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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. Jesse Rinehart for a conversation about cancer research. Dr. Rinehart is an Associate Professor of Cellular and Molecular Physiology at Yale School of Medicine, and Dr. Gore is director of hematologic malignancies at Smilow Cancer Hospital.

Gore As I host this series from time to time, I'm really struck in a way that a lot of our guests are from the Yale School of Medicine and I have to say that the departmental nomenclature has more words per sentence, per title, than any place I have ever been. Professor of cellular, molecular, physiology, any meaning there, are you a physiologist?

Rinehart I am a physiologist, and what you are witnessing is sort of the evolution of departmental nomenclatures. At the very core, we are a department of physiology and that is very much strongly rooted in the principles of medicine, but as the field and its science has progressed, you are aware that we have a much more molecular understanding of the word and the cells and the processes, so what you can notice across the nation and even the world is that these names, like the cellular and molecular infiltrating the disciplines, it is no longer microbiology, it is molecular microbiology, for example.

Gore When I was a medical student quite a number of years ago, physiology was about how the lungs were and forces in the heart and how muscles are put to work and bones, I mean we learned a little bit about cellular physiology and how the endocrine system worked and the kidneys work I guess, but it was really mostly about organ function.

Rinehart Yes and we still teach that today. We teach those basic principles, they are extremely important because the body functions exactly the same way as it did then as it does now, the difference is that we now understand the genetic basis of so many diseases and so the challenge for us as scientists, as educators in medicine, is that we take that knowledge of the genetic cause, but then we have to translate those principles right back to the top of the systems food chain, if you will. We are going to talk about systems biology and you just introduced the perfect example.

Gore Oh good. I was going to say that I guess you still need to know how the lungs work if you are going to treat asthma past beyond knowing how the smooth muscle cell in asthma is dysfunctioning, or not functioning, you need to know how the lungs work or you can lose the patient.

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Rinehart Absolutely and treatment is still very much a practice to make your patient healthy, and we still have a long way to go, what we call translate. Translate things that we understand in a basic science level so that it makes it all the way to the treatment. There is a still big challenge, even in education and in the practice of medicine, putting it altogether like that.

Gore I imagine that educating this new generation of physicians, physician scientists, basic scientists in the medical or biological human biology fields has got to be especially more challenging even than it has been, but maybe that has always been the case.

Rinehart Challenging, but extremely fun and they are very, very knowledgeable and their quest for those intricacies is really impressive, so they keep us on our toes.

Gore Put on your teacher's hat then, and I think first of all our listeners should know what physiology is, and maybe you could give us a brief thumbnail on what physiology encompasses and tell us about systems biology, which I am sure most of us don't really understand.

Rinehart Sometimes I think about physiology and explain it as the basic principles of medicine. In human medicine, it is the science behind how everything works. Physiology, as you put it earlier, is a description of different organ systems and how they work together, but the goal is to maintain the health of the organism and to maintain homeostasis, we use that term sometimes, and so as a physiologist, we try to understand those principles and I made a connection earlier back to systems biology, and many people and probably most of your listeners are aware that we have different systems, organ systems, brain, the heart, the lungs, the kidney, they have to work together, so it is really this property of working together and communication that brings systems together and that is my introduction to what is systems biology. It is understanding how many different parts work together for a common goal. Now, biology does not have goals, but biology has needs and drives and evolved properties. We need to breathe, we need to regulate our blood pressure, we need to be able to get up and walk out of the room. These things are controlled by organ systems. Any cell in your body has to do basic things. They have their own physiology and those properties come from a collection of molecules, genes, proteins and those define the system. I have just described 2 very broad levels of systems biology, putting things together, understanding how they work and those fundamental principles behind it are a major challenge.

Gore You are giving me a kind of visual, like you might see in a movie where it starts out at a very high level, then it zooms down, down, down into the eyeball and in the eyeball, now you see the retina and then you are the picture or whatever the person is seeing and then you zoom, zoom, zoom and then you see the cell and you are now in the big cell and then you

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zoom, zoom, zoom, and now you are in the nucleus and you painted this kind of very mind blowing 1960's psychedelic that may say more about me than what you said.

Rinehart That description is something that is really important for your listeners to understand about the basic science that we tried to achieve. I could produce an eyeball and I think most people would be able to say that is an eyeball, but one of the challenges is that when you go deeper and deeper into that eyeball as you just described elegantly, you start to not recognize it as an eyeball. And here is the big challenge, how can we take the information from a genome, so that is what every cell has, it is all your genes put together, DNA, how can we understand how that makes an eyeball work? When if you're studying just the DNA, you cannot even tell it is an eyeball, that is a major challenge, so systems biology on that level, on a molecular level is very, very challenging because we are looking at common parts that you cannot tell the difference fundamentally between the parts and an eyeball or a lung or a heart or a different cell, but you have to figure out how they all work together and collaborate to bring about those properties in a healthy state. So that is one of the modes of a healthy state. I am sure we will talk about the disease state later, but you can imagine the challenges are exactly the same.

Gore You are in a group that studies systems biology, or calls itself a system biology group cell. And what are the components, what kinds of scientists or does everyone take a system? I am taking the eyeball, you are taking the knee bone, I am taking the nuclear, I am taking the expression of genes, you are taking regulation. What is the systems space around you?

Rinehart We don't actually work like that, it is a very cool idea that maybe one day we all get together and we start our labs at the same time and we sort of divide up the field. We are quite honest and what I can tell you about the composition of our systems biology center is that we have a very diverse set of expertise and experts, each of us comes in with our own set of talents, our own initiatives and drives and quests in systems biology and it is all of those differences together that really allows us to weave this fabric of collaboration and we are not a group of copies and I think you are going to find that property across most departments in most universities. We build educational institutions by diverse minds and theories and thoughts in people, but what a department does and what systems biology does, is it brings people together under a common theme, so while what we do looks very different on paper, we are all looking for common answers to complex questions in systems biology and so in our center, we have engineers in the traditional sense, we have molecular engineers, the genome engineers, we have cellular biologists, physiologists like myself, we have evolutionary biologists. It turns out that you can understand the properties of complex systems by also understanding their origins, it is the essence of evolution. You can imagine all of these different fields that I just described

coming together and then we have a discussion, we say okay, where can we focus ourselves, where can we come together

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with all of our talents and really have a common problem and that was one of the fundamental driving forces to put together our center on cancer systems biology. We realized that many of us had merging products in the area of cancer research, but we also realized that working together as a group, a system, a network, we would actually be more powerful and be more productive and more innovative and so that is really how it all came together from the whole center to the center grant itself.

Gore I was looking at your curriculum vitae and publications and it seems like you have a long history in what looks to me like microbiology, which I understand that cells are cells, but microbes depending on what kind of microbes are even in the same general family of cells as most animal cells. What was your path or what is your path as you are switching from a bug guy to a human cell or animal cell and cancer guy?

Rinehart I do read on paper as a bug guy.

Gore There is nothing wrong with it.

Rinehart Absolutely not and I probably would never change, but why even call myself a bug guy, why have I done all this, because it turns out that the bugs, the bacteria are very simple, but very powerful living test tubes, so a major focus of my research career and what really inspires me is to think of ways, invent technologies or new methods or combinations of methods, to make those bacterial cells act and model the properties of human cells. I'm using them as a tool and I choose them because they are far simpler, as you just pointed out, they are different, so the differences are important because I can model a network. For example, let's take 2 human proteins that talk to each other, that is a network, like a social network, right, I can model those or place those into a bacterial cell, but then I can study just the interaction of those 2 things without the influence of the rest of the mammalian cell or the cell that they came from. So that is sort of reductionist isolation and is really important for hypothesis building and hypothesis testing. That is a fundamental reason why I am in bugs, but let me make this perfectly clear, my motivation is really to understand human health.

Gore Got it. We are going to pick up the interaction between your proteins and your bugs and human health and cancer after our break, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about systems biology with Dr. Jesse Rinehart.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore and I am joined tonight by my guest, Dr. Jesse Rinehart. We have been discussing systems biology. Jesse, before the break, you were starting with another kind of potentially mind blowing thing for me, taking human proteins that interact and it is too complicated to study them in human cells, you put them in a much simpler bacterium and watch them interact and you love that, that allusion to social network, so that you could put in, like they could have another friend protein right, and now you got a 3-way network, you know what I am getting at?

Rinehart Absolutely and I like that analogy because if you take 3 friends and you put them in a large room you will probably find each other and you will talk and so that is an important principle inside cells that we know that proteins, or friends, they find each other and they talk to each other and they form a network and we call that network and we describe it as interactions even in biology and these interactions are also a good term for how people talk to each other in a crowded room, so taking that analogy one step further, what I was trying to paint a picture of for your listeners is the fact that we can take those friends that we know, collaborate inside a mammalian cell and get them to work and act inside a bacterial cell. It is our way of controlling the room, having a lot of defined factors that we can manipulate. It is engineering too in a way, you are allowing us a lot of freedom to manipulate things and make observations, so it is really an exciting field.

Gore I guess it is not so different from social science experiments where they get 10 college students or graduate students, put them in an artificial setting, but in a room and then they test how that evolves because they could not really do it in real life when everyone is going off in every direction or something like that.

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Rinehart Yeah, that is true and part of the challenge is finding the right people in our analogy or proteins in the real world, and that brings us to the aims of using this technology in cancer. We choose proteins that we know interact in a negative fashion and we call it negative because it is driving the properties of the cancer cells, so we want to understand that more intimately and we bring that connection or those proteins together into the bacterial cell with the aim of modeling a network as it might exist in a cancer cell.

Gore It is my understanding that most proteins that are involved in driving cancer are proteins that come from normal proteins that are sometimes not acting normally. They are all human genes, these are genes that were invaded, or am I mistaken about it?

Rinehart That is correct.

Gore So these proteins all had a positive role at some point or we would have evolved to get rid of them, so how do they become negative or how do you pick a negative protein? Can you give us an example?

Rinehart I will just point out that you asked still, one of the most difficult and challenging questions, in my opinion, in cancer biology, the origins of the disease, because I think what you implied, and I agree with you, is that every cell has what should be a healthy set of genes, of proteins, and they should go along their way and be normal. So, what happens, how do you take what should be a positive network and it is now negative? Very challenging questions. What we know and what we have learned over the years is that those negative properties can form mutations in genes, so a cell has its own genome and if it acquires the right mutation, it now has a cancer genome if you will and we have discovered those, not myself, but the field has identified that, but where we are coming is we are focusing less on what is known about individual mutations, but rather once those mutations are established in the cell, what happens next, what happens to the environment and can we find the whole process of the whole network of problems and go after that in a productive sort of way.

Gore Just to back track on that, when the gene gets mutated, if it is going to turn into a part of a cancer genome, it needs to make a protein, that may be similar to what it was supposed to be, but it has got some different properties than the normal one and that is why it is behaving abnormally?

Rinehart That is correct. The gene is a template to make a protein and so if you have a gene that has one template, it makes one type of protein, but then if you change just a little bit of that template it will make a different protein and as you just pointed out perfectly, it is making something with a slight change that can alter the properties of the protein in general and

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we have learned those lessons on a simple level, it really boils down to chemistry because proteins are complex chemicals. They are assembled in a cell as long chains of defined chemistry and you can have a single change in one piece of that chemistry and it really can set the whole cell on a different track and it could even form a cancer cell.

Gore So you are studying these mutated proteins and the networks or the friends that they form and how they operate, is that right?

Rinehart Yes and we have actually taken on something a little bit more challenging than that. We are studying a property of cancer cells that we don't really understand the genetic basis, meaning that no one has identified a factor or a mutation or a set of mutations that really is responsible directly for the properties. So we are looking at how cancer cells move and then how they move aggressively. Gore Physically move?

Rinehart Physically, yes and we were talking earlier about the physiological processes of breathing and walking, well imagine that in a cell and imagine trying to study that property without knowing how the heck it is happening, cells don't have a leg for example, cells don't have what look like muscles. So to think about how is the cell changing the properties of its movement in a negative way and the negative way in cancer is it becomes invasive, right. It doesn't stay where it is supposed to stay, it moves away. So we are looking at very aggressive cancers and particular cells that move away from the solid tumor and why use the term invasive because that is exactly what they do, they leave the solid tumor and they invade the nearby tissue and so at the fundamental level, they are moving, well how are they doing that? While we have a handful of proteins that can dictate some of that movement and so it is those proteins that we have brought over into our bacterial model to just understand how they work together.

Gore I remember and again, I am very, very out of date here, I remember cell biology having proteins that were similar to some of our muscle proteins that helped move, give cells structure and move them. Am I so out of date or that is what you are talking about?

Rinehart No, I was over generalizing, so absolutely you are correct. There are fibers inside cells that you could really equate to a muscle fiber. What I was trying to point out in a very simple way is that the structures inside of the cell are not as recognizable as a human leg or something and I was just trying to paint a picture for the listeners of how do you understand how a cell moves when we don't really understand what a cell leg looks like, for example, we have to really think creatively, we have to be very inquisitive to try to figure

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out the basic principles of that movement and then understand how has that been deranged inside of a cancerous cell, right?

Gore So is it these fibers moving structures that you are studying or proteins that regulate the movement or the contraction?

Rinehart It is the second part, it is the regulation. One of the principles that we are interested in is this idea of regulation that there is a natural state of regulation that is good, where you have a little bit of movement, not too much, not too little, but if that regulation goes away, then you can force too much movement and so we imagine that these cancer cells have somehow reprogrammed that system to regulate more aggressive movement and since we believe that we are studying some of the fundamental proteins that drive that process, we can better understand the regulation.

Gore So as you said, it is all about regulation, but then it is how much is too much and that is the major challenge and do the proteins that you study confirm a particular kind of cancer?

Rinehart Yes, we are actually studying proteins that, as I drew a picture for us earlier about when you dig down deep into a cell, it is difficult to tell the difference, so we are actually using proteins that can be commonly found at other places, but we actually know that there are more of them in cancer cells and they have been uniquely repurposed in particular cells, so one area that we are looking at very intensely is brain cancer and glioblastoma in particular, there we are looking at sets of proteins that really seem to be specialized in those aggressive cancers and that specialization is different from maybe what they might look like or what they might do in another cell.

Gore Let's fantasize forward, so you figure out, let's say important features that regulate the movement and you maybe go back and validate that is operative in these brain cancer cells?

Rinehart Absolutely.

Gore And then what? What do you do with that information, it sure sounds interesting and worthwhile knowing, but does this help people with brain cancer?

Rinehart The information itself does not directly help a person with brain cancer, but what our aim is and it is something that I'm very passionate about, is when we have tested all hypothesis and we can present a new set of information, let's say the publication, that that information contains enough good leads that it can translate into the clinic. That means that we have identified a set of proteins and their properties and we really understand how they work in cancer, that is the beginnings of forming a hypothesis about how maybe to design a

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drug or a therapy to reverse that process. I really believe that what we do is provide these packets of knowledge that allow someone else to take that next step and if it is really good and we are really careful about it and we find important information, that packet of knowledge can go far and wide, it can be

disseminated to many, many laboratories or maybe even into the private sector where let's say a drug company might think, let's focus on this information, let's develop a drug that will someday impact a patient.

Gore Now I'm visualizing your system center as being part of this much bigger system that includes other cancer centers.

Rinehart For sure, you have just described how a field, let's say cancer biology in general, how that progresses. We have individual labs, investigators, publish papers, those papers are made publicly available for anyone to read, obviously experts in the field read them, but maybe someone else reads them too and I think that is how science works fundamentally, that is how we move forward.

Dr. Jesse Rinehart is an Associate Professor of Cellular and Molecular Physiology at Yale School of Medicine. If you have questions, the address is cancer-answers@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. You are on WNPR, Connecticut's public media source for news and ideas.