



Science Translational Medicine Podcast

Transcript, 18 August 2010

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Host – Annalisa VanHook

Welcome to the *Science Translational Medicine* Podcast for August 18, 2010. I'm Annalisa VanHook, and today I'm speaking with Yung-Chi Cheng about new work from his group that evaluates the efficacy of an ancient Chinese herbal remedy for treating the gastrointestinal side effects of chemotherapy. Dr. Cheng joined me on the phone from the Yale University School of Medicine.

Interviewer – Annalisa VanHook

Welcome, Dr. Cheng.

Interviewee – Yung-Chi Cheng

Thank you.

Interviewer – Annalisa VanHook

Which ancient herbal remedy did you test, and what condition is it supposed to treat?

Interviewee – Yung-Chi Cheng

This herbal remedy is based on the formula which was first established 1,800 years ago, and it is called Huang Qin Tang. And it was used for treatment of diarrhea and GI disorder[s] for many years and still used today.

Interviewer – Annalisa VanHook

the herbs eaten or is it taken as a tea?

Interviewee – Yung-Chi Cheng

Put all four herb together, and they cook it, and they drink the extract.

Host – Annalisa VanHook

Although there is anecdotal evidence that Huang Qin Tang works for treating GI ailments, there haven't been any systematic scientific studies of the effectiveness of the remedy. And so Cheng's group set about testing the efficacy of Huang Qin Tang in mice.

Interviewee – Yung-Chi Cheng

So, we want to see whether this herb can be used to alleviate side effects associated with the cancer chemotherapy, with a focus on GI disorder. But in order for us to explore that, we have to ensure that this herbal mixture will not interfere [with] irinotecan's action on the tumor.

Interviewer – Annalisa VanHook

So, this drug, irinotecan, then, it causes gastrointestinal side effects in mice that are similar to what it would do in humans?

Interviewee – Yung-Chi Cheng

In many ways they are very similar to. So, we use the tumor model and mice model to assess whether this herbal mixture will compromise chemo effect on tumor. And also, whether it will decrease the global toxicity of the mice. This include the weight loss and also mortality.

Interviewer – Annalisa VanHook

Did the herb in any way interfere with the chemotherapy?

Interviewee – Yung-Chi Cheng

It turned out not only do not detract chemo against tumor; it actually enhance the chemo action on the tumor. It also decreased the side effect of the chemo in mice. So, in essence you're increasing anticancer drug action but also decreasing anticancer drug side effects.

Interviewer – Annalisa VanHook

Did you determine how this herb mixture works – the mechanism by which that mixture of compounds relieves the gastrointestinal symptoms?

Interviewee – Yung-Chi Cheng

There are two major impact[s] in the GI tract. First, decrease the inflammatory process caused by chemo on GI tract. And the mechanism involved in decreasing this inflammatory, [there are] at least three mechanisms. One is iNOS inhibition, another is Cox2 inhibition, another is NF-κB pathway inhibition. So, these three mechanisms,[are] actually mediated through different chemicals in the herbal extract.

Interviewer – Annalisa VanHook

Did you isolate those chemicals from the herbs?

Interviewee – Yung-Chi Cheng

The for these three, we are currently trying to explore further what are the chemicals. So, we do know they are distinct, the chemicals. So, in essence this mixture not only have a multiple site of action and also have a different chemical against different actions. Okay, so that's the first aspect. The second is also enhance the recovery of the damaged tissue.

Interviewer – Annalisa VanHook

The damaged gastrointestinal tissue?

Interviewee – Yung-Chi Cheng

Yes, that's correct. And this is mediated through increasing the progenitor cells' growth. So, the progenitor is likely [to] come from stem cells. So, in essence, we accelerate stem cell/progenitor cell growth. The mechanism underlying it—at least partly—is due to

enhancement of the Wnt pathway. This mixture have action on Wnt pathway through two different mechanisms. First is increasing the transcript of several of the proteins involved in Wnt pathway. Second is to potentiate the action of the Wnt on that pathway. The chemical involved in potentiation of the Wnt pathway is a flavonoid, the chemical already been worked out, so we are in the final stage of finishing these studies.

Interviewer – Annalisa VanHook

Did you try testing these herbs individually?

Interviewee – Yung-Chi Cheng

We need all four herbs. If we delete any one of it, it's not as good. We also test each single herb; it's not as good as [when] you have four herbs. So, four herbs are required, multiple action is mediated—even in the GI—and then the mechanism is multiple ,then different chemical in these herbs is involved.

Interviewer – Annalisa VanHook

So, the components of these herbs are acting together synergistically.

Interviewee – Yung-Chi Cheng

So, it could act synergistically, in some of those actions, and additive, or antagonistic. In essence, this cannot be explained by any single chemicals in the mixture. But, deletion of any of those herbs, you have a different impact on three biological endpoints. So, it means the mechanism cannot be the same for those three biological endpoints. So, it's a totally new concept in looking to from reductionist approach.

Interviewer – Annalisa VanHook

When you took this herbal remedy into the lab – being composed of natural products and being an herbal remedy that's made by different people, how did you ensure that the batches of the herbal remedy that you were using were consistent? I mean, how did you control for that sort of thing?

Interviewee – Yung-Chi Cheng

So, started with a herbal source, okay, in collaboration between PhytoCeutica, which is a Yale-sponsored company – both Yale and I are cofounder, I have to declare – and in collaboration with a long-experienced herbal company in Taiwan, called the Sun Tan, Corporation – they choose the proper herb and then follow PhytoCeutica instruction to make GMP-type material, Good Manufactur[ing] Practice.

Interviewer – Annalisa VanHook

So, those are sort of quality-controlled, consistent products.

Interviewee – Yung-Chi Cheng

Yes, that's correct. Then you need to assess mixture – how consistent from one preparation to another. Since we have no idea what are the chemical involved and in the actions, and also what could be the potential site of actions, so we decide to use a global approach. This include[s] both chemical and the biological fingerprinting technology.

Then analyzing by software called the Phyto Similarity Index, which is create[d] by PhytoCeutica together with a colleague at Yale. And then, using this very sophisticated technology, we [are] analyzing our product. Even five years apart, different batch of herbs show Phyto Similarity Index of 0.95, with one [as a] total match, zero is no match. So, then we compare these PHY906 preparation with commercially available Huang Qin Tang from different companies. The similarity index vary from 0.65 to 0.90, okay.

Interviewer – Annalisa VanHook

PHY906 is the name you use for this herbal remedy.

Interviewee – Yung-Chi Cheng

That's correct. So, there's so, in essence, PHY906 shown to be active doesn't mean all the Huang Qin Tang are active.

Interviewer – Annalisa VanHook

Because what you can find in the herb shop is going to vary.

Interviewee – Yung-Chi Cheng

Yeah. So, that's why we keep calling [it] PHY906, we don't want [it] to be confused [with blends purchased from other providers].

Interviewer – Annalisa VanHook

Right. PHY906 is a set formulation with specific qualities that you can monitor.

Interviewee – Yung-Chi Cheng

That's right.

Interviewer – Annalisa VanHook

Have you started systematically studying this remedy in humans, how it acts in humans?

Interviewee – Yung-Chi Cheng

We have done several clinic trial in the more in the phase 1/2 stage. The first one is a randomized and placebo crossover design for colon cancer. In this placebo trial, only 17 patients is involved. This was the first-line therapy for colon cancer, so those were done in naïve, chemo-naïve patients. We have two cycles: One cycle is with or without a herbal remedy – one arm without has placebo there, so patient doesn't know, physician doesn't know. Then, the same patients switched over, the second cycle do not have [the herb]. If they do not have [the herb during] the first cycle, the second cycle they will have [the herb]. So that's what we call the crossover.

Interviewer – Annalisa VanHook

The patients receive the drug either in the first part of the study or the second part of the study, but they don't know which. And so, then, the patient's reaction to the drug is sort of gauged against that patient's own reaction to the placebo.

Interviewee – Yung-Chi Cheng

Yeah. So, the purpose of that study is to see whether we decrease the side effect with our protocol. In the patient[s] who receive chemo alone, that cycle, they have expected side effects, this including diarrhea, nausea, vomiting, fatigue. And that's a Grade 3-Grade 4, a serious one. If you looked on another arm, which received PHY906, you find out that actually substantial drop of the side effects. So, in essence, with this small number of patients, we have evidence to substantiate. This require[s] further studies.

Interviewer – Annalisa VanHook

It's the gastrointestinal and other side effects of chemotherapy that ... they get so bad that the patients will stop the chemotherapy because the symptoms are so severe.

Interviewee – Yung-Chi Cheng

That's correct.

Interviewer – Annalisa VanHook

And so, this could potentially help people be able to tolerate chemotherapy longer.

Interviewee – Yung-Chi Cheng

And also, these drugs—don't forget—in our animal studies even enhance those compounds – chemo against tumor. So, they may not only help the relief they may even have a more pronounced anticancer action of those chemo. So, by that study we found it, but unfortunately we cannot continue this study because the FDA changed the first-line protocol, so we stopped. So, now we just complete another phase I/II study—a phase 1 study at Yale. So, we're escalating the 906 dosage, see whether 906 have exerting some side effects by itself, with a fixed amount of irinotecan. So, this study is just complete, the paper is in the process [of] being written up. The conclusion: We do not see 906-associated side effects. In essence, the dosage we use do not cause additional side effects.

Host – Annalisa VanHook

Cheng's group would also like to test PHY906 on patients who are on their second round of chemotherapy.

Interviewer – Annalisa VanHook

Then, presumably then the next step is to go on to evaluate its efficacy.

Interviewee – Yung-Chi Cheng

So, now it's no longer [in what] we call the “chemo-naïve” patient – it's actually, it's a chemo-refractory patient. Those patient already been through the first-line therapy. We use those to do the study. They have tumor progression. So, in essence, it's for second-line therapy.

Interviewer – Annalisa VanHook

You'll be testing it in patients that are onto their second round of chemotherapy; the patients are getting very aggressive chemotherapy treatment.

Interviewee – Yung-Chi Cheng

That's right. So, that trial will be initiated if we have the resource.

Interviewer – Annalisa VanHook

Interviewer – Annalisa VanHook

Well, thank you, Dr. Cheng.

Interviewee – Yung-Chi Cheng

Goodbye. Have a good day.

Host – Annalisa VanHook

Yung-Chi Cheng is senior author of a Research Article published this week in *Science Translational Medicine*. That paper is by Lam and colleagues, and it's titled, "The Four-Herb Chinese Medicine PHY906 Reduces Chemotherapy-Induced Gastrointestinal Toxicity."

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