The future of drug development: the paradigm shift towards systems therapeutics

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Progress in cell biology, genetics, molecular, and systems pharmacology is the driving force behind a current paradigm shift in drug research. This paradigm shift shapes new avenues for advanced treatments that are commonly referred to as 'systems therapeutics'. Systems therapeutics differ in many ways from current drugs because they target biological networks rather than single transduction pathways, and affect disease processes rather than physiological processes. Here, we examine how the paradigm shift towards systems therapeutics will change current scientific concepts of the interactions between drugs and diseases, the organization of research and development, as well as the clinical use and therapeutic evaluations of therapeutic interventions.

Where do we come from?

For centuries, the discovery and application of medicine has been driven by myriad clinical experiences, serendipity, and empirical trial and error, with, in the early days, many therapies being isolated from natural sources. Our current therapeutic arsenal still includes many products with an origin or an initial lead in nature (e.g., paclitaxel, statins, and antimicrobial agents) and revisiting natural products for drug discovery remains actively pursued [1].

During the second half of the 20th century, progress in science (e.g., increase in synthetic organic chemistry or the development of pharmacology-based concepts of drug action) marked a 'paradigm shift' in drug research (Fig. 1). Adoption of the 'single path transduction model', describing drug effects as the result of interactions of a single drug at a single receptor, led to groundbreaking drugs, such as propranolol or cimetidine [2]. In practice, these drugs are typically applied in fixed doses according to a 'one size fits many' principle, with a major emphasis on the control of symptoms of the disease. These single receptor-based drugs, together with anti-infectives, such as penicillin or streptomycin, resulted in unprecedented progress in drug development during the decades after World War II [3].

However, in recent years, the development of new drugs on the basis of the 'single target–single drug' concept stagnated, with significantly reduced success rates and prolonged development times [4]. The stagnation in drug development also coincides with major challenges in healthcare systems worldwide. Among many factors, aging of the population has led to a significantly increased burden of disease, with seemingly infinite demands for healthcare resources, both operationally, capacity wise, and budgetary [5,6]. However, apart from demographic changes, many transformations in current healthcare systems (e.g., increased patient focus, demand for equal access, proportionate regulation, and globalization) also affect the space of drug research, the business model for the industry, and the socioeconomic dimensions of pharmacotherapy.

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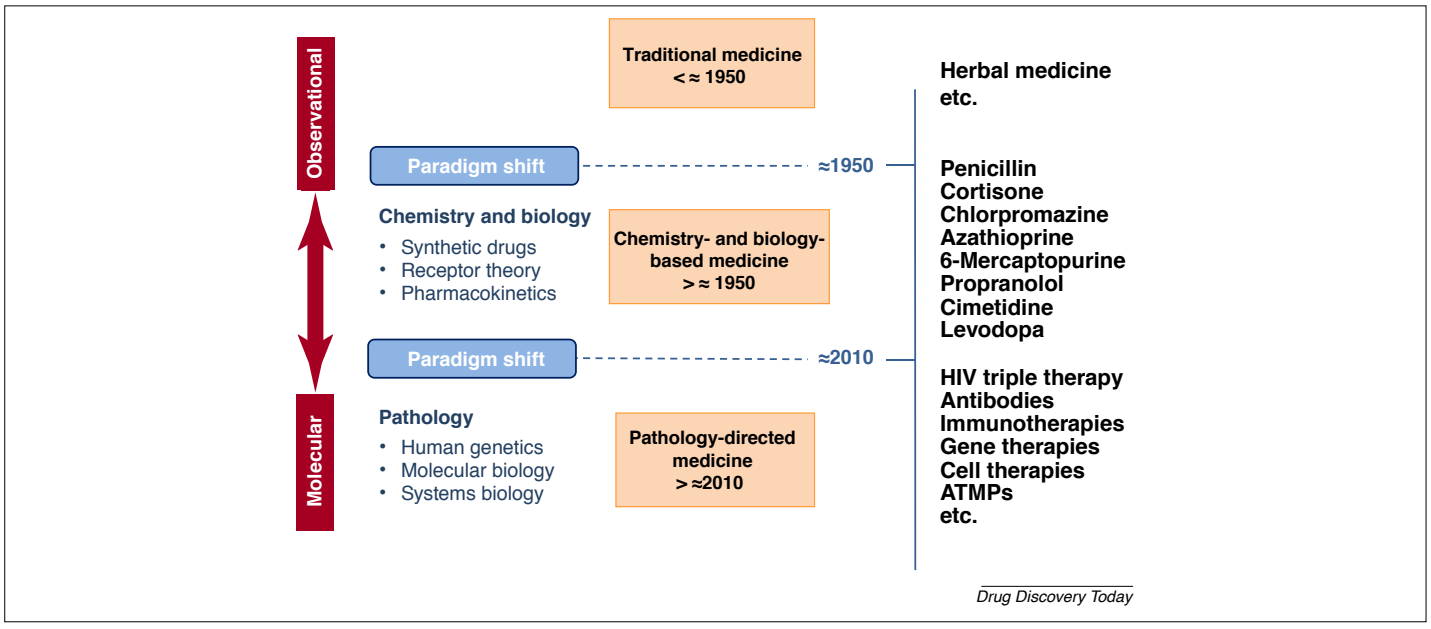

FIGURE 1

An overview of the paradigm shifts in drug development since the second half of the 20th century.

Now, more than a decade into the 21st century, through progress in cell biology, genetics, molecular, and systems pharmacology, the next paradigm shift in drug research is unfolding (Fig. 1). The adoption of 'biological network transduction models', evaluating drug effects as the result of multiple interactions in a biological network, has yielded unprecedented opportunities to understand the functioning of biological systems, to identify the molecular mechanisms of drug action, and to design therapeutic strategies aimed at modifying disease processes rather than controlling symptoms [7].

It is expected that these transitions in science and drug development will shape new avenues for an avalanche of advanced treatments reaching patients in the years to come. Conceptually, these therapeutic interventions differ in many ways from current drug treatments and are commonly referred to as 'systems therapeutics'.

Under the title 'Future Medicines For One World', the 6th FIP Pharmaceutical Sciences World Congress (PSWC) in Stockholm on May 20–24, 2017 addressed the question of how to make systems therapeutics a reality. The views presented in this paper are inspired by the PSWC 2017.[†] First, we introduce the scientific principles of systems therapeutics. Next, we discuss how the paradigm shift towards systems therapeutics might change current scientific concepts of the interactions between drugs and disease, the organization of research & development (R&D), as well as the clinical use and therapeutic evaluation of systems therapeutic interventions. We conclude with a discussion of the impact of the systems approach on pharmaceutical sciences as a scientific discipline.

The era of systems therapeutics: from single pathways towards biological networks

In recent years, progress in cell biology, genomics, proteomics, and metabolomics has revealed relevant molecular networks underpinning the functioning and defects of biological systems. Advanced insights into the molecular mechanisms and pathology of disease open windows for the design of targeted interventions aiming to prevent and/or modify the disease. For certain diseases, the refinement of diagnostics has led to the identification of multiple subtypes. For other diseases, it appears that a multitude of molecular mechanisms might cause diseases with similar, if not identical, phenotypical features [8,9]. The differentiation between subtypes of disease has major implications for the design of therapies, and the ways in which they are studied and applied in clinical practice. For example, biomarkers, such as *BRAF* mutations for predicting response to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer, drive the stratification of patients into responders and nonresponders to therapy [10].

Previously, the single path transduction model was used to describe the pharmacology of drugs in a quantitative manner, accounting for distinct properties of the behavior of biological systems, such as nonlinearity (e.g., the saturation target binding and/or activation), hysteresis (the observation that the time course of the drug effect lags behind the concentration), and, to a certain extent, individual variation [2]. However, the pathway was unable to explain other fundamental properties of systems behavior, such

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as convergence or redundancy (the observation that distinctly different molecular mechanisms might lead to the same disease with similar, if not identical, phenotypic properties), synergy and/or antagonism (the phenomenon that the combined effect of two interventions is larger and/or smaller than the sum of the effects of the two interventions separately), resilience (the relative insensitivity of the system to disease progression or drug effects), and multistationarity (the fact that the system can exist in more than one stable state). The biological network transduction model postulates that the functioning of biological systems depends on the interactions between nodes within a biological network [7]. In this manner, it can account for the aforementioned spectrum of properties of complex biological systems behavior. This is particularly relevant in the design of systems therapeutic interventions aiming at disease intervention [11]. In this context, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways in rheumatoid arthritis and other inflammatory diseases are a relevant example. Now, almost 20 years after their discovery, they are being harnessed for treating a variety of immune disorders targeting complex biological networks, also raising pertinent questions about target selectivity with impact on both efficacy and (long-term) safety [12].

Systems therapeutics differ in many ways from traditional 'one size fits many' fixed treatments (Table 1). Systems therapeutic interventions are 'precision treatments' that are: (i) stratified to account for differences in the molecular mechanism of the disease; (ii) individualized to account for factors causing interindividual variation in response; (iii) increasingly complex to describe the interactions between nodes in a biological network; and (iv) applied in a pre-emptive or preventive manner to modify disease progression. This will be accompanied by the introduction of a broader supply of therapeutic interventions. In addition to traditional small-molecule drugs, the future therapeutic arsenal will increasingly include large-molecule biologics, multitarget drugs, rational drug combinations, gene therapies, and cellular therapies. As stated above, clear examples are the treatments and immunotherapies for various types of cancer, where information with respect to the molecular mechanism of the disease constitutes the basis for the stratification of drug treatment [11,13].

TABLE 1

Features of the pharmacology-based fixed formulations versus pathology-targeted precision treatments with regard to their scientific concepts, R&D, clinical use, and therapeutic evaluations

Pharmacology-based 'fixed formulations'	Pathology-targeted 'precision treatments'
Scientific concepts	
Single drugs targeting single targets 'One-size-fits-many' fixed formulations aimed at symptomatic relief Industrial manufacturing of fixed formulations	Multitarget drugs (combinations) targeting complex biological networks Personalized precision treatments aimed at disease modification and/or cure Bedside assembly of personalized treatments
R&D	
Monodisciplinary expert teams Stand-alone research hubs Closed innovation	Interdisciplinary research teams Shared knowledge infrastructure Open innovation
Clinical use	
Treatments applied in an intuitive manner Monitoring of product quality Monitoring of treatment response on basis of limited number of clinical measures	Treatments applied in a pre-emptive and preventive manner Monitoring of process quality Monitoring of treatment response on basis of complex array of biomarkers
Therapeutic evaluations	
Data collection focus in preclinical usage space 'Big data' to identify patterns that could indicate new pathways, mechanisms of disease, and mechanisms of drug action 'Learn & confirm' based on randomized clinical trial data	Data collection focus in real-world clinical usage space 'Smart data' to assess individualized drug treatments by accounting for interindividual variation Iterative learning cycles for continuous evaluations based on RWD

'Scientific concepts' in the era of systems therapeutics

Systems therapeutics target complex biological systems and will increasingly involve multitarget drug combinations, aimed at disease modification. The design of these interventions requires the integration of drug and disease biological networks. Given their inherent complexity, the development of tailor-made systems therapeutic interventions relies on mathematical models of the functioning of the biological system. These models are based on mathematical expressions to describe interactions within biological networks and can include pharmacogenomic information to predict risk to diseases, variability in exposure, treatment response, and risk of adverse effects in real-life situations. To date, the modeling of pharmacodynamic interactions in drug development has been either largely unexplored or described by fairly simple linear functions. However, this does not do justice to the complexity of pharmacodynamic interactions, which are typically highly dimensional and nonlinear [7]. Insights into this type of behavior can be exploited in the optimization of therapeutic interventions. An example is the search for synergistic antiepileptic drug combinations [14]. The biological network model also constitutes a scientific basis for the modeling of complex patterns of disease progression and for the design of systems therapeutic interventions aimed at disease processes and disease progression [7].

Given their inherent complexity, the identification of these models and the estimation of the values of the model parameters constitute a major challenge. Therefore, progress in advanced mathematical and (Bayesian) statistical methods is a prerequisite for creating and understanding mechanistic disease models. The development of biomarkers, reflecting in a quantitative manner processes in the causal path of the disease process, will be an integral part of this approach [15].

In addition to these challenges to identifying mathematical models, complexities at the level of the disposition of drug molecules continue to be an important factor in the development of systems therapeutics interventions. In many instances, promising drug candidates need to be further optimized to overcome complexities related to the delivery of the drug to its target. This applies in particular for drugs that exert their actions on intracellular targets [16]. The progress in the identification of transporters

and their functional role in drug distribution and as determinants of drug action has been a major step forward to address these challenges [17]. The elucidation of the mechanisms involved in the intracellular disposition of foreign chemicals remains an important topic for future research. Another challenge at the level of the delivery concerns the robust co-delivery of conventional drugs and adjuvants and the administration of drug combinations. Advanced drug delivery systems are instrumental in enhancing the robustness of therapeutic interventions [18].

From a scientific point of view, the manufacturing and quality assurance of tailored-interventions is a major challenge. The production of tailored interventions will move (part of) the manufacturing from large-scale production plants [where the final product is manufactured under good manufacturing practice (GMP) conditions] closer to the patient. In these settings, healthcare professionals, in particular pharmacists, will have an important new role in the final step of the manufacturing process: the assembly of personalized treatments, using custom-made components at the bedside [19]. We see similar developments in the area of gene- and cell-based therapies, with both scientific and regulatory challenges, and tailored strategies, both in terms of disease targeting and manufacturing, are also at the heart of innovations in these fields [20].

The focus on systems approaches will shift drug research further in the direction of the clinical arena. This concerns in particular the discovery of drug targets to directly influence the disease process. Such targets can only be discovered in patients with a certain disease. Therefore, the discovery of drug targets is very much in the domain of the medical sciences. Once drug targets have been identified, aspects, such as the discovery and design of drug molecules, the delivery and targeting, the formulation and manufacturing, and ultimately the pre-clinical development and evaluation, are in the domain of the pharmaceutical sciences, whereas the ultimate clinical evaluation is again in the medical domain. Through the focus on disease mechanisms, the medical and pharmaceutical sciences will become increasingly interconnected.

Organization of 'research & development' in the era of systems therapeutics

The introduction of 'precision medicines' in the era of systems therapeutics will rely on global approaches to the conduct and organization of: (i) research activities, creating interdisciplinary research teams; (ii) increased focus on the sharing of resources; and (iii) training and education of new generations of scientists.

With the introduction of personalized systems therapeutics, drug development and clinical usage will become increasingly intertwined. To exploit the full potential of systems approaches, it is crucial that scientists and practitioners involved in drug discovery, development, manufacturing, and clinical practice collaborate in multidisciplinary research teams. To solve global health problems, such as antibiotic resistance and the TB and malaria epidemics in low and middle-income countries, global efforts to develop new therapies for patients become even more relevant. To ensure that systems therapeutic interventions can reach the patient in a timely fashion, the ways of 'working' in a collaborative environment require a rethink of current rewarding systems with regard to intellectual property and data exclusivity [21].

Open innovation models are seen as one of the solutions in progressing science to enable innovations in a challenging and multidimensional age of systems biology, from discovery until clinical use. Open innovation models will reduce current organizational boundaries to facilitate the rapid transfer of knowledge that is needed to expedite the innovation of therapies. However, working in open innovation models requires a change of mind and new incentive models in which global public health needs are better aligned with rewards for innovation. Such an environment relies on mutual trust across public and private sectors, which can be gained through public private partnerships (PPPs) of large international consortia [22]. So far, it is too early to draw up the balance sheet on such models, although there is a clear momentum for change.

Ultimately, a new generation of scientists with a multifaceted scientific background and excellent communication skills is needed. Scientists that are trained in the dual areas of medicine and technology will be more capable of working in interdisciplinary research teams because individual specialist areas will become more interweaved, which will speed up the R&D process. An example is a specially trained pharmacist who covers multiple specialist areas, and who has an important role in the development, implementation, and evaluation of systems therapeutic interventions [23]. Furthermore, this new generation of scientists would be trained to handle new technological concepts applied in the healthcare setting. In the end, the confines of individual specialist fields will become more permeable, facilitating collaborative working models around systems biology.

'Clinical use' in the era of systems therapeutics

Therapeutic interventions aimed at disease modification will be used increasingly in a pre-emptive or preventive manner, which has important implications for clinical use. To stratify treatment on the basis of the molecular mechanism of the disease and to be able to apply systems therapeutic interventions in a pre-emptive manner, detailed diagnostics will be needed that unveil the molecular mechanism of the disease in individual patients. This will go hand-in-hand with the development of mechanistic biomarkers with a high construct validity, which reflect in a strictly quantitative manner disease processes, disease progression, and the effects of therapeutic interventions. Here, new technologies in the area of 'metabolomics' are particularly important for the discovery of low-molecular-weight biomarkers [24,25].

The era of systems therapeutics will have a major impact on the role of pharmacists and healthcare professionals. For example, the design of systems therapeutics interventions will be more integrated with the healthcare process. This means that the emphasis of the work of pharmacists will increasingly focus on designing and managing healthcare processes, to deliver treatments tailored to the individual patient, rather than managing the supply and use of medicinal products.

To deliver personalized treatments to individual patients, it is crucial to obtain estimates of the values of, and the variation in, systems model parameters in real-life populations. One of the features of future clinical practice is the wealth and complexity of the data that will become available both in- and outside of the clinic. Using digital health devices for monitoring and measurement (e.g., wearables), detailed data on treatment effects can be

collected more efficiently, both in the clinical setting and in regular daily life. On the basis of these data, the structure of the underlying systems model and the values of the model parameters can continuously be updated and refined. Exciting developments in advanced learning systems, such as artificial intelligence, data integrity, and machine learning, can contribute to identifying new aspects of biological systems behavior in the near future [26]. Furthermore, data collections and measurements can be shifted to the pre-emptive space (i.e., in healthy individuals or risk groups), to monitor early signs and symptoms of the disease to prevent its progression at the earliest state.

Hence, research and practice in the era of systems therapeutics will increasingly go hand-in-hand, which will radically change the roles of healthcare professionals, and collaborations between them. Furthermore, it will bring new types of expert into clinical practice, such as data scientists and digital health technology experts.

'Therapeutic evaluations' in the era of systems therapeutics

In the systems approach, the emphasis in the regulatory approval of drugs and medicinal products is no longer on the evaluation of a product solely on the basis of data obtained in prelaunch clinical trials. The evaluation of systems therapeutic interventions is based around the process of designing and implementing tailor-made precision treatments in stratified patient populations. This requires the conceptualization of novel systems models of the functioning of the biological system, including interactions between components of biological networks. Preclinical research in the laboratory forms a unique basis for the design and evaluation of such models, as well as the extrapolation from the laboratory to the patient [27]. Characterization and prediction of the variability in pharmacokinetics, to account for eventual differences in target exposure, and variability in values of systems parameters describing the pharmacodynamics, disease processes, and interactions between the two, are key here [28,29]. This notably deviates from current standard regulatory concepts, in which drugs are evaluated in predefined, often large patient populations, followed by a binary (yes or no) regulatory decision for marketing approval. Recent regulatory science work has shown which crucial factors drive such decision processes, but we need more insights to really build a regulatory space that responds to the needs of innovation and ensure patient safety and access to medicines that work [30].

In the era of systems therapeutics, preclinical assessments and the post-marketing surveillance will amalgamate into a dynamic life-cycle approach for the evaluation of therapeutic interventions. Novel concepts of the evaluation of the clinical efficacy are particularly important for treatments that modify disease progression and that are applied in a pre-emptive or preventive treatment paradigm, because the traditional clinical trial designs and statistical techniques are unable to handle data on disease progression in a meaningful manner.

A key enabler in the movement of regulatory science towards a systems approach can be real-world data (RWD). RWD studies can generate long-term data on the safety and effectiveness of systems therapeutics interventions that require robust data collection methods in the clinical usage space. The widespread use of electronic health records can facilitate the collection of RWD and contribute to this new concept of generating knowledge. To account for the inherent complexity of the RWD (e.g., for inter-individual variation) in the real-world setting, the era of systems therapeutics cannot rely on the big data concept, but requires the integration of a 'smart data' approach [31,32]. Thus, combined with prediction models for treatment response at the individual patient level, RWD can support regulatory decision-making and facilitate the transition to a life-cycle approach. Whether RWD will deliver in the near future in terms of real evidence remains a topical question. The stakes are high, the same with the promises, and only the future will tell [33].

In the pharmacology-based era of drug development, novel therapeutic interventions are generally studied in a defined population for a finite period and often relying on randomization to increase the robustness of the assessment. During this process, a single key hypothesis about the efficacy of the drug is identified (learn) and assessed (confirm). Therefore, the current clinical drug development model is often described as 'Learn & Confirm' [34].

In the current paradigm shift towards an era of systems therapeutics, we are moving away from the 'one-size-fits-many' approach and adopting a 'precision medicines' approach, for which different models for the scientific enquiry of novel therapeutic interventions apply. The dynamic and continuous learning environment that coincides with the precision medicines approach in systems therapeutics is characterized by repeated cycles of simulations, predictions, experimental verification, and new hypothesis generation [35]. The dynamic era of systems therapeutics requires the adoption of a new model based on the continuous appraisal of efficacy and safety, which can be described as 'Iterative Learning Cycles'.

A call to action for pharmaceutical sciences and beyond

Advances in science are indicating a 'paradigm shift' and are opening radically new avenues for the development of targeted therapies with disease-modifying properties. This paradigm shift towards a pathology-based era of systems therapeutics has several important implications for the future of pharmaceutical sciences [36].

In 2015, the International Pharmaceutical Federation (FIP) proposed the following definition of a pharmaceutical scientist: 'A pharmaceutical scientist is a qualified expert in aspects of the science and technology of medical products. This includes but is not limited to the discovery, development, manufacture, regulation, and utilisation of medical products – embracing how medicines work, how safe and effective products are brought to the market, their impact on the body and their effect on the prevention and treatment of disease' (https://fip.org/pharmaceutical_sciences). In this definition, the emphasis is on the development of medical products in the broadest sense. Moreover, with its focus on aspects of the science and technology of medical products, it emphasizes the multidisciplinary nature of drug development. Pharmaceutical scientists share specialist knowledge in certain areas of the pharmaceutical sciences, with a broad understanding of drug development in general. By virtue of this qualification, they are uniquely qualified for roles in the integration of information from different sources.

The FIP definition recognizes the diversity of aspects of drug development and thereby the potential distinction between subdisciplines within the pharmaceutical sciences. However, drug development is not the exclusive domain of the pharmaceutical sciences and even less so in the coming decades, as this paper argues.

Our paper also argues that specialists are needed not only from the pharmaceutical sciences, biological sciences, or medical sciences, but also from fields such as engineering, computational sciences, and robotics. We anticipate an area where not only diagnostics and myriad treatment scenarios, including disease interception, might go hand in hand, but also where questions about equal access to these scenarios will be more pertinent on the table than ever before. The scientific and technological possibilities are huge, but whether societies are able to swallow these requires strong leadership and informed and sustainable policies.

Therefore, we close this paper with a call to action. All of the developments described here will happen in some shape or form, but will not lead to better treatments for patients by themselves alone. The paradigm shift we identify should be high on the agenda of policymakers, business leaders, and the research community as a whole. Importantly, we also need to start educating a new generation of researchers today. Only if we create the right environment and optimal incentives for a future generation of scientists to work, thrive, and innovate can we capture the full value for patients of the era of systems therapeutics that is now dawning.

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