

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



Hosts

Lynn Wilson MD

Vice Chairman and Professor
of Therapeutic Radiology

Francine Foss MD

Professor of Medical Oncology

**Yale Small Molecule Discovery
Center**

Guest Expert:

Michael Kinch, PhD

*Managing Director for the Yale Center
for Molecular Discovery*

Yale Cancer Center Answers

is a weekly broadcast on

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Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous 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 1-888-234-4YCC. This week, Dr. Wilson is joined by Dr. Michael Kinch. Dr. Kinch is Managing Director for the Yale Center for Molecular Discovery. Here is Lynn Wilson.

Wilson Let's start off by having you tell us a little bit about what you do?

Kinch I am in charge of what is known as the Yale Center for Molecular Discovery which is a recent combination of two different centers at Yale, one was known as the Yale Small Molecular Discovery Center and the other was known as the Yale High Throughput Cell Biology Center and to give you a little bit of an idea what the center does, I'll give you a little bit of an idea what my background is. I started life as a professor, I was actually a cancer researcher, and my focus was in breast and prostate cancer. We had identified novel ways of targeting metastatic cells with a type of therapeutic known as a monoclonal antibody. About 4-5 years into my professorship, after I had gotten tenure, I was approached by a biotechnology company that was interested in not only the technology we had developed, but also in asking if I would leave academia and start an oncology program at this Biotech Company. This company is known as MedImmune, which was a small biotech at the time and it grew quite large, so we went through a really fun time where the growth of the company was pretty dramatic. We increased the number of cancer programs we had from basically a handful to more than about two dozen. About five years after MedImmune, I was recruited by a gentleman by the name of Stan Cohens to be the chief scientific officer at a biotech company about a mile down the road and this was a small start-up company and the reason for raising that is that in the time that I was in academia large pharma, or biotech, and then small biotech, the field has transitioned quite a bit, which led to why I came to Yale and why I am at the Cancer Center. Large pharmaceutical companies have largely pulled out of early research and development of new therapeutics. They tend to become involved in the development of therapeutics more at the clinical stage level, after there is already some evidence from the clinic that the drug is going to be useful. The difficulty is that in the past that gap that has been formed by the drug company pulling back has been filled in by biotechnology companies. The issue is the venture capital for biotechnology companies has more or less evaporated and while there is still some out there, to a large degree investors, especially since the economic downturn, are less inclined to invest in smaller companies and that creates a real situation for new drug development because in the past, perhaps a professor might have an idea and be able to a venture capital or what is known as an angel investor to invest and then advance the drug down the road. That option is not so much of an option anymore. So what we are trying to do at the Center is to identify opportunities to advance something beyond perhaps just an initial idea that an investigator has, into something that is a bit more tangible that leads to the idea that we have in the Center of

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being able to expand these inventions as much as begin, take them further down the road then they might have otherwise with the goal not of competing with the Pfizers and the Mercks of the world, but rather to identify projects that are perhaps the best opportunities for the university, advancing to the point where the Pfizers and the Mercks or venture capitalists might be more inclined to want to license those programs.

Wilson And obviously this work is expensive and resource intensive, and with the evaporation of venture capital, who is paying for this?

Kinch That is a big issue in drug development. What we are trying to do is to find unique and creative ways for underwriting a lot of this work and that is also what I had to do in my last job in the biotechnology company, because again, the money is just not there like it was. So what we have been trying to do is to take an approach where first of all the university underwrites a substantial portion of what we do and the rationale for that is that we are tasked with generating value for the university by advancing these inventions down the road. If nothing else, providing tools for the investigator that they would not otherwise have and therefore, being able to generate new grants, new manuscripts, and other sorts of items of value to the university. In addition, what we have done very recently, just two to three months ago, is make an announcement to identify opportunities for industry to become involved in our work, and specifically what we have done is practice a model in which we worked with a major pharmaceutical company who has underwritten some other work that we do. They receive basically nothing other than the ability to get an idea of what we do. So in the past, what has occurred often is that a large company will negotiate a license with a University, for example, for a fair amount of money, that project will be taken aboard by that company and advanced. The problem that the pharmaceutical companies have had is that they invest lots of money, lots of time and resources and the project may not work out at the end of the day, perhaps something, especially early on in the life of the program, might have been not perfect and that slight imperfection became more and more of a problem and the project didn't advance, plus science is not guaranteed to work, so often times things do not work. We have basically reached out to the pharmaceutical companies to say to them, if you become involved at an earlier stage and if nothing else you monitor what is going on, they can give you a better feel as the projects evolve into whether you would want to make the investment to move into this. So our goal is to try to have a company interact with as many different projects as possible, and help us advance those program at the same time, and help the pharmaceutical company or biotech partner be able to identify which programs they would like to advance forward.

Wilson This is really fascinating information and a fascinating endeavor. How did you first get interested in this? As a young kid were you interested in science, did something happen in college?

Kinch I obviously, I think like many scientists, enjoyed science from the beginning. I had a great love for everything except, ironically, for biology. Growing up math and physics were fantastic and I held off until I believe it was late in my sophomore year, before I took my first biology class in college

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and then became immediately hooked. My interest in biology probably coincided greatly with the fact that within my family itself we had a high incidence of cancer. I lost two grandfathers as a result of colon cancer and many other relatives as well and as a matter of fact, about five years ago I found myself in the opposite seat from what I normally did at the National Cancer Institute, as we discussed before the program until very recently we lived in the Gaithersburg, Maryland area and what happened was that it turns out the high incidence of cancer within my family was the result of a genetic predisposition that our family has for two particular types of colon cancer. I had given many talks at the National Cancer Institute down in Bethesda, and it turns out that one day I found myself in the opposite seat where I was actually the subject of a genetic study of cancer and it turns out that it looks like in my particular case, I did not end up having the marker that leads to this, but it gives you a whole new appreciation for what cancer is and how it can impact your life, again you go from it being theory to all of a sudden it is a real life thing.

Wilson Not only for your family, but for yourself, it changes your perspectives on things.

Kinch Absolutely.

Wilson Tells us a little bit more about the Center. How long has it been in existence? Tell us a little bit about its expansion and growth since it started?

Kinch The Center has been around for about five or six years. It was originally started by a faculty member in the molecular cellular and developmental biology department by the name of Craig Crews, and at the time there were actually two centers, Craig founded one of these centers that was known as the Yale Small Molecular Discovery Center, and its job upon its original mandate, upon creation, was to be able to advance the discoveries of the investigators by creating new tools and specifically a set of molecules known as small molecules. Small molecules are basically just like the name sounds, molecules that are quite small, and most conventional therapeutics are small molecules and the issue is that anytime you have a chemical you need to be able to identify that you have chemicals that work in the way in which you want them to work, and do not have what is known as off target, or side effects, and so the job of the Center originally was to screen for these molecules and identify those that potentially could be research tools and potentially could also lead to something that might, down the road, be therapeutic when put into the right hands. The Center itself has actually been very successful. They have had, I think to date, more than about 80 programs have been successfully, and I believe three local biotechnology companies spun out of activities that went on at the Center and a number of different licensing opportunities have occurred. In addition, and more fundamentally, the Center has a good track record as far as being able to deliver to the investigator those tools that the investigators need for grants and for publications and for other opportunities and academic medicine as well.

Wilson What sort of growth has there been over that five years? Did it start as a relatively small group and got much bigger, where do we stand in terms of that?

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Kinch It has remained roughly the same size until the recent merger. It started off as two or three individuals and we are now up to about twelve, but approximately half of those were from another center which we can talk about a little bit later, but one of the goals that we have as a Center is to try to stay small in the lead. We want to be able to be as nimble as possible with regards to being able to have a lead group of people that can do work as well as they can, as well as is possible. One joke we have within the Center is that we strive to be number two in everything that we do, and the reason for that is that if we are number one and we are leading the development, for example, of a new technology, that takes a lot of energy and effort that we have to put into that technology that we could not put into the projects that we get from our faculty investigators. On the other hand, if we are number three or if we are number four or five and there are technologies that are very well done, it could be done elsewhere faster, better, or cheaper, and we would hire those people to do it for us. Instead we would like to be number two and be able to do something that is just beyond cutting edge and that is providing a service to the faculty that cannot be obtained otherwise and to be able to move forward with that.

Wilson I see, that is an interesting philosophy and approach. Tell us a little bit more about who exactly is involved and what are their roles in the Center?

Kinch So I lead the Center, but the day-to-day operations are actually run on the biology side by a scientist by the name of Janie Merkel who has been with the Center for about six years. To put that into perspective, I have been with the Center for about a year and a half. So Janie has really seen it through its full evolution. In addition, to Janie, on the chemistry side, we were fortunate to be able to recruit a chemist from Pfizer and he is now leading some of the more untraditional approaches towards chemistry that pharmaceutical companies have routinely practiced, but within academia have not been utilized, and so that is going to help us to be able to advance some of the discoveries that we make as far as small molecules that we discover, make them better, make them higher quality, take some of the risk out of the side effects that might otherwise have come out it and that investigator, we brought him on board from Pfizer and have been able to take advantage of having a real hybrid between academia and industry. About half of the people within the Center have a biotech background and about half are academia and that also is consistent with the fact that the way in which we operate is very different than other sorts of Centers within universities, often times what you have are Centers where an investigator will come with an idea and you have within the Center a lot of equipment and the Center head will say to the investigator, make use of the equipment as you would like. In other cases, a Center will basically take over the project from the investigator and move it forward. We have taken a little bit of different approach where we will link an individual from the laboratory that made the initial discovery with someone from the Center who will help adapt the work that is done within the laboratory to the Center and then move forward with that and that gets at a major problem because the type of experiments that are done in the laboratory day to day by a normal investigator, are very different than what, for example, the pharmaceutical industry does and it may be that in a pharmaceutical industry you have an

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experiment that is done once or twice a year for ten years where as is an investigators lab, all the work may be done in a month or two. So it takes creates a certain robustness and consistency in the experiments that occur over time. What we have done is to try to create a Center staff that allows us to do that. And we can talk more about that if you are interested after the break.

Wilson We are going to take a short break for a medical minute. Please stay tuned to learn more information about the Yale Center for Molecular Discovery with Dr. Kinch.

*Medical
Minute*

It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year and one in six American men will develop prostate cancer in the course of his lifetime. Fortunately, major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the 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. With screening, early detection, and a healthy lifestyle, prostate cancer can be defeated. 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 three 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.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my guest, Dr. Michael Kinch and we are discussing the Yale Center for Molecular Discovery. Dr. Kinch, tell us a little bit more about some of the items we were discussing during the break.

Kinch One of the things we were talking about is how we are trying to translate work that goes on in the investigator's basic research laboratory into something where there is a translational potential and opportunity for a drug to end up in a pharmaceutical company's hands. There is an interesting set of articles that have come out. One was an editorial in the Wall Street Journal and another was an article in the Journal Nature, which is one of the two or three top preeminent science journals in the world, and in both of them the former head of oncology at Amgen, my counter par at Amgen when I was at MedImmune and I knew the gentlemen quite well, has pointed out that the failure rate for academic-corporate partnerships is exceedingly high, and he has gone around and given a series of speeches, including one in New Haven last April, and what he has pointed out is that greater than 90% of all corporate academic partnerships fail utterly with no value being generated for either the academic or for the company, and furthermore, in this nature review, or nature article, he pointed out that greater than 90% of the work that is published by academic investigators cannot be reproduced in a corporate laboratory and that creates obviously lots and lots of problems because if you cannot reproduce someone's work and you cannot move it

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forward, where are the new ideas going to come from? There is the potential for there to be a lot of finger pointing, where the corporate world can look at the academic world and say well obviously you are wrong or you are only showing the most preferential data and the academic investigator can look at the corporate investigator and say well you are just incompetent and that is why you cannot reproduce the findings, and I think that our approach at the Center is that we believe that it's actually something in between and that is that fundamentally the type of research that goes on in a corporate laboratory and the type of researches that goes on in an academic laboratory are very-very different from one another, and when people talk about translational medicine, they are generally talking about translation from the bench in the laboratory to the clinic, but there is actually another translation from the investigator to the company that needs to occur and as we mentioned before, there is an appreciation of the fact that an experiment may be done in a company for many months and in some cases many years. Where as an investigator may do this experiment once or twice, or let's say even five or ten times over a month or two, and so a year later, a different student or different postdoctoral fellow, whoever is doing the experiment may have a very different approach and not be able to even reproduce the findings of their predecessor. Much less then if you now go into a corporate environment where you have a very different set of machinery with a very separate and different type of an approach. To give you an example, an investigator in an academic laboratory will often times do an experiment in centrifuge tubes, one experiment at a time, perhaps 10 or 15 different samples in an experiment. That same experiment in a corporate setting may be done 150 to 100,000 times per day for days and days and so that requires a different type of technology, a different type of translation, and that is what one of our goals is, to try to achieve that hybrid of the academic in industry approach to help from an educational standpoint making the academic investigator aware of what the constraints and the realities are within the corporate world and the other way around in the pharmaceutical industry to make them appreciate that when we say that we have given the 'good seal approval' if you will to this particular type of an experiment, they will have a greater satisfaction and believe that this is going to be able to be reproduced in their laboratories and allow them to initiate the development towards a new medicine or new drug.

Wilson It certainly sounds like there are a lot of challenges, if it was easy then it would not be as interesting and everybody would be doing it. Getting back to the small molecules, you had briefly described what a small molecule is, but what is their role in cancer?

Kinch Most conventional treatments for cancer are actually small molecules. They are molecules that are again very small. They are generally targeted for a particular activity, specifically in cancer generally to try to kill the cancer cells without killing the normal cells. Now a small molecule can be distinguished from a large molecule and there are many different types of large molecules, but perhaps the most well-known are monoclonal antibodies. Either antibodies that are given to you that are made in the laboratory, or the type of antibody that once you receive an immunization you produce it yourself. The big discriminator between small molecules and large molecules, or antibodies, is simply their size. An antibody may be what is known as 150,000 daltons, a dalton

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being a type of measurement unit, whereas a small molecule may be 200 or 300. So, it is considerably smaller in size. Again, most conventional cancer drugs are small molecules, but with the advent of Erbitux and Avastin, and other therapeutics for cancer that are monoclonal antibodies, large molecules and more targeted therapies have received a lot more press in the last few years. But still, the majority of therapeutics out there are small molecules.

Wilson I see, and what has been the growth curve for small molecules over the last five to ten years? Has it been fairly linear? Is it becoming explosive in terms of discovery?

Kinch Both in small molecule and large, and just for the record our particular Center does not distinguish among them, the growth in as far as the new drugs that have been approved and the growth with regards to new drugs that have sold very well by pharmaceutical and biotechnology companies, has really been skewed towards large molecules over the last maybe five to ten years. As a matter of fact, my background is in large molecules and there have been quite a few mergers in the last five to ten years and they continue today. Traditionally small molecule companies are acquiring large molecule capabilities, often times through mergers and acquisitions. For example, my old company, MedImmune, was purchased by AstraZeneca. That is representative of many others where GenTech for example, was purchased by Roche, and there are many other examples of that. So, one of the frustrations that I think all of us feel and one of the disappointments over the last few years has been that the approval of all drugs, small and large, has not kept pace with what would be the hope for the future, and I think with some regulatory changes and recognition of a lot of new science that has occurred in the last few years, that will improve, but at the moment, of course we are not improving things as quickly as we want to and again that is part of the reason that the Center is here, because there has been the creation of what is known as the valley of death, which is basically the valley being created, if you will, between what the basic research is that is generally done in the universities and the research that is generally done in the pharmaceutical companies that is further along in the development of the drug. In between, there is a chasm of work that no one really knows how that is going to be funded and how that work is going to be supported overtime. Compounding that is the fact that in addition to a changing regulatory environment where the FDA, its condition for approving drugs and monitoring safeties seem to be varying quite a bit over the last decade or so, is the fact that the pharmaceutical industry really is probably not going to be recognizable in 10 to 15 years compared to what it is today and what it has been in the past, and I think many companies, pretty much all companies, appreciate the fact that the industry is going to look very different in about a decade, but no one knows what it is going to look like, and no one knows what the hybrids are going to look like such as the Center that we have and others, how that is going to contribute to what the model looks like. So it is exciting time of experimentation, not just in the science itself, but also in the business of how new medicines are going to be discovered and moved forward.

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Wilson For our listeners, if you have identified a small molecule that looks very promising, tell us a little bit about the regulatory timeline between that discovery and when a human being can actually be treated with that medication or small molecule and benefit from that?

Kinch It is a great question and it is the big issue that companies face, and also keep this in mind, if you are a financial investor investing in a new biotech company, this is something that people keep in mind as well, oftentimes from when a new discovery was made, lets say that someone has identified a molecule that might be targeted in cancer, we hear about these breakthroughs all the time in the press, it can be five or ten years until the drug has gone through all of what is known as preclinical research and has reached a point where a document known as an investigational new drug application, or an IND is submitted. The importance of the IND is this is what now allows, it is the gateway that allows the clinical trials of that drug to begin, and so a good five or ten years and I believe the average is somewhere between 200 and 500 million dollars worth of investment can go into a therapeutic until it reaches that point. The vast majority of therapeutics, or attempted therapeutics, which reached that point, fail. So, I think the estimate is at least 9/10 fail for every one that gets into the clinic. Then you enter sort of the human clinical side of things and that can again last anywhere from perhaps I think the earliest that I have ever heard of is 3 to 4 years of clinical investigation up to 10 or 15 to 20 years depending on the type of trial that it is and so when you are looking at it altogether, you can be looking at 20 to 30 years from a basic discovery until the point where that drug is actually approved by the Food and Drug Administration and can be given to patients. Now some patients may be able to get it while it is in clinical trials, but again at that point it's still an experiment and it's still an investigation and so there is no guarantee of activity, but part of what our Center is attempting to do is to shorten that timeline, particularly that preclinical timeline, and there is a great deal of interest, I know at Yale Cancer Center and in the FDA, in determining how we can shorten the process while preserving the safety potential. I think Vioxx, another approved drug that subsequently ran into safety issues, has made people cautious. Rightly so, but there is clearly a balance that needs to be achieved and we are in the process of trying to determine how to achieve that in the best way possible.

Wilson What are some of the departments within the Cancer Center that you and your team have interacted with?

Kinch We have actually interacted with almost all of the different departments within the Cancer Center and many different departments within the University. We are fortunate in that we have interactions with the most basic of basic science, part of what we do is actually discovery of some of these new targets that might be targeted by small molecules or antibodies. But we also are doing other investigations, for example, on looking at drug combinations. It is pretty well established that one plus one can be equal to ten, and that if you have one drug that works well and another drug that works well, the combination of that can work really well, and so we have been working with some investigators at the Cancer Center to be able to advance some of those and

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identify what are the good combinations, likewise, one plus one can cancel each other out or even be toxic, and so we have been working with some of the later stage drugs for that. So, we have been fortunate to get to work with many different aspects of the Cancer Center.

Wilson How important is basic science in the development of these new treatments?

Kinch Basic science is key. Obviously understanding of the targets, knowing what the target is that you might be able to go after, and how it is going to work is important, but what has been interesting is that as a safety concern, the FDA is placing greater emphasis on understanding exactly how your drug is working rather than just what in the past might have been anecdotal information on how a particular molecule works. I used to teach chemotherapy to medical students in a past life and one of the things that we use to emphasize is that some of the best working cancer drugs were discovered by accident. One component of mustard gas, for example, was noticed in the trenches of World War I, some of the veterans who were exposed to mustard gas, some of their cancers got better, some got worse, and that led to this investigation and no one really knew what was happening, why it was working, in some cases until decades later, that is in the past and now it has been generally understood that you need to understand exactly how your molecule is functioning. How it is that you are going to be intervening against the cancer cell and importantly not hurting the normal cell and that is essential because again, we want to minimize the likelihood that the Vioxx like event, where you have an unforeseen toxicity that occurs. There is a real emphasis on trying to minimize if that is going to happen.

Wilson Can you give us some examples of some of the new research that you are really excited about?

Kinch There are many different opportunities. It would be hard to narrow it down to one. We have quite a few different programs where there are very fundamental differences between cancer cells and benign cells have been identified and allowed us to be able to target it. So, I think that it would be hard to limit it to one, but I believe there is great potential in the future.

Dr. Michael Kinch is Managing Director for the Yale Center for Molecular Discovery. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.