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Filed on behalf of: Benson Hill Biosystems, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BENSON HILL BIOSYSTEMS, INC.,
Petitioner,

v.

THE BROAD INSTITUTE INC.,
PRESIDENTS AND FELLOWS OF HARVARD COLLEGE &
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
Patent Owners.

U.S. Patent No. 9,790,490

PETITION FOR POST GRANT REVIEW

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1021	Fieck et al., "Modifications of the *E. coli* Lac repressor for expression in eukaryotic cells: effects of nuclear signal sequences on protein activity and nuclear accumulation," *Nucleic Acids Research*, 20(7):1785-91 (1992)
1022	United States Patent No. 8,697,359
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1024	Mali et al., "RNA-Guided Human Genome Engineering via Cas9," *Science*, 339(6121):823-26 (2013)
1025	Sandy et al., "Mammalian RNAi: a practical guide," *BioTechniques*, 39:215-24 (2005)
1026	United States Patent Application Publication No. 2013/0302401
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1028	Nair et al., "Multivalent *N*-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing," *JACS*, 136:16958-63 (2014)
1029	Ludlum et al., "Alkylation of Synthetic Polynucleotides," *Science*, 145(3630):397-99 (1964).
1030	Glen Research, *The Glen Report*, 19(1):1-16 (2007)

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1031	El-Andaloussi et al., "Exosome-mediated delivery of siRNA in vitro and in vivo," *Nat Protoc*, 7(12):2112-26 (2012)
1032	Choulika et al., "Transfer of single gene-containing long terminal repeats into the genome of mammalian cells by a retroviral vector carrying the cre gene and the loxP site," *J Virol.*, 70(3):1792-98 (1996)
1033	Bergemann et al., "Excision of specific DNA-sequences from integrated retroviral vectors via site-specific recombination," *Nucleic Acids Research*, 23(21):4451-56 (1995)
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1036	Shukla et al., "Precise genome modification in the crop species Zea mays using zinc-finger nucleases," *Nature*, 459(7245):437-41 (2009)
1037	Jinek et al., "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity," *Science*, 337(6069):816-21 (2012).
1038	Mojica et al., "Biological significance of a family of regularly spaced repeats in the genomes of Archaea, Bacteria and mitochondria," *Mol Microbiol*, 36(1):244-46 (2000)
1039	Ishino et al., "Nucleotide Sequence of the *iap* Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in *Escherichia coli*, and Identification of the Gene Product," *Journal of Bacteriology*, 169(12):5429-33 (1987)
1040	Jansen et al., "Identification of genes that are associated with DNA repeats in prokaryotes," *Molecular Microbiology*, 43(6):1565-75 (2002)
1041	Bolotin et al., "Clustered regularly interspaced short palindrome repeats (CRISPRs) have spacers of extrachromosomal origin," *Microbiology*, 151(Pt 8):2551-61 (2005)
1042	Mojica et al., "Intervening sequences of regularly spaced prokaryotic repeats derive from foreign genetic elements," *J Mol Evol*, 60(2):174-82 (2005)

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1043	Pourcel, "CRISPR elements in Yersinia pestis acquire new repeats by preferential uptake of bacteriophage DNA, and provide additional tools for evolutionary studies," *Microbiology*, 151(Pt 3):653-3 (2005)
1044	Barrangou et al., "CRISPR provides acquired resistance against viruses in prokaryotes," *Science*, 315(5819):1709-12 (2007)
1045	Haft et al., "A Guild of 45 CRISPR-Associated (Cas) Protein Families and Multiple CRISPR/Cas Subtypes Exist in Prokaryotic Genomes," *PLOS Computational Biology*, 1(6):474-83 (2005)
1046	Brouns et al., "Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes," *Science*, 321(5891):960-64 (2008)
1047	Garneau et al., "The CRISPR/Cas bacterial immune system cleaves bacteriophage and plasmid DNA," *Nature*, 468(7320):67-71 (2010)
1048	Deveau et al., "Phage Response to CRISPR-Encoded Resistance in *Streptococcus thermophilus*," *Journal of Bacteriology*, 190(4):1390-1400 (2008)
1049	Mojica et al., "Short motif sequences determine the targets of the prokaryotic CRISPR defence system," *Microbiology*, 155(Pt 3):733-40 (2009)
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1051	Nishimasu et al., "Crystal Structure of Cas9 in Complex with Guide RNA and Target RNA," *Cell*, 156(5):935-49 (2014)
1052	Deltcheva et al., "CRISPR RNA maturation by *trans*-encoded small RNA and host factor RNase III," *Nature*, 471(7341):602-07 (2011)
1053	Makarova et al., "Unification of Cas protein families and a simple scenario for the origin and evolution of CRISPR-Cas systems," *Biology Direct*, 6:38, pp. 1-27 (2011)
1054	Nam et al., "Cas5d protein process pre-crRNA and assembles into a Cascade-like interference complex in Subtype I-C/Dvulg CRISPR-Cas system," *Structure*, 20(9):1574-84 (2012)
1055	Haurwitz et al., "Sequence- and structure-specific RNA processing by a CRISPR endonuclease," *Science*, 329(5997):1355-58 (2010)

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1056	Hatoum-Aslan et al., "Mature clustered, regularly interspaced, short palindromic repeats RNA (crRNA) length is measured by a ruler mechanism anchored at the precursor processing site," *PNAS*, 108(52):21218-222 (2011)
1057	Rouillon et al., "Structure of the CRISPR Interference Complex CSM Reveals Key Similarities with Cascade," *Molecular Cell*, 52:124-34 (2013)
1058	Hale et al., "RNA-Guided RNA Cleavage by a CRISPR RNA-Cas Protein," *Cell*, 139(5):945-56 (2009)
1059	Vestergaard et al., "CRISPR adaptive immune systems of Archaea," *RNA Biology*, 11(2):156-67 (2014)
1060	Voskarides & Deltas, "Screening for Mutations in Kidney-Related Genes Using SURVEYOR Nuclease for Cleavage at Heteroduplex Mismatches," *Journal of Molecular Diagnostics*, 11(4):311-18 (2009)
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1062	Kim et al., "Genotyping with CRISPR-Cas-derived RNA-guided endonucleases," *Nat Commun*, 5:3157 (2014)
1063	Minton, "How can biochemical reactions within cells differ from those in test tubes?," *Journal of Cell Science*, 119:2863-69 (2006)
1064	Ellis, "Macromolecular crowding: obvious but underappreciated," *Trends Biochem Sci*, 26(10):597-604 (2001)
1065	Nishimasu et al., "Structural Basis for the Altered PAM Recognition by Engineered CRISPR-Cpf1," *Mol Cell*, 67(1):139-47 (2017)
1066	Shmakov et al., "Diversity and evolution of class 2 CRISPR-Cas systems," *Nat Rev Microbiol.*, 15(3):169-82 (2017)
1067	Aravind et al., "Holliday junction resolvases and related nucleases: identification of new families, phyletic distribution and evolutionary trajectories," *Nucleic Acids Research*, 28(18):3417-32 (2000)
1068	Chen et al., "Structural asymmetry in the *Thermus thermophilus* RuvC dimer suggests a basis for sequential strand cleavages during Holiday junction resolution," *Nucleic Acids Research*, 41(1):648-59 (2013)

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1069	Leenay & Beisel, "Deciphering, communicating, and engineering the CRISPR PAM," *J Mol Biol.*, 429(2):177-91 (2017)
1070	Pul et al., "Identification and characterization of E. coli CRISPR-cas promoters and their silencing by H-NS," *Mol Microbiol*, 75(6):1495-512 (2010)
1071	Kim et al., "Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins," *Genome Res.*, 24(6):1012-9 (2014)

I. INTRODUCTION

Benson Hill Biosystems, Inc. ("Petitioner") requests post grant review of U.S. Patent No. 9,790,490 ("the '490 patent"), which is assigned to The Broad Institute Inc., Presidents and Fellows of Harvard College, and Massachusetts Institute of Technology ("Patent Owners"). The '490 patent broadly claims systems for genetic engineering of eukaryotic cells using a Cpf1 CRISPR effector protein and at least one targeting nucleic acid component (*i.e.*, guide RNA).

As shown in this Petition and supported by the declaration of Dr. Chase Beisel, the claims of the '490 patent cover an incredibly broad and vast genus[1] of Cpf1 effector proteins that are required to be functional in eukaryotic cells, in that they cleave DNA. This genus of proteins encompasses a virtually unknowable number of molecules. Yet, out of the several different Cpf1 proteins disclosed in the specification only a few actually functioned in eukaryotic cells, and the specification fails to explain how or why these particular proteins were effective while others were not. Similarly, the specification fails to provide any correlation between the structure of the Cpf1 proteins and their claimed function of successfully cleaving DNA in eukaryotic cells. As such, the well-established precedent of the Federal

[1] The accompanying declaration of Dr. Chase Beisel refers to a "family" of Cpf1 proteins encompassed by the claims, instead of the more legal term "genus."

Circuit dictates that the challenged claims fail to satisfy the written description requirement of 35 U.S.C. § 112, particularly given the manifest unpredictability in the field. And for essentially the same reasons, the *full scope* of the claims is not enabled by the limited teachings in the specification. It would take complex iterative testing, of precisely the sort found by the Federal Circuit to constitute undue experimentation, to identify the genus of Cpf1 proteins that are functional within the meaning of the claims. Accordingly, because the scope of claims 1-60 of the '490 patent vastly exceeds what is described and enabled in the specification, those claims are not patentable. Each of claims 1-60 is also unpatentable for indefiniteness, as the specification provides ambiguous and often contradictory descriptions of what constitutes a "Cpf1 effector protein." Additionally, if the Board determines that the claims require no functional activity and/or that the art was sufficiently predictable to enable and describe the full scope of the claimed genus, then claims 1-60 are unpatentable for lack of practical utility and/or obviousness. Petitioner, therefore, requests cancellation of the challenged claims.

II. BACKGROUND AND STATE OF THE ART

CRISPR (**c**lustered **r**egularly **i**nterspaced **s**hort **p**alindromic **r**epeats) systems were first discovered in bacteria and archaea, where they play a role in adaptive immune responses by specifically cleaving DNA or RNA of invading foreign nucleic acids (*e.g.*, phages). Ex. 1003, ¶¶ 17-18, 22; Ex. 1007, 8-12. A key

component of CRISPR systems is the "effector protein" (also called a CRISPR-associated, or Cas protein), which cleaves target nucleic acids in a sequence-specific manner. Ex. 1003, ¶ 19; Ex. 1008, 6-7, 13-15. In most CRISPR systems, sequence specificity is provided by a "guide RNA" (gRNA; also called a CRISPR RNA or crRNA), which forms a complex with the effector protein and base-pairs with the target nucleic acid. Ex. 1003, ¶¶ 19, 21; Ex. 1009, 4, 7-9. To effect cleavage, effector proteins discovered to date require the presence of a "protospacer adjacent motif" or "PAM" sequence in the target DNA, which enables the effector protein/gRNA complex to pin-point the specific cleavage site in the target genome. Ex. 1003, ¶ 20; Ex. 1010, 1-2, 8-9.

Once the cleavage site is identified, the target DNA unwinds and base pairs with the guide RNA, and the effector protein cleaves the target DNA within the base-paired region. Ex. 1003, ¶¶ 25-26. The cleaved genomic DNA then undergoes one of two fates. The vast majority of CRISPR-induced cleavages are repaired by non-homologous end joining, which introduces small insertions, deletions, or substitution mutations at the cleavage site. Ex. 1001, 107:29-63; Ex. 1003, ¶ 27. But if a source of homologous DNA is available, the genomic DNA can undergo homology-directed repair to include the homologous DNA. Ex. 1003, ¶ 27; Ex. 1011, 1-2.

CRISPR systems are remarkably diverse, despite their common role in adaptive immunity, and show extreme variability in their effector protein compositions, as well as their genomic loci architecture. Ex. 1003, ¶ 24; Ex. 1008, 6-7, 9, 13-15; Ex. 1012, 7. Current CRISPR classification systems define two classes, six main types, and nineteen subtypes. Ex. 1003, ¶¶ 23, 28; Ex. 1013, 8-11, 15; Ex. 1008, 6-7, 13-15; Ex. 1069, 9. Each grouping is distinguished by its effector proteins and by the mechanisms of RNA processing, target recognition, and target destruction. Class 2/type II systems have received the most attention because their machinery can be packaged into a portable two-component system for biotechnological applications involving genetic manipulations. Ex. 1003, ¶ 24; Ex. 1007, 9-12; Ex. 1013, 14-19. The hallmark effector protein of class 2/type II systems is Cas9 (particularly, SpCas9 derived from *Streptococcus pyogenes*), which has become the most commonly utilized effector protein for genome editing applications. Nevertheless, despite intense efforts to characterize different CRISPR systems, by the end of 2015, major aspects of their basic biology, diversity, and evolution remained unknown. Ex. 1003, ¶ 23; Ex. 1008, 13.

The ’490 patent relates to a class 2 CRISPR system containing an effector protein called “Cpf1,” and its use in genome editing applications. The Cpf1 system was identified informatically in several bacterial genomes in 2012. Ex. 1014; *see also* Ex. 1004, 6-7, 14; Ex. 1003, ¶ 28. By the end of 2015, however, no functional

activity had yet been demonstrated for Cpf1, and it was unknown whether the genomic regions encoding Cpf1 proteins represented functional CRISPR systems. Ex. 1003, ¶ 28; Ex. 1013, 23; Ex. 1005, 7-8. Thus, the technology involved in harvesting Cpf1 proteins for genetic manipulation of eukaryotic cells was still nascent when the '490 patent was filed in 2015.

III. SUMMARY OF THE '490 PATENT

A. The Challenged Claims

The '490 patent contains four independent claims, each drawn to an engineered, non-naturally occurring system comprising: (a) a Cpf1 effector protein (claims 1 and 4[2]) or a nucleotide sequence encoding a Cpf1 effector protein (claims 2-4); and (b) an engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and hybridize with a target sequence in a eukaryotic cell (claims 1 and 4) or a nucleotide sequence encoding such a guide polynucleotide (claims 2-4). Ex. 1001, 547:49-549:26.

[2] Claim 4 is an improper duplicate of claims 1 and 2, since claim 4 merely combines the elements of claims 1 and 2 in the alternative. For similar reasons, claims 5 and 7 (which depend from claim 4 and specify elements from claim 1) are improper duplicates of claim 1, while claims 6 and 8 (which depend from claim 4 and specify elements from claim 2) are improper duplicates of claim 2.

Each of claims 1-4 recites that the system lacks a tracr sequence. Claim 1 is representative of the challenged claims, and recites:

> An engineered, non-naturally occurring system comprising
> a) a Cpf1 effector protein, and
> b) at least one engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and comprising a guide sequence, wherein the guide sequence is designed to hybridize with a target sequence in a eukaryotic cell; and
> wherein the system lacks a tracr sequence, the engineered guide polynucleotide and Cpf1 effector protein do not naturally occur together, and a complex of the engineered guide polynucleotide and Cpf1 effector protein does not naturally occur.

Ex. 1001, 547:49-61. All of the dependent claims fall within the scope of claims 1-4 and either recite additional aspects of the system (claims 5-24), delivery particles comprising the system (claims 25-28), methods of genetic modification using the system (claims 29-55), or eukaryotic cells comprising the system (claims 56-60). Ex. 1001, 549:27-552:26.

B. The Specification

The ’490 patent investigates the diversity of Cpf1-family proteins that had been deposited in public sequence databases by performing a BLAST search of the WGS database at the NCBI (presumably using one or more previously-identified

Cpf1 sequences as a starting point), which "revealed 46 non-redundant Cpf1 family proteins (FIG. 64)."[3] Ex. 1001, 444:1-3; Ex. 1003, ¶¶ 29, 33. The patent provides a sequence alignment of putative Cas-Cpf1 proteins in Fig. 38, along with a "consensus sequence" (SEQ ID NO:1033) based on that alignment. Ex. 1001, 14:1-3, 388:62-64, Fig. 38, Sequence Listing at 1408-17. An overview of Cpf1 loci alignment with the consensus sequence is shown in Fig. 39. Ex. 1001, 388:64-65. The sequence alignment reveals very little sequence conservation among the putative Cpf1 proteins. Ex. 1003, ¶ 34. While the specification explains that a protein may be considered a Cpf1 effector protein if it has "sequence homology or identity of at least 80%" (presumably to SEQ ID NO:1033; Ex. 1001, 35:37-39; Ex. 1003, ¶ 35), BLASTP alignments of SEQ ID NO:1033 with the 17 putative Cpf1 proteins that were tested in the examples show sequence identity as low *as 25%*. Ex. 1003, ¶¶ 34-35.

The '490 patent explains that 16 of the identified Cpf1 proteins were chosen for testing. Ex. 1001, 444:3-5.[4] At least *six* of the enzymes *failed* to show any

[3] Fig. 64 actually identifies 51 non-redundant putative Cpf1 proteins. Ex. 1003, ¶ 33.

[4] A careful review of the Examples and Figures indicates that 17 enzymes were actually tested. Ex. 1003, ¶¶ 42-46.

activity *in vitro* or *in vivo*. Ex. 1003, ¶¶ 47-54. *In vitro* activity (in lysate or purified protein assays) was demonstrated for only *eleven* of the enzymes. Ex. 1001, Examples 6, 13, 14, Figs. 89, 90, 100A-B, 100F, 101C, 106; Ex. 1003, ¶ 51. *In vivo* activity in eukaryotic cells was demonstrated for merely *three* of the enzymes. Ex. 1001, Examples 4, 6, 14, Figs. 88, 93, 101C, 108A-C; Ex. 1003, ¶ 54. One of those enzymes (FnCpf1), along with another enzyme that did *not* exhibit *in vivo* activity in eukaryotic cells (PaCpf1), presumably *did* exhibit *in vivo* activity in prokaryotes (*E. coli*) based on reported PAM sequences for those species. Ex. 1001, Examples 3, 4, 5, 8, Figs. 45A-E, 62A-E, 95C-E, 102D; Ex. 1003, ¶ 47. PAM sequences were determined for a total of 9 of the enzymes. Ex. 1003, ¶ 49.

C. The Prosecution History

The ’490 patent was filed on December 18, 2015, claiming priority to five U.S. provisional applications. A non-final Office Action was issued rejecting all of the elected claims for indefiniteness, lack of subject matter eligibility, and anticipation in view of the Schunder et al. paper (Ex. 1004 (“Schunder”)) that originally identified Cpf1 systems in several bacterial genomes. Ex. 1002, 6148-55.

In response, Patent Owners amended the claims to overcome the indefiniteness and subject-matter eligibility rejections. Ex. 1002, 6173-83. Regarding the anticipation rejection, Patent Owners argued that Schunder “fails to demonstrate that any of the putative [CRISPR-Cpf] components were *functional*,”

and "fails to teach or suggest elements needed to engineer an *operable F. tulerenis* [*sic*] *CRISPR-Cas system*," such as the "Protospacer Adjacent Motif (PAM), which would be required to design a functional guide." Ex. 1002, 6184 (emphasis added). Patent Owners concluded that "Schunder does not teach or suggest all of the limitations of the instant claims" or "teach one of ordinary skill in the art how to make and use the instantly claimed invention." *Id.*

An Examiner-Initiated Interview was conducted, during which the Examiner and Patent Owners discussed proposed new claims to overcome the rejections of the previous Office Action. Ex. 1002, 7664. The Examiner noted that the lack of tracr sequence in the system was a substantive and non-obvious functional and structural difference from prior art systems that required a tracr sequence, and required Patent Owners to include such language in the claims. *Id.* The agreed-upon claims were set forth in the Examiner's Amendment that was appended to the Notice of Allowance mailed July 13, 2017. Ex. 1002, 7666-77. The '490 patent issued with 60 claims on October 17, 2017.

IV. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") of CRISPR-based genome editing in eukaryotic cells at the earliest effective filing date of the claimed invention would have had skills relating to molecular biology, biochemistry, cell biology, and/or genetics. Ex. 1003, ¶¶ 59-60. Typically, a POSA would have had an M.D. or

a Ph.D. in biology, chemistry, engineering *(e.g.*, chemical engineering, biological engineering, biomedical engineering, or biochemical engineering), biophysics, or a related discipline, with a focus on genetic modification techniques and at least three years of experience working in industry and/or academia on genetic modification techniques. Ex. 1003, ¶ 60.

A POSA also would have had knowledge of various laboratory techniques and strategies used in genomic engineering, genome mining, and bioinformatic identification of proteins. Ex. 1003, ¶ 61. A POSA would have had knowledge of *in vitro* and *in vivo* assays to test the processing and function of putative CRISPR arrays. *Id*. A POSA would have known how to research the scientific literature in fields relating to CRISPR-based genome editing and have knowledge of, and skills relating to, techniques useful in such research. *Id.* A POSA would have experience using Cas9 for genome editing, including the design of gRNAs for sequence-specific DNA targeting. *Id.* Finally, a POSA may have worked as part of a multidisciplinary team and drawn upon his or her own skills as well as certain specialized skills of others on the team to solve a given problem. *Id.*

V. CLAIM CONSTRUCTION

For purposes of this Petition, each claim term recited in the ’490 patent should be construed according to its “broadest reasonable construction in light of the

specification in which it appears." *See* 37 C.F.R. § 42.100(b)).[5] System claims 1-4 (from which claims 5-60 depend) require that the Cpf1 effector protein "form[s] a complex with" a guide sequence that "is designed to hybridize with a target sequence in a eukaryotic cell . . . ." *See, e.g.*, Ex. 1001, 547:51-56. Claims 9 and 10 require the complex to "cause[] cleavage distally of the target sequence" in the eukaryotic cell, and claims 29-55 recite a "method of modifying a locus of interest having a target sequence of a eukaryotic cell" by delivering the system of claims 1-4. Ex. 1001, 549:37-43, 550:38-552:16. Thus, on their face, each of the claims of the '490 patent requires a system in which the recited Cpf1 protein exhibits effector protein function in a eukaryotic cell. Ex. 1003, ¶¶ 62, 67-68.

The specification supports this construction by teaching that the claimed nucleic-acid targeting complexes are used for "modifying (e.g., deleting, inserting,

[5] The Office's proposed "Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board," which would replace the broadest reasonable interpretation standard with the standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), have not yet gone into effect. Nevertheless, Petitioner is not aware of any differences in how the claims would be construed under a *Phillips* standard. Under either standard, the challenged claims should be found unpatentable.

translocating, inactivating, activating) a target DNA or RNA in a multiplicity of cell types." Ex. 1001, 42:3-7; *see also* 77:45-54 ("CRISPR-Cas (e.g. Cpf1) proteins and systems of the invention are used to produce cells comprising a modified target locus."), 2:42-51, 2:65-3:8, 3:57-59; 4:5-11, 4:58-66, 30:30-35, 42:15-18, 43:55-63, 64:31-40, 65:2-5, 72:59-60, 73:23-32, 77:25-36, 84:23-32, 156:29-44; 185:61-186:5. The specification explains that "upon binding of the said complex to the locus of interest the effector protein induces the modification of the target locus of interest." Ex. 1001, 4:64-66; *see also* 2:49-51, 3:5-8.

Although the patent also provides an embodiment in which catalytically *inactive* effector proteins are used in detection methods such as fluorescence *in situ* hybridization (FISH) (Ex. 1001, 156:45-67), that is certainly not the focus of the specification (Ex. 1003, ¶ 69), and the arguments Patent Owners advanced during prosecution expressly *disavowed* such embodiments. In responding to the Examiner's anticipation rejection, Patent Owners argued that the cited reference "fails to demonstrate that any of the putative components are *functional*" and "fails to teach or suggest elements needed to engineer an *operable F. tulerenis* [sic] CRISPR-Cas system." Ex. 1002, 6184 (emphases added). Patent Owners concluded that because the reference "does not teach or suggest all of the limitations of the instant claims," it "does not anticipate the claimed invention." *Id.* In addition, Patent Owners argued that the reference fails to enable the claimed invention because it

"provides no teaching or suggestion of a *F. tulerenis* [sic] PAM, which would be needed to design *functional* guides to hybridize to a target of interest." *Id.* (emphasis added). Thus, Patent Owners' arguments emphasized that functional assays are critical to showing possession of the invention, and expressly disclaimed non-functional systems.

Similarly, the Examiner required Patent Owners to amend the claims prior to allowance to recite that "the system lacks a tracr sequence," because this "was a substantive and non-obvious functional and structural difference from a system that required a tracr sequence" to function. Ex. 1002, 7664; *see also id.* at 7677 (noting that "the prior art fails to disclose or suggest such a system that lacks a tracr sequence"). Patent Owners' acquiescence to this amendment, along with their other statements made during prosecution to overcome the prior art constitute a clear disavowal of claim scope and limit the claims to those systems that actually function to cleave a target sequence in a eukaryotic cell. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013) ("When the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered."). Thus, under the broadest reasonable construction in light of the specification and prosecution history, each of the system claims *must* be functional, *i.e.*, the Cpf1 protein must form a complex

with a guide sequence and be capable of hybridizing to a target sequence in a eukaryotic cell and cleaving the target sequence. Ex. 1003, ¶ 70.

If, however, the Board were to determine that the issued claims do not require any functional aspects, then Petitioner includes additional grounds of unpatentability based on lack of practical utility under 35 U.S.C. § 101 (Ground 6) and obviousness over Schunder (Ground 7).

VI. IDENTIFICATION OF CHALLENGES

Since the '490 patent was filed under the AIA, and since this Petition is being filed within nine months of the date the patent issued, claims 1-60 are eligible for PGR and are unpatentable for lack of written description, lack of enablement, and indefiniteness. In addition, if the Board disagrees with Petitioner's proposed claim construction, claims 1-60 are unpatentable for lack of practical utility and obviousness.

Ground	*Claims*	*Legal Basis*
1	1-60	Inadequate written description under 35 U.S.C. § 112 for the genus of Cpf1 effector proteins
2	1-60	Lack of enablement under 35 U.S.C. § 112 for the genus of Cpf1 effector proteins
3	1-60	Indefiniteness under 35 U.S.C. § 112 for "Cpf1 effector protein"
4	1-60	Lack of enablement under 35 U.S.C. § 112 for the genus of systems lacking a tracr sequence
5	1-60	Inadequate written description under 35 U.S.C. § 112 for the genus of systems lacking a tracr sequence
6	1-60	Lack of practical utility under 35 U.S.C. § 101

Ground	*Claims*	*Legal Basis*
7	1-60	Obviousness under 35 U.S.C. § 103 over Schunder, the general knowledge in the art at the time, and various secondary references

The grounds are not redundant because each provides a different legal and factual basis to show the challenged claims are unpatentable.

A. Ground 1: Failure to Comply with the Written Description Requirement for the Recited Genus of "Cpf1 effector protein[s]"

1. The Specification Does Not Describe a Sufficient Number of Representative Species or Provide a Structure/Function Correlation Sufficient to Adequately Describe the Full Scope of the Subject Matter Recited in Claims 1-60

When a patent claims a genus using functional language to define a desired result, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1349 (Fed. Cir. 2010) (*en banc*). A sufficient description of a functionally-defined genus "requires [1] the disclosure of either a representative number of species falling within the scope of the genus or [2] structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." *Id.* at 1350 (internal quotation omitted).

For a claim directed to a functionally-described genus, the Federal Circuit has analogized the written description inquiry to a plot of land. *AbbVie Deutschland*

GmbH & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1299-1300 (Fed. Cir. 2014). One must ask whether the specification describes only a corner of the plot, or instead describes its full bounds, since "merely drawing a fence around a perceived genus is not a description of the genus." *Id.* at 1300. "Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *Id.* Further, it is well established that the *predictability* of the technology and the maturity of the field are important factors that need to be considered to determine whether there is sufficient written description to support a broad functionally defined genus. *Ariad*, 598 F.3d at 1351 (explaining that "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology").

Here, the claims of the '490 patent cover an incredibly broad genus of functional Cpf1 effector proteins in eukaryotic cells, encompassing an unknowable number of molecules. Ex. 1003, ¶ 74. Yet the '490 patent falls woefully short of providing sufficient written description of that massive genus. The specification identifies only 51 putative Cpf1 proteins. *See* Ex. 1001, Fig. 64, 389:1-423:63; Ex. 1003, ¶¶ 33, 75. Of those 51 proteins, only 17 were actually tested in the Examples, and *only 11* of those demonstrated any potential effector protein activity *in vitro*. Ex. 1003, ¶ 75. Thus, 35% of the putative Cpf1 proteins tested in the Examples failed to exhibit any effector protein activity *whatsoever*. *Id.* These results indicate

a high level of unpredictability as to whether any given putative Cpf1 protein will actually function as a CRISPR effector protein. Thus, while various putative Cpf1 proteins were identified, the specification provides no means other than trial and error to determine which sequences constitute functional Cpf1 effector proteins.

Moreover, of the 11 Cpf1 proteins that demonstrated activity *in vitro*, only 8 were tested in eukaryotic cells, and *only 3* of those 8 demonstrated effector protein activity in that system. Ex. 1003, ¶ 76. Thus, *only 27%* of the proteins that were even shown to have activity *in vitro* exhibited effector protein activity in a eukaryotic system, as *specifically required by the claim*. The patent does not establish that these 3, as opposed to the other proteins identified in the specification, are somehow "representative" of the claimed invention—only that they are functional, which is simply not sufficient under established precedent. Ex. 1003, ¶¶ 77-78. The patent does not describe any structural features of the 3 functional proteins that fall within the scope of the claim to set them apart from the other non-functional proteins, such as sequence identity or having particular domains. Ex. 1003, ¶ 79. Only through repetitive testing could a skilled artisan determine whether any putative Cpf1 protein is functional and thus falls within the scope of the claim. Ex. 1003, ¶ 80. Indeed, the negative results obtained for the majority of the tested Cpf1 proteins demonstrate the unpredictable nature of these enzymes when adapting them for use in non-native systems.

Subsequent studies have further revealed that only 12-25% of putative Cpf1 proteins support eukaryotic genome editing. Ex. 1015, 6; Ex. 1003, ¶ 81; *see also Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1375 (Fed. Cir. 2017) (holding that post-priority evidence may be used to show that claims covering any antibody that binds to a specific antigen are not adequately supported). These results indicate a high level of unpredictability as to whether any given putative Cpf1 protein will function as a CRISPR effector protein in eukaryotic cells. Even the inventors have acknowledged that "only a small fraction of bacterial nucleases can function efficiently when heterologously expressed in mammalian cells" (Ex. 1005, 11), which is a point that Patent Owners also successfully argued in recent interference proceedings before the Board. *Broad Inst., Inc. et al. v. Regents of the Univ. of California*, 2017 WL 657415, *2, 7, 16-17, 19 (PTAB 2017) (crediting Patent Owners' arguments that evidence of effector protein function in prokaryotic systems is not predictive of efficacy in eukaryotes).

This unpredictability was further confirmed in a recent publication that tested 16 putative Cpf1 proteins *in vitro* and in eukaryotic cells. Ex. 1006. Only 10 of the 16 tested proteins were active *in vitro*, and only four were active in eukaryotic cells. Ex. 1006, 3; Ex. 1003, ¶ 82. Of note were two Cpf1 proteins (Mb2Cpf1 and Mb3Cpf1), which were active *in vitro* but showed differing levels of activity in human cell assays. Ex. 1006, 3-4; Ex. 1003, ¶ 82. In the authors' own words: "The

apparent difference in activity between Mb2Cpf1 and Mb3Cpf1 was ***somewhat surprising*** given that these orthologs ***share a predicted homology of 94.7%***." Ex. 1006, 4 (emphasis added). The fact that the authors (several of whom are inventors of the '490 patent) failed to predict the difference in activity between two Cpf1 proteins sharing nearly 95% identity provides strong evidence of the unpredictability in the art regarding whether a particular Cpf1 protein will have activity. Ex. 1003, ¶ 82.

The Patent Owners themselves emphasized how sequence identity and/or lack thereof impacts the interchangeability of CRISPR effector proteins during the recent interference proceedings before the Board. Specifically, Patent Owners argued that *low* sequence identities among Cas9 proteins suggest that substitution of one Cas9 protein for another would be *unsuccessful*. *See* Reply 5 of Junior Party at 9, *Broad Inst., Inc. et al. v. Regents of the Univ. of California*, 2017 WL 657415 (PTAB 2017) (No. 106,048) ("the low level of homology between SaCas9 and SpCas9 and the significant structural differences between the two illustrates [*sic*] the unexpected attributes of using SaCas9."). The fact that certain Cas9 proteins are functional despite the low sequence identity with other functional Cas9 proteins demonstrates the inherent unpredictability of the technology. As such, the Patent Owners recognized that the demonstration of function for one protein in eukaryotic cells

would *not* be sufficient to lead one skilled in the art to predict that any other protein would also function in eukaryotic cells.

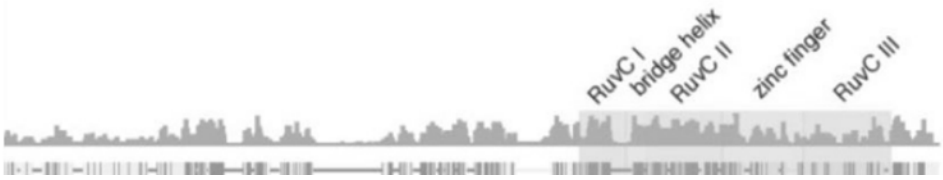
As discussed above there is nothing in the ’490 patent that explains why the 3 Cpf1 proteins that work and fall within the scope of the claims are “representative” of the claimed genus, while the other Cpf1 proteins that failed to work are not. In terms of a structure-function correlation, the ’490 patent provides no concrete guidance regarding any structural features of Cpf1 proteins that can be used to predict whether members of the claimed genus other than those specifically tested in the patent will have effector protein activity in eukaryotic cells. Ex. 1003, ¶ 83. The enzymes that demonstrated effector protein activity are diverse and are not clustered together in any clade of the phylogenetic tree. *Id.* The three proteins that were shown to work in eukaryotes share just 35%-40% identity at the amino acid level, and the patent fails to describe any feature of those sequences that is predictive of their success. *Id.*

At best, the specification merely provides a “synthetic consensus sequence” in the form of SEQ ID NO:1033 based on a sequence alignment of putative Cpf1 proteins, and explains that a protein may be considered a Cpf1 effector protein if it has “sequence homology or identity of at least 80%” (presumably to SEQ ID NO:1033). Ex. 1001, 35:37-39; Ex. 1003, ¶ 84. But BLASTP alignments of SEQ ID NO:1033 with the 17 putative Cpf1 proteins that were tested in the examples

show just 25-60% identity. Ex. 1003, ¶ 84. Notably, the three proteins that worked, AsCpf1 (SEQ ID NO:1261), LbCpf1 (SEQ ID NO:1273), and FnCpf1 (SEQ ID NO:51) share just 39%, 56%, and 52% identity, respectively, with SEQ ID NO:1033. *Id.*

While the patent also contains various functional descriptions of Cpf1 proteins, many of those definitions are internally inconsistent, and none is sufficient to identify additional members of the claimed genus. For instance, the patent describes Cpf1 proteins as containing a RuvC domain that mediates double-stranded break production. Ex. 1001, 29:49-53. In fact, the patent describes RuvC as the "only functional characterized domain" of Cpf1 proteins. Ex. 1001, 45:50-52; Ex. 1003, ¶ 30. However, RuvC domains are present in many different proteins, including Cpf1, Cas9, C2c1, and certain transposases. Ex. 1003, ¶ 85. The patent itself states that the "catalytic residues [in the RuvC domain] were identified based on sequence homology to *Thermus thermophilus* Ruv C (PDB ID: 4EP5)," which is a Holliday Junction resolvase protein. Ex. 1001, 22:24-27; Ex. 1003, ¶ 85. Thus, the presence of a RuvC domain is not a unique characteristic of Cpf1 proteins, nor is it predictive of whether a putative Cpf1 protein will have activity in eukaryotic cells. All the Cpf1 proteins that *failed* in eukaryotic cells also had a RuvC domain. Ex. 1003, ¶ 85.

Moreover, the patent is internally inconsistent regarding what even constitutes a RuvC domain in the context of a Cpf1 protein. For instance, the patent teaches that the RuvC domain is "contiguous in the Cpf1 sequence, in contrast to Cas9 where it contains long inserts" (Ex. 1001, 344:48-53; Ex. 1003, ¶ 31), yet the Figures depict the RuvC domain as comprising three different segments that are separated by other motifs (Ex. 1001, Figure 100B (reproduced below); Ex. 1003, ¶ 86).



In addition, the '490 patent elsewhere refers to "RuvC-like" domains, without explaining how, if at all, such domains differ from a *bona fide* RuvC domain. *See, e.g.*, Ex. 1001, 29:47-30:2, 343:36-39; 344:44-345:1, 346:6-15, 347:62-348:14, Example 11. Thus, a POSA is left questioning exactly what aspects of RuvC domains are present in Cpf1 proteins. Ex. 1003, ¶ 87.

Underscoring the lack of any meaningful guidance regarding which functional domains are *present* in Cpf1 proteins, the patent then attempts to characterize Cpf1 proteins by what domains are *missing* compared to other CRISPR effector proteins. Ex. 1003, ¶ 32. Specifically, the patent teaches that "Cpf1 lacks the HNH nuclease domain that is present in all Cas9 proteins . . . ." Ex. 1001, 344:48-50. Yet even this characterization is ambiguous, as elsewhere, the patent discusses various modifications that may be made to the effector protein's HNH domain to (1) reduce

off-target effects and/or enhance on-target effects; (2) weaken intra-protein interactions; or (3) strengthen intra-protein interactions. Ex. 1001, 157:36-158:40.[6] Thus, the '490 patent leaves a POSA wondering which domains can be used to identify Cpf1 proteins, let alone which might be predictive of activity in eukaryotes. Ex. 1003, ¶ 88.

Given the incredible breadth of the genus of Cpf1 effector proteins encompassed by the issued claims, and the lack of any coherent disclosure regarding structural features that are common to the members of the genus that might make them effective in eukaryotic cells, the exemplification of 3 enzymes that exhibit the claimed functionality is insufficient to establish that the inventors possessed the broad genus of all Cpf1 proteins encompassed by the claims. Ex. 1003, ¶¶ 63, 71-73, 89. When there is a substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *AbbVie*, 759 F.3d at 1300. And while there are no "bright-line rules" as to the number of representative species required to support a claimed genus, *Ariad*, 598 F.3d at 1351, the '490 patent's disclosure of only 3 exemplary species falling within the scope of

[6] Like Cpf1, the other two putative effector proteins discussed in the '490 patent, C2c1 and C2c2, also lack an HNH domain. '490 patent at 348:33-38; Ex. 1003, ¶ 88.

the incredibly broad claimed genus, with *no explanation* as to why these 3 are effective, is simply not sufficient to satisfy the written description for the broadly claimed genus.

2. Claims 12-14 Fail to Sufficiently Narrow the Scope of the Genus

Claims 12-14 each recite progressively narrower groups of bacterial species and strains from which the claimed Cpf1 effector proteins may be derived. Claim 12 limits the invention to Cpf1 effector proteins from the 51 bacterial species identified in Fig. 64, claim 13 to Cpf1 effector proteins from the 17 bacterial species tested in the Examples, and claim 14 to four specific Cpf1 effector proteins from four bacterial species. As discussed in § VI.C below, however, identification of a bacterial species as a potential source of a Cpf1 protein is not adequate description of the enzyme itself, since many bacterial species include multiple CRISPR loci with associated CRISPR effector proteins, which may or may not include Cpf1 proteins. Ex. 1003, ¶¶ 90-91. Taking just the first entry in Figure 64 (*Lachnospiraceae bacterium*), the '490 patent provides 13 different protein sequences for this bacterium alone that are between 1200-1500 amino acids long and could potentially correspond to a Cpf1 protein. Ex. 1003, ¶ 92. Thus, absent recitation of specific SEQ ID NOs in the claims, as required by 37 C.F.R. § 1.821(d) ("Where the description or claims of a patent application discuss a sequence that is set forth in the 'Sequence Listing' . . . reference must be made to the sequence by use of the

sequence identifier, preceded by 'SEQ ID NO:' in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application"), it is not clear which proteins fall within the scope of these claims, making it impossible to determine whether the inventors had possession of each and every Cpf1 effector protein encompassed by these claims.

Moreover, as discussed above, the '490 patent demonstrates activity in eukaryotic cells for Cpf1 effector proteins from fewer than 6% of the bacteria listed in Fig. 64, and fewer than 18% of those tested in the Examples. Ex. 1003, ¶ 93. And activity in eukaryotes was demonstrated only for three of the four tested proteins specifically recited in claim 14 (FnCpf1, LbCpf1, and AsCpf1). *Id.* The other enzyme (PaCpf1) was never even tested in eukaryotes, and showed little to no activity *in vitro*. *Id.* Thus, even if claims 12-14 were limited to the specific protein sequences that are disclosed in the specification, which they are not, these claims would still read on a relatively large number of enzymes that do not exhibit the claimed functionality in eukaryotic cells. Given the highly unpredictable nature of this field, such disclosures are insufficient to convey that the inventors possessed the full scope of Cpf1 proteins recited in these claims.

B. Ground 2: Claims 1-60 Fail to Comply with the Enablement Requirement for the Recited Genus of "Cpf1 effector protein[s]"

An enabling disclosure "must teach those skilled in the art how to make and use the *full scope* of the claimed invention without undue experimentation." *In re*

Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (emphasis added). To satisfy the statutory bargain underlying § 112, the scope of the claims must be "commensurate" with teachings in the specification. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1377 (Fed. Cir. 1999). "The scope of the claims must be less than or equal to the scope of the enablement." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

The need to engage in "an iterative, trial-and-error process to practice the claimed invention," where the specification provides "only a starting point, a direction for further research," precludes a finding of enablement. *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010). Similarly, where the skilled artisan "would need to assay each of at least tens of thousands of candidates" and the specification offered "no guidance or predictions about particular substitutions" that would lead to other effective members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013).

With regard to genus claims in unpredictable arts, the Federal Circuit has stated that the specification should demonstrate how to make and use species across the scope of the genus: "In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity

how to make and use other potential embodiments across the full scope of the claims." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). Thus, as is the case with the written description requirement, in order for patent claims to a genus to be enabled, the specification must enable a representative number of species falling within the scope of the genus. *Id.*

In *In re Wands*, the Federal Circuit identified the following eight factors to determine whether undue experimentation is necessary to practice the full scope of the claimed invention: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. 858 F.2d 731, 737 (Fed. Cir. 1988). Factors (4), (5), (6), and (8) have been discussed in §§ III.A, II, IV, and VI.A, respectively; the remaining factors are addressed below.[7]

1. The Amount of Direction or Guidance Presented and The Presence or Absence of Working Examples

While the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled, the inquiry is whether a POSA

[7] While factor (7) is also discussed above in the context of written description, we further discuss this factor below.

could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

For example, in *In re Vaeck*, the Federal Circuit affirmed the USPTO's nonenablement rejection of claims reciting heterologous gene expression in 150 genera of cyanobacteria. 947 F.2d 488, 495-96 (Fed. Cir. 1991). The court considered the rejection proper because cyanobacteria are a "diverse and relatively poorly understood group of microorganisms," with unpredictable heterologous gene expression, and the specification disclosed only nine exemplary genera. *Id.* at 496.

Similarly, in *Wyeth* the claims at issue covered "any structural analog of sirolimus that exhibits immunosuppressive and antirestenotic effects." 720 F.3d at 1384. As the case was decided on summary judgment, the court was required to accept the patentee's characterization of the state of the art. Thus, the Federal Circuit accepted that "a skilled artisan could ascertain whether a candidate rapamycin compound has the same macrocyclic ring as sirolimus," that "a skilled artisan could routinely determine whether a candidate has immunosuppressive and antirestenotic effects using the assays disclosed in the specification," and that "four compounds known to have the same macrocyclic ring as sirolimus at the effective filing date all

'*have* immunosuppressive and antirestenotic effects.'" *Id.* at 1384-85 (citation omitted) (emphasis in original).

Nevertheless, the Federal Circuit held that the specification did not enable the full scope of the claims. The court found "it would be necessary to first synthesize and then screen *each* candidate compound using the assays disclosed in the specification to determine whether it has immunosuppressive and antirestenotic effects." *Id*. at 1385 (emphasis in original). And, the court found there was no teaching in the specification concerning which modifications would likely be successful. *Id.* "[T]he specification . . . discloses only a starting point for further iterative research in an unpredictable and poorly understood field." *Id.* at 1386. "The resulting need to engage in a systematic screening process for each of the many rapamycin candidate compounds is excessive experimentation." *Id.*

The facts here are much more compelling than those at issue in *Vaeck* or *Wyeth*. As discussed above, the '490 patent fails to show activity for the vast majority of the claimed genus of Cpf1 effector proteins, having tested only 17 of the practically infinite number of molecules encompassed by the claims, and only showing activity for 3 of those proteins in eukaryotic cells. Ex. 1003, ¶ 101. As a result, the claims read on an unknowable number of inoperative embodiments. Of the 17 enzymes that were tested, only 11 exhibited activity *in vitro*, and *only 3* exhibited activity in eukaryotic cells, as required by the claims. *Id.* There is nothing

in the ’490 patent that guides a skilled artisan to predict *why* certain alleged Cpf1 proteins worked and why certain ones did not. *Id.* As a result, the patent fails to provide any means for identifying additional operative embodiments absent the precise type of trial and error irritative testing that was rejected by the Federal Circuit in *Wyeth*.

At best, the patent merely provides a “consensus sequence” (SEQ ID NO:1033) that those skilled in the art may use to identify other putative Cpf1 proteins having at least 80% sequence homology or identity to the consensus sequence. Ex. 1001, 35:37-39. But, as discussed above, sequence homology is not an adequate predictor of actual function in eukaryotic cells. *See* Reply 5 of Junior Party at 9, *Broad Inst., Inc. et al. v. Regents of the Univ. of California*, 2017 WL 657415 (PTAB 2017) (No. 106,048); Ex. 1003, ¶ 102. Further, those working in the field in 2015 recognized that *cas* genes evolve rapidly, which complicates the use of sequence homology for the identification and classification of CRISPR systems. Ex. 1013, 5, 7; Ex. 1003, ¶ 102. As a result, “distinct profiles for each subfamily [of CRISPR effector proteins] have to be generated” to effectively search for other family members. Ex. 1013, 10; Ex. 1003, ¶ 102. This was considered “a nontrivial task” because “fully automated identification of [CRISPR effector protein] subtypes in general is not currently feasible” and because sequence similarity searches “may result in a considerable number of false positives and false negatives,” including

proteins and domains that are not CRISPR systems. Ex. 1013, 7, 10; Ex. 1003, ¶ 102. Indeed, those in the field recognized that the analysis of CRISPR systems requires integration of "the most sensitive sequence comparison tools, protein structure comparison, and refined approaches for comparison of gene neighborhoods." Ex. 1013, 5, 7, 33; Ex. 1003, ¶ 102.

Because the '490 patent provides no meaningful guidance regarding a "distinct profile" for Cpf1 proteins, and because the techniques for determining such a profile were "nontrivial," undue experimentation would have been required to identify additional operative embodiments of the claimed invention (Ex. 1003, ¶ 103), particularly where even "routine" testing that was irritative and extensive was found not to be enabling in *Wyeth*. 720 F.3d at 1386.

2. The Predictability or Unpredictability of the Art and The Quantity of Experimentation Necessary

Even assuming the '490 patent provided sufficient guidance to enable one skilled in the art to identify additional putative Cpf1 proteins, the necessary experimentation to test each "hit" for functionality in eukaryotic cells was not considered routine, and even "routine" irritative testing that was extensive was found not to be enabling in *Wyeth*. 720 F.3d at 1386; *see also* Ex. 1003, ¶¶ 37-39, 105. To determine functionality in eukaryotic cells, a POSA must first determine the PAM requirements for the putative Cpf1-encoding gene. And as discussed below, such determinations are not trivial. Ex. 1003, ¶ 105. The gene must then be cloned

into an expression vector and transfected into eukaryotic cells along with a suitable guide RNA. *Id.* The cells must be grown to allow for protein expression and function, and then harvested and analyzed, for instance, by a SURVEYOR nuclease assay, to determine whether the Cpf1 protein resulted in cleavage. *Id.* Finally, putative indels detected by the SURVEYOR assay must be verified with sequencing data to ensure that false positive results are not taken as genuine cleavage events. *Id.* Such assays are the only way to definitively determine whether a given Cpf1 enzyme actually functions in eukaryotic cells. *Id.* And as indicated by the negative results obtained for the majority of the proteins tested in the '490 patent, whether a particular Cpf1 will demonstrate activity in eukaryotic cells is entirely unpredictable. Ex. 1003, ¶ 104. Such testing is well-beyond the sort of testing the Federal Circuit held in *Wyeth* led to a finding of non-enablement.

Further, as discussed above, a recent publication tested 16 putative Cpf1 proteins *in vitro* and in eukaryotic cells, and showed that only 10 were active *in vitro*, while only four were active in eukaryotic cells. Ex. 1006, 3. In addition, two Cpf1 proteins having almost 95% sequence homology surprised the authors by showing differing levels of activity in human cell assays. *Id.* at 3-4. The fact that the authors, several of whom are inventors of the '490 patent, failed to predict the difference in activity between two Cpf1 proteins sharing 95% identity provides strong evidence

of the unpredictability in the art regarding whether a particular Cpf1 protein will have activity. Ex. 1003, ¶ 104.

Indeed, Patent Owners themselves emphasized this unpredictability during prosecution. In responding to the Examiner's anticipation rejection, Patent Owners argued that the Schunder reference did not provide an enabling disclosure because it "fails to teach or suggest elements needed to engineer an operable *F. tulerenis* [sic] CRISPR-Cas system. For example, [the reference] fails to teach or suggest a *F. tulerenis* [sic] Protospacer Adjacent Motif (PAM), which would be required to design a functional guide." Ex. 1002, 6184. Thus, Patent Owners acknowledged that enablement of the claimed invention cannot be demonstrated absent disclosure of a functional PAM motif.

Patent Owners also emphasized the importance of PAM sequences for making and using CRISPR systems during the Cas9 interference proceedings before the Board. Specifically, Patent Owners argued that the complete lack of any discussion of PAM sequences in the interfering application demonstrates that "the inventors failed to describe information that persons of ordinary skill would have expected and required for making and using a CRISPR-Cas9 system capable of functioning against non-natural DNA targets . . . ." Opposition 4 of Junior Party at 2, *Broad Inst., Inc. et al. v. Regents of the Univ. of California*, 2017 WL 657415 (PTAB 2017) (No. 106,048); *see also id.* ("The complete lack of any discussion of PAM would

have indicated to persons of ordinary skill that the inventors failed to describe an invention configured for use against non-natural targets in a eukaryotic cell."). Thus, Patent Owners appear to understand that knowledge of the PAM requirements for a given effector protein is a pre-requisite to determining whether it will function in an exogenous system. Indeed, PAMs have been described as being "absolutely required to initiate crRNA-mediated DNA binding," even if the target sequence is completely complementary to the guide RNA. Ex. 1010, 1; Ex. 1012, 7-8, 14-15; Ex. 1003, ¶ 106.

Yet, there is no way—even *presently*—for one skilled in the art to examine a putative CRISPR effector protein sequence and arrive at its PAM requirements from the amino acid sequence itself, absent significant experimentation. Ex. 1003, ¶¶ 40-41, 107; Ex. 1012, 8. Indeed, significant variation in PAM site requirements has been observed among Cas9 effector proteins: while *Streptococcus pyogenes* Cas9 (SpCas9) prefers an NGG PAM, *Staphylococcus aureus* Cas9 (SaCas9) prefers an NNGRRT PAM. Ex. 1016, 6, 22-24, 46, 47-48, 49-50, 59-60; Ex. 1003, ¶ 108. In addition, modifications to amino acid residues within a given Cas9 effector protein can result in modified PAM site requirements for that enzyme. Ex. 1017, 5-9; Ex. 1003, ¶ 108. Thus, PAM requirements must be determined experimentally for each effector protein. But in 2015, the techniques available to make such determinations suffered significant shortcomings. Ex. 1012, 8.

The ’490 patent describes one method for determining the PAM requirements of a putative Cpf1 protein. Ex. 1001, 433:45-434:12. The assay requires sophisticated molecular biology experimentation and subsequent computational analysis. Ex. 1003, ¶ 109. In the inventors’ own use of the assay, they were successful in identifying PAM sequence requirements for only 9 of the 17 putative Cpf1 proteins tested. *See* Ex. 1001, Examples 5, 6, and 13; Ex. 1003, ¶ 109.

A 2017 publication from researchers including an inventor on the ’490 patent (Feng Zheng) attempted to engineer the AsCpf1 protein to have divergent PAM site requirements. Ex. 1018, 5. The native AsCpf1 protein utilizes a TTTV PAM motif. *Id.*; *see also* Ex. 1001, 549:65-67. The engineered Cpf1 proteins included S542R/K607R mutations resulting in a TYCV PAM requirement, and S542R/K548V/N552R mutations resulting in a TATV PAM requirement. Ex. 1018, 5; Ex. 1003, ¶ 110. Based on these teachings, one skilled in the art would conclude that amino acid differences at one or more of these positions may contribute to divergent PAM requirements. Ex. 1003, ¶ 110. Yet, an alignment of the sequences of 43 putative Cpf1 proteins, which represent only a small subset of the genus of Cpf1 proteins claimed in the ’490 patent, reveals significant diversity at each of these amino acid positions, suggesting possible differences in PAM requirements for these enzymes. Ex. 1018, 17-18; Ex. 1003, ¶ 110. Moreover, examination of the many alleged Cpf1 proteins that have already been deposited in publicly available

databases, and those that are still awaiting discovery, is likely to uncover still more diversity at amino acid positions that may affect PAM site requirements. Ex. 1003, ¶ 111.

In addition, the four amino acids mutated in Ex. 1018 likely are not the sole determinants of PAM site requirements for AsCpf1 or for other putative Cpf1 enzymes. Ex. 1003, ¶ 112. Indeed, the authors identified 64 residues within the AsCpf1 protein sequence as potentially contributing to PAM site requirements based on their analysis of the enzyme's structure. Ex. 1018, 21; Ex. 1003, ¶ 112. And additional amino acids in FnCpf1 have been shown to interact with the PAM site based on structural studies. Ex. 1019, 6-8; Ex. 1003, ¶ 112. Thus, the work that has occurred since the '490 patent filing has failed to identify either universal PAM sites for Cpf1 enzymes or methods to predict PAM site requirements for Cpf1 enzymes.

In view of this post-filing date evidence, it is clear that at the time the '490 patent was filed, the state of the art was such that PAM site requirements for a given Cpf1 enzyme could not be determined absent complicated and non-trivial experimental validation for each enzyme. And since Patent Owners acknowledged during prosecution that knowledge of the PAM requirements for a given effector protein is a pre-requisite to determining whether it will function in an endogenous system, these post-filing date analyses are strong evidence that undue experimentation would have been required to practice the claimed invention at the

time the ’490 patent was filed. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (explaining how it was proper for the court to examine “post-1987 reports to determine whether monocot cells were readily transformable in 1987”); *Amgen v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017) (noting that post-filing date evidence can be used to show that a patent does not disclose a sufficient number of representative species to support a claimed genus).[8]

3. Claims 12-14 Fail to Sufficiently Narrow the Scope of the Genus

For largely the same reasons that claims 12-14 do not sufficiently narrow the genus to overcome the written description deficiencies, these claims also do not overcome the deficiencies with respect to enablement. As discussed in § VI.C below, identification of a bacterial species as a potential source of a Cpf1 protein is not adequate identification of the enzyme itself, since many bacterial species include

[8] Claim 11, which recites that “the PAM comprises a 5’ T-rich motif,” provides no meaningful guidance regarding the PAM sequences that would be required to make and use the invention across the full scope of the claimed Cpf1 effector proteins. Absent additional information, such as sequence length and location of the thymine residues within the sequences, such a limitation is completely arbitrary. Ex. 1003, ¶ 113.

multiple CRISPR loci with associated CRISPR effector proteins, which may or may not include Cpf1 proteins. Ex. 1003, ¶ 114. Indeed, taking just the first entry on Figure 64, the '490 patent provides 13 different sequences that could correspond to potential Cpf1 proteins for this bacterium alone. Thus, undue experimentation would still be required to screen the genomes of each of the recited bacteria to identify putative Cpf1 proteins, and then test each of those putative proteins for activity in eukaryotic cells. Ex. 1003, ¶ 114.

This is especially true in view of the fact that the '490 patent demonstrates activity in eukaryotic cells for Cpf1 effector proteins from fewer than 6% of the bacteria listed in Fig. 64, fewer than 18% of those tested in the Examples, and only three of the four recited in claim 14. Ex. 1003, ¶ 115. Furthermore, the '490 patent demonstrates that Cpf1 proteins from at least 10% of the bacteria listed in Fig. 64 and 30% of the bacteria recited in claim 13 have *no activity* in eukaryotic cells. *ID.* And based on the lack of *in vitro* activity demonstrated in the patent, a POSA also would not expect activity in eukaryotic cells for another 11% from Figure 64, 35% from claim 13, and 25% from claim 14. *Id.* Thus, even if claims 12-14 were limited to the specific protein sequences that are disclosed in the specification, which they are not, these claims would still read on a relatively large number of inoperative embodiments. Given the highly unpredictable nature of this field, such disclosures are insufficient to enable the full scope of Cpf1 proteins recited in these claims.

4. Conclusion that the Claimed Invention Lacks Enablement

As set forth in detail above, the '490 patent discloses only a starting point for further iterative research in an unpredictable and poorly understood field. There is no way to determine which Cpf1 proteins would have the required activity without trial and error. Additionally, the patent provides PAM sequences for only 9 of the unknowable number of Cpf1 effector proteins encompassed by the claims, and demonstrates activity in eukaryotic cells for only 3 Cpf1 proteins out of the many hundreds of thousands of proteins covered by the claims. Given the limited number of successful examples of Cpf1 proteins disclosed in the '490 patent, the extreme unpredictability in the field, and the fact that the art is still in its infancy even today, the patent does not provide sufficient support for the broad scope of the issued claims. Ex. 1003, ¶¶ 64, 99-100, 116. Because the breath of the claims is not commensurate with the teachings in the specification, the claims should be held not enabled for their full scope.

C. Ground 3: Claims 1-60 Fail to Inform with Reasonable Certainty the Scope of "a Cpf1 effector protein"

A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Nautilus, Inc. v. Biosig. Instruments Inc.*, 134 S. Ct. 2120, 2129 (2014) (citations omitted). As a result, "[a] claim is indefinite if its legal

scope is not clear enough that a person of ordinary skill in the art could determine whether a particular composition infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003); *see also Dow Chem. Co. v. Nova Chems. Corp*., 803 F.3d 620, 633-34 (Fed. Cir. 2015) (holding claims indefinite where "there is no question that each of these four methods may produce different results").

Claims 1-60 require "a Cpf1 effector protein" or "one or more nucleotide sequences encoding a Cpf1 effector protein." Ex. 1001, 547:51, 547:64-65, 548:61-63, 549:12-13. Yet, none of the claims specifies any sequence or other structural information to identify such proteins. Ex. 1003, ¶ 123. At best, the claims merely list exemplary species from which such Cpf1 proteins may be obtained. Ex. 1001 549:47-67. However, such listings provide no meaningful guidance regarding the claimed proteins, as many bacterial species include multiple CRISPR loci with associated CRISPR effector proteins. Ex. 1003, ¶ 125. For example, claims 12 and 13 refer to *Francisella tularensis*, but that organism contains both a Cpf1 gene and a Cas9 gene. *See, e.g.*, Ex. 1020, 9-10, 18; Ex. 1004, 6-7, 14; Ex. 1005, 8; Ex. 1003, ¶ 125. Claims 12 and 13 also refer to *Smithella* sp., which contains a genomic locus with CRISPR arrays as well as a gene annotated as Cpf1 and another uncharacterized

gene. *See, e.g.*, Ex. 1005, 24; Ex. 1003, ¶ 125.[9] Thus, absent recitation of specific SEQ ID NOs, it is not clear which proteins are intended by the claims.

Nor does the specification provide any meaningful guidance regarding what is meant by the phrase "Cpf1 effector protein" in the claims, as this term is not sufficiently described in the patent or elsewhere in the prior art. The specification provides long listings of exemplary species from which the claimed Cpf1 proteins may be obtained, which include at least two species, *S. mutans* and *C. jejuni*, that do not appear to contain Cpf1 proteins at all. Ex. 1001, 7:43-9:3; Ex. 1003, ¶ 126. Specifically, BLASTP searches of the sequences provided in the patent for *S. mutans* (SEQ ID NOs:968-972) yield 100% matches to an anticodon nuclease, not a Cpf1 protein. Ex. 1003, ¶ 126. Similarly, BLASTP searches for the sequences from *C. jejuni* (SEQ ID NOs:362-365) yield 100% matches to a Cas9 protein. Ex. 1003,

[9] Although claim 14 refers to four specific enzymes (FnCpf1, PaCpf1, LbCpf1, and AsCpf1), the '490 patent provides a multitude of sequences that could correspond to those enzymes. Ex. 1003, ¶ 125. For instance, the Sequence Listing identifies at least 10 different sequences from *Francisella tularensis* that are between 1200-1500 amino acids long and could potentially correspond to FnCpf1, and at least 13 similarly-sized sequences for *Lachnospiraceae bacterium* that could potentially correspond to LbCpf1. *Id.*

¶ 126. While an applicant is entitled to be his own lexicographer, such definitions must be reasonably clear, deliberate, and precise. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Here, the sequences disclosed in the patent as allegedly corresponding to Cpf1 proteins from different species only serve to further confound the already unclear definition of "Cpf1 effector protein." A POSA is left guessing whether *S. mutans* and *C. jejuni* actually contain a Cpf1 protein, and which, if any, proteins from the other listed species may be a "Cpf1 effector protein."[10]

Aside from the ambiguous Cpf1 sequence information provided in the '490 patent, the only other information provided in the patent is: (1) that the disclosed "Cpf1-family proteins span a range of lengths between about 1200 and about 1500 amino acids" (Ex. 1001, 444:5-7; *see also* 29:49-53 (describing Cpf1 as "a large protein (about 1300 amino acids)"; Ex. 1003, ¶ 30); (2) a "synthetic consensus sequence" provided as SEQ ID NO:1033 in the Sequence Listing (Ex. 1003, ¶ 34); and (3) vague and ambiguous descriptions of various structural features that are present or absent in Cpf1 proteins (Ex. 1001, 344:44-53; Ex. 1003, ¶¶ 30-32, 36).

[10] Claims 12-14 do not include *S. mutans* and *C. jejuni*. Nevertheless, those claims are still indefinite for the reasons discussed herein, since merely listing an organism as being the source of a protein does not adequately describe the structure of that protein.

This information fails to clarify the definition of "Cpf1 effector protein." Ex. 1003, ¶ 123.

Regarding the disclosed lengths of Cpf1 proteins, ranges "between about 1200 and about 1500 amino acids" and "about 1300 amino acids" leave the reader entirely unclear as to how many amino acids must be present to define a Cpf1 protein. Ex. 1003, ¶ 124. And the "synthetic consensus sequence" and vague guidance that sequences having at least 80% identity (presumably to that consensus sequence) may be "Cpf1 effector proteins" (Ex. 1001, 35:37-39) is also unhelpful, since *none* of the Cpf1 sequences tested in the patent shares even 70% identity with the consensus sequence. As discussed above, BLASTP alignments of each of the sequences tested in the patent show just 25-60% identity to the consensus sequence. Ex. 1003, ¶ 33.

The remaining guidance provided in the patent is similarly unhelpful. The '490 patent identifies RuvC domains as the "only functional characterized domain" of Cpf1 proteins, yet RuvC domains are present in many diverse proteins. Ex. 1003, ¶ 127. In addition, the patent describes these RuvC domains as being contiguous in the Cpf1 sequence (Ex. 1001, 344:48-53), but as shown in Figure 100B (reproduced above), this description is incorrect: a bridge helix domain separates RuvCI from RuvCII, and a zinc finger domain separates RuvCII from RuvCIII. *Id.* The '490 patent also refers to "RuvC-like" domains in Cpf1, without explaining how, if at all, such domains differ from a *bona fide* RuvC domain. *See, e.g.*, Ex. 1001, 29:47-30:2,

343:36-39; 344:44-345:1, 346:6-15, 347:62-348:14, Example 11. Thus, the discussion in the '490 patent describing Cpf1 proteins as having a RuvC domain provides no meaningful guidance regarding the definition of "Cpf1 effector protein." Such a characterization leaves a POSA questioning whether any given protein having a RuvC domain is actually a "Cpf1 effector protein."

Further, as discussed above, the '490 patent states that Cpf1 proteins do *not* have an HNH domain. Ex. 1001, 344:48-50. The patent, however, then proceeds to discuss various modifications that may be made to the Cpf1 HNH domain. Ex. 1001, 158:8-64. While an applicant may disavow certain claim interpretations, "the specification [must] make[] clear that the invention does not include a particular feature . . . ." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). Here, however, the patent is internally inconsistent regarding the presence of an HNH domain in Cpf1 proteins, which only serves to further confound the definition of a "Cpf1 effector protein." A POSA would not know whether any given protein comprising an HNH domain infringes the claimed "Cpf1 effector protein." Ex. 1003, ¶ 128.

Finally, the '490 patent appears to classify Cpf1 proteins as both a Type V and a Type VI CRISPR enzyme system. *See*, *e.g.*, Ex. 1001, 2:42-56; 4:58-66; 29:12-33; 34:1-3; 34:54-35:15; 35:51-:36:5; 36:49-53; 36:65-37:22; 38:4-6; 38:17-19; etc.; *see also* Ex. 1003, ¶ 36. But Type VI nucleases (*e.g.*, C2c2/Cas13a): (1)

target RNA, whereas the ’490 patent teaches that Cpf1 targets DNA; (2) do not contain RuvC domains, whereas the ’490 patent describes RuvC as the “only functional characterized domain” of Cpf1 proteins; and (3) share virtually no sequence similarity to the “synthetic consensus sequence” provided as SEQ ID NO:1033. Ex. 1008, 6-8, 12-15; Ex. 1003, ¶ 129. Thus, because Type VI CRISPR enzyme systems encompass proteins that possess entirely different sequences and perform entirely disparate functions from Cpf1 proteins, the patent’s ambiguous classification of Cpf1 as a Type V or Type VI CRISPR enzyme system further confounds the definition of “Cpf1 effector protein.”

In view of the complete lack of any structure/function correlation disclosed in the ’490 patent for Cpf1 proteins, a POSA would be unable to interpret the metes and bounds of the “Cpf1 effector protein” recited in the claims. Ex. 1003, ¶¶ 65, 121-122, 130. As a result, the claims do not adequately apprise one skilled in the art of how to avoid infringement. For example, if a competitor uses a protein comprising a contiguous RuvC domain, does he infringe? What if the protein has an HNH domain and shares 80% sequence identity with SEQ ID NO:1033? Because the answers to these questions are not discernible from the four corners of the ’490 patent, claims 1-60 of the ’490 patent are indefinite under 35 U.S.C. § 112(b).

D. Ground 4: Claims 1-60 Fail to Comply with the Enablement Requirement for the Recited Genus of Systems "lack[ing] a tracr sequence"

Each of the issued claims requires that "the system lacks a tracr sequence." Proof of a negative, however, is difficult to establish. Ex. 1003, ¶ 95. Indeed, the '490 patent itself is internally inconsistent regarding whether the Cpf1 systems described therein utilize a tracrRNA. Ex. 1003, ¶ 55-58. For instance, the patent states that "Applicants identified two putative tracrRNAs" after conducting an RNAseq analysis of the *Francisella tularensis* Cpf1 locus, which are depicted in Figures 48-50. Ex. 1001, 425:3-8. Figure 54 further shows the localization of a "putative tracrRNA" in the FnCpf1 locus. Ex. 1001, 15:21-23. Yet elsewhere, the patent states that "we did not observe any robustly expressed small transcripts near the Francisella Cpf1 locus that might correspond to tracrRNAs" and that "after further evaluation of the FnCpf1 locus, applicants concluded that target DNA cleavage by a Cpf1 effector protein complex does not require a tracrRNA." Ex. 1001, 442:15-17, 14:60-63. Thus, only after performing a "further evaluation" using *in vitro* cleavage assays were Patent Owners able to conclude that a tracrRNA is not required for FnCpf1 to cleave DNA. Ex. 1003, ¶ 118.

Indeed, such assays are the only way to determine whether a given Cpf1 enzyme does or does not require a tracrRNA for cleavage. Ex. 1003, ¶ 119. But such assays are non-trivial. *Id.* They involve cloning the putative Cpf1-encoding

gene into an expression vector for a suitable organism (*e.g.*, *E. coli*, yeast, or human cells). *Id.* The cells must be grown to allow for protein production, then harvested and lysed. *Id.* The resulting protein lysate must then be incubated with crRNA, with and without putative tracrRNAs, along with a target DNA substrate. The DNA is then analyzed, for instance, by gel electrophoresis or DNA sequencing, to determine whether the *in vitro* reaction resulted in cleavage. *Id.* As in *Wyeth v. Abbott Labs.*, even though assays existed that could be "routinely use[d]" to test if putative Cpf1 proteins require a tracrRNA sequence, because the field was "unpredictable and poorly understood," "[t]he resulting need to engage in a systematic screening process is excessive experimentation." 720 F.3d at 1386.

Of the 17 putative Cpf1 proteins tested *in vitro*, only 11 demonstrated activity. Ex. 1003, ¶ 96. And of the 8 putative Cpf1 proteins tested in eukaryotic cells, only 3 demonstrated activity. *Id.* No reason is given as to why some of the putative Cpf1 proteins that were tested failed to cleave DNA in those assays. Given the low level of sequence identity conserved among the putative Cpf1 proteins described in the '490 patent, it certainly is conceivable that some of the tested proteins did not show activity because they, in fact, require a tracrRNA. *Id.* Some or all of the poorly conserved regions of Cpf1 proteins may, for example, be involved in protein interactions with tracrRNAs. *Id.* Indeed, we now know that another Type V

nuclease discussed in the '490 patent (C2c1) *does* require a tracrRNA despite its strong similarity to Cpf1. Ex. 1003, ¶¶ 58, 96.

The remaining question, therefore, is whether having to synthesize and screen each of an unknowable number of candidate Cpf1 effector proteins constitutes undue experimentation. In *ALZA Corp. v. Andrx Pharmaceuticals, LLC*, the Federal Circuit affirmed a judgment of nonenablement where the specification provided "only a starting point, a direction for further research." 603 F.3d 935, 941 (Fed. Cir. 2010) (internal quotation omitted). The court concluded that a POSA "would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the . . . specification." *Id.* Similarly, here, one skilled in the art would be required to perform "an iterative, trial-and-error process" involving a non-trivial assay that constitutes undue experimentation. Ex. 1003,

¶¶ 64, 99, 117, 120. Accordingly, claims 1-60 are not enabled for this additional reason.[11]

E. Ground 5: Claims 1-60 Fail to Comply with the Written Description Requirement for the Recited Genus of Systems "lack[ing] a tracr sequence"

For essentially the same reasons noted above, the challenged claims lack adequate written description for the claimed genus of systems lacking a tracr sequence. Ex. 1003, ¶ 94. Absent positive results from a DNA cleavage assay, one skilled in the art would not be able to conclude whether any given Cpf1 protein does or does not require a tracrRNA. Ex. 1003, ¶ 97. Yet the patent only provides such data for 11 putative Cpf1 proteins. *No conclusion* can be drawn regarding the unknowable number of other Cpf1 proteins encompassed by the claims based on the information provided in the '490 patent. *Id.*

[11] For largely the same reasons that claims 12-14 do not sufficiently narrow the genus to overcome the enablement deficiencies discussed in § VI.B, these claims also do not overcome the deficiencies discussed herein. Ex. 1003, ¶ 120 n.5. At best, the '490 patent demonstrates that 11 of the Cpf1 proteins encompassed by the claims lack a tracr sequence. Undue experimentation would be required to (1) identify putative CRISPR-Cpf1 systems in the remaining species, and (2) determine whether any of those systems also lack a tracr sequence. *Id.*

Based on the lack of knowledge and predictability in the art, a POSA would not conclude that the inventors were in possession of the genus of Cpf1 effector systems lacking a tracr sequence recited in the claims. Ex. 1003, ¶¶ 63, 71-73, 98. The disclosures set forth in the '490 patent provide no more than an invitation for those skilled in the art to experiment using the described technology to discover for themselves any additional Cpf1 effector systems that lack a tracr sequence. Ex. 1003, ¶ 98. But the mere description of methods for screening and identifying such systems is not sufficient to describe the structural identity of such systems. Indeed, the naked concept that Cpf1 effector systems do not require a tracr sequence is an unpatentable law of nature under 35 U.S.C. § 101. As the Patent Owner acknowledged during prosecution, it is only when that discovery is coupled with a sufficiently described artificial system that is capable of cleaving DNA for use in genetic modification can the claimed subject matter pass into subject matter that may be patentable. *See* Ex. 1002, 6182 (arguing patentability under 35 U.S.C. § 101 because "in contrast to any naturally occurring CRISPR system which targets a naturally occurring virus specific to its bacterial host cell, the claimed systems are

designed to target any nucleic acid of interest."). Accordingly, the inventors have not established that they possessed an invention as broad as recited in the claims.[12]

F. Ground 6: Claims 1-60 Lack Practical Utility

If the Board determines that the issued claims do not require a system in which the recited Cpf1 protein exhibits effector protein function in a eukaryotic cell, then the claims are unpatentable for lack of practical utility under 35 U.S.C. § 101.[13] Every patent claim must have some practical utility to satisfy the "useful" requirement of § 101, even if that utility is not specifically recited in the claim. *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed.

[12] For largely the same reasons that claims 12-14 do not sufficiently narrow the genus to overcome the written description deficiencies discussed in § VI.A, these claims also do not overcome the deficiencies discussed herein. Ex. 1003, ¶ 98 n.4. At best, the '490 patent demonstrates that 11 of the Cpf1 protein encompassed by the claims lack a tracr sequence. Such evidence is insufficient to establish that the inventors possessed tracr-deficient CRISPR-Cpf1 systems from any of the other recited bacteria. *Id.*

[13] In addition, claims 9, 10, and 29-55, which require the claimed systems to have functional activity in eukaryotic cells would become improper dependent claims under such an interpretation.

Cir. 2003). "The utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful and, accordingly, the subject matter of the claim must be operable." *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323-24 (Fed. Cir. 2009) (citation omitted). Further, "[i]f a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement." *Id*.

Here, the utility provided by the '490 patent for the *claimed* systems is for use as a tool in genetic engineering. For instance, the patent teaches that:

> The invention provides a method of *modifying sequences* associated with or at a target locus of interest, the method comprising delivering to said locus a non-naturally occurring or engineered composition comprising a putative Type V CRISPR-Cas loci effector protein and one or more nucleic acid components, wherein the effector protein forms a complex with the one or more nucleic acid components and upon binding of the said complex to the locus of interest the effector protein induces the modification of the sequences associated with or at the target locus of interest.

Ex. 1001, 2:42-51 (emphasis added). Although the patent also discloses an embodiment in which catalytically *inactive* effector proteins are used in detection methods such as fluorescence in situ hybridization (FISH) (Ex. 1001, 156:45-67), the Patent Owners expressly disclaimed such embodiments from the claims during

prosecution. Specifically, as discussed above in § V, Patent Owners' arguments in response to the Examiner's anticipation rejection emphasized that functional assays are critical to showing possession of the invention, and disavowed systems comprising catalytically inactive effector proteins from the scope of the claims. Accordingly, to be useful under § 101, the claimed subject matter must actually function in a eukaryotic cell to cleave DNA.

G. Ground 7: Claims 1-60 Would Have Been Obvious Over Schunder in View of the General Knowledge in the Art and Secondary References[14]

If the Board determines that the issued claims do *not* require a system in which the recited Cpf1 protein exhibits effector protein function in a eukaryotic cell and/or that the art *was* sufficiently predictable to enable the full scope of the claimed genus of Cpf1 effector proteins, then the claims would have been obvious in view of Schunder (Ex. 1004) for essentially the reasons advanced by the Examiner during prosecution. Schunder describes two different CRISPR systems in *Francisella tularensis* subsp. *novicida* U112, and identifies the presence of CRISPR systems in other *Francisella* strains. Ex. 1004, 6-7, 9. The second CRISPR system that Schunder identified in *Francisella tularensis* subsp. *novicida* U112 comprises a Cas9-like effector protein designated FTN1397 (Ex. 1004, 7-8), which has an amino acid sequence that is 100% identical to SEQ ID NO:51 in the '490 patent (Ex. 1003,

[14] The various secondary references are identified in the chart below.

¶ 134). Thus, Schunder discloses a system comprising each and every element of claims 1-4, except that the system claimed by the ’490 patent is engineered to function in a eukaryotic cell. Ex. 1003, ¶ 135.

But long before the ’490 patent was filed, those skilled in the art were using CRISPR systems to “easily and efficiently” edit genomes in eukaryotic and especially mammalian cells. *See, e.g.*, Ex. 1007, 7; Ex. 1003, ¶ 136. Indeed, the primary utility provided by the specification of the ’490 patent for the claimed systems is for use as a tool for genetic engineering, and in particular, for modifying eukaryotic genomes. For instance, the patent teaches that:

> The invention provides methods of genome editing or modifying sequences associated with or at a target locus of interest wherein the method comprises introducing a Cpf1 effector protein complex into any desired cell type, prokaryotic or eukaryotic cell, whereby the Cpf1 effector protein complex effectively functions to integrate a DNA insert into the genome of the eukaryotic or prokaryotic cell. In preferred embodiments, the cell is a eukaryotic cell and the genome is a mammalian genome.

Ex. 1001, 4:5-13.

To establish obviousness under 35 U.S.C. § 103, current precedent requires sufficient motivation to make the claimed invention with a reasonable expectation of success in achieving the sought after goal. *PAR Pharmaceutical, Inc. v. TWI*

Pharmaceuticals, Inc., 773 F.3d 1186, 1196 (Fed. Cir. 2014). Here, based on the prior art work with Cas9 systems, there would have been more than sufficient motivation for one skilled in the art to engineer a guide polynucleotide for use in the CRISPR system described in Schunder such that it hybridizes with a target sequence in a eukaryotic cell, as claimed in the '490 patent. Ex. 1003, ¶ 137. In addition, one skilled in the art would have been motivated to search for similar Cpf1-based CRISPR systems in other bacteria, as recited in claims 12 and 13 of the '490 patent. *Id.*

One would have been motivated to make such modifications to the systems described in Schunder, because those skilled in the art recognized that CRISPR systems "hold[] immense promise to transform basic science, biotechnology, and medicine." Ex. 1007, 7. Further, Schunder describes the sequence of certain of the very Cpf1 effector proteins that are disclosed in the specification of the '490 patent that can be used in the subject matter recited in claims 1-4 for genome modification in eukaryotic cells. Ex. 1003, ¶ 134. And if the claims require *no* functional activity and/or if the art was sufficiently predictable to describe and enable the *full scope* of the claimed genus of Cpf1 proteins, contentions which Petitioner believes are *not* accurate, then a POSA would have had a reasonable expectation of success in arriving at the invention recited in claims 1-60 by making such modifications to Schunder's system based on the general knowledge in the art at the time, as set forth

in the below chart. *See also* Ex. 1003, ¶¶ 66, 131-133.[15] Accordingly, if the claims are adequately described and enabled under 35 U.S.C. § 112, Petitioner contends that they are unpatentable in view of Schunder and the general knowledge in the art at the time.

Claim	*Teachings in the Art*
1. An engineered, non-naturally occurring system comprising a) a Cpf1 effector protein, and b) at least one engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and comprising a guide sequence, wherein the guide sequence is designed to hybridize with a target sequence in a eukaryotic cell; and wherein the system lacks a tracr sequence, the engineered guide polynucleotide and Cpf1 effector protein do not naturally occur together, and a complex of the engineered guide	Schunder provides the first disclosure of a functional CRISPR system in *F. tularensis* subsp. *novicida* comprising an effector protein having 100% sequence identity to SEQ ID NO:51 from the '490 patent, and a guide polynucleotide designed to form a complex with the Cpf1 effector protein and to hybridize with a target sequence in an invading pathogen. *See* Ex. 1004, 7, 10-13. In addition, while the '490 patent does not provide adequate disclosure to establish that all Cpf1 proteins do not require a tracr sequence for the reasons expressed in § VI.E, the '490 patent does disclose, in Examples 9 and 10, that the FTN1397 *F. tularensis*

[15] As set forth in the chart, none of the additional limitations provided in claims 1-60 provides patentable weight in view of the prior art. Indeed, most of the claims merely add limitations that represent well-known generalized knowledge concerning how to effect efficient genome modification of eukaryotic cells using such systems. Ex. 1003, ¶ 138.

Claim	*Teachings in the Art*
polynucleotide and Cpf1 effector protein does not naturally occur.	CRISPR-Cpf1 system described in Schunder inherently lacks a tracr sequence. Moreover, it was known that Type I and Type III CRISPR systems do not require a tracrRNA and instead rely on the CRISPR proteins for CRISPR RNA processing. *See* Ex. 1046, 3-6.
2. An engineered, non-naturally occurring system comprising a) one or more nucleotide sequences encoding a Cpf1 effector protein, and b) one or more nucleotide sequences encoding at least one engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and comprising a guide sequence, wherein the guide sequence is designed to hybridize with a target sequence in a eukaryotic cell; and wherein the system lacks a tracr sequence, the engineered guide polynucleotide and Cpf1 effector protein do not naturally occur together, and a complex of the engineered guide polynucleotide and Cpf1 effector protein does not naturally occur.	Schunder provides the first disclosure of a functional CRISPR system in *F. tularensis* subsp. *novicida* comprising one or more nucleotide sequences encoding an effector protein having 100% sequence identity to SEQ ID NO:51 from the ’490 patent, and one or more nucleotide sequences encoding a guide polynucleotide designed to form a complex with the Cpf1 effector protein and to hybridize with a target sequence in an invading pathogen. *See* Ex. 1004, 7, 10-13. In addition, while the ’490 patent does not provide adequate disclosure to establish that all Cpf1 proteins do not require a tracr sequence for the reasons expressed in § VI.E, the ’490 patent does disclose, in Examples 9 and 10, that the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder inherently lacks a tracr sequence. Moreover, it was known that Type I and Type III CRISPR systems do not require a tracrRNA and instead rely on the CRISPR proteins for CRISPR RNA processing. *See* Ex. 1046, 3-6.

Claim	*Teachings in the Art*
3. An engineered, non-naturally occurring vector system comprising one or more vectors comprising a) a first regulatory element operably linked to one or more nucleotide sequences encoding a Cpf1 effector protein; b) a second regulatory element operably linked to one or more nucleotide sequences encoding at least one engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and comprising a guide sequence, wherein the guide sequence is designed to hybridize with a target sequence in a eukaryotic cell; and wherein the system lacks a tracr sequence, components (a) and (b) are located on the same or different vectors of the system, the engineered guide polynucleotide and Cpf1 effector protein do not naturally occur together, and a complex of the engineered guide polynucleotide and Cpf1 effector protein does not naturally occur.	Schunder provides the first disclosure of a functional CRISPR system in *F. tularensis* subsp. *novicida* comprising a regulatory element operably linked to one or more nucleotide sequences encoding an effector protein having 100% sequence identity to SEQ ID NO:51 from the '490 patent, and a second regulatory element operably linked to one or more nucleotide sequences encoding a guide polynucleotide designed to form a complex with the Cpf1 effector protein and to hybridize with a target sequence in an invading pathogen. *See* Ex. 1004, 7, 10-13. While Schunder does not directly discuss a "first regulatory element" or a "second regulatory element," Schunder repeatedly describes the CRISPR system as "functional" and states that the leader sequence of the CRISPR array is necessary for spacer acquisition. *See* Ex. 1004, 6-8. An essential aspect of a "functional" CRISPR system is that the various components of the system (effector protein-encoding gene, gRNA, etc.) are expressed. Ex. 1003, ¶ 138 chart. Such expression requires a promoter, which is a regulatory element. *Id.* In addition, previous reports established that the leader sequence in CRISPR arrays contains a promoter. *See* Ex. 1070 at 1-3, 8-14. Thus, Schunder's discussion of "functional" CRISPR

Claim	*Teachings in the Art*
	systems inherently discloses the claimed regulatory elements. In addition, while the '490 patent does not provide adequate disclosure to establish that all Cpf1 proteins do not require a tracr sequence for the reasons expressed in § VI.E, the '490 patent does disclose, in Examples 9 and 10, that the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder inherently lacks a tracr sequence. Moreover, it was known that Type I and Type III CRISPR systems do not require a tracrRNA and instead rely on the CRISPR proteins for CRISPR RNA processing. *See* Ex. 1046, 3-6.
4. An engineered, non-naturally occurring system comprising a) a Cpf1 effector protein, or one or more nucleotide sequences encoding the Cpf1 effector protein, and b) at least one engineered guide polynucleotide designed to form a complex with the Cpf1 effector protein and comprising a guide sequence, wherein the guide sequence is designed to hybridize with a target sequence in a eukaryotic cell, or one or more nucleotide sequences encoding the at least one engineered guide polynucleotide; wherein the system lacks a tracr sequence, the engineered guide	*See* claims 1 & 2.

Claim	*Teachings in the Art*
polynucleotide and Cpf1 effector protein do not naturally occur together, and a complex of the engineered guide polynucleotide and Cpf1 effector protein does not naturally occur.	
5. The system according to claim 4, comprising the at least one engineered guide polynucleotide.	*See* claim 1.
6. The system according to claim 4, comprising the one or more nucleotide sequences encoding the Cpf1 effector protein.	*See* claim 2.
7. The system according to claim 4, comprising the Cpf1 effector protein.	*See* claim 1.
8. The system according to claim 4, comprising the one or more nucleotide sequences encoding the at least one engineered guide polynucleotide.	*See* claim 2.
9. The system according to claim 1, 2, 3, or 4, wherein the complex of the at least one engineered guide polynucleotide and the Cpf1 effector protein causes cleavage distally of the target sequence.	Presumably "target sequence" should read "PAM sequence," as cleavage occurs *within* the target sequence distal to the PAM. In addition, while the '490 patent does not provide adequate disclosure of the PAM sequences for the genus of Cpf1 proteins recited in the claims for the reasons expressed in § VI.B, Figure 104 of the '490 patent establishes that the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder inherently cleaves distal of the PAM sequence.
10. The system according to claim 9, wherein said cleavage generates a	The '490 patent establishes that staggered double stranded breaks with

Claim	*Teachings in the Art*
staggered double stranded break with a 4- or 5-nt 5' overhang.	4- or 5-nt 5' overhangs are an inherent property of the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder. *See, e.g.*, Ex. 1001, Fig. 104.
11. The system according to claim 1, 2, 3, or 4, wherein said target sequence is 3' of a Protospacer Adjacent Motif (PAM) and the PAM comprises a 5' T-rich motif.	While the '490 patent does not provide adequate disclosure of the PAM sequences for the genus of Cpf1 proteins recited in the claims for the reasons expressed in § VI.B, the '490 patent establishes that T-rich PAM sequences are an inherent feature of the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder. *See, e.g.*, Ex. 1001, Figs. 90, 100, 102.
12. The system according to claim 1, 2, 3, or 4, wherein the Cpf1 effector protein is of a bacterial species listed in FIG. 64A or FIG. 64B.	Schunder disclosed the CRISPR-Cpf1 system of *Francisella tularensis* 1, which is listed in FIG. 64A.
13. The system according to claim 12, wherein the bacterial species is selected from the group consisting of *Francisella tularensis* 1, *Prevotella albensis, Lachnospiraceae bacterium* MC2017 1, *Butyrivibrio proteoclasticus, Peregrinibacteria bacterium* GW2011_GWA2_33_10, *Parcubacteria bacterium* GW2011_GWC2_44_17, *Smithella sp.* SCADC, *Acidaminococcus sp.* BV3L6, *Lachnospiraceae bacterium* MA2020, *Candidatus Methanoplasma termitum, Eubacterium eligens, Moraxella bovoculi* 237, *Leptospira inadai, Lachnospiraceae bacterium* ND2006, *Porphyromonas crevioricanis* 3,	Schunder disclosed the CRISPR-Cpf1 system of *Francisella tularensis* 1.

Claim	*Teachings in the Art*
Prevotella disiens and *Porphyromonas macacae*.	
14. The system according to claim 1, 2, 3, or 4, wherein said target sequence is 3' of a Protospacer Adjacent Motif (PAM) and the PAM sequence is TTN, where N is A/C/G or T and the Cpf1 effector protein is FnCpf1, or the PAM sequence is TTTV, where V is A/C or G and the Cpf1 effector protein is PaCpf1p, LbCpf1 or AsCpf1.	Schunder disclosed the CRISPR-Cpf1 system of *Francisella tularensis* 1. While the '490 patent does not provide adequate disclosure of the PAM sequences for the genus of Cpf1 proteins recited in the claims for the reasons expressed in § VI.B, the '490 patent establishes that a TTN PAM sequence is an inherent feature of the FTN1397 *F. tularensis* CRISPR-Cpf1 system described in Schunder. *See, e.g.*, Ex. 1001, Figs. 90, 100, 102.
15. The system according to claim 1, 2, 3, or 4, wherein the Cpf1 effector protein comprises one or more nuclear localization signals.	Researchers have been using nuclear localization signals to target prokaryotic peptides expressed in eukaryotic cells to the cells' nuclei for decades. *See, e.g.*, Ex. 1021, 6, 9, 11. In addition, nuclear localization signals had been successfully added to Cas9. *See, e.g.*, Ex. 1022, Fig. 2B.
16. The system according to claim 2, 3, or 4, wherein the one or more nucleotide sequences encoding the Cpf1 effector protein is/are codon optimized for expression in a eukaryotic cell.	Researchers have been providing codon-optimized versions of genes to provide high-level expression of a protein in eukaryotic cells for decades. *See, e.g.*, Ex. 1023, 7, 9-11. In addition, codon optimization had been successfully applied to Cas9. Ex. 1024, 5-8.
17. The system according to claim 2, 3, or 4, wherein components (a) and (b) are on one vector.	It was well-known in the art that one or more nucleic acids can be placed on a single vector. *See, e.g.*, Ex. 1025, 8, 10. In addition, such techniques had

Claim	*Teachings in the Art*
	been successfully applied to Cas9. *See, e.g.*, Ex. 1022, Figs. 22A-B.
18. The system according to claim 2 or 4, wherein the one or more nucleotide sequences of components (a) and (b) are a single nucleic acid molecule.	*See* claim 17.
19. The system according to claim 1, 2, 3, or 4, wherein the eukaryotic cell is an animal or human cell.	Animal and human cells are merely specific categories of eukaryotic cells. In addition, use of CRISPR systems in human cells was known in the art for Cas9. *See, e.g.*, Ex. 1007, 10.
20. The system according to claim 1, 2, 3, or 4, wherein the eukaryotic cell is a plant cell.	Plant cells are merely specific categories of eukaryotic cells. In addition, use of CRISPR systems in plant cells was known in the art for Cas9. *See, e.g.*, Ex. 1022, Example 7.
21. The system according to claim 1, 2, 3, or 4, wherein the guide sequence is linked to a direct repeat sequence.	Figure 2 of Schunder (Ex. 1004, 8) shows that the guide sequence of the CRISPR-Cpf1 systems disclosed therein is linked to a direct repeat sequence.
22. The system according to claim 1, 2, 3, or 4, wherein the complex, engineered guide polynucleotide or Cpf1 effector protein is conjugated to at least one sugar moiety.	The conjugation of sugar moieties, such as N-acetyl galactosamine (GalNAc), to nucleic acid and protein molecules to facilitate their delivery into cells and improve their stability and immunogenicity was well known in the art. *See, e.g.*, Ex. 1026, [0064]; Ex. 1027, abstract, Fig. 1; Ex. 1028, 22-25.
23. The system according to claim 22, wherein the sugar moiety comprises N-	*See* claim 22.

Claim	*Teachings in the Art*
acetyl galactosamine (GalNAc) or triantennary GalNAc.	
24. The system according to claim 1, 2, 3, or 4, wherein the engineered guide polynucleotide comprises at least one modified nucleotide.	Modification of nucleotides has been known for decades. *See, e.g.*, Ex. 1029, 4-6. Further, POSAs routinely made use of modified nucleotides in genetic engineering, for example, to introduce site-specific cross-linking between and within nucleotide sequences. *See*, *e.g.*, Ex. 1030, 1-5, 14-16.
25. A delivery particle comprising the system according to claim 1, 2, 3, or 4.	The use of delivery particles, including exosomes, viral vectors, and polymeric nanoparticles made of low-molecular-weight polyamines and lipids, for introducing nucleic acids into eukaryotic cells is well known in the art. *See*, *e.g.*, Ex. 1031, 1-3; Ex. 1032, 9-10, 12-14; Ex. 1033, 7-8, 11-12; Ex. 1034, 5-8, 10-11. In addition, such techniques had been successfully applied to CRISPR systems. *See, e.g.*, Ex. 1035, 1-2, 8-10.
26. The delivery particle of claim 25, wherein the Cpf1 effector protein is complexed with the engineered guide polynucleotide.	The '490 patent establishes that this is an inherent property of the Cpf1 system disclosed in Schunder. *See, e.g.*, Ex. 1001, Examples 4, 6. A system in which the guide polynucleotide is not complexed with the effector protein would not have any utility. This was also well-established for Cas9. *See* Ex. 1071 at 1-2, 5-6.

Claim	*Teachings in the Art*
27. The delivery particle of claim 25, further comprising a lipid, a sugar, a metal or a protein.	*See* claim 25.
28. The delivery particle of claim 26, further comprising a lipid, a sugar, a metal or a protein.	*See* claim 25.
29. A method of modifying a locus of interest having a target sequence of a eukaryotic cell comprising delivering the system according to claim 1, 2, 3, or 4, to said locus of interest, wherein the guide sequence hybridizes with the target sequence whereby modification of the locus of interest occurs.	As discussed above, long before the '490 patent was filed, those skilled in the art were using CRISPR systems to "easily and efficiently" edit the genomes of eukaryotic cells. *See, e.g.*, Ex. 1007, 7. Indeed, this is the primary utility provided in the '490 patent for the clamed Cpf1 systems. *See*, *e.g.*, Ex. 1001, 4:5-13.
30. The method of claim 29, wherein the locus of interest is within a eukaryotic cell.	*See* claim 29.
31. The method of claim 30, wherein the cell is an animal cell.	*See* claim 19.
32. The method of claim 30, wherein the cell is an animal or human cell.	*See* claim 19.
33. The method of claim 30, wherein the cell is a plant cell.	*See* claim 20.
34. The method of claim 30, wherein said delivering the system comprises delivering one or more nucleotide sequences encoding the Cpf1 effector protein and one or more nucleotide	*See* claim 2.

Claim	*Teachings in the Art*
sequences encoding the at least one engineered guide polynucleotide.	
35. The method of claim 34, wherein the one or more nucleotide sequences are comprised within one or more vectors.	*See* claim 17.
36. The method of claim 34, wherein the one or more nucleotide sequences are comprised within a single vector.	*See* claim 17.
37. The method of claim 34, wherein the one or more nucleotide sequences molecules are delivered via delivery particles, vesicles, or one or more viral vectors.	*See* claim 25.
38. The method of claim 30, wherein the system or a component thereof is delivered via delivery particles, vesicles, or one or more viral vectors.	*See* claim 25.
39. The method of claim 38, wherein the system is delivered via delivery particles delivery vesicles, or one or more viral vectors.	*See* claim 25.
40. The method of claim 38, wherein the delivery particles comprise a lipid, a sugar, a metal or a protein.	*See* claim 25.
41. The method of claim 38, wherein the delivery vesicles are exosomes or liposomes.	*See* claim 25.
42. The method of claim 38, wherein the one or more viral vectors are one or more adenoviruses, one or more	*See* claim 25 (Ex. 1035 discloses adenovirus-delivered CRISPR/Cas9).

Claim	*Teachings in the Art*
lentiviruses or one or more adeno-associated viruses.	
43. The method of claim 30, wherein the Cpf1 effector protein comprises one or more nuclear localization signals.	*See* claim 15.
44. The method of claim 30, wherein the eukaryotic cell comprises a cell of a cell line or a cell of an organism and the locus of interest comprises a genomic locus of interest.	Cell lines and cells of an organism are merely specific categories of eukaryotic cells. In addition, a genomic locus is merely a specific category of a locus. Moreover, long before the '490 patent was filed, those skilled in the art were using CRISPR-Cas9 systems to "easily and efficiently" edit genomic loci of interest in eukaryotic cells from cell lines. *See, e.g.*, Ex. 1007, 7; Ex. 1022, Example 1.
45. The method of claim 30, wherein the eukaryotic cell is in vitro, ex vivo or in vivo.	*In vitro, ex vivo*, and *in vivo* are merely specific categories of eukaryotic cells. In addition, long before the '490 patent was filed, those skilled in the art were using CRISPR-Cas9 systems to edit genomic loci *in vitro*. *See* Ex. 1022, Example 1.
46. The method of claim 30, wherein the eukaryotic cell comprises a stem cell or stem cell line.	Stem cells are merely a specific category of eukaryotic cells. In addition, long before the '490 patent was filed, those skilled in the art had used CRISPR-Cas9 systems to edit stem cells. *See* Ex. 1022, 18:61-19:7.

Claim	*Teachings in the Art*
47. The method of claim 29, wherein the locus of interest is within a eukaryotic DNA molecule in vitro.	*See* claim 45.
48. The method of claim 33, wherein the method comprises obtaining a plant having a modified trait of interest from the plant cell.	Plant cells are merely specific categories of eukaryotic cells. In addition, use of CRISPR-Cas9 systems in plant cells was known in the art. *See, e.g.*, Ex. 1022, Example 7.
49. The method of claim 33, wherein the method comprises identifying a trait of interest in a plant obtained from the plant cell, wherein the trait of interest is encoded by a gene of interest.	*See* claim 48.
50. The method of claim 49, further comprising introducing the identified gene of interest into a plant cell or a plant cell line or plant germplasm and generating therefrom a plant containing the gene of interest.	*See* claim 48.
51. The method of claim 50, wherein the plant exhibits the trait of interest.	*See* claim 49.
52. The method of claim 29, wherein the modification comprises a strand break.	As discussed in Schunder, CRISPR nucleases produce double-stranded breaks. Ex. 1004, 6.
53. The method of claim 52, wherein the strand break comprises a staggered DNA double stranded break with a 4- or 5-nt 5' overhang.	*See* claim 10.
54. The method of claim 53, wherein the modification comprises integration	Integration of DNA into double-stranded breaks produced by certain

Claim	*Teachings in the Art*
of a DNA insert into the staggered DNA double stranded break.	nucleases was well known in the art. *See, e.g.*, Ex. 1036, 5, 7-8.
55. The method of claim 29, including adding a cation.	Cations, such as Mg^{2+} were known to be required for the action of Cas9. *See, e.g.*, Ex. 1037, 5-6.
56. A eukaryotic cell comprising the system of any one of claims 1-8.	Claim 56 merely recites a eukaryotic cell containing the system set forth in any of claims 1-8.
57. The cell of claim 56, wherein the eukaryotic cell is an animal cell.	*See* claim 19.
58. The cell of claim 56, wherein the eukaryotic cell is a human cell.	*See* claim 19.
59. The cell of claim 56, wherein the eukaryotic cell comprises a stem cell or stem cell line.	*See* claim 46.
60. The cell of claim 56, wherein the eukaryotic cell is a plant cell.	*See* claim 20.

VII. STATEMENT OF PRECISE RELIEF REQUESTED

As set forth above, claims 1-60 of the ’490 patent are unpatentable under one or more of 35 U.S.C. §§ 101, 103, and/or 112, so Petitioner requests review and cancellation of those claims.

VIII. GROUNDS FOR STANDING

Petitioner certifies that the ’490 patent is available for post grant review, and that Petitioner is not barred or estopped from requesting review on the grounds identified. This Petition is being filed within nine months of issuance.

IX. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party in Interest: Benson Hill Biosystems, Inc.

Related Matters: Petitioner is not aware of any judicial matter that would affect or be affected by a decision in this proceeding, but pending U.S. Patent Application Nos. 15/844,608 and 15/783,770 claim priority to the '490 patent.

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X. CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

This Petition complies with 37 C.F.R. § 42.24(d). As calculated by the "Word Count" feature of Microsoft Word 2010, it contains 16,748 words, excluding the words contained in the following: Table of Contents, Table of Authorities, Petitioner's Exhibit List, Mandatory Notices Under 37 C.F.R. § 42.8, Certification Under § 42.24(d), and Certificate of Service.

XI. CONCLUSION

Petitioner has established a reasonable likelihood that it will prevail in establishing that claims 1-60 of the '490 patent are unpatentable. The petition should be granted, post grant review should be instituted, and claims 1-60 should be found unpatentable and canceled.

Dated: July 17, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Petition for Post Grant Review of U.S. Patent No. 9,790,490**, Power of Attorney, and Exhibits 1001-1071 were served by Express Mail on July 17, 2018, in their entirety at the following correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,790,490.

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