Enhancing the Survival & Patency of Saphenous Vein Grafts using a Reverse-Xenograft Model

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Objective

•The saphenous vein graft (**SVG**) has been the conduit of choice for over 50 years, but its lack of availability makes its superior utility unreliable.

•Because of the paucity of autologous vein grafts and poor results of alternative bypass conduits, we hypothesized vein allografts can be used for patients with limb-threatening ischemia who do not have adequate vein conduit for restorative bypass surgery.

•Remodeling processes of the vein graft start within days after harvesting and grafting, leading to the formation of intimal hyperplasia; the primary cause of intermediate-phase vein graft stenosis and occlusion. Even autologous saphenous vein grafts are affected, leading to poor long-term patency, with handling and preimplantation treatment, having an impact on mean time to failure.

•Despite substantial improvements in outcomes in the past decade, graft patency and conduit availability remain the 'Achilles' heel' of this procedure.

Materials and Methods

•To study the question of how to treat vessels for implantation such that they are less "visible" to the immune system, we have developed an IRB/IACUC-approved model in which ***human saphenous vein segments are grafted into rats*** via infra-renal inter-positional aorta grafts, (Figures 1 and 2,) after subjecting the veins to various treatments intended to extend patency. This reverse xenograft model accelerates the rate of failure due to the extreme difference in species biomarkers.

•We have performed SVGs on 47 Sprague-Dawley rats, using either no pretreatment, or one of several pretreatment cocktails including various fixatives, de-cellularizing agents, nucleases, proteases and alcohols, at varying concentrations, for periods of time from 1 month to 9 months.

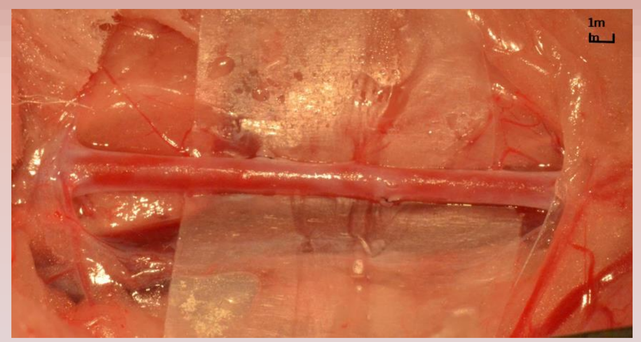

Fig. 1: Aortic Exposure in Sprague-Dawley Rat

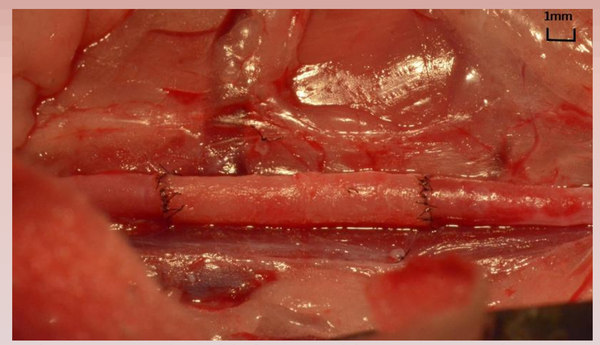

Fig. 2: Completed infra-renal human SVG into rat

Fig. 3a: Untreated human SVG after 3mo (aneurysmal)

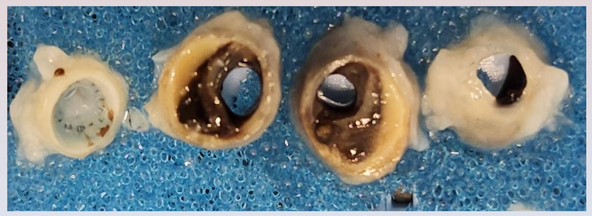

Fig. 3b: cross-sectional view at 3mo (narrow lumen)

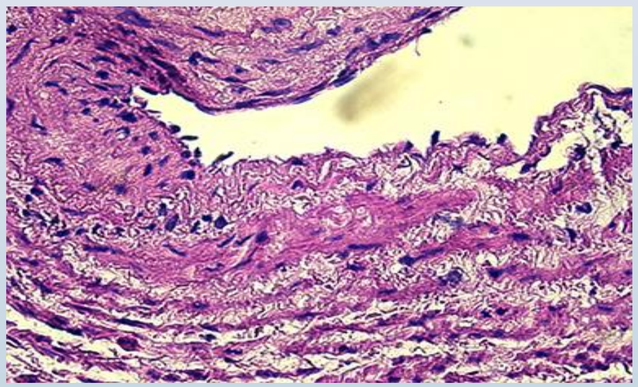

Fig. 4a: Untreated SVG at 3 months

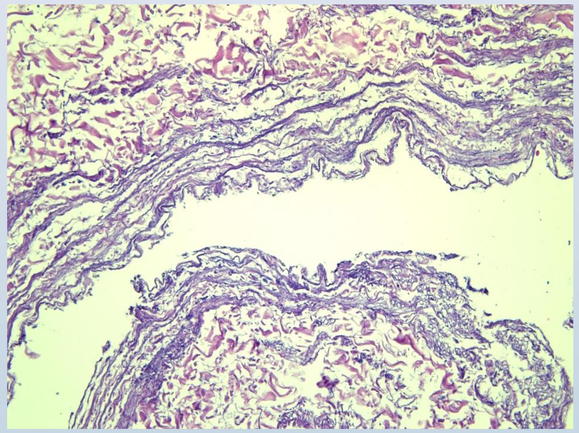

Fig. 4a: Pre-treated, (SDS & Glutaraldehyde) SVG open architecture and absence of cellular material

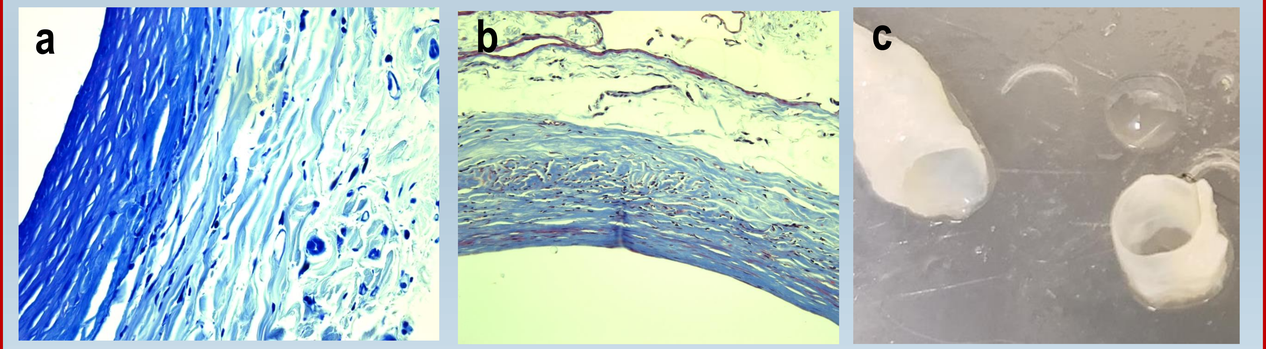

Fig. 5(a-c): 9mo of pretreated SVG (a): Diff-Quick stain (b): trichrome (20x) (c): Gross SVG harvested

Results

•As expected, preliminary data from our lab shows a **strong immune reaction** to the implantation of **untreated human SVG**. Control rats (SVGs with no pretreatment), showed serious degradation as early as 2 weeks after grafting.

•By three months, untreated veins were badly degraded and aneurysmal, and occlusion was imminent (Figure 3a and b).

•All the *pre-treated* vessels appeared *superior* to controls, with some demonstrating minimal intimal hyperplasia out to the longest time points tested. We have experimented with various methods to improve graft patency and to limit the degree of immunologic destruction of the tissue.

•Figure 4a shows a microscopic image of an untreated SV (H&E stained, 40X). Figure 4B shows a 40X H&E image of the saphenous vein after pre-treatment with SDS and Glutaraldehyde.

•Figure 5a shows a 40x Diff-Quick stained image, (5a,) and a 20X trichrome-stained image (5b,) of SVG pre-treated with SDS and glutaraldehyde after 9 months implantation in a rat.

• Figure 5c shows gross SVG harvested after 9 months with almost complete abscess of intimal hyperplasia

Conclusion

- We have successfully tested the hypothesis that human saphenous vein segments can be subjected to pre-treatment such that when they are implanted into rats, they will retain greater patency and have improved histological and physiological performance at 3, 6 and 9 months compared to controls. This research has significant implications for graft patency and retention in clinical applications.
- All the rats used for implantation of pre-treated veins showed excellent patency and suffered no ill effects out to 9 months, the longest time tested so far.
- Since the rats only life 2 and a half to three years, this is equivalent to 15-20 years in a human.
- We have shown the rapid onset of tissue destruction in an untreated graft, due to the large immunologic distance between the species in this xenograft model.
- These data suggest that such pretreatment on vein grafts in humans would improve survival and patency of the tissues.

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