

Physician scientists

Pamela Davis MD PhD, for Meeting November 12.

Victor Dzau has reminded us that although we were declared an endangered species 40 years ago, we're still here. However, we've been talking so long about the physician scientist crisis that it has had the opportunity to broaden and deepen. During this time our numbers have not increased, though numbers of PhD biomedical scientists have grown, so physicians now command a smaller proportion of the NIH budget. Fiscal pressures all around have led to such emphasis on productivity and rvu's that young physicians may not even consider turning aside from the clinic to pursue other things. **The youngest cohort of physician scientists, those age 31-40, is dwindling. The decline is even more precipitous in the 41-50 age group.** We have to ask whether we really need this endangered species at all. After all, medical education is expensive, and we are headed for a physician shortage – should we invest in someone who, if he or she succeeds, will not practice medicine even close to full time? On the other hand, research is also quite expensive. The institution must invest over 50 cents for every external dollar it receives for research, and much of that investment is in training. The timeline for payoff, if you are looking for improved health, is long, especially for lab scientists. And Bruce Alberts and his colleagues tell us we are training too many researchers anyway. Should we invest in a researcher who will dilute his or her research effort in patient care? Is the rare phenotype so precious?

We are going to have to justify our continued existence, just as our hospital systems frequently point to efficient systems with no academic component and ask us to justify the “academic” in academic medicine.

We have argued through the years, and most recently in the NIH report on the physician scientist workforce, that the special perspective a physician has on research questions and approaches makes it critical that at least a few of us translators survive. In fact, this report notes that if we examine Nobel laureates in physiology and medicine, 37% have been MDs, 41% of the Lasker award winners in basic science and 65% in clinical science are MDs. 60% of the

members of the biological science section of the NAS are MDs, and 7 of the chief scientific officers of the top ten pharma companies are MDs. Apparently such rare birds make great and impactful discoveries, profoundly influence biomedical science, and are key to developing the next generation of pharmaceuticals – and the next generation of investigators!

If we accept that physician scientists play a crucial role in biomedicine (and biomedicine, by the way, is the one industry in which the US is still clearly a leader!) then why are we unable to assure their development and growth? Why are we unable to secure the pipeline?

First, **the pipeline takes too long**. The road winds through the MD PhD of 8 years, residency, where one has the opportunity to lose touch with the science that was so cutting edge in the PhD, fellowship where one tries to recover some of that edge, or, if not an MD-PhD, acquire it in the first place, and then a protracted period of mentorship as a junior faculty member which finally ends with the first independent funding at about age 44. We and our accreditors – LCME that accredits the medical schools and ACGME that rules the residencies – need to work together to provide streamlined career paths for these special people. Indeed, there's already a push to shorten the timeline for training for primary care. Shouldn't we push for shortening the time for clinical certification for physician scientists?

If one did not have the benefit of an MSTP fellowship, there's also the little matter of medical school debt as well. One arrives at independence in one's mid-forties with a mortgage, but no house.

And, what might be the most creative years are not spent creating new knowledge.

Then, there's the problem of **instability in the research granting system**. Many bright young people don't mind competition, but when they see us sweating blood about grants and also not being funded, it is truly discouraging. Continuous worry about keeping one's lab intact is too challenging and distracting for many excellent scientists, especially those who feel a sense of responsibility toward their students and their employees.

Finally, there is the **incredible burden of dither** imposed by compliance regulations from two worlds. On the clinical side, even those in cognitive specialties have to deal with hospital and

licensing and specialty reaccreditation procedures – and if you have procedural skills, keeping up is even harder. Hospitals make you take classes in risk management and IDC-10, and fill out interminable forms for such simple things as a flu shot. No one can do that for you. A physician scientist colleague who has limited clinic time tells me that he calculated that now he spends as much time on clinical compliance as he does seeing patients. Taking into account the cost of his time and malpractice insurance, it may no longer be a value proposition for him to continue clinical activity, but then will that diminish his value as a physician scientist?

On the lab side, keeping up with clinical research certification, IACUC certification, conflict of interest, effort reporting, export controls, responsible conduct of research, lab safety certification (of varying degrees of difficulty depending on the area of science), invention disclosures, new NIH formats, regulations, page limits, technical requirements, different requirements for other federal agencies, agreements with foundations that fund us that can run to 15 pages with various restrictions, state regulations – all of it is daunting and can only be mitigated, not eliminated, by provision of appropriate administrative help.

Traditionally we think of the quintessential physician scientist as one **inspired in the clinic who goes to the lab to figure out the questions** provoked by his or her patients. Many of us were trained to think that epidemiology and clinical studies were somehow second class and not worthy of the true physician scientist. In fact, my PhD adviser had such suspicion even of basic statistics that he was fond of saying that if you had to resort to statistics to prove your case, it probably wasn't true. It was thought that clinical studies could be accomplished by any physician with half a brain and a spark of curiosity. But now, after multiple lessons from drugs that failed in phase 2 (the most common site of failure in the clinical trials continuum), we recognize that sometimes what is abundantly clear in mice is absolutely untrue in humans – in our cancer center they say “any damn fool can cure a mouse”! We recognize that the human model is the ultimate arbiter of human physiology –in the end, the intact human must be the test subject for understanding and treating human disease. Moreover, we are now challenged to conduct human studies more efficiently – it needs to be much less costly and the gold standard RCT may need to be replaced by trials of more sophisticated design - adaptive designs, Bayesian analysis, N of 1 studies. We can't spend as much money and time as we are

now to get valid answers. Patients are waiting. And we are now becoming sensitized to human variability and the fact that not all patients with particular diseases are identical or respond in the same way – from patients with cancers to monogenic diseases. In my own field of cystic fibrosis, CF delta F508 homozygotes did not respond in identical fashion to a precision drug combination recently released by the FDA – some improved, but some actually deteriorated. Could we have predicted this and identified the different responders? Should we have collected other data in the course of the trial to be able retrospectively to analyze the responses? Precision medicine needs to be incorporated into clinical trial design. The creativity required to address such questions in human subjects, who insist on outbreeding, eat when they please, take over the counter drugs without telling us, and shade their histories just a tad – well, it’s daunting. **The realm of clinical and translational research requires specialized training, and we need to embrace it - after all, the work of the translational researcher will ultimately validate – or not – our lab discoveries. This is an area in which the physician scientist excels.** In fact one can argue that only the physician can truly grasp and deal with the complexities of modern clinical and translational research. This is an area in which the CTSA program has stepped up, by training MD faculty early in their career, and by catalyzing MS and PhD programs in clinical research to train individuals during medical school or after. In this context, we should address the question of recognizing the contribution of physicians who spend most of their time in clinical medicine, yet recruit into clinical trial, oversee follow up visits in clinical trials, and often make insightful observations. How are they to be supported? But the expansion of the venue of the physician scientist does not stop with clinical research – that is, the patient and the investigator in the same room and they are both alive! There is another element emerging. **In vivo expands to being informed by in silico.** The advent of big data makes many of us worry, because big data often means very poorly vetted or poorly collected data of highly variable quality. It’s hard for many of us to believe that anything good could emerge out of such a gemisch. But, it is certainly possible to use such data to estimate the availability of subjects for clinical trials with very restrictive entry and exclusion criteria. It may be possible to compare the results from big data, analyzed in a short time, with those obtained from RCTs or prospective studies and to determine whether the directionality and

magnitude of the results match. If not, why? Big data can be subjected to validation scripts and “cleaned up” for various purposes. It is certainly useful for hypothesis generation, and may become more useful for hypothesis testing. It will certainly help us understand how the delivery of medical care works, and how it can become more efficient and achieve better outcomes. These are issues too important to leave to the administrators to determine. We can cross reference social and environmental issues with health. We can track patients with wearable devices. This, too, is a province of physician scientists. But one needs the appropriate training in informatics and the management of large data sets to succeed. Again, the CTSA's have stepped up to catalyze and encourage such training. In the realm of big data, I think that it's formulating the best question that wins the day, and I suspect that physicians will own the best questions for quite a while.

All of these areas converge in public health, implementation science, population health. These topics may better be viewed from a global perspective. We'd do well to examine world medicine – our own public health statistics are not up to those posted by other developed countries, yet our systems cost more. We can learn from other economies. We may learn from developing countries strategies to deliver care in rural areas or in the crush of our inner cities.

I would argue that the venue of the physician scientist has expanded beyond the laboratory into the clinic and into the computer. Some of the most effective physician scientists these days live in the realms of clinical and in silico studies, as well as conducting research in vitro. Moreover, **the culture of the physician scientist is also changing.** Nowadays, we solve many problems as a team. Thirty years ago, physician scientists with brilliant minds went into a 1000 sq ft lab with a few acolytes and emerged with new truths about the mechanistic operation of, say, the complement cascade, or the clotting cascade, or signal transduction in a G protein, or the development of the immune system. There were some young physician scientists in their labs who carved out a piece of the great man's work (and yes, it usually was a man!) and spun out into their own 500 sq ft kingdoms to make their fortunes. Nowadays, even in the preclinical laboratory, it's different. Specialists in various high technology areas collaborate to investigate knotty and complex problems, and each area is indispensable to the results. This is true in the laboratory as well as in the realm of clinical research, and in the arc of big data.

Nowadays, many of us consider training in **teamwork** and leadership as important as the hard science.

We are working now with a new generation of physician scientists who grew up with the idea of teamwork. It comes naturally to them, and it's up to us to reinforce it. For example, our CTSA KL2 component has a set of required didactic courses, but trainees can place out of any of them with prior training - any except leadership/entrepreneurship and team building. These have proven to be valuable for all of our trainees – and sometimes inspired collaborations right within the trainee cohort. When we accept a KL2 trainee, we plan a four-year timeline in which a major grant should be written in the third year. We provide multiple mentors, and a multidisciplinary advisory committee monitors the mentoring at six month intervals and has the authority to make changes if necessary. This follow up, originally derided as Mickey Mouse by some of our senior faculty, is now viewed as essential. Many of the grants that emerge from this system are team grants. By two years after graduation from the four year program, over 70% of our trainees have large independent research grants – mostly R01s, or U01s, but also grants from other federal agencies, or large foundation grants. We believe that our closely supervised intensive mentoring has shortened the training time and effectively launched independent careers. Of course, since there's no control group we can't definitively say that the mentoring is the secret sauce. We also think that because they are team players, their careers are more likely to be sustainable, but that too remains to be proven. Because they have been broadly trained and shown the world of possibilities, they will follow their problem where it leads, obtain the collaborators and the skills that they need, and find the answers. They will bridge the gap between the lab and the clinic, and between clinical care and public health. They will teach us to deliver care better and faster and cheaper. They will make a difference, in vivo and in silico, as much as we did in vitro in the past. They will matter. And isn't that why we want the physician scientist after all?