Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. 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 genomic causes of cancer progression and therapeutic vulnerabilities with Doctor Jason Sheltzer. Dr Sheltzer is an assistant professor of surgery and oncology at the Yale School of Medicine where Doctor Chagpar is a professor of surgical oncology.

Sure, so despite my departmental affiliation I am neither a surgeon nor an oncologist. I am a basic science researcher. I have a PhD in molecular biology and my lab studies the genetic basis of cancer development and cancer therapeutic responses from a basic or a non clinical perspective. That sounds pretty interesting, but it also sounds pretty broad.
We talk a lot on this show about the genomic and genetic underpinnings of cancer, so tell us a little bit more about your research, sure, so overall, I think that it is a really remarkable time in cancer biology. There are a ton of exciting advances happening at Yale and at institutions around the world, and there are just rapid advances in so many areas that are really directly contributing to patient care. In my own lab, we were interested in using different genetic techniques to model certain alterations in chromosomes that you commonly see in cancer. So in cancer cells most normal cells in your body have 46 chromosomes, 23 pairs of chromosomes, but for some reason cancer cells almost all have the wrong number of chromosomes. Cancer cells have 47 chromosomes or 48 chromosomes, or 140 chromosomes, and no one really understands how that happens or why? Why that contributes to tumor growth and my lab tries to generate techniques to model these chromosome changes so we can understand how they contribute to cancer.
OK, so I guess there’s a few questions to unpack there. The first is why do cancer cells have a different number of chromosomes and what impact does that have on cancer development, right? So there are two schools of thought there, so on one hand, some people think that this is just like an accident of cancer. Cancer cells do a lot of things wrong. They’re very genomically unstable. They have all sorts of errors that occur during the cell cycle, and so some scientists think that the aneuploidy, which is another word for the chromosome copy number alterations that we see in cancer, is just kind of a byproduct of things going wrong in cancer, and that it doesn’t really have a functional importance. On the other hand, other scientists believe that these chromosome copy number alterations are directly influencing the development and the progression of cancer and the idea there is that these chromosome copy number changes are influencing the number of copies of a gene you have in a cell instead of having two copies of a gene like you would
in most normal cells in your body, you may have three copies. Or four copies or 25 copies of a gene. And if that gene has tumor promoting properties, then having 25 copies of that gene might directly contribute to cancer. So a few questions. The first question is there are some congenital anomalies, some congenital conditions. So I’m thinking about things like Klinefelter syndrome or Down syndrome where people may have an altered number of copies of certain chromosomes. Does that mean that those people by definition are at increased risk of developing cancer, yeah? It’s a really interesting and important question. Down syndrome is a developmental disability caused by having three copies of chromosome 21. It’s the most common genetic cause of developmental disability in EU. Individuals with Down syndrome have a significantly greater risk of developing leukemia and other blood cancers during their lifetime. At the same time, for reasons that
I think are very poorly understood, individuals with Down syndrome actually have a significantly decreased risk of developing most solid cancers. Individuals with Down syndrome have lower rates of colon cancer, breast cancer, brain cancer, Melanoma, and I think that discrepancy is very poorly understood, and so how do you square that with the concept of the thought? At least the one school of thought of some scientists. As you point out that having a discrepant number of copies of a chromosome. So if you’ve got more copies than you’re producing more gene products, more proteins. Cancer cells are more likely to go awry that predisposes to cancer, whereas these people have a lower risk of cancer. How do you square those two phenomena? Yeah, that’s a terrific question. So in your cells, not all chromosomes are equivalent. Not all genes are equivalent. There are some genes. That when you have them present in extra copies,
they may promote cancer and there are other genes that when you have them in extra copies, they may actually suppress cancer. They prevent the development of cancer and there's a further layer of complication in that different tissues in your body are different as well, and so a gene that has a certain function in blood cells. It may have a different function, or it may have no function whatsoever in mammary gland cells. Or in neurons, and so the current commonly accepted explanation for the Down syndrome cancer phenomenon is that there are genes on chromosome 21 which promote the development of cancer in blood cells which promote the development of leukemias, which are what are commonly observed in individuals with Down syndrome. But these genes or other genes on chromosome 21. May actually suppress the development of cancer in other tissues, and it’s a really strange phenomenon, and the relationship between the copy number of these genes and the
copy number of genes in general and the development of cancer. I think there's a lot more to explore there that science doesn't yet know. And I guess the other question is if I understood you correctly earlier, you were saying that this copy number phenomenon is quite common in cancer, is that right? Yep, about 90 to 95% of cancers have the wrong number of chromosomes in them. So my next question has to do with this. Is it that there's the wrong number of copies of a particular chromosome in the cancer cell? Or is this a germline phenomenon, so we know that for example in Down syndrome it’s a germline phenomenon. You have an extra copy of chromosome 21 in all of the cells in your body, whereas it seems to me that you know most cancers are also going to acquire extra copies as they move along their cancer Genesis pathway. Yes, so it is it more that cancer cells? Acquire extra copies as they move along their cancer Genesis pathway. So I think that we can say that most of the chromosome alterations...
that occur in cancer are cymatic or they occur during the body over a lifetime and are not germ line. That is, you aren’t born with them, but they instead accumulate over time more broadly. A lot of research has been done indicating how different mutations or single base pair changes can occur over a person’s lifetime and contribute to their cancer risk overtime. In addition to these point mutations which contribute to cancer development and occur overtime, there’s increasing evidence that overtime your cells will accumulate more aneuploidy or chromosome copy number errors. As well, so if you look in cells that are isolated from say an 80 year old person and compare them to normal cells that are isolated from say 20 year old person in general the 80 year old will have significantly more aneuploidy or chromosomal errors in their tissue than the 20 year old, and this may be one of the unexplored causes of why cancer incidence increases with age. Because of these somatic chromosomal
alterations that are developed overtime and so is it. The concept that if you could somehow reverse that process or stop that process such that people did not acquire aneuploidy as they grew older, that you could actually potentially stop certain cancers. Absolutely, that would be an incredibly exciting cancer prevention strategy. If it was true, there is and we just don’t yet know again to contrast the research on aneuploidy or chromosomal changes with the research on mutations and DNA base pair changes. A lot of research has been done trying to develop strategies to delay the development of point mutations over age. People have talked about antioxidants and vitamin C as some potential strategies. I don’t think there’s good evidence for their strategies, but those are some of the strategies that have been described for the prevention of point mutations for the prevention of chromosome errors. Almost nothing is known, and this is absolutely something that my lab plans to study at Yale to see if we can prevent the development of aneuploidy overtime,
and if that would subsequently slow or delay the development of cancer. So tell us more about about that. How do you plan on doing those experiments, and what might we have to look forward to in the future? Yeah, there is a lot that we are planning to do. In general, I think that there are certain proteins that are known to control the process of chromosome segregation. These were proteins that were first discovered in simple single celled organisms. Like budding yeast Saccharomyces service, yeah, the basic process of chromosome segregation was worked out in in these simple organisms and then later research demonstrated that these same genes function in simple single celled eukaryotic organisms also function in human cells and in cancer cells. And so one of our ideas is to take some of these genes and then manipulate their expression. That is if you have genes whose role in the cell? Is to protect the fidelity of chromosome segregation, then maybe over expressing some of these genes would further protect the fidelity of chromosome segregation.
and decrease the number of errors that occur during aging. That’s some of the research that we plan to do in my lab, and so when you talk about chromosome segregation just to remember back to you know junior high biology, that’s that’s really when the the cells are replicating and they’re going to divide. That your body kind of the cell puts half the chromosomes in one daughter cell and half the chromosomes and the other daughter cell is that right? Yep, the the magic of the cell cycle is the concept of aneuploidy. When you say that there may be a lack of fidelity that that segregation processes where you know they may put 2047 chromosomes in one cell and and and 45. And the other. Yep, so during the cell cycle you have 46 chromosomes. Normally in most cells in your body during the cell cycle, each chromosome gets replicated and so you wind up with 92 chromosomes instead of 46 for a short period of time, and then those 92 chromosomes need to divide equally such that one daughter cell gets 46 chromosomes and the other daughter cell.
Also gets 46 chromosomes and if you have an error in that process and one daughter cell gets 47 and the other gets 45 instead, that produces aneuploidy, that’s a chromosome segregation error that we think can have pretty profound consequences for cancer development. Well, we’re going to take a short break and learn more about the causes of cancer progression and therapeutic vulnerability right after we take a short break. For a medical minute, please stay tuned to learn more with my guest Doctor Jason Shelter. Funding for Yale Cancer Answers comes from Astra Zeneca dedicated to advancing options and providing hope for people living with cancer. More information at Astra Zeneca Dash us.com. Over 230,000 Americans will be diagnosed with lung cancer this year and in Connecticut alone there will be over 2700 new cases. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer each day. Patients with lung cancer are surviving
thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated Comprehensive cancer centers, such as the battle two trial at Yale Cancer Center and Smilow Cancer Hospital to learn if a drug or combination of drugs based on personal biomarkers can help to control non small cell lung cancer. 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 Tag part and I’m joined tonight by my guest Doctor Jason Shelter. We’re learning about his research into the genomic causes of cancer progression and before the break Jason you were talking a lot about this concept of aneuploidy, the idea that having an incorrect number of chromosomes can predispose to cancer and some of
the work that your lab is planning on doing to kind of address. That and look at whether that is a potential target for cancer prevention. But are there other mechanisms of cancer development outside of aneuploidy, that your lab is also looking at? Yep, so in addition to the chromosome errors that occur in cancer, there are single base pair changes point mutations in the sequence of the chromosomes themselves, which have a fundamental role in driving cancer development and at the same time which also create potential therapeutic vulnerabilities or potential ways for scientists and clinicians to treat cancer so tell us more about that. Maybe give us an example of some of the things that your lab. Is working on in that vein, so there has been an absolute revolution in cancer therapy over the past 10 to 20 years previously. For most of the 20th century, the standard way to treat cancer was slash and burn was to cut it out of your body through surgery and then to burn any cells that remained with the use of radiation which
does kill cancer cells but can have very profound side effects as well.

Or with chemotherapy agents, which again can kill cancer cells, but have some pretty significant side effects as well in the past 20 years, there’s been a revolution in the development of what are called targeted therapies. That is, these are drugs, which instead of just nonspecifically killing kind of all cells that it encounters, targeted therapies are designed to inhibit specific proteins that are expressed by cancer cells.

In order to eliminate cancer cells while leaving normal tissue unharmed or relatively unharmed, my lab uses a genetic tool called crisper and crisper is a new tool for genome engineering that was recently developed just in the past seven or so years, and it allows you to make very precise modifications in the cells that you’re interested in studying.

So using CRISPR you can go into a cancer cell or a normal cell growing in a Petri dish or growing in a mouse. And then you can cut out a gene of interest. Or you can introduce a mutation into a gene of interest and then
study how cutting out that gene or introducing a mutation affects the biology of those cancer cells. We can link this then to the question of targeted therapy because we can delete a gene in cancer cells using crisper. That is, we can knock it out from cancer cells and then we can ask whether these cancer cells live or whether these cancer cells die. So just out of curiosity, when you said that we couldn’t do this before CRISPR in mammalian cells, we could only do it in single celled organisms. Why is that? What is how exactly does CRISPR work to allow you to do this in mammalian cells? What’s the difference in single celled eukaryotes? You can introduce foreign genetic material quite easy and the cells will oftentimes incorporate the foreign genetic material into their own DNA. They randomly will pick up DNA from the environment and incorporate it into their genomes, and that’s in fact unrelated to what I study. But one of the causes of the problem of antibiotic resistance among bacteria. And among eukaryotic parasites
that they have this habit of just picking up random DNA and taking it, scientists have taken advantage of that process in order to genomically modify these single celled eukaryotes to study them in the lab.

In the context of cancer, cancer cells normal cells don’t really do that. Any one of us could take a bath in a pool full of DNA, and we would not start expressing random things from the DNA that we’re swimming in. That just isn’t how mammalian cells work. Crisper is a DNA cutting enzyme, and so while you normally wouldn’t just randomly change or randomly modify DNA. In a eueryote in a mammalian cell. Because CRISPR is a DNA cutting enzyme we can use it in order to cut the DNA in a certain place in a defined manner, which allows scientists to make these modifications and cancer cells that we couldn’t before. When you use crisper say in in a mouse, does it affect all the cells in that mouse or is it a given cell or is it a few cells like how diffuse? Is the effect that you can have on a given gene? Yeah, so it depends on how you use it.
CRISPER is useful both as a research tool and itself as a potential therapeutic modality in the future. So in my lab we use CRISPR as a research tool. We want to make certain modifications in cancer cells in order to respond to see how cancer cells. Respond in addition to that, when you start thinking about using CRISPR in a mouse or in an Organism, there are potential therapeutic uses for CRISPR as well. Say to treat genetic diseases or to treat cancer itself. This is much more preliminary. There is a lot of work to do there, but for instance in some of the clinical trials that have been done and in some of the mouse work that has been done, the liver is the organ in your body. That generally detoxifies foreign matter that you receive, and so if you just inject CRISPR particles into a mouse’s body, or into a human body, they oftentimes go to the liver and they will genetically modify cells in the liver. So so tell us a little bit more about
you know you mentioned that your lab is using CRISPR to kind of figure out targets for potential cancer therapeutics. How do you take that to the next level and figure out what are those targets? How you might design drugs against them, and tell us a little bit more about the potential for this in the future. Yep, so 22,000 genes in the genome. Some of them may make good targets for cancer, and some of them may not make good targets for cancer. The first step in this process is the one that my lab is most active in. We try and use CRISPR to identify the genes and cancer cells that are required for cancer growth. If you can eliminate a gene with CRISPR and it causes cancer cells to die, then that gene might be a promising target for therapeutic development. Unfortunately, when it comes to actually developing a drug against that gene, that is a complicated process that we are still learning a whole lot about. There are some genes in the genome which code for proteins. Proteins are the functional part of the cell. The part that actually does the work. There are some proteins that are
basically like big greasy balls. They just are greasy and they don’t bind to anything and they’re very hard for something to latch onto. And something that’s you know big and greasy like that just doesn’t make a good drug target because there is nothing for a drug to bind onto. What you really want for a drug target is you want a protein that’s the part of the cell that that actually does the work that has say various binding pockets on it or holes in it where you can design a small molecule compound to actually bind in that pocket and then inhibit that proteins function. So there are some genes that are required for cancer growth but that are very very hard to generate drugs against because they’re just greasy and there’s nothing to bind onto. And then there are other proteins and cells that are possible for you to design drugs against and we want to see if we can identify those proteins in particular. And so you know, this kind of brings me back to the question that we were talking about earlier in terms of, you know I I get the whole concept of
0:25:31.926 –> 0:25:34.45 Crisper being used to look at jeans
0:25:34.45 –> 0:25:36.286 That you can specifically target
0:25:36.286 –> 0:25:38.934 To see whether they would be a good
0:25:38.934 –> 0:25:40.92 Target or a not so good target.
0:25:40.92 –> 0:25:42.97 But ultimately when you’re looking
0:25:42.97 –> 0:25:44.2 At developing drugs,
0:25:44.2 –> 0:25:46.8 It sounds like you’re developing
0:25:46.8 –> 0:25:48.36 Drugs against proteins.
0:25:48.36 –> 0:25:50.576 Which brings me back to if you know
0:25:50.576 –> 0:25:53.719 That a particular gene is involved in cancer,
0:25:53.72 –> 0:25:58.176 Genesis, uh, why not target the gene so,
0:25:58.18 –> 0:26:01.18 Especially if crisper is very
0:26:01.18 –> 0:26:04.18 Specific for a particular gene,
0:26:04.18 –> 0:26:05.758 Do you think that that I,
0:26:05.76 –> 0:26:07.524 I realize you said that earlier
0:26:07.524 –> 0:26:09.141 That this is very preliminary,
0:26:09.141 –> 0:26:13.11 But do you think that there will be a
0:26:13.207 –> 0:26:16.294 Role for that kind of gene editing?
0:26:16.3 –> 0:26:18.4 And can you really do that in?
0:26:18.4 –> 0:26:20.67 A fully mature adult organism?
0:26:21.44 –> 0:26:24.804 Yeah, that’s a great question and I
0:26:24.804 –> 0:26:26.928 Think that you’re just thinking about
0:26:26.928 –> 0:26:29.518 25 years in the future right now.
0:26:29.52 –> 0:26:32.536 So like I to go back to the
0:26:32.536 –> 0:26:35.57 Analogy or the thought experiment
0:26:35.57 –> 0:26:38.466 That I previously mentioned.
0:26:38.47 –> 0:26:41.06 If you or I were to dive
0:26:41.06 –> 0:26:43.509 Into a bath full of DNA,
0:26:43.51 –> 0:26:46.765 Nothing would really happen to us because
0:26:46.765 –> 0:26:49.558 Mammalian cells do not readily take.
0:26:49.56 –> 0:26:51.858 Foreign DNA DNA,
as itself is highly charged

deoxyribonucleic acid.

It is an acid and it won’t just normally pass from outside ourselves or outside our body into our body.

To have crisper actually enter our body, you need to develop some approach that allows a very big macromolecule with a nucleic acid component, because part of crisper is ribonucleic acid.

Actually you need to get that from your body into your body and out of your body into your body and into cancer cells and that problem of delivery getting the crisper where you want it is a pretty significant challenge right now.

With current targeted therapies and cancer, these are small molecules.

You know, maybe 50 atoms, a hundred 150 atoms and they will pass through cell membranes quite readily, and so it’s much easier to get them to cancer cells where they can do the work of inhibiting cancer cell growth.

At the same time as we develop improved techniques to get nucleic acids into the body, for instance.

People I’m sure are familiar with
the mRNA vaccines for COVID-19, which involved getting nucleic acids into cells in your body as those types of approaches for delivery improve will have ways to use CRISPR for cancer treatment as well. Doctor Jason Shelter is an assistant professor of surgery and oncology at the Yale School of Medicine. If you have questions, the address is cancer answers at yale.edu and past editions of the program are available in audio and written form at Yale Cancer Center 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 and Astra Zeneca.