Lymphangioleiomyomatosis (LAM), a slowly progressive disease affecting mostly young and middle-aged females [1], is one of the few orphan lung diseases that has attracted major attention in recent years from both clinicians and researchers [2], with rapidly evolving progress. With an estimated prevalence of one in 400,000 adult females aged 20–69 yrs for the sporadic form [3] and ~30% of patients with tuberous sclerosis complex [4] (tuberous sclerosis complex itself has a prevalence of one in 5,800 live births [5]), LAM is indeed a rare disease according to the European definition (prevalence was less than one out of 2,000 persons). However, similar to what has been witnessed for idiopathic pulmonary hypertension some years ago, the organisation and care of LAM patients has improved considerably. Reference centres have been established in many countries for the care of patients suffering from rare diseases, either for rare pulmonary diseases as a whole including LAM, or specifically for LAM (LAM clinics). One initiative funded by the 7th Framework Programme of the European Commission is in the progression to establish European networks of centres of expertise (coordinator: T.O.F. Wagner, Frankfurt, Germany; LAM coordinator: S.J. Johnson, Nottingham, UK). Furthermore, basic and translational research has made tremendous progress, and some medical therapy may be envisioned in the near future. Hence the hope is forming that LAM may no longer be an orphan in the coming years; the sooner the better.

Since the first reports of LAM in 1937 and the first comprehensive descriptions of LAM patients in 1974 to 1975 [6, 7], our understanding of the disease has dramatically improved (table 1). Further progress in disease description has been obtained from retrospective series of patients [9–13] and from registries [16], but mainly from the LAM registry of the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA), the largest LAM registry to date. Established in 1997 and coordinated by J. Moss, it has produced advances in knowledge on baseline characteristics of patients [16], rate of decline in lung function [28], lung transplantation [29] and comorbidities such as osteoporosis [30]. Since this date other registries have been established in several countries and internationally [31], with the objective of fostering collaboration between clinicians, researchers and patients. For instance, a large national registry is being launched in France under the auspices of the Comité National contre les Maladies Respiratoires. As in the field of pulmonary hypertension [32], registries are increasingly recognised as an appropriate way of studying aspects of the disease that cannot be addressed by clinical trials, including long-term survival with therapy when available, comparative analysis of various clinical phenotypes, clinical pathological correlation studies, exploratory analysis of potential effect of drugs [33] and biomarkers.

In the present issue of the *European Respiratory Review*, Harari et al. [34] review the most important and recent progresses made in the pathogenesis and management of LAM. The important messages for clinicians from this review comprise of: 1) recently adopted diagnostic criteria; 2) typical imaging pattern and pathology for LAM; 3) modalities of management of pneumothorax and chylothorax; 4) management of angiomylipoma; and 5) current therapeutic options for pulmonary LAM. This article nicely complements a recent systematic review by a European Respiratory Society Task Force, which produced comprehensive guidelines for the diagnosis and management of LAM, one of which was proposed definitions for LAM [35].

The diagnosis of LAM is now considered definite in the presence of: 1) characteristic high-resolution computed tomography (HRCT) lung changes; and 2) lung biopsy fitting the pathological criteria for LAM, angiomylipoma of the kidney, thoracic or abdominal chylous effusion, lymphangioleiomyoma or lymph-node involved by LAM [35]. Characteristic HRCT findings are multiple (>10) thin-walled, round, well-defined, air-filled, evenly distributed pulmonary cysts, 2–5 mm in diameter and up to 30 mm in size [35]. Criteria for the diagnosis of probable or possible LAM are also available. The importance of international criteria for LAM should not be underestimated, as they are the basis on which robust therapeutic evidence is being built by ad hoc trials.

Since the publication of these guideline criteria, data have accumulated stating that the serum level of vascular endothelial growth factor (VEGF)-D may contribute to the diagnosis of LAM, with a reported sensitivity of about 70% of a serum VEGF-D level >800 mg·mL⁻¹ and excellent specificity [22, 36, 37]. It is probable that measurement of the serum level of VEGF-D will be especially useful to confirm the diagnosis, thereby obviating the need for a video-assisted lung biopsy in those patients with typical chest imaging and obstructive ventilatory defect yet absence of renal angiomylipoma.
chylous effusion or tuberous sclerosis complex. Serum VEGF-D can contribute to differentiate LAM from other multiple cystic lung diseases and may have to be included in the diagnostic algorithm of LAM in the near future. Further guidelines are currently being produced by a joint Task Force of the American Thoracic Society and the European Respiratory Society.

Currently, treatment of LAM is mostly supportive, with bronchodilators, supplemental oxygen if needed, treatment of complications, including pneumothorax, and lung transplantation if appropriate. Hormonal therapy (mostly using progesterone) should not be used routinely in patients with LAM, and anti-oestrogen interventions are not recommended [35]. Yearly follow-up of asymptomatic renal angiomyolipomas is performed by ultrasound measurement or magnetic resonance imaging, whereas embolisation (or occasionally nephron sparing surgery) should be considered in the case of bleeding and for angiomyolipomas $>4$ cm in diameter, or with renal aneurysms $>5$ mm, which are at an increased risk of bleeding [35].

The pathogenesis of LAM had remained largely elusive until the discovery in 2000 by E.P. Henske and co-workers that LAM cells carry bi-allelic mutations within the TSC2 gene, a tumour suppressor gene that encodes tuberin [18]. The same mutations in TSC2 were found both in the angiomyolipomas and in abnormal smooth muscle cells (LAM cells) from the lung tissue [18]. This observation itself emanated from the occurrence of LAM in $\sim30\%$ of patients with tuberous sclerosis complex [4], a dominant inherited disease caused by germline mutations in the TSC1 or TSC2 genes. In pulmonary LAM, as in renal angiomyolipomas, TSC2 mutations cause the constitutive activation of the phosphoinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR)/S6-kinase pathway and largely drive the proliferation of LAM cells [38]. Another milestone in LAM research has come from the observation that LAM cells from the receiver can repopulate a donor lung after transplantation [39], suggesting that LAM cells can travel to the lung, despite LAM lesions being histologically benign. This theory of “benign metastasis” [20] has since been supported by the isolation of LAM cells (harbouring loss of heterozygosity of the TSC2 locus) from the peripheral blood, urine, chylous ascites and pleural effusions of females with the sporadic form of LAM using a density gradient centrifugation separation [21]. LAM cells can also be found in the bronchoalveolar lavage fluid [40]. Circulating LAM cells express chemokine receptors and CD44v6, a splice variant of surface integrin associated with cancer metastasis [41]. Many other processes can contribute to LAM cell metastasis through disruption of cell adhesion, migration, motility, survival, resistance to anoikis and protease expression, several of which are enhanced by oestrogens [38]. A third milestone in LAM research was the recognition of the role of the lymphatic system in mediating the metastasis of LAM cells, which in circulation are organised in clusters surrounded by lymphatic endothelial cells [42–44]. In addition to its use as a diagnostic marker, secretion of VEGF-D (a growth factor for lymphatic endothelial cells) by LAM cells seems to contribute to LAM pathogenesis and may become a target for LAM therapy. Overall, LAM is now considered as “driven by a confluence of prometastatic factors that include mTOR activation, lymphatic recruitment, extracellular matrix remodeling and oestrogen promoted cell survival” [38]. It is anticipated that further progress in LAM pathogenesis may arise from genomics including genomewide association studies.

Recent advances in LAM pathogenesis, namely identification of activation of the PI3K/Akt/mTOR pathway as a key player, have prompted clinical trials in LAM within a short period of time. Sirolimus (or rapamycin) inhibits the mTOR complexes mTORC1 and to a lesser extent mTORC2, and was shown to reduce tumour size of renal carcinoma developing in rats carrying a germline mutation of TSC2 [45]. Sirolimus therapy for 1 yr decreased angiomyolipomas in patients with sporadic LAM or tuberous sclerosis complex by half [27]. mTOR inhibitors are also used in astrocytomas associated with tuberous sclerosis complex [23, 46]. Although trials have proved to be challenging to carry out in pulmonary LAM [47] due to the paucity of patients with progressive disease and relative difficulties in measuring progression of disease, preliminary observations suggest that sirolimus might improve pulmonary function or inhibit the decline in pulmonary function [27, 48]. Clinical trials are currently in progress to assess the effect of mTOR inhibitors (sirolimus and everolimus) in patients with LAM and obstructive pulmonary disease (ClinicalTrials.gov registration numbers NCT00414648 and NCT01059318). However, mTOR inhibitors only partially reverse abnormalities observed in vitro in LAM cells; they may cause a variety of side-effects and their safety profile is still poorly known in the context of LAM. Thus, mTOR inhibitors should not be routinely prescribed outside clinical trials for pulmonary LAM [35]. Other candidate pathways and drugs need to be explored. Matrix metalloproteases are thought to contribute to the cystic destruction of the lung parenchyma in LAM and may offer another therapeutic target. Studies are conducted to evaluate the effect of doxycyclin, an oral inhibitor of metalloproteases [47]. The integrin CD44v6 and VEGF-D may also represent effective targets for therapy.
Such tremendous progress would not have been possible without LAM patients and patient associations who have raised funds, organised meetings, facilitated collaboration, advocated for improved registries, provided biological material for research and established worldwide networks of support and information for patients and clinicians. Most of all, patients have taught us the experience of living with LAM and what major effects this disease has on the patient’s life [49]. Interaction with patients is the best stimulus for LAM researchers to develop innovative therapies for LAM and eventually to improve quality of life and survival of patients with LAM.

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STATEMENT OF INTEREST

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