UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
APOTEX INC., and APOTEX CORP.,
EMCURE PHARMACEUTICALS LTD.,
HERITAGE PHARMA LABS INC.,
HERITAGE PHARMACEUTICALS INC.,
GLENMARK PHARMACEUTICALS, INC., USA,
GLENMARK HOLDING SA,
GLENMARK PHARMACEUTICALS, LTD., MYLAN LABORATORIES LIMITED, TEVA PHARMACEUTICALS,
FRESENIUS KABI USA, LLC and WOCKHARDT BIO AG,
Petitioners,

v.

ELI LILLY & COMPANY
Patent Owner.

Case IPR2016-00318
U.S. Patent No. 7,772,209

VIDEOTAPED DEPOSITION OF PATRICK J. STOVER, PH.D.
Chicago, Illinois
Friday, February 10, 2017

Reported by: PAULA CAMPBELL, CSR, RDR, CRR, CRC

Job No: 118359

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February 10, 2017
9:11 A.M.

Videotaped discovery deposition of PATRICK J. STOVER, Ph.D., held at the offices of BRINKS GILSON & LIONE, 455 North Cityfront Plaza Drive, Chicago, Illinois, pursuant to notice before Paula Campbell, CSR, RDR, CRR, CRC.

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ALSO PRESENT:
Robert Zellner, Videographer

VIDEOGRAPHER: Good morning. This is the start of tape labeled number one of the videotaped deposition of Patrick J. Stover, Ph.D., in the matter of Sandoz, Inc, et al., versus Eli Lilly and Company in the United States Patent and Trademark Office, before the Patent Trial and Appeal Board, Case Number IPR2016-00318.

This deposition is being held at Brinks Gilson & Lione at NBC Tower, 455 North Cityfront Plaza Drive, Suite 3600, Chicago, Illinois, 60611, on February 10th, 2017, at approximately 9:11 A.M.

My name is Robert Zellner, from TSG Reporting, Inc., and I am the legal video specialist. The court reporter is Paula Campbell in association with TSG Reporting.

And will counsel please introduce yourselves for the record?

MR. KRINSKY: David Krinsky of Williams & Connelly, LLP on behalf of Patent Owner Eli Lilly and Company. With me is James Leeds of Eli Lilly and Company.

MS. LYDIGSEN: Laura Lydigsen of Brinks

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P. STOVER

Gilson & Lione for petitioner, Sandoz Inc., and with me is Bryan Richardson, also of Brinks Gilson & Lione.

VIDEOGRAPHER: Thank you.

Will the court reporter please swear in the witness?

REPORTER: Would you please raise your right hand.

P A T R I C K S T O V E R,

called as a witness, having been duly sworn, was examined and testified as follows:

MR. KRINSKY: And just before we begin, to make it clear for the record, I understand there are a number of other parties who are on the telephone who will be identified by e-mail later?

MS. LYDIGSEN: Correct. We will contact them.

EXAMINATION

BY MR. KRINSKY:

Q. All right. Good morning, Dr. Stover.

A. Good morning, David.

Q. Have you ever been deposed before?

A. I have not.

P. STOVER

Q. Okay. Well, I'll give you the -- you have probably heard this from your counsel, but just so you understand the flow of the proceedings --

A. Sure.

Q. -- I'm here to ask you questions. Your answer suggests that one rule that perhaps you need to get used to is I'll ask questions, your counsel will object if she has an objection, and then, you should give your answer, but for the court reporter's sake, we should all try to avoid talking over each other. I will try not to interrupt you. You try not to interrupt me. It will go more smoothly that way.

A. Certainly.

Q. And regardless of whether your counsel objects, you're obligated to answer my questions unless she instructs you not to answer and you follow her instruction.

A. I understand.

Q. You're not a medical doctor, are you?

A. I am not.

Q. You have a -- you have a Ph.D.?

A. I do.

Q. What is that Ph.D. in?

P. STOVER

A. Biochemistry -- biochemistry and molecular biophysics.

Q. And what do you see -- for purposes of this proceeding, how would you categorize your expertise? What do you see yourself as an expert in --

A. Certainly.

Q. -- for today's purposes?

A. Absolutely. I am an expert in folate metabolism. I think I am recognized as one of the global leaders in that area, just in terms of knowledge of the metabolism and the work that I have contributed to that field.

My Ph.D. focused primarily on enzymology. So I am very familiar with enzymes, how enzymes are analyzed, how inhibitors are designed, how inhibitors are characterized.

My current position is Director of the Division of Nutritional Sciences at Cornell University. I've been there since 1994. Prior to that -- in the Division of Nutritional Sciences, so I am a -- also considered an expert in nutrition and human nutrition, and I did my post doc at UC Berkeley in the Department of Nutritional Sciences.

So my background, I guess, I would put in

P. STOVER

three spheres. One is in knowledge of one-carbon metabolism, including folate and B-12, and the functioning of enzymes and enzymology, and in the broader area of nutrition.

Q. Do you have a familiarity with the drug pemetrexed?

A. I do.

Q. Is that something you have been familiar with prior to your work on this case?

A. Yes, I actually acquired that compound from Lilly in some publication -- a characterization of an enzyme called methylenetetrahydrofolate synthase, and we used that drug, along with other Lilly drugs, to try to understand the trafficking of folate and how it's trafficked intracellularly, how decisions are made of whether the folate to make purines or goes to make thymidylate.

Q. And when --

(A short interruption in the proceedings was had.)

BY MR. KRINSKY:

Q. When was that roughly?

A. Oh, that paper was published in '90 -- or no, in 2008, I believe. Martha Field is the first

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author.

Q. So that was published at a time when pemetrexed was already an approved anticancer therapy?

A. I can't speak to that. It was my understanding as it was, but I'm not a clinician.

Q. And you don't have any particular experience in the area of oncology?

A. I don't. I work with veterinary oncologists to try to understand how folate metabolism changes during cellular transformation. Much of my research focuses on uses of cancer models. So I am interested in how cellular transformation modifies the metabolic pathway to achieve the goals of the cancer cell.

So I have made transgenic mice where we have altered metabolism. We have crossed those mice to colon cancer models and measured things like tumor number, tumor multiplicity, so forth and so on.

So our cancer work is limited to a fundamental understanding of how nutrition interacts with genetics in cancer.

Q. So is it fair to say that you've done work

on sort of the pure science underlying the biochemistry of cancer, but not -- you haven't done work directly on human cancer treatment?

A. That would be absolutely correct. I have done work with some agencies in terms of expert guidance and consulting on the role of folate and cancer risk at the population level, but we are not talking about treatment. We are talking about prevention there.

Q. And just to be clear in what you're talking about, you are talking about the effects of folate on the incidence of cancer in the population?

A. That's correct, but it would include effects not only on incidence but on mortality at the population level.

Q. Okay. From -- from your standpoint as -- as a biochemist and an expert in folate metabolism, how does pemetrexed work to treat cancer?

A. So pemetrexed is known as a multitargeted antifolate. It's -- there is a long generation of these antifolates. Early in the 1940s, when Lederle Labs first elucidated the structure of folate and synthesized folic acid, almost immediately thereafter they began to design inhibitors or

analogs that would inhibit DNA synthesis, because they knew that this compound that they had isolated from biological material was needed for DNA synthesis. Almost immediately they came out with compounds to try to inhibit DNA synthesis.

So pemetrexed is a multitargeted antifolate. It has a hierarchy in terms of its targets. It binds most tightly to thymidylate synthase, but also is an effective inhibitor of dihydrofolate reductase, and it also has weaker -- this is all relative of course, it's a hierarchy -- weaker affinity for -- for FGAR transformylase.

Q. Is FGAR transformylase sometimes known as GARFT?

A. It is.

Q. I'm going to call it that for simplicity's sake.

A. We'll call it GARFT, absolutely.

Q. And thymidylate synthase is often referred to as TS?

A. Well, actually now the nomenclature they like TYMS, but I'll -- happy to go with TS.

Q. Okay. I think -- I think we lawyers settled on TS a while ago.

A. Okay. There you go. Well, we had too, but then these, you know, boards who change the names of genes for this and that changed it to TYMS.

Q. Okay. Well, we'll -- we'll go with TS for today, if that's all right.

A. That's fine.

Q. What is the relevance of pemetrexed's ability to inhibit these various enzymes to the treatment of cancer?

A. I'm sorry. Could you repeat?

Q. What is the relevance of pemetrexed's ability to inhibit these various enzymes to the treatment of cancer?

MS. LYDIGSEN: Objection. Vague.

A. The -- they are folate analogs. So they are structurally similar to substrates of folate-dependent enzymes. They bind to those enzymes in a competitive way so that the natural substrate can't bind, and they tend to bind more tighter than the natural substrate, thereby they inhibit the activity.

And in the case of TS, they prevent the synthesis of thymidylate, which is one of the four required bases for DNA synthesis.

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P. STOVER

Q. So pemetrexed has the effect, then, of inhibiting DNA synthesis?

A. Correct.

Q. And in order to divide, cancer cells need to perform DNA synthesis?

A. That's correct.

Q. And so, the idea then is that the pemetrexed kills the cancer cell, because it can't make DNA?

MS. LYDIGSEN: Objection to form.

A. It's more complicated than that. What you actually get is stalling of the replication fork that triggers other cellular events, among those is -- can be a ptosis or other biological event. So it isn't -- it's more complicated than you're describing it.

Q. Okay. But the -- is it fair to say that the primary mechanism by which pemetrexed works on cancer cells is by inhibiting DNA synthesis?

A. That's the leading hypothesis and the most likely explanation. I would agree with that.

Q. And that would have been the understanding of a person of ordinarily skill in the art in this case?

P. STOVER

A. I would agree with that.

Q. How does -- you understand that one of the issues in this case surrounds the toxicities that pemetrexed had been observed to cause prior to 1999?

A. I didn't address that in my declaration.

Q. You understand that pemetrexed does cause toxicities?

A. Yes, I do.

Q. And how does pemetrexed cause toxicities?

MS. LYDIGSEN: Objection. Outside the scope.

A. Pemetrexed is a multitargeted antifolate. So not only does it inhibit its primary target, or at least its highest affinity target, TYMS, but it targets other enzymes as well, as I indicated.

Toxicities, depending on the nature of the toxicity, could originate from any off-target effect. Calling -- if we are referring to the target effect as the inhibition of TS.

Q. Are you familiar with a particular toxicity called neutropenia?

A. I am not an expert in neutropenia, no.

Q. Okay. So do you know how pemetrexed causes neutropenia?

P. STOVER

A. I -- I am not an expert in how pemetrexed causes neutropenia, no.

Q. Okay. So to the extent other experts in this case have opined that pemetrexed can cause neutropenia by inhibiting DNA synthesis, you don't agree with that opinion?

A. I have --

MS. LYDIGSEN: Objection. Outside the scope.

A. I have no opinion on that.

Q. Is the same true of other particular hematological toxicities?

MS. LYDIGSEN: Objection. Outside the scope.

A. Which would you be referring to, to a megaloblastic anemia or -- which -- which --

Q. Any other hematologic toxicity.

A. Rapidly dividing cells require DNA synthesis. So if you impair DNA synthesis, you will have -- you are more likely to have both chromosomal abnormalities in those cells as well as lower rates of cell division proliferation.

Q. So one of the mechanisms by which pemetrexed can cause, and would have been understood

P. STOVER

to be able to cause, toxicities is by inhibiting DNA synthesis in noncancerous but rapidly dividing cells; is that fair?

A. That would be a hypothesis. Pemetrexed has off-target effects that can have other effects, such as its effects on dihydrofolate reductase.

Q. Well, and dihydrofolate -- you say off-target, but does dihydro -- excuse me.

Does dihydrofolate reductase inhibition have any bearing on pemetrexed's ability to treat cancer?

MS. LYDIGSEN: Objection. Outside the scope.

A. I need clarification in terms of what you are meaning in terms of treating cancer.

Q. Well, a few moments ago we discussed the, at least at a very general level, and I understand there is -- there is underlying complexity --

A. Absolutely.

Q. -- we discussed at a general level the way in which by inhibiting TS pemetrexed can treat cancer.

A. Correct.

Q. My question is: Does pemetrexed's

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