A Biocompatible Polyester Designed for Facile Biofunctionalization

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Statement of Purpose: Aliphatic polyesters such as polyglycolide and lactide have been widely used as tissue-engineering scaffolds and drug delivery matrices. However these synthetic polyesters lack biofunctional groups for defined interactions with cells and tissues. One way to address this drawback is the introduction of functional groups, which will allow facile modifications with biomolecules that afford controlled interactions with cells and tissues. Efficient synthesis of functionalizable polyesters, however, is still a major challenge that greatly limits the availability and widespread applications of functionalizable synthetic polyesters. We have designed and prepared a linear functionalizable polyester poly (sebacoyl diglyceride) (PSeD) (**Fig.1**), which can be viewed as a linear analog of poly(glycerol sebacate) (PGS) [1]. PSeD is designed to retain the good biocompatibility of PGS but with a refined structure so as to facilitate biofunctionalization. PGS has a branched structure with most of its secondary hydroxyl groups converted to ester groups. The distinct synthesis method of PSeD by an epoxide ring opening reaction leads to a well defined polymer structure with longer linear backbone and free hydroxyl groups. The facile biofunctionalization of PSeD has been demonstrated by esterification of the free -OH groups with glycine and a hexapeptide IKVAVS as representatives of biomolecules.

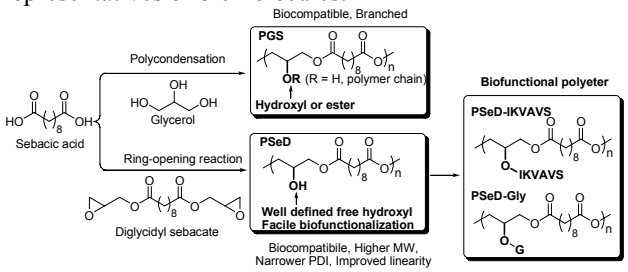


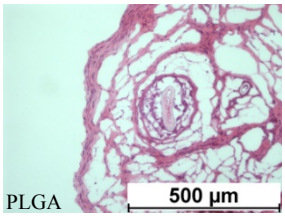
Fig. 1. Design of PSeD and PGS.

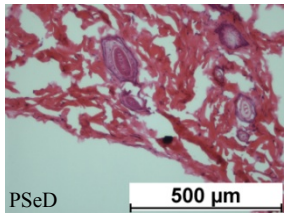
Methods: Diglycidyl sebacate was prepared via esterification of sebacoyl chloride by glycidol. PSeD was synthesized by an epoxide ring-opening reaction. Dicyclohexylcarbodiimide mediated coupling reaction attached glycinate and IKVAVS to PSeD. The resultant polymers were characterized by NMR, FTIR, DSC, and GPC. The *in vitro* and *in vivo* biocompatibility of PSeD were evaluated by MTT assay using baboon smooth muscle cells (TCPS as a control) and subcutaneous implantation in Sprague Dawley rats (PLGA as a control). The capability of PSeD-IKVAVS at promoting neurite extension was examined by culturing differentiated PC12 cells on its surface using laminin as the control.

Results: Under optimized conditions, PSeD was produced in 90% yield. PSeD exhibits several unique advantages over PGS prepolymer (table 1): better defined structure with more free -OH groups and much higher linearity (according to NMR analysis); higher molecular weight; narrower polydispersity (PDI); and longer shelf life. PSeD exhibited good *in vitro* and *in vivo* biocompatibility (**Fig. 2**). Biofunctionalization of PSeD by laminin epitope IKVAVS provided a neuroactive polymer that was comparable to laminin (**Fig. 3**).

Table1: Comparison of PSeD and PGS prepolymer

Polymer	*Branching*	*Mn (kDa)*	*PDI*	*Shelf life*
PSeD	10%	16.6	2.5	> 1 year
PGS	55%	9.0	9.3	< 3 months





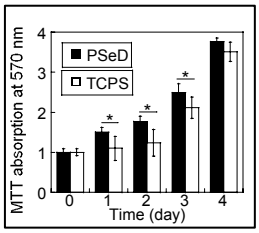
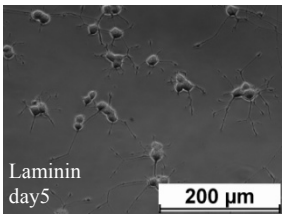
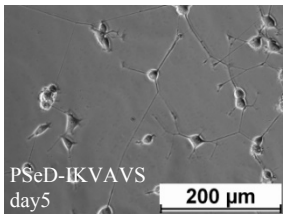


Fig. 2: Biocompabiliy of PSeD as tested by MTT assays and histological analysis of SC tissue (H&E). Unlike PLGA, there is no distinct fibrous capsule around PSeD implants retrieved at day15. Delamination of the tissue was a cryosection artifact.





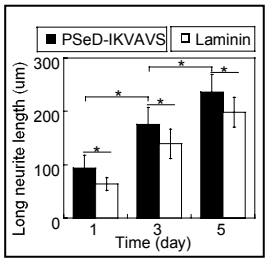


Fig. 3. PC12 cells cultured on PSeD-IKVAVS formed extensive networks and displayed longer neurites than that on laminin. 20 longest neurites from 10 random images on each surface per day were measured.

Conclusions: A linear functionalizable and biocompatible polyester bearing free hydroxyl groups was designed and synthesized in two simple steps without protection or deprotection. The resultant polyester can be readily biofunctionalized with amino acid and oligopepetide. Furthermore, the synthetic strategy is general and can be used to synthesize other glycerol-based linear polyesters. We expect this new design platform will lead to a diverse family of biodegradable and bioactive polymers with versatile mechanical, physical, chemical, and biological properties tailored for a wide range of biomedical applications.

References:

1. Wang YD. *et al.* Nat. Biotechnol. 2002;20(6):602-606.