

# **Opening the Black Box of Peer Review**

Jonathan P. Saxe

Many of you are probably very familiar with the hard work that goes into writing a paper and preparing it for submission, but what about after you click "submit?" As editors, my colleagues and I at *Cell Stem Cell* understand that navigating the peer review and paper revision process can be daunting and mysterious. As part of our efforts to promote transparency in our editorial practices, we thought it would be helpful to publicly discuss the broader principles and procedures that we apply to all submitted papers. I'll do that in this Backstory, using two papers that were co-submitted to *Cell Stem Cell* and published late last year to walk you through our editorial processes. We'll also discuss the reviewer comments and resulting correspondences to illustrate key points along the way. The papers are from the groups of Jim Wells (https://www.cell.com/cell-stem-cell/fulltext/S193459091830393X) and Jianwen Que (https://www.cell.com/cell-stem-cell/fulltext/S1934590918303941), and the editorial team and I thank the authors and reviewers of these papers for allowing us to openly utilize these materials in this fashion.

### **Dual Presubmissions Lead to Coordinated Peer Review**

In September 2017, I received an enquiry from Jim Wells and Jianwen Que asking if *Cell Stem Cell* would be interested in their papers (Supplemental Information, Document S1, section I). Their groups had been working independently to derive esophageal organoids from human pluripotent stem cells, and after becoming aware of each other's work, they decided to coordinate their submissions. As you can see (Supplemental Information, Document S1, section II), the editorial team and I thought the papers were interesting and we encouraged submission. To us, presubmission enquiries are an opportunity for authors to quickly gather editorial feedback about the fit of a paper for a given journal based on its topic, specific findings, and systems utilized. Presubs can be sent simultaneously to multiple journals, and we welcome enquiries submitted through our website form or sent to our journal email and personal cell.com

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The Jianwen Que and Jim Wells groups model esophagus tissue development (left) using human PSC-derived organoids (right).



### addresses (listed on our journal's webpage). As you can see in my reply (Supplemental Information, Document S1, section II), these enquiries also give us a chance to ask questions that we think could come up during peer review and highlight any special circumstances; in this case, I briefly outlined some points that we think about when considering co-submitted papers.

You may wonder how it happens that closely related papers are often published together. Often, this is simply because authors independently submit similar papers around the same time. We can then review them on serendipitously similar timelines and may be able to coordinate their publication in a given issue. In other cases, such as here, the authors chose to co-submit their manuscripts. This kind of coordination can be advantageous, since two papers can provide a synergistic message and independently validate each other's main findings. However, we do look for each paper to independently meet our publication standards, and we will not publish a weaker study simply because it was co-submitted with a stronger one.

When papers are submitted to *Cell Stem Cell*, all editors receive an email containing the title, authors, and abstract, and we briefly discuss them during our frequent editorial meetings to keep up with all of the papers entering our system. *Cell Stem Cell* two pages to handling editors who read them in depth and assess their suitability for formal peer review. The criteria for suitability vary by journal and by specific subfield, but in general we weigh what the paper is teaching a sorad readership, so we look for innovative findings that resonate with multiple fields. We also assess technical quality, whether the study has obvious holes, and whether it might be a good fit for our journal if those holes are filled. The handling editor then presents the paper to the Editor-in-Chief and the rest of the editorial team, with a recommendation to review or reject without review. Other team members might add their own perspective and/or additional background, highlight related papers they handled to ensure consistency in how we proceed with papers touching on similar topics, and suggest potential reviewers.

Drs. Que and Wells co-submitted their studies a month after their presubmission enquiry. During our initial evaluations, our editorial team noted the clear interest in deriving tissuespecific organoids from human pluripotent stem cells, especially as human esophageal organoids had not been previously reported. In a group discussion following my in-depth evaluations, we noted the different approaches used by these groups for organoid derivation and the distinct biological lessons they taught us about esophageal development. We thought each paper was interesting on its own and that together they put forth a strong message about new ways to model human tissue-specific epithelial development, and we therefore sent them out for peer review.

When we send papers out for review, we provide authors with the option of immediately sharing their submitted manuscript and its "under review" status on our pre-publication server Sneak Peek (https://www.cell.com/sneakpeek). Both groups decided to post their papers, which you can view (at https://papers.ssrn.com/sol3/papers.cfm?abstract\_id=3155797 and https://papers.ssrn.com/sol3/papers.cfm?abstract\_id=3155722) and see how they have evolved as a result of the review process.

We recruit reviewers with subject and technical expertise that cover the main points that a paper is making, while also gathering broader perspective about its wider interest. With co-submitted papers, we try to have the same reviewers look at both, although that may vary if each paper has unique aspects. Here, three reviewers with expertise across esophageal biology and development and broader knowledge of epithelial biology, organoids, and endodermal tissue models agreed to review them both.

#### Making Sense of Mixed Reviews

As you can see (Supplemental Information, Document S1, sections III and IV), we received surprisingly mixed reviewer comments on the papers. Reviewer 2 thought both studies were very strong, and reviewer 1 felt similarly about the Que study and raised relatively minor concerns with it. However, reviewer 1 noted substantial concerns with several aspects of the Wells paper and resultantly recommended against inviting a revision. In stark contrast, reviewer 3 thought that the conclusions in the Wells paper were supported by the underlying data and that the work would be

"...coordination can be advantageous, since two papers can provide a synergistic message and independently validate each other's main findings."

### Cell Stem Cell Backstory



Jim Wells' team.

important for the field once properly revised, but raised a host of technical issues with the analyses in the Que paper and resultantly recommended against publishing it in our journal. So, how do we integrate such disparate feedback to arrive at fair and consistent editorial decisions for each paper?

As editors, we must carefully look at the scientific merits of the reviewer comments, and our decisions are not simply based on the most negative (or positive) reviews. Instead, we assess the reviewers' individual concerns and look for common themes among their comments, and then weigh those against the broader message of the paper and each reviewers' specific expertise. We also think about how much work it might take to address those issues and integrate all of that with the reviewers' perspectives on how a paper's findings may advance the field, in terms of broader knowledge as well as potential practical or therapeutic applicability. We then arrive at a decision that can come in several flavors, and we present the paper and our recommendations to the team for further discussions.

We encourage a "major revision" when the reviewers are enthusiastic about a paper and raise experimental issues that seem addressable within a discrete time frame of a few months. We reject papers with extensive technical issues or that seem unlikely to change how readers think about the topic at hand, since extensive revisions still won't make them a good fit for our journal. Many other papers, however, lie in a middle ground and we think about these a little differently. They may be making an interesting point but still need a lot of work, for instance to rule out alternate explanations or provide further insights, that we and the reviewers think is necessary for the paper to move forward at Cell Stem Cell. However, the best ways to resolve such issues aren't always obvious, and we also understand that there might be other factors that authors need to consider. What if a student or post-doc is leaving the lab soon, or what if you have a grant deadline coming up and need to have the paper published before that? It is often possible to publish faster, and with lessextensive revisions, in one of our sister journals rather than putting a lot of time and effort into revising a paper that may or may not end up published in Cell Stem Cell. In these situations, we often write an "open-door rejection" that clearly explains our thoughts and gives authors flexibility in proceeding. If authors decide to revise their paper with the intention of resubmitting it to us, we encourage emailing us to discuss a point-by-point rebuttal of the reviewers' critiques so we can ensure that critical points will be addressed. These discussions can be especially helpful to prevent significant misguided effort, and we may consult with reviewers about whether proposed experiments, if successful, might resolve their concerns.

What does this look like in practice? The team and I felt both studies fell in this middle ground, since the reviewers liked them both but also thought key aspects of each needed to be developed substantially. We also took a step back to ensure we were making consistent decisions between the papers, and we noted similar overall levels of enthusiasm for them. Taking this all together, open-door rejections for each seemed appropriate and also gave the authors freedom to continue coordinating with each other. I explained these points in the decision letters (Supplemental Information, Document S1, sections III and IV) and offered both sets of authors the opportunity to transfer their papers to *Cell Reports* if they did not want to revise the paper in the way we and the reviewers felt they needed to.

#### **Appealing Decisions and Finding Clear Paths for Revision**

Shortly afterward, I received emails from both sets of authors stating that they thought they could address the major concerns that the reviewers raised, and each followed up with a point-by-point rebuttal letter detailing their plans (Supplemental Information, Document S1, sections V, VI, and VII). We find it helpful to discuss revision plans at this point since we can resolve any misunderstandings about the major issues that arose during the review process, gain a sense of whether the authors think those issues are experimentally addressable and what their plans are for doing so, and how long that might take. Authors may raise potentially significant sticking points and we can provide our perspective about those as well. In other cases, discussions at this stage are an important reality check about whether a revised paper would even be a good fit here before authors invest a significant amount of time and energy into revisions. As you can see in their correspondences (Supplemental Information, Document S1, sections VI and VII), the Wells group raised reasonable counterpoints about the requests for further xenograft experiments, and both sets of authors were concerned about resolving questions about whether their esophageal organoids modeled bona fide human tissue at the molecular level. They also outlined their plans for addressing the other issues that came up, and we gave them encouraging feedback and clarifications about some specific questions (Supplemental Information, Document S1, section VIII).

The authors wrote to us again once they had completed their revisions to ask about resubmission. We make decisions about reconsidering rejected papers based on completed revisions, and when evaluating rebuttals we ask ourselves several questions. Do those revisions adequately address the technical critiques that reviewers raised? If the reviewers felt that the paper fell short of providing a clear conceptual breakthrough or exciting mechanistic insights, do the revisions now provide that? Did the reviewers indicate willingness to look at a revised paper, or were they clear in recommending the paper for another journal? Every situation is unique and we encourage authors to clearly explain how their revisions address the critiques raised in their response letters; when disagreeing with a specific point, it is best to do so constructively and from a scientific perspective rather than from a combative one.

In their detailed response letters (Supplemental Information, Document S1, sections IX and X), the authors described how they addressed the reviewers' comments, although not all experiments were successful (e.g., attempts to achieve orthotopic organoid engraftment to assess potential repopulation capacity). We do not necessarily require authors to resolve all of the reviewers' issues in order to re-review a paper, and in this case requiring a positive result for this experiment did not seem like a reasonable expectation given the state of the art in the field. We therefore agreed to formally reconsider both papers and asked reviewers 1 and 3 to re-review them; since reviewer 2 had mentioned in their review that they did not need to re-review it, we considered the authors' responses to their minor comments ourselves. Reviewer 1, who was previously positive about the Que paper but critical of the Wells paper, recommended accepting both revised papers. Reviewer 3 was largely positive about the authors' revisions but continued pressing a previous point about comparing organoids to primary human tissue that was not sufficiently resolved by the new RNA expression analyses. So what is a fair decision at this point?

In general, we consider papers through a single round of major revisions, and if there are substantial remaining issues we close the door to further consideration. That may seem harsh, but at this point in the process it is very clear whether the main conclusions of the paper are fundamentally sound or not. We really try to avoid repeated cycles of revisions and review, since those are very frustrating for authors, frequently do not result in a positive final recommendation, and



Jianwen Que's group.

substantially increase the timeline for publication (in our journal or another). We do make exceptions on a case-by-case basis when there is significant reviewer interest and a clear set of further experimental revisions.

In their re-reviews, two of three reviewers were very positive about both papers. The remaining issue about transcriptomic comparisons of organoids to their *in vivo* counterpart tissue was important but also seemed addressable through re-analyses of existing data and some additional, feasible experiments, so we gave both authors a minor revision. This decision does not mean that we will publish a paper but as you can see from our decision letters (Supplemental Information, Document S1, sections XI and XII), they do express editorial enthusiasm about moving forward toward publication. The authors then emailed us to describe how they were planning on resolving these outstanding issues and their plans seemed very reasonable to us (Supplemental Information, Document S1, sections XII and XIV); at this phase we do think it is important to resolve remaining critiques, particularly those central to a paper's main findings, but we want to ensure that can be done quickly and not unnecessarily delay publication.

We may ask reviewers to look over the further revisions or assess them at an editorial level; with the Que and Wells papers we felt that the new data (Supplemental Information, Document S1, sections XV and XVI), when considered in the broader context of each paper, appropriately resolved the outstanding points, and we told both sets of authors that we would proceed with publishing their papers (Supplemental Information, Document S1, sections XVIII and XVIII). This is the home stretch, as manuscripts still have to pass through a series of checks to ensure that they conform to our Production and STAR Methods requirements and an image forensics analysis to check for issues with figure preparation before publication, but at this stage they are accepted in principle.

### Conclusions

The decision of both sets of authors to share and co-submit their papers was very helpful here. By doing so, they shared limited and valuable samples to address what turned out to be a significant sticking point (comparisons of their organoids with *in vivo* tissue), which may not have been feasible without such coordination. As editors, we strive to thread the needle between being as transparent as possible and maintaining author confidentiality unless, as in this case, authors explicitly allow us to discuss their papers with a coordinating group. While we did publish the Que and Wells papers in *Cell Stem Cell*, this sort of cooperation is also helpful in situations where we may reject one (or both) paper(s) as we can help authors understand important factors in our decisions which we might not otherwise be at liberty to discuss (again,

to maintain confidentiality of other authors). That will not make a disappointing decision any less painful, but it would hopefully mitigate frustration by providing a clearer explanation for the underlying reasons.

The *Cell Stem Cell* team and I hope this story demonstrates the value of open communication between authors and between editors and authors. We are always happy to discuss appeals and revision plans if they are rooted in a scientific rationale; we cannot promise that authors will agree with our decisions or advice, but we will listen to what authors have to say. We also hope that this serves as a useful tool for examining paths to publication, and that by openly sharing our thinking during many of the different steps along the way, the publishing process is now a little less mysterious.

#### SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.stem.2019.05.017.

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