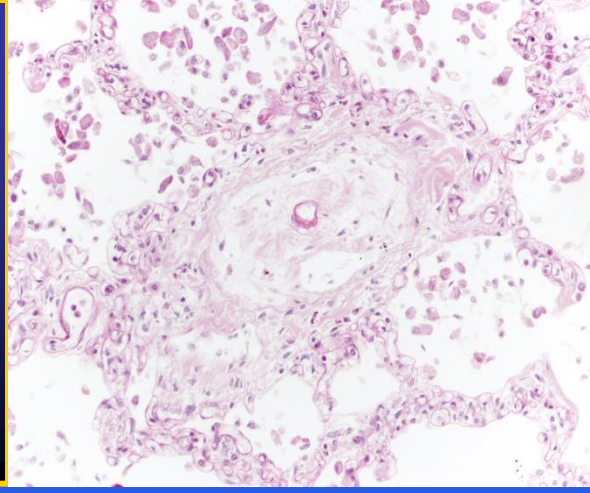
Orphan Lung Diseases



Sergio Harari

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

Roche

What is a "rare disease"?

❖ *Europe:* a disease is considered as *rare* when it affects 1 person per 2,000 (Prevalence <0.05%)

What is an "orphan disease"?

The term "orphan" denotes diseases that either because of their rarity or paucity of therapeutic options are less well understood by patients and their caregivers

Du Bois RM . Am J Respir Crit Care Med 2002; 166: 1157

Global effort against rare and orphan diseases

- ***Increasing incidence of rare diseases and growing research efforts***
- Translational research
- Rare diseases and common therapies
- Rare diseases and exposure to drugs or toxins

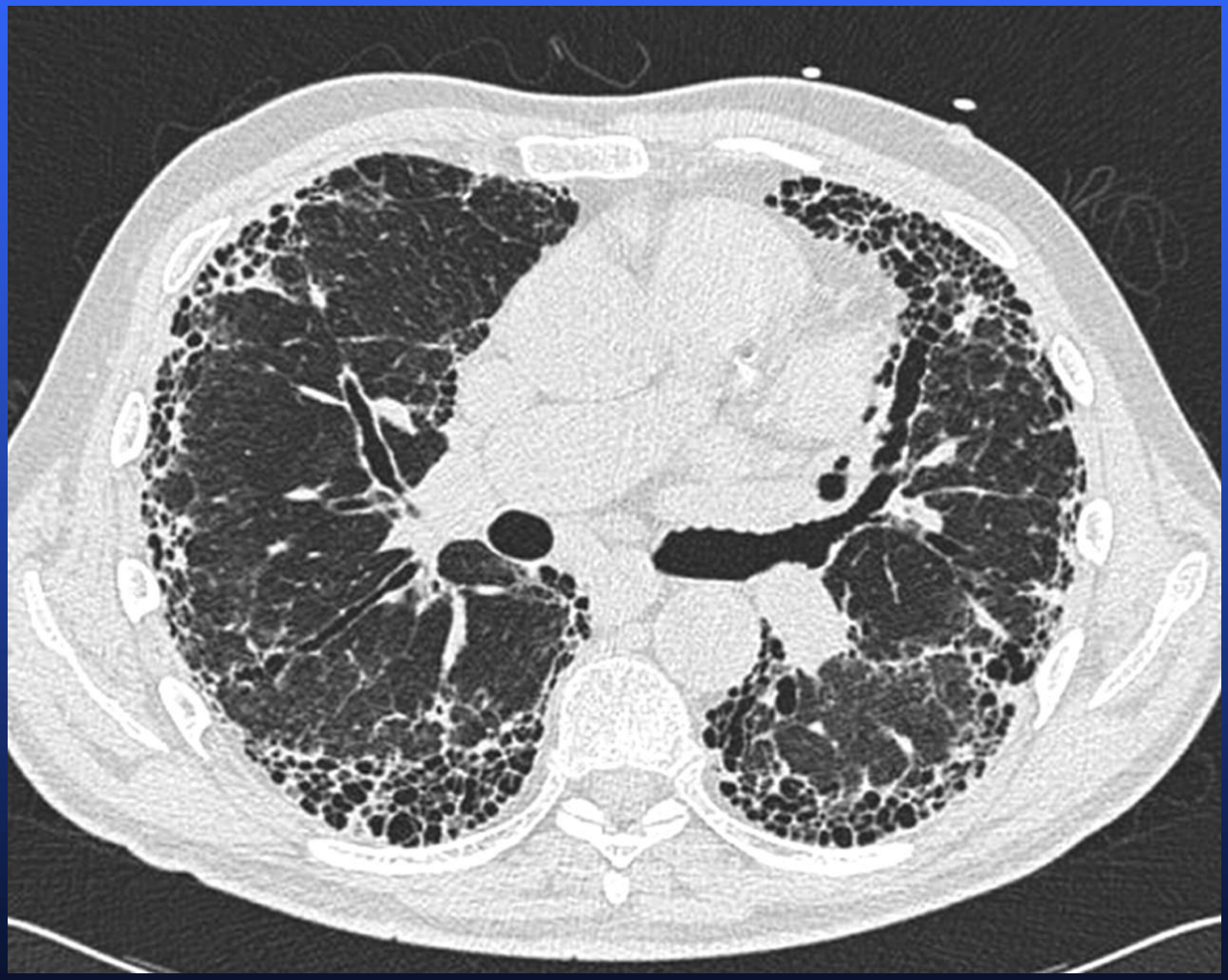
Papers published on rare pulmonary diseases in ERS publications from 1990 to June 2013

	1990-1999	2000-2009	2010-2013
Sarcoidosis	93	107	48
Idiopathic pulmonary fibrosis	44	104	73
Lymphangioleiomyomatosis	7	12	9
Pulmonary Langerhans' cells histiocytosis	2	4	8
Idiopathic pulmonary hypertension	2	54	28
Vasculitis	14	9	5

Harari S, Humbert M, Cottin V; Eur Resp Rev, 2013

Global effort against rare and orphan diseases

IPF



American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Am J Respir Crit Care Med 2011; 183:788

Guidelines for diagnosis and clinical management of IPF evidence-based

The quality of the available evidence was determined according to the ATS GRADE

GRADE = **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation

European Respiratory *review*

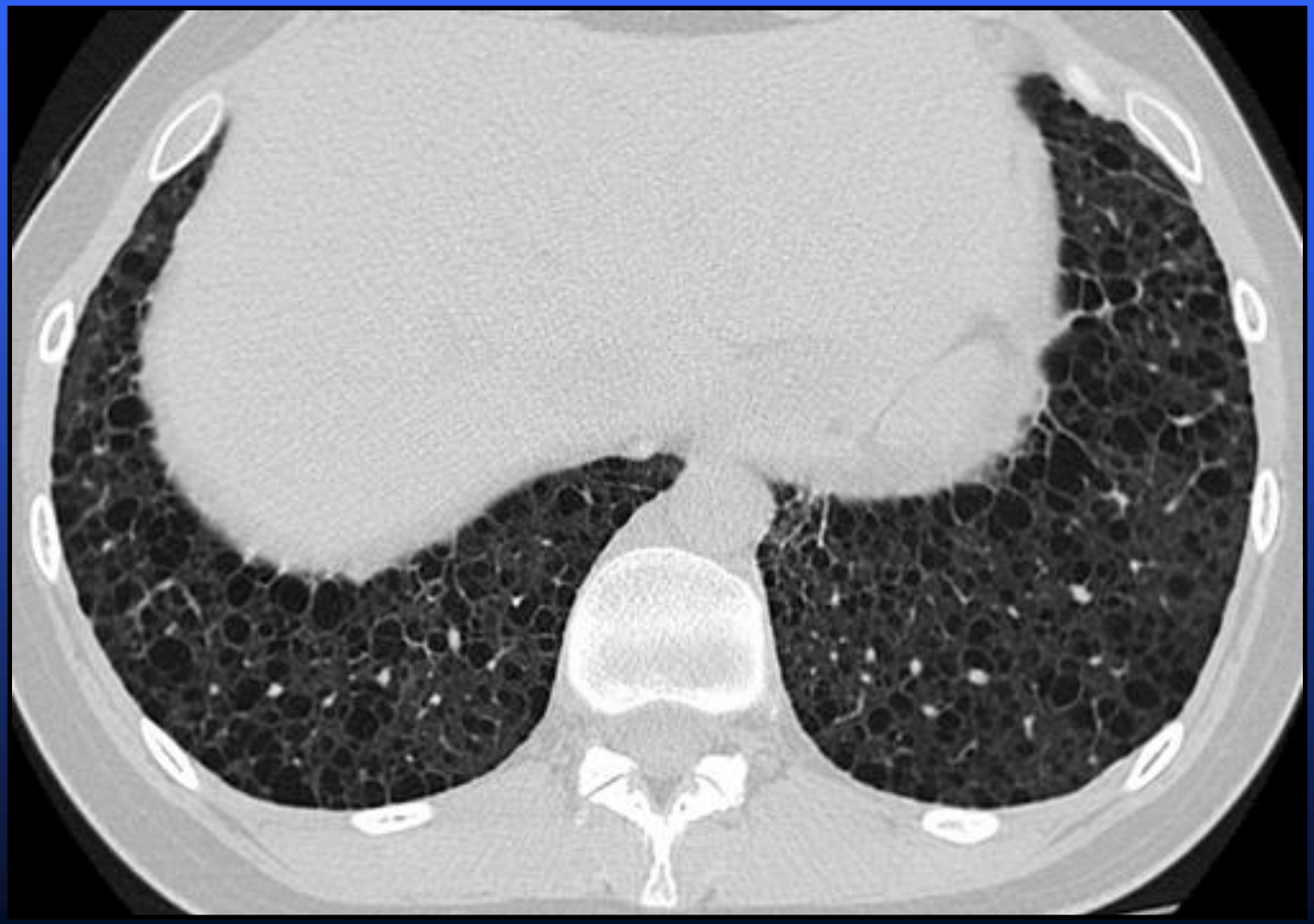
Changing the idiopathic pulmonary fibrosis treatment approach and improving patient outcomes

"The first major step forward has been the European approval of pirfenidone for patients with mild-to moderate IPF. Pirfenidone has demonstrated statistically significant and clinically meaningful effects in clinical trials".

Cottin V. Eur Respir Rev. 2012;21:161-167

Global effort against rare and orphan diseases

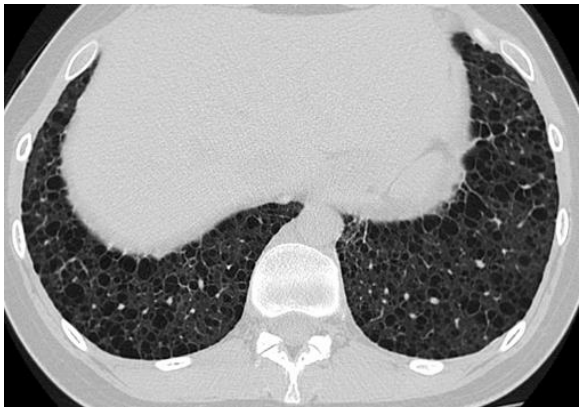
LAM



LYMPHANGIOLEIOMYOMATOSIS

- Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years.

- It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours (e.g. renal angiomyolipomas, lymphangioleiomyomas)



- It can be sporadic (3,5-8/million women) or associated with TSC (30-40% of patients), an autosomal dominant syndrome characterised by hamartoma formation in multiple organ systems, cerebral calcifications, seizures and cognitive defects

LYMPHANGIOLEIOMYOMATOSIS

➢ LAM shares so many genetic, molecular, and pathological aspects with a neoplasm that it can be referred to as *a slow progressive tumor*

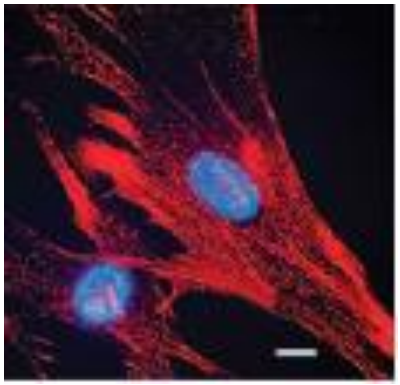
- Mutations
- Inappropriate growth and survival
- Metastasis via blood and lymphatic circulation
- Infiltration
- Tissue destruction
- Sex steroid sensitivity

➢ It has a good biomarker for diagnosis, monitoring of disease and prediction of answer to therapy: VEGF-D

➢ It has an effective and relatively safe treatment which can stop or slow down the progression of the disease: sirolimus (mTOR inhibitor)

- Side effects: Mouth ulcers, diarrhea, upper respiratory infections, hypercholesterolemia, acneiform rash
- Non responders

LAM cells



Smooth muscle actin

The multisystem manifestations of LAM are believed to result from metastatic dissemination of abnormal smooth muscle-like cells: LAM cells.

- In tissues, LAM cells are heterogeneous, ranging from small and round or spindle-shaped to large and epithelioid.

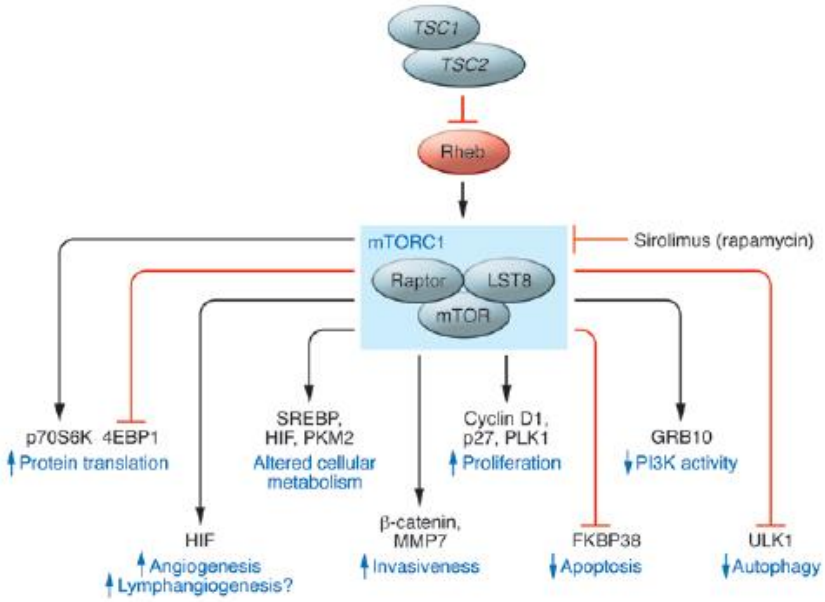
- LAM cells do differ from normal smooth muscle cells by the presence of gp100, a glycoprotein found in melanoma that reacts with a monoclonal antibody, HMB45.

- In blood, they can be enriched by flow-cytometry using CD45 and CD235a antibodies to remove leukocytes and red blood cells *(Crooks et al, 2004).*

- Two cell surface proteins, CD44v6 and CD9, have been identified for the isolation of disseminated LAM cells from BALF, urine and chylous effusions *(Cai et al, 2010).*

LAM cells

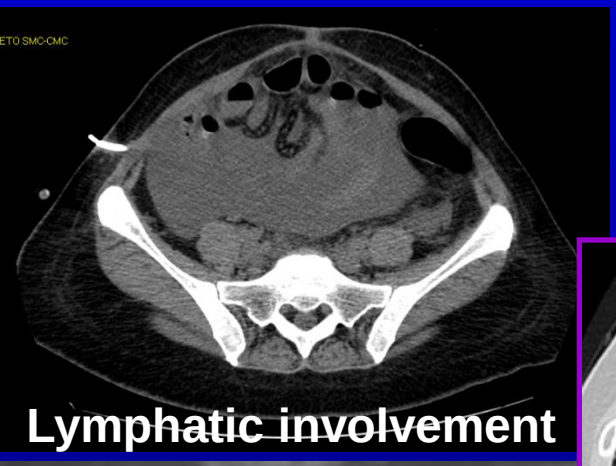
- LAM cell growth is caused at least in part by mutational inactivation of the tumor suppressor genes Tuberous Sclerosis Complex 1(TSC1) or TSC2.
- The mutations found most frequently in sporadic LAM is TSC2 loss of heterozygosity (LOH) on chromosome 16p13 .
- Loss of TSC2 protein function results in hyperactivation of the mTORC1 signaling pathway leading to dysregulated cell growth and cell viability.

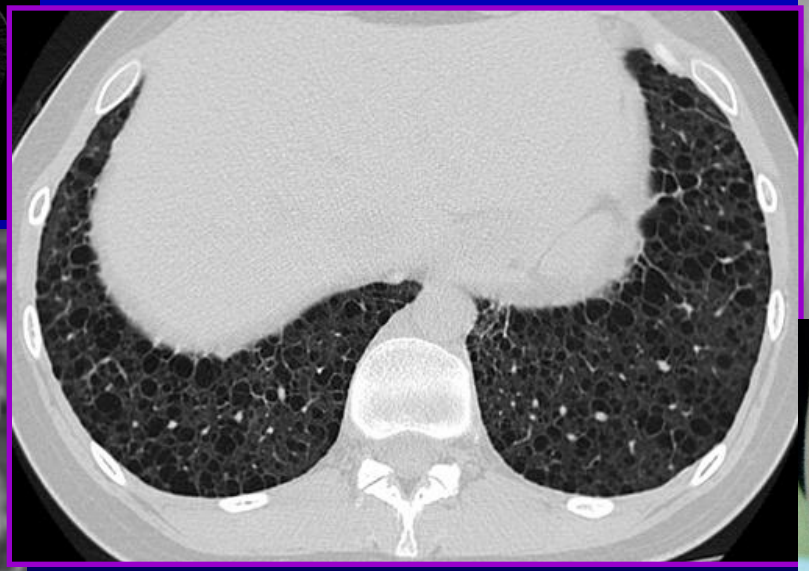


Henske EP, McCormack FX, JCI, 2012

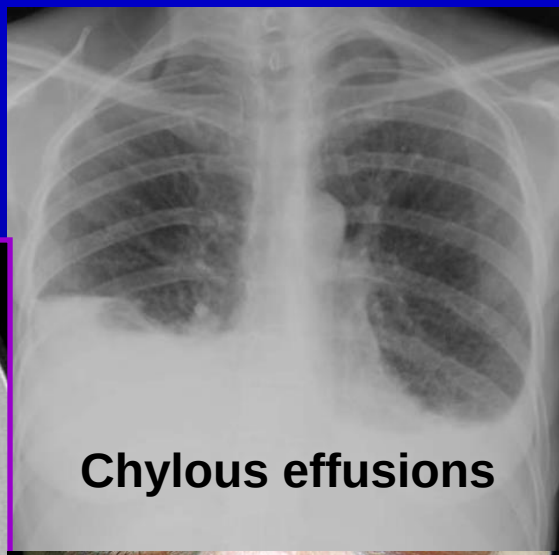
Definite diagnosis

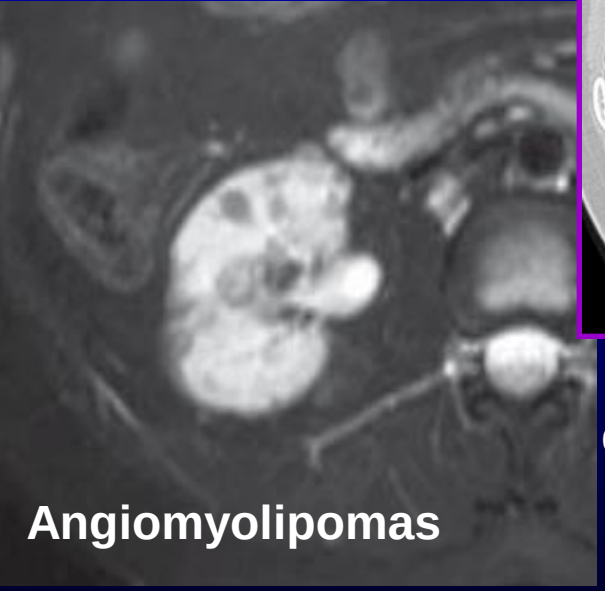
ERS guidelines 2010

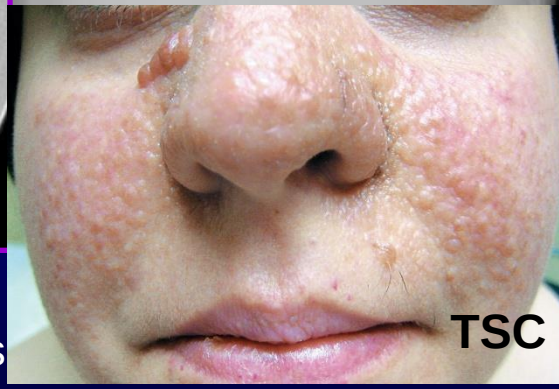




Numerous thin-walled lung cysts distributed diffusely throughout the lungs without sparing of lung bases







Johnson SR, ERJ 2010

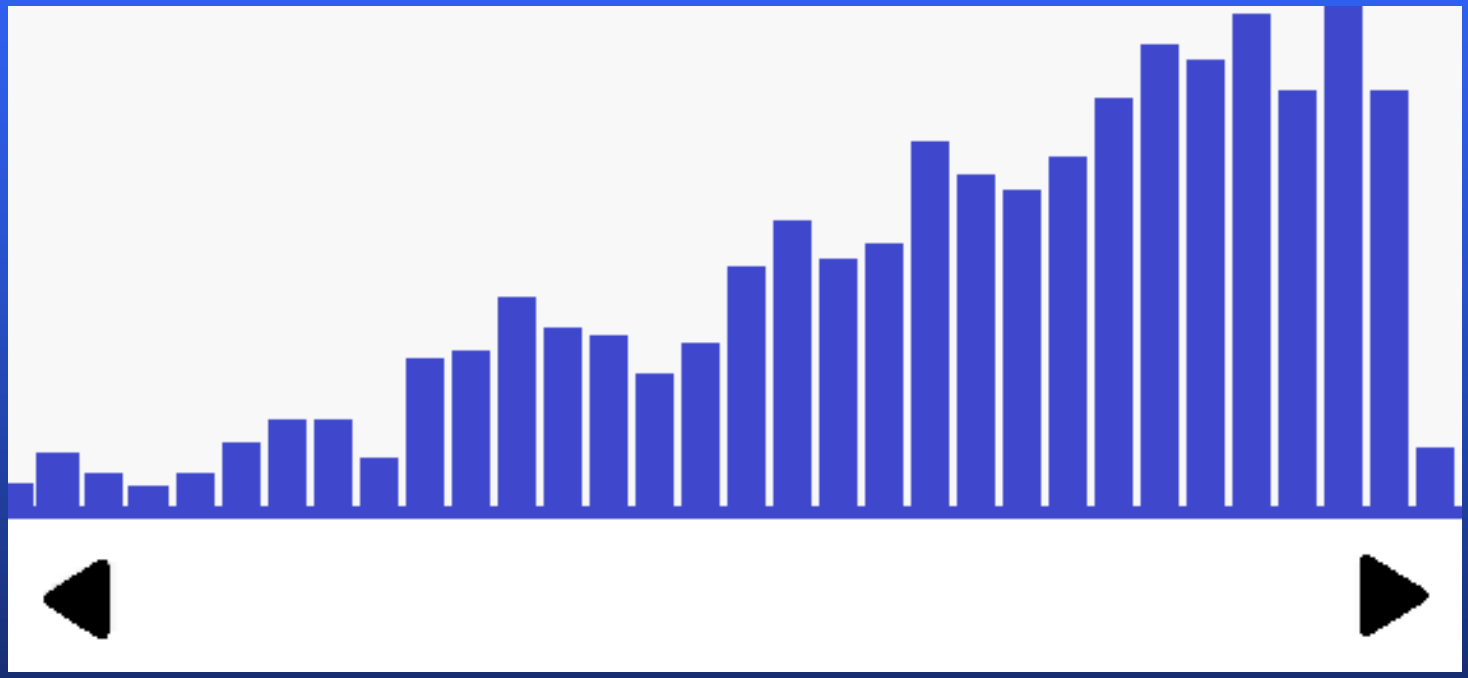
European Respiratory *review*

Lymphangioleiomyomatosis: what do we know and what are we looking for?

Recent progress in our understanding of the molecular pathogenesis of LAM and muscle cell biology provides a foundation for the development of new therapeutic strategies. Inhibitors of mTOR and inhibitors of MMPs and angiogenesis are the most promising areas of research.

Harari S et al. Eur Respir Rev. 2011;20:34-44

Pubmed search: results by year



From 1988 to 2015

LAM – clinicalTrials.gov

Status	Study	Study type	Study design
Completed 2000-2008	Treatment With Octreotide in Patients With Lymphangioleiomyomatosis	Interventional Phase II	Efficacy Study Single Group Assignment Open Label
Completed 1999-2008	Official Records of Patients Diagnosed With Lymphangioleiomyomatosis	Observational	
Completed 2002-2006	Rapamycin Therapy for Patients With Tuberous Sclerosis Complex and Sporadic LAM	Interventional Phase II	Non-Randomized Safety/Efficacy Study Single Group Assignment Open Label
Completed 1997-2003 Last update 2006	Lymphangioleiomyomatosis (LAM) Registry	Observational	Observational Model: Natural History
Completed 2007-2009	Trial of Efficacy and Safety of Sirolimus in Tuberous Sclerosis and LAM (TESSTAL)	Interventional Phase II	Safety/Efficacy Study Single Group Assignment Non-Randomized Open Label
Completed 2009-2010	Pulmonary Hypertension in Lymphangioleiomyomatosis (LAM-PH)	Observational	Observational Case-Only Retrospective
Completed 2006-2011	Efficacy and Safety of Sirolimus for Treating Lymphangioleiomyomatosis (MILES)	Interventional Phase III	Safety/Efficacy Study Parallel Assignment Randomized Double Blind

LAM – clinicalTrials.gov

Status	Study	Study type	Study design
2011-	Trial of Aromatase Inhibition in Lymphangioleiomyomatosis (TRAIL)	Interventional Phase II	Efficacy Study Parallel Assignment Randomized, Double Blind
Completed	Doxycycline In Lymphangioleiomyomatosis (LAM)	Interventional Phase IV	Allocation: Safety/Efficacy Study Parallel Assignment Randomized,Double Blind
Completed	RAD001 Therapy of Angiomyolipomata in Patients With TS Complex and Sporadic LAM	Interventional Phase I Phase II	Safety/Efficacy Study Single Group Assignment Open Label
Completed	A Study to Determine the Effectiveness of Escalating Doses of RAD001 (Everolimus) in Patients With Lymphangioleiomyomatosis	Interventional	An exploratory, open label, non-randomized, within-patient
Active, not recruiting 2008-	Long Term Follow Up for RAD001 Therapy of Angiomyolipomata in Patients With TSC and Sporadic LAM	Interventional Phase I Phase II	Safety/Efficacy Study Single Group Assignment Open Label
Completed	Efficacy and Safety of RAD001 in Patients Aged 18 and Over With Angiomyolipoma Associated With Either TSC or Sporadic LAM (EXIST-2)	Interventional Phase III	A Randomized, Double-blind, Placebo-controlled
Ongoing 2012-	Safety Study of Sirolimus and Hydroxychloroquine in Women With Lymphangioleiomyomatosis (SAIL)	Interventional Phase I	Safety study Open label

Patients organisations

Country/Region/Town	Name
AUSTRIA/Wien/WIEN	**Österreichischer Verband der Herz- und Lungentransplantierten**
FRANCE/POITOU-CHARENTES/ SAINT BENOIT	**FLAM - France Lymphangioléiomyomatose**
GERMANY/Sachsen/LEIPZIG	**LAM Selbsthilfe**
ITALY/Friuli Venezia Giulia/PAVIA di UDINE	**LAM Italia**
ITALY/Sicilia/CATANIA	**AILAM - Associazione Italiana Linfangioleiomiomatosi - ONLUS**
NETHERLANDS/Braband/AALBURG	**LAM Netherlands**
SPAIN/Galicia/VIGO	**AELAM - Asociación Española de Linfangioleiomiomatosis**
UNITED KINGDOM/Nottinghamshire/NOTTINGHAM	**LAM Action**
UNITED STATES/Ohio/Cincinnati	**The LAM Foundation**
UNITED STATES/Massachusetts/Cambridge	**LAM Treatment Alliance**
AUSTRALIA/Bondi Junction	**LARA – LAM Australasia research alliance**
NEW ZEALAND/Auckland	**New Zealand LAM Charitable Trust**
CANADA	**LAM Canada**

ERS TASK FORCE

European Respiratory Society guidelines for the diagnosis and management of Lymphangioleiomyomatosis - 2010

- Aim: to produce evidence based, consensus guidelines for the diagnosis, assessment and treatment of patients with LAM.

- Grading of recommendation strength used was the 2004 American College of Chest Physicians health and science policy grading system

Eur Respir J 2010; 35: 14–26

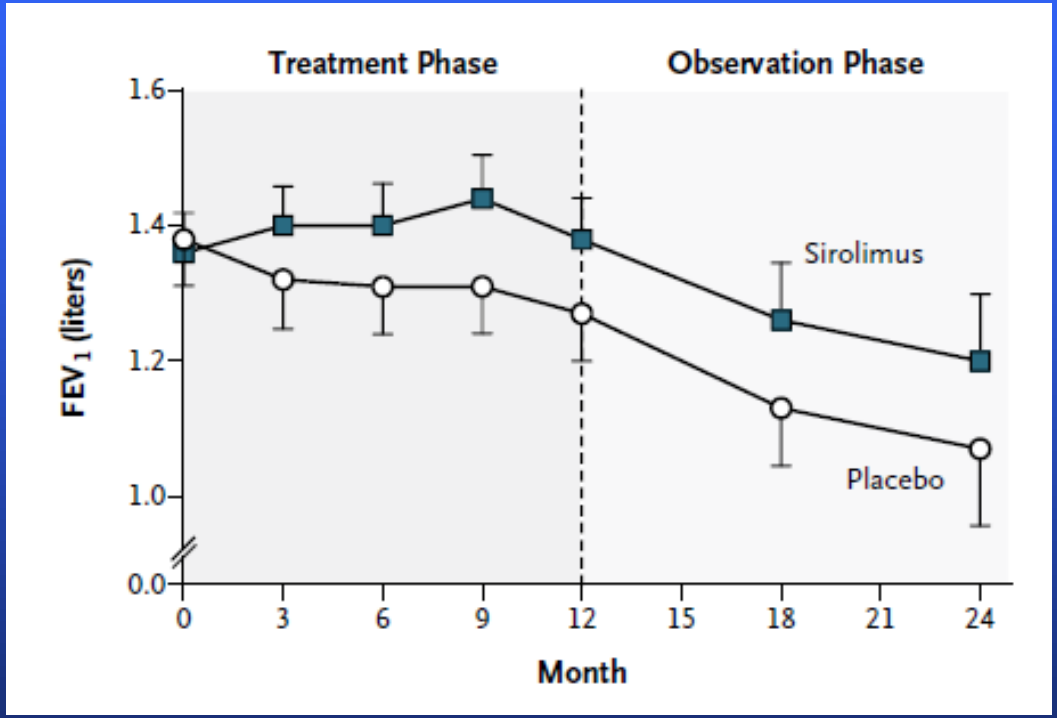
Treatment

mTOR inhibitors

2011	**MILES** (Sirolimus)	Randomised, double-blind, placebo-controlled	Efficacy and safety for sirolimus in LAM
2011	**TESSTAL** (Sirolimus)	Non-randomized, open label trial	Efficacy and Safety rapy for renal angiomyolipmoas in TSC-LAM and S-LAM
2013	**EXIST-1** (Everolimus)	Randomised, double-blind, placebo-controlled	Efficacy and safety in subependymal giant cell astrocytomas
2013	**EXIST -2** (Everolimus)	Randomised, double-blind, placebo-controlled	Angiomyolipoma response in TSC or S-LAM
2015	***RAD001X2201*** *(Everolimus)*	*Open-label, within-patient multiple dose escalation in LAM*	*Waiting for results*

The MILES trial: a milestone

- Stabilization of lung function during the treatment period
- After discontinuation of sirolimus, the decline in lung function resumed and paralleled that in the placebo group

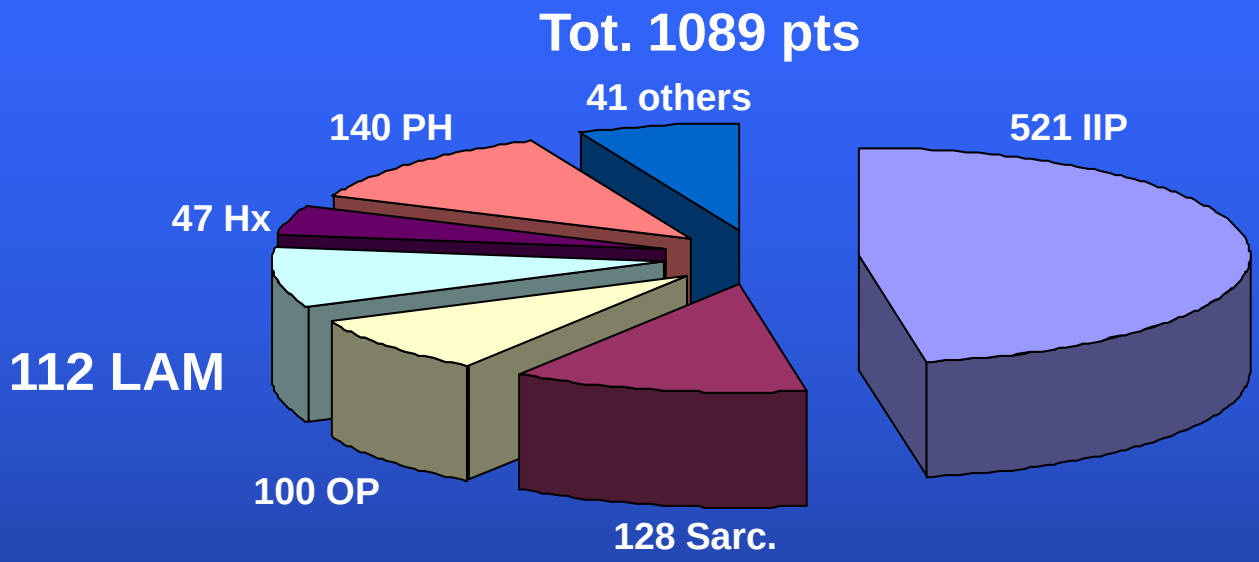


More common adverse effects:
Mouth ulcers, diarrhea, upper respiratory infections, hypercholesterolemia, acneiform rash

McCormack FX, NEJM 2011

Rare Lung Diseases

Ospedale San Giuseppe Experience (2001- 2014)



Mean age at diagnosis: 36 years

18 pts in post-menopausal age, 20 TSC-LAM

45 pts treated with Sirolimus

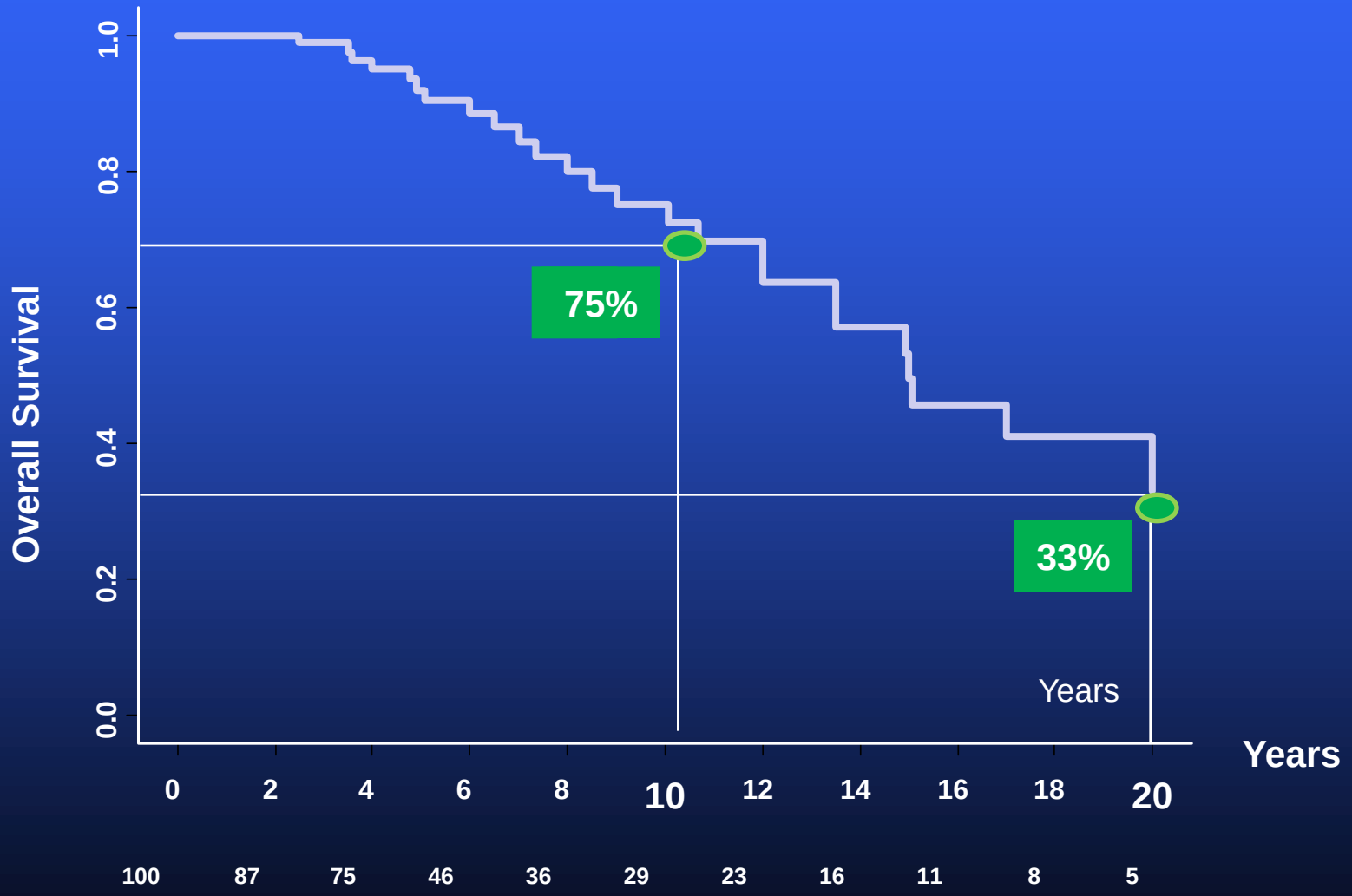
- FEV1 change in pre-treatment period: - 119 ml/year
- FEV1 change in treatment period: + 84 ml/year

3 pts showed declining lung function after two year treatment period

3 pts discontinued the therapy because of adverse events

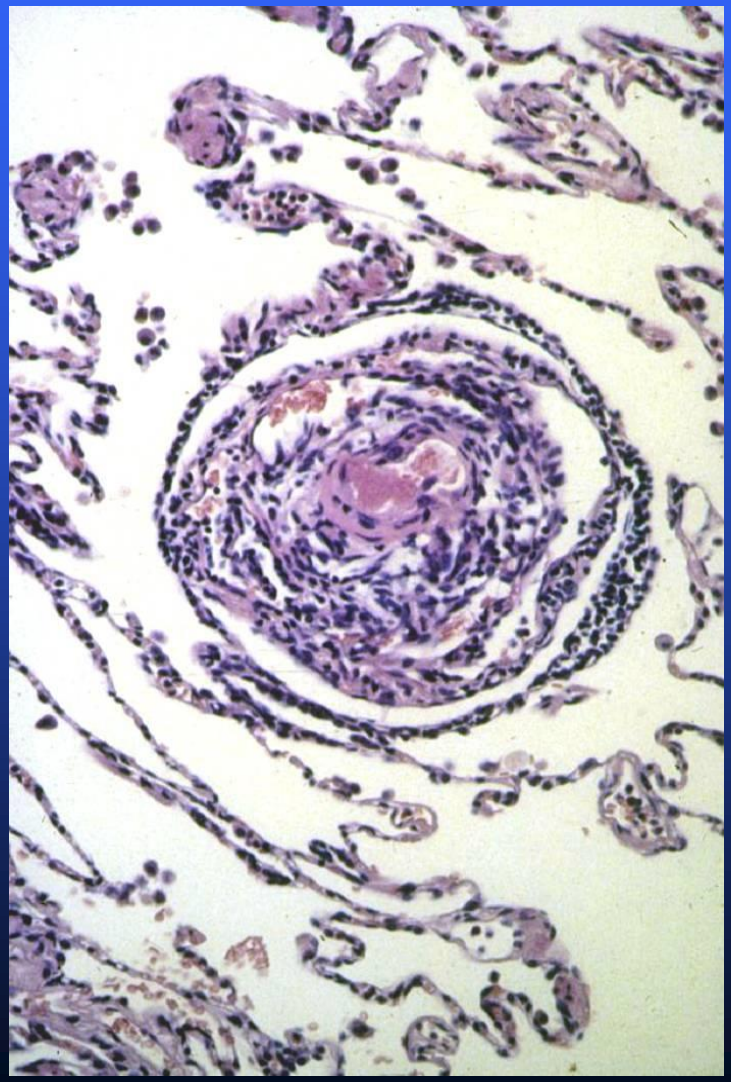
Overall survival in 100 patients

Ospedale San Giuseppe experience



Global effort against rare and orphan diseases

PAH



PAH - Prevalence

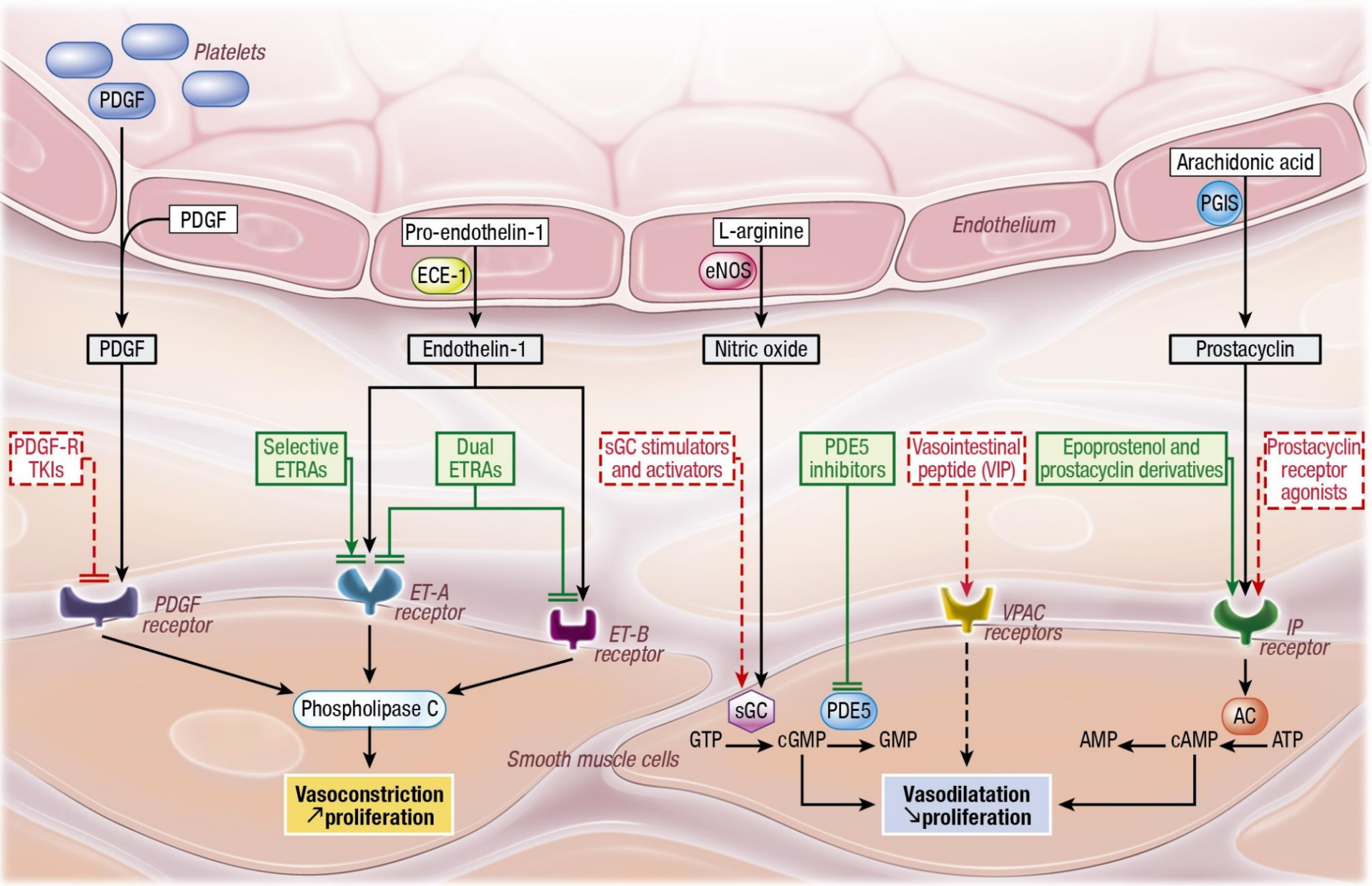
Orphanet Report Series (Update, June 2013)

Estimated prevalence = 1.5 cases per 100.000

Sources: - Websites: Orphanet, e-medicine, GeneClinics, EMA and OMIM ;

- Medline is consulted using the search algorithm: «Disease names» AND Epidemiology[MeSH:NoExp] OR Incidence[Title/abstract] OR Prevalence[Title/abstract] OR Epidemiology[Title/abstract] ;
- Medical books, grey literature and reports from experts are also important sources of data

Current and Emerging Targets and Therapies in PAH



O'Callaghan DS et al, Nat Clin Practice Cardiol 2011; 19:526-538

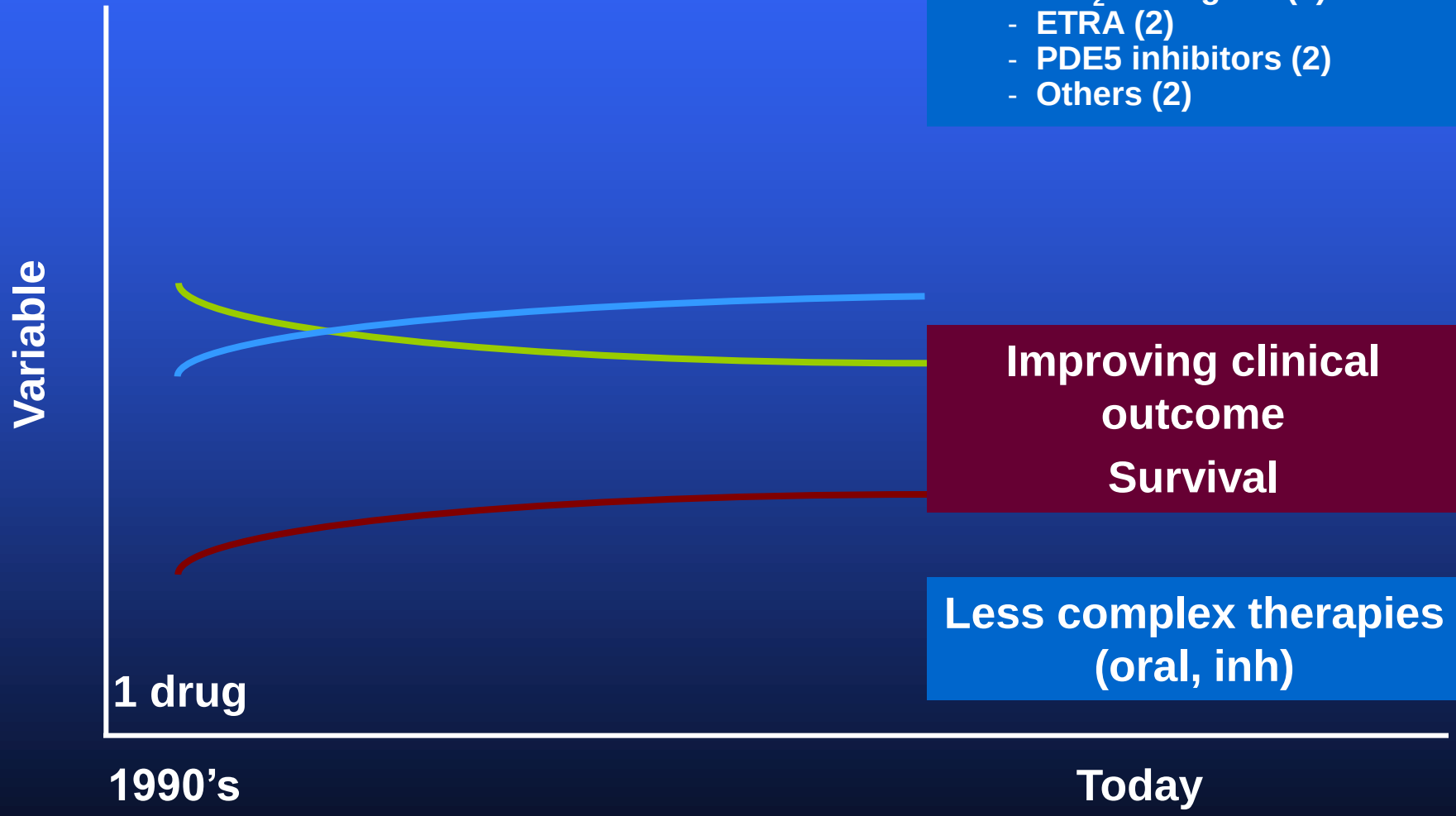
PAH - What progress in the last 20 years?

Lung transplantation

iv epoprostenol

10 drugs available

- PGI_2 analogues (4)
- ETRA (2)
- PDE5 inhibitors (2)
- Others (2)



Improving clinical outcome

Survival

Less complex therapies (oral, inh)

Drugs approved for PAH in Europe

Endothelin pathway	Prostacyclin pathway	NO / cGMP pathway
▪ **ERA dual (ET_A&ET_B)** ▪ **ERA selective(ET_A)**	▪ **Prostanoids** ▪ **IP receptors agonists**	▪ **PDE-5 inhibitor** ▪ **sGC stimulators**
Bosentan	Epoprostenol IV Epo thermostable IV	Sildenafil
Ambrisentan	Iloprost inhaled	Tadalafil
Macitentan	Treprostinil SC (IV*)	Riociguat
	Oral Selexipag	

*** IV Treprosinil as 2nd line Tx when SC not tolerated.**

Oral Selexipag not yet approved

Recent morbidity-mortality trials in PAH

TRIAL	Inclusion Period	Maximum Follow-up
Seraphin (n=742) : Primary end-point met Macitentan vs placebo 64% pre- treated with PDE5-inh or Prostanoids	1.5 year	3 years
Griphon (n=1156) : Primary end-point met Selexipag vs placebo 80% treated with PDE5-in and or ERA	3.5 years	3 years
Ambition (n=605) : Primary end-point met Ambrisentan+Tadalafil vs monotherapy	3.8 years	3 years

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

A multicenter, double-blind,randomized, placebo-controlled, event driven, phase 3 trial.

742 Patients randomized in three arms

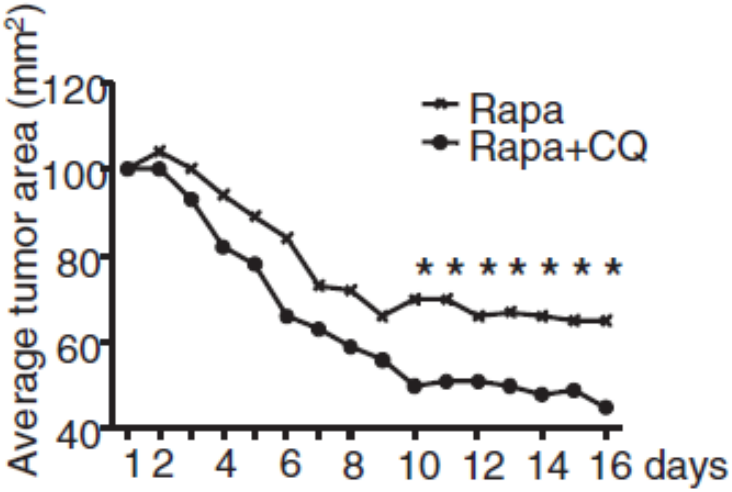
Primary end point: time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension.

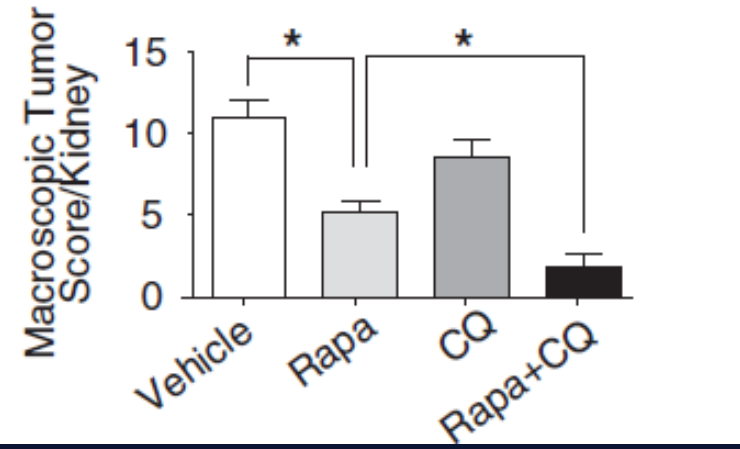
Pulido T et al, NEJM 2013

Global effort against rare and orphan diseases

- Increasing incidence of rare diseases and growing research efforts
- ***Translational research***
- Rare diseases and common therapies
- Rare diseases and exposure to drugs or toxins

From bench to bedside
LAM: a good model





The combination of mTORC1 and autophagy inhibition (using rapamycin and chloroquine) is more effective than either treatment alone in inhibiting the survival of tuberin (TSC2)- null cells, growth of TSC2-null xenograft tumors, and development of spontaneous renal tumors in Tsc2+/− mice

Thus dual inhibition of mTORC1 and autophagy is a potential therapeutic strategy for TSC and LAM patients.

Parkhitko A et al, PNAS 2011

From bench to bedside
LAM: a good model

OPEN ACCESS Freely available online

PLOS ONE

MicroRNA-21 is Induced by Rapamycin in a Model of Tuberous Sclerosis (TSC) and Lymphangioleiomyomatosis (LAM)

Anil J. Trindade, Douglas A. Medvetz, Nicole A. Neuman, Faina Myachina, Jane Yu, Carmen Priolo, Elizabeth P. Henske*

mTOR-inhibition by Rapamycin upregulates miR-21, a pro-survival miR

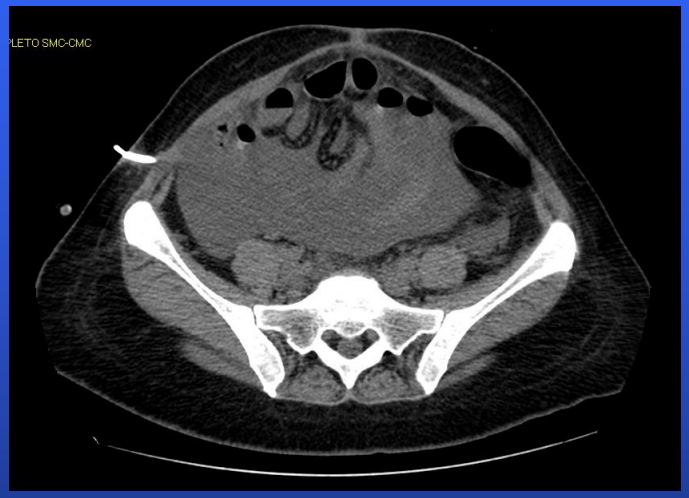
- **pro-survival effects of miR-21 may partially explain why there is a resumption of disease upon treatment discontinuation in LAM patients treated with Rapamycin**.
- miR-21 is a known regulator of smooth muscle morphology, promoting a de-differentiated state marked by growth and migration
- is possible that miR-21 induces a pro-inflammatory state that promotes the survival and metastasis of TSC2-deficient LAM cells.

Could suppression of miR-21 in conjunction with Rapamycin represent an effective therapeutic strategy for TSC and LAM?

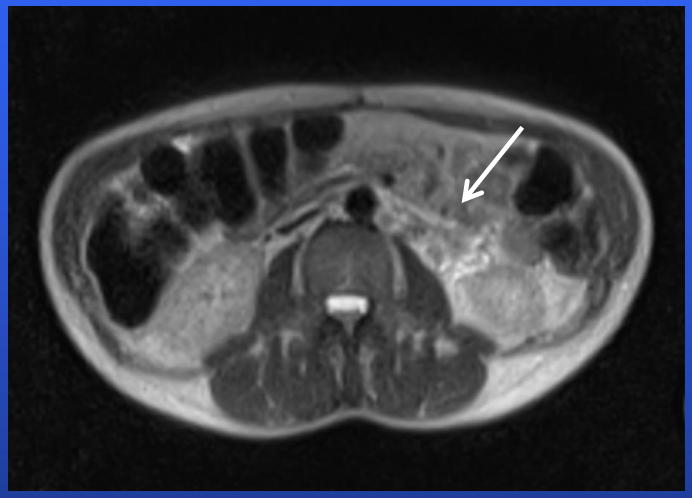
Trindade AJ et al, PLOS 2013

A 39 years old woman with mild lung disease and a large abdominal lymphangioleiomiomas was referred to our centre for recurrent chylous ascites after every attempt of oral feeding

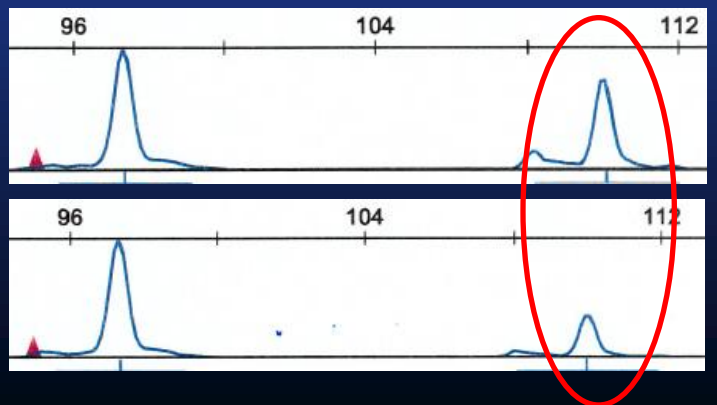
Before sirolimus

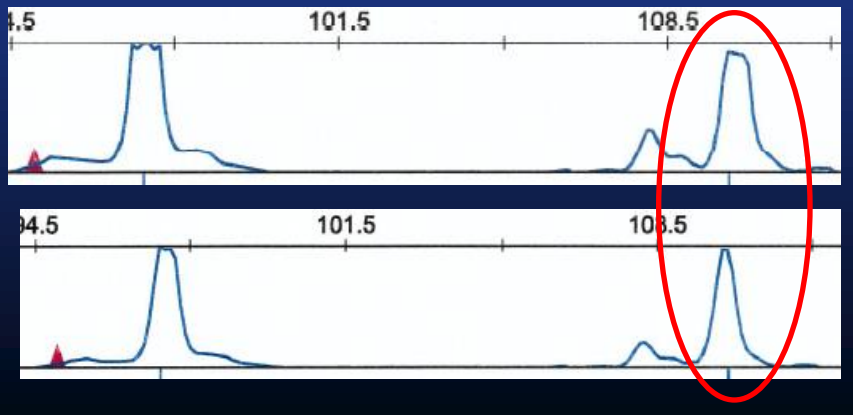


After 3 months of sirolimus



Serum VEGF-D: 4490 pg/mL ⟶ 1 558 pg/mL





Global effort against rare and orphan diseases

- Increasing incidence of rare diseases and growing research efforts
- Translational research
- ***Rare diseases and common therapies***
- Rare diseases and exposure to drugs or toxins

Rare diseases and “famous” therapies *Beta-blockers*

Beta-blockers and Portopulmonary Hypertension

10 patients - After beta-blockers (propanolol or atenolol) withdrawal:

- Improvement in exercise tolerance (Walk distance during 6MWT)

- Improvement in hemodynamics (increase in CO with no change in mPAP resulting in decreased pulmonary vascular resistance)

Provencher S et al, Gastroenterology 2006

Rare diseases and “famous” therapies
PAH and *Beta-blockers*

European Respiratory *review*

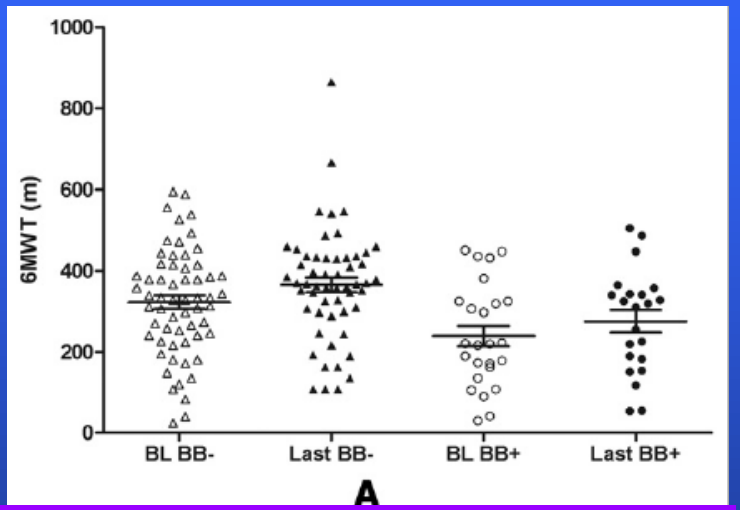
By common clinical consensus, beta-blocker use in PAH is contraindicated.
Neverthless there are several indicators of increased sympathetic activity affecting the right ventricle in PAH.

Could a low-dose of a newer selective beta-blocker might be a tolerable option to abolish the detrimental effects of sympathetic overdrive in PAH?

Handoko LM, Eur Resp Rev 2010

Rare diseases and “famous” therapies
PAH and *Beta-blockers*

Beta-Blocker statistics at baseline (n = 26)	
Type of β-blocker used	
Metoprolol	54%
Atenolol	8%
Bisoprolol	27%
Propranolol	4%
Acebutolol	4%
Nadolol	4%
Metoprolol-equivalent dose (mg), median (interquartile range)*	100 (50–100)



Most patients tolerate beta-blockers well and they do not appear to exert detrimental effects in clinical, functional, and hemodynamic outcomes in patients with PAH.

Although use of bradycardiac agents such as beta-blockers do carry the theoretical risk of decreasing cardiac output, careful use of beta-blockers in selected patients may be safe in those who do not demonstrate any adverse clinical effects.

So PPS et al, Am J Cardiol 2012;109:1504 –1509

Rare diseases and “famous” therapies
LAM and Statins

Evidence of RhoA GTPase activation in LAM-derived and human TSC2-null cells suggested that HMG-CoA reductase inhibitors statins can be used as potential adjuvant agents.

Combined treatment of rapamycin with simvastatin but not with atorvastatin showed a synergistic growth inhibitory effect on TSC2-null cells

Atochina-Vasserman EN et al, Am J Respir Cell Mol Biol, 2013 Aug

Rare diseases and "famous" therapies
ILD and Statins

- In a large cohort of smokers from COPDGene statin use was positively associated in ILA (odds ratio, 1.60; 95% confidence interval, 1.03–2.50; P ¼ 0.04) after adjustment for covariates
- Statin administration aggravates lung injury and fibrosis in bleomycin-treated mice
- Statins enhance NLRP3-inflammasome activation by increasing mitochondrial reactive oxygen species generation in macrophages.

Statins may influence the susceptibility to, or progression of, ILD

Xu JF et al, AJRCCM 2012; 185: 547-556

Global effort against rare and orphan diseases

- Increasing incidence of rare diseases and growing research effort
- Transalational research
- Rare diseases and common terapies
- ***Rare diseases and exposure to drugs or toxins***

Rare diseases and exposure to drugs or toxins

- In the last three decades strong association between PAH and the use of anorexic drugs (mainly derivatives of fenfluramine) has been found

Douglas JG et al. Br Med J (Clin Res Ed) 1981; 283: 881–883
Brenot F et al. Br Heart J 1993; 70: 537–541.
Abenhaim L et al N Engl J Med 1996; 335: 609–616.

- Fenfluramine derivatives are potent serotonin (5-HT) uptake inhibitors and interact directly with the 5-HT transporter. 5-HT acts as growth factor for pulmonary artery smooth muscle cells

Eddahibi S et al. Respir. Res 2002; 3:9
Eddahibi S et al. Chest 2002; 121: Suppl. 3, 97S–98S.
Eddahibi S et al. J Clin Invest 2001; 108: 1141–1150 .

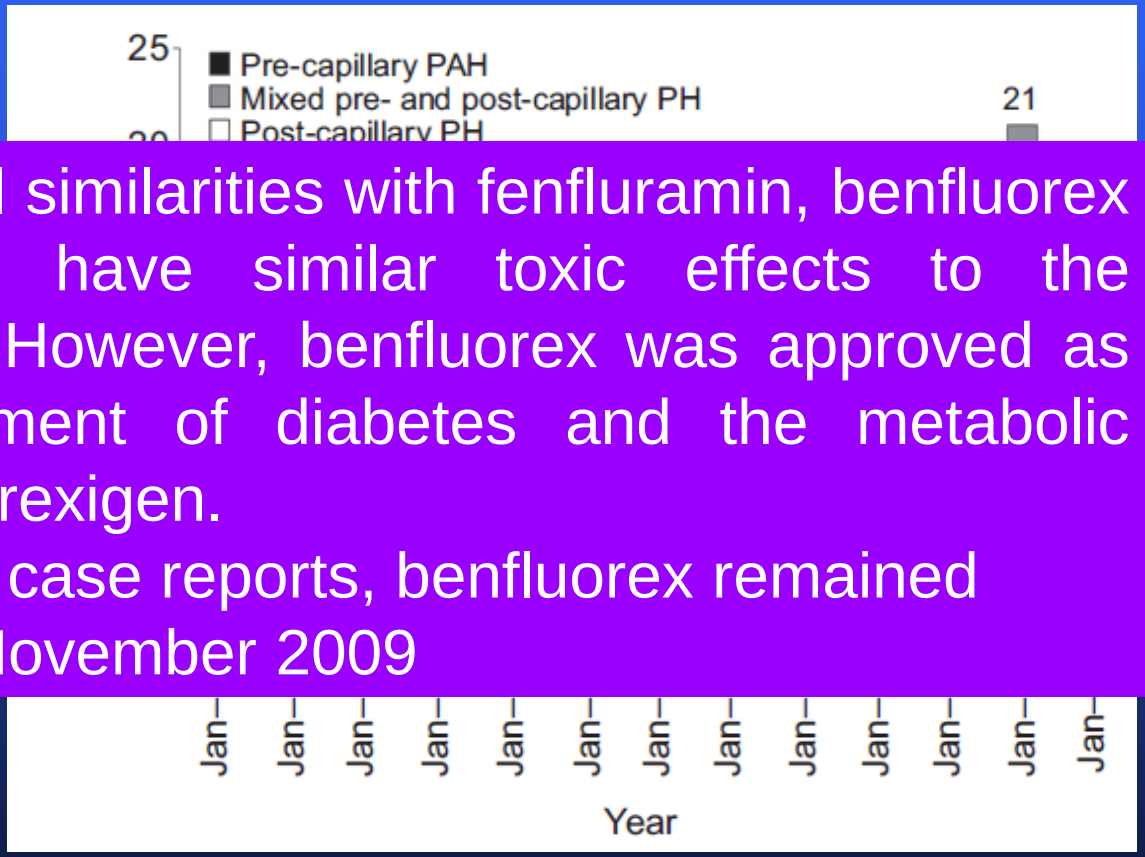
Rare diseases and exposure to drugs or toxins

Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases

R. Souza*, M. Humbert*, B. Sztrymf*, X. Jaïs*, A. Yaïci*, J. Le Pavec*, F. Parent*, P. Hervé*, F. Soubrier#, O. Sitbon* and G. Simonneau*

Souza R, Eur Respir J 2008; 31: 343–348

Rare diseases and exposure to drugs or toxins



Given its pharmacological similarities with fenfluramin, benfluorex would be expected to have similar toxic effects to the fenfluramine derivatives. However, benfluorex was approved as an agent for the treatment of diabetes and the metabolic syndrome and not an anorexigen.

As a result, and inspite of case reports, benfluorex remained available in France until November 2009

Savale L et al, Eur Respir J 2012; 40: 1164–1172

Difficult conditions of common diseases

- Difficult-to-control asthma
- Severe refractory asthma
- Severe eosinophilic asthma

European Respiratory *review*

REVIEW RARE DISEASES AND ORPHAN DRUGS

Severe refractory asthma: an update

Bel EH et al. Eur Respir Rev. 2013;22:227-235

Conclusions

- **In the last two decades "a global effort" against orphan and rare diseases has been made leading to a progress in diagnosis and treatment.**
- **Translational research has become essential to find new approaches for diagnosis and treatment of rare diseases**
- **Patient organizations and registries are very important to support and improve both basic and clinical research on rare diseases (e.g. LAM associations)**
- **Research into rare diseases may be limited by a relative inability to capture sufficiently large patient populations.**