Title: **The Biggest Challenge in Science remains the Scientist**
Catch phrase for twitter:
#According_to_a_meta-study_scientists_are_certifiably_responsible
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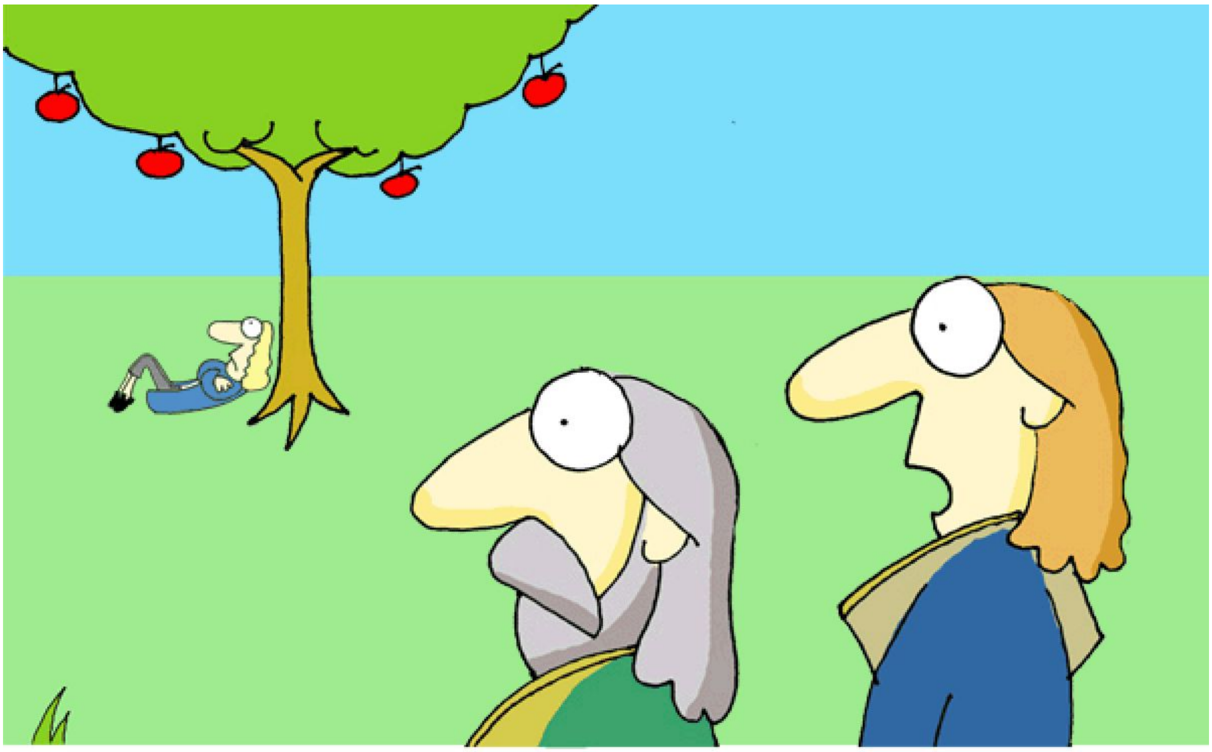

“Reviewers have asked him to reproduce the experiment.”

Preclinical research is, by definition, preclinical. It’s the groundwork, the preliminary research of finding and evaluating treatments before testing them on humans. Medical researchers are in a constant race to translate laboratory findings into clinical trials against constraints in time and resources. The challenges can be categorized into two groups. On one hand, scientists deal with multiple factors and effects (number of targets, drugs, doses and treatment regimes) which implies a broad and parallel approach. On the other hand, clinical development is expensive and exposes patients to unknown risks which implies a limited and specialized approach. The first group of challenges thus is how to find potential treatments, the second group is how to make sure a treatment really works.

For the first group, scientists use exploratory research to generate a series of pathophysiological theories translating data into assumed connections between causes and effects. Strategies can evolve and change over the course of time, as during investigations new findings may arise. The use of small sample sizes allows to test strategies in parallel.

However, small sample sizes lead to random variations that may result in large effect sizes and lower the positive predictive value (PPV), possibly wasting resources in clinical research. To overcome this problem, confirmatory research is inevitable. Confirmatory research aims to conclusively and reliably test a pre-specified relationship between variables. Its outcome decides over clinical trials. In contrast to exploratory research, confirmatory research requires a more stringent methodological approach and must be optimized for reliability. Larger sample sizes minimize the effect of random variations such as false positive error. These two approaches complement each other: intervention strategies established by exploratory research should be tested by confirmatory studies before clinical trials. Unfortunately few preclinical studies use confirmatory testing.

Moreover, most studies are conducted with certain errors or irregularities and may sometimes generate conclusions that contradict even within the same line of research. Thus the necessity for a new method arises. Combining the data of several related studies, meta-analysis uses statistical methods to come up with an estimate close to the unknown truth hiding behind the data. It also uses statistical power to resolve the uncertainty when reports disagree. But to what extent is this analysis informative? Meta-analysis cannot correct for poor design and/or bias in the original studies. For example, unreported data and manipulation in the size of samples (attrition of animal model and masking of outliers) weaken the power of this method. All these limitations have driven analysts to refine the criteria by which a certain study is included in meta-analysis. But has this resolved the issue? Unfortunately, not. So, what else can be done?

A new scientific discipline that conducts research on research is evolving. The field of meta-research cuts across all disciplines, drawing from a wide range of methodologies and theoretical framework. Meta-research focuses on: how to perform research, reporting standards, reproducibility, evaluation and how to reform the reward and incentive system. Meta-research interfaces with many other established disciplines such as epistemology, psychology, ethics and research synthesis methods (meta-analysis). The search-string database “Scopus” maps the meta-research literature and identifies its key players. It comprises 79 terms that capture the thematic areas described above and allows the identification of meta-research-relevant publications.

Meta-research as a growing interdisciplinary field requires continuous updates and refinements. Initiatives such as the Meta-Research Innovation Center at Stanford (METRICS) and the Cochrane Collaboration were launched within the last few years. METRICS has recruited a large number of faculties within/without biomedicine in an attempt to connect the different elements of this field and enhance their synergy. In addition, METRICS started building a meta-research community through speaker series, curriculum development, regular workshops and by creating an interactive online platform to inform and connect researchers.

As research relies on each of its components, every single one is essential and must be trustworthy. Transparent complete reporting of the raw data and a clear experimental methodology are of paramount importance. To improve the effectiveness of quality control in preclinical trials, guidelines (e.g. ARRIVE/IMPROVE) were developed. Compliance with these guidelines shows promising results. In addition emphasizing awareness among students results in a well informed and better equipped generation of scientists who are able to conduct studies with precision, accuracy and reliability.

Although meta-research seems to be a powerful tool to improve experimental practice and design, publication bias still drives a lot of research facilities into malpractice. Only collaboration between the different scientific institutions can minimize the risk of violations and consequently provide a more reliable basis for clinical trials in the interest of better healthcare.

References

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