We welcome the opportunity to respond to the commentaries on our paper—The Mouse that Trolled—by Hardy, Sarnoff, and Cordova and Feldman. Their comments are academic criticism in the very best sense. We also take the opportunity to update on recent legal actions, which we had not predicted. This opportunity enriches our narrative history of the patenting of the APPswe mutation for early onset Alzheimer’s disease, and we hope the continued saga is of interest.

HARDY’S POLICY CHANGE

We find it heartening that Prof. Hardy concurs with our main points and learned from his experience in deciding years later not to patent mutations on another Alzheimer’s-related gene, TREM2. His point that the financial benefits redound to the discoverers and inventors, but not to the donor families of the DNA that enabled those discoveries, is very well taken. It is not necessarily a flaw in the patent system, which is designed to reward only some of the steps involved in socially beneficial innovation, but it points to an asymmetry and injustice of the innovation system as a whole in the way the fruits of innovation are distributed. Those who contribute tissue and information are treated as altruistic ‘donors’ eligible only for non-financial rewards. Those intangible benefits can be substantial if someone contributes to a scientific advance or technological breakthrough in the form of novel diagnostics or therapies, but the system does not...
provide ‘donors’ with any of the financial benefits. Yet the same system of innovation treats those who do research and development and those who put products and services on the market as motivated primarily by financial reward. Each of these frameworks—an idealistic Mertonian science with only intangible rewards, and a Kitchean prospect theory of financially driven patent incentives—leaves out important elements in how innovation actually works. For many scientists, including by his comment John Hardy, the advance of science and medicine are strong incentives, often far stronger than the financial ones. Indeed, one lesson from this tale is that the pure science and pure capitalism frameworks are each, taken on their own, inadequate to explain how to optimally motivate the various players in innovation.

**ANOTHER MOUSE TROLLS**

We corroborate that Prof. Hardy learned about our paper only after it was published. He then initiated correspondence with us that has given us valuable insight. His perspective as a scientist on events and policies is a welcome addition. Despite not seeking patents on TREM2, he has not, as it turns out, escaped the patent battles over Alzheimer’s-related genes.

After Hardy’s note appeared in the *Journal*, in December 2015, the University of South Florida (USF) filed two additional lawsuits asserting a patent that Prof. Hardy and his collaborator Karen Duff assigned to USF when they were on faculty there (US Patent 5898,094). The Duff–Hardy patent claims transgenic mice that have the APP-swe mutation along with another mutation in PSEN1 that is also associated with familial Alzheimer’s disease. Prof. Hardy now works at University College London’s Institute of Neurology, London. Prof. Duff now works at Columbia University’s Medical Center. Prof. Hardy learned of these recent suits through us, not through USF, the plaintiff enforcing his patent.

One suit was filed against the US Government in the US Court of Federal Claims on December 18, 2015 (case 15–1549C). It seeks recompense for the distribution of transgenic mice under NIH grants and cooperative agreements, as discussed in our article. US law gives the federal government the right to use patented inventions for government purposes, but also obligates the government to give fair recompense to patent holders (28 USC § 1498). As the suit alleged, the NIH signed a 2011 ‘authorization and consent’ agreement with Jackson Laboratories (JAX) with funding to distribute transgenic mice of many kinds, including those with mutations in Alzheimer’s-related genes. While Alzheimer’s mice constitute a small fraction of the strains available through JAX, but are an important research priority. USF is seeking compensation for the transgenic mice claimed in the Duff–Hardy patent that have been distributed under the federal grants and cooperative agreements. The USF complaint lists nine mouse strains that include a PSEN1 mutation, and that it claims infringe the asserted patent. Those mouse strains were donated by researchers at the University of California at Irvine, Stanford

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4 Robert K. Merton, *Science and Technology in a Democratic Order*, 115 J. LEGAL. POL. SOCIO. 126 (1942); reprinted as *SCIENCE AND DEMOCRATIC SOCIAL STRUCTURE* IN MERTON’S SOCIAL THEORY AND SOCIAL STRUCTURE (1949, 1957, and 1968), and finally reprinted as *THE NORMATIVE STRUCTURE OF SCIENCE IN THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS* (University of Chicago Press) (1979).

5 Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J. L. & ECON. 265, 290 (1977).
University, University of Florida, and Northwestern University and are distributed by JAX.

So far as we can determine from searches of databases on US federal grants, and corroborated by Prof. Hardy, federal funds were not used in the research that gave rise to the Duff–Hardy patent, so it is not subject to the government use rights of the Bayh–Dole Act (35 USC § 18).

The second lawsuit was filed against JAX on December 22, 2015 in the US District Court for the Middle District of Florida (8:15-cv-02916-MSS-EAJ). It alleges patent infringement. It seeks treble damages for willful infringement and requests an injunction against JAX from distributing transgenic mice claimed in the patent.

The parallels with the story of our article are striking, but there are important differences. First, in our story, the purported inventor of the patents on the APPswe mutations was Michael Mullan. One of our points was that the US Patent and Trademark Office granted claims to transgenic mice incorporating the mutation based on sequence of the mutation alone, whereas it actually took many years to develop a mouse model. Mullan himself never did so; others took the baton and advanced the science to produce mouse models of Alzheimer’s disease. In contrast to Mullan, Duff and Hardy became leaders in Alzheimer’s mouse transgenics, and we cited their 1995 *Nature* paper in our article. We argued that the Mullan patents might well be deemed invalid if challenged for failing to meet the enablement or written description requirements for patentability (35 USC § 112). Those arguments would not apply with the same force to the Duff–Hardy patent in the USF suits.

Another important difference is that the Duff–Hardy patent was assigned to USF. This comports with Florida state law obligating state employees to report inventions and assign patent rights to their state university employers. That did not happen with the Mullan patents. A jury decided that Mullan did not have rights to assign because he excluded Hardy as a legally necessary coinventor, and even if he had such rights, he was subject to Florida state law, under which the patent should have been managed by the University, not licensed to the Alzheimer’s Institute of America without the University’s knowledge. These are important differences that distinguish the Mullan patents at the center of our article from the USF suits.

**ACADEMIC TROLLING**

The more important point about the USF suits is that a university is suing the government and a non-profit research institution for distributing research tools. Many academic research institutions produce patented and unpatented research tools in the process of doing science. Indeed, our forthcoming patent landscape of the mouse research tools identified 7179 granted US patents up to 2007, most of which were maintained over their lifetime, and most of which were held by academic research institutions. Patent claims included mouse genes and their human orthologs, transgenic mouse strains, derivative cell lines, and associated methods. If USF succeeds in its suits, will it induce similar actions by other academic institutions? We have no idea whether this

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6 Tania Bubela et al., *Governance of Biomedical Research Commons to Advance Clinical Translation: Lessons from the Mouse Model Community*, in *GOVERNING MEDICAL RESEARCH COMMONS* (K. Strandburg, M. Madison & B. Frischmann eds., Cambridge University Press (2016) (in press).
will become commonplace, but to date it has not been standard conduct of universities, and it could set a fateful precedent.

Cordova and Feldman focus their commentary on the possible threat of patent trolling by non-practicing entities, noting ‘numerous patents that could be deployed with the same techniques that patent trolls have used in the technology sector’ and issue a warning: ‘it is clear, however, that there will be similar examples [to the case we described] in the future’. That warning has already been borne out by the USF suits—but with a twist. USF did not license its patents to a non-practicing entity to litigate on its behalf, but has itself filed the lawsuits in question. USF cut out the middle man. We concur with Cordova and Feldman that these cases should ‘make us think deeply about the role that the public expects universities to play in society’.

These cases will be worth following closely, since their success could require considerable restructuring of academic research practices. By asking for an injunction, USF urges the court to shut down JAX distribution of the nine strains absent a licensing arrangement with USF. The USF complaint is silent on whether there is any other source for the transgenic mice. USF is not suing a competitor, but the world’s main non-profit source of a research tool used to study and develop possible treatments for Alzheimer’s disease. Whether this is a bargaining tactic or an incompletely thought-through strategy—seeking a standard remedy from traditional patent infringement litigation to a situation in which the defendant is not a competitor, where an injunction would make Alzheimer’s research tools unavailable—may come to light as the case progresses. The cases are being brought by Jerry Stouck, who ‘specializes in litigation against federal government agencies on behalf of contractors’.  

If USF were to prevail, and especially if other research institutions were to follow USF’s lead in seeking revenues for distribution of patented research tools from other non-profit and government institutions, then repositories such as JAX would need to become clearinghouses for patent rights as well as research tools, and would have to track uses to allocate royalties—raising transaction costs. JAX and most other repositories have deliberately eschewed the role of royalty collector and allocator. JAX requires depositors to agree, whether they hold patents or not, that their mouse lines will be distributed using Simplified Conditions of Use to non-profit researchers. Depositors may decide to distribute to industry users. If depositors allow distribution to industry, JAX merely acts as a broker, distributing the line once it receives evidence of an agreement between the depositor and the industry user. This suit challenges the JAX distribution model.

HOW DOES PATENT EXCLUSIVITY MAP TO RESEARCH?
The two new USF suits also bear directly on points raised by Sarnoff about the need to restore a domain of scientific activity free from infringement liability. He notes that the US Court of Appeals for the Federal Circuit made clear in Madey v. Duke University (307 F.3d 1343–1349, 2002) that research, including research at non-profit academic institutions, is subject to infringement liability for ‘making and using’, even if not

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7 Jerry Stouck, Right and Wrong Ways to Use Others’ Patents, NATIONAL DEFENSE BLOG, 2008, http://www.nationaldefensemagazine.org/archive/2008/June/Pages/Ethics2293.aspx (accessed Jan. 9, 2016).
8 David Einhorn & Rita Heimes, Creating a Mouse Academic Research Commons, 27 (10) NAT. BIOTECHNOL. 890, 891 (2009).
'selling', a patented invention. Our colleagues Wesley Cohen, Ashish Arora, Charlene Cho, and John Walsh note that, in practice, most academic researchers pay little attention to patent rights in their research, with a few exceptions, and that patent rights generally do not impede research. More suits like the USF suits against the US Government and JAX could change that.

One solution is to restore the traditional ‘research exemption’ from infringement liability. The European and Australian law enables research on an invention to see how it works, but Sarnoff urges a broader conception: ‘Patents simply did not and should not extend to scientific research’. This would apply even to commercially driven research so long as it does not ‘actually compete in the marketplace for use of the patented invention nor commercially benefit in its own production operations from using the invention’.

The US research exemption was created in common law, not by statute, starting with Justice Joseph Story’s dicta in cases before the Massachusetts Circuit Court at the time of Napoleon (1813). In Europe and Australia such research use is codified. Sarnoff’s comment rekindles a long-standing debate about having a research exemption similarly codified in US law. The issue is, however, a lack of consensus about how to set its boundaries. Too broad an exemption undermines patent incentives for research tools that are most efficiently developed as commercial products and services. Some storied patents in biotechnology were on platform technologies. Think recombinant DNA ($255 million revenues for University of California and Stanford), Columbia’s cotransformation patents ($790 million), polymerase chain reaction ($300 million for Cetus and $2 billion for Roche), and now patent battles over CRISPR and families of DNA-cutting enzymes. A too-narrow exemption fails to serve its intended purpose of freeing research from infringement liability. Lack of a statutory research exemption in US law is not entirely from want of trying. A 1990 House bill, HR 101–5598, proposed a research exemption; early 2007 drafts of what became the America Invents Act of 2011 also proposed to exempt some research uses from infringement liability.

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9 John P. Walsh, Wesley M. Cohen & Charlene Cho, Where Excludability Matters: Material versus intellectual property in academic biomedical research, 36 Res. Pol’y 36 (8): 1184, 1203 (2007); John P. Walsh, Ashish Arora & Wesley M. Cohen, Effects of Research Tool Patents and Licensing of Biomedical Innovation, in PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285, 340 (Wesley M. Cohen & Stephen A. Merrill eds, National Academies Press) (2003).

10 Niels Reimers, Tiger by the Tail, 17 CHEMTECH. 464–71 (1987), reprinted in 7 J. ASS’N. UNIV. TECH. MANAGERS 25, 47; M.P. Feldman, A. Colaianni & C.K. Liu, Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program, in 22 INTELLECTUAL PROPERTY MANAGEMENT IN HEALTH AND AGRICULTURAL INNOVATION: A HANDBOOK OF BEST PRACTICES (Anatole Krattinger ed., Oxford) (2007); Sally S. Hughes, Making Dollars Out of DNA, 92 ISIS 541, 575 (2001).

11 Alessandra Colaianni & Robert Cook-Deegan, Columbia University’s Axel Patents: Technology Transfer and Implications for the Bayh-Dole Act, 87(3) THE MILBANK Q. 683, 715 (2009).

12 Joe Fore, Ilse R. Wiechers & Robert Cook-Deegan, The Effects of Business Practices, Licensing and Intellectual Property on the Development and Dissemination of the Polymerase Chain Reaction: A Case Study, 3 J. BIOMED. DISC. & COLLABORATION 1, 7 (2006).

13 Jacob S. Sherkow, The CRISPR Patent Interference Showdown Is On: How Did We Get Here and What Comes Next?, STANFORD LAW SCHOOL LAW AND BIOSCIENCES BLOG (2015), https://law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/ (accessed Jan. 9, 2016).
Sarnoff’s suggestion builds on articles in legal journals: a seminal 1989 article by Rebecca Eisenberg,14 and an article by Suzanne Michel in 1992 specifically addressed the exemption’s applicability to federally funded inventions;15 as did a series of articles by Rochelle Dreyfus, Donna Gitter, Janice Mueller, and Maureen O’Rourke just before and after the Madey decision.16 Perhaps, at some point, a window of opportunity will open for congressional action.

The alternative to statutory change is case law. However, given the considerable turmoil and uncertainty about how to interpret jurisprudence over patentable subject matter (35 USC § 101)—Bilski v Kappos, Mayo v Prometheus, Assoc. Molec. Pathol. v Myriad, and Alice v CLS Bank—and the tug-of-war between the Supreme Court and the Court of Appeals for the Federal Circuit, seeking certainty from case law may be a vain hope.

COSTS OF LITIGATION
Sarnoff also wishes we had included more information about ‘the actual costs imposed and the research that was foregone because of the patent threats’. We dearly wish we could comply more fully. Assessing what research has not taken place entails dubious counterfactual speculation, although we did gather ample evidence that the field of Alzheimer’s genetics was rife with conflict and fear of litigation. Our efforts to contact Swedish researchers, for example, led to a response from a lawyer who explicitly noted that his client feared litigation. Our interviews were covered by a Certificate of Confidentiality from the NIH, and several interviews were emphatically off the record. Moreover, given the litigious climate, we would not have trusted answers to questions about what research someone wanted to conduct but did not, given the strong incentives to either exaggerate or underplay the damage in an adversarial ethos.

The surveys fielded by Walsh and Cohen do ask questions about projects not pursued, although for a much broader range of science and scientists. That survey methodology, however, fits poorly with a case study such as ours. We nonetheless agree with Sarnoff’s desire for more reliable and methodologically rigorous empirical data about real costs of patent policies.

One aspect of costs has, however, been illuminated by Alzheimer’s Institute of America (AIA) v Avid Pharmaceuticals: the costs of defending against litigation. In our article, we bemoaned the lack of access to litigation costs, since many of the relevant records were sealed. There is now a public record of some costs. When Judge Savage ruled the case was ‘exceptional’ and directed that AIA pay Avid’s legal costs, the court appointed a special master to assess those costs. Gene D. Cohen, the Special Master, mediated a request for fees from Avid’s legal team and AIA’s challenge to those fees. He reviewed only this one case, not the dozen others that preceded it, so it is a substantial underestimate of the overall litigation costs recounted in our article. And the costs are only those

14 Rebecca S. Eisenberg, Patents and the Progress of Science: Exclusive Rights and Experimental Use, 56 U. CHI. L. REV. 1017, 1086 (1989).
15 Suzanne T. Michel, The Experimental Use Exception to Infringement Applied to Federally Funded Inventions, 7 BERKELEY TECH. L. J. 369, 410 (1992).
16 Donna M. Gitter, International Conflicts over Patenting Human DNA Sequences in the United States and the European Union: an Argument for Compulsory Licensing and a Fair-Use Exemption, 76 N.Y.U. L. REV. 1623, 1637 (2001); Janice M. Mueller, No ’Dilettante Affair’: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools, 76 Wash. L. Rev. 1, 17 (2001); Maureen A. O’Rourke, Toward a Doctrine of Fair Use in Patent Law, 100 COLUM. L. REV. 1177, 1205 (2000).
of the defendant, not those of the plaintiff. They are nonetheless illustrative. Avid’s legal team requested $6,867,219.31; the Special Master reduced this by $2923,901.61 and recommended that AIA pay $3,943,317.70 to Avid.\textsuperscript{17} The story is not over, as Avid has filed objections to some of the reductions and takes particular umbrage at bearing full costs of the Special Master’s services, with a five-page account of the protracted and apparently unpleasant mediation process for deciding the fees.\textsuperscript{18}

THE BOTTOM LINE

The patent battles are a side-show in research on Alzheimer’s disease, which is a major biomedical research priority. The tale of the Mullan patents was an unusual case of trolls who fished with an invalid patent for inventions that they never made under patent ownership that was tainted by shenanigans. The new cases are still about trolling, with a state university suing government and a non-profit research institution for revenues from distributed research tools. A recent article by authors from JAX emphasizes the central importance of mouse models in understanding Alzheimer’s disease.\textsuperscript{19} We end by echoing Duff and Hardy’s final sentence about what’s truly important: ‘expanding and distributing colonies of mice should be a priority.’\textsuperscript{20}

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\textsuperscript{17} Gene D. Cohen (Dec. 22, 2015), ‘Report and Recommendation of the Special Master’ in the US District Court for the Eastern District of Pennsylvania (Civil Action No. 2:10-cv-6908-TJS).

\textsuperscript{18} C. S. Marion (Jan. 5, 2016), ‘Avid Pharmaceuticals’ Objection to the Recommendation of the Allocation of Fees of the Special Master’ (Civil Action No.2:10-cv-69087-TJS).

\textsuperscript{19} Kristen D. Onos et al., Toward More Predictive Genetic Mouse Models of Alzheimer’s Disease, \textit{BRAIN RES. BULL.} (2015), \url{http://dx.doi.org/10.1016/j.brainresbull.2015.12.003} (accessed Jan. 9, 2016).

\textsuperscript{20} Karen Duff & John Hardy, \textit{Mouse Model Made}, 373 \textit{NATURE} 476, 477 (1995).