Current concepts in the pathogenesis and clinical management of lymphangioleiomyomatosis

Donal O'Malley[a,b], *Nishant Gupta*[c] *and Cormac McCarthy*[a,b]

Purpose of review
Lymphangioleiomyomatosis (LAM) is a systemic, low-grade, metastasizing neoplasm that predominantly affects women. This review demonstrates recent progression in this rare disease, from improved understanding of pathogenesis, to novel treatments. We provide an overview of recent advances that are shaping the future of LAM diagnostic and treatment approaches.

Recent findings
Understanding the role of hormonal pathways, immune system interactions, mechanistic target of rapamycin (mTOR) signalling inhibition and the LAM microenvironment is creating opportunities for combination therapies with curative potential. Evidence supporting the uterine origin of LAM cells has renewed interest in hormonal signalling pathways, while potential immune evasion mechanisms of LAM cells are under investigation. More complete blockade of mTOR pathways by newer generation agents, as well as research into the crosstalk between LAM cells and their surroundings is informing development of novel combination therapies with disease modifying potential. Biomarker identification beyond vascular endothelial growth factor D (VEGF-D) is essential for diagnostic, prognostic and treatment decision making. Cellular mapping using single-cell RNA sequencing and spatial transcriptomics, as well as integration of artificial intelligence into diagnostic and therapeutic development pathways, has the potential to significantly advance our understanding of this rare disease.

Summary
LAM research demonstrates how sustained investigation in rare disease can advance from preclinical mechanistic insights to targeted treatments. Understanding the role of hormonal pathways, immune system interactions, mTOR signalling inhibition and the microenvironment is creating opportunities for combination therapies with curative potential. Advancements in technology, including single cell analysis, spatial transcriptomics and artificial intelligence are accelerating the discover of biomarkers and therapeutic targets, positioning LAM for significant clinical advances in the coming years.

Keywords
cystic lung disease, lymphangioleiomyomatosis, mechanistic target of rapamycin, sirolimus

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a systemic, low-grade, metastasizing neoplasm that predominantly affects women, occurring either sporadically or in association with tuberous sclerosis complex (TSC) [1,2▪,3]. Recent years have witnessed significant advances in our understanding of this rare disease. Key discoveries include insights into disease pathogenesis such as the role of multiple immune evasion mechanisms and evidence supporting the uterine origin of LAM cells. The establishment of mechanistic target of rapamycin (mTOR) inhibitors as first line therapy was a pivotal development in LAM treatment. Current research extends beyond their established role in reducing lung function decline, exploring potential benefit in subsets of LAM patients who might not otherwise qualify for treatment based solely on lung function criteria. Furthermore, novel biomarker development and investigation of new therapeutic pathways is evolving rapidly. This review provides an overview of the most recent advances in LAM, exploring current

[a]Department of Respiratory Medicine, St. Vincent's University Hospital, [b]School of Medicine, University College Dublin, Dublin 4, Ireland and [c]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati, Cincinnati, Ohio, USA

Correspondence to Cormac McCarthy, MD, PhD, FRCPI, UCD School of Medicine, Education and Research Centre, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland. Tel: +353 1 221 3323; e-mail: cormac.mccarthy@ucd.ie

Curr Opin Pulm Med 2025, 31:000–000

DOI:10.1097/MCP.0000000000001185

1531-6971 Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

KEY POINTS

- This review demonstrates how sustained research in rare diseases such as lymphangioleiomyomatosis (LAM) can advance the understanding of disease pathogenesis, leading to improved diagnostic and treatment options, with for example evidence of uterine origin renewing interest in hormonal signalling mechanisms.
- The search for novel biomarkers beyond vascular endothelial growth factor D remains essential for improving diagnostic accuracy, prognostication, treatment decisions, and establishing endpoints for future clinical trials.
- Preclinical research about LAM cells' immune evasion mechanisms and their interactions with surrounding tissues are laying the groundwork for promising combination therapies, that could potentially induce disease remission rather than merely slowing progression.
- Improvement of recognized effective treatment pathways is essential, with newer-generation mechanistic target of rapamycin inhibitors offer more complete blockade of central pathogenic pathways.
- Advanced technologies like single-cell RNA sequencing, spatial transcriptomics, and artificial intelligence will significantly enhance understanding of LAM pathophysiology and identify the most promising targets for future clinical trials.

new insights into pathogenesis, outlining recent advancements in therapy and identifying potential future therapeutic approaches.

RECENT DEVELOPMENTS IN THE CLINICAL CARE OF LYMPHANGIOLEIOMYOMATOSIS

Epidemiology and clinical features of lymphangioleiomyomatosis

LAM typically presents in women of reproductive age and clinical features include diffuse cystic lung disease (virtually all patients), spontaneous pneumothorax (~half of the patients), chylous effusions (~20% of patients, more in sporadic LAM compared to TSC-LAM), and renal angiomyolipomas (AMLs) (~30–40% of patients with sporadic LAM and 80–90% of patients with TSC-LAM). Until recently, the prevalence of LAM was estimated to range between 3.4 - 7.8 cases per million women; however, more recent analyses have revealed the prevalence of LAM to be closer to approximately 20 cases per million women [4▪,5▪,6▪].

Current diagnostic standards in lymphangioleiomyomatosis

Diagnostic criteria for LAM require computed tomography (CT) imaging displaying characteristic cystic lung disease (Fig. 1) and one or more of the following: TSC, AMLs, chylous effusions, lymphangioleiomyomas or a serum vascular endothelial growth factor D (VEGF-D) level greater than or equal to 800 pg/ml [7]. In cases of diagnostic uncertainty, transbronchial lung biopsy provides a safe and effective means of obtaining a definitive tissue diagnosis, with yields of approximately 50–60%, especially following review by an expert pathologist [7,8▪]. Transbronchial cryobiopsies can also aid diagnosis of LAM; although the yield and overall safety of this procedure needs to be better studied in patients with cystic lung disease [9]. Serum VEGF-D is a validated biomarker in LAM and values exceeding 800pg/ml, combined with characteristic CT findings, provide diagnostic specificity of almost 100% [10–12].

LAM is seen in approximately one-third of women with TSC with prevalence approaching almost 80% by the age of 40 years and represents a major source of morbidity and mortality in women with TSC [13,14,15▪]. Current TSC Clinical Practice Guidelines recommend performing a chest CT scan to screen for the presence of LAM in all adult women with TSC [16▪]. However, screening practices in TSC vary substantially across centres and LAM screening is not uniformly performed in women with TSC [4▪]. For instance, an analysis of the UK LAM Centre cohort revealed that over 75% of patients were diagnosed only after becoming symptomatic [17▪]. More proactive and uniform screening for LAM in women with TSC is a major unmet need that can be readily accomplished and might lead to more timely therapeutic interventions.

Current therapy of lymphangioleiomyomatosis

The Multicenter International LAM Efficacy of Sirolimus (MILES) trial demonstrated that treatment with sirolimus leads to stabilization of lung function decline and reduction in serum VEGF-D levels [18,19]. Based on these results, sirolimus has been approved by regulatory agencies in more than 40 countries as a treatment of LAM. Clinical guidelines recommend initiating sirolimus in LAM patients with FEV1 below 70 percentage predicted, FEV1 decline exceeding 90 ml per year or problematic chylous effusions [18]. While the sirolimus dose in the MILES trial was adjusted to maintain trough levels between 5 and 15 ng/ml, with an average dose and trough of 2 mg daily and 7 ng/ml, respectively,

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

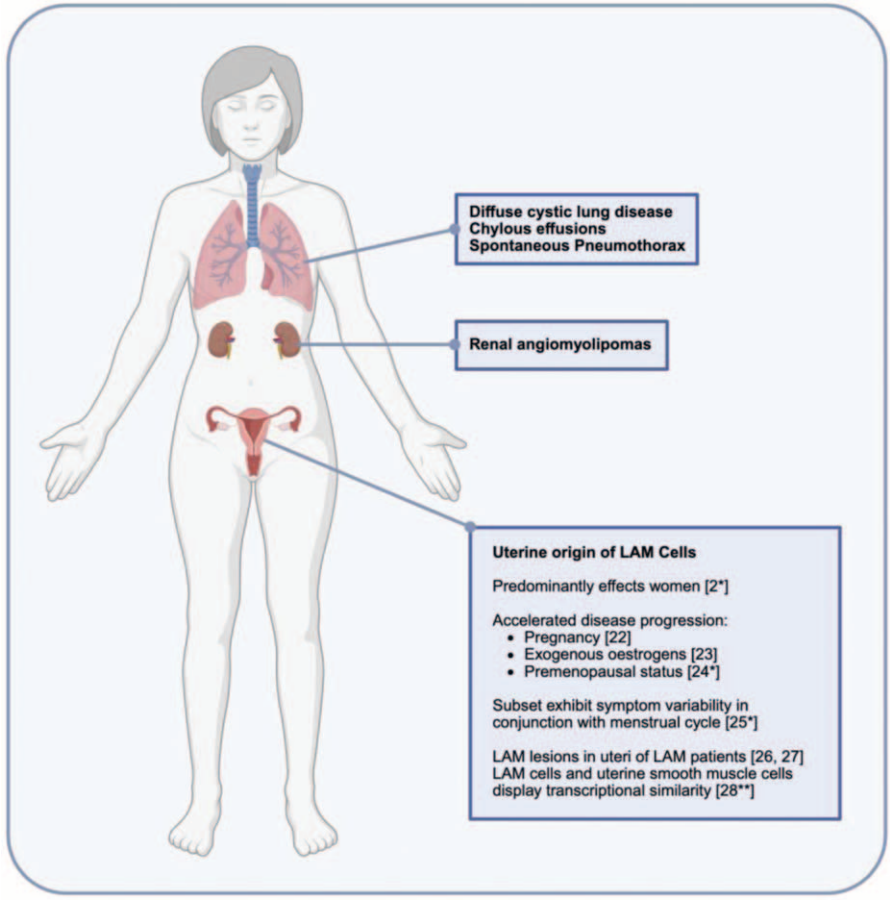

FIGURE 1. Evidence for the uterine origin of LAM Cells. LAM typically presents in women of reproductive age and clinical features include diffuse cystic lung disease, spontaneous pneumothorax, chylous effusions and renal angiomyolipomas. LAM cells arise from an extrapulmonary source and metastasise to the lungs via blood and lymphatics. Recent evidence has strongly suggested a uterine source of origin for LAM cells [28▪▪]. LAM, lymphangioleiomyomatosis.

recent evidence suggests that treatment with low dose sirolimus (1 mg daily, trough <5 ng/ml) might also be an effective option for many patients with reduced risk of adverse effects [18,20]. While long term studies have demonstrated sustained stabilization in lung function over 5 years with favourable tolerability, the treatment is not curative and lung function decline resumes upon drug discontinuation [18,21], highlighting the need to develop novel remission inducing treatment strategies, whether in isolation or in combination with sirolimus.

NEW DEVELOPMENTS IN LYMPHANGIOLEIOMYOMATOSIS PATHOGENESIS

Uterine origin of lymphangioleiomyomatosis cells

The pathophysiology of LAM is driven by activated mTOR signalling due to mutations in the TSC genes driving the clonal proliferation of abnormal smooth muscle like cells (LAM cells) that arise from an extrapulmonary source and metastasize to the lungs via blood and lymphatics. Several clinical observations point to a central role of female sexual hormones in the disease pathogenesis (Fig. 1): LAM is seen almost exclusively in women [2▪], accelerated disease progression has been reported during pregnancy [22] and following exposure to exogenous oestrogen [23], lung function declines faster in premenopausal women with LAM compared to postmenopausal women [24▪], and a subset of patients with LAM exhibit cyclical variability in their symptoms coinciding with the hormonal fluxes of menstrual cycle [25▪]. LAM lesions were noted in the uteri of 90% of patients with LAM versus none in controls [26,27]. Recent single cell and single-nuclei RNA sequencing performed on lungs and uterine tissue obtained from LAM patients demonstrated remarkable transcriptional similarity between the LAM cells and uterine smooth muscle cells, and strongly suggests a uterine source of origin for LAM cells [28▪▪].

1531-6971 Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Despite the strong evidence linking female sexual hormones to disease pathogenesis, therapeutic interventions targeting hormonal pathways have demonstrated mixed results and current guidelines recommend against the routine use of hormonal therapy in patients with LAM [12]. The only randomized controlled trial of hormonal antagonism studied an aromatase inhibitor (letrozole) in postmenopausal women with LAM. While the use of letrozole was safe, the study was underpowered to detect efficacy [29]. Identifying the optimal subset of LAM patients who might benefit from hormonal blockade and conducting a proper controlled trial of hormonal blockade in LAM remains a high priority future need.

The lymphangioleiomyomatosis microenvironment

Recent research has helped unravel the complex pathophysiology of LAM, particularly regarding cellular senescence and immune evasion mechanisms. LAM cells exhibit a senescent phenotype dependent on mTOR hyperactivity, potentially promoting loss of lung parenchymal structures similar to that seen in idiopathic pulmonary fibrosis [30▪]. Within LAM nodules, alveolar type II epithelial cells demonstrate enhanced proliferation and express fibroblast growth factor 7 that may facilitate cross talk with LAM-associated fibroblasts [31▪]. Advanced disease may be less responsive to mTOR inhibition due to the evolution of LAM nodules, where fibroblasts might outnumber LAM cells [32▪].

Multiple mechanisms of immune evasion have been identified in the pathogenesis of LAM. Natural killer cells have been implicated in the LAM microenvironment, with reduced levels of natural killer group 2D (NKG2D) positive natural killer (NK) cells correlating with lung function decline [33]. Checkpoint inhibition has shown potential in preclinical models, with evidence of upregulation of programmed cell death protein 1 (PD-1) expression [34▪]. Combination treatment in similar models, with checkpoint inhibition targeting Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) [35▪], or addition of Toll-like-receptor agonists to PD-1 inhibitors has demonstrated enhanced outcomes [36▪]. These findings suggest checkpoint inhibition might be a future therapeutic strategy in LAM.

MTOR SIGNALLING AND THERAPEUTIC TARGETING

LAM cells express melanocytic markers, such as Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB), whose expression depends on mTORC1 signalling. The constitutively released GPNMB ectodomain can be measured in serum, with significantly higher levels in LAM preclinical models suggesting a role in tumour cell growth enhancement [37▪]. Analysis of The Cancer Genome Atlas has revealed mTORC1 hyperactivity associated with immune checkpoint upregulation, leading to suppression of cytotoxic CD4+ T cell activity and decreased survival [38▪]. Chimeric antigen receptor (CAR) T cell therapy targeting ganglioside 3, an immunogen implicated in mTORC1 activation, has shown potential for tumour reduction in mouse models [39▪].

Next generation bi-steric mTORC1 inhibitors have demonstrated superior efficacy and lower tumour relapse rates in LAM models compared to sirolimus, by eliminating phosphorylated 4EBP1, a rapalog resistant protein, and inducing higher rates of apoptosis [40▪]. Prevention of growth in LAM-associated fibroblasts has been demonstrated by the bi-steric mTORC1-selective compound RMC-5552, with more durable inhibition compared to sirolimus [41▪]. These findings demonstrate the therapeutic potential of more completely targeting mTORC1 hyperactivity in LAM that has previously been underexplored.

The benefits of mTOR inhibitors in LAM extend beyond lung function stabilization. A notable observation is the near complete resolution of chylous effusions and reduction in renal AMLs and lymphangioleiomyomas following treatment with mTOR inhibitors [42–45]. Recent studies across the US and China have demonstrated a substantial reduction in the risk of spontaneous pneumothoraces in women with LAM following treatment with sirolimus [46▪▪,47▪▪], suggesting recurrent pneumothorax might be an independent indication to initiate treatment with sirolimus. Survival benefit following treatment with sirolimus has also been demonstrated in recent LAM cohort analyses [48▪▪,49▪].

NOVEL BIOMARKERS IN LYMPHANGIOLEIOMYOMATOSIS

Clinical and physiological measures

Premenopausal patients with LAM exhibit faster decline in lung function compared to postmenopausal women with LAM, although both groups exhibit a beneficial response to sirolimus treatment [24▪]. Baseline lung function can also help in prognostication [50▪]. Recently, a LAM calculator has been developed that can help predict the future rate of decline in FEV1 in treatment-naïve patients with LAM by using readily-available clinical data such as

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

age at diagnosis, menopausal status and lung function [51▪]. This model can be freely accessed at: https://anushkapalipana.shinyapps.io/testapp_v2/. Approximately 25–30% of women with LAM report cyclical respiratory symptom variability associated with the hormonal fluxes of menstrual cycle [25▪]. Patients with this trait tend to be more symptomatic and might respond favourably to hormonal therapy compared to patients without cyclical symptom variability.

Imaging-based biomarkers

Multiple groups have demonstrated the ability to quantify the cyst burden on chest CT scans, which has the potential to become a useful measure to gauge disease severity and assess disease progression and treatment response [50▪,52▪▪]. Cyst burden on chest CTs has demonstrated prognostic value; patients with greater cyst burden on CT imaging tend to exhibit more rapid pulmonary function decline [24▪,50▪]. Sirolimus treatment can help slow the increase in lung cyst volume [53▪]. Novel MRI-based imaging techniques, both hyperpolarized 129Xe as well as oxygen enhanced MRI scans, have demonstrated utility in assessing functional properties in addition to structural imaging in patients with LAM and represent a radiation-free modality to monitor lung disease in LAM [54▪,55▪]. There remains a critical need to develop sensitive nuclear medicine-based imaging modalities that can help quantify LAM cell burden in patients. Recent advances in machine learning techniques show promise in distinguishing LAM from other cystic lung diseases, suggesting a potential role for artificial intelligence-based programs to aid in more timely recognition of LAM (as well as other rare cystic lung diseases) and help combat the ubiquitous problem of delayed diagnosis that is common to all rare diseases [56▪].

Serological biomarkers

While serum VEGF-D has helped tremendously to attain noninvasive diagnostic confirmation of LAM and obviate the need for lung biopsy in several patients, elevated VEGF-D levels are seen in ~60% of patients with LAM and there remains an unmet need to develop diagnostic biomarkers that can help confirm the diagnosis of LAM in the remaining 40% of patients, whether in isolation or in combination with VEGF-D.

In addition to its role as a diagnostic biomarker, serum VEGF-D also has utility as a prognostic and predictive biomarker and might also be helpful as a dosing biomarker to guide personalized dosing of sirolimus for individual LAM patients. Similar to VEGF-D, serum VEGF-C levels decreased following treatment with sirolimus and rose again after treatment was withheld, suggesting it might also be a useful biomarker to predict treatment responsiveness [57▪].

Improved understanding of the molecular pathogenesis of LAM has helped uncover several other candidates with potential for clinical utility as biomarkers, such as endostatin, IGFBP4 and GPNMB [28▪▪,37▪,58▪]. Fibroblast growth factor 23, involved in serum phosphate homeostasis, has shown potential in identifying patients at risk of progressive disease [59▪]. The vitamin D binding protein axis has demonstrated promise in disease monitoring, with levels correlating with disease severity and progression. Lower vitamin D binding protein levels are associated with reduced lung function and more active disease, suggesting a protective role that may influence prognosis [60]. Matrix metalloproteinases (MMPs), particularly MMP-9, MMP-2 and MMP-7, have been postulated in the pathogenesis of tissue remodelling in LAM and have been found to be elevated in the serum of LAM patients [61▪,62,63▪]. MMP-2 shows promise in differentiating LAM from other cystic lung diseases, especially when combined with VEGF-D as a composite biomarker [64▪▪]. Preliminary studies of moesin, a cytoskeleton protein, have revealed elevated serum levels and potential to improve LAM differentiation from other cystic lung disease in combination with VEGF-D [65▪]. Other emerging areas of interest include altered lipid metabolism and the potential use of lipid metabolites as novel biomarkers [66▪]. Data derived from single cell RNA sequencing performed on human LAM lungs has revealed multiple novel pathways and biomarker candidates with relevance to LAM. These data have been compiled in an easy-to-use web-based interface (The LAM Cell Atlas) that can be freely accessed: https://research.cchmc.org/pbge/lunggens/LCA/LCA.html [67▪]. Combining these data with other modalities such as proteomics, perhaps augmented by artificial intelligence, could further aid biomarker discovery in LAM (see Table 1).

NOVEL AND EMERGING THERAPEUTIC PATHWAYS

Recently completed clinical trials

Autophagy related studies have explored the relationship with mTOR inhibition, with the Sirolimus and Autophagy Inhibition in LAM (SAIL) trial of Sirolimus combined with Hydroxychloroquine demonstrating potential lung function benefits [68]. Preclinical studies of resveratrol with sirolimus

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. Potential novel biomarkers

Clinical	
Menopausal status	Faster lung function decline in premenopausal versus postmenopausal patients [24▪]
Baseline lung function	Lower risk of progression with higher baseline lung function [50▪]
Cyclical symptom variability	Symptom variability with menstrual cycle may indicate hormonal therapy response [25▪]
Imaging	
Cyst burden on chest CT	Greater cyst burden associated with more rapid lung function decline [24▪,50▪]
MRI-based imaging	Allows assessment of functional properties in addition to structural imaging [54▪,55▪]
Machine learning AI models	Allows differentiation of LAM from other cystic lung diseases [56▪]
Serological	
VEGF-C	Associated with mTOR inhibitor treatment response [57▪]
Endostatin	Associated with lung function decline [58▪]
GPNMB	Higher in LAM serum and decreases with mTOR inhibition [37▪]
FBGF23	Associated with lung function decline [59▪]
Vitamin D binding protein	Associated with lung function decline [60]
MMP-2	Improves differentiation of LAM from other cystic lung disease [64▪▪]
Moesin	Improves differentiation of LAM from other cystic lung disease [65▪]

AI, artificial intelligence; LAM, lymphangioleiomyomatosis.

showed promise in blocking sirolimus induced autophagy upregulation, with a subsequent phase 2 trial demonstrating favourable safety and tolerability profile, and modest improvement in health-related quality of life measures [69,70▪]. Src kinases, whose degradation is promoted by autophagy, are increased in LAM lung tissue, with potential roles in abnormal cell degradation and invasion [71]. Src inhibition in the form of Saracatinib has been studied in early phase trials in LAM and the results are awaited [72].

Other recent areas of investigation include the COX-2 inhibition in LAM (COLA) study, which established the safety of Celecoxib in treatment naïve LAM patients and displayed VEGF-D lowering potential in some patients [73▪▪]. Statins demonstrated inhibition of MMPs (MMP-2, MMP-3 and MMP-3) and reduction of lung tissue damage in preclinical models, however a phase II study of simvastatin in combination with mTOR inhibition revealed FEV1 decline [74,75▪▪]. Nintedanib, a multiple tyrosine kinase inhibitor used to treat pulmonary fibrosis, led to stabilization of lung function decline in a recent early phase study [76▪▪].

Ongoing clinical trials

Ongoing studies of interest include the Safety and Durability of Sirolimus for Treatment of LAM (MIDAS) study, examining long-term sirolimus therapy, while the Multicenter Interventional Lymphangioleiomyomatosis Early Disease (MILED) trial is investigating whether early, low dose sirolimus can prevent disease progression in patients with preserved lung function [77,78]. Loratadine, promising given the increase in histamine metabolite Methylimidazoleacetic acid in LAM, is under investigation in a phase II trial [79] (See Table 2).

Potential agents with promise

In addition to bi-steric mTORC1-selective compounds and immune checkpoint inhibitors, there are several other promising candidates based on preclinical studies. Targeting lymphangiogenesis via vascular endothelial growth factor receptor (VEGFR) signalling has shown promising results in LAM preclinical models, demonstrating growth inhibition of tsc2-null lesions, reduced immune cell recruitment and decreased VEGF-D levels [80]. Targeting tyrosine kinase pathways such as Src and Syk kinases might also offer therapeutic potential [71,81]. The role of STAT-1 and STAT 3 in LAM cell survival has been explored in preclinical models, prompted by the emergence of the HOX-PBX gene network as a critical factor in LAM cell survival [82▪]. STAT1 inhibition with Fludarabine displayed potential benefit on LAM cell survival, particularly in synergy with mTOR inhibition [83▪].

Existing therapeutic agents may have potential applications in the treatment of LAM. Mast cell recruitment in LAM nodules appears to contribute

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2. Clinical trials

Agent	Trial	Outcome
Recently completed		
Hydroxychloroquine	Sirolimus and autophagy inhibition in LAM (SAIL)	Sirolimus and hydroxychloroquine combination well tolerated. Potential beneficial lung function effects [68].
Resveratrol	Safety and efficacy of combined resveratrol and sirolimus in LAM	Sirolimus and resveratrol combination well tolerated. Modest improvement in health-related quality of life [70▪].
Saracatinib	Safety and efficacy of saracatinib in subjects with LAM (SLAM-2)	Results awaited [72].
Celecoxib	COX-2 inhibition in LAM (COLA)	Celecoxib well tolerated in treatment naïve patients. Potential effect on VEGF-D levels [73▪▪].
Simvastatin	Safety of simvastatin (SOS) in patients with pulmonary LAM and with TSC	mTOR inhibition and simvastatin well tolerated. Associated with decline in FEV1 [75▪▪].
Nintedanib	Nintedanib for patients with LAM	Nintedanib well tolerated. Potential stabilization of lung function [76▪▪].
Ongoing		
Sirolimus	Multicenter interventional LAM early disease trial (MILED)	To determine if early, low dose sirolimus prevents progression in patients with preserved lung function [77].
Sirolimus	Safety and durability of sirolimus for treatment of LAM (MIDAS)	An observational study examining long term mTOR inhibitor therapy [78].
Loratadine	Loratadine associated with rapamycin in patients with LAM	To evaluate the safety of loratadine in combination with sirolimus [79].

LAM, lymphangioleiomyomatosis.

to disease progression through tryptase release, with sodium cromoglycate a potential treatment through its tryptase inhibition properties [84▪]. Similarly, neutrophil elastase (NE) inhibition, in the form of sivelstat, displays therapeutic potential, with high NE expression correlating with tumour progression in LAM preclinical models [85]. Future therapeutic targets also include the inhibition of mRNA translation driven by mTORC1, with several compounds targeting this pathway in various stages of preclinical and clinical development [86▪].

CONCLUSION

LAM is an exemplar rare disease where sustained research efforts have advanced our understanding of the disease pathogenesis and offered multiple novel treatment approaches. Evidence supporting the uterine origin of LAM cells has renewed the interest in exploring hormonal signalling in the disease pathogenesis, improved understanding of the mechanisms by which LAM cells evade detection by the immune system has suggested potential role of immunotherapeutic approaches, newer-generation mTOR inhibitors offer the prospect of better and more complete blockade of the central pathogenic pathway driving LAM, and understanding the crosstalk between LAM cells and their surroundings such as the lymphatic endothelial cells and the pulmonary parenchymal microenvironment will help develop novel combination therapies to halt disease progression, and hopefully induce remission, in patients with LAM. The search for novel biomarkers in addition to VEGF-D is essential to further improve diagnostic accuracy, aid prognostication, assist therapeutic decision making and also act as endpoints for future clinical trials. Comprehensive cellular mapping of LAM by utilizing state-of-the-art technologies such as single cell RNA sequencing and spatial transcriptomics including early disease specimens in addition to the current data derived from explants obtained at the time of lung transplantation will tremendously advance our understanding of LAM. Lastly, exploration and integration of artificial intelligence to better understand the key molecular perturbations in LAM can help identify the most promising targets for the next phase of clinical trials in LAM.

Acknowledgements

None.

Financial support and sponsorship

None.

1531-6971 Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. McCormack FX, Travis WD, Colby TV, *et al.* Lymphangioleiomyomatosis: calling it what it is: a low-grade, destructive, metastasizing neoplasm. Am J Respir Crit Care Med 2012; 186:1210–1212.
2. ■ McCarthy C, Gupta N, Johnson SR, *et al.* Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management. Lancet Respir Med 2021; 9:1313–1327.

This review provides a comprehensive overview of the pathophysiology, clinical presentation, diagnostic pathways and management of LAM, acting as a valuble, easy to access resource for clinicians.

3. Ryu JH, Moss J, Beck GJ, *et al.* The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 2006; 173:105–111.
4. ■ Lynn E, Forde SH, Franciosi AN, *et al.* Updated Prevalence of Lymphangioleiomyomatosis in Europe. Am J Respir Crit Care Med 2024; 209:456–459.

This study presents updated prevalence data for LAM in Europe, helping to establish more accurate estimates of disease burden in European populations. This is essential for healthcare planning, resource allocation, and raising awareness among clinicians about the true frequency of LAM.

5. ■ Gupta N, Johnson SR. Lymphangioleiomyomatosis: no longer ultra-rare. Am J Respir Crit Care Med 2024; 209:358–359.

This editorial discusses how LAM should no longer be classified as "ultra-rare," and that current prevalence estimates should be treated as minimum estimates.

6. ■ Kimura Y, Jo T, Hashimoto Y, *et al.* Epidemiology of patients with lymphangioleiomyomatosis: a descriptive study using the national database of health insurance claims and specific health checkups of Japan. Respir Investig 2024; 62:494–502.

This epidemiological study utilises Japan's national health insurance database to analyse patterns and distribution of LAM, contributing insights into population incidences and prevalence of LAM.

7. Gupta N, Finlay GA, Kotloff RM, *et al.* Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. Am J Respir Crit Care Med 2017; 196:1337–1348.
8. ■ Koba T, Arai T, Kitaichi M, *et al.* Efficacy and safety of transbronchial lung biopsy for the diagnosis of lymphangioleiomyomatosis: a report of 24 consecutive patients. Respirology 2018; 23:331–338.

This study evaluates the efficacy and safety of transbronchial lung biopsy in LAM, establishing its role in the diagnostic algorithm and potentially reducing the need for more invasive diagnostic methods.

9. Gupta N, Wikenheiser-Brokamp K, Zander D, *et al.* Successful diagnosis of lymphangioleiomyomatosis with transbronchial lung cryobiopsy. Lymphology 2017; 50:154–157.
10. Young LR, Inoue Y, McCormack FX. Diagnostic potential of serum VEGF-D for lymphangioleiomyomatosis. N Engl J Med 2008; 358:199–200.
11. Young LR, Vandyke R, Gulleman PM, *et al.* Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. Chest 2010; 138:674–681.
12. McCormack FX, Gupta N, Finlay GR, *et al.* Official American Thoracic Society/Japanese Respiratory Society Clinical Practice guidelines: lymphangioleiomyomatosis diagnosis and management. Am J Respir Crit Care Med 2016; 194:748–761.
13. Moss J, Avila NA, Barnes PM, *et al.* Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med 2001; 164:669–671.
14. Cudzilo CJ, Szczesniak RD, Brody AS, *et al.* Lymphangioleiomyomatosis screening in women with tuberous sclerosis. Chest 2013; 144:578–585.
15. ■ Zak S, Mokhallati N, Su W, *et al.* Lymphangioleiomyomatosis mortality in patients with tuberous sclerosis complex. Ann Am Thorac Soc 2019; 16:509–512.

This research investigates mortality in TSC LAM, providing important prognostic information for this subgroup, guiding screening and intervention approaches for this population.

16. ■ Northrup H, Aronow ME, Bebin EM, *et al.* Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol 2021; 123:50–66.

This paper presents updated international diagnostic criteria for TSC, including TSC-LAM, with surveillance recommendations and management guidelines.

17. ■ Johnson J, Somerfield W, Johnson SR. Lymphangioleiomyomatosis in patients with tuberous sclerosis: a national centre audit. Orphanet J Rare Dis 2024; 19:137.

This national centre audit examines LAM specifically in patients with TSC, providing insights into this distinct subpopulation. This study helps clarify differences between sporadic LAM and TSC associated cases.

18. McCormack FX, Inoue Y, Moss J, *et al.* Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011; 364:1595–1606.
19. Young L, Lee HS, Inoue Y, *et al.* Serum VEGF-D a concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial. Lancet Respir Med 2013; 1:445–452.
20. Ando K, Kurihara M, Kataoka H, *et al.* Efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis. Respir Investig 2013; 51:175–183.
21. Yao J, Taveira-DaSilva AM, Jones AM, *et al.* Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis. Am J Respir Crit Care Med 2014; 190:1273–1282.
22. Hayashida M, Yasuo M, Hanaoka M, *et al.* Reductions in pulmonary function detected in patients with lymphangioleiomyomatosis: An analysis of the Japanese National Research Project on Intractable Diseases database. Respir Investig 2016; 54:193–200.
23. Oberstein EM, Fleming LE, Gómez-Marin O, *et al.* Pulmonary lymphangioleiomyomatosis (LAM): examining oral contraceptive pills and the onset of disease. J Womens Health (Larchmt) 2003; 12:81–85.
24. ■ Gupta N, Lee HS, Young LR, *et al.* Analysis of the MILES cohort reveals determinants of disease progression and treatment response in lymphangioleiomyomatosis. Eur Respir J 2019; 53.

This analysis of the MILES cohort identifies key determinants of disease progression and treatment response in LAM, helping refine patient selection for mTOR inhibitor therapy and establishing disease prognostic indicators.

25. ■ Shaw BM, Kopras E, Gupta N. Menstrual cycle-related respiratory symptom variability in patients with lymphangioleiomyomatosis. Ann Am Thorac Soc 2022; 19:1619–1621.

This investigation explores how respiratory symptoms in LAM patients fluctuate during the menstrual cycle, highlighting the hormonal influence on disease presentation, which may inform future treatment timing or hormonal intervention strategies in LAM patients.

26. Prizant H, Sen A, Light A, *et al.* Uterine-specific loss of Tsc2 leads to myometrial tumors in both the uterus and lungs. Mol Endocrinol 2013; 27:1403–1414.
27. Hayashi T, Kumasaka T, Mitani K, *et al.* Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients. Am J Surg Pathol 2011; 35:1776–1785.
28. ■■ Guo M, Yu JJ, Perl AK, *et al.* Single-cell transcriptomic analysis identifies a unique pulmonary lymphangioleiomyomatosis cell. Am J Respir Crit Care Med 2020; 202:1373–1387.

This single-cell transcriptomic analysis identifies a unique pulmonary LAM cell type with distinct genetic characteristics, advancing understanding of LAM cellular pathology and potentially identify new therapeutic targets.

29. Lu C, Lee HS, Pappas GP, *et al.* A phase II clinical trial of an aromatase inhibitor for postmenopausal women with lymphangioleiomyomatosis. Ann Am Thorac Soc 2017; 14:919–928.
30. ■ Bernardelli C, Ancona S, Lazzari M, *et al.* LAM cells as potential drivers of senescence in lymphangioleiomyomatosis microenvironment. Int J Mol Sci 2022; 23:7040.

This research explores how LAM cells may drive cellular senescence in the LAM microenvironment, offering insights into disease mechanisms and progression and potentially identifying interventions targeting senescence.

31. ■ Clements D, Miller S, Babaei-Jadidi R, *et al.* Cross talk between LAM cells and fibroblasts may influence alveolar epithelial cell behavior in lymphangioleiomyomatosis. Am J Physiol Lung Cell Mol Physiol 2022; 322:L283–Ll293.

This paper investigates communication between LAM cells and fibroblasts and how this cross-talk influences cell behaviour within the LAM microenvironment, which could reveal new therapeutic approaches targeting cellular communication.

32. ■ Miller S, Stewart ID, Clements D, *et al.* Evolution of lung pathology in lymphangioleiomyomatosis: associations with disease course and treatment response. J Pathol Clin Res 2020; 6:215–226.

This study examines the evolution of lung pathology in LAM and identifies clinical-pathological correlations which help predict outcomes and optimise therapeutic approaches based on specific pathological features.

33. Osterburg AR, Nelson RL, Yaniv BZ, *et al.* NK cell activating receptor ligand expression in lymphangioleiomyomatosis is associated with lung function decline. JCI Insight 2016; 1:e87270.
34. ■ Maisel K, Merrilees MJ, Atochina-Vasserman EN, *et al.* Immune checkpoint ligand PD-L1 is upregulated in pulmonary lymphangioleiomyomatosis. Am J Respir Cell Mol Biol 2018; 59:723–732.

This research demonstrates upregulation of the immune checkpoint ligand PD-L1 in LAM tissue, suggesting a potential role for novel immunotherapy approaches.

35. ■ Liu HJ, Lizotte PH, Du H, *et al.* TSC2-deficient tumors have evidence of T cell exhaustion and respond to anti-PD-1/anti-CTLA-4 immunotherapy. JCI Insight 2018; 3:e98674.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

This study demonstrates preclinical evidence of LAM model respond to combined immunotherapy, providing preclinical evidence as a potential treatment.

36. Amosu MM, Jankowski AM, McCright JC, *et al.* Plasmacytoid dendritic cells ■ mediate CpG-ODN-induced increase in survival in a mouse model of lymphangioleiomyomatosis. Am J Respir Cell Mol Biol 2024; 71:519–533.

This research demonstrates that Toll-like receptor agonists in combination with PD-1 inhibitors demonstrate favourable outcomes in preclinical models, exploring aspects of the immune system that could be leveraged for therapeutic benefit in LAM.

37. Gibbons E, Taya M, Wu H, *et al.* Glycoprotein non-metastatic melanoma ■ protein B promotes tumor growth and is a biomarker for lymphangioleiomyomatosis. Endocr Relat Cancer 2024; 31:e230312.

This study identifies glycoprotein nonmetastatic melanoma protein B as both promoting tumour growth and serving as a potential biomarker for LAM, which could lead to new diagnostic approaches and targeted therapies of this molecular pathway.

38. Liu HJ, Du H, Khabibullin D, *et al.* mTORC1 upregulates B7-H3/CD276 to ■ inhibit antitumor T cells and drive tumor immune evasion. Nat Commun 2023; 14:1214.

The study reveals important interactions between the mTOR pathway and immune checkpoint upregulation in LAM preclinical models, potentially informing future novel treament approaches.

39. Thomas A, Sumughan S, Dellacecca ER, *et al.* Benign tumors in TSC are ■ amenable to treatment by GD3 CAR T cells in mice. JCI Insight 2021; 6: e152014.

This preclinical study demonstrates that benign tumours in TSC respond to treatment with GD3 CAR T cells, exploring a novel immunotherapy approach.

40. Du H, Yang YC, Liu HJ, *et al.* Bi-steric mTORC1 inhibitors induce apoptotic ■ cell death in tumor models with hyperactivated mTORC1. J Clin Invest 2023; 133:e167861.

This research reports that bi-steric mTORC1 inhibitors induce apoptotic cell death in tumour models with hyperactivated mTORC1 signalling, with potential to improve outcomes compared to current treatments in LAM.

41. Evans JF, Ledwell OA, Tang Y, *et al.* The bi-steric inhibitor RMC-5552 reduces ■ mTORC1 signaling and growth in lymphangioleiomyomatosis. Am J Respir Cell Mol Biol 2025; 72:643–652.

This study investigates the bi-steric inhibitor RMC-5552 and its effects on mTORC1 signalling and growth in LAM, representing an important advancement in potential therapeutic options for LAM.

42. Zhan Y, Shen L, Xu W, *et al.* Functional improvements in patients with lymphangioleiomyomatosis after sirolimus: an observational study. Orphanet J Rare Dis 2018; 13:34.

43. Taveira-DaSilva AM, Hathaway O, Stylianou M, *et al.* Changes in lung function and chylous effusions in patients with lymphangioleiomyomatosis treated with sirolimus. Ann Intern Med 2011; 154:797–805; w-292-793.

44. Bissler JJ, Kingswood JC, Radzikowska E, *et al.* Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013; 381:817–824.

45. Bissler JJ, McCormack FX, Young LR, *et al.* Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008; 358:140–151.

46. Cheng C, Xu W, Wang Y, *et al.* Sirolimus reduces the risk of pneumothorax ■■ recurrence in patients with lymphangioleiomyomatosis: a historical prospective self-controlled study. Orphanet J Rare Dis 2022; 17:257.

This study demonstrates that sirolimus reduces the risk of pneumothorax recurrence in patients with LAM, offering guidance for clinicians and potentially changing standard practice for this subgroup.

47. Cortinas N, Liu J, Kopras E, *et al.* Impact of age, menopause, and sirolimus on ■■ spontaneous pneumothoraces in lymphangioleiomyomatosis. Chest 2022; 162:1324–1327.

This study examines how age, menopause, and sirolimus treatment affect the occurrence of spontaneous pneumothoraces in LAM patients, helping to stratify these risk factors, which could guide individualised preventive strategies.

48. Xu W, Yang C, Cheng C, *et al.* Determinants of progression and mortality in ■■ lymphangioleiomyomatosis. Chest 2023; 164:137–148.

This research identifies key determinants of disease progression and mortality in LAM, identifying prognostic indicators which could help identify high-risk patients who might benefit from more aggressive intervention or closer monitoring.

49. Sakurai T, Kanou T, Funaki S, *et al.* Effect of mTOR inhibitors on the mortality ■ and safety of patients with lymphangioleiomyomatosis on the lung transplantation waitlist: a retrospective cohort study. Respir Investig 2024; 62:657–662.

This retrospective cohort study evaluates how mTOR inhibitors affect mortality and safety outcomes in LAM patients awaiting lung transplantation, with potential to influence pretransplant management protocols for this patient population.

50. Gupta N, Lee HS, Ryu JH, *et al.* The NHLBI LAM registry: prognostic ■ physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis. Chest 2019; 155:288–296.

This analysis of the NHLBI LAM Registry identifies prognostic physiologic and radiologic biomarkers, providing valuable insights into disease progression.

51. Palipana AK, Gecili E, Song S, *et al.* Predicting individualized lung disease ■ progression in treatment-naive patients with lymphangioleiomyomatosis. Chest 2023; 163:1458–1470.

This study develops a prediction model for individualised lung disease progression in treatment-naive LAM patients, enabling more personalised treatment planning and could help identify patients who would benefit most from early intervention.

52. Gopalakrishnan V, Yao J, Steagall WK, *et al.* Use of CT imaging to quantify ■■ progression and response to treatment in lymphangioleiomyomatosis. Chest 2019; 155:962–971.

This study demonstrates how CT imaging can be used to quantify disease progression and response to treatment in LAM, providing an objective measures of disease burden to monitor patients.

53. Kim C, Do KH, Cha J, *et al.* Effects of sirolimus in lymphangioleiomyomatosis ■ patients on lung cysts and pulmonary function: long-term follow-up observational study. Eur Radiol 2020; 30:735–743.

This observational study examines the effects of sirolimus on lung cysts and pulmonary function in LAM patients, providing important data on long term treatment response and impact on disease progression, which could inform monitoring protocols.

54. Walkup LL, Roach DJ, Hall CS, *et al.* Cyst ventilation heterogeneity and ■ alveolar airspace dilation as early disease markers in lymphangioleiomyomatosis. Ann Am Thorac Soc 2019; 16:1008–1016.

This research uses imaging to search for early disease markers in LAM, to potentially establish earlier diagnosis and intervention by identifying presymptomatic disease features.

55. Bhattacharya I, Ramasawmy R, Javed A, *et al.* Assessment of lung structure ■ and regional function using 0.55 T MRI in patients with lymphangioleiomyomatosis. Invest Radiol 2022; 57:178–186.

This study utilizes MRI technology to assess lung structure and regional function in LAM patients, exploring a novel nonradiation-based imaging technique that may provide functional information beyond conventional CT scanning.

56. Jonas A, Muelly M, Gupta N, *et al.* Machine learning to distinguish lymphan- ■ gioleiomyomatosis from other diffuse cystic lung diseases. Respir Investig 2022; 60:430–433.

This research applies machine learning techniques to distinguish LAM from other diffuse cystic lung diseases, which could lead to computer-assisted diagnostic tools to help radiologists identify LAM with greater confidence.

57. Gupta N, Hagner M, Wu H, *et al.* Serum vascular endothelial growth factor C ■ as a marker of therapeutic response to sirolimus in lymphangioleiomyomatosis. Ann Am Thorac Soc 2021; 18:174–177.

This study investigates serum VEGF-C as a potential biomarker of therapeutic response to sirolimus in LAM, contributing to the search for biomarkers to guide diagnosis and management.

58. Lamattina AM, Poli S, Kidambi P, *et al.* Serum endostatin levels are associated ■ with diffusion capacity and with tuberous sclerosis- associated lymphangioleiomyomatosis. Orphanet J Rare Dis 2019; 14:72.

This study demonstrates that serum endostatin levels are associated with pulmonary function and TSC LAM, contributing to the understanding of LAM pathophysiology.

59. Esposito AJ, Imani J, Shrestha S, *et al.* Lymphangioleiomyomatosis: circulating ■ levels of FGF23 and pulmonary diffusion. J Bras Pneumol 2023; 49: e20220356.

This research examines the relationship between circulating levels of FGF23 and lung function in LAM, which may help identify new pathways involved in LAM pathophysiology.

60. Miller S, Coveney C, Johnson J, *et al.* The vitamin D binding protein axis modifies disease severity in lymphangioleiomyomatosis. Eur Respir J 2018; 52.

61. Ancona S, Orpianesi E, Bernardelli C, *et al.* Differential modulation of matrix ■ metalloproteinases-2 and -7 in LAM/TSC cells. Biomedicines 2021; 9:1760.

This study investigates the role of MMP-2 and MMP-7 in preclinical models, exploring how these proteins are dysregulated and potentially contribute to cyst formation and tissue destruction, adding to the understanding of the mechanism of LAM lung damage.

62. Odajima N, Betsuyaku T, Nasuhara Y, *et al.* Matrix metalloproteinases in blood from patients with LAM. Respir Med 2009; 103:124–129.

63. Terraneo S, Lesma E, Ancona S, *et al.* Exploring the role of matrix metallo- ■ proteinases as biomarkers in sporadic lymphangioleiomyomatosis and tuberous sclerosis complex. A pilot study. Front Med (Lausanne) 2021; 8:605909.

This study explores the role of matrix metalloproteinases as potential biomarkers in LAM, with potential in diagnostic and therapeutic approaches targeting tissue remodelling .processes.

64. Revilla-López E, Ruiz de Miguel V, López-Meseguer M, *et al.* Lymphangio- ■■ leiomyomatosis: searching for potential biomarkers. Front Med (Lausanne) 2023; 10:1079317.

This paper presents a broad investigation into potential biomarkers for lymphangioleiomyomatosis, aiming to identify clinically useful tools for diagnosis, monitoring, and treatment approaches in LAM.

65. Song X, Cai H, Peng W, *et al.* The role of moesin in diagnosing and assessing ■ severity of lymphangioleiomyomatosis. Respir Res 2024; 25:57.

This research evaluates the role of moesin, in diagnosing and assessing severity of LAM and it's potential use in monitoring treatment response.

66. Bottolo L, Miller S, Johnson SR. Sphingolipid, fatty acid and phospholipid ■ metabolites are associated with disease severity and mTOR inhibition in lymphangioleiomyomatosis. Thorax 2020; 75:679–688.

This study demonstrates that sphingolipid, fatty acid, and phospholipid metabolites are associated with disease severity and response to mTOR inhibition in LAM,

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

identifing potential metabolic biomarkers and suggesting potential metabolic pathways as therapeutic targets in LAM.

67. Du Y, Guo M, Wu Y, *et al.* Lymphangioleiomyomatosis (LAM) cell atlas. Thorax ■ 2023; 78:85–87.

This research presents a comprehensive LAM Cell Atlas, providing a detailed characterisation of cell types, enhancing our understanding of LAM gene expression.

68. El-Chemaly S, Taveira-Dasilva A, Goldberg HJ, *et al.* Sirolimus and autophagy inhibition in lymphangioleiomyomatosis: results of a phase I Clinical trial. Chest 2017; 151:1302–1310.

69. Alayev A, Sun Y, Snyder RB, *et al.* Resveratrol prevents rapamycin-induced upregulation of autophagy and selectively induces apoptosis in TSC2-deficient cells. Cell Cycle 2014; 13:371–382.

70. Gupta N, Zhang B, Zhou Y, *et al.* Safety and efficacy of combined resveratrol ■ and sirolimus in lymphangioleiomyomatosis. Chest 2023; 163:1144–1155.

This clinical trial investigates the safety and efficacy of combining resveratrol with sirolimus in LAM, representing an effort to develop combination therapies that might enhance efficacy or reduce side effects in LAM management.

71. Tyryshkin A, Bhattacharya A, Eissa NT. SRC kinase is a novel therapeutic target in lymphangioleiomyomatosis. Cancer Res 2014; 74:1996–2005.

72. Hanania N. Safety and efficacy of saracatinib in subjects with lymphangioleiomyomatosis (SLAM-2). https://clinicaltrials.gov/study/NCT02737202?a=4 [Accessed April 2025]. Baylor College of Medicine; 2020.

73. El-Chemaly S, Taveira-DaSilva A, Bagwe S, *et al.* Celecoxib in lymphangio- ■■ leiomyomatosis: results of a phase I clinical trial. Eur Respir J 2020; 55:1902370.

This clinical trial reports results of celecoxib treatment in LAM, evaluating the safety profile and preliminary efficacy to explore repurposing an established medication as a potential new therapeutic approach.

74. Goncharova EA, Goncharov DA, Fehrenbach M, *et al.* Prevention of alveolar destruction and airspace enlargement in a mouse model of pulmonary lymphangioleiomyomatosis (LAM). Sci Transl Med 2012; 4:154ra134.

75. Krymskaya VP, Courtwright AM, Fleck V, *et al.* A phase II clinical trial of the ■■ Safety Of Simvastatin (SOS) in patients with pulmonary lymphangioleiomyomatosis and with tuberous sclerosis complex. Respir Med 2020; 163:105898.

This clinical trial examines the safety of simvastatin in patients with LAM, representing an effort to identify new treatment options by repurposing existing medications with known safety profiles.

76. Harari S, Elia D, Caminati A, *et al.* Nintedanib for patients with lymphangio- ■■ leiomyomatosis: a phase 2, open-label, single-arm study. Lancet Respir Med 2024; 12:967–974.

This study evaluated nintedanib for patients with LAM, exploring a mechanistically distinct therapeutic approach targeting fibrotic aspects of LAM pathophysiology.

77. McCormack FX. Multicenter Interventional Lymphangioleiomyomatosis (LAM) Early Disease Trial (MILED), vol 2024. https://clinicaltrials.gov/study/NCT03150914 [Accessed April 2025]. University of Cincinnati; 2024.

78. McCormack F. Safety and Durability of Sirolimus for Treatment of LAM (MIDAS). https://clinicaltrials.gov/study/NCT02432560 [Accessed April 2025]. University of Cincinnati; 2024.

79. Bordas-Martínez J, Herranz C, Vicens-Zygmunt V, *et al.* Design of phase II, randomized, placebo-controlled study of loratadine associate with rapamycin in patients with lymphangioleiomyomatosis (LAM). Eur Respir J 2020; 56:3401.

80. Atochina-Vasserman EN, Abramova E, James ML, *et al.* Pharmacological targeting of VEGFR signaling with axitinib inhibits Tsc2-null lesion growth in the mouse model of lymphangioleiomyomatosis. Am J Physiol Lung Cell Mol Physiol 2015; 309:L1447–1454.

81. Cui Y, Steagall WK, Lamattina AM, *et al.* Aberrant SYK kinase signaling is essential for tumorigenesis induced by TSC2 inactivation. Cancer Res 2017; 77:1492–1502.

82. Olatoke T, Wagner A, Astrinidis A, *et al.* Single-cell multiomic analysis ■ identifies a HOX-PBX gene network regulating the survival of lymphangioleiomyomatosis cells. Sci Adv 2023; 9:eadf8549.

This single-cell multiomic analysis identifies the HOX-PBX gene network as regulating LAM cell survival, revealing potential new therapeutic targets operating through developmental pathways not previously linked to LAM.

83. Olatoke T, Zhang EY, Wagner A, *et al.* STAT1 promotes PD-L1 activation and ■ tumor growth in lymphangioleiomyomatosis. bioRxiv [Preprint] 2024. doi: 10.1101/2024.12.11.627871.

This study demonstrates that STAT1 promotes PD-L1 activation and tumour growth in LAM, suggesting potential for immunotherapy targeting the PD-1/PD-L1 axis.

84. Babaei-Jadidi R, Dongre A, Miller S, *et al.* Mast-cell tryptase release con- ■ tributes to disease progression in lymphangioleiomyomatosis. Am J Respir Crit Care Med 2021; 204:431–444.

This research shows that mast-cell tryptase release contributes to disease progression in LAM, suggesting anti-inflammatory or mast cell-directed therapies could be beneficial in LAM management.

85. Taya M, Garcia-Hernandez ML, Rangel-Moreno J, *et al.* Neutrophil elastase from myeloid cells promotes TSC2-null tumor growth. Endocr Relat Cancer 2020; 27:261–274.

86. Evans JF, McCormack FX, Sonenberg N, *et al.* Lost in translation: a neglected ■ mTOR target for lymphangioleiomyomatosis. Eur Respir Rev 2023; 32:230100.

This review discusses neglected mTOR targets for LAM treatment, potentially identifying new directions for developing more effective mTOR-targeting strategies.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.