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Abstract

Amidst the Fourth Industrial Revolution, the emerging fields of biofabrication and biomanufacturing are transforming life sciences and healthcare. These sectors are benefiting from a synergy of engineering biology, sustainable manufacturing, and integrated design principles. The field of biofabrication in the United Kingdom is emerging as a pivotal force in bioscience and healthcare, propelled by cutting-edge research and development. Concentrating on the production of biologically functional products for use in drug delivery, in vitro models, and tissue engineering, research institutions across these regions are dedicated to innovating solutions that adhere to ethical and safety standards while prioritizing sustainable and affordable technologies that are rapidly deployable to a wide range of sectors, from food, to pharma and healthcare systems.

Main text

The Fourth Industrial Revolution, often referred to as Industry 4.0, has seen a transition period from 2000-2010 and is characterised by the fusion of electronics, robotics, and biology [1]. Integrating domains such as artificial intelligence, biotechnology, the internet of things, and 3D printing/ biofabrication is leading to rapid and global technological advancements that improve productivity and promote economic growth. In particular, technological advances have transformed the life science and biomedical sectors. These innovations have brought significant economic and health benefits in the short and medium terms, including a steady rise in life expectancy since the 1980s [2]. Although continued progress is critical to tackle diseases, prepare for future pandemics and improve healthy ageing, some of the impact of the healthcare industry cannot be ignored. For instance, the healthcare industry was responsible for twice as many carbon emissions as the aviation industry in 2019 [3, 4]. In addition, more than 100 million animals were used in research and testing globally in 2015 [5], and in 2022, 2.76 million scientific procedures were carried out on animals in the UK [6]. With less than 10% of drugs making it through this pipeline to clinical translation [7], these practices are unethical and unsustainable. The field of Engineering Biology will play a key role in supporting broadly future innovations in healthcare technologies and the pharmaceutical field, from the design and manufacturing of more affordable cell therapies, to improved in vitro models for therapeutics development and the design of next generations of vaccines and antibiotics.

Biofabrication will play a key role in Engineering Biology, and enabling the full impact of this field on technology development, translation, scale up and broad commercialization. This includes the application of techniques such as 3D bioprinting, tissue engineering, and directed assembly, which are used to produce biologically-based products using living cells and organisms [8]. These techniques can be applied in vitro to model healthy and disease phenotypes as well as in vivo for tissue and organ replacement. A 2023 report by the World Health Organization considered 3D bioprinting an emerging technology that could help solve global health challenges by increasing the supply of organs and tissues for drug screening and transplantation within the next 10 years [9].

Biofabrication is the process of constructing functional biological structures with living cells and biomaterials, whereas biomanufacturing employs biological systems for scalable production. In particular, biofabrication offers the potential to harness the vast potential of biology without the necessity of genetic modification. The immediate impact of both biofabrication and biomanufacturing emerges from the development and application of advanced biomaterials. Numerous "bio-inert" medical devices that have improved millions of lives and are still used today such as prosthetics, stents, and dental implants [10]. More recently, the focus has been on "bioactive" biomaterials that can harness the host response as a resource to enhance tissue-biomaterial adhesion [11], stimulate local tissue regeneration [12], or release targeted therapeutic agents [13]. The global market for these biomaterials/ bio-products was estimated at over 150 billion USD in 2022 and is expected to grow by 15% annually until at least 2030 [14]. Biofabrication has the potential to open up avenues for personalised medical solutions by using patient-derived cells to engineer a wide range of tissues [15], including bone [16], kidney [17], and myocardium models [18, 19]. This level of control over genetic background and tissue structure has allowed investigation of historically underrepresented demographics, including sex-specific differences in cardiac tissue [20, 21] and kidney [17] disease phenotypes. Although strategies addressing ethnic diversity have also been proposed [22], greater diversity is still needed with the vast majority of induced pluripotent stem cell (iPSC) lines being of European descent [23]. Effective use of the available biofabrication and biomanufacturing techniques can help reduce the pervasive gender and ethnicity biases still present in many biomedical studies [24]. Increasing the efficacy of diagnostic tools, improving patient outcomes, and extending medical device lifespans can save the NHS from significant costs associated with missed diagnoses and repeat visits.

The applications of biofabrication and biomanufacturing are vast and not just limited to healthcare and the life sciences. The food, sensor, farming, construction, and fashion industries can use affordable bioprinting and other biofabrication technologies to improve their productivity, and to develop new products. For example, the UK agriculture market alone was estimated at 7.9 billion GBP in 2022 [25]. These industries offer a large market for biofabrication to exploit. Small and medium-sized enterprises (SMEs), which make up 99% of all EU businesses [26], frequently face challenges in developing proprietary techniques and navigating the complex approval process for genetic engineering. Biofabrication offers a promising alternative that does not depend on genetic modification, providing affordable and accessible engineering biology solutions. The fair distribution of biofabrication technologies is crucial, as it allows SMEs to realize their full potential and contribute significantly to the industry.

Figure 1 highlights a range of different research groups from across the UK that are at the forefront of Industry 4.0 in the biofabrication fields. Research groups in this review are grouped by region to give a geographical breakdown of where key biofabrication technologies are being developed and utilised. As shown in Figure 1, the British Isles are home to a wide range of biofabrication techniques that are improving the efficiency and accuracy of lab-grown biologically-based products, including tissue engineering for a wide range of organ systems, sustainable polymers, hydrogels, smart fibres, nanoclays, and bioactive implants. With the size and rapidly evolving nature of the field, this review should not be considered an exhaustive list of biofabrication research being carried out in the UK, but instead should be considered a snapshot of popular biofabrication sub-themes being explored on these isles.

Looking to the future, biofabrication is poised to become a cornerstone of the rapidly evolving field of engineering biology. In the near to medium term (3-5 years), pursuing engineering biology through biofabrication which does not involve genetic modification could expedite ethical compliance and public acceptance, thereby facilitating quicker return on investment on the healthcare products and biotechnologies to be developed. Over the longer term (5-10 years), the integration of synthetic biology with biofabrication, alongside advances in tissue and cell engineering and scalable sustainable manufacturing, is expected to significantly enhance the value and safety of end products. This, in turn, may streamline regulatory processes due to heightened safety and efficacy. The success of these endeavors hinges on robust biofabrication and biomanufacturing sectors, ensuring swift adoption of new technologies and sustaining the UK's leading position in this domain. Additionally, the advancement of supporting infrastructure and specialized postgraduate education programs is crucial for preparing future experts, and sustaining robust biosecurity measures and bioeconomy development in the UK and the EU.

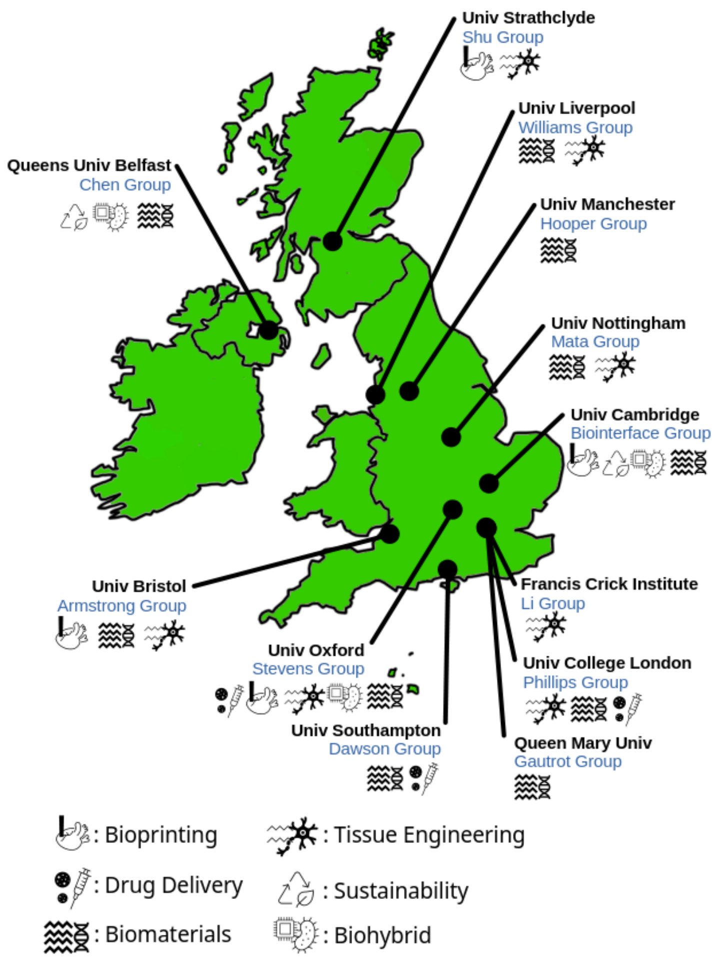

Figure 1. A non-exhaustive regional breakdown of biofabrication and biomanufacturing groups from around the UK as of March 2024.

References

[1] M. Xu, J. M. David, and S. H. Kim, “The Fourth Industrial Revolution: Opportunities and Challenges,” IJFR, vol. 9, no. 2, p. 90, Feb. 2018, doi: 10.5430/ijfr.v9n2p90.

[2] “National life tables – life expectancy in the UK: 2020 to 2022,” Office for National Statistics (ONS), statistical bulletin, Jan. 2024.

[3] R. Bosurgi, “Climate crisis: Healthcare is a major contributor, global report finds,” BMJ, p. l5560, Sep. 2019, doi: 10.1136/bmj.l5560.

[4] Global Carbon Project, “Supplemental data of Global Carbon Project 2019.” Oct. 10, 2019. doi: 10.18160/GCP-2019.

[5] K. Taylor and L. R. Alvarez, “An Estimate of the Number of Animals Used for Scientific Purposes Worldwide in 2015,” Altern Lab Anim, vol. 47, no. 5–6, pp. 196–213, Nov. 2019, doi: 10.1177/0261192919899853.

[6] “Annual Statistics of Scientific Procedures on Living Animals Great Britain 2022,” Home Office, Jul. 2023.

[7] C. H. Wong, K. W. Siah, and A. W. Lo, “Estimation of clinical trial success rates and related parameters,” Biostatistics, vol. 20, no. 2, pp. 273–286, Apr. 2019, doi: 10.1093/biostatistics/kxx069.

[8] W. Sun et al., “The bioprinting roadmap,” Biofabrication, vol. 12, no. 2, p. 022002, Apr. 2020, doi: 10.1088/1758-5090/ab5158.

[9] “Imagining futures of 3D bioprinting,” World Health Organization (WHO global health foresight series), Geneva, 2023.

[10] N. Huebsch and D. J. Mooney, “Inspiration and application in the evolution of biomaterials,” Nature, vol. 462, no. 7272, pp. 426–432, Nov. 2009, doi: 10.1038/nature08601.

[11] S. J. Rego, A. C. Vale, G. M. Luz, J. F. Mano, and N. M. Alves, “Adhesive Bioactive Coatings Inspired by Sea Life,” Langmuir, vol. 32, no. 2, pp. 560–568, Jan. 2016, doi: 10.1021/acs.langmuir.5b03508.

[12] G. Koller, R. J. Cook, I. D. Thompson, T. F. Watson, and L. Di Silvio, “Surface modification of titanium implants using bioactive glasses with air abrasion technologies,” J Mater Sci: Mater Med, vol. 18, no. 12, pp. 2291–2296, Dec. 2007, doi: 10.1007/s10856-007-3137-z.

[13] N. Zanjanizadeh Ezazi et al., “Fabrication and Characterization of Drug-Loaded Conductive Poly(glycerol sebacate)/Nanoparticle-Based Composite Patch for Myocardial Infarction Applications,” ACS Appl. Mater. Interfaces, vol. 12, no. 6, pp. 6899–6909, Feb. 2020, doi: 10.1021/acsami.9b21066.

[14] ‘Biomaterials Market Size, Share & Trends Analysis Report By Product (Natural, Metallic, Polymer), By Application (Cardiovascular, Orthopedics, Plastic Surgery), By Region, And Segment Forecasts, 2023 - 2030’, Grand View Research, 2023. [Online]. Available: https://www.grandviewresearch.com/industry-analysis/biomaterials-industry

[15] A. C. Fonseca et al., “Emulating Human Tissues and Organs: A Bioprinting Perspective Toward Personalized Medicine,” Chem. Rev., vol. 120, no. 19, pp. 11093–11139, Oct. 2020, doi: 10.1021/acs.chemrev.0c00342.

[16] C. Arrigoni, M. Gilardi, S. Bersini, C. Candrian, and M. Moretti, “Bioprinting and Organ-on-Chip Applications Towards Personalized Medicine for Bone Diseases,” Stem Cell Rev and Rep, vol. 13, no. 3, pp. 407–417, Jun. 2017, doi: 10.1007/s12015-017-9741-5.

[17] M. Van Daal, M. E. Muntinga, S. Steffens, A. Halsema, and P. Verdonk, “Sex and Gender Bias in Kidney Transplantation: 3D Bioprinting as a

Challenge to Personalized Medicine," Women's Health Reports, vol. 1, no. 1, pp. 218–223, Apr. 2020, doi: 10.1089/whr.2020.0047.

[18] T. Eschenhagen, C. Mummery, and B. C. Knollmann, "Modelling sarcomeric cardiomyopathies in the dish: From human heart samples to iPSC cardiomyocytes," Cardiovascular Research, vol. 105, no. 4, pp. 424–438, Apr. 2015, doi: 10.1093/cvr/cvv017.

[19] C. Kim et al., "Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs," Nature, vol. 494, no. 7435, pp. 105–110, Feb. 2013, doi: 10.1038/nature11799.

[20] R. Lock et al., "A framework for developing sex-specific engineered heart models," Nat Rev Mater, vol. 7, no. 4, pp. 295–313, Apr. 2022, doi: 10.1038/s41578-021-00381-1.

[21] V. Regitz-Zagrosek and G. Kararigas, "Mechanistic Pathways of Sex Differences in Cardiovascular Disease," Physiological Reviews, vol. 97, no. 1, pp. 1–37, Jan. 2017, doi: 10.1152/physrev.00021.2015.

[22] E. A. Chang et al., "Derivation of Ethnically Diverse Human Induced Pluripotent Stem Cell Lines," Sci Rep, vol. 5, no. 1, p. 15234, Oct. 2015, doi: 10.1038/srep15234.

[23] S. Ghosh, R. Nehme, and L. E. Barrett, "Greater genetic diversity is needed in human pluripotent stem cell models," Nat Commun, vol. 13, no. 1, p. 7301, Nov. 2022, doi: 10.1038/s41467-022-34940-z.

[24] J. Y. Kim, K. Min, H. Y. Paik, and S. K. Lee, "Sex omission and male bias are still widespread in cell experiments," American Journal of Physiology-Cell Physiology, vol. 320, no. 5, pp. C742–C749, May 2021, doi: 10.1152/ajpcell.00358.2020.

[25] ‘National Statistics Summary’, Department for Environment, Food, & Rural Affairs, Feb. 2024.

[26] “A European industrial strategy: Unleashing the full potential of European SMEs.” European Commission. Directorate General for Communication, Mar. 2020.