**Canon Fodder—A Case for Contrarian Science**

Gerald W. Dorn II

Cannon fodder are expendable soldiers deployed as “food” for enemy cannon fire when there is no hope of ultimately prevailing: generals dispose of “worthless” soldiers by sacrificing them to the cannon. Here, I adopt the term Canon fodder to describe contrarian scientific concepts dismissed because they do not conform to conventional wisdom: reviewers dispose of “unworthy” science by sacrificing it to the canon.

It is a rare opportunity to be invited to opine to one’s peers on a topic of choice. Actually, my peers are my chosen topic. Specifically, peer review. Twenty-five years ago, I eschewed job security as an interventional cardiologist in favor of academic research. Consequently, I needed NIH R01 funding. After my initial attempts failed spectacularly, one of my mentors (it was Jeff Robbins or Rick Walsh, or perhaps both) provided surprising guidance: I should compose my grant application with 4 specific aims, then discard the most exciting aim and submit what remained. This would avoid provocation in favor of the conventional and acceptable. It was sage advice from highly successful senior investigators (I learned this the hard way, by initially disregarding it and suffering the consequences).

I envisioned testing the neurohormonal hypothesis of heart failure by expressing in cardiac myocytes a signaling molecule common to neurohormonal pathways postulated to mediate pathological hypertrophy. I would use the then-new mouse α-myosin heavy chain (α-MHC) promoter to drive cardiac-specific expression of the α subunit of heterotrimeric G-protein, Gq, the common proximal transducer for angiotensin II (type 1), endothelin, and norepinephrine (α-adrenergic) signaling.

I reasoned that cardiomyocyte-specific activation of Gq signaling would circumvent hemodynamic effects (eg, hypertension) of Gq-coupled neurohormones. If the planned Gq signaling would recapitulate features of pathological hypertrophy and heart failure, then cardiomyocytes were autonomously responding to neurohormonal signaling, thus proving the neurohormonal hypothesis. My first postdoctoral fellow, Drew D’Angelo, prepared the transgene construct and arranged for mouse oocyte injection while I put the plan on paper and submitted it to NIH.

Five months later, the pink sheets arrived. The score was terrible; the reviewer was gentle, but unambiguous: “This will never work.” He/she explained how, as a consequence of the well-known “α- to β-myosin heavy chain switch”, any pro-hypertrophic transgene driven by the α-MHC promoter would turn itself off well before physical hypertrophy ever occurred. The goal of recapitulating pathological hypertrophy using cardiomyocyte-autonomous genetic manipulation was therefore unobtainable using the proposed transgenic system. This unavoidable outcome, completely obvious to those even passingly familiar with the field, constituted a fatal flaw.

Hundreds of α-MHC driven cardiac hypertrophy genetic mouse models later it is clear that this logic, based on the conventional wisdom of 2 decade ago, was erroneous. Counter-regulation of α- and β-MHC in murine heart disease is less of a switch than a shift. Proportional expression of fetal β-MHC mRNA increases dramatically in mouse pathological hypertrophy and heart failure, but it remains a minor isoform, and α-MHC continues to be expressed robustly. I suggested this in an amended grant proposal and included data showing how α-MHC–driven Gq expression recapitulated features of pressure overload hypertrophy in the absence of pressure overload.

The study section replied: “Because (as the committee previously explained) this transgenic hypertrophy experiment can never succeed, we must conclude that the applicant has made some egregious mistakes in his phenotypic analyses.” Conventional wisdom prevailed in the face of contrarian data.

This personal anecdote demonstrates how common knowledge is at best incomplete, is sometimes completely wrong, and is therefore subject to evolution and revolution. My story ended happily. The third time the application was reviewed, contemporaneous with publication of our second paper exploring how hearts directly respond to neurohormonal activation of cardiomyocyte Gq-coupled signaling, the NIH review was brief and enthusiastic: “The applicant has already accomplished much of what we told him he could not; let’s just give him the money” (at least that is how I remember it).

We are discomforted when familiar concepts are disputed, but it is better to embrace hypotheses and results that challenge conventional wisdom. Some exciting new ideas will be wrong. For every revolutionary scientific idea like RNA interference, there are others that prove to be fundamentally unsound (eg, cold fusion, water with memory, and genetically reprogramming stem cells by changing pH). Thus, it may be that the greatest impact of peer involvement is as the crucible wherein experimental findings are validated (or not) through independent replication.

Bad science should be judged as such, but we should welcome notions that defy convention. It is easy to attack new ideas by appealing to conventional wisdom because the “canon fodder” argument is impossible to rebut. “This will never work” is one example, but there are other forms. The most egregious instance in my experience is: “If this were true then someone else would already have reported it” (anonymous New England
Journal of Medicine reviewer). The implicit argument was that everything was already known about the topic.

A more insidious form of intellectual conservatism is the insistence on “template science,” that is, minor experimental variations according to a well-established template. These studies are easy to design and evaluate because they do not require much thinking. Consider the gene knockout mouse. Years ago, a proponent of this approach insisted that the only way to truly understand the function of factor X was to knock it out. This proposition proved so powerful that it moved beyond conventional wisdom to a level of acceptance comparable with natural law, but I am pretty sure it is wrong. Parallelism in biological pathways and functional redundancy between related factors limits the use of gene ablation for functional interrogation. For example, Gq signal activation through cardiomyocyte-directed Gαq overexpression led us to conclude that this factor was a transducer of pressure overload hypertrophy. Consequently, cardiomyocyte-specific knockout of Gq should inhibit hypertrophy induced by microsurgical aortic banding. It did not, because functionally redundant Gα11 was present and compensated for absent Gq. Combined ablation of both Gq and Gα11 in the heart was required to establish that Gq signaling was necessary for pressure overload hypertrophy. There are many examples where the phenotype produced by ablation of a gene does not provide accurate or complete information on the relevant biological activities of that gene. Indeed, because critical functions are likely to be conserved within family members, it is sometimes niche functionality that is exposed by individual gene ablation. We recently demonstrated this for the closely related novel protein kinase C isoforms PKCδ and PKCe. Instead of “we knocked out gene A and X did not happen, therefore gene A does not regulate X” it is useful to consider alternate explanations for negative results and to conservatively interpret positive findings.

The points made above are not new or surprising. Ironically, conventional wisdom now is that our past reliance upon conventional wisdom was counterproductive. Accordingly, peer review of grant proposals or manuscripts emphasizes novelty and innovation. The problem is universally recognized and appropriate processes are in place, but human nature is difficult to change and there is a definite comfort zone for evaluating and accepting new scientific findings, outside of which one encounters resistance. In 2001, I wrote an overview for Circulation of the controversy generated by Olson’s and Molkentin’s description of the calcineurin pathway leading to heart failure, a scientific dispute that seems surprising in hindsight.

One of the mechanisms developed by the NIH to expand the diversity and innovation of their extramurally-funded grant portfolio is the Transformative R01, or TR01. I was privileged to serve on this study section earlier this year, and I found both the grant application and review processes to be refreshingly unconventional. The application format was brief and concept-driven. The review committee members were leaders in their fields and diverse in their areas of expertise. Remarkably, grants were assigned to individuals who were not authorities on the specific research topic. Thus, I evaluated TR01 applications on imaging, endocrinology, and implantable biosensors, whereas cardiac grants were reviewed by others. As explained to us by NIH staff, the approach of having experts evaluate proposals outside of their areas of expertise was intended to promote science that takes new approaches and contradicts established paradigms, while avoiding critiques based on technical or conceptual nonconformity. (Of course, the counterargument is that nonexperts are less likely to recognize incremental science; it will be interesting to see what fruit the program bears.) The discussions were interesting, but I was surprised at how often the consensus opinion regressed to conventional norms. As a nonexpert, I recall being particularly enthusiastic about one proposal that took a different approach to cancer immunotherapy. After the 3 assigned reviewers provided their evaluations, the discussion was opened up to the other committee members. One individual, an authority in the area, declared: “This will never work.”

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