Dr. Balajee : ... in case of mass casualty incidents, several hundreds and thousands of people are likely to be exposed to ionizing radiation. We have to increase the search capacity so that we can provide a rapid biodosimetry to people who are exposed during this mass casualty incidents, radiological nuclear. So keeping this in mind, so we initiated a game, it's called the dicentric chromosome challenge game. Till to date, the game has been played by more than a thousand individuals from so many biodosimetry laboratories around the globe. I'm quite excited about this, and this is one way of training people how to score dicentric chromosomes. It's a game, so people will be interested to try out and we also give a score, so people are always trying to play and improve their scoring.

Speaker 2: This is the ORISE Featurecast, a special edition of Further Together, the ORAU podcast. Join your host, Michael and Jenna for conversations with ORISE's research program participants and their mentors as they talk about their experiences and how they are helping shape the future of science. Welcome to the ORISE Featurecast.

Michael Holtz: Happy Wednesday! And welcome to another episode of Further Together, the ORAU podcast. I'm Michael Holtz with my co-host as ever, Jenna Harpenau. Jenna, how are you?

Jenna Harpenau: I'm doing great. How are you?

Michael Holtz: I'm good. It's a new year. It's 2021, high expectations.

Jenna Harpenau: Yeah, very. Although I don't know, maybe we should have some low expectations and just let 2021 exceed our expectations.

Michael Holtz: You might be right. I saw a meme on social media that was like, "We're all going to walk in really quietly and we're not going to touch anything. Just let it happen."

Jenna Harpenau: Yep. I feel the same way.

Michael Holtz: So maybe that's what we should do. Well, I'm really excited today. We have Dr. Balajee with us today to talk about his latest research, and this is a project that was funded by ODRD, or ORAU Directed Research and Development funding, and it's related to DNA damage on 3D genome. I'm just going to let him tell us because...

Jenna Harpenau: They're always doing the coolest stuff over there.

Michael Holtz: I know, they really are. So Dr. Balajee, welcome back. You've been here before, so welcome back to Further Together, the ORAU podcast.

Dr. Balajee : I'm excited to be here, Michael and Jenna, and thank you very much for having me here.

Michael Holtz: Tell us a little bit about who you are.

Dr. Balajee : I work as the technical director for the cytogenetic biodosimetry laboratory. So it's a part of REAC/TS. We do radiation biodosimetry for exposed people. So when we get the blood samples from exposed people, so we do an assay known as dicentric chromosome assay and then we estimate the absolved radiation dose. So this is what predominantly we do at the CBL. Besides, we do a lot of research projects to enhance the biodosimetry capabilities of CBL. So in this context, we reach out to other university partners to initiate and develop a lot of exciting research projects which would help us in the future.

Michael Holtz: Okay. And you just had a manuscript published that you were a co-author of in December in a publication called Nature Communications and it's Radiation Induced DNA Damage and Repair Effects on 3D Genome Organization. So basically, we're talking about radiation damage to DNA. Talk about your research project. How did this come to be? And I guess all of the things, what you found? Et cetera.

Dr. Balajee : With pleasure, Michael. I'm going to tell you a short story how all these collaborations started initially.

Michael Holtz: Okay.

Dr. Balajee : So I'm really glad that our fruitful collaboration with UDK resulted in a very good publication in the Nature Communications. Our collaborations started way back in 2016 with the ODRD pilot award. ODRD requested partnership with a member university and I was desperately looking for a partner. After several hours of browsing, I found Dr. Rachel McCord, whose research on 3D genome organization appealed to me very much. Luckily for me, she was hired by UDK as an associate professor just a few months before I contacted her. So luckily for me, I found the partner and we started working on this 3D genome organization.

Before I go into any details, I will tell you how complex of a genome organization is. So each cell's nucleus contains a two meters long DNA which has to be packaged in a space with six microns. Imagine what kind of complexity we are dealing with. So we are really interested in this genome organization, how DNA is packaged and how it functions in different activities. So with the novel technology such as chromosome confirmation capture technique, we actually analyzed the interacting regions, how the genome is organized into different domains and what would be the interaction of these domains after ionizing radiation exposure. So this is what we did in this Nature Communications.

So our conclusion is that the third organization, we call it topologically associating domains. So they changed a little bit, much more so in the DNA repair proficient cells compared to DNA repair deficient cells. And as you know, the dicentric chromosome assay which we use reflects the exchange between two chromosomes of DNA breaks. So we can also map that using this technology, and this 3D genome organization is variable conserved. What I mean by 3D genome organization is the packaging of this long DNA into very small instructional and functional units. So this organization seems to be disorganized or altered in many disease states like cancer. So cancer cells have distorted 3D genome organization.

So this research has a lot of scope. You can analyze this for different disease states, and how they are altered and how this alterations in structure leads to pathological conditions. So it is really exciting, not only for radiation, but you can also use for a wide variety of applications, basically human disease, biology.

Michael Holtz: That is really exciting. I know you focused on ionizing radiation exposure. For those of us who don't work in the radiation space on a daily basis, talk about what ionizing radiation exposure means.

Dr. Balajee : So radiation that causes ionization like X-rays or gamma rays. And so, when we are exposed or when cells are exposed, it ionizes a lot of molecules and atoms. So during this ionization process, large amount of energy is deposited and that can cause a lot of damage to the DNA. Basically, when you go for a dental X-ray or any kind of medical diagnostic procedures, it involves a little bit of ionizing radiation, so we are constantly exposed to ionizing radiation. And we also get radiation from space, we call it cosmic radiation, which is quite harmful. And also, some of the fruits and vegetables we consume, they also contain traces of radioactivity. So we are continually exposed to radiation, probably most of them at very low doses, they do not cause any harm to our bodies, but when the dose exceeds, then it's a problem because it can break the DNA which is the blueprint of life.

So once the DNA's broken, most of the times it's rejoined properly, but sometimes they may misrejoin, giving out a lot of chromosome elaborations like we see, like the dicentric chromosome let's say, which we use at the CBL is actually reflecting misrejoining of breaks in the DNA. So we do have efficient repair missionary, but sometimes when the damage exceeds the threshold, then we get into trouble. And we always score this chromosome elaborations or DNA misrejoining as a surrogate for absolve radiation dose. So you can actually estimate the dose based on the extent of damage.

Michael Holtz: Okay. Which is obviously really important to the work?

Dr. Balajee : It's very, very important. There are a lot of accidents that keep happening with the diagnostic exposure, so REAC/TS is actually supporting all this at 24/7 basis. So people have all kinds of questions about radiation exposure and some incidents that might have happened to them. People go to dental X-ray or something like this, and then they say they have some adverse effects, and then... People have all kinds of concerns. And so, from the internet, people read quite a lot about radiation accidents like Fukushima and Chernobyl and all the effects on organisms, not necessarily humans, but also fish and all kinds of mammals, so they're really scared, so I can understand their concern. But the diagnostic radiation is pretty harmless, but we need it for diagnosis, so there is no way to avoid radiation. So radiation has become part and parcel of our life. So when the dose exceeds, that's where the problems come.

Michael Holtz: This was something you've been wanting to do for several years, and you said since like 2016, you were looking for a partner. And you've touched on this a little bit, what is the value of ODRD to (A.) Helping you find a partner, but then being able to conduct this kind of research?

Dr. Balajee : A really good question, Michael. So I always give tremendous appreciation to ODRD funding mechanism, because ORAU has more than a 125 member universities, and those universities have excellent researchers and faculty members and they do research on a wide variety of aspects. So finding a partner may be difficult sometimes because of the vast number of member universities, but it is always very advantageous to advance the science at ORAU. We may not have all the facilities and resources to carry out research, but this collaboration through ODRD funding is really paving the way for increasing the collaboration, so it is really excellent.

And I have been fortunate enough to get ODRD funding almost every year until this year because they suspended the funding because of COVID pandemic. But all this projects, which I got through ODRD have been tremendously useful and some of the projects are still ongoing. So for example, we submitted two research proposals to Department of Defense DOD, and one to NASA, a bit to Ohio State University. So we are not only looking for cytogenetic markers, but we are also looking at molecular biomarkers that can predict radiation exposure. As I mentioned this before, dicentric chromosome assay is the gold standard, no doubt, but it takes quite a bit of time, so 72 hours, sometimes four days for getting the results. So we are looking for an alternative. What if, in case of radiological emergencies, we have to provide rapid biodosimetry, so DCA is not the way because it is too time consuming and labor intensive. So we are looking for alternative.

So using molecular markers such as micro RMA which is a small piece of RNA that changes in expression of the radiation exposure. So you can use that as a surrogate for quickly telling people to what dose they are exposed to, so we are actually looking for options. So for doing all this, ODRD has helped a lot, otherwise I would not have found all this interesting partners from member universities. So in short, ODRD has played a major role in my research and also for ORAU.

Michael Holtz: Right. Absolutely. And I know for this particular project, your collaborator was just up the road, as we say, and at [crosstalk 00:15:29], so.

Dr. Balajee : Yeah, Dr. Rachel McCord. So I was really happy to find her because she is very close, and having a collaborator in the same city is really important. You can exchange ideas, you can call on them if you have any queries or concerns and the exchange of research materials like cell lines and other staff, it worked great. I mean, we continued to collaborate and we have a lot of projects in mind for the future, so that is going to continue. So we are even planning to submit a hedge proposal on this. So NASA is also very much interested in understanding the chromatin structure and the disease outcome in astronauts. With the Mars missions around the corner, they are very concerned about the cosmic radiation.

Space radiation is several fold, more harmful than X-rays and gamma rays which we use for diagnosis. So they have really tremendous amount of energy and basically they can drill a hole in your brain. That kind of powerful radiation is cosmic radiation. So yeah, they're always looking out for preventive measures and also markers to determine the extent of radiation exposure. So this is going to be great.

Jenna Harpenau: Dr. Balajee, you mentioned something a little bit earlier if there were some kind of a radiation event you would be looking for a group of people that would help you out and be able to quickly identify the markers if people have been exposed. Can you talk a little bit more about that and how you help train people and how you make that tribe of people that you trust to look at the test and look at the markers and, I guess how you prepare?

Dr. Balajee : Yeah. I'm glad that you asked this question, Jenna. That is one of our main goal for the CBL. In case of a mass casualty incidents, several hundreds and thousands of people are likely to be exposed to ionization radiation. And so, knowing the exposure dose is very critical for taking the appropriate medical countermeasures. So in this regard, we would like to increase the such capacity of a dicentric chromosome scores. Even though I talked about a lot of molecular markers for biodosimetry, still the dicentric chromosome I'd say is the gold standard. So DCA is well preferred over any of the biodosimetry technologies existing now. So we have to increase the such capacity so that we can provide a rapid biodosimetry to people who are exposed during this mass casualty incidents, radiological or nuclear. So keeping this in mind, we initiated a game, it's called the dicentric chromosome challenge game and full credit goes to Don Hanlon and his team. So they developed this game with our assistance.

And this project was funded by ORISE director's office and my sincere thanks to them for funding this exciting project. And we developed this game and the game was launched in July of this year. And we initially requested other participants of the ERC summer program, basically six teachers joined a CBL for training. So we requested them to try out the game, so they were marvelous, they did a fabulous job and they even presented at a poster based on their finding and they also gave a tremendous inputs for improving the game.

So till to date, the game has been played by more than 1000 individuals from so many biodosimetry laboratories are on the globe. I'm quite excited about this, and this is one way of training people how to score dicentric chromosomes. It's a game, so people will be interested to try out and we also give a score. So people are always trying to play and improve their scoring. So what we have in mind, and those people who scored more than 90%. So we will recruit them in a registry, so we will enroll them and whenever we need their help, we can contact them. So we will just ask them to give their contact information, email address and the Institute address and all so we can contact them when we need help with dicentric chromosomal assay scoring. So this is the idea, I'm quite excited about this.

In addition to this, we are also initiating a lot of avenues, networking. So we are interested in initiating a cytogenetic biodosimetry network in the US, so there are already four or five potential labs and we have to find a way to initiate this and then do this on a regular basis. We have to do interlaboratory comparison exercise and all, so those labs are ready when the situation demands. So, that's the idea.

Michael Holtz: That's great. I actually played the game, Dr. Balajee, and I had to do it twice but I did very well the second time, so.

Dr. Balajee : Yeah.

Jenna Harpenau: Add Michael to your list.

Michael Holtz: Right?

Dr. Balajee : Yes. No, his name is already enrolled. So whoever plays, I think, but only the top scholars are enlisted in that. So-

Jenna Harpenau: There you go, Michael, it's a challenge for 2021.

Dr. Balajee : Yeah.

Michael Holtz: Right? Exactly.

Dr. Balajee : It's a challenge for 2021.

Michael Holtz: Exactly.

Dr. Balajee : And I wish more people from ORAU try this game. But we have got really good response and there are certain improvements to be made to the game. Actually, I'm looking out for funding to improve the game, so I'm really interested. There are some technical problems and issues, and Don is really optimistic in improving this game, provided we have some funding from some other sources, but I am on that. And hopefully, we will get some funding to make this game a perfect one so many people can try and learn dicentric chromosome scoring and that will work to our advantage in the future, I believe.

Michael Holtz: Right. That's exciting. The one thing that I've learned playing the game is not to overthink it. Truly like, "Here's what a dicentric chromosome looks like. Here's what you're looking for."

Dr. Balajee : Yeah. But we selected almost very good pictures, but in reality, chromosome preps are not always the same from different people. After all, we use the white blood cells, lymphocytes and we get very good chromosome perhaps from some people but I cannot say the same for other people because we have intrinsic variations. Some people's blood cells grow much better in culture than others due to various reasons. But we put the best ones so we don't want to scare away people. So they have to see good pictures first and then gradually will improve the complexity, so that's the idea. So we have different levels, low, medium and high levels.

Michael Holtz: My challenge is to get to the high level.

Dr. Balajee : So high level, I think what we are planning is, so you will see chromosomes all over the place overlapping with each other and it gives the impression that it is a dicentric chromosome but it is not, because it's simply overlapping with each other. So yeah, gradually building up the level so that you know exactly, because not every time you are going to get the perfect prep for dicentric chromosome.

Michael Holtz: Sure, sure. Dr. Balajee, is there anything you want to add that we haven't talked about?

Dr. Balajee : I pretty much summed up everything, but there are a few projects that are ongoing now. So one is the lipidomic profiling, basically lipids in our body. So that is a field known as metabolomics. So there is a recent paper on metabolomics after ionization radiation exposure. So when we are exposed to radiation, there are a lot of changes in lipid profiles. When you go for do a blood test, so they do the lipid profile. You are aware of this, saturated fatty acids, non-saturated fatty acids, cholesterol, the LDL, HDL. So the lipid profiles, they change after radiation exposure and we have a way of detecting them for radiation exposure. So this project we initiated with Oak Ridge National Lab, Dr. John Kao, he's collaborating with us. And Oak Ridge National Lab, they developed a device known as [Pen Doc 00:00:25:40]. So you have to just touch the sensor and it'll give you the lipid profile.

So we are actually developing a lot of signatures, lipid signatures for identifying the exposed people. And so, if we have some lipid markers, we can quickly tell who is exposed to radiation, who is not. So I'm quite excited about this project. We have even written a white paper and we plan to submit to all the funding agencies, like NASA DOD, DOE, and the BARDA, DARPA to name a few. So I'm quite excited. So with funding, we will be able to accomplish some of the lipid signatures for ionizing radiation exposure. And the cool thing about this is it doesn't take too much time because we have a Pen Doc device, all you have to do is touch the sensor and it'll give you the lipid profile. Probably a fraction of a second, you get you a lipid profile.

Michael Holtz: So you don't have to get a needle stick, you don't have to get a-

Dr. Balajee : No, no, nothing. I mean, this is like a pen, a Pen Doc, it's like a pen. You would just touch the tip of the pen, that's all. No, no, there is no... Nothing.

Michael Holtz: Oh my goodness.

Jenna Harpenau: That's very cool.

Dr. Balajee : Yeah, that's very cool. And we are also trying to use this technology for finding out people who are intrinsically radiation sensitive. We have a radio sensitive population. Of course the number varies anywhere from five to 10 percent of the human population and they are radiation sensitive, so you have to be really careful. So if such people develop cancer, then you have to moderate the dose, you cannot use the regular dose which you use for normal people. These people are radiation sensitive so you have to adjust the radiation therapy. And so, for the screening, I think this Pen Doc would be very useful, they don't need to go through laborious procedures, but just to touch the Pen Doc and then you get the signature. So, probably I'm over-exaggerating a little bit, but I think this is a potential possibility for the future. So once we have radiation specific lipids that change after exposure, we can use them as a surrogate for biodosimetry. So, that's an idea.

Michael Holtz: That's exciting.

Dr. Balajee : Yeah. And last but not the least. So I'm collaborating with the Columbia University Medical Center and everybody is talking about COVID-19. So what are the damages caused by this virus to our body? And we are planning to submit a proposal which is not completely finalized for ODRD. So we plan to examine the residual damage on those people who got infected with COVID-19. They might have recovered now, but we don't know what kind of damage was caused to their blood cells, white blood cells. And if such patients are also radiation sensitive, something changed in them that made them more radiation sensitive or not. So we are planning to submit this proposal so we can use the standard technologies for screening this COVID-19 patients to find out whether anything changed after this infection. So I'm quite excited about this.

Michael Holtz: That is exciting and certainly would be useful information.

Dr. Balajee : Yeah, because most of the viruses, they cause DNA damage and chromosomal damage. So we don't know anything about this so we thought it's better to investigate those people who got infected with the COVID-19 to see they have any residual damage left behind. So if it is promising, then we will expand this study. So right now, it's quite exciting.

Michael Holtz: You are always doing some of the coolest research, Dr. Balajee.

Dr. Balajee : No. Thank you, Michael. Thank you, Jenna. So this kind of encouraging words actually motivate me, so I need this. I need boosting all the time.

Michael Holtz: Well, we're here-

Dr. Balajee : If nobody cares, and then I think, "Oh, probably I'm not doing anything interesting. I'm not going to attract people's attention." So when people tell all these good things, that really motivate me and inspire me to do more, so that is really important. And so, you have to be really generous to appreciate someone, you have to have a big heart to appreciate someone, so I really, really appreciate your gesture, thus it needs a little bit more to come out and appreciate someone I know how valuable it is.

Jenna Harpenau: Well, we learn something every time we talk to you, so you're helping us.

Michael Holtz: Definitely.

Dr. Balajee : Yeah. There are so many things to tell, and sometimes when you talk, it doesn't come to your mind and then probably when they get off, "Oh, I should've mentioned this. I should have mentioned that." And before I close-

Michael Holtz: Well, we can always have you back.

Dr. Balajee : Yeah, before I close, I would like to thank, definitely Dr Iddins, REAC/TS director and the entire team. They have been a tremendous support to me in whatever research avenues I undertake and so I really, really should mention this. Every one of them is so helpful to me, as for actually make me going further and further with research. So I would not have done all this without their help, so.

Michael Holtz: Sure, absolutely.

Dr. Balajee : And I also think ORAU and all the people I interact with. Like I mentioned, many times before, ODRD has done a phenomenal thing to me personally and scientifically. Without their funding, I would not have ventured into many of these exciting possibilities. So again, thanks to the ODRD team for funding all my research so far.

Michael Holtz: Well, we look forward to having you back to talk about more research funded by ODRD or others, so.

Dr. Balajee : Absolutely. I'll be glad to come on and share my latest things on research and I can also tell you how successful I am or how unsuccessful I am. Not everything works in science, sometimes you have to work hard and...

Michael Holtz: That's part of the process, right, I mean...

Dr. Balajee : Yes, that is part of the process. And that is a process of evolution, when you do something wrong, and then you learn your mistake, and then rectify them and move on. So if you think a particular project is really worth doing, so you don't really bother about the setbacks but you find a way to proceed with that because our overall goal is really what we're pursuing, so that's very important.

Michael Holtz: Absolutely. Dr. Balajee, thank you so much for spending your time with us today.

Dr. Balajee : Oh, I'm happy to do this and thanks to you and Jenna for having me on this podcast. I really enjoyed pretty much.

Michael Holtz: Well, we will have you back soon. Thank you so much.

Jenna Harpenau: Yeah.

Michael Holtz: Thank you. Thank you both.

Speaker 2: Thank you for listening to the ORISE Featurecast. To learn more about the Oak Ridge Institute for Science and Education, visit orise.orau.gov or find us on Facebook, Twitter, and Instagram at ORISE connect.