Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.

Welcome to Yale Cancer answers with your host doctor in East JGP are Yale Cancer answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer this week.

It’s a conversation about the molecular mechanisms of cancer with Doctor Daryl Klein.

Doctor Klein is an assistant professor of pharmacology at the Yale School of Medicine, where Doctor Chad Power as a
professor of surgical oncology.

So Darrell maybe we can start off by you telling us a little bit more about yourself and what it is exactly that you do.

Yeah, I mean I think. My path to become a medical researcher involves my personal backstory and my love of competition. In some ways, I feel like I've been destined to study kinases and cancer and their mechanisms and and with the hope of developing useful cancer therapeutics. And my career trajectory if you will.

As a medical scientist, I began long before my formal training.
I grew up in New Jersey just outside of Philadelphia, and at a young age, my sister was diagnosed with MLE or chronic myeloid leukemia. Kimberly, my sister, was diagnosed with a blood cancer that’s rare in children at that time. Over 40 years ago now, Peter Noel at the University of Pennsylvania in Philadelphia was studying the driving mutations that lead to CML. And he discovered a chromosome alteration that he dubbed the Philadelphia chromosome and kmle patients, like my sister and the results.
of that change.

Is that a new protein is made a fusion of a tyrosine kinase signaling protein?

That’s that’s stuck in the on position, and that instructs cells to.

To divide and grow and thus cancer.

And that protein became a target for drug discovery and it really heralded the era of precision medicine that specifically targeting a single. You know bad protein with a drug and that was really exciting.

And in 2001 there was this huge success with. The mat neighbor or Gleevec, and that became the first drug that was developed to target a
specific kinase to treat a disease, and in this case, someone. And patients treated with this drug can live long lives with controlled disease. Unfortunately for you know, Kimberly, it was just the beginning of understanding this disease. And there were no therapeutics, and that meant you know, little could be done, and. In this powerlessness drives me to find ways to spare other families similar devastation and to better understand cancer.
I really have spent a large part of my career investigating the molecular basis for oncogenic signaling. And you know on that path I attended the University of Pennsylvania for my undergrad in my PhD, and my medical degree, and I did clinical rotations at the Children’s Hospital of Philadelphia Chop. So I was walking the same halls as Peter, Noel and my parents and my sister years before. I joined the MSTP or medical Scientist training program and. This was funded by the NIH,
the National Institutes of Health, to grant to train a group of physicians, also to be researchers, and the goal of that program is basically to link basic science findings to the clinic. The bench to the bedside and to lab progress into useful therapeutics as rapidly as possible. And I think the success of Leave Act was just the beginning of targeting kinases. These these tires and kinases other kinases and cancer. And so when I was at Penn, I studied under Professor Mark Lemon.
He was working on those other kinases that lead to different cancers. And you know, to see how they might cause cancer and how we might leverage understanding their mechanisms to develop new therapeutics. I also mentioned you know my my desire for you know competition. And when I first joined Mark's
lab at Penn and was first introduced to lab research, I realized there that. Scientific researches is intensely competitive and I think it makes Olympic sport seem safe by comparison and I love that and I loved everything about that. And then the problem is in sensually in science. You’re competing with unknown competitors and and an unknown number of teams and the rules of the game are undefined and you don’t even know when the conversation started. So,
and certainly your competitors have
more money and resources than you do,
so you’re always the underdog and and
that excites me and I like that.
You know an example.
When we started the project will chat
more about in a little bit.
We were certain that you know
half a dozen other groups in the world
were already working on it and and we
didn’t know how far along they were.
And so all you know is what you don’t know.
And if you want to win,
you have to work nonstop like 24/7.
I once spent 50 hours straight in the lab
when I was a grad student without sleeping.
And then you know that was exciting to me. That’s something you can’t do in sport after the game you go home, but science is a years long competition with no timeouts and the intensity is off the charts so. I think that that frames kind of. Why I became a medical researcher and why? Why I love doing the work that I do. So let’s take a step back for a bit. I mean, that sounds really inspiring and and interesting in terms of how this kind of came full circle. How you? Had this experience.
with your sister and then went on to become a scientist that’s hopefully making a difference in the lives of other patients like her. But for our audience, I should also mention that while I trained as an MDP MD PhD physician scientist, I’ve actually chosen a path devoted entirely to research. So during training, when I find myself engaging with patients...
and talking to them about the unfortunately limited treatment options. I found that difficult and frustrating and all I wanted to do was rush back to the lab and find new potential therapeutic avenues. So I made a choice to devote myself entirely to lab work, but at the same time I’m still working with other physicians, scientists and clinicians to help bridge our discoveries. Kinases are often drivers of cancers and the one that I’ve
been working on recently ALK and
a plastic lymphoma kinases is a
well known cancer related protein.
And much like the protein involved
in my sisters of Mle,
it’s a tyrosine kinase and
basically tyrosine kinases instruct
the cells to grow and divide,
and if this is unregulated
that leads to cancer.
So ALK well, unlike the Siml case, ALK is.
Is A is a receptor tyrosine kinase.
So what that means is ALK is
located in a different part of
the cell than the CML kinase.
So if it if a cell were an ocean,
the CML kinase would be a submarine and ALK would be more like an aircraft carrier at the surface and so this. Localization difference has therapeutic implications. As you might imagine, you can’t target a submarine the same way you would target in an aircraft carrier. So in the clinic we use small molecule. You know missile like drugs that can dive deep into the ocean to reach that kinase whereas for ALK we have an opportunity to use antibodies that can target it at the cell surface, so more like a.
You know a B52 bomber. It's been known for years that ALK is a driver of neuroblastoma. Now neuroblastoma is a cancer of the peripheral nervous system. It's one of the more common pediatric cancers that accounts for more than 10% of childhood cancer mortality. But clinically useful therapeutics have been slow to develop, and I think one of the key reasons for this slow development of treatments is likely the lack of a structural framework for the target alcc. Simply put, we have no idea what it
looked like or how it functioned.

It was a complete mystery before our work.

I mean the fact that ALK is expressed on neuroblastoma cells but is not present.

On healthy tissue makes Alk a veritable oncogenic beacon.

That's a perfect target for precision medicine.

In each case the protein. Specifically, if you're targeting the protein specifically, it should have little side effects outside of the cancer itself.
And the hope is that if we can target this kinase alken neuroblastoma. That we might have the same positive outcomes for neuroblastoma that we see for patients with KMEL. So you know one of the things that always fascinates me is how you find these things to begin with. I mean, how do we know that these kinases play a role in cancer? How does that? How do you figure that out? How do you know which kinases are submarines and which kinases are our aircraft carriers, I mean. And how did you figure out that these were important anyways?
How does that happen?
That’s a good question.
That’s certainly outside of my lab’s expertise.
A lot of that is done through genomic work and associating certain genes with certain disease phenotypes, and so where my lab’s expertise comes in pretty much after the fact.
Once these associations are known.
That’s where we come in to help define bio physically and structurally, exactly how these kinases and uncle genes are acting, and hopefully if we have a molecular
picture of that how we might design and develop therapeutics to. To stall that and prevent disease. So when you say that it kind of all starts with understanding what genes are expressed in what genes aren’t. I mean it, it sounds like the progress we make in terms of cancer medicine is really investigators. Building on other investigators’ work. So somebody you know maybe was sequencing some genes and found that some genes were overexpressed in some cancers versus not. And then other people kind of discovered that gene was associated with a protein like.
A kinase and then you look at that kinase and say well where is it and how can we target it? Is that kind of how that works? That's exactly right, right? I mean, it's work of a tremendous number of individuals with differing expertise. Certainly the approach my lab takes is just one cog in that machine, one that's a bit further down, and probably less than the discovery stage. But one that is keenly important to understand the mechanism of how molecules work,
which can then give us insight into how we might target these and develop therapeutics. Around their function.

And then the other question that I often have is. OK, so you know you discover this kinase and you discover that it’s important in cancer. Why is it that some kinases are important in some cancers but not in others? Why? Why do you have these genes for these kinases to begin with? And why are they differentially expressed?

Cancer often recapitulates the paradigms that are important and during development.
So all of these kinases are crucially important in the stages of development and help patterning and complex tissues. After that, they aren’t used so much in adulthood, and it’s only during cancer that a lot of these developmental pathways are reawakened, and they can be reawakened in different tissues and different places, but they all lead to the same thing. Basically once you turn on a kinase on your turning on the growth instructions and
when that's not counterbalanced,

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that's how cancer develops.

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Well, we’re going to take a

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short break for a medical minute,

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but when we come back,

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let’s learn more about the molecular

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mechanisms of cancer and how exactly

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we target these differentially

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expressed kinases to actually

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make a difference for patients,

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please stay tuned for more with

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my guest doctor Daryl Klein

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funding for Yale Cancer Answers comes

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from Smilow Cancer Hospital with an

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event focused on nutrition for cancer

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survivorship presented by the Smilow
Cancer Care Center in Trumbull.

April 14th Register at Yale Cancer Center.

Org or email cancer answers at Yale.

The American Cancer Society estimates that nearly 150,000 people in the US will be diagnosed with colorectal cancer this year alone.

When detected, early colorectal cancer is easily treated and highly curable, and men and women over the age of 45 should have regular colonoscopies to screen for the disease.

Patients with colorectal cancer have more hope than ever before, thanks to increased access to advanced
therapies and specialized care.

Clinical trials are currently underway at federally designated Comprehensive Cancer Centers. Such as Yale Cancer Center and its Milo Cancer Hospital to test innovative new treatments for colorectal cancer tumor. Gene analysis has helped improve management of colorectal cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents, resulting in more patient specific treatment. More information is available at yalecancercenter.org you’re listening to Connecticut Public Radio.
Welcome back to Yale Cancer answers. This is doctor in East Egg part and I'm joined tonight by my guest doctor, Daryl Klein. We're learning more about the molecular mechanisms of cancer and right before the break Daryl was telling us about this profoundly inspiring story of his sister who is diagnosed with CML, which really started his journey on becoming a physician scientist, and one who is particularly interested in these molecules called kinases, which really work. To activate the growth of cancer
cells and so you know Darrell before the break you were mentioning that eurolab really after we know that you know a kinase is involved in a particular cancer is really involved in looking at its structure and kind of how to target it. Is that right? Exactly, my lab is a structural biology lab, so you know, we’re sensually photographers. But we take pictures of very tiny things, molecules and proteins, and so this. Requires specialized equipment cameras if you will. That use X rays and electrons rather
than light in the visual spectrum that we’re used to.

Many people know DNA, so let’s start there.

People have heard of DNA and Watson and Crick and they’re double Helix.

And DNA is basically a cookbook with 10s of thousands of recipes, mostly protein recipes,

ALK is one of these recipes.

And the recipe in the DNA cookbook tells us the ingredients and the order to make alcc.

But one big problem with this DNA cookbook.

Is it not illustrated,
So we have no idea what the final product will look like. So you know my lab follows the recipe to take pictures of the final products to. To illustrate this, this DNA cookbook. So we take molecular photographs of the protein and also the mutants that are found in cancer. And in these pictures give us a better understanding of how things supposed to look like and how it changes in cancer. And in this can inform us about approaches to. Designing targeted therapeutics. So my lab just reported the structure of the protein ALK in nature.
That’s the tyrosine kinase that’s important in neuroblastoma.

And this gave us a first look at this unique uncle Gene and it’s, you know it’s going to be impossible for me to relay the complexities here. But if we stick to our Analogy of the the cell is an ocean, it’s. It’s not unreasonable to say that Alcc did actually look a bit like an aircraft carrier. I mean it had this. Unusual a long gated structure and it probably lies parallel to the to the surface, so it’s like an aircraft carrier floating on the water.
Or the surface of a cell.
And and furthermore,
we can see how it actually gets activated.
Basically two of these aircraft carriers line up next to one another and in that position they’re then capable to sell to send their their growth signals, which ultimately end up being cancerous growth signals. To the neuroblastoma cell. Uncontrolled ALK activation like this leads to cancer and it and it results from the tumor continuing to express this developmental out gene along with its stimulatory ligand. Our research reveals an approach
to shutting off ALK and that it can be quite straightforward. Potentially if we use our structure as a blueprint, we can see clear areas where we would want to target this. This aircraft like molecule. I mean there’s certain vulnerabilities that are revealed in the structure that we can strategically target and and you know sync this aircraft carrier, and so my lab now is designing potent antibodies. That specifically target these regions in ALK, and you know there’s small
molecules currently out there in use for Neuroblastoma, as well as many other different cancers that are driven or partially dependent on kinases. And compared to small molecule therapeutics antibodies, I think can offer a great benefit. The small molecule drugs that are now currently in use like prison and learn Latin. They target the intracellular. The actual kinase domain of the protein out. And one problem with these types of inhibitors is that you can’t keep fooling the cancer for very long. They the cancer figures out this...
trip quite fast that you’re trying to inhibit it in this domain, and the cancer makes changes that diminish the drugs impact. Whereas I think the antibody approach is a more brute force approach and it’s harder for the cancer to overcome this, the strategy of inhibition. I think the therapeutic future will likely use a combination of these two to completely dismantle the machinery. In some ways you know cancer can be viewed as having some of the
similar challenges that we see for SARS, Co V2 and both use similar strategies to overcome disease.

Both you know cancer and viruses mutate rapidly. And they can evolve to different inhibitor approaches. And just as we use antibodies through vaccination or or directly injecting recombinant antibodies and small molecules to overcome COVID.

Now we have a new blueprint for ALK to help us overcome similar challenges in cancer and in particular neuroblastoma.

And it sounds like when you know the the
structure of these aircraft carriers. But you can be very specific about targeting those particular molecules as opposed to normal cells. So you might have a bomber that only targets, a mechanism whereby these two aircraft carriers can't line up together that really wouldn't apply in any other situation, and you can try to get more precise or more targeted therapies. Is that right?
That's exactly right, and remember that I said that you know, since alpha is expressed only on neuroblastoma cells but not present on healthy tissue, it really makes targeting ALK the perfect for you know. Set up for precision medicine and then a layer on top of that, which I think you were just referring to is now that we know the detailed structure and blueprints of this. And that’s exactly what we’re trying to do. We’re trying to design antibodies that specifically block areas on the protein that are.
00:24:07.210 --> 00:24:09.850 involved in important for it’s activation.

00:24:09.850 --> 00:24:12.754 That is precisely where the ligand

00:24:12.754 --> 00:24:17.150 binds to activate the receptor and

00:24:17.150 --> 00:24:19.990 getting back to how it’s activated.

00:24:19.990 --> 00:24:22.762 Where we see the the two molecules

00:24:22.762 --> 00:24:24.998 lining up side-by-side to each other,

00:24:25.000 --> 00:24:27.085 we’re designing antibodies that can

00:24:27.085 --> 00:24:29.624 block that interface to prevent it

00:24:29.624 --> 00:24:31.940 from being activated that is being

00:24:31.940 --> 00:24:33.600 activated independent of ligand.

00:24:33.600 --> 00:24:36.197 Which could be caused by certain mutations,

00:24:36.200 --> 00:24:38.780 which is further research that we’re

00:24:38.780 --> 00:24:41.900 doing now or or with the ligand.

00:24:41.900 --> 00:24:45.278 So we’re using all this information

00:24:45.278 --> 00:24:47.530 to specifically design antibodies

00:24:47.530 --> 00:24:50.000
that are tailored to this molecule
and the type of mutations or mechanisms that activate it specifically in neuroblastoma.
And so as you design these antibodies in these treatments,
you’re doing that in the lab. How? How does it actually get into patients?
How does it affect people like your sister? Because that’s where the story really started and how long
does that whole process take? You’re right, that’s a that’s certainly a long process and you know
Cancer Research is so matured and so specialized now that it really requires
you know effort to put these discoveries into usable formats and for others to build upon and meaningful ways. And just as the NIH created that MSTP program to link basic science and patient care now I think we need similar links between basic science researchers. I mean, the you know RNA biologist and chromosome researcher and. And in the biophysicist like me trying to link up with the model Organism biologist to test the a lot of these and preclinical setups. We all speak a different scientific dialect and we have different perspectives,
so you know how do we work together
and in one answer to that is is,
you know being part of the Yale Cancer Biology Institute that I’m a part of.
You know we really bring together desperate researchers among those interested in cancer.
And so you know now I have and and
being a physician scientist so you know
now there’s a cohort of people and
colleagues that I can work with that
can bring our developing antibodies that we have into preclinical testing quite rapidly to see if they do.
So good activity in vivo and then that hopefully can be rapidly leveraged
into reaching the patients that desperately need these treatments.

Sounds very much like you had mentioned earlier, but this is kind of a microcosm for the macrocosm of how science works, that your lab puts together. People who all kind of come at the problem of ALK from a slightly different vantage point. The work in your lab kind of builds on the work of other people’s labs, and so maybe in the last few minutes that we have, you could tell us kind of a little bit about.
How that works in the grand scheme of things?

I mean, it sounds like.

One of the things that we’ve realized with the pandemic is that the world is shrinking, and hopefully the scientific discovery bounces around fairly easily.

How does that collaboration work?

I think it is. It is certainly a challenge and I think you know getting researchers to talk to each other and work together is an important part of that. And like you said, I think you know during the pandemic and having people communicate in different ways like we are now through zoom and other things.
Maybe the world is shrinking a bit and I think that’s a good thing for science and that’s a good thing for research because. Of course, all of us working independently and making advances. We don’t want them to go unnoticed by the people next in that chain that you were talking about. That’s necessary to make the leap to bring these discoveries to their therapeutic potential.

Doctor Daryl Klein is an assistant professor of pharmacology at the Yale School of Medicine. If you have questions,
the address is canceranswers@yale.edu
and past editions of the program are available in audio and written.
F arm at yalecancercenter.org.
We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public radio funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.