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A pharma perspective on the systems medicine and pharmacology of inflammation

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ABSTRACT

Biological systems are complex and comprehend multiple scales of organisation. Hence, holistic approaches are necessary to capture the behaviour of these entities from the molecular and cellular to the whole organism level. This also applies to the understanding and treatment of different diseases. Traditional systems biology has been successful in describing different biological phenomena at the cellular level, but it still lacks of a holistic description of the multi-scale interactions within the body. The importance of the physiological context is of particular interest in inflammation. Regulatory agencies have urged the scientific community to increase the translational power of bio-medical research and it has been recognised that modelling and simulation could be a path to follow. Interestingly, in pharma R&D, modelling and simulation has been employed since a long time ago. Systems pharmacology, and particularly physiologically based pharmacokinetic/pharmacodynamic models, serve as a suitable framework to integrate the available and emerging knowledge at different levels of the drug development process. Systems medicine and pharmacology of inflammation will potentially benefit from this framework in order to better understand inflammatory diseases and to help to transfer the vast knowledge on the molecular and cellular level into a more physiological context. Ultimately, this may lead to reliable predictions of clinical outcomes such as disease progression or treatment efficacy, contributing thereby to a better care of patients.

1. Moving systems biology beyond cellular pathways to impact medical treatment

Biological systems comprehend multiple scales and are sheer complex by nature. After millions of years of adaptation, organisms are inherently robust to internal and external changes thanks to multiple feedback controls, redundancy, modularity and structural stability [1]. Due to this intrinsic robustness, traditional research approaches have difficulties in describing the behaviour of these systems because they tend to reduce complexity too much. In contrast, systems biology claims to integrate knowledge at various levels and to describe a biological system in a comprehensive way. Specifically, systems biology integrates boundary conditions of a biological system, e.g. the physiological context and its modulations that may result in a patho-physiological situation. This is of critical relevance when addressing medical and clinical questions. Nevertheless, systems biology approaches that concentrate on a single level of a biological system, e.g. the molecular level or the cell, thwart the full power of systems biology.

The importance of the physiological context is particularly obvious in inflammation: an originally localised process might get out of control and spreads out, causing systemic responses that – in the worst case – can be fatal. In inflammation, as well as multiple other diseases, a vast knowledge exists at the molecular and cellular level. It has been widely recognised that special efforts are required to bring this comprehensive scientific knowledge from the bench to the bedside [2,3].

2. Pharmaceutical R&D workflow to identify novel compounds

The integration of pharmacological effects on any level into a systems biology approach can be considered as transition into the area of systems pharmacology. It is a challenging task to integrate emerging experimental findings on e.g. a disease, a mode of action, in the course of an R&D project in order to contribute to the sustainability of the R&D process as such [2].

The discovery and development of a new compound is characterised by two major consecutive phases: preclinical and clinical, and there are challenges and opportunities for mathematical

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modelling at multiple steps in both phases [4]. The preclinical phase usually starts with the identification of a suitable target, followed by the identification of a lead compound (often using high-throughput assays), i.e. a (bio-)chemical structure that influences the target in a (thought-to-be) desirable way. This can be for instance blocking or activating the target receptor or enzyme. This lead compound is evaluated and optimised further in different *in vitro* assays and potentially structural modelling support to assess efficacy and toxicity at the subcellular and cellular level. Safety and efficacy of the modified lead compound are investigated in experimental animal models which also supports finding dose–response relationships in an *in vivo* setting. Thus, the capital interest during preclinical development is (a) identifying novel compounds that are potent and selective (and hopefully effective and safe in later stages), (b) discerning dose–response relations and (c) finding a suitable first-dose in man. If a compound succeeds in all of these former steps, it may then transition into the phase of clinical investigation. In clinical phase I, appropriate doses are tested in healthy individuals to establish levels that are not associated with major unwanted side effects. Then, the efficacy of a compound is tested in medium-size group of patients, usually against placebo in phase II and then against a benchmark in a bigger group in phase III. Benchmark refers to the standard therapy at the time of starting the clinical study, e.g. a benchmark drug or a benchmark regimen. Group sizes in clinical phases are carefully planned to achieve statistical significance. If therapy with the test compound is at least non-inferior to the standard therapy at the time, it may be approved by the regulatory agencies and launched to the market. Depending on the indication and the risk-benefit of the drug, rare side effects may only be discovered after approval and market launch during phase IV trials or pharmacovigilance and may lead to warnings and market withdrawal.

The average cost in time and resources in discovery and development of a new drug that reaches the market has been estimated to be ~13 years and ~1.8 billion USD [5]. In addition, in the US, only 10% of the candidate applications of new compounds that enter the clinical phase are finally approved by the FDA [6]. The high failure rate during clinical development indicates the challenge of assessing safety and efficacy in early non-clinical stages of the pipeline to avoid later attrition.

3. Experimental and modelling approaches to pharmacokinetics and pharmacodynamics

At the beginning of new drug life cycle, models of molecular and cellular processes support the identification and evaluation of new drug targets. However, in order to support further developments in pharma R&D, modelling efforts have to be carried out beyond these levels. After the successful identification of a suitable compound with a specific selectivity and potency profile *in vitro*, evaluation continues in a more physiological context addressing both potential efficacy and toxicity to the final therapeutic context. In the course of this, establishing a dose–response relationship is generally broken down into two parts: first, the pharmacokinetics (PK) of a drug, establishing (and understanding) the relationship between a given dose and the resulting drug concentration-time profile in the plasma or at the target site; second, the pharmacodynamics (PD) of the drug, establishing (and understanding) the relationship between a given drug concentration-time profile and the resulting effect. Quantitative descriptive compartmental models, often enriched with nonlinear mixed effect parts, are traditionally used to support the analysis of clinical data. This encompasses derivation of characteristic parameters and rigorous quantification of population variability as well as identification of covariates that describe population variability such as body weight or disease status in particular [7,8]. Quantifying and understanding variability is important in the context of the therapeutic window, plan clinical studies, or stratification of populations and treatments. Physiologically-based pharmacokinetics and pharmacodynamics (PBPK/PD) modelling takes a more mechanistic approach and yields generally more complex compartmental models. As many parameters cannot be identified based on a single set of PK data, independent *a priori* knowledge on physiology such as organ volumes, composition, and blood flow rates is employed to build an individual organism.

In PBPK/PD modelling, parameters describing drug properties and parameters describing the organism are separated which is useful in many respects. For instance, it allows continuous integration emerging data to keep a model well informed (e.g. continuous learning). Also, by adjusting physiological parameters, simulation scenarios can be extrapolated or translated to new settings, e.g. rat versus man, adult versus newborns, or healthy versus diseased. This is generally difficult using descriptive models [9]. Variability in PBPK/PD modelling can be predicted based on known physiological variability. However, the rigorous quantification of variability in a PBPK/PD model given PK/PD data is challenging and computationally demanding, but being worked on [10].

Despite early works in PBPK/PD mainly addressed the PK of a compound from a mechanistic perspective, these models rather left the PD in the empirical side. Systems pharmacology is now developing towards integration of mechanistic PD models to support translational research [11–13]. Overall, this approach can support rational decision-making in diverse stages of the pharmaceutical R&D pipeline: to further qualify targets or lead compounds along with *in vitro* characterisation, to simulate the PK/PD of a compound in animals, to optimise the first-in-man dose, to simulate drug–drug interactions or PK/PD of drugs in special populations or to plan the design of clinical trials [14,15].

4. Systems pharmacology of inflammation

An inflammatory response comprehends a myriad of intertwined events at different levels of resolution – from molecules to the whole organism – and this should be reflected by a systems pharmacology model. Accordingly, systems pharmacology models of inflammation need to integrate different stages of inflammation together with the PK and PD of relevant drugs (Fig. 1). However, the degree of mechanistic detail at each level that is mandatory for an adequate description depends on the data available and the questions addressed.

Several research groups are aiming towards such an integrated understanding and, for example, develop PK models of anti-inflammatory compounds combined with signalling pathways at the intracellular level leading thus to PK/PD models with high mechanistic detail. For instance, Foteinou and co-workers [16] nested a simplification of Hoffman's NF-kB regulation model [17] into a more complex model that also included lipopolysaccharide (LPS) inflammatory signalling influenced by a coupled PK model of corticosteroids to simulate treatment. Dwivedi et al. [18] evaluated different therapies in Crohn's disease by coupling antibody PK models to interleukin-6 signalling pathways. These models were tested in a variety of scenarios simulating the systemic response using different doses, treatment regimens and under different initial conditions. Results provided novel insights into improved interventions by considering alternative doses, a different time window of intervention, a combination of therapies, or even novel therapeutic targets. Other researchers have applied systems pharmacology approaches to describe the adverse effects that may arise in anti-inflammatory therapy. Fang and collaborators [19] combined a bottom-up mechanistic PD model into a