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Filed: February 28, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER
Junior Party

(Applications 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168;16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374),

v.

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE,
Senior Party

(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, 9,840,713, and Application 14/704,551).

Patent Interference No. 106,115 (DK)

Decision on Priority
37 C.F.R. § 41.125(a)

Before, SALLY GARDNER LANE, JAMES T. MOORE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge.*

Summary

In this interference we determine that The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College ("Broad") have priority over The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier ("CVC") with respect to Count 1 – a single RNA CRISPR-Cas9 system that functions in eukaryotic cells. CVC fails to provide sufficient, persuasive evidence of an earlier reduction to practice or conception, as they are legally defined, of each and every element of Count 1 before Broad's evidence of reduction to practice. Thus, we determine that CVC's currently involved claims are unpatentable under 35 U.S.C. § 102(g).[1] Furthermore, we are unpersuaded by CVC's arguments that Broad's involved claims are unpatentable under 35 U.S.C. § 102(f) for failure to name the correct inventors and we exercise our discretion in declining to take up CVC's arguments regarding inequitable conduct. We enter judgment against CVC, finally refusing CVC's claims involved in this proceeding.

I. Introduction

The same parties were before us previously in Interference 106,048. CVC was involved in that interference based on claims to a CRISPR-Cas9 system that cleaves DNA without restriction to the environment (*e.g.,* encompassing *in vitro* environments outside of a cell and prokaryotic cell environments), whereas Broad

[1] Patent interferences continue under the relevant statutes in effect on 15 March 2013. *See* Pub. L. 112-29, § 3(n), 125 Stat. 284, 293 (2011).

was involved based on claims that were limited to the system in a eukaryotic environment. (*See* Interference 106,048, Senior Party Clean Copy of Claims, Paper 12, Replacement Broad Clean Copy of Claims, Paper 17, and Decision on Motions, Paper 893, 2:4–7.) That interference was terminated without a determination of unpatentability or judgment against either party because it was held, on motion by Broad, that the parties' involved claims did not interfere. (*See* Interference 106,048, Decision on Motion, Paper 893.) Specifically, it was held that CVC's claims to a CRISPR-Cas9 system without restriction to environment do not anticipate or render obvious Broad's claims limited to a eukaryotic environment. (*See id.*)

Subsequent to an affirmance of that decision by the Federal Circuit,[2] at least some of CVC's involved applications were issued as patents with claims to a method of cleaving DNA with a CRISPR-Cas9 system having a single RNA component, without restriction to the environment. (*See, e.g.,* U.S. Patent 10,266,850; *see* CVC Opp. 5, Paper 2567, 37:4–6.) There is no dispute in this proceeding over the patentability of those claims or that the CVC inventors were the first to invent a CRISPR-Cas9 system with a single guide RNA to cleave DNA in a generic environment.

CVC now presents claims to a CRISPR-Cas9 system having a single RNA component in a eukaryotic cell environment. (*See* Junior Party's Clean Copy of Claims, Paper 7.) These claims were determined to interfere with the same Broad

[2] *See Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286 (Fed. Cir. 2018).

claims involved in Interference 106,048 upon declaration of the current proceeding. (*See* Declaration, Paper 1.) Thus, the priority dispute before us now is which party's inventors were the first to invent a CRISPR-Cas9 system with a single guide RNA able to cleave or edit DNA to affect gene expression in a eukaryotic cell. (*See id.* at 12–13, Count 1.) Our focus is the determination of priority of invention of the subject matter of Count 1 under 35 U.S.C. § 102(g). *See* 35 U.S.C. § 135(a) ("The Board of Patent Appeals and Interferences shall determine questions of priority of the inventions . . . .").

A.

Following the preliminary motions phase of this proceeding, CVC as junior party was accorded benefit of the filing date 28 January 2013 of its provisional application 61/757,640. (*See* Redeclaration, Paper 878.) Broad was accorded benefit of the filing of date 12 December 2012 of its provisional application 61/736,527. (*See id.*) Both parties have filed motions arguing for dates of conception and reduction to practice earlier than their accorded benefit dates. CVC filed Substantive Motion 2 (Paper 1579), which was followed by Broad's opposition (Paper 2569) and CVC's reply (Paper 2744). Broad filed Substantive Motion 5 (Paper 2118), which was followed by CVC's opposition (Paper 2567) and Broad's reply (Paper 2745).

CVC was also authorized to file a motion arguing that Broad's involved patent and application claims are unpatentable for failure to name the correct inventors. CVC filed Substantive Motion 3 (Paper 1558), which was followed by Broad's opposition (Paper 2475) and CVC's reply (Paper 2743).

We take up motions in the order that secures the just, speedy, and inexpensive resolution of the proceeding. *See* 37 C.F.R. § 41.125(a). The parties presented oral arguments on 4 February 2022. (*See* Transcript, Paper 2862.)

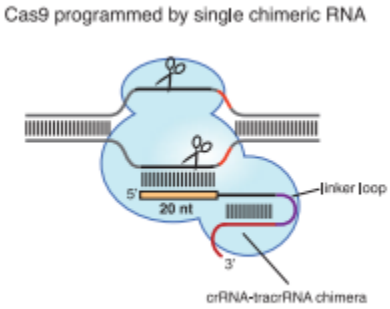
B.

Count 1 is a "McKelvey count,[3]" which includes a claim of an involved Broad application and a claim of an involved CVC application directed to a CRISPR-Cas9 system having a single RNA component, which along with the protein Cas9, can cleave a DNA molecule to alter gene expression or modulate transcription of a targeted gene in a eukaryotic environment. (*See* Declaration, Paper 1, 12–13.)

Briefly, a CRISPR-Cas9 system uses two RNAs and a protein to target a DNA molecule and cleave it at a specific sequence. Count 1 is limited to a system in which the two RNAs are fused into a single RNA molecule, sometimes referred to as a "single guide RNA," "sgRNA," or "chimeric RNA." In Broad's terminology the single guide or chimeric fused RNA comprises a "guide sequence" fused to a "tracr sequence" and in CVC's terminology it comprises a "targeter-RNA" (also called a "crRNA") fused to an "activator-RNA" (also called a "tracrRNA"). Under both parties' terminology, the fused RNA hybridizes to the

[3] *See Melrose v. Graham Packaging Co.,* Interference No. 106,050, 2017 WL 4280697, at *12 (P.T.A.B. Sept. 22, 2017) ("The count is a so-called McKelvey count, now familiar in interferences. Notwithstanding the disjunctive combination of claims, the count represents a single patentable invention.") The use of such a count in interference proceedings was pioneered by the Honorable Frederick E. McKelvey, of the Board.

targeted DNA to achieve specific cutting of the targeted DNA. Jinek 2012[4] (Ex. 3202) provides a schematic figure of the system, which is reproduced below.



(Jinek 2012, Ex. 3202, 820, Fig. 5A.)

Count 1 recites Broad patent 8,697,359, claim 18 or CVC application 15/981,807, claim 156. (*See* Declaration, Paper 1, 12.) Broad patent 8,697,359, claim 18 recites:

> The CRISPR-Cas system of claim 15, wherein the guide RNAs comprise a guide sequence fused to a tracr sequence.

(*Id.* at 12.) Broad patent 8,697,359, claim 15 recites:

> An engineered, programmable, non-naturally occurring Type II CRISPR-Cas system comprising a Cas9 protein and at least one guide RNA that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell, wherein the DNA molecule encodes and the eukaryotic cell expresses at least one gene product and the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

[4] Jinek et al., "A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity," SCIENCE, 337: 816–21 (2012).

(*Id.* at 13.) CVC application 15/981,807, claim 156 recites:

> A eukaryotic cell comprising a target DNA molecule and an engineered and/or non-naturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-—CRISPR associated (Cas) (CRISPR-Cas) system comprising
>
> a) a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein; and
>
> b) a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises:
>
> i) a targeter-RNA that is capable of hybridizing with a target sequence in the target DNA molecule, and
>
> ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,
>
> wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides; and
>
> wherein the single molecule DNA-targeting RNA is capable of forming a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule.

(*Id*.) Both the CVC and Broad portions of Count 1 recite either a "eukaryotic cell comprising" a CRISPR-Cas9 system (claim 156 of CVC application 15/981,807) or a CRISPR-Cas9 system "in a eukaryotic cell" (claim 18 of Broad patent 8,697,359). Both portions also recite the ability of the CRSIPR-Cas9 system to cleave or edit DNA in the eukaryotic cell to alter gene expression. The Broad portion of Count 1 recites "wherein . . . the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered" and the

CVC portion of Count 1 recites "whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule." A complete invention includes these elements of Count 1.

C.

"[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice." *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). When evaluating the testimony of an inventor, we look to corroborative, independent evidence to avoid to safeguard against inventors who might otherwise "be tempted to remember facts favorable to their case." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1346 (Fed. Cir. 2017).

As senior party, the Broad inventors are presumed to have invented the subject matter of the count before junior party CVC. (*See* 37 C.F.R. § 41.207(a).) Each party, though, bears the burden of providing a showing, supported by appropriate evidence, of the motions it asserts. (*See* 37 C.F.R. § 41.208(b) and § 41.121(b).) We evaluate the parties' arguments and evidence of dates of conception and reduction to practice to determine whether the preponderance of the evidence supports the presumptions of junior and senior party. (*See* 37 C.F.R. § 41.2017(a)(2).)

II. CVC Motion 2 - Priority

CVC asserts an earliest date of actual reduction to practice date (9 August 2012) and conception date (1 March 2012) before Broad's accorded benefit date (12 December 2012). (*See* CVC Motion 2, Paper 1579; *see* Redeclaration, Paper 878.) We look to the evidence presented by the parties of the activities and ideas of CVC's named inventors, Jennifer Doudna, Ph.D., Martin Jinek, Ph.D., Emmanuelle Charpentier, Ph.D., and Krzysztof Chylinski, Ph.D., to determine if the preponderance of evidence supports these dates.

A.

An actual reduction to practice requires proving that the inventors constructed an embodiment of the count, meeting all its limitations, and that they determined the invention would work for its intended purpose. *Cooper*, 154 F.3d at 1327, citing *UMC Elecs. Co. v. United States*, 816 F.2d 647, 652 (Fed.Cir.1987). "[W]hen testing is necessary to establish utility, there must be recognition and appreciation that the tests were successful for reduction to practice to occur." *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 594–95 (Fed.Cir.1997). Because testing is necessary to know whether a CRISPR-Cas9 system cleaves or edits DNA, we look to whether the evidence CVC presents shows that the inventors recognized and appreciated the results of the 9 August 2012 experiment as an embodiment meeting all the limitations of Count 1.

CVC first argues that an embodiment of Count 1 was actually reduced to practice by 9 August 2012 in an experiment in zebrafish embryos performed by Florian Raible, Ph.D., who reportedly was the research group leader at the Center of Molecular Biology at the University of Vienna in 2012. (*See* CVC Motion 2,

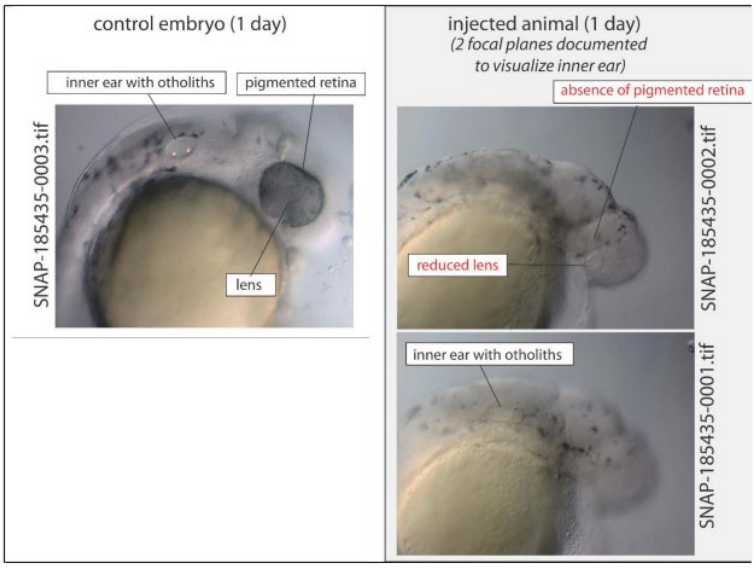
Paper 1579, 22:1–27:15; *see* Raible Decl., Ex. 4294, ¶ 2.) Dr. Raible testifies that he had significant first-hand experience with other gene editing systems such as zinc-finger nuclease (ZFN) technology and transcription activator-like effector nucleases (TALE nucleases or TALENs), including microinjecting them into fertilized eggs of the zebrafish. (Raible Decl., Ex. 4294, ¶ 7.)

Dr. Raible testifies that on 28 June 2012, he sent an e-mail to Dr. Charpentier to show his interest in using the sgRNA CRISPR system in a fish model. (*See* Raible Decl., Ex. 4294, ¶ 14, citing Exs. 4799, 4801, 4802.) Exhibit 4799 is a copy of an e-mail dated 28 June 2012, reflecting Dr. Raible's testimony that he agreed to experiments in an *in vivo* context. (*See* Ex. 4799.) CVC presents the testimony of Dr. Charpentier and a corroborating copy of an email dated 29 June 2012, as evidence that Dr. Doudna approved these experiments. (*See* CVC Motion 2, Paper 1579, 22:5–6, citing Charpentier Decl., Ex. 4351, ¶ 62, Ex. 4804.)

CVC presents evidence of the plans Dr. Chylinski and Dr. Raible made to design CRISPR systems, including the required "NGG" sequence adjacent to the target DNA sequence (called the "PAM sequence"), for targeting the *rx3* gene (also called *chokh/chk*), which regulates eye formation. (*See* CVC Motion 2, Paper 1579, 22:7–23, citing Ex. 4810, Ex. 4294, ¶¶ 21–27.) Mutation of the *rx3/chokh/chk* gene is reported to result in a specific, diagnostic eyeless phenotype, which could be distinguished from generalized developmental problems due to causes other than the disruption of a specific gene. (*See* Raible Decl., Ex. 4294, ¶¶ 22–26.)

CVC argues that in July 2012, Dr. Chylinski and Dr. Raible did preliminary studies and that by 19 July 2012, Dr. Raible performed a first test of a CRISPR-Cas9 system in zebrafish. (*See* CVC Motion 2, Paper 1579, 22:19–25, citing Raible Decl., Ex. 4294, ¶¶ 33–49.) Dr. Raible testifies that he did not detect the expected phenotype from this first test, but instead found some non-specific developmental effects, such as the lack of a head. (*See* Raible Decl., Ex. 4249, ¶ 49, citing Ex. 4337.)

CVC cites further to Dr. Raible's and Dr. Chylinski's testimony about experiments using the fish model with a new *rx3* target sequence. (*See* CVC Motion 2, Paper 1579, 22:25–23:7, citing Raible Decl., Ex. 4294, ¶¶ 52–53, Chylinski Decl., Ex. 4348, ¶¶ 123–124.) On 8 August, 2012, Dr. Raible reportedly performed a second zebrafish experiment and on 9 August 2012 he reportedly identified at least one fish allegedly with the targeted mutation. (*See* CVC Motion 2, Paper 1579, 23:8–16.) In his supporting testimony, Dr. Raible's indicates that one of the 30 embryos he injected with one concentration of the test solution showed the characteristic eyeless morphological phenotype expected for the homozygous *rx3*/*chokh*/*chk* mutant fish. (*See* Raible Decl., Ex. 4294, ¶¶ 54–55.) Dr. Raible testifies that he documented the mutant embryo and the wild type embryo, citing to several different exhibits. (*See* Raible Decl., Ex. 4294, ¶ 55, citing Exs. 4913–4915.) Dr. Raible provides a compilation of several images from these exhibits, which is reproduced below.



(Raible Decl., Ex. 4294, ¶ 55, citing Exs. 4913–4915.)

In his declaration, Dr. Raible summarizes that he

> prepared [the animal with the homozygous *rx3/chokh/chk* phenotype] on August 8, 2012, on behalf of the CVC inventors by injecting into the animal a preformed complex of the Cas9 protein and two single-guide RNAs that included crRNA and tracrRNA sequences where the crRNA sequence targeted the *rx3/chokh/chk* locus. This fish indicated to me that there was successful site-specific DNA cleavage in a zygote injected with the inventors' CRISPR-Cas9 system. The inventor's CRISPR-Cas9 system thus worked as predicted in zebrafish using previously known methods for delivery and analysis.

(Raible Decl., Ex. 4294, ¶ 56.) Dr. Raible testifies that within a few days of obtaining the results he informed Dr. Chylinski. (*See* Raible Decl., Ex. 4249, ¶¶ 57–58.) CVC does not direct us to contemporaneous evidence showing that Dr. Raible considered the results of the 9 August 2012 experiment to have been successful. Although Dr. Raible is not an inventor and, therefore, his testimony does not necessarily need to be corroborated, contemporaneous evidence carries

more weight in supporting his understanding at the time of the experiment, particularly where CVC argues that his understandings inure to the inventors' benefit. (*See* CVC Motion 2, Paper 1579, 26:16–24.)

Dr. Chylinski testifies that he learned of Dr. Raible's results on 9 August 2012 and e-mailed Dr. Charpentier about them. (*See* Chylinski Decl., Ex. 4348, ¶ 127, citing Ex. 4911.) Dr. Charpentier testifies that on a phone call Dr. Chylinski conveyed to her, "consistent with his email," that Dr. Raible had reported positive results of an eyeless phenotype in zebrafish, reflecting successful gene modification using the sgRNA CRISPR-Cas9 system. (Charpentier Decl., Ex. 4351, ¶ 70, citing Exs. 4911, 4912.) Exhibit 4911 is a copy of an e-mail from Dr. Chylinski to Dr. Charpentier, dated 9 August 2012. In the e-mail Dr. Chylinski states:

> Potentially good news about fish. We tested the NLS-tagged Cas9 that we just got from Martin as the normal protein was not giving anything conclusive. It looks like GFP expression in medaka is much lower in the embryo although there are still problems with toxicity and so on, so it will require some more optimization form their site. Anyway, there is a hint it might work but we shouldn't be overexcited now.

(Ex. 4911.) In a reply e-mail, Dr. Charpentier responded "ok. i give you a call now then." (Ex. 4912.)

Broad argues that Dr. Chylinski's e-mail of 9 August 2012 does not indicate he appreciated or recognized that the results of Dr. Raible's zebrafish experiment were successful. (*See* Broad Opp. 2, Paper 2569, 48:15–49:13.) First, Broad argues that the e-mail refers to experiments in "medaka," a type of fish distinct from the zebrafish embryos Exhibits 4913–4915. (*See* Raible Decl., Ex. 4294,

¶¶ 52–55.) Furthermore, Broad argues that Dr. Chylinski never characterized the fish experiments he discusses as being a success. Instead, he refers to a "hint" and cautions about being "overexcited now." (Exs. 4911, 4912.)

We agree with Broad that Dr. Chylinski's 9 August 2012 e-mail to Dr. Charpentier does not characterize any fish experiment as successful and that it is not clear to which results Dr. Chylinski refers because he mentions medaka, not zebrafish. We agree with Broad that by itself, neither Dr. Chylinski's e-mail of 9 August, nor Dr. Charpentier's response demonstrates that either recognized and appreciated Dr. Raible's 9 August 2012 experiment was an actual reduction to practice of an embodiment of Count 1. The e-mail of Exhibit 4911 also fails to adequately support Dr. Raible's declaration testimony that he considered the experiment of 9 August 2012 to be successful at the time.

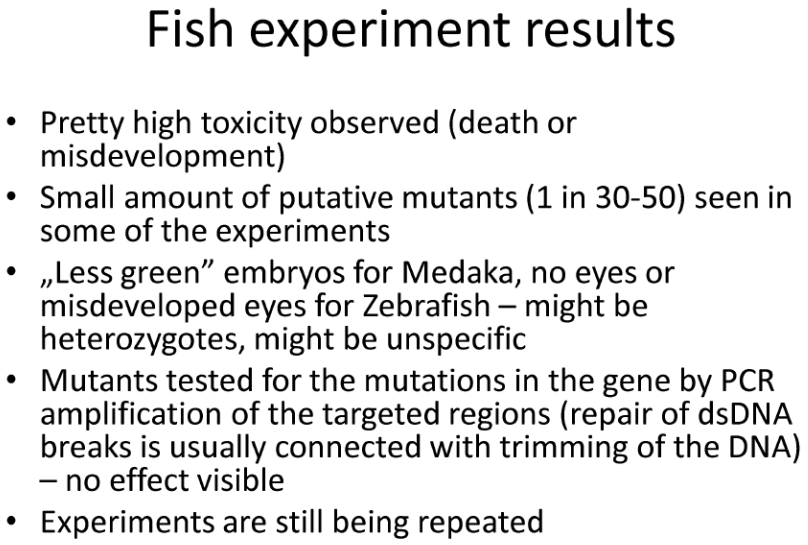
CVC cites further to Exhibit 5139 as evidence supporting Dr. Charpentier's and Dr. Chylinski's appreciation that the fish embodiment worked for its intended purposes and met all the limitations of Count 1. (*See* CVC Motion 2, Paper 1579, 23:17–21.) Exhibit 5139 is a copy of an e-mail dated 29 August 2012, from Dr. Charpentier to recipients including Dr. Chylinski, asking for a slide presentation summarizing strategies for *in vivo* targeting in bacteria and fish that had been done so far. (*See* Ex. 5139.) We agree with Broad that Exhibit 5139 only requests information and does not provide any indication of the results of these experiments or the inventors' understanding of them. (*See* Broad Opp. 2, Paper 2569, 49:14–20.)

Dr. Chylinski testifies that on 31 August 2012 he prepared a slide for Dr. Charpentier that included a summary of the strategies for *in vivo* targeting in

fish at the time. (*See* Chylinski Decl., Ex. 4348, ¶ 129, citing Ex. 4916; *see* CVC Motion 2, Paper 1579, 23:18–23.) Dr. Chylinski testifies:

> We believed that these effects were the result of our sgRNA CRISPR-Cas9 system's activity in the fish, though we had not confirmed an effect on the targeted regions by sequencing. Ex. 4916. While my fish experiment result summary noted that the effects of possible incomplete GFP loss in the medaka might be the result of "heterozygotes" or "unspecific" effects, the zebrafish eyeless phenotype indicated that we had successfully used our sgRNA CRISPR-Cas9 system to target and cleave target DNA within the zebrafish. Ex. 4916. The reference to repeating experiments indicated that a journal publication would require multiple experiments and a second molecular detection assay.

(Chylinski Decl., Ex. 4348, ¶ 129.) Exhibit 4916 is a copy of an e-mail dated 31 August 2012, from Dr. Chylinski to Dr. Charpentier, with an attached slide presentation. Page 10 of Exhibit 4916 is reproduced below.



This slide states that "a small amount of putative mutants" were seen in some experiments, states that the "no eyes or misdeveloped eyes for Zebrafish," which

"might be heterozygotes, might be unspecific," and indicates that there is no visible effect of testing for mutations by PCR. (*See* Ex. 4916, 10.)

We are not persuaded that Exhibit 4916 supports Dr. Chylinski's testimony that he recognized the zebrafish eyeless phenotype "indicated that we had successfully used our sgRNA CRISPR-Cas9 system to target and cleave target DNA within the zebrafish." (Chylinski Decl., Ex. 4348, ¶ 129.) CVC argues that Exhibit 4916 shows that Dr. Chylinski summarized the positive results as indicating "'putative mutants' including 'no eyes or misdeveloped eyes for zebrafish,'" but fails to mention that Dr. Chylinski included the possibility that these mutants were "unspecific." Exhibit 4916 does not indicate that Dr. Chylinski favored the explanation of heterozygosity over unspecific effects or that he was convinced the phenotype was due to specific editing of the *rx3* gene by a CRISPR-Cas9 system. We agree with Broad and find that, contrary to CVC's argument, Exhibit 4916 does not indicate an acknowledgement of positive results by Dr. Chylinski. (Broad Opp. 2, Paper 2569, 43:2–14.) Exhibit 4916 does not indicate that Dr. Raible informed Dr. Chylinski of any experiments he believed were successful as of the end of August 2012.

CVC cites to Dr. Chylinksi's testimony on cross-examination that he recalled Dr. Raible "describing the phenotypes he observed." However CVC does not direct us to any part of Dr. Chylinski's deposition that indicates he considered Dr. Raible's results to show that the CRISPR-Cas9 system had cleaved DNA in a zebrafish embryo to cause an alteration of gene expression in a zebrafish embryo. (*See* CVC Reply 2, Paper 2744, 25:9–13, citing Chylinski Depo., Ex. 6202, 101:14–102:3.)

CVC also argues that by 9 August 2012 Drs. Chylinski and Charpentier appreciated that a fish cell embodiment of the count worked for its intended purpose. (*See* CVC Motion 2, Paper 1579, 23:15–16.) In its Reply Brief,[5] CVC argues that Dr. Charpentier stated she was "convinced" the CRISPR/Cas9 system would work in Dr. Raible's fish experiments. (*See* CVC Reply 2, Paper 2744, 13:14–18, 22:6–8.) In support, CVC cites to a statement in Dr. Charpentier's declaration citing Exhibit 4807. (*See* Charpentier Decl., Ex. 4351, ¶ 60.)

Dr. Charpentier reports that Exhibit 4807 is a copy of an e-mail that was reportedly never sent, but has a date of 28 June 2012 and appears to be from Dr. Charpentier to Dr. Raible, among other cc'ed recipients. (*See* Charpentier Decl., Ex. 4351, ¶ 60; *see* Ex. 4807.) The message is in response to Dr. Raible's offer to collaborate and his plan for experiments using a CRISPR/Cas9 system in fish, as well as a worm model, including a plan for experiments. (*See* Ex. 4807.) Dr. Raible refers to what might be expected "if the stunning efficiency of the CRISPR/Cas system you observed in vitro translates to the in vivo scenario . . . ." (*Id*.) Apparently in reply, Dr. Charpentier indicates she is glad that Dr. Raible is interested in doing fish experiments as a collaboration and then states: "Wit[h] regard to the system, we are indeed convinced." (*Id*.) Dr. Raible does not refer to any actual results. Nor does Dr. Charpentier.

[5] We note that CVC relied on Exhibit 4807 for the first time in it Reply Brief as support for an argument that Dr. Charpentier was "convinced" the system would work in fish cells, even though the exhibit was available when CVC Motion 2 was filed. (*See* Motion 2, Paper 1579, I-24.)

Neither Dr. Charpentier nor CVC provides an explanation why Dr. Charpentier's words in Exhibit 4807 indicate she was convinced of positive results for Dr. Raible's fish experiments. Instead, Dr. Charpentier and CVC merely quote the words "indeed convinced" without relating them back to Dr. Raible's message. Without further explanation of how Dr. Charpentier's comment relates to positive results using a CRISPR-Cas9 system in a fish cell, the e-mail fails to corroborate Dr. Charpentier's testimony or to support CVC's argument that Dr. Charpentier was "convinced" that the fish system would work. We note further that CVC does not direct us to comments by any of the CVC inventors that they were "convinced" or similarly persuaded that the CRISPR-Cas9 system had worked *after* Dr. Raible presented his results to Dr. Chylinski.

In general, we find that CVC over-emphasizes isolated words by its inventors to argue that they recognized and appreciated Dr. Raible's results. We are further persuaded that CVC over-interprets the inventors' recognition and appreciation of Dr. Raible's results because neither Dr. Doudna nor Dr. Jinek remembers learning of them at the time. (*See* Doudna Depo, Ex. 6204, 169:10–15; *see* Jinek Depo., Ex. 6207, 75:16–78:9; *see* Broad Opp. 2, Paper 2569, 47:17–48:5.) It is unlikely that Dr. Doudna or Dr. Jinek was told of results understood by Drs. Chylinski and Charpentier to be the first successful gene modification in a eukaryotic cell by a CRISPR-Cas9 system and forgot it. (*See* Doudna Depo., Ex. 6204, 269:16–22 (Q Okay. All right. Well, you would have been keenly interested in learning if there had been success since you were working as quickly as possible to try and show that CRISPR-Cas9 worked in eukaryotic cells for genome editing, right? A I would have been interested in all of the experiments we

had underway at the time.").) Instead, Dr. Doudna testified that getting the genome editing a CRISPR-Cas9 system to work in a fish cell would have been of broad interest and would be publication-worthy in a high-impact journal in 2012. (*See* Doudna Depo., Ex. 6204, 163:3–12.) Thus, if Dr. Doudna had been told that Dr. Raible's experiment in August 2012, or at any other time, was successful, she would have remembered it. We note, too, that no zebrafish experiments were included in CVC's provisional applications filed 19 October 2012 and 28 January 2013. (*See* Broad Opp. 2, Paper 2569, 50:5–8.) The lack of communication by Drs. Chylinski and Charpentier regarding Dr. Raible's 9 August 2012 zebrafish experiment and lack of reference to it later indicates to us that the CVC inventors did not consider it to be a success or a reduction to practice of Count 1 because Dr. Raible did not communicate any success to them.

Both parties present the opinion testimony of witnesses who have experience with zebrafish models. CVC presents the testimony of Cecilia Moens, Ph.D. (*see* CVC Motion 2, Paper 1579, 24:1–26:15, citing Moens Decl., Ex. 4343) and Broad presents the testimony of Phillippe Mourrain, Ph.D. (*see* Broad Opp. 2, Paper 2569, 45:1–46:22, citing Mourrain Decl., Ex. 3447). Neither party disputes the qualifications of the other's witness, but the witnesses provide divergent opinions on the results of Dr. Raible's 9 August 2012 experiment.

Dr. Moens testifies that the eyeless phenotype Dr. Raible obtained in the 9 August 2012 zebrafish experiment was consistent with cleavage of the *rx3* gene and demonstrated that the CRISPR-Cas9 system he injected into the embryos was capable of cleaving or editing a target DNA to modulate transcription of at least one gene encoded by the target DNA. (*See* Moens Decl., Ex. 4343, ¶¶ 45–58, 70–

72.) Dr. Moens testifies that visual verification of the phenotype is sufficient to prove, with a high level of confidence that the *rx3* gene was successfully targeted, even without molecular analysis, such as PCR, to verify cleavage. (Moens Decl., Ex. 4343, ¶ 49.)

Dr. Mourrain testifies that Dr. Raible and others in the field would have used genetic testing to confirm mutations of the *rx3* gene. (*See* Mourrain Decl., Ex. 3447, ¶¶ 23–60.) Dr. Mourrain testifies further that the phenotype shown in the images from Dr. Raible's 9 August 2012 experiment was not what would have been expected from targeted cleavage of the *rx3* gene because a combination of characteristics were not present. According to Dr. Mourrain, the pictures presented by Dr. Raible were taken earlier in development than when these characteristics would be assessed. (*See* Mourrain Decl., Ex. 3447, ¶¶ 94–102.) In general, Broad argues that Dr. Raible's 9 August 2012 zebrafish experiment was a failure. (*See* Broad Opp. 2, Paper 2569, 40:11–47:10.)

Although both witnesses appear to be qualified in light of their credentials and experience, we need not determine which witness is correct because "there is no conception or reduction to practice where there has been no recognition or appreciation of the existence of" new subject matter. *Silvestri v. Grant*, 496 F.2d 593, 597 (CCPA 1973). Expert testimony can shed light on what the inventors did, such as whether their results demonstrate every limitation of a count, but we look for an appreciation of the results *by the inventors* or their agents. Thus, even if, as Dr. Moens testifies, one zebrafish embryo demonstrated targeted mutation of the *rx3* gene by a CRISPR-Cas9 system, if her testimony does not indicate the CVC inventors or Dr. Raible recognized or appreciated this result, the one embryo

would not indicate a reduction to practice by the inventors. In *Heard v. Burton*, 333 F.2d 239, 1505 (CCPA 1964), the court held that there was no reduction to practice where Heard never recognized what he had made, even though years later, after Burton's filing date, his company tested it and determined it was a particular form of alumina recited in the count. *See also Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1065 (Fed. Cir. 2005) ("it is not enough that a party adduce evidence that objective test results comport with an inventor's testimony concerning his state of mind. Rather, there must also be evidence that the junior party timely interpreted or evaluated the results, and understood them to show the existence [of] the invention."). Because neither party's witness can testify to what the CVC inventors or Dr. Raible were thinking at the time, we are not persuaded that either's testimony sheds light on whether the CVC inventors reduced an embodiment of Count 1 to practice by 9 August 2012.

In addition to not being persuaded that the CVC inventors recognized and appreciated the results of Dr. Raible's experiment, we are not persuaded by the contemporaneous evidence, specifically Dr. Raible's subsequent work, that Dr. Raible appreciated these results. (*See* Broad Opp. 2, Paper 2569, 44:14–23, 46:23–47:7.) According to his testimony, Dr. Raible attempted at least two other experiments using an sgRNA CRISPRCas9 system to target the *rx3* gene. (*See* Raible Decl., Ex. 4294, ¶¶ 70–73.) One experiment produced an eyeless embryo that also had non-specific development delay, which Dr. Raible characterized in his declaration as "more likely than not the product of successful DNA cleavage." (*See* Raible Decl., Ex. 4294, ¶ 72.) The other experiment "did not yield clearer results" than the previous experiment. (*See id.* at ¶ 73.)

But then, by 12 September 2012, Dr. Raible ended the project without any publication identified to us by CVC. He testifies:

> While I was happy to have helped the inventors validate their sgRNA CRSIRPCas9 system in zebrafish, I did not believe that merely showing successful cleavage in a eukaryote using only routine techniques, with no special parameters to introduce a nuclease into eukaryotic cells, would be a publication-worthy discovery. That was a trivial and expected result. I felt that to justify expending additional resources on these experiments, I needed results suggesting that the efficiency of CRISPR-Cas9 *in vivo* could compete with ZFNs and TALENs. I believed that other labs with more resources would likely generate such data before I would be able to, for instance by being able to perform massive parallel sequencing on targeted gene loci, bypassing the need to rely on the presence of length variants identified by PCR.

(*See id.* at ¶ 74.) This testimony contrasts sharply with Dr. Raible's views in June 2012, when he stated:

> Given the massive interest in simple methods for genome editing, we would expect that the establishment of a CRISPR/CAS-based genome editing system in any fish system would be of broad interest, and therefore a short article in a high-impact journal would not be unlikely as a result (provided the results match the expectations based on the in vivo data).

(Ex. 4799, 2.) It also contrasts with CVC's representation that there was a "race to publish on the implementation of CVC's sgRNA CRISPR-Cas9 system . . . ." (CVC Opp. 5, Paper 2567, 2:8–9.) Given the apparent importance of the experiments Dr. Raible was performing it is unclear why he abandoned them if he believed the CRISPR-Cas9 system designed by the CVC inventors was producing positive results in fish cells. It seems more likely that Dr. Raible's abandonment of

the project indicates that he did not recognize any success in 2012. (*See* Broad Opp. 2, Paper 2569, 47:1–7.)

CVC fails to direct us to persuasive evidence that any of the CVC inventors or Dr. Raible recognized or appreciated the results of the 9 August 2012 zebrafish experiment as demonstrating specific cleavage of a targeted DNA with an sgRNA CRISPR-Cas9 system to affect gene expression in a eukaryotic cell. Although Dr. Raible testified for this proceeding that one fish embryo indicated the CVC inventors' system had worked as predicted, no other evidence highlighted by CVC demonstrates he had this understanding in August 2012. (*See* Raible Decl., Ex. 4294, ¶ 56.) The evidence CVC presents shows that Drs. Chylinski and Charpentier were aware of Dr. Raible's results, but does not show that they considered the results to show success or that they relayed this information to either Dr. Doudna or Dr. Jinek. CVC does not direct us to evidence, beyond his testimony for this proceeding, that Dr. Raible communicated his understanding that the experiments were successful to any of the CVC inventors. Furthermore, Dr. Raible continued his allegedly successful experiment with only two other experiments and then abandoned the project, despite, in his words, the "massive interest" in field. (Ex. 4799; *see* Raible Decl., Ex. 4294, ¶¶ 70–74.)

Without persuasive evidence that either the inventors or Dr. Raible recognized the 9 August 2012 zebrafish experiment was successful, we are not persuaded that any inurement indicates an actual reduction to practice of an embodiment of Count 1. (*Contra* CVC Reply 2, Paper 2744, 16:2–4.) *See Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 593, 595 (Fed. Cir. 1997) (where there was not sufficient or persuasive evidence that the workers actually communicated

the results or had a basis to know whether the results were positive, their work did not inure to the benefit of the inventors or prove reduction to practice).

Accordingly, we are not persuaded that the CVC inventors or Dr. Raible actually reduced to practice an embodiment of Count 1 by 9 August 2012.

CVC asserts later dates of actual reduction to practice by 31 October 2012, 1 November 2012, 5 November 2012, and 18 November 2012. (*See* CVC Motion 2, Paper 1579, 27:16–35:9.) As discussed below, we are persuaded that the Broad inventors reduced to practice an embodiment of Count 1 by 5 October 2012 – a date prior to any of CVC's other asserted dates. Thus, we need not render a decision on CVC's later dates because even if we found the evidence supporting them to be persuasive, they would not change our overall analysis of priority. Instead, we look to whether CVC presents evidence to persuade us that it had a date of conception earlier than Broad. *See Cooper*, 154 F.3d at 1327 ("[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice.").

B.

CVC argues that its inventors had a complete conception of an embodiment of Count 1 by 1 March 2012. (*See* CVC Motion 2, Paper 1579, 4:13–20:23.) Conception requires a "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986); *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200,

1206 (Fed. Cir. 1991) ("Conception requires both the idea of the invention's structure and possession of an operative method of making it."). "An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Burroughs Wellcome Co. v. Barr Lab., Inc*., 40 F.3d 1223, 1228 (Fed. Cir. 1994).

The inventor need not know that the invention will work for conception to be complete because determining it works is part of reduction to practice. *See id.* Even when the invention is in an uncertain or experimental art, where the inventor cannot reasonably believe an idea will be operable until some result supports that conclusion, "[a]n inventor's belief that his invention will work or his reasons for choosing a particular approach are irrelevant to conception." *Id*. Thus, we do not base a determination of conception on facts regarding the state of the art or the inventor's beliefs of what will happen, but on the facts of how specific and settled the inventor's ideas were at the time asserted.

Under facts "where results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error" there has not been a complete conception. *Alpert v. Slatin,* 305 F.2d 891, 894 (CCPA 1962). "Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Burroughs*, 40 F.3d at 1228. Similarly, a conception may not be complete "if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and

permanent reflection of the complete invention as it will be used in practice." *See id.* at 1229. "When a research plan requires extensive research before the inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred." *Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001).

In such cases it is the factual uncertainty about whether the idea was complete in the mind of the inventor, rather than a generalized uncertainty surrounding experimental sciences or a specific field of art, that undermines conception. *See id.* For example, under the facts of *Hitzeman* it was not the general state of the art, but statements made by the inventor during prosecution and subsequent publications that revealed he had not conceived of the complete subject matter of the count and considered it not to have been reasonably expected by one of ordinary skill in the art. *Id.* at 1357. The *Hitzeman* court found that claiming the result of a biological process with "no more than a hope, or wish," that the process would be performed, when it had never before been achieved, was insufficient to establish conception. *Id.* at 1356–57.

CVC begins by asserting that before 1 March 2012, its inventors had identified the necessary and sufficient components of a CRISPR-Cas9 cleavage complex that could cleave any chosen target DNA *in vitro*. (*See* CVC Motion 2, Paper 1579, 5:6–6:10.) CVC states that the inventors learned that the PAM sequence was necessary and learned that they could truncate the lengths of the crRNA and tracrRNA, while maintaining a functional *in vitro* CRISPR-Cas9 system. (*See id.* at 6:21–7:7.) According to CVC, the inventors understood before

1 March 2012 that they could program their system to target and cleave any target DNA molecule of choice. (*See id.* at 7:8–13.)

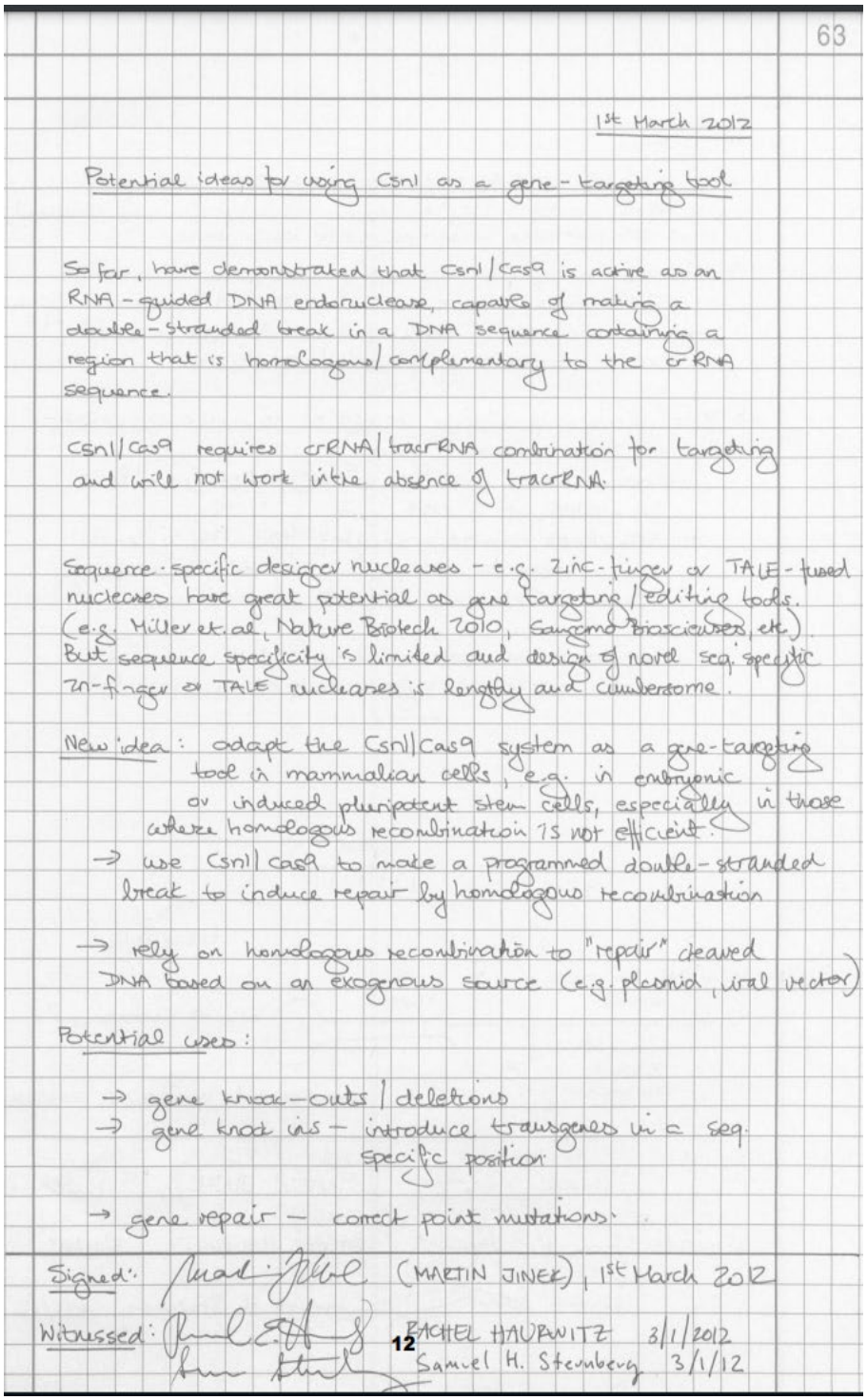
CVC continues with the argument that by 1 March 2012 the inventors had conceived of a CRISPR-Cas9 system in eukaryotic cells. (*See* CVC Motion 2, Paper 1579, 7:17–13:2.) CVC relies on the testimony of Dr. Doudna and Dr. Jinek that by 1 March 2012 they had discussed and developed a schematic diagram of a CRISPR-Cas9 system including a single guide RNA or "sgRNA," or "chimeric RNA" with the crRNA and tracrRNA present on a single RNA molecule. (*See* CVC Motion 2, Paper 1579, 7:18–23, citing Jinek Decl., Ex. 4349, ¶¶ 30–32; *see* Doudna Decl., Ex. 4350, ¶¶ 41–44.) This single RNA would form a complex with Cas9 to target and cleave DNA that is complementary to the protospacer region of the crRNA. (*See id*.) Dr. Doudna testifies that she "believed that the engineered sgRNA CRISPR-Cas9 system we had designed could target and modify DNA in both prokaryotes and eukaryotes, including mammalian cells." (*Id.*, ¶ 44.)

In support of their testimony, Drs. Jinek and Doudna cite to Exhibit 4406, which is e-mail correspondence between them dated 1 March 2012. In the e-mail, Dr. Doudna states: "I'm very excited about the Csn-1/Cas9-based genome targeting ideas we discussed yesterday, this will be fabulous if it works." (Exs. 4406 and 4405.) Dr. Doudna states further that she thought "it would be good to demonstrate that the single-RNA guide works to direct DNA cleavage by Csn1/Cas9 in vitro ASAP, . . . and then proceed with the experiments necessary to show that this strategy will actually work in mammalian cells." (Exs. 4406 and 4405.) The e-mails between Drs. Jinek and Doudna demonstrate that they planned experiments to show that the single-guide RNA CRISPR/Cas9 system would work

in mammalian cells.

CVC, as well as Drs. Jinek and Doudna, cite further to pages of Dr. Jinek's notebook memorializing their ideas on 1 March 2012. The pages are reproduced below.

Interference 106,115



63

1st March 2012

Potential ideas for using Csn1 as a gene-targeting tool

So far, have demonstrated that Csn1/Cas9 is active as an RNA-guided DNA endonuclease, capable of making a double-stranded break in a DNA sequence containing a region that is homologous/complementary to the crRNA sequence.

Csn1/Cas9 requires crRNA/tracrRNA combination for targeting and will not work in the absence of tracrRNA.

Sequence-specific designer nucleases - e.g. Zinc-finger or TALE-fused nucleases have great potential as gene targeting/editing tools. (e.g. Miller et al, Nature Biotech 2010, Sangamo Biosciences, etc) But sequence specificity is limited and design of novel seq. specific Zn-finger or TALE nucleases is lengthy and cumbersome.

New idea: adapt the Csn1/Cas9 system as a gene-targeting tool in mammalian cells, e.g. in embryonic or induced pluripotent stem cells, especially in those where homologous recombination is not efficient.

→ use Csn1/Cas9 to make a programmed double-stranded break to induce repair by homologous recombination

→ rely on homologous recombination to "repair" cleaved DNA based on an exogenous source (e.g. plasmid, viral vector)

Potential uses:

→ gene knock-outs/deletions
→ gene knock-ins - introduce transgenes in a seq. specific position

→ gene repair - correct point mutations.

Signed: (MARTIN JINEK), 1st March 2012

Witnessed: RACHEL HAURWITZ 3/1/2012
Samuel H. Sternberg 3/1/12

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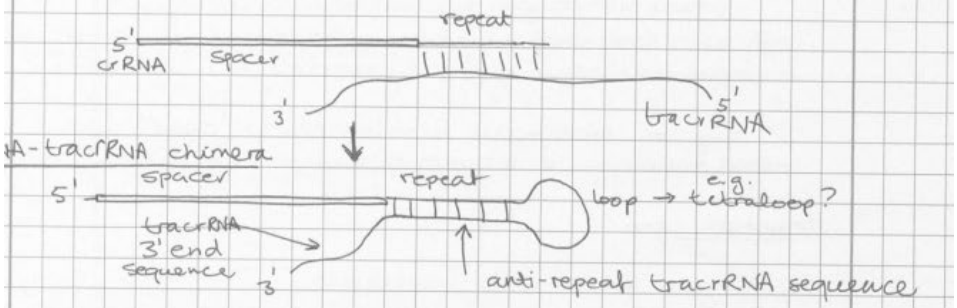
Strategy

→ Csn1/Cas9 activity requires the crRNA guide and tracrRNA (most likely functioning as a positioning element) that are partially base-paired to each other

→ one way would be to supply Csn1, together with a crRNA-encoding gene and a tracrRNA-encoding gene as separate constructs – either all on separate plasmids/vectors, or on a single plasmid/viral vector.

→ But another possibility would be to make a crRNA-tracrRNA chimera (fusion).
- know already that the mature crRNA can be truncated at 3' end
- tracrRNA can be truncated from the 5' end.
- system seems to work as long as some base-pairing between crRNA and tracrRNA is maintained.

⇒ Therefore could make a chimeric RNA containing a crRNA/tracrRNA hybrid hairpin



Signed: (MARTIN JINEK), 1st March 2012

Witnessed: RACHEL HAURWITZ 3/1/2012

Samuel H. Sternberg 3/1/12

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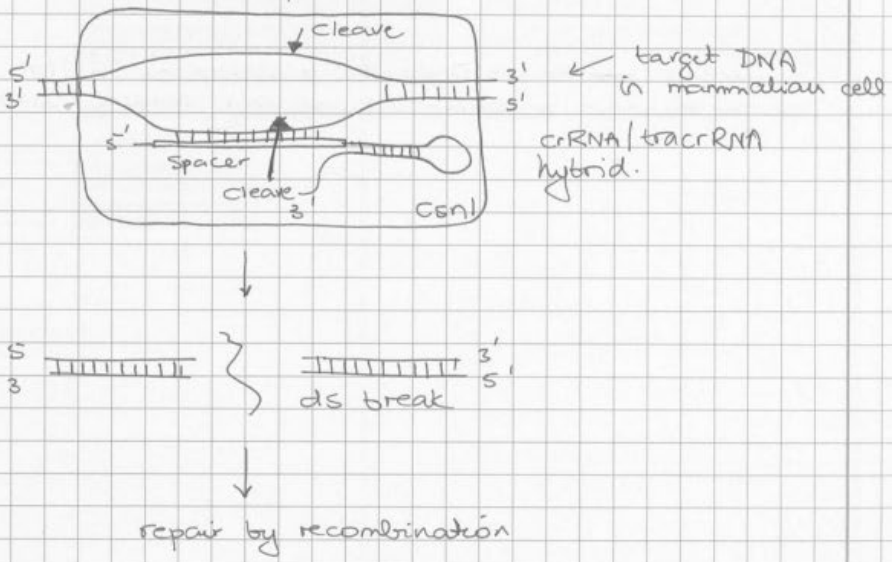
Interference 106,115

65

Next set of experiments

→ test that crRNA/tracrRNA hybrid constructs work in vitro

→ test whether the strategy can be used to induce DSBs in mammalian cells in a sequence-specific fashion.



Signed: (MARTIN JINEK), 1st March 2012

Witnessed: RACHEL HAURWITZ · 3/1/12

Samuel H. Sternberg 3/1/12

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(Ex. 4381, 12–14.) These notebook pages corroborate the CVC inventors' testimony that they had developed a CRISPR-Cas9 system, including a crRNA-tracrRNA fusion, for targeting a sequence homologous or complementary to the crRNA sequence. (*See* Ex. 4381, 12–13.) The pages indicate that Drs. Jinek and Doudna had the "New idea" of "adapt[ing] the Csn1/Cas9 system as a gene-targeting took in mammalian cells, e.g. in embryonic or induced pluripotent stem cells . . . ." (Ex. 4381, 12.) The pages also indicate that the CVC inventors had a plan to "test whether the strategy can be used to induce DSBs in mammalian cells in a sequence-specific fashion." (Ex. 4381, 14.)

CVC cites to the testimony of Yannick Doyon, PhD.,[6] to support the argument that its inventors' conception was complete because each element of Count 1 was included in Dr. Jinek's notebook pages. (*See* CVC Motion 2, Paper 1579, 8:17–12:8, citing Doyon Decl., Ex. 4345, ¶¶ 70–82.) Specifically, Dr. Doyon testifies that the system the CVC inventors depicted has a Cas9 protein and a single molecule DNA-targeting RNA capable of hybridizing to a target sequence to cleave the DNA. (*See* Doyon Decl., Ex. 4345, ¶¶ 74–76.) CVC cites further to Dr. Doyon's opinion that Dr. Jinek's notebook shows evidence of having

[6] Dr. Doyon terrifies that he is an Associate Professor in the Department of Molecular Medicine at Université Laval, Québec, Canada. (*See* Declaration of Yannick Doyon, Ph.D. ("Doyon Decl."), Ex. 4345, ¶ 13.) Dr. Doyon testifies that he has extensive experience in the field of genome editing using ZFNs, TALENs, and CRISPR-Cas9 systems and his publications, patents, and grants reflect his testimony. (*See id.* at ¶ 14; *see* Ex. 4346.) Broad does not raise any objection to Dr. Doyon's qualifications. We find him to be qualified to present opinion testimony on the subject of interference.

conceived of a "eukaryotic cell comprising a target DNA molecule and an engineered Type II CRISPR-Cas system," because statements in the notebook refer to "mammalian cells," "embryonic or pluripotent cells," and gene knock-outs/deletions" as well as "gene knock-ins" and "gene repair." (*See* Doyon Decl., Ex. 4345, ¶¶ 77–80; *see* CVC Motion 2, Paper 1579, 9:3–12.)

CVC argues that its inventors' conception was definite and permanent as of 1 March 2012 because it did not change between conception and subsequent reduction to practice. (*See* CVC Motion 2, Paper 1579, 12:9–13:2.) Specifically, CVC argues that the sgRNA CRISPR-Cas9 system depicted in Dr. Jinek's notebook is a "blueprint" of the sgRNA design that was published by the inventors in Jinek 2012 (Ex. 3202), used in their reductions to practice, and disclosed in their patent applications. (*Id.* citing Doyon Decl., Ex. 4345, ¶¶ 83–85.) CVC presents a side-by-side comparison of diagrams depicting an sgRNA from Dr. Jinek's notebook entry of 1 March 2012 (Ex. 4381), Figure 5B of the Jinek 2012 publication (Ex. 3202), and Figure 38A of CVC provisional application 61/757,640 ("P3," Ex. 3004), which it argues are the same. (*See* CVC Motion 2, Paper 1579, 12:13–18.) Dr. Doyon supports this argument by testifying that "[t]he single-guide CRISPR-Cas9 system for eukaryotic cells that the CVC inventors contemplated by March 1, 2012 is the same as the single-guide CRISPR-Cas9 system that the CVC inventors later used to induce double- strand breaks in the DNA of mammalian cells using ordinary skill and routine techniques." (Doyon Decl., Ex. 4345, ¶ 83.)

CVC argues that further evidence of its inventors' conception on 1 March 2012 occurred on 11 April 2012, on 28 May 2012, and on 28 June 2012, after the inventors were diligently working towards a reduction to practice. (*See*

CVC Motion 2, Paper 1579, 14:2–20:23.) First, CVC asserts that by 4 April 2011 the inventors had conducted the first *in vitro* test confirming an sgRNA could form a functional DNA-cleavage complex with Cas9 and cleave targeted DNA. (*See id.* at 14:8–10, citing Jinek Notebook, Ex. 4381, 84–86 (indicating that "chimeras A are all functional").) After that test, CVC highlights an invention disclosure form ("IDF") reportedly drafted by Dr. Jinek on 11 April 2012, as evidenced by a copy of an e-mail from Dr. Jinek to Dr. Doudna with that date. (*See* CVC Motion 2, Paper 1579, 14:11–16, citing Ex. 5105.)

CVC asserts that the IDF "shows that the inventors understood the PAM sequence and its expected role in CRISPR-Cas9-mediated DNA cleavage in a eukaryotic cell" because it referred to using a CRISPR-Cas9 system in eukaryotic cells such as oocytes, embryos, human ES cells, and iPSC lines (CVC Motion 2, Paper 1579, 15:8–10, citing Ex. 5105, 18, 23–28, Jinek Decl., Ex. 4349, ¶¶ 72–74; Doudna Decl., Ex. 4350, ¶ 60.) CVC asserts further that by 11 April 2012, its inventors had selected truncated crRNA and tracrRNA components for a CRISPR-Cas9 system. (*See* CVC Motion 2, Paper 1570, 15:17–16:15.)

CVC argues that the IDF provides conventional techniques for reducing the invention to practice and optimizing it. (*See* CVC Motion 2, Paper 1579, 16:16–17:1, citing Ex. 5105, 23–24.) The IDF lists techniques of introducing DNA or RNA encoding components of the system into cells, by direct microinjection of oocytes, and embryos, transfection of cultured cells, electroporation of cultured cells, transduction of cells using viral vectors and *Agrobacterium*-mediated transformation of plants. (*See* Ex. 5105, 24.)

Broad argues that the IDF "simply consists of laundry lists of methods for

introduction and generic statements" regarding useful components without any definite or permanent idea for implementation of the invention. (Broad Opp. 2, Paper 2569, 32:17–20.) Broad cites to Dr. Jinek's cross-examination testimony that as of 1 March 2012, he understood achieving sgRNA and Cas9-mediated genome editing in eukaryotic cells would only require expressing or delivering these components to the cell "using straightforward application of basically methods for expression of RNAs and proteins in eukaryotic cells," such as had been used for TALENs and zinc finger techniques. (Jinek Depo., Ex. 6207, 92:6–9; *see, generally, id.* at 92:10–95:1; *see* Broad Opp. 2, Paper 2569, 32:15–33:2.) CVC does not direct us to more explanation or details of the processes that the CVC inventors understood, at the time, would be needed to achieve a functional sgRNA CRISPR-Cas9 system in a eukaryotic cell.

The IDF demonstrates that the CVC inventors planned to use their sgRNA CRISPR-Cas9 system in eukaryotic cells, but does not provide many details of how the inventors envisioned such a system would be operable. Instead, the IDF and Dr. Jinek's testimony indicates that as of 1 March 2012 the inventors assumed that what was known about other genome editing systems such as TALENs and zinc fingers would be applicable to a CRISPR-Cas9 system.

CVC cites further to experimental work supporting the asserted conception date of 1 March 2012, noting that "[w]hile diligently working towards an [actual reduction to practice], the inventors understood that the Doudna and Charpentier labs were not equipped to do testing in eukaryotic cells, but collegial labs at [University of California] and [University of Vienna] would be able to test the system in eukaryotes much faster." (CVC Motion 2, Paper 1579, 17:2–4.) The

CVC inventors testify that they contacted other scientists: David Drubin and Aaron Cheng to test sgRNA CRISPR-Cas9 in human cells and Florian Raible to test sgRNA CRISPR-Cas9 in zebrafish cells. (*See* Doudna Decl., Ex. 4350, ¶ 62, Jinek Decl., Ex. 4349, ¶ 75, 78; Charpentier Decl., Ex. 4351, ¶¶ 57–58; Chylinski Decl., Ex. 4348, ¶¶ 115.)

CVC argues that by 28 May 2012 its inventors had constructed sgRNAs for programming CRISPR-Cas9 systems to target genes from eukaryotic organisms adjacent to PAM sequences in eukaryotic cells, specifically in human cells. (*See* CVC Motion 2, Paper 1579, 17:11–19:9.) Dr. Jinek's testimony and his notebooks, cited by CVC, show that he had a plan to use his sgRNA constructs to target the CTLA gene in human cells. (*See* Jinek Decl., Ex. 4348, ¶¶ 124–128; Jinek Notebook, Ex. 4382, 1, 2.) CVC argues that this CLTA-targeting sgRNA CRISPR-Cas9 construct is the same system the inventors used to ultimately reduce an embodiment of Count 1 to practice in human cells. (*See* CVC Motion 2, Paper 1579, 19:7–9.) CVC argues further that a first year graduate student was able to reduce the invention to practice in human cells using conventional methods with only a few weeks of training. (*See* CVC Motion 2, Paper 1579, 13:23–14:1.)

CVC next points to evidence from 28 June 2012 as further support for the inventors' conception. (*See* CVC Motion 2, Paper 1579, 19:10–20:23.) CVC cites to e-mails between Drs. Charpentier, Chylinski, and Raible on that date discussing a plan to inject sgRNA/Cas9 into zebrafish embryos as an RNA/protein complex. (*See* CVC Motion 2, Paper 1579, 19:19–20:12, citing Ex. 4799; Chylinski Decl., Ex. 4348, ¶¶ 115–1116, Charpentier Decl., Ex. 4351, ¶¶ 57–59, Raible Decl., Ex. 4294, ¶¶ 14–16.) According to CVC, the inventors' reduction to practice in

zebrafish required only routine injection of sgRNA and Cas9 protein into zebrafish embryos. (*See* CVC Motion 2, Paper 1579, 13:8–14.)

Broad opposes CVC's arguments regarding conception, arguing, in general, that the CVC inventors lacked a "definite and permanent idea of the complete operative invention" as it would have been applied in practice. (Broad Opp. 2, Paper 2569, 30:13–39:16.) According to Broad, the 1 March 2012 diagram in Dr. Jinek's notebook was merely a "naked idea," without a definite plan. (*See id.* at 32:1–4.) Broad also asserts that the CVC inventors encountered multiple failures throughout 2012 when they attempted to use their sgRNA CRISPR-Cas9 system in human cells and zebrafish embryos. (*See id.* at 30:13–39:16.)

According to Broad, these failures prompted them to consider changing material aspects of the system in an attempt to find a strategy that could work. (*See id.*) Broad argues that these failures also indicate the CVC inventors had not expressed their ideas in such clear terms as to enable those skilled in the art to make the invention. (*See id.* at 33:24–34:5, citing *Coleman v. Dines,* 754 F.2d 353, 359 (Fed. Cir. 1985) ("Conception must be proved by corroborating evidence which shows that the inventor disclosed to others his 'completed thought expressed in such clear terms as to enable those skilled in the art' to make the invention.").)

Broad argues that instead of providing directions sufficient to reduce to practice a functional sgRNA CRISPR-Cas9 system in human cells by 28 May 2012, the CVC inventors were "merely guessing at solutions to fundamental problems." (Broad Opp. 2, Paper 2569, 35:2–37:19.) Broad first cites to a copy of e-mail correspondence dated 16 August 2012, with the subject line "Re: unfortunate results," in which Dr. Cheng reported to Dr. Doudna, Jinek,

and Drubin that experiments targeting the eukaryotic gene CTLA in cells failed. (*See* Ex. 4943; *see* Broad Opp. 2, Paper 2569, 35:13–15.) The exhibit shows a response from Dr. Doudna: "Shucks! I guess it would have been too easy of it worked the first time . . . I'll think on this and get back to you - my quick take is maybe try again with improved Cas9 expression?" (Ex. 4943.)

Broad cites further to a copy of e-mail correspondence dated 14[7] September 2012, with the subject line "Re: no good news," in which Dr. Cheng wrote to Dr. Doudna: "Unfortunately no cleavage for any RNA chimeras despite using the codon-optimized Cas9 constructs this time See attached." (Ex. 4988; *see* Broad Opp. 2, Paper 2569, 35:16–36:1.) The exhibit shows that Dr. Doudna responded with generalized suggestions about repeating the experiment with increased amounts of plasmid, concluding:

> Since there are so many variables in these experiments I think we have to try to move forward in a stepwise fashion as much as possible.
>
> As for RNA localization I think we're hoping that the Cas9 protein binds the RNA such that the RNP is transported into the nucleus I wonder if having a too-efficient NLS on Cas9 is actually counterproductive if it means that Cas9 is transported before it has a chance to find and bind the guide RNA. . . Thoughts?

(Ex. 4988.)

[7] The quoted language is from an e-mail dated "Sep 15, 2012 at 4:03 AM," but the response from Dr. Doudna is dated "Friday, September 14, 2012 6:43 PM." (Ex. 4988.) Although it is not clear whether different time zones account for this discrepancy, it does not change our analysis of the inventors' ideas in mid-September.

In a copy of an e-mail dated 11 October 2012, Dr. Doudna responded to news about a failed experiment with codon-optimized and non-codon optimized Cas9 with a CLTA6 RNA chimera, stating:

> Hi Alex and Aaron - thanks for sending your results although it's disappointing not to see Cas9-mediated cleavage in these experiments. Aaron I'm wondering if you think there is anything different about the way you did the experiment back in August when it appeared that there was some cleavage with the CLTA6 guide? Or could that result have been due to a contamination, say with the ZFN sample -? And it will be interesting to see the result from the RNA transfection experiment. Is it worth trying the transfections again with the codon-optimized Cas9? As we have discussed I still think the problem may be with the assembly and localization of the Cas9 RNP - either due to degradation of the guide RNA failure to assemble with Cas9 or failure of the RNP nuclear localization. I will think on this on my way back to SF tonight and we can meet soon to discuss.

(Ex. 5043; *see* Jinek Decl., Ex. 4349, ¶ 230.)

Broad cites yet further to a copy of e-mail correspondence also dated 11 October, in which Dr. Jinek wrote to Dr. Doudna:

> Re mammalian cells - Based on the latest set of results, I suspect we have a problem with our RNA design. Either we are not targeting the right piece of DNA (due to chromatin structure etc), or the problem lies with the RNA design per se. Given that the ZFN has no problems cleaving the same region (+/- 30 bp), the former is probably the lesser concern at this point. On the other hand, there could be a number or reasons for the latter including:
>
> -RNA is not made at sufficient levels
>
> -RNA is expressed strongly but turns over too fast to associate with Cas9 posibly due to degradation by exonucleases
>
> -RNA is stable but does not associate with Cas9 at the right place and at the right time.

> For the next set of experiments I think we should switch to CMV vectors cloning today and explore alternatives to our first-generation RNA design - e.g. modify the hairpin length introduce extensions at the 5' and 3' termini. Or possibly block potential degradation from either end by introducing hairpins etc.

(Ex. 5041; *see* Broad Opp. 2, Paper 2569, 36:2–6.) Dr. Doudna responded:

> As for Cas9 in mammalian cells I completely agree with your analysis and suspect that one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic.
>
> It would be great to test some alternate designs of the guide RNA in vitro - perhaps this is something Alex could do using target plasmids you already have available? Maybe we could also try this in cell extracts? We can discuss further tomorrow - 10 am OK?

(Ex. 5041.) And Dr. Jinek responded:

> I agree that we should explore various alternate RNA designs for targeting in cells. As for the in vitro experiments - I thought that this was what Steve Lin was going to do. Maybe it would be good to bring him on board for this as well at this stage. Then things could be parallelized and Alex could focus more on the mammalian cell work. When Enbo gets back he could then help out with IPs and Northerns because we will need to check whether the RNAs are associating with Cas9 in vivo. Anyway, let's talk tomorrow.

(Ex. 5041.)

Broad cites to a copy of further e-mail correspondence dated 17 October 2012, in which Dr. Doudna wrote to Dr. Jinek, Dr. Cheng, and other scientists at Berkley:

> I think that doing the experiment with cell extracts to test whether the

> transfected Cas9 is active is a critical control. We should perhaps also be preparing some of the other Cas9's for mammalian expression in case they work better for some reason (i.e. folding or faster/better RNP assembly).

(Ex. 5053; *see* Broad Opp. 2, Paper 2569, 36:6–10.)

From these e-mails, Broad concludes that instead of having a definite and permanent idea of an embodiment of Count 1, the CVC inventors were engaged in "guesswork" and "returned to the drawing board." (Broad Opp. 2, Paper 2569, 36:10–11.) According to Broad the CVC inventors had to redesign their components and strategy beyond what would have been routine techniques for one of ordinary skill in the art and did not have a definite and permanent idea of the invention by 1 March 2012. (*See id*. at 37:18–19.)

CVC does not directly address these e-mail statements in its Reply Brief, arguing only that Broad "cites correspondence with its colleagues *as evidence of CVC's reasonable diligence*, which . . . Broad barely challenged." (CVC Reply 2, Paper 2744, 18:15–17.) CVC does not provide any reason why these communications are not also evidence the inventors' thoughts and understandings around CVC's asserted conception date.

CVC asserts that the 28 June 2012 design of a CRISPR-Cas9 system complex for use in zebrafish embryos is evidence of the 1 March 2012 conception. (*See* CVC Motion 2, Paper 1579, 19:10–20:23.) As discussed above, we are not persuaded that the CVC inventors' recognized and appreciated the result of Dr. Raible's zebrafish experiments. Although CVC argues that the inventors' design of sgRNAs to target genes in zebrafish is evidence of their earlier

conception, we are not persuaded that these designs represent a definite and permanent idea of the invention because we are not persuaded the CVC inventors understood that reducing the invention to practice in zebrafish using this design would have required only routine skill by 28 June 2012. (*See* CVC Motion 2, Paper 1579, 20:18–23.) Thus, we agree with Broad that CVC's evidence of conception by 28 June 2012 in the design of sgRNAs for a CRISPR-Cas9 system in zebrafish is not persuasive evidence of a definite and permanent idea of the invention by the CVC inventors due to the, at least perceived, subsequent experimental failures of this design.

In general, CVC argues that Broad "fabricates an illusion of doubt in the inventors' minds by cataloging snippets from various CVC documents . . . . These simply reflect that the inventors understood and considered these routine implementation issues during the process and, at all stages, had a plan to address them." (CVC Reply 2, Paper 2744, 10:12–15.) We disagree, given the inventors' actual statements about problems with design and questions about what to do next. CVC cites to the inventors' declarations as evidence that they had a plan to address the issues they encountered, but their statements prepared for this proceeding do not reflect these contemporaneous communications.

For example, CVC cites to Dr. Doudna's declaration statement that her "familiarity with multiple systems that had been used successfully to target and modify genes in eukaryotes made it clear to [her], before March 1, 2012, that the CRISPR-Cas9 system that [they] had engineered would work in eukaryotes." (Doudna Decl., Ex. 4350, ¶ 40; *see* CVC

Reply 2, Paper 2744, 10:15–16.) But her contemporaneous statements on 11 October 2012 that "one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic" (Ex. 5041) or that there was contamination from controls (Ex. 5043), as well as suggestions to "test some alternate designs of the guide RNA" (Ex. 5041), does not indicate she knew how to solve this problem to make a functional system at the time.

> Similarly, Dr. Jinek testified for this proceeding that his experience with RNAi and knowledge of RNA biology led me understand that issues such as potential degradation and nuclear localization are the types of problems that could be addressed though routine experimentation by, for example, adjusting the amount of RNA, modifying the RNA to improve expression or stability, or optimizing the delivery method.

(Jinek Decl., ex. 4349, ¶ 230; *see* CVC Reply 2, Paper 2744, 10:15–16.) But, his contemporaneous statements on 11 October 2012 of "a problem with our RNA design" and suggestions to "switch to CMV vectors cloning today and explore alternatives to our first-generation RNA design – e.g. modify the hairpin length introduce extensions at the 5' and 3' termini. Or possibly block potential degradation from either end by introducing hairpins etc." do not indicate he had a definite and permanent idea of a function system at the time. (Ex. 5041.)

Dr. Chylinski (Ex. 4348, ¶¶ 22–24) and Dr. Charpentier (Ex. 4351, ¶ 26) also testify to their knowledge of using RNAs in eukaryotic cells and of other gene editing systems, such as TALENs and zinc fingers, but CVC does not direct us to anything other than these generalized statements to show specific instructions for

overcoming the problems encountered through October 2012. (*See* CVC Reply 2, Paper 2744, 10:15–16.) For example, CVC does not direct us to evidence that either Dr. Chylinski or Dr. Charpentier provided Dr. Raible with specific instructions that would have produced positive results in his fish embryo experiments. CVC does not direct us to evidence that any of the inventors had a definite and permanent idea of an sgRNA CRISPR-Cas9 system that would work to edit DNA in a eukaryotic cell, particularly when they encountered what was perceived as design problems in their system at that time. (*Contra* CVC Reply 2, Paper 2744, 10:15–16.)

CVC argues further that its inventors did not encounter "perplexing intricate difficulties arising every step of the way" or "unduly extensive research or experimentation" when applying CVC's sg RNA CRISPR-Cas9 system in eukaryotic cells. (*See* CVC Reply 2, Paper 2744, 17:19–23, quoting *Rey-Bellet v. Englehardt*, 493 F.2d 1380, 1386 (CCPA 1974) and *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994).) Given the inventors' comments from August to October of many "unfortunate results" (Ex. 4943), "problem with our RNA design" (Ex. 5041), and "so many variables in these experiments" (Ex. 4988) it is not clear how CVC comes to this conclusion.

CVC argues that "[i]t is irrelevant whether . . . some experiments performed by CVC's colleagues in other eukaryotic cell types (e.g., nematodes) had not yet succeeded," whether there were doubts about the results of other experiments (citing experiments in medaka fish), or whether collaborations in yeast, mice, or plants had not yet started. (CVC Reply 2, Paper 2744, 18:1–5.) CVC argues that "[t]he question is not whether some colleagues' experiments succeeded or failed,

but rather whether the inventors' conception of Count 1 was complete." (*Id.* at 18:5–7.) We agree with this last statement – the relevant question is whether the inventors had a complete conception of Count 1. But, we disagree that the other facts are irrelevant to that question and that they cannot provide insight into what the inventors were thinking at the asserted date of conception. We disagree that reports of repeated failures and correspondence reviewing the possible problems, searching for solutions, and questioning their designs do not provide an insight into what the inventors thought on 1 March 2012 and after.

We find the facts related to the CVC's inventors' asserted conception on 1 March 2012 and the further evidence of 11 April 2012, 28 May 2012, and 28 June 2012 to be different from the facts of inventorship presented in *Burroughs*. In that case, the confirmatory testing was "brief" and followed the "normal course of clinical trials." *Burroughs*, 40 F.3d at 1230. In contrast, CVC argues its inventors had the materials for an actual reduction to practice in human cells on 28 May 2012, but allegedly completed it, after diligent work, on 31 October 2012 – over five months later – after encountering many problems and trying many times. (*See* CVC Motion 2, Paper 1579, 17:11–19:9, 27:16–33:23.) Contrary to CVC's argument, we find that the CVC inventors engaged in a "prolonged period of extensive research, experiment, and modification" following the alleged conception on 1 March 2012. *Burroughs*, 40 F.3d at 1230. The evidence shows that, at best, the CVC inventors encountered one unrecognized positive result and several failures with zebrafish embryos and several months of failed experiments and doubt with human cells. Given that the scientists performing these experiments were of at least ordinary skill, we are persuaded that the

communications surrounding these experiments reflect "uncertainty that so undermines the specificity of the inventor's idea that it [was] not yet a definite and permanent reflection of the complete invention as it [would] be used in practice." *Id.* at 1229.

We do not base our decision on a lack of reasonable expectation of success by the CVC inventors that the system would be capable of editing DNA in a eukaryotic cell. (*See* CVC Reply 2, Paper 2744, 4:6–19, 19:14–20.) And we agree with CVC that the decision in the prior interference 106,048, which determined that those of ordinary skill in the art would not have been a reasonable expectation of success in a functional eukaryotic CRISPR-Cas9 at the time, is not directly relevant to the inquiry before us now. (*See id.*, 4:23–5:3.) Accordingly, we are not persuaded by either party's evidence of what those in the art expected at the time. (*See* Broad Opp. 2, Paper 2569, 18:23–24:12; *see* CVC Reply 2, Paper 2744, 22:18–24:6.)

Instead, we base our decision on the facts that the CVC inventors encountered multiple experimental failures before they recognized any success, even as late as mid-October 2012. Although the CVC inventors developed a system on 1 March 2012 that they hoped would work in eukaryotic cells, the preponderance of the evidence demonstrates that they did not have a definite and permanent idea of how to achieve that result as of that date or by the later dates CVC asserts support that date because of their perception of these multiple failures.

CVC argues that a system with the same sgRNA sequence, promoter, nuclear localization sequence, cell type and methods asserted to be evidence of conception when designed on 28 May 2012 were ultimately shown to be functional

in Example 2 of its provisional application 61/757,640 ("P3"), filed 28 January 2013, which we determined to be a constructive reduction to practice. (*See* CVC Motion 2, Paper 1579, 17:11–19:9; *see* CVC Reply 2, Paper 2744, 7:6–21.) CVC argues that this evidence is therefore necessarily sufficient to demonstrate conception, citing *Haskell v. Colebourne*, 671 F.2d 1362 (CCPA 1982). (*See* CVC Reply 2, Paper 2744, 7:9–14.)

Haskell, though, presented a much simpler fact pattern, wherein the disclosure in a pre-filing patent application draft was held to be adequate evidence of conception when nearly the same application, filed a few days later, was a sufficient constructive reduction to practice. *See id.* at 1366–67. There was no evidence of experimental failures and uncertainty between the drafting of the application and the filing of the final application days later in *Haskell*. We decline to interpret *Haskell* as a creating a blanket rule that when elements are later shown to be sufficient to establish a constructive reduction to practice in a benefit application, conception must necessarily have occurred, as CVC asserts. (*See* CVC Reply 2, Paper 2744, 7:9–14.) Rather we look to all of the evidence presented, including evidence of experimental failures and uncertainty to determine what the inventors understood about the system at the dates asserted. The inventors' activities in the eight months from their initial description of the materials on 28 May 2012 to the constructive reduction to practice allegedly using these materials on 28 January 2013 indicates to us they had sufficient uncertainty that undermines CVC's arguments of a definite and permanent idea of an sgRNA CRISPR-Cas9 system to be used in a eukaryotic cell.

We acknowledge CVC's argument that in the end only routine materials and techniques, as described by the CVC inventors, were required for a sgRNA CRISPR-Cas9 that can edit DNA in eukaryotic cells, but we look to what the CVC inventors understood as evidence of their conception, not what others might have understood later. (CVC Reply 2, Paper 2744, 7:15–10:11.) The *Hitzeman* court explained:

> *Nunc pro tunc* conception involves the situation where an inventor actually possessed a claimed device at the time of his alleged conception, but failed to recognize the device's inventive features at that time. As articulated in cases such as [*Heard v. Burton*, 333 F.2d 239, 242–44 (1964)], an inventor who failed to appreciate the claimed inventive features of a device at the time of alleged conception cannot use his later recognition of those features to retroactively cure his imperfect conception.

Hitzeman, 243 F.3d at 1358–59; *see also Cooper*, 154 F.3d at 1331 ("The rule that conception and reduction to practice cannot be established *nunc pro tunc* simply requires that in order for an experiment to constitute an actual reduction to practice, there must have been contemporaneous appreciation of the invention at issue by the inventor." (citing *Estee Lauder,* 129 F.3d at 593).)

Count 1 requires not just the mechanics of a CRISPR-Cas9 system (RNAs, vectors, transfection or microinjection techniques), but also that the system causing "expression of the at least one gene product is altered" in a eukaryotic cell or a system that "is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule" in a eukaryotic cell. (*See* Declaration, Paper 1, 12–13.) Therefore, it is not sufficient for CVC to show only that its inventors conceived of the mechanics

of a CRISPR-Cas9 system. To have conceived of an embodiment of Count 1 they must have had a definite and permanent idea of an operative invention, that is of a system they knew would produce the effects on genes in a eukaryotic cell recited in Count 1.

C.

There is no dispute in this proceeding that the CVC inventors conceived of a generic sgRNA CRISPR-Cas9 system by 1 March 2012 and we note that CVC's patent rights to that invention are not at issue here. (*See* CVC Opp. 5, Paper 2567, 37:4–6.) Rather, the issue before us now is CVC inventor's conception of a CRISPR-Cas9 system that works in eukaryotic cells. CVC fails to direct us to persuasive evidence that the testing of CVC's CRISPR-Cas9 system was merely confirmative as in *Burroughs Wellcome.* Instead, we find the subsequent course of experimentation, especially repeated failures, reveal the inventor's uncertainty, which undermines a definite and permanent idea. Thus, CVC fails to persuade us that its inventors had a conception of an embodiment of Count 1 by 1 March 2012.

As explained above, we are also not persuaded that the CVC inventors either reduced to practice an embodiment of Count 1 by 9 August 2012 or that Dr. Raible performed experiments that inured a reduction to practice to them by that date.

Accordingly, we DENY CVC Motion 2 for priority.

III. Broad Motion 5 – For judgment based on priority

Broad argues that its inventors actually reduced to practice an embodiment of Count 1 by 5 October 2012. (*See* Broad Motion 5, Paper 2118, 20:10–21:12, 36:11–39:15.) Broad asserts earlier dates in July and August 2012 as well, but we

need not consider whether Broad's evidence regarding these dates is sufficient because, in light of our decisions in regard to CVC's priority arguments, an actual reduction to practice by the Broad inventors by 5 October 2012 demonstrates priority before any post-9 August 2012 date CVC asserts. That is, if we determine that the Broad inventors had an actual reduction to practice of an embodiment of Count 1 by 5 October 2012, Broad will have persuaded us that it is entitled to priority over CVC.

We look to the activities and ideas of the Broad inventors, Feng Zhang, Ph.D., Le Cong, Ph.D., Fei Ran, Ph.D., Patrick Hsu, Ph.D., Randall Platt, Ph.D., and Neville Sanjana, Ph.D., to determine whether the preponderance of the evidence shows that by 5 October 2012 they constructed an embodiment of Count 1, meeting all its limitations and that they recognized and appreciated it would work for its intended purpose. *See Cooper*, 154 F.3d at 1327; *see Estee Lauder Inc.*, 129 F.3d at 594–95. We look to other evidence presented by Broad as background to the asserted reduction to practice on 5 October 2012.

A.

Broad presents the testimony of Dr. Zhang that by 7 February 2011 he had learned of CRISPR systems and was considering them as a tool for genome editing. (*See* Zhang Decl., Ex. 3424, ¶ 50; *see* Broad Motion 5, Paper 2118, 7:18–23.) A copy of e-mails dated 5–7 February 2011, from Dr. Zhang to Le Cong provides a link to a paper in Science magazine and states:

> Let's keep this confidential. I have a feeling that this could work very well in mammalian systems and can completely replace any kind of FokI system. I ordered the cascade and nuclease genes for synthesis so we should be able to test them shortly after you get back. I did a pretty thorough patent search and

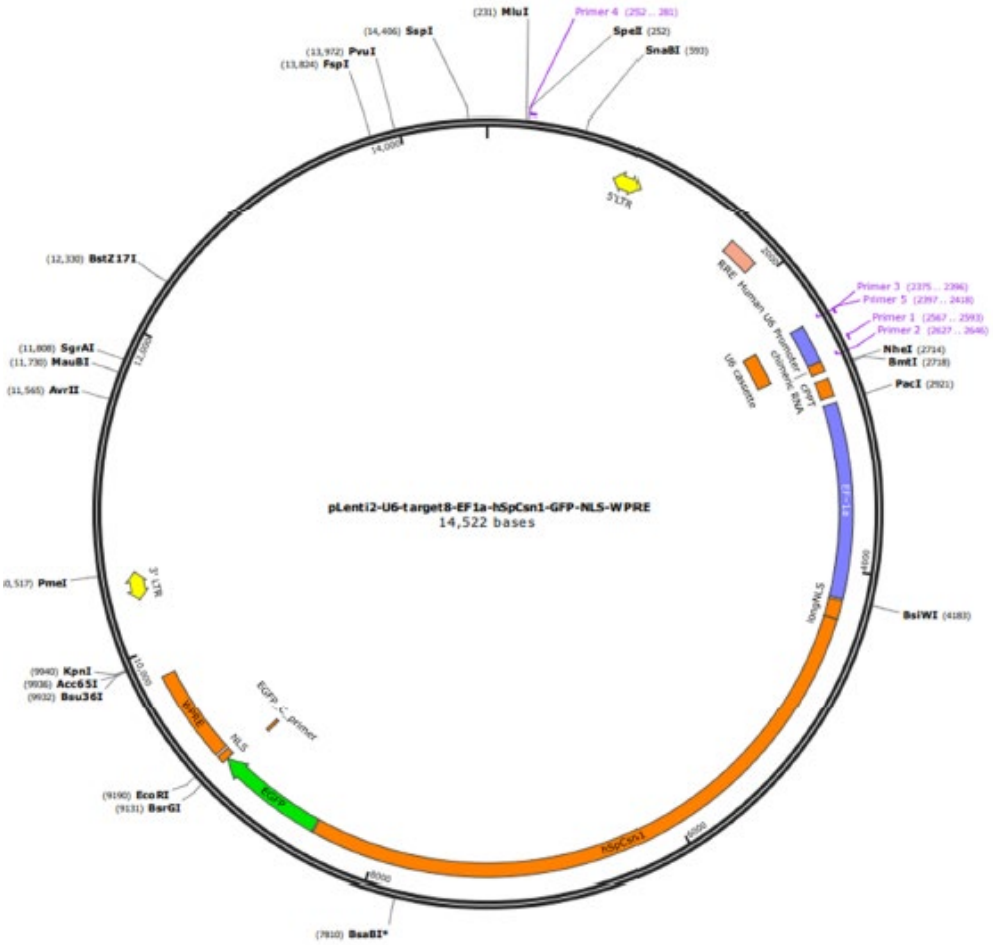
> it doesn't seem like anyone has thought about using this as a nuclease system for catalyzing homologous recombination.

(Ex. 3832.) It is not clear from the e-mail that Dr. Zhang is referring to a CRISPR system because it cannot be discerned to which Science magazine paper Dr. Zhang refers, but the e-mail corroborates his testimony that he was contemplating using a non-mammalian nuclease system in eukaryotic cells by February 2011.

Dr. Zhang testifies that in April 2011, after reading a published article by Deltcheva *et al.* (Ex. 3214), he recognized the three components of a CRISPR system were the Cas9 protein, the crRNA, and the tracrRNA. (*See* Zhang Decl., Ex. 3424 ¶¶ 66–67; *see* Broad Motion 5, Paper 2118, 8:11–18.) Deltcheva includes a figure of a model of "tracrRNA-mediated crRNA maturation involving RNase III and Csn1," with a legend stating: "tracrRNA can bind with almost perfect complementarity to each repeat sequence of the pre-crRNA. The resulting RNA duplex is recognized and site-specifically diced by RNase III in the presence of Csn1, releasing the individual repeat-spacer-repeat units (first processing event)." (Deltcheva, Ex. 3214, 605.) Dr. Zhang explains that the "Csn1" protein is the same as the "Cas9" protein, or "cas5" protein, and that he uses the terms interchangeably. (*See* Zhang Decl., Ex. 3424, ¶¶ 60, 66.)

Dr. Zhang testifies that he designed vectors to express chimeric RNA constructs for use in a CRISPR-Cas9 system, which included various configurations of hSpCas9 and chimeric RNA for testing in eukaryotic cells. (*See* Zhang Decl., Ex. 3424, ¶¶ 133–140.) Dr. Zhang presents a plasmid map of the hSpCas9 system with chimeric RNA, which he asserts was used successfully. (*See* Zhang Decl., Ex. 3424, ¶ 141, citing Ex. 3770, 128.) Exhibit 3770 is a copy of an

e-mail, dated 17 July 2012, from Dr. Zhang to Grace Gao and Dr. Cong, with attachments, including the plasmid diagram named "pLenti2-U6-target1-EF1a-hSpCsn1-GFP-NLS-WPRE.sbd" on page 128 and reproduced below.



Andrew Ellington, Ph.D.,[8] Broad's witness, explains that the map of plasmid

[8] Dr. Ellington testifies that he is a Professor in the Department of Molecular Biosciences at the University of Texas and in the Howard Hughes Medical Institute. (Ellington Decl., Ex. 3430, ¶ 11.) Dr. Ellington testifies that he has

pLenti2-U6- target8-EF1a-hSpCsn1-GFP-NLS-WPRE includes a sequence called "Chimeric RNA" in the upper, right-hand side, which has a 20 nucleotide guide sequence capable of hybridizing to a target sequence in the genome, a tracr mate sequence, a GAAA linker, and tracr RNA sequence, all of which would be expected to be expressed from the U6 promoter. (*See* Declaration of Technical Expert Andrew Ellington in Support of Broad ("Ellington Decl."), Ex. 3430, ¶¶ 33, 34; *see* Broad Motion 5, Paper 2118, 24:13–17.)

Broad cites to the testimony of both Dr. Zhang and Dr. Cong about experiments starting on 17 July 2012 to target the mTH gene, a gene Dr. Zhang testifies he was studying in regard to neuronal and brain function, using vectors to express hSpCas9, with nuclear localization signals, and chimeric RNA in mouse cells. (*See* Broad Motion 5, Paper 2118, 13:14–18, citing, *e.g.*, Zhang Decl., Ex. 3424, ¶ 143, and Cong Decl., Ex. 3425, ¶ 25; *see* Zhang Decl., Ex. 3424, ¶ 124.) According to Broad and the inventors' testimony Dr. Cong transfected separate cultures of mouse cells, incubated them, and lysed them to obtain genomic DNA for a Surveyor assay[9] to show genetic modification. (*See* Cong Decl., Ex. 3425,

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extensive experience in the fields of biomolecular engineering and synthetic biology, particularly with engineering nucleic acid and protein systems. (*See id.* at ¶ 10.) Dr. Ellington's publications, patents, and grants reflect his testimony. (*See* Ex. 3431.) CVC does not raise any objection to Dr. Ellington's qualifications. We find him to be qualified to present opinion testimony on the subject of interference.

[9] Dr. Ellington explains that the Surveyor assay was used to detect and quantify cleavage of the mTH genomic target used in the CRISPR-Cas9 experiments by the Broad inventors. (*See* Ellington Decl., Ex. 3430, ¶ 36.) Briefly, the Surveyor assay detects small insertions or deletions (called "indels") using an enzyme to cleave DNA at such mismatches and then imaging the resulting fragments,

¶ 25.) Drs. Zhang and Cong reportedly obtained results from these experiments on 20 July 2012 and from further experiments on 21 July 2012, which Dr. Cong allegedly characterized as "very promising . . . but because the second gel is 1%, it's hard to tell." (Ex. 3773; *see* Broad Motion 5, Paper 2118, 13:14–14:5, citing Zhang Decl., Ex. 3424, ¶¶ 140–149; *see* Cong Decl., Ex. 3425, ¶¶ 26–33.)

Broad presents another e-mail dated 22 July 2012, in which Dr. Cong wrote to Dr. Zhang: "For CRISPR, the expected size for the particular target seq of No.7 of mTH is 250bp + 380bp, and our faint band at least one of them is just below the 400bp marker, the other one is also seems to be around 250bp, so it's very promising." (Ex. 3775; *see* Broad Motion 5, Paper 2118, 13:19–14:5; *see* Zhang Decl., Ex. 3424, ¶ 151; s*ee* Cong Decl., ¶ 32.) Broad argues further that on 23 July 2012, Dr. Zhang wrote that the "the most critical thing for us to do now is to verify that we are indeed getting cutting with the U6::mTH-l/EFla::2xNLS-Csnl-GFP construct. Once that is confirmed we will be able to plan the rest of the experiments much more easily." (*See* Ex. 3777; *see* Broad Motion 5, Paper 2118, 13:19–14:1; *see* Zhang Decl., Ex. 3424, ¶ 153.)

Broad argues that in addition to visualizing results on gels, the inventors also analyzed the activity of the chimeric RNA CRIPR-hSpCas9 system on the mTH gene with sequencing analysis. (*See* Broad Motion 5, Paper 2118, 15:1–16:13, citing Zhang Decl., Ex. 3424, ¶¶ 163–69; Cong Decl., Ex. 3425, ¶¶ 44–57.) Broad relies on Dr. Cong's testimony that by 28 July 2012 samples from colonies

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separated by size, on a gel. (*See id.*)

containing genomic DNA fragments of the 27 July 2012 experiment were submitted to Genwiz for sequencing. (*See* Cong Decl., Ex. 3425, ¶¶ 44 and 46, citing Exs. 3781 and 3782.) Exhibits 3781 and 3782 are copies of e-mails dated 30 July 2012 from a Genwiz e-mail address to Dr. Cong indicating that samples had been received. (*See* Exs. 3781 and 3782.)

Dr. Zhang testifies that on 31 July 2012 he accessed and analyzed the sequencing results from the 25 July 2012 mTH target experiment and recognized that two colonies showed small insertions or deletions, or "indels," at the expected modification site. (*See* Zhang Decl., Ex. 3424, ¶ 165, citing Ex. 3784.) He also testifies that he understood that these indels would result in a frameshift in the DNA target sequence that would result in a change in expression when the mTH target was expressed, such as by introducing a premature stop-codon. (*See id.*) Exhibit 3784, which is a copy of an e-mail, dated 31 July 2012, sent by Dr. Zhang to Dr. Cong, states in part: "Hi Le, I took a look at the data. It is very promising. There are two clones that had modifications. See attached. Feng." (Ex. 3784.) Exhibit 3830 is a copy of an e-mail, dated 31 July 2012, in which Dr. Cong responds to Dr. Zhang, stating: "There is a better example in plate 3 sequencing results! Will send you summary later. I am looking at the results with David." (Ex. 3830.)

CVC argues that this evidence, as well as evidence of earlier asserted reductions to practice, is insufficient to establish it as an actual reduction to practice. (*See* CVC Opp. 5, Paper 2567, 46:7–51:20.) In general, CVC argues that Broad fails to provide contemporaneous evidence, such as laboratory notebooks or electronic notes of the experimental design, protocol, conditions, or other details of

the experiment, fails to provide contemporaneous evidence that Dr. Zhang appreciated that the embodiment worked for its intended purpose, and fails to provide sufficient corroboration of the inventors' testimony. (*See id.*) CVC argues further that the results of the experiments reported were not properly controlled, were contaminated, and that the electronic notebook records have no associated metadata and are unreliable. (*See id.*)

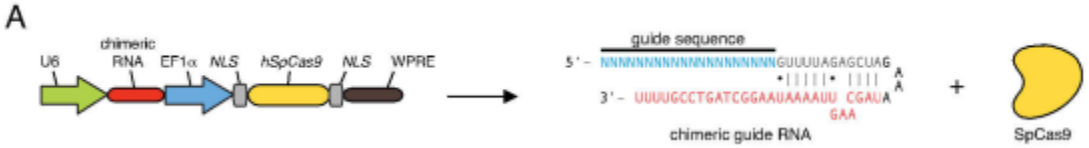
We note that much of the inventors' testimony we cite above is supported by copies of e-mails presented by Broad, while other testimony Broad presents appears to lack corroboration. Nevertheless, as discussed above, we need not review the evidence Broad presents regarding these experiments as a reduction to practice in July 2012 because we need only consider the assertions of an actual reduction to practice on 5 October 2012 to evaluate Broad's priority case. Accordingly, we do not make a determination of the sufficiency of this evidence alone to support Broad's priority argument, but look to it for background to the asserted 5 October 2012 reduction to practice.

Broad argues that Dr. Zhang reported the results for the July 2012 experiments in the 5 October 2012 manuscript submitted to Science magazine. (*See* Broad Motion 5, Paper 2118, 16:21–23, 36:12–39:15, citing Ex. 3564.) Exhibit 3564 is a copy of a manuscript entitled "CRISPR-Assisted Mammalian Genome Engineering," and naming Le Cong, David Cox, F. Ann Ran, Shuailiang Lin, Robert Barretto, Wenyan Jiang, Luciano Marraffini, and Feng Zhang as authors. (*See* Exhibit 3564.) Exhibit 3564 has the header "Submitted Manuscript: Confidential" and the date "October 5, 2012." (Ex. 3564.)

According to Broad, the manuscript is evidence that the experiments

presented were done at least prior to 5 October 2012. (*See* Broad Motion 5, Paper 2118, 37:1–7.) Broad argues further that Dr. Zhang's decision to prepare a manuscript for submission to the journal Science, which would then undergo extensive peer review, indicates he recognized and appreciated that his results demonstrated successful use of a chimeric RNA CRISPR-Cas9 system to cleave DNA in a eukaryotic cell. (*See id*.)

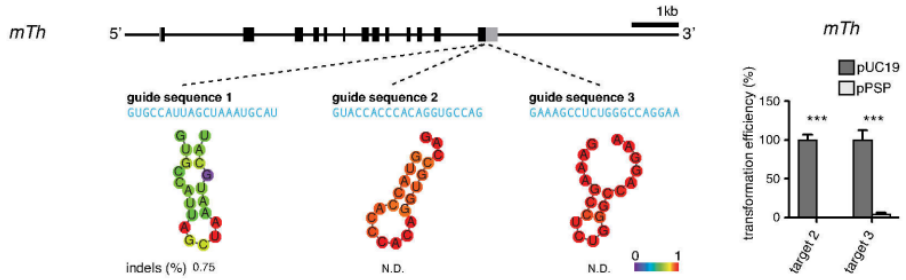
Broad cites to Dr. Zhang's testimony that one of the systems he described in the manuscript (Ex. 3564) is an "hSpCas9" system with chimeric RNA. (*See* Zhang Decl., Ex. 3424, ¶ 180.) Dr. Zhang points to Figure 2A of the manuscript, which is reproduced below.



(Ex. 3564, 15; *see* Zhang Decl., Ex. 3424, ¶ 180.) Dr. Zhang testifies that he designed this system earlier, citing to the e-mail dated 17 July 2012, to Dr. Cong and other Broad personnel, including plasmid maps and sequences as attachments. (*See* Zhang Decl., Ex. 3424, ¶ 182, citing Ex. 3770.) Dr. Zhang testifies further that his chimeric RNA design differed from that in Jinek 2012 (Ex. 3202), authored by CVC inventors, by having four extra U nucleotides on the 3' end of the tracr segment because he used a U6 promoter. (*See* Zhang Decl., Ex. 3424, ¶ 180.)

Broad argues, citing to Dr. Zhang's testimony, that the 5 October 2012 manuscript memorializes the July 2012 mouse cell experiments. (*See* Zhang Decl., Ex. 3424, ¶¶ 173–175; *see* Broad Motion 5, Paper 2118, 17:7–18:3, 37:11–16.)

Broad points to a portion of Figure 2B of the manuscript, which is reproduced below.



(Ex. 3564, 15.) The legend for Figure 2B indicates that it is a

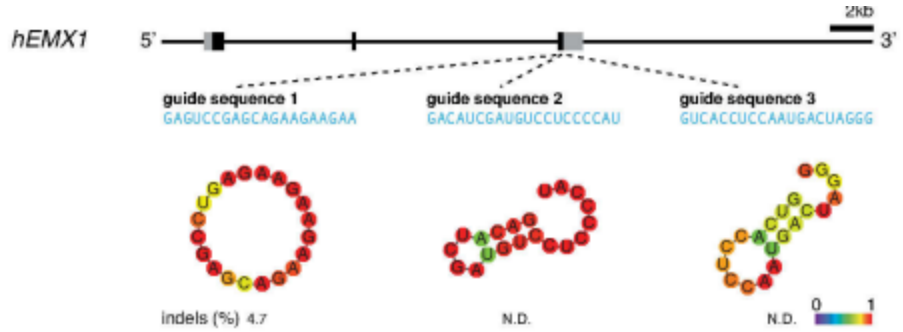
> [s]chematic showing guide sequences targeting the human EMXJ, PVALB, and mouse Th loci as well as their predicted secondary structures. The modification efficiency at each target site is indicated below the RNA secondary structure drawing (EMXJ, n = 216 amplicon sequencing reads; PVALB, n = 224 reads; Th, n = 265 reads). Each base is colored according to its probability of assuming the predicted secondary structure, as indicated by the rainbow scale.

(Ex. 3564, 12.) Broad points to the notation of an indels (%) of 0.75 for one of the constructs targeting the mTH gene. (*See* Broad Motion 5, Paper 2118, 37:11–13.)

Broad argues that the indel % of 0.75 reported in the 5 October 2012 manuscript is consistent with the two positive results received from sequencing data for the repeat experiment in July 2012 because two positive results out of 265 sequencing reads provides a percentage of 0.75. (*See* Broad Motion 5, Paper 2118, 18:1–3; *see* Cong Decl., Ex. 3425, ¶ 57: "The indel% of 0.75 listed in the manuscript for the first mTH target sequence is consistent with the two positive results we received in the Genewiz data, divided by the 265 reads (i.e., 2/265 =

0.0075) that were reported. This is consistent with my recollection that we included our successful use of Dr. Zhang's hSpCas9 system with chimeric RNA to target the mTH target sequence 1 in our manuscript.").)

Broad argues further that Dr. Zhang described other experiments in human cells with his hSpCas9 system and chimeric RNA in the 5 October 2012 manuscript, citing to other portions of Figure 2B relating to the hEMX1 target in a human cell. (*See* Broad Motion 5, Paper 2118, 38:7–39:2.) This portion of Figure 2B is reproduced below.



(Ex. 3564, 15.) The text of the 5 October 2013 manuscript supporting this portion of Figure 2B recites:

> We then explored the generalizability of CRISPR-mediated cleavage in eukaryotic cells by targeting additional genomic loci in both human and mouse cells by designing chimeric RNA targeting multiple sites in the human EMXJ, PVALB, as well as the mouse *Th* loci. We achieved 6.3% and 0.75% modification rate for the human *PVALB* and mouse *Th* loci respectively, demonstrating the broad applicability of the CRISPR system in modifying different loci across multiple organisms (Figure 2B, Table 1). However, we were only able to detect cleavage with one out of three spacers for each locus.

(Ex. 3564, 5.) The manuscript indicates that indels (%) of 0.75 for one construct targeting the mTH gene and an indels (%) of 4.7 for one construct targeting the hEMX1 gene demonstrate that the CRISPR system works for modifying different loci across multiple organisms.

Broad argues that acceptance of and reviewers' comments about the 5 October 2012 manuscript are evidence that Dr. Zhang's experiments were successful and achieved the biological function required in Count 1: "the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered" or "cleaving or editing the target DNA molecule." (Declaration, Paper 1, 13; *see* Broad Motion 5, Paper 2118, 39:3–13.) Specifically, Broad cites to comments including:

> The authors report for the first time the milestone implementation of a bacterial CRISPR system in human cells, and show it can be used for RNA-guided DNA cleavage and genome engineering. Specifically, Le Cong et al. show that two distinct type II CRISPR-Cas systems (based on Cas9 from primarily S.pyogenes and to a lesser extent S. thermophilus) can cleave several targets in human (EMX1, PVALB) and mouse (Th) cell lines. Results show compellingly and thoroughly that the system they developed based on Cas9, crRNA and tracr RNA, or on Cas9 and chimeric RNA is functional and efficient in vivo, for cleavage and inducing mutations at the target site.

(Ex. 3836, 3.) Broad cites further to another comment:

> Jinek et al. (2012) and Gasiunas et al. (2012) showed recently that the Cas9-crRNA complex of the type II CRISPR-Cas system acts as an RNA-guided DNA nuclease where the specificity is programmed by crRNA and Cas9 executes cleavage. The flexibility in RNA programming coupled with a Cas9 ability to generate doublestranded DNA breaks (DSB) set a stage for genome editing using Cas9-crRNA

> complexes. Le Cong et al. now provide experimental evidence that Cas9-crRNA complex can be employed for the mammalian genome engineering. This is a breakthrough paper which may be a game changer in the genome editing field. Le Cong et al reconstituted Cas9-crRNA interference system in mammalian cell lines and show that Cas9 nuclease introduces DSB at the sites targeted by crRNA. They obtained a functional Cas9-crRNA complex in mammalian cells through the heterologous expression of individual components and showed that they are transported to the nucleus and introduce a DSB in DNA. Authors show that Cas9-crRNA cleavage results in the formation of indels which support repair through the error-prone NHEJ pathway. To make precise edits in the genome authors used a nicking Cas9 mutant to stimulate homologous recombination which is an error-free gene repair pathway. Work is technically sound, experiments make a logical flow and in general paper reads well.

(Ex. 3836, 3–4.) The reviewers' comments indicate to us that not only did the Broad inventors recognize and appreciate the positive results of an engineered Type II CRISPR-Cas system targeting DNA in eukaryotic cells to specifically cleave DNA molecules and alter gene expression, others in the field confirmed the results.

Broad cites to Dr. Ellington's testimony to show that the experiments of July 2012 are reported in the 5 October 2012 manuscript show an actual reduction to practice of each and every element of the half of Count 1 that recites claim 18 of Broad patent 8,697,359. (*See* Broad Motion 5, Paper 2118, 24:17–20, citing Ellington Decl., Ex. 3430, Charts A and B.) Dr. Ellington testifies that the description of Figure 2(A) in the manuscript meets the element of an engineered, programmable, non-naturally occurring Type II CRISPR-Cas9 system. (*See* Ellington Decl., Ex. 3420, 62, 67, 85, Chart A.) Dr. Ellington explains that

Figure 2(A) provides a schematic diagram of a vector that can be programmed to target multiple genomic loci by driving the expression of a synthetic crRNA-tracrRNA chimera (chimeric RNA), having a 20-bp guide sequence corresponding to the protospacer in the genomic target site, as well as a SpCas9, which do not naturally occur together. (*See id.*)

Dr. Ellington also cites to Figure 2B of the 5 October 2012 manuscript, specifically the results provided for targeting of the mTH gene as evidence that the inventors' work meets the element of a CRISPR-Cas9 system with a chimeric RNA and Cas9 protein that achieve "targeting and hybridizing to a target sequence of a DNA molecule." (*See* Ellington Decl., Ex. 3430, 69, Chart A.) Dr. Ellington quotes the language of the manuscript: "Schematic showing guide sequences targeting the human EMX1, PV ALB, and mouse Th loci as well as their predicted secondary structures." (*Id.*)

Dr. Ellington cites further to the use of HEK 293FT or N2A cells in the manuscript as evidence of the inventors' reduction to practice of a CRISPR-Cas9 system as recited in Count 1 in a eukaryotic cell. (*See id.* at 74, citing Ex. 3564, October 5, 2012 manuscript, Ex. 3564, 20.) In support of the element of the Cas9 protein cleaving the DNA molecule of a gene expressed in a eukaryotic cell and altering expression of at least one gene product, Dr. Ellington again cites to the statement in the 5 October 2012 manuscript that:

> We then explored the generalizability of CRISPR-mediated cleavage in eukaryotic cells by targeting additional genomic loci in both human and mouse cells by designing chimeric RNA targeting multiple sites in the human . . . as well as the mouse Th loci. We achieved 6.3% and 0.75% modification rate for the human PVALB and mouse Th loci

respectively.

(Ellington Decl., Ex. 3430, 80, 83, Chart A, quoting 5 October 2012 manuscript, Ex. 3564, 5.) Dr. Ellington cites further to the statement in the manuscript that "[t]he modification efficiency of each target site is indicated below the RNA secondary structure drawing" in support of the element of the Cas9 protein cleaving DNA molecules. (Ellington Decl., Ex. 3430, 80, 83, Chart A, quoting 5 October 2012 manuscript, Ex. 3564, 12.) And Dr. Ellington cites to Table 1 of the 5 October 2012 manuscript, which reports the results of gene targeting with two different species of Cas9 protein, in three different genes, representing mouse and human, with indel % ranging from 0.75 to 6.4. (*See* Ellington Decl., Ex. 3430, 84, Chart A, quoting 5 October 2012 manuscript, 18, Table 1.)

Dr. Ellington provides similar testimony regarding the half of Count 1 that recites claim 156 of CVC application 15/981,807. (*See* Ellington Decl., Ex. 3430, 93, 94, 99, 101, 109, 111, Chart B.)

CVC does not put forth an argument, or direct us to evidence to support an argument, that the 5 October 2012 manuscript prepared by the CVC inventors fails to memorialize an actual reduction to practice of each and every element of Count 1 as of that date.[10] Nor does CVC put forth an argument, or direct us to

[10] CVC denies Broad's statements of material fact ("SMFs") regarding the 5 October 2012 manuscript, but fails to explain why or cite evidence to the contrary in its opposition. (*See* CVC Opp. 5, Paper 2567, Appendix 2-11, response to Broad SMF 53 ("Dr. Zhang also reported his successful results with his hSpCas9 system in the October 5, 2012 Manuscript submitted to Science. . . .

evidence in support of an argument that the 5 October 2012 manuscript does not represent experiments performed by the Broad inventors. In the absence of such arguments, we are not persuaded that any deficiencies CVC asserts regarding Broad's evidence of reductions to practice before 5 October 2012, for example in July, negate the evidence of the submitted manuscript as representing an actual reduction to practice by the Broad inventors by 5 October 2012. (*See* CVC Opp. 5, Paper 2569, 44:6–51:20.) As Broad argues, the manuscript itself is corroboration that the Broad inventors performed the experiments reported therein and appreciated the results and the reviewers' comments indicate that the experiments were conducted at least to standards acceptable to those of ordinary skill in the art. Because Broad presents persuasive evidence that the 5 October 2012 manuscript memorializes each and every element of a system and eukaryotic cell as recited in Count 1, which CVC does not dispute, we are persuaded that it is sufficient evidence of an actual reduction to practice by the Broad inventors.

B.

CVC opposes Broad's motion for priority, in general, on the asserted basis that the CVC inventors derived the system of Count 1 entirely from CVC.[11] (*See* CVC Opp. 5, Paper 2567, 1:2–3.)

To prove derivation a party must "establish prior conception of the claimed

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Response: Denied."); *see also id.* at Appendix 2-11 – 2-14, responses to Broad SMFs 54, 55, 65–69.)

[11] Broad argues that CVC's arguments are untimely and improper because they should have been presented as a substantive motion for judgment under 35 U.S.C. § 102(f). (*See* Broad Reply 5, Paper 2745, 1:10–13, 8:20–10:9.) Whether or not

subject matter and communication of the conception to the adverse claimant." *Price v. Symsek,* 988 F.2d 1187, 1190 (Fed. Cir. 1993) (explaining that although the ultimate question of whether a patentee derived an invention from another is one of fact, the determination of whether there was a prior conception is a question of law, which is based upon subsidiary factual findings). "Communication of a complete conception must be sufficient to enable one of ordinary skill in the art to construct and successfully operate the invention." *See Hedgewick v. Akers*, 497 F.2d 905, 908 (CCPA 1974). Thus, to prove derivation, CVC must first establish that its inventors conceived of the claimed subject matter before the Broad inventors.

In its Opposition, CVC argues that its inventors conceived of the invention of Count 1 before Broad's asserted conception date of 26 June 2012 and that Drs.

CVC's derivation argument was properly presented as an opposition, CVC bears the burden of proving its elements. We note that CVC mischaracterizes the Board's Memorandum of 25 March 2021, by stating "the PTAB instructed CVC not to file a separate motion." (CVC Reply 2, Paper 2744, 28:23–24.) Instead, when asked whether CVC should raise its derivation allegations in a separate motion, the Board "offer[ed] no opinion" and directed CVC to the Interference Rules and Standing Order for guidance. (*See* Memorandum, Paper 2474.) The Board also noted that because the schedule was well underway, a request to file a motion would likely have been denied. (*See id.*) The Memorandum did not indicate that derivation is properly raised in an opposition if, as Broad argues, the facts on which the allegation is based were known when the parties had an opportunity to seek authorization for proposed motions at the outset of the interference. (*See* Broad Reply 5, Paper 2745, 9:23–10:9; *see* Junior Party List of Intended Motions, Paper 19 (not requesting or mentioning a motion for derivation).)

Doudna and Charpentier received the Nobel Prize for their work. (*See* CVC Opp. 5, Paper 2567, 1:7–14, 31:9–33:11.) In support of this earlier date of conception, CVC refers to the evidence it presents in CVC Motion 2, arguing for priority, stating that "[b]y June 26 [Broad's asserted date of conception], the CVC inventors had not only filed CVC's first provisional application, but were well on their way towards an actual reduction to practice in eukaryotes . . . ." (*See* CVC Opp. 5, Paper 2567, 31:22–23.) CVC does not direct us to evidence that overcomes our determination, discussed above, that the CVC inventors encountered multiple experimental failures before they recognized any success in eukaryotic cells, even as late as mid-October 2012. CVC does not address its inventors' experimental failures in its opposition.

CVC argues that "the completeness of CVC's conception before June 26 is further confirmed by the fact that Zhang claims to have quickly and easily applied CVC's sgRNA CRISPR-Cas9 system in eukaryotic cells, once he learned of CVC's invention from Marraffini." (CVC Opp. 5, Paper 2567, 33:4–7; *see also* 6:1–22.) As explained above, though, neither conception nor reduction to practice can be established *nunc pro tunc*. *See Hitzeman*, 243 F.3d at 1358–59; *see also Cooper*, 154 F.3d at 1331. Regardless of any success by the Broad inventors, the preponderance of the evidence presented by the parties demonstrates that the CVC inventors' experimental failures reveal uncertainty undermining a definite and permanent idea of an sgRNA CRISPR-Cas9 system that edits or cleaves DNA in a eukaryotic cell. CVC attempts to shift our focus to the activities of other, competing inventors, rather than on the activities of its own inventors. We are not

persuaded that these other activities are evidence of the CVC inventors' ideas or of their conception.

Similarly, we are not persuaded by CVC's argument that because the Broad inventors were able to reduce to practice an embodiment of Count 1 "quickly and easily," the CVC inventors had a complete conception. (*See* CVC Opp. 5, Paper 2567, 6:1–6:12.) The Broad inventors' activities and ideas do not inure to CVC, at least because CVC never submitted anything to the Broad inventors for testing. *See Genentech, Inc. v. Chiro Corp.*, 220 F.3d 1345, 1353 (Fed. Cir. 2000) (inurement requires at least (1) conception by the inventor, (2) expectation of success by the inventor, and (3) "the inventor must have submitted the embodiment for testing for the intended purpose of the invention."). None of the facts presented by either party indicates that the CVC and Broad inventors worked together on a eukaryotic CRISPR-Cas9 system and CVC raises derivation only as an opposition to Broad's priority motion. *See Applegate v. Scherer*, 332 F.2d 571, 573 (CCPA 1964) ("An originality or derivation case . . . is quite unlike a case involving independent invention, between whom true priority must be decided.").

CVC cites to *Applegate* to argue that a party who identifies a compound, not the party who tested it and showed that it worked, is the inventor. (*See* CVC Opp. 2, Paper 2567, 4:5–16; 34:20–35:23.) CVC argues that under *Applegate*, there is no rule requiring proof that a biological invention works before there can be conception. (*See id.*) We agree. We disagree, though, that *Applegate* is otherwise informative in light of the facts before us. There is no issue in *Applegate* of whether Scherer fully conceived of the subject matter of the count because the evidence shows he named the compound of interest, he asked Scherer to test it for

its intended purpose, and Scherer obtained the results in the normal course of testing. *See id.* at 572–73. Unlike the facts before us, *Applegate* does not address repeated experimental failures and their effect on a determination of conception or derivation.

Furthermore, we also decline to accept CVC's argument that the Broad inventors contributed nothing to the invention of Count 1. (*See* CVC Opp. 5, Paper 2567, 6:23 ("The record shows that Zhang contributed *none* of the elements of Count 1."). Broad raises technical reasons why the Broad inventors had success when other eukaryotic CRISPR-Cas9 systems failed. (*See, e.g.,* Broad Opp. 2, Paper 2569, 36:18–37:14 (arguing that Dr. Zhang chose to use a U6 promoter that would produce a tracrRNA in eukaryotic cells that was four nucleotides longer than the tracrRNA the CVC inventors in their *in vitro* experiments); *see* Broad Motion 5, Paper 2118, 12:4–9.) Although CVC fails to dispute the difference between these technical details of the parties' systems, we need not make a determination on the merits of Broad's arguments because CVC's failures before Broad's success by 5 October 2012 indicate there must have been differences.

According to CVC, any technical aspects of Broad's system were merely routine techniques used by those of ordinary skill and were not inventive. (*See* CVC Opp. 5, Paper 2567, 20:20–22:10.) CVC argues further that any choices made by Dr. Zhang, such as choice of promoter, codon optimization, addition of nuclear localization signals, are not recited in Count 1 and are not required for reduction to practice. (*See* CVC Opp. 5, Paper 2567, 22:11–30:15.) CVC's argument discredits the limitation in Count 1 of a *functional* fused or covalently linked RNA CRISPR-Cas9 system in eukaryotic cells that alters the expression of

at least one gene product, cleaves or edits a target DNA molecule, or modulates transcription of a one gene encoded by the target DNA molecule. (*See* Declaration, Paper 1, 13.) Although Count 1 does not recite the various technical features that are needed to obtain this function, conception and reduction to practice require any necessary technical features. Therefore, we disagree with CVC that the determination of the necessary technical features of a system are irrelevant to conception or reduction to practice, even if each feature, in isolation, was known to those of ordinary skill. We disagree that the Broad inventors' ideas of the necessary features of a functional eukaryotic system as recited in Count 1 are irrelevant to a determination of priority.

Even if CVC invented a generalized sgRNA CRISPR-Cas9 system, for which they hold numerous patents undisputed in this proceeding (*see* CVC Opp. 5, Paper 2657, 37:4–6; *see* Broad Reply 5, Paper 2745, 3:18–19), and they had an intention and hope that a CRISPR-Cas9 system would work in eukaryotic cells (*see* CVC Opp. 5, Paper 2657, 10:1–18:17), we are not persuaded that the determination of technical features necessary to achieve success is irrelevant. Instead, determination of those features indicated that the Broad inventors had a definite and permanent idea of a system in eukaryotic cells, which lead them to an actual reduction to practice earlier than the CVC inventors.

CVC argues that even if the Broad inventors contributed the "eukaryotic aspect of Count 1 . . . Zhang cannot be an inventor of Count 1 because the eukaryotic element is just one of several features, including the sgRNA feature." (CVC Opp. 5, Paper 2567, 5:1–7.) According to CVC, to win an interference, a party must have invented the entire invention as embodied in the combination of

elements recited in the count. (*See id.* at 5:7–11.) CVC cites to *Alexander v. Williams*, 342 F.2d 466, 468 (CCPA 1965), where Bendix inventors were found to have not conceived of the entire count when it had been disclosed to them by General Electric inventors. (*See* CVC Opp. 5, Paper 2567, 5:1–11; 36:9–23.)

We do not see how this case or argument benefits CVC because even though the Broad inventors learned of a guide RNA comprising a guide sequence fused to a tracr sequence from a public presentation given by CVC inventors in June 2012 (*see* CVC Opp. 5, Paper 2567, 1:7–13; *see* Marraffini Depo., Ex. 5262, 38:4–10 (confirming that the linker sequence Dr. Marraffini disclosed to Dr. Zhang was presented publicly by the CVC inventors)), the CVC inventors had only used this system *in vitro* at the time.

Given the subsequent failures and lack of a clear plan by the CVC inventors to achieve a functional CRISPR-Cas9 system in eukaryotic cells, it is not clear to us why CVC now emphasizes the need to have conceived of the entire count to prevail on priority. (*See* Broad Reply 5, Paper 2745, 24:1–17.) Unlike the facts of *Alexander*, and as explained above, we determine that to show conception of Count 1 a party must show conception of the count element of a CRISPR-Cas9 system that achieves cleavage or editing of a gene to alter expression from a gene in a eukaryotic cell. *Compare Alexander*, 342 F.2d at 470–71 (finding that the count element of mounting cams on a common shaft was not "the essence of the invention" and was the losing party's only contribution). Because we find that the CVC inventors did not conceive of every element of Count 1 on 1 March 2012, we are not persuaded that the CVC inventors could have divulged the complete subject matter of Count 1 to the Broad inventors. *Contra Alexander*, 342 F.2d at 468

("One undisputed fact of great significance, we think, is that the General Electric inventors were the first to conceive the invention defined by the count."), *see also id.* at 471 ("In this case Bendix had not even rendered partial aid since the General Electric inventors had first conceived every element of the count.").

CVC's arguments and evidence presented in its opposition to Broad Motion 5 do not persuade us that its inventors had a complete conception of the invention of Count 1 prior to 5 October 2012 – the date that we are persuaded the Broad inventors achieved a reduction to practice of the invention of Count 1. Without a prior conception, CVC's argument that Broad derived the system recited in Count 1 entirely from CVC fails.

C.

Broad has persuaded us that its inventors achieved an actual reduction to practice of an embodiment of Count 1 by 5 October 2012. CVC has failed to persuade us that its inventors achieved either an actual reduction practice or a complete conception of an embodiment of Count 1 before that date. CVC also fails to persuade us that Broad derived the invention of Count 1 from the CVC inventors.

Accordingly, we GRANT Broad Motion 5.

Judgement against CVC will be entered separately.

IV. CVC Motion for Incorrect Inventorship – CVC Motion 3

CVC argues that judgement should be entered against Broad because all of Broad's involved patents and applications are invalid under 35 U.S.C. § 102(f) for failure to name all of the correct inventors. (*See* CVC Motion 3, Paper 1558.) A

determination of inventorship requires two steps performed as a claim-by-claim analysis: first a construction of each asserted claim to determine the subject matter encompassed and then a comparison of the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to determine whether the correct inventors were named. *See Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1302 (Fed. Cir. 2002). We look to the sufficiency of CVC's evidence in support of its argument that the contributions of the named inventors on Broad's patents and applications does not match the scope and content of the subject matter claimed.

CVC's arguments are ultimately based on a sworn declaration prepared by Thomas J. Kowalski (the "Kowalski Decl.," Ex. 4295), Broad's former prosecuting patent attorney, in an opposition proceeding in the European Patent Office regarding inventorship of PCT application claims. (*See* CVC Motion 3, Paper 1558, 2:17–3:3.) The declaration provides a list of named individuals and their alleged contributions. (*See* Kowalski Decl., Ex. 4295, ¶ 16.) The declaration refers in general to patent applications filed by Broad, but does not provide an analysis of individual claims and does not list or discuss Broad's currently involved patents or applications. (*See* Kowalski Decl., Ex. 4295, ¶ 14.)

CVC provides Chart 1, which lists PCT application claim language allegedly corresponding to reported inventive contributions, as well as CVC's interpretation of the "corresponding representative claim language in Broad's involved U.S. patents or application." (*See* CVC Motion 3, Paper 1558, 4:9–5:2.) Neither Chart 1, not specific claim phrases, appear in the Kowalski Declaration.

CVC argues that the inventors named on Broad's involved patents and application is inconsistent with Mr. Kowalski's findings. (*See* CVC Motion 3, Paper 1558, 6:11–9:2.) CVC provides Chart 2, which lists Broad's involved patents and application and the individuals who CVC asserts should have been named. (*See id.* at 7:3–9:2.)

We are not persuaded that the Kowalski Declaration is sufficient evidence that Broad's involved patents and applications incorrectly name inventors because CVC never compares the alleged contributions of the people named in Kowalski declaration with Broad's involved patent and application claims, as properly interpreted. CVC repeatedly notes that Broad's PCT application and Broad's involved patents and application claim priority to the same original provisional application and, thus, "originate from a common source." (*See* CVC Motion 3, Paper 1558, 6:12–14, 11:14–16, *see also id.* at 12:12–13, 13:6–7, 13:22–23.) To the extent CVC is asserting that the Kowalski Declaration is relevant to Broad's involved claims, this argument is unpersuasive. Claiming benefit to the same provisional application says nothing about what is claimed in later applications. Broad's involved patents and application may claim different inventions from the PCT applications, regardless of their lineages. Without an actual analysis of Broad's involved claims and the alleged contributions of each asserted co-inventor, CVC's argument is completely unpersuasive.

Furthermore, neither CVC nor the Kowalski Declaration provides a detailed explanation of the contributions done by the people named. Mr. Kowalski testifies that he "review[ed] the claims as a statement of inventive concepts disclosed in the application and for a provisional application the subject matter in the disclosure

(and claims, if present)." (*See* Kowalski Decl., Ex. 4295, ¶ 5.) Mr. Kowalski then states that he conducted interviews and "invite[d] the individual to provide any additional information, e.g., additional documents, that support his contribution to the invention or inventions." (*Id.* at ¶ 9.) Mr. Kowalski concludes that he assessed all of the information, considering "the nature of the invention, e.g., whether the invention requires simultaneous conception and reduction to practice and the state of the prior art, and who did what when." (*Id.* at ¶ 10.) But none of this information is included in the declaration. The declaration includes only brief conclusions, of no more than a sentence, indicating to which inventions the named individuals "contributed in a not insubstantial manner. . . ." (*See id*. at ¶ 16.)

For example, the declaration states that Dr. Cong and Randall Platt contributed to "CRISPR-Cas9 system adapted in for uses in eukaryotic cells," but that Patrick Hsu, Fei Ran, and Shuailiang Lin, contributed to "the CRISPR-Cas9 system for *certain* uses in eukaryotic cells." (Kowalski Decl., Ex. 4295, ¶ 16 (emphasis added).) Mr. Kowalski did not provide an explanation of the difference between "uses in a eukaryotic cell" and "*certain* uses in a eukaryotic cell," if there is any difference. He provided no more substantive information beyond the short phrases and did not compare these contributions to any specific claim language.

CVC acknowledges this lack of information for at least some of the people identified by Mr. Kowalski, stating: "The declaration does not specify precisely to which systems and methods of use in eukaryotes Ran, Hsu, and Lin contributed, but, in the absence of clarification, it is reasonable to assume that whatever aspects they did contribute are reflected in the claims of PCT/US2013/074611." (CVC Motion 3, Paper 1558, 10:22–25.) We decline to adopt the CVC attorney's

assumptions. Furthermore, we do not find CVC's arguments to be persuasive of any contribution regarding Broad's currently involved patent and application claims.

CVC cites to the testimony of Scott Bailey, Ph.D., to support its argument that a skilled artisan would have found that inventive contribution by Platt, Cong, Ran, Hsu, and Lin, as identified in the Kowalski Declaration and claimed in Broad's application PCT/US2013/074611, is also claimed in Broad's involved patents and application. (*See* CVC Motion 3, Paper 1558, 11:1–4, citing Bailey Decl., Ex. 4341, ¶¶ 30-35.) Dr. Bailey is an Associate Professor in the Department of Biochemistry and Molecular Biology at Johns Hopkins Bloomberg School of Public Health. (*See* Bailey Decl., Ex. 4341, ¶ 9.) Dr. Bailey does not testify to any particular expertise in patent law, instead applying "U.S. legal principles that have been provided to me by counsel." (Bailey Decl., Ex. 4341, ¶ 17.) In fact, Dr. Bailey has never done an inventorship analysis. (*See* Bailey Depo, Ex. 6208, 18:7–11 ("Q. Have you ever conducted an inventorship analysis for purposes of patents or applications filed in the United States Patent and Trademark Office? A. I have not."), *see* Broad Opp. 3, Paper 2475, 18:3–23.) We do not find Dr. Bailey to be qualified to testify about the legal aspects of inventorship. Thus, we give his conclusions little weight. His testimony is, though, that he works in the field of molecular mechanisms of CRISPR systems, and his publications and grants support this. (*See* Bailey Decl., Ex. 4341, ¶ 14; *see* Bailey *Curriculum Vitae*, Ex. 4342.) Thus, to the extent he testifies about what one of skill in the art would have understood at the time, we find him qualified.

Dr. Bailey's testimony highlights the vagueness of the Kowalski Declaration. Dr. Bailey testifies that Mr. Kowalski determined that "Ran, Hsu, and Lin made inventive contributions to 'certain' uses of or methods of using the CRISPR-Cas9 systems in eukaryotic cells, although he [presumably Mr. Kowalski] does not specify what 'certain' means." (Bailey Decl., Ex. 4341, ¶ 31.) According to Dr. Bailey, "it is reasonable to assume that whatever aspects Ran, Hsu, and Lin did contribute are reflected in the claims of [the PCT application], which do not recite specific uses that are distinct from the basic use of CRISPR-Cas9 systems in eukaryotic cells." (Bailey Decl., Ex. 4342, ¶ 31.) Thus, even though Dr. Bailey does not understand Mr. Kowalski's conclusions, he accepts that Ran, Hsu, and Lin are inventors of uses of CRISPR-Cas9 systems in eukaryotic cells.

Dr. Bailey continues, testifying that "the contributions regarding the use of CRISPR-Cas9 systems in eukaryotic cells, as identified in the Kowalski Declaration and claimed in [PCT application], are also claimed in the involved Broad patents and application." (Bailey Decl., Ex. 4341, ¶ 33.) To come to this conclusion, Dr. Bailey provides a chart listing "Inventive Contributions According to Kowalski Declaration," being "in eukaryotic cells," and matches this phrase to claim language in Broad's involved claims that refers to eukaryotic cells. (Bailey Decl., Ex. 4341, ¶ 33.)

Dr. Bailey concludes:

> as a technical matter, I view the claims of the [the PCT application] and claims of the involved Broad patents and application as being directed to the same invention, even if they use different words. So, if Mr. Kowalski is correct that Platt, Cong, Ran, Hsu, and Lin "contributed in a not insubstantial manner" to the subject matter claimed in [the PCT application],

> they must necessarily also have "contributed in a not insubstantial manner" to the subject matter claimed in the above-listed involved Broad patents and application.

(Bailey Decl., Ex. 4341, ¶ 35.) CVC argues that it "presented the—now unrebutted—testimony of its scientific expert, Dr. Bailey, that those same technical contributions Kowalski identified are recited in the claims of the Broad's involved patents and application." (CVC Reply 3, Paper 2743, 1:10–12.)

Because Dr. Bailey testifies that he is not certain of the technical contributions Mr. Kowalski identified, beyond the short phrases Mr. Kowalski used, and because Dr. Bailey merely matches words in Broad's involved claims, we are not persuaded that his testimony indicates anything about the contributions of the named people or Broad's claims or what one of ordinary skill would have understood about them. Neither Dr. Bailey nor CVC explains, for example, how the "certain uses in eukaryotic cells" referred to by Mr. Kowalski compare to the scope of Broad's involved claims.

Dr. Bailey's testimony, to the extent he is qualified to give it, is unpersuasive because it is not supported by any explanation or reasoning other than a blind acceptance of the vague conclusions in the Kowalski Declaration and a comparison to isolated phrases in Broad's involved claims. Furthermore, the Kowalski Declaration does not refer to or provide an analysis of Broad's involved patent or application claims. Thus, we give little to no weight to either Dr. Bailey's testimony or the Kowalski Declaration in regard to the inventorship of Broad's currently involved claims having the phrase "eukaryotic cells."

The Kowalski Declaration is similarly unpersuasive regarding the phrases "co-delivery to the nucleus," "*in vivo* applications," and "ortholog design." (Kowalski Decl., Ex. 4295, ¶ 16; *see* CVC Motion 3, Paper 1558, 11:18–13:24.) Mr. Kowalski provided no more substantive information beyond these short phrases and did not compare these contributions to any specific claim language. Again, there is no discussion of Broad's involved claims or even of the specific claim language of the PCT applications to which Mr. Kowalski refers. Dr. Bailey again provides only a blind acceptance of the vague conclusions in the Kowalski Declaration and a comparison to isolated phrases in Broad's involved claims. (*See* Bailey Decl., Ex. 4341, ¶¶ 37–54.) Neither Mr. Kowalski nor Dr. Bailey provide an actual analysis of what the named individuals did and how those contributions contribute to subject matter within the scope of Broad's involved claims as properly interpreted.

CVC argues that Broad does not present evidence or information to respond substantively to CVC's arguments and does not explain why it did not identify the people named in the Kowalski Declaration as inventors. (*See* CVC Reply 3, Paper 2743, 1:21–2:1.) Broad need not do so because CVC carries the burden of proving the inventorship of Broad's patents and applications is incorrect. *See* 37 C.F.R. § 41.208(b) ("To be sufficient, a motion must provide a showing, supported with appropriate evidence, such that, if unrebutted, it would justify the relief sought. The burden of proof is on the movant."). CVC fails to do so.

CVC argues that because Mr. Kowalski was Broad's own attorney and he provided sworn testimony "based on subject matter—and not on a claim-by-claim basis," on which Broad previously relied in European opposition proceedings,

Broad cannot argue that the analysis is insufficient and must be bound by it here. (*See* CVC Reply 3, Paper 2743, 5:11–19.) CVC argues further that Mr. Kowalski's Declaration is an admission that can be used against Broad in this proceeding. (*See id.* at 6:20–9:23.) These arguments are unpersuasive because the Kowalski Declaration does not persuade us that the findings therein are necessarily relevant to Broad's involved claims. CVC argues that Dr. Bailey's analysis determined that the "relevant claims as a whole" recite the same features as the claim language and specification disclosure of the relevant PCT applications, but as explained above, we find Dr. Bailey's analysis to be insufficient because he merely matched words in Mr. Kowalski's determinations with the words in Broad's currently involved claims. (CVC Reply 3, Paper 2743, 12–23.) Neither Dr. Bailey nor CVC provides an analysis of Broad's involved claims, beyond the recitation of some words. Thus, their declarations do not provide us with sufficient evidence of who invented Broad's involved claims.

Patent issuance creates a presumption that the named inventors are the true and only inventors. *See Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998). CVC's burden is to overcome this presumption with sufficient evidence. CVC fails to meet its burden and to persuade us that we should determine any of Broad's issued patent claims, or pending application claims, are unpatentable under 35 U.S.C. § 102(f).

Accordingly, we DENY CVC Motion 3. This decision renders Broad Contingent Responsive Motion 6 moot.

V. CVC Miscellaneous Motion 7 – To Exclude Evidence

CVC requests that certain exhibits submitted by Broad be excluded. (CVC Motion 7, Paper 2789.) Specifically, CVC argues that the following declarations should be excluded: Benjamin Davies (Ex. 3435), Mark Kay (Ex. 3436), Alan Lambowith (Ex. 3437); Paul Simons (Exs. 3438 and 3440); Erez Lieberman Aidan (Ex. 3439), Greg Hannon (Ex. 3441 and 3442), Mark Isalan (Ex. 3443), Caixao Gao (Ex. 3446); Adam Bogdanove (Ex. 3449), Thierry VandenDriessche (Ex. 3450), Bryan Cullen (Ex. 3451), Paula Cannon (Ex. 3452), portions of the Third Declaration of Ronald Breaker (Ex. 3448). (*See id.* at 1:19–2:22.) CVC asserts that either the declarants were not made available for cross-examination or the declarations contain statements of in admissible hearsay. (*See id.* at 3:5—9:12.)

We do not rely on any of these declarations to reach our decisions. Thus, CVC's request is moot.

CVC also asserts that Exhibits 3681, 6107, and 6116 should be excluded because they are third party books and are inadmissible hearsay. (*See id.* at 9:15–10:23.) Again, we do not rely on any of these exhibits to reach our decisions. Thus, this request is also moot.

Accordingly, we DISMISS CVC's motion to exclude evidence.

VI. Broad Miscellaneous Motion 9 – To Exclude Evidence

Broad requests that portions of the re-direct testimony of Dr. Phillip Zamore should be excluded as being outside the scope of cross examination. (*See* Broad Motion 9, Paper 2793.)

Because we deny CVC's motions and grant Broad Motion 5 without relying on Dr. Zamore's cross-examination, Broad's request is moot.

Accordingly, we DISMISS Broad's motion to exclude.

VII. Inequitable conduct

CVC asserts inequitable conduct during prosecution of the applications that became the involved Broad patents and requests authorization to file a motion arguing that it renders Broad's claims unpatentable. (*See* Junior Party's List of Intended Motions, Paper 19, 15:15–22:12; *see* CVC's Additional Justifications Supporting Authorizing a Motion for Unpatentability Due to Inequitable Conduct, Paper 2856, 1:13–5:8.) Specifically, CVC asserts that Dr. Zhang made affirmative material misstatements during prosecution of the applications that became Broad's involved patents and applications by submitting allegedly false declarations. (*See id.*)

Under the circumstances of this case, we decline to take up CVC's arguments of inequitable conduct because they are not directly related to the issue of priority for the subject matter of the current count. CVC filed claims that provoked an interference, a proceeding primarily to determine priority between parties. Our mandate is to determine priority, whereas determinations of unpatentability for other reasons is discretionary. *See* 35 U.S.C. § 135(a) ("The

Board of Patent Appeals and Interferences shall determine questions of priority of the inventions and may determine questions of patentability.").

CVC has had an opportunity to oppose any facts presented by Broad in this proceeding with contrary evidence. Thus, if the facts CVC asserts regarding inequitable conduct are related to Broad's priority case, CVC has had an opportunity to present them. CVC does not allege any inequitable conduct by counsel for Broad or any of Broad's named inventors during this proceeding. Instead, CVC's basis for asserting inequitable conduct would seek to cancel Broad's claims for reasons unrelated to Broad's arguments for priority. Accordingly, in this proceeding, we exercise our discretion to decline to consider issues that are not related to priority.

No further motions are authorized.

VIII. Conclusion

We deny CVC Motion 2 for judgment based on priority.

We deny CVC Motion 3 for judgment based on improper inventorship.

We grant Broad Motion 5 for judgment based on priority.

We dismiss as moot Broad Motion 6 for correction of inventorship.

We dismiss as moot CVC Motion 7 to exclude evidence.

We dismiss as moot Broad Motion 9 to exclude evidence.

We enter judgment separately in accordance with these decisions.

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