



Division of Plastic and Reconstructive Surgery

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Trama-related Lymphedema: A Novel Role for Retinoic Acid-based Therapy

Alex K. Wong, MD, FACS

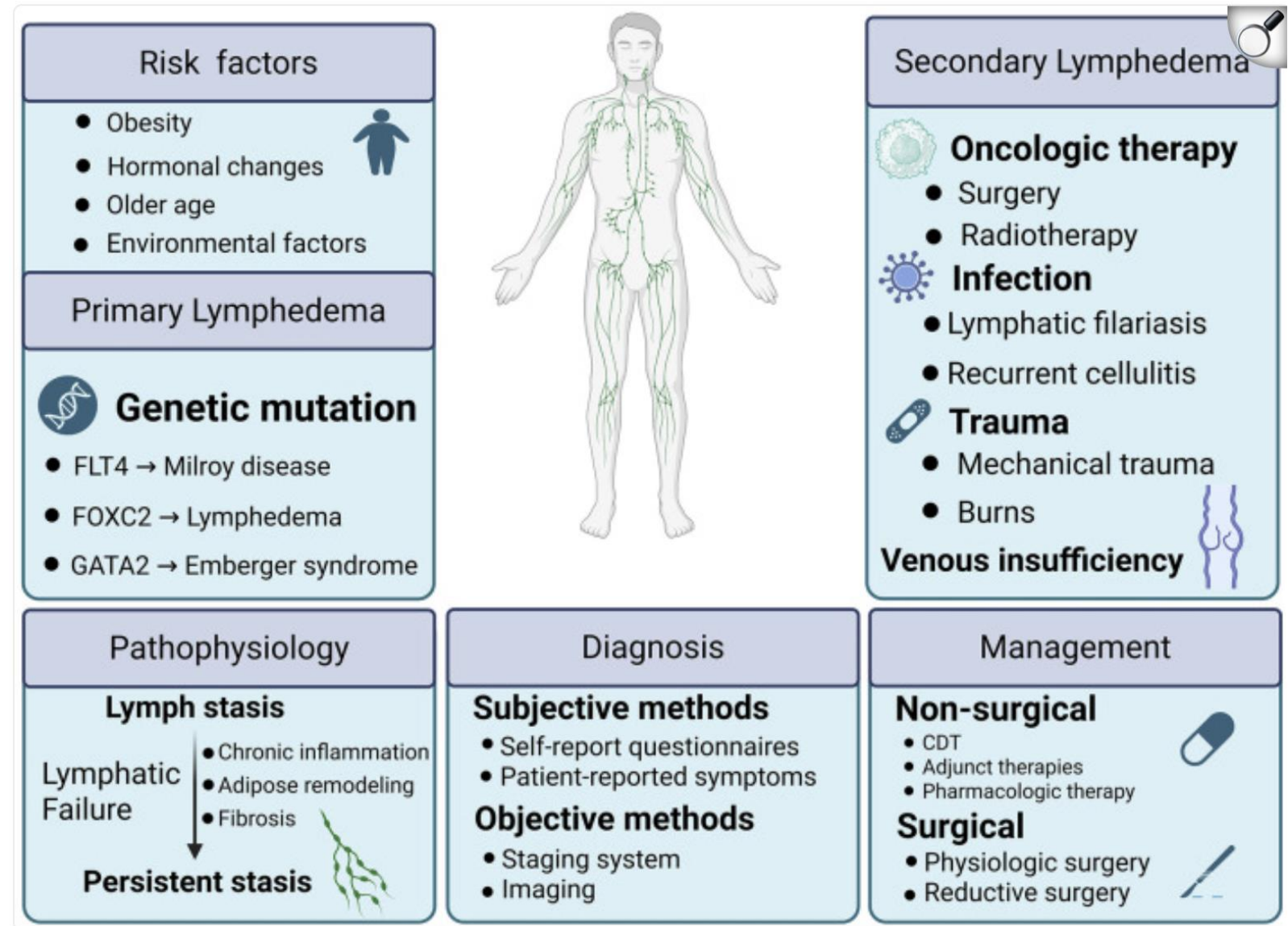
MHSRS: Cellular Therapeutics for Trauma (August 6, 2026)

Disclosures

Dr. Wong is Founder & CEO of LymphaGEN, Inc.

Introduction

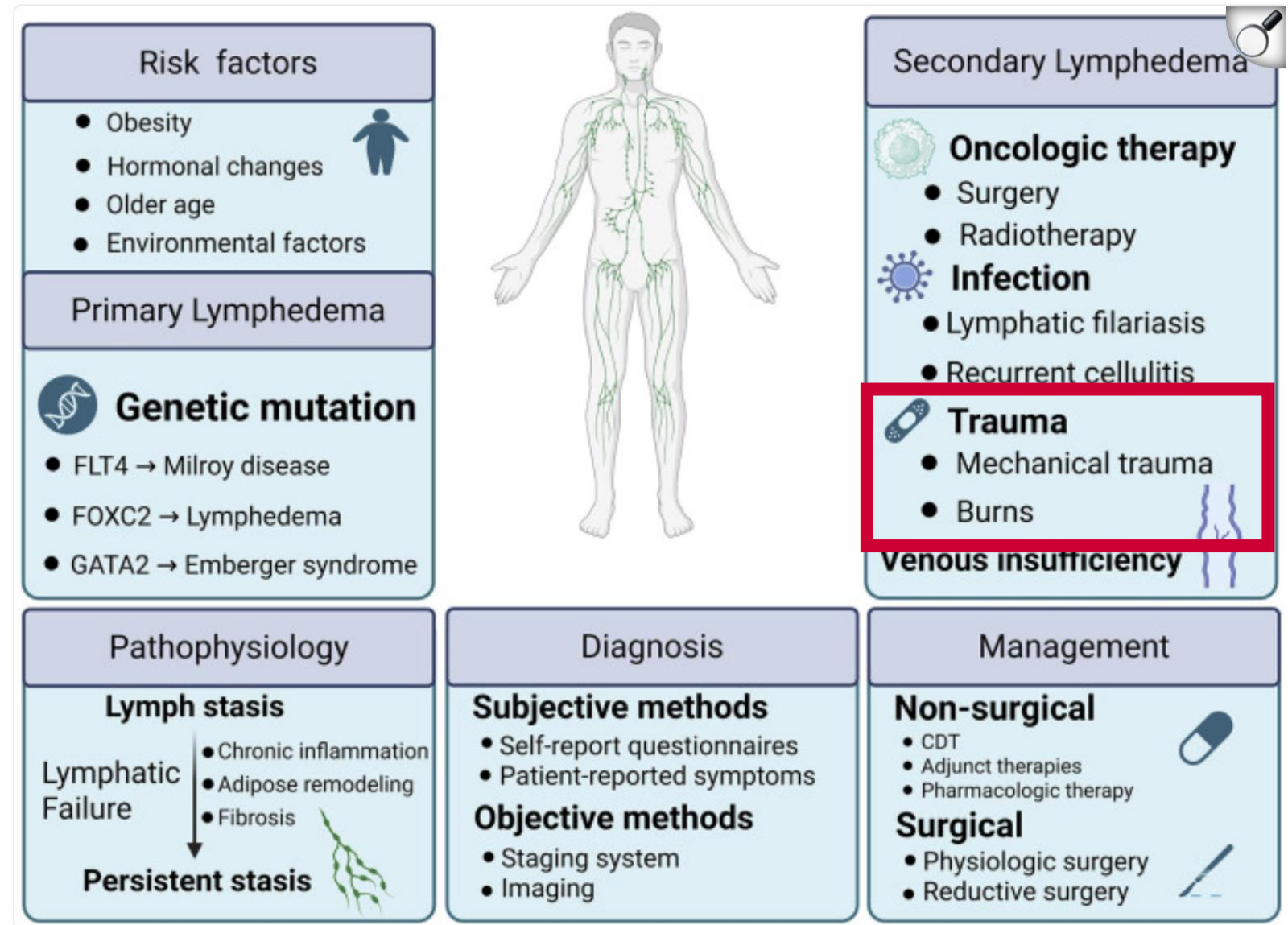
- Lymphedema is chronic accumulation of protein-rich fluid due to impaired lymphatic drainage
- Two types: primary (genetic) and secondary (acquired)
- ~ 250 million people affected around the world



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Trauma Related

- Lymphedema is the chronic accumulation of protein-rich fluid due to impaired lymphatic drainage
- Two types: primary (genetic) and secondary (acquired)
- ~ 250 million people affected around the world
- **After trauma to extremity, 25-50% have chronic lymphedema**



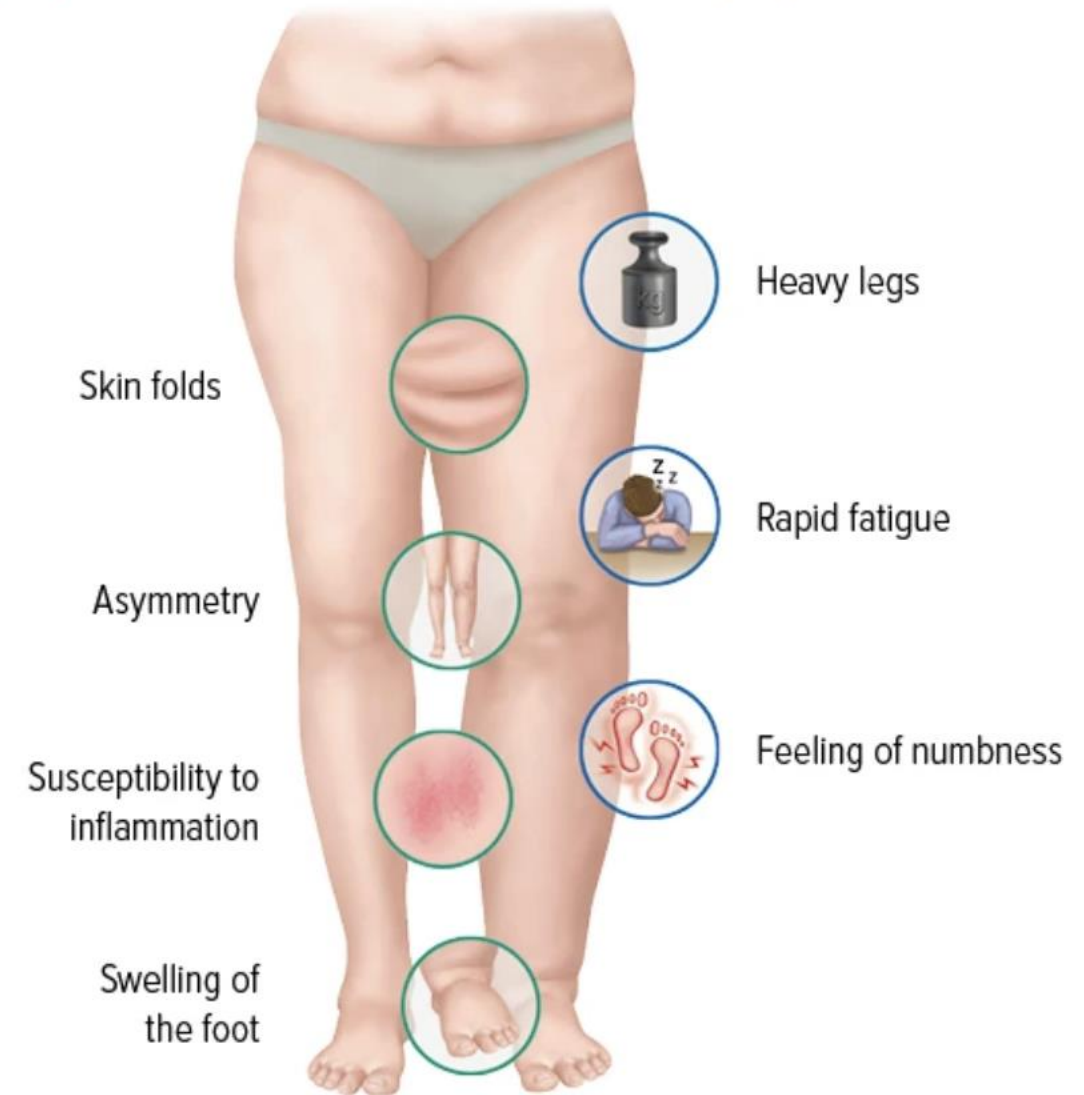
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Clinical Symptoms

- Feeling of heaviness/fullness
- Pitting edema
- Pain and tightness decreased ROM & mobility
- Recurrent cellulitis
- Worse when dependent
- Long term risk for angiosarcoma >10 years

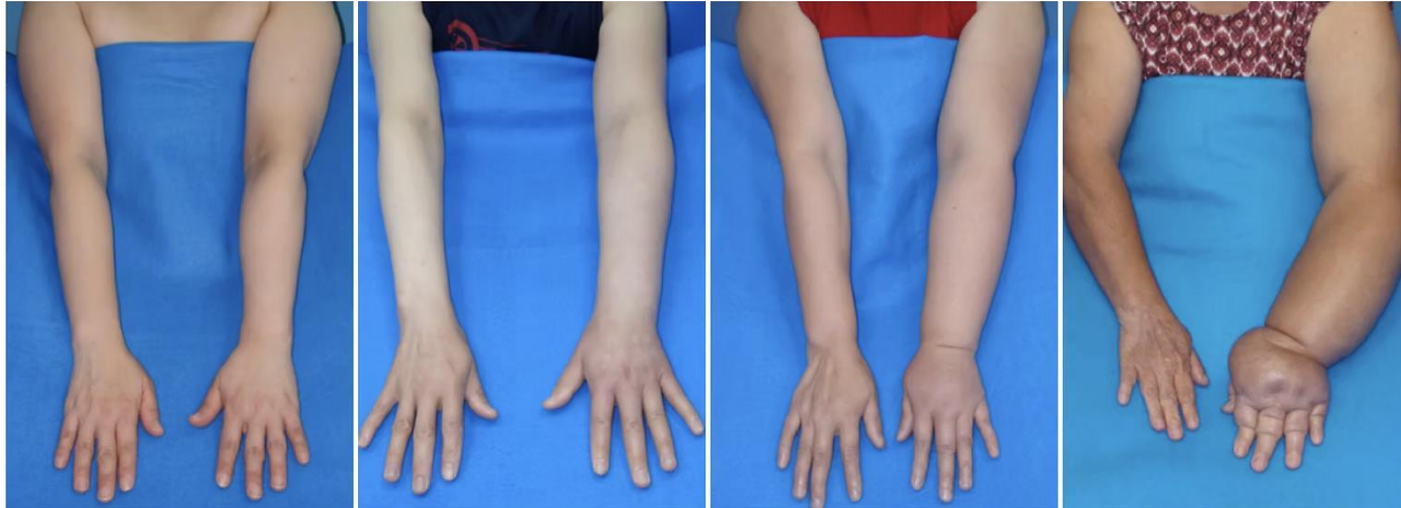
Externally symptoms
lymphoedema

Internally symptoms
lymphoedema



From Juzo.

Clinical Examples



Stage 1

Stage 2

Stage 3

Stage 4



Management of Lymphedema



Non-surgical treatments

Complete decongestive therapy

Manual lymph drainage

Compression therapy

Exercise

Skin care

Compression garments

Advanced pneumatic
compression therapy

Laser therapy

Surgical treatments

Reductive techniques

Direct excision

Liposuction

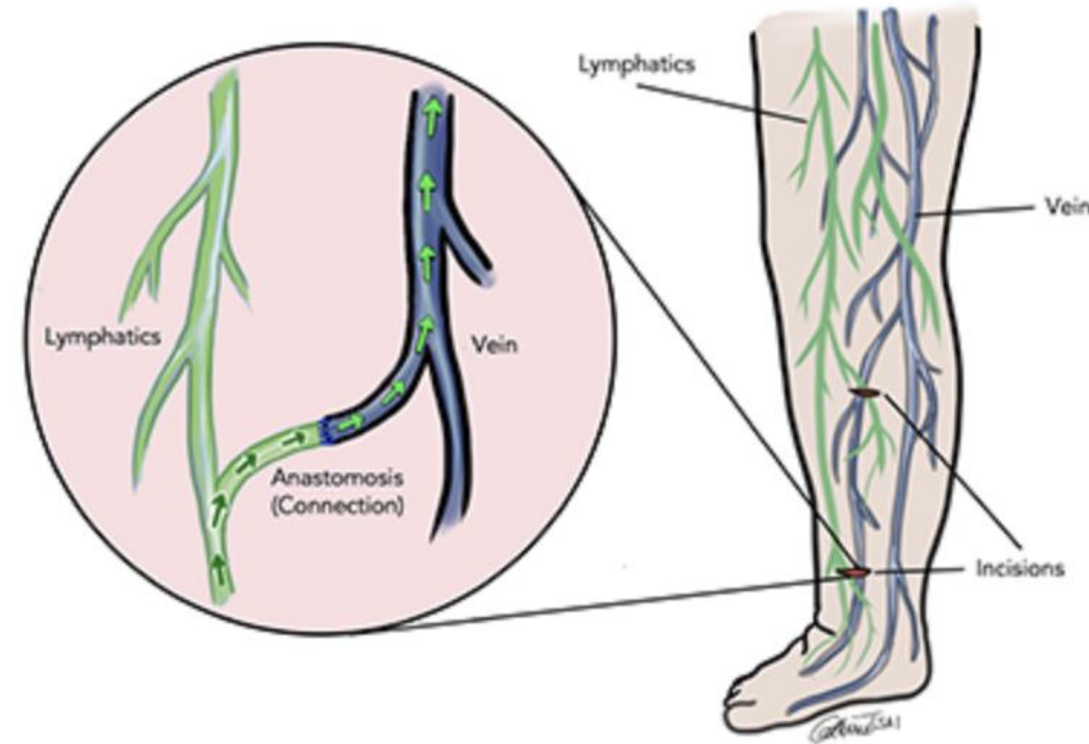
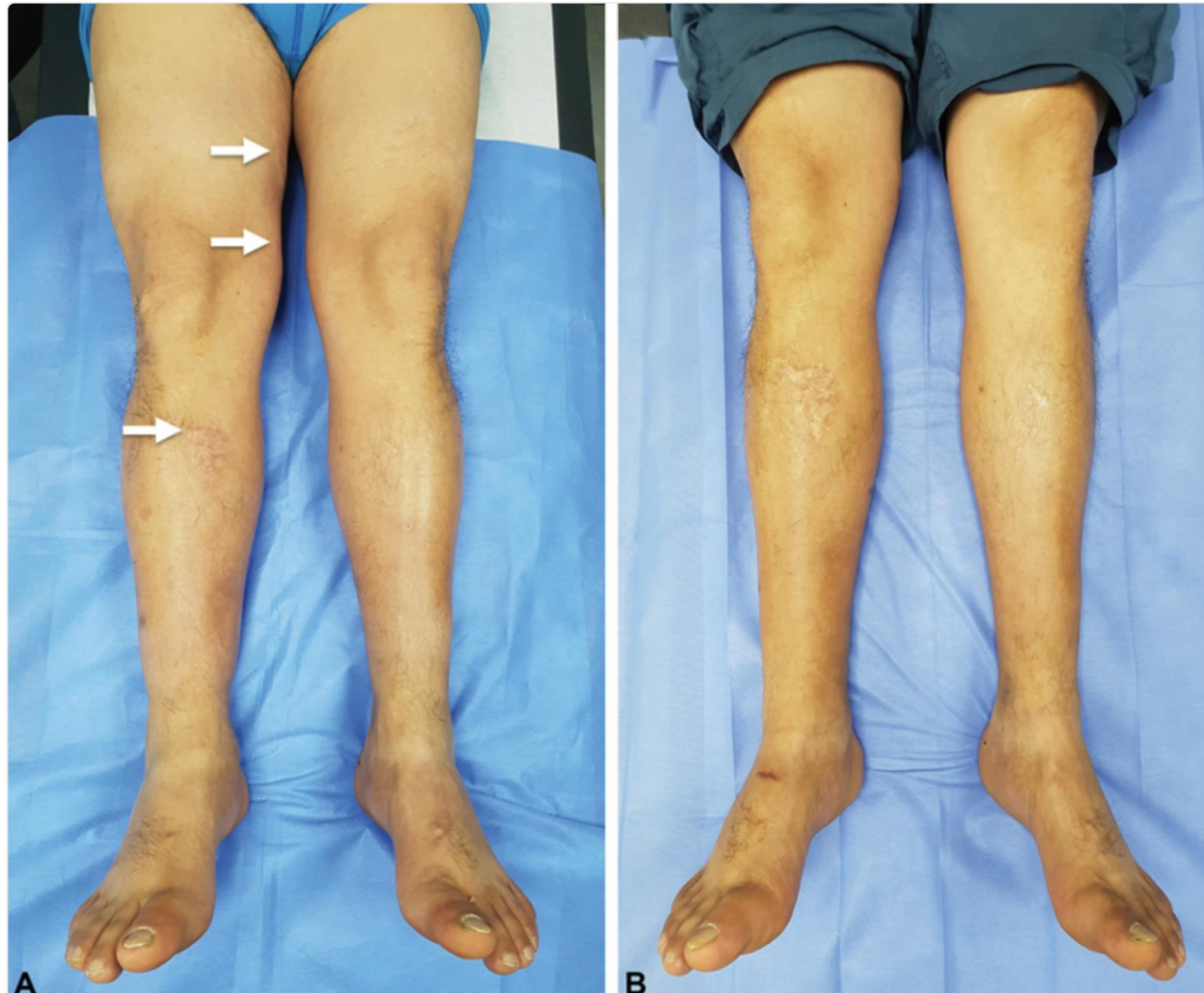
Physiological techniques

Lymphatico-lymphatic by-pass

Lymphatico-venous by-pass

Lymph node transfer

Microsurgical Treatment of Lymphedema



A 58-year-old male patient with 6 years of right lower limb posttraumatic lymphedema after a tiger attack treated with three lymphovenous anastomosis.

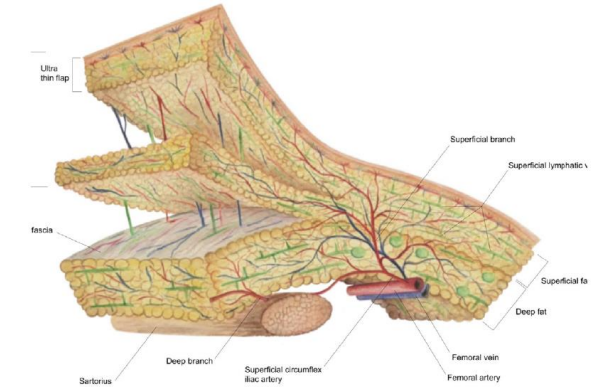
(A) Preoperative excess volume (PEV) was 13.35%. (B) Thirteen months after surgery, PEV was 7.37% and the reduction of excess volume was 44.7%

Arch Plast Surg 2023 Aug 2;50(4):422-431.

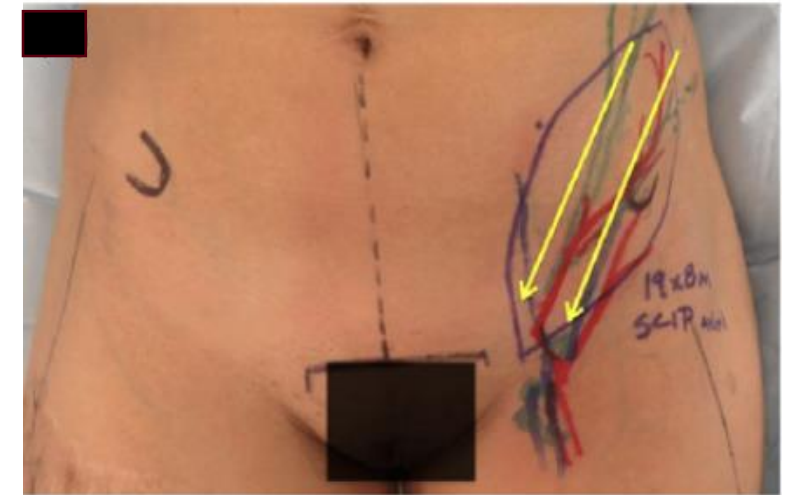
Microsurgical Treatment of Lymphedema



Case 3. (A) Preoperative picture. (B) Twenty-month postoperative picture. A 42-year-old male patient with 10 months of right upper limb posttraumatic lymphedema and chronic ulcer after a degloving injury treated with local flaps. Scarred tissue was excised and reconstruction was performed with TEAR approach using SCIP-IX. (A) Preoperative excess volume (PEV) was 19.25%; (B) Twenty months after surgery, PEV was 5.55% and the reduction of excess volume was 71.17% (patient 2 in [Table 2](#)). SCIP-IX, superficial circumflex iliac artery perforator lymphatic vessels; TEAR, total extremity anatomy reconstruction.

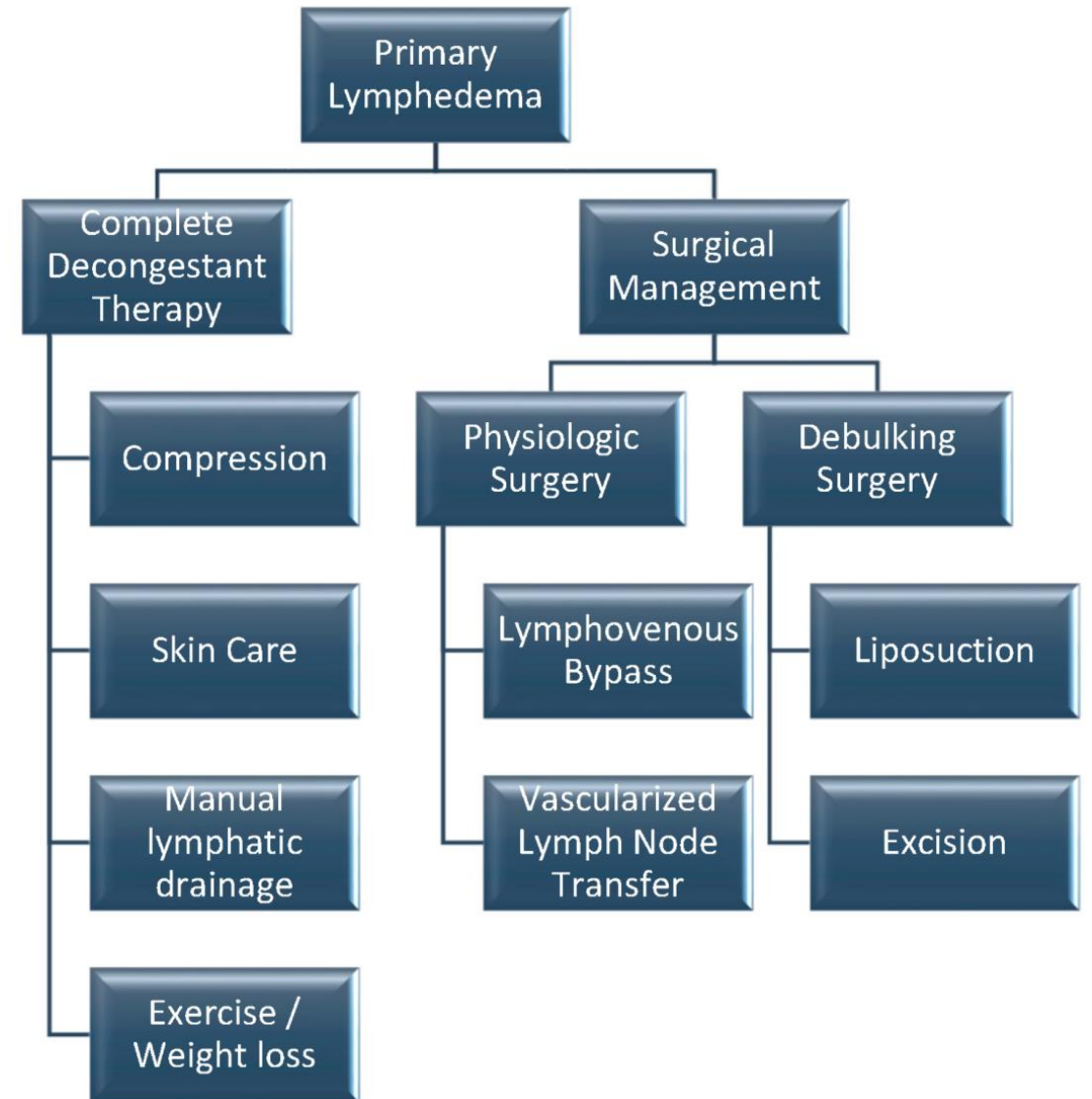


Post-traumatic lymphedema treatment with superficial circumflex iliac artery perforator lymphatic free flap:

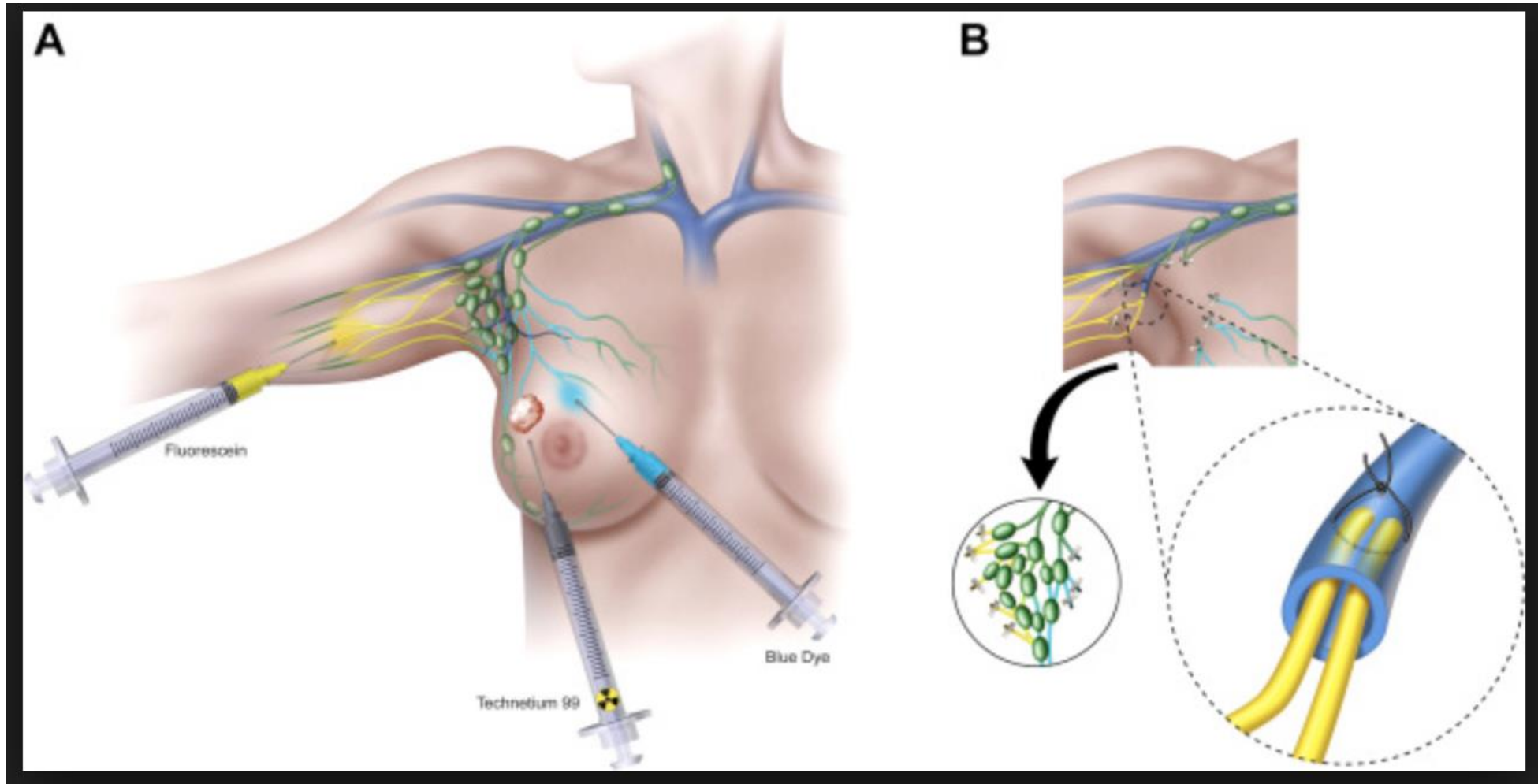


Management of Lymphedema

- Benefits of treatments
 - Symptomatic relief
 - Slow disease progression
 - Improve symptoms
 - Reduce limb size
 - Improve QoL
- But... there is **NO CURE**

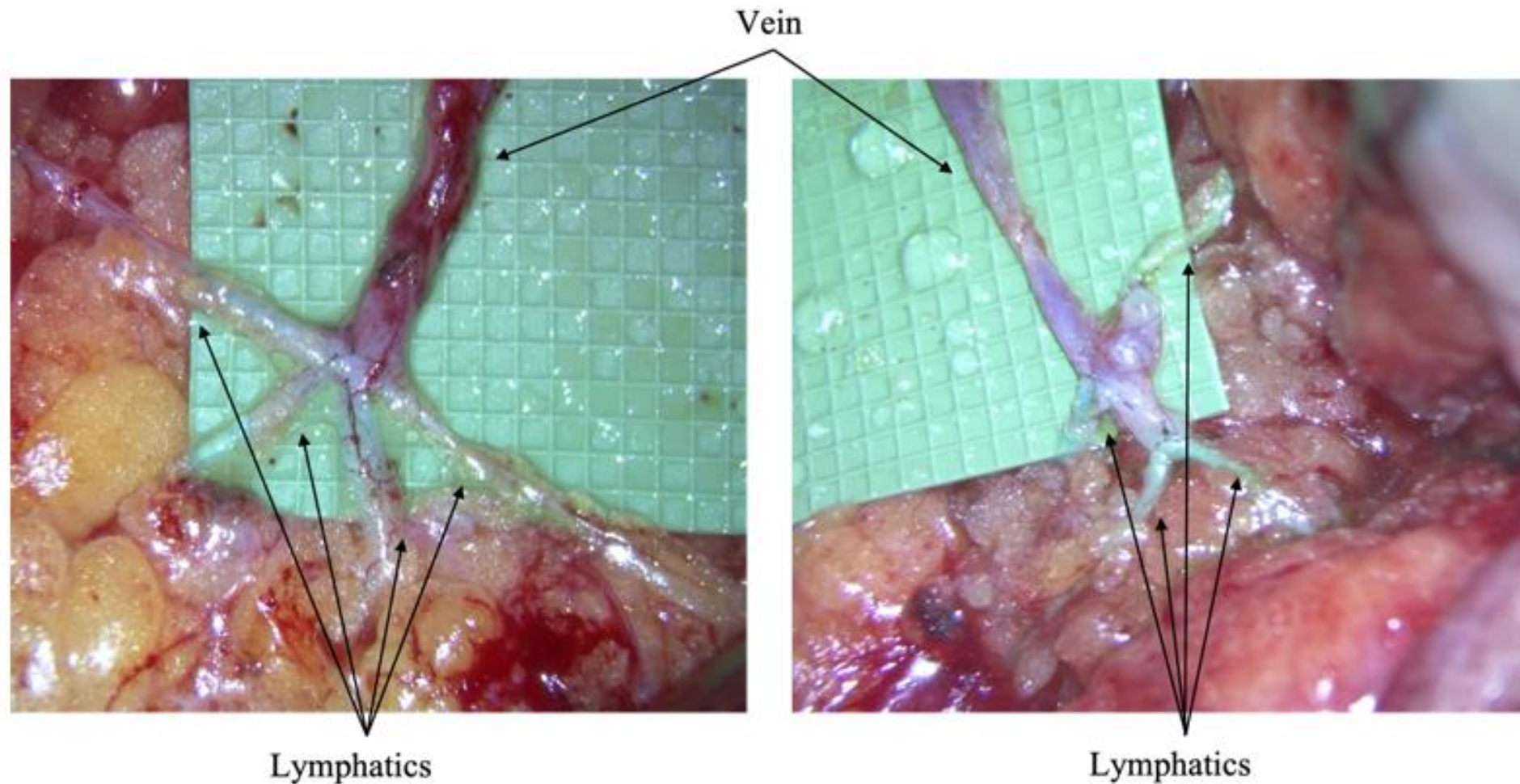


Surgical Procedure to Prevent Lymphedema



- Lymphatic Microsurgical Preventing Healing Approach (LYMPHA)

Immediate Lymphatic-Venous Reconstruction (ILR/LYMPA)



Mitigate Lymphedema by Stimulating Lymphatic Regeneration?

- Since lymphedema results from surgical lymphatic disruption & obstructed flow of lymph fluid...
 - Microsurgical expertise is limited...
- Hypothesis: Can we prevent lymphedema by stimulating lymphangiogenesis & lymphatic regeneration with adjuvant pharmacologic therapy?

Ideal Characteristics for Pro-Lymphatic Drug

- Nontoxic
- Bio-compatible / bio-degradable
- No side (off target) effects
- Efficient distribution to site / tissue bed of action
- Consistent action
- Easily and predictably metabolized or eliminated
- Inexpensive to make

9-*cis* Retinoic Acid Prevents Lymphedema

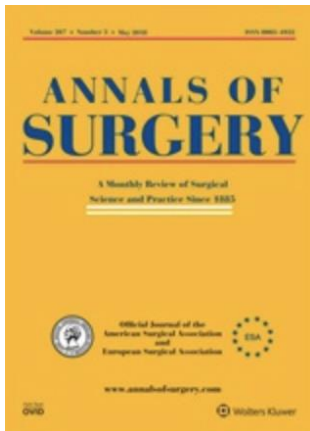


2012

9-Cis Retinoic Acid Promotes Lymphangiogenesis and Enhances Lymphatic Vessel Regeneration : Therapeutic Implications of 9-Cis Retinoic Acid for Secondary Lymphedema

Inho Choi, Sunju Lee, Hee Kyoung Chung, Yong Suk Lee, Kyu Eui Kim, Dongwon Choi, Eun Kyung Park, Dongyun Yang, Tatiana Ecoiffier, John Monahan, Wen Chen, Berenice Aguilar, Ha Neul Lee, Jaehyuk Yoo, Chester J. Koh, Lu Chen, Alex K. Wong and Young-Kwon Hong

ORIGINAL ARTICLE

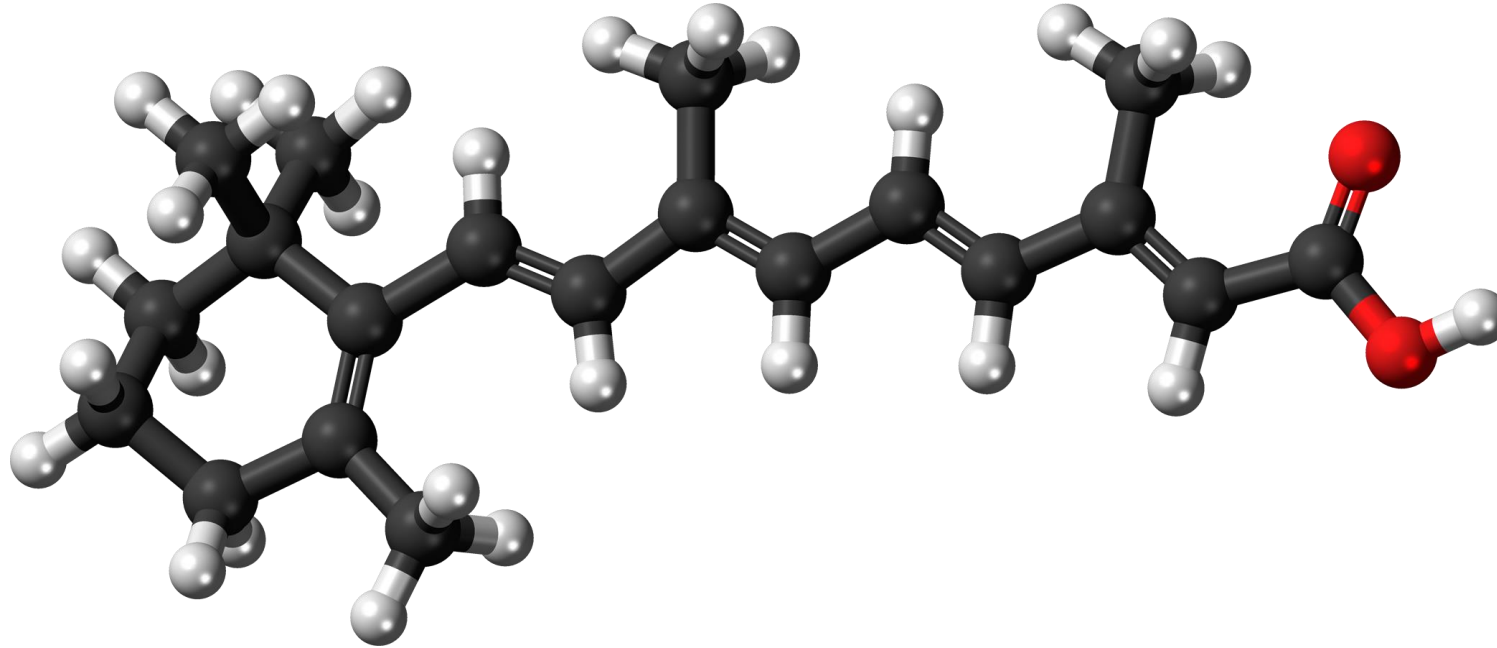


2016

Prevention of Postsurgical Lymphedema by 9-*cis* Retinoic Acid

Athanasios Bramos, MD,* David Perrault, BS,* Sara Yang, BA,† Eunson Jung, BA,† Young Kwon Hong, PhD,†^a and Alex K. Wong, MD, FACS*^a

9-cis Retinoic Acid (alitretinoin)

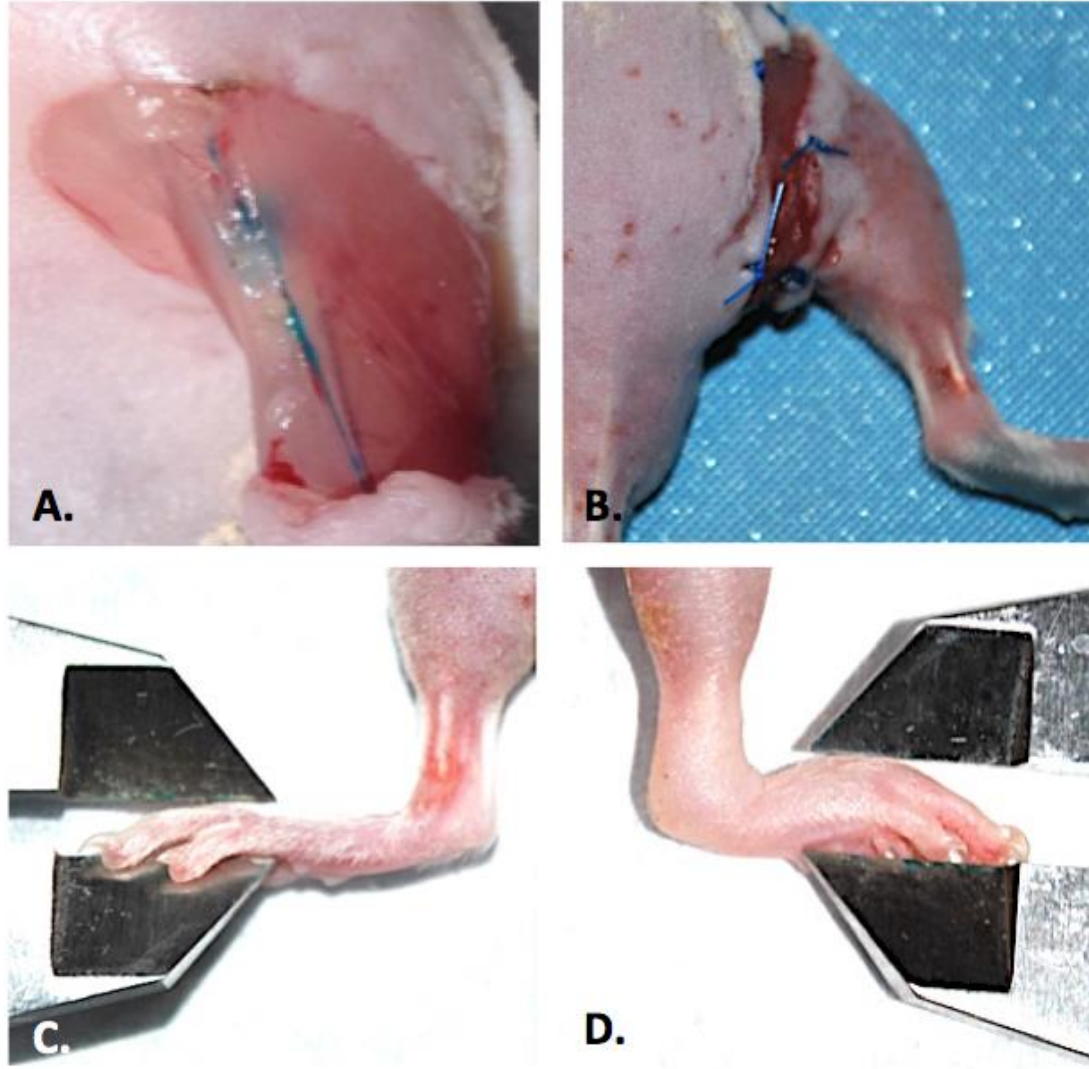


Properties	
Chemical formula	$C_{20}H_{28}O_2$
Molar mass	300.43512 g/mol
Appearance	yellow to light orange crystalline powder with characteristic floral odor ^[1]
Melting point	180 to 182 °C (356 to 360 °F; 453 to 455 K) crystals from ethanol ^[1]
Solubility in water	nearly insoluble
Solubility in fat	soluble

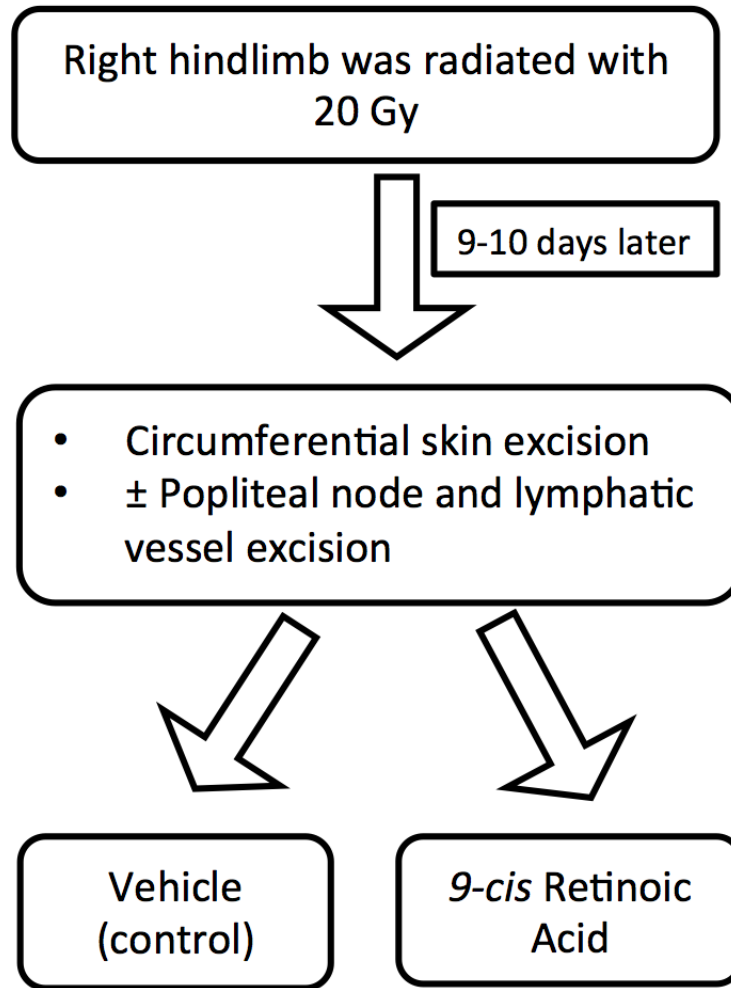
- Metabolite of vitamin A
- Required for development of chordate animals → Involved in axial pattern signaling
- **FDA approved (topical)** for:
 - Kaposi sarcoma skin lesions
 - Severe chronic hand eczema



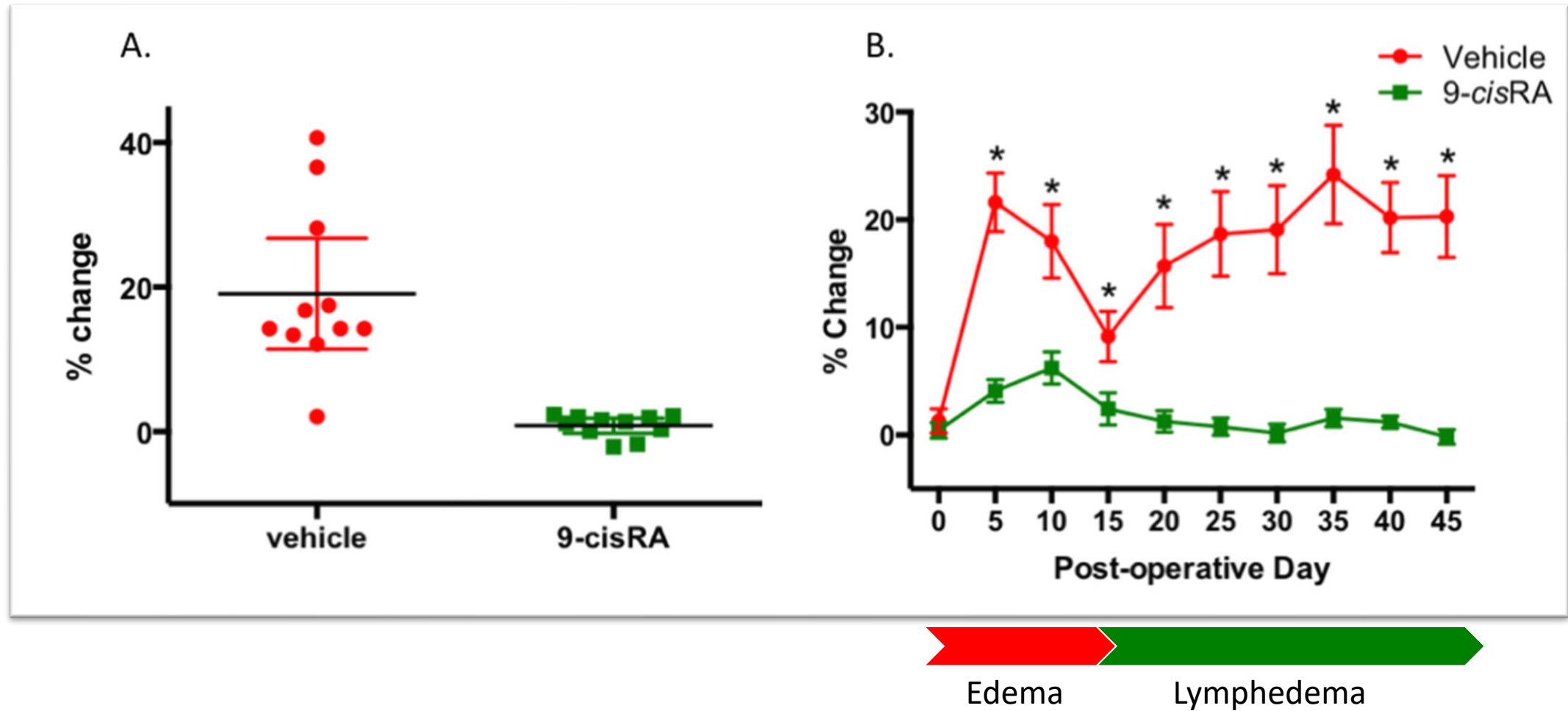
Hindlimb Model of Post-Surgical Lymphedema



9-cis RA Mitigates Lymphedema

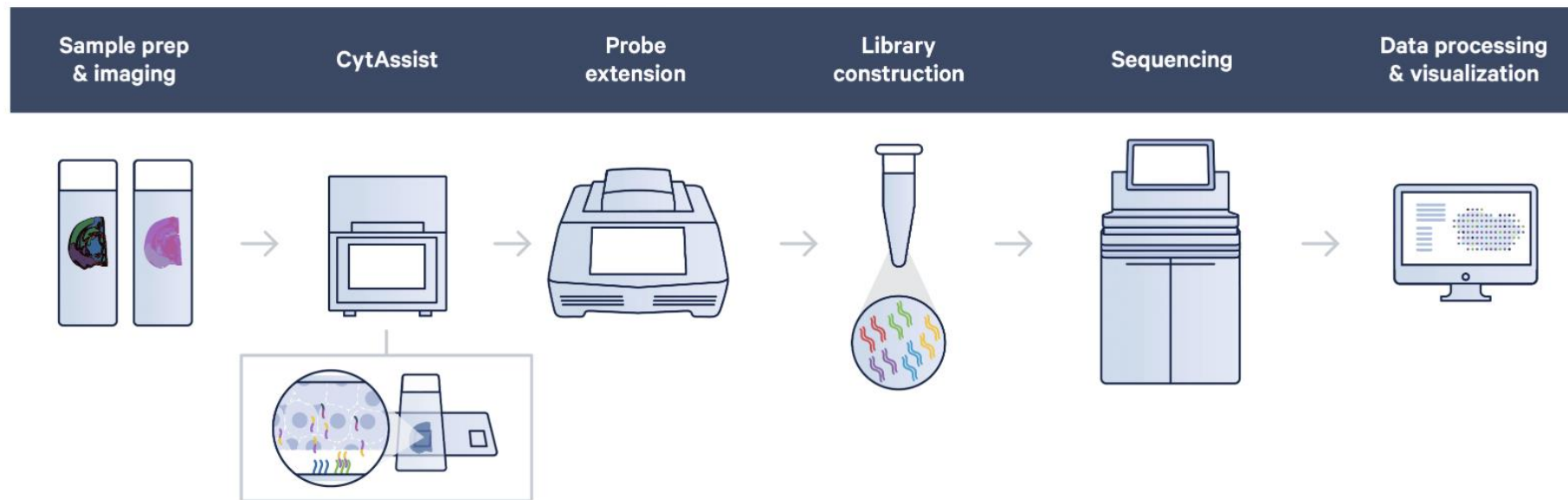


9-cis RA Mitigates Lymphedema



How Does 9-cia RA Affect Lymphatic Endothelial Cells *in vivo* ?

- Spatial Transcriptomics
 - Measure gene expression within tissue samples while preserving the spatial coordinates and structural context of the cells



Overview of the 10x Visium workflow, image provided by 10x Genomics.

Spatial Transcriptomics Identifies IGFBP5 in Treated Distal Tissue

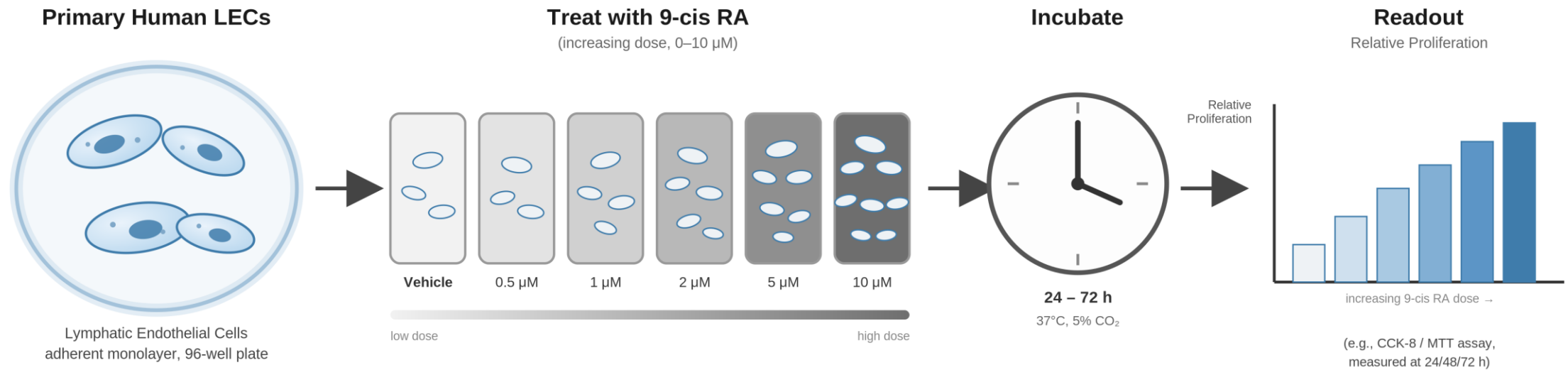
Top differentially expressed genes

- IGFBP5
- Eef2
- Col1a2
- Cst3

We focused on IGFBP5 as a candidate mediator of 9-cis RA-induced lymphangiogenesis.



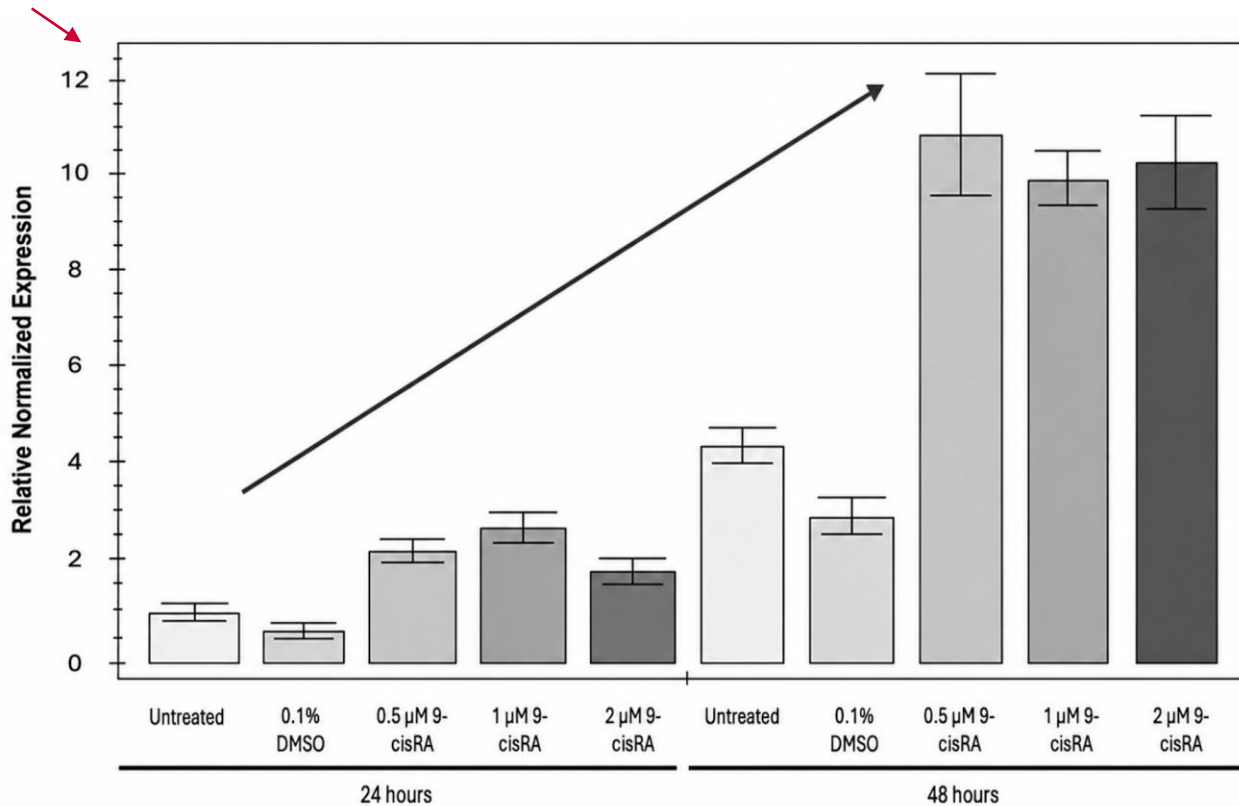
Assessment of IGFBP5 Expression by in LECs and other Cell Types *in vitro*



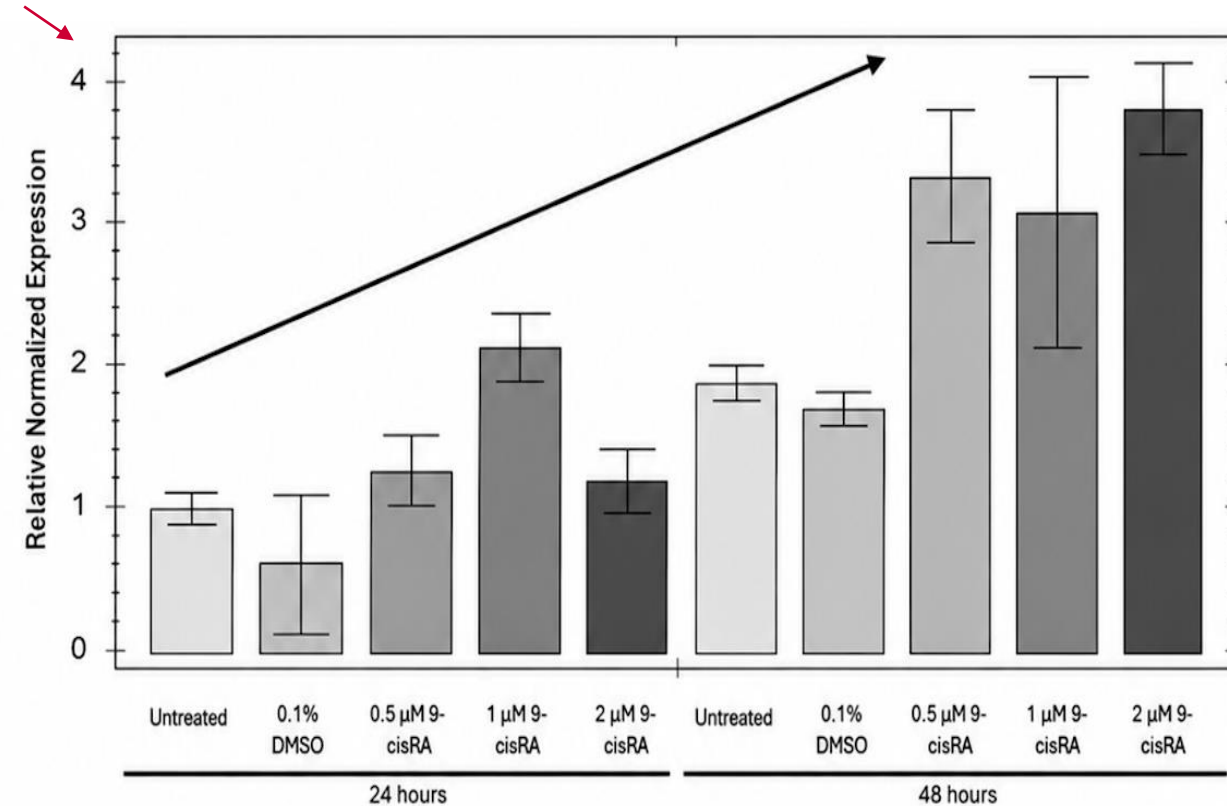
Experimental workflow: dose-response effect of 9-cis retinoic acid on primary human lymphatic endothelial cell proliferation

9-cisRA Preferentially Induces IGFBP5 in LECs

LECs

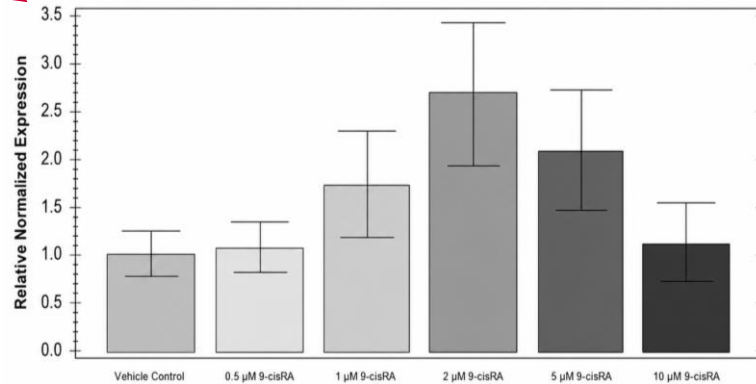


HUVECs

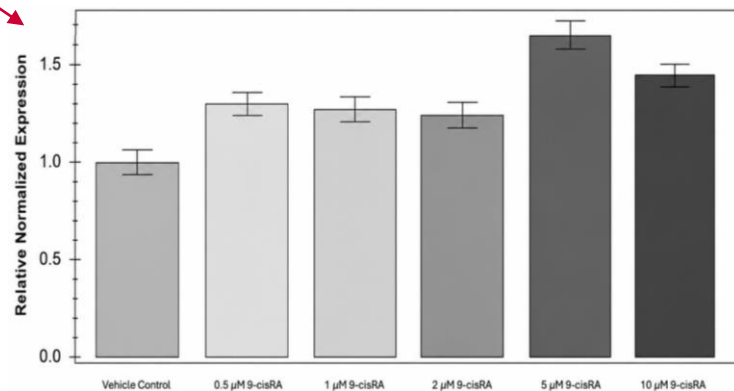


9-cisRA Does Not Significantly Affect IGFBP5 in Other Cell Types

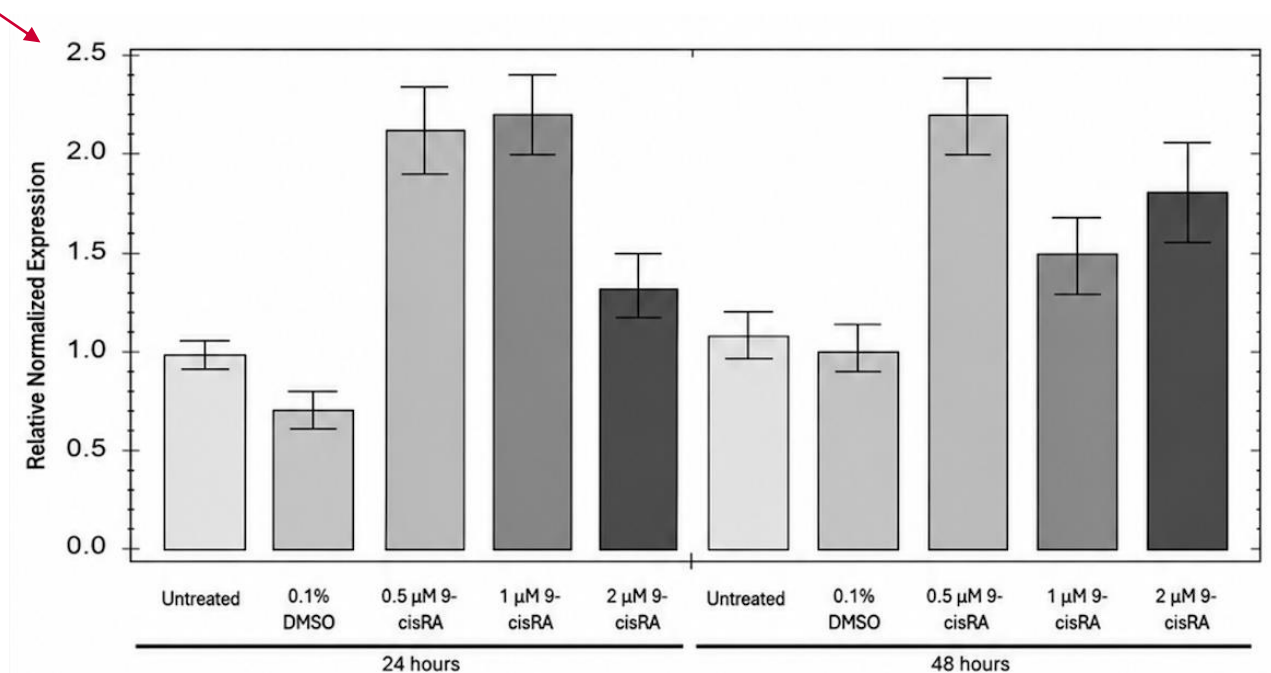
Lymphocytes



Adipocytes



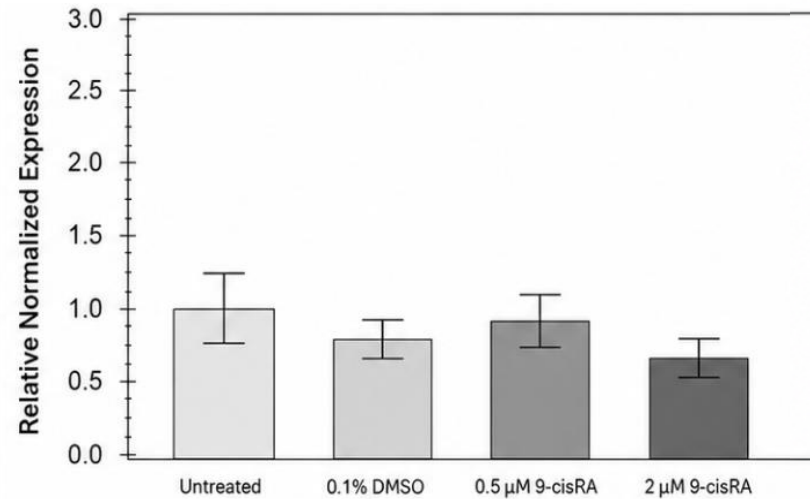
Fibroblasts



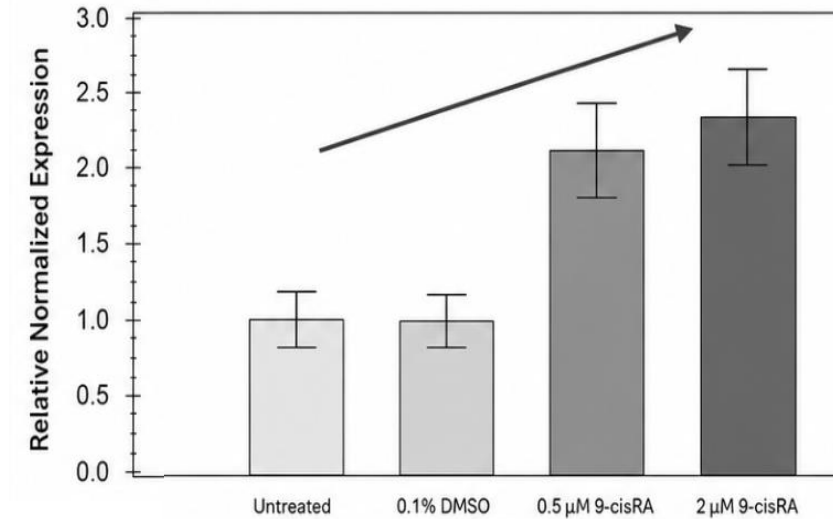
9-cisRA Selectively Activates IGF2 in LECs

LECs

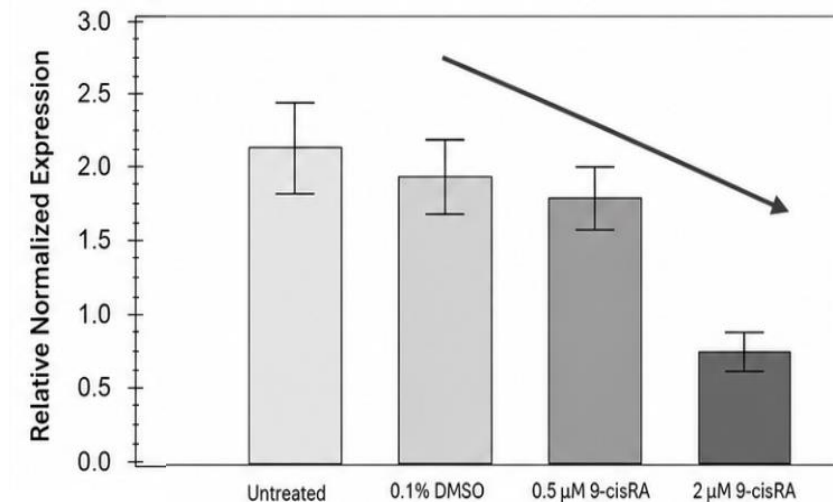
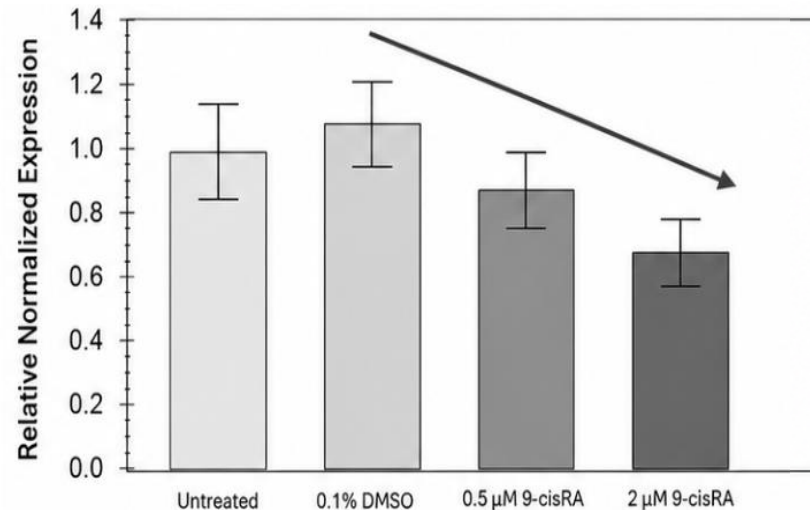
IGF1



IGF2

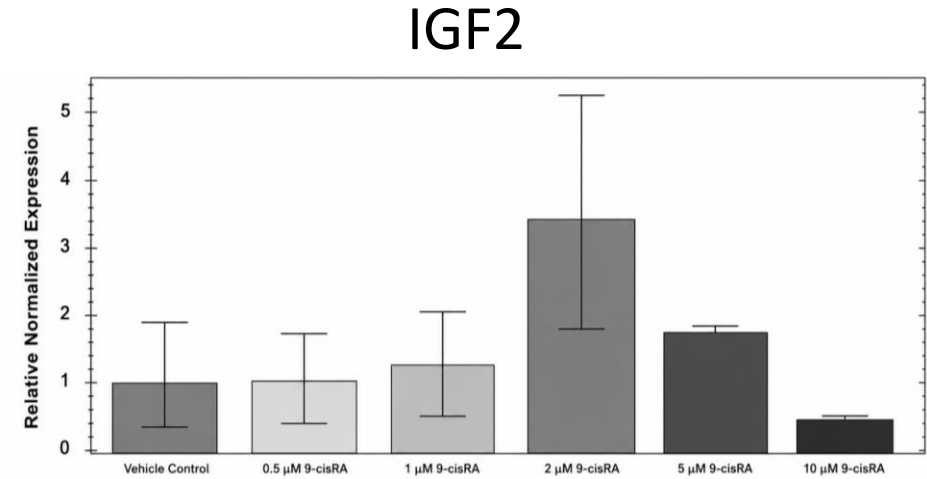
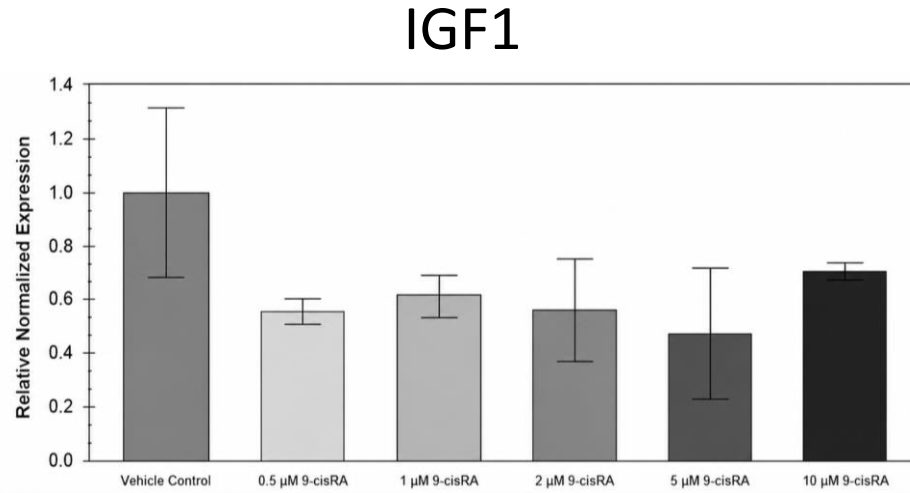


HUVECs

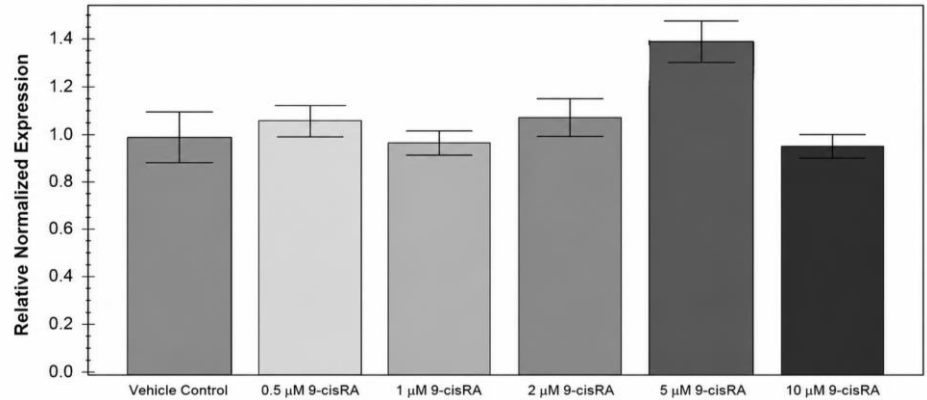
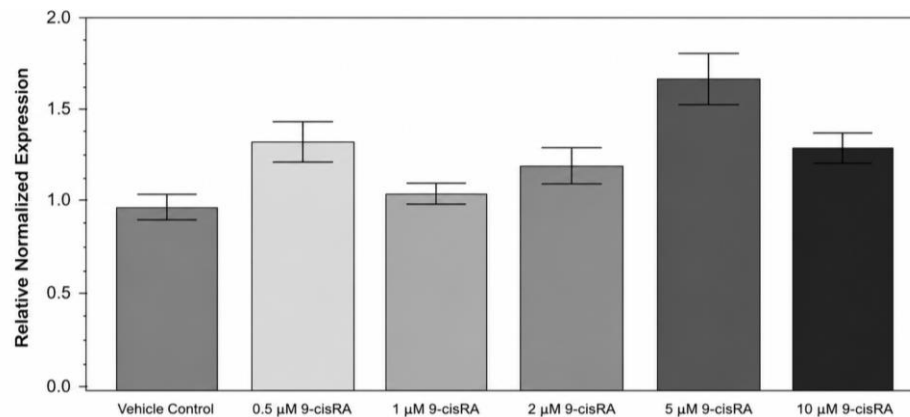


9-cisRA Does Not Significantly Alter IGF1/IGF2 in Other Cell Types

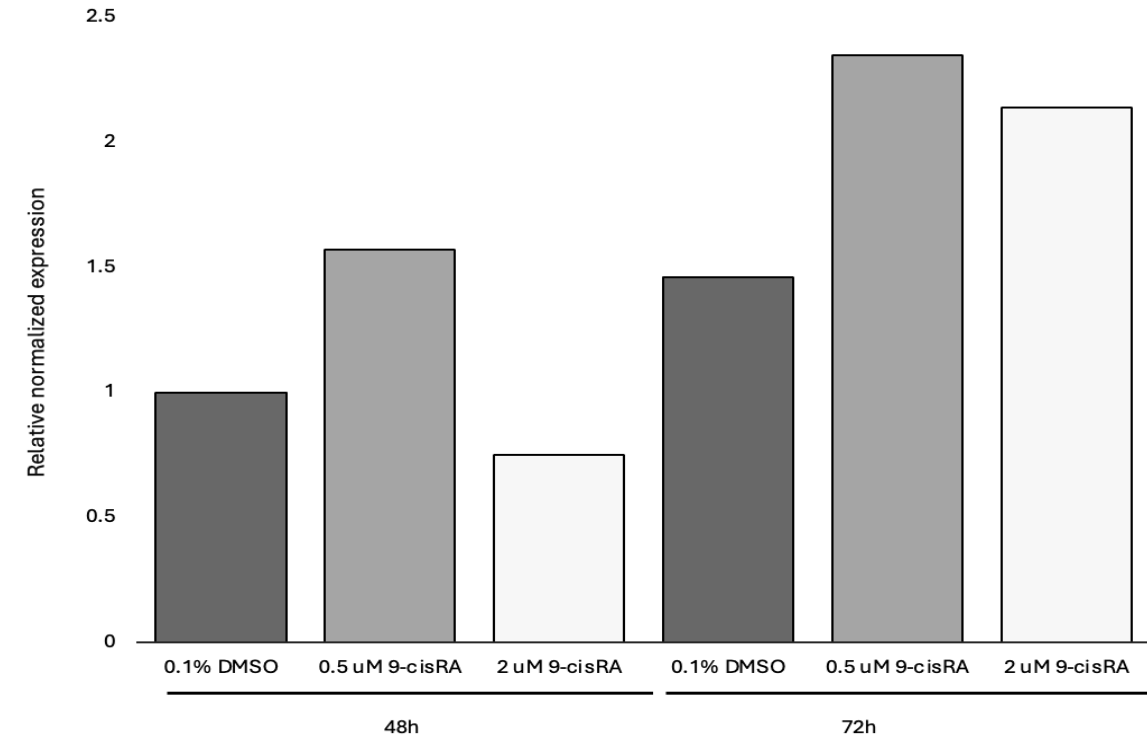
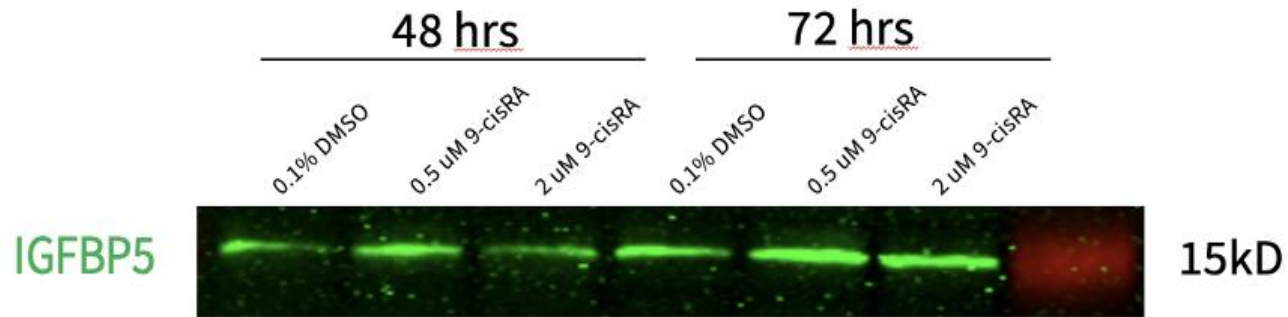
Lymphocytes



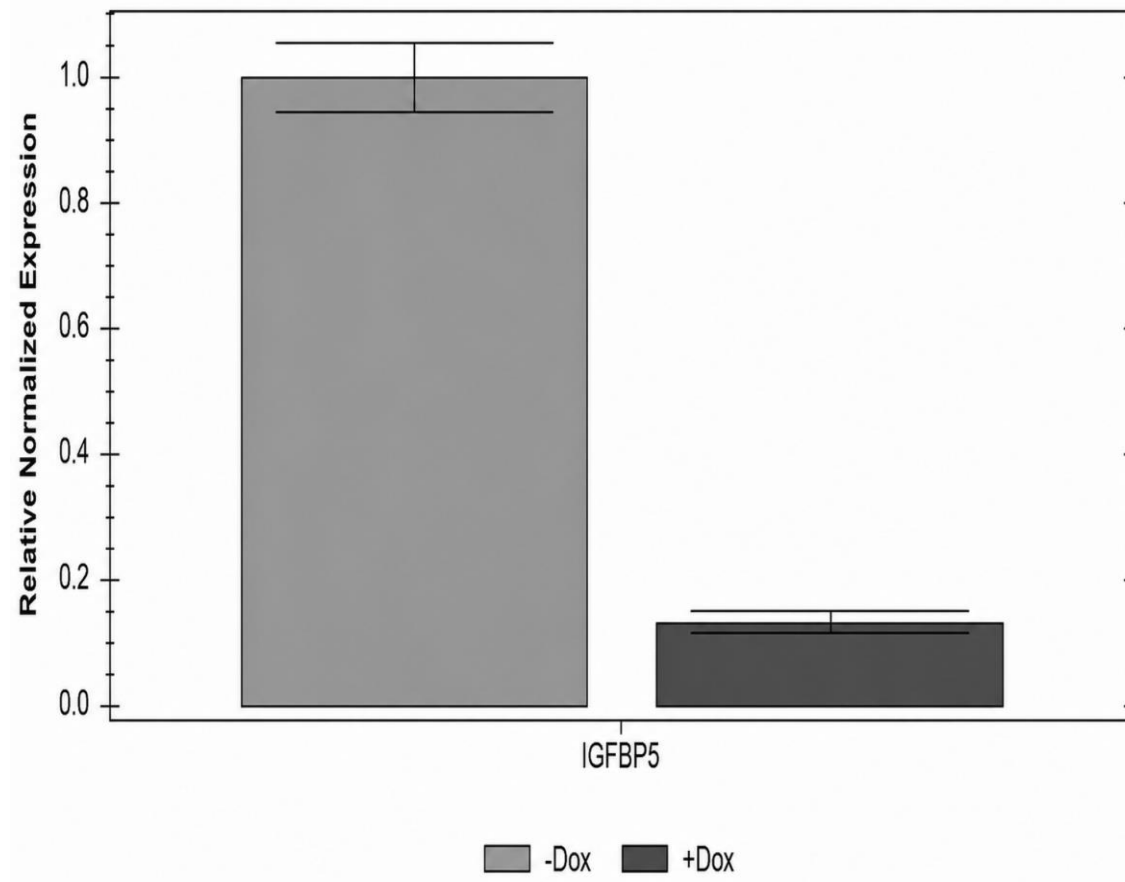
Adipocytes



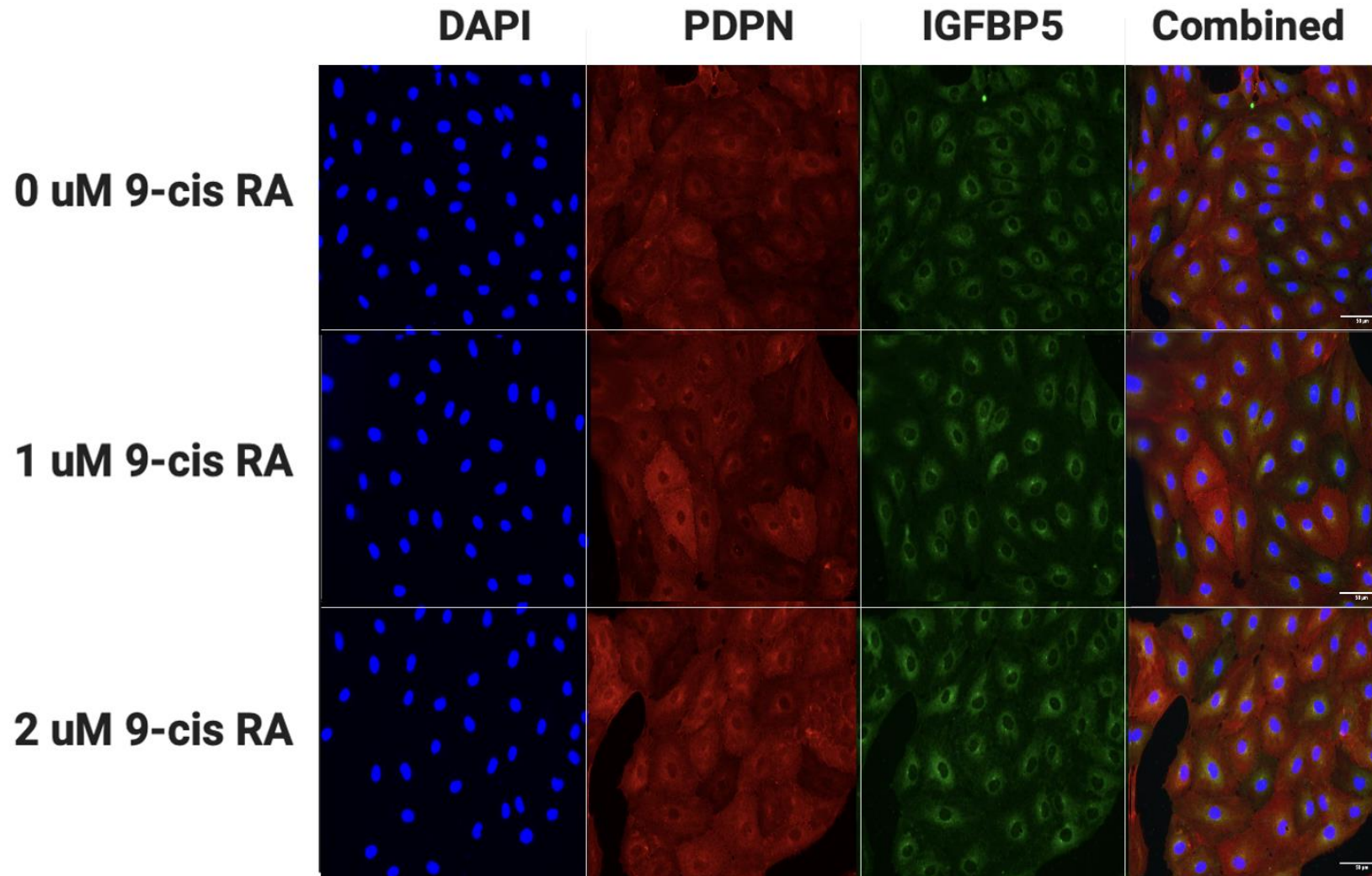
9-cisRA Increases IGFBP5 Protein in LECs



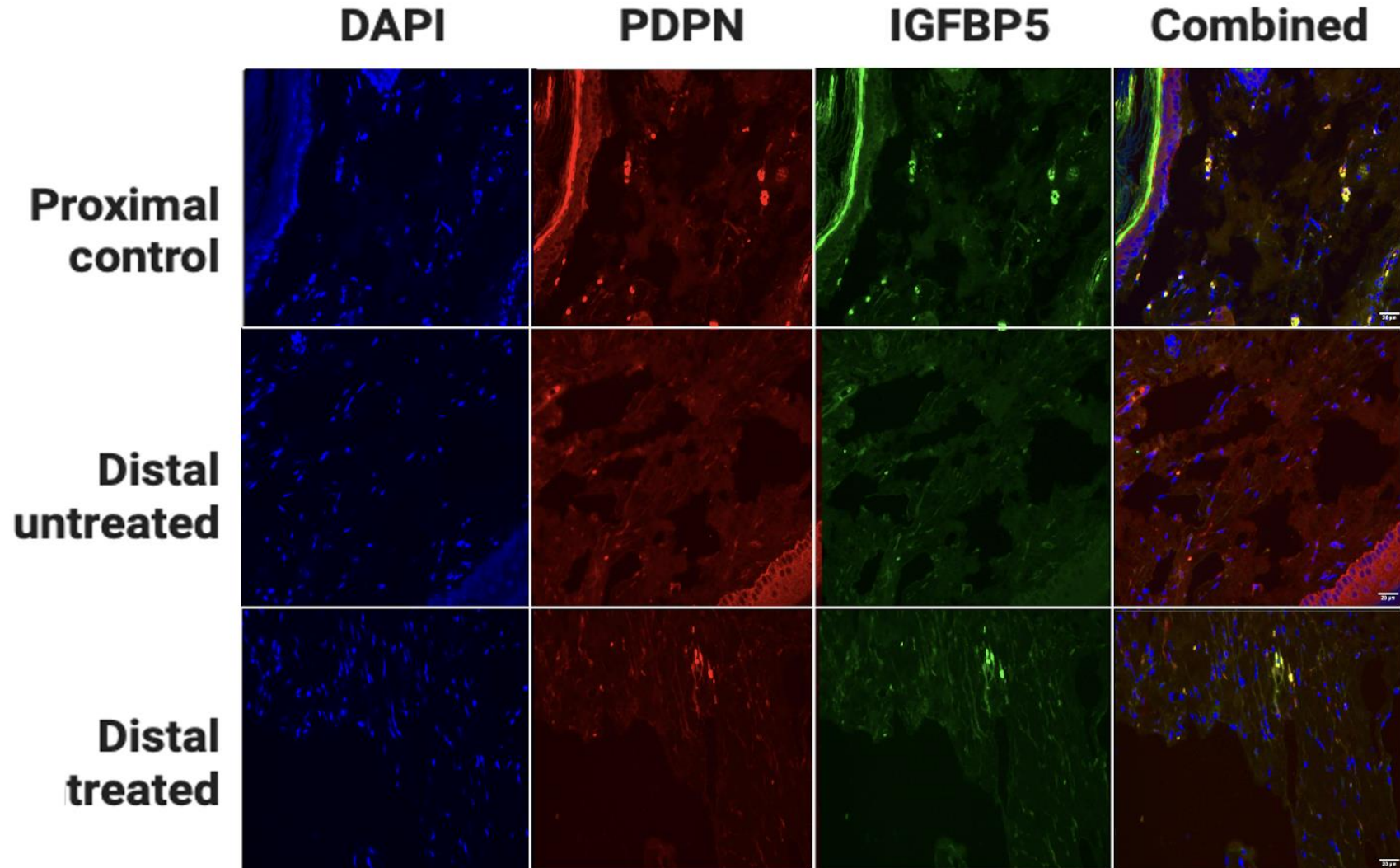
IGFBP5 Knockdown Impairs LEC Proliferation



IGFBP5 Localization in LECs *In Vitro*



IGFBP5 Colocalizes with Lymphatic Endothelium *In Vivo*

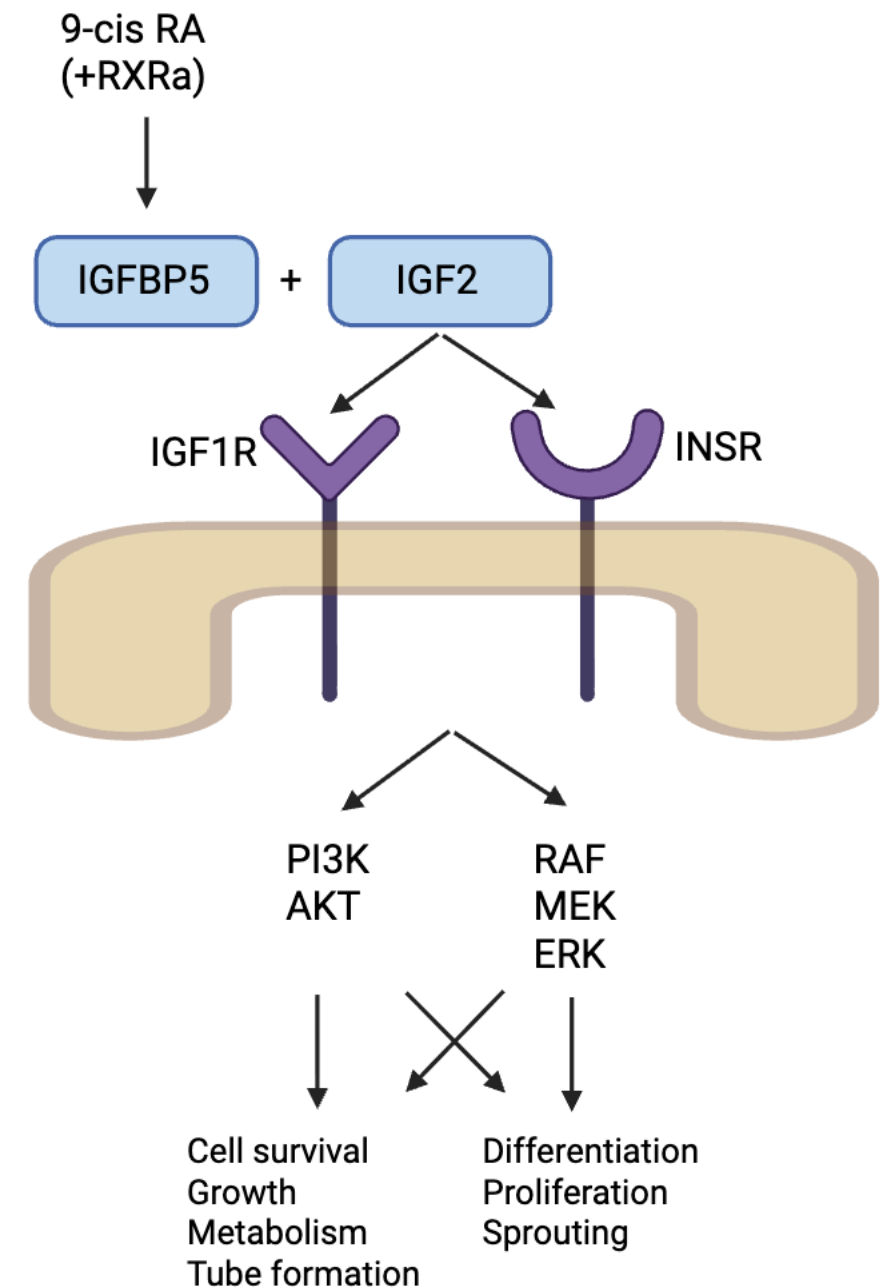


Understanding the Mechanism

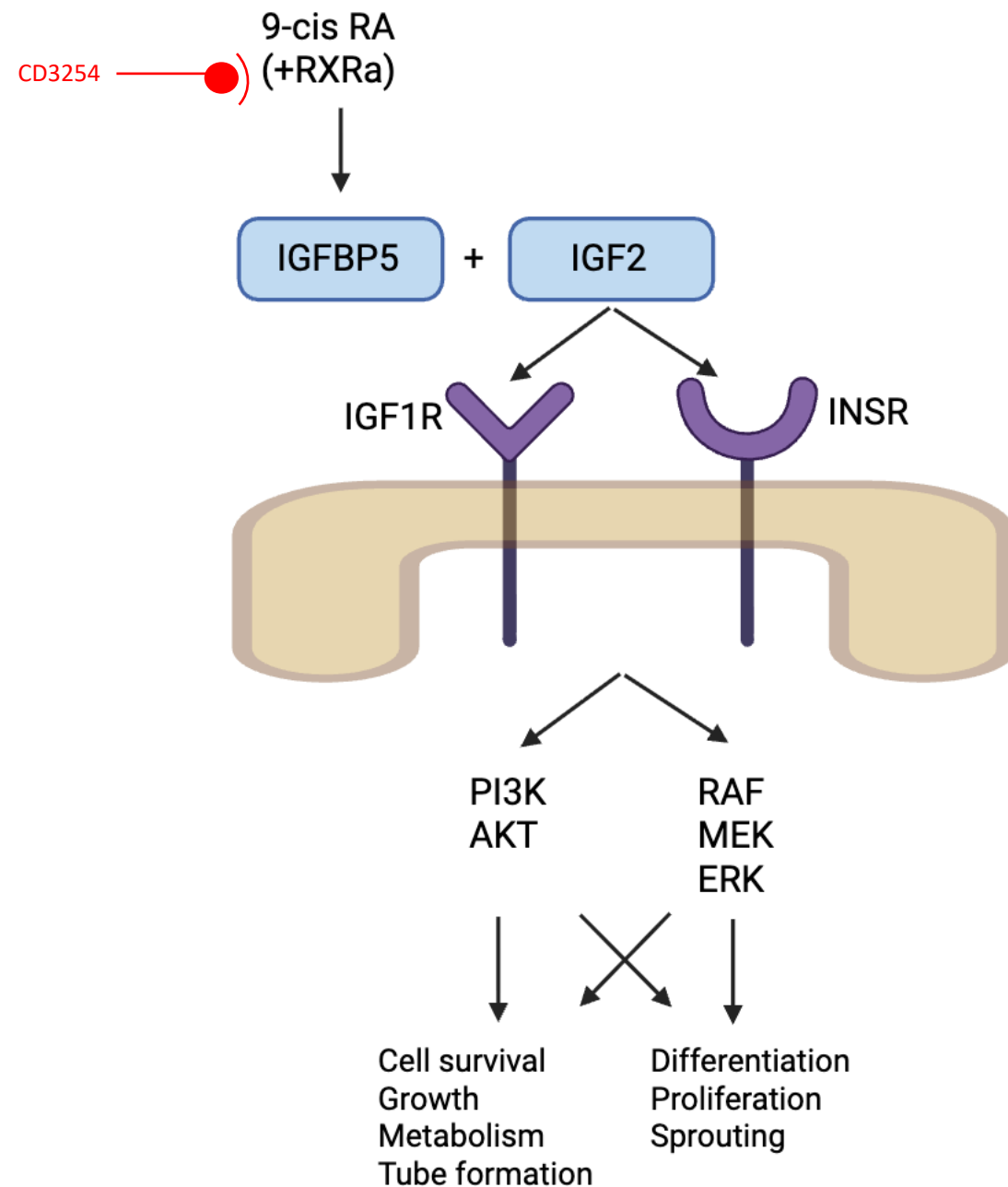
Proposed Mechanism of 9-cisRA-Induced Lymphangiogenesis

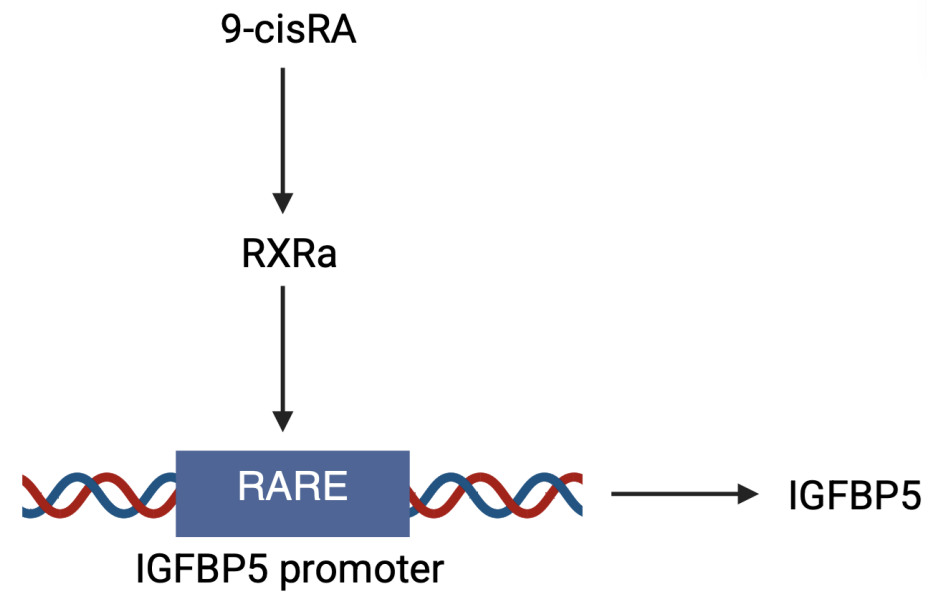
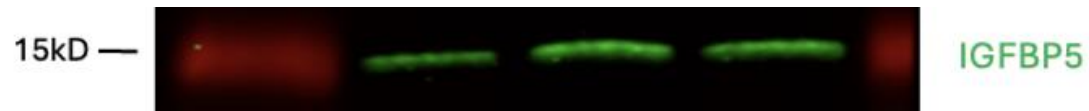
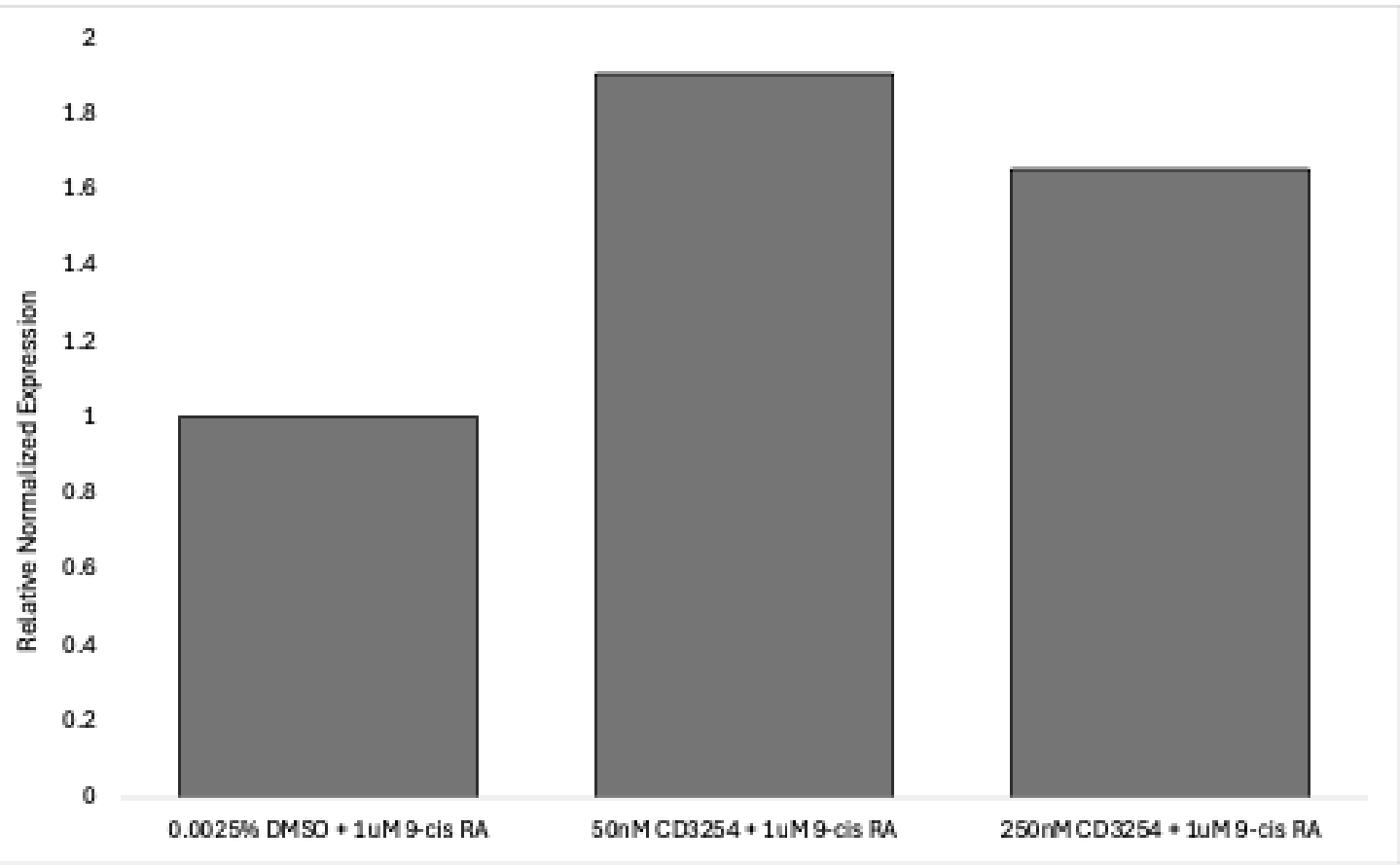
Two mechanistic questions:

- 1) Upstream: How does 9-cisRA induce IGFBP5?
- 2) Downstream: How does IGFBP5 affect LEC signaling?

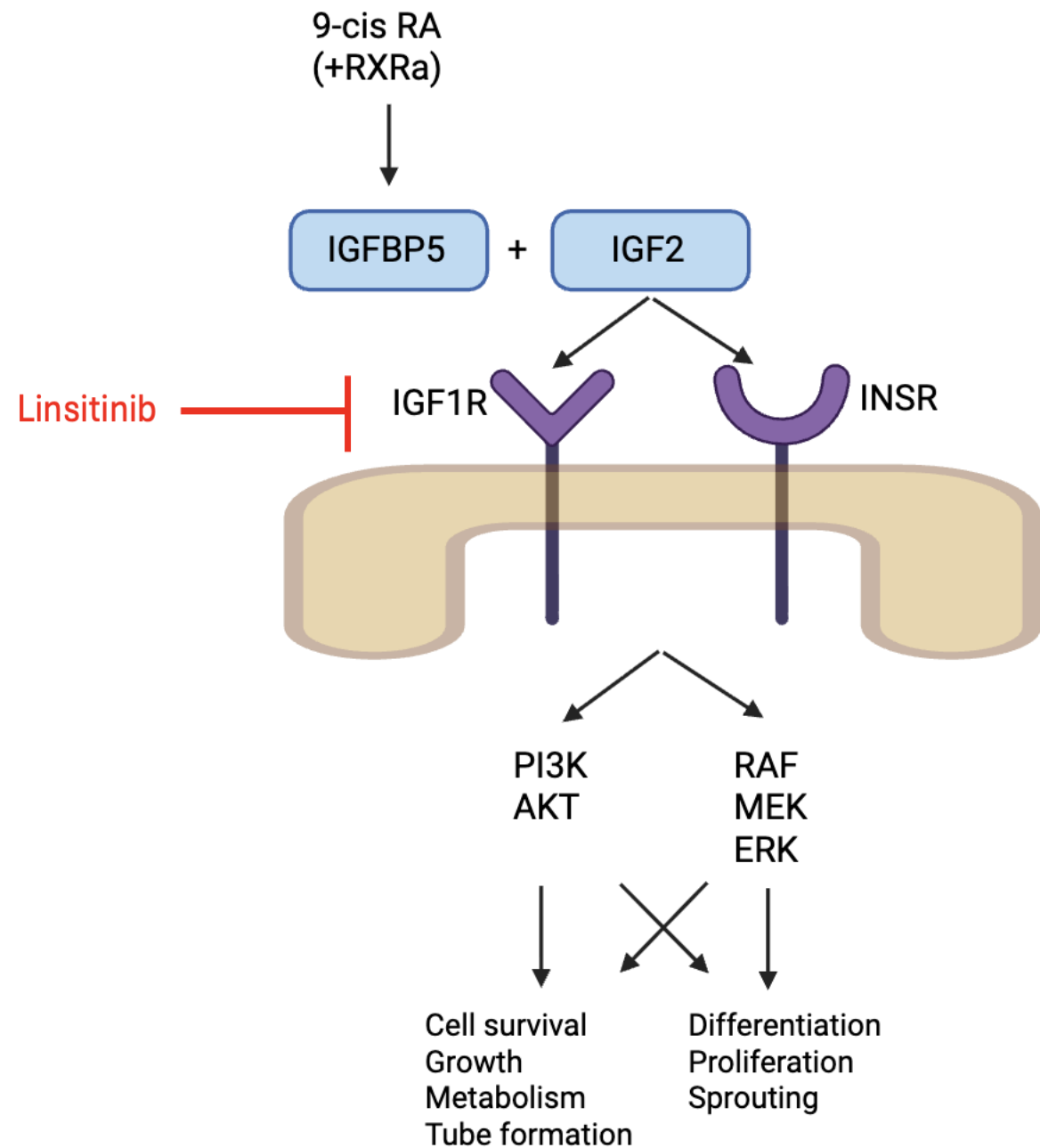


Testing RXR-alpha as an Upstream Regulator of IGFBP5

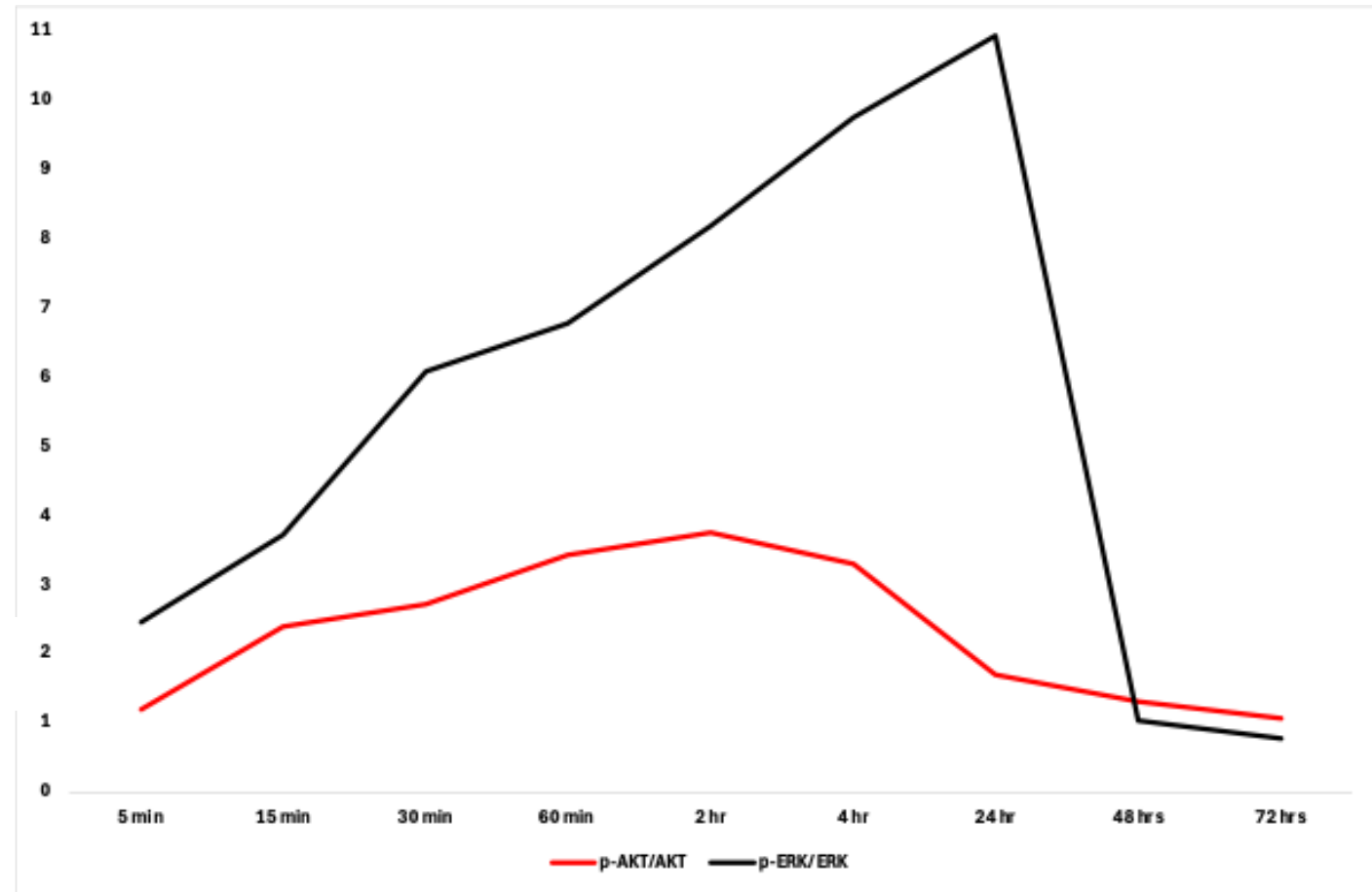
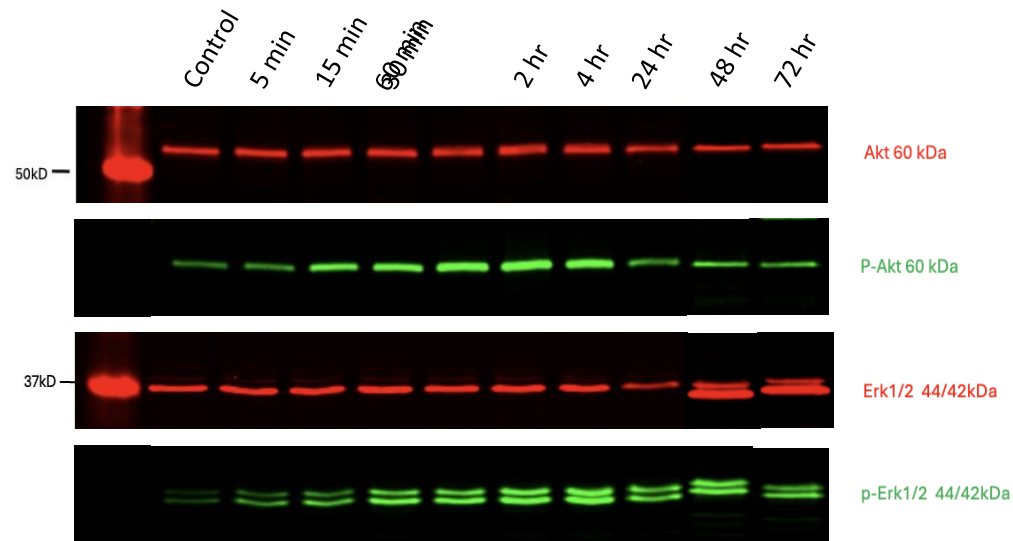




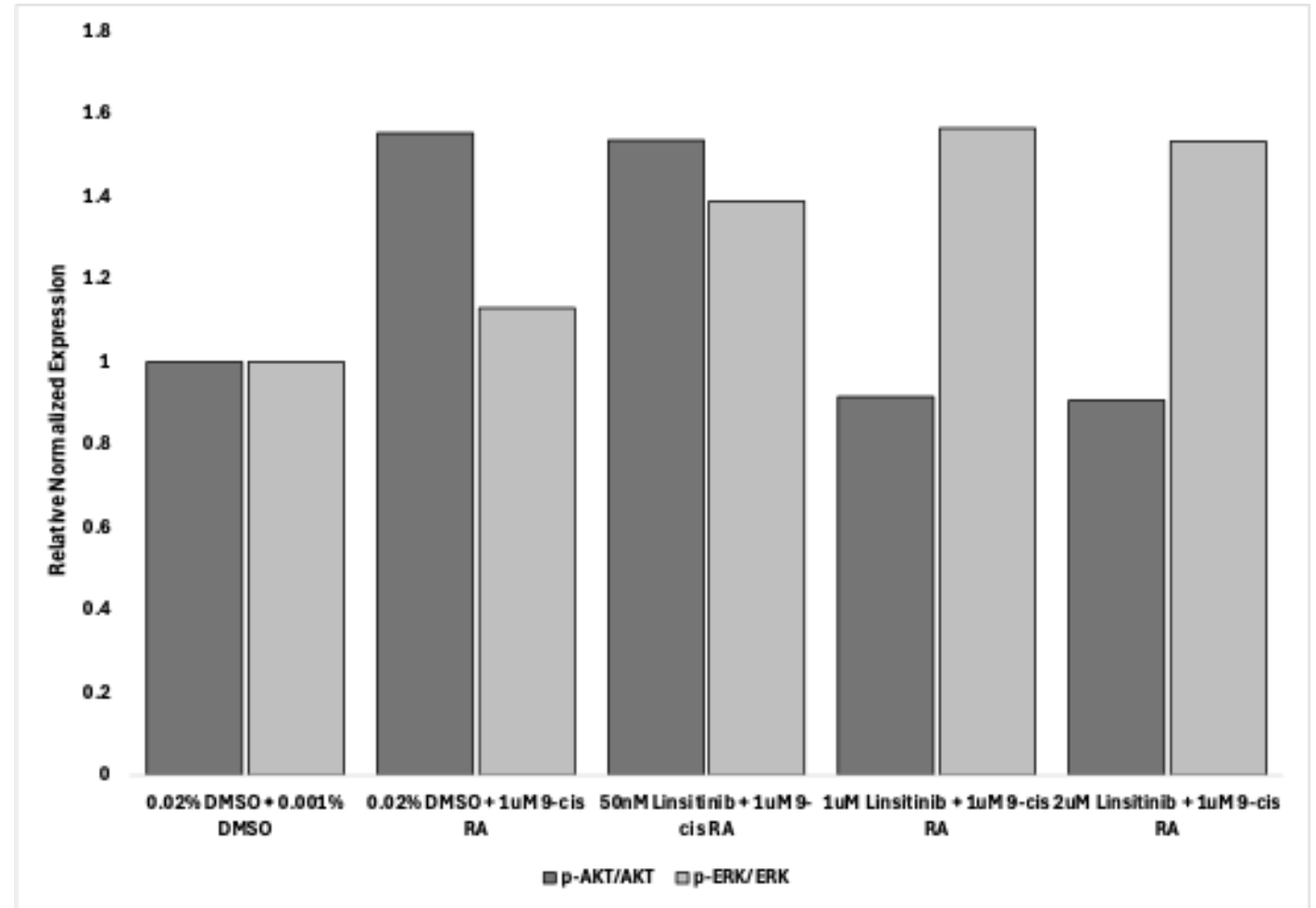
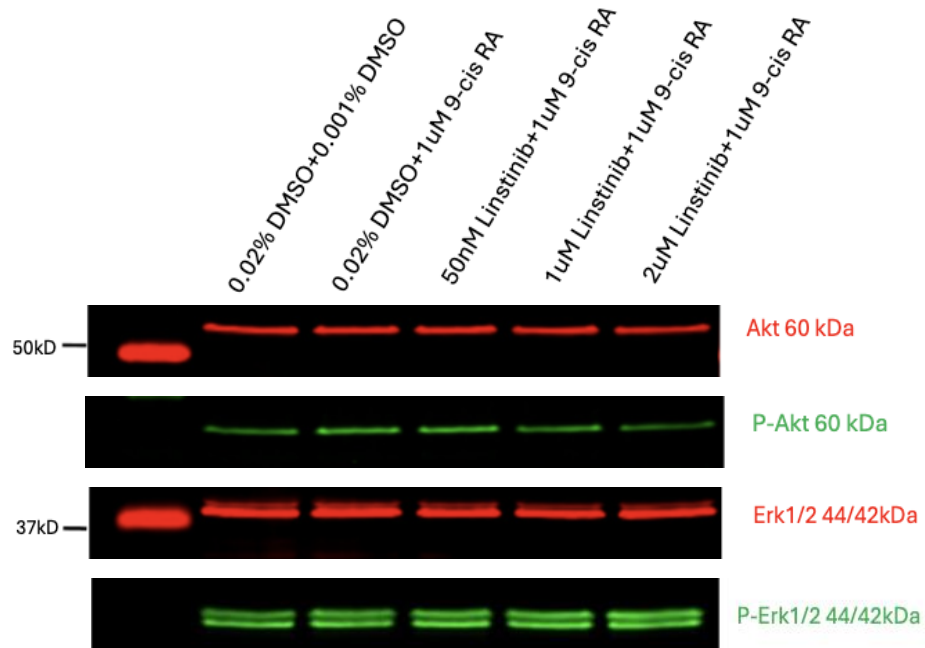
Testing the IGF Axis Downstream of 9-cisRA and IGFBP5



9-cisRA Transiently Activates AKT and ERK Signaling



IGF1R/INSR Blockade Suppresses AKT but Not ERK Signaling



Conclusions and Future Directions

- 9-cisRA mitigates lymphedema and promotes lymphatic remodeling in vivo.
- Spatial transcriptomics identifies IGFBP5 as a candidate mediator in treated distal tissue.
- 9-cisRA induces an LEC-specific IGFBP5/IGF2 response.
- IGFBP5 is secreted by LECs and supports LEC proliferation.
- RXR-alpha and IGF-axis signaling may link 9-cisRA to downstream AKT/ERK activation.
- **Future direction:** Validate IGFBP5 function in vivo using IGFBP5 knockdown/knockout models.



Division of Plastic and Reconstructive Surgery

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Acknowledgements

Nihal Sriramaneni, Ping Shu, Wan Jiao, Jessica Damanski, Alexander Lemenze