REGENERATIVE MEDICINE
2024, VOL. 19, NO. 12, 611–616
https://doi.org/10.1080/17460751.2024.2437281

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PERSPECTIVE

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Artificial intelligence powers regenerative medicine into predictive realm

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ABSTRACT
The expanding regenerative medicine toolkit is reaching a record number of lives. There is a pressing need to enhance the precision, efficiency, and effectiveness of regenerative approaches and achieve reliable outcomes. While regenerative medicine has relied on an empiric paradigm, availability of big data along with advances in informatics and artificial intelligence offer the opportunity to inform the next generation of regenerative sciences along the discovery, translation, and application pathway. Artificial intelligence can streamline discovery and development of optimized biotherapeutics by aiding in the interpretation of readouts associated with optimal repair outcomes. In advanced biomanufacturing, artificial intelligence holds potential in ensuring quality control and assuring scalability through automated monitoring of process-critical variables mandatory for product consistency. In practice application, artificial intelligence can guide clinical trial design, patient selection, delivery strategies, and outcome assessment. As artificial intelligence transforms the regenerative horizon, caution is necessary to reduce bias, ensure generalizability, and mitigate ethical concerns with the goal of equitable access for patients and populations.

ARTICLE HISTORY
Received 25 September 2024
Accepted 29 November 2024

KEYWORDS
artificial intelligence; healthcare; machine learning; manufacturing; regeneration; stem cell; systems biology; tissue engineering

Οι έξυπνοι μαθαίνουν από όλα και από όλους, οι μέτριοι από τις εμπειρίες τους – Σωκράτης

Smart people learn from everything and everyone, average ones from experience … – Socrates
(Greek Philosopher; 469 BC – 399 BC)

1. Regenerative medicine today

The portfolio of increasingly mature regenerative biotechnologies continues to grow and diversify [1,2]. Across therapeutic classes and clinical indications, innovative regenerative therapies offer disruptive approaches that aspire to restore the form and function of a failing organ and rebuild recipient's health [3]. Immersing into diverse healthcare sectors, the expanded regenerative toolbox aims to enrich contemporary treatment options beyond the symptom mitigation scope of more traditional therapies. Notably, regenerative approaches aim to offer disease-modifying or even curative options for notoriously recalcitrant conditions and otherwise incurable maladies [4]. Currently, emerging regenerative care solutions touch a record number of human lives around the globe through regimented clinical trials and real-world practices, projecting past the originally stated goals of structural and functional repair to achieve quality-of-life objectives [5–13]. With this evolving backdrop, regulatory approvals have been sought more frequently across clinical specialties. These efforts are exemplified by practice-transformative regenerative immunotherapies introduced for the management of B-cell lymphomas, B-cell lymphoblastic leukemia, and multiple myeloma in haemato-oncology; for addressing ocular burn-induced limbal stem cell deficiency in ophthalmology; or for complex fistula repair and Crohn's disease treatment in gastroenterology and surgery [14–16]. Cartilage-derived chondrocytes for cartilage repair, and mesenchymal stem cells [17] in graft-versus-host disease, are also now registered therapies [6,7,18]. However, the incomplete understanding of the nature and/or cause of treated disease entities, amplified by only a partial characterization of applied biotherapies, have hindered a broader uptake in practice, jeopardized notably by mixed, and often unpredictable clinical outcomes [19–21]. Accordingly, there is a pressing need to enhance the precision, efficiency, and effectiveness of regenerative approaches to reach standards realized with more conventional armamentaria in human medicine. Notable examples include the continuous need for: (i) optimized cell biotherapeutics endowed with predictable regenerative potency and functionality; (ii) improved tissue engineered scaffolds, custom-designed, and offering desirable tissue interaction properties for enhanced outcome; (iii) targeted selection of suitable patient populations most likely to favorably respond to a regenerative regimen; (iv) comprehensive surveillance of recipient responses following a regenerative intervention in order to maximize longitudinal follow-up; and (v) through iterative considerations, realizing accelerated cycles of next-generation discovery and development that leverage the growing clinical experience enabling in turn expedited advances and adding value to overcome diverse challenges that span the regenerative science and practice continuum.

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Article highlights

Regenerative Medicine Today and Current Challenges

- The regenerative medicine armamentarium continues to grow.
- Regenerative therapies touch a record number of lives.
- Incomplete understanding of the nature and/or cause of treated disease entities and partial characterization of biotherapies have resulted in mixed, often unpredictable clinical outcomes, hindering a broader uptake.
- Data science and bioinformatics usher a next phase in the evolution of the field, helping to overcome recognized constraints.

Machine Learning and Deep Learning

- Artificial intelligence encompasses the domains of machine learning and deep learning with attributes pertinent in addressing uncertainties in the precision, efficiency, and effectiveness of regenerative pipelines.
- Machine learning relies on fitting predictive models to empower classification, regression, and/or clustering of high-dimensional inputs.
- Deep learning relies on neural network architectures capable of extracting features from raw data and processing them to offer an output to be used sequentially for higher-order analysis.

AI Empowered Regenerative Medicine

- Use of artificial intelligence domains is expected to enhance the technological, translational, and clinical readiness of regenerative medicine approaches.
- Artificial intelligence-augmented omics analysis can help refine biotherapy development.
- Integration of artificial intelligence into the manufacturing know-how is particularly valuable in ensuring quality control and assuring scalability.
- Machine learning models can be fed process parameters from bioreactors to enable identification of predictive variables critical for development, optimization, and upscaling of complex biomanufacturing processes and procedures.
- Deep learning trained for morphometric profiling can automate manufacturing ensuring quality and scalability.
- Collectively, incorporation of artificial intelligence in advanced manufacturing processes can reduce technical requirements and help close the readiness gap.

AI in Assessment of Regenerative Therapies

- Artificial Intelligence informs the translation of regenerative technologies, enhancing clinical assessment of regenerative therapy outcomes.
- Clinical trial design may be augmented with artificial intelligence approaches which take advantage of available real-world datasets to improve trial designs by helping reduce bias, increase diversity, and guide therapeutic indications and candidate selection.

Future Perspective

- Artificial intelligence holds promise in facilitating the advancements across regenerative science and medicine specialties.
- As artificial intelligence is increasingly applied, several potential pitfalls need to be addressed including algorithmic bias, overfitting of the training data, and data security.
- Artificial intelligence is gradually embraced across regenerative medicine pipelines with the potential to propel emerging biotherapeutics toward clinical service-line integration.

2. Current challenges

Case in point, early regenerative protocols and pioneering clinical development plans did not discern the regenerative aptitude of delivered biotherapeutics and did not necessarily consider distinct underlying disease substrates presenting distinctive, often idiosyncratic therapeutic requirements [22,23]. Moreover, the recognized shortcomings in delivery strategies and the commonly imprecise best candidate identification have confined the regenerative care pathways to an empirical paradigm [24–26]. Regenerative practice has in fact largely relied on experience-guided algorithms based on inference from trial-and-error iterations rather than on the fidelity of evidence-based and guideline-directed, reliable care pathways. In this context, ongoing optimizing endeavors have been multi-pronged, ranging from deciphering the regeneration-permissive intimacy of disease substrates to decoding the mode of regenerative action, and ultimately delineating clinical predictors and biomarkers of therapeutic response [27–29]. Despite ongoing advances, translation of regenerative science into standardized clinical applications with dedicated and validated care pathways continues to be impeded by mixed results across specialties, including in gastroenterology, neurosurgery, orthopedics, or dermatology attributed in part to differences ensuing from the selection of patient candidates in the absence of definitive clinical guidelines, non-standardized regenerative material sourcing, variable delivery strategies, and non-harmonized outcome measures [30–33] Data science and bioinformatics have ushered a next phase in the evolution of the field attempting to overcome traditional constraints. Indeed, progress in data mining and information engineering — exemplified by multiomics-based dissection of disease substrates, biotherapeutic profiles, and repair links — have offered the opportunity for more advanced solutions [34]. This includes the launch of fit-for-purpose biotherapies, fine-tuned delivery options, or informed selection of recipient candidates [35–37]. As such, regenerative medicine continues to benefit from the prospect of integrating predictive measures, adding value to the reliability of the discipline and its impact on contemporary clinical care [38]. Markedly, regenerative medicine is increasingly recognized not only as a traditionally reactive healthcare option but rather as one presenting a proactive potential able to bring benefit early, even at a pre-clinical disease stage [39]. Ultimately, successful implementation and seamless integration of regenerative choices into mainstream healthcare systems requires ensuring validity (i.e., safety and efficacy) and utility (i.e., sustained benefit over standard of care) of introduced curative therapies while achieving equitable access and sustainable adoption for the broad benefit of patients and populations [40].

3. The era of machine learning and deep learning

The wealth of 'big data' sets, the progress with data analytics, and the increased fluency and applicability of sophisticated informatic languages have collectively offered an unprecedented opportunity to harness the expanding artificial intelligence technologies and develop modern platforms capable of augmenting the processes of discovery, translation, and application across the regenerative science and medicine spectrum. Artificial intelligence, an umbrella term for software that aspires to mimic and/or augment human cognition, encompasses the domains of 'machine learning' and 'deep learning' with both offering unique and pertinent attributes [41]. Specifically, machine learning relies on fitting predictive models, i.e., algorithms, with recognized value in dealing with complex and large datasets to empower classification, regression, and/or clustering of high-dimensional inputs [42]. Machine learning is readily applicable across the entirety of the innovation pipeline. Case in point, unsupervised machine learning algorithms are a cornerstone of omics analysis, supporting an unbiased assessment of distinct disease states [43] even when preceding overt disease manifestation in efforts that explore and exploit disease risk signatures [44]. Machine learning, in unison with dimensional reduction, can help distill intricate and multiparametric readouts, allowing identification of distinct (e.g., patient) cohorts correlating with discrete (pre) clinical endpoints and/or patterns [45–47]. Capable of extracting features from raw data and processing them to offer an output to be used sequentially for higher-order analysis, deep learning relies on neural network architectures comprised of interconnected 'neurons' performing a function on an input and providing a discerning output [42]. Deep learning applications in medicine are diverse, spanning from computer vision, natural language processing, and reinforcement learning with recognized value for advanced imaging, electronic health record utilization, and robotic interventions, respectively [48]. Deep learning has been used for high throughout drug candidate screening [49], predicting therapeutic response [50,51], imaging-based diagnostics [52], or in aiding with triaging and clinical decision support [53]. Indeed, the integration of artificial intelligence methodology in regenerative medicine could significantly impact the next iteration of the discovery science to clinical application spectrum [54].

4. AI empowered regenerative medicine

Use of artificial intelligence domains is expected to enhance the technological, translational, and clinical readiness of regenerative medicine approaches [55]. Case in point, artificial intelligence presents broad utility in the discovery and development of new biotherapeutics. Moreover, it facilitates advanced at-scale manufacturing [56]. Systems interrogation has enabled identifying stem cell signatures associated with a boosted regenerative outcome in the setting of organotypic considerations [57]. Integration of these approaches with deep learning-based high-throughput morphometric analysis could foster an iterative refinement of the biotherapeutic discovery-development-diffusion cycle [58]. In fact, high-throughput 'omics technologies are a proven exemplar that has aided in the dissection of regenerative signals produced by reparative stem cell populations, facilitating, in turn, to gain insight into means that would streamline cell-free alternatives reduced to the essence of the required and sufficient regenerative signaling information. Artificial intelligence application can aid in genome annotation, gene and protein identification, prediction of binding locations and protein–protein interactions. Multidimensional data processing and integration helps the charting of molecular expression profiles needed for classification of disease status and prediction of therapeutic impact [59–63]. Unsupervised machine learning of protein expression patterns following dimensionality reduction has documented, for example, the rescue of the infarcted myocardial proteome returning toward a pre-infarcted state following regenerative therapy intervention [59]. Artificial intelligence can further foster clinical development programs of biotherapies through aided cell function monitoring to automate interpretation of readouts [64] informing fit-for-purpose therapy refinement [59]. For example, a deep learning model trained on individual preclinical or clinical trial datasets leveraging mesenchymal stromal cells for cartilage repair was able to identify factors associated with targeted repair and to offer the opportunity for therapeutic refining [65].

5. AIenhanced manufacturing of regenerative biotherapeutics

In conjunction with the discovery-development axis, integration of artificial intelligence into the manufacturing know-how is particularly valuable in ensuring quality control and assuring scalability, prerequisites in the clinical-grade manufacturing workflows. For example, machine learning models can be fed process parameters from bioreactors to enable identification of predictive variables critical for development, optimization, and upscaling of complex biomanufacturing processes and procedures [66,67]. Informed manufacturing practices may help target the underlying drivers of heterogeneity that hinder translation during scale-up [66,68]. Case in point, translation of morphometric profiling empowered by deep learning trained on microscopic images can automate manufacturing. Namely, a high-speed laser coupled with deep learning enables high-throughput cell purification, facilitating the maintenance of high-quality pluripotent stem cell lines free from spontaneously differentiating progeny [69]. Subsequently, models trained on tracking differentiation and manufacturing enable automated detection of the most desirable cell populations, ready for on-demand applications [70]. Beyond stem cells, artificial intelligence can help guide the development of optimal matrices such as those based on hydrogels and used in tissue engineering and hybrid regenerative products [71]. Collectively, incorporation of artificial intelligence in advanced manufacturing processes can reduce technical requirements and help close the readiness gap [72] to promote a mass customized outlook for personalized regenerative care [73]. Yet, leveraging artificial intelligence for regenerative applications is still in its infancy [71]. Thus, the responsible and ethical use of artificial intelligence will require interdisciplinary collaboration, ethical oversight and review, and consistent transparency [74–77].

6. AI in clinical assessment of regenerative therapies

Artificial Intelligence informs the translation of regenerative technologies, enhancing clinical assessment of regenerative therapy outcomes. For instance, artificial intelligence helps to identify prospective imaging biomarkers [78]. Synergized with large regenerative medicine trials, these efforts have identified imaging-based biomarkers associated with benefit from cell therapy [5,38] helping to map useful biomarker panels that stratify patients most likely to respond to a regenerative treatment option [79]. At macro level, clinical trial design may be augmented with artificial intelligence approaches which take advantage of available real-world datasets to improve trial designs by helping reduce bias, increase diversity, and guide therapeutic indications and candidate selection [80]. Following therapy delivery, machine learning may also help track therapeutic response. Hence, artificial intelligence platforms are poised to help transform regenerative science and medicine, augmenting, and accelerating biotherapeutic development, informing targeted delivery, and refining outcome monitoring for the express purpose of extending healthspan for patients and populations.

7. Future perspective

In the context of steady longevity gains, the healthspan-lifespan gap is widening worldwide, underpinned by a rise in the burden of chronic noncommunicable diseases, a global phenomenon [81,82]. Regenerative medicine is anticipated to contribute to modern strategies rolled out to compress the healthspan gap that undermines healthy living [81]. In this regard, artificial intelligence holds promise in facilitating the advancements across regenerative science and medicine specialties to narrow the widening healthspan-lifespan gap and contribute to a healthy longevity horizon [82]. Notwithstanding, a sustainable and equitable regenerative care outlook requires ethical and transparent deployment of artificial intelligence-driven prediction models following careful consideration of challenges and pitfalls by multi-national public and private stakeholders, and demonstrable integrity and reproducibility through data, model and code sharing. Several potential pitfalls, including algorithmic bias, may be introduced during the training process [83]. Indeed, artificial intelligence forecasts are highly dependent on the accurate and high-quality data input [84]. Overfitting of the training data may result in models that perform well during training, but are not generalizable in real-world clinical and societal applications [85]. This is of particular relevance for minorities and groups traditionally underrepresented in biomedical studies, including the elderly, as training data of sufficient volume or quality may be missing in these populations [86]. In this context, the application of algorithms must be conscientiously applied to prevent bias and treatment inequities. These emerging points of vulnerability require rigorous collection of high-quality training data that are representative of demographics, including vulnerable populations; in parallel, regular performance assessment of models is required [83]. It is equally important to prevent unauthorized scraping of deposited data sets, thus respecting data frontiers in line with patient consent and privacy. Leveraging open access data sharing can help expand available training data sources. However, differences in analysis pipelines may add heterogeneity in information gleaned from previously analyzed datasets [87]. In line with the importance of high-quality information-rich data, accurate models require cleanly annotated training datasets with a rigorously defined ground truth to enable accurate learning [88]. Deep learning models are attractive as they allow abstraction of relevant features of importance; however, these 'black box' models are obscure and have limited interpretability, which may hinder applicability in clinical decision-making in part attributed to challenges with accountability and undetected bias [89]. Thus, translatability into the clinic across healthcare systems may be best achieved by leveraging the simplest model to reach the desired outcome. In addition, the use of artificial intelligence models will require access to vast amounts of private personal and health information which poses data security concerns due to the risk of breaches and inappropriate use [83]. Caution is necessary as large language models may influence medical knowledge, with risk for misuse and important downstream ramifications [84]. Artificial intelligence is being gradually embraced across regenerative medicine pipelines with the potential to further propel emerging biotherapeutics toward clinical service-line integration. Assuring inclusive and distributed governance will be paramount at the age of augmented intelligence models capable of reasoning as artificial intelligence powers regenerative medicine into the predictive realm.

Acknowledgments

The authors recognize the Marriott Family Foundation for invaluable support in advancing the principles and practices of regenerative medicine. Andre Terzic is a Mayo Clinic Distinguished Investigator.

Author contributions

Concept and design: Armin Garmany & Andre Terzic
Manuscript writing and approval: Armin Garmany & Andre Terzic
Administrative support and supervision: Andre Terzic
Andre Terzicisa member of the *Regenerative Medicine* Editorial Board. They were not involved in any editorial decisions related to the publication of this article, and all author details were blinded to the article's peer reviewers as per the journal's double-anonymized peer review policy.

Disclosure statement

Andre Terzic is a co-inventor on regenerative sciences related intellectual property disclosed to Mayo Clinic. Mayo Clinic and Andre Terzic have interests in Rion LLC. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
No writing assistance was utilized in the production of this manuscript.

Funding

Work in the authors' laboratory is supported by the Marriott Family Foundation. Armin Garmany is supported by the National Institute of General Medical Sciences (T32 GM145408). Andre Terzic acknowledges the National Institutes of Health grant award (R01 hL134664).

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