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ROLE OF PRECLINICAL STUDIES IN CLINICAL RESEARCH

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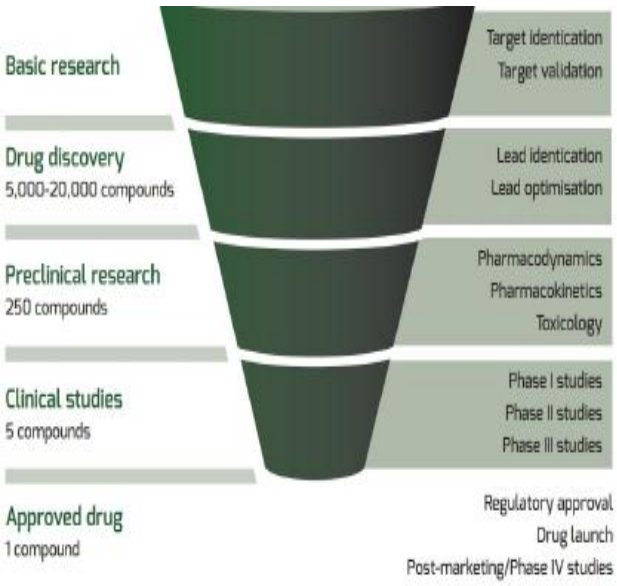
ABSTRACT
The process of developing a novel drug is very time consuming and costly. To increase the chances of successfully completing a clinical trial leading to the approval of a new drug, the choice of appropriate pre-clinical models is of utmost importance. Identifying a safe, potent, and efficacious drug requires thorough preclinical testing, which evaluates aspects of pharmacodynamics, pharmacokinetics, and toxicology in in vitro and in vivo settings. Nevertheless, merely a small fraction of investigational new drugs tested in clinical trials after passing pre-clinical evaluation eventually lead to a marketed product. Hence, there is a need for optimizing current standard pre-clinical approaches to better mimic the complexity of human disease mechanisms. In order to ensure relevant results applied in clinical contexts, effective development and careful selection of modeling frames for preclinical trials are crucial. The purpose of this research is to study a variation in the time line between in vitro, in vivo and silicone models, and the limits of pre-clinical treatment trials.

KEYWORDS: Drug, Pharmacodynamics, Pharmacokinetics, Toxicology, Clinical trials, Pre-clinical models.

INTRODUCTION
Preclinical studies aim at providing information about safety and efficacy of a drug candidate before testing it in humans. Furthermore, they can provide evidence for the compounds biological effect and usually include both in vitro and in vivo studies. Preclinical studies have to comply with the guidelines dictated by Good Laboratory Practice to ensure reliable result and are required by authorities such as the FDA before filing for approval as IND. Insights into the compound's dosing and toxicity thresholds are necessary to assess if it is justified and sufficiently safe to continue with clinical trials and are given by studies on pharmacokinetics, pharmacodynamics, and toxicology. The perfect preclinical model precisely mimics human illness.

The assessment and validation of preclinical models with special reference to principle and methods applied in pre-clinical studies with objectives to study the difference between in vitro, in vivo & silicon models and outlining Pre-clinical tests time line along with studying the limitations of preclinical studies in pharmacodynamics treatments.



Obtaining relevant results from preclinical studies with a high degree of general is ability requires appropriate preclinical models that are as comparable to the target population as possible. Typically, this involves a series of experiments using in vitro, in vivo, and more recently, also in silico models.

In vitro models – The in vitro models are studying the drug in a Petridis. In vitro experiments are a reasonably effective, quick, and cost efficient method of preclinical research. Those experiments utilize cell, tissue, and organ cultures, or concentrate on specific cell components such as proteins or other biological macromolecules. In vitro studies permit close control and monitoring of laboratory settings and also provide mechanistic proof for the Investigational compound's mode. While having the potential to provide mechanistic insights, in vitro models are constrained by the fact that isolated cells may not behave in a Petridis as they would within the body where they partake in crosstalk and interaction with millions of other cells. Consequently, more sophisticated preclinical models are required to establish investigational compound's safety profile before transitioning to a clinical setting.

Preclinical studies models

In vivo models – In vivo studies consider the complete organism based on various animal models. Similar to studies in humans, animal testing is tightly regulated in most countries and permission from local ethical review boards is required to ensure that no unnecessary harm is done to the experimental subjects. Recent developments have refined the use of animal models in drug discovery through non-invasive imaging technologies, micro sampling, and telemetric control. Naturally, monitoring laboratory settings is much more difficult for in vivo experiments and, due to the dynamics of the living organism; substances can behave differently from what is a predicted based on finding obtained in a test tube. Typically, in vivo experiments are conducted in a rodent (e.g, rat, guinea pig, hamster) and non-rodent model to conform with FDA criteria. Mice, rodents, and dogs are among the most commonly used animal models although research of primates (e.g., chimpanzees, chimpanzees, etc.) is conducted rarely and usually with larger molecules.

In silico models–the computer's role in drug development- Progress in bioinformatics over the past decades has made in silicon studies enticing such that they frequently precede or accompany in vitro and in vivo studies. In silico models are based on computer simulations that provide details on how an investigational compound could behave in subsequent in vitro and in vivo experiments.

In drug production, preclinical development, also called preclinical tests and nonclinical studies, is a period of study that starts before clinical trials (testing in humans) can begin, and during which critical efficacy, iterative testing and drug safety data are gathered, usually in laboratory animals. The key aims of preclinical studies are to decide a starting, stable dose first-in-human testing and determine possible toxicity of the product, which usually involve new medical technologies, prescription medications, and diagnostics. The purpose of a preclinical study is to gather evidence in support of the safety of the new medication. Preclinical studies are expected before clinical trials in humans can be started.

Preclinical Tests Timeline

The following table outlines the typical duration for various types of preclinical studies and the preferred timing relative to clinical trials they support.

Pre/Non-clinical Study	Duration	Time	Clinical Study Supported
Safety pharmacology Toxicokinetic pharmacokinetic studies Single dose acute toxicityor dose escalation study in two speciesLocal tolerance studies using relevant route of administration	3 weeks, depending on kinetic data, 14 days A few hours to several weeks depending on sample and test type	Prior to Phase I. Information should be available by the time early Phase I trials are completed	Phase 1 or 2
Repeated dose toxicity studies in one rodent and one non-rodent model	Should equal or exceed the durationof Phase I/II studies: (minimum 2 weeks,maximum12 months, generally months for biotech-derived products) and to support Phase III: 1 month, 3 months,6 months	Prior to Phase I and Prior to Phase III	Phase I/II: 2 weeks to12 months, Phase III:< 2 weeks< 1 month > 1 month
Genotoxicity studies	Variable	Complete prior to start of Phase II and all pediatric clinical trials	
Reproductive toxicity studies	(> 1 month- long repeated dose toxicity studies	Not required if repeated dose toxicity studies	Phase I/II (males, and females not of

	required prior to tests).	including evaluatin of male and female reproduct ive organs have been done.	child- bearing potential)
	Pre- mating treatment interval of 4 weeks for males and 2 weeks for females.	Complete all female reproduct ive toxicity and genotoxi city studies prior to Phase I/II studies. Pre- and postnatal develop ment study prior to marketin g approval.	Phase I/II (pregnantfemales and females of childbearing potential)
	Continue treatment throughou t mating for males and at least through implantati on for females.	Complete prior to pediatric studies.	Pediatric clinical trials
	Collect and evaluate data through two or more generatio ns.		
Carcinogenicity studies	Variable	Prior tol ong-term pediatric trials. Not usually needed unless there is cause for concern.	Pediatric clinical trials
Juvenile animal safety studies	Variable	When previous safety data are insufficie nt	Pediatric clinical trials
Supplementary toxicity studies	Variable; dependen t on previous toxicity studies	Required if previous findings indicate special concern	

To improve drug development outcomes, it is important to review when preclinical pharmacodynamics and safety models have successfully predicted human responses and when they have not. In a recent issue of the BJP, Bugelski and Martin examined the concordance between preclinical and human data for biopharmaceuticals targeted to cell-surface proteins. The cases are interesting and several trends emerge.[1] The pharmacodynamics of biopharmaceuticals in non-human primates is largely predictive; the use of surrogates in rodents may be similarly predictive, allowing for more conservative use of non-human primates. While overall concordance of preclinical toxicology data and clinical safety was poor, this is largely a reflection of the immunomodulatory biology of the majority of the biopharmaceuticals evaluated.

The ultimate aims of preclinical research are to reliably model, in animals, the desired biological impact of a medication in order to predict treatment outcome in patients (efficacy), and to classify and describe all toxicities associated with a drug in order to predict adverse effects in people (safety) for informed risk evaluation. Currently, the results of preclinical trials are more accurate, and are best summarized as providing evidence for the intended biological effect of a medication (pharmacodynamics) and providing insight into possible toxicities to create a human starting dose at which no significant adverse reactions are likely to occur and allow for control of any undesired effects.

In two articles in a recent issue of BJP, Bugelski and Martin examine the concordance between preclinical and human data for biopharmaceuticals.[2] They provide an organized summary of the preclinical and human data on the 15 currently approved monoclonal antibodies and fusion proteins targeted to cell-surface proteins.[3] In their general study, they find that they are well-compatible with human pharmacology in mice receiving substitute molecules or non-human primates that receive cross-reactive human bio pharmaceutics but that they are poorly compared with pharmacodynamics received by genetically impaired mouse and all three models with harmful human results.

The pharmacodynamics of rodents' surrogates and the medicinal physics of human primates have not been uncommon to man. Generally speaking, the reason for moving a new treatment into the clinic is based on the biological impact expected by animals. The interesting finding of the study is that rodent substitutes are comparatively predictive. This conclusion suggests that the development of adequate substitutes to assess the biologic effect required by rodents is worthwhile and offers support in preclinical trials for reducing the use of non-human primates. Although the data set for substitutes for the rodent is small and cases in which the substitute or rodent model does not replicate circumstances or reactions in people/primates, the prediction of human pharmacodynamics alone is premature in assume that rodent models would be sufficient.

The investigators observed that mice’s consuming subrogate molecules or non-human primates received cross-reactive human biopharmaceutical drugs were in

poor agreement with human adverse effects. However, the finding mostly reflects the immunomodulatory biology in most cell-surface biopharmaceutical products. The writers stressed that certain medications are immunosuppressive, due to the mechanism of action and preclinical models.[3]

Severe clinical trials of efalizumab and tocilizumab contained bacterial, virus, fungal and other opportunistic infections, not reported in non-human or rat pre-clinical studies.[4] It is little wonder that preclinical modeling does not forecast the harmful consequences of immunosuppression, since pathogens in regulated laboratory environments are quite different from the pathogens in a range of environmental conditions in a root or nonhuman primate. A number of monoclonal antibodies, including muromonabe, that target lymphocytes, have induced cytokine release syndrome that rodents and non-human primates have also not predicted. The best-documented example of inability to predict cytokine release is the CD28 unique TGN1412 antibody that led to life-threats in a phase I clinical trial, leading to the activation of the T-cell, to acute cytokine release syndrome. In the non-human primate research, the acute cytokine reaction was reported.[5] Follow-up in vitro studies have shown that non-human primates fail to imitate the human in vivo reaction due to variations in the reactivity of non-human primate and human white blood cell TGN1412.[6]

This inability to foresee immunomodulation outcomes (immunosuppression and cytokine release) seems to be the main explanation why most biopharmaceuticals mentioned in this paper differ between the preclinical and clinical safety findings. In this respect, it is important to remember that there was consensuses among at least one of the pre-clinical models of clinical side effects among the four medicines (cetuximab, panitumumab, abciximab and trastuzumab) which are not immune modulate.

DISCUSSION

The results of the experimental shortcomings and the data series, not as per the models, may be more reasons of a weak harmony between preclinical toxicology and human welfare. The hazard detection and subtle symptoms observed by patients (headache, discomfort, tiredness, etc.) could not be seen in animals in the pre-clinical toxicology tests. Moreover, any adverse effect which is only seldom observes in patients would be very difficult, considering higher dosage doses and longer drug-handling periods, to detect in preclinical trials due to functional constraints of the scale of the tests.

Preclinical studies are not allowed to diagnose unusual events, especially in non-human primates. In preclinical trials the use of young, stable animals is usually the contrast to biopharmaceuticals in human patients for indications of inflammation and oncology. Nor is it surprise that trials in ordinary animals fail to identify any of the most significant human adverse effects due to contact with concurrent therapy, such as an elevated risk of heart failure following doxorubicin and cyclophosphamide care in patients with trastuzumab.[7]

In order to explain where our pre-clinical models are more or less predictive, we need to collect sufficiently clinical evidence for cell-field biopharmaceutical products. The pharmacodynamics of biopharmaceuticals is largely predictive in non-human primates; the use of the suitable substitutes in rodents can be equally predictive, thereby enabling non- human primates to be used more conservatively. For efficient outcomes, measures such as pre-clinical routines should be taken where they may be less predictive and in order to take educated decision in the field of drug discovery new and clinically relevant additional pre-clinical trials should be considered.

CONCLUSION

Despite all attempts to identify relevant animal models to guarantee a meaningful translation benefit, preclinical testing is indispensable; as medicines are given to human beings, they usually have distinct pharmacodynamics properties. There is therefore clearance for the use of only one out of five research drugs studied in clinical studies. Some reports also claim that just 9% of preclinical compounds are preclinical effective. The failure to evaluate effectiveness in Phase II and Phase III trials shows that pre-clinical models are currently used to properly imitate tumors-heterogeneity, holster causes, and pathways for drug-resistance. However, for human subjects to be protected in clinical trials, preclinical testing is imperative. Effective creation and careful selection of modeling frameworks for preclinical trials are essential to ensure appropriate findings that are applied in clinical settings.

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