Next Generation Therapeutics: Stem cell to Drug discovery

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Stem cell biology has captured the imagination of biologists, tissue engineers, pharmaceutical company scientists, and indeed the general public, largely because of the prospect it seems to offer of manipulating cell fate to treat disorders for which there is no other effective therapy. In recent years, one of the most promising applications for stem cell biology has been in drug discovery. Stem cells are increasingly being used in new and innovative ways to improve the drug discovery process – including academia, biotech start-ups and large pharmaceutical companies. In this seminar we'll take a look at how stem cells are being used in the drug discovery process – from disease modelling, to target identification, through to compound screening, and toxicity testing. Further, provide information on stem cell technologies and how they are shaping the pharmaceutical industries. The interest in stem cell biology as a route to novel therapeutic drugs arose from the convergence of **3 separate lines of investigations**:

1) There is evidence that pathways that regulate embryonic development and, hence, act in large part on tissue stem and progenitor cells are also disrupted in adult disease.
2) Control differentiation of embryonic stem cells and small molecule regulators of differentiation.
3) Major advance was the reprogramming of adult cells to induced pluripotent stem cells (iPSCs). The iPSC technology offers the prospect of capturing cells derived from a large number of specific types of pre-diagnosed adult patients, potentially at any age, and a correspondingly large number of controls in a format that can support an industrial level of screening, efficacy, and safety studies.

Disease modelling: Drug discovery relies on having accurate models of human disease. Historically, disease modelling has been restricted to animal models, simple single cell organisms such as yeast, and immortalized human cancer cell lines. Animal models do not fully approximate human physiology, and studies cannot be sufficiently scaled for large-scale, comprehensive phenotypic testing. Ground-breaking work by Shinya Yamanaka in 2006 helped circumvent these issues, by showing that genetic reprogramming could turn terminally differentiated adult cells back into an embryonic like state. These resultant stem cells, called induced pluripotent stem cells (iPSCs), share many features of embryonic stem cells (ESCs), including pluripotency. **Compound screening:** Translating complex stem cell derived in vitro models into large scale, reproducible phenotypic assays that allow the screening of thousands of compounds, is a vital yet challenging step in stem cell-based drug discovery. **Toxicity screening:** While stem cell-based models are incredibly useful in early-stage disease specific phenotypic screens, stem cells can also be an incredibly useful tool for identifying off-target adverse effects of drugs already in development. Identifying such effects early on in the drug development pipeline can be much more cost-effective than identifying these effects later in animal studies – or during clinical studies. These include cardiac toxicity screens, and liver toxicity screens. It is hoped that screening for toxicity early on in the drug development process will make it easier to re-design compounds to reduce their toxicity.

Summary

The drug discovery process as practiced in most pharmaceutical companies is inefficient, at best, and, in the past decade or so, has struggled to meet the need for new drugs. In addition, there have been a number of famous cases in which already marketed drugs have been found to have unanticipated side effects. Standard preclinical drug safety testing relies exclusively on administering drugs to two non-human animal species, and it is possible that safety studies on validated human cells might help avoid unexpected drug toxicities. Stem cells offer the remarkable capacity to generate an unlimited source of disease relevant cell types to perform large-scale phenotypic screens and also identify off-target toxicities.