Yale CANCER CENTER answers

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Using Immunotherapy to Fight Cancer

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about bioengineering and immunotherapy with Dr. Tarek Fahmy. Dr. Fahmy is Associate Professor of Biomedical Engineering and of Immunobiology at Yale School of Medicine. Here is Dr. Steven Gore.

Gore Let us start of by telling me a little bit about what it is a biomedical engineer does?

Fahmy Biomedical engineering is a very wide profession in the scope and the breadth of what they do, for example, diagnostic devices that we are all familiar with like magnetic resonance imaging, MRI, CT scan, x-ray equipment, all of these things were actually originally designed by what we call now, biomedical engineers. Biomedical engineering in the sense of biomolecular engineering is a very new area in biomedical engineering and that refers to the idea of taking small things, not big equipment, proteins, small molecules and tailoring them so that they can be more therapeutic in the body and less toxic by side effect standards, so biomolecular engineering is a very hot area actually.

Gore It is always good to be in a hot area, especially if you planning for funding, I would guess?

Fahmy It is great.

Gore How does one train if they want to be a biomedical engineer, does one train as an engineer or a biologist, how does that work?

Fahmy That is a great question. As an example, my training is very bizarre. I actually have a hybridized training background. I started off as a chemical engineer and I worked at DuPont for a number of years making the polymers that we all use and love and then I shifted into immunopathology at Hopkins. I did my graduate work in immunology and then I decided I wanted to do my postdoctoral work in something that was an intersect between chemical engineering and immunology or biology in general and of course that means biomedical engineering and that is how I ended up in that field. For biomedical engineering now, training is well established in the sense of the core tracks that people can get training in, in order to do different things. For example, biomechanics, orthopedic engineering specialties, there is bio-imaging as we were talking, the MR, magnetic resonance, CT and then of course, there is the biomolecular engineering which is a very exciting topic.

Gore And do people study this at the level of a college education or is this mostly postgraduate?

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Fahmy It is actually undergraduate now. You can do it as undergraduate, major in biomedical engineering. At Yale, we have a fantastic program. It trains students' right out of high school in biomedical engineering and of course you specialize more as you evolve into the graduate studies.

Gore It was also a very popular undergraduate major at Johns Hopkins, so I guess we must have overlapped, you and I.

Fahmy That is right.

Gore So all you high school people who are of course listening to this fascinating show who are kind of science geeks but are fascinated by the techno aspect of it, look into bioengineering as a potential interesting field if that is something that floats your boat as you hear what Dr. Fahmy does. So that is really interesting, thanks for that little background because it is something I have always wondered about, especially having so many years at Hopkins where we would see a lot of these biomedical engineering students.

Fahmy Biomedical engineering at Hopkins is one of the best programs in the country.

Gore I knew a lot of the students went to medical school, so I was never really sure, butthey seem to be doing some really fantastic stuff, so you are a biomedical engineer focusing on molecular immunobiology?

Fahmy That is right.

Gore Tell us about that.

Fahmy It is interesting, actually the scope of immunology and engineering, it was surprising to me how much there is in terms of overlap. I know it sounds at the very surface, like very different subjects, but once you delve into the area, obviously you see that there are quite a bit of commonalities. For example, one of the things that I used to do when I was a chemical engineer when I worked in DuPont was I worked with things called bioreactors or chemical reactors, more generally, and those are basically big tanks with an input, something flows in, something flows out, something happens in that tank that gives you a product and that is what we call a chemical reactor. It sounds a lot fancier than it is.

Gore Is this like a beer brewing machine?

Fahmy Like a beer brewing machine.

Gore I think we have all seen those tanks, right.

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Fahmy That is exactly right.

Gore They are building one in Branford, right now as a matter of fact, a big brewery. Stony Creek, but I digress, go ahead please.

Fahmy But those are great examples of what we call bioreactors. There is fermentation happening inside.

Gore I was joking, but I guess I got it right.

Fahmy Absolutely and in fact the simpler ones, the ones that I work with, are actually less sophisticated in the sense that you had chemicals that float into a vessel that actually spontaneously reacted with each other and then you got something coming out which was a product. There were no bacteria in there like breweries or there was no fermentation process. There was no real skill in the sense that the ingredients needed to be worked on internally within the vessel.

Gore It was just a way of making a new chemical basically.

Fahmy A new chemical. An ideal example would be if you take hydrogen and oxygen and you mix them together, you get water, but of course that has to happen under certain conditions.

Gore Like turning on a faucet. That would be actually a better example.

Gore I am sorry.

Fahmy By the way, I do not mean to simplify any of this.

Gore We try to keep this totally simple because that is my job really, so please.

Fahmy I do not want any chemical engineers out there to hate me.

Gore But those of us who are not engineers really appreciate the nuts and bolts here.

Fahmy From the standpoint of a reaction, that is really the key thing, what happens within a container and cells do that all the time. There are input cells, there is output which could be an input of sugar for example and output could be energy or it could be motion or it could be collection of cells that have the same input and then collectively have the same output, give rise to tissue that have a specific function. So cells, every single cell in our body is essentially a chemical reactor, a lot more sophisticated than the ones I use to play with at DuPont, but immunobiology refers to a class of cells that are basically floating around in our body, keeping us protected all the time, those cells are what we call our defense cells and their input is stuff that does not belong inside the body.

8:18 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

Their output is basically a way to get rid of those things. They either zap their target or they send the alarm signals or they do all sorts of different functions to alert not only other cells that there is a foreign agent, but also to clear that agent.

Gore For an example, if somebody has been vaccinated against a particular thing, let's say measles, if he has had the measles vaccine and if one is exposed to the measles virus, then the measles virus or parts of it would be an input to the immune cells and then the immune cell which has been trained by the vaccine reacts.

Fahmy That is right.

Gore It gets rid of the measles; is that the simple way of thinking about it?

Fahmy Another excellent example, and not even that simple, that is exactly how it works, that is how vaccines work, that is why we all get flu shots. We train our bodies to recognize something before we actually see the real thing and we train our bodies to recognize our simple bits and pieces of what we think is going to be the next flu pathogen that we will get hit with. Unfortunately, that does not work a lot of times like with HIV and cancer, there are no really good vaccines for cancer, malaria, and the list goes on.

Gore Ebola.

Fahmy Ebola, that is right.

Gore Which is a hot topic right now.

Fahmy The idea is to train our immune system to recognize what is foreign and protect us from it if we get exposed to it.

Gore So how do engineers get involved with that?

Fahmy What is the big issue then if it is as easy as injecting the body with what we call an attenuated form of the pathogen, or something that is not as harmful as the virus or the bacteria?

Gore Yeah, I thought you just go to Walgreens and pay your 20 dollars. Who needs an engineer?

10:24 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

Fahmy It would be great if it was like that for everything. There would be no issues, but in fact it turns out to be a little more difficult in the sense that there are a lot of viruses out there, Ebola being a prime example, that have learned to hide in the body and hide very well, so they can evade the immune response and then there are other viruses that are actually intelligent, they actually invade or get inside the immune cells, a good example of that is HIV. HIV hides in what we call CD4 positive T-cells and those are T-cells that actually are extremely important for protection generating the antibodies that protect those against different kinds of pathogens.

Gore And that is why patients with HIV are at risk of developing infections?

Fahmy Exactly, that is because their CD4 T-cells are not as primed for functioning as well. There is something in there, though the cells are not completely dysfunctional, they are not functioning as normal. They are more susceptible to different infections and bad things can happen if they get exposed to very dangerous pathogens. So where an engineer comes in is when you try to educate the immune system in a better way than just throwing in bits and pieces of things you want the body to recognize. The idea is, if you were to miniaturize yourself and get inside the body and see how the new cells work, and by the way, scientists do this all the time because they have great microscopes and they can look at cells very close up and they see how things work, you would notice that what happens with a pathogenic invasion is that there are certain cells that are professionals at eating things that are foreign to the body. They gobble things up and then they interact with other cells and so there is this crossed awkward discussion between different cells to assess how dangerous is that thing that just got gobbled up.

Gore Like Pac-Man cells.

Fahmy Precisely, in fact, if you can imagine a Pac-Man eating something and then going and talking to Mrs. Pac-Man, for example. That basically spells out how the immune response will develop. Now where engineers come in is essentially trying to enable that discussion. What we do in the lab is we try to create a discussion between those cells such that the output or the end result will be a very robust, very strong immune response to what got eaten or what we call phagocytosed or cleared by those phagocytic cells that are floating in the blood.

Gore So how do you get the cells to talk better to each other?

Fahmy That is interesting. If you notice viruses, bacteria, all sorts of things that get inside the body are actually particles. Very small particles. Viruses are particles in the range of between 10 to 100 nanometers in diameter. A hair follicle, for example, is almost a million nanometers and so 1000th of the diameter of a hair follicle is what a typical virus or bacteria in one dimension will be in terms of size and our bodies have learned to recognize particles. The problem now with vaccines, is that when we get immunized we actually do not get these particulate vaccines. We get bits and pieces of molecules that we think are very important for the immune system to recognize, so the

14:39 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

idea with biomolecular engineering in the vaccine area is, how do you then create a safe particulate form of that piece so that it can be recognized and responded against?

Gore I want you to hold on to that particular thought. We are going to take a short break for a medical minute. Please stay tuned to learn more information about the very fascinating field of bioengineering and immunotherapy with Dr. Tarek Fahmy.

Medical Minute *There are over 13 million cancer survivors in the United States and over a 100,000 here in Connecticut. Completing treatment for cancer is an exciting milestone but cancer and its treatment can be a life changing experience. Following treatment, cancer survivors can face several long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers to keep cancer survivors well and focused on healthy living. The Survivorship Clinic at Yale Cance Center focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.*

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by our guest, Dr. Tarek Fahmy and we are discussing immunotherapy and bioengineering. Tarek, before the break you were telling me that our immune system, if I understand it, is trained to recognize particles and you are trying to build different kinds of particles.

Fahmy That is the idea, the motivation for developing vaccines at least using biomaterial. The biomolecular engineers are trying to develop particulate vaccines and that is actually one of the big thrusts of our program.

Gore What are you trying to vaccinate against?

Fahmy We are trying to develop a vaccine currently against a variety of different things, specifically what we call the flaviviral class of antigens which are basically West Nile and dengue fever. And also Japanese encephalitis, these are all classes of what we call flaviviruses. The reason we are focused on that is because there is no vaccine. Of course, there are things that we are very interested in to collaborate extensively with folks here at the Yale School of Medicine, Dr. Priti Kumar, for example, trying to develop an HIV vaccine. Developing these vaccines entails us trying to create a system that is both safe once injected but also very effective, and it turns out in short that if you take a piece of a virus that is important for recognition or neutralization, or that can induce an immune response and you are to package that into a nanoparticle.

18:17 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

Gore I am excited to know what that is.

Fahmy It is actually a very simple idea. The idea of making nanoparticles is if you can imagine oil and water.

Gore They do not mix.

Fahmy They do not mix, but what happens if you really mix them.

Gore You get little bubbles.

Fahmy You get little droplets and bubbles, but then what happens if you really sonicate that or you basically put in a lot more energy.

Gore No idea, I have never done that.

Fahmy If you mix the hell out of it, you will basically end up with very small bubbles.

Gore Okay.

Fahmy That is really it.

Gore Smaller than a hair follicle?

Fahmy Smaller than a hair follicle, and that is one of the simplest ways of making a nanoparticle.

Gore We pay you to do that?

Fahmy You pay me to do that.

Gore I could have figured that out.

Fahmy Well, the tricky part is how do you now stabilize that? Because if you leave that solution alone for a while you are going to get separation and so how do you stabilize that system?

Gore I do not know, how do you do it?

Fahmy You wrap it with a polymer, or each individual bubble with something we call a stabilizer and that is where a lot of interesting things can happen because the stabilizer can actually be made so that it can have certain addressable molecules that would end up basically targeted to specific cells of interest.

19:40 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

Gore Can you give us an example? I am not getting this.

Fahmy Yeah, a good example is cancer immunotherapy for example where there are certain cells in the body that unfortunately change structure or mutate in some form or another and then of course, they can grow and then that is when a tumor develops and so the question becomes, how can you target that tumor site or target those cancer cells and the idea of using a nanoparticle becomes very attractive there because if you can now attach something to the surface of these particles that would target those cancer cells and you load up that particle with a chemotherapeutic drug, then you end up with a lot of that drug in that location and you do not suffer the side effects, not you, God forbid, but just to speak of.

Gore I realize that is just a simplified thing and I have wrapped it with this stabilizer, right?

Fahmy That is right.

Gore And the stabilizer is what targets the cancer cells or is there is an antibody on it?

Fahmy Exactly, you put something on the stabilizer that would basically recognize the tumor cells and a typical thing would be an antibody and we use a lot of antibodies.

Gore And then I would inject these particles into the patient?

Fahmy Yes.

Gore And the antibodies are going to find the cells?

Fahmy That is the idea.

Gore And then what happens?

Fahmy So then you end up delivering a lot of drug.

Gore Because you have got chemo attached too.

Fahmy You have got chemo inside the particles. So when you are mixing the oil and the water, you are essentially sprinkling in the drug of interest, and so when you form these bubbles, the drug is going to be entrapped within those bubbles, then you are wrapping it around with your antibody and stabilizer combination and you end up with basically what we call a targeted nanoparticle, a very simple conceptual idea actually, that has been around for a while.

21:53 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

Gore For some reason I am picturing in my mind Julia Child's Kitchen, which is in the basement of the Smithsonian.

Fahmy Yeah.

Gore You remember Julia Childs, the French chef, and she is mixing this and mixing that, but I realize it is probably a little less mad scientist than that.

Fahmy It is actually almost the same.

Gore So all the teenagers who like to cook who want to do science should go into bioengineering as well.

Fahmy And the best biochemists are actually cooks and very good cooks are usually excellent, excellent biochemists or biomolecular engineers.

Gore This is great. This is a whole vocational training episode of Yale Cancer Center Answers. Seriously though, that is fascinating, but are you also trying to turn on the immune system to attack cancer cells or are some people doing that, is that part of this kind of approach?

Fahmy That is exactly what we are very focused on now, that is something that I am personally very passionate about. Now you have this interesting carrier that can be addressed to cancer cells, what do you put inside?

Gore With the carrier being the nanoparticle?

Fahmy Yes. I would say for many years people have tried different chemotherapeutic drugs. In fact, there is a company now that is actually going through phase II clinical trials with targeted delivery of docetaxel, which is a drug, and so the field is finally evolving to the clinical realm and you will see products in the future, I think in the next five years, in the clinic using nanoparticles to deliver chemotherapeutic drugs to cancer cells, prostate cancer cells is the clinical trial that is ongoing right now. It is fascinating and it is an excellent improvement, but I think that does not take advantage of what we can actually do with these things in the sense of using our innate defenses to eradicate the unnatural growth. What happens with immunity, unfortunately, in cancer is that they become really dumb, those immune cells that are patrolling around and supposed to be looking for pathogens when something mutates or changes. We have a fantastic immunobiology department that is investigating this in a lot more breadth and depth than what I am saying, but something happens that neutralizes those immune cells. They become un-functional or neutral and in a sense, the cancer cells, the tumor environment is actually pretty intelligent, it knows how to sequester itself away from our defenses, otherwise, it would not last for too long and so what is it that is being sent to neutralize those immune cells? There are a number of candidate molecules that have

25:01 into mp3 file http://yalecancercenter.org/podcasts/2015%200125%20YCC%20Answers%20-%20Dr%20Fahmy.mp3

been proposed, Dr. Richard Flavell, for example, is one of the pioneers on these signals that are being sent out from cancer cells that neutralize immunity and one molecule that is important, a master regulator of immunity, is actually TGF beta.

Gore Okay.

Fahmy That is the name of the molecule transforming growth factor beta. So, that neutralization is one component and what we are trying to do with nanoparticles is we are trying to deliver to those cancer cells something that makes them not send out these immune system inhibitors. At the same time, we are also packaging them with other molecules that actually activate immunity. Imagine that you are trying to give a speech, and you want your audience to be very excited and responsive to your speech.

Gore I do not feed them lunch first, that is my technique.

Fahmy That is an excellent example and that is one thought, you take away their ability of being lethargic.

Gore Right.

Fahmy But then at the same time, you may want to just feed them all Red Bull or something or give them hot coffee.

Gore Electric shocks.

Fahmy Shocks or something, and so it is this combination that I think is very important in the sense of awakening the immune response against the cancer and you can do that very effectively if and only if you have a way to target those molecules to the cancer cells.

Gore Do you have a way?

Fahmy That is where the nanoparticles come in. And the nanoparticles then would package both these inhibitors as well as stimulators.

Gore So you have got the TGF beta inhibitor.

Fahmy And then you have the T-cell stimulator.

Gore All in the same particle?

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Fahmy Correct

Gore But they go into different cells, right?

Fahmy They are addressed now to the tumor cells in general. And so what happens is they are latching on to tumor cells and then they are releasing their components. They are releasing their cargo, slowly over time and so you end up with at least localized immune effect or immunostimulant effect.

Gore And the T-cells around there start to react?

Fahmy The T-cells start to react and the cancer cells become very non-suppressive. And at the same time, we are getting this interesting immune stimulation by T-cells and so within a short period of time, those cancer cells are cleared from the body. Now, notice there is really no chemotherapy here and there is no directed drug delivery in the sense of classical drugs that we use currently in the clinic. All we are really doing is trying to awaken the immune system to what is wrong and that idea is being exploited with a lot more vigor with other kinds of what we call check-point inhibitors, other kinds of things that are being developed at Yale Cancer Center for immunotherapy. A classical example of this idea of suppressing the immune system is using the antibodies, anti-PD1 therapy right now, which is being developed by Dr. Lieping Chen, and that is trying to basically awaken but also suppress the tumor cells' ability to fight an immune response.

Dr. Tarek Fahmy is Associate Professor of Biomedical Engineering and of Immunobiology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at calecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.