Enabling personalized cancer medicine decisions: The challenging pharmacological approach of PBPK models for nanomedicine and pharmacogenomics (Review)

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Abstract. The existing tumor heterogeneity and the complexity of cancer cell biology critically demand powerful translational tools with which to support interdisciplinary efforts aiming to advance personalized cancer medicine decisions in drug development and clinical practice. The development of physiologically based pharmacokinetic (PBPK) models to predict the effects of drugs in the body facilitates the clinical translation of genomic knowledge and the implementation of *in vivo* pharmacology experience with pharmacogenomics. Such a direction unequivocally empowers our capacity to also make personalized drug dosage scheme decisions for drugs, including molecularly targeted agents and innovative nanoformulations, i.e. in establishing pharmacotyping in prescription. In this way, the applicability of PBPK models to guide individualized cancer therapeutic decisions of broad clinical utility in nanomedicine in real-time and in a cost-affordable manner will be discussed. The latter will be presented by emphasizing the need for combined efforts within the scientific borderlines of genomics with nanotechnology to ensure major benefits and productivity for nanomedicine and personalized medicine interventions.

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1. Introduction

Currently, the development of powerful and smart high-throughput tools in translational medicine along with nanotechnological applications enabling information-based medicine have revived the hope for the broader application of pharmacogenomics (PGx) for most, if not all, individual patients (see Table I for term definition) (1-10). By extending such a notion from PGx to routine healthcare and drug prescription (Rx), it means that this transition is better served by achieving pharmacotyping (PTx) in drug delivery (6,8,9). Further support is gained through expanding the clinical application of innovative approaches and technicalities happening in the era of: i) genomic profiling; ii) biomedical imaging; iii) synthetic, biology-based, cell engineering to advance drug delivery entities; iv) population-based modeling as predictive tools of pharmacokinetic (PK) parameters of drugs (absorption, distribution, metabolism and excretion; ADME) and v) innovative approaches and tools on patient electronic data

Table I. Definition of terms.

CYP genetic variation refers to various genetic polymorphisms existing in cytochrome P450 (CYP) drug metabolizing enzymes that contribute to altered PK behavior due to dysfunction of drug metabolism and thus to limited drug therapy outcomes.

Personalized medicine joins the gap between the clinical setting and various health-related basic disciplines with genomics in a way to increase precision of prognosis, diagnosis, and therapy outcomes of individuals in an affordable way. The latter implies in real-time the stratification of patients suffering the same complex illness (e.g., cancer, cardiovascular disorders), thus referring to the clinical translation of genomic knowledge into practical clinical utility for disease risk assessment, diagnostic profiles, therapeutic delivery and new drug development approaches.

Pharmacogenomics (PGx) bridges the gap between pharmacology and genomics toward unveiling the pharmacological response heterogeneity, providing the promise of the clinical implementation of molecular knowledge into the pharmacokinetic/ pharmacodynamic (PK/PD) level as well as moving drug prescription to pharmacotyping (e.g. the individualized drug selection dosage schemes based on specific patient clinical characteristics and genetic make-up).

Pharmacotyping (PTx) applies to drug prescription (Rx) and describes the process where the physician's selection of specific drugs and their dosage schemes is also based on each individual patient's genetic make-up.

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management, clinical support and routine healthcare. These scientific breakthroughs empower the speed and the productivity in developing innovative molecularly targeted drugs and nanotheranostics with improved clinical safety and efficacy profiles (11-20). The latter coincides with the movement from an Rx process mainly based on the physician's own experience into a more highly digitized and integrated workflow platform to aid the administration of individualized drug dosage schemes for personalized medicine.

As a matter of fact, the interdisciplinary infrastructure and methodologies needed to broadly enable PTx in the clinical setting is depicted in Fig. 1 (for a more extensive overview see Ref. 7). In particular, such a diagrammatic presentation exemplifies the environment to maximize outcomes and achieve improved efficacy and safety profiles of clinical practical utility for personalized medicine decisions. That means that the proper translational capacity for all the involved disciplines and technologies has to be clinically validated in terms of precise clinical diagnosis and drug prescription dosage scheme selection by healthcare practitioners. The latter refers to advancements such as: i) the 'omics'-related for molecular diagnostics and PGx; ii) the computerized/information-based platforms in data and text mining for bioinformatics and biostatistics; and iii) the PK/pharmacodynamic (PK/PD) guidelines for pharmacovigilance, molecular and clinical pharmacology. By enabling this direction, the establishment of PTx in drug prescription is served. Last, but not least, the integration of nanotechnology, imaging technologies and advanced cell therapies impacting nanomedicine applications are also better facilitated and implemented in the clinical setting, as shown in Fig. 1.

Following such a roadmap in Rx it must also be considered that the inter-individual response heterogeneity (patient phenotype) noted in clinical pharmacology and the incidence of adverse drug reactions (ADRs) are related to various factors and parameters affecting the risk/benefit therapeutic ratio that refer to: i) the molecular pathophysiology of diseases as well as their severity; ii) the co-administration of medicines that might result in drug interactions; iii) any existed co-morbidities; iv) the functional status of vital organs, i.e. liver and kidneys contributing to PK behavior of drugs; v) the age of the individual patient; vi) the person's lifestyle, i.e. smoking, caffeine intake; vii) the patient's compliance (adherence) to the physician's guidance to prescribed therapy; and also viii) the personal genetic make-up, or alternatively, the existing human genome variability in genes involved in PK/PD processes ensuring drug effects in the body; i.e. the genetic polymorphism of various gene alleles referring to drug metabolizing enzymes, transporters and receptors (21-32). Simultaneously, the successful address of such PK/PD issues represents the gold-standard target upon developing drug nanodelivery vehicles.

2. The economic burden and cost-effectiveness of PGx to enable personalized cancer medicine decisions

It has been estimated that drug response heterogeneity for marketed drugs significantly contributes to the increase of healthcare costs, the rate of in-patient hospitalization and mortality index (33-37). Although there is a widespread interest in personalized medicine, the broad application of PGx testing implies that the validation of the clinical improvement outcome must be clearly demonstrated in a cost-effective manner. Undoubtedly, however, only a limited number of studies have addressed cost-effectiveness issues of PGx applications in the clinical setting (38-41). To this end, recent studies assessing the pharmacoeconomic benefits of thiopurine methyltransferase (TPMT) PGx testing have shown a favorable cost-effectiveness ratio, by analyzing either the outcome achieved in children suffering from acute lymphoblastic leukemia (ALL), or relevant pharmacovigilance data referring to the emergence of ADRs (39,41). On the contrary, the lack of standardized PGx economic models has undoubtedly emerged in the case of CYP genetic variation, by trying to evaluate the economic burden vs. the clinical benefits of PGx testing upon prescribing antipsychotics in routine healthcare (38). In addition, the complexity in undertaking a trial-based evaluation of the cost-effectiveness of PGx tests such as the application of TPMT for prescribing azathioprine in patients suffering autoimmune diseases has recently been shown (40). Moreover,
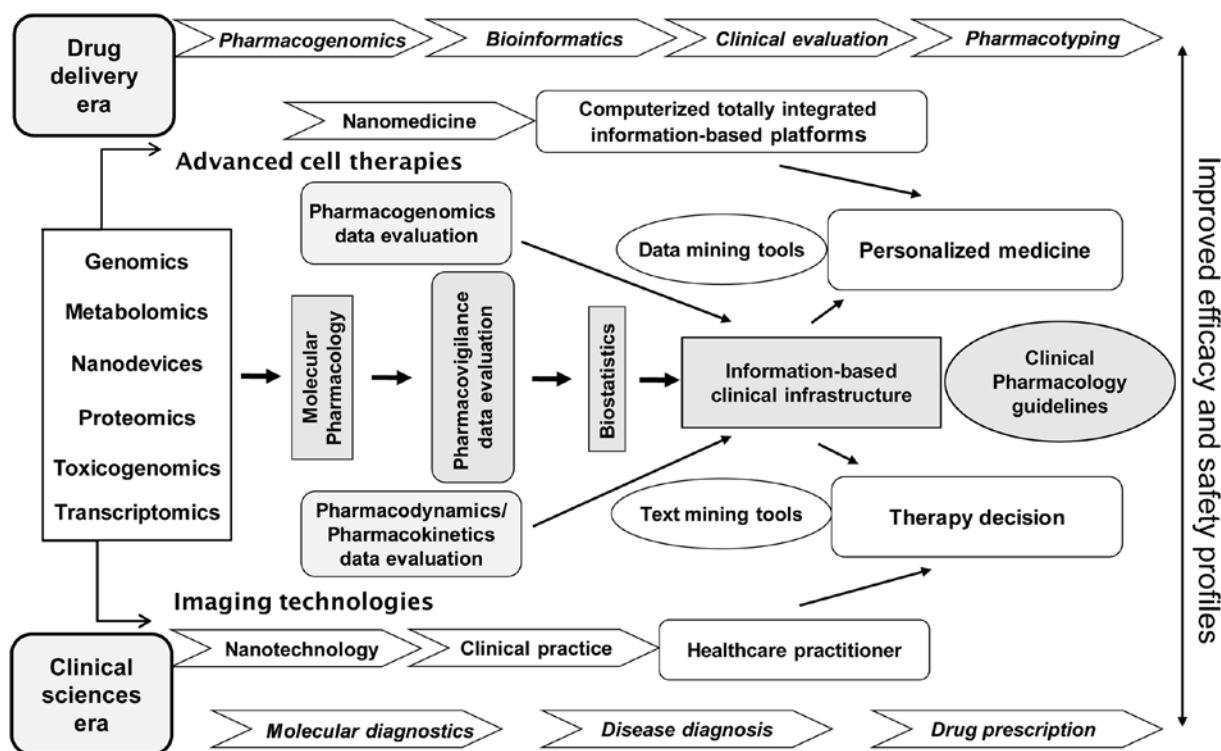
Figure 1. Depiction of scientific efforts and methodologies contributing to personalized medicine decisions toward advancing broader drug prescription profiles (see text for details).

the economic evaluation of PGx testing is now considered a main barrier hindering the implementation of clinical practice with PGx knowledge. Importantly, before moving toward the routine application of PGx concepts in the healthcare system and establishing PTx, the clear demonstration of the economic benefits gained must be addressed to accompany the already assured clinical benefits of any PGx testing. Such a direction will allow cost-effectiveness analysis to document the relative cost/benefit ratios of PGx interventions compared to current clinical practices and create the framework for healthcare providers to make reimbursement decisions. Importantly, the limited evidence accumulated thus far in analyzing the economic value of personalized medicine tests also restricts any proper informed decision-making and assessment of genomic priorities (42). Complementary, in order to advance practical clinical utility of personalized medicine decisions, the cost-effectiveness in addition to the clinical effectiveness of PGx tests for decision makers should simultaneously be undertaken in a robust and timely manner (43).

3. Development of PBPK models and advanced *ex vivo* pharmacological assays to support PTx and implement clinical pharmacology guidelines

The PK and PD behavior of drugs is known to be affected by either drug interactions or genetic polymorphism of genes involved in drug actions, thus leading to altered plasma therapeutic concentrations (inefficiency or toxicity) and also to modulated receptor affinity (sensitivity) (8,9). The future application of physiologically based pharmacokinetic (PBPK) models to shape the practical utility of personalized/stratified

medicine and ensure PTx is shown in Fig. 2. Indeed, the accuracy and predictability potential of the applied methodologies and model approaches for assessing the drug plasma concentration-time profile and clearance in humans has been recently verified (44,45). This, however, implies the development of algorithms to improve the statistical power and robustness upon mathematical integration and PBPK modeling of drug effects by facilitating the clinical exploitation and inference of genome-wide association studies and PGx tests (46-48). In contrast, PGx knowledge for drugs is now considered an integral part of therapeutics and drug development, since a number of predictive PGx biomarkers to assess the safety and clinical efficacy profiles of individual marketed drugs have been validated by drug regulatory agencies (e.g. the FDA and EMA) (32,49). To this end, the development of PBPK models, implemented together with system pharmacology approaches (assessing predictive PGx biomarkers), represents a promising platform where in real-time the assessment of both patient- and drug-related factors can be inter-correlated for individual patient populations. Alternatively, the latter means the elaboration of a multidisciplinary environment in order to assess both drug interactions and PGx data to be effectively incorporated to guide Rx, thus achieving PTx.

The need to empower the predictive capacity of *ex vivo/in silico* pharmacological assays, particularly for complex and multifactorial diseases (e.g. cancer) to advance translational medicine capacity, still represents an unmet need upon new drug development efforts. The demand for obtaining improved productivity outcomes in the preclinical phase is further stressed by analyzing data from specialized sources referring to registered medicines under development and in
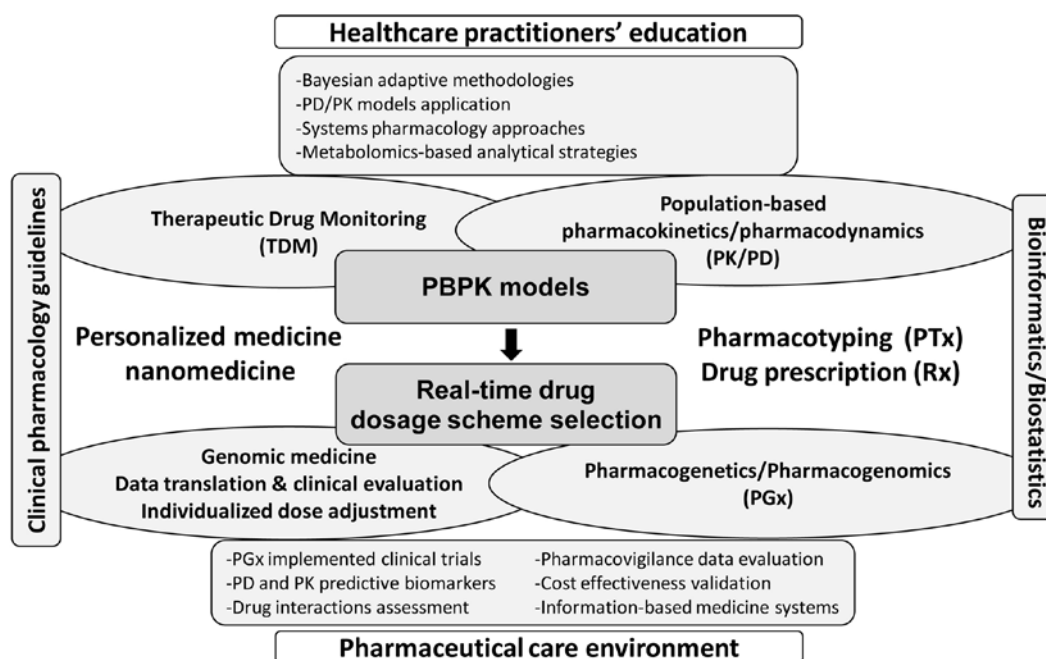
Figure 2. A scheme of pharmacotyping in the drug prescription process is depicted within the context of personalized medicine and nanomedicine. Specific research and/or clinically-oriented methodologies are presented with focus on PBPK modeling to allow real-time drug dosage-scheme selection toward achieving personalized medicine broader utility decisions in drug delivery and therapeutics (see text for details).

clinical trials (50,51). However for example, by considering the era of innovative anticancer therapeutics, a major question then is raised amenable to further analysis pending on how to better succeed in this task? At first, the development of predictive biomarkers applied as companion diagnostics of molecularly targeted anticancer drugs to achieve personalized treatment currently represents an established practice toward assessing tumor genetic make-up variability. Secondly and in contrast, it is a well-established notion in clinical practice that pharmacological response variability is also attributed to various drug-, patient- and/or environmental-related factors (8). The former has been successful to date in clinical practice through mainly *in vivo* pharmacology advancements and the latter through PK developments. By taking both such notions into consideration, it is clear that in achieving a broadly successful personalized cancer therapy option, both tumor cell and genome variability as well as individualized drug dosage scheme delivery (e.g. PTx) have to be inter-correlated and simultaneously applied in routine clinical practice (8,9,32). In addition, importantly, the potential to accelerate such innovative anticancer therapeutic developments, in a way to match the personalized cancer therapy needs and expectations in clinical practice, will require specific collaborative attempts between academia, industry, and regulatory agencies (19,52). In other words, the previously gained experience from both *in vivo* pharmacology experimentation and therapeutic drug monitoring methodology both in research and clinical practice have to be implemented with suitably designed, validated and developed molecular diagnostics to elucidate the missing links in knowledge for personalized medicine decisions. To this end, pharmacologists must positively work to advance broader practical utility decisions by directing and guiding the establishment of a research-based, regulatory-oriented

and clinically-focused personalized medicine environment for various pharmacological classes of therapeutics and illnesses (8,9,32). To this end, if the successful development of quantitative PGx models for translation medicine is achieved, than the genetically-guided drug dose adjustment can be best utilized to improve drug development and routine clinical practice outcomes (52-54). In fulfilling this task of practical clinical utility, the inter-convergence of genomic with clinical information can occur and bring together clinicians and scientists of basic sciences, thus accelerating the pace of PTx in Rx.

By taking into consideration the deficit in scientific knowledge, the approach to accelerate the development of more powerful innovative anticancer therapeutics is by discovering methods by which to improve early clinical anticancer drug evaluation through structured and rational trial designs that incorporate predictive PK, PD, PGx and intermediate end-point biomarkers (51). In addition, it is also crucial to discover ways to enrich methodologies facilitating the integration of PGx into know-how strategy of the mainstay drug development pipeline (55). The latter implies that the suitable organization and application of population-based PK/PD *ex vivo* pharmacology modeling is also vital to support the integration of genomic knowledge in routine clinical practice and Rx by hastening the movement toward personalized medicine (56). Moreover, it is evident from the previously gained *in vivo* pharmacology experience in drug development that the efficient clinical translation of genomic knowledge coincides with successfully addressing the issues related to the adjustment of clinical pharmacology guidelines toward personalized medicine concepts. Alternatively, the implementation of clinical pharmacology guidelines with PGx knowledge through the development of advanced PBPK models represents one of the most crucial

Table II. Application of PBPK models in selected nanomedicine studies.

Nanoformulation	PBPK model application	Ref.
Silver nanoparticles	Mouse whole-body PBPK model	(93)
PLGA nanoparticles	Mouse semi-mechanistic PBPK model	(158)
Nano-TiO$_2$ particles	Human whole-body PBPK model	(94)
Aluminum nanoparticles	*In vitro-in vivo* extrapolation (IVIVE) PBPK model in a population of rat alveolar macrophages	(159)
Quantum dots	Mouse whole-body PBPK model	(160)
[99m]Tc-labeled nanoparticles	Human whole-body PBPK model	(161)
Silver nanoparticles	Rat whole-body PBPK model	(162)
Gold-dendrimer composite nanodevices	Mouse whole-body PBPK model	(163)
Nanocarrier-mediated delivery of various drugs	Semi-mechanistic PBPK model of hepatocellular carcinoma (HCC) tumor cells	(164)
PEG-coated PAA nanoparticles	Rat whole-body PBPK model	(165)
Metal nanoparticles	Rat-whole body PBPK model	(166)
Gold nanoparticles	*In vitro* and *in silico* methods for assessing the pulmonary translocation and biodistribution of NPs towards replacement of *in vivo* studies	(167)
PEG-Gold nanoparticles	Mouse membrane-limited whole-body PBPK model	(168)
Silver nanoparticles of different sizes	Rat-PBPK model of 2 and 5 compartments	(162)

PBPK, physiologically based pharmacokinetics.

elements for enabling the practical utility of personalized medicine and applying PTx concepts for drug delivery worldwide (8,9). This direction also necessitates overcoming barriers hindering efficient clinical translation and implementation of PGx knowledge from bench to bedside. To this end, it is notable that PGx guidelines for dose recommendation schemes of specific pharmacological drug classes have already been initiated and proposed (57-62). To foster the applicability and practical utility of these methodologies through the use of PBPK/PGx models, the assessment of any ethical, social and cost-benefit impacts should also be addressed before the transfer of techniques used in genomic-related research laboratories to diagnostic laboratories (8,9,32,54). Subsequently, the modeling of the tumor microenvironment will be outlined to further stress the usefulness of the application of PBPKs in the era of nanomedicine and personalized medicine.

4. Model-based approaches for enabling the development of cancer-targeted delivery of nanomedicines by simulating tumor microenvironment heterogeneity

One of the most challenging issues in pharmacology and therapeutics relates to the capacity of predicting the PK profile of any administered drug to individual patients and thus to estimate the cellular concentrations reached at the site of action referring either to the diseased organ, or tissue in order to be within the therapeutic ratio range. This prediction of the behavior of drugs plays fundamental and crucial roles in the development of stratified and personalized treatment decisions. Indeed, the latter offers opportunities for pharmacologists and clinicians to generate models and test different scenarios of the effects of drugs on the lesion (organ or tissue) by taking

into consideration all the variants, including different genomic backgrounds that eventually might contribute to variation in the pharmacological response and clinical phenotype. Particularly for cancer therapy, tumor microenvironment heterogeneity represents a main obstacle hindering the development of innovative anticancer therapeutics and also limiting the clinical outcomes achieved thus far (19,63,64). Particularly for solid tumors, the role of the lesion microenvironment, blood flow, vessel leakage, oxygen supply, size, specific gene expression and growth rate have been found to play an important role in therapeutic outcomes since they are related with drug delivery (i.e. PK) and consequently with pharmacological action (i.e. PD) (65-68). Despite the fact that chemotherapy dosage schemes in oncology always take into consideration various patient characteristics (i.e. body weight), the applied therapeutic protocols and scaling of the dose are based on nomograms and the optimum fitting of the patient to them instead of considering additional tumor characteristics. Although limited attempts to apply PBPK models for nanoformulations have to date been made (see Table II), the dynamics of such a methodology and the way by which specific factors crucial for the PK profile of nanomedicines could be quantified in models have recently been presented (69,70). Alternatively, the recent advancements in translation medicine, nanomedicine and personal genome sequencing permit the implementation of cancer genome testing into the clinical setting, a fact with major opportunities for personalized therapeutic decisions in oncology; i.e. precision cancer medicine to overcome therapy obstacles and ameliorate the negative outcome that oncologists face in their practice (71-74). Moving forward, the genuine application of PBPK modeling in such an innovative cancer therapy era could help to elucidate tumor heterogeneity properties and

predict drug behavior through simulation of individual patient tumor characteristics and drug properties. A better understanding of the microenvironment complexity, phenotypic diversity and genetic heterogeneity of tumors through PBPK modeling may lead to the development of early approaches in the drug discovery process that will minimize the attrition rate and increase the productivity outcome for novel anticancer therapeutics. An example of personalized cancer therapy is application of tamoxifen for estrogen receptor-positive breast cancer patients (75,76). Tamoxifen is a pro-drug that undergoes extensive hepatic and gut wall metabolism thus forming metabolites with different response effects (77). Moreover, CYP2D6 function and genetic polymorphism has been proven to be the rate-limiting step upon the formation of its main active metabolite 4-hydroxy-N-desmethyltamoxifen (endoxifen). As a consequence, CYP2D6 PGx knowledge allows the prediction of the individual patient pharmacological response and hence the clinical outcome of tamoxifen-treated breast cancer women (75,77,78). In parallel, the clinical impact of drug-drug interactions with concomitant use of selective serotonin reuptake inhibitors such as paroxetine, a strong CYP2D6 inhibitor, has also been described (79,80). Such clinical PGx knowledge has been applied in tamoxifen-based PBPK approaches in order to provide a more precise clinical understanding of any required *in vitro-in vivo* extrapolation regarding a drug's PK profile evaluation (81). Consequently, tamoxifen-based PBPK modeling provides the opportunity for infrastructure creation for assessing whether potential co-administration of endoxifen with tamoxifen could successfully address genetic variability chemotherapy issues and achieve a sustained pharmacodynamic profile in treated breast cancer patients (82). At the same time, this knowledge appears to stimulate the design of multiscale mechanistic PK/PD model-based approaches for individualizing the therapeutic dosage schemes for tamoxifen and other anticancer drugs, such as temozolamide for glioblastoma, thus introducing a new era for modern PTx in cancer therapeutics (83,84). The latter obviously may also help to apply the predictive capacity of cancer chemotherapy-based PBPK models in nanomedicine development to achieve optimum nanoformulation concentration profiles needed in tumor-targeted cells. In contrast, scientific interdisciplinary efforts in the era of nanomedicine hold promise to seize the opportunity to apply novel model-based approaches and enhance the capability for designing and analyzing the properties and the pharmacological effects of cancer therapeutic nanoformulations (82,85). Indicatively, there is on-going research on nanoparticles loaded with tamoxifen for the development of nanoformulations with improved PK profiles and tumor-targeted delivery, thus attempting to overcome the PK/PD and PGx issues negatively impacting the clinical outcome, as mentioned above (86,87). Furthermore, in order for the broad exploitation of such innovative approaches, nanoformulations of anticancer drugs such as paclitaxel, docetaxel, cisplatin and doxorubicin are in development and under clinical evaluation (88-91).

In addition to drug-improved profiles and clinical research, recently published model-based PK studies describe the impact of the physicochemical properties of nanoformulations and theranostics on their *in vivo* kinetic profile as delivery systems and/or therapeutic molecules in tumors (69,92). The

combination of the above observations already positively affects the development of novel nanomedicines where their construction, size and physical properties contribute to their targeted delivery to the lesion site. Moreover, it is indicative of the future perspectives presented for the era of nanotechnology and the adoption of all possible data and parameters (model-based, biological, pharmacological and technological) in order to develop nanoformulations with desired PK/PD properties to ensure maximum clinical outcome for most, if not all, patients. To this respect, PBPK modeling represents for complex and multifactorial diseases, such as cancer, an essential and fruitful tool with which to advance future research regarding the disposition of nanoformulations at the site of their action in the body (70,93,94). This needed collaboration from various scientific disciplines of pharmacology, *in silico* modeling and pharmaceutical nanotechnology shows a tremendous potential for designing sophisticated and clinically effective and safe nanomedicines with either diagnostic and/or therapeutic modality (95-98). Importantly, the usefulness of such nanomedicine-focused PBPK models could directly be exploited for specific cancer (or other disease-related) patient groups such as the pediatric population to help solve issues of pediatric drug development and administration dosage scheme protocols (99). In addition, moving forward, a similar beneficial approach could eventually occur to impact the area of protein cancer therapeutics and relevant formulations, since the peculiar characteristics of this type of drug and their behavior in the body, clearly requires a suitable simulation design and the predictive capacity of more complex PBPK models (i.e. including immune system) to enhance productivity, drug behavior profiles and clinical outcomes (100-102).

5. Moving toward the implementation of PBPK models in nanomedicines: The case of tumor modeling and cancer therapy

Undoubtedly, the early applicability of PBPK models for the development of small-molecule drug entities has advanced the predictive capability of their subsequent PK/PD effect profiles which has eventually enhanced the productivity outcomes within the new drug development era (103). Currently, however, PBPK modeling extends toward covering the administration of therapeutic proteins based on the continuously increasing number of biopharmaceuticals reaching the market (102,104,105). From the mechanistic perspective, modeling and simulation of PBPK are implemented by the central idea that the drug molecules of interest (small chemicals or proteins) are subject to PK processes within the body described by distribution, metabolism and elimination routes in addition to the absorption mechanisms applied for small chemicals. By considering that these PK processes could be described mathematically, a number of differential equations have been applied to mechanistically express the underlying biological phenomena in a way that all body organs are linked through blood circulation. The suitable clinical validation of this approach then creates a framework where knowledge of clinical utility is generated from data covering *in silico*, *in vitro* and/or *in vivo* methodologies and experimentation upon new drug development. The main challenge still refers to the need for mutual understanding of

both mathematics and biology from the users in order to avoid developing models which could be unrealistic or provide false results (106-108). Importantly in the case of nanomedicines, PBPK approaches are considered more complex based on the characteristics of the nanoparticles that make them different from small-molecule drugs and therapeutic proteins, since their PK profile is controlled by more multifaceted and interrelated relationships between the nanosystem and body physiology (109,110). Nanostructured vehicles are designed either as solid nanoparticles consisting of polymers or inorganic materials or as liquid-based formulations that could be described as nanoemulsions. Such nanosystems are then loaded with small chemical drug molecules, therapeutic proteins, imaging probes or other relevant compounds (small RNA molecules, e.g. siRNAs/miRNAs) to cover a wide-range of medical uses from imaging to therapeutic applications (70,111-115). One of the driving forces for developing nanosystems for drug targeted delivery relies on their drug-loaded capacity for improved *in vivo* PK/PD profiles due to advanced metabolic stability and membrane permeability that could lead to improved bioavailability (for *per os* administration) and also to a prolonged pharmacological effect at the site of action with limited toxicity (116-118). Although these pharmacological advantages have intrigued the research on developing nanomedicines they also obstruct the straightforward application of PBPK approaches as they are applied today. This is due to several reasons which are also attributed to the characteristics of nanomedicines in order to obtain the above features of improved PK profiles. For example, it is easily conceivable that for the various systems of nanomedicines (i.e. dendrimers, nanocrystals, emulsions, liposomes, solid lipid nanoparticles, micelles and polymeric nanoparticles) different PBPK considerations should be implemented, since they represent different drug-release systems. The latter also adds more complexity to the models, since for each one a different mechanism of drug release exists depending on the administration route - i.e. absorption through gut for *per os* delivery, release in the blood stream for intravenous infusion, or even release on the site of action for targeted administration. For example, in the typical setting of the PBPK approach, the controlled or sustained drug release systems are related with mechanisms of gut absorption (transporters, enzymes) or of other routes (i.e. skin, lungs) in order to predict the concentration of the drug that reaches the blood circulation which thereafter is used to further estimate the tissue concentrations, the PD profile on the site of action, and the elimination profiles (119-121). In contrast to nanomedicines, which act as drug nano-carriers, the controlled release often appears to be in the blood stream or in the site of action (i.e. tumor lesion, microenvironment) (122-126). These mechanisms add more complexity to the systems since additional parameters are involved, such as the mechanism of the release from the nanocarrier and the permeability into the site of action for each specific diseased tissue targeted, but also the drug's characteristic distribution such as solubility in plasma, plasma to tissue ratio and fraction of binding into tissue. In addition, the nanoparticle concentrations in systemic circulation and/or in the organ locally should be linked with drug release profiles related to either top-down or bottom-up PBPK models. The latter presents added complexity toward

validation due to the difficulty to collect *in vivo* and clinical data for nanomedicines that act as carriers for targeted drug release. Taking into consideration the recent advancements in PGx approaches, then the use of PBPK modeling for nanomedicines also requires suitable adjustment to address drug-specific genetic PK/PD information. For example, issues that need to be addressed include the impact of polymorphisms of phase I and II drug metabolizing enzymes on the controlled/sustained release over time of the drug from its nano-carrier into the systemic concentration (implying changes in the rate of the enzymatic reaction), since it is unclear whether it remains the same or even similar as for cases with classical sustained release systems for prolonged absorption (120,127).

Based on the molecular knowledge accumulated thus far for epithelial-mesenchymal transition (EMT) and the known histological architecture of the tumor cells within the tissue, one can consider to build such a core PBPK model by suitably developing algorithms that incorporate parameters referring also to the metastatic behavior of malignant cells such as: i) cell adhesion molecule levels (e.g. for adherent junctions E-cadherin, for focal adhesion junctions integrin β1, and for desmosomal junctions desmoglein-3); ii) the neovascularization extent (angiogenesis level) and the computationally depicted histological structure in the tumor area that could also contain measurable additional molecular markers involved in these processes [e.g. expression levels of vascular endothelial growth factor (VEGF), αvβ3 integrin]. The clinical validation of any relevant adhesion molecule specification as metastatic biomarker, however, is needed for each tumor type, as recently shown in the case of oral squamous cell carcinoma (128). Finally, taking into consideration the known histological, genomic and cellular heterogeneity that exists within the tumor in various organs, one can further add information to specific components depending on the desired target diseased tissue (63). All the above parameters could contribute to the design of additional compartments (representing primary and metastatic tumor sites) although, to date, there are no published data available combining PBPK and metastatic tumors despite the fact that clinical trials are already executed for metastatic tumors and nanoparticles based on the preclinical data available (129).

Furthermore, much work exists for tumor growth modeling (usually for xerographs) and how they can possibly be coupled with PBPK approaches regarding the estimation of chemotherapy concentrations in tumor compartments and the improved adjustment of dosing regimen (83,130-132). Moreover, in addition to xenograft-based models, there is much effort toward the development of multi-scale *in silico* models aimed at the improved comprehension of tumor growth and the underlying mechanisms that lead to diverse outcomes of tumor lesions (133-141). Although both approaches sometimes require a tedious and time-consuming process due to the required individual extrapolation of data and validation of various factors contributing to cancer pathophysiology, diversity and modeling, they show encouraging results towards improved, personalized or stratified approaches to cancer treatment particularly for novel chemotherapeutic drug delivery schemes. The application of nanomedicines to prevent cancer metastasis provides new opportunities toward the development of improved therapies (142-146). It must also

be emphasized that these approaches could be implemented at two levels of personalized approaches. The first level could be the stratification of patients based on primary and metastatic tumor regions and the second one the individual dosage regiments as proposed by *in silico* clinical trial models based on PBPK approaches. In addition, by successfully generating a metastatic behavior-based PBPK model, its application to assess the PK/PD profile of novel therapeutics very early in the drug developmental process may lead to improved productivity of drug candidate products with enhanced efficacy and clinical safety profiles, particularly in the more complex cases of metastatic tumors.

From the above mentioned, more focused efforts are needed toward establishing the optimum PK/PD correlations regarding the nanosystem physicochemical properties, the biological environment and the underlying molecular markers for balancing benefit-to-risk ratio in the preclinical/clinical development process. Drug-release kinetics either in systemic circulation or in the local diseased-tissue microenvironment (e.g. pulsatile vs. continuous release) is a crucial factor affecting the efficacy of nanomedicines and their safety behavior. It is thus urgent that a more thorough understanding of human physiology and pathophysiology and the interactions of biological systems with therapeutics be achieved. The latter implies a direction where the enhancement of pharmacological translational efficiency is facilitated through exploitation of the underlying developmental biology dynamics, the cellular diversity and the genomic heterogeneity for individual patients and for most illnesses. To successfully move on, the nanosystem formulation platforms, the pharmacological and preclinical assessment methodologies as well as the clinical development design must comply with such interdisciplinary research scheme requirements to readily overcome various obstructing parameters from bench to the clinic. Recently published work for cancer nanosystem platform methodologies and PBPK modeling add new insights to such a direction. In one study, the polymeric nanoparticle design platform was based on a combinatorial nature of simultaneously assessing their physicochemical diversity (size, surface hydrophilicity, targeting ligand density, drug loading and drug release) with the best clinical performance profiling for PK, biodistribution and efficacy upon encapsulation with chemotherapeutic agents (129). Importantly, the designed docetaxel-loaded polymeric nanoparticles targeted to the prostate-specific surface antigen exhibited similar PK, biodistribution, and safety profiles in three animal species (mice, rats and monkeys). In particular, their PK characteristics achieved much higher plasma concentrations of docetaxel for an extended duration that coincided with prolonged circulation in the vasculature and controlled release pattern in the body. To this end, docetaxel-loaded polymeric nanoparticles have been tested in humans with promising results confirming the previous data observed in animal species, whereas a phase II clinical trial is now running to evaluate their PK/PD behavior in patients with advanced metastatic prostate cancer (ClinicalTrials.gov Identifier: NCT01812746). In another similar study using the bisphosphonate ligand alendronate to target bone cancer lesions, the successful formulation of targeted polymeric nanoparticles for the controlled delivery of bortezomib to diminish off-target effects and increase

tumor cell concentration was achieved (147). Bortezomib, a proteasome inhibitor, is clinically used for the therapy of multiple myeloma, a cancer primarily originating in bone marrow resulting in osteolytic lesions. Again, these bone microenvironment-targeted polymeric nanoparticles loaded with bortezomib have shown a favored PK/PD profile in terms of high retention, accumulation and bone homing capacity as well as enhanced survival and decreased tumor burden in mouse models of multiple myeloma. In a third study, the development of a PK model to quantify the effect of vascular physiology and permeability in individual patients for cancer nanotherapeutics was conducted (69). Notably, the specific particle size range of cancer nanosystems and the timed drug release profile were found to be crucial predictive rate-limiting formulation factors in order for the benefit-to-risk ratio to be maximized and clinically validated. The latter was correlated with the enhanced permeability and retention effect, attributed to the tumor microenvironment vascular pore size along with that exhibited for normal tissues, meaning that both normal physiology and pathophysiology of the vasculature contributed to the PK/PD cancer nanotherapeutic behavior. Unanimously, these results present evidence that the exploitation of PBPK modeling early in the development of cancer therapy nanomedicine represents the required solid ground and suitable framework for increasing the productivity later on in clinical phases and ensuring better efficacy and safety profiles for the respective marketed nanotherapeutics.

Based on the above, a proposed tumor-focused PBPK model for nanomedicines (PBPK-NM) is presented in Fig. 3. This vital need for successfully addressing the different PK behaviors of nanoparticles and thus nanomedicines in the body compared to that of their small-molecule drug counterparts, has already led the FDA to initiate projects such as 'PBPK Modeling of Nanomedicine' in order to apply computational modeling approaches to assess the safety of nano-scale materials. In particular, liposomal doxorubicin (Doxil), the first nanomedicine that entered the market and is used in the clinic for various solid tumors (ovarian cancer and myeloma) has been selected. The project launched in November 2014 is currently at the half of the road stage and it is expected to be concluded at the end of 2015 aimed at the development of computational approaches to be utilized to monitor Doxil in the blood and in different sites of the body (http://www.accessdata.fda.gov/FDATrack/track-proj?program=nctr&id=NCTR-OSC-PM-PBPK-Modeling-of-Nanomedicine).

6. Future perspectives in advancing PBPK models to ensure practical clinical utility of cancer therapeutic interventions and PTx

The predictive capacity of PBPK models allows them to also be successfully applied in assessing impacts on dose and particle size as well as on the *in vivo* performance of nano-formulations, either for medicines under development or for marketed drugs (148). However, fundamental issues exist that are hampering the advancement of personalized medicine and that highlight the lack of emerging predictive tools that could serve as a decision support mechanism for physicians to personalize treatment (149,150). Particularly, this seems even more difficult for drug delivery by attempting to unify knowl-
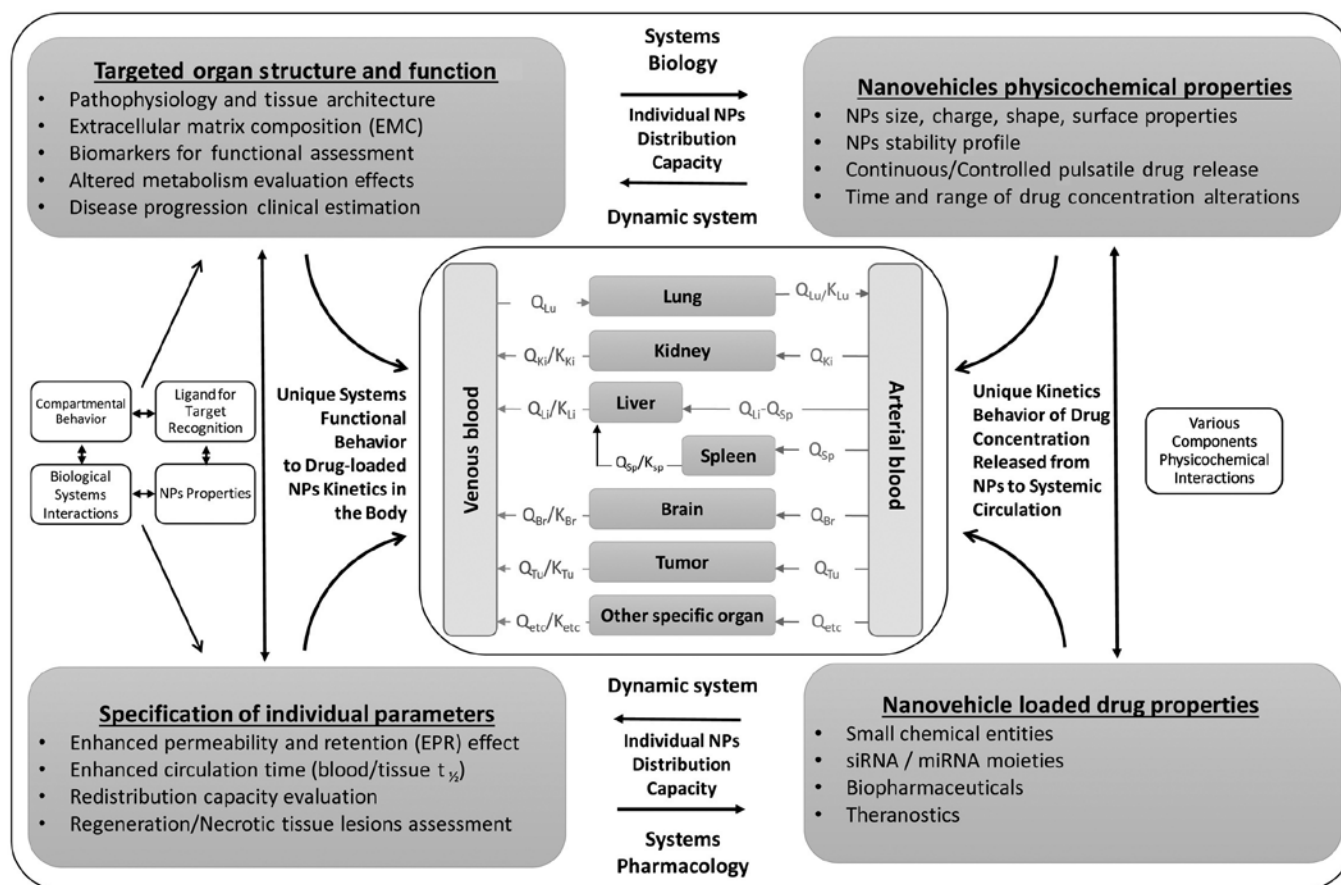
Figure 3. Diagrammatic illustration of a proposed population-based pharmacokinetic model for nanomedicines (PBPK-NM). The depiction of the complex and dynamic interactions between nanovehicle physicochemical behavior, loaded drug properties and specific architecture and function of the targeted organ shown is adapted for tumor therapy. In particular, the two crucial components in the PBPK-NM model represent: i) the system dynamics (systems biology), i.e. the interaction between the targeted organ structure and function and nanovehicle properties; and ii) the pharmacological dynamics (systems pharmacology), i.e. the loaded drug properties and the specific organ parameters contributing to the PK/PD outcome. These two component interactions modulate the unique behavior of systems to drug-loaded NP kinetics in the body, as well as the unique kinetic behavior of the drug concentration released from NPs to the systemic circulation. The latter can lead to an individual distribution capacity for the drug-loaded NPs and a unique system functional behavior to it, which definitely enables a strong potential for stratified and personalized treatment. Q, The blood flow in the various organs; K, the partition coefficient of the loaded drug for a specific organ with Lu, Ki, Li, Sp, Br, Tu, representing lung, kidney, liver, spleen, brain and tumor, respectively.

edge from heterogeneous data derived e.g. from personal genome sequencing, structural, functional and chemical genomics applications, as well as the PK/PD drug profiles including the clinical setting. In contrast, PBPK models represent platforms where organ- and tissue-specific parameters, genomic variation data and physicochemical drug properties can be efficiently inter-correlated to allow the prediction of PK/PD drug behavior in the body for specific populations or individual patients. Importantly, the enrichment of the predictive capacity of PBPK models towards empowering individualized drug response phenotype decisions could be achieved through incorporation of: i) genome-wide drug-target molecular interactions; ii) temporal and spatial scale macromolecular conformation state behavior; iii) drug-driven molecular circuit pathways; and iv) in real-time monitoring the impact of environmental and clinical parameters. To this end, the structure-enabled integrative modeling to effectively predict QT interval prolongation and minimize the drug-induced arrhythmia profile of delivered medicines in the clinical setting has been recently exemplified (150). The latter implements crucial clinical information related to molecular, genomics, pharmacological and chemical drug-

related aspects including those of pharmacovigilance that have been previously established in regulatory legislation for the arrhythmogenic behavior of drugs (8).

As far as drug delivery is concerned, new tools are tilting health-care control from physicians to patients with the paradigm of the delivery of insulin using telemedicine (151). Three dimensional (3D) printing technologies emerge as an innovative approach to design pharmaceutical dosage forms for personalized medicine (152). Recently, 3D printing was used for the production of tablets capable of satisfying regulatory tests and matching the release of standard commercial tablets (153). Remote controlled capsules (RCCs) have been extensively used in the field of site-specific drug delivery using micro-electronic mechanical system (MEMS) technology 154). MEMS combined with medical devices (e.g. contact lenses) can be used for ocular diagnostics (155). Finally dosing devices and solid dosage forms might allow oral individual drug therapy (156).

The availability of information science technologies aimed to develop advanced tools and databases for electronic health records for patients raise the question of whether virtual population profiles gained from epidemiologic

recorded data with data generated from the patients and/or hospital driven databases and relative software could match. The latter, if occurred, would permit the fitting of modeled data of virtual profiles with profiles of real life patients and thus initiate personalized or stratified medicine approaches. Moreover, it will also advance the next step for the development of unique decision-making tools or for novel approaches during R&D but also for PTx procedures. However, the absence of a roadmap on how the regulatory environment in drug development and healthcare is gaining major clinical benefit and economic value from personalized medicine applications has clearly restricted the required evidence to informed decision-making and assessment of genomic priorities (42). It is therefore of important priority to work and present evidence by establishing infrastructure and methodologies capable of confirming cost-effectiveness in addition to clinical effectiveness in a robust and timely manner for decision makers (43); and by doing so, the parallel advancement of PBPK models will empower the translation capacity and practical clinical utility of personalized medicine decisions, thus benefitting healthcare and stabilizing PTx worldwide (157). These new technologies are expected to revolutionize existing healthcare and drug delivery, in a way to enrich personalized medicine capabilities and precision for broader clinical utility of translational medicine therapeutic interventions worldwide.

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