Lymphangioleiomyomatosis of the lung

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History:

34 yo female patient, suspicion of lymphangioleiomyomatosis

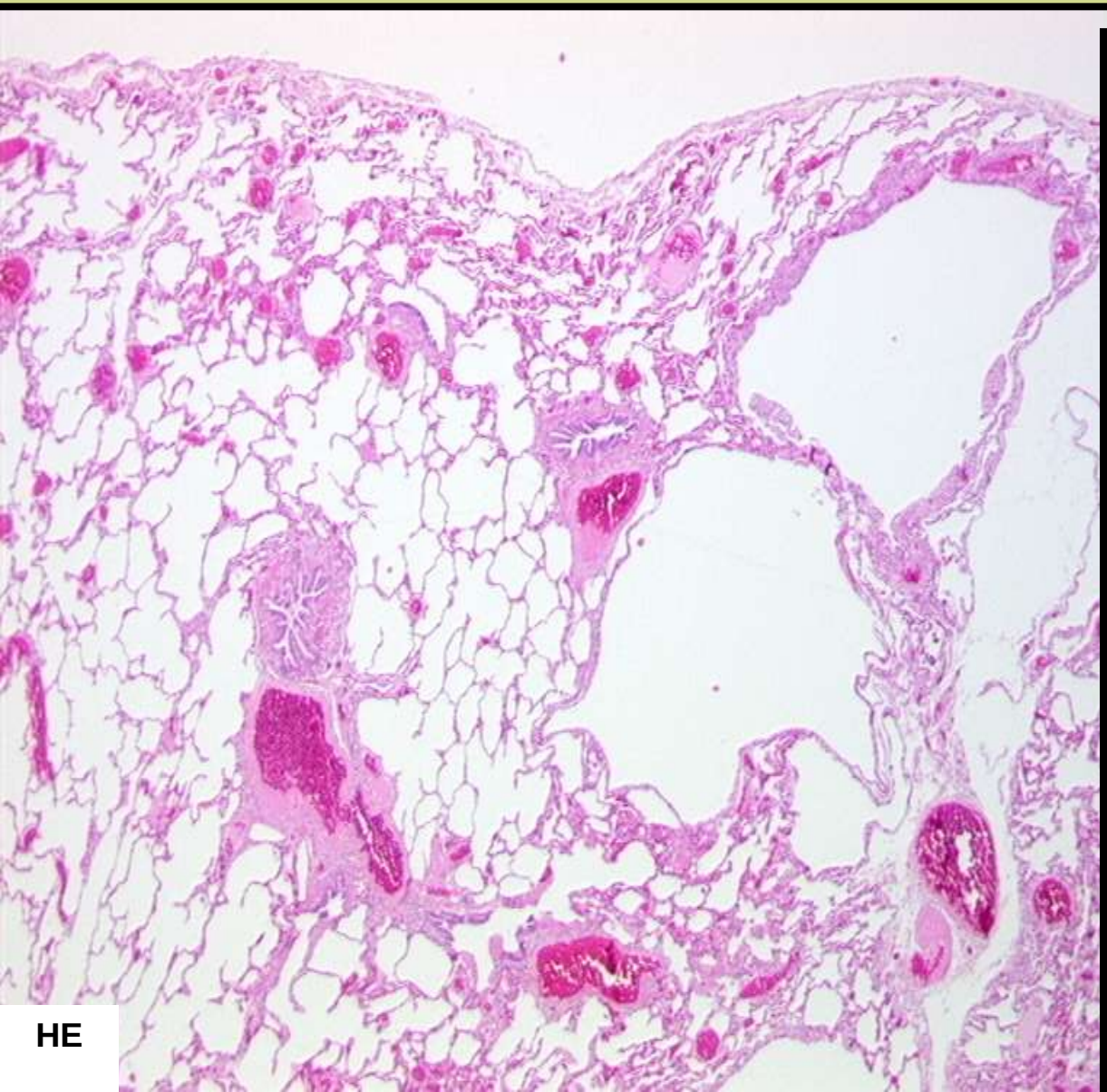
Macroscopy:

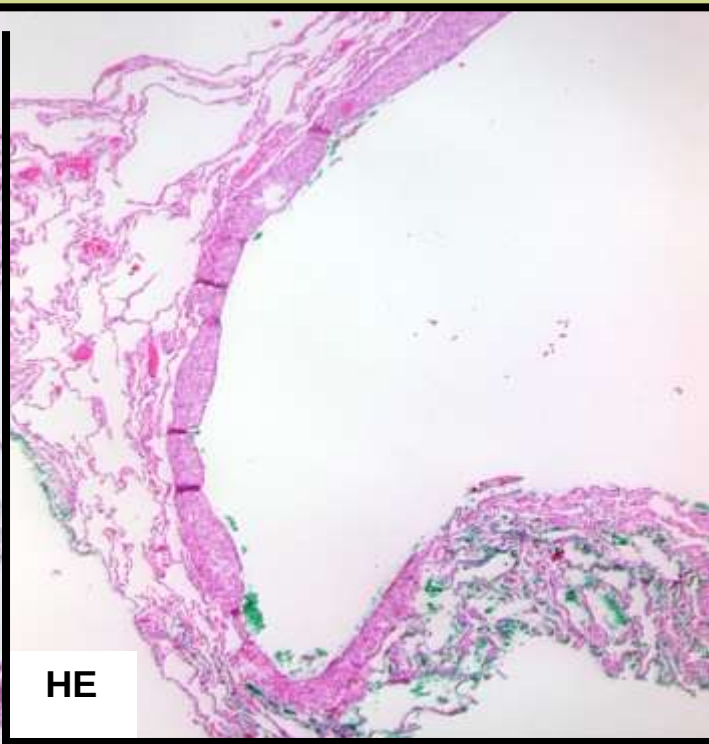
Lung resection specimen of segment V of left upper lobe of the lung 4 x 4 x 2 cm in size

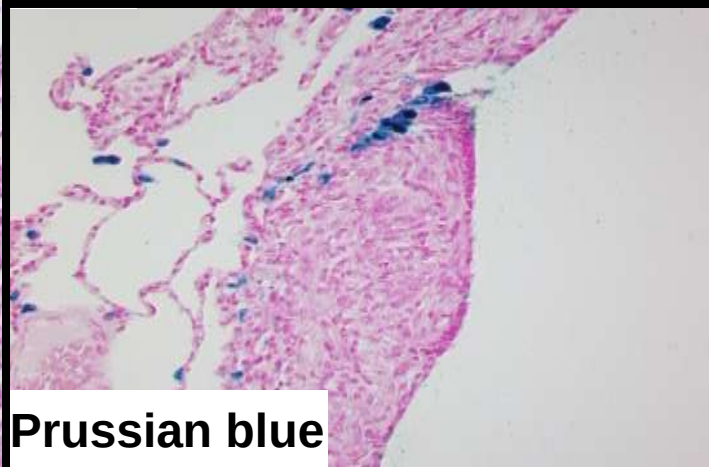
Histology:

H 09713/11

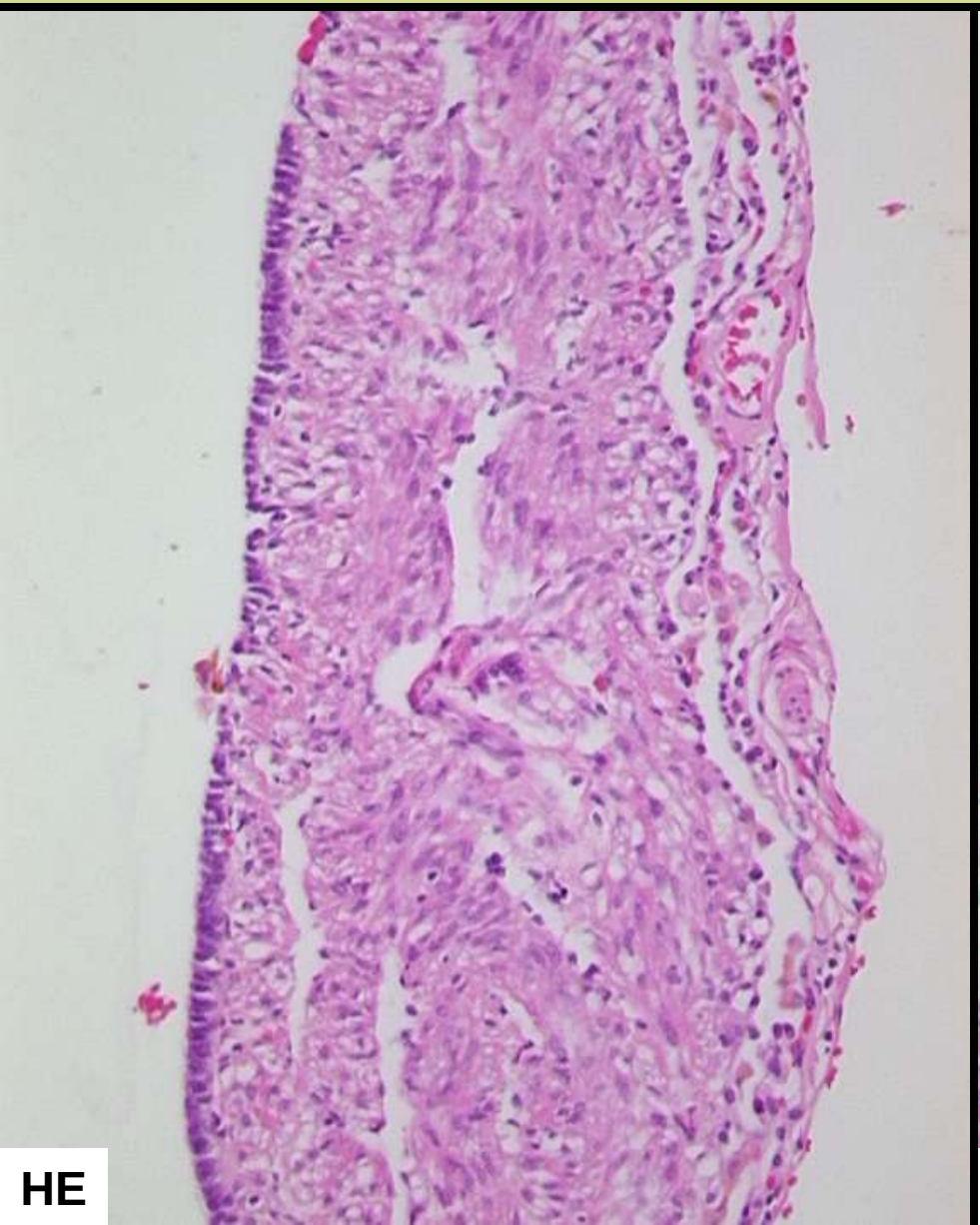
Histology (H 09713/11)

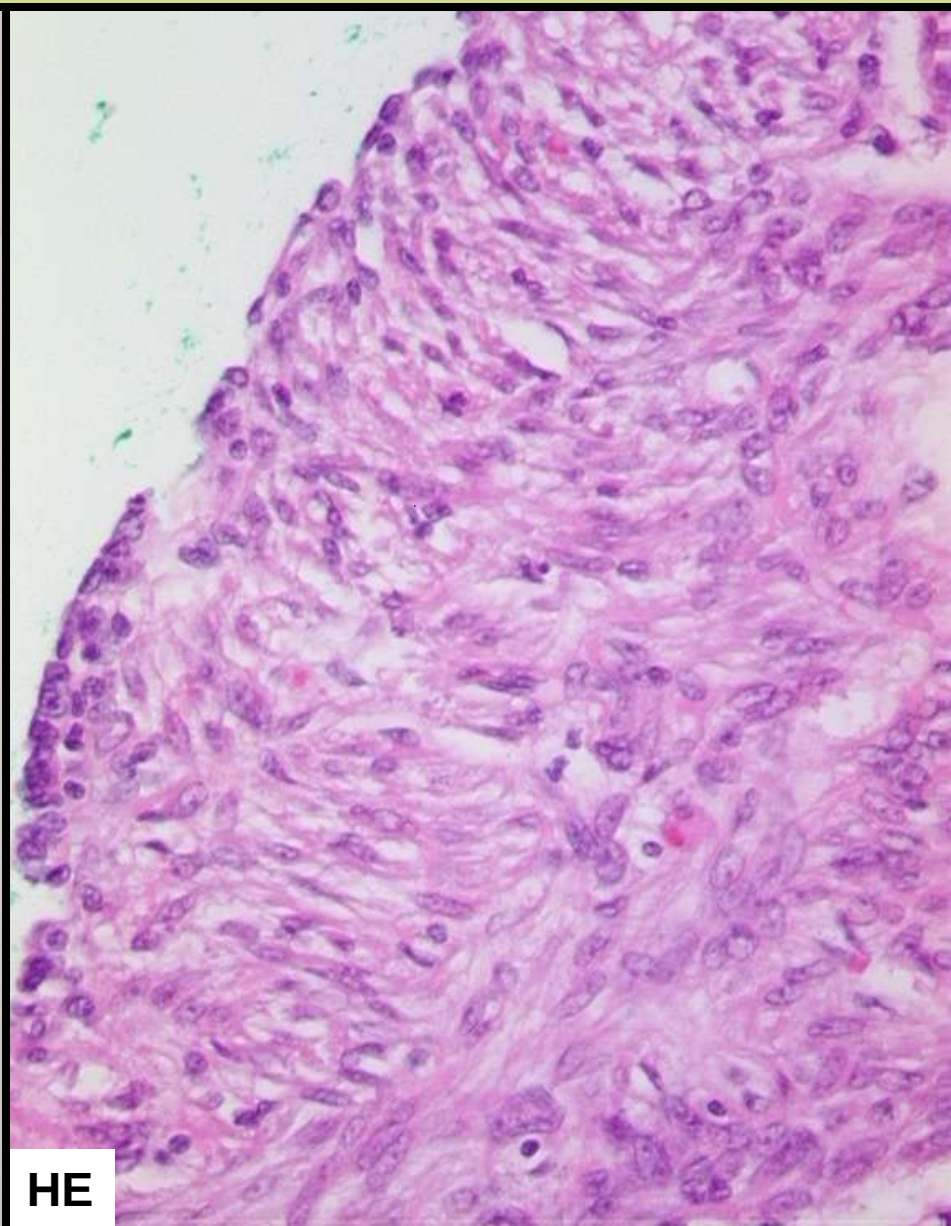




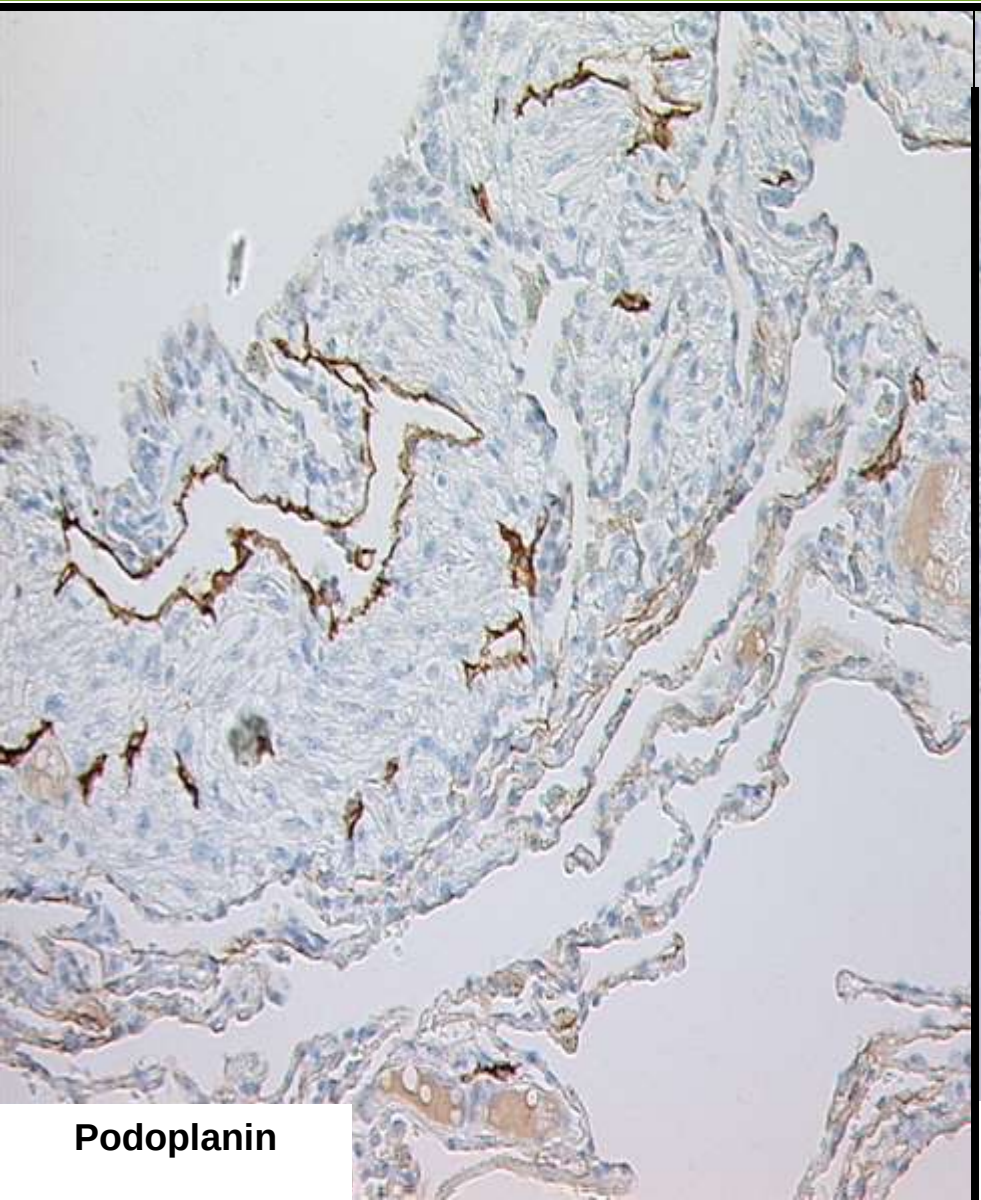


Histology (H 09713/11)

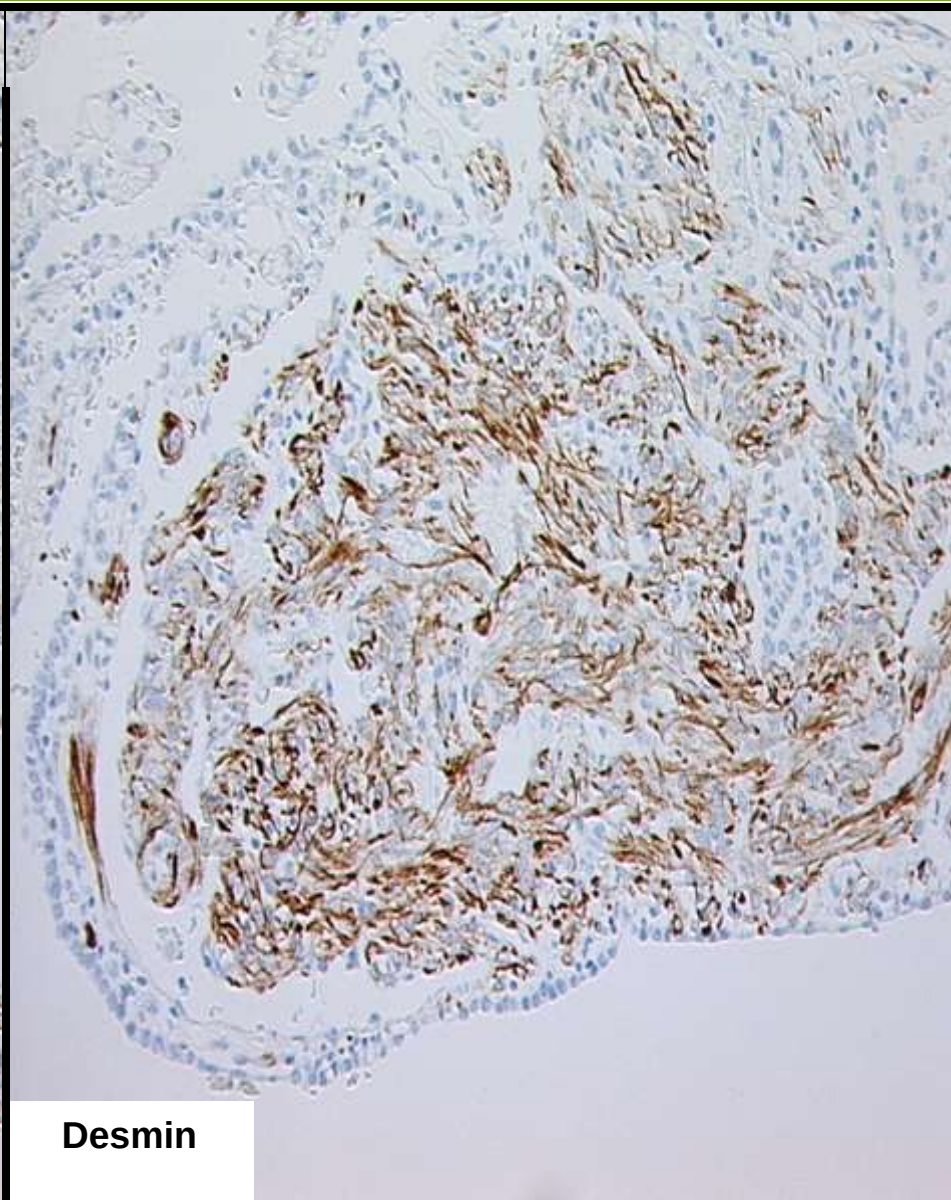




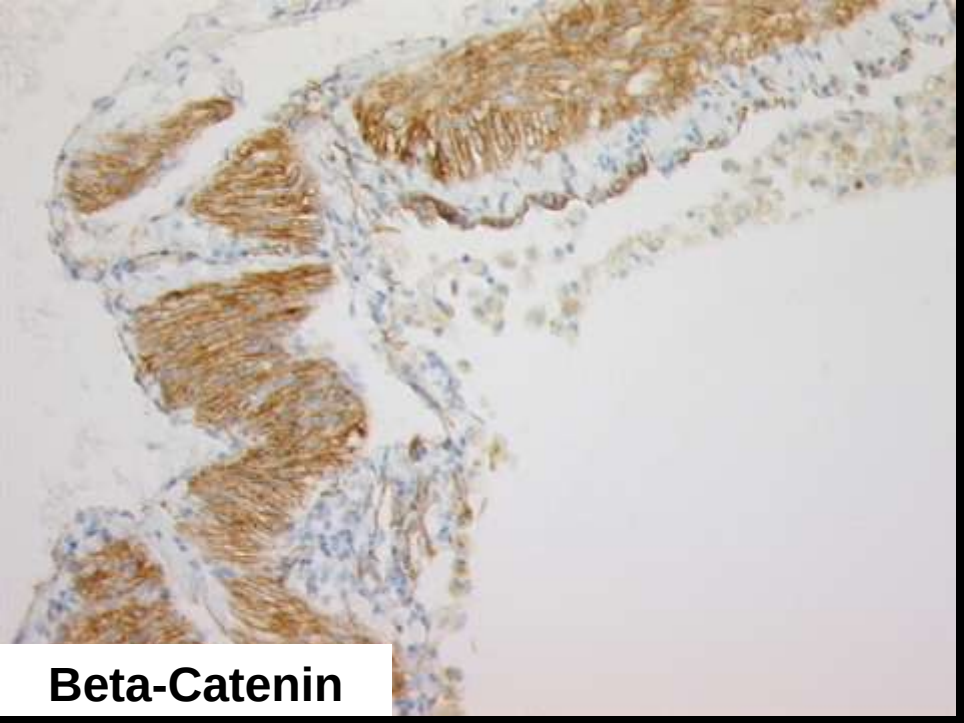
Immunohistology (H 09713/11)

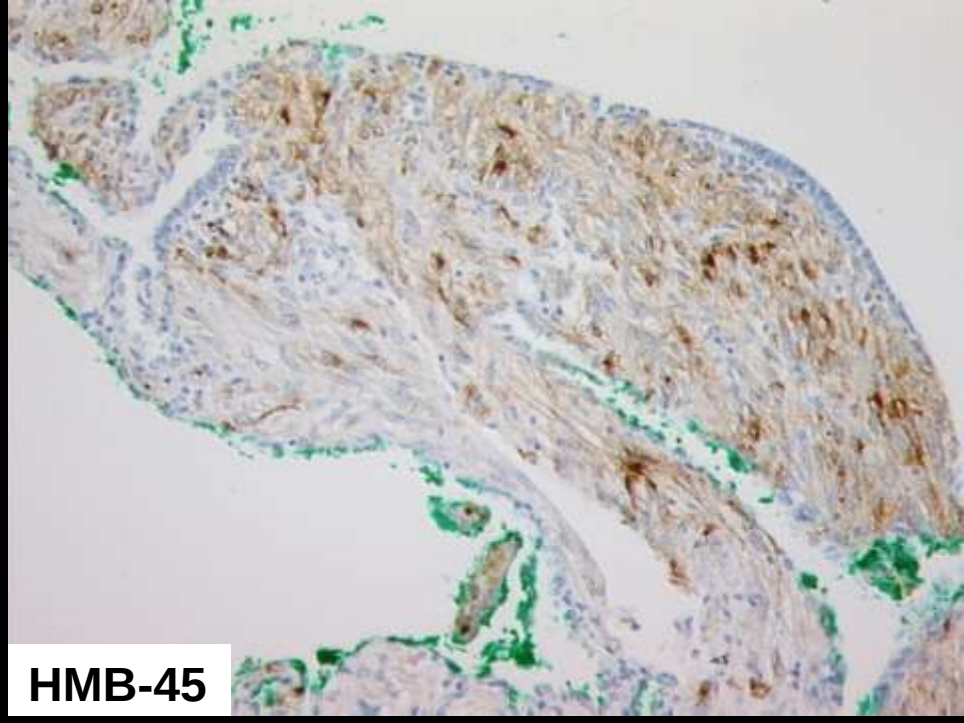


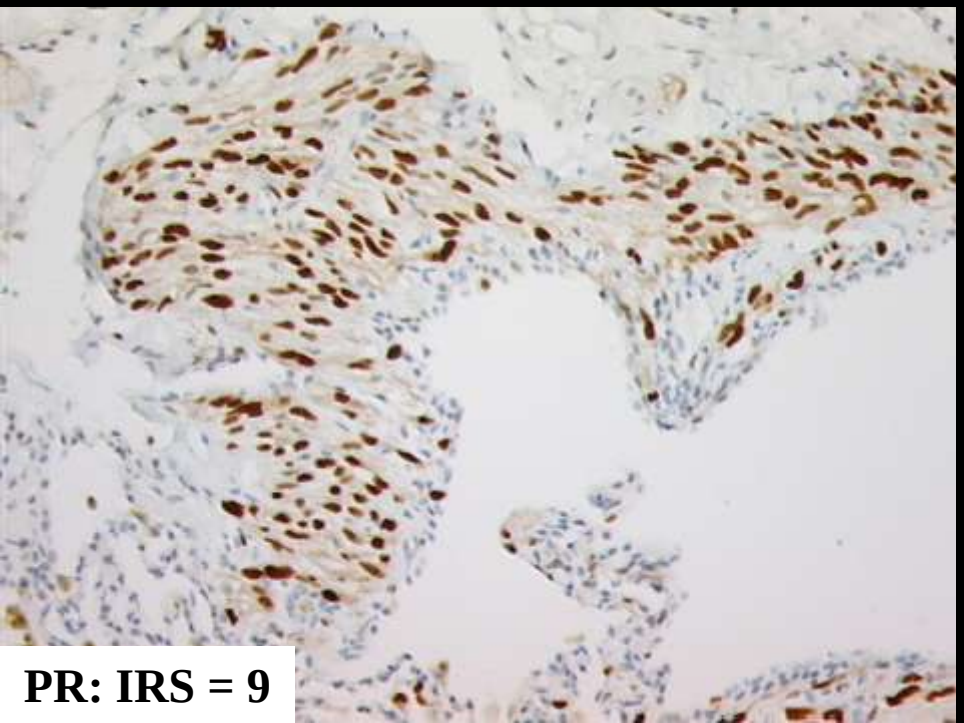
Podoplanin

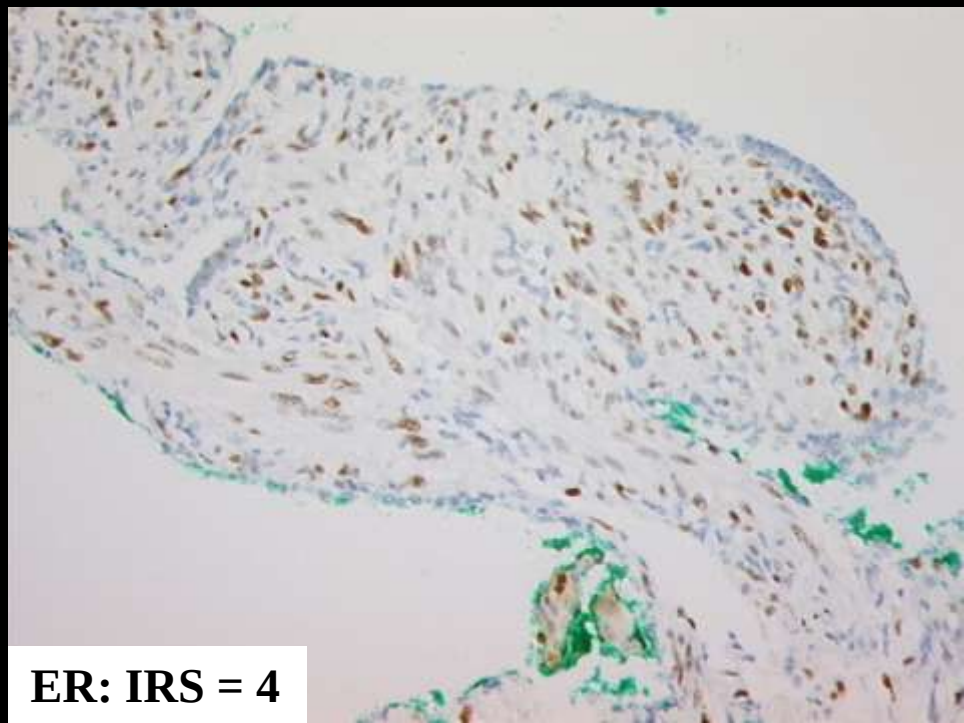


Desmin


Beta-Catenin

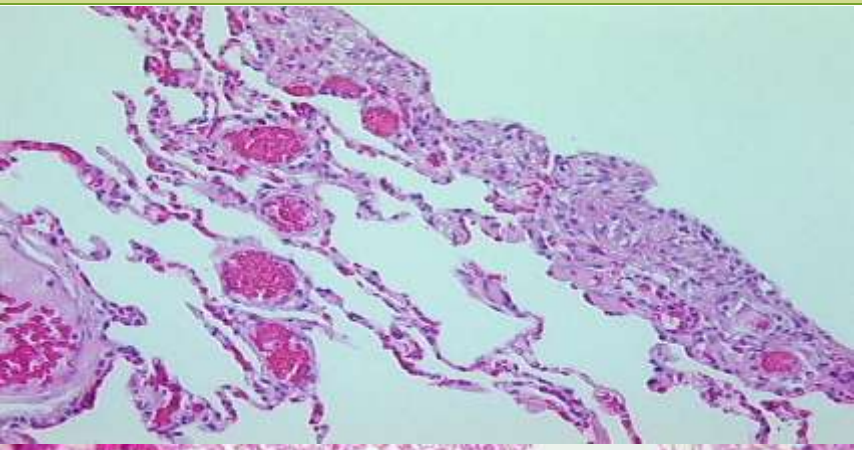

HMB-45

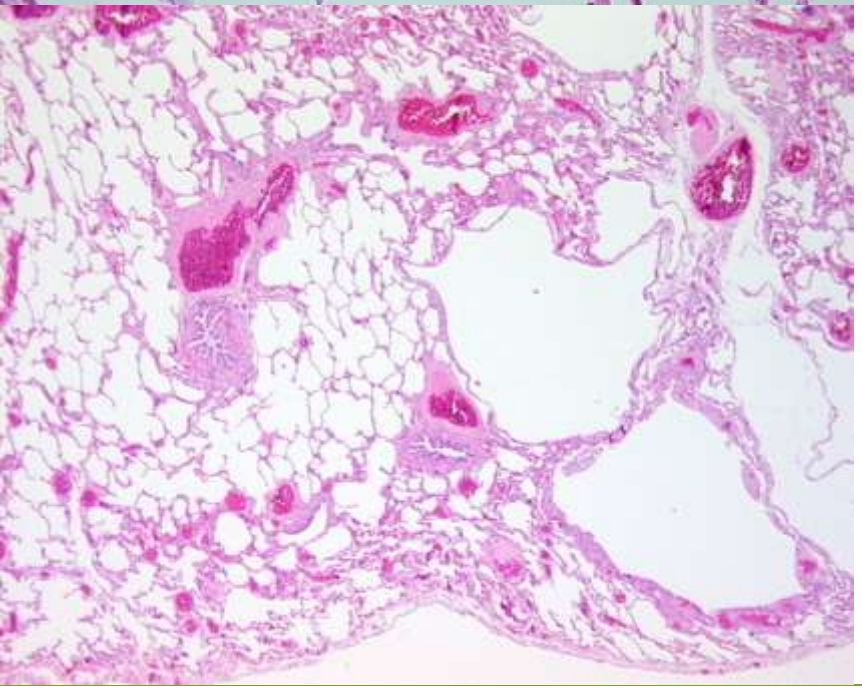

PR: IRS = 9


ER: IRS = 4

Summary of histology lung resection specimen segment V (H 09713/11):

Atypical lung resection specimen of the segment V of the left lung with **lymphangioleiomyomatosis (LHS Score 1)** as well as fresh and old bleedings





LAM HISTOLOGY SCORE (LHS Score)

* **Semiquantitative assessment of lung damage respectively lung affection with cystistic lesions and infiltration of LAM cells (prognostic parameter)**

	10-year survival
* Score 1: under 25 %	nearly 100 %
* Score 2: 25-50 %	74,4 %
* Score 3: over 50 %	52,3 %

Matsui et al. 2001: Am J Surg Pathol 25(4): 479-484

LYMPHANGIOLEIOMYOMATOSIS

* affects nearly exclusively **women in reproductive age**
* Incidence 1-2,6 cases / 1000000 women (often misdiagnosed !)
* Described in the 60´s in the literature for the first time

  Cornog JL et al. Cancer 1966;19:1909-1930
* **Outcome variable**, median survival time of 8-10 years after diagnosis

LYMPHANGIOLEIOMYOMATOSIS

* Monoclonal proliferation of immature respectively abnormal smooth muscle cells in the lungs, in the wall of lymphatic vessels (partially also in bronchioles) in and lymp nodes in the thorax and retroperitoneum) with progressive cystic destruction of the lungs

* Pathognomonic **HMB-45 expression (melanocytic marker)**

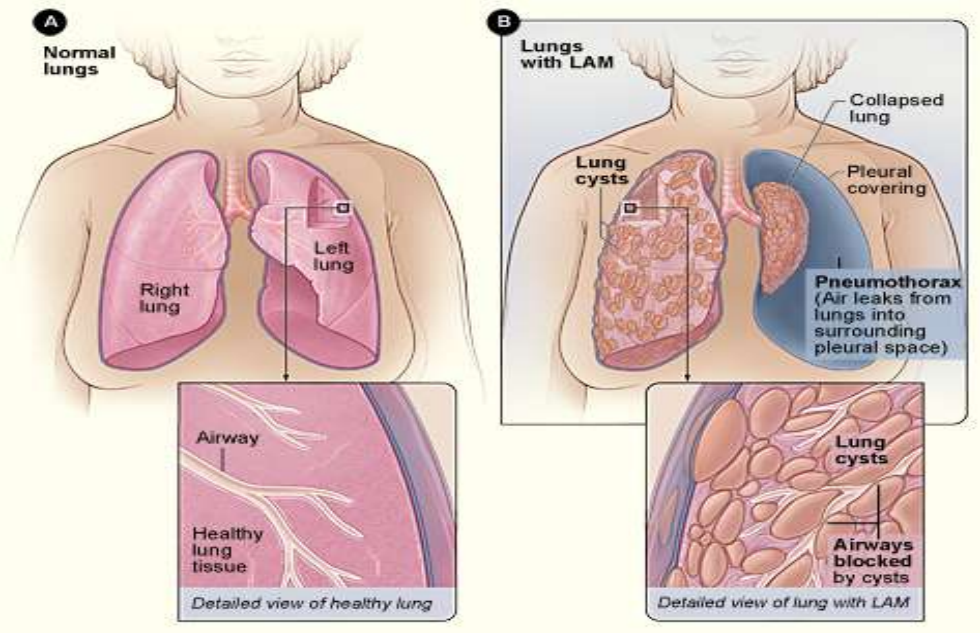
LYMPHANGIOLEIOMYOMATOSIS

Clinical picture:

* **pneumothorax**

  (highest incidence among CLD

* **dyspnea on exertion**



* **Extrapulmonary manifestations of LAM (often before lung manifestation): Angiomyolipoma (in 40-80% of patients with lymphangioleiomyomatosis !),** chylous ascites, abdominal lymphadenopathy and lymphangioleiomyomas

PEComa
perivascular epitheloid cell tumour

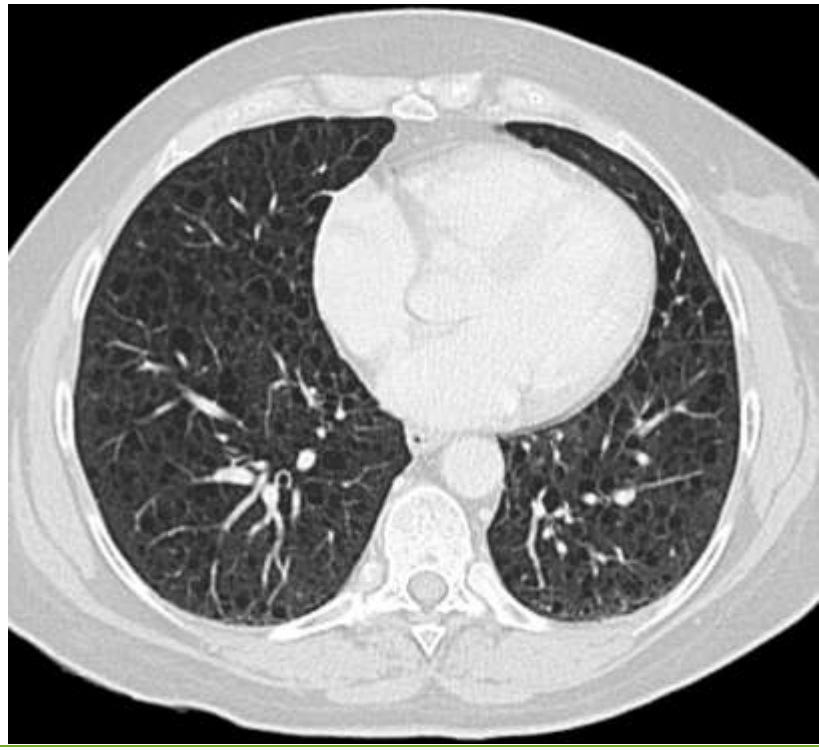
- Mesenchymal tumor with relatedness to smooth muscle cells and melanocytes (**positivity for melanocytic and myogenic markers**), origin from vessel walls and mainly benign course
- Angiomyolipoma
- **Lymphangioleiomyomatosis**
- High prevalence of angiomyolipoma in lymphangiomyomatosis!
- Clear cell sugar tumour of the lung

LYMPHANGIOLEIOMYOMATOSIS

Radiology

* Multiple thin-walled diffuse cysts up to 2 cm in size, no preference of a certain part the the lung

* <u>however:</u> in up to 20% of cases unsuspicious radiologic finding!



LYMPHANGIOLEIOMYOMATOSIS

Therapy: no effective treatment options!

Harari S et al. 2011; Eur Respir Rev 20: 119, 34-44

*** Estrogen blocker (not proofed !)**

*** Progesteron preparation (consider in single cases with rapid progression)**

*** Ultima ratio treatment: lung transplantation (better survival rate of LAM-patients than in other patient groups after lung transplantation)**

LYMPHANGIOLEIOMYOMATOSIS

- **Sporadic form** (mainly with more pronounced clinical symptoms)
- In **tuberous sclerosis (30-40 % of patients)**
- Associated with mutations of genes of tuberous sclerosis TSC1 or TSC2 with consecutive proliferation of immature respectively abnormal muscle cells

Genes of tuberous sclerosis
TSC1 and TSC2 tumor suppressor gene

- **Hamartin:** Protein product of **TSC1** gene (reorganization of actin cytoskeleton)
- **Tuberin:** Protein product of **TSC2** gene (negative regulator of cell cycle progression)
- **Hamartin-tuberin complex: negative regulator of mTOR**
- Loss of TSC function results in mTOR activation
- Hypothesis: Rapamycin (mTOR inhibitor) could influence LAM progression ?

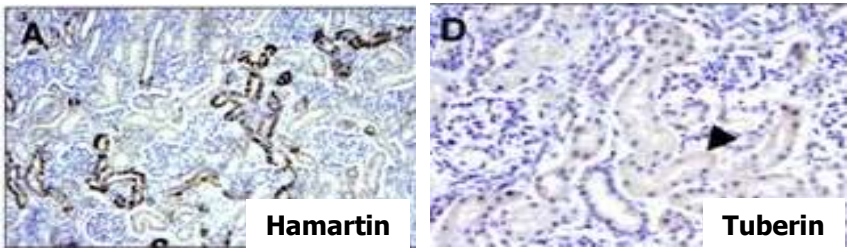
Angiomyolipoma and tuberous sclerosis
-Molecular pathogenesis and consecutive therapeutic approach-

Normal:

Tuberin

Hamartin

Rheb-GDP/GTP

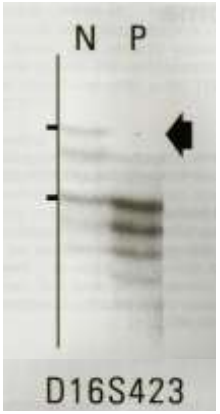


Proximal tubule

Tuberous sclerosis/AML:

~~**Tuberin**~~

Hamartin



LOH of TSC2 gene locus

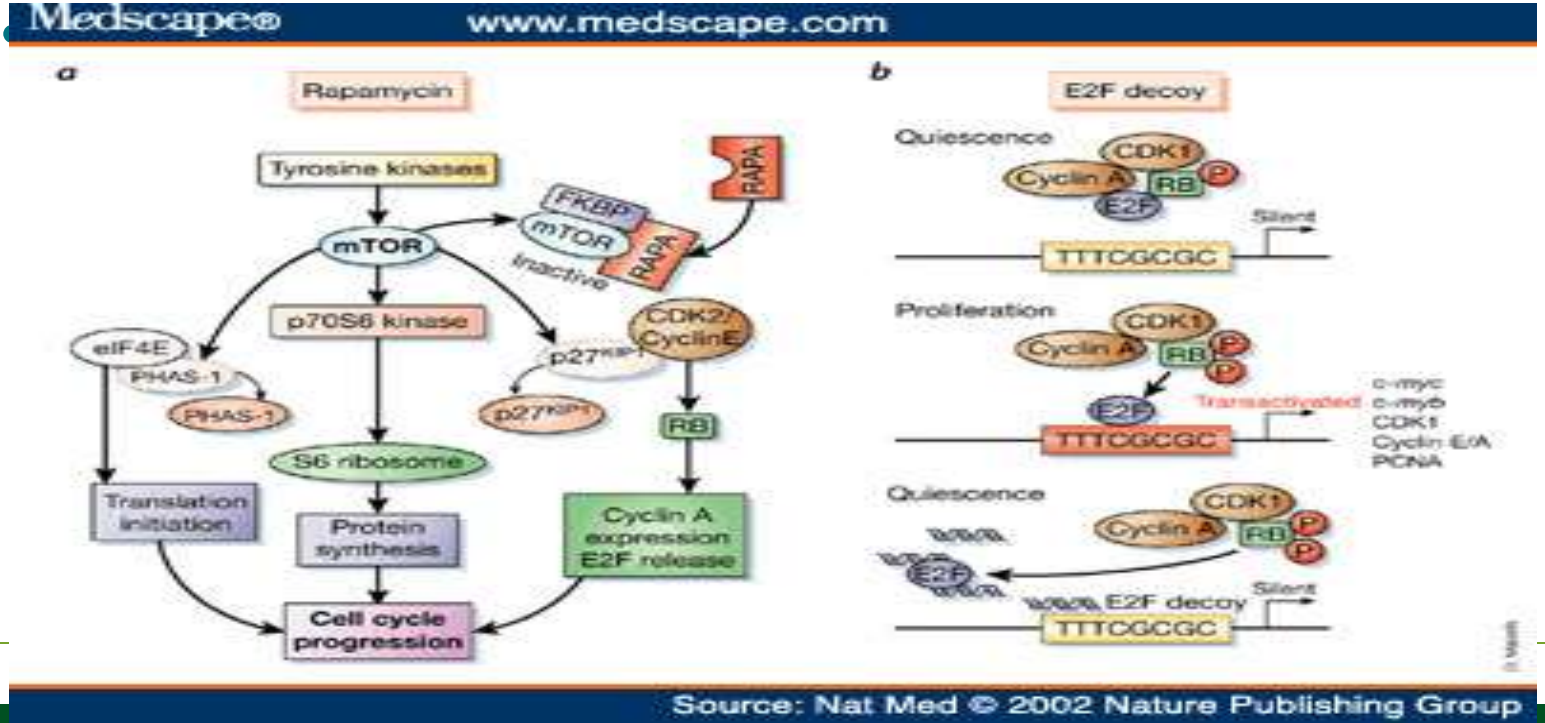
Loss of tuberin

Phosphorylation and persistant activation of mTOR

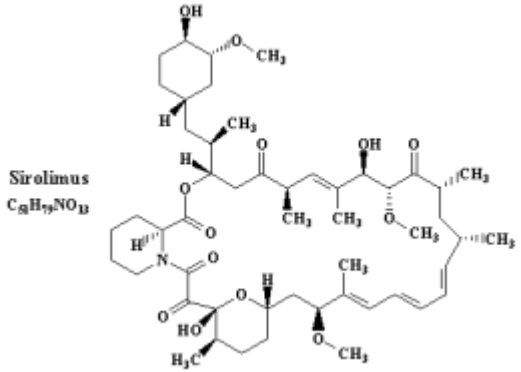
Protein synthesis and cell growth

mTOR (mammalian target of rapamycin)

- 282 kDa **intracellular serine/threonin kinase**
- **Central regulator of cell proliferation and cell cycle**



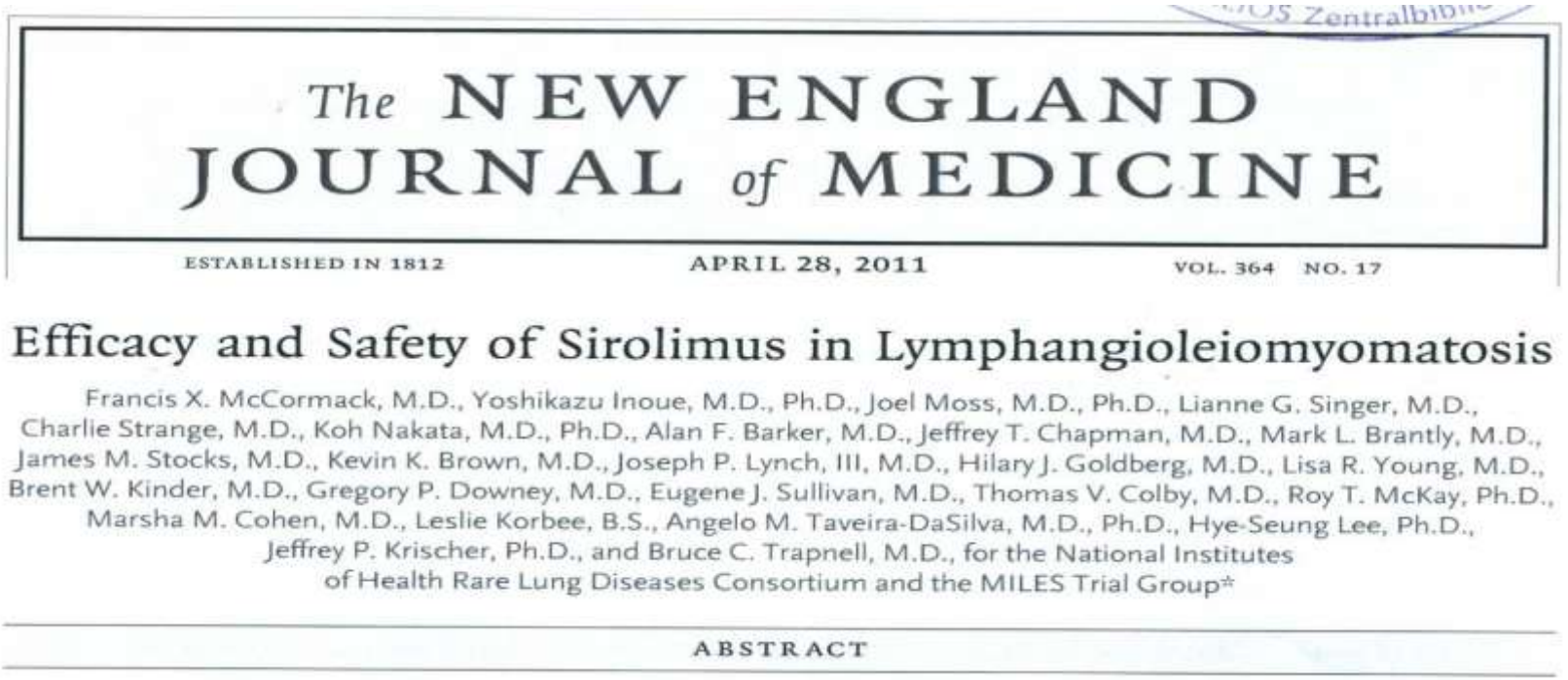
Sirolimus (Rapamycin)



- Immunosuppressive with macrolid structure
- **<u>Antiproliferative effects (mTOR inhibitor)</u>**
- Particularly susceptible to inhibition of mTOR are T-cells, <u>cells of blood vessels and lymphatic vessels, smooth muscle cells and tumor cells</u>

LYMPHANGIOLEIOMYOMATOSIS

mTOR inhibition: promising new therapeutic option



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Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

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ABSTRACT

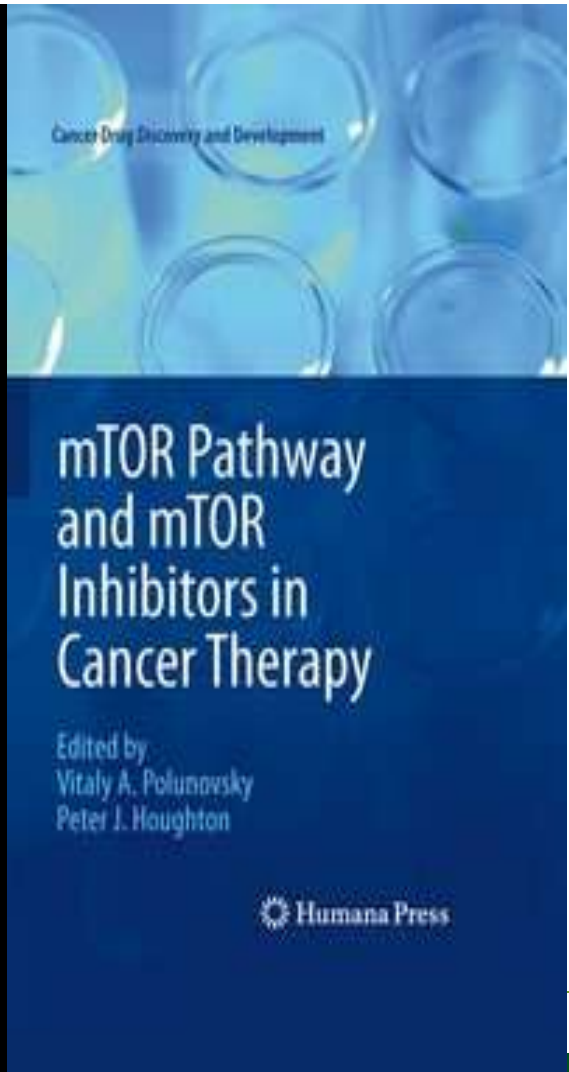
In patients with LAM, sirolimus stabilized lung function, reduced serum VEGF-D levels, and was associated with a reduction in symptoms and improvement in quality of life.

Therapy with sirolimus may be useful in selected patients with LAM.

mTOR inhibition:
a new mode of action in oncology

Auf mTor Aktivierung basierte Tumorerkrankungen

Erkrankung	Genetik, Pathologie	mTor Einbindung
TSC	TSC1, TSC2, versch.Organe	TSC1+2 inaktiviert Rheb
LAM (Tumorsyndrome)	TSC2, Muskelzellen der Lunge	TSC1+2 inaktiviert Rheb
PJS (Tumorsyndrome)	STK1/LKB1 Darmtumoren	STK1 aktiv. AMPK, ⬆ TSC2
Prostata	PTEN	PTEN Verlust, ⬆ Akt
Mamma	PTEN, AKT, HER2 Amplifikation	PTEN Verlust, ⬆ Akt
Lunge	PTEN, HER2, LKB1	PTEN Verlust, ⬆ Akt
Blase	PTEN	PTEN Verlust, ⬆ Akt
Melanom	PTEN	PTEN Verlust, ⬆ Akt
RCC	vHL, PTEN	⬆ AKT
Ovar	PTEN, PI3K, AKT, HER2-Ampl.	PTEN Verlust, ⬆ Akt
Endometrium	PTEN, PI3K, AKT, HER2-Ampl.	⬆ AKT
Schilddrüse	PTEN, PI3K, AKT, HER2-Ampl.	PTEN Verlust, ⬆ Akt
Gehirn (Glioblastom)	PTEN	⬆ AKT
CML	BCR-ABL Translokation	⬆ AKT



SUMMARY

Lymphangiomyomatosis: rare differential diagnosis of cystic lung diseases

In young women with pneumothorax, angiomyolipoma of the kidney or tuberous sclerosis LAM should always be considered as a differential diagnosis

Exact and early diagnosis and differentiation from other (diffuse) cystistic lung diseases is important due to different therapeutic approaches

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Thank you for your attention!

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