Update in Experimental DVT Vein Wall Injury

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DISCLOSURES:
None

Overview – human and exptl PTS

- Clinical background and need for new Rx
- Imaging of human post DVT veins
- Antiproliferative agent to prevent PTS
- Nanoparticles

Mainstays of medical therapy for DVT

- Rapid and therapeutic anticoagulation
  - Prevent recurrent DVT; promote resolution
- Leg elevation and compression
- Iliac vein stenting
  - CTRACT in progress
- ? Invasive techniques to clear thrombus?
  - Still defining the most appropriate patients

Vein wall remodeling in patients with acute deep vein thrombosis and chronic postthrombotic changes

J Thromb Haemost 2017; 15: 1989-93.

Case series of DVT and ctls
N = 35 acute DVT
N = 15 chronic PTS
N = 32 controls

High resolution duplex with stnd protocol, multiple segments

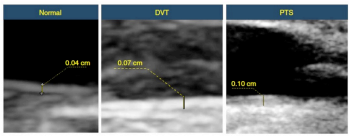

Fig. 1. High-resolution ultrasound images demonstrating significant wall thickening in patients with acute deep vein thrombosis (DVT) and postthrombotic syndrome (PTS) as compared with normal. [Color figure can be viewed at wileyonlinelibrary.com]

Vein wall remodeling in patients with acute deep vein thrombosis and chronic postthrombotic changes

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Means

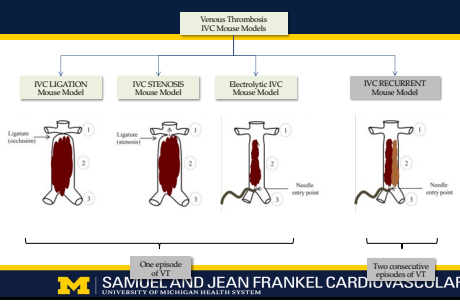
Controls = 0.37 mm
Acute DVT = 0.63 mm
PTS = 0.85 mm

Table 2 Vein wall thickness measurements

	Acute DVT			PTS			Control		
Vein segment	*N*	Mean (mm)	95% CI (mm)	*N*	Mean (mm)	95% CI (mm)	*N*	Mean (mm)	95% CI (mm)
Common femoral	19	0.74	0.70–0.77	6	1.02	0.81–1.22	90	0.42	0.41–0.43
Proximal femoral	18	0.68	0.65–0.70	5	0.91	0.83–0.99	59	0.38	0.37–0.39
Mid-femoral	16	0.66	0.64–0.68	4	0.89	0.71–1.07	76	0.38	0.37–0.39
Distal femoral	16	0.68	0.64–0.71	12	0.88	0.75–1.01	91	0.39	0.38–0.40
Proximal popliteal	16	0.66	0.63–0.69	20	0.93	0.79–1.06	86	0.39	0.38–0.40
Distal popliteal	18	0.67	0.64–0.70	20	0.81	0.71–0.90	77	0.39	0.37–0.40
Posterior Tibial	19	0.53	0.51–0.54	5	0.65	0.54–0.73	57	0.31	0.29–0.32
Peroneal	22	0.53	0.50–0.55	9	0.66	0.62–0.77	59	0.31	0.29–0.32
Proximal	103	0.68	0.67–0.69	67	0.89	0.84–0.94	515	0.40	0.39–0.40
Calf	51	0.52	0.51–0.53	11	0.66	0.59–0.72	106	0.32	0.31–0.33

CI, confidence interval; DVT, deep vein thrombosis; PTS, postthrombotic syndrome.

Mouse IVC Animal Models



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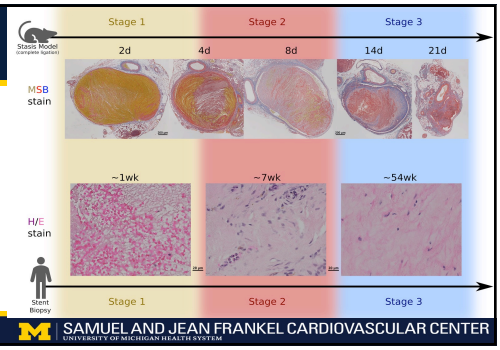
Mouse and human



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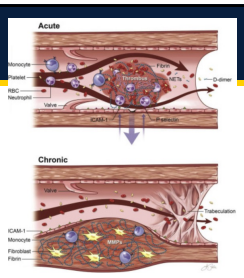
Venous thrombus resolution

Fibrinolysis
Phagocytosis
Neovascularization
Angiogenesis

Fibrosis
Vessel wall remodeling

Early influx of PMN with later influx of monocyte/macrophages

Highly dependent on immune cell recruitment and function.



Audu CO, Gordon AE, Obi AT, Wakefield TW, Henke PK. J Vasc Surg Venous Lymphat Disord. 2020 Mar;8(2):299-305.

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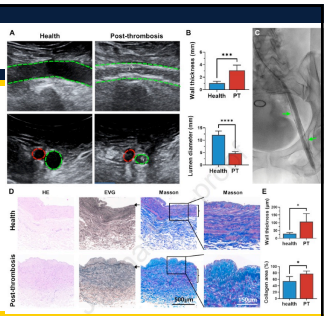
Title: Antiproliferative agent attenuates post-thrombotic vein wall remodeling in murine and human subjects

Human cohort of PTS patients
N = 4 healthy and PTS biopsies

JTH 2024 in press



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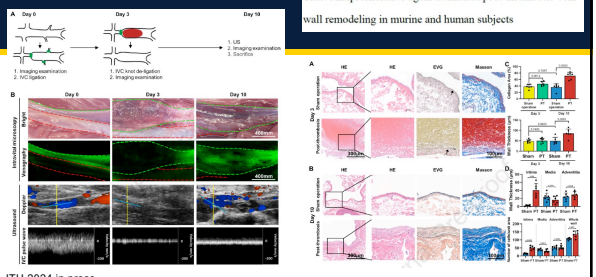

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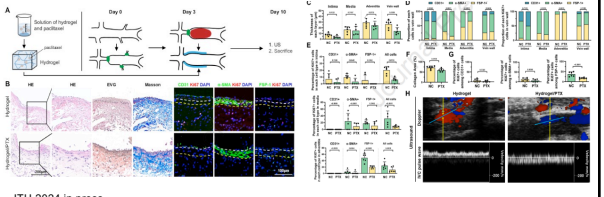
Hydrogel with Paclitaxol peri-adventially



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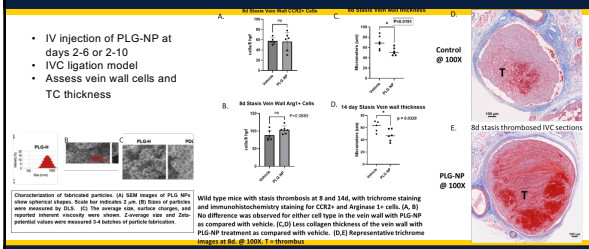
PLGA-NP and post VT vein wall fibrosis

- IV injection of PLG-NP at days 2-6 or 2-10
- IVC ligation model
- Assess vein wall cells and TC thickness



Characterization of fabricated particles. (A) SEM images of PLG NPs show spherical shapes. Scale bar indicates 2 μm. (B) Sizes of particles were measured by DLS. (C) The average size, surface charges, and reported inherent viscosity were shown. Z-average size and Zeta-potential values were measured 3-4 batches of particle fabrication.

Wild type mice with stasis thrombosis at 8 and 14d, with trichrome staining and immunohistochemistry staining for CCR2+ and Arginase 1+ cells. (A, B) No difference was observed for either cell type in the vein wall with PLG-NP as compared with vehicle. (C,D) Less collagen thickness of the vein wall with PLG-NP treatment as compared with vehicle. (D,E) Representative trichrome images at 8d. @ 100X. T = thrombus

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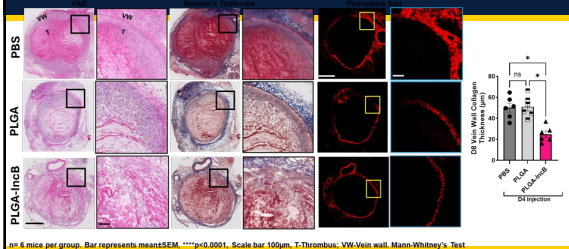
Anti-CCR2 Nanotherapy Reduces D8 Vein Wall Fibrosis



n= 6 mice per group. Bar represents mean±SEM. ****p<0.0001. Scale bar 100μm. T-Thrombus; VW-Vein wall. Mann-Whitney's Test

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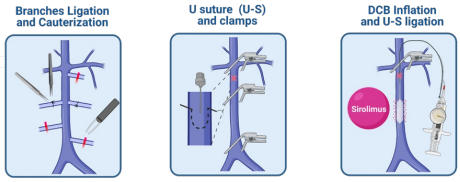
New model of rat post thrombosis with PTA

Moreno, Obi, Luke, et al.

New model of post VT to allow balloon and stenting



Animal: Sprague Dawley rats (male). **Age:** 15 weeks (adult). **Weight :** 500 grams ✖ U-stitch and Insertion Point

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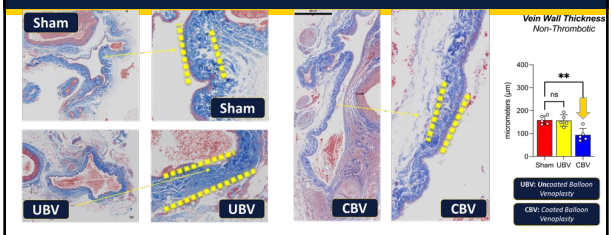
Rat post thrombosis PTA with Sirolimus



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Insights from experimental post-thrombotic syndrome and potential for novel therapies

Table 1. Potential avenues for novel therapies to reduce development of or treat PTS

Pathways involved in development of PTS	Molecular target(s)	Current state of investigation	Mechanisms involved
Endothelial to mesenchymal transformation	CCR7, Endothelin-1, TGFb	mice	Cellular response to injury, fibrosis
Leukocyte recruitment/venous inflammation	CAMs, CCR2, CXCR2	Mice, primates	Cellular trafficking, cellular activation
Inflammatory cytokine signaling	TLR-9, IL-6, IL-6R$_{sr}$	Mice, rats	Cellular activation
Fibrinolysis	Fibrin, uPA, plasmin, PAI-1	mice	Thrombus clearance, maturation
Vein wall matrix metabolism	MMP-2 MMP-9	Mice, rats	Fibrosis

Abbreviations: CAMs, cell adhesion molecules; CCR2, cystine-cysteine receptor2; CCR7, cystine-cysteine receptor7; CXCR, cysteine - x - cysteine receptor2; IL6, interleukin6; MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor-1; TLR, toll-like receptor; uPA, urokinase plasminogen activator.

Translational Res 2020;225:95

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Summary

- PTS causes a fibrotic vein wall response that varies from person to person
- All animal models suffer from non upright position and thus no hydrostatic pressure effects
- The fibrotic response may respond to antiproliferative and monocyte specific NP agents
- Timing of administration and how delivered will be key

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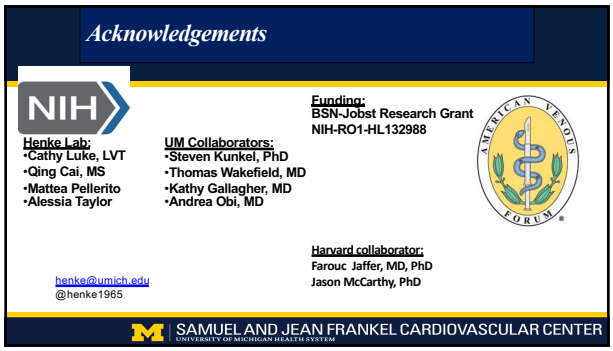
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