COMMENTARY

Problems with the Drug Discovery and Development Process: An Outsider's Viewpoint

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DESCRIPTION

Preclinical drug development

The major problem as I see it in the Preclinical Drug Development is utilizing biochemical, cell culture, healthy animal models, and diseased animal models and trying to mimic to a large degree the human diseases. Although clearly these models have their utility, the specificity to the human model is quite limited. First, although there is 98% DNA homology between mouse and human models, the 2% difference appears to be a large difference in DNA sequence. For example, genes for human cytokines are "knocked-in' to make a mouse more like a human. Another example of trying to mimic the human model with an animal model is the mouse xenograft model of cancer in which the human tumour of interest is grafted into a mouse.

The problem is that in the mouse model they have chosen to graft the tumour into is a mouse model that does not have an immune system. Clearly, the idea of taking a human tumour and grafting it into a mouse would seem very specific and robust of a disease model. On the other hand, maybe the scientists in question should use a mouse with an intact immune system and therefore examine the effects of the tumour alone on disease progression and survival.

Clinical trials

Clearly Phase I Clinical Trials appear to be intact and 10-100 patients would appear to be an appropriate number of patients to study efficacy and safety in a diseased population. This is from a statistical standpoint. As I understand it; however, Phase I Clinical Trials are commonly performed in healthy volunteers. Phase II and Phase III Clinical Trials in my opinion are complete overkill with regard to the number of patients utilized from a statistical standpoint. Phase II Clinical Trials utilize 100-500 patients while Phase III Trials utilize 1000s of patients. These studies are likely way overpowered from a statistical standpoint. What that means both from an efficacy mainly but also a safety standpoint is there is too much time, resources, and money wasted in collecting data on 500-1000s of patients.

From a statistical standpoint for efficacy the fewer patients utilized in a study that shows a statistical benefit of an intervention like a drug, the larger in the effect (effect size). In Physiology, we frequently use 6-12 healthy subjects in a nutritional supplement and/or exercise intervention and show efficacy. From my standpoint, having 500-1000s patients with disease enrolled for only a safety perspective, is again overkill. A researcher, clinician, and/or nurse should be able to do document severe and high number of side effects if they are present in 100 patients with the disease in question.

An additional measure, with regard to Clinical Trials, would be the addition of Exploratory Clinical Trials to the already present Phase I Clinical Trials. That is patients could be added one by one if side effects are low in number and severity. The Exploratory Study could be accelerated at a high rate when the first few patients show no significant and numerous side effects. In essence, I believe their needs to be a restructuring of the Drug Development process.

Again, I am an outsider to the Pharmaceutical Industry but have extensive clinical trial experience with nutritional supplements, exercise interventions, and FDA approved drugs.

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