Tim:

Everyone, thank you all for being here. My name is Tim. I'm a postdoc at MIT. And I'm one of three people who work on glimps podcast. And you can check us out at glimpse.mit.edu. If you want to hear our other episodes. I want to thank also some of our funding that makes this possible. So the postdoc association of MIT has given us funding. So without further ado, here is our guest, Angelika Amon. Angelika has won a lot of awards, and she's an extremely important scientist in her field. But just from my perspective, I joined the department, the same department where she is, and everyone from her lab, and all the work that her lab puts out is just really extraordinary. It's completely outside of my field, but it's been really exciting to get to know her and her lab members. She's an extraordinarily accomplished scientist, but it's most important to what people are like one on one. So how is it how it's gonna go, she's gonna introduce her working on what she does in the lab, and then I'm going to ask her a couple questions briefly. And then we're going to open it up to you all. So you all can ask your questions. And for that part, I just want to point out, you'll ask the question, and then I'll just repeat it into the mic so that it actually gets recorded. So without any further delays, please Angelika it's an honor having you and please tell us about what you work on.

**Angelika:**

Thank you, Tim. Thank you for having me. You guys hear me? Perfect. I'm actually nervous. Unlike for my lectures, I actually prepared for this. Yeah, I have like, little cheat cards here. And so Tim asked me that, you know, I should start out for 10 minutes telling you a little bit what we're doing. And I decided what I'm going to do is I'm sort of giving you sort of the historical perspective here. Now I'm an old lady, so old people like historical perspectives. And so I started out studying how cells divide, and specifically how the genetic material that is Sort of assembled into chromosomes how they are divided up during cell division, and cell division, specifically chromosome segregation was and continues to be my passion.

But what sort of Tim and I talked about today is that we are going to talk about condition a disease condition known as aneuploidy. And basically what that means for the non biologists here is, you all have 46 chromosomes, 23 pairs, and if you don't have those 46 if you have too few to too many, that is, first of all bad news for you. And secondly, it's called in aneuploidy. That's the only complicated word you have to remember for tonight.

And so, the way I got into studying this condition of Having too few or too many chromosomes was that, you know, as any card carrying academic scientists, I have to write a lot of grants. And all NIH grants have what's called a significant section. And what the significant sections are is basically you have to tell people why they should care about what you do. And what all my friends who study chromosome segregation will do is well, understanding the mechanisms by which chromosome segregate or are divvied up between the two daughter cells is super important, because when you make a mistake, you become an employee of too few or too many chromosomes. And that causes cancer. You know, I wrote this dutifully to make sure that the tax dollars are coming in. But you know, it always bugged me because I didn't really understand how having too few or too many chromosomes, how that would actually lead to cancer. And so now a number of years ago, the lab where we decided, you know, maybe we should study this. Maybe we should try and actually understand how having too few or too many chromosomes actually causes cancer.

And we figured that that was an important question, because I should tell you that 90% of all human tumors have either too few or too many chromosomes. What I want to do is I want to put this number in perspective for you. There is mutations I'm sure you guys all know this mutations changes in the genetic code of your genes causes cancer. There are genes that we know when you mutate them are involved in causing cancer. The most popular one among all the cancers is a gene called p53. p53 gene is mutated about 50% of cancers. And so runner up number two, the RAS gene mutated and about 30% of cancers. As you can see, having the wrong chromosome number is way more prevalent among cancers than any point mutations, any other genetic alteration. And what I want to tell you here is actually historically quite interesting, if you ever wanted to know. Well, one was actually the first hypothesis that was put forth to explain where cancer is coming from. It actually came from the realization that cancer cells have the wrong chromosome number. There was a very famous German scientist. His name was Theodore Bovary, who together with his wife, Marcella O'Grady, who by the way, was the first woman who were received an advanced degree from MIT. They proposed a hypothesis what they said that making a mistake when divvying up your chromosomes and therefore becoming aneuploid causes cancer. And so, my team, they're all sitting over there, some of them are sitting over there. They were like, let's try and figure out whether this is true and how this works. So the problem with studying chromosome gains and chromosome losses in cancer is it's difficult. Because cancers I probably you probably know this, I don't have to tell you this cancers have a lot of genetic changes. They have a myriad of point mutations were at base in your DNA code is changed, what pieces of your genome are lost what other pieces I amplified. And we realized that if we want to understand how a losing and gaining chromosomes contributes to cancer, if we started this in cancer, it's going to be very tricky. So we wanted to study this a normal cells. And so we generated model systems, meaning cell lines, Cell systems where we were induced, losing or gaining chromosomes and then we simply ask, but what happens to these cells? What happens to cells that lose or gain chromosomes? That was the simple question. We first did this in baker’s yeast, you should ask me afterwards of why on earth we are studying baker's yeast. One reason is because I'm a lover of wine. But they are actually all and look, we have lots of levels of beer in our lab too. But there are actually much better reasons than that. And then, subsequently, we also started this in mouse cells and in human cells.

And when we started studying this, we made a surprising discovery. And that's what I love about science. You're always surprised, okay. So what we realized is every single experiment We did. When you change the chromosome number, you're gaining a chromosome, you're losing your chromosome. The cells got really sick or they died. Shoot, okay. So losing or gaining chromosomes is really, really bad for normal cells. So that was interesting. We thought, that's interesting. Let's figure out why. We did this. A lot of graduate students and postdocs in the lab studied of why aneuploid cells are sick. And I'll give you you know, 5 years worth of research in like three sentences, please don't be depressed. Basically, what happens is aneuploidy is a disease of imbalance. What do I mean by this? We have 46 chromosomes 23 pairs of chromosomes, all these chromosomes have genes, and you have two copies of each gene, that's a good thing.

When you lose or gain chromosomes, you change the number of genes in your cells, okay? And when there's too few or too many genes, there's too few or too many gene products, okay? And all of a sudden, everything was perfectly in balance, two of each, all of a sudden you have three of this one of this bad news, things are imbalanced, the cells get confused. They get really stressed out, many of them die, and the rest of them is really, really stress. Okay, so that was cool. We know imbalancing your genome stresses cells frequently kill cells. But I hope you appreciate that we were sort of at a dead end because You know, remember, we started studying this weird thing? Because we wanted to understand how it caused cancer. I don't have to tell you that cancer is a disease of excessive cell growth. So how can a condition that make cells really, really sick, all of a sudden contribute to a disease that's actually characterized by excessive gross growth? Right? So we had a puzzle at hand. And we're scratching our heads and we were confused, and maybe some of us are still confused. But we sort of clearly the one conclusion that we could draw from all these studies was, Well, one thing we know if any point you're having the wrong chromosome number, promotes cancer progression promotes cancer as a disease. It probably cannot do it by promoting cell division. Okay, it must do in some other way. And then the key question, of course, was, what is this other way?

Okay. And again, I'm super lucky. I have these really smart students and these really smart postdocs, and they figured it out. They basically showed over the years, that really there are two reasons why aneuploidy or having the wrong chromosome number is good for cancer. The first thing that we discovered is that what inequality does is it increases the ability of cells to change. So how do cells change? cells can change when you alter their genetic makeup? So some students in the lab found that when you're aneuploid, basically what happens is that your genome becomes more change. More, as scientists we say more mutable, okay? It increases the frequency with which cells can change. And apparently, and obviously, that if you have the ability to change or shape shift more easily, right, then you can acquire new traits, new characteristics more easily. And we reasoned, and some of us some of the students in lab still study this, reasoned that this ability to change could help the cancer, for example, when it moves from the primary site to a metastatic site write for breast cancer cell to live in the bone, you know, as a metastatic disease in the bone or in the liver, you have to have new traits you have to be able to survive in a new site. And data in the lab suggests that perhaps inequality helps with that and this increased mutability. The second way in which inequality helps cancer is because changes in the gene copy number itself, you know, changing gene copy number by changing chromosome number that allows cells to adapt better to new environments. It basically allows cells to do things that normal cells cannot. Okay? And sort of this adaptability. This is what this what we call evolvability, really, we believe helps cancer cells to do things that a normal cell would not be able to do. It allows them to survive. And the conditions for normal cells would not to end in that way and aneuploidy promotes too much metastasis. So that's where we're at right now. There's obviously a lot more questions that we still need to understand.

Do you want to sort of give you a little bit of an outlook of where we're going from there?

**Tim:**

Sure

**Angelika:**

Sorry. That was a rhetorical question.

**Tim:**

Positive reinforcement.

**Angelika:**

We recently made a remarkable discovery. We made the discovery that when you change your chromosome number, when cells change their chromosome number that doesn't go unnoticed. It turns out, your immune system knows, magically somehow that a cell is aneuploid. Okay? And it clears those bad cells out of your body. Well, we now want to understand is, how does that work? Okay. What is it about this any bad cells that the immune system can say, aha, you have the wrong chromosome numbers. Okay. You're at a related question. I told you. The vast majority of cancers are aneuploid. So it's somehow, at some point, this immune recognition is lost. Right? How does that work? We have no idea.

Other important questions that we're addressing is how do changes in chromosome number, promote metastasis? How do they promote resistance to traditional chemotherapies, and so forth? And then, obviously, another key question is I told you having the wrong chromosome number makes cells sick. You know, all these cancers are aneuploid. Somehow they must evolve tolerance to the aneuploid state. How do they do that? How do they all of a sudden, say, well, it doesn't matter whether I have all this hodgepodge of chromosomes, I'll divide happily anyway. If we understand how tolerance training for the evolve, we might have the opportunity to now think therapeutically target these cells. And that's, of course, something that's sort of the big, long term goal of the lab, sort of, at some point in the distant future, will we be able to develop therapies to develop strategies to specifically target he's aneuploid. So imagine you have a drug that selectively kills aneuploid cells. What a wonder drug that would be. The good news is the vast majority of your cells are you put, that's a good thing. Okay. So most of your tissues, all of your tissues, all the cells in there have the right chromosome number. Only cancer cells have the wrong chromosome number only they are in a play. And so if we had a drug that selectively killed those cells, it would work against many different types of cancers, right? Importantly, it would have very little side effects because it wouldn't touch all the normal cells in your body. And so down the road, if you have me again in 20 years, probably not. But if some imagine you had thinking, I'm hoping that I'll be able to tell you that we have started to find these kind of drugs and have started to understand how they work. That's what we do. That's where we came from and where we gonna go. All right.

**Tim:**

Wow, that was, I feel like I'm an expert on aneuploidy now. So I have a two part question for you. First, coming off of what you just said about how cancer cells somehow not only can apparently survive in an endpoint state, but rather, almost every cancer cell that we see is actually aneuploid. Do you think it's, is there an evolution within the tumor at an early stage? Where cell divisions are going wrong? There's they're going wrong every time every time. And chromosomes are just shuffling around shuffling and shuffling around until there's like a jackpot kind of combination of, you know, to two extra chromosome three and like zero chromosome seven and four extra chromosome 11. And that combination works. But all the other ones don't work.

**Angelika:**

That's a great question. I think maybe that's actually exactly how we think about this. So the vast majority of chromosome gains and losses are detrimental, meaning they do not work, right. But then that could be this rare, magical carrier type that helps you do something that you normally cannot do. So Becca Silverman, who's actually here in the audience, she actually has done a very interesting experiment. She has asked Very simple question of when, during the process of tumorigenesis, as the cancer arises and develops, when does an employee do rise? When does it happen? When does it actually happen when, during that etiology? When do you actually arise it? And so the way she did this is she got patient samples of what we call pre malignant lesions. These are growths, like warts, for example, that are growing, but they're not tumors yet. And she asked a very simple but very important question. Are those early pre malignant stages aneuploid or not? And the answer was very clearly they are not. So what Becca believes is that very early on the mutations that do get allow you to proliferate right and you sort of proliferate in place. But then when a cancer wants to do something special, yeah, that's when it comes in.

**Tim:**

Okay. Okay, so the second part of my question is, at any point state that you knew, as you know, and as many of us probably know, aneuploidy exists in humans. I, you can correct me if I'm wrong, but I believe that any aneuploidy of any chromosome except for 21 is lethal in the embryo. Yeah.

**Angelika:**

No trisomy 13, and trisomy 18 survive to term.

**Tim:**

So there’s trisomy 13, 18, and 21. That state is permissive for an embryo to grow into term, right. So what do we know? I might my question is just in contrast to the cancer question, are there shuffling chromosomes around like crazy? What do we know about those three that permits the embryo to actually develop in humans?

**Angelika:**

So the answer is very simple. For, those are the smallest chromosomes in, in humans, in terms of they have the fewest number of genes on them. So the reason why they survive is because changing the copy number of this small number of genes is compatible with survival. But the larger chromosomes, for example, in the mouse, none of the trisomies survive. So well, not at all, not as well, maybe some circumstances 19 but all the other ones are lethal. So actually, humans are little bit unusual that we actually do have three trisomies that that survived to term. But what I also find very fascinating is that most people actually don't know is that over 80% of trisomy 21 fetuses actually do not survive to term. So it's, you know, I actually think what it's a fascinating question is, is sort of what's different about the 16% that then can actually live to an age of 50-60 years old.

**Tim**

Right. So it's actually, there must be some adaptation.

**Angelika:**

Yeah, very much. So. And I think, and we, we do not understand that at all. That's what we call phenotypic spread. Where are you know, some embryos die, as you know, very, very early during embryogenesis. And then others live to 60 years of age. Wow.

**Tim:**

So I want to open it up to questions soon. But I want to ask actually, really, I want to move a little bit away from this particular topic. Because I know that a lot of your work is actually on yeast, and that's where you started doing your research. And I read a really interesting commentary recently that was discussing this idea or this phrase that we read a lot in the scientific literature where something is “conserved from yeast to humans.” And this this author was sort of taking issue with that phrasing because yeast have evolved along their path from you know, the time of single celled organisms, humans have evolved along their path from the time of single celled organisms. So there isn't actually like a straight line from yeast to humans that we can draw. So in an evolutionary sense, it doesn't sort of make sense this person made the same claim about flies and about mice. I'll send you the citation. And so I just wanted to know, I wanted to get some of your perspective as someone who has a lab who actually does research on yeast and on mammalian cells and on mice and with human samples, so kind of bridging these different scales about sort of what are the fundamentals of the biology that you can uncover and use that are still important for human biology. So I can send you that reference.

**Angelika:**

really take it, you know, obviously, cells do not have brains, right. So obviously, if you're interested in synaptic function and system systems, neurobiology, budding yeast is not the ideal model system. I grant you that. But if you're interested in basic eukaryotic cell biology, the way a yeast cell divides is the same way a human cell divides. And Paul Nurse, he actually won the Nobel Prize for showing that he took a yeast cell that was defective in a particularly cell division gene. And he stuck the human version of that gene into the yeast cell and it worked. Okay, so clearly cell division secretion, DNA replication, autophagy, yada, yada via all of this, you know, we all basically do it the same way. And I can't stand this arrogance of these, like mammalian biologists, “Ooo, I have three genes and your yeast guys only have one therefore, we are special.” I mean, come on, right? I mean, so you cannot excels the eukaryotic cell and they do things fundamentally the same way.

And you're right, in the lab, we're using multiple model systems and we have a very pragmatic approach right? If, if the question can be a addressed in both yeast cells, mice cells and human cells, I'd be stupid to do it in a human cell. You can do so much better experiments in yeast. The experiments are so much so much more precise, the amount of manipulation that you can do is just so much more superior to anything you can do in mammalian system. Obviously, if I'm interested in how cells interact with the immune system, obviously, we're not going to study that. So, you know what, it's very clear. What we do is basic cell biology about aneuploidy or aging or mitochondrial function in a chromosome segregation. We do lots of different things, right? We do that in yeast. And if we want to study something, you know, that's unique to multicellular organisms. We do that in a mouse and we do that in humans.

**Tim:**

Great. Okay. So we've taken up some time now. So I think hopefully, some good questions have bubbled up in your brains. I think the easiest way to do this is Angelika just call on someone and ask you a question and I'll be sure to repeat it into the mic. Okay, I'll call on someone saying I just wanted to give you the power right here.

Okay, so the question is Do people who have a trisomy syndrome that we spoke about, do those people have high rates of cancer?

**Angelika:**

As with everything in science, the answer is not straightforward. Okay? So if you're interested in the cancer rate of solid tumors, like colon cancer, lung cancer, and so forth, individually, so we only know about trisomy 21, because trisomy 13 and trisomy 18 they die very at a very young age, so there's just not enough time to develop cancer. But in trisomy 21, there's a lot of very good epidemiological studies out and they suggest that solid tumors are significantly reduced in people with trisomy 21, which sort of I would argue will actually be consistent with the idea that generally inadequate cells are less fit. So there is some higher barrier to transformation. However, interestingly, they are prone a highly susceptible to very specific cancers, one of which is called transitional myeloproliferative disorder, which is sort of a precursor to AML (acute myelocytic leukemia). And that is a highly, highly I think a 20 fold increase compared to the normal population. And people are studying why that is and people have begun to identify genes that are important for, you know, when triplicated you know, are important for this disease. And actually we're studying in the Becca actually in the lab is studying exactly that question. So you can ask her.

**Tim:**

More questions, young lady,

Okay, so the question is why is it that in your opinion an experiment in yeast, if you can do the experiment, that's superior to the same experiment in human cells? Yeah.

**Angelika:**

You know what I tell my students when I when they joined the lab, and we're discussing of what is it that they want to do? I tell them, doing your PhD in baker's yeast is really hard. Because the only rate limiting factor is your brain and not all students can take it right. And what I'm trying to tell them when I say this is that the experimental versatility and the tools that we have in yeast are unmatched by anything else. You know, you probably heard about CRISPR and Cas9 and now we have this uncanny ability to manipulate the mammalian genome. It's nothing compared to yeast. Like these guys in the lab, just snicker right? And so that's the kind of experiments we can do with the precision with which we can ask questions. There's nothing like it, and it makes me really, okay it annoys me that people just keep saying well, the times of model organisms model systems are are counted right? We are now should all study some tissue culture cell line, you know, who came from God knows what and evolve for 40 years to live on a plastic dish, you know? And if you believe that that teaches you anything about human physiology, I strongly beg to differ. So I'm a big fan of model organisms because the only limitation is your own the ability to ask a question, and to be curious, right in. I just don't ever want to miss this. I really don't. And obviously, I do appreciate that sort of translational aspect is important and I do appreciate that, you know, some questions cannot be addressed in yeast and for that, obviously, we need to use other systems. But I will always be a yeast geneticist at heart. Right.

**Tim:**

More questions. Right here?

That's a great question. So the question is about how have you examined apoptosis which is regulated cell death? In aneuploid cells? Is that right? Yeah. Yeah. All right.

**Angelika:**

Um, I told you earlier that our general experiments used chromosomal segregation in primary cells meaning in not in tissue culture cells, but in cells that are directly coming from a tissue from either a person or from a mouse, that it's generally detrimental. And we of course, asked whether that is due to increased apoptosis, but what we generally see is that rather than inducing apoptosis, having the wrong chromosome number really induces a stage called senescence, which is basically a cell a state where a cell sort of stop dividing, they sort of sit there.. You know, they sort of sit there and they don't do anything anymore. And, you know, that basically, “I'm done with this.” Right. And that's, that's really what senescence is, is all about. Having said this, we have done some drug screens where we're looking as I mentioned earlier, we're starting to look for a compounds that specifically kill aneuploid cells. And we have found drugs that increase apoptosis in aneuploid cells. How that works, how you decide whether you go the senescence path or the apoptotic path. I think people generally don't really understand that yet. And we actually don't understand how that works in the context.

All right, we probably one more question which I think Colles I've ignored you for long enough. Yeah. So Colles is asking if we say 10 years in the future in terms of therapies that would target aneuploid cells. Could you silence aneuploid chromosomes? Yeah. So chromosomes which are there in too high numbers?

**Anelika:**

It's a great question. This is not work by by our lab, but by Jeannie Laurence at UMass Worcester. And obviously that question has been around for a long time in a trisomy 21 field, where people have of course, trisomy 21, is a condition known as Down syndrome, where an individual has three copies of chromosome 21, instead of the normal two. Of course, there was and continues to be a lot of interest in, in silencing that third copy of chromosome 21 to sort of perhaps reverse some of the adverse effects of having an extra copy of chromosome 21.

Jeannie Laurence at UMass Worcester tried that by exploiting some biology of the X chromosome. So some of you probably most of you probably know this women have two X chromosomes. Men have one X chromosome and one Y chromosome. And the way this works, it's not that women just have twice as much of all the X chromosome genes. It actually turns out that there is a mechanism by which one of the X chromosomes is silenced in women, so that the dosage of X chromosome genes is the same in men and in women, okay with a few exceptions but details okay. Decades of work have actually revealed a gene called Xist, which sits on the X chromosome, and silences you know, from which the silencing spreads. Okay, so you can shut down the entire X chromosome nearly from this one locus on the X chromosome called the Xist locus. Really cool biology from Jeannie Lawrence, which is really cool. And that really changed the trisomy 21 research field. She moved that Xist gene from the X chromosome to that extra copy of chromosome 21 and silenced the extra copy of chromosome 21. And the cells really returned to normal. And the reason why this had such tremendous implications for the field of trisomy 21 research is because until then, you know, everybody sort of assumed you Know, your egg gets fertilized, it has an extra copy of chromosome 21. There's a lot of development that goes wrong. And by that time that child is born, there's really nothing you can do anymore. Okay, because you know, all these developmental pathways went array astray because they had an extra copy of chromosome 21. And what genius work showed was that a lot of those fields, these traits that are all these defects that happened from this extra copy of chromosome 21, were reversible. And that was actually really, you know, an eye opening discovery, because it sort of told the field, hey, if you can find a way for doing this systemically in an organism, you know, you could really fundamentally change the lives of these individuals. How you would do that after person is born and there's 10 to the I don't know cells, I don't know. But what that results just said is that it might be worth a try.

**Tim:**

Cool. So we should wrap up and thank you all so much for sitting patiently.

**Angelika:**

Thank you for listening.

**Tim:**

This has been really fun and thank you especially Angelika.

**Angelika:**

Thank you for having me.

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