Identifying Novel Drug Treatment Options for Pediatric Osteosarcoma

Osteosarcoma is highly metastatic and drug-resistant cancer. The survival rate for metastatic osteosarcoma remains less than 20 percent for the last 40 years. Tomoo Iwakuma, MD, PhD, is leading research focused on the elucidation of mechanisms underlying osteosarcoma progression and the discovery of novel drugs against this osteosarcoma. His laboratory has identified a lead compound that specifically killed canine and human osteosarcoma cells lacking the activity of the tumor suppressor p53, with minimal impact on non-tumor cells. Join us as we visit with Dr. Iwakuma about this promising research.

Featured Speaker:

Tomoo Iwakuma, MD, PhD

Tomoo Iwakuma, MD, PhD, is Director of the Translational Laboratory Oncology Research Program at the Children's Mercy Research Institute and the Frank B. Tyler Professor of Cancer Research and Adjunct faculty, Department of Molecular & Integrative Physiology, at Kansas University Medical Center. Dr. Iwakuma's research focuses on cancer progression.

Learn more about Tomoo Iwakuma, MD, PhD (http://www.kumc.edu/school-of-medicine/cancer-biology/faculty/tomoo-iwakuma-md-phd.html)

Transcription:

Dr. Michael Smith (Host): So our topic today is identifying novel drug treatment options for osteosarcoma. My guest is Dr. Tomoo Iwakuma. Dr. Iwakuma is the Director of Translational Laboratory Oncology Research at Children’s Mercy. Dr. Iwakuma, welcome to the show.

Dr. Tomoo Iwakuma (Guest): Thank you very much.

Host: So I know you were involved in an important research study. Why don’t you tell us a little bit about that study and what prompted you to do this.

Dr. Iwakuma: Sure so this research is supported by Braden's Hope and related to the novel therapeutic compound that can specifically kill the cancer cell, which in this case is osteosarcoma cells lacking the most frequently mutated human gene called p53, tumor suppressor p53.

Host: And so this study was specifically looking for any – multiple compounds that might be able to achieve your goals, is that correct?

Dr. Iwakuma: Correct. So why I’ve been doing the osteosarcoma is I am originally orthopedic surgeon in Japan and then I had a clinical practice by treating the patient with osteosarcoma. The current therapeutic modality has a limitation and I knew in the end, you know, aggressive osteosarcoma, you have no treatment options, so nothing you can offer to the patient. I really don’t like that. So I want to discover the novel strategy, or novel compound, novel drug that can kill the cancer cells, especially in

my case osteosarcoma. That is most frequent type of bone cancer.

Host: So when you were going into this research, when you decided that this was something you wanted to study, did you already have in mind some compounds that might be able to work in this specific case of osteosarcoma?

Dr. Iwakuma: That is a great question. Actually this research initially started with Meet West Cancer Alliance Collaboration with medical doctor, hematology oncology doctor, Dr. Joy Fulbright at Children's Mercy and then we wanted to find out the compound that specifically kills osteosarcoma cells both in canine and human osteosarcoma cells but doesn't kill the normal non-tumor cells. So to do that we started the Life Chemical Library Screen, basically compound library screen. This library contains many, many, many unknown and the known including FDA approved compounds. So then we just did the test or screen. Then we identified many of the potential candidates, which only killed canine and human osteosarcoma cells but did not kill the non-tumor cells. That is in collaboration with high throughput screening core facility in KU.

Host: Once you were able to identify – I guess from that initial research, looking into that library of compounds. How many compounds are we talking about that you initially were looking at and how many were you able to identify as candidates?

Dr. Iwakuma: Over 150,000 compounds we started with. So then –

Host: Wow, that's a lot of work.

Dr. Iwakuma: Right, a lot of work and I have to give credit to the high throughput core facility, you know? And then we picked out 176 compounds as candidates.

Host: Wow, 176 out of the 150,000?

Dr. Iwakuma: Correct.

Host: Where are you at with these 176 compounds? What's the next step to?

Dr. Iwakuma: So many validation procedures and we narrow down one compound. It's called a KU compound.

Host: So you've identified out of that initial 150,000 compounds, you've identified the KU compound. This is the one that is going to give, what you believe to be the best therapeutic outcome?

Dr. Iwakuma: Yes, there's great potential I would say. So we confirmed this KU compound only kills the cancer cells but doesn't kill the normal cells. So eventually we found multiple, multiple osteosarcoma cells – cell lines available, and then turns out this compound has only killed a certain population of the osteosarcoma cells. Even osteosarcoma cells, if the osteosarcoma cells carry the wild type p53, this compound doesn't kill. So normal cells always have wild type p53, most of the time, so that's why it didn't kill, but even osteosarcoma cells which have the wild type p53, this compound doesn't cure it, but if the cell lacks the wild type p53, this compound kills it. So this means this compound is cancer specific,

that is the most important part. Our body has wild type p53, intact p53. Only cancer lose the wild type p53 activity, right?

Host: Right, so this is a very highly specific targeted therapy that at least that's the potential.

Dr. Iwakuma: Exactly, so then, what is ideal – if you think about what is the ideal chemotherapy drug? Currently chemotherapy drugs kill both the normal cells and the cancer cells but this drug, I expect it to only kill the cancer cells lacking p53 activity. Wild normal cells have the intact p53, that's why it doesn't kill. Does that make sense?

Host: Yes absolutely, so what you have found, or at least the potential compound, the KU compound is one that is going to be very therapeutic, very efficacious, yet at the same time going to keep side effects down, the toxicity is going to be lower with this compound.

Dr. Iwakuma: Yes, toxicity is a key one, yes.

Host: That's exciting news.

Dr. Iwakuma: It is exciting. I'm very excited about this. [laughter] So one important thing with this, how often cancer cells or osteosarcoma cells lose the p53 activity, so recent genome-wide sequencing result, not our group result, but other groups show that almost over 85% of osteosarcoma have some abnormality in the tumor. 85% so that's very high.

Host: Which means that gives you a large potential patient population you're going to be able to treat.

Dr. Iwakuma: Right, correct. Moreover, generally as I said, p53 is the most frequently mutated gene in human cancer. So over 50% of human cancers lose the p53 activity. So that's why –

Host: That's all cancer, that 50% is all cancer?

Dr. Iwakuma: All cancer, all cancer, 50%, so you would expect half of the patients to have benefit from this.

Host: Right, I can see why you're so excited.

Dr. Iwakuma: Yep, yep. So even this drug – this compound could work for other types of cancer. As a part of my study, I checked other types of cancer, head and neck cancer and liver cancer and colon cancer. It's like that. If the cell has wild type p53 it's very hard to kill, but if the cell lose wild type p53, it done. So it doesn't select the type of cancer.

Host: Right, very nice. So Dr. Iwakuma, let me ask you this then. Obviously this is still at – you're at the very basic science research phase of this. What's your hope now. This sounds like something we need to move into some clinical trials. What do you see here? Give us your vision.

Dr. Iwakuma: So Braydon's Hope, it really supports our research to bring this compound to the clinical trial. So then we checked whether this compound has any stability, portability, and efficacy in cells or

even in bodies. So we found this compound unfortunately it metabolizes very quick in the human body. So now we understand which part of the structure, clinical structure, we need to modify. We know it now. We learned it. We know where the breaking point. Where is the breaking point, where we need to modify, we know that.

Host: And that's then going to help with the bioavailability of the KU compound.

Dr. Iwakuma: Exactly. It's going to help the bioavailability. It will be much more stable in our body and it keep killing the cancer, that's our hope.

Host: So Dr. Iwakuma, let me ask you, very exciting work, right? This is fascinating to me and I'm glad that we've had a chance to talk. Has some of this been published yet or presented?

Dr. Iwakuma: Well we kind of briefly presented this last to the American Cancer Society – Research Society, AACR.

Host: Is there plans to publish?

Dr. Iwakuma: Oh yes.

Host: There should be right? You're very excited about this. This is a great finding.

Dr. Iwakuma: And I want to know why this drug only cures the mutant – p53 lacking cancer cells. Why not –

Host: Yeah, interesting question, right? Yeah.

Dr. Iwakuma: Why not killing the wild type p53 cells?

Host: Yeah, that's very intriguing and I look forward Dr. Iwakuma to follow your research and see where this goes.

Dr. Iwakuma: We do have some preliminary data. We have some ideas, but once we confirm the mechanism of action then we will publish, probably in a year or so.

Host: That sounds fantastic. Dr. Iwakuma, I want to thank you for the work that you're doing at Children's Mercy. This is very impressive. I look forward to reading your publication on the KU compound and I want to thank you for coming on the show today. You're listening to Transformational Pediatrics with Children's Mercy Kansas City. For more information, you can go to childrensmercy.org, that's childrensmercy.org. I'm Dr. Mike Smith, thanks for listening.