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Opinion

# Bridging the Gap between Pre-Clinical and Clinical Studies in Cancer Research

**Ratna Kumari***

DBT BIOCARe Scientist, India

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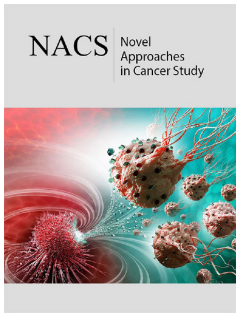


***Corresponding author:** Ratna Kumari, DBT BIOCARe Scientist, India

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**Abstract**

In spite of successful basic and pre-clinical cancer research findings its translatability into clinics is significantly low. Unfortunately, most of the clinical trials in oncology are unsuccessful and lead to pharmacological drug attrition. The complex nature of cancer biology and limitations due to pre-clinical research tools makes pre-clinical cancer research prone to irreproducibility. Pharmacological development of drugs heavily relies on the published data for drug target biology and irreproducible findings are the key factor behind high failure rates of clinical trials. Consequently, there is an urgent need to revisit the pre-clinical cancer research strategies to achieve a greater clinical success.

## Introduction

With the advent of new technologies over the decades the field of Cancer Research has reached its pinnacle of success. Despite the success of basic and pre-clinical cancer research most of the clinical trials do not succeed with expected outcome. Basically, pre-clinical studies play an enormously important role when it comes to decide whether a drug is safe, effective, and ready for clinical trials or not. The evaluation of human specific drugs through pre-clinical studies is extremely crucial for the success of clinical trials. Unfortunately, the translatability of pre-clinical cancer research is significantly low than other therapeutic areas [1-2]. It is now a well-established fact that the clinical trials in cancer have the highest failure rate. Indeed, many significant pre-clinical findings based on which the clinical trials are designed are not actually reproducible [1]. Consequently, there is an urgent need to revisit the pre-clinical cancer research strategies to achieve a greater clinical success.

The successful translation of pre-clinical cancer studies depends on various factors, and traditionally the way pre-clinical studies are done is already falling short of standard. The major challenges while moving research findings from pre-clinical phase to clinical phase are the following:

A. Reproducibility of pre-clinical findings: Our ability to translate pre-clinical cancer research is remarkably low primarily because most of the clinical trials designed are based on pre-clinical findings which are actually non-reproducible in many cases [1]. It occurs because of inherently complex nature of cancer biology and limitations due to pre-clinical research tools. Maintaining an optimal research environment is another important factor contributing towards the reproducibility.

B. Evaluation of tumor response in pre-clinical models and in clinical trials: Evaluation of tumor response and drug treatment response plays an important role in the success of the clinical trial and ultimately lead to approval of the anti-cancer drug. The main anti-tumor response criterion in pre-clinical animal models is the shrinkage of tumor size and is done mostly after sacrificing animals thereby eliminating the impact of anti-tumor agent on the overall survival of animals. However, in clinical trials tumor assessment is carefully selected and done based on the purpose of trial. Early phase clinical trials estimate the safety and identify evidence of biological drug activity, such as tumor size reduction. In later phase efficacy studies commonly assess whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms. In clinical trials a careful selection of endpoints based on tumor assessment plays a significant role.

C. Multi-model pre-clinical research strategy: Use of suitable pre-clinical model advances the chance of successful pharmacological drug development. Use of one narrow experimental model might be enough to get a publication, but it is not at all good for pre-clinical/clinical development of a drug. Pre-clinical studies incorporating a number of well-characterized cell-lines, *In-vivo* animal models, and biospecimens represents heterogeneity in tumors and provide stronger evidence. Furthermore, the underlying hypothesis of the study complemented with multi-model analysis and presentation of entire data set supports clinical development of drugs.

D. Pre-clinical drug development and drug attrition rate in clinical trial: The quality of pre-clinical strategies for drug development is the key behind registration new cancer medicines and its ultimate approval. Less drug dose optimization before it moves into further crucial clinical trials and less assurance regarding relationship between early end points and late/regulatory end points funnel into pharmacological drug attrition.

E. Patient driven correlative science approach: For a successful new molecular targeted drug development; the results from pre-clinical studies should be robust enough to withstand the rigorous challenges of clinical trials. To achieve this, the pre-clinical studies should be complemented with patient driven correlative science which entails correlating pre-clinical studies with the biospecimen based research. Such correlative studies have potential to reduce the failure rates in pharmacological drug development process.

F. Clinical trial design**:** Resolving the fundamental issues regarding clinical trial design and proper planning eliminates most of the errors in clinical trials. Finding the right patient who will benefit from the new drug under clinical trial is one of the biggest challenges [3]. As in most cases clinical trials are conducted prospectively and selecting patients prospectively is one of the big reasons behind high failure rates of clinical trials.

G. Quality of published literatures: The whole drug development process relies heavily on the published literatures describing basic and preclinical studies regarding drug target and biology [4]. Even in the earliest stage of drug development the cost of investment activities is substantial, so the validity of published literatures plays an extremely important role. The in-depth understanding of potential drugs targets would surely reduce the drug attrition rate.

Addressing these systemic issues would improve the translatability of projects being transferred from academia to industry/clinical settings. To maximize the effect and reduce high phase II failure rates the pre-clinical drug development should be carried in close collaboration between Scientists, Physicians, Patients Advocates, and Patients. The pre-clinical studies should always be associated with multiple models (*In-Vitro*, *In-Vivo*, and Clinical Samples) and there should be equivalent opportunities to present negative data as well. In essence, the success of clinical trials for pharmacological development of a drug depends upon the sustainable pre-clinical research strategies.

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