CLAIMS

What is claimed is:

1. A biocompatible tissue filler, comprising hyaluronic acid (HA), silk protein or silk protein fragments (SPF), and an anesthetic agent, wherein a portion of the HA, a portion of the SPF, or both, is modified or cross-linked by one or more linker moieties comprising one or more of an alkane or alkyl chain, an ether group, and a secondary alcohol,

wherein the silk protein or silk protein fragments have an average weight average molecular weight ranging from 1 kDa to 250 kDa,

wherein the modified or cross-linked HA or SPF comprises a linker or cross-linking moiety comprising a polyethylene glycol (PEG) chain, and

wherein modification or cross-linking is obtained using a cross-linking agent and/or a cross-linking precursor which is a polyethylene glycol diglycidyl ether.

2. The tissue filler of claim 1, having a degree of modification (MoD) of 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, 10.0%, 10.1%, 10.2%, 10.3%, 10.4%, 10.5%, 10.6%, 10.7%, 10.8%, 10.9%, 11.0%, 11.1%, 11.2%, 11.3%, 11.4%, 11.5%, 11.6%, 11.7%, 11.8%, 11.9%, 12.0%, 12.1%, 12.2%, 12.3%, 12.4%, 12.5%, 12.6%, 12.7%, 12.8%, 12.9%, 13.0%, 13.1%, 13.2%, 13.3%, 13.4%, 13.5%, 13.6%, 13.7%, 13.8%, 13.9%, 14.0%, 14.1%, 14.2%, 14.3%, 14.4%, 14.5%, 14.6%, 14.7%, 14.8%, 14.9%, 15.0%, 15.1%, 15.2%, 15.3%, 15.4%, 15.5%, 15.6%, 15.7%, 15.8%, 15.9%, 16.0%, 16.1%, 16.2%, 16.3%, 16.4%, 16.5%, 16.6%, 16.7%, 16.8%, 16.9%, 17.0%, 17.1%, 17.2%, 17.3%, 17.4%, 17.5%, 17.6%, 17.7%, 17.8%, 17.9%, 18.0%, 18.1%, 18.2%, 18.3%, 18.4%, 18.5%, 18.6%, 18.7%, 18.8%, 18.9%, 19.0%, 19.1%, 19.2%, 19.3%, 19.4%, 19.5%, 19.6%, 19.7%, 19.8%, 19.9%, or 20.0%.

3. The tissue filler of any one of claims 1 to 2, wherein the polyethylene glycol diglycidyl ether has an average M_n of 500, 1000, 2000, or 6000.

4. The tissue filler of any one of claims 1 to 3, wherein the polyethylene glycol diglycidyl ether has from 2 to 25 ethylene glycol groups.

5. The tissue filler of any one of claims 1 to 4, wherein the anesthetic agent is lidocaine.

6. The tissue filler of any one of claims 1 to 5, wherein the concentration of anesthetic agent in the tissue filler is from 0.001% to 5%.

7. The tissue filler of claim 5, wherein the concentration of lidocaine in the tissue filler is 0.3%.

8. The tissue filler of any one of claims 1 to 7, wherein the tissue filler further comprises water.

9. The tissue filler of any one of claims 1 to 8, wherein the total concentration of HA in the tissue filler is from 10 mg/mL to 50 mg/mL.

10. The tissue filler of any one of claims 1 to 9, wherein the total concentration of HA in the tissue filler is 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, 20 mg/mL, 21 mg/mL, 22 mg/mL, 23 mg/mL, 24 mg/mL, 25 mg/mL, 26 mg/mL, 27 mg/mL, 28 mg/mL, 29 mg/mL, or 30 mg/mL.

11. The tissue filler of any one of claims 1 to 10, wherein the silk protein is silk fibroin.

12. The tissue filler of any one of claims 1 to 11, wherein the silk protein is silk fibroin substantially devoid of sericin.

13. The tissue filler of any one of claims 1 to 12, wherein the SPF have an average weight average molecular weight between 5 kDa and 150 kDa.

14. The tissue filler of any one of claims 1 to 12, wherein the SPF have an average weight average molecular weight selected from between 6 kDa and 17 kDa, between 17 kDa and 39 kDa, and between 39 kDa and 80 kDa.

15. The tissue filler of any one of claims 1 to 12, wherein the SPF have low molecular weight, medium molecular weight, or high molecular weight.

16. The tissue filler of any one of claims 1 to 15, wherein the SPF have a polydispersity of between 1 and 5.0 or between 1.5 and 3.0.

17. The tissue filler of any one of claims 1 to 16, wherein a portion of the SPF are modified or cross-linked, wherein the degree of modification or cross-linking of the modified or cross-linked SPF is between 1% and 100%.

18. The tissue filler of claim 17, wherein the degree of modification or cross-linking of the modified or cross-linked SPF is between 1% and 15%.

19. The tissue filler of any one of claims 17 to 18, wherein the degree of modification or cross-linking of the modified or cross-linked SPF is one or more of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, and 15%.

20. The tissue filler of any one of claims 1 to 19, wherein the tissue filler is a gel or a hydrogel.

21. The tissue filler of any one of claims 17 to 20, wherein the total concentration of SPF in the tissue filler is from 0.1 mg/mL to 15 mg/mL.

22. The tissue filler of any one of claims 17 to 21, wherein the total concentration of SPF in the tissue filler is 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 1.5 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 3.5 mg/mL, 4 mg/mL, 4.5 mg/mL, 5 mg/mL, 5.5 mg/mL, 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.5 mg/mL, 8 mg/mL, 8.5 mg/mL, 9 mg/mL, 9.5 mg/mL, 10 mg/mL, 10.5 mg/mL, 11 mg/mL, 11.5 mg/mL, 12 mg/mL, 12.5 mg/mL, 13 mg/mL, 13.5 mg/mL, 14 mg/mL, 14.5 mg/mL, or 15 mg/mL.

23. The tissue filler of any one of claims 1 to 22, wherein the tissue filler is a dermal filler.

24. The tissue filler of any one of claims 1 to 23, wherein the tissue filler is biodegradable.

25. The tissue filler of any one of claims 1 to 24, wherein the tissue filler is injectable.

26. The tissue filler of any one of claims 1 to 25, wherein the tissue filler has a storage modulus (*G'*) of from 25 Pa to 1500 Pa.

27. The tissue filler of any one of claims 1 to 26, wherein the tissue filler has a complex viscosity from 1 Pa·s to 10 Pa·s.

28. A tissue filler of any one of claims 1 to 27 for use in therapy.

29. A method of cosmetic treatment in a subject in need thereof, comprising administering to the subject an effective amount of a tissue filler of any one of claims 1 to 27.

30. The tissue filler of claim 28, or the method of claim 29, wherein the tissue filler is to be administered into a dermal region of the subject.

31. The method of claim 29 or claim 30, wherein the method is an augmentation, a reconstruction, correcting a defect or imperfection of a body part, region or area.

32. The method of any one of claims 29 to 31, wherein the method is a facial augmentation or a facial reconstruction.

33. The tissue filler of claim 28, or the method of any one of claims 29 to 32, wherein the tissue filler resists biodegradation, bioerosion, bioabsorption, and/or bioresorption, for at least 3 days, 7 days, 14 days, 21 days, 28 days, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months.

34. The tissue filler of claim 28, or the method of any one of claims 29 to 33, wherein administration of the tissue filler to the subject results in a reduced inflammatory response compared to the inflammatory response induced by a control tissue filler comprising a

polysaccharide and lidocaine, wherein the control tissue filler does not include silk protein fragments (SPF).

35. The tissue filler of claim 28, or the method of any one of claims 29 to 34, wherein administration of the tissue filler to the subject results in increased collagen production compared to the collagen production induced by a control tissue filler comprising a polysaccharide and lidocaine, wherein the control tissue filler does not include silk protein fragments (SPF).