PKPD relationships and dose rationale in analgesic drug development : towards the prediction of target engagement

Taneja, A.

SECTION IV

CONCLUSIONS AND PERSPECTIVES

CHAPTER 10

Analgesic drug development at the crossroads -
Where do we go from here?
Thesis summary, conclusions and perspectives

ANALGESIC DRUG DEVELOPMENT AS IT STANDS TODAY

Chronic pain is a significant health problem that greatly impacts the quality of life of individual patients and imparts high costs to society. Despite intense research effort and progress in our understanding of the mechanistic and molecular basis of pain, chronic pain remains a significant clinical problem that has few effective therapies [1]. In fact, existing analgesics are relatively ineffective, have a high side-effect burden and do not reduce pain in all treated individuals. While a statistically significant reduction in pain in pivotal trials can result in an investigational analgesic obtaining regulatory approval, these treatments are palliative in nature making pain symptoms more manageable, with global pain scores reducing by 30% at best in responders [2-4]. However, even in successful phase 3 analgesic trials, at the end the majority of subjects are still eligible to enter the same trial [5].

Experts across different disciplines acknowledge the unmet needs in analgesia and recommend strategies for enhancing analgesic drug development. Nevertheless, both treatment and research into chronic pain are greatly compromised by the fact that there is no objective diagnostic test that can complement the subjective assessment of chronic pain conditions. Currently, there are no concrete diagnostic measures that enable early diagnosis, prevention or prophylaxis of a syndrome that endures for long periods of time.

While there has been exploration of different treatment options, including novel putative mechanisms of action for analgesia, there has been wide-spread reluctance on the part of the pharmaceutical industry to take novel products further into development without demonstrating the efficacy of analgesics based on behavioural measures, which reflects the current status at which this pathological condition or syndrome is clinically detectable. As a consequence, efforts in drug development have been geared to the design of the clinical trials (e.g., FDA's Analgesic Clinical Trials Innovation, Opportunities, and Networks - ACTION Initiative)[6], under the assumption that better trial designs will yield more successful results. This hypothesis is questionable in view of the frequent failures of clinical efficacy trials of opioid drug products, considering the well-established effectiveness of these products from literally thousands of years of clinical experience. In this thesis, we have brought a different perspective to the evaluation of chronic pain by emphasising the role of pharmacology and target engagement as the basis for translational research and clinical evaluation of novel molecules in humans. Throughout the various chapters we have highlighted some important conceptual and experimental flaws in the way that pain signalling and pharmacological activity are characterised and translated across species and disease conditions. The common denominator of the work presented here is the requirement for accurate characterisation of exposure-response relationships, without which the dose rationale for the progression of a molecule cannot justified, whether drugs are aimed at symptomatic relief, disease modification or prophylaxis. In addition to a comprehensive review of the mechanisms underlying pain signalling and symptoms, the work developed here focuses on three

different aspects of research underpinning the use of pharmacokinetic-pharmacodynamic relationships. First, we have explored the requirements for the characterisation of behavioural measures of pain during the early screening of candidate molecules, shedding light onto the shortcomings of experimental protocols commonly used in preclinical research. Then we introduced the prerequisites for the parameterisation of pain behaviour to ensure accurate translation of the pharmacological properties across species as well as for bridging across different phases of development. Lastly, an attempt was made to model clinical response in chronic inflammatory pain and to establish correlations between symptom improvement and the underlying pharmacological effects using biomarkers. In addition our work showed how clinical trial simulations can be used as a design tool, enabling the evaluation of a variety of scenarios that disentangle the contribution of pharmacology from the confounding effects of placebo and disease dynamics.

CHRONIC PAIN AS A NOCICEPTIVE SIGNALLING DISORDER

An overview of the ongoing research efforts in neuropathic and chronic inflammatory pain was presented in **Chapter 1**. We have shown that in addition to practical challenges, there are still several methodological issues that hinder the development of novel medications for the treatment of chronic pain. The most common problem is clearly the lack of construct validity of the experimental protocols used to assess drug effects. Pain experiments focus on transient behavioural models of pain, which do not necessarily reflect what is occurring in chronic pain patients. A new paradigm is proposed for the identification of relevant targets and candidate molecules in which pain is coupled to the cause of sensorial signalling dysfunction rather than to the symptoms. We have also shown that early diagnosis, timing of the intervention and reversibility of the underlying processes cannot be disentangled from each other and ultimately determine the success or failure of a treatment. It is therefore essential to understand the changes in the nervous system that result in the pain experience and consider the need for interventions before symptoms evolve. Consequently, one needs appropriate measures of patient response that are crucial in establishing patterns of response. On the other hand, such experimental protocols will remain of limited value unless relevant pathophysiological changes can be detected at the prodromic phase, i.e., before the metamorphosis from acute injury to chronic pain. This discussion is further extended to the limitations and flaws in the current paradigm for the screening and selection of compounds in drug development and used as a foundation for the subsequent chapters in this thesis. Here we have also highlighted the fact that the measures of pain perception currently used in experimental modelsedo not bring to light all involved pathways, which creates an important translational gap across species.

MODEL-BASED ANALYSIS OF PAIN BEHAVIOUR IN PRE-CLINICAL INVESTIGATIONS

As discussed in **Chapter 2**, the translational value of pre-clinical models of pain has been the subject of heated debate [7]. The generally held view is that these models lack construct or predictive validity and are only able to replicate symptoms [8, 9]. Moreover coarse behavioural endpoints such as the threshold to paw withdrawal (allodynia) or paw withdrawal latency (hyperalgesia) are employed as surrogates for evaluating analgesic activity. Despite these limitations, we have highlighted how further understanding of the pharmacology and target engagement can be relevant for the progression of a molecule into humans.

Using recent examples from published literature, we have emphasised the requirements for the assessment of concentration-effect relationships in pre-clinical species, including important changes in experimental procedures in standard screening protocols. Among other factors, we have indicated the importance of pharmacokinetic sampling and expressing drug properties such as potency in terms of exposure (EC_{50}), rather than dose (ED_{50}). Poor experimental design can lead to inaccuracies in parameter estimation and consequently to biased selection and ranking of candidate molecules during screening. In this context, we have introduced how mathematical and statistical models can be used as a tool to describe biological system and drug properties in a quantitative manner. Hierarchical or population models were proposed as the basis for identifying the different sources of variability as well as to assess treatment effects and disease progression. In addition, here we bring in the concept of biomarkers as an intermediate step between drug action and behaviour, which can be integrated in a systematic manner by pharmacokinetic-pharmacodynamic modelling, enabling the characterisation of exposure-response relationships and consequently providing mechanistic underpinning, be it for the purpose of interspecies translation or determination of the therapeutic dose levels in patients.

EXPERIMENTAL PAIN MODELS: UNTRANSLATABLE YET INFORMATIVE

An important assumption underlying the work presented in this thesis was that some of the limitations of the current practice of pre-clinical research may be overcome by model-based analyses, in that **it facilitates the evaluation and discrimination between drug and system-specific properties**. Furthermore, it can be envisaged that estimates of potency that are based on concentrations rather than doses will be more informative, allowing for more accurate comparisons between compounds of the same class and possibly enhancing the predictive value of such estimates. Another premise of our work was that standardised experimental protocols are not designed to ensure the informative value of the data collected or optimally discriminate between molecules or dose levels. Given the empirical

nature of pain experiments, standardisation procedures simply attempt to increase the reproducibility of measurements. Hence, efforts were made to evaluate the impact that such improvements could represent to the development of novel molecules for the treatment of chronic pain.

As indicated previously in the scope of this thesis, the lack of suitable markers of pharmacology is compounded by poor data integration at the time candidate molecules are selected. We have shown that whilst the assessment of concentration-response relationships across the different phases of development is a *sine qua non* condition to understand treatment effects and variability, accurate estimation of PKPD parameters is not guaranteed. PKPD relationships must have predictive validity or value for the target population, both in qualitative and quantitative terms. Such considerations are not formally embedded in the requirements for evidence generation, and consequently lead to experimental protocols, which are often not informative or eventually even biased[8].

Two experimental models of pain behaviour were selected to illustrate the aforementioned concepts. First, the threshold to paw withdrawal to a normally non-noxious stimulus was measured as a marker of the anti-allodynic effect in the complete Freund's adjuvant (CFA) model, a well-known experimental animal model of inflammatory pain. In the second case, the change in flinching frequency observed after injection of formalin was selected as a marker of drug effect. The pain response in this model is based on spontaneous behaviour, rather than on the threshold for a painful stimulus. In addition, the pain reaction produced by formalin results from a conditioned motor response, reflecting higher cognitive function than simple withdrawal responses [10]. It has also been demonstrated that drugs with different mechanisms of action can be differentiated in terms of the type and magnitude of the effects on the flinching behaviour. We have hypothesised that for this reason the formalin-induced model is likely to show some construct validity as compared to other experimental models based on short duration stimuli [11]. From a methodological perspective, we have demonstrated that the choice of parameterisation is as critical as the precision of model parameters. Undoubtedly, the limited availability of data during the screening of compounds leads to two important statistical issues, namely parameter identifiability and poor precision.

In **Chapters 4 and 5** we showed therefore how efficacy can be reliably assessed for gabapentin and pregabalin. To prevent model and parameter identifiability issues, an approach was proposed based on the use of a binary response as parametric filter for drug screening. Our analysis showed that it is possible to dissect system from drug-specific features, allowing the assessment of potency as parameter of interest for two paradigm compounds. The aim was to decrease the uncertainty on EC_{50} estimates as well as on the corresponding inter individual variability. ED-optimality was therefore applied in combination with a logistic regression model describing the relationship between drug exposure and response

to evoked pain in rats, enabling us to take parameter uncertainty into account [12]. The design variables selected for optimisation included the dose levels and sampling times required for the characterisation of the analgesic effects. Moreover, information regarding system-specific model parameters and relative *in vitro* potency data were also incorporated as priors during optimisation. Our analysis also shed light onto the implications of the empirical choice of dose levels, which are often too high to allow accurate estimation of drug potency *in vivo*. Moreover, despite the wide range of doses used in the experiments, simulated concentration profiles of gabapentin were not significantly different from each other. Relative bioavailability was found to decrease nonlinearly from 100 % at 10 mg/kg to 9 % at 300 mg/kg. In contrast to results from typical experiments in which ED_{50} is calculated, irrespective of the underlying exposure levels, protocol optimisation procedures clearly showed the importance of optimised sampling and dose schemes. EC_{50} values for gabapentin and pregabalin were 1400 and 897 ng/ml, confirming that the relative difference potencies observed *in vitro* are also seen *in vivo*. Overall, these findings demonstrate that protocol optimisation does represent an improvement in terms of parameter precision and bias. We anticipate that these procedures will provide the basis for further validation of experimental models of pain in terms of sensitivity and specificity, i.e., enabling the characterisation of the false positive and false negative rates during the screening process.

The advantages of model parameterisations based on drug- and system-specific properties was further explored in **Chapter 6**, where we investigated the feasibility of developing a semi-mechanistic model to describe the effects of a wide dose range of gabapentin (i.e., 0 – 100 mg/kg) on formalin-induced pain, which is characterised by two peaks of flinching behaviour. The first peak of hypersensitisation was described by a mono-exponential declining function, whereas the second, prolonged phase of nociception was best parameterised by an indirect response model with a time variant synthesis rate. Drug effect was parameterised as an I_{max} function. Here, however, the drug effect represented a covariate on pain response. The approach contrasts to traditional parameterisation of drug effects in indirect response models where it is applied to the synthesis or the elimination rate of the disease [13]. Yet, our choice of parameterisation has a mechanistic basis, given that gabapentin is known to have no disease-modifying effects. Interestingly, the mean IC_{50} values of 7510 ng/ml were found to be in the same log order of magnitude as those reported by Lockwood *et al.* and Whiteside for gabapentin in clinical studies [14, 15]. On the other hand, despite high exposure levels, gabapentin did not completely suppress the behavioural effects induced by formalin. This apparent discrepancy appears to reflect the somewhat limited efficacy in neuropathic pain patients.

Whilst concrete improvements in the estimation of drug- and system-specific parameters were demonstrated by the use of a model-based approach, our endeavour thus far to characterise behavioural endpoints as a measure of drug effects has highlighted the

implications of the lack of biomarkers as an intermediate step for the translation of the pharmacological properties across different phases of development. Undeniably, there is a pressing need to obtain early signals of efficacy by means of biomarkers, which could be used not only as *"scaling factors"* to translate drug effects from pre-clinical species to humans, but also as a tool for extrapolating drug effects across populations during drug development, i.e., from health to disease conditions. The points-to-consider for the use of biomarkers as the basis for the dose rationale were presented in the subsequent section of the thesis.

Biomarker-guided dose selection and prediction of clinical response

As indicated in the introduction, to address the escalating attrition rate in drug development, focus must be given to two key approaches in parallel [16]. The first is better target selection, taking into account the pathways as well as the timing of diagnosis and intervention. The second is the routine pursuit of early proof-of-concept studies, preferably already in Phase I or in human tissue, in which biomarkers or surrogate endpoints could be employed as markers of efficacy and safety. Despite the evidence from other therapeutic areas supporting such an approach [17, 18], chronic pain protocols have remained primarily based on clinical scales without any reference to the underlying pharmacology or target engagement [19, 20]. Clearly, the integration of biomarkers of pharmacology into drug development also offers the possibility to eliminate part of the bias that arises from empirical evidence using nonspecific behavioural measures.

In **Chapter 7**, we made therefore an attempt to show that opportunities exist for truly characterising the clinical pharmacological profile of novel molecules in humans when biomarkers are used as *predictors* of efficacy, enabling mechanistic insight into the exposure-response relationships and consequently better rationale for the therapeutic dose range. Moreover, the assessment of pharmacokinetic-pharmacodynamic relationships using biomarkers can provide a stronger basis for personalised medicine.

Here data from GW406381, a cyclo-oxygenase (COX) inhibitor was used to illustrate the concept of biomarker-guided dose selection and emphasise the importance of gaining insight into the clinical pharmacology of the compound as the basis for the dose rationale. The choice of the COX-2 system as a paradigm was dictated by the various reports arising from the withdrawal of different drugs from the market, for which the clinical pharmacology profile was clearly known to determine efficacy and safety. Data from a phase I, randomised double-blind single dose followed by a 10-day repeated dose study in healthy male subjects were available for the analysis. Doses of 35 or 70 mg GW406381 were administered orally under fasting conditions. Plasma concentrations of GW406381 and PGE_2 (prostaglandin E_2) as well as thromboxane B_2 (TXB_2) were measured at regular intervals throughout the study.

The analysis was performed in two stages. First, a compartmental pharmacokinetic model with first order absorption was used to describe the time course of drug concentrations in the plasma. Then an I_{max} model was fitted to the prostaglandin data to describe the exposure-response relationships.

From a methodological standpoint, by integrating pharmacokinetic data from a Phase I trial with PGE_2, as determined by an *ex vivo* assay, we have illustrated how biomarkers can be used to guide dose selection in subsequent phases of drug development. It is noteworthy to mention that our analysis was successful despite the high variability in PGE_2 data. Mean potency estimates (IC_{50}) were 43.25 ng/ml, with IC_{80} and IC_{95} values reaching 103.43 and 275.58 ng/ml respectively. In addition, the high variability in pharmacokinetics and pharmacodynamics observed in healthy subjects exposed an important limitation of using *in vitro* potency as a benchmark to compare compounds in early clinical development, which does not reflect differences in selectivity or metabolic activity *in vivo*. In fact, Fries *et al.* showed that despite the higher potency of rofecoxib relative to celecoxib *in vitro*, their *in vivo* selectivity is likely to be the same [21]. Likewise, the *in vitro* potency of GW406381 was estimated to be approximately 30 times as high as rofecoxib. However, the optimal recommended dose range proposed from our simulations lies between 150-250 mg, while that for rofecoxib is 25-50mg. This is mostly explained by the inter-individual differences in pharmacokinetics. Given the proposed therapeutic range (i.e., <80% and < 95% inhibition), it was found that a b.i.d. regimen allowed peak concentrations to remain above the IC_{95} for a shorter time and at much higher dosages, without significant effect on trough concentrations, which were comparable to those achieved with a q.d. regimen.

With the help of simulation scenarios we have also demonstrated how biomarkers can be used to explore dose adjustment in special populations. The simulated clinical scenarios included factors known to have potential effect on the pharmacokinetics and pharmacodynamics of GW406381, namely hepatic impairment, metabolic induction and systemic inflammation. Our results showed that moderate to severe hepatic impairment or metabolic induction do lead to significant changes in exposure and consequently in dose adjustments to ensure target exposures are achieved and maintained during the course of therapy. Conversely, increases in baseline levels of PGE_2 appeared to require no changes in dosing regimen.

In brief, this analysis allowed for the evaluation of the dose rationale taking into account the benefit-risk balance, which depends not only on the total dose level, but also on the dosing regimen [22]. Such a balance is likely to be achieved when PGE_2 is maintained above 80% but below 95%. Under these conditions, chronic treatment would effectively block the inducible fraction of the available COX-2 pool, whilst allowing for the residual or basal activity of PGE_2 and other COX-2 related prostacyclins, which have an essential role in normal tissue homeostasis and repair.

In the last part of this thesis, we have expanded the concept of biomarker-guided dose selection to Phase 2 clinical trials to gain further insight into the relationship between biomarkers and overt pain symptoms. By applying the mechanistic classification proposed by Danhof *et al*. [23], it was possible to unravel a putative exposure-biomarker response relationship for GW406381. To this purpose, ACRn scores from a large clinical trial in rheumatoid arthritis patients were used. Even though the utility of the ACRn as an index of clinical improvement is beyond doubt, its correlation with the underlying pharmacological activity following administration of a COX-2 inhibitor has not been established. In **Chapters 8** we have progressed with the use of biomarkers from health to disease and attempted to ascertain whether biomarkers could be correlated with ACRn. In spite of the limited number dose levels that were tested in the trial (0, 10, 35 and 50 mg, administered orally as a once daily dosing regimen), our objective was to show how longitudinal modelling can provide the basis for inferences about the pharmacological effects underlying clinical response. An integrative approach was therefore proposed in which information was derived about the whole time course of treatment response. This contrasts with current practice, in which efficacy is determined by comparing the differences in clinical response at completion of treatment only. The time course of the pain response was best characterised by a Weibull function with an I_{max} model describing the drug effects. We could identify a responder phenotype in the population, which included all individuals who displayed at least a 25% decrease in ACRn from baseline at the end of the study. Interestingly, the percentage of responders was not dose proportional, which reflects the impact of high pharmacokinetic and pharmacodynamic variability. Whilst direct evidence of efficacy could not be obtained from higher dose levels, these findings are in agreement with the predicted levels of target engagement, as determined by the PGE_2 inhibition. Based on the premise that pharmacological activity translates into clinical analgesia when PGE_2 inhibition reaches a threshold of at least 80%, it appears that the doses selected for the clinical study were sub-therapeutic. According to the analysis of the biomarker response, the therapeutic doses for GW406381 were likely to be between 100 and 250mg/day.

Our endeavour to evaluate the predictive value of a model-based approach for the dose selection of analgesic drugs would not be complete without further characterisation of the correlation between biomarker and clinical response [24]. In **Chapter 9** we explore therefore the putative relationship between prostaglandin inhibition (PGE_2) and the ACRn scores in rheumatoid arthritis patients. In addition to demonstrating the suitability of PGE_2 as a proxy for target engagement (i.e., COX-2 inhibition), inferences about the correlation between biomarker and clinical response provide better insight into the causes of variability in a large population. Using the pharmacokinetic and pharmacokinetic-pharmacodynamic models previously developed in chapters 7 and 8 simulations were performed of the time course of the clinical response (ACRn) and PGE_2 concentrations. The hypothetical experimental

protocol was based on a typical clinical trial in rheumatoid arthritis, with treatment duration of 6 weeks and five hundred patients per dose level. A range of doses from 10 to 400 mg GW406381 was considered in our exercise to ensure accurate characterisation of the potential sources of variability. Patients were classified as responders or non-responders based on the simulated response at completion of treatment. Our results showed a wide variation in the time course of the core set measures, irrespective of the initial baseline conditions, with predicted PGE_2 inhibition over 80% at doses greater than 250mg. Furthermore, the proportion of responders increased in a non-linear fashion across the simulated dose levels, with a decrease of 50% in the median ACRn at doses >100mg/day. The availability of such a correlation represents a stronger basis for the dose rationale in efficacy trials, which have been primarily been determined by evidence of treatment response based on overt symptoms, rather than on the underlying concentration-effect relationships.

In conclusion, we have shown that modelling and simulation can facilitate the translation of experimental findings across different phases of drug discovery and development, improving the dose selection and the design of experimental protocols. To this end, we have demonstrated that the availability of longitudinal data is paramount. However, experimental protocols must be based on sampling schemes that allow for the accurate characterisation of pharmacokinetics, biomarkers and efficacy. Moreover, the choice of appropriate model parameterisations, which enable discrimination between drug and system-specific parameters, offers the possibility to systematically explore drug effects taking into account the historical evidence for system-specific properties. In fact, we have shown that statistical priors can be used to reduce uncertainty during parameter estimation and protocol optimisation and as such enable further understanding of the underlying variability in experimental data. Furthermore, using paradigm compounds with known analgesic activity, we have underlined how essential concentration-effect relationships are for the dose rationale in humans. It provides the basis for evaluating the effect of influential covariates on drug exposure and response.

Albeit a preliminary exercise, in which modelling and simulations are used as inferential tools, the approach presented throughout this thesis represents a shift from the empiricism which has dominated selection of candidate molecules, the rationale for the therapeutic doses and the design of Phase 2b and 3 trials for chronic pain conditions. The critical point here is that drug response cannot be expected without sufficient target engagement. On the other hand, further increases in exposure do not yield additional efficacy when maximum pharmacology has been reached. Undeniably, the use of pharmacokinetic-pharmacodynamic models makes target engagement a central component in the development of analgesic drugs.

Future perspectives

Drug development has traditionally been considered a linear process beginning with target selection and ending with regulatory approval [1, 25]. This creates a sequential approach to decision making, in which there should be learning at each step, i.e., knowledge from a previous step informs the subsequent one (see Figure 10.1). Currently, however, as shown throughout this thesis each step appears to occur in isolation and there is little or no integration and accrual of information from preceding steps.

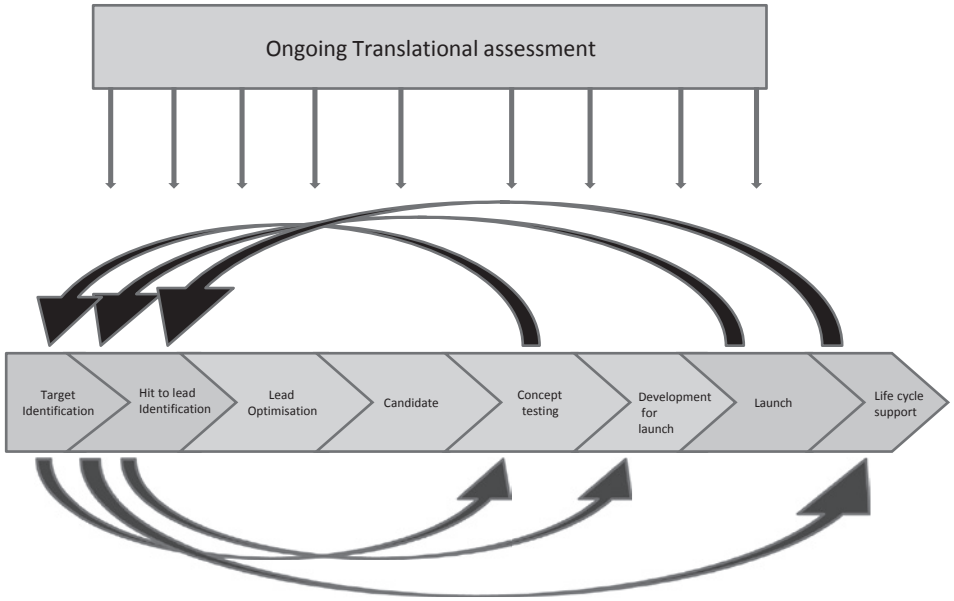

Figure 10.1: Translational steps in drug discovery and development. The standard linear model of drug development is depicted, for illustrative purposes only. Translational activity is bidirectional. Translational assessment needs to start early and requires constant updating according to progress in both directions 'including reverse translation'. Adapted with permission from [25].

From a clinical and biological perspective, an approach is required that allows us to depart from the current fragmented strategy, which focuses on individual signal transduction pathways, to studying pain as a system based-approach [26]. Moreover, efforts must be made to detect the underlying signalling disorder that precedes the overt pain experience. Prophylactic or pre-emptive treatments are needed to ensure normal tissue homeostasis is maintained after onset of injury and subsequent acute inflammatory response. In this context, drug development programmes will have to consider co-development of diagnostic markers.

Clearly, the issue in the evaluation of neuropathic pain conditions is whether existing or new experimental models may ever provide us the basis for translating drug effects from animals to humans without evidence of common biological substrates. Yet, a model-based approach is essential to optimise the design and interpretation of preclinical experiments, making it more informative. The availability of models will also contribute to mechanistic inferences, enabling systematic integration of data and information from a vast range of experimental protocols, including *in vitro* human cell and tissue cultures. In fact, Woolf and collaborators have proposed a new approach to analgesic drug development, in which human genetics is employed to validate potential analgesic targets. Some examples include the role of polymorphisms in voltage-gated sodium channel Nav1.7 and GTP cyclohydrolase-1, which have been linked to decreased pain perception. Likewise, other approaches are being considered which entail early exploration of the pharmacology of the compound (proof of principle) in humans (see Figure 10.2). Irrespective of differences in choice of tools or research protocol, all proposals are unanimous on the role of mechanistic biomarkers to guide development [1], [26].

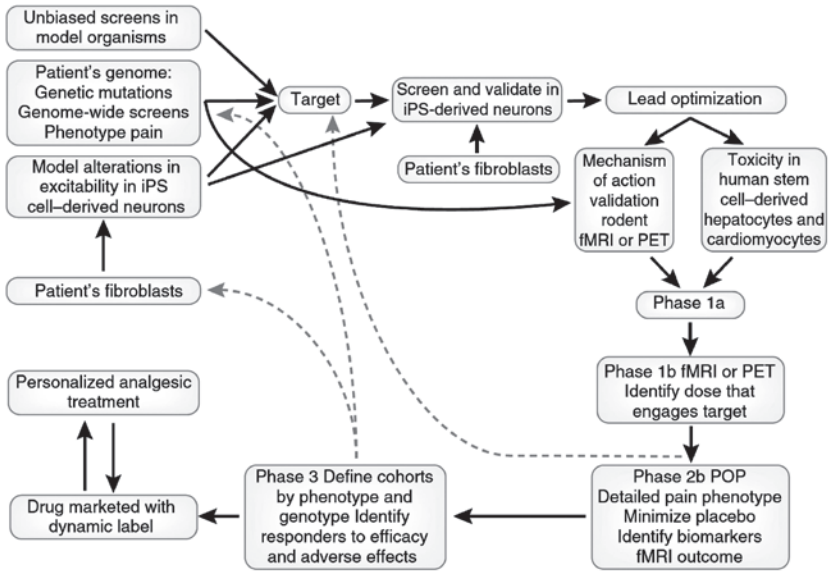

Figure 10.2: A proposed new analgesic development pathway. The preclinical and clinical distinction must be abolished. The choice of a target must be driven by data from patients using unbiased screening techniques. Screening and validation must focus on the native human target expressed in human cells relevant to the target's action in pain; preclinical toxicity studies must be done in human cells; Phase I must include pharmacokinetic data showing engagement or target occupancy. Phase 2b must be designed to differentiate true efficacy by detailed phenotyping, use of appropriate biomarkers and outcome measures. Phase 3 should be a confirmatory step to identify responders and assess the clinical impact of patient heterogeneity. iPs= induced pluripotent cell, PET=positron emission tomography, POP=proof of principle, fMRI= functional magnetic resonance imaging. *Adapted with permission from* [1].

Currently there is no validated biomarker for chronic pain. In fact, the identification and use of biomarkers for CNS disease are more challenging than other diseases [27] due to the inaccessibility of the brain. A number of reviews have summarized the current state of the art of imaging pain in the brain [28]; [29, 30] but none have evaluated the potential of using imaging to discover and define biomarkers of pain and their potential application in drug development.

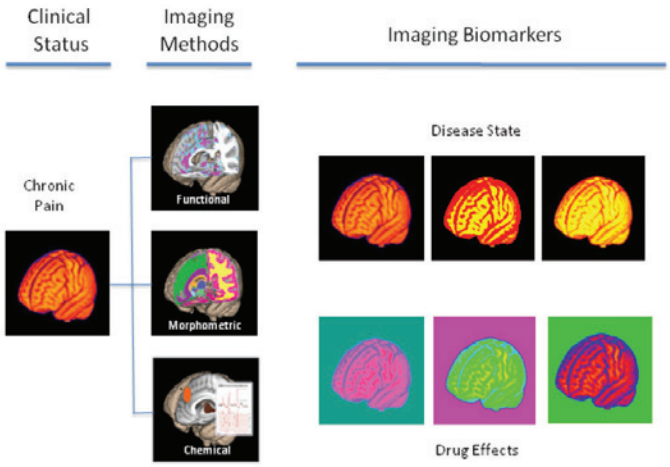

Figure 10.3: Imaging biomarkers or disease state and drug effects. Functional biomarkers may include specific fMRI signals for pain based on evoked or resting state connectivity patterns. Morphometric biomarkers include changes in volume or thickness of brain gray matter or alterations in white matter integrity. Chemical biomarkers include specific chemical changes in brain regions related to disease state or drug effect (*adapted with permission from* [37]).

Developments in functional imaging will unquestionably facilitate the identification of biomarkers of pain and help us to better understand the role of various brain areas in the expression of pain, especially in processes that are associated with neuroplasticity, which is a critical step for the development of chronic pain [31]. In conjunction with physiological (sensory) challenges it may be possible to anticipate signalling disorders before symptoms emerge. Collectively, a refined understanding of abnormal activity or connectivity of synaptic elements may allow us to more effectively target interventions in patients who are likely to later experience chronic pain [32]. In the context of drug development, these advances may also improve translational go/no go decision making between the laboratory and early clinical trials. However, a reductionist approach needs to be avoided in that further understanding of the pain syndrome cannot be achieved by functional imaging alone. When integrated with clinical subjective assessments [33], genetic [34], metabolomics [35], or proteomics [36], such evidence could provide orthogonal views that together may improve the predictive value of pain biomarker strategies. The challenge to be overcome as for any

chronic disease that requires prolonged dosing is that one will need to differentiate the early direct effects of the drug from chronic effects on brain systems that are associated with longer-term effective treatment.

Irrespective of the advancements in the field of imaging and proteomics as an important step to generate evidence of target engagement and possibly of markers of disease progression, pharmacokinetic-pharmacodynamic models can play an essential role as translational tool, providing guidance for the introduction of novel research protocols aimed at reducing uncertainty about the potential clinical relevance of candidate molecules and enabling selection of the putative therapeutic dose range and transition from the pre-clinical phase to humans. Through the use of systems pharmacology, pathways associated with signalling processes can be better mapped and system-specific parameters disentangled from drug-specific properties. Under the assumption of common substrates in experimental and disease conditions, modelling can be used to predict target engagement and consequently the downstream pharmacological effects. It is also conceivable that *scaling factors* could be identified to describe potential differences, such as receptor density, between experimental protocols and disease conditions in humans. Similar concepts have been recently applied for antipsychotics, for which *in vitro* receptor occupancy in rats has been scaled all the way to clinical efficacy [38, 39]. As already proposed in this last section of this thesis, quantitative techniques could then be used further explore the role of phenotypic differences and other influential factors (covariates) on pharmacokinetics and response, thereby supporting dose selection and other label claims (Figure 10.4).

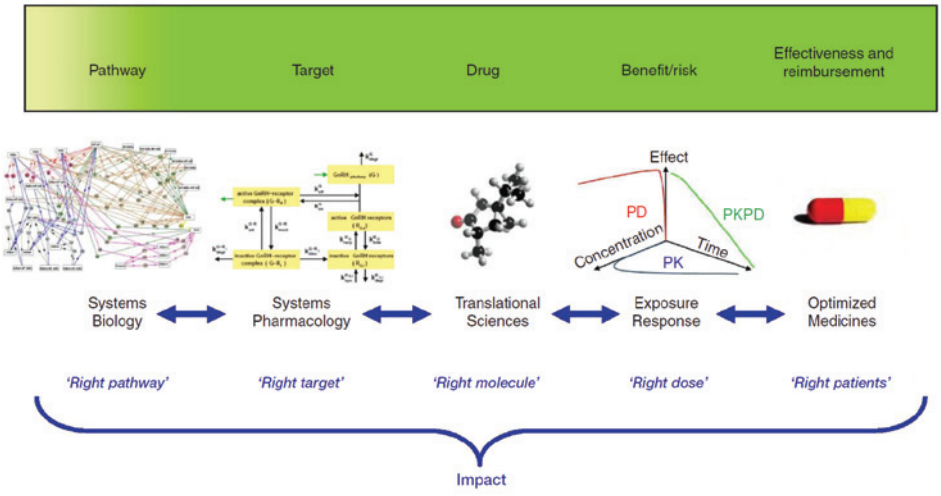

Figure 10.4: An integrated model-based approach across drug discovery and development, from systems biology all the way to exposure-response modelling. Adapted with permission from [40].

A slightly different scenario can be envisaged with regard to the challenges one faces in the evaluation treatment effects in chronic inflammatory pain, for which a few biomarkers exist and imaging technology is already being used. The challenge will be to reach consensus about the importance of revisiting current guidelines, which dismiss the role of pharmacological activity as the basis for dose selection and exclude the concept of learning and confirming as the paradigm for drug development. Undoubtedly, the use of simulation scenarios will play an increasingly important role in the evaluation of the impact of heterogeneity in target population as well as of variability in pharmacokinetics, pharmacodynamics and response to intervention. In this context the integration of statistical models that describe trial design factors, such as drop-out and censoring, with mechanism-based models describing the underlying progression of the disease will be of great value [41]. Finally, we envisage that further advancements in the prediction of pain response can be obtained by expanding the concepts to multiple endpoints as well as by incorporating fully mechanistic models to the pharmacometric framework proposed in this thesis.

REFERENCES

1. Woolf, C.J., *Overcoming obstacles to developing new analgesics.* Nat Med. **16**(11): p. 1241-7.
2. Hauser, W., F. Petzke, and C. Sommer, *Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome.* J Pain. **11**(6): p. 505-21.
3. Moore, R.A., *et al*., *Pregabalin for acute and chronic pain in adults.* Cochrane Database Syst Rev, 2009(3): p. CD007076.
4. Gilron, I. and T.J. Coderre, *Emerging drugs in neuropathic pain.* Expert Opin Emerg Drugs, 2007. **12**(1): p. 113-26.
5. Straube, S., *et al*., *Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports.* Rheumatology (Oxford). **49**(4): p. 706-15.
6. Dworkin, R.H. and D.C. Turk, *Accelerating the development of improved analgesic treatments: the ACTION public-private partnership.* Pain Med. **12 Suppl 3**: p. S109-17.
7. Blackburn-Munro, G., *Pain-like behaviours in animals - how human are they?* Trends Pharmacol Sci, 2004. **25**(6): p. 299-305.
8. van der Worp, H.B., *et al*., *Can animal models of disease reliably inform human studies?* PLoS Med. **7**(3): p. e1000245.
9. Taneja, A., *et al*., *Translation of drug effects from experimental models of neuropathic pain and analgesia to humans.* Drug Discov Today.
10. Le Bars, D., M. Gozariu, and S.W. Cadden, *Animal models of nociception.* Pharmacol Rev, 2001. **53**(4): p. 597-652.
11. Koganei, H., M. Shoji, and S. Iwata, *Suppression of formalin-induced nociception by cilnidipine, a voltage-dependent calcium channel blocker.* Biol Pharm Bull, 2009. **32**(10): p. 1695-700.
12. Dodds, M.G., A.C. Hooker, and P. Vicini, *Robust population pharmacokinetic experiment design.* J Pharmacokinet Pharmacodyn, 2005. **32**(1): p. 33-64.
13. Dayneka, N.L., V. Garg, and W.J. Jusko, *Comparison of four basic models of indirect pharmacodynamic responses.* J Pharmacokinet Biopharm, 1993. **21**(4): p. 457-78.
14. Lockwood, P.A., *et al*., *The use of clinical trial simulation to support dose selection: application to development of a new treatment for chronic neuropathic pain.* Pharm Res, 2003. **20**(11): p. 1752-9.
15. Whiteside, G.T., A. Adedoyin, and L. Leventhal, *Predictive validity of animal pain models? A comparison of the pharmacokinetic-pharmacodynamic relationship for pain drugs in rats and humans.* Neuropharmacology, 2008. **54**(5): p. 767-75.
16. Paul, S.M., *et al*., *How to improve R&D productivity: the pharmaceutical industry's grand challenge.* Nat Rev Drug Discov. **9**(3): p. 203-14.
17. Le Tourneau, C., J.J. Lee, and L.L. Siu, *Dose escalation methods in phase I cancer clinical trials.* J Natl Cancer Inst, 2009. **101**(10): p. 708-20.
18. Parulekar, W.R. and E.A. Eisenhauer, *Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: theory and practice.* J Natl Cancer Inst, 2004. **96**(13): p. 990-7.
19. European Medicines Evaluation Agency, *Guideline on Clinical Medicinal Products Intended for the Treatment of Nociceptive Pain*, Committee for Medicinal Products For Human Use (CHMP), Editor. 2007, EMEA: London. p. 3-10.
20. European Medicines Evaluation Agency, *Guideline on Clinical Medicinal Products Intended for the Treatment of Nociceptive Pain*, Committee for Medicinal Products For Human Use (CHMP), Editor. 2002, EMEA: London. p. 3-10.
21. Fries, S., *et al*., *Marked interindividual variability in the response to selective inhibitors of cyclooxygenase-2.* Gastroenterology, 2006. **130**(1): p. 55-64.
22. Weir, M.R., *et al*., *Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program.* Am Heart J, 2003. **146**(4): p. 591-604.
23. Danhof, M., *et al*., *Mechanism-based pharmacokinetic-pharmacodynamic modelling-a new classification of biomarkers.* Pharm Res, 2005. **22**(9): p. 1432-7.
24. Wang, Y., *Extracting Knowledge from Failed Development Programmes.* Pharm Med, 2012. **26**(2): p. 91-96.

25. Wehling, M., *Assessing the translatability of drug projects: what needs to be scored to predict success?* Nat Rev Drug Discov, 2009. **8**(7): p. 541-6.
26. Mao, J., *Current challenges in translational pain research.* Trends Pharmacol Sci. **33**(11): p. 568-73.
27. Hayes, R.L., *et al*., *Translation of neurological biomarkers to clinically relevant platforms.* Methods Mol Biol, 2009. **566**: p. 303-13.
28. Hanbing L., R.T.a.S.E., *Magnetic Resonance Imaging of Pharmacological Systems.*, in *Imaging in CNS Drug Discovery and Development: Implications for Disease & Therapy*, Becerra .L, Hargreaves R, Borsook D., Editor. 2009, Springer-Verlag: New York.
29. Matthews, P.M., G.D. Honey, and E.T. Bullmore, *Applications of fMRI in translational medicine and clinical practice.* Nat Rev Neurosci, 2006. **7**(9): p. 732-44.
30. Tracey, I. and P.W. Mantyh, *The cerebral signature for pain perception and its modulation.* Neuron, 2007. **55**(3): p. 377-91.
31. Borsook, D., L. Becerra, and R. Hargreaves, *Biomarkers for chronic pain and analgesia. Part 1: the need, reality, challenges, and solutions.* Discov Med. **11**(58): p. 197-207.
32. Borsook, D., *et al*., *Pain and analgesia: The value of salience circuits.* Prog Neurobiol. **104**: p. 93-105.
33. Scholz, J., *et al*., *A novel tool for the assessment of pain: validation in low back pain.* PLoS Med, 2009. **6**(4): p. e1000047.
34. Edwards, R.R., *Genetic predictors of acute and chronic pain.* Curr Rheumatol Rep, 2006. **8**(6): p. 411-7.
35. Serhan, C.N., *Systems approach to inflammation resolution: identification of novel anti-inflammatory and pro-resolving mediators.* J Thromb Haemost, 2009. **7 Suppl 1**: p. 44-8.
36. Niederberger, E., H. Kuhlein, and G. Geisslinger, *Update on the pathobiology of neuropathic pain.* Expert Rev Proteomics, 2008. **5**(6): p. 799-818.
37. Borsook, D., L. Becerra, and R. Hargreaves, *Biomarkers for chronic pain and analgesia. Part 2: how, where, and what to look for using functional imaging.* Discov Med. **11**(58): p. 209-19.
38. Johnson, M., *et al*., *Mechanism-based pharmacokinetic-pharmacodynamic modelling of the dopamine D2 receptor occupancy of olanzapine in rats.* Pharm Res. **28**(10): p. 2490-504.
39. Pilla Reddy, V., *Translational PKPD modelling in Schizophrenia*, in *Pharmacokinetics, Toxicoogy and Targeting*. 2012, University of Groningen: Groningen. p. 302.
40. van der Graaf , P., *Pharmacometrics and Systems Pharmacology.* CPT:Pharmacometrics and Systems Pharmacology, 2012. **1**(e8).
41. Smith MK, F.J., Kowalski KG, Hutmacher MM and Ewy W, *Decision-making in Drug Development: Application of a model-based framework for assessing trial performance*, in *In: Clinical Trial Simulations: Applications and Trends*, K.H.a.P. C, Editor. 2011, Springer: San Fransisco. p. 61-85.