Stem-Cell Aging and Pathways to Precancer Evolution

Catriona Jamieson: [MUSIC] I'm going to tell you a story about dirt. You never know where you're going to find the newest discoveries. We have colleagues who are undaunted by difficulty, who have come up with a molecule that is the first ADAR1 inhibitor ever to be made that was propelled into the clinic by somebody who's in the front row, and this is named after her Rebecca Moors. Thank you very much. Rebecsinib is the name of the drug. And this is what happens when people never, ever, ever give up Gan Base, and that is a Japanese term for never giving up.

We're all here to talk about how we get stem cells that go from aging to pre cancer to cancer stem cells. How do we unravel this complex puzzle and actually intercept it before people go from a pre cancer condition like a myeloproliferative neoplasm that you heard. Noah talk about to a full blown cancer, and how much of this is human specific biology that's actually stress induced. When I'm in clinic, people say, How much did stress have to do with me getting this disorder? We really want to unravel this. Unfortunately, we can do this in the hematopoetic or blood forming stem cells because they're readily accessible. You heard Allison say, it's hard to get a piece of your brain. People don't really want to voluntarily give that up, but they will give up some blood, in some cases, some bone marrow.

We've been working on how these disorders where you make too many of one type of blood cell, whether it's white blood cells, red blood cells, or platelets for start. They often start at the level of a hematopoetic stem cell or blood forming stem cell. These were discovered in 1961 by Tila McCullough in Canada because people were worried about nuclear proliferation. They thought that radiation would wipe out our entire bone marrow. Then Tila McCullough discovered these cells called hematopoetic stem cells, and Irv Weissman was able to find the surface markers that allowed us to isolate that. Since then, that was back actually in 1992, we've been uncovering where these mutations start. Why do we care about stem cells? Stem cells are supposed to regenerate our tissues, but they can also regenerate cancer if they've gone awry. We've been targeting the pathways that allow these stem cells to take the initial step between being abnormal. Actually been able to clone themselves.

I'll talk specifically about inflammation dependent base editing enzymes and their role in myeloproliferative neoplasm progression to acute myeloid leukemia. This all starts with these stress enzymes that are human specific. Humans evolve to protect our stem cells from repetitive elements, these retroviruses, like human endogenous retroviruses, and long interspersed nuclear elements, lines and herbs. This is biology that was ignored for a long time because we couldn't sequence it. They're repetitive elements that were really hard to see, but they're very very important for telling our stem cells how to behave when you're undergoing stress. They tell us to mobilize our stem cells and they tell our stem cells to clone themselves. But when they do this too much, the enzymes that were supposed to prevent this active retrotransposition or activation of lines and herrves actually start to mutate our DNA. Those are APOBEC or RNA, that's ADR. We have these repressors of retrotransposons or repetitive elements that dark genome that when they're activated for too long can actually lead to pre cancer and cancer.

Why does this have anything to do with space? Like Allison, I was looking at the NASA twin study. This was published in science in 2019. You see that Scott Kelly came back two inch taller than his brother Mark. Amazing. You get to be taller. Apparently, your skin gets better. According to Peggy Whitson, you lose your wrinkles. The only thing is, Scott Kelly after almost a year in space compared to his brother Mark that didn't spend much time in space, came back with immune dysfunction. Premalignant changes in the blood that look like they were just the beginning of a pre leukemic disorder, and the same inflammatory growth factors that we know

can activate these enzymes, ADAR and APOBEC that comutate our RNA and DNA respectively.

Now we've completed nine missions to the ISS. We're thrilled to be able to work with our implementation partners and NASA. To be able to see in an accelerated time frame how stem cells age, how they become pre malignant and malignant. That's something that is all detectable now thanks to the work we've done with NASA and our implementation partners. We've developed these canaries, as I like to call them, the cancer and aging stem cell nanoboeactor, artificial regenerative intelligence enhanced systems.

My dad was a coal mining engineer, and he always taught us that you take a canary into a coal mine because they're much more sensitive to carbon monoxide. This is our equivalent. It's like a canary or carbon monoxide sensor of stem cell stress. We made this with Space Tango. We've got the Space Tango here, team today. Hey, Twyman, Paul, we've got a number of you here because we just did de integration of Space 633 for us and Allison Motr's mission, as well. Basically, this is a little incubator, it's a cube lab. You see here you've got this flask for the media. You've got the nanobioeactors that we made here. All of these experiments have been directed by our stellar Mission specialist Jessica Pham.

Basically, we can put stem cells in these little nanobioeactors, and then image them with his microscope. We can see when stem cells are asleep, they're supposed to be asleep, 80% of the time to maintain their full activity. When they're in cycle, they're green, when they dividing their yellow. You see how small this pediatric blood bag is? That has all the stem cells we need to actually we reproduce all the blood cells in our body if we had to use this as a therapeutic avatar or Theotar as I'm calling it. This is a splicing reporter, so we can see in real time and space and on the ground whether or not the stem cells are splicing too much, they turn green. Then we can see have they activated this malignant gene called ADAR1, which is here in green in tumor organoids.

We did this all so we could see, are we seeing accelerated stem cell aging in space, as was suggested by Scott Kelly coming back looking about 10 years older than his brother, at least from a blood stampoint. We did this study NASA funded WispacTango. We were able to see that stem cells age faster, probably 10 years faster in space than on the ground. The most notable finding was that in flight, there was activation of what we call the dark genome with the cells that had been in flight here and red compared to ground controls. We talked about activation of the dark genome or ADAR sader of the genome because you inherit it. That seemed to catch the attention of CNN, NBC, all these other groups because they thought this was cool.

The thing is, we didn't just invent this. We have this. Our DNA is littered with all of these vistigial retroviruses. They have been part of our genome for thousands and thousands of years. They should stay quiet, but they get activated under conditions of stress, and they lead to this stress biology that can induce accelerated stem cell aging and pre cancer. We were feeling very Debbie Downer about this whole thing. We thought that once aging has started, there's nothing that can stop it. This is a freight train. Actually, this is thanks to our friends in the audience from Axiom Pinar. Hello. Here you are. Our bio repository team, Inga, Gan Jessica, the whole Lab. We were able to study whether this is true in astronauts.

We looked at the axiom two, three, and four crew members. They're all superhuman. They all seem to have this idea that everything will work out. I don't know if this is part of astronaut training or whether they were just genetically built to be like this. But we decided to ask the question, do they age faster from a stem cell level in space? We looked at Axiom 2 crew members. I had been there for 10 days, Axiom 3, 21 days, Axiom 4, 20 days. We were able to look at before, during and after return from space to see what their stem cells did. We're able to do this for all of us now, by the way. If you wanted us to look at your stem cells in your blood to see if you're stressed or not, we can actually do it.

We can take two little vials of blood. We can separate out the purified stem cells that are CD 34

positive and then do whole genome sequencing to look for mutations with Ludmil Alexandrovs lab, whole transcriptome, or single cell RNA sequencing, and then look at aging of those stem cells. When we first looked at the data, I thought, here we go. We're seeing accelerated aging. It Patrick Chang, because I always love to point him out. And Claire Engstrom in the lab said, actually, there's this other population of stem cells that comes up in flight in response to stress that is a more primitive stem cell. I remember saying to Patrick and Claire, it's not a stem cell. It looks too primitive.

But it turns out just a little while before we made this discovery, Dominique Bone found this population of EPCR positive stem cells that is ten to 100 times more capable of regenerating our bone marrow. I just hadn't read the paper. Went back, read the paper, and said, Holy moly, this is what the astronauts are doing. They're mobilizing this highly regenerative stem cell population in response to stress, not just space stress, but they even do it a little bit on the ground in anticipation of launch. This is something that we can test in all of us now, and it's a marker of resilience. It turns out that that stem cell population may outcompete the mutated stem cells. Those stem cells, we think of being mutated by activation of that enzyme I mentioned, APOBEC3C.

We're able to see, are your stem cells revving up and regenerating or are they being corrupted by this enzyme, APOBEC3C and getting mutations that we can detect. Ten days in space is not so bad. Three weeks, we start to see mutations. But for people that can mobilize this regenerative stem cell population, it seems to outcompete the bad. How is it that we can detect and expand those cells and prevent pre cancer from becoming full blown cancer? One way is to detect APOBEC3C and reverse that. We're working on it. But we decided to start at the end of this story, target this malignant enzyme that works in a human specific way to corrupt our stem cells, and that's called ADR P150. The reason that's so bad is it allows cancer stem cells to clone themselves and evade the immune system.

Now, AR1 is something that our lab discovered back in 2012, actually, as something that allows cancers to clone themselves. This became something that a lot of groups worked on and started to look at ADAR high as bad AML. If you're high in ADAR, you don't live as long with AML, multiple myeloma, liver cancer, breast cancer, 20 different cancers, if you activate this. But that way it wasn't just a story about cancer cloning itself. It was a story about cancer evading the immune system because if ADR is turned on, it turns off interferon in the tumor micro environment, so the T cells go, let those guys go, gives the cancer a hall pass. We started saying there's no time to wait. We have to strike at cancer just as it's getting started or ideally before it really takes off, blasts off, pun intended.

Here's Jessica working at ISS PF, preparing our tumor organoids for flight. We started testing cancers in space with Axiom 1. We showed the tumor organoids tripled in size in just ten days. But perhaps most importantly, in addition to tripling in size, they activated that enzyme ADAR 1. That gave us an opportunity to target this enzyme. Here's Walter Villada. He's an astronaut. He's doing our experiments with breast cancer organoids. He's comparing two drugs Fedratnib and Rebecsinib and that rebecsinib is the drug that very specifically prevents ADAR 150 from being activated, whereas Fedratnib is a weak ADR inhibitor. We wanted to compare the two. Basically, what we found in that study is Rebecsinib behaved as a cancer kill switch. If you're not growing, you're dying. The tumor organoids just stopped growing. Then we said, that was in a cell line. What about metastatic breast cancer from patients?

We found this is Day 4 of our Axiom 4 mission. The Rebecsinib stop the growth of these tumor organoids. They have that ADAR green fluorescent protein reporter in there. Looked very similar to genetic knockdown of ADAR. But I think the surprise was really glioblastoma multiforme. GBM is the most malignant brain tumor in adults. It affects 13,000 people annually. It has a 100% mortality rate, usually within 18 months. There's nothing that works to stop this freight train. We were amazed when Rebeknb low doses seemed to stop this tumor from propagating. The ADAR knockdown wasn't even as dramatic.

The other disease that responded exquisitely, sensitively was secondary AML that has evolved from a myeloproliferative neoplasm. You see this forms this almost solid tumor cluster of disease. This is Day 5, and flight hot just stopped growing and couldn't be propagated. Then Jessica and Wen showed that if you transplant the cells that have come back from fletum or treated with vehicle control, they still grow the leukemia. But the ones that were treated with Rebecsinib have trouble doing them. We've got an active investigational new drug application now. The company AspRA will be taking forward to that phase one clinical trial with Rebecsinib for treatment of patients with myelofibrosis or secondary AML. But the idea is that it could expand to a number of other ADR activated malignancies, and the way to accelerate the implementation of this more expanded trial is because of space. We only got this accelerated view into how cancers evolve because of our NASA ISS missions.

So basically, what we're looking at are these twin crises in cancer. The number one cause of death from cancer is actually the cancer comes back. The reason it can do that is our stem cells get exhausted if they don't make a proper immune system and they can't see the cancer anymore. We're tackling these twin crises in cancer with our NASA crew members and the undaunted axiom crew members. We're thrilled to be able to work with Red wire, Space Tango, axiom BioServe. And we just signed an MOU with VAST, so we're thrilled about that. Thank you, Ken, propelling us forward together with Meg and the whole team at VAST.

But the point, I guess, of all of this is to say, what Noah was telling us, it's our collective responsibility to make sure that never should there be a person that has to worry about the cost of care. We need to make therapies more effectively. This drug was found in the dirt in Japan. It's a bacterial metabolite, so it's a soil bacterium that Jim LeClair and Mike Burkhardt were able to purify. But this is the dawn of a brave new era where we can do this. Bigger, better, faster, smarter, and faster includes spaceflight. I just wanted to thank everyone for being here and for recognizing that this is just that pivot point in time where we all have to do this together. Thank you [APPLAUSE]

FEMALE_1: Amazing talk as always. I guess my question is on EPCRs. I used to work on this. You said that it's resilience, that it's part of the resilience that maybe expressed on them. I guess my question would be, Hey, what do you think the mechanism that would lead to that resilience? Is it just a stress? Is it something else that the bone marrow of the science is sense and then the other way we know maybe ways that we can mobilize those cells. Will that be actually a way for us to increase resilience or would we want to avoid it actually?

Catriona Jamieson: All what we're working on now. It looks like there are three populations in there. There's one that doesn't express APOBEC. It's not a pure population, so it doesn't look like it can mutate itself as readily. We do think it is sensitive to a mechano sensor called Piezo 1. That is something that Fubi in the lab has an agonist and an antagonist for. It's a way of expanding this population. It's also ADAR high and line and Herve high. So not all of these retrolaments are bad, it's just when they're activated for too long. So they are part of normal regeneration. We do want to learn how to expand them. You certainly have your whole PhD on this. Yes, please, we'd love to work with you, but we don't think this is just for blood stem cell biology.

We think it's going to be important very early in neural stem cell biology, skin stem cell biology. Cancer, you know, takes a highway. It hijacks these stem cell pathways. So we're trying to dial it down where you see it in cancer, but it could also be the other side of the coin where we can enhance regeneration, provided we can control.

FEMALE_2: For the drug resenative, where does the bacteria? You said it comes from dirt in Japan. Who found this bacteria in dirt in Japan? That's really interesting.

Catriona Jamieson: It's such a great question. This comes down to basic science. There was a scientist working in Japan that said, Wait, what's this? This drug seems to kill cancer and was

working with cell lines. Then Japanese company ESIESAI decided, maybe this will be something, but it turned out it's really hard to make. We had no idea. When you start on this difficult journey, you never know how hard it's gonna be. But a friend of mine who actually invented Fedratnib that drug that's now known as Anbeic said, Cat, when you have a problem, go back to the beginning. When you lose your keys or lose your cell phone, where does it come from in the first place?

It turns out that bacterium has an enzyme that makes the drug. We were able to find the enzyme, clone it, make it fully synthetically. I think, as Allison was alluding to, we have a lot of natural products and go back to them and say, can we make this even more effectively. So it was a very clever thing. It's kind of like immune checkpoint inhibitors. They were discovered 20 years before that Nobel Prize was given. So some of these things take a while to incubate, and the point with precision medicine now is we can see it faster, and we can develop things faster. I think we just need to put our minds together and be open minded about the next set of cancer curing drugs.

FEMALE_3: With the experiments and space, at what magnification or what full do you expect drugs to get approved? How much faster?

Catriona Jamieson: It's such a great question. Actually, I was on a full day workshop with the FDA and NASA. So the FDA wants to regulate this. They're seeing things are happening very quickly. And so, you know, as you can see, the FDA is really trying to look at approvals based on organoid models. Two more organoid models that started April 10 of last year where they said a lot of these immune based therapies actually aren't predicted based on animal models, and we can predict them based on patient derived little mini tumors. They're in it to win it. I think when they talk about a fast path or acceleration fast path to approval, it can be as little as three years from first patient treated. I've seen that with one drug called Sprycell where it was three years from first patient treated.

I know because I treated one of the first patients when I was at Stanford. But I think we can really demand that this be done faster. I think the reason is faster is patients really thoughtful and are giving their blood, their bone marrow or their tumor tissue, sometimes sequentially. And that's allowing us to see how cancers evolve over time and actually dial back the clock to pre cancer and say, wait a minute. This started at this pre cancer stage. So now we have genomics and RNAC, and we can make it very precise and have a stellar stem cell fitness portal, the stellaridome, that you'll hear from Peter Devolt about from Epic. So I think we should all have access to these data in real time, and I think it will accelerate approvals pretty dramatically.

You think about usually it takes 10 years. Minimum to get from an idea to an FDA approved therapy. We're trying to shorten that timeline to three, hopefully. With AI, we'll be able to get some early indications of what's likely to work, but it's not going to replace natural intelligence, which is regenerative, neurostem cell based, and we network because we bounce ideas off each other. Thank you [MUSIC]