UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE,
(Patents 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641 and Application 14/704,551),

Junior Party,

v.

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, and EMMANUELLE CHARPENTIER,
(Application 13/842/859)

Senior Party.

Patent Interference No. 106,048 (DK)

Held: December 6, 2016

BEFORE: RICHARD E. SCHAFER, SALLY GARDNER LANE, DEBORAH KATZ, Administrative Patent Judges.

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The above-entitled matter came on for hearing on Tuesday, December 6, 2016, commencing at 10:00 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE SCHAFER: Good morning. This is the oral argument in Interference 106,048, The Broad Institute, et al. versus The Regents of the University of California, et al. The time for argument has been set for 20 minutes for each side.

Who will be arguing for Broad?

MR. TRYBUS: I will, Your Honor. Steven Trybus from Jenner & Block on behalf of Broad.

JUDGE SCHAFER: How much time would you like to reserve for rebuttal?

MR. TRYBUS: I'd like to reserve five minutes.

JUDGE SCHAFER: Five minutes?

Who will be arguing for The University of California?

MR. WALTERS: I will, Your Honor. Todd Walters from Buchanan Ingersoll & Rooney.

JUDGE SCHAFER: How much time would you like to reserve for rebuttal?

MR. WALTERS: I'd like to reserve three minutes, Your Honor.

JUDGE SCHAFER: Three minutes?

Do the parties have any demonstratives for us?

MR. TRYBUS: Yes, Your Honor.

MR. WALTERS: Yes, Your Honor.

JUDGE SCHAFER: If you could bring them up and if you could give a set to the court reporter.

(Demonstratives were handed out.)

JUDGE SCHAFER: Okay. Mr. Trybus, if you'd like to begin your argument.

MR. TRYBUS: Good morning, Your Honors.

I think there's no substantial dispute on our Motion 3. The Junior Party is entitled to benefit because Example 1 meets Count 1. And on our Motion 5, the briefing sets forth the reasons why the claims at issue there should be de-designated.

I'm going to spend my time, unless Your Honors have any questions, on our Motion 2 with regard to no

interference-in-fact and why it was not obvious to use CRISPR in eukaryotic cells as of December 2012.

Now, as a bit of background, when the Broad scientists began working in this field, their focus was on gene editing in mammalian cells. So not surprisingly the claims in the Broad patents and application at issue have limitation to use in eukaryotic cells.

Now, Senior Party provoked this interference. They had presented over 3,000 claims to the Office, including claims that had eukaryotic limitations and including copying our claims, but they chose to elect the group of claims that they did, none of which have a eukaryotic limitation for this interference. So if there is an interference-in-fact, Your Honors, it's reasonable that the count contained eukaryotic limitations.

Now, on the no interference-in-fact point, the key issue that has developed through the briefing is whether the use of CRISPR in eukaryotic cells was obvious after the Jinek 2012 article published as Senior Party alleges.

And the reason that this is the issue that has come is that the parties agree that prior to the Jinek 2012 article, there was no reasonable expectation of success. I'd refer Your Honors to slide 30 in our materials.

JUDGE SCHAFER: What was the name of the article again?

MR. TRYBUS: Jinek 2012 article.

JUDGE SCHAFER: Yeah, the Jinek 2012 article. Is that essentially coextensive with the claims with University of California's claims?

MR. TRYBUS: The Jinek 2012 I recall, Your Honor, sometimes it gets used as a proxy for some of the provisional applications. The Jinek 2012 article has disclosures that are somewhat like P2. The P1, their first provisional, is a -- is somewhat different and -- okay. That was not what I wanted to project. Sorry about that.

I apologize, did I answer Your Honor's question?

JUDGE SCHAFER: No, I'm not sure. Because for no interference-in-fact or interference-in-fact, we're comparing claims in the nature of double patenting type of thing, so that's why I want to know if the Jinek art was, in fact, essentially the same as the University of California's claims, which is we're starting out as presumed prior art.

MR. TRYBUS: Right. So, Your Honor, with regard to that, the Jinek 2012 article like their claims do not -- does not have information about eukaryotic cells. It has information about in vitro experiments. So in that sense it is an appropriate vehicle in terms of talking about what would or wouldn't have been obvious over their claims.

Because, Your Honor, so prior to Jinek 2012, one of their two duplicative experts, Dr. Greider -- and this is at slide 30. It's in the record at Exhibit 2013 at page 79 of the deposition. She

was asked the question, prior to the disclosure of Jinek 2012, was there a reasonable expectation of success? And her answer was, without knowing what the essential components are, and Senior Party's position is that Jinek 2012 discloses those essential components, that there was no expectation of success.

Now, Senior Party asserts really that Jinek 2012, though, changed everything and that essentially everything in this field, certainly their argument is that the eukaryotic cells -- work in the eukaryotic cells would have been obvious after the Jinek 2012 argument or, sorry, article published and they really make two points in support of that.

They say, first of all, that as a matter of scientific fact essentially that it was required for that information and it was required for someone to be able to do in eukaryotic cells and they also talk about work by other laboratories that came after the Jinek 2012 article.

Now, they say that the Jinek 2012 article was specifically significant, and this is from their declarations, because the tracrRNA, the CRISPR RNA and Cas9 form a complex which can cleave DNA outside of eukaryotic cells. And they go so far as to say that even our work depended entirely -- and that quote depended entirely is from pages 13 and 14 of their opposition on the Jinek 2012 and this simply isn't true.

Now, Senior Party had put together as one of its exhibits a timeline to try to prove this and they started with that

timeline with Jinek 2012. We've modified the timeline a little bit and I've put it up on the board here. It's Exhibit 2313. It's also slide 41 in your materials, Your Honors.

And what the record evidence shows is that Dr. Zhang had already -- and Dr. Zhang is the lead inventor for The Broad, but he had already started working on this prior to the time of Jinek 2012. So in early 2011 he had an information disclosure statement where he disclosed that. That's in the record along with Paper 53, our priority statement.

And he had an NIH grant that he submitted in early 2012 prior to Jinek 2012 in which he described the use of a CRISPR-Cas9 complex with Cas9, the crRNA and the tracrRNA for use with eukaryotic cells and that successful work on that was ultimately reported in the Cong, et al. article, which is the last part on the board published in January 3rd, 2013, which was the point at which a person of ordinary skill in the art really was able to have a reasonable expectation of success.

Let me just point out very quickly two pieces of evidence that we didn't put on the board, but there are other things that precede Jinek 2012. For example, in March 2012 another group, Vilnius University, and their patent application is in the record at 1479, Exhibit 1479, they filed an application reporting DNA cleavage using the complex in test tubes much like the work of Senior Party here.

And as far back as 2010 in the Garneau article, which is Exhibit 1153, there was a showing that Cas9 was an RNA-guided protein that cleaved DNA. So we submit, Your Honors, that it was not necessary for the Jinek 2012 disclosure in order to work in eukaryotic cells.

The second piece that Senior Party asserts that Jinek 2012 supposedly has relevance is the fact that there were several groups that after the Jinek 2012 argument conducted work in eukaryotic cells and those are on the board here, but we need to remember that the issue -- and Your Honor's question got to this in part is the question is whether our claims were obvious over their claims and the other pieces of prior art to the person of ordinary skill in the art based on what was known in the art.

Now, the articles here from these labs we cover this extensively in our brief, so I'm not going to go through it in that much detail, but these are all people of extraordinary skill. These are not people of ordinary skill.

And the other fact is that these groups did not use the molecules and -- the molecules in Jinek 2012 and conventional techniques. Rather, the Mali group and the Hwang group, they did not use molecules from Jinek 2012. They used the molecule that was their own and the Cho group, which is set forth there, used nonconventional means to drive the system in a way to find any hint of cleavage in eukaryotic cells.

And these groups certainly did not think that they were doing something that was just an obvious extension of the Jinek 2012 article because they all published in major journals and they all filed -- many of them filed for patent applications.

Now, we do have I think very good objective contemporaneous evidence, Your Honors, of what the state of the art was in 2012 and this is in the slides and I also have a board that summarizes three of the slides here. These are comments that were made contemporaneously or about the 2012 materials.

So I'd first refer to what's on the top of this board. It's also in the demonstratives at slide 34. It's a quote from Exhibit 2207 at 3 and it's an interview with Dr. Doudna, one of Senior Party's lead inventor, talked about -- and she was talking about the Jinek 2012 article and she said there was a problem. We weren't sure if the CRISPR/Cas9 would work in eukaryotes, plant and animal cells.

And she goes on to say in that quote why that is and the fact of the matter is because what she talks about is the difference in the nucleus because the interest wasn't getting into the nucleus of the eukaryotic cells and obviously the prokaryotic system does not have that issue.

Now, the next quote on the board, this is also slide 37 in your materials, this is from Exhibit 2230 at page 3. Dr. Doudna here is talking again about these issues, realized that it would be a profound discovery if you could get a powerful gene therapy

technique to work in human cells. So there was motivation. But despite that motivation, Dr. Doudna in this quote shows that she experienced many frustrations trying to get it into human cells.

Now, we actually know that the work that Senior Party did, the initial work, they obviously had the material that was in Jinek 2012 before the public did because they did that work. As a matter of fact, I think they would say they had that work prior to the time they filed their first provisional in May of 2012, but we know from their priority statement that they did not -- they don't contend that they actually got this to work in eukaryotic cells until many, many months later in October 2012.

So despite their superior knowledge, their skill and the motivation, even Senior Party was not able to make this work very easily. This is the antithesis of something that would have been obvious.

JUDGE KATZ: So let me ask sort of as a follow-on to Judge Schafer's question, on the -- California's claims, UC's claims cover sort of arguably three or four different environments. There's a generic claim.

MR. TRYBUS: They are environment free is the way I often refer to it, yes, or generic to environment. They could cover use in prokaryotic cells or eukaryotic cells or in vitro use, yes, Your Honor.

JUDGE KATZ: But that's a limited set of possible environments. It's not like it's completely unlimited. So why --

what -- how do you argue that it wouldn't be obvious just to try each one of those and if it works, which it did, where is the nonobviousness?

MR. TRYBUS: Well, Your Honor, I think that there was motivation to try, but I don't think it would have been obvious to try because there was no reasonable expectation of success with regard to this. What the record shows in this evidence including, for example, these quotes including the quote that I was going to get to from Jinek 2013 where they talk about the fact that it was not known whether such a bacterial system could be moved into eukaryotic cells. So the question really was that. Obviously the system in its natural environment was in prokaryotic cells
and there was a question of this.

And in Dr. Simons' declaration on our behalf, he laid out a number of different things. And as a matter of fact, one of the other issues that comes up is also their expert, Dr. Carroll, at the same time, and this is in Exhibit 1152. He wrote an article at the time and he talked -- he said that only attempts to apply the system will address the concerns of whether this can be done or not.

So on the record here what we have is we have a number of pieces of evidence with regard to how easy it was. Senior Party, as a matter of fact, makes an assertion that most prokaryotic

proteins could be moved into eukaryotic cells, but I think the record belies that contention.

Because the examples that they put forward, Your Honors, they only put forward four examples of proteins and they were protein-only examples and they're very different than the CRISPR-Cas system, which of course is a combination of a protein and an RNA. I think that there is much more relevant evidence with regard to what the person of ordinary skill in the art would have been and I point to two things.

The first of which that I would point to is work that had been done years earlier on CRISPR-Cas by Drs. Sontheimer and Marraffini. Their work is shown in Exhibit 1161. And they had made sort of similar statements of the wish or hope or plan of putting things in eukaryotic cells and they were never able to do so. There was never any indication that they were successful at all.

And the person of ordinary skill in the art would have been aware of that prior idea that this would be a good thing to do and would be something that one would try to do, yet it was an utter failure and the person of ordinary skill in the art would have that in mind.

Another thing that the person of ordinary skill in the art would have in mind is the work with Group II introns or targatrons, which also has a protein component and an RNA component. So I believe it's more analogous to what is at issue

here than the protein-only examples that Senior Party used. And what -- I'm sorry, Your Honor.

JUDGE KATZ: So the work of Sontheimer was with a different CRISPR system.

MR. TRYBUS: It was.

JUDGE KATZ: And how is that -- that's also a three-component system, there was a protein and RNAs or how does that -- it's a Type III system I think?

MR. TRYBUS: Your Honor, I know I don't have much time so I'm not trying to blunt your question, but without going through the details of the fact that there are differences between the different types of CRISPR systems, I still think that the person of ordinary skill in the art would have had in mind the idea that Sontheimer and Marraffini had said that they were going to move CRISPR systems or were going to try to move CRISPR systems into eukaryotic cells and were not able to do so.

And likewise with regard to the Group II introns or targatrons as they're called, what we saw is that after decades of research in this, and again a person of ordinary skill in the art would understand this and would have known this, these were not moved into eukaryotic cells to any level whatsoever.

Senior Party -- one of Senior Party's experts, Dr. Carroll, in one of the quotes that we have in the briefs and in our demonstratives said that it was inefficient and one of our experts, Dr. Breaker, said that it was, in fact, an utter failure, that persons

of ordinary skill in the art would have taken that as an utter failure.

And, Your Honors, I think the other piece that comes to be with this is that it was certainly very appropriate I think that the persons of ordinary skill in the art had the skepticism because these more relevant pieces provided the skepticism and what later developments show is that that skepticism was well deserved.

Because if what was able to be shown later, and this is Exhibit 2233, the Ran article, shows six Type-II Cas9 ortholog systems, all of which work in vitro and only one of which is able to work in eukaryotic cells. So from a manner of science, ultimately the answer is that not all of these systems work.

So a person of ordinary skill in the art had no reason upfront to think that there was going to be an expectation of success. We agree, we don't dispute and as a matter of fact we would affirm -- we affirmatively use the fact there was a tremendous motivation and that explains why a number of groups might have been motivated to try to see whether they could get this profound discovery, but that was the sort of thing that it was.

They were looking for a profound discovery. The materials, the comments at the time belie this idea now in the interference that this was all obvious. The Jinek 2012 turned the tide in terms of things.

In fact, the other thing that has proven out is the article is published on -- sorry, the board isn't up anymore. The article is

published on January 3rd, 2013 were when persons of ordinary skill in the art started working in eukaryotic cells with the CRISPR system.

And for Junior Party, Broad alone, there have now been over 36,000 requests for reagents from Addgene and the Cong, et al. article there has been cited over 2,000 times. That was the point where with a showing that CRISPR Cas9 actually worked in eukaryotic cells, a person of ordinary skill in the art was able to take the system and work with it.

The Jinek 2012 article did not provide that kind of change in the situation. It was -- there was no reasonable expectation of success prior to Jinek 2012 and there was no reasonable expectation after 2012 all the way through the date of December 12, 2012, the filing of our provisional patent application.

JUDGE SCHAFER: Okay. Thank you, Mr. Trybus. We'll hear what Mr. Walters has to say.

MR. TRYBUS: Thank you.

JUDGE SCHAFER: We had some questions for you. We'll give you your full five minutes.

MR. TRYBUS: Thank you, Your Honor.

MR. WALTERS: If you can give us a second to set up here, please.

JUDGE SCHAFER: Yes, go ahead.

MR. WALTERS: I'm trying to get a signal here.

JUDGE SCHAFER: We'll wait until you're ready.

MR. WALTERS: Thank you.

We'll get started. Thank you.

Your Honors, today UC intends to focus on its Motion 3 and Motion to Substitute the Count. In the process we hope to explain why you should deny Junior Party's Motion of No Interference-in-fact and why you should grant UC's Motion for Benefit.

Just very quickly, as to Sontheimer, Sontheimer never did any in vitro experiments to identify the necessary and sufficient components. Sontheimer was a situation where it was a research plan. He didn't have the full set of components necessary. That's why it didn't work for Sontheimer. We are different here.

JUDGE KATZ: Mr. Walters, did it ever -- he was using the Type III system; is that correct?

MR. WALTERS: He was using the Type III system. It was not the Type-II CRISPR-Cas system.

JUDGE KATZ: Right. Does the Type III system work in eukaryotes?

MR. WALTERS: No one has ever identified the necessary and sufficient components of that system.

JUDGE KATZ: So nobody has tried.

MR. WALTERS: No one has tried.

JUDGE KATZ: Okay.

MR. WALTERS: Your Honors, I'd like to refer to slide 4, please, and in slide 4 you will see a comparison of the counts. And there are two major differences in Count 1 as compared to Count 2 that I'm going to focus on today.

One is the eukaryotic cell limitation and the other is the single-molecule limitation. And what we are saying is in this interference going forward, the count should not have a limitation to the method being in eukaryotic cells and what we're saying is that the count should include the single molecule limitation. That's why we presented Count II the way that we did.

I will first focus on why the count should not include the eukaryotic environment limitation. First of all, there is no dispute that all of Broad's claims are limited to the eukaryotic environment limitation. There's also no dispute that none of UC's claims include that limitation. There's no dispute that if there is an interference-in-fact in this case, then performance of the method in eukaryotes would be obvious in view of UC's claims.

The reason for that is the test for an interference-in-fact is a two-way test. If there is an interference-in-fact here, then Broad's claims would be unpatentable in view of UC's claims and none of UC's claims have an environment to eukaryotic limitation.

Moreover, there is no dispute that UC has proffered proofs in this case that fall outside of Count I and Broad has made

no substantive argument that the proofs that we proffered do not fall within proposed Count 2.

Thus, UC should not be able to prevent -- I'm sorry, Broad should not be able to prevent UC from obtaining its claims to its separately patentable invention based on generic proofs and the eukaryotic limitation should not be included as well.

Now, why were you correct that the eukaryotic cell limitation was obvious in view of the claims? The answer lies with what was obvious to one skilled in the art once the necessary and sufficient components of the system were known. And here as you heard earlier, there was no dispute that the counts in UC's claims describe the necessary and sufficient components of the Type-II CRISPR-Cas DNA cleavage system, no dispute.

Objective evidence of what would happen once those necessary and sufficient components is available in this record. If we could go to slide 12, please.

In slide 12 you will see that Broad's own experts says that Jinek 2012 was the first publication to disclose the necessary and sufficient components for DNA cleavage.

Moreover, if we can go to slide 13, Broad's expert -- and you heard Mr. Trybus earlier say that there's no dispute that there was motivation to move that system into eukaryotic cells, no dispute on motivation.

If we can go to slide 13.

If you read Broad's specification and ask them how did they do it, they used conventional techniques to move the CRISPR-Cas system into eukaryotic cells. It says it over and over and over again in their specification.

And if we could look at slide 18, I'm sorry, 19, you can see that Broad's expert also said that use of NLSs and codon optimization was conventional.

Slide 20. The use of promoters and vectors was conventional.

Slide 21. The use of microinjection is conventional.

So at the relevant time when the necessary and sufficient components were first disclosed, there was motivation in a means to be able to get it into eukaryotic cells doing conventional methods. The only thing left was to do it.

JUDGE LANE: Mr. Walters, if this was conventional, then why did one of your own inventors talk about this being a big problem, encountered frustrations? Can you explain that difference there?

MR. WALTERS: Thank you for asking that question, Your Honor.

If we could go to slide 47.

Broad has made much ado about statements from Dr. Doudna and, indeed, Dr. Doudna has been interviewed hundreds of times regarding the CRISPR technology. However, what Broad does not do is point you to any statement where Dr.

Doudna, in fact, said she didn't believe it was going to work in eukaryotic cells.

The frustrations that you mention, we don't know what the context and the only quote is many frustrations. It may -- we don't know the context of that and, moreover, the objective evidence at the time if you look just a month earlier -- well, actually let's stay on this slide -- she said at the time of Jinek 2012 in June of 2012 that it's a very real possibility to move it into eukaryotic cells.

And a month before that, if we could go to the next slide, UC's first provisional had already been filed where the inventors, and Dr. Doudna is one of the inventors, specifically said that you can move the system into eukaryotic cells. Moreover, within six months of that, Dr. Doudna and others, along with many other groups that didn't have the benefit of UC's first provisional application, were able to successfully move the system into eukaryotic cells.

So there is no statement in the record that she did not believe that it was going to work in eukaryotic cells.

JUDGE KATZ: Are there any statements in the record that anybody said they did believe it would work, something like it would be likely to work?

MR. WALTERS: If we can go back to the previous slide.

Right there Dr. Doudna says, it is now a real possibility.

JUDGE KATZ: Does that rise to the level of an expectation of success, is a possibility an expectation that it will work or is it just a question of whether it will work or not?

MR. WALTERS: I think it is an indication that she believed that it would work, but you don't even have to rely on these interpretations of statements. Let's look at what actually happened after the publication of Jinek 2012.

If you look at the publication date, it was June 28 of 2012. There were one, two, three, four, five, six different groups within six months who were able to successfully move the system from an in vitro environment, as disclosed in Jinek 2012, into a eukaryotic cell environment. And what did each of those groups do?

If we go to slide 90.

Slide 90 is an interesting slide. It shows in the first column where disclosures are in the UC first provisional application and it goes through and says -- it shows you where various portions of the method are disclosed in the application. But if you look at each of these other groups, they did it in the very same way that's described in the UC application, but they didn't even have the benefit of the UC application to perform the methods that way that shows that those skilled in the art, once they had the necessary and sufficient components, all thought it would work and performed the method using conventional methods.

JUDGE KATZ: But doesn't that go more to that they had a motivation to when they did it? Did Dr. Doudna -- I mean, it seems like she had the information. Did she get it to work immediately after she had the information in eukaryotic cells?

MR. WALTERS: So Dr. Doudna has a lab where she does crystallography. She was not set up to do work in cells immediately, but she did ultimately successfully perform the method in eukaryotic cells because she published in early 2013 as well.

JUDGE KATZ: So she didn't have a motivation to do it at the time after she did -- after Jinek 2012 or after she had done the experiment.

MR. WALTERS: She was absolutely motivated to do it at the time. Everyone wanted to move the system into eukaryotic cells. There's no dispute on motivation here. The question is -- I'm sorry, I interrupted.

JUDGE KATZ: Was she able to, though, immediately after she determined the necessary components, was Dr. Doudna able to have the system working in eukaryotic cells immediately after her in vitro experiments?

MR. WALTERS: When she performed those experiments in the six-month period after the publication of Jinek 2012, yes, she was able to successfully do that.

JUDGE KATZ: Within six months.

MR. WALTERS: Within six months, yes.

Your Honors, if you look at slide 20, please. I'm sorry, 21, please. 24 please, I apologize.

Now, Broad's expert on cross examination, Dr. Simons said, no one does an experiment without a belief that it might work under certain circumstances. In here what Broad wants you to believe is that all of these groups went and performed this experiment, all these experiments, a multitude of them, prepared patent applications and manuscripts and none of them had a reasonable expectation that the experiments were going to work.

JUDGE KATZ: But the flip side of that is, do you think that anytime a scientist performs an experiment, is there an expectation that meets the legal definition of a reasonable expectation of success?

MR. WALTERS: I think when people perform experiments, they have that expectation. If they had no --

JUDGE KATZ: But the legal definition.

MR. WALTERS: If they had no reasonable expectation of success, they would modify the experiment in the first place.

JUDGE SCHAFER: Why would you do that, why wouldn't you start with what people know? Why wouldn't you start with, okay, we want to -- we have to get this stuff into the cell nucleus and we have techniques for getting stuff into the nucleus? So why wouldn't we try those first, hoping to get a result? I can understand the hope. I don't know if I'm buying this statement that anybody who doesn't experiment has a belief it will

work. They certainly have a hope that it will work. I believe that.

MR. WALTERS: Well, here also the evidence of record shows that other prokaryotic systems have been successfully moved into eukaryotic cells and Broad has not offered one single example that does not work in eukaryotic cells.

JUDGE KATZ: If we go back to the Sontheimer, the Type III CRISPR-Cas, it seems that there would have been the same motivation there. It was a similar type of system people were looking at. In fact, Sontheimer wrote a prophetic application because he wanted also to get a system that would work in eukaryotic cells.

MR. WALTERS: But remember the difference with Sontheimer is he never did the in vitro experiments to determine what the necessary and sufficient components were of the complex.

JUDGE KATZ: Or maybe they just weren't successful and so he didn't put them in his application.

MR. WALTERS: You can look at the Sontheimer application and see they never did those in vitro experiments to show what the necessary and sufficient components were. They don't disclose them in there. That's the problem with Sontheimer.

JUDGE KATZ: Okay.

MR. WALTERS: If we might go to the issue of the single-molecule invention. Broad admits that all of UC's claims

are directed to the single-molecule invention. Broad admits that it also has claims directed to the single-molecule invention. The only question is how many of its claims are limited to the single-molecule invention.

You should know -- if we could put up slide 51, please.

You should know that the single-molecule invention is not -- is a unique format not found in nature, first of all.

Secondly, if we can look at slide 52, what we're talking about with the single-molecule invention -- I'm putting a laser pointer, oh, that does not work on the screen, but in slide 52 it's the portion of the slide encircled in red that shows a covalent bond between a first RNA molecule and a second RNA molecule.

JUDGE KATZ: Were such linkers known in the art before? I think they were called -- they had a name tetra loops. Is that --

MR. WALTERS: Well, there is a reference to hairpins. You hear the term hairpins, but what was not known at the time was if you modified -- and if you see -- if you look at the A portion of this figure, you see a two-molecule system having two separate RNA molecules.

What was not known at the time of the invention is if you modify the three prime end of the top RNA molecule and you modify the bottom five prime end of the bottom RNA molecule referred to as the activator that you would still get Cas9 binding. That was unpredictable at that time.

Because if you modified those ends -- and this was known in the art. If you modify those ends, even slightly, even slightly and as Dr. Breaker has said during cross examination, just the orientation of the end can keep a protein from binding to the RNA molecule.

Here there was no expectation that if you put a linker on that you would have binding to the Cas9 in the first instance and even if you had binding to the Cas9 that it would then cleave DNA once the system was targeted to the DNA.

JUDGE KATZ: But there was an expectation that the whole system would work in an entirely different environment. That's your position, that there was an expectation that the system would work in a eukaryotic environment, the entire system with a protein and two RNAs, but that there was -- that there was an expectation, but there was no expectation by making a small modification to the two RNAs that then -- there was no expectation that that would work.

MR. WALTERS: That is correct.

JUDGE KATZ: That's your position.

MR. WALTERS: That's correct, Your Honor, yes, and that's because of looking at what the Cas9 is binding to doesn't change going from an in vitro environment to a eukaryote environment. But if you change the binding portion of the molecules, then that has a significant impact on whether or not the Cas9 will bind in the first place.

JUDGE KATZ: So was it known that just the binding of the RNA to the protein would make the system functional or were there other cellular environments or other things that had to do with the system being functional? Are you sort of saying that once the RNA bound to the protein, that was the only thing that people of skill in the art would have wondered about whether the system would work?

MR. WALTERS: Well, it has to -- the protein has to bind to the RNA molecule and you have to be able to target that complex to DNA. That's just hybridization. And then the Cas9 will cleave the DNA, just like it does in the bacterial environment.

JUDGE KATZ: So how do you address the differences in the DNA between a prokaryote and eukaryote?

MR. WALTERS: The differences in the DNA between them?

JUDGE KATZ: Between -- there are differences.

MR. WALTERS: That's right. The guide sequence that you would use in the system would be different with DNA in a eukaryotic cell and you would change that guide sequence so that it would hybridize to what you wanted to hybridize. That was not --

JUDGE KATZ: Right, the DNA differences and how the DNA is presented in a prokaryotic cell or in vitro for that matter versus in a eukaryotic cell. I'm talking about chromatin

structure and things like that. How do you address those differences?

MR. WALTERS: Not one of the other authors indicated that chromatin was a problem. Chromatin never was deemed to be a problem. It didn't prevent them from doing their experiments. Nothing in the record says that chromatin was an impediment. In fact, there are other articles where we point out other proteins that was in the presence of chromatin and it didn't prevent them from working as well.

Your Honors, because the single-molecule invention is separately patentable, you should -- and because Broad has claims directed to that invention, you should include that limitation in the count as well.

Should you find that the single-molecule limitation does not render the claims separately patentable, at a minimum you should take out the eukaryotic limitation from the count. You could do that in a number of ways. Remove the eukaryotic limitation from the current count or you could do a McKelvey (phonetic) count. But in any case, we shouldn't allow obvious claims to go forward in this interference when there are proofs that would render those claims obvious. Thank you.

JUDGE SCHAFER: Thank you. We had some questions. We will give you your full rebuttal.

Mr. Trybus.

MR. TRYBUS: Thank you, Your Honors.

With regard to the question of the obviousness of the work in the eukaryotic cells, I don't think that the sort of expressions of possibility are anything like meeting the legal test of reasonable expectation of success.

I think what we have here is the sort of situations that in prior cases are being talked about as a thought to vary all the parameters or try numerous possibilities where the prior art gives only general guidance. None of these things were known and there was only the barest of general guidance with regard to this.

And the fact that six months later the group succeeded with regard to some of these things is not relevant to what a person of ordinary skill in the art would have been thinking prior to addressing that and they would have been thinking that the differences between prokaryotic cells and eukaryotic cells including, for example, the chromatin in the nucleus and the tightly-wound nature of the DNA as well as a number of other concerns that were set forth by Dr. Carroll and echoed by Dr. Simons in his declaration. Those things all go to that.

With regard to one of Senior Party's arguments that they continually talk about in the briefing and again today, talking about that the -- that they were the first to identify the necessary and sufficient components with regard to this, the sufficient components had already been identified prior to that time, so there was the ability.

For example, Dr. Zhang had the ability to do some work. There was no need with regard to knowing exactly what was necessary, but still the persons of ordinary skill in the art would have focused on the fact that there wasn't any guidance as to how to move this system into a eukaryotic cell.

There was a question for Mr. Walters with regard to the question -- I'm moving now, sorry, to the single guide issue. And from a technical perspective, the Breaker declaration, which is Exhibit 2010, lays out the fact that the GAA tetra loop was known in the prior art and so it was not at all surprising that one could link two pieces of RNA together and that when linked together that was able to be functional with regard to this.

And more to the point of the changing of the count here, inclusion -- excuse me, inclusion of the single-molecule language excludes all of Broad's early proofs and Senior Party realizes that that that's the case because the prosecution record, the public prosecution record of our patents shows that our early work was not done with a single guide but was done with a dual-molecule format.

When Your Honors authorized Senior Party to bring one motion on changing the count, you warned Senior Party that that count should be just and they didn't choose. They chose among a number of different counts that they had suggested and they chose a count that, instead of being fair to both parties, was fundamentally unfair, unjust to Broad because it would eliminate

all of our earliest proofs because we did work in the -- excuse me, with the dual guide rather than the single guide.

And the other point that Senior Party made with regard to the count was that it excludes some of its work. But one of the things that is clear actually from the evidence that they submitted with regard to -- they submitted some parts of a notebook in Exhibit 1507 that shows work with a single guide, but in those pages, when you look at it, you realize that that's a replication.

Those pages refer back to dual guide work that was done before. This is an experiment -- I think it's number 18 and it refers back to a 17. And when you look at the information that's there, it's clear it says at the bottom of the last page I think that it mirrors the dual guide material that they were doing.

So they were working both in dual guide and single guide. The only reason that Senior Party is suggesting the single guide limitation I believe is to exclude our proofs, our earliest proofs, because it was very well-known that that was not what our earliest proofs were involving.

Unless Your Honors have further questions, I have nothing further.

JUDGE SCHAFER: Okay. Thank you, Mr. Trybus.

MR. WALTERS: Could I have slide 25 come up?

Your Honors, in Broad's Motion For No Interference-in-Fact, the only date that they assert as the relevant date is December 12 of 2012. At that time -- and they say that at

page 7, page 21 and in facts -- two facts on 82-2. In addition, Broad's expert said that the date that's relevant is December 12 of 2012. That you can look at slide 9 in our demonstratives.

If you consider the 2012 date, December of 2012, and you look at how many others had already been able to accomplish this by that point, it's not even plausible that those skilled in the art did not have a reasonable expectation of success nor that they could not do it. There was no special sauce here.

If we could look at slide 90 again. If you look at slide 90, you'll note from UC's first provisional application that UC disclosed the necessary and sufficient components. UC disclosed the use of vectors and NLSs and promoters and all of those conventional techniques. They also disclosed Chimera A. And Chimera A was a chimera that allowed them to perform the method in vitro, but then all these other groups without the benefit of UC's provisional application described how to move it into eukaryotic cells in the very same way. There was no special sauce that was pulled out of any of these publications to say that it made it work.

Now, what Broad has indicated is that no one used Chimera A and the point to the guide sequence, that is what's being targeted. Well, that has to change. What you target, you change the guide sequence or that the targeter portion of the molecule might have been a little longer in some cases. The reason for that is the natural targeter is a little longer. It depends

on how much you want to truncate that, but Chimera A generally was all the same. It's all the same. There's no special sauce here.

As to the GAA tetra loops, Broad offers that those tetra loops were well-known. And if you look at the references that they're relying upon, the tetra loops are used for crystallography experiments. One doesn't want to make a crystal and use a crystal in a eukaryotic cell for this purpose. Crystallography experiments are different.

The other thing they talk about adding a tetra loop for is to do an mfold analysis. Mfold has nothing to do with this invention. Mfold allows you to determine the stability of a molecule. And, oh, by the way, the stability analysis that was done by Dr. Breaker, he admits he provides no explanation of what he did. He didn't use the right cassette in the program. You can see that testimony in his transcript.

But the use of those tetra loops for crystallography just has nothing to do with what we're talking about here today.

JUDGE SCHAFER: Okay. Thank you.

MR. WALTERS: Thank you, Your Honors.

JUDGE SCHAFER: Okay. The case is submitted and the arguments are complete. Thank you.

(Concluded at 10:54 a.m.)

Patent 8,697,359, et al., Application 14/704,551 and 13/842/859
Patent Interference 106,048 (DK)

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