi Palazzo delle Stelline

Nuove terapie e quale futuro per l'ipertensione polmonare

Roberto Cassandro

U.O. di Pneumologia e Terapia Semi Intensiva
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe - MultiMedica, Milano

NO Conflict of interests disclosures

MARIO

ANTONIO

Dg di ipertensione arteriosa polmonare idiopatica a 50 anni

Terapia massimale

Deceduto dopo 4 anni dalla diagnosi

Dg di ipertensione arteriosa polmonare idiopatica a 52 anni

Terapia di combinazione

Stabile a 6 anni dalla diagnosi

Early diagnosis and Genetic role

Genomics approaches permitted to identify several genes involved in in the predisposition to develop PAH

BMPR2 (central actual role)

- *ALK1 (ACVRL1)*
- *ENG*
- *SMAD9*
- *TBX4*
- *KCNK3*
- *CAV1*
- *EIF2AK4*
- *SMAD4*
- *SMAD1*
- *KLF2*
- *BMPR1B*
- *GDF2 (BMP9)*
- *KCNA5*

Early diagnosis and Genetic role

Actually the reason why BMPR2 signalling is reduced in PAH and how the alterations influence the pathogenesis needs to be understood too

Even if genetic mutation is not the only responsible of PAH development, pre symptomatic screening of individuals with known mutations in PAH-predisposing genes could potentially lead to earlier diagnosis and treatment of PAH

Early diagnosis

Even if PAH tissue access is a clear limitations since lung biopsy carries prohibitive risks in most PAH patients,

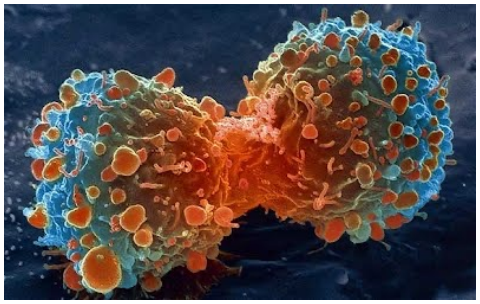
there is a clear need to identify well validated circulating biomarkers

Early diagnosis

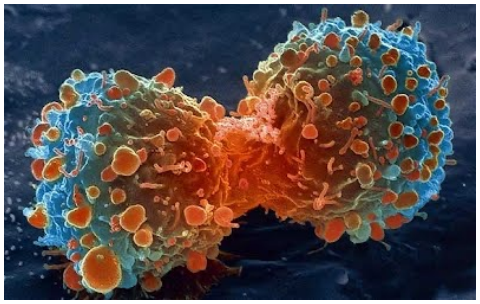
Rhodes et al. performed a proteinomic analysis in 143 PAH patients in follow-up for 2 years, 75 of them for 2.5 years

They identified that the measurements of a combination of nine circulating proteins can be used to stratify PAH patients at high risk of mortality

Rhodes et al. Lancet Resp Med 2017; 5:717-726



Pathogenesis

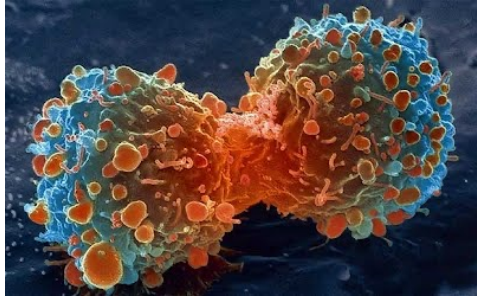


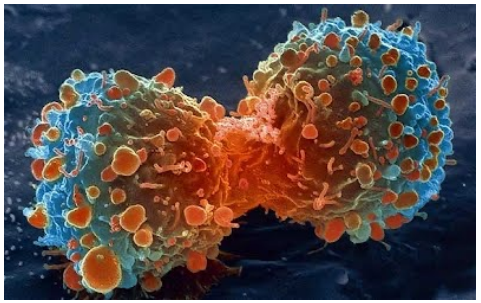
Inflammation and immune disorders appear to be a common denominator for all form of PAH

Pulmonary vascular lesions are characterized by inflammatory infiltrates and their better knowledge could help to identify panel of key inflamamtory mediators to distinguish different PH/PAH clinical phenotypes

The role of autoimmune mechanisms linked to complement activation in the genesis of pulmonary vascular lesions

Pathogenesis





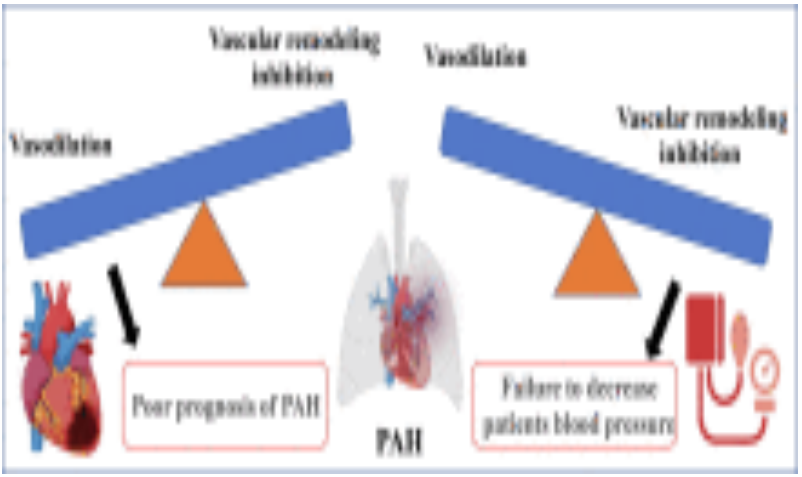
Cancer like

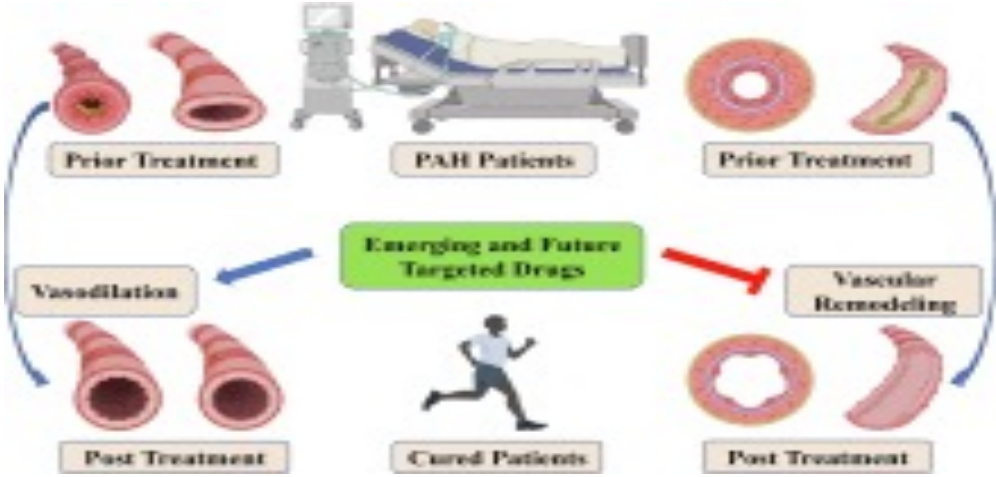
Vascular cells acquire a cancer–like phenotype such as their hyperproliferation and resistance to apoptosis, lead to pulmonary vascular obstruction and remodeling

Antivascular remodeling stategies are centered around a plethora of classical antitumor targets

Guignabert C et al. Eur Resp Rev 22;130 2013; 543-551

Therapy
General considerations





Active vasoconstriction, as well as vascular remodeling, leads to PAH.

It is now accepted that curative therapeutic options for PAH must address not only vasoconstriction, but also vascular remodeling.

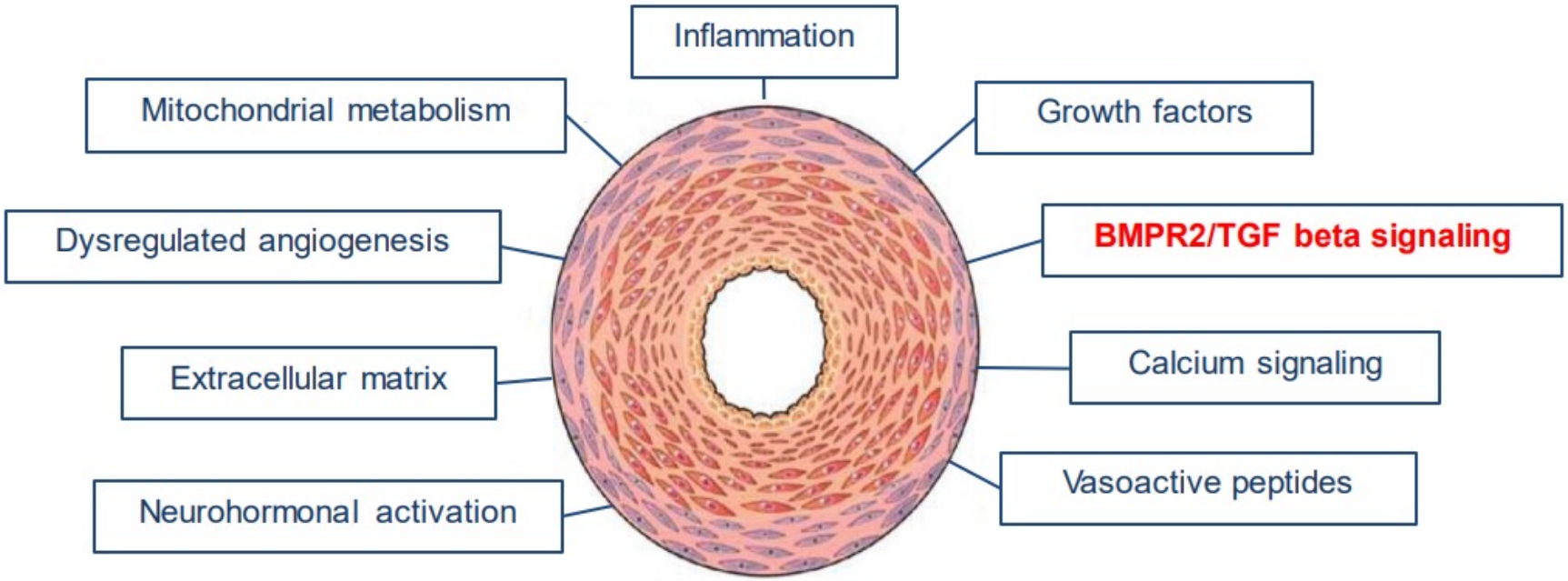
Therefore, natural products, combination therapies, and hybridization drugs are being developed to regulate vasoconstriction and vascular remodeling simultaneously

Therapy

General considerations

New advances in technologies and understanding, contributing to a therapeutic strategy switch from ‘symptom-based’ to ‘pathology-based’ treatments, will speed the development of a valuable new generation of drugs for PAH treatment in the near future

Therapy
New future pathways



Therapy
New actual future pathways

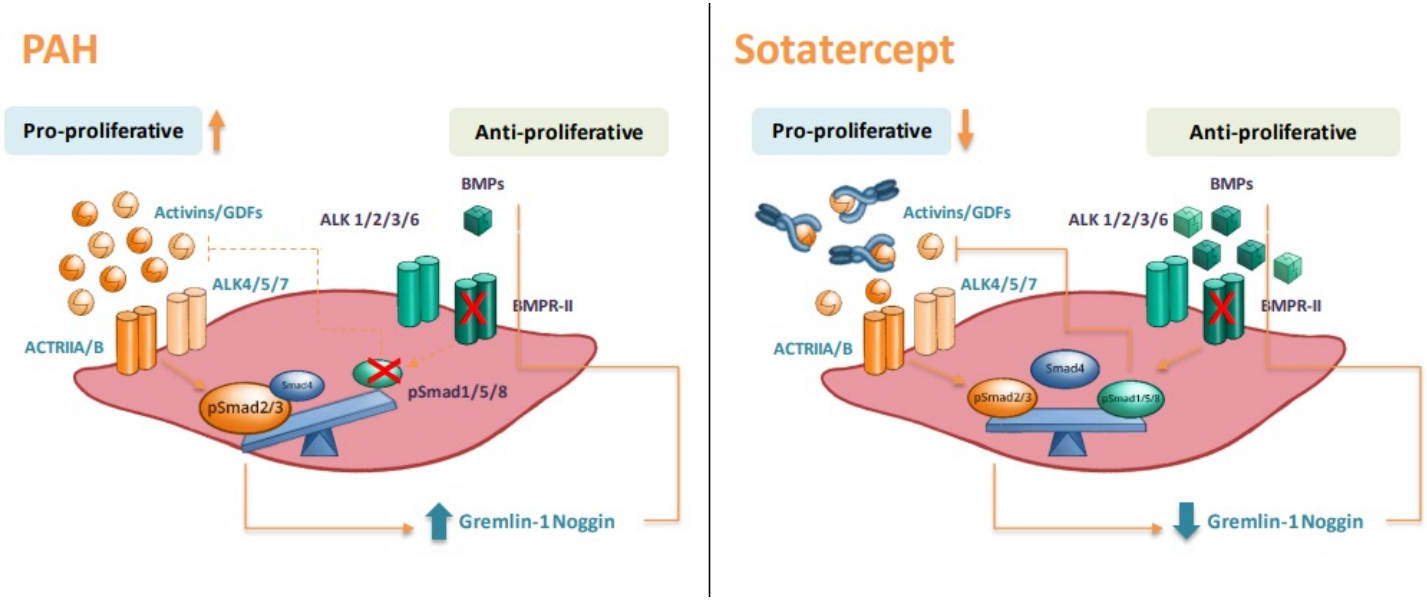
Sotatercept

Sotatercept for the Treatment of PAH

- BMPR-II is a serine/threonine receptor kinase
- It has been evaluated in healthy volunteers, in patients with hematologic disorders, and in patients with conditions characterized by a dysfunctional TGF-β superfamily signaling pathway, including bone loss, chemotherapy-induced anemia, multiple myeloma, myelodysplastic syndromes, β-thalassemia, and end-stage kidney disease
- Reduced BMPR-II expression is linked to PH
- BMPR-II expression is downregulated in all types of PAH
- Imbalanced BMPR-II signaling is a molecular driver of PAH

M. Humbert et al. NEJM 2021

Sotatercept for the Treatment of PAH

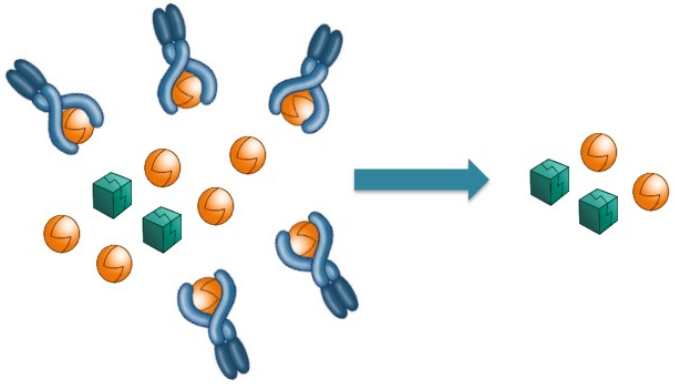


ACTRIIA-Fc

Selective for

Activin A
Activin B
GDF-11
GDF-8

Traps Smad2/3 ligands in PAH



The overall result is that antiproliferative signaling is reduced, shifting the balance toward proproliferative activin–Smad2/3 signaling, which leads to pulmonary vascular remodeling

M. Humbert et al. NEJM 2021

Clinical trials with sotatercept
Our experience

		Target Population	Endpoints
PULSAR	**Phase 2** **Efficacy & Safety** n=106	• WHO FC II-III • Background SOC therapies	• 1° PVR • 2° 6MWD
STELLAR	**Main Phase 3** **Registrational Study** n=284	• WHO FC II-III • Background SOC therapies (mono, double, or triple)	• 1° 6MWD • 2° Multicomponent improvement
HYPERION	**Phase 3 Early Intervention*** n~442-662	• WHO FC II or III • Diagnosed < 6 months • REVEAL Lite 2 risk score ≥6 • Background double or triple combo	• 1° TTCW • 2° Multicomponent improvement
ZENITH	**Phase 3 Late Intervention** n~166	• Advanced WHO FC III-IV • REVEAL 2.0 risk score ≥10 • Stable on maximum-tolerated double or triple therapy for >30 days	• 1° Time to death, lung transplant or PAH-related hospitalization of ≥24 hours
SOTERIA	**OLE Long-term Follow-up** n~700-900	• Any ongoing or previous Sotatercept PAH clinical study	• 1° Safety and tolerability • 2° 6MWD, FC, PVR, OS, NT-proBNP

Therapy
New actual future pathways

Imatinib

Clinical trials
Our experience

Inhaled Imatinib Pulmonary Arterial Hypertension Clinical Trial (**IMPAHCT**) or A Phase 2b/3, Randomized, Controlled, 24-week Dose Ranging and Confirmatory Study of AV-101 in Patients with PAH

IMPAHCT

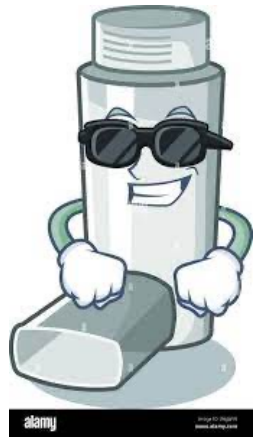
Clinical efficacy of oral imatinib mesylate in the treatment of PAH was observed in Functional Class II-IV patients in the Phase 3 IMPRES trial, in which the primary endpoint, **six minute walk distance (6MWD**), as well as secondary endpoints measuring pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), cardiac output (CO), and N-Terminal Prohormone-B Natriuretic Peptide (NT-proBNP) all showed statistically significant and therapeutically relevant improvements on top of the maximal standard of care (Hoeper et al., 2013).

Oral imatinib was not well tolerated and further clinical development was halted.

IMPAHCT

Given the demonstrated clinical efficacy of oral imatinib in PAH, Aerovate is developing a dry powder inhaled imatinib, AV-101, to target the delivery of imatinib to the diseased organ, the lungs.

Inhaled administration of AV-101 is expected to provide rapid local exposure of respiratory tissue to imatinib with a lower dose and lower systemic exposure compared to oral tablets



IMPAHCT- Study design

Study AV-101-002 is a Phase 2b/3 study design where recruitment of subjects will continue as the study progresses from Phase 2b to Phase 3

The Phase 2b and 3 datasets will be kept separate.

The objective of the study is to establish an optimal dose based primarily upon the change in PVR assessed by right heart catheterization (RHC) and the safety and tolerability of AV-101 as evaluated in the Phase 2b Part of the study.

The optimal dose will be taken into the Phase 3 Part of the study where the placebo-corrected change in 6MWD after 24 weeks of treatment will be used as the primary endpoint.

Except for PVR and 6MWD, all secondary endpoints will be similar across the Phase 2b and Phase 3 Parts of the study including NT-proBNP, multi-component improvement score, WHO Functional Class (FC), clinical worsening, REVEAL Lite 2 risk score, Quality of life (QoL), transthoracic echocardiogram (echo) parameters, and safety and tolerability.

All subjects will be given the opportunity to enter into a blinded Follow-up Long-Term extension (LTE) study

Therapy
New actual future indications

Inhaled trepostinil in ILD-PAH

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease (INCREASE)

326 pts affected by IIP (92 IPF) and PH (documented by RHC) were randomized to receive inhaled treprostinil (72 µg 4 times a day) or placebo for 16 weeks.

Primary end point: change in 6MWD

Secondary end points: change in NT-proBNP level from baseline to week 16;

the time to clinical worsening, evaluated from the time of randomization until the patient's withdrawal from the trial or the time until the occurrence of:

hospitalization for a cardiopulmonary indication;

a decrease in 6-minute walk distance greater than 15% from baseline,

death from any cause,

lung transplantation

Nathan SD Lancet Respir Med. 2021

INCREASE study - Results

Patients in the inhaled treprostinil group had a placebo corrected median improvement from baseline in 6MWD of 21 m

Treated group compared to placebo showed a 38% of reduction in NT-proBNP ($p < 0.001$), a 34% reduction in risk for exacerbation of ILD ($p=0.03$) and a 39% reduction in time to first clinical worsening event ($p<0.001$)

Inhaled Treprostinil was well tolerated and the safety profile was consistent with previous study.

Post- hoc analysis: In patients with ILD and associated pulmonary hypertension, inhaled treprostinil was associated with improvements in FVC versus placebo at 16 weeks. This difference was most evident in patients with idiopathic interstitial pneumonia, particularly idiopathic pulmonary fibrosis

Nathan SD Lancet Respir Med. 2021

Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study

Overall, Inhaled treprostinil was associated with a placebo-corrected improvement in FVC of 28·5 mL (p=0·35) at week 8 and 44·4 mL (p=0·21) at week 16.

Analyzing each subgroup in 92 IPF pts it was greater: asignificant placebo-corrected improvement in FVC (84.52 mL p=0.11 and 168.52 mL,p=0.0108 at Weeks 8 and 16, respectively compared to placebo) was observed

This change was greater in IPF patients than in CTD–ILD and CPFE patients, leading to the hypothesis that inhaled treprostinil might reduce fibrosis, contributing to the improvement of 6MWD

Nathan SD Lancet Respir Med. 2021

Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study

The mechanism by which treatment with treprostinil to an increase in FVC is unclear.

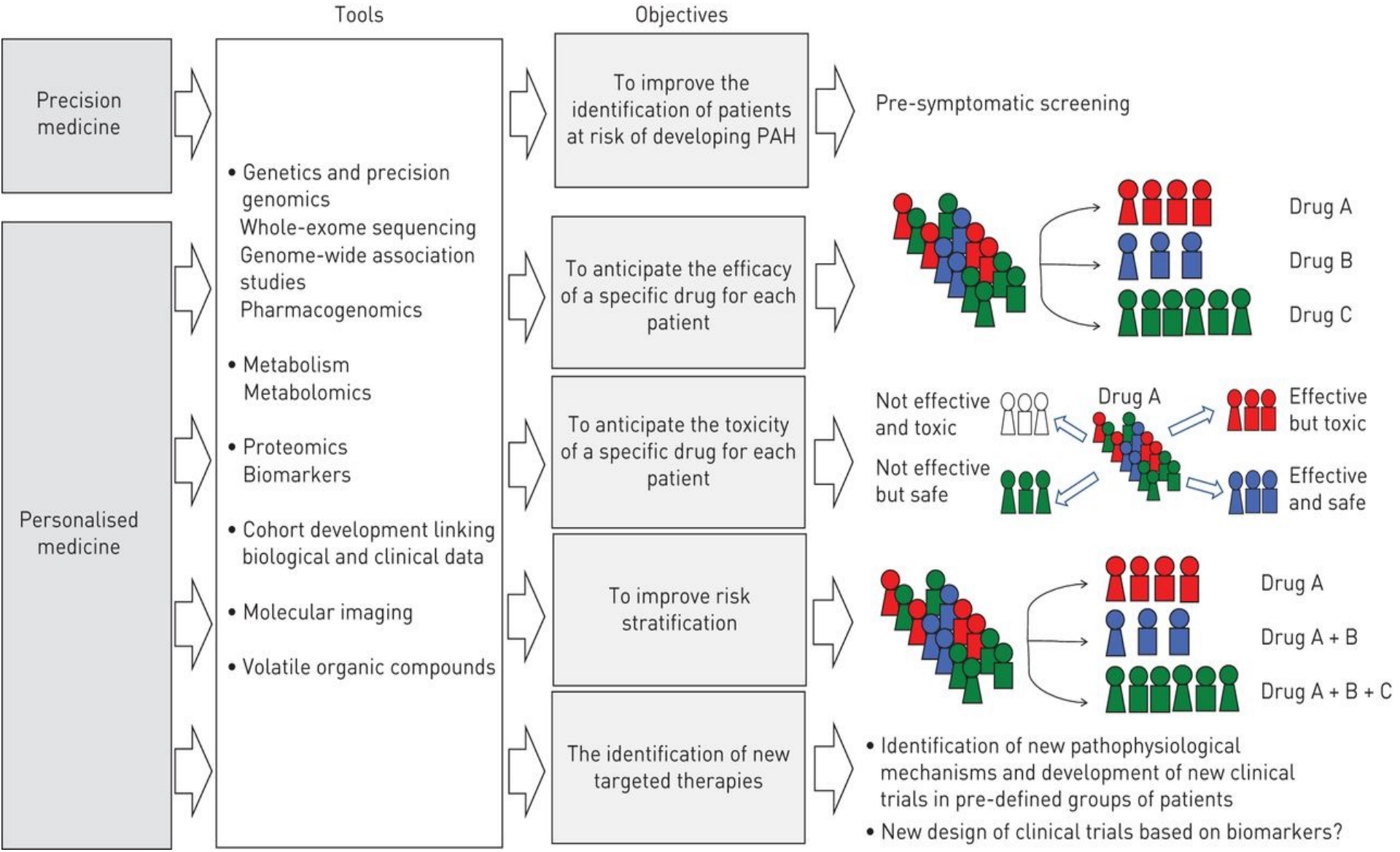
Improvement in FVC could be based on changes in vessel compliance with treatment, but no data about DLCO were analyzed

Possible role of the endothelium in triggering epithelial fibrotic changes, as well as the possible direct antifibrotic action of trepostinil, which has been shown to reduce recruitment of fibrocytes to sites of vascular remodelling and to suppress profibrotic fibroblast activity in mice (Lambers C *Sci Rep* 2018, Nikitopoulou I *Pulm Circ* 2019).

A new clinical trial will be ……

Nathan SD *Lancet Respir Med* 2021

Conclusions



Savale L et al. Eur resp Rev 2018; 13-27

MARIO

52 anni
Dg genetica di ipertensione arteriosa polmonare idiopatica a 50
20 anni
Terapia personalizzata
Guarito

ANTONIO

54 anni
Dg genetica di ipertensione arteriosa polmonare idiopatica a 52
20 anni
Terapia personalizzata
Guarito












GRAZIE