

Assignment 10: Biomaterials and Host Integration

Cell and Tissue Engineering

Problems

1) The company Baxter received approval for its Fibrin Sealant (Tisseel®) in July, 2000 for application in surgical procedures. Features of this produce can be found at the website (<http://tisseel.com/us/index.html>). This material is being evaluated for a number of tissue engineering applications. Consider its use as a possible material in which to deliver tendon cells to a defect between bone and avulsed tendon. With regard to this prospective biomaterial application, please answer the following questions. Remember to give references when appropriate.

a) What type of biomaterial is Tisseel® and what are its components?

Tisseel® a fibrin sealant, is made mostly of human fibrinogen (91 mg/ml for a total protein concentration of 110.5 mg/ml), a clottable protein, and thrombin (a protease protein which causes fibrinogen to polymerize) combined with aprotinin and calcium chloride.

b) What reaction does Tisseel® undergo to form a sealant?

Upon injection, fibrinogen is converted into fibrin by the splitting of fibrinogen into fibrin monomers and fibrinopeptides involving thrombin-mediated proteolytic cleavage. The fibrin monomers aggregate into fibers creating a fibrin clot. Further concerted action of thrombin and calcium ions stabilizes the clot by cross-linking fibrin fibers. (Kattula et al.).

c) How quickly does Tisseel® degrade?

According to Baxter's technical sheet, the clot produced by Tisseel® is very similar to a natural blood clot, and will dissolve naturally. Aprotinin in Tisseel® increases the longevity of the clot. Depending the size of the clot it can take few hours to days for a natural clot to degrade physiologically.

d) What surface properties would be desirable for such an application? Does the product have such properties?

Different surface properties such product should provide are

Tunable stiffness:

- Cells in the extracellular matrix can induce stiffening of fibrin gels via myosin-driven cell contraction (Litvinov and Weisel).
- Fibrin formed in the presence of vessel wall components displays a reduced stiffness allowing easier degradation. In the other hand, histone-DNA complexes added to fibrin increases its rigidity and show slower fibrinolysis (Litvinov and Weisel).

High deformability:

- When stretched fibrin shrinks dramatically due to a molecular structural transition.
- Elastic modulus increases several-fold when fibrin is polymerized by thrombin and crosslinking happens between fibrin fibers.

Promotes clotting:

- It has been shown that platelets sense the stiffness of the underlying fibrin/fibrinogen substrate and higher substrate stiffness leads to increase platelet activation, adhesion and spreading (Litvinov and Weisel).

By combining fibrinogen with thrombin, Tisseel® exhibits all these desired properties.

- e) What bulk properties would be desirable for such an application? Does the product have such properties?

Fibrin is a viscoelastic polymer. When compression increases, the fibrin network density increases, the fibers reorient in the compression plane direction and as result of fiber crisscrossing happenings, the number of shorter fiber segments increases significantly transforming the whole network into a planar-like structure perpendicular to the compression direction. At low strains, the stress is linearly proportional to strain and at larger strains, the slope of the stress-strain curve increases exponentially. This is important as under stress blood clots, not only, fibrin will tend to stretch rather break but also as fibers are stretched, the stiffer fibers distribute the strain load to the less strained fibers increasing the elasticity factor (Litvinov and Weisel). By combining fibrinogen and thrombin, Tisseel® acts as a dynamic mesh which is important to promote hemostasis or for wound sealing.

- 2) In lecture 1 we discuss the use of lithographic methods for tailoring biomaterials at the cellular level. Please briefly describe one technique each for tailoring biomaterials at the subcellular and supracellular length scales. 2-3 sentences each MAX.

Subcellular

In molecular imprinting a template molecule is imprinted in a polymer matrix. The template molecule is then removed in part or entirely leaving behind cavities complementary to the template in size, shape and chemically. The cavity is then used as a selective binding site for the templated molecule (Ertürk and Mattiasson).

Supracellular

In a solvent casting-particulate leaching technique, a polymer is dissolved in a solvent and casted into a mold which could contain a porogen. Upon solvent evaporation, the porogen is dissolved producing a porous scaffold, for example a structure mimicking the bone marrow niche (Sola, Antonella et al). Particles such as salt is used to tune the pore size, pores can also be formed using foaming agent.

3) Name the immunomodulatory strategy based on the description:

a) Encapsulation of cells with semipermeable material

Physical immunoisolation

b) Blocking co-stimulators of T-cell activation

Tolerance induction

c) Use of corticosteroids

Pharmacological treatment

d) Forced expression of human proteins in xenograft cells

Genetic modifications

References:

Question 1 adapted from Tissue Engineering, Palsson and Bhatia

Tisseel®:

<https://www.medicines.org.uk/emc/product/1801/smpc>

<https://www.medicines.org.uk/emc/product/1801/smpc#INDICATIONS>

<https://docs.google.com/viewer?url=https%3A%2F%2Fwww.medicines.org.uk%2Femc%2Ffiles%2Fpil.1801.pdf>

Sola, Antonella et al. "Development of solvent-casting particulate leaching (SCPL) polymer scaffolds as improved three-dimensional supports to mimic the bone marrow niche." *Materials science & engineering. C, Materials for biological applications* vol. 96 (2019): 153-165. doi:10.1016/j.msec.2018.10.086

Ertürk, Gizem, and Bo Mattiasson. "Molecular Imprinting Techniques Used for the Preparation of Biosensors." *Sensors*, vol. 17, no. 2, Feb. 2017, p. 288. *DOI.org (Crossref)*, <https://doi.org/10.3390/s17020288>.

Kattula, Sravya, et al. "Fibrinogen and Fibrin in Hemostasis and Thrombosis." *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 37, no. 3, Mar. 2017. *DOI.org (Crossref)*, <https://doi.org/10.1161/ATVBAHA.117.308564>.

Litvinov, Rustem I., and John W. Weisel. "Fibrin Mechanical Properties and Their Structural Origins." *Matrix Biology*, vol. 60–61, July 2017, pp. 110–23. *DOI.org (Crossref)*, <https://doi.org/10.1016/j.matbio.2016.08.003>.



Rubric

Question	Component	Total Point Value
1	a	2
	b	2
	C	2
	D	2
	E	2
2	Subcellular	6
	Supracellular	6
3	A	2
	B	2
	C	2
	D	2