

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



Hosts

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**Researching New Ways to
Treat Ovarian Cancer**

Guest Expert:

Gil Mor, MD, PhD

*Professor of Obstetrics, Gynecology &
Reproductive Sciences*

Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening I will be sitting in for Ed and Francine and my guest is Dr. Gil Mor. Dr. Mor is a Professor in the Department of Obstetrics And Gynecology at Yale School Of Medicine where he leads the reproductive immunology unit. He joins me this week to talk about his research into the understanding of ovarian cancer.

Barber Dr. Mor, welcome to Yale Cancer Center Answers.

Mor Thank you Bruce Barber.

Barber How did you find yourself at Yale?

Mor I was very interested in understanding the role of the immune system in promoting or controlling cancer and that is some of the work that I did during my training at the National Institute of Health, and I came to Yale in order to expand this field of what we call reproductive immunology, that is the interaction between the immune system and reproductive organs both in the normal as well as in the pathologic. While here, I established collaboration with the members of the gynecologic oncology department and expressed my interest in ovarian cancer.

Barber Where did you do your original training?

Mor My training was done in Israel. I come from there. I went to medical school at the Hadassah Medical School in Jerusalem and my received my PhD at the Weizmann Institute in Rehovot.

Barber What caught your interest in this kind of science to begin with?

Mor One of my frustrations when I was practicing medicine, especially in Israel, is when you confront a patient you read from a book what you have to do and many times that does not work, so I decided instead of reading a book, I may like to write the book, and that is the reason I moved to science.

Barber That is great so you started off as a regular physician?

Mor Exactly, when I was doing my residency I started doing research and then, against the good advice of my wife, I went to become a PhD. During my residency I started doing the research and I did my PhD.

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- Barber And you teach medical students I would imagine?
- Mor We have medical students that come to us and I teach medical students, as well as graduate students. My life has a combination of graduate students plus doctoral fellows. I like to work with medical fellows so it is a nice combination from the basic science to the clinical physicians.
- Barber If you could treat me as a new medical student, and I am just learning about reproductive endocrinology and ovarian cancer, how would you explain to me basically the workings of that aspect of physiology?
- Mor There is the idea that in a patient with cancer, in general, the immune system has been suppressed, so it is a weak immune system. But in reality, it is the opposite. The immune system is functioning normal, but when we take tumors, and it does not matter what type of tumor, it can be ovarian cancer tumors or breast cancer tumors, there are a lot of immune cells inside those tumors and guess what, those tumors, instead of dying because of the presence of the immune system, they are growing. There have been many clinical trials with vaccines against tumors and they have been successful in inducing an immune response, so the immune system is activated, but instead of the tumor dying and the patient being safe, we have the opposite. The tumor grows, so that has been a puzzle for me and I wanted to understand why the immune system in the tumor environment instead of killing the tumor, it's helping the tumor to grow.
- Barber This is obviously very important in ovarian cancer because, correct me if I am wrong, it is very hard to detect ovarian cancer.
- Mor Exactly, there are two major aspects in understanding this disease. One is that the disease is detected in late stages because of the location of the ovaries it is impossible to do a mammography or to do a self-examination, so when the patient goes to the physician they will discover a mass in the abdomen but that means that that abnormal growth is quite big in order to be detected by the examination, or when the patient goes to do an imaging analysis like a CT scan or an ultrasound he will detect it only when the mass is big. Unfortunately, when that mass is able to be seen by this approach the disease may have spread and then things get much more complicated. We know that early detection means survival, late detection unfortunately brings many complications.
- Barber It is a great way for you to devote your scientific background, to figure out how to either shrink these tumors, or to have them just not grow in the first place.
- Mor Exactly, this is the design that we have been working on in the lab because when you develop a test of early detection, the question that we will have is what do we do? We wanted to detect the tumor early, but also have an answer of how do we treat it? How do we prevent the disease

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from coming? We developed a test for early detection that is a combination of proteins. This has been characterized and is now with the FDA and is offered in Europe in a few countries like Spain, Italy, and Denmark, and the main concept is that this blood test can look at the patient in multiple phases, so during a long time, to see if these markers change and it will tell us if something abnormal is going.

Barber It seems to me that we are focusing more on the proteins?

Mor Yeah.

Barber Is this a recent development?

Mor This is one of the interesting things in science, we go by cycles. There was a cycle when everything was genomics and not proteins; proteins were not important anymore, and because there were so many PhDs studying about gene regulation and genomics, there were hardly any PhDs that knew what a protein was. Now, we know that the genes are important, but the genes don't solve everything. You can find a genetic mutation, but that is not a death sentence. With a gene mutation you can live without developing a cancer, so, the gene is a base, but it does not determine exactly what is going to happen in your life. The environment, the way we live, affects how the cells communicate with each other and to communicate with one another, they use proteins, not genes, so now we are using the language to communicate, with that communication we will have a good relationship, a good friendship, and it is exactly the same, the language in this antibody are proteins, so good proteins, good communication, bad proteins bad communications, bad friendships.

Barber When did you start studying this communication method of proteins?

Mor I am a cell biologist in my basic science. I always have been interested in the cell and I knew that the cells need to communicate with each other to live. If I put two cells in a Petri dish the first thing that they will do is to send projections to touch each other. Once they touch each other they start growing, that is the reason you like to hug your wife, you like to touch your children, physical contact. Communication is the secret of life, at least in my point of view.

Barber What are you finding about the difference in that communication when cancer is present?

Mor That has been one of the major questions, why a cell suddenly becomes crazy. I am going to talk to you about a very specific aspect, there are many hypothesis, many aspects, but I want to focus on what we are working on, and it is one word and is called inflammation and inflammation is

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related to repair. If we do not have an inflammatory process we would be dead. When you cut your skin the reason that your skin will be cured immediately, exactly as it was before, is because there is an inflammatory process that repairs your skin. Inside of our organs, inside of our tissues, we are all the time dying, so all the time we need to have that inflammatory process for repair. As with everything in life, there is a range that is good and that is bad. There is good inflammation, and there is also bad inflammation. The bad inflammation is chronic inflammation, if you continue cutting your skin in the same place; you are going to have a tumor there. Now specifically about ovarian cancer, what is the connection between inflammation and ovarian cancer? Multiple ovulations, so when a woman every month ovulates, it is cutting the surface of the ovary in order to allow the ova to come out and then what it needs to do, it needs to repair and to repair is inflammation. A woman that is ovulating every single day from the age of 13 to 35 has a classical chronic inflammation, each time it is repair and wound, repair and wound, and the repair, I forgot to tell you, tells the cells to grow.

Barber So that is the protein, that is the communication.

Mor Exactly. Inflammation is the language that is saying there is a hole here, start growing and heal, but if you start talking too much, you will get tired of me. You would not like to listen any more to what I say and that is exactly what happens. Those cells that are telling them all the time to repair, say, I am tired of that now leave me alone. Then, they behave independently and then become abnormal cells.

Barber This is fascinating and it must be quite rewarding as you start to figure out this language.

Mor Indeed it is fascinating because it also helps us to start designing new ways of how to prevent and new ways of how to treat. For example, in terms of prevention of ovarian cancer, one of the factors, again there are many epidemiological studies, but I will focus on what is leading us to understand the biology. One of the preventions of ovarian cancer is, for example, pregnancy. Why pregnancy protects ovarian cancer is because you do not have ovulation. You do not have the chronic inflammation. The other interesting thing that I have always been questioning in my head is that tubal ligation is a protection for ovarian cancer. What I mean by tubal ligation is that you are closing the communication between the uterus and the lower female reproductive tract with a peritoneum, the abdomen where the ovaries are located so when a woman has a tubal ligation, the risk of ovarian cancer decreases significantly. We think now we understand the reasons and there are two potential things. One is that in a movement coming from the lower reproductive tract to the abdomen can carry bacteria and bacteria or microorganisms can induce a local inflammation, a chronic inflammation, and then again, would be the bad communication we were talking about a few minutes ago, and that would lead to transformation of cells. An example

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is endometriosis. I think some of my colleagues have discussed endometriosis and that is a condition of inflammation in the abdomen. That is a risk for ovarian cancer, and what we are finding is potentially that ovarian cancer is not originated in the ovaries.

Barber This is fascinating, we must hear more, but we have to take a break. I am speaking with Dr. Gil Mor who is Professor in the Department of Obstetrics and Gynecology and leads the reproductive immunology unit at Yale.

Medical Minute

It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year and over 200 new cases will be diagnosed in Connecticut alone. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam, and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses 3-dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting network

Barber Welcome back to Yale Cancer Center Answers. We are speaking with Dr. Gil Mor about ovarian cancers and we want to move now into the stem cells. First let's start off with what is the definition of a cancer stem cell?

Mor I always like to say that we as scientists and physicians sometimes are very dogmatic. When I studied in medical school, they taught me and I learned in all the books that a tumor is originated by one cell that got crazy and started dividing like crazy, then they build this mass of fast-dividing cells so all the biology that we have developed and all the therapies that we have developed so far are based on that concept of cells dividing fast, so chemotherapy kills fast dividing cells but if you see what the situation is you will find that a patient will go to surgery, the physician will remove everything that he or she can see, and then they go to chemotherapy. The patient goes home free of disease with no tumor left. Six months later, one year or two years later, the disease comes back, and not only does it come back, it recreates again the original tumor. So, if the concept is that one cell divides multiple times, how can we have this recreation? To summarize many years of work in a few minutes, is we were right, but we were wrong. We have been studying only one small part of the tumor biology. There is another component that we never accepted that exists and that is that the tumor is not a mass of fast dividing cells. It is a well-organized structural organ

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and what I mean by that is that it's a hierarchy of cells. There is one cell that is the progenitor, the leader, that recreates a tumor or recreates the organ and then you have the soldiers that are those mass fast dividing cells. Chemotherapy kills only those fast dividing cells, the soldiers. It does not kill those progenitor cells, they are chemo resistant, and not only that, these progenitor cells give origin to another type of progenitors and they can migrate. They can attach to other parts of the body, or the abdomen in the case of ovarian cancer. They will stay there resting, sleeping, and by factors that we are just discovering they suddenly wake up and they recreate again the tumor, and you have the metastasis.

Barber Wow! So these progenitors, are those stem cells?

Mor Exactly. I use the word progenitors because for many people it is a little confusing, when I tell you stem cell, you think it may be cells coming from the embryo, etc. The meaning of a stem cell, it means a cell that has the capacity to recreate the multiple types of cells that make an organ.

Barber It is like the boss.

Mor It is exactly like the boss, or the general.

Barber The cells are the soldiers, as you mentioned before, and so you are now trying to figure out how to keep these other generals from going off and going to sleep and then waking up and forming tumors in other parts of the body?

Mor Exactly. The big advance in our research is that we recognize first of all what is the capacity of the enemy and we recognize that this is not just a mass, it is well organized, as I mentioned to you before. Now, recognizing which one is really the important target. Now, we need to develop therapies. I want to make very clear that I do not imply that chemotherapy has to be replaced, we need to kill the soldiers, and we need to kill the fast dividing cells. What we need now is specific therapies that will kill the soldiers. Unfortunately, today from what I know there is nothing approved in the clinic that can really kill those cells.

Barber The generals.

Mor The generals. So our research now is focused on working with people from Yale who have great pharmacology and chemistry departments who are synthesizing new compounds. We work with many pharmaceutical companies. We have a continuous screening process, why because we have isolated those cells we grow them today in the lab. That is a big step so we have those cells, the generals, so we are screening new drugs that can kill those generals.

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Barber How long has it been since you could grow those generals, those stem cells in the lab?

Mor We have had those cells for almost three years.

Barber This is cutting edge stuff.

Mor: Completely, this is completely new.

Barber Absolutely amazing, and I can tell you are very passionate about this, but I can also tell that you have always been this sort of person that challenges the conventional way.

Mor This brings me back to what you asked at the beginning. If my thoughts were to practice medicine in the regular way, I never would have gone to do a PhD during my residency.

Barber So this was the kind of guy you have always been?

Mor Always.

Barber I would imagine it takes people like you as scientists, in addition to, as you mentioned before, the people that are working and established these great new drugs, Herceptin or something like that, that really are having a great deal of success killing the soldiers and doing as little damage to the healthy tissue as possible, but in science we really need people who are thinking in new ways don't we?

Mor Absolutely, and this is important also because I do not want to create a new religion and that is our tendency, to think this is the only way. Biology, medicine, is the integration of different views. Again, we are humans, so we like to think that only the way that we are doing this or finding that is the answer for everything, no, the new medicine, the new science, is integrational, where you bring people from different fields and put them together, for example, we are working with people with biophysics knowledge to develop new ways to deliver drugs, with the chemistry people who have different concepts, and with immunologists, so bringing new aspects to an old question.

Barber It has been a theme in our conversation, and that is communication and that is what I am learning is so important in science, it is in the collaboration and different people thinking in different ways about things and sharing those ideas.

Mor Collaboration is the most important thing, and I am going to tell you one of the problems that we have in biomedicine. When a new discovery from the lab, wants to go to the clinic, it may take 10 to 15 years, and it is not because this is so difficult, it is just because there is no communication.

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The language that PhD's speak, or the basic scientist, is a completely different language than the clinician, or the MD speaks. And it is simple, when we are at medical school we are trained that if you come in with a stomachache or problem, I have to fix your problem quickly. I need to send you back so you can go back to your normal life. You do not want me to start analyzing you. You want a solution. The MD is trained to give a quick solution. Now if you go to a PhD with your problem, he or she will not try to give an answer. They will try to dig the problem to make it more complicated to make bigger and bigger and bigger questions. So when you put a PhD and MD front to front and the MD brings the question and the PhD is bringing more questions, then you say I cannot talk to this person.

- Barber It is just like the proteins that allow the conversation between the cells, so it does not exist so we need to build that in our research.
- Mor That is one of the unique things about Yale and our medical school because our medical students are trained, they go to the lab, they learn the language of the PhD and when they go to the clinic they learn the language of the MD and they function as the communicators or translators. That is the reason is called translational research.
- Barber I never knew that, I have heard that term used and that is the whole bedside to bench communication.
- Mor The translation is because they speak different languages.
- Barber And is that unique to Yale and is this new, is this part of the culture of the medical school?
- Mor I think that Yale is one of the leading medical schools in this idea that all medical students spend a good amount of time doing research and that is very important that those medical students continue doing some basic science and not just moving to do clinical studies, because as long as our medical students are exposed, even for a short period of time to the language of lab, they are going to be able to do collaborative work when they are practicing their medicine.
- Barber That has got to be so exciting for you to be part of this where there is obviously a great deal of growth going on, you just opened the Smilow Cancer Hospital. Are you involved at all with the West Campus, which looks like just unbelievable lab space?
- Mor We are excited to see how the expansion of Yale is allowing us to bring new technologies. Our collaboration started, for example, with the physicians from gynecologic oncology; Dr. Thomas Rutherford, and Dr. Peter Schwartz. We started learning how to communicate, how to talk, and we created this beautiful nice protein interaction. Also, we have many fellows who came to the lab.

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They learned the language and now I continue collaborating with them, for example, Dr. Silasi, he was one of my fellows and he learned the language. Now he is 100% clinician, but he knows what we need. And he is involved all the time in the collaborating projects so it works and we do new clinical trials. We try new approaches and so on.

Barber Dr. Gil Mor is a Professor in the Department of Obstetrics and Gynecology at Yale School of Medicine where he leads the reproductive immunology unit.

If you have questions or would like to share your comments, visit yalecancecenter.org where you can also subscribe to our pod cast and find written transcription of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.