Lymphatic Forum 2025
Oral Abstracts

Lymphatic Development and Differentiation

Lyve1-driven Nras^{Q61R} expression causes edema, enlarged lymphatic vessels, and hepatic vascular defects in embryonic mice

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Key Ideas:

- NRASQ61R expression in lymphatic endothelial cells disrupts lymphatic development and function
- Hyperactive NRAS signaling drives lymphatic and sinusoidal vessel enlargement
- NRASQ61R expression in endothelial cells can drive certain phenotypes seen in KLA

Connexin 37 and cell cycle regulation of lymphatic valve morphogenesis

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Key Ideas:

- Cx37 in lymphatic endothelial cells is required for lymphatic valve morphogenesis
- Lymphatic valve forming regions reside in distinct cell cycle states from the adjacent lymphangion
- Cx37 maintains the cell cycle state of valve forming regions through the CDK4/6 inhibitor p27

Lymphatic Fluid Regulation

Distinct role of dural and leptomeningeal macrophages in maintaining cerebrospinal fluid drainage to meningeal lymphatic vessels

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Key Ideas:

- Macrophages are widely present in the leptomeninges and dura mater of meninges
- Leptomeningeal and dural macrophages play distinct roles in maintaining optimal CSF drainage
- Leptomeningeal and dural macrophages can be targeted using different approaches

Identification of Slc22a1 (Oct1) as a novel marker of lymphatic muscle cells

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Key Ideas:

- Single cell sequencing identified a specific marker for lymphatic smooth muscle cells
- Lymphatic smooth muscle cells express different genes than those of arteries and veins
- A new reporter mouse allows the specific visualization of lymphatic smooth muscle cells

Store-operated calcium entry in mouse lymphatic muscle cells: A new paradigm to explore

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Key Ideas:

- Store operated calcium entry in lymphatic muscle cells
- scRNASeq of lymphatic muscle cells
- Fluid regulation

The thrombin receptor PAR1 orchestrates changes in lymphatic endothelial cell junction morphology to augment lymphatic drainage during lung injury

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Key Ideas:

- The lung lymphatic endothelial cells transition from zipper to button junctions during lung injury
- Transition to button junctions in lung lymphatic collecting vessels augments lymphatic drainage
- Transition of lung lymphatic junctions during injury is dependent on the thrombin receptor PAR1

Lymphatic-Immune Crosstalk

Modulation of lymphatic endothelial nitric oxide regulates the progression of cardiometabolic heart failure

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Key Ideas:

- Lymphatic endothelial Hba regulates heart structure during heart failure
- Lymphatic endothelial Hba regulates immune cell presence in the heart during heart failure
- NO chelation in LECs suppresses genes related to lymphangiogenesis and cell junction maintenance

Investigating the mechanisms of *Helicobacter hepaticus* mediated lymphangiogenesis and tertiary lymphoid structure formation

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Key Ideas:

- Bacterial driven tertiary lymphoid structure formation
- role of lymphatic vessels in response to bacteria
- role of lymphatic vessels in tertiary lymphoid structure formation and maturation

Lymphatics in Metabolism

Lymphatic endothelial Piezo1–TRPV4 signaling in obesity

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Key Ideas:

- First evidence of elementary Ca^{2+} influx events occurring through TRPV4 channels in intact LECs
- LEC TRPV4 channel activity contributes to lymphatic endothelial dysfunction in obesity
- LEC Piezo1–TRPV4 signaling axis in MCLVs

The functional roles of TGFβ signaling in regulating cardiac lymphangiogenesis and cardiac repair after myocardial ischemia

Esteban Delgado, Long Do MS, Liam Flynn BS, Erhe Gao MD, PhD, Emily Megill BS, Nathaniel Snyder PhD, MPH, Xiaolei Liu PhD

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Key Ideas:

- TGFβ negatively regulates cardiac lymphangiogenesis and cardiac repair after MI
- TGFβ negatively regulates CPT1A-mediated fatty acid oxidation in LECs
- Enhancing fatty acid oxidation in LECs under TGFβ stimulation prevents changes in LEC activities

Young Investigator Session

A novel RAS inhibitor suppresses abnormal characteristics induced by NRAS Q61R in *vitro*

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Key Ideas:

- KLA is a rare lymphatic anomaly with poor prognosis, linked to NRASQ61R mutations
- RMC-7977, a RAS(ON) inhibitor, blocks MAPK/PI3K signaling in NRASQ61R EPC
- RMC-7977 reduces proliferation, migration, and Ang-2 levels, supporting RAS inhibitors for KLA

The role of the lymphatic system in cardiac growth, repair and regeneration

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Key Ideas:

- Epicardial-lymphatic interactions shape regenerative responses
- Lymphatic regulation of epicardial signalling in heart regeneration
- Epicardial-lymphatic interactions shape regenerative responses

The Notch3+ stroma in gut lymphatic-muscle development and stem cell homeostasis

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Key Ideas:

- Villus smooth muscle (SM) originates from PDGFRα+ fibroblast-to-myofibroblast transition
- NOTCH3 within the PDGFRα+ lineage governs MLC assembly and dietary fat absorption
- NOTCH3 within the PDGFRβ+ lineage regulates MLC homeostasis and ISC function via WNT signaling

Metabolically driven iPSC differentiation to generate robust and functional lymphatic endothelial cells

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Key Ideas:

- iPSC differentiation to LEC
- lymphedema treatment
- lymphangiogenesis

Lymphatic Disease Detection and Therapeutics

Preliminary results of the European multicentric phase III trial regarding sirolimus in slow-flow vascular malformations

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Key Ideas:

- Sirolimus can improve patient's quality of life in 85% of the cases
- Sirolimus increased feasibility of surgery or sclerotherapy in 20 (15%) patients
- Not all patients report a recurrence of symptoms after sirolimus arrest

Lymphatic Malformation and Pathobiology and Clinical Trials

Marfan Syndrome impairs the formation and function of lymphatic vessels in the mitral valves causing the progression of myxomatous valve degeneration

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Key Ideas:

- Lymphatic vessels are hypoplastic in mitral valves (MVs) of Fbn1 heterozygous mutant mice
- Lymphatic drainage function is defective in MVs of Fbn1 heterozygous mutant mice
- VEGF-C156S rescues lymphatic defects in MVs and ameliorates MV thickening in Fbn1 mutant mice

KRAS mutations in lymphatic malformations degrade lymphatic valves through the plasminogen activator pathway and MMPs

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Key Ideas:

- Mice that express the KRAS-G12D mutation have a severe loss of lymphatic valves & chylothorax
- KRAS-G12D upregulates components of the plasminogen activator pathway and several MMPs
- Active MMPs degrade the lymphatic valve ECM core

Lymphatics, Cancer, and Metastasis

Transcriptomic analysis of tumor LECs and migratory leukocytes – A comparison between cold and hot tumors

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Key Ideas:

- scRNA-seq reveals the plasticity of LEC subclusters in murine melanoma models
- LECs regulate leukocyte trafficking and immunosuppression in tumors
- The immune-interacting LEC subset is significantly enhanced in T cell-inflamed tumors

Comprehensive 3D statistical atlases for predicting lymphatic drainage in breast cancer and cutaneous melanoma

Hayley M Reynolds PhD[1], Tharanga Jayathungage Don PhD[1], Cameron Walker PhD[2], Josephine Situ BE[2], Poppy Buissink BE[2], Annie Mu ME[1], Robert Finnegan PhD[3], Thiranja Prasad Babarenda Gamage PhD[1], David K V Chung MD[4]

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Key Ideas:

- Lymphatic drainage of the skin and breast is highly variable between patients
- Statistical atlases can predict sites of lymphatic drainage and therefore cancer metastasis
- Statistical lymphatic atlases could be used for medical education, treatment planning and follow-up

Lymphatic Dysfunction in Human Diseases

Liver lymphatic changes in biliary atresia from diagnosis to transplant

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Key Ideas:

- Intrahepatic lymphatics expand in biliary atresia, a pediatric cholestatic liver disease
- Increased lymphatic vessel density is associated with longer survival with native liver in BA
- LEC expression of PD-L1 increases throughout disease progression in BA

Adipose tissue expansion in obesogenic conditions can occur via Piezo2 in capillary lymphatic endothelium

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Key Ideas:

- Piezo2 is highly expressed in lymphatic capillary endothelium
- Flt4 expression is regulated by Piezo2, possibly working through KLF2
- Piezo2 and Flt4 expressions are lost in obesogenic conditions, as well as after siMAF knock-down