Ask A Biologist Vol 076 (Guest Charles Arntzen)

Tobacco Plants to the Rescue

If you are a tobacco plant, you have a bad reputation. The link to cancer and other health related diseases is cause for any person to avoid you. But there is another side to this plant. Dr. Biology sits down with biologist **Charlie Arntzen** to talk about how tobacco plants are helping scientists produce treatments for viruses like Ebola.

Transcript

Dr. Biology: This is "Ask A Biologist," a program about the living world, and I am Dr. Biology. It's an unlikely hero. After all, it's been shown to be the leading cause of lung cancer. Its use increases the chances of many other cancers. In the United States alone, one in five deaths are related to tobacco use. So how does the tobacco plant go from villain to hero? Here's part of the story.

In 2014, an outbreak of the Ebola virus struck West Africa. Two US aid workers who were providing medical assistance during the outbreak became infected with the virus. Their chances of survival looked poor. Next, enter an experimental drug developed by a group of scientists who've been using our tobacco-plant villain to develop a cure for diseases, including Ebola.

One of our researchers who had been pioneering the use of plants for vaccines is Charles Arntzen. Charlie, as he prefers to be called, is a professor in the School of Life Sciences at Arizona State University and the Biodesign Institute of Infectious Diseases and Vaccinology, also at ASU.

Today, we'll get a chance to learn more about the tobacco-plant story and what might be possible in the not-too-distant future. Welcome to the show, Charlie Arntzen, and thank you for visiting with me today.

Charlie Arntzen: Dr. Biology, it's fun to be here.

Dr. Biology: I've heard you're called a "pharmer." That would be spelled p-h-a-r-m-e-r. What is pharming?

Charlie: First of all, I did grow up on a farm with an f, but pharming with a ph is the production of pharmaceuticals in plants. It's a relatively new idea, although I started working on this over 20 years ago. It's really only caught on in a commercial sense or practical sense over the last 8 to 10 years.

Dr. Biology: Can you walk us through, I call it a quick lesson in plant genetics? Why I'm mentioning this is, I'd like to know how do you get a plant to make the ingredients for a medicine?

Charlie: We've tried two approaches. One is GMO approach where you introduce genes into plants - we did it with potatoes, for example -- and cause those plants to produce a new protein that

has pharmaceutical value. More recently, over the last eight years, we've gone to a synthetic-biology approach.

We genetically change plant viruses. You take out bits of a plant virus that has genes out of it and replace those genes with some protein that we want to produce. The one that's been most interesting over the last few years -- or ones -- are genes that cause a tobacco plant to produce monoclonal antibodies.

Dr. Biology: OK, let's go in to monoclonal antibodies.

Charlie: We all produce antibodies in our body. Every time we're exposed to an infectious agent, a virus or bacteria, our body's immune system kicks in and we make antibodies. In the case of something really nasty like the Ebola virus, we don't want to be exposed and cause our immune system to respond, because it may not respond fast enough and we might die.

What we do is short circuit the process by finding genes that cause the production of antibodies. It sounds simple. It's relatively complex because we isolate those genes from mice that have been exposed to Ebola. The mice are quite resilient. They don't die when they are exposed to Ebola, but their immune system works and so they produce antibodies.

We go in, get the cells out of the mice that are making antibodies, purify that DNA and now we've got the genetic information on how to make an antibody. We call them monoclonal because it is one specific type of antibody, an antibody that we test and prove reacts with the Ebola virus itself.

Dr. Biology: While we're talking about viruses and our immune system, I just want to remind everyone that on "Ask A Biologist" we have a fun story. It's actually a comic book called "Viral Attack," and it's a great way to get introduced to how the immune system works. It's something that is in comic-book form, but you can dig deeper and get into the real science whenever you want to.

It's just something for people to know and the address is askabiologist.asu.edu/viral-attack. It's a great way to learn about how the body actually has battles going on just about every day.

Charlie: Right.

Dr. Biology: Let's get back to your pet plant. When we look at the history of tobacco, it's not been the best plant for human health until now. Why use tobacco plants?

Charlie: We tried a number of different plant species, but there's two advantages in particular to tobacco. First of all, a lot of genetics has been done because the farmers who grew tobacco had to produce something that grew quickly and it was profitable for them.

A disappointment to farmers but something that makes us happy is, tobacco has all sorts of pathogens or diseases that cause problems to the tobacco plant. Many of these are viruses. Again, because this has been a cash crop, there's been a lot of work on these viruses in the past. All we have to do is go back, look at the scientific literature.

From that literature we can learn about viruses like tobacco mosaic virus. We know now, based upon the research of others, which genes in this virus cause it to replicate. That is, reproduce itself

very fast in a tobacco plant. We know which of these genes we can take out and change them all and put in something else. What we do is, essentially, make a synthetic plant virus.

Taking parts of authentic tobacco viruses, keeping the ones that are essential so that it is, if you will, a virus. But then adding to it genes that encode the proteins that we want as a therapeutic to treat patients that have Ebola.

Dr. Biology: That's interesting because we talk about this process, and the work that you did lead to the Ebola drug ZMapp that was used to treat the two health workers that had become infected with the virus. I think a lot of people, they get this news on the evening news and The Times. I think that they get the impression that this breakthrough happened overnight.

Charlie: Ah, I wish it had, but that's not the way things work in developing a pharmaceutical. We began this study back in 2002. It was a collaboration between researchers at Arizona State University and a company in San Diego called Mapp. Actually, that's where the "Mapp" comes from in ZMapp, the therapeutic that was produced. We teamed up.

Our expertise was in a synthetic virology, how do you put genes together in a way that they'll work in plants? Our friends over in San Diego were antibody engineers. They knew how to take a gene from a mouse and reconstruct that gene, so that it now encodes a protein that's identical to what a human being would make. We swapped this information back and forth.

I think if it had not been for an Ebola outbreak in 2014 in Africa, probably nobody, except a few intense biologists, would know what we have done, what we spent 12 years doing -- that is, taking all this information, using a bunch of skill sets, teaming them together and then, finally, manufacturing this therapeutic which, I'm delighted to say, has saved lives.

Dr. Biology: It was actually very unexpected to you, wasn't it?

Charlie: It was. It had been 12 years in the making. If I had predicted a year ago when we would see this being tested in humans, I'd say another three to four years. It's simply because that's the way pharmaceutical testing goes. We don't produce drugs in this country that haven't been thoroughly vetted and tested for safety and all these sorts of things.

I'd just expected that we would have to continue this sort of research. But there's something about a crisis and in this case, a humanitarian desire to use the best technology we had at the time. That allowed us to use ZMapp to treat these people in Africa.

Dr. Biology: If you started in 2002, then 2014 we got to use this ZMapp, that's 12 years. Even then it was faster than you would've been able to do without the outbreak of Ebola?

Charlie: Absolutely. I would say in big pharmaceutical companies, from the first discovery to getting an approved product, it's more common to be 15, 18, even 20 years before the product is finally safely tested and everything is ready to go, to give the consumer a very good product.

Dr. Biology: While we're talking about Ebola, I'd like to clear something that can be confusing about the virus. Most people know that it's bad, but it's not highly contagious because it's not an

airborne virus. Actually you need quite a bit to become infected. You have to have close contact with some bodily fluid such as blood or vomit that contains the virus.

However, if you catch the virus, there's a very high risk of death. It can be as high as 90 percent. In the recent West Africa outbreak, there was a 55-percent death rate. It's one of those things that, there was a bit of a scare in the sense that it could've been a pandemic. But that doesn't diminish the fact that, how efficient a killer it can be, once it gets into the human body.

Charlie: Correct.

Dr. Biology: Let's go back to tobacco plant. Can you use it for things other than medicine? Of course, we know smoking and chewing tobacco [laughs] but let's go to some good things. Can you use tobacco plants for other things?

Charlie: The research that's been going on far has primarily been to express monoclonal antibodies, particularly cancer drugs. So many of the modern generation of cancer therapeutics are monoclonal antibodies, and they're still very expensive in use. So expensive that really it's the US and Europe and Japan and a few wealthy nations that have access to these new categories of protein drugs for cancer.

What the scientific community is saying, "We need new manufacturing systems, so that we can reduce the cost of protein drugs." Make such things as Herceptin or Rituxan. Very good and important cancer drugs, but can we produce them at a cost that the rest of the world would have access to this wonderful technology that we've developed in the US?"

Dr. Biology: So with your tobacco plants, because they've been developed over the years and using genetic techniques, whether they were before the age of transgenics -- you know, the old fashion way -- selective breeding of the plants...

Today, they're a crop that grows very fast and has a lot of what we call "mass." That's what makes it a really good plant for this kind of a process. If you you're able to use that you get a lot of material out of it.

Charlie: Correct.

Dr. Biology: Are there other plants besides tobacco that are suited for pharming?

Charlie: There's a company in Israel called Protalix that uses carrots to produce a human enzyme to treat something called Gaucher's disease. It's an inherited disease. Terrible, usually begins affecting children when they're young. It's a terrible disease.

Anyway, the reason that people are affected is, they're missing a gene that causes them to not be able to make an important metabolic protein. What's been done by this company is to produce this human enzyme in carrot cells, grown in fermentation, purify the human protein and simply inject it into people, essentially eliminating that terrible disease.

Dr. Biology: So we have carrots and we have tobacco, very good. Is there another plant out there that comes to mind?

Charlie: There might be many others that...there has been research on a variety of other plants. I think the important point here is, it's not the plants. It's really what product you are going to produce. When we look at new pharmaceuticals, what's changing now is, if we had a new cancer drug...

In the past we would have had a narrow selection probably only GMO mammalian cells, genetically modified -- say, cultured cells going in fermenters. That was really the only route that was cost-effective for us to go. Now we're adding a new approach of using plants as an alternative -- less costly to establish, quicker to get large amounts of new material et cetera.

I don't think it's a species of plants. It's just this broad platform technology. I would say the people who get these new cancer drugs or antibodies, or anything produced in tobacco or carrots or whatever, they're never going to think about, "Did it came from a plant?"

It's not the important issue. They're going to ask, "Is it good? Is it safe? Is it highly effective?" That's our task, is to make sure it is.

Dr. Biology: Interestingly enough, even though a lot of our medicines and therapeutics have come from plants in the past -- aspirin is a really good example, historically -- we don't necessarily equate plants and medicines as much as we should.

I mean, they're a bedrock of what we're doing. Since we've been working with the tobacco plants and we have something that attacks the Ebola virus, and then you talked about the cancer-treatment drugs, what else?

Charlie: The major other area that we're looking at -- this was other groups -- is producing vaccines in plants. This is sort of the emerging frontier of trying to expand vaccine use around the world to get rid of terrible old diseases like dengue and malaria and other things, for which there are no current vaccines.

A critical thing for global public health is, we have to produce these vaccines at relatively low cost, and preferably in easy ways to administer, such as an oral vaccine. Our particular focus here at ASU is to try to use tobacco plants to make a vaccine that would prevent stomach flu -- something caused by a virus called Norovirus, but stomach flu.

It's something that's needed around the world. We're focusing on coming up with an oral delivery mechanism to protect young people and also the elderly who suffer greatly from this disease.

Dr. Biology: Once you find a process, the plant you deal with, the modifications you have to do with the plant, is there an advantage to being able to grow the plant locally and process it? Is it a process that can be done by developing countries?

Charlie: We've been working with developing countries. In particular, people in our lab have trained, have gone to South Africa, have gone to Malaysia, South Korea, China. The whole idea here is, this is a robust technology that is relatively low in capital cost to get established.

Our goal is to set up manufacturing so that drug development, and particularly vaccine development, is done in country in the developing world. The logic here is, that creates jobs locally.

It generates an interest in local governments in maintaining these public health programs long term. Ultimately, while I believe greatly in philanthropy, it's much better to create an incentive in country to produce your own medicines, rather than being totally dependent on someone giving it to you year after year.

Dr. Biology: I mentioned a little bit about the history of plants, brought up aspirin. Let's talk a little bit more about the history of plants and medicines.

Charlie: Plants have been used as a source of medicines for centuries, and still are. Things like ginseng for example are widely used, especially in Asian cultures. For us to make a transition and use something like a tobacco plant to derive medicines, for me, is not a strange concept because I see the continuity that has gone on over the centuries.

It just happens that today, we've got the additional tool of genetic modification. We can move genes around. We can make a synthetic virus which causes the plants to do something new. I think it's the best of using modern technology and an approach that's been valuable for centuries, and just marrying the two to come up with a new way of producing therapeutics.

Dr. Biology: The work that you've done started, in this particular case -- you've done a lot of work over the years -- but in 2002 is when you first started this.

There is a debate, at times, between what we call basic research -- that's the study of a particular system or an area of science for the sake of understanding how it works -- and then there's applied research where someone is out trying to do something that has what we would call a purpose, an applied purpose.

It seems like we're getting a fusion of those or a compression of that occurring. How would you put into perspective your role and your view on what you do in the basic sciences, the basic research you do, and getting it to this point, for example, where ZMapp becomes available?

Charlie: Let me try to put that in a context of the word creativity. I think in basic research, it's an exploratory area. It's an intellectual pursuit and you are getting fundamental knowledge. In contrast, applied studies are, more or less, how do you do something specific in a way that achieves a goal that you want.

Creativity, I believe, is bridging these two things. That's where you build upon the basic tools, could be of biology, it can be of physics. Physicists work with engineers and that's where the creativity comes in.

A biologist can work with somebody in the pharmaceutical industry. The creativity is linking the basic science to a problem that needs to be solved. That's where I find the greatest joy in the research I do, is trying to span these areas in something I call just the creative activity.

Dr. Biology: Why I like to bring that up is, the applied research or the applied mode really can't function if you don't have the basic research, because that's the foundation of it. As you said, it's that linkage.

It's that creativity of looking at what basic knowledge we've acquired, and the techniques and the things that we need to do -- what is the outcome that we need, and pulling all those together. Do you see more collaboration between the different disciplines than when you first started out in biology?

Charlie: I think the whole information revolution has made it so much easier for scientists and non-scientists to collaborate and identify goals and work together. Yes, in the biological sciences the multi-disciplinary approach to what we do is absolutely the most exciting, most interesting part of the field.

Dr. Biology: Let's mention a few of your collaborators here. I know you have quite a few at ASU alone. Let's go through them.

Charlie: At ASU we have developed a network of scientists that work together. Some of them are very basic molecular biologists. We have some virologists, who are interested in how viruses can be restructured. We have biochemists who have to purify proteins. We have protein chemists who analyze what we get out of it.

Besides that, we work with companies. One of them is this company in San Diego that does antibody engineering. They're really, really good at understanding how antibodies work in the immune system. We also work with a manufacturing company in Kentucky that knows how to grow tobacco. Their specialty is purifying proteins out of tobacco, making them very clean and perfect for use as medicines.

We have a whole range of people. I should also mention we work with clinicians, who take the proteins we produce, do human clinical trials, usually first animal pre-clinical trials. It's all this combined expertise that's necessary to move a basic discovery from our lab bench all the way to a therapeutic that's going to help someone.

Dr. Biology: With the cancer drugs that you talked about that could be developed with the use of the tobacco plants, do you see those also as being able to do what we call "personalized medicine?" Will we be able to do more custom types of medicines, in particular with the cancers? What we're learning is, not everybody's cancer is the same.

Charlie: One of the exciting things about using plant biology for cancer therapy is the cost of doing this first batch of material is relatively low. It makes it more feasible to do personalized therapeutic design. In fact, this is being researched at the present time by a company called Icon Genetics.

They're working on non-Hodgkin's lymphoma, where every patient has cancer, but a slightly different cancer. You need to identify the particular type of cell that is deranged, if you will. Then design a therapeutic exactly for that cancer cell. It's being shown now that plants are feasible to do this, because for a modest cost, you can grow a small section of plants in a growth room.

Then from that set of plants purify a drug designed specific for patient A, and another set of plants for patient B. Most importantly, you can do this in a cost-effective way so you can end up with a therapeutic that's not going to break the bank.

Dr. Biology: When we do the personalized touch, the key here is to make sure it's very targeted, it kills the cancer cells without killing all the other cells. That's what's been a challenge with us for a long time with most of our cancer treatments. How do we get rid of the cancer without killing off the patient?

Charlie: Most chemotherapy agents are really just toxins that kill a broad range of cells. Our focus in the next 20 years is going to be narrow that target range down. Find chemotherapy agents that are more specific for specific cells, and even going down to specific individuals in the population.

Dr. Biology: On "Ask A Biologist," none of my biologists get out of here without three questions. I'm going to launch into the first one. When did you first know you wanted to be a biologist?

Charlie: I think I maybe grew up with the idea of being a biologist, but growing up on a farm you didn't quite think of it that way. I was interested in living things and what we fed animals and how crops grow. When I went off to college I decided I was going to be an engineer because that's what all my friends were going to be, was an engineer.

It was only after spending some years in college and switching majors a few times that I said what really continues to fascinate me is the life sciences. I did study with a plant pathologist early on and it got me hooked.

Dr. Biology: Do you remember what year that was? Was that your sophomore year?

Charlie: I think it probably was somewhere between sophomore and junior year because I was working in the summer in a greenhouse setting at the University of Minnesota. It was a wonderful place to get stimulated by all the professors around. Each of them seemed to be very excited about his or her projects that they were doing. I could just see how much fun it was.

Dr. Biology: So it was the idea of actually doing and not just studying that got you hooked?

Charlie: I think it was the research opportunity that got me hooked.

Dr. Biology: OK, now I'm going to take it all away, all right? You can't be a biologist! A lot of my biologists like to teach, so I'm going to take that away from you. If you could be anything or do anything, what would you do, or what would you be?

Charlie: I've always thought it'd be fun to be an architect. Architects, seems to me, sit back, think about the needs and then come up with a plan that meets the expectations of their client, if it's a big company or it's a family trying to build a home. Then, in the end, you get to see what it looks like when it's done. That must be, for architects, very, very satisfying.

Dr. Biology: The last question. What advice would you have for a young biologist or perhaps someone who, let's put it this way, maybe someone was an architect that always wanted to be a biologist. How would you advise them to either switch careers or get into the career of biology?

Charlie: Interesting question. I guess if I were advising someone who made a decision they wanted to be in biology, the first thing I'd tell them is, "Study something basic." Study biochemistry or microbiology or anatomy or ecology.

Get at the basic principles, because when you do, it leads you into things that are very satisfying. Once you see a problem ahead, you've got the tools with which to attack that problem and come up with solutions.

Dr. Biology: With that, Charlie, I'd like to thank you for visiting with me today.

Charlie: Dr. Biology, it's always fun.

Dr. Biology: You've been listening to Ask A Biologist and my guest has been Charles Arntzen, biologist and professor in the School of Life Sciences and the Biodesign Institute Center for Infectious Diseases and Vaccinology, both of which are at Arizona State University.

For those of you who might like to explore more about Arntzen's work, visit the podcast web page on the Ask A Biologist website. There, we'll have a companion story on his work.

Ask A Biologist podcast is produced on the campus of Arizona State University and is recorded in the Grassroots Studio, housed in the School of Life Sciences, which is an academic unit of the College of Liberal Arts and Sciences.

Remember, even though our program is not broadcast live, you can still send us your questions about biology using our companion website. The address is askabiologist.asu.edu, or you can just Google the words "Ask A Biologist." I'm Dr. Biology

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