Strategies for Innovation and Interdisciplinary Translational Research

Research and Career Benefits and Barriers

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Abstract: Following is a portion of the proceedings of the panel and audience discussion from the AFMR-Translational Medical Research Development Workshop at EB08.

Key Words: strategies, innovation, interdisciplinary research, translational research, career, workshop discussion


Below is a summary of questions, comments, and ideas discussed among the panel speakers and with workshop participants at the EB2008 American Federation for Medical Research Translational Medical Research Workshop, Strategies for Innovation and Interdisciplinary Translational Research: Research and Career Benefits and Barriers.

CARROTS AND THE STICKS: REWARD SYSTEMS AND CONNECTING WITH THE “BIG PICTURE”

Question: I am a surgery resident and also getting a PhD in 2009 by The American Federation for Medical Research and Federation of American Societies for Experimental Biology are part of making those interactions. For example, many (meeting) talks are very (narrowly) focused, and you do not see where they fit into the big picture. In a big lecture hall, you could get someone who has the 10 thousand foot view of science on the topic to introduce people doing these focused things in that area and then integrate it into the big picture to give a more complete thought. What do you think?

Dr. Mark Benedyk (MB): What you are describing is akin to what I experienced when I went to my first Drosophila genetics conference in grad school. Not only are there specialized geneticists who work in yeast, flies, worms, and mice, but in the Drosophila community, there are neuronal geneticists who study sensory neurons, developmental people, etc. The result is a sad Babel that precludes collaboration and effective communication and is ultimately derived from what people are rewarded for. Everybody here spoke about compensation schemes or incentives for interacting with other people, but at the end of the day, if you are trying to get tenure, somebody is going to say, “What kind of publications have you put together in those extremely specialized journals that you are supposed to publish in?” That is part of the problem. I will be kind of radical here and say, I think tenure is the root of this problem. It is an interesting conundrum, where you are working toward a position in which you never really have to work again so that you can eventually gets things done that really count towards your scientific goals. That is the kind of situation corporations consider all the time. Parts of our bonuses come from a team goal, and the team component of that goal gets more enhanced the higher in the organization you go. Maybe there should be team goals in universities. I do not know.

Question: You hit on exactly what needs to change—how things are rewarded. Another problem is the whole first authorship, last authorship issue. If we just had senior authors, listed alphabetically, and junior authors, listed alphabetically, then you would not have graduate students and research residents laboring 24-7 on something just to have someone else come along and say, “I’m taking first authorship of that.” Then the student/resident has spent 2 years and has nothing to show for it.

Dr. Lars Berglund (LB): I am very sympathetic to that. I have been engaged quite a lot in our own university on how to actually deal with this. First and last authorship is one thing, but there is also the issue of identifying contributions. It is your expertise in some area that makes an important contribution to a number of studies. It may not be as a first or second or third, or last author, but I have argued it is as valuable as many other things because it is a key skill or competency that is contributed. A good example is biostatisticians, who are involved in a number of studies, bring their unique skills to them and improve the quality of the studies. It is an ongoing debate and not something we can (fully) control, particularly in a system like the University of California. I had a very interesting experience going from a private university (Columbia) to a public university (University of California). Issues of transparency come up, and with that, a very slow system to change.

Dr. Marc Facciotti (MF): If I can just add 2 things regarding tenure. I think Lars (Berglund) is somebody that supports interactions and would not have any problems voting for the advancement of somebody who was really interactive with other people. There are individuals in these big institutions that want to see a lot of interaction, but for some reason, (perhaps because of the institution size, etc) are held back. In contrast, the Institute for Systems Biology is academically structured (people have titles like assistant professor, associate professor or full professor, etc),
but nobody is tenured. The reward system is set up to favor people interacting at the Institute. You are rewarded for doing exciting science, and it does not matter as much whether or not 3 other people at the institute plus somebody else in Kentucky contributed to that. If you were a key player, that is seen as a positive. It is not counted against you that you were not the senior author on every publication that came out of your laboratory. There is an understanding among the faculty there (at Institute for Systems Biology) that this is the philosophy they want to use.

Dr. William Mobley (WM): I would like that a lot. I think part of the system we have is based upon a superficial perspective of what actually went into the paper. We count publications, we count first authorships, we count last authorships, but what we should count is the work product and the genius and innovation involved. I think we can evolve to a system where we could list names alphabetically and then we might list at the end of papers the names of those people who principally contributed the ideas, who principally did the work, who paid for it, who set up a house for it to go, and so on. It would not be very difficult. All the authors would have to say, “Yes, I agree with everything about all the authorship issues.” So when you looked at the paper, you could say, “This was done in Dr. Jones’s laboratory, but pretty clearly it was M.E. Anderson who really had the idea and Mary Jones who worked with...” It is doable and knowable, and a way to make it easy to resolve the authorship issue and to make sure people get credit.

A second issue is how much do we want innovation and new concepts?—A lot. We always have. We have always prided ourselves on pushing for the cutting edge, cool science. That has never been a problem. How important is excellence? It is really important to us. We have always rewarded excellence or have tried to. What we have not done very well is define the pieces of the puzzle that make it excellent and innovative. We have not been clearly defining who has been responsible for what. It has always been the first author and the last author or the corresponding author. So I think we could define this better.

Finally, I think we have to say, “How much do we care about solving difficult problems like helping people who are sick?” If the answer is, “A lot”—then we will understand that to carry out research that is meaningful across scales requires teamwork. So one of the criteria for tenure would be how good a team player the candidate is. I have never heard anybody ask that question in a tenure process. To solve real problems, team play will be essential. No one of us can possibly know all we need to know across multiple domains. And I definitely think we need to more properly reward the young people who do the work. I know cases in which investigators have put their name on a paper that come out of other people’s laboratories just because they made available an antibody or some other reagent. Well, guess what, on the bottom line of the paper under the new system it would just state that this person “gave me an antibody.” It even resolves that little problem.

(Follow up note: Several journals [such as Journal of the American Medical Association] have adopted this contribution-based approach in their manuscript submission processes and require designation of the type of contribution by each author. In practical terms, how will the contributions be fairly assessed and are there as many or more risks in this approach for the junior as compared with the more senior participants?)

INDIVIDUAL RECOGNITION AND INTELLECTUAL PROPERTY

WM: I love the incubator idea because it still plays upon the individual genius and the individual energy of an investigator—a champion for the new company who thinks about it day and night and wants it to prosper. Obviously, he/she needs a team, but maybe it was not a team that came up with the idea. I think most really great ideas do not come from teams, but from individuals within teams. My guess is great ideas come because thousands of people talk about something and 1 or 2 people get a great idea. How do you prosecute the idea? I love that the incubator keeps that champion in place working and makes it possible for that person to succeed. So Pfizer (La Jolla, CA) is doing this—could the National Institutes of Health (NIH) do this? Could the NIH convene those discussions? In addition, how does the incubator deal with institutions and intellectual property issues?

MB: These types of financing vehicles (the Pfizer Incubator [TPI], the Novartis Option Fund and some of the other nontraditional vehicles Big Pharma are creating) are coming about from a broader consensus that Big Pharma is going to go through big changes in the next 10 years, and needs to do things differently. Huge amounts of revenues are going to disappear because of patent expirations. For example, Lipitor is going off patent in about 2 years. How is Pfizer going to deal with a $13-billion gap in revenue? And the population has also changed. We have a lot more elderly people. For example, your average budget for a development project including a multi-study, global, multisite clinical trial for an Alzheimer product is about $300 million. Given the financial crisis and issues at the Food and Drug Administration, how do you tackle discovery of new Alzheimer products in a climate where the business model for pharmaceutical companies is in the midst of significant restructuring? Times have changed, so we have a compelling need to break the mold and do something different. NIH, I think they have tried. The problem with NIH is that they try by saying, “We are going to create a new grant.” But that is like saying, “I’m going to solve pollution by making a new car,” as opposed to saying, “I’m going to improve transportation.” I do not know how to generate enough momentum to break the inertia toward these types of solutions.

Regarding (intellectual property and) our working with institutions (eg, the University of California system). I recently spent time at San Diego State University, the quieter, smaller sister to the University of California in San Diego. They have a really interesting system. They have a foundation that administers all the intellectual property out of a range of different State University campuses and are very easy to deal with licensing-wise. In the absence of this type of model, I think that at University of California system schools you need to find a champion principal investigator to drive the system in the way that you want it to go. Last year I was informed, about a tech transfer consortium akin to the California State University System with 5 schools in New York; Columbia, Rockefeller, Einstein, New York University, and, I think, Cornell Medical. People are realizing that there has to be more cross-fertilization between industry and the clinic and basic science. Administratively, you have to provide channels so that intellectual property can leak the academic world and go to broader audience. That is one way to do it.

ACADEMICS AND INDUSTRY: BRIDGING CULTURES TOWARDS COMMON GOALS?

Question: I am an assistant professor, and before this, I was in Biotech. I see the NIH roadmap initiatives and the Pfizer incubator, which I find really interesting and attractive, and am trying to understand where I fit into this scheme. I see a gap between the incubator and what NIH is doing. To give an example, I started a tool company for drug discovery. We raised $40 million and had a series of compounds for rheumatoid
arthritus that we sold to a large Pharma company. I left to go into academics and thought I would be well positioned for the road map grants. However, I found out it is much harder than I thought to get those grants. I submitted a grant on assay technology. The review panel did not think there was need for a new assay. A year later, I licensed it to a company. So, I am not sure if I am just a really bad grant writer, which is very possible, but there was a disconnection between the review panel (mostly academics)—thinking the world did not need this assay—and a company (the biggest seller of this type of technology) saying this was a useful assay. Do you see a disconnection between what the incubator is offering and the roadmap initiatives? Do you see a way to blend them? Do you see this (the incubator) growing bigger?”

MB: I left academia after attending the Rockefeller University, and at the time when I decided to leave academia, that was considered a terrible thing to do. I had heard that a classmate, who was extremely intelligent and whose father is an academic luminary was (also) going to leave the academic track and go to Harvard Business School. I remember meeting her in the elevator, and saying, “A friend told me you are going to Harvard Business School.” She just turned white. There was (is) a cultural gulf between academia and industry, which I think is unfortunate. Having worked at a company focused on neurological disease I saw incredible, high-quality basic science going on—which I do not know you could see anywhere in academia. Likewise, often you see a squandering of resources in big and small pharma that would not happen in academia. Perhaps, this is due to people hiring too many other people like themselves. So, if you did a stint in industry, there may be a mixture of both disdain and jealousy from people that read your grant proposals. I only say that because that has been my experience. Likewise, if you are an academic and you come to Big Pharma, there is often a view that you must be completely impractical and unable to focus on product development.

Question: Do you see Pfizer reaching out to work with NIH and the roadmap initiatives in increasing ways?

MB: I do not know to what extent specifically they are doing that, but in that spirit, I sat down yesterday with the [Chief Scientific Officer] of the Oncology Business Unit (Pfizer), and he is developing a network of thought leaders and accessing tissue banks and cancer centers all over the world to help drive a lot of what he is doing at Pfizer. We cannot internally fund open-ended basis research at Pfizer, but we can fund it externally. We can strategically look 3–5 years forward and try to see where trends are going, and in that context, yes, there is a movement to do that.

LB: I think you bring up a really important point when you said that “people like people like themselves.” I think that is partly true, because you probably think like people like yourself. I am interested in developing -for our trainees and maybe even our medical students—a way to get immersed in the thinking of companies. Would there be interest, in principle, in internships or shorter rotations of researchers within companies like The Pfizer Incubator or in at the (Pfizer) research parts—to give people a sense of the culture, and how companies are thinking, and people in the company would (also) get a sense of what we are thinking? I think it could have a broader scope in trying to bridge this gap which exists and is not beneficial.

MB: It is not beneficial. I know at Genentech, there are Genentech fellows and postdocs. I think, but do not know, that that is the case (too) in Big Pharma. However, I do know they are trying to embrace that model so that there is less of a 2-culture system and more integration. There is value in that mind set—in cross-fertilization—because very often people do not realize they are working on really interesting science and get tunnel visioned. They do not realize that there are other issues at play in developing drugs, be they proteins or small molecules. To keep that in the back of your mind, the whole time you are working on a project is, I think, very valuable.

WM: I got to hear about one of the roadmap initiatives when I was on council—a chemical library roadmap initiative. The idea was that people would write grants and NIH would pay groups to do high-throughput screening to develop drugs. The budget was maybe 2 million (dollars) a year for the whole country—quite a small amount given the typical budget for such work, at least as practiced in a Pharma company. I was critical because I thought that what they were attempting to do was not something that the academic environment normally supports. They were attempting to duplicate the terrific ability of industry to do this. So, if there were real champions for linking of missions (of academe and industry), sharing of resources and capabilities and technology—and forget about the compounds for the moment—just “here is how you do this…”—then I think the roadmap might make a very important contribution. My sense of the roadmap is that it is developing tools, reagents, and technologies, but not necessarily new ideas. It is not a problem-solving exercise rather it appears largely to be an infrastructure building activity. Though much needed, I would suggest the addition of projects in which disease-related studies were pursued in an interdisciplinary fashion.

Question: A big concern of mine is the NIH compound collection. In biotech, we had our fifty thousand compound collection, and more than 50% of our hits were false-positives. However, we only figured out that when a chemist resynthesized them. That is not happening with PubChem compounds that are being screened yet a company would be able to recognize that.

MB: I agree. Having worked with a company that just did high-throughput screening and assay development, I see some NIH initiatives and think, “This is like a 1970s version of what we did (in industry) in the mid 1990s.” So, what do people get out of this? I think the point about there not being an end goal (in the roadmap initiatives) of solving a big problem but just creating stuff (tools, etc), is a realization that came to a lot of disease foundations in the last few years. If you talk to the Cystic Fibrosis Foundation or other foundations involved in diabetes or retinal degeneration, they are no longer funding research here, there, and everywhere. They are trying to fund a “virtual company” to develop therapies that will solve problems that affect a lot of people. That is a really different way of thinking about things, and I do not think it has that model has yet been embraced by the NIH.

Question: Would The Pfizer Incubator be interested in work that uses existing Pfizer drugs for new applications? Does the incubator deal with those kinds of projects?

MB: I can tell you that Pfizer Incubator is on the campus of Pfizer Global Research & Development in La Jolla, California, and I always have Pfizer people saying, “Hey, I have a great idea. I want to start a company in the Incubator.” My response is, “Quit your job at Pfizer and come up with the idea and then come to the Incubator. Because if it is already in Pfizer, it is a Pfizer-owned idea. Depending on the intellectual property aspect of the idea you have in mind, it either may be a viable Incubator opportunity or not. But I do not know more (specifics), so I cannot really say any more.”

NEW APPROACHES—DEFINING MISSIONS, GOALS, AND SUCCESS

LB: Not necessarily defending NIH, but I think it speaks to the fact that people do what they know to do. Program people at
NIH know grant mechanisms and therefore they speak to grant mechanisms. But, I actually see this, at least the NIH’s Clinical and Translational Science Award (CSTA), as somewhat of a daring experiment. You try to turn things around someway or another. You probably do not know what you are looking for, but you try. If you give some institutions throughout the country a task to do, they will probably come up with some things that are going to be useful. Taken together, you will get some way that may progress things. I can attest to my personal experience now 1.5 years into this, I find it interesting to be able to implement this program in various ways, without exactly being told how to do it. No one told us to do workshops and link pilot rewards and demand that people come across from different domains. We could have done anything. So there is a certain amount of new, uncovered territory here and what I have come to appreciate is actually the importance of teams. I think we are sometimes erroneous, limiting this to faculty. There are enormous skills in staff, and I think the universities really do not know how to deal with this and how to reward staff because our activities rest on skilled staff. I tell faculty, “You don’t get a lot of money but you get fractional access to staff.” That is something we might learn from industry where I suppose you have better ways of dealing with staff.

MB: I know you said it has been a year and a half. You know The Pfizer Incubator is kind of an experiment. It is interesting because Pfizer is going through all these tumultuous changes and I have been there 10 weeks and there are already a lot of changes at TPI. I just had a board meeting in San Francisco for TPI last week and my first question was, “What is the goal of TPI? How do I measure success? How do I avoid failure?” For me, the biggest failure would be that I invest in companies and 3 years down the road people at Pfizer ask, “What are you doing? Why did you do this? We cannot use any of this stuff.” So, my first task is to poll everybody internally and say, “What is it you guys need? Not now, but 2 or 3 years from now. Do you have some targets you are not accessing? Or is there a kind of problem that we can solve with different kinds of technology? Can we look at that?” and fill in that strategic return on investment. So for the CSTA, I would have to ask, as well, what is success? How do you measure that success?

LB: One way is essentially to take words (said) here, to put the patient in the center. How can we actually bring things more to the patient? More incremental goals would be to get more funding to certain areas. Can we help faculty create more funding, create more interdisciplinary wealth? I think, already we have some success there. Probably, sort of like the middle author thing, these people would have gotten 90% of that success anyhow, but because they could involve these infrastructures, they had enough in place to convince the study section. Another thing is we have really seen energized medical students at our place applying for some of this funding. That would bring in mentors and more people into research. But ultimately, it would have to be how well, do we nurture the trainees we have into independent funding. That is a longer perspective as you brought up. So those are a couple of the goals and there is a committee that looks at evaluations.

WM: So you think about big institutional efforts to raise funds and we sometimes get lost in the translation, literally. In an exercise at Stanford, I found that we were missing the patient centric focus. So I did just what you (Mark Benedyk) did. I asked, “What are we going to say? What is the hypothesis here and why would anybody give us money? Who are we really?” One of us said, “we want a research intensive university with excellent people and staff and we all really care a lot about research and teaching and clinical care.” The hospital CEO said, “No, we help sick people.” The first person said, “Well, yes I said that.” I would argue that one measure of the success of CSTA is that everybody in that school, every doctor, every nurse, not just the CEO would say, “Now we know how better to serve our patients. It is about the patients after all.” That would be an amazing marker of success because everybody would be aligned under that incentive. It may be that your best audience for that is the medical students who, in my view are completely okay with that goal. They believe it in their heart and do not have the issue of tenure and the other issues that preoccupy faculty members. They are free of these concerns and can focus on the most important questions. Would not it be terrific to immunize them against worrying about all the derivative issues that we deal with?

Dr. Deborah Zucker (DZ): We have talked about how you bring things from research into products and about looking in a much more focused way to something tangible at the end. Do you see some of the same mechanisms that potentially promote this—stifling some of the creativity that has to happen as an underpinning to this? For example, the Human Genome Project—when that was first proposed there was a lot of discussion about the money going to sequencing the human genome as opposed to going to the small labs that were spending a lot (of time) to sequence a single gene, but then were looking at its proteins, functions, and so on. So how do you envision balancing directed research with some of the needed creativity or innovation?

WM: So the question presumes zero sum game and I do not like that. I reject the zero sum game because the innovation that comes from an individual laboratory has been our strength. Saying, “Look, you could either have cake or you can have a fork,” does not work. You have to have the cake and the fork. You have to make science and you have to use science. When the Roadmap is brought up I hear, “Oh, the roadmap is depriving all our young investigators of RO1 funding.” I hope that is not true, but we as scientists have a responsibility to explain to congress why it has to be both—AND. We have to be also accountable for how we use our funds. If we are committed principally to our own careers then congress has every right to say, “It is not going to be both.” But if we are committed to our patients, I would hope that Congress will respond by saying, “Here are the additional funds that are needed to solve these important problems, but you must be accountable for their most effective use.” NIH has to change, to be the accountable, transparent entity that Congress and the people should demand of it.

MB: With respect to your question, you know, there is a fundamental tension in universities. They are not project development houses—they are universities. I think that some of you (academics) have to stick to your guns and do what you are supposed to do per your mission and per your charter. I do not think that there is some implicit loss of creativity when you are focused on a goal. That is the underlying subtext of what you just asked, right? I do not think that is true.

DZ: I am not disagreeing with you. I think it depends on how you formulate your goal. When you have a broad goal, there are a lot of things that can contribute to that. The more narrowly focused your goal is, the more narrowly focused your work will likely be. Even there, you have lots of ways to innovate to get to that goal. What are the focus and boundaries? You need boundaries to get to something in the end, but at the same time, you need to have space because we do not know today what may be the thing we need for 10 years down the road.

MB: I think there is a mythology in academia that proposes that lack of project management and good management skills and interaction with other groups is the price we pay for our unbounded creativity. I think that in industry it is the opposite, that we need to control everything and focus it and that is the
It is perhaps being (more) clear about what assumptions we are making and maybe breaking them down when they need to be broken down—but also realizing that there are some underlying aspects (missions/goals) that do need to be attended to. It is a combination, and I think we are at a point of trying to figure out the balance because currently it is not on track.

MB: Right.

**INVOlVING CLINICIANS—FROM RESEARCH TO PRACTICE TO NEW RESEARCH**

*Question:* Personally, I am very grateful that this workshop was organized. For many years, efforts were not to develop integrated sciences or to promote translational medicine. Rather a very individual approach to small tasks was promoted. I think that the beginning of medicine was translational medicine because the great name scientists were interested at the same time in experimental science and in the clinics. It is very good that now NIH promotes translational medicine. I come from Poland and we have a saying, “the onset is always difficult,” but we just have to overcome these difficulties—and to convince the scientists that translational medicine is what people are expecting from us—sponsors are not interested in very specialized findings. It is essential to promote translational medicine to have more understanding by our society about how our science is important. I expect that NIH is also promoting translational medicine among clinicians because I think that the understanding of this kind of science among clinicians is also very poor. What actions are promoting this kind of science among clinicians, to make them very positive about cooperating with the experimental scientists?"

**DZ:** Other than NIH, for example, the Centers for Medicare & Medicaid Services, which pays for a lot of Medicare and Medicaid (also) has gotten into research. So, for the second (T2) translational step, there is a lot more interest in effectiveness research and health services research. The Agency for Healthcare Research and Quality does (fund) a lot of work on what happens in the clinics and about putting evidence and research results into practice. The Agency for Healthcare Research and Quality and now Centers for Medicare & Medicaid Services are interested in trying to use information garnered in clinics to help inform us about what research is needed and how well things actually work. For example, side effects, phase 3 and 4 studies, and getting more information from clinicians about the heterogeneity of responses among their patients to particular medications. I do not know if that is the type of thing you are talking about, but it is one aspect of T2 translational research that is being promoted.

**LB:** One thing that is becoming pretty scarce is our physician scientists, which actually are true physician scientists, who have a leg in each part. The NIH has recognized that to some extent, and they are trying to have more training programs and more funding for these people. If they are in medical school going into a training program, they help with decreasing debt. You might perhaps argue that these larger clinical translational science awards are meant to stimulate this, but it is not a direct stimulus on having a bigger cadre of physician scientists. I think other entities are doing their part. The Howard Hughes Medical Institute has promoted their PhD students to get a better sense of the medical area, not necessarily making them physicians but exposing them to the field of medicine to increase translational aspects. I think many leading organizations are seeing this as a problem.

**WM:** There is a huge problem regarding the investment that can be made by clinicians (in research) because in an academic medical center, many of the clinical faculty members are extremely busy seeing patients. There is a huge push to see more patients to cover their salaries. It is great that they see a lot of patients but it is very difficult for them to have a rich scholarly life at the same time. When they are as busy as they are, it compromises the ability to access them, to learn from them and to bring them new ideas. So this is another piece of the puzzle that has to be dealt with. How do you get clinicians—especially clinicians, but even sometimes clinician scientists—to participate more fully with the process of creating and using new knowledge? Theoretically, they might play a terribly important role—they could play a huge role in designing clinical trials that are more effective, use much more effective markers of disease progression, and so on. All those things are possible. We need those people to be involved, but the message that they too often get is that they need to see more patients. That is antithetical to bringing them along as full partners. So I think that that has to change. And how is that going to change? We have to tackle the busted health care system in America. I do not care how great our technology or medicine is, this will mean little if access is not universal. So, we have a number of significant issues that have to be addressed. It is essential that there be a bipartisan effort to really fix health care.

**Comment:** One of the difficulties may be that not many medical doctors decide to work in science, or experimental physiology or pathology. It would be very good to encourage students studying medicine to start to work in some experimental disciplines. It may be very difficult of course, because salaries are not comparable. Some effort should be made in this direction.

**DZ:** We have to end now. I want to thank all the panelists very much and thank the audience also for your participation. Thank you all very much.