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It is Time to Re-evaluate the Peer Review Process for Preclinical Research

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Issues and Challenges with Peer-Review

In 2011, Ploegh wrote an outstanding comment in *Nature* entitled “End the Wasteful Tyranny of Reviewer Experiments”.^[1] Ploegh eloquently explained how time and money are wasted in responding to peer review that goes *beyond* the task of deciding if the premise of the work is worthy of publication. Unfortunately, little has changed since then!

Peer review was intended to assure that published studies were based on a sound hypothesis, valid methodology, and logical interpretation of results. However, peer review has morphed into what is often a “wish list” of experiments that the authors must successfully complete to achieve their goal of publication. Once a manuscript is revised, it is re-reviewed by the original reviewers: this is appropriate in principle as the reviewers are already familiar with the work and are in the best position to determine if the manuscript has been improved. The reviewers must be satisfied with the authors’ responses. If not, 1) more work is requested or, 2) the paper is rejected. Thus, authors feel pressure to appease the reviewers. And herein lies a major problem.

Although reviewer queries are an integral aspect of the peer-review process, not all reviewer queries improve manuscripts. As stated by Ploegh, the review/revision process is frequently not cost/time-efficient. A critical question remains: Are manuscripts of *significantly greater value* after review, revision, and possibly another round of the same? In an informal survey of colleagues in the cancer field, most believe that extensive revisions (estimated to take 6–24 months) improve the value of manuscripts by only 0–20% (one author stated that extensive revisions for high-impact journals actually *decreases* the manuscripts’ value by ~10%, as the delay in publication impedes the timely dissemination of knowledge).

In terms of cost-efficiency, reviewer comments seem to have become more complex and difficult to respond to, and the cost (for supplies and personnel) and time can drain laboratory resources. For example, we had a manuscript published in a high-impact journal after we persevered through 19 months of revisions; in our estimate, we spent over \$220,000

(salary and experiments) to satisfy the reviewers' requests. The manuscript probably improved by ~10%, and none of the principal findings changed.

On many occasions, the reviewers' wish list coerces authors to present a *perfect* story; if one is to get over the "hump" and have the manuscript accepted, one *must* provide *positive* results when addressing reviewer queries. Elizabeth Iorns, Co-Director of the Reproducibility Initiative, points out that rarely, if ever, does an author report a negative result when responding to a query (personal communication). We believe that the current peer review process can play a role in fostering a culture of selective reporting or, worse, even falsifying or fabricating data in order to appease reviewers.^[2] While peer review is essential to assure data reproducibility, the pressure on authors to provide the data that reviewers *prefer* to see affects data reproducibility and the integrity of our research enterprise; in turn, this may impact clinical trials and/or patient care. The principle of "publish or perish" is stronger than ever, and furthermore, publishing in a few select journals—the "CNS" journals (*Cell*, *Nature*, *Science*, and related journals) has become almost essential to the careers of young investigators in some fields. The possibility that the payoffs and "perverse academic incentives" ^[3] for publishing in these journals are so high that it tempts authors to provide results that appease reviewers; this occurs at the cost of breaches in the ethical conduct of science.

In addition, it is important to recognize that not all peer review is altruistic. Reviewers sometimes request additional experiments that seem designed to support work done in their own laboratories and, in turn, lead to the referencing of the reviewer's publications. There is also speculation among investigators that some peer reviewers continue to submit new queries on subsequent reviews so that publication is delayed long enough that they have time to "scoop" the authors.^[4]

In spite of a suboptimal peer review system, most investigators in our scientific community agree that peer review is important and necessary to maintain high standards in publishing. Although there have been efforts to publish manuscripts prior to review and then have the community conduct post-publication peer review, this has not been implemented in the biomedical arena. Thus, pre-publication peer review remains the cornerstone of publishing the highest quality data.

An important issue is that most scientists never receive any *formal* training on how to review manuscripts. We list several resources that may train peer reviewers.^[5–8] The senior author of this manuscript has been a peer reviewer for >25 years but has never been asked whether he has received any training in peer review. While referees in various other aspects of life, such as sports, have to undergo rigorous training to be able to adjudicate in their respective fields, there are rare opportunities for formal training in peer review. This is especially troublesome because peer review may determine whether an article that has the potential to affect clinical care and/or drug approval is published. Suboptimal peer-review may allow publication of sketchy, but sexy data, leading to either lack of reproducibility, failed clinical trials, or both. "Closed-minded" peer-review may also "miss" a potentially interesting observation since it may not be a sensationalized finding, but one that is still important to the

field. Delays in scientific publishing are having profound effects on dissemination of knowledge and negatively impacting the careers of many investigators.^[4]

Suggested Guidelines for Scientific Peer Review

What can the scientific community do to solve or mitigate these problems? We think that the onus lies on us all: authors, reviewers, publishers, and editors.

For Authors

We believe that the following requirements must be met by authors prior to manuscript submission to assure that reviewers' time is used efficiently. 1) The authors must present a coherent *story* that was hypothesis-driven and supported by experiments that either support or refute the underlying hypothesis (again, negative findings have merit). 2) Methodology must be detailed enough to facilitate attempts at validating the experiments in other laboratories. 3) The report must show results of all experiments conducted to test the underlying hypothesis, even if results were "negative", and all studies leading to the ultimate premise of the work must be reported. 4) The study must use appropriate statistical techniques, and not seek the test that is best suited to obtain the almighty $P < 0.05$. 5) The authors must avoid making sensationalized claims that are not directly supported by the data.

For Reviewers

There are basic principles of peer-review that reviewers should follow: 1) Accept manuscripts for review only if there is no conflict of interest and you have no inherent or subconscious bias; 2) Be punctual and finish the review process within a reasonable period (as outlined by the journal); 3) Be honest in accepting or refusing a manuscript for review based on your knowledge base in the area: not every reviewer is an expert in all aspects of her/his field. All of these, if done wrong, can lead to unnecessary delays or biases in manuscript reviews and dissemination of knowledge.

As stated above, the purpose of peer-review is to assure that published manuscripts contribute meaningful information to the scientific community. When reviewing manuscripts, reviewers should focus on the major premise of the work, and determine whether the data support the conclusions. When revision is necessary, reviewers should *prioritize* the few studies or analyses that must be done to support the premise of the paper, while listing interesting but non-essential studies as "suggestions".^[9] It is not mandated that these suggestions be addressed in the current study; however, if these studies have already been done, they could easily be added to the manuscript. In addition, such suggestions could be the basis of the author's next paper, because input from expert reviewers can influence continued progress in a field. Perhaps this openness in sharing ideas and suggestions could accelerate research overall. After all, our primary goal is to advance knowledge, and the more ideas and suggestions provided by experts, the more likely we are to make an impact on the lives of our patients!

Probably the most important aspect is what *not* to do: do not penalize authors for reporting negative results. Do not ask authors for additional studies that will not further support the conclusions of the paper. Avoid asking for a wish list of studies that you would like to see,

but that doesn't address the premise of the work. If a paper is interesting, but not within the purview of the journal, be complimentary and suggest an alternative journal; don't overwhelm the authors with negative comments. Negative comments should be reserved for incompetent research and unethical behavior.

For Journals, Editors, and Institutions

All of the above (in the prior 2 sections) requires a culture change, of which the first step would be training of peer reviewers and editors. We may not be able to re-train the current generation of reviewers, but as we move forward, tutorials in peer review should be a requirement for successful completion of any medical and graduate education program. This should also be initiated by journals via a short tutorial or even on-line video.

How can we decrease the burden of peer review while optimizing the value? Peer review requires a great deal of time and effort, with little reward other than fulfilling our moral obligation to serve the scientific community. Publishers and editors should devise a system where peer review is less burdensome and asks the reviewers to focus on the key message of the manuscript. As mentioned above, a template separating *essential queries* vs *suggestions* may help in prioritizing additional studies. Editors should utilize a *line item veto* of requests for additional studies that are not critical to the underlying message of the work.

We propose to allow only *three* categories for initial decisions: 1) accept; 2) accept with minor modifications; or 3) reject (Table 1). If reviewers find that a study is timely and important, they should do everything possible to have the information disseminated rapidly to the scientific or medical community. It is very easy for reviewers and editors to request major revisions, but this leaves the authors in limbo (and perhaps even without sufficient funding for other studies). If a few experiments can be done in a reasonable time frame to fill in small gaps and/or further validate findings, or if data can be re-analyzed to address some minor issues, then it is appropriate to request revisions. But if there are major flaws in the study that requires substantial work to validate the authors' claims, the manuscript is apparently not ready for publication and should be rejected.^[9] We strongly suggest that editors refrain from manuscripts being sent back multiple times with requests for major and lengthy revisions, without a guarantee of acceptance for publication. Thus our recommendations above remove the commonly used category of "major revisions required". Editors must clearly state that appropriate responses to essential queries are required for acceptance; anything short of that may lead to a rejection, keeping with our recommendations that lengthy, costly, and repeated revisions should be discouraged.

The process of submitting, reviewing, and revising manuscripts (*and repeat as directed*, as stated on many shampoo bottles) often takes far too long; the same holds for grant submissions, reviews, revisions, and activation of funding. Each and every delay in publication (and grant approval) has a domino effect on the entire research enterprise and, ultimately, advances in important fields, such as cancer care. In the US alone it is estimated that about 1,650 people die each day of cancer.^[10] To rapidly facilitate new knowledge, we must determine if published studies are sound enough that they can serve as the foundation of additional studies that will, in turn, benefit patients. We need to use our time and

resources (including financial support) more efficiently and, most importantly, we must restore integrity and a sense of urgency in the field of research!

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Table 1

Proposed Reviewer Decisions and Rationale For Each Category

Reviewer's Decision	Basis for decision making
Accept	Timely and important study done properly and ethically that needs rapid dissemination within the scientific community.
Accept with minor Modifications	Basic premise of study is strong and true. Appropriate for a study where 1) a few experiments can be done in a reasonable time frame to fill in small gaps, 2) further validation of key findings re needed, and/or 3) if data needs to be re-analyzed to address some minor issues or statistical concerns.
Reject	Major flaws in the study that would require substantial work (and cost) to prove the authors' claims; i.e. the manuscript is not ready or thorough enough for publication. This approach avoids requests for major and lengthy revisions without a guarantee of acceptance for publication.