Canon Fodder—A Case for Contrarian Science

Gerald W. Dorn II

Canon 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 Gqα transgenic mice developed 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 prohypertrophic 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 Gqα 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...
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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