Applying Agriculture to Medicine: Therapeutics and Treatment

Q&A

MODERATED BY
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Rick Borchelt: In our session this morning, we discussed the intersection of biomedicine and agricultural biotechnology and what will be required to fulfill the promises of biotechnology that we are currently making. We may be foreshadowing next year's NABC conference—that biotechnology is at a crossroads between science and society. People of more-primitive or traditional cultures understand the power of liminal places. Initiations, for example, are done on high mountain tops or on seashores or in caves—at physical boundaries. In these societies, animals that regularly cross these boundaries are venerated.

I would like to engage the panel in some discussion of these boundary issues and how they are affecting their work, particularly in the areas of infrastructure, funding, and culture. Then we will take questions from the audience.

Irwin, please discuss the concept of physical proximity as an infrastructural constraint.

Irwin Goldman: It's a challenge that we have met before—there is a track record at the Land Grant Institutions and possibly some of the federal institutions. The granting agencies need to recognize the need for collaborative effort, which is most easily achieved when scientists are physically in the same place. I agree that it is a formidable challenge, but our institutions are set up in the United States in a way that makes that a little more possible than otherwise.

Borchelt: Harry, Mich—do your institutions support that kind of collaborative activity?

Mich Hein: I have not been in an academic institution since I left this institution, so I can't speak to what has transpired in academia over the last 20 years. But I worked at Monsanto and at PPG Industries for about 10 years and then at the Scripps Research Institute for about 10 years. Industry brings together people from disparate fields into relatively small groups to solve specific problems. The Scripps Research Institute, which was a biomedical research institute for many years and then in about 1985 expanded to include chemistry, in-silico chemistry for protein modeling, and also brought plant biology into the fold. That institution had probably 300 investigators in close physical proximity working on the cutting edge in five or six core disciplines, from which grew work on oral vaccines from plant systems. I think that the lessons from those successes could be applied to academic institutions where there is expertise in agriculture and basic science.

Borchelt: Harry, you are in one of the nation's premiere medical research institutions. Is there a medical culture issue that you find difficult to address with your colleagues—do they see this as a reversal to the shamanic days of dosing people with herbs?

Harry Preuss: Yes, we see a great deal of resistance. At one point I was getting together with the people who work with AIDS, and we had a proposal to look at the potential for monolaurin to affect HIV, which is an encapsulated virus. There had been some preliminary evidence that it could be useful. So, the idea of using coconut oil was just too much. But, we assured them that, with their cooperation, they would be watching the patients. Patients on standard therapies whose viral counts had remained very high were fed macaroons—I think that turned them off too. We said that we would feed them the macaroons—obviously we didn't think there would be any risk unless they liked them and ate too many—then do the viral counts a month later. I was amazed to find that they didn't want to bother.

Then, one of my colleagues at Georgetown had some patients with ovarian cancers and I talked about the potential of using maitake mushroom on those patients. He had just finished an unsuccessful regimen with gemcitabine and the other oral poisons they were using on the patients, and I remember his comment was, "Well I don't want anyone to know that I'm working with a mushroom." I said tell them that you are working with a beta-glucan—look it up in the literature and you will find a great deal of literature on beta-glucans as a stimulatory agent in cancer—but I never could get him interested. I look at this as lost time. I'm the type of individual if I am not putting the patient at risk I will try it and see what happens. They are very closed-minded, but they're starting to come around. We have had some lectures on mushrooms and people are starting to say, "Maybe there is some benefit." It's a slow process.

Borchelt: Is there an education issue at the postgraduate or postdoctoral level that would be helpful in this?

Preuss: Well Georgetown just received an NIH-funded grant to include alternative medicine in its teaching program. I am part of that, and sometimes I shudder because I don't like to be linked with *alternative* medicine. I usually tell people I practice medicine, it works or it doesn't work—the thought that you are in alternative medicine is very pejorative. So, I don't like that terminology, but certainly it includes working with supplements and nutraceuticals.

It took us 5 years to convince colleagues at the American College of Nutrition that we should be looking more at botanicals. Sure, you hear people on the radio and the television making exorbitant claims—but I put the idea before our group that this is what we were supposed to be doing, if there are some sham concepts out there then part of our job is to expose them. We should look at everything, and take the good and go on and do more work with it, and expose what is bad. But it's hard to win them over.

Goldman: On the question of education, I think that students are increasingly trying to choose the border or the boundary areas between fields. It is a humbling experience to make the jump to another discipline because there is so much new terminology and so much to learn. But, judging from the graduate applications that we see, students want to bridge gaps. Whether we need formal programs, I'm not sure, but students are choosing to work in collaborative groups that have already established a record of obtaining grants and running projects across a variety of disciplines. So, the student then needs to double her or his training. They need training in medicine and in the agriculture, which makes it more burdensome. But we are starting to see that, and I think it's a very positive indicator of educational opportunities.

Borchelt: Mich, where are you finding your workforce for Epicyte?

Hein: That is a very difficult question to answer. We literally have to look everywhere. We have found people principally who have experience in the biopharmaceutical industry already. Our best source of workforce are people who have worked in the gaps between existing disciplines and people who have used multiple disciplines in problem-solving. At Scripps they have a very interesting graduate program that is multi-disciplinary—macromolecular and cellular biology, and biochemistry—where the students have to use multiple disciplines. They do everything from in-silico protein prediction to molecular genetics and organismal studies. We have to find people who already have such experience or we have to spend 2 years training them.

Borchelt: I don't want to put you all on the spot, but Mary Clutter is in the audience today and I'm sure she would appreciate your thoughts on how to take better advantage of synergies between agricultural biotechnology and medical biotechnology. How would you go about designing or redesigning part of the granting process so that it captures those synergies in ways that may not be possible today?

Hein: One way to do that would be to engage more industry-trained scientists. Not business-development people who may be involved with small business innovation research (SBIR) programs, but rather the scientists who are deep in the core biotechnology and medical industries and, for that matter, even the agricultural industry, and get them on grants panels, because a lot of the cutting-edge and interdisciplinary research is being seen by those people. Recently we have been fairly successful in getting SBIR grants, but when we were trying to do this work 10 years ago at Scripps, we were being reviewed largely by academics and our proposals to make antibodies in plants came back with one-sentence reviews that it wouldn't work. Yet there were people in industry who had been working on similar systems and who understood that it would work. So, I suggest enriching the pool of people who are reviewing the science.

Preuss: I have been seeking support through industry mainly. Originally my research covered the area of nephrology and hypertension, which is what I am trained in. Then I started working on supplements and natural products, and my attempts to get grants when I was working with chromium were almost futile. I was working on chromium and on fractions of maitake, when rezalin came out. One of the manufacturers who gave us support said, "Why are they allowing rezalin out? It's a drug that has been killing people in Japan." I couldn't tell him why, and now it's off the market having caused a lot of liver problems. I have had a lot of difficulty working with natural products. Therefore, I go to manufacturers and usually they are interested and will put up some money to study their products.

Goldman: In relation to the communication issue that we spoke of earlier—when you have groups from disparate fields coming together and proposing projects they essentially speak different languages. One aspect that needs to come across very clearly is how these groups are going to collaborate. On the other hand, there are examples of where the flow of information—even from the production agronomist to the food chemist who is going to extract the compounds to the medical professional who is going to test the compounds—is well presented. That kind of dialogue has to happen first, with communication well established, in order to be successful. So, somehow, in addition to making modifications in the granting process, we need to initiate the dialogue—not

just because the money is available—by providing forums like this for people to get together and start to make inroads.

Borchelt: I'd like to open discussion up to the audience now.

Kitty Smith (USDA Economic Research Service, Washington, DC): We heard yesterday that most people get their information on food and health from television, which, while Lea Thompson thought that was a good thing, I wonder about it. And today in his introduction I thought I heard Randy Woodson make a negative reference to *Prevention* magazine where most of the contributors have a whole bunch of educational initials behind their names. I'm wondering, for those of you who are working on the borders between plants and human health, what are good references for those of us who can't read biochemistry journals?

Hein: I don't think there are any. You have pointed to a key issue and, as I suggested earlier, communication channels really need to be improved. I don't know what role the USDA might have in that process. The extension service might be a reasonable place to look to, as a system that is already working. I find that television is not particularly informative on these issues. In my experience, discussions on television always have a controversial fulcrum to get people's attention, which doesn't necessarily provide the best light. In terms of what people read, I would say the most accurate information with a broad scope is in journals like *Nature Biotechnology*, but that isn't something that the general public is going to read. So we need a way to bridge that gap. In some metropolitan areas where biotechnology industry is burgeoning, some newspapers are taking things into their own hands and doing a good job. In San Diego we have the *North County Times*, which has an entire section every Sunday on science and technology, written by Bradley Fikes who does an excellent job. But that is a single regional area—there is a need for something similar to be broadly accessible.

Borchelt: The situation actually is even worse than indicated by Susan Borra and Lea Thompson yesterday. I just finished chairing a 3-year blue-ribbon panel on the future of science communication funded by the Department of Energy and NASA, and we found that most people get their science, health and technology information from regional and local television, which probably has the highest error rate of any of the media that we looked at. We also found from the work of Jon Miller at Northwestern University that there is a particular audience out there—we call them science attentives, probably 20 or 25 million strong—who will dig past that, who will look behind *USA Today*. They get most of their references from the Web, which is a growing area that I suspect probably wasn't surveyed quite as directly in Susan's work. We are finding that the Web provides

a safety net for science and technology information. When people hear something on television, many then consult the Internet. This is particularly true of ages up to about 45. Not an ideal situation clearly.

Bob Peterson (Montana State University, Bozeman, MT): I lead the Agricultural Risk Assessment Program at my home institution and I want to follow up on Mich Hein's comments. Before joining Montana State I was in the private sector and worked for several years with the evolving regulations regarding plant-based biopharmaceuticals, vaccines, antigens in particular, and antibodies. I think there is some confusion in comments of yesterday and today in terms of thinking that some of these products will be regulated as foods. When you are talking about producing non-food proteins in food crops the regulations are very different and the field production is in no way capricious—it will be regulated as one step in the plan of production of a vaccine, antibody or other pharmaceutical. Even the title *Foods for Health* is confusing. In terms of the products that Dr. Hein was talking about, they are not considered foods any more, and they will not be regulated as foods. They will come under special regulations, which are still evolving, to prevent them from entering food channels. Vaccines will not be administered through food, at least in the United States, the way these regulations are evolving.

Hein: Those points are very well taken. I didn't go into detail about the regulatory process and I really appreciate you making the point. But, we as a company, and I think most other organizations public or private in the United States that are developing plant-based systems for producing pharmaceuticals, are very much aware of the need to maintain the integrity both of the food chain and of the pharmaceutical-manufacturing process. This is a new arena in which regulations and infrastructure are evolving, and part of the challenge for us as a small organization lies in not having the infrastructure of large pharmaceutical companies to interact with the agencies. So we need to take baby steps and we've done that. But the process is frustrating because of the cost in time and dollars. We are all interacting closely with the Biotechnology Industry Organization (BIO) as well as with the federal regulatory agencies to ensure that we are practicing good stewardship. I know of no one actively engaged in the industry today who would diverge from that. We are specifically looking at making drug molecules. On the issue of vaccines—a field I worked in for about 10 years then made a conscious choice to leave until we know significantly more about the impact of edible molecules on the immune system—progress has been made in the last 6 years on which John Howard will probably enlighten us.

Samuel Lehrer (Tulane University, New Orleans, LA): I want to comment on the problems of interactions of various scientific disciplines. In major cities,

medical centers were placed in areas of high population to provide patients for teaching students. Take Chicago or New York, and it is the case with Tulane in New Orleans and with Temple in Philadelphia—all of these medical centers are removed from universities, and that is a problem. Developing interdisciplinary programs is the way to go, but it takes real effort. People just don't feel like traveling 10 or 15 minutes to a seminar or to a discussion. Mich's point about the study sections is a good one. I think study-section diversity—groups that review grants—has been a real issue over the last 10 to 20 years. Maybe it is just bitter grapes on my part in terms of getting grants, but certainly the granting agencies need to make more of an effort to expand the pool of people in study sections so that they can take on new projects and encourage new ideas.

Two quick questions for you Mich: what are the sources of your antibodies, and are you planning to use the plant as a delivery system or just for production?

Hein: I'll answer the last part first. For the products that we are developing today, we are looking at two delivery methods. One is actually parenteral—highly purified injectable drugs, approved by the FDA, tested in clinical trials. And we are also looking at topical applications for prevention and therapy of mucosal infective and inflammatory disorders. While those formulations will contain highly purified antibodies they will have other excipients in them, much as other topical products. So they might be in gels or in lubricants. From the standpoint of production, we looked at many species of plant, most of which are capable of being used for manufacture. But, we made a conscious decision to focus on one, to make the system work. We chose maize, corn, because much of the technical know-how was already in place. And we chose the endosperm, specifically because it has a small number of soluble proteins, all of which are well characterized and none of which is known to be harmful to humans. Also, handling procedures were already available. People know how to grow it and we know a lot about the germplasm. But others are using different species and many of them work. We originally worked with tobacco because it was a great experimental organism. We will stick with corn for the near term, although we are still evaluating others.