



Cancer Research in Action

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July 30, 2017

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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, Dr. Gore is joined by Dr. Mark Lemmon for a conversation about cancer biology. Dr. Lemmon is the David A. Sackler Professor of Pharmacology and Co-Director of the Cancer Biology Institute at Yale School of Medicine, and Dr. Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore When I was coming up in training in the late 1980s and then as a young faculty member in the 1990s, everyone was extolling advances in genetics and molecular biology, we are going to transform cancer, and what I saw, and of course my vision I think was rather limited or unimaginative, I saw a lot of genes being sequenced back in the day very painstakingly, and it was very interesting to see how various genes were contributing to cancer, but I did not get how that was really ever going to do anything, has that promise borne fruit?

Lemmon I think it has actually set the stage for what is going to be some serious revolutions and they have already started in this area. And I felt pretty much the same. I grew up as a biochemist, kind of hidden in the depths of a cold room purifying proteins and just being interested in what proteins do in life. And so, for me when I saw the sequencing and the genetics, really giving cancer molecular description so we could actually hook this particular molecule to this particular cancer or this particular change in a molecule to a cancer, that really got me excited to start thinking about doing biochemistry of these. That is really what pulled me away from being, some would say a boring biochemist in some senses, to doing cancer biology, which is really what brought me to Yale too. I had been a chair of biochemistry at UPenn until a couple of years ago. So, I think in terms of cancer, those pieces of information, the genes identified, the mutations identified are crucial because they are really giving you the nuts and bolts of what has gone wrong in the cancer cells, in the cancer systems. And, that is where the clues are going to come and they already are for how to fix it. If you look at the modern targeted cancer therapeutics, most of them are predicated on a particular genetic change of mutation in the epidermal growth factor receptor, for example which has changed in about 10% of lung cancer cases and is targeted with drugs and several examples of that sort. So, I think it opened up the opportunity to really do some biochemistry of the cancer system.

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- Gore What percent of cancers have the on-switch which is turned on, like you mentioned this particular growth factor receptor where if you had a drug that turned off the switch, it would kind of be simple concept. Are most cancers like that?
- Lemmon No, they are not actually, I would say. Actually, it depends of course on how you would argue it, but I think what we have learned is that it is rare that a given cancer through its entire history is dependent on one on-switch. There are key oncogenes that change, RAS of course is important in a very large number of cancers. EGFR interestingly was the first cell surface marker associated with cancers back in the 80s actually, when that was found, and people spent many, many years trying to figure out ways of inhibiting it, and finally those were approved – cetuximab, Erbitux in the 1990s, but of course what has happened with all of those examples is that once you start to attack that particular problem, that particular target, resistance develops. What that tells you is that it was not just that, there are other components or other components can take over. So, it is really not a single driver. What has happened is the cells have gotten screwed up in some senses, and it is almost as if control systems have just become out of control. A term for that is to lose robustness. So, what happens if you would start to hit one, like EGF receptor, then another will take over because the system is sufficiently plastic that you select for changes that would enhance cell growth, so you almost argue that treating the attacking EGF receptor or one of these targets is a bit like attacking one of the symptoms rather than the causes, and you end up in a game of whack-a-mole where if you hit EGF receptors, something else will come up, so you have to hit that and then something else will come up and you have to hit that. It is a bit like if your car is overheating and there is steam coming out of the hood, you could make the argument that attacking the EGF receptor was a bit like sealing up the hood so you do not see the steam anymore. I think in the next phase we need to really understand what is causing the ability of the system to be able to get out of control.
- Gore So, these cancer cells are driven by one of these mutations that we have a drug for, and then some resistance mechanism emerges, do you think that these cells are sort of mutating as they go along or are there are cells in the mix that were in a minority population that had this other mutation like a resistant bacterium in a culture that then grows out, do we understand that at all.
- Lemmon I do not think we completely understand it. There are different schools of thought about it, including the idea that the changes that allow resistance will emerge under the pressure of the initial drug, a bit like a bacterium situation. There are cases where that seems to have been documented. There is also a strong argument and quite a lot of data to suggest that the resistance mutations preexist in the population and they are selected out. But there is also another set of observations that suggest that once you take a cancer cell that is driven by an oncogene product out, and the idea would be if

you shut down the oncogene product, which might be EGF receptor, might be BCR-ABL, might be ALK, the things that we have targeted therapeutics for, if you actually look at those cells and look at how they respond to the drug, oftentimes they will start to express the various things we associate with resistance, almost as if that is a stress response. So, I think there are a variety of different possible mechanisms and we do not quite understand it and that is the kind of frontier I think in this field just not.

Gore Am I getting from you that you are really advocating understanding sort of the underlying mutation maker or genetic unstabilizer at the heart of these cancers?

Lemmon That is a very important part of it. I think there are two ways you can go about it, and Yale has a lot of great work in this arena and thinking about how to stop the mutations from continuing. The mutation makers if you like, there are a variety of those at the level of DNA repair would be one potential Achilles heel. So, that is one aspect and could help. But I think another way of thinking about it is that rather than thinking about the individual drivers, potentially we could think about what controls the network, what controls the whole system. It is almost like if you imagine a particular set of messages in the internet will cause a particular event, a targeted therapeutic is a bit like shutting down those messages. If instead we could start to think about how to fix the internet, so it only does what we want, that would be another possibility, thinking about controlling or reigning in the networks. To do that, we really need to start broadening our view and start thinking about the cell, the cancer cell, and its environment as a very complex network. We are a long way away from this, but I think it is the next frontier of cancer research, asking how did growth control signals relate with metabolism, which is providing the energy source for the cell and how are the proteins that control growth linked with the RNA messages, which is actually another that is untapped in terms of regulation and how do all of those within the cell itself relate with the environment of the cancer cell, and that is a very fundamental issue. There is a lot of feedback between the cancer cell and the environment in a general sense depending upon where it is, but there is also of course the immune system which is really an area of huge research here at Yale and elsewhere. So that makes the system even bigger. And these are really big challenges, and it is like taking biochemistry and squaring it or cubing it or sticking it to the power of 4. I think that we really have got to understand the biochemical systems at this rather large level, which is actually what we are trying to do or is a key goal of the Cancer Biology Institute of Yale, to have a component of that.

Gore Can you make that a little more comprehensible for those mortals among us? I am getting a picture of like a whole ecosystem or a biome or something, that you are

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seeing the cancer living in a host environment with an immune system and metabolism going on and somehow I think I am hearing that you want to find an Achilles heel that would sort of poison the ecosystem and make it go away. Is that right?

Lemmon Either that or the complete opposite. Because in a sense, to poison the ecosystem would probably be horribly toxic and would probably damage the ecosystem.

Gore Because the host would suffer.

Lemmon Precisely. I think another way to simply, if we could just get a sense of what are the key controllers, we could potentially correct it or provide alternative mechanisms of keeping the system in check, that type of thing. And I think that may not be possible, but the key is that we actually try to understand what are the regulatory principles of this network in some senses.

Gore Once a cancer develops, hasn't it already sort of plugged in, taking advantage of that ecosystem and milked it to its own advantage where things seem a little out of control?

Lemmon Yes, out of control is the key. If you could actually create more control, in a sense, that is what is being done in current immunotherapies that seem to work. The situation there is that the tumor cell which is out of control from an immunological perspective is shutting down the immune system so it does not get attacked, and in that sense from the point of view of the immunological ecosystem, it is indeed out of control. And so, the current immunotherapies are really blocking that out of control nurse, if you like, so that the immune system can come and take care of these cells. And so that is the kind, does that make sense, that is the kind of concept behind, just trying to restore or strengthen the elements that would return the system to being under control.

Gore But even there, in the situations where the immune response has turned back on and tumors respond, not all patients are being cured, is that right?

Lemmon Yeah, absolutely. I mean there are going to be a very large number of ways of doing this, which is why we really need to keep going and to understand the aspects of the network in general. Let me give you another example of one that is really not tapped at all, and that is the messenger RNAs for example really have not been considered very much as a control system, yet we know that those get very much shortened in cancer. And so perhaps, one could think of an approach of just lengthening messenger RNAs which would restore a whole bunch of control systems. So, that is one idea looking at the level of RNA transcripts. So, there are a variety of different untapped principles that we really need to think about.

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Gore This is heavy stuff and super interesting, and right now we are going to have to break this thought for a short medical minute. Please stay tuned to learn more about cancer biology, ecosystems and networks with Dr. Mark Lemmon.

Medical Minute

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Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis, or 3D mammography, is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org.

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Mark Lemmon and we are discussing the field of cancer biology. You know, Mark, prior to the break, you kind of overwhelmed me with this vision of these complicated systems. I remember when I was studying biochemistry in college and we were doing intermediary metabolism, I had made this huge piece of paper where I drew all these different cycles and arrows how this one fed into the other, I was studying in a library at 2 in the morning for some exam and I was standing on a chair looking down at this thing, and I was not even drug influenced honestly, maybe coffee, and there was this really exciting swirling orb thing about how, like for a second I felt like I got it, but I probably did not really understand very well, and this is kind of the image I am getting about the way you are trying to put together cancer biology.

Lemmon In a sense, yeah. I have to say that when I was at college, I had them all pinned up in my college room actually. For some reason, none of the girls wanted to come back.

Gore Family show, Mark.

Lemmon But I mean, it is complex. I think the stars have aligned in some senses for it because we do have access now through sequencing to have a large amount of information, and computationally, these kinds of systems can be dealt with. So, I think the systems are too complex for us to just simply intuit them, but computational modeling of them

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can actually work, which if you think about it, that is the way we think about traffic for example. We do not really understand how traffic flows, but we have good computer models for it. and I think it is much the same as going to be true in the context of what is going on with growth control and cancer if we fully understand in a sense that we can draw out a pathway when we were college kid, but we can actually do what if's and so forth with a computer model. I think that is the level of which we will have to understand it given our feeble minds.

Gore So, you have been engaged since you have been here in building an institute in cancer biology, and what is your concept of how or what does that mean really, I mean what is your concept of how an institute, which is going to have several scientists right, what is that going to do to sort of crack these systems?

Lemmon I think it is a matter of combining discipline. So, we have great cancer research here at Yale, which is patient proximal, so the clinical aspects of cancer research here at Yale are fantastic. That then links very nicely to a large number of different arenas of more basic cancer research from cancer cell biology to immunology, etc. And I think in a sense going back to what we were discussing at the beginning, what we need to do is just take that to a slightly higher resolution, start to think about what are the interactions between the molecules and so forth. This is almost an engineering problem in some senses. And so, when you start thinking about it in that way, you realize that one needs to combine disciplines. We need to have people who can think about the systems and yet from an engineering perspective talking to the cancer biologists, we need to have chemists also involved in that conversation, so I think what the cancer biology institute is really all about, we are out on the West Campus at Yale, is linking other elements of research at Yale to what is going on proximal to the cancer clinics. I guess it is a clearing house for different disciplines where we cannot just do biology, we cannot just do chemistry, we cannot just do engineering to solve this problem, we need to involve all of those components.

Gore Is part of that going to be this computer computational piece?

Lemmon We have a very strong interaction actually right across the road on the West Campus. There is a systems biology institute, which does exactly that. It is interested in these complex systems using computer models and so forth. So, yeah, absolutely that will be a key part of it.

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Gore And do you think that as an institute, is everybody going to be working on sort of communal problems, like have everybody working on this particular protein or that particular system or how is that going to work?

Lemmon No, I think it is really about control principles. The bottom-line is that when you think about a cancer cell sitting in its environment, the way it is controlled is through its signaling through its metabolism for production of energy supply, through its interactions with the immune system, through the control of its gene expression where all of those basic things that we think about in biology. So, we will have a faculty member of research group associated probably with each of those arenas, so what each member will be doing is thinking about control of cancer cells. That is the problem, how to bring cancer cells back under control I suppose. So, that is the problem, but just doing it from a different perspective where all of the perspectives are interlocked because you cannot think about the metabolism without thinking about the signaling. You cannot think about the signaling without thinking about gene expression. So, they are all interlocked at that level, but at the moment, those disciplines are to some extent separated, so the idea is by bringing people who are interested in each of those disciplines together to think about cancer that will create kind of a hope, a holistic view of how the cancer cell interacts with this environment and what are its weak points so we can attack.

Gore Fascinating. Can you tell me an anecdote at all about something that you are working on right now that is particularly making you excited?

Lemmon Getting back to the beginning actually, as I said, I started off a biochemist just trying to understand how molecules work, and what we do as biochemists is study how fast reactions go, how well the mechanisms of these reactions, things that most people are not that excited about, and there is a particular example where we are working on a kinase, which is a type of enzyme that sticks phosphate groups onto tyrosines and amino acids and proteins.

Gore Well, that sounds really boring but it is really important, right?

Lemmon A very key reaction.

Gore That is like an on-and-off switch?

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Lemmon It is indeed an on-and-off switch, and what we are doing with this enzyme in trying to understand it was measuring what is called K_m for ATP, it is kind of thing that undergraduates fear for the most part.

Gore Yeah, some big equation that has a dividing in and a bunch of multipliers and stuff right?

Lemmon Right. Anyway, we measured it. You ask a graduate student to do that and they will often groan.

Gore Roll their eyes.

Lemmon Indeed. And so, you are measuring that for a couple of different variants of this kinase called ALK, anaplastic lymphoma kinase, which is interesting and one of the reasons you go into it is we know that it is mutated in about 10-15% of kids with neuroblastoma. It is a driver mutation in neuroblastoma and indeed is being targeted with several ALK inhibitors at the moment, which are actually looking very promising. But the key question is that we are having meetings, as biochemists, we are having meetings with clinicians and one of the issues that arose is the one mutation brings with it susceptibility to one of the drugs that are currently being tried for targeting ALK. Another mutation brings with it resistance to that drug, so just understanding this from a clinical perspective is key, and the answer seems to be that one increases the K_m for ATP, makes ATP bind more weakly and the other does the opposite, and so it was really the K_m for ATP is the issue that defines resistance of sensitivity to this particular drug that has been used in kids with neuroblastoma, and those that have the higher K_m for ATP actually do to some extent respond. So, that was actually one of my most exciting days in biochemistry, talking to clinician who is running in a clinical trial about K_m for ATP, something I never thought I would do. And having heard we write the trial in terms of concentration of drug to overcome this problem. So, really nitty-gritty biochemistry, plugging into making decisions about how to move forward in clinical trials. I think that is what a lot of this is about at the moment.

Gore That is really interesting you say that Mark, because I review a lot of clinical trials both in some of my capacities here but also when reviewing grants and so on for the National Cancer Institute, and I think that a lot of clinical scientists and pharma companies often see a target looks appealing, they have a drug and want me to use this drug to turn off the switch, and there is very little consideration in my experience in terms of really looking at the biochemistry, looking at what concentrations are going to be really useful and whether this is even a feasible concept, even though you have got a target and you have got a drug, it does not mean that A plus B is going to give you the outcome, especially in a complex system like a human being.

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Lemmon Absolutely. And I have learned enormous amounts from looking at how this has moved forward recently. There is a particular example of inhibitors for BRAF in melanoma, which has I think taught us all huge lessons. And the idea there is that in melanoma, which was an untreatable disease not so long ago, there are now particular mutations, in this case it is a different amino acid from the tyrosines, but there is a particular mutation that is found in I think about 50% of melanomas, and inhibitors of a BRAF were developed, and they have substantial value really where I can transform people's lives, again resistance is an issue down the road, but what was very interesting with these was that when they were applied to patients, patients in one particular setting would have these inhibitors which are supposedly shutting off the system, it would actually activate the system instead in the context of having an activated RAS or something else to. The so-called RAF paradox, by inhibiting this pathway, you can actually elevate growth signaling effectively. And that is complex and really makes you think, and it is clear that the only way to understand that is from the point of view of the networks, and what that has done, and I would like to give a plug for this actually in some senses, is enhanced this approach of so-called reverse translational research where understanding what happens with the drug in the clinic, then informs the basic science, so we did not really understand how RAF does its signaling in the cell before this, but trying to understand this weird, important and problematic phenomenon in the clinic has really taught us a huge amount about how that particular signaling aspect works and ends up of course like everything being way more complicated than we expected, but the upshot of that is that now with the enhanced understanding, we can be much more sophisticated about the drugs that we apply in that system, so the reverse translational research back to the lab is now coming forward to the clinic, and so I think this interplay between the basic mechanistic biochemistry, the basic science and the clinical aspect is important and that works both ways. I think clinicians really do well to talk a lot to the basic scientists, but I think it is incredibly important that the basic scientists actually think about what is going on in the clinic and engage in the clinical questions and problems.

Dr. Mark Lemmon is the David A. Sackler Professor of Pharmacology and Co-Director of the Cancer Biology Institute at 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. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on WNPR, Connecticut's public media source for news and ideas.