# Glycerol-based biodegradable polymers and their applications in regenerative medicine

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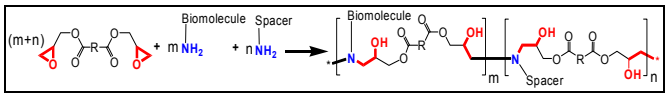
**Introduction:** Glycerol is a very simple yet essential biomolecule with three –OH groups, which make it a very versatile building block for polymeric biomaterials. The goal of my research is to delineate platform technologies of using glycerol and its derivatives to introduce distinct properties to synthetic biomaterials. My early effort has been focused on using glycerol itself as the monomer of a lightly crosslinked biodegradable elastomer - poly(glycerol sebacate) (PGS). The first part of this presentation will illustrate the usefulness of PGS as a scaffold material for blood vessel tissue engineering. More recently, my laboratory has been using glycerol derivatives as a facile tool to polymerize amine-containing biomolecules. One series of the resultant poly(amino-glycerol ester)s (PAGEs) with integrated neurotransmitter functionalities were found to be neuro-active. The second part of this presentation will illustrate the potential of PAGEs in nerve regeneration.

**Methods:** PGS was synthesized and fabricated into tubular scaffolds as previously described.[1, 2] The scaffolds were seeded with primary baboon smooth muscle cells (BaSMCs) and cultured for 7 days before seeding of baboon endothelial progenitor cells (BaEPCs). The constructs were evaluated mechanically and histologically after 21 days.

Poly(amino-glycerol ester)s were synthesized by direct condensation of the corresponding diglycidyl esters and primary amines in *N,N*-dimethylformamide at 60 °C in the presence of equimolar $Mg(ClO_4)_2$ catalyst (**Scheme 1**).[3] The diglycidyl esters were synthesized by oxidation of diallylesters obtained by esterification of dicarboxylic acids in allyl alcohol. The primary amines used for this research were leucine ethyl ester, dopamine, and 2-aminoethyl acetate. All reagents were purchased form Alfa Aesar (Ward Hill, MA). Neuro-activity of the polymers was tested with rat dorsal root ganglia explants. *In vivo* biocompatibility was tested by IM implantation next to sciatic nerve in rats.




**Scheme 1**. The synthesis of PAGE.

**Results/Discussion:** To test the potential of using PGS as scaffold material for small artery tissue engineering, we have cocultured BaSMCs and BaEPCs in PGS tubular scaffolds to produce bioartificial arteries (5 mm inner diameter) with physiologic compliance (**Fig. 1A**). Histological and biochemical analysis revealed simultaneous synthesis of collagen and elastin (**Fig. 1B**). The latter has been elusive in tissue engineered arteries using adult cells.

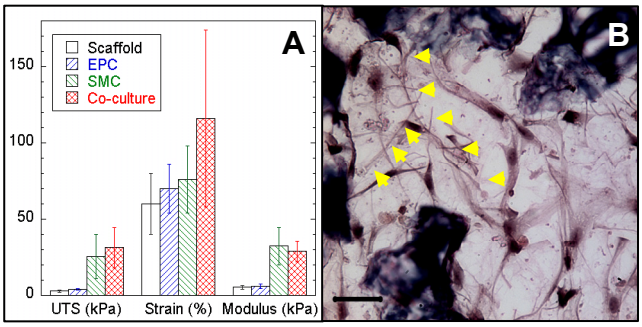



**Figure 1**. (A) Culture of cells, especially coculture of SMCs and EPCs, significantly improved the ultimate tensile stress, strain, and modulus of the constructs. The improved strain suggested that functional crosslinked elastin fibers were synthesized. (B) The presence of elastin fiber revealed by Verhoff's stain in constructs co-cultured for 21 days. 200x.

To demonstrate the potential of neurotransmitter-based PAGEs, we have created series of polymers with dopamine- and acetylcholine-like functional groups. The composition of the polymers was systematically varied using leucine ethyl ester as the inert spacer. The resultant polymers with the optimal composition promoted extensive neurite outgrowth and synapse formation from explanted rat dorsal root ganglia (**Fig. 2**). Preliminary *in vivo* studies revealed that the polymers caused little fibrosis or nerve degeneration.

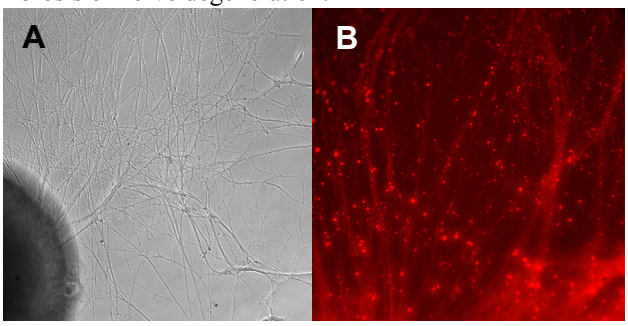



**Figure 2**. Extensive neurite outgrowth and synapse formation observed on explanted rat dorsal root ganglia cultured on (A) dopamine- and (B) acetylcholine- based poly(amino-glycerol ester)s. The ganglia were observed by phase contrast microscopy in A and fluorescent microscopy using anti-synapsin in B. Magnification for both images are 200X.

**Conclusions:** We have demonstrated that glycerol and its derivatives can be a very versatile tool to introduce bioactivity to synthetic polymers. Further development of these materials may provide new treatment strategies in regenerative medicine.

**References:**

1. Wang, Y., *et al.*, Nat. Biotechnol. 2002, *20*, 602-606.
2. Gao, J., *et al.*, Tissue Eng. 2006, *12*, (4), 917-925.
3. Gao, J., *et al.*, Proc. Natl. Acad. Sci. U. S. A. 2006, *103*, 16681-16686.