

Unconventional Wisdom

Steven L. McKnight^{1,*}

¹Department of Biochemistry, UT Southwestern Medical Center, Dallas, TX 75390-9152, USA

*Correspondence: steven.mcknight@utsouthwestern.edu

DOI 10.1016/j.cell.2009.08.016

Science is an “endless frontier,” and opportunities for transformative discovery abound. The young scientist will profit by paying mind to two forms of balance: the contrast between depth and breadth in training, and the contrast between hypothesis-driven research and random inquiry into the unknown.

When asked to compose a brief article to be directed toward an audience consisting of young scientists, my first reaction was—geez, young scientists don't need advice at all, they rule. The majority of genuinely profound discoveries made over the millennia have come from young scientists. There are numerous reasons for this. The young mind is maximally acute, and the young scientist is minimally distracted. It's sink-or-swim for the young scientist, so he or she is hungrier and fights harder to bring home the bacon. Finally, the young scientist brings little baggage to a problem. I would trade the supposed wisdom gained from a longstanding career in science for the combination of naiveté and exuberance any day. For these reasons, the best advice I can give comes from one of Bob Dylan's songs on his *Planet Waves* album: “may you stay, forever young.”

The starting point I was given posed the question of where I thought the best opportunities for discoveries might lie in the years ahead. The answer to this question is simple—scientific opportunities abound everywhere. Of course, we hope to someday understand the molecular basis of memory and the magic of regeneration, but these are only two of hundreds of watershed opportunities for transformative discovery standing in front of us in the decades to come.

Let's consider two contrasting articles, published by eminent scientists, that influenced me early during my own career. The first was authored by the renowned geneticist Gunther Stent. Having used Stent's wonderful textbook on genetics (Stent, 1963) during my undergraduate training at the University of Texas, I viewed Stent as a scientific icon.

Subsequently, Stent published an essay in *Science* that argued that the field of molecular biology was washed up, done, kaput (Stent, 1968). Yes, by then the genetic code had been cracked, Crick's central dogma had been confirmed, and the nature of the gene was understood in atomic detail. On the other hand, I was just entering the field of biological research, and I viewed the subdiscipline of molecular biology as having unlimited promise. Much to my dismay, a scientist of Stent's stature had argued the field was dead.

The second article of influence was an essay published in *Cell* by Charles Yanofsky wherein he questioned whether the field of microbiology might be at the end of its rope (Yanofsky, 1991). At the time, the lion's share of attention and grant funding were going toward studies of eukaryotic organisms, and Yanofsky wondered whether the end was near for studies of prokaryotes. Yanofsky, however, came to the exact opposite conclusion from Stent—instead of announcing the demise of microbiology, he boldly predicted that the well was far from dry. Looking back on what has been discovered in the field of microbiology over the past three decades—quorum sensing, molecular mechanisms of pathogenesis, riboswitches, genome sequences, thermophiles and extremophiles, the microbial flora inhabiting our bodies, and so on—Yanofsky's forward-reaching conclusion could not have been more spot on.

Naming where the most exciting breakthroughs will come from in the ensuing decades is way beyond what I could possibly muster! In this regard, I pay special homage to an early president of the Carnegie Institution of Washington, Vannevar Bush. It was his words that

so beautifully described science as the “endless frontier” (Bush, 1945). Those two words gave me plenty of inspiration to overcome any discouragement transiently resulting from the diametrically opposing conclusion of Stent. They are as true today as they were in 1945 when penned by Dr. Bush.

Reasoned advice to the young scientist is to be careful not to become overly focused. Yes, to be competitive, the young scientist must be at the top of the game in his or her chosen field. On the other hand a scientist broadly exposed to disciplines outside of his or her chosen field will enjoy distinct advantages. The subdisciplines of biological and biomedical research evolve rapidly, and it is often the case that the most radical of transformations to a field come from outsiders who bring a combination of fresh perspectives and naiveté. It is for this reason that medical students—if they choose in a genuine and dedicated manner to have a career in science—can sometimes be equally prepared for extended success as PhDs. Medical students have to learn anatomy, physiology, pathology, genetics, biochemistry, pharmacology, immunology, and other fields of science required to understand how the human body operates. Modern PhD programs often focus the training of young scientists so acutely that, as a subdiscipline matures, liability to extinction becomes a genuine threat. For the PhD student, one should consider the benefits of attending seminars—while in graduate school and during post-doctoral training—orthogonal to what is being studied in the training laboratory. The much stronger tendency for a young trainee is never to miss the seminars most closely related to his or her

research, even though the young scientist already has a 99% mastery of that particular subdiscipline. Bottom line, the breadth of your scientific training will be of equivalent value to its depth.

The question is not where to explore for new opportunities on the horizon of science, but instead, how to go about looking for them. Here the balance of “inductive inquiry” (I^2) and “hypothesis-driven” (HD) approaches becomes the crux. A recent article written by Francisco Ayala beautifully recounts how the plusses and minuses of the two approaches have been debated by philosophers over the past several centuries (Ayala, 2009). The I^2 approach, in its most pure form, entails adventure into uncharted territories—neither guided nor bridled by hypothesis. The HD approach is built on scholarship and smarts and is fundamentally driven by theory. If X and Y facts are understood, this knowledge should facilitate the hypothesis essential for solving the unknown Z. Scientists, just like most people, are far more comfortable with the known than the unknown. If one can embark on an adventure with known variables in pocket, the comfort factor alone will nudge the endeavor in favor of the HD direction.

Another influential factor perennially favoring the HD side of the equation is money. Except in the most unusual of circumstances, other people are making the decision for us as to where we get to explore. Science requires money, and money is doled out by committees that evaluate our research plans. Proposals thin on HD, no matter how open and uncharted the territory chosen for inquiry, tend to be rejected. As such the I^2 approach almost always loses out to the HD approach when it comes to funding decisions. Bottom line, conventional wisdom almost always prevails—this, I advise, is something you will have to constantly fight in order to carve out a truly innovative career in science.

Any research endeavor we might choose to pursue is, of course, an I^2 /HD blend. As articulated by Charles Darwin, “Let theory guide your observations,” otherwise one “might as well go into a gravel pit and count the pebbles and describe the colors. How odd it is that anyone should not see that observation must be for or against some view if it is to be of any

service” (Darwin, 1903). A scientist cannot easily shed the knowledge causing him or her to proceed on an adventure without bearing elements of scholarship, theory, and bias. If, however, this knowledge is sufficiently acute and dominating, it likely leads the adventure in the same direction being pursued by many other scientists. Put in other words, the dominating hypotheses in all fields—like the Pied Piper of Hamelin—tend to channel scientists into the same directions. A buffering of the power of the HD approach requires a purposeful squinting of the eyes so that a dose of I^2 flavor can be added to the mix. Please understand that I am not advocating the mindless data gathering that has become trendy with the advent of “omics” technologies (DNA microarrays, whole genome association scans, and the like). These approaches do little more than count and color Darwin’s pebbles. What I instead recommend is fresh scientific inquiry into under-appreciated biological or medical phenomena that presently exist in a mystic state.

Central to my argument favoring inductive inquiry is the attitude that we know so little about biology that we cannot even anticipate the nature of major discoveries to unfold in the future. Others, no doubt, are more perceptive than I. But I can legitimately say that I had no clue that eukaryotic genes would be segmented into introns and exons, that RNA could perform catalytic reactions, and that small RNAs would be able to self-amplify and profoundly regulate biological pathways in organisms ranging from spinach to worms to humans. Cast in a different light, I pose the question of whether our biomedical research enterprise would be better or worse off had every single specific aim of every single grant ever submitted to the NIH been perfectly completed if—in payment to the devil—we had to give up the totally unanticipated discoveries that were never once written as a specific aim in any grant application?

So, if one buys into the utility of the foggy, eye-squinting I^2 approach, how might a young scientist pursue this course and decide what to do? The actual choice of direction is the easiest problem to solve. One simply has to look where the trends are headed and go the other way. Here, for conceptual purposes only,

I suggest a “pin the tail on the donkey” approach. A randomly assembled chart is printed up containing squares labeled with all of our 20 to 30 thousand genes. Of these, we know lots about some, a bit about others, yet almost nothing of the remainder. We slap on a blindfold then throw the dart against the wall. Chances are reasonably good that the dart will land on an “unknown” gene—as long as the contestant does not peek around the blindfold and aim the dart at the squares adorned with the comfortable names that already appear every day in the literature. That the unknown gene does something critical is supported by the fact that it’s been kept in place by hundreds of millions of years of evolution. That every gene and every protein are both interesting and important is incontrovertible. This being the case, why would anyone want to work on a gene or protein already staked out by dozens of other scientists?

Why do we choose to be scientists? Most fundamentally, we do so because science offers us the chance to make a discovery—no matter how large or small—never before conceived by another human. Two hundred years ago, the opportunity for discovery is what drove a band of adventurous souls to join Meriwether Lewis and William Clark to sail up the Missouri river in hopes of finding a passage across the northwest. Nothing, I propose, can be more rewarding than the sheer joy of discovery. It is notable, however, that those mavericks who signed on with Lewis and Clark experienced 99% slog to the 1% of their time spent miraculously stumbling over new valleys or passages. Scientific research, likewise, is a head-bumping slog. If we are lucky, the slog is periodically punctuated by unbridled joy. In this time of tight grant funding and a challenging job market, the best I can offer is to encourage young scientists to trust your instincts and stay on your uniquely chosen path.

I close with a personal reflection. When I was a youngster, I loved sports and could think of nothing better than a career in professional athletics. The reason for this was not based on talent—had it been, I’d perhaps now be a retired football player coaching at some high school or college. No, the reason for this was that I simply loved sports. I was unafraid of training and working to foster

my ambitions for achievement because it never felt like work at all. As, through adolescence, I came to realize that my innate talents in athletics were clearly inadequate for a professional career, I was haunted by the question of what I might do for a living. Out of serendipity, I found my way into the field of biological research. Lo and behold, I found that chasing scientific adventure was hardly work at all but instead was a joyous endeavor not unlike what I'd experienced at an earlier stage of my life in athletics. To the young scientist, I leave this final

question. Does science feel like a job, or is it the case that vocation matches avocation, such that you can't wait to get to the lab, such that it does not feel like work at all? If so, nothing can stop you and may you indeed "stay, forever young."

ACKNOWLEDGMENTS

I thank Cori Bargman, Don Brown, Joanne Chory, Mike Dyer, Charlie Emerson, Joe Goldstein, Rich Losick, Mort Meyerson, Mark Ptashne, Bill Neaves, Mike Rosen, Peter Walter, Xiaodong Wang, Charley Yanofsky, and trainees in the McKnight lab for invaluable input on the composition of this Essay.

REFERENCES

- Ayala, F.J. (2009). *Proc. Natl. Acad. Sci. USA* 106, 10033–10039.
- Bush, V. (1945). *Science, The Endless Frontier: A Report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development* (Washington, DC: United States Government Printing Office).
- Darwin, F. (1903). *More Letters of Charles Darwin* (London: Murray).
- Stent, G.S. (1963). *Molecular Biology of Bacterial Viruses* (San Francisco: W.H. Freeman and Co.).
- Stent, G.S. (1968). *Science* 160, 390–395.
- Yanofsky, C. (1991). *Cell* 65, 199–200.