

As scientists, we hold a position of responsibility in society based on specialized knowledge we have and seek to expand. This responsibility extends across scientific fields, but for biomedical scientists entrusted with taxpayer's dollars given in the hope that our research will eventually improve global health, there is a special duty to the broader society. This year's ethics cases address multiple aspects of this responsibility. These range from recognizing and dealing responsibly with potentially hazardous materials, to promoting sound, reproducible research and communicating it effectively to both the public and research community. Scientists feel pressure from inside --competition within and between labs -- as well as from outside --citizens expecting their investment in science to rapidly translate into better treatments and health. While competition and pressure fuel innovation, they can also lead to short-sighted decisions to cut corners in order to achieve career goals and secure ongoing funding. In labs, cutting corners can lead to problems with reproducibility. In society, especially in the current social media environment with news constantly going "viral", the pressure to act on preliminary, poorly validated or clinically unproven new results can be misleading, counterproductive and even dangerous. The anti-vaccine movement and its claims of causation in autism provides a good example of this danger.

As you go through the 2017 research ethics cases, consider what pressures you may be experiencing in your own work and how you can maintain high quality standards. Do not lose sight of the broader impact your work might have on society, even if you are not involved in clinical research. Think about what you can do to make the consequences of your research relevant and effectively communicated to the public.

Deciding What Study Results to Publish and Transparency in Research Publication

Dr. Wyck is the lead investigator for a cohort-based case-control study of the genetic and environmental factors related to Parkinson's Disease (PD) that compares 1,000 patients with 1,000 matched controls. Her team's analysis discovers that having a history of head trauma ($p=0.005$), high blood pressure ($p=0.01$), or exposure to agricultural pesticides ($p=0.04$) is related to 25-60% higher risk of PD. Surprisingly, Dr. Wyck found that current cigarette smokers were at 40% lower risk of PD as compared to non-smokers ($p=0.02$). The analysis also indicated that non-smokers exposed to second-hand smoke had 12% lower PD risk as compared to non-smokers without exposure to second-hand smoke, but this association was not formally statistically significant ($p=0.07$).

Dr. Wyck is concerned that the findings for smoking exposure may have a negative impact on public health by discouraging people from quitting (i.e., as a way to avoid developing PD). While preparing the study manuscript, she is considering whether or not to report the findings related to smoking (and if so, how to address those findings in the discussion).

Questions:

1. Should Dr. Wyck report all of her findings, including those related to smoking? Why or why not? What if the result for smoking was opposite; i.e., it was related to *higher* PD risk?
2. Should she only report findings with p-values <0.05 ?
3. Which findings should Dr. Wyck emphasize in title, abstract, and discussion?
4. How should she discuss the apparent protective association with smoking; e.g., should she speculate on possible mechanisms, such as nicotine's role in increasing brain dopamine levels?
5. What, if anything, should the authors say about the second-hand smoke finding?
6. What aspects of the many health risks associated with smoking are relevant to the findings?

Handling Select Agents

Several years ago, Dr. Antonelli completed his postdoctoral training in the NIH laboratory of Dr. White and returned to his home country to run his own lab. Drs. Antonelli and White continued to collaborate and in 2009 Dr. Antonelli brought Dr. White a viral construct to use in their joint projects. The original virus was the Newcastle Disease Virus (NDV), a virulent chicken virus, which is extensively used in immunology to induce interferon expression in dendritic cells.

Dr. White did not have any written agreements in place to receive these materials, nor did he consider the material to be a select agent because it was only a chicken virus and is generally assumed to pose no hazard to human health (although it can still cause mild conjunctivitis and influenza-like symptoms). Also, Dr. Antonelli had confirmed in an email that no vaccinations or special handling precautions were needed for this virus, leading Dr. White to assume it was the less virulent *LaSota* strain of NDV, which would not require registration.

Dr. White and the other members of his lab, including postdocs and graduate students, continued to work with the virus for several years and published two papers. However, the methods section of both papers - copied largely from an early article by White and Antonelli - indicated that the construct was based on the highly virulent *Herts* strain of the NDV, indicating that it was in fact a select agent (and should therefore have been registered). Unfortunately, Dr. White did not realize this, as he usually only focuses on editing the abstract, introduction, results and discussion sections of the manuscript drafts from his fellows.

No one ever pointed out to Dr. White that they likely were dealing with the virulent strain of NDV, and it went unnoticed until the "Clean Sweep" initiative at the NIH in 2014, led by the NIH's Division of Occupational Health and Safety. At that time, it turned out that Dr. White had no proof that the virus was harmless, meaning that that he and his fellows could have been exposed to, or inadvertently released, a potential biohazard.

Questions:

1. What are the risks associated with research on select agents? How does one know if something is a select agent or a dual-use agent? Can animal pathogens be select agents?
2. What are Material Transfer Agreements (MTA), why are they important? Was it appropriate for Dr. Antonelli to bring a viral clone to the United States and share it with Dr. White without getting the proper documentation? What other ethical and legal problems do you see in this case?
3. Whose responsibility was it to check the manuscript methods section and make sure that the virus construct used was safe for use in the lab (or alert the group if it was not)?
4. How would you react if it turned out that you have been using a poorly characterized (and potentially harmful) bacterium or virus? How would you deal with the paper(s) that used this construct and provided questionable (erroneous?) info?

Resources:

<https://www.selectagents.gov/SelectAgentsandToxinsList.html>
<http://osp.od.nih.gov/office-biotechnology-activities/biosecurity>
<https://osp.od.nih.gov/biotechnology/biosafety-guidance-and-resources/>

Research Competition and Reproducibility

Dr. Park is a tenure-track investigator searching for a novel method to de-differentiate cells from adult tissues to produce stem cell lines that might be used in organ regeneration. At his third-year tenure-track review, the committee expresses a concern that he has no recent high-impact publications.

Part 1

Dr. Park presents his postdoctoral fellows, Drs. Sanchez and Aero, a list of the ten most-promising chemicals and growth factors he has identified for further testing. As motivation, he reminds them that whoever successfully publishes such a breakthrough approach will have a great career. After the initial screening indicates that a derivative of trichostatin A is the most promising compound, Dr. Park assigns both fellows to work on this chemical separately, using the same commercially available cell line. At first, the fellows get along collegially and have some productive discussions about how to design their experiments, but they have a falling out when Dr. Sanchez suggests that they collaborate on both projects and share first-author status.

After four months of independent, intense (and secretive) experimentation by the two postdocs, Dr. Aero presents at a lab meeting beautiful preliminary results demonstrating that incubating isolated adult cells with the compound produces de-differentiation and rapid cell proliferation, and that removal of the drug results in fully functional re-differentiation. Dr. Sanchez, however, can show only a weak, seemingly toxic response to the drug, and she wonders to herself whether Dr. Aero may have sabotaged her experiments. She notices that both her experimental and control cells have abnormally high death rates and suspects that someone is tampering with her experiments. One morning she discovers that her incubator was set at 40°C, and that the set points had also been altered so as not to trigger the alarm when the temperature exceeded 37.5°C (36-37°C is the optimal temperature for growing these cells).

Questions:

1. Should the head of a lab put two trainees on the same project? What are the advantages and disadvantages?
2. What can or should Dr. Sanchez do if she suspects that her work has been tampered with? Should she talk to Dr. Park about this?
3. What should Dr. Park do if Dr. Sanchez claims that her work has been sabotaged?
4. Is tampering with an experiment unethical? Does it fit the definition of research misconduct?
5. If the group is successful in discovering an agent that can induce de-differentiation, this discovery could be patentable and could have significant economic value. Should they pursue a patent prior to making any decisions regarding publication?

Part 2

After Dr. Park warns the fellows not to sabotage each other's experiments, Dr. Sanchez is also able to demonstrate that the drug produces de-differentiation, but the effect size is only 50% of Dr. Aero's experiments. He asks them to both repeat their experiments and they both obtain results which are similar to those they obtained earlier. Dr. Park decides that the group has successfully replicated the experiments, and they submit a paper to a high impact journal reporting Dr. Aero's impressive findings. The paper lists Dr. Aero as the first author, followed by Dr. Sanchez, two graduate students, and Dr. Park. The paper does not include data from Dr. Sanchez's experiments and only reports data from Dr. Aero's two experiments. It says that the group has replicated his findings, with data available upon request.

Questions:

1. Does Dr. Sanchez' experiment constitute a successful replication of Dr. Aero's work?
2. Should they have reported the results of both experiments?
3. Should they have attempted to determine why Dr. Sanchez' experiments consistently had a much smaller effect size than Dr. Aero's? What factors could lead to different outcomes in such experiments?
4. Is failure to report Dr. Sanchez's results data falsification?

Part 3

The paper is accepted for publication and is highlighted with an accompanying editorial. The institute prepares a press release and several reporters interview Dr. Park. Based on the promising findings, Dr. Park's lab chief prepares a compelling departmental application on the urgent need for a next-generation sequencer and bioinformatics support. The request is funded unusually rapidly because of the potential high impact of the work, even though other labs with long-term consistent productivity had competing requests for the funds.

Questions:

1. What responsibilities do lab chiefs and supervisors have in this type of situation?
2. How do we prepare trainees and other researchers for professional survival and career success in the current competitive research environment while instilling and preserving high ethical standards?
3. How can competition for limited resources be made fairer?

Part 4

Another lab headed by Dr. Williams tries to repeat Park's work using commercially available cell lines but is not able to obtain the larger effects reported in the paper and cannot determine why; their effect size is closer to that of Dr. Sanchez. They contact Dr. Park and ask for their protocols, samples, and primary data of Drs. Sanchez and Aero. They conduct a genetic analysis of Dr. Aero's and Dr. Sanchez's cell lines and detect some variations. They suspect that Dr. Aero's cell line may have mutations that made it more sensitive to the trichostatin A derivative, and plan to investigate this hypothesis in future work.

Questions:

1. How did the failure to report Dr. Sanchez's experiments impact the reproducibility of this research and the overall understanding of the effects of the trichostatin A derivative on de-differentiation?
2. What other biological factors could contribute to the source of the differences?

Societal Aspects of the Responsible Conduct of Research

Part I

You are a post-doctoral fellow working with a prominent senior investigator on a project examining risk factors for dementia. You, as first author, and the lab are drafting the report of an investigation of the association between flu vaccination and dementia. In reviewing the manuscript, you notice that the data summarized in one of the tables are not consistent with the raw data in the chart reviews. In particular, the time between last exposure to the vaccine and date of dementia diagnosis for several patients is substantially shorter than what your own records indicate. This shorter latency implies a stronger link between vaccination and disease than would be observed otherwise. You request a meeting with the PI where you indicate that the data in the table do not match those in the chart reviews. You are told somewhat dismissively that some statistical adjustments had to be applied to “smooth” the data, that these methods are standard and have been validated, and that you shouldn’t worry about these apparent discrepancies.

Questions:

1. What are your responsibilities as a coauthor for understanding analyses performed on data? Should you investigate this further? If so, what steps would you take?
2. Are there risks to you as a young researcher in this situation? Should you be worried that continuing to voice your concerns might impact your relationship with the PI?
3. Should you be concerned that the data were perhaps manipulated to generate more interesting findings?

Part II

Despite your concerns, the main findings of the study are published in a respected medical journal. Several prominent dementia researchers immediately refute the primary findings and conclusions, and request access to the primary data. After a while, a formal NIH misconduct investigation is launched and finds sufficient evidence of data falsification to warrant retraction of the paper. Despite the scientific criticism and discrediting of the study, however, both traditional and social media had already translated the findings into the message that an increase in dementia in the elderly is linked to taking the flu vaccine. Consequently, there is now a decrease in flu vaccine compliance not just in the elderly, but in all age groups.

Questions:

1. In what ways do news or social networks communicate scientific results differently from the scientific literature? To what extent are authors of research papers and other scientists responsible for the eventual public dissemination of messages derived from the primary studies and publications?
2. Do you think the scientific literature is self-correcting and, if so, to what extent does this also apply to the much larger lay literature?