Delivering patient relevant healthcare and patient centric drug discovery and innovation based approach globally is the new and emerging requirement. It means, the very starting material, knowledge and data is to be connected with the patient and only patient. Conventional methods relying on extrapolation of data from animal systems and models is slowly going to be a thing of the past as the emerging field of human stem cells and their role in drug discovery and development is quickly gaining momentum.

S Dravida, A Soorneedi Transcell Biologics

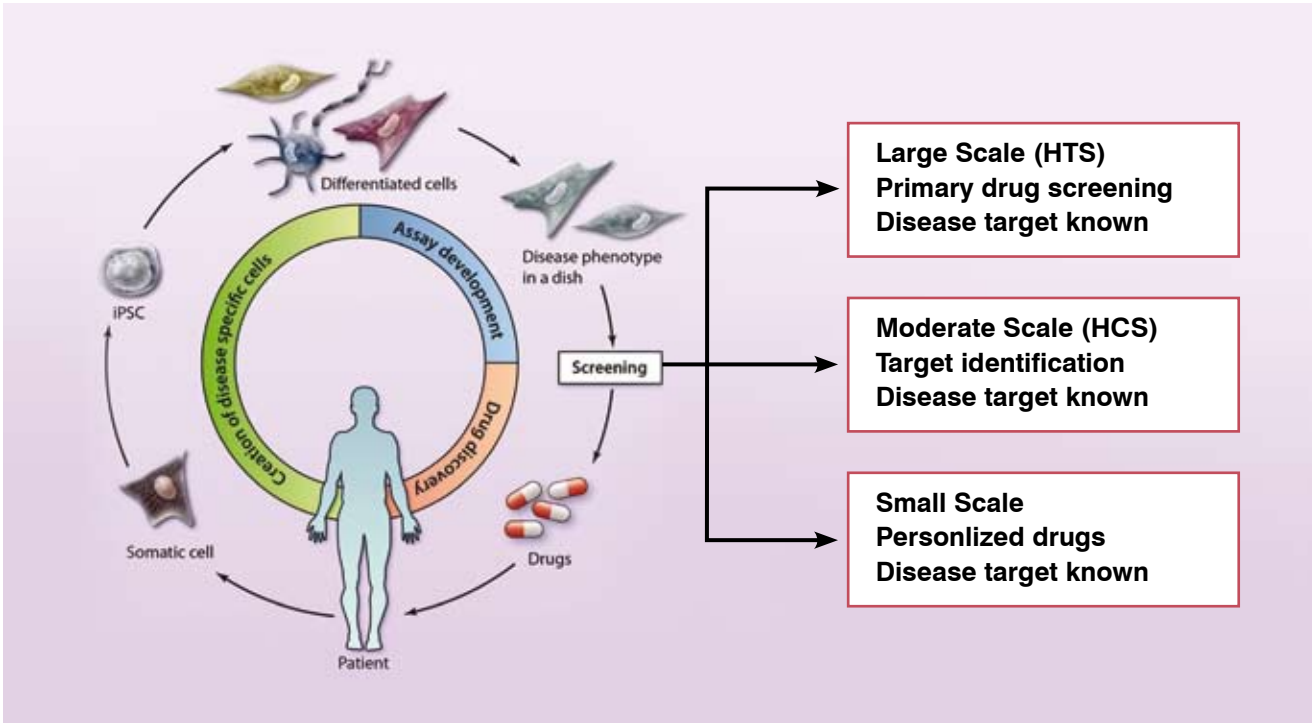
Emerging Directions in R&D of Drug Discovery and Development

The patient specificity paradigm

Using stem cells as platforms for drug discovery not only allows us to recreate the microenvironment usually found inside the body but it also allows us to decipher the molecular intricacies that play an important role in the success of precision medicine and ways to further improve it.

Traditional drug discovery practice includes the early phases of research (Pre-Discovery stage), Discovery phase 1 (Identification of hit molecules), Discovery phase 2 (Lead and Optimisation), Discovery phase 3 (Pre-clinical safety and efficacy) leading to Development stage involving clinical trials. The early stages of the process is known to take approximately upto six years and then, researchers hope to identify, develop a suitable drug candidate to further optimise in the lab, animal models, and then in clinics for another ten to twelve years. The story of drug discovery from academic or clinical research or from the commercial sector, till date has been revolving around the elusive 'Target', which is anything within a living organism to which a druggable candidate is directed, resulting in the function that is expected of in a disease state.

Ninety nine per cent of the hypothesis-driven drug research is centered around known and tested targets (biased) from the literature or in the mind of the lead researcher; thousands of



compounds accessed from shared libraries or made libraries from the known drug scaffold/chemistry are screened, followed by hunting for molecules that would dock in, which is a wild goose chase. Recent advances in molecular medicine and tools to enhance computational capacity have claimed to have enabled researchers to only understand the inner workings of human disease to extrapolate in research on validated Targets. The traditional high throughput (computational) screening process which is very popular during the early phases of research can leverage automation between validated target points and large number of drug-like compounds. Very recent emerging thought process -driven direction in early phases of drug research is to develop patient specific drugs taking into consideration the patients history. The introspection and interruption points could be the starting materials (both chemistry and biology) along with the process employed. The promise of personalised medicine (or precision medicine) is to get the right treatment to the right patient at the right dose the first time, through the use of targeted/selected therapies with desired outcomes. Equipped with phenotype screening platforms to discover the desired functions, the pre-discovery phase has a great opportunity to integrate patient sourced samples, especially in oncology and neurodegenerative diseases drug research. These emerging advancements not only offer selectivity/ targeted relevant options to patients but also nicely complement complexity to the R&D process directed towards functional multi-target discoveries on the patients for the patients.

The R&D in valid in taking hits to leads and optimising leads traditionally again is very target-centric with repetitive screening performed on either easily available animal or transformed cell based or engineered artificial reporter assay platforms. These are far away from the natural biological systems and the data obtained need extrapolation to the patient and the human disease indications. Although phenotypic assays validate drug candidates in intact and relevant biological platforms, integration of patient sourced and prepared biological platforms in optimising leads is relevant minimising any false positive data at this stage of crucial discovery process, setting stage for successful drug development in clinics.

Pre-clinical animal-based safety and efficacy phases of drug research is the only known and applied procedure for investigational new drug candidate that has passed the preliminary stages of research and validation. This approach comes under heavy criticism from many anti-animal usage groups advocating actively against the use of animals for drug testing. It was reported that approximately 20 million animals are used annually in medical experiments or for testing drug candidates. Depending on animal research and testing to discover drugs for humans is expensive, time-consuming, unreliable and not patient relevant. Extrapolation of information/ data from animal research to developing patient specific drugs has always had erratic baseline in anatomy, organ structure/function, metabolism, drug absorption. Despite the fact that several

hundreds of animals are used for testing a single drug candidate, generating volumes of safety data, approximately 95 per cent of the drug candidates do not pass clinical trials while the disease burden continues to rise.

It is to the common man's and the patient's knowledge that in spite of several hundreds of animals used for testing one drug candidate and the volumes of safety and efficacy data generated on all the investigational new drugs till date, approximately 95 per cent of the drug candidates that enter human clinical testing fail while the disease burden has continued to rise. The recent discovery of human donor sourcing and inducing pluripotency has revolutionised the very approach and the hypothesis of integrating human/donor/patient stem cell based systems to evaluate the safety and efficacy of drug candidates pushing the data generated closer to reality and not extrapolation, that has always resulted in desperate situations for clinics. The behaviour of cells in phenotypic assays is monitored microscopically, providing sub-cellular ultra deep resolution of biological responses that the human cells display to drugs. Human tissues from donors can provide yet another approach, as well as animal models. Additionally, as the liver plays a critical role in how the body metabolises drugs and produces key proteins, the existing animal models are being used to study physiology and pharmacology in an intact system, patient, or donor derived stem cell coaxed liver models with both the complex micro-architecture and diverse cell makeup developed in the lab as platforms for drug evaluations.

During the century-old drug discovery and development research, investigators have uncovered certain important and expensive reasons that led the R&D process to a dead end and setbacks from finding the holy grail. Target biased and based approach, in silico methods of high throughput assays along with the discovery on non-patient systems, coupled with extrapolating to the human disease have surfaced to be the stumbling blocks. Integrating nature-inspired new and complex stereochemistry addressing the undruggable /druggable targets, functional phenotype based high throughput screening along with privileged biology having high physiological relevance, such as those that use human primary cell types, organoids derived from such primary cell types, stem-cell derived cells, and/or patient cells, are the emerging directions that are proven to increase predictive validity, improving R&D productivity.

Drug discovery and development using patient sourced biological platforms and predictive models embracing genomics inspired target identification has to become the new norm and direction with highest probabilities of success predicted. This practice while helping improve the precision of novel drugs would also benefit the R&D sector economically.

Target tricks don't work in drug discovery and development anymore….

Do or Do not! There is no try.. is the new order for drug hunters!

AUTHOR BIO

A Scientist by profession, **Subhadraw Dravida** led global stem cell research and commercialisation initiatives in regenerative medicine and drug discovery domains for over 12 years. She holds over two dozen patents in the field of regenerative medicine and has significant expertise in converting promising research into business opportunities.