prepared by the mixed biological ink system enhanced by alginate and extracellular matrix have been proved to promote cell proliferation and differentiation and angiogenesis in vivo (Figure 1.9).

Xie et al. [82] explored the potential application of 3D printing technology in drug screening in vitro. They successfully constructed a liver cancer model in a 3D structure made from a mixture of gelatin and sodium alginate. In the process of long-term culture in vitro, its tumorigenic potential and histological characteristics were preserved, which provided a platform for screening anticancer drugs in vitro.

Ma et al. constructed a multi-scale hierarchical bioactive calcium silicate nanowire/alginate composite hydrogel scaffold for tendon-to-bone interface tissue engineering. Three-dimensional printing technology was combined with mechanical stretching methods to introduce biomimetic reinforcement structures from nano- to micrometer- to micro-scale in this composite hydrogel, which significantly improved the mechanical properties. Experiments showed that the biochemical and topographical characteristics of the composite hydrogel provided a favorable microenvironment for rabbit bone marrow mesenchymal stem cells and tendon stem cells to promote their directional alignment and induced differentiation. The composite scaffold significantly promoted the regeneration of tendon–bone tissue in vivo, especially in the fibrocartilage transition zone. Therefore, this multi-scale structural design provides an innovative strategy for the engineering of functionalized tendon–bone tissues [83].

Zhu et al. prepared a multifunctional nanocomposite bioink for extrusion bioprinting using amine-functionalized copper (Cu), oxidized alginate, gelatin, and mesoporous bioactive glass nanoparticles (ACuMBGNs). This ink has good rheological properties and structural stability. Rapid cell spreading and high survival were supported by the reversible dynamic microenvironment and cell adhesion ligands introduced by aminated particles. Osteogenic differentiation and angiogenesis of mouse bone marrow stromal stem cells (BMSCs) were promoted in the bioprinted scaffolds without additional growth factors. This nanocomposite biomaterial is expected to be a superior platform for bioprinting complex three-dimensional matrix environments for superior cell support [84].

References

1 Dekamin, M.G., Karimi, Z., Latifidoost, Z. et al. (2018). Alginic acid: a mild and renewable bifunctional heterogeneous biopolymeric organocatalyst for efficient and facile synthesis of polyhydroquinolines. *Int. J. Biol. Macromol.* 108: 1273–1280.

2 Lee, K.Y. and Mooney, D.J. (2012). Alginate: properties and biomedical applications. *Prog. Polym. Sci.* 37: 106–126.

3 Cao, L.Q., Lu, W., Mata, A. et al. (2020). Egg-box model-based gelation of alginate and pectin: a review. *Carbohydr. Polym.* 242: 116389.

4 Czuban, M., Srinivasan, S., Yee, N.A. et al. (2018). Bio-orthogonal chemistry and reloadable biomaterial enable local activation of antibiotic prodrugs and enhance treatments against infections. *ACS Cent. Sci.* 4: 1624–1632.

5 Ke, Y.H., Zhu, J.M., Chu, Y.H. et al. (2022). Bifunctional fusion membrane-based hydrogel enhances antitumor potency of autologous cancer vaccines by activating dendritic cells. *Adv. Funct. Mater.* 32: 2201306.

6 Zhao, Z.P., Li, Q., Qin, X.H. et al. (2022). An injectable hydrogel reshaping adenosinergic axis for cancer therapy. *Adv. Funct. Mater.* 32: 2200801.

7 Wu, Y.H., Yao, Y., Zhang, J.M. et al. (2022). Tumor-targeted injectable double-network hydrogel for prevention of breast cancer recurrence and wound infection via synergistic photothermal and brachytherapy. *Adv. Sci.* 9: 2200681.

8 Li, Z.T., Ding, Y.Y., Liu, J. et al. (2022). Depletion of tumor associated macrophages enhances local and systemic platelet-mediated anti-PD-1 delivery for post-surgery tumor recurrence treatment. *Nat. Commun.* 13: 1845.

9 Zhu, Z.Q., Wang, L., Peng, Y.O. et al. (2022). Continuous self-oxygenated double-layered hydrogel under natural light for real-time infection monitoring, enhanced photodynamic therapy, and hypoxia relief in refractory diabetic wounds healing. *Adv. Funct. Mater.* 32: 2201875.

10 Gan, J.J., Sun, L.Y., Chen, G.P. et al. (2022). Mesenchymal stem cell exosomes encapsulated oral microcapsules for acute colitis treatment. *Adv. Healthc. Mater.* 11: e2201105.

11 Zhang, D., Li, Q., Chen, X.W. et al. (2022). An injectable hydrogel to modulate T cells for cancer immunotherapy. *Small* 18: e2202663.

12 Delcassian, D., Luzhansky, I., Spanoudaki, V. et al. (2020). Magnetic retrieval of encapsulated beta cell transplants from diabetic mice using dual-function MRI visible and retrievable microcapsules. *Adv. Mater.* 32: 1904502.

13 Hasani-Sadrabadi, M.M., Sarrion, P., Pouraghaei, S. et al. (2020). An engineered cell-laden adhesive hydrogel promotes craniofacial bone tissue regeneration in rats. *Sci. Transl. Med.* 12: eaay6853.

14 Whitehead, J., Griffin, K.H., Gionet-Gonzales, M. et al. (2021). Hydrogel mechanics are a key driver of bone formation by mesenchymal stromal cell spheroids. *Biomaterials* 269: 120607.

15 Hung, B., Gonzalez-Fernandez, T., Lin, J.B. et al. (2020). Multi-peptide presentation and hydrogel mechanics jointly enhance therapeutic duo-potential of entrapped stromal cells. *Biomaterials* 245: 119973.

16 Hasturk, O., Smiley, J.A., Arnett, M. et al. (2022). Cytoprotection of human progenitor and stem cells through encapsulation in alginate templated, dual crosslinked silk and silk-gelatin composite hydrogel microbeads. *Adv. Healthc. Mater.* 11: e2200293.

17 Qian, B., Yang, Q., Wang, M.L. et al. (2022). Encapsulation of lyophilized platelet-rich fibrin in alginate-hyaluronic acid hydrogel as a novel vascularized substitution for myocardial infarction. *Bioact. Mater.* 7: 401–411.

18 Panebianco, C.J., Rao, S.J., Hom, W.W. et al. (2022). Genipin-crosslinked fibrin seeded with oxidized alginate microbeads as a novel composite biomaterial strategy for intervertebral disc cell therapy. *Biomaterials* 287: 121641.

19 Theocharidis, G., Rahmani, S., Lee, S.M. et al. (2022). Murine macrophages or their secretome delivered in alginate dressings enhance impaired wound healing in diabetic mice. *Biomaterials* 288: 121692.

20 Jeon, O. and Alsberg, E. (2013). Regulation of stem cell fate in a three-dimensional micropatterned dual-crosslinked hydrogel system. *Adv. Funct. Mater.* 23: 4765–4775.

21 Gonzalez-Pujana, A., Vining, K.H., Zhang, D.K.Y. et al. (2020). Multifunctional biomimetic hydrogel systems to boost the immunomodulatory potential of mesenchymal stromal cells. *Biomaterials* 257: 120266.

22 Liu, H.T., Wang, Y.Q., Wang, H. et al. (2020). A droplet microfluidic system to fabricate hybrid capsules enabling stem cell organoid engineering. *Adv. Sci.* 7: 1903739.

23 Liao, J.F., Tian, T.R., Shi, S.R. et al. (2017). The fabrication of biomimetic biphasic CAN-PAC hydrogel with a seamless interfacial layer applied in osteochondral defect repair. *Bone Res.* 5: 17018.

24 Öztürk, E., Arlov, O., Aksel, S. et al. (2016). Sulfated hydrogel matrices direct mitogenicity and maintenance of chondrocyte phenotype through activation of FGF signaling. *Adv. Funct. Mater.* 26: 3649–3662.

25 Liao, I.C., Moutos, F.T., Estes, B.T. et al. (2013). Composite three-dimensional woven scaffolds with interpenetrating network hydrogels to create functional synthetic articular cartilage. *Adv. Funct. Mater.* 23: 5833–5839.

26 Moshaverinia, A., Xu, X.T., Chen, C. et al. (2014). Application of stem cells derived from the periodontal ligament or gingival tissue sources for tendon tissue regeneration. *Biomaterials* 35: 2642–2650.

27 Mredha, M.T.I., Guo, Y.Z., Nonoyama, T. et al. (2018). A facile method to fabricate anisotropic hydrogels with perfectly aligned hierarchical fibrous structures. *Adv. Mater.* 30: 1870060.

28 Campbell, K.T., Stilhano, R.S., and Silva, E.A. (2018). Enzymatically degradable alginate hydrogel systems to deliver endothelial progenitor cells for potential revasculature applications. *Biomaterials* 179: 109–121.

29 Hao, T., Li, J.J., Yao, F.L. et al. (2018). Injectable fullerenol/alginate hydrogel for suppression of oxidative stress damage in Brown adipose-derived stem cells and cardiac repair (vol 11, pg 5474, 2017). *ACS Nano* 12: 10564.

30 Anker, S.D., Coats, A.J.S., Cristian, G. et al. (2015). A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure (AUGMENT-HF trial). *Eur. Heart J.* 36: 2297–2309.

31 Leor, J., Tuvia, S., Guetta, V. et al. (2009). Intracoronary injection of in situ forming alginate hydrogel reverses left ventricular remodeling after myocardial infarction in swine. *J. Am. Coll. Cardiol.* 54: 1014–1023.

32 He, Y.N., Li, F., Jiang, P. et al. (2023). Remote control of the recruitment and capture of endogenous stem cells by ultrasound for in situ repair of bone defects. *Bioact. Mater.* 21: 223–238.

33 Zheng, A., Wang, X., Xin, X.Z. et al. (2023). Promoting lacunar bone regeneration with an injectable hydrogel adaptive to the microenvironment. *Bioact. Mater.* 21: 403–421.

34 Wang, C.R., Jiang, X., Kim, H.J. et al. (2022). Flexible patch with printable and antibacterial conductive hydrogel electrodes for accelerated wound healing. *Biomaterials* 285: 121479.

35 Wang, T., Yi, W.W., Zhang, Y. et al. (2023). Sodium alginate hydrogel containing platelet-rich plasma for wound healing. *Colloids Surf. B* 222: 113096.

36 Choi, S., Moon, J.R., Park, N. et al. (2023). Bone-adhesive anisotropic tough hydrogel mimicking tendon enthesis. *Adv. Mater.* 35: 2206207.

37 Liu, H.S., Hu, X.L., Li, W. et al. (2023). A highly-stretchable and adhesive hydrogel for noninvasive joint wound closure driven by hydrogen bonds. *Chem. Eng. J.* 452: 139368.

38 Yao, S.S., Zhao, Y.Q., Xu, Y.F. et al. (2022). Injectable dual-dynamic-bond cross-linked hydrogel for highly efficient infected diabetic wound healing. *Adv. Healthc. Mater.* 11: e2200516.

39 Wang, C.P., Wang, X.Y., Dong, K.Y. et al. (2016). Injectable and responsively degradable hydrogel for personalized photothermal therapy. *Biomaterials* 104: 129–137.

40 Patrick, P.S., Bear, J.C., Fitzke, H.E. et al. (2020). Radio-metal cross-linking of alginate hydrogels for non-invasive imaging. *Biomaterials* 243: 119930.

41 Zhu, Y.L., Ma, Z.J., Kong, L.Z. et al. (2020). Modulation of macrophages by bioactive glass/sodium alginate hydrogel is crucial in skin regeneration enhancement. *Biomaterials* 256: 120216.

42 Ren, J.L., Yin, X.J., Chen, Y. et al. (2020). Alginate hydrogel-coated syringe needles for rapid haemostasis of vessel and viscera puncture. *Biomaterials* 249: 120019.

43 Jons, C.K., Grosskopf, A.K., Baillet, J. et al. (2022). Yield-stress and creep control depot formation and persistence of injectable hydrogels following subcutaneous administration. *Adv. Funct. Mater.* 32: 2203402.

44 Ji, D., Park, J.M., Oh, M.S. et al. (2022). Superstrong, superstiff, and conductive alginate hydrogels. *Nat. Commun.* 13: 3019.

45 Hwang, J.C., Kim, M., Kim, S. et al. (2022). In situ diagnosis and simultaneous treatment of cardiac diseases using a single-device platform. *Sci. Adv.* 8: abq0897.

46 Asadi-Korayem, M., Akbari-Taemeh, M., Mohammadian-Sabet, F. et al. (2021). How does counter-cation substitution influence inter- and intramolecular hydrogen bonding and electrospinnability of alginates. *Int. J. Biol. Macromol.* 171: 234–241.

47 Fujita, S., Wakuda, Y., Matsumura, M., and Suye, S.I. (2019). Geometrically customizable alginate hydrogel nanofibers for cell culture platforms. *J. Mater. Chem. B* 7: 6556–6563.

48 Kaassis, A.Y.A., Young, N., Sano, N. et al. (2014). Pulsatile drug release from electrospun poly(ethylene oxide)-sodium alginate blend nanofibres. *J. Mater. Chem. B* 2: 1400–1407.

49 De Silva, R.T., Dissanayake, R.K., Mantilaka, M.M.M.G.P.G. et al. (2018). Drug-loaded halloysite nanotube-reinforced electrospun alginate-based nanofibrous scaffolds with sustained antimicrobial protection. *ACS Appl. Mater. Interfaces* 10: 33913–33922.

50 Dodero, A., Alloisio, M., Castellano, M., and Vicini, S. (2020). Multilayer alginate-polycaprolactone electrospun membranes as skin wound patches with drug delivery abilities. *ACS Appl. Mater. Interfaces* 12: 31162–31171.

51 Mulholland, E.J., Ali, A., Robson, T. et al. (2019). Delivery of RALA/siFKBPL nanoparticles electrospun bilayer nanofibres: an innovative angiogenic therapy for wound repair. *J. Control. Release* 316: 53–65.

52 Tang, Y.D., Lan, X.Z., Liang, C.F. et al. (2019). Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing. *Carbohydr. Polym.* 219: 113–120.

53 Hajiali, H., Summa, M., Russo, D. et al. (2016). Alginate-lavender nanofibers with antibacterial and anti-inflammatory activity to effectively promote burn healing. *J. Mater. Chem. B* 4: 1686–1695.

54 Dodero, A., Scarfi, S., Pozzolini, M. et al. (2020). Alginate-based electrospun membranes containing ZnO nanoparticles as potential wound healing patches: biological, mechanical, and physicochemical characterization. *ACS Appl. Mater. Interfaces* 12: 3371–3381.

55 Chen, Y.H., Cheng, C.H., Chang, W.J. et al. (2016). Studies of magnetic alginate-based electrospun matrices crosslinked with different methods for potential hyperthermia treatment. *Mater. Sci. Eng. C* 62: 338–349.

56 Alloisio, M., Dodero, A., Alberti, S. et al. (2022). Electrospun alginate mats embedding silver nanoparticles with bioactive properties. *Int. J. Biol. Macromol.* 213: 427–434.

57 Lashkari, M., Rahmani, M., Yousefpoor, Y. et al. (2023). Cell-based wound dressing: bilayered PCL/gelatin nanofibers-alginate/collagen hydrogel scaffold loaded with mesenchymal stem cells. *Int. J. Biol. Macromol.* 239: 124099.

58 Wang, W., Liu, M.Y., Shafiq, M. et al. (2023). Synthesis of oxidized sodium alginate and its electrospun bio-hybrids with zinc oxide nanoparticles to promote wound healing. *Int. J. Biol. Macromol.* 232: 123480.

59 Hu, W.W. and Lin, Y.T. (2022). Alginate/polycaprolactone composite fibers as multifunctional wound dressings. *Carbohydr. Polym.* 289: 119440.

60 Apsite, I., Uribe, J.M., Posada, A.F. et al. (2020). 4D biofabrication of skeletal muscle microtissues. *Biofabrication* 12: 015016.

61 Yeo, M. and Kim, G. (2019). Nano/microscale topographically designed alginate/PCL scaffolds for inducing myoblast alignment and myogenic differentiation. *Carbohydr. Polym.* 223: 115041.

62 Formica, F.A., Öztürk, E., Hess, S.C. et al. (2016). A bioinspired ultraporous nanofiber-hydrogel mimic of the cartilage extracellular matrix. *Adv. Healthc. Mater.* 5: 3129–3138.

63 Hazeri, Y., Irani, S., Zandi, M., and Pezeshki-Modaress, M. (2020). Polyvinyl alcohol/sulfated alginate nanofibers induced the neuronal differentiation of human bone marrow stem cells. *Int. J. Biol. Macromol.* 147: 946–953.

64 Sadeghi, M., Falahi, F., Akbari-Birgani, S., and Nikfarjam, N. (2023). Trilayer tubular scaffold to mimic ductal carcinoma breast cancer for the study of chemo-photothermal therapy. *ACS Appl. Polym. Mater.* 5: 2394–2407.

65 Joo, G., Park, M., Park, S.S. et al. (2022). Tailored alginate/PCL-gelatin-β-TCP membrane for guided bone regeneration. *Biomed. Mater.* 17: 045011.

66 Li, W.R., Chen, P.E., Pan, Y.X. et al. (2022). Construction of a band-aid like cardiac patch for myocardial infarction with controllable HS release. *Adv. Sci.* 9: e2204509.

67 Bombin, A.D.J., Dunne, N., and McCarthy, H.O. (2023). Delivery of a peptide/microRNA blend electrospun antimicrobial nanofibres for wound repair. *Acta Biomater.* 155: 304–322.

68 Chen, X.Q., Zhu, Q.M., Wen, Y.S. et al. (2022). Chemical modification of alginate via the oxidation-reductive amination reaction for the development of alginate derivative electrospun composite nanofibers. *J. Drug Deliv. Sci. Technol.* 68: 103113.

69 Soto-Quintero, A., González-Alva, P., Covelo, A., and Hernández, M.A. (2022). Study of the in vitro degradation and characterization of the HaCat keratinocytes adherence on electrospun scaffolds based polyvinyl alcohol/sodium alginate. *J. Appl. Polym. Sci.* 139: e52775.

70 Molina, M.I.E., Chen, C.A., Martinez, J. et al. (2023). Novel electrospun polycaprolactone/calcium alginate scaffolds for skin tissue engineering. *Materials* 16: 136.

71 Ashraf, S.S., Parivar, K., Roodbari, N.H. et al. (2022). Fabrication and characterization of biaxially electrospun collagen/alginate nanofibers, improved with *Rhodotorula mucilaginosa* sp. GUMS16 produced exopolysaccharides for wound healing applications. *Int. J. Biol. Macromol.* 196: 194–203.

72 He, S., Fang, J., Zhong, C.X. et al. (2022). Controlled pVEGF delivery via a gene-activated matrix comprised of a peptide-modified non-viral vector and a nanofibrous scaffold for skin wound healing. *Acta Biomater.* 140: 149–162.

73 He, S., Fang, J., Zhong, C.X. et al. (2022). Spatiotemporal delivery of pBMP2 and pVEGF by a core-sheath structured fiber-hydrogel gene-activated matrix loaded with peptide-modified nanoparticles for critical-sized bone defect repair. *Adv. Healthc. Mater.* 11: e2201096.

74 Van Belleghem, S., Torres, L., Santoro, M. et al. (2020). Hybrid 3D printing of synthetic and cell-laden bioinks for shape retaining soft tissue grafts. *Adv. Funct. Mater.* 30: 1907145.

75 Jia, W.T., Gungor-Ozkerim, P.S., Zhang, Y.S. et al. (2016). Direct 3D bioprinting of perfusable vascular constructs using a blend bioink. *Biomaterials* 106: 58–68.

76 Pataky, K., Braschler, T., Negro, A. et al. (2012). Microdrop printing of hydrogel bioinks into 3D tissue-like geometries. *Adv. Mater.* 24: 391–396.

77 Kirillova, A., Maxson, R., Stoychev, G. et al. (2017). 4D biofabrication using shape-morphing hydrogels. *Adv. Mater.* 29: 1703443.

78 Jeon, O., Bin Lee, Y., Lee, S.J. et al. (2022). Stem cell-laden hydrogel bioink for generation of high resolution and fidelity engineered tissues with complex geometries. *Bioact. Mater.* 15: 185–193.

79 Bolívar-Monsalve, E.J., Ceballos-González, C.F., Chávez-Madero, C. et al. (2022). One-step bioprinting of multi-channel hydrogel filaments using chaotic advection: fabrication of pre-vascularized muscle-like tissues. *Adv. Healthc. Mater.* 11: e2200448.

80 Liang, J.C., Zeng, H.J., Qiao, L. et al. (2022). 3D printed piezoelectric wound dressing with dual piezoelectric response models for scar-prevention wound healing. *ACS Appl. Mater. Interfaces* 14: 30507–30522.

81 De Santis, M.M., Alsafadi, H.N., Tas, S. et al. (2021). Extracellular-matrix-reinforced bioinks for 3D bioprinting human tissue. *Adv. Mater.* 33: 2005476.

82 Xie, F.H., Sun, L.J., Pang, Y. et al. (2021). Three-dimensional bio-printing of primary human hepatocellular carcinoma for personalized medicine. *Biomaterials* 265: 120416.

83 Ma, H.S., Yang, C., Ma, Z.J. et al. (2022). Multiscale hierarchical architecture-based bioactive scaffolds for versatile tissue engineering. *Adv. Healthc. Mater.* 11: 2102837.

84 Zhu, H., Monavari, M., Zheng, K. et al. (2022). 3D bioprinting of multifunctional dynamic nanocomposite bioinks incorporating Cu-doped mesoporous bioactive glass nanoparticles for bone tissue engineering. *Small* 18: 2104996.