Published in final edited form as:

Brain Res Bull. 2023 January ; 192: 203–207. doi:10.1016/j.brainresbull.2022.11.020.

Reframing the perception of outliers and negative data in translational research

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Abstract

Negative results can be a source of disappointment for scientists, yet their publication is needed for scientific progress, in particular for cutting-edge translational research of novel therapeutics. This manuscript is directed to scientists, junior and senior, that produce and review data for publication. It discusses the difference between 'negative' or 'unexpected' data and 'useless' data, re-evaluates the importance of the experimental design to generate valuable data and proposes strategies to work with and report negative results. Overall, it aims to reframe the perception of working with, reporting and reviewing unexpected data as an opportunity to provide rationale for innovative ideas, prevent the misuse of limited resources and, ultimately, strengthen the reputation of a scientist.

Keywords

Biologics; Cell therapy; Experimental design; Negative data; Outliers; Translational research

1. Progress in translational research depends on sharing results

Antibiotics, one of the first biologic therapies, have transformed medicine (Lobanovska and Pilla, 2017). But this breakthrough may not have happened if Professor Fleming, instead of trying to understand what happened to one of his standard bacterial cultures that became moldy, had thrown away the Petri dish. He identified the fungus as *Penicillium notatum* as the cause of his failed experiment, and named 'penicillin' the antibacterial molecule that it produced. Fleming's decision to publish his carefully collected results (Fleming, 1929) led the team of Drs. Florey and Chain to isolate, generate and test penicillin in animals and humans. Afterwards, penicillin got to be mass produced and was nicknamed "the wonder drug", saving troops lives at the end of World War II. For this discovery, Fleming, Chain and Florey received the 1945 Nobel Prize for Medicine.

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Conflict of interest

The author declares no conflict of interest.

Novel biologics present exciting opportunities to provide relief for patients with namely uncurable diseases. The path towards developing a successful therapy meanders, as translational researchers identify leads and discard failures, and through this process, publications, patents and funding related to the research may emerge that directly impact a scientist's professional career in academia or industry. Thus, it is easy for a scientist to be disappointed by data that do not look as expected and decide to bury the results. Yet, carefully obtained and analyzed negative data are useful for the scientific community, including the individual scientist.

Most investigators agree that negative or unexpected results are valuable and should be shared. When Echevarria and colleagues (Echevarría et al., 2021) asked a group of European researchers working on RNA therapeutics whether negative results are worth sharing with the scientific community, 82 % agreed that they should be shared. Interestingly, when the same investigators were asked if they have ever published negative results only 14 % responded yes. Although no investigator was opposed to publishing their negative data, they rationalized not doing it because "it is too time consuming" (53 %) or "negative results are less cited than positive results" (26 %).

Results that do not support the proposed scientific question are disappointing, as it takes time, effort and funds to identify a compelling scientific question, perform the experiment, collect and analyze the produced data (Fig. 1). At that moment, it is good practice to remember that the goal of an experiment is to test a hypothesis, and data are only evidence to support or refute it (Nimpf and Keays, 2020). In this context, results, regardless of the outcome, inform about the feasibility of an approach and next research steps. Unexpected data (like a moldy Petri dish) are very different from useless data. Their main difference is how the data are obtained and analyzed. The successful clinical translation of new therapeutic strategies depends on unbiased, replicable data production, collection and reporting. As detailed by Yarborough and colleagues (Yarborough et al., 2018), the quality of the preclinical research that informs human trials has an ethical impact on the patient volunteers.

Today scientists should not have to hesitate about submitting for publication their carefully obtained negative or unexpected results. Funding agencies and journal editors are urging scientists to enhance rigor and reproducibility in research and reviewers to commit to unbiased evaluations (Nimpf and Keays, 2020; PLOS, 2020; Weintraub, 2016). The latest example of this need has been the discovery of tampered western blot images in a 2006 Nature publication by Lesné and colleagues (Lesné et al., 2006). The highly cited article supports the clinical translation of targeting beta-amyloid accumulation as a therapy for Alzheimer's disease and has shaken the field, as it exposed the pressures in academia to support favored axioms (Grimes, 2022; Piller, 2022).

This manuscript is directed to scientists, junior and senior, that produce and review data for publication. It discusses the difference between 'negative' or 'unexpected' data and 'useless' data, re-evaluate the importance of the experimental design to generate valuable data and proposes strategies to work with and report negative results. The suggestions are based on my long-term experience successfully publishing negative results (e.g., (Emborg

and Colombo, 1994; Emborg et al., 2001; Mancinelli et al., 2021; Ohshima-Hosoyama et al., 2012). Overall, this paper aims to reframe the perception of working with, reporting and reviewing unexpected data as an opportunity to provide rationale for innovative ideas, prevent the misuse of limited resources and, ultimately, strengthen the reputation of a scientist.

2. Negative results are not “useless” data

Results are termed ‘positive’ when they support the driving hypothesis and ‘negative’ if they counter it. Both are informative when they are produced by unbiased experiments with methods that prevent tainting the results with personal preferences. ‘Unexpected’ results are produced by unbiased experiments and can be part of a dataset that proves or not a hypothesis. As their name suggests, unexpected data are surprising and point out at something different, maybe an alternate mechanism or subsystem.

For the purpose of this discussion, ‘useless’ data are defined as the results obtained by a biased or poorly performed experiment. While human error (e.g., use of a wrong buffer, a mislabeled drug, or an un-calibrated instrument) can produce unusable data, a trackable honest mistake can help identify a solution to a problem.

3. The experimental design is a key tool for generating valuable data

A well thought-out experimental design is the key to fend off useless data. The process starts with the development of a valid hypothesis with true equipoise, especially relevant for translational research testing new therapies. The term equipoise refers to balance across experimental groups being compared and it is most frequently used in relationship to the design of clinical trials (London, 2017). Achieving equipoise depends on using unbiased methods. It requires proper experimental controls, randomization and blind assignment to groups being compared, predefined inclusion and exclusion criteria and matching across populations, as well as a priori stated hypothesis and power analysis, blind data collection and analysis (Kimmelman et al., 2009).

Trained personnel and appropriate supervision are needed to accomplish the processes delineated in the experimental design and generate trustworthy data. The hands-on scientists are as important as using good quality materials and properly maintained equipment. Standard operating procedures take time and effort to be written but they are a worthy investment, as they facilitate training and enhance replicability. Fillable forms help produce careful records of who, when and how an experiment was done, which are essential elements to understand variables and outcomes. Furthermore, if the ultimate goal of a project is to file for a patent (uspto.gov, 2022) or submit an Investigational New Drug or an application to the Food and Drug Administration (fda.gov, 2022), those hardworking files are indispensable resources.

4. Planning studies in nonhuman primates require additional considerations

Research in nonhuman primates provides invaluable data for clinical translation. Their complex behavior, physiology and anatomy, as well as their outbred nature and close genetics to humans, can provide insight on efficacy and toxicity of novel therapies, especially for neurological disorders (Izpisua Belmonte et al., 2015). As such, the highest standards for unbiased research and strict adherence to the ethical tenets of animal use are expected for studies in nonhuman primates (Academy of Medical Sciences, 2006).

An interesting dilemma arises for the evaluation of first-in-class technologies. Institutional authorization of monkey studies requires that a description of potential adverse effects is included in the animal protocol, yet they may not be clear for novel therapies. A solution is to plan a feasibility experiment in a few subjects, in order to test the procedure, optimize parameters and have preliminary data to inform subsequent tests. In order for this type of experiment to provide useful results, the experimental plan needs to include safeguards to ensure unbiased data collection and analyses, even if the preliminary study does not include a control group. Examples are videorecording of monkeys' behavioral tests for later evaluation by an independent blind scientist, randomization of unilateral treatments to use the same subjects as controls, or obtaining material from a monkey tissue bank for comparison.

Feasibility studies in monkeys can be reported as part of a publication to explain how the controlled study was developed and, in some cases, they can stand alone to support or negate further investigations. We have used this approach for initial testing of cell therapies for Parkinson's disease in macaques. Our results in 3 hemiparkinsonian, cyclosporine-immunosuppressed animals showed limited survival of human embryonic stem cells -derived dopaminergic neuroprogenitors (Emborg et al., 2013a). We used the data from our failed study as a rationale to get funding from the Parkinson Foundation for a similar project, but instead using autologous induced pluripotent stem cells. Our results demonstrating cell survival and safety of the autologous grafts (Emborg et al., 2013b) supported a National Institute of Health proposal to study the efficacy of the approach (Tao et al., 2021).

5. Positive and negative results have to be checked and outliers reported

Blind data collection and analyses minimizes the risk of biased results, but they do not protect against mistakes, therefore positive and negative outcomes need to be checked. The active participation of supervisors in the experimental process and their expressed commitment for obtaining accurate results rather than the desired results, facilitates communication when problems arise, build trust between team members, and overall improves the quality of the research. Random sampling of records and raw data can be performed in a limited amount time to identify patterns and problems.

Outliers, the data that fall outside the groups, are part of every, or almost, every experiment. An outlier is a data point that is different from the pattern of data (NIST/SEMATECH,

2012). Outliers often contribute to negative results. Scatterplots and boxplots can help detect stray data points. Technical errors can be recognized by going over the experimental records, data collection and analysis. Outliers can be removed from analyses due to human mistake, unbiased application of a priori defined inclusion and exclusion criteria, or statistical tests (e.g., Grubb test) (GraphPad Software, 2022). In general, outliers should be reported, and, if needed, the reasons used for data omission of the analyses should be stated.

6. All authors are responsible for the contents of a paper

In 2011, Fang and Casadevall (2011) published an editorial article assessing the relationship between their newly minted ‘retraction index’ (frequency of publications being retracted due to scientific error or misconduct for a journal in a given year) vs. the ‘impact factor’ (frequency of an average article of a journal is being cited in a given year) across different journals. The authors found a range of frequency of retractions between journals that strongly correlated with the journal impact factor. The reasons for the high number of retractions in journals, such as the New England Journal of Medicine, Cell, Science and Nature varied from technical mistakes to plagiarism. Maybe the high number of retractions in these journals were due to a greater level of scrutiny. Or, maybe investigators were willing to cut corners or turn a blind eye in order to get a paper in a high impact journal.

It is the burden of each author to ensure that their contribution to a manuscript is accurate, although their responsibility does not stop with their section. The criteria for authorship recommended by the International Medical Journal Editors (ICJME) (ICMJE, 2022) includes an “agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved”. This agreement is predicated on authors being able to identify the contributions of each co-author and trust their integrity. This statement implies that all authors critically read the manuscript and agree to its contents before submission, which is other recommendation of the ICJME.

7. Strategies for writing a report with negative data

Despite the overall agreement between scientists about the importance of publishing negative results and the numerous articles encouraging it, the actual pursuit of getting a negative results paper published can be a challenging, draining experience. Mehta’s publication on a limited failure of genome editing (Mehta et al., 2019) made the author reflect on the current “toxic” definition of scientific success and the forces feeding a bias towards publishing positive results (Mehta, 2019).

Against this bleak backdrop, reframing how manuscripts with negative results are prepared for publication can facilitate the writing and smooth out the peer-review process. A first consideration is whether the negative data should be reported as a stand-alone study or as part of a dataset containing positive results. The latter alternative nullifies the conundrum of publishing negative data and can overall add depth to a project, but the studies should complement each other and the investigators involved in each section need to agree to the approach and a blended authorship.

If we start from the premise that the experiment was driven by a compelling hypothesis, followed a carefully crafted experimental design, and rigorous data analyses, the writing process can be expedited by tapping into those documents. The introduction sets the tone of the manuscript. Thus, a properly referenced rationale for the study, demonstrating the scientific value and validity of the proposed question is critical, which will lead to stating the a priori formulated hypothesis. As negative results often contradict current assumptions, the study methods may undergo greater scrutiny. Providing the detailed methods with a description of the overall experimental design, and the rigorous statistical planning and analyses will ease the reviewers' concerns. A similar effect will be achieved by striving for results transparency, for example by plotting individual data points and describing outliers. A thoughtful discussion considering how the utilized methods and findings compare to previous publications, as well as stating possible limitations or caveats to the utilized approach will enrich the final product of the research. The Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, which have been revised in 2020 (Percie du Sert et al., 2020), are an excellent resource when preparing manuscripts, regardless of whether the results are positive or negative.

8. There are many journal options for manuscript submission

As seasoned investigators know, the selection of a peer-reviewed journal for manuscript submission requires some strategic planning, which is especially important for successfully publishing negative results. Every scientist wishes to publish in high impact journals, yet producing the type of research that will be attractive for these journals is difficult, regardless of positive or negative results.

A good place to start is by making a list of potential journals based on the background references for the study. Asking co-authors and collaborators for journal suggestions can also help identify hidden gems as well as sift through unviable alternatives. Submission of a negative results study to journals dedicated to this type of outcomes, such as "Positively Negative" or "Journal of Negative Results" can be a viable option (Nimpf and Keays, 2020). Searching the journals' websites for their mission and target audience follows, as matching the research topic to the scope of the journal is critical to avoid an editorial rejection. Reviewing the editorial board of candidate journals is a task not to be neglected. If the report goes against what the editors published in the past, it may be wiser to choose another journal. Some editors encourage inquiries about the suitability of a submission, which can be easily accomplished and can save time and effort. The journal's request for suggestions of managing editors, potential and opposed reviewers is a chance to work with co-authors to propose knowledgeable unbiased scientists. For investigators concerned about reviewers' objectivity, some journals offer double-anonymized reviews, in which both reviewers and authors are not identified (PLOS, 2020) or open reviews, in which reviewers' comments are published or reviewers' have an interactive role when providing feedback (e.g., Frontiers in aging) (Frontiers, 2022).

An alternative path for studies at risk of generating negative results is to register the research before performing the experiment (Center for Open Science, 2022). The advantage is clear: manuscripts that pass the pre-study peer review are accepted in-principle, as long as they

keep to the original plan, maintain scientific rigor and, overall, produce a high quality submission. This approach should not be taken lightly as it requires investigators foresight and commitment to fulfill the prescribed procedures (Ledgerwood, 2018; Nosek et al., 2018).

A word of caution is needed against predatory journals. In their insightful commentary Grudniewicz and her colleagues from 10 different countries (Grudniewicz et al., 2019) stated that “Predatory journals and publishers are entities that prioritize self-interest at the expense of scholarship and are characterized by false or misleading information, deviation from best editorial and publication practices, a lack of transparency, and/or the use of aggressive and indiscriminate solicitation practices.” The above mentioned approach for identifying journals, including checking the journal’s website and discussing with co-authors, also works for spotting predatory practices and avoiding falling into an editorial trap that only aims to profit from researchers (see also (Happe, 2020)).

9. The reviewer’s role in generating a trustworthy body of research

After the conditions of well-produced, unbiased research and appropriate journal selection are met for submission of a negative results manuscript, the publication fate of the article is left to the peer reviewers.

Editors select the reviewers and count on them for providing quality feedback. Agreeing to review a manuscript implies that the reviewer has the knowledge and time to do it. The reviewer also agrees to be unbiased, and to keep confidentiality during the process (Rockwell, 2014). Interestingly, scientists that were affected by a biased against publishing negative results, as reviewers they may conscious or unconsciously reject papers presenting negative or contradictory results in favor of manuscripts confirming current axioms.

Editors have devised a number of approaches aiming to increase transparency and minimize optimism bias in publications. Double blind reviews, open reviews and pre-registered studies are proposed as alternative ways to minimize ‘cliques’ in research and maximize exposure to different ideas (Frontiers, 2022; PLOS, 2020). Ultimately, increasing reviewers self-awareness of potential biases with appropriate training and mentoring will help improve the fairness and quality of the reviewing practice (Catlow, 2017).

10. Conclusions and final thoughts

Progress in the development of novel therapies depends on having a complete picture of what strategies work and which ones are not worth pursuing, in order to prevent the misuse of limited resources and the clinical translation of potentially harmful therapies. Scientists, who interchangeably play the role of authors and reviewers, need to commit to honestly appreciating negative results by supporting their publication. The strategies highlighted in this manuscript aim to facilitate the process and encourage the sharing of unexpected data for the benefit of science as well as the individual scientist.

Acknowledgments

This work was supported by the Kellett Award from the University of Wisconsin and NIH grants P51OD011106, UG3NS111688, U34AG068466 and R61NS115102. The funding agencies did not have any role in the preparation of this article.

Data availability

No data was used for the research described in the article.

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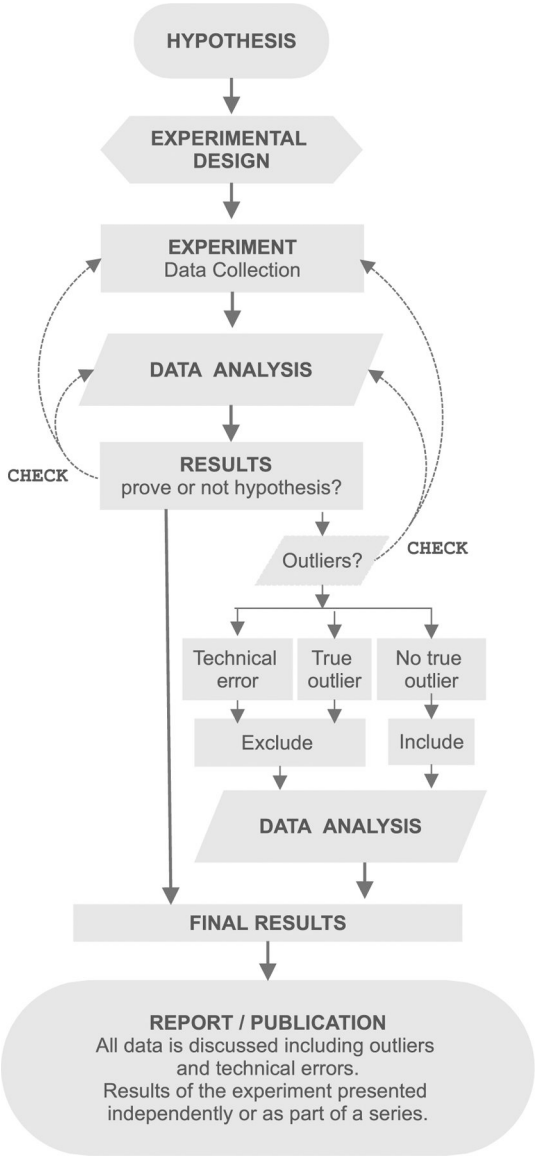

Fig. 1.
Flowchart of the experimental process.