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Clerk (00:01):

[Inaudible] ARCH Development versus OSI Pharmaceutical. . . . We're ready Mr. Sullivan, whenever you are.

Peter Sullivan (01:12):

Good morning, and may it please the court. Peter Sullivan for Dana Farber Cancer Institute and ARCH Development. There are three points on appeal. I'm going to start with the Akinaga grounds. The board below found that the combination of Akinaga , [inaudible] and tan in light of the knowledge of a person of ordinary skill in the art, rendered claims 1, 2, 3, and five of the five, 12 patent obvious. And it's part—part of that determination, there was an issue that I want to focus on 'it's—it's that the board held that a person of ordinary skill in the art, knew that UCN-01 'was an inhibitor—a tyrosine kinase inhibitor, and humans and animals and that's with respect to c-Src, but also with respect to other tyrosine kinase inhibitors. We submit that was a decision without substantial evidence in the record. Now, there were three inferential jumps that the board makes in connection with finding that UCN-01 is a tyrosine kinase inhibitor.

Peter Sullivan (02:20):

It starts with Akinaga—the Akinaga reference reports that there is inhibition of something called V, viral Src. The v-Src is a mutant kinase that is found in the Rous sarcoma chicken virus... It's found in chickens. It's not found in humans. And Akinaga reported that in a test of the actual substrate of V SARC, not in cells, but like an in vitro test of the substrate that there was inhibition by UCN-01. The rest of the art 'that's used in order to come to the conclusion that UCN-01 is a tyrosine kinase inhibitor in humans and in animals, comes largely from expert testimony and staurosporine art. And staurosporine is a—is another drug—another treatment drug, that has a structural similarity to UCN-01, but they're not the same.

Judge (03:25):

Close cultural similarity.

Peter Sullivan (03:27):

Yes, yes. 'They're—they're—

Judge (03:28)

And you sort of semi disparaged the testimony, but this testimony counts and was believed.

Peter Sullivan (03:37)

We—it was, it was believed that their structural similarity and that may lead someone to look at that drug.

Peter Sullivan (03:42):

But the conclusion that was made your honor, is that that drug would act the same way as UCN-01. And that's a leap too far. And what we pointed out below to the board, was that there's actually record evidence in another Akinaga reference. It's Akinaga 1991, and that reference actually compare it. UCN-01 to staurosporine, it showed there was an—a host of differences having to do with specificity, potency, and activity. The kinds of things that you worry about when you're trying to figure out whether something inhibits tyrosine kinases. So, staurosporine was shown to not be similar in its function to UCN-01.

Peter Sullivan (04:32):

The other piece of evidence that was used to support a conclusion that UCN-01 was a staurosporine—was a tyrosine kinase inhibitor was referenced to Robinson. Robinson is also a staurosporine reference. It's actually the—the goal of the investigators in Robinson

Judge (04:58)

What about the Sanaev reference? If I've not mispronounced it.

Peter Sullivan (05:03)

Sanaev? We—we're all just guessing about that, judge. Sanaev is a UCN-01 reference, that reference talks about four unknown proteins, and it finds them one of its tests that there's a phosphorylation. What phosphorylation will tell you is that may be an indication that there is tyrasine kinase inhibition taking place. But it can also be increased phosphatase activity. And both experts agreed that you need to understand whether there was increased phosphatase activity before you can conclude that this was tyrosene kinase inhibition and doctor—

Judge Lourie (05:44):

This patent—this patent is expired, correct?

Peter Sullivan (05:44):

It is. Dr—Dr. Allen Espin's testimony on that point is found at appendix 2135, lines nine to 15 And Sanaev and Akinaga are the only two UCN-01 references. The rest of them are stars pouring references. So—

Judge (06:12):

And staurosporine differs from UCN only by a hydroxyl group. It's pretty close?

Peter Sullivan (06:19):

Right. Exactly. Its—let me get the actual statement about the difference because there—it notes that the difference actually in Okanaga 91, the investigators note that that actual difference in hydroxyl may be the precise reason why there's a difference in function. So—in so far as it's different, that difference was being described as the reason why staurosporine doesn''t act the same way that UCN-01 does.

Judge 2 (06:47):

Since it's the only difference between the two, it would have to be, inferentially, the basis for a difference in function, right?

Peter Sullivan (06:56):

That's what the investigator said. And I would agree with that presumption.

Judge 2 (07:02):

Okay.

Peter Sullivan (07:11):

Okay. There—there are two other grounds. One is alternative ground for relief based on the Hamana art, and then 'there's—and then there's a constitutional argument that we've raised. So going to the Hamana grounds, the person of ordinary skill in the art the, the grounds for Hamana were a person of ordinary skill in the art, plus Hamana, plus McGahn would render the claims that are asserted of the factual patent invalid. And the board correctly noted that the term cell death apoptosis should be equated to cell killing, and it should not be broadened to include induction of a differentiation pathway. And in that case, as Judge Lourie mentioned, this is an expired patent. The plain construction was on the basis of Phillips. And—and in this case, the court construed—the board construed that cell death was not to include differentiation and that the report and reason—the reason why that's important, 'is Hamana's art talks about converting 'benzidine negative cells to benzidine positive cells taking cancerous cells and converting to non-cancerous cells. It doesn't talk of cell killing. So,because the court—the board construed claims to, to—to exclude differentiation, that was the basis for concluding that the Hamana, the art would not be relevant. And it wouldn't—it would not be—the board were not reject, find it unpatentable, the claims on the basis of the Hamana art.

Judge (08:59):

You mentioned a constitutional argument we've already held that reexamining granted patents is—is not taking or... Is not unlawful.

Peter Sullivan (09:15):

Right. 'That's—in the Patlex decision, your honor. Yes...As we mentioned in our reply brief the Patlex decision relied in part on Supreme court precedent that included [Inaudible] substantially advances aspect of the takings clause. Subsequent Supreme court cases, including the Lingl case, L I N G L versus Chevron held that in a takings clause, we presume that the con—congressional—the Congress was provided an adequate basis. It has a law that's appropriate, whereas in the due process—due process case, you look at both the government interest and whether it's a rational basis to achieve that interest. And the takings clause—so to the extent Patlex is relying on cases involving substantial—substantial advances and the policy behind the court—legislation. It was—it—it—it can be reexamined because that law is no longer right. And—and the Supreme court took—took pains to correct that law in the Lingl case. So our position is that Patlex can be reexamined in light of the Supreme court case, and the takings clause case can be decided. We—as I said, the constitutional law issue involves both the due process and taking supplies. Both of those—

Judge (10:40):

Well, certainly due process and the extensive reexamination review process.

Peter Sullivan (10:48):

I'm sorry, your honor?

Judge (10:49):

It's certainly due process in, the IPR process.

Peter Sullivan (10:55):

It's, we're arguing substantial—substantive due process, which is rarely granted. We understand that. The basis is whether there's a legitimate government interest in a rational basis to go forward. The government's interest as expressed through this quarter and through Congress you know, looking at the statute has been that there is both dubious patents out there, and that we want to strengthen the patent community. And we submit that this—this IPRs do not have a rational basis for that second part. There was nothing in the IPR statute, it strengthens already valid patents. We can be examined—this patents expired, but you can take a patent, you can have it examined by an IPR, by a party, and then you can come through that. And then another party can come right back. There's no—there's no super presumption of validity. There's nothing that says, okay, we went through this process now it's stronger. No, 'it's just—it's just subject to more and more—more and more challenges. We submit that, that means that—that that second part that Congress talked about, wasn't met in the IPR challenge. And for those who had applied for patents under the prior regime its— it's unfair to them to be subjected to this new process. I see I'm in my—

Judge (12:19):

Okay, let's hear from the other side. Thank you.

Judge (12:32):

So you are splitting time with the government?

Brian Matsui (12:34):

That's correct, your honor.

Judge (12:35):

And they are arguing just the constitutionality question?

Brian Matsui (12:38):

That's correct, your honor. May it please the court, Brian Matsui, and I'm presenting argument for both appellees here, and I'm going to address the patentability issues. This is a straightforward, substantial evidence appeal. Even though the board made numerous factual findings, based upon the prior art adopted our claim charts in full, credited our expert in his 114 page declaration, and found ARCH's expert in his seven page declaration, not persuasive. ARCH raises no legal challenges to patentability. Instead, it raises two narrow substantial evidence issues. There's substantial evidence to support both of the findings that are challenges, but the court only needs to address one to affirm on the patentability issues. And that's the UCN-01 is a tyrosine kinase inhibitor. And we know that UCN-01 is a tyrosine kinase inhibitor because of the board found Akinaga says so. It says that at appendix 32 and appendix 29 that table one in Akinaga expressly states that UCN-01 inhibits VSRC.

Judge (13:52):

That's VSRC not CSRC.

Brian Matsui (13:54):

That's correct. Your honor.

Judge (13:55):

Their argument is predicated entirely on the distinction.

Brian Matsui (13:58):

That's true, but Akinaga says that VSRC is a tyrosine kinase. And the '512 patent itself says that VSRC is a tyrosine kinase.

Judge (14:10):

So you don't think that the inference needs to be made that the CSRC is the same as VSRC.

Brian Matsui (14:22):

Not at column 19 line 28—

Judge (14:26):

Operates equivalently?

Brian Matsui (14:29):

Not at column 19 line 28 the patent discloses, the genistein, a compound, is a tyrosine kinase inhibitor because it inhibits VSRC. So the patent itself is treating VSRC as a tyrosine kinase inhibitor as a tyrosine kinase. But, but more importantly, this is a factual finding here. The board found as a matter of fact, at appendix 33, that a person of ordinary skill in the art would understand that a compound that inhibits VSRC would inhibit CSRC. It found Dr. Keith's testimony not persuasive, and it credited and quoted our expert's testimony saying there similarities between the VSRC and CSRC such that a skilled artisan would understand that the compound that inhibits VSRC also inhibits CSRC. That's one reason, in addition to the fact that Akinaga says VSRC is a tyrosine kinase that their argument fails.

Brian Matsui (15:25):

But another reason why their argument fails is because of the Sinai reference. The Sinai reference says that UCN-01, and the board made findings about this at appendix 29 and at appendix 29 and at 33 that the Sinai—sorry, 35—the board said that Sinai discloses that UCN-01 inhibits multiple tyrosine [inaudible] kinases. And it did experiment testing on human breast cancer cells to determine that it led to decreased tyrosine phosphorylation of at least four proteins when UCN-01 is applied to human breast cancer cells. And the board found as a matter of fact, based upon this reference and based upon our expert's testimony that a person of ordinary skill in the art would understand that UCN-01 is a tyrosine kinase inhibitor, and that's being applied to two cells right there. So that's additional substantial evidence that supports the board's decision here in this case where they found ARCH's experts, testimony not persuasive. That should resolve the appeal because there is no need then to look to any other art when you have references that explained that UCN-01 is a tyrosine kinase inhibitor, and it doesn't—and I think that it's important also to look, to take a step back and look at the—what the board did here in this case. The board's rehearing decision, which ARCH really, wholly ignores, rejected the very premise of ARCH'S argument that it depends upon—that its ruling depends upon any difference between VSRC and CSRC.

Judge (17:21):

I noticed some references to protein kinase inhibitor, as opposed to tyrosine kinase. Tyrosine, of course, is not a protein. It's an amino acid, which is a component of a protein. Is that difference of any significance to us here?

Brian Matsui (17:36):

No, because the fact that UCN-01 is also a protein kinase inhibitor doesn't mean that it's not a tyrosine kinase inhibitor, as well. A lot of this art is showing that these compounds inhibit multiple different enzymes or proteins, and that's all that's being shown here. The board here had the evidence before and made a determination on the facts, based upon the significant evidence in the prior art and in our expert's

testimony that UCN-01 is a tyrosine kinase inhibitor. There's nothing in the '512 patent that requires a particular tyrosine kinase inhibitor. It just lists a number of examples. It doesn't say that it needs to inhibit tyrosine kinases with any sort of degree. It just says any tyrosine kinase inhibitor, any low molecular weight tyrosine kinase inhibitor. Now, I just would also like to briefly touch upon the motivation argument that ARCH raises.

Brian Matsui (18:37):

Because again, that's another issue that the court does not need to reach because as ARCH has said you needed to look at the [inaudible] art in order to determine whether or not UCN-01 is a tyrosine kinase inhibitor. But you don't need to do that because, again, Akinaga and Sinai explained that UCN-01 is a tyrosine kinase inhibitor, and the board made a finding of that on its rehearing decision at 43 and 44 where it says its decision doesn't depend upon any of the [inaudible] art. So given that, that's enough right there to affirm the board's decision.

Judge (19:16):

Now the link between the VSRC and C is, is based on the testimony, which the board accepted and believed.

Brian Matsui (19:26):

That's correct, your honor. And it's the same thing for the motivation argument. If the court needed to reach the motivation to combine argument, that's another factual finding that supported by substantial evidence where the board found ARCH's evidence not persuasive. It looked at the fact that our expert testified that UCN-01 in [inaudible] have a similar mechanism of action. They both inhibit kinases by interfering with ATP binding. They both have similar effects on the cell cycle and they are structurally similar. The board was perfectly well within its rights to weigh that evidence and make a factual finding and determine that a person of ordinary skill in the art that has this Akinaga reference, which basically discloses—it does disclose everything. Adding a DNA agent to a tyrosine kinase inhibitor to enhance cell death, the person with ordinary skill in the art that wanted to learn more about UCN-01 would look at the [inaudible] art. If there are no further questions we would ask the court to affirm.

Catherine Allen (20:44):

Thank you, your honor. May it please the court. Catherine Allen, on behalf of the United States, we intervene to address the constitutional issues. And I would just like to start out by responding to a couple of points that the other side made. First, is that the due process question here is whether there is any rational basis for Congress's decision to apply inter parties review to patents that issue prior to the AIA. They agree that it serves the purpose of weeding out erroneously. granted patents. That ends the due process question. Also, they dispute Patlex citation of cases that look to congressional purpose. And I just want to point out that those citations are in the due process portion of the opinion. And there's no question that—sorry, there's no dispute that the due process question is whether Congress had a rational basis for this application of the statute. So Patlex is still a good law on, on that issue. And we think it forecloses the due process question here. But, in addition, we think that there's no takings problem because, the cancellation of a patent through IPR rests on a determination by the agency that the patent holder never had a valid property interest, and the patent wouldn't actually be canceled until this court affirms that determination. And in that sense, it's really no different than when a district court determines that a patent is invalid.

Judge (22:11):

What do you say as to the failure to raise this issue before the board? Had the issue had been raised before the board, what would the board have been empowered to do about?

Catherine Allen (22:25):

Yes, your honor. If the issue had been raised before the board and the board determined that there was—that the board agreed with the constitutional challenge, it could have declined to institute inter parties review in this case.

Judge (22:38):

So you think that this is something that needs to be raised prior to the institution of the IPR?

Catherine Allen (22:47):

Well, that would be the best time to raise it, but in addition, the board could terminate the proceedings, and, in effect, reconsidering the institution decision if it was raised later in the proceedings. But, I think the fundamental point is that they—

Judge (22:59):

Do you think that the board, in effect has the power to entertain a constitutional argument—sorry—it was a constitutional challenge to the statute that the board is charged with enforcing?

Catherine Allen (23:12):

Yes, your honor. I do think it does section 314A does not require the agency to Institute inter parties review in any case. So it's clear that the agency does have discretion as the Supreme court recognized in Cuozzo to declined to institute—that decision is committed to the agency's discretion. And I would point out that the Supreme Court in Thunder Basin and, more recently in 2012 in Elgin, made clear that the sometimes quoted statement that agencies don't have jurisdiction to consider constitutional issues is not mandatory. And we think here, justice in, in Ray DBC , it would not have been futile for the party to raise it and therefore the issue should be considered forfeited.

Judge (23:56):

But, just to finish the point, then. Are you saying that the board does have the authority, quite independent of its right to decline to institute, but it does have authority to rule on a constitutional challenge to the statute? Or are you saying that well, it can always decline and thereby avoid the problem altogether?

Catherine Allen (24:26):

Well, your honor, I think—it's clear that Congress authorized the board to make institutes—or authorized the agency to make institution decisions. And—

Judge (24:33):

My question really goes to whether the board—if the board wants to be perfectly transparent about this and say "we would institute this, but for the fact that we think that statute is unconstitutional and we think it's unconstitutional, therefore we declined to institute." Is that a lawful act in your view in the view of the department of justice for the board to take?

Catherine Allen (24:58):

Yes, your honor. We think the board could issue a decision when it declines to institute—sorry—if the board agreed with the constitutional challenge, it could decline to institute and issue a decision explaining that the reason it was declining to institute—

Judge (25:13):

And that would be unreviewable, under Cuozzo, by us?

Catherine Allen (25:16):

Yes, your honor. I do think that because that's committed to the agency discretion that if—if the court, if the agency found that there was a constitutional problem, that would be unreviewable. But of course, the agency has addressed this issue in a different case that is also pending before this court. And there the agency rejected the retroactivity challenge, and the issue is now properly presented to this court in that case. And that obviously is reviewable. If there are no further questions. Thank you.

Peter Sullivan (25:50):

I'll start with the constitutional issues. The court obviously can see this, hear this case in the interest of justice, if it believes it's important and proper to do so. The property interest here is broader than the government is professing. It's not just those who have invalid patents. It's all patent holders are under the same regulatory disability of having to deal with a quasi judicial additional judicial administrative process. A process that has a lower bar to institution than the substantial new question of patentability line that was drawn for reexamination. And that also has the additional disability of having institution be granted when there's competing testimony under 42 CFR 108. When the board is confronted with conflicting expert testimony on an issue, it is instructed to weigh that in favor of institution. So, the bar is lower.

Judge (26:48):

Suppose that the Congress decided that the clear and convincing evidence test in district court was really too onerous for patent challengers and decided to convert the test into one for by a preponderance. Do you think that would be constitutionally invalid?

Peter Sullivan (27:07):

If retroactively applied? On the basis of retroactivity, I would. I would also believe that's the case. At some point, the process drives the results. You know, the fact that this IPR has been so popular to tell us all that maybe something's different than it was with the old reexamination regime. Patent holders certainly feel that way. It changes the calculus for licensing negotiations. I represent two cancer institutes. They have to everyday they're on the lines with licensing decisions, and those decisions are affected by the fact that a large pharmaceutical company could just throw you into re-exam where IPR, excuse me, and have to go through a mid six-figure challenge before you get to enforce, like we have here. I like to turn just for a couple more points on a couple of things about [inaudible]. Judge Lourie, of course, it's critical that it's, there's a difference between proteins and tyrosine kinases.

Peter Sullivan (28:01):

[Inaudible] does not identify what tyrosine kinase have been inhibited. How could someone of ordinary skill in the art know that it's a tyrosine kinase inhibitor without knowing what the tyrosine kinases that are being inhibited. That's the point? This evidence doesn't get us far enough to make the leap because there's inferences upon inferences upon inferences. And I want to go, I want to close with the cell cycle. I got a minute. The irony of this case is that this is a classic hindsight reconstruction. If you look at Akinaga, Akinaga talks about cell cycle and says that the fact that compound A MMC and compound B UCN-01 act on two different parts of the cell cycle is a good thing because perhaps it's a one, two punch. The fact that one is not interfering with the other is a good thing, whatever Akinaga thought. That's what it said. That was the state of the art. The inventors here believed that tyrosine kinase inhibition was a counteracting move. They saw the cell cycle arrest in G2 to be a negative, not a positive. And they went looking for a drug that would counteract that negative aspect. That's contrary to what Akinaga was looking at. When we talk about the problem to be solved, Akinaga was looking at it way different than the inventors of the '512 patent were. Time. Thank you.

Clerk (29:35):

Thank you. We thank both sides in the cases submitted.