

Review

# Integrating Artificial Intelligence for Academic Advanced Therapy Medicinal Products: Challenges and Opportunities

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**Abstract:** Cell and gene therapies represent promising new treatment options for many diseases, but also face challenges for clinical translation and delivery. Hospital-based GMP facilities enable rapid bench-to-bedside development and patient access but require significant adaptation to implement pharmaceutical manufacturing in healthcare infrastructures constrained by space, regulations, and resources. This article reviews key considerations, constraints, and solutions for establishing hospital facilities for advanced therapy medicinal products (ATMPs). Technologies like process analytical technology (PAT), continuous manufacturing, and artificial intelligence (AI) can aid these facilities through enhanced process monitoring, control, and automation. However, quality systems tailored for product quality rather than just compliance, and substantial investment in infrastructure, equipment, personnel, and multi-departmental coordination, remain crucial for successful hospital ATMP facilities and to drive new therapies from research to clinical impact.

**Keywords:** bioprocess; advanced therapy medicinal products (ATMPs); artificial intelligence (AI); cell and gene therapies; bench-to-bedside delivery; personalized medicine; GMP facilities; quality systems



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## 1. Introduction

Advanced therapy medicinal products (ATMPs) like cell and gene therapies are innovative treatment approaches that modify patients' genes, cells, or tissues to treat disease. 'Academic advanced therapy' in the context of ATMPs refers to those developed within academic institutions, including medical centers and hospital environments. This approach contrasts with industrial ATMP development, focusing on pioneering innovative treatments and bridging the gap between basic research and clinical application. Academic institutions play a crucial role in the translational process, emphasizing a blend of scientific discovery and practical healthcare outcomes. These centers convert laboratory discoveries into viable therapies, integrating innovative treatment development within academic research frameworks, distinct from commercial pharmaceutical manufacturing [1]. However, ATMPs remain experimental, requiring an initial translation from laboratories to clinical trials to demonstrate safety and efficacy. The personalized nature of many ATMPs, using autologous or allogenic patient cells, adds manufacturing complexity compared to traditional pharmaceuticals. Each patient-specific batch must be rapidly produced in small quantities and under stringent aseptic conditions. Strict guidelines like good manufacturing practices (GMPs) are essential for ensuring quality. The implementation of GMPs is mandatory to secure approval from regulatory agencies for the production and use of ATMPs.

Traditionally, pharmaceutical companies have possessed the infrastructure and expertise to manufacture therapies for clinical trials under GMPs. However, the personalized nature of most autologous/allogenic ATMPs has required academic medical centers to develop their own in-house GMP facilities, to enable bench-to-bedside translation and patient access within the same institution. However, constructing GMP facilities within hospitals faces considerable constraints. Here, we review the key challenges academic

medical centers must address in establishing ATMP manufacturing, as well as emerging solutions to facilitate the clinical translation of innovative new therapies.

This article aims to explore the multifaceted role of artificial intelligence techniques such as machine learning and computer vision in the ATMP manufacturing revolution. It seeks to provide a global view of the current state of AI integration, specifically the application of subfields such as natural language processing and predictive modelling, carrying out a detailed search for information on the benefits that these technologies provide and the challenges entailed, particularly in relation to GMP compliance and optimization of hospital ATMP facilities. Through this exploration, this paper will illuminate the dynamic interplay between specialized AI applications and ATMP manufacturing, highlighting how this integration of specific capabilities such as automated image analysis and adaptive control can advance the field, while ensuring safety, effectiveness, and regulatory compliance.

## 2. Advantages of On-Site Hospital Facilities

Having GMP facilities located directly within academic hospitals provides major advantages for producing autologous/allogenic ATMPs. Proximity allows cell-based therapies to be rapidly manufactured on-site and delivered directly to patients. This avoids risks associated with transporting fragile cell products long distances between external manufacturing sites and hospitals [2]. This closeness not only preserves the integrity of cellular products but also simplifies logistics, reducing both the costs and risks associated with transporting products over long distances. Furthermore, the alignment of manufacturing with clinical schedules allows for flexible batch planning, accommodating rapid changes due to production dynamics or patient needs [3,4]. On-site facilities also enable the smooth translation of therapies from laboratory discovery to clinical trials. Once safety has been established in early phase studies, hospital facilities can continue providing patient access through expanded access programs.

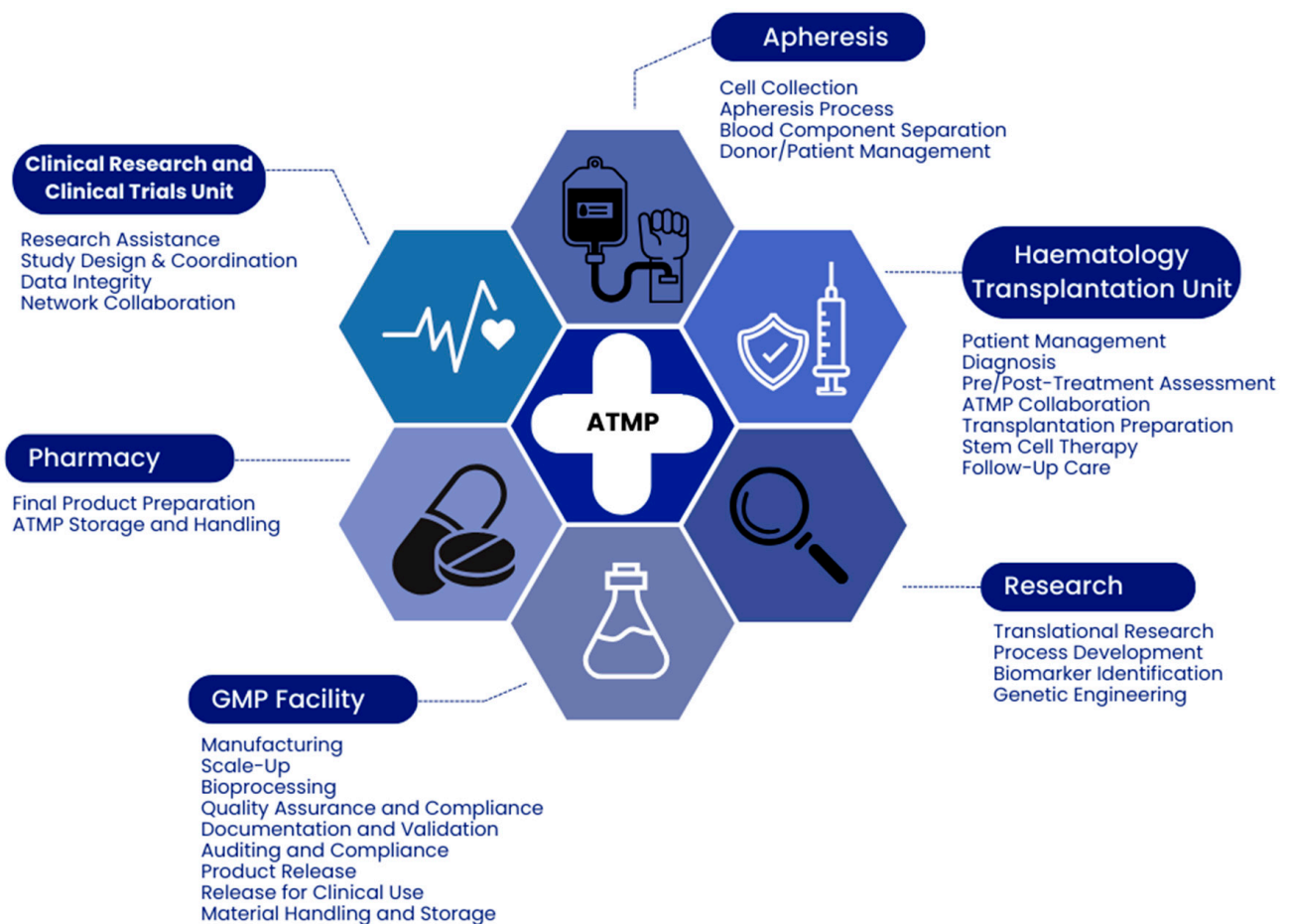
One of the major disadvantages faced by hospital facilities is limited space. Hospitals must integrate cleanrooms and manufacturing equipment into existing infrastructure not designed for production. Facilities must be strategically designed to make optimal use of available space. The use of isolators and closed systems can limit the need for larger cleanrooms [5,6]. Careful planning allows the creation of multi-product facilities that segregate therapies like viral vectors or gene-modified cells. Despite space restrictions, on-site locations remain ideal for the frequent manufacturing of personalized cell therapies requiring rapid delivery in small batches [3].

### 2.1. Implementing GMPs in Hospitals

While proximity provides clear advantages, implementing pharmaceutical manufacturing and GMPs within healthcare settings also poses challenges. Hospital staff are generally unfamiliar with the extensive GMP documentation, training in bioprocesses, and oversight required for clinical cell and gene therapy production [7]. Quality systems within healthcare focus on ensuring optimal medical services, whereas pharmaceutical GMPs aim to guarantee consistent product quality and safety [8]. Extensive GMP training and ongoing specialized personnel education are essential to bridge this gap.

The manufacturing of autologous/allogenic ATMPs integrates key hospital units, as depicted in Figure 1, to streamline the entire production and administration process. A clinical research and clinical trials unit spearheads the development of clinical research projects, ensuring meticulous research support and data integrity. Close to this is the hematology department, which is crucial for patient management in cell-based therapies, covering diagnosis, pre-treatment assessments, and collaboration for ATMP application. Notably, the transplantation unit within this department specializes in the preparatory and follow-up care for stem cell therapy [9]. Research areas like translational research and process development bridge the gap between laboratory research and clinical application, facilitated by innovative research fields such as biomarker identification cell therapy and genetic engineering. The apheresis unit plays a vital role in the initial collection of cellular

materials, ensuring expert handling of apheresis and patient care. In the sphere of product preparation, the pharmacy department is pivotal for the final formulation and storage of ATMPs, maintaining optimal conditions until clinical use. At the heart of manufacturing is the GMP facility, encompassing a comprehensive spectrum from manufacturing to quality assurance, as well as adhering to strict documentation and compliance standards. The synergy among these units, as visualized in Figure 1, is essential for the construction, qualification, validation, and maintenance of GMP facilities. This coordinated approach ensures that hospital activities, including the handling of biological samples and adherence to GMP requirements, maintain product quality throughout all manufacturing phases. Continuous communication across these units fosters an awareness of GMP regulations, which is crucial for staff members not typically versed in pharmaceutical standards [3,10].



**Figure 1.** Presents a cohesive overview of the operational framework surrounding advanced therapy medicinal products (ATMPs). At the core of the illustration is the ‘ATMP’, with surrounding nodes representing various specialized units. Each hospital unit is integral to the ATMP development and application process, highlighting the collaborative nature of this advanced medicinal ecosystem.

Quality system adaptation in hospitals, specifically focusing on product quality, safety, and efficacy, is key to implementing GMPs in hospitals. Excessive procedures solely for regulatory compliance can impede operations. A risk-based approach (RBA) in hospitals can concentrate quality efforts on critical factors affecting products and patients [8]. This method facilitates translating ATMPs to clinical practice, while ensuring compliance with pharmaceutical manufacturing standards within complex hospital environments [3,11,12]. This approach helps to identify priority areas where the quality system can be optimized without compromising product quality or patient safety in any case. This enables hospitals to avoid unnecessary regulatory procedures that are solely for the sake of regulatory compliance and that do not contribute to operational efficiency or patient care. This

balanced approach ensures that, while regulatory standards are fully met, the primary emphasis remains on safeguarding patient health and ensuring the efficacy of ATMPs. In essence, adapting a quality system using RBA perspectives is not only about meeting regulatory requirements but also about enhancing the quality of healthcare delivery in the challenging and dynamic environment of hospitals [13].

## 2.2. Investment in Infrastructure and Personnel

Significant investment in infrastructure, equipment, and personnel is essential when establishing in-house GMP facilities [14]. Constructing, qualifying, and maintaining pharmaceutical cleanrooms requires extensive capital. Specialized manufacturing and monitoring equipment suited for cell processing must be purchased and qualified. The costs of infrastructure, alongside expenses for consumables and testing, highlight the value of efficient facility designs that maximize productivity.

Recruiting personnel with appropriate backgrounds in cell therapy process development, GMP manufacturing, quality control, quality assurance, and regulatory experience is crucial but challenging given this field's novelty. Finding personnel with experience in clinical cell bioprocessing is not always simple. Staff availability can limit capacity, so manufacturing strategies maximizing operator productivity can enable hospitals to meet clinical demand within personnel constraints [5]. Extensive planning and financial investment are critical for establishing the necessary infrastructure, staff, training, and multi-departmental coordination for hospital ATMP facilities, to effectively transition new therapies from research to clinical application. This transition is especially pertinent when integrating emerging technologies like AI, where financial considerations are paramount. The study by Harrison et al. underscored the importance of economical scalability in cell therapy manufacturing, highlighting the potential of small-scale microfactories as a cost-effective approach before progressing to larger-scale macrofactories [15,16]. This model calls for careful economic assessment, particularly in automating processes to enhance efficiency and reduce costs, while maintaining quality control and managing the variability in donor cell characteristics. This strategy of balancing innovation with sustainability can serve as a template for AI integration in ATMP manufacturing, and it may even promote and facilitate clinical integration [17,18]. Infrastructure, equipment, and personnel training represent substantial investments, especially for smaller-scale academic facilities involved in the production of CAR-T cells, a type of ATMP. These upfront investments are pivotal due to the high costs associated with CAR-T cell manufacturing, which can reach approximately USD 400,000 per therapy production. However, integrating AI in this process offers a promising opportunity to reduce these costs. AI's ability to analyze and interpret data can significantly improve the efficiency and cost-effectiveness of CAR-T cell production by automating the multi-step manufacturing process, allowing comprehensive data collection. Such automation not only directly lowers high manufacturing costs but also aids in optimizing logistics and scaling production. Moreover, AI technologies could assist in identifying suitable patients for therapy, monitoring therapy progression, and predicting treatment responses. However, creating an AI-based CAR-T cell therapy system also raises challenges such as data privacy, data security, and the requirement to integrate AI systems into existing workflows. Ultimately, reducing contamination incidents and batch failures through AI can boost usable outputs, with forecasts suggesting that the total cost of goods may decrease by up to 18%, thus enhancing process sustainability. These benefits cannot be realized until there are verifiable use cases, combined with increased maturity in major capabilities such as blockchain technology and digitalization, highlighting the clear economic incentives and reduction in barriers to AI adoption of ATMP manufacturing [19,20].

Additionally, it is a fact that decentralized manufacturing has emerged as a crucial strategy in the cell and gene therapy arena, not just revolutionizing production landscapes but also addressing staffing and training challenges. Thus, a decentralized model refers to distributing production across multiple hospital nodes, while on-site facilities refer to the presence of manufacturing capabilities within each individual hospital. This decentralized



paradigm complements on-site facilities by enabling production to occur in smaller, dispersed facilities across locations, rather than consolidated in one large, centralized facility. The decentralized network model allows hospitals to reap the benefits of on-site production, while distributing resources and sharing expertise across nodes. Through dispersing production across multiple locations, this inherently meets the demand for personalized treatments. The pivotal role of automation in this new paradigm complements the indispensable expertise of trained human operators, ensuring the management of process variability and adherence to stringent quality standards within ‘smart cell factories’. This approach synergizes with the need for highly skilled personnel in cell therapy process development, GMP manufacturing, and regulatory compliance. It also aligns with the integration of AI and other emerging technologies, which are essential for economical scalability, as discussed in the study by Harrison et al. Decentralized manufacturing not only enhances operator productivity but also democratizes the value chain, generating socioeconomic benefits through job creation. Additionally, it offers a strategic framework for academic facilities involved in CAR-T cell production, addressing the substantial upfront investments in infrastructure and training. Incorporating AI into decentralized systems promises to reduce manufacturing costs, optimize logistics, and scale production, while ensuring data privacy and security. This model presents a sustainable solution, balancing innovation with efficiency, as well as setting a template for future advancements in ATMP manufacturing [21].

### 3. Enhancing Hospital Facilities with New Technologies

Emerging technologies present opportunities to enhance the capabilities of hospital ATMP facilities within ever-present space, time, cost, and personnel constraints. Process analytical technology (PAT) is a pivotal advancement employing advanced in-line monitoring and process control to optimize manufacturing [22]. By continuously analyzing physicochemical parameters like pH, dissolved oxygen, and temperature—as well as metabolites and nutrient concentrations, such as glucose and glutamine, and byproduct concentrations, such as lactate and ammonia—bioreactors can be automatically controlled, decreasing manual operations [23,24]. This approach is complemented by the application of advanced sensory technologies, particularly fluorescent optical sensors, as highlighted in recent research [25]. These sensors are instrumental for real-time monitoring, enabling the quantification of analytes of interest during bioprocessing. This capability for early detection is crucial for identifying deviations from method parameters, facilitating timely countermeasures and ensuring consistency in individualized batches. The integration of PAT with state-of-the-art sensory technologies underscores the increase in biomanufacturing efficiency for enhanced control methods in the complex cellular manufacturing environments of cell and gene therapy. Automated cell counting and viability analysis and product concentration reduces delays when waiting for quality control results before proceeding to the next manufacturing step. PAT enables real-time process adjustments and consistency between individualized batches [26]. Building upon the principles of PAT, a recent study [27] made significant strides toward enhancing the capabilities of in-line monitoring and process optimization in biomanufacturing. This research introduced a pioneering automated method for creating Raman spectroscopy models using Python and Bayes optimization. This innovation represents a significant leap in the field, dramatically improving the accuracy of models and simplifying the complexities associated with monitoring a diverse range of compounds. The study’s approach notably broadened the scope of detectable compounds in cell cultures. It successfully constructed models for almost every amino acid and extended this capability to components traditionally elusive to Raman spectroscopy, such as metal ions, oxygen, and carbon dioxide. This expansion in the range of detectable compounds is pivotal, as it enhances our understanding of cell culture environments and allows for more precise control over the manufacturing process. Highlighting the precision of this method, the study’s models, particularly for glucose concentration, demonstrated remarkable accuracy, with a correlation coefficient ( $R^2$ ) of

0.93 and a root mean square error of 0.23. Such precision in monitoring is critical in the biomanufacturing sector, where the maintenance of optimal culture conditions directly influences product quality and yield. Moreover, the method's ability to model various compounds, including those indicative of stress markers like BiP and oxidative glutathione, opens up new possibilities for monitoring a wide array of culture characteristics. This capability is instrumental for real-time monitoring and feedback control, ensuring the continuous adaptation and optimization of culture conditions. It aligns directly with the objectives of PAT, whose fundamental focus is to maintain consistency and quality across batches through real-time process adjustments. The integration of this method with advanced AI technologies further underscores its potential. Exploiting the power of AI, this approach can create more comprehensive and precise models for a broad spectrum of parameters, extending beyond traditional medium components and metabolites. This synergy between Raman spectroscopy modelling and AI technologies provides sophisticated and efficient monitoring and control mechanisms in biopharmaceutical manufacturing, aligning with the industry's move towards more automated, precise, and intelligent process management systems.

Continuous manufacturing, producing therapies in an uninterrupted flow rather than individual batches, shows promise for integration into hospital facilities. One example that has been demonstrated is interrupted cell culture production of viral vectors [28,29], as well as perfusion systems that enable constant harvesting of cellular products [30]. Ongoing downstream processing steps are also being integrated, to develop end-to-end production. Compared to batch manufacturing, continuous processes require smaller equipment footprints, allowing hospitals to increase productivity within the given space constraints. The verification and validation methods enabled by PAT support can ensure quality control in real time. The research by Williams et al. [31] exemplified the profound impact of PAT in biopharmaceutical manufacturing, particularly in the optimization of cell and gene therapy processes. Their study employed the Ranger system, a novel refractometry-based PAT, which demonstrated its efficacy in real-time monitoring of metabolic activity within HEK293T cell cultures during the production of lentiviral vectors. This system's ability to rapidly discern the relationship between bioreactor pH and culture metabolic activity, and to adjust the pH accordingly, resulted in a notable 1.8-fold increase in metabolic activity compared to an unoptimized process. However, it also revealed a particular aspect of cellular response: increased metabolic activity did not correspond to increased lentiviral vector production, highlighting the complexity of these biological systems and the importance of sophisticated process control. Furthermore, through metabolic flux modelling, Williams et al. uncovered how low-pH environments caused a significant metabolic shift in cells, redirecting cellular resources from growth towards managing environmental stress and adverse conditions. These insights underscore the capacity of PAT, not only in enhancing process efficiency, but also for enriching our understanding of the underlying biological mechanisms, thus contributing to a continuous improvement in quality control and process optimization in real time [31].

Artificial intelligence (AI) and machine learning (ML) have the potential to facilitate and enhance the analysis of the vast amount of data generated during PAT monitoring and throughout manufacturing steps [20,32]. By detecting patterns and correlations, AI models can identify critical bioprocess parameters, predict deviations, and determine potential actions, aiding biotechnologist personnel. Intelligent algorithms can also support the automation of elements of batch record reviewing, equipment maintenance, prevention campaigns, and contamination risk analysis. AI-based automation of cell and gene therapy manufacturing, sample tracking, and environmental monitoring of the cleanroom will increase hospital facilities' consistency and oversight. Recent research has exemplified AI's aptitude for tackling personalized medicine's intricacies. Schmitt et al.'s study described predictive machine learning algorithms that can anticipate individual patient-specific therapy response rates based on biomarker and genomic data analysis [19]. Meanwhile, Li et al., [33] discussed an AI digital platform that automates cell therapy production track-

ing and shows enhanced consistency between autologous batches. This concept is in line with advanced AI-powered microfluidic technology, which has significantly enhanced both fundamental biological research and translational clinical diagnosis. The implementation of AI in microfluidic technology, as highlighted in a recent study, enables the processing of the large-scale data obtained in high-throughput assays. These AI models can analyze multimodal datasets including images, videos, electric signals, and sequences from microfluidic devices. They offer the capability not only to collect data, but to understand and interpret it, ultimately facilitating fundamental and translational research in fields like single-cell genomics, cell signaling, and cell type discovery. Beyond mere planning, real-time learning systems, as demonstrated in microfluidics, can dynamically optimize continuous bioreactor parameters, adjusting to variability between patient cell samples. This capability is especially crucial in single-cell biology, where AI models extract cellular features from various modalities and use deep learning algorithms for more intuitive data processing and uncovering hidden connections among data. These advancements in AI model development tailored for single-cell biology signify a new era, where AI not only enhances data processing and feature extraction, but also aids in interpreting the underlying structure of big data in cell analysis, including cell counting, sorting, and classification. The integration of AI into cell therapy manufacturing, as explored by Li et al., [33] has led to the creation of an automated high-throughput genome editing platform that revolutionizes the consistency and efficiency of producing autologous batches. This cutting-edge platform leverages AI to streamline the gene editing process in mammalian cells, radically transforming the traditional labor-intensive methods into a rapid, high-throughput, and error-minimized operation. The pivotal achievement of this innovation is the chromatin accessibility enabled learning model (CAELM), an AI learning model that accurately predicts the efficiency of cytosine base editors (CBEs). By integrating both chromatin accessibility and sequence information, CAELM offers a profound enhancement in predicting in situ base editing outcomes [33].

This advanced model stands out for its precision and reliability, surpassing existing predictive tools like BE-Hive in its correlation with actual base editing efficiencies. The strength of CAELM is evident in its Pearson's correlation values, which range from 0.42 to 0.87, demonstrating a high level of predictive accuracy critical for the development of genome editing-based therapeutics. This transformative approach not only accelerates the scientific research in base editing, but also permits more accurate and efficient therapeutic applications, marking a significant step in the intersection of AI and biomedicine [33,34].

#### 4. Scaling Gene and Cell Therapy ATMPs from Research to the Clinic with AI

Gene and cell therapies show immense potential as advanced medicinal therapies, but scaling initial proof-of-concepts into robust clinical processes poses difficulties and limitations. The sensitivity of living systems means research protocols often fail when directly applied at the larger volumes required for patient treatments. Healthcare centers developing gene therapy ATMPs must optimize this scale-up, to progress from early studies to clinical manufacturing. AI and real-time metabolomics analysis can allow enhanced process understanding, to bridge the research-to-clinic scale-up gap.

During initial studies, gene delivery mechanisms and editing efficiency are evaluated at laboratory scale. However, small-scale conditions rarely translate directly to the larger volumes required for patient doses. Cell growth kinetics, vector productivity, and other critical quality attributes commonly diverge during scale-up. Extensive empirical optimization trials have traditionally been needed to adapt processes to clinical scale. AI technologies offer tools to accelerate scale-up by revealing key biological factors affected by production volume. ML algorithms integrating multivariate data can identify patterns linking process parameters to cell health across scales [35]. This model-driven approach rapidly highlights stress factors impairing growth or productivity when scaling up batches. AI control systems can then automatically optimize dynamic feeding, pH, dissolved oxygen, and other bioreactor parameters based on continuous metabolite monitoring.

Cellular metabolism provides integral indicators of the biological effects of gene engineering and culture environment. High-throughput metabolomics profiling coupled with AI analysis elucidates metabolic phenotypes and clarifies discrepancies between research and clinical protocols. Tracking key metabolites and pathways disrupted during scale-up highlights target areas for process improvements. For instance, glutamine limitation or build-up of lactate may only occur above certain volumes. AI modelling can integrate multi-omics datasets with process data to reveal the metabolic shifts responsible for reduced clinical-scale productivity. This understanding enables tailored nutrient supplementation or gene modifications, to restore a favorable metabolism. Additionally, real-time biosensors monitoring metabolites allow adaptive AI control systems to dynamically optimize nutrients and parameters throughout production. Maintaining cultures in ideal metabolic regimes enhances process robustness during scale-up.

## **5. Analysis of the Role and Potential Impact of AI in Academic ATMP Manufacturing, with Additional Details on the Key Advantages AI Can Provide**

### *5.1. Process Monitoring*

The personalized nature of autologous ATMPs results in inherent variability between patient cell samples used for manufacturing. This variability in starting material can propagate through the process, making achieving consistency between individualized batches challenging. Conventional bioprocess monitoring typically relies on manual and periodic offline sample analysis. AI enables improved real-time process oversight through advanced sensor instrumentation coupled with intelligent algorithms continuously analyzing data for patterns predictive of critical quality attributes.

Multivariate AI models imply that machine learning algorithms can integrate data streams from arrays of in-line sensors and bioreactors probe analyzers, to identify inter-relationships between bio-parameters and product quality. This higher-resolution view allows slight process deviations to be detected earlier and corrections to be made through automated feedback control, rather than periodic and manual sampling. Thus, AI process monitoring provides complete tracking and mapping of the multidimensional course of cell bioproduction. ML techniques can also incorporate spectroscopic [36], imaging, and other process data, to build predictive models of final product critical quality attributes such as identity, purity, and potency [37]. This real-time predictive capability facilitates standardized quality and reduced variability within and between batches, as well as reduced batch failures.

In the exploration of AI's impact on ATMP production, we can observe distinct advantages and challenges, as outlined in Table 1. Enhanced process monitoring and the automation of manufacturing tasks are among the key benefits, leading to increased efficiency and reduced workload for biotechnologists. Moreover, AI's dynamic control and adaptability allow fine-tuning cell culture conditions, thus ensuring batch consistency, which is critical for patient-specific treatments. On the other hand, issues such as data security concerns and the requirement for specialized personnel present noteworthy obstacles, potentially hindering AI's integration.

A further analysis is presented in Table 2 of the ATMP production process with and without AI integration. It is evident that AI integration significantly enhances process monitoring and manufacturing efficiency, offering a more sophisticated approach to data management, which traditional methods lack. The enhanced quality and consistency afforded by AI contribute to better control of product integrity; nonetheless, there are higher investment and costs required for implementing such advanced technologies. The need for personnel training and expertise remains an essential consideration to fully realize the potential of AI in this field.



**Table 1.** Advantages and disadvantages of AI in ATMP production.

Advantages of AI in ATMP Production	Disadvantages of AI in ATMP Production
<b>Enhanced Process Monitoring</b> Real-time oversight and data analysis for maintaining consistency and quality.	<b>Data Security Concerns</b> Risks associated with patient data privacy and data integrity in AI systems.
<b>Automation of Manufacturing Tasks</b> Increases efficiency, precision, and scalability, reducing the workload of biotechnologists.	<b>High Initial Investment</b> Significant upfront costs for AI integration and infrastructure development.
<b>Dynamic Control and Adaptability</b> AI systems can adjust to the variability in patient cell samples, optimizing batch consistency.	<b>Limited Data in Early Development</b> AI models may lack accuracy in early stages due to insufficient data for machine learning.
<b>Improved Data Management</b> Effective handling of large datasets, enhancing process comprehension and decision-making.	<b>Requirement for Specialized Personnel</b> Need for staff with expertise in AI and bioprocessing, who can be scarce.
<b>Systems Biology Integration</b> AI aids in understanding complex biological relationships, enhancing predictive medicine.	<b>Regulatory Challenges</b> Ambiguity in regulatory compliance for emerging AI applications in healthcare.

**Table 2.** Comparison of ATMP production with and without AI integration.

Aspect of ATMP Production	With AI Integration	Without AI Integration
<b>Process Monitoring</b>	Enhanced real-time monitoring and analysis using AI algorithms.	Relies on manual and periodic offline sample analysis.
<b>Manufacturing Efficiency</b>	Higher efficiency and scalability due to automation and dynamic control.	Less efficient, often limited by manual operations and static processes.
<b>Data Management</b>	Advanced handling of large and complex datasets, facilitating better decision-making.	Traditional data management, potentially leading to slower and less informed decisions.
<b>Quality and Consistency</b>	Improved product quality and batch consistency through predictive models and real-time adjustments.	Potential variability and quality issues due to lack of real-time monitoring and control.
<b>Investment and Costs</b>	Higher initial investment but potential long-term cost savings through efficiency and reduced error rates.	Lower initial costs but potentially higher long-term operational expenses.
<b>Personnel Training and Expertise</b>	Requires staff trained in AI and data science.	Relies more on traditional bioprocessing skills.

### 5.2. Automation

The manufacturing of ATMPs involves numerous supplementary operations beside the bioprocess itself, including supply chain management, sample tracking, the changeover between batches, contamination control, equipment maintenance, regulatory compliance adherence, quality control, batch record reviewing, and data management. AI enables automation of many tasks, to enhance precision and consistency, increase efficiency, allow scalability according to production demands, improve cost-effectiveness, and reduce biotechnology personnel workloads. Robotic process automation can replicate and mimic administrative and repetitive activities like data entry, basic data manipulation, and report generation. ML algorithms can schedule planned equipment calibration, preventive maintenance, and cleaning procedures based on the runtime. Cleanroom environmental monitoring data analyzed by AI models can provide alerts on contamination risks and suggest corrective actions, to avoid batch losses or disruptions to production.

Automated microscopy employing computer vision techniques permits precise characterization of cells. The searching of batch records by an AI makes use of natural language processing and provides appropriate results related to valuable data. Augmented reality helps operators carry out critical manual operations, in order to minimize mistakes. Multi-faceted AI-driven automation can be used to address the spatial and staffing limitations

that academic ATMP facilities often experience. Flexible cell-factories able to manufacture multiple individualized therapies in accordance with the specific requirements of a health-care center can also be encompassed within ML methods, instead of following large-scale production. With intelligent automation, workforces can become more productive using limited staffing, while facilities can be made more efficient.

### 5.3. Dynamic Control

Adaptive bioprocess control systems are critical for ATMP manufacturing, given the inevitable variability between patient cell samples. Traditional bioreactors rely on feedback and control loops tracking setpoint values [38,39]. However, the optimal parameters and tolerances may differ for each autologous batch's unique biologic characteristics. AI allows more advanced control schemes that continuously recalculate in real time the ideal setpoint based on multivariate analysis. ML algorithms can discover relationships between sensor data, bioprocess parameters, and critical quality attributes of the products in bioreactors. Through this approach, a prediction model of the final product's quality can guide dynamic adjustments of process variables in real time, leading to maximized batch consistency and robustness.

Hybrid AI strategies combine mechanistic first-principles models of cell growth and metabolism with data-driven ML models that capture the existing variability in the data. These models are commonly used for research and learning purposes, to gain insights into the intrinsic behavior of biological systems. Thus, adaptive model predictive control integrates these models to continuously re-optimize process parameters based on current state measurements of the process. Thus, as more batches are produced, semi-supervised ML can improve the controller model. AI control systems are particularly well-suited for handling the high variability and lack of expertise that are frequently experienced during early ATMP process development and technology transfer, because of their capacity for self-learning. The capability of AIs in handling complexity allows flexible and sophisticated adaptive control, especially when dealing with the specific needs of tailored batches [40].

### 5.4. Data Management

ATMP manufacturing fundamentally relies on synthesizing various databases, starting from the clinical status of the incoming patient sample and ending with the final product testing results. The correlation between clinical indicators and production factors can have an impact on product quality and treatment outcomes. Traditional data infrastructure faces challenges due to the vast amount of data produced. This data comes from various sources: sensors in process arrays, omics analyses, and electronic records. Additionally, the need to track and trace this data adds to the complexity, creating stress and pressure on existing systems. In this regard, AI can provide tools suited for managing and handling heterogeneous structured, unstructured, and semi-structured data. ML is efficient for identifying imperceptible patterns and correlations within massive datasets. AI can integrate electronic batch records, processing data, laboratory results, clinical data, and other sources into contextualized knowledge that enhances process comprehension. Well-known techniques such as natural language processing permit mining unstructured textual records. AI can enhance data management through dimensionality reduction, noise filtering, missing data imputation, and real-time data cleansing, to consolidate relevant information from discordant sources and that is apparently unrelated into usable and applicable models, guiding decision making and controlling adjustments to optimize each personalized batch. Thus, the integration of AI's multifaceted capabilities, including knowledge contextualization, data mining, dimensionality reduction, and real-time data management, highlights its strengths for advancing process understanding and facilitating optimal real-time decision-making for the production of personalized gene therapy ATMPs.

### 5.5. Systems Biology and AI

The aim of systems biology is developing complex models that integrate data from multiple disciplines, in order to explain complex biologic relationships or transactions. This is contrary to the reductionist approach of the twentieth century that gave insight into some areas but not in full regarding the comprehension of complexities and interpretation of non-structured elements. In addition to other methods, systems and network biology offer a unique approach to analyze multi-omics data. This method integrates various data types to uncover new patterns and behaviors in complex molecular and cellular networks. It does this by utilizing machine learning (ML) algorithms, which helps in understanding these complex biological systems more effectively. Network biology empowered by AI is important for describing the associations within normal and dysfunctional phenotypes. It aspires to clearer, explicit, and deterministic models, in order to further predictive, preventive, and personalized medicine. The large volume of multi-omics data makes functional integration impracticable manually, necessitating advanced analytics like network analysis, Bayesian methods, and multivariate techniques—now powered by AI.

### 5.6. Advanced Control Systems Leveraging AI

Recently, bioreactors have employed automatic proportional-integral-derivative (PID) control for parameters like temperature, while others require manual regulation [41]. The progress in control strategies, optimization algorithms, and software systems has been significant. Contemporary bioreactors often incorporate SCADA systems requiring a human-machine interface [42,43]. Newer systems are starting to implement adaptive model-based controllers, providing two key advantages: (i) optimizing constraints and control signal ranges; (ii) dynamically adjusting actions based on control outcomes and system changes. Their strength is in continuously recalculating the optimal next steps during operation. The development of distributed control systems in communication protocols is gradually progressing. The combination of increased computing power and a wider array of algorithms now allows the implementation of iterative control techniques. This employs an extensive pool of data obtained during monitoring and a deeper understanding of cell culture behavior, facilitating the creation of more precise and sensitive AI-driven models using systems that integrate ML algorithms, computer vision, and the other AI techniques described above. Basically, AI plays a central role in managing the variability and complexity within the ambit of ATMP manufacturing. It is undeniable that AI can greatly benefit academic ATMP production, but previously it required proficient control over different facets. As previously discussed, AI can enhance process monitoring, automation, control, and data integration for personalized therapies. However, implementing AI in this sector clearly demands rigorous oversight of technology capabilities, data accuracy, personnel competencies, and regulatory adherence.

A cross-functional understanding of AI maturity is crucial. Models like the Artificial Intelligence Optimization Team's [40,44,45] AI maturity level characterization model allow an organization to evaluate its current AI proficiencies across manufacturing categories, identifying gaps [46]. This assessment enables strategic roadmaps for developing capabilities required for AI tools. Rather than algorithm development, the focus is on integrating AI into operational functions. Structured maturity evaluation also tracks progress over time.

AI depends on quality data [47] and data integrity, which are critical for patient information. Systems that ensuring privacy and effective data governance are essential before launching any AI initiatives. Data security vulnerabilities require specific and exhaustive risk analysis, as well as controls for AI/ML applications. For instance, the authentication of data provenance, quality, and security as just as important a qualifier for infrastructure. AI models continue to stay in line with changing processes by constantly curating and maintaining data. High-quality data and its integrity are crucial in AI implementation in a clinical environment as this entails sensitive patients' information. As the basis of any health AI-driven initiative, it is essential to establish strong systems, which will also guarantee privacy safety and management procedures. AI and machine learning apps that

deal with medical data contain a high level of data security vulnerabilities, which require comprehensive risk assessment and customized controls specific for AI/ML in medicine.

However, within the scope of processes controlled by AI, especially the initial steps such as academic ATMP process development, this may be considered a disadvantage of applying ML techniques. The batches of data mined and collected from industries such as pharmaceuticals manufacturing can train and improve numerous ML models. Nevertheless, when the number of batches is limited, such as in academic production, the quality of training a better model becomes limited.

Therefore, in this scenario, ML algorithms may not be able to take all possible scenarios into consideration, resulting in inaccuracies in application. Under such circumstances, predictions become inaccurate, there is less adaptability to changing conditions, adaptability is low, and the insight into underlining processes is minimal, since this depends on insufficient data. Consequently, in order to improve the effectiveness of ML applications, it is imperative to increase the quantity of manufacturing batches or find alternative means to increase data collection. One available alternative is consolidation of a Healthcare center network established to, not only to improve health outcomes among patients, but also enhance ATMP quality. Within this network of hospitals, various nodes would collaborate by exchanging information and sharing expertise, to advance ATMP manufacturing without compromising on quality and safety.

Focusing on data sharing between the nodes in a network via the implementation and usage of blockchain technology for secure data sharing can enable an encrypted system for data distribution, which can be a tool for information exchange that is suitable for being validated by regulatory agencies. This immutable and private process would ensure that both raw or processed data are available for ML analysis and enhanced cell processing. This innovative application of blockchain's immutable and private framework could not only enhance data security but also update the process of data sharing, ensuring accuracy and integrity in the handling of sensitive data across the network [48–50].

Reskilling biotechnologist staff to implement augmented intelligence, while managing additional risks, is critical. AI success requires personnel fluent in its applications and limitations, especially for regulated manufacturing. Cross-functional collaboration between biotechnologists and AI experts can promote effective adoption of AI and ML. Thus, institutional cybersecurity defense requires a deep bench of talent specialized in AI/ML data risks. Specialized personnel combining computational proficiency with bioprocessing expertise remain scarce yet essential for overseeing responsible AI adoption. Most researchers lack formal data science training, while data analysts are often detached from manufacturing realities. Fostering collaborative groups between bioengineers, computer scientists, and clinicians could promote the development of truly tailored systems. Academic curriculums must also evolve, integrating statistics and bioinformatics skills with traditional knowledge. Some leading educational institutions have already implemented introductory data science courses into cell and gene therapy majors. For current personnel, institutions could offer continuing education programs through partnerships with technical universities (<https://www.theattcnetwork.co.uk>, accessed on 14 January 2024). Proactive reskilling builds the competencies needed to securely apply AI towards enhancing ATMP translation, rather than simply reducing costs. Therefore, investment in people and expertise is crucial, along with cutting-edge technology.

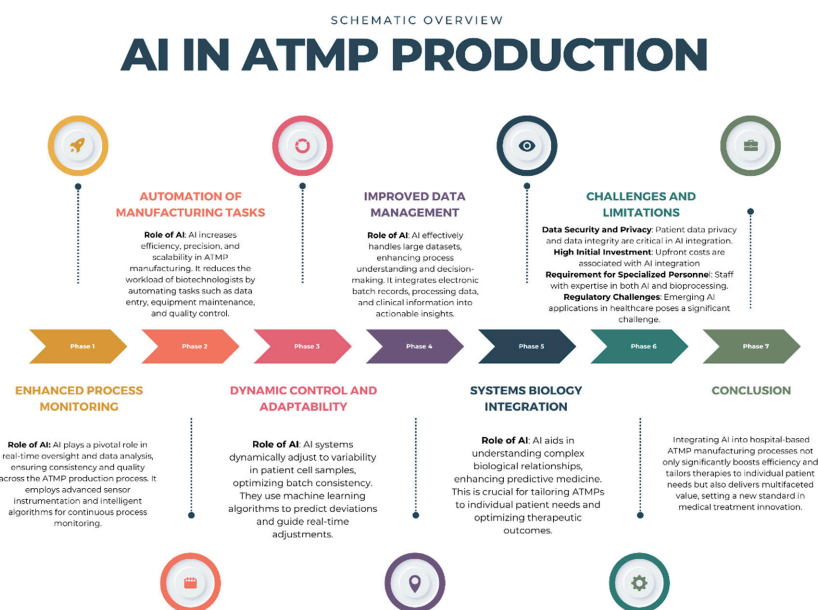
Regulatory authorities encourage AI when the benefits are demonstrated with proper GMP governance. However, ambiguity exists around emerging applications. Continuous communication, documented risk management, and a focus on enhancing quality help ensure compliance. Ultimately, AI for ATMPs requires synchronized integration across technology, data, people, regulation, and health care objectives—comprehensive management of this convergence would allow a controlled evolution toward more intelligent manufacturing [51].

Furthermore, a focus on product quality improvement must be a priority in AI integration. However, if appropriately designed and adjusted, AI systems can make processes

more efficient, less prone to error, and consistent, thus improving product quality and safety. This is a proactive approach that guarantees compliance, while ensuring the healthcare system provides safe and quality services to patients.

Achieving the successful implementation of AI in relation to the manufacturing of ATMPs relies on the synchronous integration of various spheres. These areas include the implementation of cutting-edge technological solutions in healthcare, responsible data management, health practitioner cooperation, strict regulation compliance, and the alignment of AI strategies with other academic and public health players. Proper management of this diverse convergence is a challenge, as each requires explicit leadership, operational procedures, and well-defined roles and responsibilities that are coherent in a complex academic–hospital ecosystem [52].

In synthesizing the critical factors for the successful implementation of AI within the domain of ATMP manufacturing, we must acknowledge the intricate network of interdisciplinary collaboration. This involves the integration of advanced technological solutions, meticulous data management, healthcare professionals' engagement, adherence to rigorous regulatory frameworks, and strategic alignment with academic and public health initiatives. Managing this multifaceted convergence demands clear management, precise operational protocols, and well-articulated roles within the complex academic–hospital ecosystem. Furthermore, in the advanced control systems section, we elaborated on how these systems build upon previously described AI capabilities like process monitoring, automation, and dynamic control, to implement more sophisticated control algorithms. While those previous AI applications provided valuable data analysis, adjustments, and modelling, advanced control systems leverage that foundation to continuously recalculate optimal parameters using hybrid mechanistic and machine learning models. This enables a higher level of adaptive and model predictive control that goes beyond basic feedback loops to provide fully customized bioreactor optimization tailored to the unique characteristics of each individual batch in real time. Thus, the distinguishing features of advanced AI control were clarified compared to the other previous functionalities of AI discussed in the paper. Figure 2, 'AI in ATMP production', provides a structured visual overview of these interdependencies and outlines the dynamic roles of AI throughout the ATMP production cycle. It is presented here as a precursor to our concluding thoughts, reaffirming the transformative impact and the multifarious challenges of AI integration in advancing the field of ATMPs.



**Figure 2.** Visual overview of the integration of AI in ATMP production, detailing its roles, benefits, and challenges, and concluding with the potential enhancements in hospital-based ATMP efficiency and patient outcomes.



## 6. Conclusions

The emerging field of advanced therapy medicinal products represents a new frontier in personalized and innovative treatments, with enormous therapeutic potential. However, manufacturing customized cellular and gene therapies poses profound challenges, requiring extensive adaptation of conventional biopharmaceutical production paradigms. The intrinsic constraints of hospital-based facilities further intensify the difficulties in clinically translating these novel ATMPs. Constructing on-site modular GMP infrastructure can enable bench-to-bedside delivery but demands substantial optimization of design, quality systems, staffing, and coordination across hospital departments. While a monumental undertaking, the integration of academic research, pharmaceutical manufacturing, and clinical medicine made possible by hospital ATMP facilities can drive scientific discoveries toward direct patient impact.

Emerging technologies like process analytical monitoring, continuous production, and AI can further enhance process control, automation, and oversight, to overcome limitations. In this regard AI holds tremendous promise for allowing academic ATMP facilities to overcome constraints of limited space, staffing, patient-specific variability, and decentralized manufacturing. Intelligent algorithms can monitor processes in real time, automate ancillary tasks, enact sophisticated adaptive control, and synthesize the breadth of data involved in patient-specific production.

Early applications have demonstrated AI's utility for automated analysis and enhanced productivity. Visionary initiatives will make AI a transformational technology, ensuring these innovative personalized medicines realize their full therapeutic potential. However, fully realizing the clinical promise of personalized ATMPs ultimately relies on synergistic partnerships across disciplines, to pioneer new treatments while maintaining demanding quality standards. Improving patient outcomes should motivate explorations into AI-driven automation. Beyond operational metrics, focusing innovation on maximizing therapeutic safety and efficacy requires integrating manufacturing data with clinical databases through processes that maintain privacy safeguards.

Real-world evidence can help us understand how the quality of a cellular product impacts how it works. Using advanced analysis, connections can be made between treatment procedures and side effects, or how changes in cellular phenotype during production can affect their survival after being transplanted. By contextualizing technical data into patient impacts, development can shift from simply engineering robotic bio-factories toward purposeful design tailored for healing. Focusing on clinical outcomes can continually re-center personalized medicine innovations on whole persons rather than products. The accelerating advancement in novel biotherapeutics in hospital-based manufacturing facilities can allow continued progress in providing patients access to transformative medicines tailored to their unique needs.

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## References

1. Johanna, I.; Daudeij, A.; Devina, F.; Nijenhuis, C.; Nuijen, B.; Romberg, B.; de Haar, C.; Haanen, J.; Dolstra, H.; Bremer, E.; et al. Basics of advanced therapy medicinal product development in academic pharma and the role of a GMP simulation unit. *Immuno-Oncol. Technol.* **2023**, *20*, 100411. [[CrossRef](#)]
2. Elverum, K.; Whitman, M. Delivering cellular and gene therapies to patients: Solutions for realizing the potential of the next generation of medicine. *Gene Ther.* **2020**, *27*, 537–544. [[CrossRef](#)]
3. Iancu, E.M.; Kandalaf, L.E. Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting. *Curr. Opin. Biotechnol.* **2020**, *65*, 233–241. [[CrossRef](#)]
4. Bersenev, A.; Fesnak, A. Place of Academic GMP Facilities in Modern Cell Therapy. *Methods Mol. Biol.* **2020**, *2097*, 329–339. [[CrossRef](#)]
5. McGuirk, J.; Waller, E.K.; Qayed, M.; Abhyankar, S.; Ericson, S.; Holman, P.; Keir, C.; Myers, G.D. Building blocks for institutional preparation of CTL019 delivery. *Cytotherapy* **2017**, *19*, 1015–1024. [[CrossRef](#)]

6. Amini, L.; Silbert, S.K.; Maude, S.L.; Nastoupil, L.J.; Ramos, C.A.; Brentjens, R.J.; Sauter, C.S.; Shah, N.N.; Abou-El-Enein, M. Preparing for CAR T cell therapy: Patient selection, bridging therapies and lymphodepletion. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 342–355. [[CrossRef](#)]
7. Abou-El-Enein, M.; Römhild, A.; Kaiser, D.; Beier, C.; Bauer, G.; Volk, H.D.; Reinke, P. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: A novel tailored model for optimizing performance and estimating costs. *Cytotherapy* **2013**, *15*, 362–383. [[CrossRef](#)]
8. Viganò, M.; Giordano, R.; Lazzari, L. Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regen. Med.* **2017**, *12*, 803–813. [[CrossRef](#)]
9. Jackson, M.R. Accommodating clinical trials and other externally manufactured cellular therapy products: Challenges, lessons learned and creative solutions. *Cytotherapy* **2022**, *24*, 37–44. [[CrossRef](#)]
10. Sutherland, V.; Buffo, M.J.; Whiteside, T.L. Impact of contracted manufacturing organization protocols on operations in an academically based Current Good Manufacturing Practice facility. *Cytotherapy* **2022**, *24*, 32–36. [[CrossRef](#)]
11. Coppens, D.G.M.; Hoekman, J.; De Bruin, M.L.; Slaper-Cortenbach, I.C.M.; Leufkens, H.G.M.; Meij, P.; Gardarsdottir, H. Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. *Cytotherapy* **2020**, *22*, 592–600. [[CrossRef](#)]
12. Priesner, C.; Hildebrandt, M. Advanced Therapy Medicinal Products and the Changing Role of Academia. *Transfus Med Hemother.* **2022**, *49*, 158–162. [[CrossRef](#)]
13. European Commission. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. *Eur. Comm. J.* **2017**, *4*, 1–32.
14. Digiusto, D.L.; Melsop, K.; Srivastava, R.; Tran, C.A.T. Proceedings of the first academic symposium on developing, qualifying and operating a cell and gene therapy manufacturing facility. *Cytotherapy* **2018**, *20*, 1486–1494. [[CrossRef](#)] [[PubMed](#)]
15. de Wilde, S.; Guchelaar, H.-J.; Zandvliet, M.L.; Meij, P. Clinical development of gene- and cell-based therapies: Overview of the European landscape. *Mol. Ther. Methods Clin. Dev.* **2016**, *3*, 16073. [[CrossRef](#)]
16. Chauca Strand, G.; Bonander, C.; Jakobsson, N.; Johansson, N.; Svensson, M. Assessment of the clinical and cost-effectiveness evidence in the reimbursement decisions of new cancer drugs. *ESMO Open* **2022**, *7*, 100569. [[CrossRef](#)]
17. Harrison, R.P.; Medcalf, N.; Rafiq, Q.A. Cell therapy-processing economics: Small-scale microfactories as a stepping stone toward large-scale macrofactories. *Regen. Med.* **2018**, *13*, 159–173. [[CrossRef](#)]
18. Gladwell, D.; Ciani, O.; Parnaby, A.; Palmer, S. Surrogacy and the Valuation of ATMPs: Taking Our Place in the Evidence Generation/Assessment Continuum. *Pharmacoeconomics.* **2024**, *42*, 137–144. [[CrossRef](#)]
19. Bäckel, N.; Hort, S.; Kis, T.; Nettleton, D.F.; Egan, J.R.; Jacobs, J.J.L.; Grunert, D.; Schmitt, R.H. Elaborating the potential of Artificial Intelligence in automated CAR-T cell manufacturing. *Front. Mol. Med.* **2023**, *3*, 1250508. [[CrossRef](#)]
20. Hort, S.; Herbst, L.; Bäckel, N.; Erkens, F.; Niessing, B.; Frye, M.; König, N.; Papantoniou, I.; Hudecek, M.; Jacobs, J.J.L.; et al. Toward Rapid, Widely Available Autologous CAR-T Cell Therapy—Artificial Intelligence and Automation Enabling the Smart Manufacturing Hospital. *Front. Med.* **2022**, *9*, 913287. [[CrossRef](#)]
21. Harrison, R.P.; Ruck, S.; Medcalf, N.; Rafiq, Q.A. Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities. *Cytotherapy* **2017**, *19*, 1140–1151. [[CrossRef](#)]
22. Gerzon, G.; Sheng, Y.; Kirkitadze, M. Process Analytical Technologies—Advances in bioprocess integration and future perspectives. *J. Pharm. Biomed. Anal.* **2022**, *207*, 114379. [[CrossRef](#)]
23. Majors, B.S.; Betenbaugh, M.J.; Chiang, G.G. Links between metabolism and apoptosis in mammalian cells: Applications for anti-apoptosis engineering. *Metab. Eng.* **2007**, *9*, 317–326. [[CrossRef](#)]
24. Ahmed, S.; Chauhan, V.M.; Ghaemmaghami, A.M.; Aylott, J.W. New generation of bioreactors that advance extracellular matrix modelling and tissue engineering. *Biotechnol. Lett.* **2019**, *41*, 1–25. [[CrossRef](#)]
25. Harrison, R.P.; Chauhan, V.M. Enhancing cell and gene therapy manufacture through the application of advanced fluorescent optical sensors (Review). *Biointerphases* **2017**, *13*, 01A301. [[CrossRef](#)] [[PubMed](#)]
26. Jaccard, N.; Griffin, L.D.; Keser, A.; Macown, R.J.; Super, A.; Veraitch, F.S.; Szita, N. Automated method for the rapid and precise estimation of adherent cell culture characteristics from phase contrast microscopy images. *Biotechnol. Bioeng.* **2014**, *111*, 504–517. [[CrossRef](#)]
27. Tanemura, H.; Kitamura, R.; Yamada, Y.; Hoshino, M.; Kakihara, H.; Nonaka, K. Comprehensive modeling of cell culture profile using Raman spectroscopy and machine learning. *Sci. Rep.* **2023**, *13*, 21805. [[CrossRef](#)] [[PubMed](#)]
28. Yang, Z.; Paes, B.C.M.F.; Fulber, J.P.C.; Tran, M.Y.; Farnós, O.; Kamen, A.A. Development of an Integrated Continuous Manufacturing Process for the rVSV-Vectored SARS-CoV-2 Candidate Vaccine. *Vaccines* **2023**, *11*, 841. [[CrossRef](#)] [[PubMed](#)]
29. Payne, J.; Cronin, J.; Haer, M.; Krouse, J.; Prospero, W.; Drolet-Vives, K.; Lieve, M.; Soika, M.; Balmer, M.; Kirkitadze, M. In-line monitoring of surfactant clearance in viral vaccine downstream processing. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 1829–1837. [[CrossRef](#)] [[PubMed](#)]
30. Moreira, A.S.; Cavaco, D.G.; Faria, T.Q.; Alves, P.M.; Carrondo, M.J.T.; Peixoto, C. Advances in Lentivirus Purification. *Biotechnol. J.* **2021**, *16*, 2000019. [[CrossRef](#)]
31. Williams, T.; Kalinka, K.; Sanches, R.; Blanchard-Emmerson, G.; Watts, S.; Davies, L.; Knevelman, C.; McCloskey, L.; Jones, P.; Mitrophanous, K.; et al. Machine learning and metabolic modelling assisted implementation of a novel process analytical technology in cell and gene therapy manufacturing. *Sci. Rep.* **2023**, *13*, 834. [[CrossRef](#)]

32. Odeh-Couvertier, V.Y.; Dwarshuis, N.J.; Colonna, M.B.; Levine, B.L.; Edison, A.S.; Kotanchek, T.; Roy, K.; Torres-Garcia, W. Predicting T-cell quality during manufacturing through an artificial intelligence-based integrative multiomics analytical platform. *Bioeng. Transl. Med.* **2022**, *7*, e10282. [[CrossRef](#)]
33. Li, S.; An, J.; Li, Y.; Zhu, X.; Zhao, D.; Wang, L.; Sun, Y.; Yang, Y.; Bi, C.; Zhang, X.; et al. Automated high-throughput genome editing platform with an AI learning in situ prediction model. *Nat. Commun.* **2022**, *13*, 7386. [[CrossRef](#)]
34. Gao, Z.; Li, Y. Enhancing single-cell biology through advanced AI-powered microfluidics. *Biomicrofluidics* **2023**, *17*, 51301. [[CrossRef](#)]
35. Emerson, J.; Kara, B.; Glassey, J. Multivariate data analysis in cell gene therapy manufacturing. *Biotechnol. Adv.* **2020**, *45*, 107637. [[CrossRef](#)]
36. Kern, S.; Wander, L.; Meyer, K.; Guhl, S.; Mikkula, A.R.G.; Holtkamp, M.; Salge, M.; Fleischer, C.; Weber, N.; King, R.; et al. Flexible automation with compact NMR spectroscopy for continuous production of pharmaceuticals. *Anal. Bioanal. Chem.* **2019**, *411*, 3037–3046. [[CrossRef](#)] [[PubMed](#)]
37. Feng Báez, J.P.; George De la Rosa, M.V.; Alvarado-Hernández, B.B.; Romañach, R.J.; Stelzer, T. Evaluation of a compact composite sensor array for concentration monitoring of solutions and suspensions via multivariate analysis. *J. Pharm. Biomed. Anal.* **2023**, *233*, 115451. [[CrossRef](#)]
38. Rathore, A.S.; Mishra, S.; Nikita, S.; Priyanka, P. Bioprocess Control: Current Progress and Future Perspectives. *Life* **2021**, *11*, 557. [[CrossRef](#)]
39. Jabarivelisdeh, B.; Carius, L.; Findeisen, R.; Waldherr, S. Adaptive predictive control of bioprocesses with constraint-based modeling and estimation. *Comput. Chem. Eng.* **2020**, *135*, 106744. [[CrossRef](#)]
40. Sarker, I.H. AI-Based Modeling: Techniques, Applications and Research Issues Towards Automation, Intelligent and Smart Systems. *SN Comput. Sci.* **2022**, *3*, 158. [[CrossRef](#)] [[PubMed](#)]
41. Chevalier, M.; Gómez-Schiavon, M.; Ng, A.H.; El-Samad, H. Design and Analysis of a Proportional-Integral-Derivative Controller with Biological Molecules. *Cell Syst.* **2019**, *9*, 338–353.e10. [[CrossRef](#)]
42. Mitra, S.; Murthy, G.S. Bioreactor control systems in the biopharmaceutical industry: A critical perspective. *Syst. Microbiol. Biomanuf.* **2022**, *2*, 91–112. [[CrossRef](#)]
43. Mujawar, S.; Deshpande, A.; Gherkar, A.; Simon, S.E.; Prajapati, B. Introduction to Human-Machine Interface. In *Human-Machine Interface*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2023; pp. 1–23, ISBN 9781394200344.
44. Zheng, Y. Optimization of computer programming based on mathematical models of artificial intelligence algorithms. *Comput. Electr. Eng.* **2023**, *110*, 108834. [[CrossRef](#)]
45. Heaton, H.; Fung, S.W. Explainable AI via learning to optimize. *Sci. Rep.* **2023**, *13*, 10103. [[CrossRef](#)]
46. Cheng, Y.; Bi, X.; Xu, Y.; Liu, Y.; Li, J.; Du, G.; Lv, X.; Liu, L. Artificial intelligence technologies in bioprocess: Opportunities and challenges. *Bioresour. Technol.* **2023**, *369*, 128451. [[CrossRef](#)] [[PubMed](#)]
47. Arinez, J.F.; Chang, Q.; Gao, R.X.; Xu, C.; Zhang, J. Artificial Intelligence in Advanced Manufacturing: Current Status and Future Outlook. *J. Manuf. Sci. Eng.* **2020**, *142*, 110804. [[CrossRef](#)]
48. Lam, C.; van Velthoven, M.H.; Meinert, E. Developing a Blockchain-Based Supply Chain System for Advanced Therapies: Protocol for a Feasibility Study. *JMIR Res. Protoc.* **2020**, *9*, e17005. [[CrossRef](#)] [[PubMed](#)]
49. Singh, R.; Dwivedi, A.D.; Srivastava, G. Internet of Things Based Blockchain for Temperature Monitoring and Counterfeit Pharmaceutical Prevention. *Sensors* **2020**, *20*, 3951. [[CrossRef](#)] [[PubMed](#)]
50. Moosavi, J.; Naeni, L.M.; Fathollahi-Fard, A.M.; Fiore, U. Blockchain in supply chain management: A review, bibliometric, and network analysis. *Environ. Sci. Pollut. Res. Int.* **2021**. [[CrossRef](#)]
51. EMA. Multi-annual AI workplan 2023–2028 HMA-EMA Big Data Steering Group. **2023**, 1–13. Available online: <https://www.ema.europa.eu/en/news/artificial-intelligence-workplan-guide-use-ai-medicines-regulation> (accessed on 1 February 2024).
52. EMA. Reflection paper on the use of artificial intelligence in lifecycle medicines. *Eur. Med. Agency* **2023**, *31*, 1–17.

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