**Submission # 1:**

| | |
|---|---|
| **Date** | 12/3/2019 |
| **Names:** | Andrew B. Maksymowych |
| **Organization:** | University of Pennsylvania |
| **Email:** | amaks@ehrs.upenn.edu |
| **Comment:** | To Whom it may concern:<br>We are submitting a comment to the NExTRAC.<br>Please see attachment. |
| **Attachment:** | December 3, 2019<br><br>Comment submitted to the NIH NExTRAC Committee:<br><br>We are submitting this comment to respectfully caution the NExTRAC Committee to exercise due diligence in fulfilling their charge to address Novel and Exceptional Technologies. In the process of providing recommendations to the NIH Director and encouraging a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies please do not overlook 'exceptional technologies' that may have emerged but have not been adequately addressed in the regulatory sphere.<br><br>The NIH has been funding and encouraging gene therapy studies in vertebrate animals, primarily humans, since 1990. The research community and NIH have a cooperative history regarding recombinant nucleic acid research, specifically Human Gene Transfer, spanning nearly thirty years. This successful partnership culminated in the FDA approving two biologic gene therapies in 2017, one in 2018 and more to date. The potential for bringing gene therapy into the clinic appears to be without limits as the FDA projects a nearly exponential increase in IND applications in the next several years. A significant proportion of these IND applications will be for gene therapies leveraging new gene editing tools / platforms being discussed by this committee (CRISPR, Base Replacement & PRIME, for e.g.)<br><br>In April of 2019, the NIH Office of Science Policy ceded oversight of human gene therapy studies to the FDA and left *NIH Guidelines* compliance in the hands of local IBCs in order to expedite gene therapy trials by eliminating duplicative reporting and compliance requirements. Successes in human gene therapy trials also translate to an incentive to extend these technologies to veterinary medicine. At institutions like the University of Pennsylvania, where a research environment exists allowing cooperation |

among medical and veterinary colleagues, the desire to explore the utility of approaches from human medicine to veterinary medicine is strong. This collaboration significantly increases the likelihood of positive impacts and novel approaches benefitting both human and animal health (development of platform technologies like Universal CAR T cells).

One compliance issue that has not been adequately addressed in the regulatory sphere and one that has become a significant impediment to veterinary research is exemplified by a bottleneck inadvertently created by the NIH Office of Science Policy regarding gene therapy in client owned animals. According to an interpretation issued by the NIH Office of Science Policy, the *NIH Guidelines* do not address "*the intentional release of recombinant or synthetic organisms outside of a contained laboratory setting*." Is this interpretation correct? Not all veterinary gene therapy studies result in release of recombinant material into the environment. To argue that ALL do is an overly conservative interpretation of the *NIH Guidelines*. Such a determination must be based upon what technology is being used and upon a comprehensive risk assessment by the IBC. NIH Office of Science Policy guidance to the veterinary research community states that compliance with the *NIH Guidelines* mandates that research in client owned animals that involves "*release* (to their owners; into the environment) *of animals that have been administered recombinant or synthetic nucleic acid molecules requires approval by another Federal agency with oversight*." The veterinary research community is being referred to the USDA or FDA for this Federal approval. Effectively, the NIH Office of Science Policy ceded *NIH Guidelines* compliance to include approvals "*for release from containment*" from two Federal agencies that do not possess a statutory mechanism to address these requests. In our experience, both the USDA and the FDA have been exceedingly supportive and cooperative in helping us navigate this compliance dilemma. The FDA has provided an administrative path forward regarding veterinary agents that fall under their oversight. According to the interagency MOU (signed, 2012 USDA/APHIS; 2013 DHHS/FDA), oversight of veterinary agents that act through an immune mechanism fall to the USDA, which according to Federal law does not oversee basic research and has no regulatory oversight with respect to agents that are not seeking licensure. In this instance, pilot studies in client owned animals proposing to investigate gene therapy approaches for various cancers, fungal infections, hemophilia, and retinal disorders have effectively been stalled. Attempts by multiple veterinary schools seeking clarification of the opinion, meetings with the USDA, FDA and the NIH Office of Science Policy, and a request for clarification by Council on Government Relations (COGR) have not returned a satisfactory result.

Our cautionary example is one where technology has surpassed an ageing regulatory framework, which results in an inability to adequately respond to the needs of the research community and the National Cancer Institute that has funded this kind of research, threatening loss of funds and potentially the careers of researchers.

Our contention is that the NIH Office of Science Policy or another "single entity" be assigned the responsibility to review risk assessments for veterinary gene therapy pilot studies in client owned animals. If this is not tenable, then empower local IBCs, which have the experience and expertise, to make decisions regarding this research. Finally, one solution may be that 'technologies' that are currently being utilized in human gene trials, or ones that have been approved by the FDA, be deemed as having undergone adequate review and approval, and be allowed for use in veterinary studies in client owned animals, with no further review beyond registration and approval by the IBC.

We thank the Committee Chair and NExTRAC Committee membership for their time and consideration.

**Maureen O'Leary, Ph.D., MBA, CBSP(ABSA)**
Executive Director Environmental Health & Radiation Safety
University of Pennsylvania

**Andrew B. Maksymowych, M.S., Ph.D., RBP(ABSA)**
Associate Director for Biological Safety Programs,
Institutional Biosafety Officer
University of Pennsylvania

**Colleen Kovacsics, Ph.D., RBP(ABSA)**
Associate Biosafety Officer
University of Pennsylvania

**Submission # 2:**

| | | |
|---|---|---|
| **Date** | 12/6/2019 | |
| **Name** | Gerald L. Epstein | |
| **Organization:** | | |
| **Email:** | Public Comment Delivered Orally | |
| **Comment:** | Good afternoon, I guess. I'm Gerald Epstein from the National Defense University, who I'm clearly not speaking for in any way. I want to thank all of you for a fascinating meeting. I just had a couple of observations, drawing on things that I picked up along the way, that I'd like to share with you, and maybe they're already coming out.<br><br>The first, on Carrie's question of, when does something graduate from "emerging"? Does that mean it doesn't need oversight? And I just wanted to caution against "emerging" equating to "needing oversight". I think we also said "emerging" also refers to unfamiliarity or uncertainty, and there may be things that we're more familiar with and more certain with, which still need oversight. But there are other mechanisms which exist for that, or should exist for that. But I think the need for oversight doesn't equate with emergence.<br><br>The second is that the consideration, or the awareness, or the assessment of a risk does not imply that any particular policy approach ought to be taken to deal with that, and I think a real corruption of the policy process is when people are so concerned about one possible policy solution that they go back upstream and deny the problem that the solution is trying to address, and I would really -- I may be naïve. I would like to say these are two different processes. And maybe in the real world of Washington, they're connected. But I would like to live in a world where we analyze problems and then figure out what to do about them, and one doesn't necessarily determine the other.<br><br>The third is about this quest for evidence. Obviously, we want evidence. We're seeking evidence, we want to use evidence, we want to increase the evidence that's available. But we also have to recognize that evidence may not be, and possibly cannot be, available for many of the things we're talking about. In the national security world, where I spend more of my time, I don't think there's any evidence for any American citizens who ever died in a nuclear weapon detonation. This country spends trillions of dollars on that problem. And so, there may be things that we look for evidence, we try to improve our evidence, but there may be areas where we have to go by plausible analysis, as opposed to evidence.<br><br>And then finally, Carrie, I think at some point you said, what you're really looking for is enforced thoughtfulness, maybe, as a different word. I think it's actually exactly right. I broadened it a little bit, not necessarily just enforced thoughtfulness among people doing research, but objective, multicentral enforced thoughtfulness, and you want to bring these different perspectives into view, and you'd like to have | |

| | | |
|---|---|---|
| | some of that analysis done by people other than the ones who are benefitting from doing the direct work. But in an era like this, that may be -- I don't want to say that's all we can hope for. I don't want to set my bar that low, but it's certainly something to aspire to, and then maybe go beyond. | |

**Submission # 3:**

| | |
|---|---|
| **Date** | 12/6/2019 |
| **Name** | Raul Medina |
| **Organization:** | Texas A&M University |
| **Email:** | rfmedina@tamu.edu |
| **Comment:** | Community engagement should not be just a way to find out if one should or should not conduct specific research projects or science-based interventions. Instead, we should think about community engagement as a way to understand why a community will favor or oppose specific science-based interventions (i.e., understanding the nuances and complexities). Understanding the reasons a community oppose specific projects may allow researchers to identify deficiencies in communication but also may allow researchers to realize that they may not have answers to some community concerns. This realization may open new lines of research (social science as well as basic science research questions), point to needed interdisciplinary collaborations (e.g., involving ethicist, social scientists), and start needed dialogues that may affect how both parties (i.e., scientists and communities) think about implementing or stopping science-based initiatives. As Zach said: Both parties should be willing to change their minds and their time-lines. |
| **Attachment:** | |