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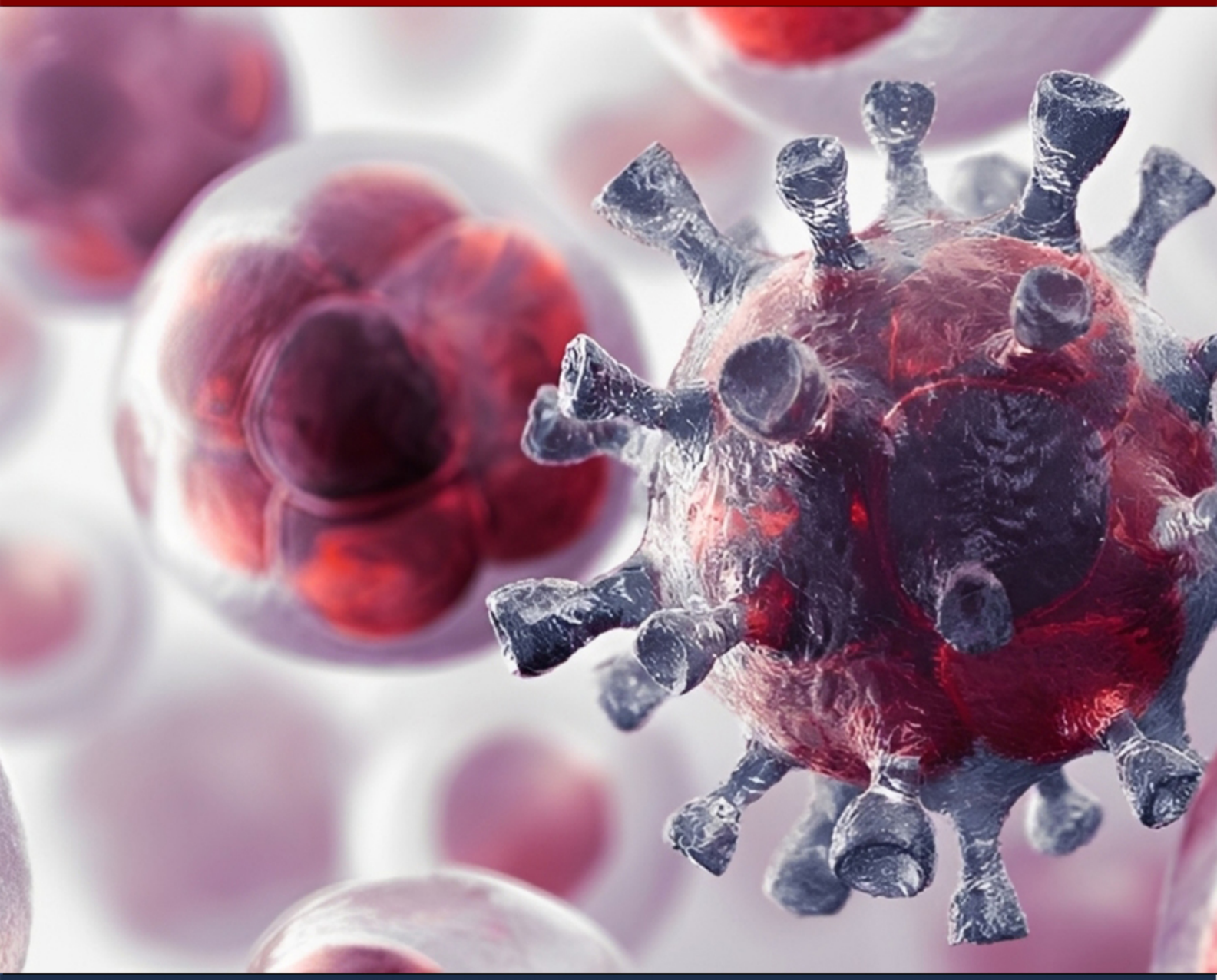

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Artificial Intelligence and Machine Learning in Personalized Treatment Planning: Mechanistic Insights and Applications in Advanced Therapies

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Abstract:

AI and ML are revolutionizing personalized medicine by facilitating predictive, adaptive, and mechanistic treatment planning. Conventional approaches of therapy are, however, rarely tailored on the patient's molecular and cellular individuality (as well as systemic variability), with suboptimal clinical efficacy and increased toxicity. AI and ML algorithms exploit high-dimensional data such as genomics, transcriptomics, proteomics, metabolomics, imaging and longitudinal clinical records to discover predictive biomarkers , to optimize the selection of therapy and to deliver interventions in real time. In oncology they are being applied to understand tumour heterogeneity, predict resistance to therapy and develop immunotherapeutic approaches. In gene and cell therapy, ML algorithms drive optimal CAR-T cell production, gRNA selection in CRISPR based therapies, predict cellular persistence and efficacy. It applies in auto-immune, metabolic and cardiovascular diseases for dynamic dosing and monitoring. Challenges consist of data harmonization, model interpretability, applications in clinical workflow, and regulatory adherence. We outline future directions that include multi-modal data fusion, federated learning, explainable AI and reach toward beyond therapeutic modalities. The convergence of AI and ML with molecular medicine has the unprecedented ability to significantly increase precision, effectiveness and safety in advanced therapy applications, providing a paradigm shift toward truly personalized care.

Keywords: Artificial Intelligence, Machine Learning, Personalized Medicine, Advanced Therapies, Cellular Functions.

INTRODUCTION

The development of personalised medicine requires the emergence of computational methods, with the capacity to integrate highly-complex biological and clinical data for therapy optimization on an individual basis. The procedures of classic therapeutics/ medicine typically do not consider between-patient heterogeneity from genomic differences, through epigenetic regulation, to transcriptomic and proteomic variations, as well as immune system disparities and dynamic interactions with the tumor environment or true pathology (disease state) (1).

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This variability causes differences in responses to the current high dose of care standard treatments, with the consequent increase in drug side effects and generally less effectiveness. Enter Artificial Intelligence (AI) and Machine Learning (ML), which have unparalleled potential to tackle these problems by capitalizing on high-dimensional data sets to discover predictive relationships, optimize therapy selection, and catalyze adaptive real-time interventions (1).

The third pillar of success AI and ML algorithms leverage on diverse learning paradigms from supervised learning (predictive modeling), unsupervised learning (clustering molecular phenotypes) and reinforcement learning (adaptive dynamic therapy) (2). In the oncology domain, AI models merge genomic, transcriptomic, proteomic and metabolomic data to infer (subclonal) populations in heterogeneous tumors. For instance, SC-RNAseq combined with ML allows for the identification of cell populations that contribute to therapy resistance, e.g. those expressing efflux transporters, anti-apoptotic proteins or immunosuppressive ligands (3). The combination of spatial transcriptomics and predictive modeling offers an understanding of where immune and stromal cells sit within tumors in order to guide immunotherapy treatment selection and delivery strategies facilitating beneficial CD8+ cytotoxic T cell infiltration into immunologically "cold" niches. Such predictive models enable the development of personalized therapies that predict how tumors will evolve and resistance against them can be broken (4).

For gene and cell therapy, ML models are used to maximize ex vivo manufacturing by leveraging high-dimensional flow cytometry and transcriptomic datasets in the determination of T cell subsets with favorable persistence, cytotoxicity, immune stimulatory capacity, as well as adoptive transfer capability in CAR-T treatment. In like manner to RNA-seq, models have been used in CRISPR for gene editing to predict gRNA efficiency at the target, off-target effects and chromatin accessibility; identifying those sequences that allow maximal precision of edit. Finally, ex vivo protocols are also optimized by reinforcement learning-based strategies that titrate delivery to the right balance of cell viability and editing efficiency for better therapeutic impact (5).

Applications may not be restricted to oncology and could also treat autoimmunity/inflammation, as diversity amongst individuals with immune activation could make such diseases harder to treat. ML-enabled multi-omics integration will also facilitate patient stratification by immune cell populations, cytokine expression, and epigenetic patterns to predict response to biologic therapy and the dynamic tuning of dosing protocols (6). In cardiovascular and metabolic diseases, AI models combine genomics, metabolomics, imaging and continuous physiological monitoring to predict adverse outcomes, tailor regenerative therapies and dose drugs in a patient-specific manner. For instance, predictive algorithms for stem cell transplantation-mediated myocardial repair can identify ideal cytokine cocktails, oxygenation environments and scaffold attributes to achieve lineage-specific differentiation and incorporation of the tissue (7).

With integration of artificial intelligence and access to wearable and implantable sensors that continuously measure physiological parameters such as glucose, heart rate variability, oxygen saturation, and circulating biomarkers, there is the potential for real-time adjustment of therapy. Longitudinal data streams are processed by ML to forecast bouts of disease, modulate drug dosage in real time, and spark off early interventions to prevent untoward events (8). In diabetes control, Reinforcement learning algorithms adjust insulin dosing given continuous glucose monitoring, leading to the minimization of hypoglycaemic events with adequate glycaemic correlation. Also in the oncologic setting, predictive monitoring can be used for dose adjustment according to early measurement of treatment resistance or system toxicity (9).

Integration of multi-modal data is a key to reach precision therapy as molecular and physiological signals are commonly dependent. Network-based models predict that key points in signaling pathways for intervention are the most effective when intervention is targeted for clinical success. Such mechanistic insight informs the development of combinatorial therapy, so that several pathways can be simultaneously targeted to combat compensatory mechanisms underlying treatment resistance. AI further enables simulation of the cellular and tissue level responses, predicting downstream effects of molecular interventions on organ function and systemic homeostasis (10).

Despite these advantages, challenges remain. Data sets from various sources, in high-dimensional space, must be harmonized/normalized and undergo careful quality control to avoid introducing biases. Interpretable AI paradigms are necessary to filter the "black box" model predictions down into actionable clinical decisions, and maintain clinical trust in predictions. Ethical and regulatory constraints such as those on patient privacy, algorithmic bias, and transparency need to be considered for broad clinical adoption. The continuation of work in the federated learning, multi-center data aggregation and real-time model retraining is increasing the robustness and generalizability of models (11).

In summary, AI and ML combine cellular,

molecular and clinical inputs to produce predictive, adaptive and mechanistic insights that inform personalized therapy. They tailor selection, dosage, and time of therapy administration, and enable adjustment to individual patient responsiveness. These capabilities place AI-driven strategies at the core of advanced therapies, underpinning precision applications across oncology, gene and cell therapies, autoimmune and inflammatory conditions, cardiovascular disorders and regenerative medicine. By transforming complex biological data to actionable knowledge, AI and ML are shaping the concept of personalized treatment planning.

AI and ML in Oncology

Heterogeneity is a key barrier to achieving robust and durable therapeutic responses, as both interpatient (i.e., across different individuals) and intratumoral (variations within the tumors of an individual patient) heterogeneity can impact sensitivity to treatment, immune evasion, as well as the evolution of resistance mechanisms. Artificial Intelligence (AI) and Machine Learning (ML) models offer powerful cutting-edge utilities to unravel this complexity by incorporating multi-omics data, such as genomics, transcriptomics, proteomics, epigenomics and single-cell sequencing in parallel to clinical and imaging datasets (12). Such integrated models can identify subclonal populations that underlie therapy resistance, characterize their molecular footprints, and predict their kinetics under a targeted selection of therapeutic intervention. For example, ML approaches can recognize cancer cells expressing high levels of ATP-binding cassette (ABC) transporters that actively excrete chemotherapeutic drugs, or cells that have increased expression of anti-apoptotic BCL-2 family members that block programmed cell death; paving the way for rational development of drug combinations targeting both survival signals and cytocidal effects (13).

Aside from the inherent resistance, immune escape in the TME is an additional obstacle. Spatial transcriptomics and imaging data processed via ML pipelines provide a mapping of the distribution of immune cells, stromal elements, and tumor-infiltrating lymphocytes at submillimeter resolution as well as regions with low or absent immune cell infiltration, referred to as “cold” tumors (14). These findings will help guide the choice and sequencing of various immunotherapies, such as checkpoint inhibitors and adoptive T cell therapies, by estimating their chances of T cell infiltration and effector function in these niches. AI models also incorporate quantitative characteristics, such as tumor mutational burden, neoantigen landscape, regulatory T cell density, myeloid-derived suppressor cells (MDSC) prevalence and cytokine milieu to predict more accurately than classic biomarkers alone the responses to PD-1 /PD-L1 or CTLA-4 blockade (15).

Predictive algorithms could also model clonal changes during tumor evolution, predicting the probability of resistance development in single agents and so tailoring combinations. Such models also consider various pharmacokinetic and pharmacodynamic effects, such as inhomogeneous penetration of drugs within tumors, presence of hypoxic niches, or pH heterogeneity that may influence both cytotoxic activity as well as immune activation. Incorporating these mechanistic features allows for personalized therapeutic approaches that adjust dynamically to tumor progression, striving to optimally balance efficacy with off-tumor toxicity (16).

Together, AI and ML in oncology allow for deep characterization of tumor heterogeneity, resistance mechanisms and immune dynamics to support precision guidance of therapy. Through integration of molecular profiling alongside the spatial, functional and temporal context, such computational strategies offer actionable findings for personalized treatment schedules design instilling maximal therapeutic effect with minimal systemic toxicity (17).

AI and ML in Gene and Cell Therapies

Systems to interrogate this complexity are essential in optimizing and tailoring gene-and cell-based therapies, a field where Artificial Intelligence (AI) and Machine Learning (ML) has emerged as a necessary computational tool to cope with highly- dimensional data spanning cellular phenotypes, transcriptomic profiles, epigenetic landscapes, and functional readouts. In the setting of chimeric antigen receptor T cell (CAR-T) and other ACT, ML algorithms are applied to single-cell RNA sequencing, surface proteomic profiling and functional cytotoxicity assays in order to identify novel T cell subsets with greater therapeutic potential (18). These algorithms are able to identify types of populations that display enriched stem-like memory phenotypes, augmented proliferative potential, exhaustion resilience and cytotoxic superiority (which will ultimately drive a selective amplification of T cells expectedly capable of surviving in vivo with potent and sustained anti-tumor action after infusion). For instance, predictive clustering of single-cell transcriptomes enables the isolation of cells with high expression of IL-7R and TCF7-the markers best associated with long-lived memory T cells-and not solely terminally differentiated or senescent phenotypes-a factor which correlates with their decreased persistence (19).

More than phenotypic selection, the ML models intrinsic optimality and portrait cytokine signaling, metabolic evasion or response to intracellular stress.

Algorithms combine information on mitochondrial functional capacity, glycolytic flux and oxidative phosphorylation to generate a model that robustly predicts cellular resilience following ex vivo expansion while enhancing yield and function of therapeutic cells (20). These models also guide the development of culture media, cytokine supplements and co-stimulatory tactics that promote maximal expansion while limiting acquisition of inhibitory or exhausted phenotypes. Reinforcement learning paradigms are particularly suited to successively tuning of these multi-parameter culture conditions, adjusting inputs on-the-fly depending upon predicted cell state transitions in order to achieve high viability and functionality (21).

In CRISPR gene editing and other gene therapeutics, AI and ML models are crucial to predict guide RNA (gRNA) activity and reduce off-target effects. Predictive approaches utilize maps of chromatin accessibility, nucleosome occupancy, DNA methylation and histone modification states to predict cleavage efficiency at target sites as well as the risk for off-target activity (22). These models can include thermodynamic parameters, sequence context and structural factors to further optimize gRNA design for maximum on-target activity. Cohort 'WiKi gRNA selection' yield gRNA that are iteratively optimized according to high-throughput screens (gRNAs favouring efficient editing while preserving cell viability and minimal genome perturbation) (23).

Nevertheless, ML models also optimize ex vivo gene editing workflows by modeling delivery modalities viral vectors, electroporation or lipid nanoparticles and their effect on transduction efficiency, cytotoxicity and immune activation. These (predictive) analyses optimize vector dose, electroporation settings and incubation times to minimize trial and error while maintaining robustness (24). Furthermore, as a complementary monitoring tool following editing, AI-derived quality control pipelines will track transcriptomic and proteomic signatures in the edited cells for signs of aberrant cellular stress responses or induction of DNA damage pathways, further strengthening safety before cellular infusion into patients (25).

In addition, multi-omic implementation with AI can predict personalized patient responses for gene and cell therapies. Through integrating single-cell phenotypes, systemic immunogenomic profiles, and tumor antigen landscapes, algorithms are capable of predicting the persistence and responsiveness of CAR-T cells in individual patients, potentially assisting in determining optimal therapy selection, conditioning regimens and combination strategies. For instance, ML models might predict the risk of cytokine release syndrome from pre-infusion immune profiling, guiding personalized preconditioning or cytokine blockade (26).

AI and ML in Autoimmune, Metabolic, and Cardiovascular Disorders

AI and ML are increasingly employed in complex chronic diseases such as chronic obstructive pulmonary disease (COPD), where the heterogeneity among patients, multifactorial pathophysiology and quasistatic progress of disease complicate clinical decision-making (27). For autoimmune diseases, ML approaches use high-dimensional datasets such as immune cell phenotyping, cytokine profiles, transcriptomics and epigenetic marks in order to stratify patients based on predicted therapeutic response. For example, specific subpopulations of T helper 17 (Th17) cells or regulatory T cells (Tregs) that distinguish responders to biologics which block TNF-α, IL-6 and/or IL-17 are known (28). Incorporating serial biomarker data Longitudinal biomarkers can be used by ML models to dynamically modulate the dosing regimens in such a way that therapeutic level of treatment effect is maintained, while simultaneously reducing systemic immunosuppression and side effects like opportunistic infections or cytopenia. Reinforcement learning algorithms also allow tailored therapy, by updating predictions in real time when new patient-specific immunological data is acquired, thereby guiding precise tuning of cytokine blockage or co-stimulatory suppression (29).

Metabolomic, microbiome profiling or continuous glucose monitoring have been incorporated into predictive models for predicting improvement and deterioration in metabolic diseases as well as hypoglycemic episodes and the impact of pharmacologic treatments (GLP-1 receptor agonist, SGLT2 inhibitor) (30). Mathematical descriptions of molecular and cellular phenomena link germinal empirical observations (e.g., functional capacity of pancreatic β-cells), hepatic triacylglycerol flux, adipocyte inflammation, insulin-receptor signaling to individual therapy responses and the quest for statistically optimal combinations of interventions. Such approaches provide both guidance on appropriate choice of pharmacotherapy, but can also inform on how dietary, exercise and circadian interventions impact metabolite levels locally within a cell and systemically (31).

Application of AI to integrate multi-modal datasets in the context of CVD management is also beneficial. Predictive models incorporate genomic variants, circulating biomarkers and echocardiographic or cardiac MRI imaging data, as well as that obtained by wearables (e.g., heart rate variability, activity level and blood pressure). These models are designed to predict acute events such as heart failure decompensations, arrhythmias and thromboembolic

events in order to facilitate preemptive interventions. Cellular effectors like endothelial function, stress response of the cardiomyocyte as well as platelet activation profile are presented in a second step to fine-tune risk-stratification and guide tailored anticoagulation and/or anti-arrhythmic or re-generative therapies (32).

Artificial Intelligence and Machine Learning The regenerative medicine recipes also leverage AI and ML to fine-tune the cellular-based therapy or tissue-level therapy into higher-order precision. Predictive algorithms will allow highly stimulating in vitro modelling of stem cell and progenitor differentiation potentials using a combination of molecular markers, epigenetic instrumentalisation and ECM interactions for enhanced tissue repair (33). Indeed, parameters of the scaffold stiffness, porosity and degradation kinetics are mathematically adjusted to enable an optimal engraftment potential, cell viability and paracrine signaling respectively. Similarly, ML-guided design-of-experiments methods are used to systematically identify cytokine/growth factor mixtures that support angiogenesis, reduce fibrosis as well as functional tissue architecture. Iconic examples of such redemption include computational design optimized therapeutic regenerative strategies that have shown improved recovery, when applied in preclinical settings (e.g., for myocardial infarction and liver failure/ musculoskeletal injury) resulting from better cellular integration and function compared to their not optimised counterparts (34).

In autoimmune, metabolic and cardiovascular diseases, AI/ML provides an environment for linking molecular, cellular or systemic observations to predictive models for individualized treatment intervention. By dynamically modeling the interplay of immune networks, metabolic pathways and tissue repair programs it enables personalized adaptive therapy selection, optimization of regenerative and pharmacologic strategies as well as identification of toxicities early – thus closing the chasm between mechanistic insight and patient-specific clinical translations (35).

Multi-Modal Data Integration and Mechanistic Modeling

The arrival of high-dimensional multi-omic data has revolutionized precision medicine into a field where complex biological systems can be statistically modeled entirely. AI and ML models can take into account from genomics, transcriptomics, proteomics, metabolomics, epigenomics to spatial imaging and clinical phenotyping via integration into mechanistic frameworks, the dynamic behavior of cells, tissues and organs in health or disease (36). This integration enables the identification of master regulatory nodes in signalling pathways, transcriptional networks and intercellular communication circuits that represent high value therapeutic targets. In oncology, the integrated network-based ML models can unfold these interactions for some ON nodes including receptor tyrosine kinases (RTKs), downstream PI3K/ AKT/mTOR effectors, apoptotic regulators and immune checkpoint molecules, to identify nodes of combined modulation that may override adaptive resistance (37).

Mechanistic models further facilitate systematic combinatorial therapy design. Computational assessment of co-targeting effects on multiple pathways e.g., the combination of BCL-2 inhibitors and PI3K blockade in chemoresistant tumor subclones with AI-models could predict superior synergistic cytotoxicity, and/or safer killing with reduced off-target toxicity. In immuno-oncology, integrated models that include spatial mapping of immune infiltrates, cytokine gradients and checkpoint expression may predict T cell recruitment rates, exhaustion dynamics and tumor microenvironment manipulation to stratify optimal timing / dosing in setting of checkpoint inhibitors/ adoptive cell therapies (38).

When time is included into the models, predictive accuracy may be increased. Single-cell RNA-seq and proteomic data longitudinally may also be injected into the model to simulate cellular trajectory, clonal evolution, phenotypic plasticity under therapeutic pressure (39). These models forecast the spread of resistant subpopulations and permit anticipation adjustments in treatment schedules. Spatially resolved data as generated from multiplex immunohistochemistry or imaging mass cytometry now allows AI algorithms to learn about the intercellular interactions within tissue microenvironment and identify local pockets of immune suppression, hypoxia or metabolic deprivation affecting therapeutic effector functions (40).

Combining molecular and functional characteristics is one of the advantages in predicting chemosensitivity. Organ-specific pharmacokinetics and pharmacodynamics can be simulated by ML models including cellular-level responses such as apoptotic susceptibility, mitochondrial stress, or oxidative damage in hepatocytes, cardiomyocytes or renal tubular cells (41). This information can inform the prediction of dose-limiting toxicities and the determination dose scheduling. For example, in the development of cardiometabolic targeted therapeutics, predictive models that integrate metabolomic flux analysis with noninvasive imaging of the heart and electrophysiological measurements can predict arrhythmic risk or myocardial stress prior

to clinical presentation (42).

Multi-modal AI models also relate to regenerative medicine and the integration of mechanistic models for stem cell differentiation trajectories, scaffold biomechanical properties, cytokine gradients and vascularization kinetics. This integration is expected to optimize the combinations of differentiation cues, biomaterial properties and paracrine signaling for engraftment, tissue repair and functional restoration. Computational modeling can predict when angiogenic networks form in engineered tissues, when fibrosis emerges and how to tailor the kinetics of scaffold degradation to coincide with the rate of tissue remodeling (43).

Together, integration of multi-modal data and mechanistic models facilitate system-level description of complex biological characters for prediction and personalized/adaptive therapies. Connecting cellular and molecular mechanisms with patient-specific phenotypes, AI-driven models enable rational therapy design, combinatorial optimization, safety testing in the continuum from preclinical predictions to clinical advanced therapy implementations in oncology as well as regenerative medicine, metabolic diseases, cardiovascular disease and autoimmune disorders (44).

Real-Time Therapy Adaptation

Finally, as wearable and implantable biosensors are virtually integrated with AI-based reinforcement learning schemes, it has become possible to personalized in real-time therapy to an extent never achieved before that disease management can no longer be viewed as static schedule-based intervention but rather adaptive dynamically through time regimens (45). These sensors continuously record high resolution physiological and molecular signals such as heart rate variability, pressure, electrocardiography (ECG), glucose levels, interstitial oxygen saturation, lactate concentrations or cytokine/metabolite fluxes to provide a real time actionable data stream. In cancer, new sensor platforms to detect tumor-specific biomarkers like circulating tumor DNA fragments, exosomal microRNAs or cytokine changes characteristic of immune activation could provide early indicators of response or resistance to therapy (46).

RSL algorithms analyze this high-dimensional temporal information to predict impending disease exacerbations, tailor effective therapies dosing and suggest early interventions (47). For example, in diabetes treatment, continuous glucose monitor sensors used with insulin pumps and AI algorithms modify the dosage of insulin delivery depending on trends in glucose levels, meal consumption, physical exertion or stress indications. Cellular modeling inherent to both of these algorithms includes β-cell function, insulin sensitivity in peripheral tissues and hepatic glucose output enabling accurate titration at a patient level with the aim of avoiding hypoglycaemia or hyperglycaemia (48).

Implantable hemodynamic monitors that monitor intracardiac pressures, electrocardiographic conduction patterns and activity are used to provide real-time data to predictive models in cardiovascular disease predicting arrhythmias, exacerbations of heart failure or thromboembolic events. Adaptive AI-directed therapy can modulate diuretic, anti-arrhythmic or anticoagulant dosing and therefore therapy before clinical symptoms appear. The predictive capability is further improved by mechanistic models that include stress markers for cardiomyocytes, endothelial function and platelet activation, which may act as early warning signs for adverse events (49).

In oncology, reinforcement learning models use real-time biomarker readouts (for example circulating tumour DNA levels, cytokine profiles and immune cell function) to adapt the dosing of chemotherapy or schedules for immunotherapy1. Simulations of tumor progression, immune trafficking rate and apoptosis fraction at a cellular resolution allow for identification for optimal timing (when to intervene), and intensity (how much to do), that can minimize toxicity while maximizing the degree of anti-tumor activity (50). The ongoing surveillance for markers of immune activation, such as IFN-γ, IL-2, and granzyme B to monitor this balance provides an opportunity to ensure just-in-time adjustment of checkpoint inhibitor therapy or adoptive cell infusions while preserving effective antitumor control (cf., the use of tryptophan depleting cytotoimmunoblocks)44; with adjustments to maintain a favorable benefit-to-risk ratio for developing cytokine release syndrome (51).

Furthermore, in the field of regenerative medicine and advanced cell therapies, biosensors used in combination with ML platforms monitor metabolic activity, viability and differentiated state of transplanted cells or engineered tissue. Temporal feedback allows for growth factor, scaffold degradation kinetics or local microenvironmental cues to be adaptively modulated, thereby promoting engraftment, vascularization and functional recovery. Spatial and temporal profiling dynamics of oxygen tension, pH gradients, and paracrine signaling factors guide adaptive changes facilitating adjustments to tissue context evolution around induced therapeutic interventions (52).

CHALLENGES AND LIMITATIONS

Although there have been significant progress in the use of AI and ML for personalized treatment planning, various scientific, technical, clinical challenges need

to be resolved in order to ensure successful and safe clinical application. A significant challenge is the heterogeneous nature and dimensionality of data (53). The resolution, accuracy, and completeness of multi-modal data (which may include genomics, transcriptomics, proteomics, metabolomics, imaging or continuous physiologic signals) can differ. Sampler-dependent sample conditioning, batch effects in sequencing or proteomics assays, and sensor inhomogeneities can contribute to biases degrading the modeling accuracy. Robust and reproducible predictions across patient populations and clinical sites depend on effective data harmonization, normalization, and preprocessing pipelines which can minimize such sources of variability (54).

Standardization and Interoperability is also a key challenge. For clinical integration, AI-based systems and applications need to interface with EHRs, LIMS (laboratory information management systems), medical imaging platforms. However, the differences in data formats, annotation protocols and measurement units make it harder to train models as well as doing real-time inference. Standard ontologies, reference datasets and shared QC metrics are crucial to enable cross-institutional model validation and regulatory approval (55).

Overcoming these challenges will require interdisciplinary interaction among computational scientists, clinicians, regulatory agencies and ethicists. Developments in standardised data workflows, explainable AI, secure sharing protocols and extensive validation studies will be vital to fully unlock the potential of AI- and ML-based automated personalised treatment planning across oncology, regenerative medicine as well as for autoimmune, metabolic and cardiovascular pathologies (56).

FUTURE PERSPECTIVES

The future of the AI- and ML-based personalized treatment planning will revolutionize advanced therapies that incorporate multi-scale molecular, cellular and tissue information with real-time monitoring of patient. One innovative direction is federated learning, which allows multi-central data integration yet without the necessity for centralizing sensitive patient information. By training models on decentralized data, federated approaches maintain privacy while utilizing a more heterogeneous population, leading to better generalization and robustness. This is especially essential in cancer and rare genetic diseases where multi-institutional data are required to capture subclonal diversity, low frequency mutational profiles, and treatment resistant phenotypes (57).

Multi-modal mechanistic modeling is another frontier. Next-generation AI platforms will incorporate genomics, transcriptomics, proteomics, metabolomics, epigenomics and spatial imaging and functional sensor data into overall representations of the disease states (58). These models will have the potential to define regulatory nodes, emerging properties of cell networks and test in silico combination therapies. As a specific example for cancer, combining insights into tumor mutational burden, immune cell infiltrate patterns, cytokine gradients or drug pharmacokinetics in a mechanistic model might help to refine timing of checkpoint inhibition administration or adoptive cell infusion scheduling/combination with targeted chemotherapy. Likewise, in metabolic disease a combination of continuous glucose monitoring, β-cell functional assays and hepatic metabolic flux data could support cellular-level mechanism-driven adaptive glucose therapy by AI (58).

There will be real-time adaptive therapy beyond the trained reinforcement learning–based systems currently in use. Implantable biosensors, microfluidic drug delivery, and AI predictive algorithms will be incorporated into future devices to dynamically control therapeutic interventions at molecular and cellular levels (59). For instance, changes in cytokines following CAR-T therapy or immunomodulatory therapy can drive automatic modulation of dosing or co-administration of checkpoint inhibitors to minimize toxicity and still maintain ideal immune activation. These closed-loop systems will utilize mechanistic models to predict cellular compensatory responses, e.g. T cell exhaustion or tumor immune evasion, or fibroblast mediated fibrosis in a regenerative trial (60).

More specific therapeutic domains are expected, such as neurodegenerative diseases, infectious diseases and tissue engineering. You could imagine using AI models to parse single-cell transcriptomics, epigenomic landscapes and extracellular vesicle signaling in Alzheimer's, Parkinson's or viral infections to design precision interventions in any of those conditions (61). In regenerative medicine, mechanistic AI will facilitate the optimization of scaffold properties, growth factor release kinetics and cell differentiation cues for a range of therapeutic endpoints including tissue repair, angiogenesis and functional recovery. Incorporation of patient-specific molecular signatures into scaffold and cellular models will afford truly personalized regenerative paradigms (62).

Explainable AI (XAI) and mechanistic transparency will be crucial to realize these advances for the clinic. Interpretable output that clusters predictive readouts with underlying cellular and molecular events are needed for clinicians. For example, AI-generated predictions will need to distinguish if, and how suspected tumor resistance

is generated (63). For example due to increased expression of ABC-transporters, up-regulation of checkpoint ligands or direct metabolic rewiring in cancer sub-clones. Transparent models would assist in regulatory approval, therapy selection and improved patient safety through rationalized evidence-based justification for intervention titration (64).

Ultimately, the integration of AI, ML and multi-modal mechanistic modeling with real-time adaptive monitoring is expected to permit personalized therapy at the cellular and molecular level leading to maximum efficacy while minimal systemic toxicity. Next generation frameworks will integrate genomic, transcriptomic, proteomic, and functional read-outs into cohesive predictive and interpretable treatment algorithms defining a new era of personalized, mechanistically guided precision medicine (65).

CONCLUSION

Artificial intelligence and machine learning are transforming personalized treatment planning, merging cellular, molecular and clinical data into predictive, adaptive and mechanistically informed networks. These tools make it possible to choose therapies with precision, monitor dynamic dosing, and tailor timing of administration to patient physiology (whether human or murine), molecular parameters, and disease state. Using multi-modal datasets, real-time tracking and mechanistic modeling, AI-based methods can predict drug response by predicting adverse effects and guiding clinical intervention. We believe that as these platforms mature, they have the potential to change the practice of oncology and regenerative medicine, autoimmune and metabolic diseases, cardiovascular disease, ushering in a new era of much more personalized and effective/safe advanced therapeutics.

Authors's Contribution

Maryam Diansaei, Parisa Haghpour: data curation; editing and review. The authors read and confirmed the final manuscript.

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Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

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Biomaterial Innovations for Controlled Drug Release in Advanced Therapies

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Abstract:

The incorporation of biomaterials in controlled drug delivery systems has redefined the advanced therapeutic modalities for the capability to modulate therapeutic agents with high precision, resulting in improved efficacy and reduced side effects. This survey examines the versatile utility of biomaterials (hydrogels, nanoparticles and bioactive scaffolds) for advanced therapeutic modalities with special focus on cellular and molecular responses. We also cover the physicochemical properties, such as biodegradability, biocompatibility and responsiveness to environmental triggers leading it to become a controlled release systems. Clinical and preclinical researches highlight these systems as promising platforms in oncology, regenerative medicine, and gene therapies. Nevertheless, obstacles remain in the areas of scaling production, reproducibility and meeting regulatory requirements. Next steps include the design of multifunctional biomaterials for co-delivery of multiple therapeutic agents, on-line monitoring of drug release, and incorporation with advanced manufacturing technologies toward clinical translation.

Keywords: Biomaterials, controlled drug delivery, advanced therapies, hydrogels, nanoparticles, bioactive scaffolds.

INTRODUCTION

Over the years, drug delivery has greatly evolved to meet the growing sophistication of therapy and shortcomings in traditional routes of administration. Conventional systemic administration approaches lead to low bioavailability, fast elimination, nonspecific localization in vivo, and deleterious systemic side effects for small-molecule drugs, biologics and nucleic acid-based therapeutics (1, 2). These constraints often require increased dosing to obtain clinical efficacy, increasing side effects and lowering patient compliance. In this regard, biomaterials-mediated drug delivery systems may represent a pivotal approach to increasing the specificity, efficiency and safety of ATMP.

By encapsulating agents into synthetic polymers, lipids, inorganic nanostructures, or their hybrids these systems can offer controlled release profiles, enzymatic protection, improved tissue accumulation and selective intracellular delivery resulting in

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the possibility to use classes of therapies thus far restrained by pharmacokinetic/biodistribution issues (3).

Biomaterial-mediated delivery strategies work at the molecular level and take advantage of specialized physicochemical and biological attributes to enhance therapeutic efficiency. Nanoparticles, hydrogels and bioactive scaffolds bind to cells through receptor mediatated endocytosis or via micropinocytosis, or even by direct membrane fusion bringing about excellent transfer of cargo into the cytoplasm or directly into the nucleus (4). Lipid nanoparticles containing siRNA or CRISPR-Cas components have been shown to very efficiently modulate gene expression in hepatocytes, immune cells or tumor cells, and the great knockdown or protein expression has also been achieved with low immunogenicity. Polymeric carriers, including PLGA nanoparticles, protect protein or peptide during systemic circulation and provide sustained protein delivery at sites (5). Natural or synthetic polymer-based hydrogels allow spatiotemporal regulation of molecular release, thereby enabling phenomena, such as stem cell differentiation, angiogenesis, immune modulation and extracellular matrix remodelling (6). These agents can be designed to be responsive to the physiological triggers, namely pH, redox potential temperature and enzymatic activity getting site-specific or stimuli triggered drug release. Tumor-targeting and pH-sensitive nanocarrier If the pH of the tumor microenvironment is acidic, we can produce pH-sensitive nanoparticles that target tumors. redox-responsive This type of carrier can take advantage of increased glutathione levels in tumor cells to trigger release in cells which makes releasing behaviors more precise and minimizes off-target toxicity (7).

Advanced biomaterials are of special importance for regenerative medicine, oncology, immunotherapy and gene therapy. In tissue engineering, co-delivery systems of scaffolds or injectable gels and growth factors (e.g., VEGF, FGF, BMP-2, neurotrophic factors) have promoted bone4, heart5 and nerve6 regeneration in preclinical models (8). Bioactive scaffolds offer physical support as well as release the therapeutic vesicles in a controlled manner, and can act as a conduit for progenitor cells to proliferate, differentiate and organize tissues. In oncology, nanoparticles coated with tumor-specific receptor ligands, antibodies or peptides preferentially accumulate in malignant tissue resulting in a higher therapeutic index of chemotherapeutics and gene-silencing agents (9). Lipid23,24 or polymeric25–27 nanoparticles which deliver siRNA or immunomodulators to the TME have shown strong therapeutic effects against tumors in preclinical models whilst reducing systemic side-effects. Co-delivery systems allow synergistic modulation of multiple pathways, including the combination with chemotherapy and gene silencing or immunomodulatory cytokines for concurrent tumor suppression due to treatment and regain of antitumor immune responses (10). In immunotherapy, biomaterial delivery of antigens, checkpoint inhibitors or cytokines to DCs and T cells has proven beneficial in immune activation and tumour specific responses whilst reducing systemic inflammation. In the field of gene therapy, there is also a need for efficient and accurate intracellular delivery of CRISPR-Cas system or mRNA so as to achieve targeted gene editing or precise expression of therapeutic proteins with minimal off-target effects (11).

Recently, clinical translation has proved the feasibility and efficacy of biomaterial-mediated delivery systems. Lipid nanoparticles for mRNA vaccine delivery, whose material precision is facilitated by the very nature of genomic RNA itself (e.g., near-atom high-resolution structures), have exhibited potent immune responses and excellent safety records in phase 3 human studies, thereby demonstrating that precise biomaterial-mediated delivery at scale is feasible (12). Interstitial injection of hydrogels and bioactive scaffolds have been tested in preclinical models of heart, musculoskeletal, and neural injury to promote tissue repair and functional recovery. Clinical phase 1 studies of siRNA-loaded nanoparticles targeting hepatocytes or immune cells have shown that downregulating a target gene is achieved in an organ with little toxicity. Concurrent visualization of therapeutic biodistribution and activity in real time via integrated imaging agents or biosensors can inform treatment kinetics and facilitate patient-tailored dose engineering. Nevertheless there are still huge challenges such as mass manufacture, reproducible characterisation, pharmacokinetics and immunagenicity as well as regulatory conformity (13). Optimization of the process parameters in the synthesis of nanoparticles, fabrication of hydrogel, and preparation of scaffold together with strict quality control and safety assessment is required for clinical application (14).

Molecular and cellular intricacies in the context of biomaterial drug delivery systems emphasize revolutionary applicability. Advanced delivery systems provide for regulated intracellular delivery, targeting the disease sites with precision, and modulating signaling pathways, immune responses and regeneration processes (15). Functionalization with targeting ligands, stimulus-responsive materials and co-delivery of multiple therapeutics can further tailor therapeutic responses in intricate pathophysiological conditions. Integrating with high-throughput characterization, computational

modeling as well as multi-omics profiling is essential for rationally designing personalized biomaterials to meet patient-specific therapeutic needs in a safe and effective manner. These methods together enable the development of precision treatments that can be customized to the molecular and cellular composition of any given patient, which broadens applicability for therapeutic applications including oncology, regenerative medicine, immunotherapy , and gene therapy (7).

This review aims to be a comprehensive, data-rich summary of late developments in biomaterial design for controlled drug release in advanced therapies. It emphasizes mechanistic understanding of the interaction between biomaterials and cellular/molecular systems that drive therapeutic efficacy, tissue regeneration, and immune response. The review also covers engineering solutions, preclinical and clinical evidence as well as translational considerations with a focus on design criteria and strategies to materialize precise, multifunctional and clinically meaningful therapeutic effects. Integrating from molecular mechanisms to materials science and translational applications, in this review, we bring the field of biomaterial-mediated controlled delivery to its status quo and introduce its transformative power in shaping next-generation advanced therapies toward precision medicine.

Hydrogels in Controlled Drug Delivery

Hydrogels are a class of multifunctional biomaterials, which have been widely studied in controlled drug delivery systems, because of their distinctive physicochemical properties and close resemblance to the extracellular matrix. Constructed from interconnected polymeric networks that can absorb large amounts of water, hydrogels offer a hydrated, tissue-mimicking environment that maintains the stability and bioactivity of enveloped biomolecules (small molecules, peptides, proteins, nucleic acids) and even cells (16). The mechanical characteristics, porosity and degradation rates of hydrogels are adjusted through polymer identity, crosslinking density and the introduction of functional groups to achieve precise modulation of drug loading and release profiles. Diffusion, swelling, gel degradation and environmentally induced release enable hydrogel-mediated delivery of therapeutic agents in such a way that the peak drug concentration at the target site is significantly higher than non-localized treatment and side effects on healthy tissue are reduced (17).

The design of stimuli-responsive or “smart” hydrogels is one of the most important advancements in the field of hydrogel. These systems utilize physiological or disease condition-directed stimuli including pH (acidic/alkaline microenvironments), temperature, enzymatic activity, ionic strength that influence drug release (17). They are often pH-responsive hydrogels in which ionizable polymeric groups cause swollen or shrunken state depending on acidic micro-environment like that of tumor tissues or inflamed area. preclinical studies have shown that these pH-sensitive hydrogels loaded with Dox obtain higher intratumoral drug retention and antitumor efficacy than the systemic administration of free drug, and alleviate cardiotoxicity and hematological toxic effects (17). Thermosensitive hydrogels, generated from polymers such as poly(N-isopropylacrylamide) or poloxamers, display a sol-gel transition at physiological temperature and can be injected into the body in liquid phase to quickly solidify at an injury site. This feature has been exploited in cardiac tissue engineering, and injectable hydrogel drug carriers releasing VEGF and FGF resulted in orientation of capillary sprouts and functional improvement after myocardial infarction; histology indicated that the rubbery polymer supported organized capillaries formation at the expense of fibrotic scarring (18).

Enzyme-mediated hydrogels have been considered as a more sophisticated approach, especially in diseases where protease activity is increased. For example, matrix metalloproteinase (MMP)-sensitive hydrogels can deliver entrapped growth factors, cytokines or chemo- therapeutics specifically to areas with increased proteolytic activity such as a tumor or in amed cartilage. Such targeted release increases local drug levels while decreasing off-target exposure, thereby increasing the therapeutic index (19). In musculoskeletal regenerative models, MMP-sensitive hydrogels-encapsulated BMP-2 + MSCs promoted bone regeneration of critical-size defects that resulted in complete bridging by weeks following implantation as assessed micro-CT and histologically, with formation of vascularized bone. Similarly, bioresponsive hydrogel-based delivery system has been developed in SCI model to promote axon regeneration and locomotor function recovery through locally controlled neurotrophic factor release, which indicates possible application of bioresponsive features in neural tissue engineering (20).

Injectable and in situ-forming hydrogels offer further benefits including minimally invasive application, ability to match irregular defect geometry and continuous local therapeutic delivery. In OA models, a syringeable hyaluronic acid based hydrogel loaded with anti-inflammatory cytokines and growth factors following intra-articular injection, decreased synovial inflammation alongside ameliorating cartilage integrity and joint functioning. Physical characteristics of the hydrogel matrix, including stiffness, porosity and degradation profile can be fine-tuned to mimic specific tissue-specific micro-environment and may play a role in orchestrating the

maintenance of therapeutic performance as well as tissue integration (21). Hydrogels have also been developed to co-deliver multiple therapeutic agents in combination, which may act synergistically. For instance, co-encapsulation of angiogenic agents with anti-inflammatory cytokines in a single hydrogel matrix can both enhance vascularized tissue regrowth and control immune responses, which is especially beneficial for ischemic injury and chronic wound healing (22).

Mechanically, hydrogels not only influence the kinetics of drug release, but act upon cell behavior. Cell adhesion, migration and proliferation as well as cell differentiation are largely controlled by hydrogel 3D-structure and mechanics. In a regenerative context (stem cell-based therapies), hydrogels also act as protective vehicle for the exchanged transplanted cells facilitating their survival, engraftment and prolonged paracrine signaling (23). VEGF-releasing MSC-laden hydrogels have been shown to augment endothelial cell proliferation and tubulization in vitro as well as angiogenesis in vivo, demonstrating the interplay between material design and cellular responses. In addition, functionalization of hydrogels with cell-adhesive peptides or growth factor-binding domains may sequester signaling cues to promote specific cell fate decisions and tissue regeneration (24).

Hybrid hydrogels containing particles or exosomes have also been investigated in the context of combination delivery strategies in recent translational studies. Drug loaded nanoparticles encapsulation in a hydrogel matrix can also allow for an ordered or staged release and preserve structure integrity at the target site49. Exosome-loaded hydrogels have also been used for controlled delivery of regenerative vesicles to preclinical injury models of the heart and brain, to extend their bioavailability and enhance paracrine effects (25). Imaging analysis indicated robust exosome retention in hydrogel scaffolds that was retained longer compared to injection, which coupled with tissue repair and functional improvements (26).

From a therapeutic point of view, studies using hydrogel-based systems have revealed good safety and biocompatibility profiles, with few reports of immunogenicity or systemic toxicity in preclinical and early-phase investigations (27). These advancements in manufacturing have made it possible to create hydrogels with reproducible mechanical properties, tunable porosity and controlled spatial presentation of therapeutics using 3D printing and microfluidic assisted crosslinking. Such developments enable patient-tailored adaptations, which enables hydrogels to be fine tuned to match the anatomic and biophysical needs of individual lesions or organs. Thus, combining 3D VP and real-time monitoring of the hydrogel delivery system with imaging contrast agents or biosensors combined in polymer network would enable further possibilities to monitor therapeutic release, tissue response and treatment effectiveness toward personalized medicine (28).

Nanoparticles for Targeted Drug Delivery

Nanoparticles have recently been recognized as one of the most promising platforms for controlled and targeted drug delivery with many advantages over conventional therapeutic approaches. Due to their small size (submicron), high surface-area-to-volume ratio and controllable physicochemical features, NPs can encapsulate a broad range of therapeutic agents such as hydrophilic and hydrophobic small molecules, peptides, proteins, nucleic acids and even organelles or extracellular vesicles (29). Nanoparticle encapsulation shields fragile drugs from inactivation by enzymes, hydrolysis, or clearance and so increase systemic bioavailability, extend circulation time. Such protective role holds particular importance when it comes to nucleic-acid therapeutics such as siRNA, mRNA or CRISPR-Cas building blocks that are otherwise prone to rapid degradation in the blood circulation and poor cellular internalization (30).

An important benefit of nanoparticles is their ability to encapsulate drugs and deliver them in a targeted manner, which can be facilitated either passively or actively. Passive targeting is mediated through the enhanced permeability and retention (EPR) effect, in which nanoparticles tend to accumulate in tumoral tissues or inflamed areas because of leaky vasculature and insufficient lymphatic drainage (31). Active targeting consists in chemically or physically conjugating the nanoparticle surface with ligands, antibodies, peptides, aptamers or small molecules that specifically bind to receptors on target cells. For example, folic acid-modified nanoparticles selectively accumulate in folate receptor-rich tumors leading to an enhanced intracellular chemotherapeutic compounds (e.g., doxorubicin or paclitaxel)'s delivery and lower systemic toxicity (32). In addition, nanoparticles with a peptide sequence RGD present on their surface are targeted to integrin-expressing endothelial cells in order to improve homing of particle to tumor vasculature, whereas antibodies against HER2 or EGFR ensure receptor-mediated endocytosis in breast and lung cancer cells, respectively (33).

Various types of nanoparticles have been widely studied for their application in therapeutic strategies. Polymeric NPs constructed by biodegradable polymers such as PLGA, PLA, chitosan, or PEGylated polymers offer their ability of sustained release through hydrolysis or enzymatic degradation while the surface properties

can be tailored to improve circulation half-life and cellular uptake (34). Liposomes, with their ability to form phospholipid bilayers, are especially favored as drug carriers of hydrophobic and amphiphilic drugs and their composition can be engineered for pH-dependent or temperature dependent release. Dendrimers, which are highly branched synthetic polymers with controlled surface functionality, allow accurate multivalent drug conjugation and can co-deliver nucleic acids or chemotherapeutic agents together as opportunities for combination therapies (35). Furthermore, inorganic nanoparticles like gold, silica or iron oxide have been also used as multimodal theranostic platforms where drug delivery is associated with imaging or photothermal therapy. For instance, chemotherapeutics-conjugated gold nanoparticles facilitate dual drug delivery and near-infrared-triggered photothermal ablation with improved tumor cell killing and healthy tissue preservation (36).

The size, shape, surface charge and composition of nanoparticles greatly affect their mechanistic properties. Particles between 50 and 200 nm show the highest blood half-life and superior tumor penetration, whereas smaller (200 nm) might be retained by the mononuclear phagocyte system. Surface charge affects cellular uptake and bio-distribution; weakly cationic particles enhance entry to anion-expressing cell membranes while strong positive or negative charges can result in opsonization and rapid elimination (37). The surface chemistry can also be tailored to have stealth characteristics (e.g., PEGylation) that prevent macrophage recognition, extend half-life in the circulation and increase bioavailability at the target site (38).

In the latest preclinical research, nanoparticles have emerged as promising drug delivery vehicles for combination therapies for synergistic therapeutics. For instance, polymeric NPs co-encapsulating chemotherapeutics and siRNA suppressing the oncogenic pathways showed more potent inhibition of tumor growth and reversed drug resistance in murine breast and pancreatic cancer models (39). Likewise, liposomes containing both immune-modulators and tumor antigens also enhance DC activation and increase anti-tumor immune responses - a sign of the intersection between drug delivery and immunotherapy. Mechanistic studies demonstrate that nanoparticle-based co-delivery improves cellular trafficking, achieves synchronized release profiles, and controls cytotoxic and immune pathways in a spatiotemporal manner (40).

Nanoparticle-enabled drug delivery approaches have also passed the preclinical phase and entered clinical assessment. Various formulations of these have been approved with regard to regulation, such as liposomal doxorubicin and PEG-liposomal irinotecan, or siRNA containing lipid nanoparticles for transthyretin mediated amyloidosis. Current clinical trials are investigating polymeric and lipid nanoparticles as carriers for mRNA vaccine, oncolytic agents, targeted chemotherapeutics and gene editing therapies (41). Nanoparticle dosing is in general well-tolerated as shown in Phases I trials where less systemic toxicity verses free drug control is evident, an improved target accumulation can be observed and pharmacodynamic effects are measurable as gene knock-down, protein expression or tumor regression. Corresponding imaging studies with radiolabeled nanoparticles have measured biodistribution showing selective accumulation in target organs and clearance profiles depending on size and surface characteristics (42).

Notwithstanding these encouraging results, a number of challenges still exist for the clinical translation of nanoparticle-mediated delivery systems. Differences with particle size, the coating on surfaces and loadings of therapeutics can cause heterogeneity in therapeutic efficacy and pharmacokinetics. Large-scale production with uniform quality and batch-to-batch reproducibility is still a technical challenge, especially for complex multifunctional nanoparticles (42). Immunogenicity, cumulative toxicity and accumulation in off-target organs i.e. liver/spleen/lung are the concerns which must be carefully evaluated preclinically. In addition, the interactions of nanoparticles with this protein corona, which forms upon exposure to blood components may influence their biodistribution and cellular uptake so that a rational approach to surface design and characterization is required (43).

These challenges are being solved by advances in engineering approaches. Precisely designed synthesis strategies (eg, microfluidic-assisted nanoprecipitation and controlled self-assembly) ensure that particle size and cargo loading are reproducible. Surface engineering approaches including ligand conjugation, PEGylation and zwitterionic coatings also enhance targeting specificity, circulation temperance and immune evasion. Such small packages that open during a change of pH, temperature, redox potential or an enzymatic event provide temporal and spatial control of therapy and minimize non-target toxicity Khorasani, 2025 #47). Nanoparticle incorporation within hydrogel or scaffold constructs could lead to improved localized delivery and retention, therefore contributing to tissue regeneration, longer term immunomodulation or combinatorial approaches (44).

Mechanistically, NPs are not solely carriers but also drivers of cellular pathways. Endosomal trafficking and cytoplasm delivery, as well as cellular signaling, will be induced by the

internalization through endocytosis, micropinocytosis or receptors. In the case of nucleic acid therapeutics, escape from endosomes/lysosomes is essential to deliver the payload in the cytosol or nucleus and various strategies like pH-responsive polymers or fusogenic lipids have been utilized to enhance delivery efficiency (45). Nanoparticles containing chemotherapeutics can activate the intrinsic and extrinsic apoptosis pathways, whereas co-delivery of drugs with immune modulators can promote M1-like macrophage polarization, improve DC activation, and trigger CD8+ T cells. These multi-faceted effects have shown how nanoparticles may be able to coordinate complex molecular and cellular injury responses in the overall improvement of therapeutic efficacy (46).

Therefore, in the field of advanced therapy, there is no double that nanoparticles have an extremely reversible and multifunctional platform. Nanoparticles can improve the efficacy, decrease systemic toxicity, and regulate molecular and cellular pathways through encapsulating, protecting, controllably releasing various therapeutic agents in combination with active targeting and responsiveness to stimuli (47).

Bioactive Scaffolds in Regenerative Medicine

Bioactive scaffolds are considered to be essential platforms in tissue engineering and regenerative medicine, offering a structural support as well as providing biochemical signals and controlled release of therapeutic agents toward the injury (or diseased) sites. These scaffolds are conceptualized not just as passive structures, but as interactive ecm substrates that can influence the cells with instructive cues, modify the microenvironment, and encourage tissue-specific maturation (48). The choice of the material composition and architecture, as well as functionalization strategies, are crucial to mimic relevant features from the extracellular matrix (ECM) such us resistance and porosity that collectively affect cell adhesion growth and migration. Natural polysaccarides such as collagen, fibrin, hyaluronic acid and chitosan are often used because of their close resemblance to ECM structures, enzymatic degradation ability and in support of bioactive motifs. Synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polyethylene glycol (PEG), present tunable mechanical performance, predictable degradation kinetics, and consistent reproducible manufacturing process, which makes them clinically scalable (48).

One of the characteristic properties of bioactive scaffolds is that they can integrate controlled release for drugs. Growth factors, cytokines, nucleic acids and small molecules can be incorporated into the scaffold matrix or conjugated to polymer chains for controlled time- and space release. For example, bone scaffolding that allows the controlled release of bone morphogenetic proteins (BMP-2, BMP-7) has demonstrated enhanced osteogenesis in critical-sized bone defect models as indicated via micro-computed tomography showing robust bone bridging and organized lamellar formation within weeks post-implantation (49). Also, the regeneration of cartilage has been improved by fibrin or collagen scaffold supplemented with transforming growth factor-beta (TGF-β) or insulin-like growth factor-1 (IGF-1) that stimulates chondrocyte proliferation and extracellular matrix deposition. These scaffolds frequently rely on a combination of diffusion-based release and matrix degradation to maintain therapeutic delivery over days to weeks, mirroring the time scales involved in tissue repair mechanisms (50).

Novel scaffolds include multi-layer and/or gradient architectures which allow for the sequential delivery of more than one bioactive agents. For instance, aided angiogenesis and osteogenesis is provided by biphasic scaffolds through the VEGF incorporated outer layer and BMPs inner structure to achieve vascularized bone regeneration (51). Preclinical evidence also shows that biomaterials with these dual-delivery systems can not only increase the quality of tissue formation, but also biomechanical-characteristic improvement (evaluated by tensile and compressive test) of the regenerating tissues. In wound healing, bioactive scaffolds loaded with vasculgenic agents and anti-inflammatory cytokines enhance re-epitheliazation, decrease scar formation, and guide granulation tissue development (52). In diabetic wound animal studies, collagen scaffolds loaded with platelet derived growth factor (PDGF) or stromal cell-derived factor-1 (SDF-1), have demonstrated increased neovascularization and more rapid closure rates vs. untreated controls, suggesting the translational implications of bioactive scaffolds in chronic tissue repair (53).

Cell interactions with bioactive scaffolds are crucial to regeneration. Scaffolds not only entrap stem cells, progenitor cells, or genetically modified cell populations against the adverse microenvironment of injured tissue but also release paracrine signalings that promote repair (54). For instance, MSC-seeded scaffolds have been demonstrated that they enhance local production of angiogenic factors including VEGF and HGF which improves vascularization and tissue infiltration. Neural stem cell-seeded scaffolds that are engineered to release neurotrophic factors such as brain-derived neurotrophic factor (BDNF) or nerve growth factor (NGF), likewise promote axonal extension and synaptic connectivity in SCI models, culminating in functional tests for

locomotor recovery (55). At a cellular level, 3 d scaffolds were shown to modulate cell morphology, cytoskeletal arrangement and mechanotransduction pathways which in turn altered downstream gene expression and differentiation paths. The stiffness, porosity and topography of scaffolds can all be tailored to direct the stem cells towards osteogenic, chondrogenic or neurogenic lineages, enabling a customizable design toward tissue specific regeneration strategies (56).

The integration of bioactive scaffold with other advanced delivery systems also contributes to increase their therapeutic potential. Nanoparticle-loaded scaffolds combine the sustained release of the scaffold matrix and the possibilities to tune release kinetics and targeting by nanoparticles. For instance, scaffolds loaded with polymeric-nanoparticle-delivery of siRNA to pro-fibrotic genes have been shown to achieve site-specific gene silencing in a fibrotic tissue model and prevent scar formation while facilitating regeneration (57). In the same way, exosome-loaded scaffolds have been designed for controlled delivery of regenerative vesicles, resulting in longer retention time at the injury site and enhanced paracrine activity. In cardiac regeneration models, MSC exosomeladen hydrogels increased myocardial contraction force, decreased infarct region, and increased the number of capillaries by combining scaffold architecture with physiologically active payload (58).

Processes of designing bioactive scaffolds have advanced to achieve control over microarchitectural features and mechanical performance. With electrospinning. 3D bioprinting, and microfluidic-assisted scaffold fabrication, the resultant scaffolds are produced with aligned fibres, defined porosity, and spatial control of bioactive biomolecules that closely replicate the native tissue architecture (59). These techniques allow the production of “patient-specific” grafts matching anatomical defects and promoting engraftment, though engraftment with functional integration have been challenging. In addition, the integration of biosensors or imaging agents into scaffolds could enable in situ real-time monitoring of effector release, tissue response and cellular activities to facilitate personalized regenerative therapies (60).

In animal models, bioactive scaffolds have been effective in the context of different tissues (e.g.: bone, cartilage, cardiac, neural or dermal tissue). Critical-size bone defect models made with hydroxyapatite-collagen scaffolds that released through 8–12 weeks BMP-2 and VEGF could meet the needs of complete bridging, and biomechanical testing showed the recovery of structural integrity (61). Fibrin-based TGF-β3-loaded scaffolds facilitated hyaline cartilage formation in articular cartilage defect models, as evidenced by histology showing type II collagen and proteoglycan deposition. In spinal cord injury animals that received aligned nanofiber scaffolds expressing NGF or BDNF, axonal regeneration and re-myelination were observed accompanied by recovery of locomotor function (62). In PDGF-loaded and antimicrobial peptide-incorporating dermal scaffolds, the current study found that wound closure was faster and infection rates were lower in full-thickness excisional wound models which demonstrated versatile and clinical impact on scaffold-based delivery systems.

Mechanism of action Mechanistically, bioactive scaffolds work through sustained release of bioactive molecules, modulation of cellular activity and host tissue integration (63).

In summary, bioactive scaffolds provide an excellent and versatile platform in regenerative medicine to direct intricate molecular and cell signaling activities that drive tissue repair and regeneration. By coupling controlled release features with tunable mechanical properties and bioactive cues, these scaffolds improve treatment efficiency in various tissues (64). With the combination of scaffold engineering and novel delivery vehicles, nanoparticles or exosomes for example, regenerative intervention can be fine tuned both in space and time to optimize regenerative outcomes and blur the boundary between molecular precision and tissue functional restoration (65).

Challenges and Future Directions

However, in spite of the great progress made on these biomaterial-based drug delivery systems, numerous hurdles still exist for their translation from the preclinical stage into broad clinical applications. A fatigue of the snippet is the production scalability and reproducibility (66). A large number of biomaterial systems, including hydrogels, nanoparticles and bioactive scaffolds depend on intricate physicochemical features, polymer composition and processing methodologies to deliver sustainment release, targeted delivery and bioactivity. Differences in the molecular weight of the polymer, crosslinker density, particle size distribution or encapsulation efficiency can have a large impact on pharmacokinetics, biodistribution and therapeutic effects (67). High throughput and standardized manufacturing processes for batch-to-batch reproducibility are yet to be fully established, especially for intricate multifunctional systems that incorporate a wide spectrum of therapeutic agents or responsive elements (68).

In the future, multifunctional biomaterials with refined spatiotemporal delivery of drugs will be designed that may combine the two at the level of both molecular and cells. These smart systems can carry combination drugs (e.g., small molecules, proteins,

nucleic acids, and exosomes) and provide on-demand clustering in response to endogenous or exogenous triggers like pH change, enzymatic activities, temperature increase, and mechanical forces. For instance, stimulant-responsive nanoparticles sequestered in hydrogel scaffolds can facilitate temporal or combinational delivery of immune modulatory and regenerative factors, yielding tissue repair and functional improvements in multiple disease models (69).

Together, these developments seek to address current challenges and confirm biomaterial-based drug delivery systems as dependable, accurate and safe platforms for advanced therapies. Integration of multifunctional materials, stimuli responsive design, scalable manufacturing, and in vivo monitoring will collectively position the next generation of biomaterial therapeutics to meet urgently unmet clinical demands across oncology cancer therapy, regenerative medicine, immunotherapy, and gene-mediated therapies (70).

CONCLUSION

Biomaterials developments have revolutionized drug delivery, thereby facilitating the precise, site-specific and sustained therapeutic approaches for complex diseases. Using stimuli responsive materials, multifunctional scaffolds and new fabrication methods these platform systems can deliver drugs, proteins, nucleic acids and cells constituents that also modify molecular and cellular pathways providing increased efficacy and reduced systemic toxicity. The main bottlenecks lie in the scalability, reproducibility, long-term biocompatibility, and regulatory issues for clinical application. Work on smart, multi-functional and patient-specific biomaterials along with real-time monitoring and controlled cargo release will pave the way for these platforms to become indispensable for safe, effective and personalized advanced therapies.

Authors's Contribution

Yasaman Vojgani, Mohadeseh Sadeghinia: Conceptualization; editing and writing. The authors read and confirmed the final manuscript.

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Modern Management of Acute and Chronic Pain: Pharmacological and Non-Pharmacological Approaches

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Abstract:

Acute and chronic pain continues to cost billions of dollars to society and affects people's functionality and quality of life. Contemporary studies chronic pain remains to bedefined as a complexity of bio-psycho-social-spiritual dimensions of pain. However, contemporary clinicians continue to report clinical challenges of balanced pain management. One of the reviewers sought to outline the contemporary approaches to pain management. Specific emphasis was given to pharmacotherapy, novel drugs and scientifically validated non-pharmacological approaches.

In the initial management of pain, the scientifically validated nurse employs non-opioid analgesics, and a carefully prescribed antidepressant, anticonvulsant, and adjunctive biological therapies. The report refers to the individual pain management advancements and precision medicine as the paradigm shift in healthcare. In addition, the use of newly researched, and the reviewed pain management devices can adjunctively be used to address chronic pain, including advanced neuromodulators, and anti-inflammatory biologics.

Keywords: Acute pain, chronic pain, Multidisciplinary pain management, Pharmacological therapy.

INTRODUCTION

The biological nociception and inflammation process in combination with the neural processing is in contact with the psychological ones, mood states, stress, coping, and social factors, including cultural background, social support and environmental conditions that continue up to three months later. This chronic condition is acquired during the process of constant medical problems or changes in the nervous system that induce maladaptive events; it can only be cured after the body is healed. The body maintains chronic pain even after the normal recovery duration and develops three major pain conditions, namely neuropathic pain, centralized pain syndromes and chronic postoperative pain (1).

The comprehensive impact of acute and chronic pain on the quality of life, everyday activities, sleep habits, work efficiency, and the psychological states determine the need to keep medical personnel constantly updated on existing pain management practices that consider every aspect of the pain manifestation (2).

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This review has the primary objective of synthesizing evidence-based methods of contemporary pain management to treat acute and chronic pain conditions. Review analyzes pharmacological treatments, rehabilitative and behavioral treatments, integrative medicine/systems and technology-based pain management system with particular focus and attention towards the combination of these methods to patients. The combination of these modalities of patients.

Pathophysiology of Acute and Chronic Pain

Acute Pain

Acute pain occurs when specific sensory neurons become activated. These sensory neurons are known as nociceptors, and they respond to damaging stimuli that are mechanical, thermal, or chemical in nature. These receptors are located in both somatic and visceral tissues (3). Their sensitivity may become heightened with the presence of a tissue injury, ischemia, or inflammation. The pain from these conditions also has significant biological protective and adaptive function. Nociceptive pain signals warn individuals to move away from damaging stimuli and facilitate adaptive rest and healing. In a normal situation, acute pain has a natural self-limited duration, and resolves when tissue damage heals and the inflammatory mediators clear (4). The biological processes associated with acute pain are well defined and include the sequence of transduction, transmission, modulation, and perception which are the result of the complex interaction of the peripheral and central nervous systems. The sequence of transduction begins when the nociceptors change noxious stimuli into electrical impulses.

This process within the spinal cord is mediated through a modulation dynamic balance of inputs that are both excitatory and inhibitory (5).

Chronic Pain

Chronic pain is generally considered to be pain that lasts for longer than three months. This extends beyond the period in which tissue is anticipated to heal. Frequently it gets diverted from its primordial protective function. The way it actually works is complicated, for many reasons. It's a combination of what goes on in our nerves, brain and state of mind (6).

A few of the key ways chronic pain occurs: Central sensitization. This causes our nerves in the brain and spinal cord to become too sensitive. Neuroinflammation is another factor. This is due to flam (active) glial cells and inflammatory chemicals. We also observe issues in pathways that would otherwise mute pain signals. This has made it more difficult for our bodies to naturally regulate or cease pain (7).

An abnormal signal can also be caused by nerves in the body's limbs or extremities experiencing damage. This can lead to neuropathic pain. One thing that means something is the role our minds play. Fearing to move, thinking negatively, feeling upset and low can all keep pain going or make it worse." This can result in unhelpful pain behaviors and a delay in getting better (8).

Pharmacological Management

Non-Opioid Analgesics

Acetaminophen, or paracetamol, is still a drug of first choice for mild-to-moderate pain. This involves such things as headache and muscle aches, osteoarthritis and fever. It likely works by blocking something called prostaglandin synthesis in the brain and by messing with serotonin pathways. The side effects, when taken in reasonable amounts, are pretty benign (8). That makes it a good choice for older individuals or those who cannot take NSAIDS. Only one thing, be careful not to overdose. Overdoing it can damage the liver, especially if someone drinks a lot of alcohol or doesn't eat well — or already has a liver problem (9).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, such as ibuprofen, naproxen, diclofenac, and COX-2 selectives (such as celecoxib) are effective in treating pain and inflammation.Topical NSAIDS avoid the gastrointestinal tract.Loose bodies can be removed using this method. Their analgesic, antipyretic and anti-inflammatory effects are due to inhibition of COX enzymes, which lead to a decrease of prostaglandin synthesis (10). NSAIDs offer better analgesic efficacy compared with acetaminophen in inflammatory pain, but their use entails significant hazards (gastrointestinal ulcers and bleeding, renal insufficiency, worsening hypertension, and increased cardiovascular events), especially if they are used for a long time or at high dose. Selective COX-2 agents are low in GI toxicity and high on cardiovascular ones (11).

With a view to get the most benefit and minimise harm, physicians could use the lowest effective dose for the shortest duration needed, to consider gastroprotection in high-risk cases (e.g. by proton pump inhibitors), and they should be cautious when prescribing NSAIDs to individuals with renal disease, congestive heart failure or previous ulcer disease (12). In summary, non-opioid analgesics are the mainstay drugs in multimodal pain management and are frequently co-administered with other modalities to provide additive benefit and minimize opioid consumption.

Opioids

Opioids such as morphine, oxycodone,

hydromorphone, fentanyl and tramadol continue to be among the most effective analgesics for severe pain including acute pain following surgery or trauma, end-of-life care related to cancer and other terminal illness and some types of chronic/unresolved pain such as cancer pain. Their analgesic activity is predominantly due to stimulation of mu-opioid receptors in the brain and spinal cord, resulting in reduced transmission and perception of nociceptive signals (13).

Though effective, use of opioids for pain management has been limited in part by a host of known risks and negative consequences. Major concerns include:

Risk of opioid addiction, abuse, and misuse: Opioid analgesics are commonly associated with the risk of psychological dependence (addiction) as well as physical dependence or tolerance that may predispose to overdose in some patients receiving such medications for the relief of chronic pain (14).

Tolerance and dependence : Patients may become tolerant to the stimulating and analgesic effects of the medication, which results in a need for ever-higher doses and an associated increase in adverse side-effects (15).

Opioid-induced hyperalgesia (OIH): Somewhat ironically, chronic opioid exposure may increase sensitivity to pain, as the result of plastic changes in the central nervous system.

Side effects: Constipation, nausea, sedation, respiratory depression, endocrine dysfunction and cognitive impairment are frequent side-effects (15).

Current approaches to the clinical use of opioids now focus on a risk–benefit protocol of prescribing. Opioid therapy should only be initiated if the anticipated benefits clearly outweigh risks of treatment, and after non-opioid analgesics and non-pharmacologic treatments have been considered or attempted (16). In summary, opioids play a critical but limited role in the treatment of pain through appropriate patient selection and careful monitoring.

Adjuvant analgesics Adjuvant or adjuvant analgesic drugs are a chemically disparate group of compounds that were first registered for non-pain indications, but which have subsequently become established in pain management based on their action against specific pathophysiological mechanisms. They are of particular interest in long-standing pain, in particular neuropathic and mixed pains like those produced by the type or volume of abnormal processes or injuries during which conventional analgesics (such as NSAIDs or opioid medications) proved to be of limited efficacy (17).

Antidepressants

Some antidepressants have been established as basic treatments for neuropathic pain, fibromyalgia, and chronic musculoskeletal syndromes.

Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, function mainly by promoting descending inhibitory tracts with increased serotonergic and noradrenergic transmission for analgesia. They also might modulate sodium channels with an additional analgesic effect. They can be effective, but they have anticholinergic and sedative side effects that preclude use in elderly or CV patients (18).

Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, offer similar analgesic effects with a more favorable side-effect profile. Duloxetine, in particular, has a strong evidence base for its use in diabetic neuropathy, chronic low back pain and osteoarthritis and is recommended as first-line treatment prioritised over some other agents across many long term pain conditions (19).

Anticonvulsants

Drugs such as gabapentin and pregabalin are now well established in the treatment of neuropathic pain, which includes postherpetic neuralgia and diabetic peripheral neuropathy. Their mechanism of action is through attenuation of voltage-gated calcium channels leading to diminishment in excitatory neurotransmitter release and diminished neuronal hyperexcitability (20). These agents have the potential to maintain and possibly improve sleep quality, a key aspect of comprehensive pain treatment; however, sedation and dizziness are frequent dose-limiting side effects (21).

Muscle Relaxants

Muscle relaxants such as cyclobenzaprne, tizanidine or baclofen may be helpful adjuncts in the treatment of those patients with myofascial pain, acute muscle spasm, or chronic musculoskeletal pain. Their main efficacy is to relax the muscle and enhance functional activity. Owing to risks of sedation, tolerance and scant long-term evidence, they are generally recommended for short term or targeted use as an adjunct to a wider rehabilitation programme (22).

Topical Agents

Local treatments provide pain relief at the site of origin with little systemic absorption and should thus be preferable in patients with comorbidities or polypharmacy. Lidocaine patches are active in focal neuropathic pain, especially postherpetic neuralgia and postoperative nerve injury (23). Capsaicin, either in low-concentration creams or high-dose patches, causes desensitization of nociceptive fibers by prolonged depletion of substance.There are also differences between them, with topical NSAIDs such as diclofenac gel offering anti-

inflammatory analgesia for osteoarthritis and soft tissue injuries, but having lower gastrointestinal risk than systemic NSAID (24). Together, the adjuvant analgesics expand the therapeutic horizon for chronic pain. They provide further rationale for personalized, multimodal and mechanistic therapy that has become a cornerstone of contemporary pain medicine by targeting different influences from neuronal hyperexcitability to disrupted descending inhibition (25).

Emerging Pharmacological Therapies

Innovations in pain neurobiology are the basis for recent development of new pharmacological approaches directed to specific molecular mechanisms that are involved in chronic and drug-resistant pain. These new treatment modalities hold tremendous potential for patients with inadequate response to traditional analgesics (26).

Cannabinoids

Cannabinoid treatments – including products produced from whole plant extracts (e.g. preparations from cannabis species that have specifically been bred and/or designed for medicinal purposes, such as Sativex and others containing THC) or isolated compounds (e.g. THC, cannabidiol) - are receiving more attention in the chronic neuropathic pain space (27). CB1 and CB2 receptors are involved in pain modulation, decreasing nociceptive transmission and inflammation, but also central sensitization. While there is evidence for small benefits in neuropathic conditions (including multiple sclerosis pain), cognitive symptoms, treatment effects, and variations in the quality of products continue to be issues. Studies are currently carried out to achieve the most effective and safe mix of cannabinoids as well as preferred, interacting delivery pathways (28).

Monoclonal Antibodies Targeting CGRP

CGRP: The migraine peptideCalcitonin gene–related peptide (CGRP) is a key player in migraine pathophysiology. Newer forms of mAbs—such as the CGRP-neutralizing mAb erenumab and the calcitonin gene-related peptide receptor–targeting antibodies fremanezumab, galcanezumab, and eptinezumab have been shown to significantly decrease the frequency of migraine occurrence and intensity in multiple patients (29).

Sodium Channel Blockers

Selective inhibition of voltage-gated sodium channels has become a prospective approach for neuropathic pain, and Nav1. 7 inhibitors. Mutations in the Nav1. 7 channel have a congenital insensitivity to pain-or conversely, severe chronic pain-syndrome, and thus is an attractive drug target. Several Nav1. 7 are under clinical trials. Outcomes have been mixed, but continued design-process optimisation of selectivity and pharmacokinetics could produce viable agents in intractable neuropathic pain.

Gene and Cell-Based Therapies

Gene and cell-based therapies are the next frontier of pain medicine. Potential future applications are in gene silencing applications (such as siRNA, CRISPR based approaches) to knock down pain-related ion channels or inflammatory mediators and some cell-based therapies with the help of designer stem cells or glia modulators in order to restore normal neuronal function. While each of these avenues is still highly experimental, now early preclinical work points to a dramatically transformative role in chronic neuropathic and inflammatory pain (30).

In total, emerging pharmacological steps take this trend towards precision pain medicine which intervene in certain molecular pathways and mechanisms. Advancements of such therapeutic approaches could have dramatic implications in treatment of patients with refractory and complex pain pathologies(29, 30).

Non-Pharmacological Approaches

Physical and Rehabilitative Therapies

Physical and rehabilitative therapies play a frequent part in non-pharmacologic management of pain, especially in musculoskeletal, post-surgical and chronic pain states. These therapies are focused on rediscovering function, increasing mobility and relieving pain with as little medication dependence as necessary (31).

Physiotherapy

Physiotherapy offers tailored therapeutic plans to target individual needs. Procedures may comprise therapeutic exercise, postural re-education, gait training and neuromuscular re-education for enhancing joint stability, flexibility and physical function respectively (32). Patient education is also a priority in physiotherapy, providing the patient with ways to be involved actively in their treatment and strategies for self-help to avoid reinjury or escalating pain levels (33).

Exercise Programs

Exercise is an integral part of any rehabilitation plan and can be customized to the patient's pain presentation and ability level. Endurance training, resistance work, and flexibility exercises not only enhance muscle strength, endurance and range of motion but also modify central pain processing by neurophysiological means (34). Physical activity

is found to decrease pain intensity, improve psychological well-being, and increase quality of life in patients with chronic musculoskeletal and neuropathic pain (35).

Manual Therapy

Manual therapy techniques, including joint mobilization, soft tissue manipulation, and myofascial release, aim to alleviate musculoskeletal dysfunction, improve tissue elasticity, and reduce localized pain. These hands-on interventions may also complement exercise therapy by enhancing mobility and facilitating the performance of functional movements (36).

Heat and Cold Therapy

In combination, physical and rehabilitation interventions provide a comprehensive strategy to address pain by targeting the functional limitations as well as perceived sensory aspects of pain. The inclusion of such programmes in a multimodal approach may be effective for enhancing mobility, global physical function and quality of life, among patients experiencing acute or chronic pain (37).

Psychological Interventions

Pain is more than just a sensory perception; it is highly influenced by cognitive, affective, and behavioral components. Psychological treatment Emotional and cognitive aspects of pain (e.g., locust control) Coping ability Disability Quality of life These techniques are especially beneficial in chronic pain syndromes, because aberrant thoughts and emotions often make the experience of pain worse (38).

Cognitive Behavioral Therapy (CBT)

CBT is a time-limited, manualized intervention focusing on pain-related thoughts, beliefs and behaviors. CBT challenges and changes unhealthy thoughts or belief systems that patients hold, including catastrophic thinking, fear-avoidance behaviors and unrealistic beliefs about pain intensity (39). Several studies have demonstrated a marked effect of CBT in reducing the severity of pain, enhancing functional status, and decreasing concurrent psychological distress with anxiety and depression. CBT is efficacious for a broad range of chronic pain problems, such as low back pain, osteoarthritis, and neuropathic pain (40).

Complementary and Integrative Therapies

Complementary and integrative treatments have emerged as important adjuncts to current pain care, especially for chronic, complex pain conditions. These do not stop at symptom reduction, but consider the biopsychosocial consequences of pain, such as emotional distress and functional status and quality of life. They can improve the efficiency of traditional treatments and reduce drug dependency when added in a multimodal treatment design (41).

Acupuncture

And acupuncture, a staple of traditional Chinese medicine, is the insertion of tiny needles at targeted sites on the body to regulate pain signaling pathways. Mechanistically, it is likely to activate endogenous opioid systems, serotoninergic and noradrenergic descending inhibitory pathways and local anti-inflammatory response that result in attenuation of nociceptive input and central sensitisation. Well-performed clinical trials have showed its effectiveness in chronic low back pain, osteoarthritis, migraines and neuropathic pain (42).

Chiropractic Care

Chiropractic care and treatment, which include spinal manipulation and mobilization is focussed on restoring musculoskeletal alignment and enhancing joint function. Evidence indicates that these methods may alleviate mechanical back and neck pain, as well as related disability, and increase spinal motion when used in conjunction with other therapies such as exercise targeting the patient and education (43).

Massage Therapy

Massage therapy is the manipulation of soft tissues of the body using hands-on techniques to decrease muscle tension, increase circulation and induce a state of relaxation. Research has shown a reduction in musculoskeletal pain, anxiety and fatigue and overall patient well-being and functional status improvement (44).

Individually and collectively, these complementary and integrative therapies represent safe, non-invasive, patient-centered treatment options for pain that complement conventional management. These interventions address pain from several different angles, and as part of a multidisciplinary approach to the treatment of pain, they help patients take back control over their health and achieve long-term relief from pain (45).

Multimodal Pain Management

Multimodal pain management is a holistic, evidence-based approach using a variety of treatment modalities to maximize analgesia and functional outcomes while reducing the potential harm associated with unimodal therapies such as opioids (46). By attacking several physiological and psychological mechanisms at the same time, multimodal strategies realize additional or synergistic effects beyond the sum of individual interventions and may be given in

reduced doses with reduced side effects (46).

An illustrative multimodal regimen is:

Non-opioid analgesics (acetaminophen, NSAIDs) for the management of peripheral nociceptive and inflammatory mechanisms. Regional anaesthesia or nerve blocks acting by targeted blockade of the pain pathway in an acute or perioperative situation, thus reducing systemic analgesic requirements (47).

Functional recovery because of physiotherapy and rehabilitation, including exercise, manual therapy and functional retraining to enhance mobility of the joint; strengthening the muscles supporting the neck region and treating musculoskeletal factors contributing to pain. Psychological interventions (e.g., cognitive-behavioral therapy, mindfulness-based treatments, biofeedback) that target the affective-cognitive components of pain and reduce catastrophizing and increase coping (48).

Education of patients, enabling individuals to comprehend their pain and participate in self-management and compliance with management plans (and better long-term outcomes, and behavioural prevention) (49).

Multimodal treatments have become the accepted standard of care for postoperative as well as chronic pain; this reflects a transition from monotherapy to comprehensive, mechanism-oriented and patient-centered approaches (50). Evidence is clear that combining pharmacologic, interventional, rehabilitative, psychological and complementary therapies results in better pain relief as well as functional recovery, quality of life, patient satisfaction and long-term sustainability with less opioid consumption and its associated complications (51).

CONCLUSION

Comprehensive pain control, both acutely and chronically, is a multidisciplinary effort based on the patient. Both pharmacological and interventional therapy, along with rehabilitation, psychological care and other alternative support, contribute to the complex web of pain. Multimodal approaches increase analgesic efficacy, functional recovery and quality of life while decreasing opioid requirement and related risks.

Pain medicine of the future will be integrated, evidence-based and personalized, using clinical expertise and technology in combination with patient engagement to address the multifaceted biological, psychological and social dimensions of pain to foster relief, resilience and function.

Authors's Contribution

Mahnaz Saremi: Conceptualization and Review; Farnoosh Honarmand: editing and writing. The authors read and confirmed the final manuscript.

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Precision Neurology in Multiple Sclerosis: Contemporary Advances and Future Perspectives

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Abstract:

Multiple sclerosis (MS) is a heterogeneous chronic autoimmune disease of the central nervous system that comes with a variety of variants in presentation, progression, and response to treatment. The advent of precision neurology presents a possibility of stratifying diagnosis, prognosis, and treatment options that fit biological personalities. This review examines the existing and developing methods of personalized care in MS in the context of genomic understanding, the discovery of new biomarkers, and pharmacogenomics Genetic variants that affect drug response, pathogenesis, and outcome have been identified using advances in next-generation sequencing and genome-wide association studies. Neuroimaging, cerebrospinal fluid, and blood-based biomarkers have the potential to diagnose earlier, predict disease activity, and monitor treatment with therapeutic efficacy. Pharmacogenomic experiments are playing an increasingly large role in determining patient-specific treatment choice, using these evaluations to optimize efficacy without adversely affecting the patient. The role of such tools in clinical practice has the potential to transform precision neurology as they will offer more specific data-driven treatment opportunities and improve patient outcomes. Questions that have not been answered are the validation of the novel biomarkers, ethical implications of using genomic data, and development of what are sound clinical decision-making algorithms. The aim of this review article is to provide a comprehensive overview of the genetic basis, biomarker-driven strategies, and precision neurology approaches in multiple sclerosis, highlighting current advances, clinical challenges, and future perspectives in personalized therapy.

Keywords: Multiple Sclerosis, Precision Neurology, Personalized Medicine, Genomics, Biomarkers.

INTRODUCTION

Multiple sclerosis (MS) is a CNS immune-mediated disease and it still is the most common cause of non-traumatic neurological disability in young adults globally (1). It is estimated that between 2.8 million people worldwide have MS as a result of an intricate interaction between genetic, environmental and immunologic factors, which eventually lead to the demyelination, axonal, and neurodegeneration (2). The disease itself has many and variable signs and symptoms-such as visual problems, motor and sensory loss, mental lapse, and lack of energy-that differ widely among patients. The extent of this individuality in disease presentation influences the course of illness, clinical response to disease and the ability of the physician to provide optimum patient

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care to that individual patient (3).

In the last twenty years, disease-modifying therapies (DMTs) have become available and have dramatically changed the therapeutic landscape of MS, preventing relapse and delaying disability in a large number of patients. However, a considerable part of the patients will show partial efficacy or no reaction at all (4). Further, the danger of adverse effects administered through treatment, along with the disparity of drug tolerance highlights the drawback of the standard one-fits-all model of treatment. This diversity relates to the true biological diversity of MS, is the place where the genetic predisposition to diseases, actions of the immune system, and exposure of the environment meet leading to generation of specific disease patterns on case by case basis in each patient (5).

Accurate neurology involves combining multidimensional data, including genomic and molecular markers, extensive imaging scales and phenotypic analysis, to determine specific diagnostic, prognostic and therapeutic interventions (6). In MS in particular, advances in the next generation sequencing technologies and genome-wide association studies (GWAS) have been able to pinpoint hundreds of genetic variants that relate to susceptibility and disease course. The introduction of parallel developments in biomarker discovery, in cerebrospinal fluid and whole blood-based assays, and imaging-derived markers has also helped in further stratification of patients on the basis of risk and responsiveness (7).

Also significant is that the emergence of pharmacogenomics is starting to shape the tailored therapeutic approach by associating genetic make-ups with differences in drug metabolic processes and effectiveness, as well as the possibility of individualized intervention selection (8). Collectively, these advances herald a paradigm shift in the management of MS- the traditional population based management to a model that uses data to develop personalized interventions aimed at providing maximum treatment benefit at minimum risk of harm (9).

This review summarizes the existing marks on precision neurology in MS with a focus on genetic discoveries, the discovery of new biomarkers, and pharmacogenomic use applications. Moreover, it discusses the prospects and challenges of transferring these tools to clinical practice, with a special focus on limitations related to the process of validating biomarkers, ethical issues concerning genomic data, and designing effective decision-making models that could be easily understood by clinicians. By drawing the line of these tendencies, this paper intends to explain how precision neurology can revolutionize the process of managing MS within one decade..

Genomic Insights into Personalized Medicine for Multiple Sclerosis

There are important interactions between genetic risk factors and environmental exposures that contribute to risk of developing MS. As an example, the risk of the disease in individuals possessing HLA-DRB1* 15:01 is significantly higher when the vitamin D levels are low, which once again proves that the forces of environment and genetics interact with each other in an additive way (10). Other known environmental factors include Epstein Barr virus (EBV) infection and smoking, and childhood obesity, which in various cases may interact with susceptibility loci to influence the development and pathology of the disease. There is a need to understand these gene environment interactions in order to help in detection of high risk individuals and formulating preventive strategies that can be adjusted to the individual genetic backgrounds (11).

Gene–Environment Dynamics

Combined risks of MS based on genetic predisposition and environmental exposures play an important role in regulating MS risk. As an example, persons with the HLA-DRB1* 15:01 risk factor are 12-fold more likely to develop the disease when vitamin D levels are low, highlighting the importance of interplay between genetics and environmental risk factors (12). Other environmental contributors are the EpsteinBarr virus (EBV) infection, smoking, and childhood obesity, which may combine with susceptibility alleles to affect the onset and severity of disease. The analysis of these gene-environment interactions is critical to targeting high-risk individuals and minimizing the risk using the preventive strategies focused on the individual genetic background (13).

Epigenetics

Besides the inherited differences of DNA, epigenetic alterations of DNA Shah that change gene expression, but do not change the DNA sequence, are significant players in MS pathophysiology (14). The functional change in spinal cord is associated with altered patterns of DNA methylation, histone modifications, and non coding RNAs, including microRNAs and long non coding RNAs, which regulate immune innate responses, myelin stability and inflammatory processes (15). These changes are, e.g., aberrant DNA methylation of immune regulatory genes, which can alter T-cell activation, as well as microRNAs, which have been shown to be linked to demyelination and neurodegeneration. It is also likely that epigenetic mechanisms mediate any effects of the environmental exposures, another complexity in individualized risk assessment and therapy design (16).

Rare Variants and Familial MS

Although common variants with GWAS are said to capture a significant proportion of MS heritability, rare variants may have very strong effects especially in cases with familial origin, or in individuals with early onset of the disease (17). Though uncommon, monogenic contributions also have been seen in immune regulation-related genes, myelin biology genes, and genes related to repair to the central nervous system. Included in this category are rare variants in genes encoding proteins important in loss of function such as IL7R, TYK2 or PRKRA which can cause highly penetrant familial MS phenotypes (18). The discovery of these rare variants by the use of whole-exome or whole-genome sequencing can help one understand the disease mechanism processes as well as facilitate precision neurology since it is applicable in high-risk families (19).

Integration into Precision Neurology

Combining prevalent susceptibility mutations, rare mutations, epigenetic variation, and gene-environment interaction can be used to generate patient-specific molecular characterization to capture factors relevant to the onset and progression of MS (20). These integrative profiles offer a multidimensional picture of the disease biology of an individual, including his/her inherited genetic makeup, acquired epigenetic features and the modification grounded upon environmental exposures. By using these profiles, clinicians and researchers can classify patients in risk categories, anticipate disease progress, and refer to those who are likely to be affected by early and/or high-efficacy interventions (21).

The molecular signatures also enable prognostic prediction as demonstrated in highlighting pathways conferring an aggressive disease, rapid accumulation of disability or poor treatment response (22). An example is the fact that a patient that had high-risk HLA alleles, epigenetic dysregulation in their immune genes, and had high-risk environmental exposures may be fast-forwarded to a period of close monitoring and commencement of disease-modifying therapies (DMTs) as early as possible. Conversely, those with molecular profiles which may be characterized as lower risk perhaps are candidates who can receive less aggressive disease therapeutic interventions and still retain disease control without incurring the potential adverse effects which otherwise would have occurred (23, 24).

Moreover, the patient-specific molecular profiling allows a framework within which precision therapeutic treatment decisions are made. By understanding which immune processes and pathways are most active in each patient-T- and B-cell activation, cytokine signaling, or myelin repair pathways-therapies can then be personalized to interrupt the processes that are driving the disease in a patient (25). This can not only maximize effective treatment but also reduce unneeded treatment, toxicity as well as healthcare expenditures. There is no doubt that the combination of genetic, epigenetic, and environmental information is one of the ultimate components of precision neurology, with the potential to shift the current approach towards MS management, which is rather generalized and one of trials and errors, into a novel mechanism-based mechanism (26).

Biomarkers for Diagnosis and Prognosis

Biomarkers have become an invaluable addition to the personalized management of multiple sclerosis (MS) as they provide objective and quantitative measures and can be used to supplement standard clinical scores (27). In contrast to symptom-based measures which do not reflect early neurodegenerative processes or subclinical disease activity in MS, biomarkers offer a view into the underlying gnathophysiology of MS (28). They will allow physicians to identify the occurrence of disease at a more tender phase, to track the progression of the disease and to improve efficacy of an intervention action due to the presence of a higher level of specificity (29).

Personalized treatment plans based on biomarkers can be supported through identification of the particular trends of immune dysregulation, neuroaxonal damage, and tissue repair in the individual (30). Moreover, biomarkers play important roles in clinical trials as well as in practice. They offer standardized endpoints in the assessment of novel therapies, speed drug development and make comparative effectiveness studies possible. In combination with genetic and epigenetic information, biomarkers will be incorporated into holistic patient-specific molecular characterizations, which will form the basis of precision neurology. Here, the discovery and testing of reliable and repeatable biomarkers is one measure toward changing how MS is managed; moving the modal of care as a reactive and symptomology-oriented model to a proactive and mechanism-oriented and patient-specific model of treatment (31).

Imaging Biomarkers

Diagnostics and longitudinal monitoring of multiple sclerosis (MS) is based solely on magnetic resonance imaging (MRI), which has become invaluable in terms of insights into both local and diffuse pathology in the central nervous system (CNS) (32). Standard MRI scanning protocols, such as T1-weighted scans, T2-weighted scans, and fluid-attenuated inversion recovery (FLAIR) allow accurate identification and characterization of demyelinating lesions to aid in

the diagnosis and classification of the disease. In addition to detecting lesions, higher order MRI can be used to quantitatively assess brain lesion burden, whole brain atrophy, and microstructural integrity in the white and gray matter which provide a more in-depth measurement of the disease effect (33).

Imaging techniques like magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), and susceptibility-weighted imaging (SWI) have an increased sensitivity to selected pathological characteristics (34). MTI can be used to evaluate myelin density and tissue integrity, DTI has the capacity to measure microstructural changes in axonal systems and connectivity, and iron deposition and microhemorrhage can be identified using SWI which are emerging as indications of chronic inflammation and neurodegeneration (35). These sophisticated MRI measures have been shown robust correlations with clinical disability measures and cognitive outcome measures in addition to long-term disease progression findings, highlighting their prognostic significance. Comparisons of sequential longitudinal MRI studies allow detection of changes that may be otherwise undetectable and offer objective parameters of response to therapy as well as stratification of the risk (36).

PET imaging is increasingly seen as a complementary modality, especially tractors to targets in microglial activation, astrocytic activation and other inflammatory processes. PET can be used to visualize immune cell activity in vivo and allows one to see active neuroinflammation that would not be visible with conventional MRI alone (37). This aptitude can be of particular use in determining early disease activity and progressive cases of MS and in assessing the impact of immunomodulatory treatment at a cellular level. Combined with MRI in hybrid MRI-PET, the structural and functional information may be merged, which would allow a multidimensional assessment of CNS pathology (38). The integrated imaging methodology makes the disease monitoring process highly accurate, facilitates individualized treatment planning and gives rise to predictive biomarkers that help understand the process of disease progression and response to treatment (39).

Fluid Biomarkers

Biomarkers in cerebrospinal fluid (CSF) and blood are minimally invasive and highly informative markers of multiple sclerosis (MS) originating at its molecular and cellular levels. Of these, neurofilament light chain (NfL) has been found to be a especially useful biomarker (40). NfL is secreted into the CSF and the bloodstream upon acute injury to neurons and other axons and is an early, dynamic biomarker of neuroaxonal damage. High NfL levels are consistently predictive of clinical relapses, the activity of MRI lesions, and the rate of disability progression, multiple studies have established it as a potent indicator of disease activity and a predictor of enhanced eventual severity (41).

The finding of oligoclonal bands (OCBs) in CSF continues to be a hallmark diagnostic of MS wherein B-cell production of immunoglobulins is happening within the central nervous system and is indicative of continuous immune activity (42). The OCBs serve to confirm diagnosis, especially CNS lesions of early or unusual areas, and are a measure of ongoing inflammatory involvement. In addition to classical markers, blood-based biomarkers are the area increasingly explored as they offer the advantages of minimum invasiveness and are adaptable to longitudinal follow-up. blood-borne microRNAs, cytokines, and chemokines have the potential to report on the immune system dyslysis, as well neuronal death, providing dynamic insight into disease pathophysiology (43).

Other new biomarkers, including glial fibrillary acidic protein (GFAP), a fibrillary acidic protein that indicates astrocytic activation, and chitinase-3-like protein 1 (CHI3L1), which has been linked to chronic inflammation and neurodegeneration, hold some promise to differentiate progressive MS and possibly measure therapeutic response (44). Longitudinal awareness of such biomarkers makes it possible to consider dynamic risk stratification and use that knowledge to tailor treatment regimens when appropriate. The combination of biomarkers that measure fluids with imaging biomarkers and gene-specific data can offer a three-dimensional edge with regard to patient-specific disease surveillance. “Such detailed profiling helps precision neurology make precision earlier, targeted treatment, long-term result for MS patients improve (45).

Integrative Approaches

The combination of imaging and molecular biomarkers is a key element to precision neurology in multiple sclerosis (MS), allowing a more-detailed picture of disease activity, prognosis and sensitivity of response to treatment. Structural and functional Brain Imaging data in combination with molecular signatures i.e. cerebrospinal fluid (CSF) and blood biomarkers will allow clinicians to build comprehensive patient-specific profiles which they can use to both risk stratify and plan specific individual treatment (46). Moreover, directing the intensity of therapies, integrated biomarker profiles may predict response to treatment, risk of rapid progression, and selection of patients in clinical trials of new therapies. As an illustration, it is shown how an advanced MRI measure, with brain atrophy, microstructural integrity, and lesion load, can be combined with a molecular marker, such

as GFAP, CHI3L1, or specific cytokine profiles, to identify subgroups that may be candidates to receive a targeted immunomodulatory or neuroprotective approach (47). The multidimensional nature of the pain-related studies enables preemptive measures to be taken before irreparable structural damage is incurred to the neurological system, maximizing immediate efficaciousness and long-term results (48).

Additionally, the ability of biomarker signatures to predict clinical outcome (such as relapse frequency, disability progression, and cognitive performance) will be valuable to make informed treatment decisions (49). Dynamic monitoring is also a possible approach to this integrative strategy whereby changes in biomarker over time can lead to changes in therapy sooner, helping to increase compliance and overall quality of life. Overall, the combined use of imaging and molecular biomarkers is helping move the management of MS toward a paradigm of nonreactive, symptom-based care towards proactive, data-driven, and patient-centered care (50). Further discovery, validation and standardisation of imaging and fluid biomarkers will play an essential role in the unleashing of the promise of precision neurology with the ability to design interventions specifically tailored to the needs of a given patient to improve prognosis, increase efficacy of therapies, and promote long-term neurological health of patients with MS (51).

Pharmacogenomics and Individualized Therapy

The field within precision neurology that is developing quickly is called pharmacogenomics that focuses on the variable effect of drugs on drug metabolism, efficacy and safety, and how genetic variability produces this variable effect (52). In MS, there are notable individual differences in the response to disease-modifying drugs DMTs, so-called, which include interferon-beta, glatiramer acetate, natalizumab , fingolimod, and the new B-cell depletion treatments. Knowledge of the genetic factors of these responses permits more specific, person centered treatment plans (53).

Drug Safety Prediction

Genetic polymorphisms will also be discussed, as they play a key role in modulating risk of adverse drug reactions in multiple sclerosis (MS) related to both the pharmacokinetics, or absorption, distribution, metabolism, and excretion of drugs, and the pharmacodynamics, or the way the body responds to therapy (54). Genetic variants in enzymes that drug-metabolizing enzymes, such as CYP2C9, CYP3A4, and NAT2 can largely change the metabolism of orally administered drug-modifying treatments (DMTs), possibly lead to drug accumulation, hepatotoxicity, or subtherapeutic concentrations that reduce therapeutic effects (55). Likewise, polymorphisms in drug transporter genes, such as the members of the cone of ATP binding C (ABC) family can alter distributions and clearance of drugs and contribute to inter-individual variability in therapeutic effects (56).

DNA-based genetic variants have also been implicated in the development of hematologic toxicities during the use of immunomodulatory or immunosuppressant therapy, such as leukopenia, lymphopenia or neutropenia (57). Some polymorphisms in genes that control the T-ABC and B-cell regulation, cytokine signaling, or immunological checkpoints may be associated with causing patients to become significantly more immune suppressed causing complications such as infections. Their identification can allow clinicians to individualize treatment dosage, increase monitoring in the laboratory, or substitute other agents with less toxicity prior to initiating treatment (58).

In addition to increasing safety, pharmacogenomic testing will enable proactive intervention of suspected adverse effects, improve patient compliance through minimized drug-related adverse events, and will lead to long-term success in treatment (59). With pharmacogenomic testing integrated into clinical practice, clinicians will be able to apply toward a personalized, mechanistic approach to optimize efficacy toward a minimum of toxicity. This intervention represents the logic of precision neurology more generally, in which genetic information is used to inform safer and more effective patient-specific treatment interventions in MS (60).

Treatment Sequencing

Pharmacogenomic information is increasingly helping tailor choice and sequencing of disease-modifying therapies (DMTs) in multiple sclerosis (MS), and thus there is a trend towards a more personalized and patient-centered decision-making process (61). Genetic markers are capable of predicting individual responses to initial therapies e.g. interferon-β or glatiramer acetate. Those with genotypes putting them at low risk of responding can perhaps benefit by early escalation to high-efficacy DMTs, such as natalizumab or sphingosine-1-phosphate receptor modulators to avoid taking relapses and delay disease progression (62). On the other hand, patients who carried genetic signatures that indicate susceptibility to treatment with first-line therapies can receive disease control without any exposure to higher-risk treatment, with the potential for minimal adverse events and a potentially more important control of disease (63).

This genotype-based approach can accommodate an individual, graded treatment regimen that affords maximum value to both safety and therapeutically effective benefit. By incorporating

pharmacogenomic data into their clinical decision-making processes, clinicians will be able to predict suboptimal responses and actively modify therapy before it occurs and avoid the need to use trial-and-error methods (64). The benefit of this approach is that it not only optimizes clinical outcome but improves patient adherence and satisfaction due to the avoidance of unnecessary toxicity. The end result is that, given the customization of treatment regimens to suit the biological characteristics of an individual, pharmacogenomics offers the potential of precision neurology in bringing target-specific patient-centered neurological care to MS patients (65).

Emerging Therapies

Newer treatment modalities, such as B-cell depletion agents (ocrelizumab, ofatumumab) will likewise provide new opportunities to apply pharmacogenomics. Variants of genes that affect B-cell activation, Fc receptor activity, or immune checkpoints may regulate susceptibility to therapeutic effects and adverse events, such as risks of infection (66). Pharmacogenomic profiling would assist in selecting patients who have a higher probability of a positive response to these therapies, and those patients at higher risk of complications to facilitate individual therapy planning. The introduction of pharmacogenomics into the clinical trial of innovative products can also help to speed up biomarker discovery, correlating with response, which will then guide personalized treatment (67).

The combination of drug safety forecasting, treatment sequencing and pharmacogenetics present an opportunity where precision neurology can evolve beyond an empirical treatment decision towards data-guided therapy decision-making. Providing MS patients with such approaches can not only improve treatment efficiency but also reduce the toxicity, increase adherence, and provide better long-term outcomes of patients with MS (68).

Challenges and Ethical Considerations

Although precision neurology in the context of multiple sclerosis (MS) holds tremendous potential, there are a number of ways in which techniques have to be further improved before they are applicable to clinical practice (69). First, there is real need to validate and to standardize biomarkers and genetic tests. Numerous prospective biomarkers, albeit promising in research studies, are not extensively validated longitudinally using a wide variety of populations. Lack of rigorous standardization can result in inter-laboratory variability and assay inconsistency which can limit clinical utility and reproducibility (70).

Second, utilization of pharmacogenomic-based therapy has logistical and cost-related limitations. Ensuring infrastructure, specialized knowledge, and maintenance is demanding, expensive, and recurring with genomics and multi-omics profiling (71). This does not mean that all low-resource settings will have access to such technologies and this may further elucidate existing care disparities. Moreover, interpretation and translation of complex genetic data into clinically actionable decisions is problematic and requires decision-support and clinician education (72).

Precision neurology is also based on ethics. The privacy of data, the issue of informed consent about genomic and biomarker information collection, and the safety of the data are a source of concern. Those people who undergo genetic tests have to be made aware of the possible consequences of the genetic test, such as incidental findings and the chance of genetic discrimination (73). Besides, the availability of more sophisticated diagnostic and therapeutic means should be made even on the fairer grounds so that the breakthrough of precision neurology can be offered to all patients, rather than only those who are connected to specialized centers and have access to private healthcare (74).

Last but not least, the proposed combination of multi-omics and biomarker data with the development of individualized care pathway adds the element of clinical decision-making complexity. Along with empowering the clinicians and patients to make more informed decisions, rich data sources have the potential to result in information overload, calling instead to evidence-based guidelines and decision-support frameworks (75).

Future Directions

Precision neurology of MS will change the face of treatment by making multidimensional data coherently intelligible and clinically useful. Further development of genomics, transcriptomics, proteomics and metabolomics will allow a further fine-tuning of the disease mechanism and better classification of patients and the discovery of novel therapeutic targets (76). Standardized biomarker panels that have been validated across populations will allow them to be used to diagnose early, predict outcome, and help in the selection of individualized treatment (77).

It is possible that emergent treatments will make increasing use of patient-specific molecular data. As another example, the discovery of immune pathway dysregulation in a specific patient could inform the decision regarding the choice of specific targeted DMTs or combinations of DMTs, eliminating repeated trial-and-error tests. Imaging and fluid biomarkers allow monitoring, in real-time and subsequent modification of treatment regimens that can be conducted with respect to the disease (78).

Ethically and practically, with precision neurology will come dependable patient-consent mechanisms, data security and equal distribution (79). Multi-institutional consortia and international efforts will be indispensable to pooling of data, standardizing procedures, and confirmation of results in different populations. Clinician, patient, and stakeholder education will also assist in making informed decisions and lead to the use of individualized strategies (80).

Overall, the advancing intersection of genetic knowledge, biomarker discovery, and pharmacogenomics is a guide to achieving real individual care of individuals with MS. Using these tools, precision neurology can not only enable the most effective treatment delivery and management but also change the paradigm of providing this care in favor of responding proactively to assessing and confronting individual, rather than reactively treating the disease (81).

CONCLUSION

Using precision neurology, aspects of genetic knowledge, biomarkers, and pharmacogenomics can be used to transform the care of multiple sclerosis and help physicians perform personalization. These provide greater certainty in estimating disease course, progression and choice of therapies, and optimize benefits and minimize toxicity.

The issues that still persist are biomarker validation, uniformity of the assays and ethical handling of patient data. These problems must be addressed and the access to more personalized approaches expanded as a way of realizing the full potential of precision neurology. Personal, data-informed interventions hold promise of improved patient outcomes and deliver a new reality in MS.

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Nanoparticles for Drug Delivery in SLE: Targeting Inflammation Nanoparticles as Tools for Modulating the Immune Response in SLE

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Abstract:

Systemic lupus erythematosus is a chronic autoimmune condition characterized by immunological dysregulation, leading to the production of autoantibodies and subsequent organ dysfunction. The CD154/CD40 signaling pathway is crucial to the pathophysiology of systemic lupus erythematosu, since it facilitates T cell-dependent B cell activation, resulting in the generation of autoreactive B cells and the production of detrimental autoantibodies. Recent breakthroughs in nanotechnology have generated novel options for modulating immune responses in systemic lupus erythematosus, offering potential therapeutic strategies for accurately targeting specific immunological pathways while reducing adverse effects. Nanoparticles (NPs) have emerged as potent instruments in SLE therapy due to their capacity to target immune cells, encapsulate pharmaceuticals, and alter immunological signaling. This review analyzes the utilization of nanoparticles to modulate immune responses in systemic lupus erythematosus, with a particular focus on the CD154/CD40 pathway. We analyze various methodologies, including targeted drug delivery, immune cell modulation, and the induction of immunological tolerance, highlighting key research that has demonstrated the effectiveness of nanoparticles in reducing autoimmune responses and mitigating disease symptoms. Despite promising results in preclinical models, challenges such as biocompatibility, immunogenicity, and scalability remain. The progression of nanoparticle-based therapeutics presents a promising future for enhanced, targeted, and personalized treatments for systemic lupus erythematosus.

Keywords: Systemic lupus erythematosus, CD154/CD40, Nanoparticles, personalized treatments.

INTRODUCTION

Systemic lupus erythematosus, often known as SLE, is a chronic autoimmune disorder that affects the entire body. In this condition, the immune system mistakenly attacks the body's own tissues, which results in extensive inflammation and damage to the tissues. A condition known as systemic lupus erythematosus (1) is characterized by the development of autoantibodies that create immune complexes (2). These immune complexes cause damage to a number of organs, including the kidneys (lupus nephritis), skin (malar rash), and joints. Multiple factors contribute to the development of systemic lupus erythematosus (1), which is characterized by a combination of genetic predisposition, environmental triggers, and abnormal immunological responses. SLE is caused by the activation of autoreactive T and B cells, which are responsible for the generation and maintenance of a pool of pathogenic autoantibodies. This is the central mechanism underpinning SLE (3).

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The interaction between CD154 (CD40L) on T cells and CD40 on B cells is a mechanism that plays a significant role in the activation of both T and B cells in systemic lupus erythematosus (1, 4). The communication between CD154 and CD40 is essential for the activation of B cells that are dependent on T cells. This activation results in the creation of autoreactive B cells, plasma cells, and pathogenic autoantibodies. It has been demonstrated that disrupting this pathway has the potential to be a therapeutic target for systemic lupus erythematosus (1) in animal models (5). As a result of their one-of-a-kind physical and chemical qualities, nanoparticles (NPs) have emerged as a potentially useful instrument for influencing the immune system. These properties include a high surface area, biocompatibility, and the capacity to traverse biological barriers (6). They are capable of being engineered to distribute medications or biologics in a regulated and targeted manner, which has the potential to reduce the side effects that are typically associated with conventional therapy (7). In this review, the role of nanoparticles in modifying immunological responses in systemic lupus erythematosus (1) is discussed, with this review concentrating specifically on the CD154/CD40 signaling pathway. Key research will be discussed, notable findings will be highlighted, and future directions for nanoparticle-based therapeutics in the treatment of SLE will be identified with regard to the debate.

Pathophysiology of SLE and the Role of CD154/CD40 Signaling

The Immunological Basis of SLE

Systemic lupus erythematosus (1) is marked by heightened activation of the innate and adaptive immune systems, leading to the generation of autoantibodies that attack self-antigens. These autoantibodies create immune complexes that accumulate in diverse tissues, including the kidneys, skin, and joints, inciting inflammation and resulting in tissue damage. A hallmark of SLE is the breakdown of immunological tolerance to self-antigens, resulting from dysregulated interactions between T cells and B cells (8). CD4+ T cells are essential in this process by facilitating B cell activation via the CD154/CD40 signaling pathway. CD154, or CD40 ligand, is temporarily expressed on activated T cells and interacts with CD40 receptors on B cells (9). This binding triggers a series of processes, such as B cell activation, improved survival, immunoglobulin class-switching, and differentiation into plasma cells that generate autoantibodies. These autoantibodies are pivotal to the pathogenesis of SLE, as they attack self-antigens and facilitate immune complex development and tissue inflammation (10). The CD154/CD40 interaction is essential for the formation and maintenance of autoreactive B cells in systemic lupus erythematosus (1). As a result, therapeutic approaches targeting the disruption of this route have demonstrated potential. Preclinical investigations have shown that inhibiting CD154/CD40 signaling decreases the generation of harmful autoantibodies, reduces inflammation, and lessens disease severity. This route remains a central emphasis in the advancement of targeted treatments for SLE (11).

The CD154/CD40 Signaling Pathway in SLE

The CD154/CD40 signaling pathway is pivotal in coordinating the activation and functional modulation of T cells and B cells, which are crucial contributors to the pathophysiology of autoimmune disorders including systemic lupus erythematosus (1). CD154, or CD40 ligand, is a temporarily expressed molecule located on the surface of activated CD4+ T lymphocytes. It attaches to CD40, a receptor consistently found on B cells and other antigen-presenting cells, initiating a series of downstream signals (12). This relationship enables essential activities in B cells, including as activation, clonal expansion, improved survival, immunoglobulin class flipping, and differentiation into plasma cells that generate antibodies (13). In the context of SLE, this pathway becomes aberrant, resulting in the emergence of autoreactive B cells. These B cells generate autoantibodies that attack self-antigens, resulting in immune complexes that accumulate in diverse tissues, including the kidneys, skin, and joints. Inflammation and tissue damage are characteristic features of SLE. The CD154/CD40 axis is essential for proper immune responses and is directly involved in the disruption of self-tolerance and the continuation of autoimmunity in SLE (14). Therapeutic modulation of this system has demonstrated encouraging outcomes in experimental lupus models. The application of monoclonal antibodies targeting CD154 has been shown to efficiently obstruct CD154/CD40 interactions, consequently reducing the activation and survival of autoreactive B cells. This inhibition diminishes the synthesis of harmful autoantibodies, alleviates systemic inflammation, and lessens tissue-specific symptoms of the disease (15). In lupus nephritis, a serious consequence of SLE, the suppression of CD154/CD40 signaling has demonstrated considerable advantages. Experimental models of lupus nephritis indicate that blocking this pathway decreases immune complex deposition in the kidneys, reduces inflammatory infiltrates, and maintains renal function. The results indicate that the CD154/CD40 pathway is a vital therapeutic target for

managing systemic autoimmunity and for preventing or mitigating organ-specific damage in SLE (16). The significance of this route has stimulated continuous investigation into therapeutic drugs that regulate CD154/CD40 signaling. Present techniques encompass monoclonal antibodies, fusion proteins, and tiny compounds specifically engineered to selectively disrupt this interaction. These strategies seek to inhibit autoimmune reactions while maintaining the immune system's capacity to fight infections, therefore enhancing the safety and efficacy of treatments for SLE and other autoimmune illnesses (17).

Nanoparticles as Tools for Modulating the Immune Response in SLE

Nanoparticles are materials sized between 1 and 1000 nm, possessing distinctive features that render them exceptionally appropriate for targeted medication delivery and immunomodulation. These characteristics encompass a substantial surface area-to-volume ratio, the capability to encapsulate both hydrophilic and hydrophobic substances, and the potential to traverse biological barriers, including the blood-brain barrier and the endothelium barrier of inflamed tissues (18). Furthermore, nanoparticles can be designed with surface changes that facilitate the precise targeting of immune cells, including T cells, B cells, and antigen-presenting cells (APCs) (19). Nanoparticles are being investigated for several therapeutic applications in systemic lupus erythematosus (1), specifically for the transport of immunosuppressive agents and biologics, control of immune cell activation, and induction of immunological tolerance. In the modulation of the CD154/CD40 signaling pathway, nanoparticles can be designed to administer therapeutic drugs that obstruct this pathway or suppress the activation of autoreactive immune cells (20).

Nanoparticles for Targeted Drug Delivery in SLE

A significant improvement in the treatment of systemic lupus erythematosus (1) is the application of nanoparticles for targeted medication delivery. Conventional therapy for systemic lupus erythematosus (1), including corticosteroids, immunosuppressive drugs such as cyclophosphamide, and biologic medicines like rituximab, have shown helpful in controlling disease activity (21). Nonetheless, prolonged usage is linked to considerable systemic adverse effects, including as widespread immunosuppression, heightened susceptibility to infections, and cumulative organ toxicity. These constraints highlight the necessity for novel therapeutic strategies that reduce undesirable effects while improving treatment effectiveness (22). Nanoparticles provide an innovative approach by facilitating the targeted delivery of therapeutic medicines to impacted tissues. These minuscule, manufactured particles can be tailored to transport pharmaceuticals directly to locations of inflammation and immune complex accumulation, such as the kidneys, skin, and joints, which are frequently affected in systemic lupus erythematosus (1). By localizing the medication payload at these locations, nanoparticles can augment therapeutic efficacy while minimizing off-target exposure and systemic toxicity (23). The capacity to functionalize nanoparticles with certain surface ligands or antibodies significantly improves their targeting efficacy. For example, nanoparticles may be coated with chemicals that specifically identify and attach to biomarkers uniquely present on inflammatory endothelium cells or activated immune cells in regions affected by lupus. This tailored delivery enhances medicine absorption at the inflammatory site while preserving healthy tissues, therefore minimizing the chance of side effects (24). In lupus nephritis, a severe form of systemic lupus erythematosus (1) marked by immune complex deposition and inflammation in the kidneys, nanoparticles can be designed to preferentially concentrate in renal tissues. Research has shown that nanoparticle-based delivery systems can efficiently transport immunosuppressive medications, such as tacrolimus or mycophenolate mofetil, to the kidneys, resulting in enhanced renal function and less systemic toxicity relative to conventional drug formulations (25). Moreover, nanoparticles can function as vehicles for combination therapy, facilitating the simultaneous delivery of numerous medications with synergistic effects. For instance, nanoparticles can concurrently administer corticosteroids to mitigate inflammation and biologic medicines to obstruct specific immunological pathways, offering a comprehensive strategy for disease management (26). Besides drug delivery, nanoparticles are being investigated as diagnostic instruments and for their capacity to directly modify immune responses. Some nanoparticles are engineered to trap circulating autoantibodies or block dendritic cell activation, so targeting the fundamental immunological dysregulation in SLE (27). The adaptability of nanoparticles, along with progress in nanotechnology and materials science, has created new opportunities for the formulation of safer and more efficacious medicines for systemic lupus erythematosus (1). Although clinical translation remains nascent, the promise of nanoparticle-based techniques to transform SLE therapy is substantial,

promising more focused, individualized, and less toxic therapeutic alternatives in the future (28).

Polymeric Nanoparticles for Controlled Release of Immunosuppressive Drugs

Polymeric nanoparticles, composed of materials like polylactic-co-glycolic acid (PLGA), are among the most extensively researched nanoparticles for drug delivery applications. These nanoparticles are biodegradable, biocompatible, and can be engineered to encapsulate a range of pharmaceuticals, including corticosteroids, immunosuppressants, and non-steroidal anti-inflammatory medications (NSAIDs) (29). The primary benefit of employing polymeric nanoparticles is their capacity for regulated and prolonged drug release, which diminishes the necessity for frequent dosing and mitigates the danger of adverse effects. Dai et al. (2018) conducted a study revealing that PLGA nanoparticles infused with corticosteroids effectively targeted inflammatory tissues in lupus-prone mice, resulting in decreased inflammation and enhanced organ function (30). The research emphasized the capacity of these nanoparticles to mitigate systemic adverse effects commonly linked to high-dose corticosteroid therapy, including weight gain and immunological suppression.

Liposomes for Delivery of Biologic Therapies

Liposomes, a category of lipid-based nanoparticles, serve as a highly promising delivery mechanism for biologic medicines, such as monoclonal antibodies, in the management of SLE (31). These spherical vesicles, formed from phospholipid bilayers, exhibit remarkable biocompatibility and versatility, rendering them optimal carriers for many therapeutic medicines. Rituximab, a biologic agent, is an anti-CD20 monoclonal antibody that specifically targets and depletes B lymphocytes, which are integral to the pathophysiology of SLE (32). Although rituximab has shown effectiveness in treating SLE, its therapeutic application is constrained by inadequate pharmacokinetics, fast elimination, and off-target consequences, including systemic immune suppression and infusion-related responses (33). The liposomal encapsulation of rituximab provides multiple benefits that mitigate these limitations. Encapsulating rituximab in liposomes dramatically prolongs the drug's circulation period in the bloodstream, facilitating sustained therapeutic levels and enhanced bioavailability. Liposomes can be modified on their surface using agents like polyethylene glycol (PEG) or targeting ligands to augment stability, diminish immune recognition and clearance, and boost specificity for B cells or inflamed tissues. These characteristics improve the targeting efficacy of rituximab, ensuring it accumulates more efficiently at locations of disease activity while reducing its effect on non-diseased tissues (34). Encapsulated rituximab demonstrated improved targeting of CD20-expressing B cells, leading to more efficient elimination of autoreactive B cells implicated in SLE. The liposomal formulation extended the drug's therapeutic effects, decreasing the required frequency of administration. The utilization of liposomal encapsulation significantly reduced off-target immune suppression, hence maintaining the functionality of non-pathogenic immune cells and diminishing the likelihood of infections and other adverse consequences linked to conventional rituximab therapy (35). Advancements in research may facilitate the creation of liposomal formulations customized for particular patient requirements, perhaps leading to personalized therapy in systemic lupus erythematosus (1). Clinical trials are essential to confirm these preclinical results and determine the safety, efficacy, and scalability of liposomal biologics in human subjects. Nonetheless, the application of liposomal encapsulation signifies a pivotal advancement in attaining more efficient, tailored, and safer treatments for SLE (36).

Modulation of CD154/CD40 Signaling Using Nanoparticles

Therapeutic strategies targeting the CD154/CD40 axis have shown efficacy in animal models and human studies; however, earlier clinical trials were halted due to thromboembolic complications associated with anti-CD154/CD40 antibodies. The review notes that second-generation antibodies directed against CD154 or CD40 are showing promising results in advanced stages of clinical testing (37).

Additionally, a 2024 study by Zhang et al. developed a biodegradable nanoparticle small interfering RNA (siRNA) delivery system (siCD40/NPs) to effectively deliver CD40 siRNA. This nanoparticle-based approach was shown to suppress alloimmune responses, indicating potential therapeutic applications in modulating immune responses in autoimmune diseases like SLE (38). These findings underscore the potential of nanoparticle-based strategies in targeting the CD154/CD40 pathway, offering a promising avenue for developing more effective and safer therapies for SLE (39).

CD154-Targeted Nanoparticles

One approach for modulating the CD154/CD40 pathway involves the development of nanoparticles functionalized with anti-CD154 antibodies. These nanoparticles can specifically bind to CD154 on activated T cells, preventing its interaction with CD40 on B cells. The study demonstrated that these nanoparticles effectively blocked T-B cell interactions, leading to a reduction in autoantibody production

and alleviation of disease symptoms. The selective inhibition of CD154/CD40 signaling without causing broad immune suppression represents a significant advantage over traditional therapies (40).

Induction of Immune Tolerance Using Nanoparticles Another promising approach in nanoparticle-based therapies for SLE is the induction of immune tolerance. Immune tolerance refers to the immune system's ability to recognize self-antigens as non-threatening, thereby preventing the development of autoimmunity. In SLE, tolerance to self-antigens is broken, leading to the activation of autoreactive T and B cells. Nanoparticles have the potential to restore this tolerance by delivering self-antigens in a way that induces a tolerogenic response rather than an autoimmune reaction (41).

Nanoparticles for Treg Induction

Regulatory T cells (Tregs) are a subset of T cells that play a critical role in maintaining immune tolerance by suppressing the activation of autoreactive immune cells. A major challenge in autoimmune diseases like SLE is the failure to maintain adequate levels of Tregs, which exacerbates immune dysfunction. Nanoparticles can be used to promote the expansion of Tregs or enhance their function, providing a novel strategy for treating autoimmune diseases (42).

A study by *Wang et al. (2019)* demonstrated that nanoparticles functionalized with self-antigens, such as DNA or nucleosomes, could be used to induce a tolerogenic response in dendritic cells (DCs). These DCs then promoted the expansion of Tregs, which suppressed the activation of autoreactive T and B cells. The induction of Tregs in this manner reduced autoantibody production and alleviated lupus symptoms in a murine model. This approach provides a potential strategy for resetting the immune system in SLE by restoring immune tolerance (43).

Moreover, *Ding et al. (2021)* reported that nanoparticles encapsulating an antigenic peptide derived from self-proteins in SLE (such as nucleosomes) were capable of inducing Treg differentiation in the context of autoimmune disease. This induction led to decreased autoreactive immune responses and reduced disease severity in lupus mice. These findings suggest that nanoparticle-based delivery systems could be used not only to modulate the immune response but also to induce long-term immune tolerance, which could potentially reduce the need for long-term immunosuppressive treatments (44).

Challenges and Limitations of Nanoparticle-Based Therapies in SLE

Despite the promising preclinical data, there are several challenges and limitations in the development and clinical translation of nanoparticle-based therapies for SLE.

1. Biocompatibility and Safety

The biocompatibility of nanoparticles is a key consideration in their therapeutic use. Although many nanoparticles are made from biocompatible materials such as lipids and PLGA, the long-term effects of nanoparticle accumulation in tissues and organs remain unclear. Non-biodegradable nanoparticles may persist in the body, leading to potential toxicity or inflammation. Furthermore, the surface properties of nanoparticles, such as their charge, size, and surface modification, can influence their interaction with immune cells and affect their biocompatibility (45).

In some cases, nanoparticles may induce unwanted immune responses, such as the activation of complement pathways or the generation of antibodies against the nanoparticles themselves. This could lead to inflammation or hypersensitivity reactions. Therefore, extensive preclinical safety studies are essential to assess the biocompatibility and potential toxicity of nanoparticles before clinical application (46).

2. Immunogenicity

While nanoparticles offer a unique advantage in terms of targeting specific immune cells, their immunogenic potential must also be considered. Nanoparticles, especially those derived from synthetic materials, may be perceived as foreign entities by the immune system, triggering an immune response against the particles. This could lead to the development of anti-nanoparticle antibodies, which could reduce the efficacy of treatment over time. Additionally, the activation of the immune system in response to nanoparticles could worsen the underlying autoimmune pathology in SLE (47).

To mitigate immunogenicity, nanoparticles must be carefully designed to avoid recognition by the immune system. This can be achieved through surface modifications such as PEGylation (the attachment of polyethylene glycol) or coating with biocompatible molecules that reduce immune recognition. Such modifications have been shown to improve the circulation time and reduce the immunogenicity of nanoparticles, making them more suitable for clinical use (48).

3. Scale-up and Manufacturing Challenges

Another significant challenge in the clinical translation of nanoparticle-based therapies is the scale-up and manufacturing process. Producing nanoparticles with consistent quality, size, and surface characteristics on a large scale can be complex and costly. The manufacturing process must also ensure that the nanoparticles are stable, reproducible, and free from contaminants. Furthermore, the process

must be adaptable to produce nanoparticles that can carry various therapeutic agents, such as small molecules, biologics, or self-antigens (49).

The regulatory approval process for nanoparticle-based therapeutics is also complex. Nanoparticles are classified as drug delivery systems, and their approval requires rigorous testing for safety, efficacy, and pharmacokinetics. This includes evaluating the long-term effects of nanoparticles in humans, which can be time-consuming and costly (50).

4. Targeting Specific Immune Cells

While nanoparticles can be engineered to target specific immune cells, achieving precise targeting remains a challenge. In SLE, the immune dysregulation involves multiple cell types, including T cells, B cells, and dendritic cells, which all play a role in disease pathogenesis. The ability to selectively target and modulate the activity of these different cell populations with high precision is a key hurdle for nanoparticle-based therapies. Further research is needed to identify the most effective targeting strategies and ensure that nanoparticles are delivered to the appropriate cells or tissues (51).

Targeting the CD154/CD40 Axis and Immune Tolerance with Nanoparticles

The targeting of the CD154/CD40 signaling pathway offers a promising strategy for modulating autoreactive immune responses in systemic lupus erythematosus (1), given its central role in B cell activation. Several studies have explored nanoparticle-based approaches to selectively target and modulate this pathway, aiming for more precise and effective treatments (52).

Tolerogenic Nanoparticles for B Cell Modulation

The findings demonstrated that this approach reduced activated B cell numbers, lowered autoantibody production, and alleviated kidney inflammation in a murine lupus model. This study emphasizes the potential of nanoparticle-based therapies to selectively modulate immune responses, offering targeted strategies that minimize systemic immune suppression (53).

Inducing Immune Tolerance with Nanoparticles

Nanoparticles are also being explored for their ability to induce immune tolerance in SLE, particularly through the expansion of regulatory T cells (Tregs). By delivering self-antigens or regulatory signals to immune cells, nanoparticles can promote tolerance to self-antigens, which could help restore immune homeostasis in autoimmune diseases (54).

2. Nanoparticles for Targeting Specific Immune Cells in SLE

Achieving cell-specific targeting is a major challenge in autoimmune therapy, but nanoparticles provide an exciting solution by enabling precise targeting of specific immune cell populations. This precision reduces the risk of broad immune suppression while improving therapeutic efficacy and safety (55).

Targeting Dendritic Cells with Nanoparticles

These DC-targeted nanoparticles modulated the immune response by inhibiting autoreactive T cell activation and promoting Treg expansion. As a result, the study observed a significant reduction in autoantibody production and improved kidney damage in lupus mice. This research underscores the potential of nanoparticle-based therapies to selectively target DCs, thereby preventing the initiation of autoimmune responses (55).

Targeting B Cells with Nanoparticles

B cells play a central role in SLE pathogenesis through the production of pathogenic autoantibodies. Li et al. (2017) investigated the use of nanoparticles functionalized with anti-CD40 antibodies, which block the CD40/CD154 interaction that is essential for B cell activation. These nanoparticles specifically targeted activated B cells in lupus-prone mice, preventing their activation and autoantibody production. This targeted inhibition of B cell activation led to a reduction in kidney inflammation and overall disease symptoms, highlighting the precision of nanoparticle-based approaches to modulate B cell function in SLE (56).

3. Nanoparticles for Gene Delivery in SLE

Gene therapy is emerging as a novel approach for modulating immune responses in autoimmune diseases like SLE. Nanoparticles can be used to deliver genetic material, such as small interfering RNA (siRNA) or CRISPR/Cas9 components, to specific immune cells, offering a powerful strategy for treating SLE at the molecular level (57).

Future Directions and Conclusion

Nanoparticles represent a promising therapeutic tool for modulating immune responses in SLE. By offering the ability to target specific immune cells and tissues, nanoparticles could provide more effective, personalized, and less toxic treatments for SLE. Targeting the CD154/CD40 signaling pathway through nanoparticles has shown great potential in preclinical studies by reducing autoantibody production and alleviating disease symptoms. Additionally, nanoparticles can be used to promote immune tolerance through the expansion of regulatory T cells, providing a novel strategy for treating autoimmune diseases like SLE (58).

Despite the promising results from preclinical models, there are significant challenges in translating nanoparticle-based therapies into clinical practice. These challenges include ensuring the biocompatibility and safety of nanoparticles, minimizing their immunogenicity, overcoming manufacturing hurdles, and achieving precise targeting of immune cells. However, with continued advancements in nanotechnology, biomaterials, and drug delivery systems, nanoparticles hold great potential to revolutionize the treatment of SLE and other autoimmune diseases (59).

CONCLUSION

Nanoparticle-based therapies represent a rapidly advancing and highly promising frontier for the treatment of systemic lupus erythematosus. Although translational challenges persist including issues of safety, immunogenicity, manufacturing, and targeted delivery ongoing innovations in nanotechnology and biomaterials continue to narrow these gaps. By enabling precise modulation of dysregulated immune pathways and reducing the systemic toxicity associated with conventional immunosuppressive drugs, nanoparticles have the potential to reshape the therapeutic landscape of SLE. With sustained interdisciplinary collaboration across immunology, materials science, and clinical research, nanoparticle-driven strategies may soon evolve into safe, effective, and personalized interventions for patients with SLE and other autoimmune diseases.

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Sanaz Khosravi Ghareh Cheh : Conceptualization; editing and writing.

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Consent for publication

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Organs-on-Chip as a Platform for Patient-Specific Drug Testing

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Abstract:
Organs-on-chip platforms represent a transformative approach to patient-specific drug testing and the advancement of personalized medicine. Traditional preclinical models, including 2D cell culture and animal studies, often fail to recapitulate human physiology, tissue architecture, and cellular heterogeneity, leading to high attrition rates in drug development. OoC systems integrate microfluidic technology with human-derived cells to recreate organ-level microenvironments, including tissue-specific mechanical cues, perfusion, and multicellular architecture. These platforms allow high-fidelity modeling of cellular, molecular, and functional responses to therapeutics under physiologically relevant conditions. Patient-derived cells can be incorporated into OoC systems to generate individualized pharmacodynamic and pharmacokinetic profiles, enabling the identification of responders, non-responders, and potential adverse reactions before clinical administration. Multi-organ and "body-on-chip" systems facilitate the study of systemic drug interactions, metabolite production, and organ-specific toxicity with unprecedented precision. Integration with high-content imaging, omics technologies, and machine learning enhances the predictive capability of these systems, allowing quantitative assessment of drug response at the cellular and molecular level. Despite challenges in standardization, scaling, and regulatory adoption, OoC technology holds immense potential to revolutionize preclinical testing, reduce reliance on animal models, and accelerate the development of personalized therapies with improved safety and efficacy.

Keywords: Organs-on-chip, microfluidics, patient-specific therapy, precision medicine, drug testing.

INTRODUCTION

The development of effective therapeutics has long been constrained by the limitations of traditional preclinical models. Conventional 2D cell cultures fail to replicate the three-dimensional architecture, mechanical forces, and multicellular interactions that define native tissues (1). Similarly, animal models often diverge from human physiology due to species-specific differences in metabolism, immune response, and drug sensitivity, resulting in poor translation of preclinical findings to the clinic. High attrition rates in drug development, particularly in oncology, cardiovascular disease, and neurodegenerative disorders, underscore the need for more predictive,

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patient-specific testing platforms. Organs-on-chip (2) technology has emerged as a powerful solution, integrating microengineering, tissue engineering, and human-derived cells to create physiologically relevant, dynamic microenvironments that mimic organ-level function.

OoC platforms utilize microfluidic channels to maintain controlled fluid flow, recapitulating shear stress, nutrient gradients, and perfusion found in vivo. These devices enable co-culture of multiple cell types in defined architectures, supporting cell-cell and cell-matrix interactions critical for tissue homeostasis and response to drugs. Mechanical cues, such as cyclic stretching in lung or cardiac models, replicate the physical forces experienced by tissues, influencing cellular differentiation, signaling, and metabolism (3). By leveraging patient-derived primary cells, induced pluripotent stem cells (iPSCs), or organoids, OoC systems can capture inter-individual genetic and epigenetic variability, allowing the creation of personalized platforms for drug screening (4).

One of the primary advantages of OoC systems is their capacity to provide quantitative readouts of drug response at the cellular and molecular level. High-content imaging enables real-time visualization of cell morphology, proliferation, apoptosis, and organ-specific functional markers. Integration with transcriptomic, proteomic, and metabolomic profiling facilitates mechanistic insights into drug action, off-target effects, and compensatory signaling pathways (4). For example, liver-on-chip systems can model cytochrome P450–mediated metabolism, predicting patient-specific pharmacokinetics and potential toxic metabolites. Similarly, tumor-on-chip platforms capture intra-tumor heterogeneity and tumor-stroma interactions, enabling assessment of chemotherapy or immunotherapy efficacy in specific subclonal populations. Endothelialized vascular networks within chips permit modeling of barrier integrity, drug transport, and immune cell infiltration, providing insight into vascular toxicity and immune-modulatory effects of therapeutics (5).

Multi-organ and body-on-chip models expand the scope of OoC technology by allowing the study of systemic interactions. For instance, coupling liver, kidney, and cardiac chips facilitates evaluation of drug metabolism, nephrotoxicity, and cardiotoxicity in a single integrated system, approximating human pharmacokinetics more accurately than single-organ assays. Such systems also allow modeling of secondary organ effects, drug-drug interactions, and sequential metabolic processes that occur in vivo (6). In oncology, coupling tumor and liver chips enables investigation of metabolite-mediated cytotoxicity or resistance, providing patient-specific insights into drug efficacy and safety. Similarly, gut-liver chips can model first-pass metabolism, microbiome-mediated biotransformation, and nutrient-drug interactions (7).

OoC platforms have demonstrated robust capacity to recapitulate complex cellular and molecular phenomena. Tumor chips reveal heterogeneity in proliferative indices, apoptotic rates, and expression of drug resistance genes. Cardiac chips reproduce beat rate, contractile force, and electrophysiological properties in response to inotropic drugs. Brain chips recreate blood-brain barrier function, neurovascular coupling, and neuronal excitability, enabling study of neuropharmacology and neurotoxicity (8). These systems also allow modeling of immune-tissue interactions, including recruitment of T cells, macrophages, and NK cells, critical for immunotherapy assessment. Incorporation of patient-derived cells permits exploration of polymorphisms affecting receptor expression, transporter function, and signaling pathways, providing a mechanistic basis for inter-patient variability in drug response (9).

Integration of OoC with machine learning and high-dimensional analytics further enhances predictive capabilities. AI algorithms can analyze time-series imaging, gene expression, and metabolic data to predict drug response, identify early toxicity signals, and guide combination therapy design. Mechanistic modeling coupled with AI enables simulation of intracellular signaling networks, enabling rational selection of therapeutic targets and drug doses (10). Reinforcement learning algorithms have been used to optimize flow rates, nutrient delivery, and drug scheduling in real time, improving tissue viability and experimental reproducibility. By combining mechanistic insights with patient-specific cellular data, these platforms move toward truly personalized pharmacology (11).

Despite these advances, several challenges remain. Standardization of chip design, cell sourcing, and culture conditions is required to ensure reproducibility. Scaling up production for high-throughput screening and integration with clinical workflows presents technical and logistical challenges (12). Long-term culture stability, immune competence, and vascularization remain areas of active research. Regulatory acceptance of OoC-derived data as a surrogate for human clinical trials is ongoing, requiring demonstration of reproducibility, predictive accuracy, and mechanistic validity (13).

Organs-on-Chip Technology in Oncology

Tumor-on-chip platforms provide a transformative approach for modeling cancer biology by replicating the complexity of the tumor microenvironment in vitro. These devices integrate patient-derived tumor cells with stromal fibroblasts, endothelial cells, and immune cell populations, creating a

three-dimensional, perfused microenvironment that closely mimics in vivo conditions (14). Microfluidic channels enable the establishment of physiologically relevant oxygen and nutrient gradients, reproducing hypoxic cores and proliferative edges that drive tumor heterogeneity and influence drug response. Such gradients are critical, as hypoxic tumor regions often exhibit elevated expression of HIF-1α, VEGF, and drug efflux transporters, contributing to therapy resistance (15).

Tumor-on-chip systems allow dynamic monitoring of apoptosis, proliferation, and cell migration in real time. Integration with live-cell imaging and high-content fluorescence microscopy enables quantification of cytotoxic T cell infiltration, NK cell activity, and immune checkpoint expression (e.g., PD-L1) at single-cell resolution (16). By incorporating patient-derived immune cells, these platforms can simulate autologous immune-tumor interactions, facilitating evaluation of immunotherapy strategies such as checkpoint blockade or CAR-T cell cytotoxicity. This capability is particularly important given the inter-patient variability in neoantigen landscape, regulatory T cell density, and cytokine milieu, which can influence responsiveness to immunomodulatory therapies (17).

Crucially, tumor-on-chip models allow investigation of molecular determinants of drug resistance. Genes associated with multi-drug resistance, including ABCB1, ABCC1, and ABCG2, as well as anti-apoptotic factors such as BCL-2, MCL-1, and survivin, can be tracked longitudinally. Real-time monitoring of these markers under chemotherapeutic pressure reveals emergence of resistant subclones and informs rational combination strategies to circumvent resistance (18). Additionally, spatial mapping of subclonal populations enables identification of regions with high proliferative capacity, quiescent cells, or stem-like tumor-initiating cells, which are often refractory to conventional therapies (19).

These platforms also permit testing of novel drug delivery systems, including nanoparticle-based carriers and targeted biologics, under physiologically relevant flow and shear conditions (20). Perfused tumor chips facilitate evaluation of drug penetration, retention, and metabolism in heterogeneous tumor tissue, providing predictive insights into pharmacokinetics and therapeutic efficacy that are unattainable with static 2D cultures. In multi-drug studies, these systems allow dynamic assessment of sequential or combination regimens, optimizing dosing schedules to enhance cytotoxicity while minimizing off-target effects (21).

Ultimately, tumor-on-chip technology bridges the gap between conventional in vitro assays and patient-specific clinical responses. By capturing cellular heterogeneity, immune interactions, and molecular resistance mechanisms, these systems offer a robust platform for precision oncology, enabling predictive testing of chemotherapeutic and immunotherapeutic strategies and guiding personalized treatment decisions (22).

Organs-on-Chip for Cardiac and Neurovascular Models

Cardiac organs-on-chip (2) platforms integrate induced pluripotent stem cell (iPSC)-derived cardiomyocytes with endothelial and supporting stromal cells to recapitulate human cardiac physiology in vitro (23). These microphysiological systems enable real-time measurement of contractile force, calcium transients, and electrophysiological properties, including action potential duration, conduction velocity, and arrhythmogenic potential (24). By combining microfluidic perfusion with cyclic mechanical stretch, cardiac OoCs simulate physiological preload and afterload conditions, reproducing cardiac workload and hemodynamic stress. Such dynamic stimulation enhances cardiomyocyte maturation, including sarcomere organization, mitochondrial function, and ion channel expression, which is critical for accurate modeling of patient-specific responses to cardioactive drugs or cardiotoxic chemotherapeutics (25). For example, perfused cardiac chips have successfully predicted doxorubicin-induced cardiotoxicity, demonstrating dose-dependent decreases in contractile amplitude, prolonged action potential duration, and early biomarkers of apoptosis such as caspase-3 activation, correlating with clinical cardiotoxicity observed in patients (26).

Neurovascular and brain-on-chip models emulate the complex architecture and function of the central nervous system, including neuronal networks, glial populations, and the blood-brain barrier (BBB) (27). Endothelial cells, pericytes, and astrocytes are co-cultured in microfluidic channels to form tight junctions with selective permeability, allowing studies of BBB transport, drug penetration, and efflux mediated by P-glycoprotein and other transporters. Integration of microelectrode arrays permits measurement of neuronal excitability, synaptic activity, and network oscillations in response to pharmacological interventions (28). These platforms enable patient-specific modeling of neurodegenerative disorders, epilepsy, and ischemic injury by incorporating iPSC-derived neurons from individual patients, capturing genetic and epigenetic variations that influence disease progression and therapy response (29).

Importantly, cardiac and neurovascular OoCs facilitate simultaneous evaluation of drug efficacy and toxicity across organ systems. Multi-organ

platforms connecting cardiac, hepatic, and neurovascular chips allow assessment of systemic pharmacokinetics, metabolism, and off-target effects, providing a predictive framework for personalized medicine (30).

Multi-Organ Integration and Systemic Pharmacology

Multi-organ organs-on-chip systems represent a paradigm shift in preclinical modeling by recapitulating inter-organ interactions, systemic pharmacokinetics, and dynamic drug responses in a physiologically relevant, human-specific context. By interconnecting multiple organ-specific chips—such as liver, kidney, heart, gut, and lung—through microfluidic perfusion channels, these platforms emulate circulation-mediated transport of drugs, metabolites, and signaling molecules, enabling mechanistic studies of organ-organ crosstalk and systemic toxicity (31). Liver-kidney-cardiac tri-culture systems allow simultaneous evaluation of hepatic drug metabolism, nephrotoxicity, and cardiotoxicity, providing an integrated readout of safety profiles that cannot be captured by single-organ models (32). Such systems have revealed metabolite-dependent cardiotoxicity, where hepatic biotransformation of chemotherapeutic agents produces reactive intermediates that impair cardiomyocyte contractility, prolong action potential duration, and induce apoptosis, reflecting patient-relevant adverse events observed in clinical trials (33).

Gut-liver chips provide a platform to investigate microbiome-mediated drug metabolism, first-pass metabolism, and nutrient-drug interactions. By incorporating commensal microbiota alongside intestinal epithelial cells and liver hepatocytes, these systems capture the enzymatic activity of bacterial and host metabolism, including phase I and phase II reactions, allowing precise prediction of bioactive metabolites and their systemic effects (34). Multi-organ platforms also enable patient-specific predictions of adverse drug reactions by integrating iPSC-derived cells from individual donors. Coupled with high-throughput readouts of electrophysiology, metabolic flux, cytokine secretion, and gene expression, these systems can simulate complex pharmacodynamics and pharmacokinetics, including variable absorption, distribution, metabolism, and excretion (34). Real-time monitoring allows optimization of dosing regimens, sequential or combination therapies, and identification of off-target effects prior to clinical administration. Integration with computational models further enhances predictive capacity, providing quantitative metrics such as clearance rates, metabolite concentrations, and tissue-specific exposure, which inform personalized treatment planning (35).

By bridging molecular, cellular, and systemic physiology, multi-organ OoC systems provide a robust framework for translational pharmacology, reducing reliance on animal models, enhancing mechanistic understanding, and supporting the development of patient-specific, safe, and effective therapeutic strategies (36).

Future Perspectives

The next generation of organs-on-chip platforms is poised to integrate increasing levels of physiological and cellular complexity, bridging the gap between in vitro models and human in vivo responses. Advanced OoC systems are expected to incorporate immune competence by integrating patient-derived immune cells, enabling dynamic modeling of immune surveillance, inflammation, and immunotherapy responses (37). The next generation of organs-on-chip platforms is poised to integrate increasing levels of physiological and cellular complexity, bridging the gap between in vitro models and human in vivo responses. Advanced OoC systems are expected to incorporate immune competence by integrating patient-derived immune cells, enabling dynamic modeling of immune surveillance, inflammation, and immunotherapy responses. Integration of artificial intelligence (AI) and machine learning (ML) with OoC data streams will enable real-time adaptive dosing, predictive modeling of organ-specific toxicity, and optimization of combinatorial therapies (38). ML algorithms trained on high-dimensional functional, transcriptomic, proteomic, and metabolomic data can identify patient-specific biomarkers of drug response, simulate dose-response curves, and predict adverse events with greater accuracy than traditional models. Reinforcement learning strategies can iteratively adjust microfluidic flow, drug concentration, or exposure duration to optimize therapeutic outcomes in silico before in vitro or clinical application (39).

High-throughput OoC arrays combined with multi-omics readouts will facilitate population-scale patient stratification, enabling identification of responders and non-responders, elucidation of mechanisms underlying inter-individual variability, and evaluation of rare adverse events (40). These capabilities will support precision pharmacology by providing actionable insights for personalized treatment planning, including optimal dosing regimens and combinatorial strategies. Federated learning approaches can integrate multi-center OoC datasets without sharing patient-identifiable information, preserving privacy while expanding the statistical power and generalizability of predictive models (41).

For widespread adoption, standardization of fabrication protocols, culture conditions, and readout

metrics remains critical to ensure reproducibility and reliability. Regulatory alignment, including definition of performance criteria and validation frameworks, will be essential for clinical and industrial translation (42). As these systems mature, they have the potential to revolutionize preclinical drug testing, reduce reliance on animal models, and accelerate the development of patient-specific therapies with improved safety and efficacy (43).

CONCLUSION

Organs-on-chip platforms provide a transformative, patient-specific approach to drug testing and personalized medicine. By integrating human-derived cells, microfluidics, mechanical cues, and multi-organ interactions, these systems recapitulate physiological and pathological states with high fidelity. Coupled with high-content analytics, omics technologies, and AI, OoC enables predictive modeling of drug efficacy, toxicity, and pharmacokinetics at the cellular and molecular levels. Future developments in multi-organ integration, adaptive monitoring, and mechanistic modeling promise to further accelerate precision therapeutics, reduce reliance on animal models, and enhance clinical translation of safe and effective patient-specific therapies.

Authors's Contribution

Farnaz Roshan Mehr and Fatemeh Gabeleh: data curation; editing and review. The authors read and confirmed the final manuscript.

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Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

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Dye Selection	Excitation and Emission
Reaction Volume	10 µL to 30 µL
Chemistries Supported	SYBR, Probe, HRM
Thermal System	Six Peltiers made from two ceramic plates with semi-conductor elements, 96-well
Thermal System Temperature Range	25.0 – 99.9°C Heating: 6.0°C/sec Cooling: 3.0°C/sec (Median), 2.5°C/sec (Average) Accuracy: ± 0.2°C or better at typical annealing, amplification, and denaturation temperatures
Dynamic Range	9
Experiment Types	Quantitative PCR with dye, Quantitative PCR with probe, Allele Discrimination with HRM, Allele Discrimination with probe, Comparative Quantitation, User Defined
Uniformity	± 0.4°C
Data Acquisition Time	<3 seconds for all
Cq Uniformity	Cq St Dev <0.20 at fast cycling (5s 95°C/10s 60°C)
Electrical Power (input)	100 – 240VAC, 50/60Hz, 1100VA
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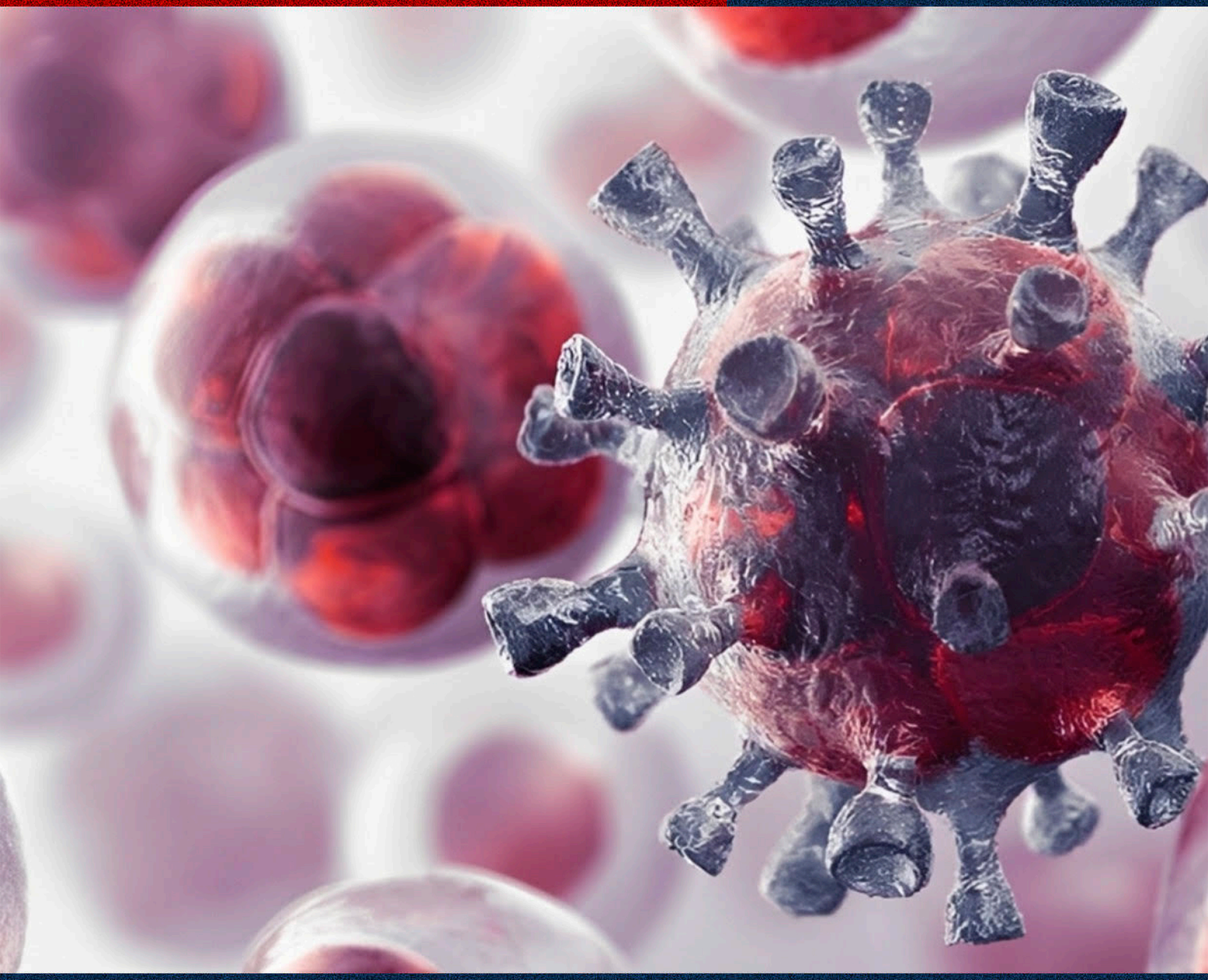

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