Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and AstraZeneca. Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it's a conversation about the use of nanoparticles to treat skin cancer with doctors Michael Girardi and W. Mark Saltzman.

Doctor Girardi is a professor of dermatology and Doctor Saltzman is a professor of biomedical engineering, Cellular and Molecular Physiology and of Chemical Engineering at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

So maybe we'll start off by having both of you tell us a little bit about yourselves and what you do. Mike, maybe I'll start with you. Sure, I run a research laboratory with a big focus on skin cancer and strategies to try to prevent skin cancer formation and to treat it. And how about you, Mark?

I'm a professor in the Department of Biomedical Engineering.
My training is in chemical engineering, but for my research career and my teaching career I’ve mainly focused on how to apply principles from chemical engineering to make new products for medicine. This is such an unusual marriage and something that I love about academia is that we can take disciplines that are truly dispersed on the surface and make them collide and have really fascinating things happen. Mike, tell me a little bit more about how your research evolved and how you got to meet Mark? You know we have a really rich environment for exchange of ideas and just a tremendous breadth of faculty that is very welcoming to folks getting together. Discussing how different perspectives and takes on research can be combined. Mark and I have had a chance to see each other at various meetings and conferences here and then we really hit it off on Mark’s technology of using nanoparticles to deliver anti tumor agents.
And a thought bomb went off in my head regarding all the potential applications in the skin which is so accessible and such a burden on our society in terms of the number of skin cancers and the challenges in controlling these and treating them.

And so I reached out to Mark after one of his talks and he was very receptive. We had a wonderful meeting and brainstorming session and that was several years ago and we’ve really grown with our possibilities and directions research-wise in putting our heads together.

Mark tell us a little bit more about your research and this drug delivery mechanism that you have and the talk that spurred everything on? I’ll start back almost 30 years ago when I first got interested in this field, we had discovered that there were some polymers, some polymer materials, plastics that one could implant in the skin or put in contact with human tissues, and they’re very inert. And the key discovery was that you could combine these materials with drug molecules.

So that you could make such things like implants that you could
place in contact with tissues or implant into tissues and they would slowly release the drug molecules that you had embedded into them, and so that really started me on a path to thinking about how you could both expand the range of materials that you could use in this fashion, and more importantly, how you could marry this technology to treat different diseases. And we really focused a lot on cancer because of the potential to create drug delivery systems that would be more effective at treating cancer. But at the same time would be safer and we could use the materials to sort of focus the drug action on the tumor cells rather than on normal tissue. And I think the possibilities for this really expanded about 15 years ago, when we discovered you could make not only implants, but you could make tiny tiny particles of these polymer materials and anti cancer drugs. So we call those nanoparticles because their size is measured in the nanometers. They’re very small, so the particles that Mike and I have been using are about the same size as a virus.
So because they’re so small you can administer them easily in a variety of different settings. You can inject them easily through a needle, for example. Or you could suspend them in a solution and infuse them or apply them topically on the skin so that gives you a lot of possibilities and thinking about how you’re going to match this delivery system to the particular tumor that you’re trying to treat and the other thing about being tiny tiny particles is that they’re much smaller than tumor cells, and so they can actually enter into tumor cells and once they’re in the tumor cell, they’ll start releasing slowly their drug, and this allows the drug, the source of the drug, to be released very near its site of action, which for anti-cancer drugs is often in the nucleus of the cell, and so this gives you another level of control or design that you can introduce into the delivery system in order to match them most effectively to treat the particular tumor that you’re interested in. And so Mike, tell us more about...
You know, it certainly sounds like this technology that Mark has is incredibly innovative, but has so many possible applications. So how did you really think about its utility in terms of skin cancer?

I took a broad approach at first. As to the potential applications in the skin topical application, for example, to improve sunscreen performance. Injection into tumors to improve delivery of anti tumor agents to skin cancers, but also about the potential to stimulate the immune system against cancer. How these could facilitate delivery of those agents.

Mark and I also talked about the various inflammatory diseases of the skin and how we might use agents that are anti inflammatory and better deliver overall immune system in a negative way.

And throughout the entire body, so it’s about local delivery. It’s about increasing drug availability in terms of cancer. We have a huge burden with basal cell carcinoma.
These are a huge number of cancers across the world that outnumber all cancers combined in their occurrence, and often are treated by surgery or multiple surgeries on the same patient. An individual can develop many of these over a lifetime if they are fair skinned and have a lot of sun exposure. There is squamous cell carcinoma which presents another set of problems. They can be numerous as well, but they can also have a small chance of traveling throughout the body. They tend to be deeper as well. Melanoma not as common as basal cell and squamous cell carcinoma. But a whole other set of problems is that this is a real killer of young people. Melanoma is something that has a very high risk of metastasis after it obtains a certain level of depth. There are clear, unmet needs in some patients who have intermediate depth Melanoma that has already metastasized to regional lymph nodes. And there are challenges in treating these patients without necessarily giving them something aggressive.
and systemically delivered.
Chemotherapy to the entire body.
So all of these potential challenges
in the world of skin cancer
have areas that could be
potentially leveraged with this technology.
Mark and I have
been really trying to look at all
of the possibilities and begin
to develop research programs
and strategies to address them.
Mark, a couple of things that struck me when
you were talking about this
technology, one is that these
nanoparticles are so small that they can
actually be engulfed by the tumor
and have a mechanism of action
at their nucleus, essentially,
really targeted therapy,
delivered to the source of the tumor.
But my question there is,
how targeted can it be?
I mean can you make these
nanoparticles such that the tumor cells
and only the tumor cells engulf them?
How does that work?
That’s a great question and I think
there’s several different aspects to that.
The one that we’ve been talking about
so far and a major
one that Mike and I have been exploring is to put the particles as close to the tumor cells as possible. To physically target them, inject them into a tumor, for example. And that’s possible with the skin cancers that Mike is mentioning, because they’re so accessible, they’re on the surface of the skin, at least some of them are exclusively on the surface of the skin, and dermatologists are very comfortable with using needles to inject locally in the skin and they’re very talented as well, and so that makes a reasonable form of targeting. But you could also make it more targeted and one possible way to make it more targeted is to take the nanoparticles and engineer the surface properties of them. And one of the aspects of the technology that we’ve exploited in many of the projects that we worked on is to make the particles themselves very sticky to proteins. Or tumor cells that have a lot of proteins on their surface.
And so when you inject these sticky particles they will tend to be taken up by whatever cells are near the site where you've placed them and this allows the vast majority of the particles to stay in a tumor if you inject them right into the skin tumor, for example.

And so that's one one way to augment the targeting that local delivery naturally provides you. A second way would be to not just use physical properties like stickiness of particles to make them attractive to tumor cells, but to make them specifically adhesive to tumor cells. So in that case, if you knew that there was a protein on the tumor cell surface that was expressed very abundantly in the tumor cells and not in normal cells, you could put some chemicals that bind to that protein on the surface of the nanoparticle. So this might be an antibody. Or an antibody fragment that is specific for that protein that's highly enriched on the tumor cell. Then that gives you an additional
level of targeting. And it’s even possible to think about administering those highly targeted particles systemically and asking them to find the tumor for you instead of you using the needle to find the tumor yourself. And that’s been a very active area of study over the past 10 to 15 years or so, and it turns out to be hard to achieve practically for reasons that we could discuss. But it’s also a method of targeting. I would like to get into how exactly we target things and what are the challenges that are being faced in this really exciting area, but first we need to take a short break for a medical minute, so please stay tuned to learn more about nanoparticles and skin tumors with my guests Doctor Michael Girardi and Doctor Mark Saltzman.

Funding for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com. Over 230,000 Americans will be diagnosed with lung cancer this year and in Connecticut alone.
there will be over 2700 new cases. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. Each day, patients with lung cancer are surviving thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated Comprehensive cancer centers, such as the BATTLE II trial at Yale Cancer Center and Smilow Cancer Hospital to learn if a drug or combination of drugs based on personal biomarkers can help to control non small cell lung cancer. More information is available at yalecancercenter.org. You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is Doctor Anees Chagpar and I’m joined tonight by my guest doctor Michael Girardi and Doctor Mark Saltzman. We’re talking about research looking into using nanoparticles to treat skin tumors and right before the
break we were talking about how these nanoparticles are so small and how we can try to make them really attack tumor cells rather than normal cells.

So Mike, Mark was talking about how we can make nanoparticles sticky. We can try to get them in an area where these cancers exist. What have you explored in terms of trying to treat these skin cancers? What are the exciting developments and where are we with this research?

So I think there’s several features that we’re really leveraging about the sticky type particles and these will bind to proteins. Any proteins they come in contact with but what’s really special about the tumor microenvironment is that it’s very protein rich tumor cells secrete a lot of proteins. They create their own matrix. This is helpful for them.

We think they perceive it as such so they can grow so they can begin to want to travel if we personify the tumor cells that way, and so these particles will bind to both tumor matrix proteins and bind to the surface of the tumor cells, so this really not only gets...
the drugs into the tumor cells, but creates anti-tumor agents all around the tumor. We think this is really important for trying to target and eliminate the tumor. We also have worked on strategies and how we deliver these tiny particles beyond the simple syringe and needle strategy, which is actually quite effective in and of itself. But for certain tumors, ones that are more broad but thin and shallow, they can create surgical challenges to cut out a large piece of skin when something is really not that deep. That lets us wonder if there is a way to deliver these agents, for example over a larger area, but not as deep and so Mark and I have explored strategies using what’s called micro needling or micro needle pads, and so the particles might be loaded into these hollow very tiny needles and in many cases they can be made to be painless because they just don’t get to the depth where they’re going to trigger the nerve endings and
these pads could be applied and the particles can be delivered in that fashion. We’ve also looked at strategies where we’ve accelerated fluid that contains the nanoparticles in a way that can push them with a high pressure system through the surface of the skin into a tumor. Kind of like a high pressure micro waterjet, so we’re really looking at ways that we can empower health care providers to be able to use this technology to best serve their patients. But in a number of different tumor settings, different tumor types, different tumor sizes, and different tumor depths. That’s really interesting, and I guess the other way to do this is, as you both were talking about earlier, was injecting this systemically. So I would think intravenously to try and hone these nanoparticles to their target whether it’s an antibody or other mechanism to try to find these cancer cells and target them that way. Mark, you know another concept that you had mentioned,
or I think Mike had mentioned before the break was using nanoparticles to kind of prime the immune system. Often on this show we’re talking about immunotherapy and the fact that these cancers kind of evade the immune system whose job it is really to get rid of things that we don’t want in our body, whether it’s infections, or whether it’s tumor cells. Tell us a little bit more about how you can engineer nanoparticles to trigger the immune system, and how that’s working in treating cancer? I’d be happy to start addressing that, but Mike is really the expert on that part, but so I’ll talk about the parts that I know and maybe he can follow up. One of the interesting things about some of the cells of the immune system is that their naturally bagocytic and part of their job is to take up particles from the environment and to sample them to look for danger signals, and so you can exploit those cells by creating nanoparticles that look like the natural kinds of things that they would take up and ingest.
And you can do that by controlling the size of the particle and by controlling its surface to make it most attractive to those macrophages or antigen presenting cells. But in addition, you could further augment the activity of those particles by putting in the kind of danger signals that they might find from a microorganism and that revs up their immune activity. And so we've been exploring that and also exploring the idea that you could present these signals to immune cells in a variety of different ways, either by slowly releasing them, or by presenting them in different fashions on the surface or the interior of the particle and looking to see if by changing the way that the particle is engineered with these signals for the immune system, if that changes the speed or the aggressiveness that you can introduce into the immune response. So Mike, do you want to kind of pick up on that?
I mean, oftentimes when we’re thinking about generating an immune response, we kind of talked about two kinds of systems. One that’s a more generalized immune response, and one that’s more targeted. Talk a little bit about how you envision nanoparticles really working in terms of the immune response against cancers.

Yeah, I think it’s a critical question. I think that cancer therapy today is about targeting the tumor and it’s about manipulating the immune system to maximize the effects of the tumor targeting strategies. No cancer therapy can ignore today what’s going on with the immune system.

It’s too powerful an ally in the fight against the cancer and there’s obstacles to overcome, so let me explain. That first dichotomy is that we have evolved to recognize foreign substances, including antigens on tumor cells and we can stimulate the heck out of that process through agents, as Mark has described, that might be considered dangerous signals, molecules that might be for example,
normally found on infectious agents, molecules that might be produced by our own cells when they have sensed that they are infected, for example. We can begin to try to trick the immune system in looking at the cancer cells in a way that makes them appear as if they’re a foreign infection, whether that be viral resemblance or bacterial resemblance or others. And we can do that in a general way, and so those are common molecules that are found on a bunch of microorganisms, so we can just introduce those types of compounds into the nanoparticles. Then we can try to facilitate how they’re seen by the immune system in a more optimized way. In a more specific way, we might try to load what are called tumor antigens, so these might be real signatures on very specific types of cancers, and they may be even specific to each patient. In this way, we’re trying to stimulate a very directed killer T cell response. That’s akin to a vaccine, for example.
these days for a bunch of other reasons, and so we can use nanoparticles to develop anti tumor vaccines that could more specifically stimulate the immune system to attack the cancer. And on another consideration though, we have to realize that tumors evolve and grow to try to suppress the immune system. And this is a major consideration in treating cancer, immune checkpoint inhibitors or something, for example, that are delivered throughout the body to try to alleviate some of these controls that the tumor has put on the immune system. But we can also try to target that with nanoparticles locally. So for example, there are immune cells that try to suppress the antitumor effects, and these need to be dealt with in a way, especially at the tumor site, so that the tumor can become what we call hot and not cold. Hot, meaning it can be recognized by the antitumor immune system more readily. And it sounds like you have so many possibilities in terms of how you can fashion these nanoparticles, so you can
target the tumor on one side and potentially attract the immune system on the other side and get these two systems in close proximity to each other in addition to delivering drugs.

Now the other thing that you mentioned before the break was using nanoparticles relating to skin cancers, but more on the prevention side.

So Mark talk a little bit about using nanoparticles to make sunscreens more effective.

Yeah, I’d be happy to do that and that was one of the first big projects that Mike and I worked together on and it was quite successful.

So the idea was that we knew that we could make these nanoparticles that would adhere to tissues and we tested them to see if you just suspended these particles, these sticky particles and you put that water on the skin would adhere and in fact they did. And they adhered very strongly to the skin. You could put some particles on the skin and then you could wash the skin extensively and the particles would just stay there and resist removal with washing.
And so we knew that there was something special about that technology, because if you can apply something topically to the skin and it stays there for a long time, that might have some value.

And so in the second phase we learned that one could take common sunscreen ingredients and load them at very high levels inside these nanoparticles, so that the nanoparticle itself was 50 percent, 60% sometimes even 70% sunscreen agent. And then if you apply those to the surface of the skin, they stuck. They don’t penetrate into the skin. They don’t wash off very easily, but they’re sitting on the skin now in a position to be between the skin and any ultraviolet light that falls on the skin, and so they could be very effective at screening that ultraviolet light and absorbing it without anything ever entering your body and they stay on there for a long time.

And so we did a number of studies trying to understand how this works and trying to perfect it using combinations of sunscreens so that we could block all wavelengths of ultraviolet
light and ultimately did a small pilot clinical trial here at Yale showing that indeed you could put these on the surface of the skin of volunteers that they were completely safe and that they would perform just as well as the kinds of sunscreens that you can buy at the drugstore. So we’re very excited about that and new ways to use technology to prevent skin cancer. And my grandparents all worked on farms and so are very familiar with the devastating effects of skin cancer.

Doctor W. Mark Saltzman is a professor of biomedical engineering, cellular and molecular Physiology and of chemical engineering and Doctor Michael Girardi is a professor of dermatology at the Yale School of Medicine. If you have questions the address is canceranswers@yale.edu. And past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to
learn more about the fight against cancer here on Connecticut Public radio funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and AstraZeneca.