Science Translational Medicine Podcast

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Host – Angela Colmone
Hello, I'm Angela Colmone. Welcome to the *Science Translational Medicine* Podcast for October 17th, 2012.

In this show, I will be speaking with Ashok Saluja of the University of Minnesota about a potential new treatment for pancreatic cancer.

Pancreatic cancer is one of the most deadly human cancers. Ninety-five percent of people diagnosed with this cancer will not be alive in five years. One reason for this dismal cure rate is that pancreatic cancer grows without any symptoms at first, which means it is often quite advanced when it is finally discovered. In more than 80% of patients, the tumor has already spread when they are diagnosed, and it can't be completely removed by surgery. The standard of care for metastatic pancreatic cancer is gemcitabine, which only helps a small percentage of patients, so new drugs are desperately needed. Ashok Saluja and his team have synthesized a new drug called Minnelide that successfully treats mice transplanted with human metastatic pancreatic cancer.

Here now is Dr. Saluja on the line to tell us more.

Interviewer – Angela Colmone
Welcome, Dr. Saluja, and thanks for joining us.

Interviewee – Ashok Saluja
Hello, Angela. Nice to be with you.

Interviewer – Angela Colmone
So how did you come up with Minnelide as a potential drug for pancreatic cancer?

Interviewee – Ashok Saluja
We've been working on pancreatic diseases for the last 30 years. About 15 years back, we started working on a set of proteins known as heat shock proteins and particularly Hsp70. What we discovered is that if you upregulate Hsp70 in mice and rats and cells, then those mice and rats have protected against pancreatitis, which is a benign disease of the pancreas but is inflammation and very painful. From those studies, which we've been doing for the last 15 years, we had proposed that Hsp70 protects cells from dying. About eight, nine years back, we started thinking about pancreatic cancer, which as you described, is probably the most deadly cancer known to humankind. And none of the chemotherapies or any drugs work for that. And we kind of reasoned—knowing what we know about heat shock proteins—that maybe these tumors don't respond to

chemotherapy because they might have too much of this protein—the good protein—Hsp70, which protects cells. And it turns out that was the case. These pancreatic tumor cells have too much of Hsp70. Once we figured out that's what it is, we started looking for inhibitors for Hsp70, because if we inhibit this overexpressed protein in tumor cells then that should decrease the tumor size and start killing these cells. It turns out that there were not many inhibitors known to inhibit Hsp70. In fact, actually there was only one compound, Quercetin, which was known to inhibit Hsp70 five, six years back. And that's not a very good compound because you need very high doses, which become toxic. We found for the first time that a natural compound, triptolide, which is derived from a plant in China, is very effective in inhibiting heat shock protein 70 in tumor cells.

Interviewer – Angela Colmone
And what stopped triptolide from working as a clinical therapeutic?

Interviewee – Ashok Saluja
Triptolide, which was very effective in killing tumor cells, had problems because it's not soluble in water; it's soluble only in DMSO and alcohol. That limits its clinical utility. So we—in collaboration with the Medicinal Chemistry department at University of Minnesota—we modified this compound and produced a novel new compound, which we call Minnelide, that is coming from Minnesota and triptolide.

Interviewer – Angela Colmone
Is Minnelide as effective as triptolide in treating preclinical models of pancreatic cancer?

Interviewee – Ashok Saluja
So Minnelide is a water-soluble form of triptolide, which is very effective in not only killing the tumor cells in culture but also in many different animal models. It is as effective, if not more effective.

Interviewer – Angela Colmone
How does Minnelide compare to the current standard of care, to gemcitabine?

Interviewee – Ashok Saluja
Good question. We have compared head-to-head comparison with the current state-of-the-art therapy gemcitabine, or Gemzar—it's sold as Gemzar by Eli Lilly—which as you had mentioned, is effective only in a very small percent of patients. In fact, the data suggests that gemcitabine adds about six weeks to the survival for pancreatic cancer patients. When we did head-to-head comparison with gemcitabine and Minnelide, Minnelide is far more effective than gemcitabine.

Interviewer – Angela Colmone
That's fantastic. So why is it necessary to look in multiple animal models before moving new drugs into the clinic?

Interviewee – Ashok Saluja
First of all, there's really no perfect model to study any disease process for that matter and particularly not for pancreatic cancer or any cancer. Every model adds something. For example, when we take human cell lines, we cannot grow them as tumors in immune-competent regular mice, or black mice which we call, because the mice will reject them because of the immune reaction. So we have to put them in immune-incompetent mice, which we call nude mice. And in those mice, then these cells will grow, and we can check the effect. So if you have human cell lines, then you have to use immune-incompetent or nude mice, which certainly has the advantage because we are using the human cell lines. But the disadvantage there is these mice are unlike human beings, where we have immune reaction and where we can—with the immune reaction—we can form stroma. We can surround the tumor cells with the adult cells, whereas in nude mice that doesn't happen. So in order to take care of that, we have to use some immune-competent mice, and for that we have to use genetically modified models, which somewhat recapitulate what happened in patients, except these are mouse cells. So that's an advantage and at the same time that is a shortcoming of that. The third model which one can use is where we take fresh tumor cells—fresh tumors—and implant them into animals and mice. And that probably we think is the most realistic situation to the patient. So one has to use multiple models and in sum total of all of these models is what I think should lead to a successful drug discovery. However, I want to stress that just because something works in animal models, that does not mean it will necessarily work in humans.

Interviewer – Angela Colmone
So what's the next step in moving Minnelide into treating patients?

Interviewee – Ashok Saluja
This is a long process. We need to have the FDA approval to start clinical trials. And we are getting very close to that. As a matter of fact, just last month, we had what we call pre-IND meeting with FDA, and it was quite positive. They want us to do one more small bridging study, which is underway, and it should be done in the next three, four months. So we are hoping that in the beginning of next year—hopefully in February/March—we will have this drug for the first time in humans.

Interviewer – Angela Colmone
Dr. Saluja, thank you so much for joining us today and congratulations on a fascinating paper.

Interviewee – Ashok Saluja
Thank you.

Host – Angela Colmone
That was Ashok Saluja of the University of Minnesota. Check out his paper on the *Science Translational Medicine* Web site at stm.sciencemag.org.

I'm Angela Colmone, thanks for listening!

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