No. 2024-1408

United States Court of Appeals for the Federal Circuit

REGENXBIO INC., THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,

Plaintiffs-Appellants,

v.

SAREPTA THERAPEUTICS, INC., SAREPTA THERAPEUTICS THREE, LLC,

Defendants-Appellees.

Appeal from the United States District Court for the District of Delaware,
Case No. 1:20-cv-01226-RGA

REPLY BRIEF OF REGENXBIO INC. AND THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

Susan E. Morrison
morrison@fr.com
FISH & RICHARDSON P.C.
222 Delaware Avenue, 17th Floor
Wilmington, DE 19801
Telephone: 302-652-5070

Deanna J. Reichel
reichel@fr.com
FISH & RICHARDSON P.C.
60 S. 6th St., Suite 3200
Minneapolis, MN 55402
Telephone: 612-335-5070

Attorneys for Plaintiff-Appellant REGENXBIO INC.

Amy M. Dudash
amy.dudash@morganlewis.com
MORGAN, LEWIS & BOCKIUS LLP
1201 N. Market Street, Suite 2201
Wilmington, DE 19801
Tel: (302) 574-3000

Julie S. Goldemberg
Julie.goldemberg@morganlewis.com
MORGAN, LEWIS & BOCKIUS LLP
2222 Market Street
Philadelphia, PA 19103
Tel: (215) 963-5095

Attorneys for Plaintiff-Appellant, The Trustees of the University of Pennsylvania

CERTIFICATE OF INTEREST

Counsel for Appellant REGENXBIO Inc. certifies the following:

1. Provide the full names of all entities represented by undersigned counsel in this case.

   REGENXBIO Inc.

2. Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

   N/A

3. Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

   BlackRock, Inc.

4. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

   Fish & Richardson P.C.: Casey M. Kraning, Brian Coggio, Kurt L. Glitzenstein, Jeremy T. Saks, John R. Lane, J. Peter Fasse

5. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

   No

6. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

   N/A

August 29, 2024 *_/s/ Susan E. Morrison_*
Susan E. Morrison

CERTIFICATE OF INTEREST

Counsel for Appellant The Trustees of the University of Pennsylvania certifies the following:

1. Provide the full names of all entities represented by undersigned counsel in this case.

The Trustees of the University of Pennsylvania

2. Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

N/A

3. Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

N/A

4. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

Morgan Lewis & Bockius LLP: Janice Logan, Eric Kraeutler

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N/A

August 29, 2024 */s/Julie S. Goldemberg*
Julie S. Goldemberg

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

INTRODUCTION

Sarepta asks this Court to affirm the first-ever decision finding claims covering laboratory-made genetically engineered cultured host cells patent ineligible under 35 U.S.C. §101, even though all parties agree those cells do not occur in nature. But the district court's decision contravenes precedent from the Supreme Court and this Court, and as pointed out by amici, will stifle innovation in the biotechnology industry if allowed to stand.

The University of Pennsylvania developed the claimed cultured host cells, which must contain a genetically engineered recombinant nucleic acid molecule that includes at least two components never found together in nature: one that encodes a particular portion of an adeno-associated virus (AAV) and another that comes from an organism other than AAV. Appellant REGENXBIO, in partnership with the University, uses the claimed cultured host cells in its research efforts to develop gene therapy product candidates for a variety of diseases. Appellants' partners also use licensed cultured host cells in the research and development of gene therapies, including several available to patients today. *See* https://www.regenxbio.com/who-we-are/pioneers-in-gene-therapy/.

This case was brought because Sarepta continues to use Appellants' groundbreaking invention, but refuses to take a license it initially sought.

Sarepta's aim in denigrating both Appellants and the invention here is to continue to use it for free. But it is Sarepta, not Appellants, that asks this Court to change the law. And it is Sarepta, not Appellants, that rewrites the claims to ignore many of their limitations. Under Supreme Court precedent, the '617 patent claims cover patentable subject matter, and the district court's decision to the contrary must be reversed.

ARGUMENT

The district court's decision, finding claims to laboratory made, genetically-engineered cultured host cells that are undisputedly not natural to be patent ineligible under section 101, fails to follow cases from this Court and the Supreme Court, including *Chakrabarty* and *Myriad*. Although the district court cited the "markedly different" standard from *Chakrabarty*, it failed to properly apply it, instead analogizing the claims here to those in *Funk*. Relying on *Funk*, the district court found, without scientific support, that "[t]aking two sequences from two different organisms and put[ting] them together is no different than taking two strains of bacteria and mixing them together." Appx10 (citation omitted). But under the district court's reasoning, neither the patent-eligible bacteria from *Chakrabarty*, which incorporated four naturally occurring DNA plasmids into a single bacteria, nor

the patent-eligible cDNA claims in *Myriad*, which spliced together pieces of natural DNA without changing their sequence, would be patentable.

In an attempt to support the outcome below, Sarepta rewrites both the claims and the law. Specifically, Sarepta ignores claim limitations, focusing on a single limitation to the exclusion of all others; it ignores the state of the law, crafting a new, unsupported test; and it ignores science, likening the claimed cultured host cells to mere "containers." Both the district court's decision and Sarepta's arguments here conflict with binding precedent. The district court's decision must be reversed.

I. SAREPTA'S ARGUMENTS FOCUS ON CHARACTERIZATIONS OF THE CLAIMS INSTEAD OF THE CLAIM LANGUAGE

Sarepta fails to address the '617 patent claim language as a whole, instead isolating a single limitation—a specific AAV sequence—and ignoring the remaining limitations. But this Court must address the full claim language. *Synopsys, Inc. v. Mentor Graphics Corp.*, 839 F.3d 1138, 1149 (Fed. Cir. 2016) ("The § 101 inquiry must focus on the language of the Asserted Claims themselves."). Sarepta's failure to consider all claim limitations is fatal to its arguments that the claims recite an unpatentable natural product under section 101.

A. The Claims of the '617 Patent Require More than the AAVrh10 Sequence

The district court's opinion and Sarepta's arguments regarding the claims' lack of structural differences from a natural product focus on a single limitation regarding AAVrh10 sequences, but the claims do *not* recite those sequences alone. It is the claimed composition "as a whole" that is the proper focus of the eligibility analysis, using the markedly different test. *See, e.g.*, *Bilski v. Kappos*, 561 U.S. 593, 611 (2010) ("*Diehr* emphasized the need to consider the invention as a whole, rather than 'dissect[ing] the claims into old and new elements . . . in the analysis.'" (citation omitted)); *Chakrabarty*, 447 U.S. 303, 309-10 (1980) (analyzing Chakrabarty's claimed bacteria in its entirety rather than looking at the individual DNA plasmids); *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1312 (Fed. Cir. 2016) ("[T]he claims are considered in their entirety to ascertain whether their character as a whole is directed to excluded subject matter" (quotation omitted)).

The asserted claims have two laboratory-created aspects: genetically engineered host cells grown in culture, which contain a genetically engineered recombinant nucleic acid molecule that has at least two components chemically spliced together, one that encodes the capsid sequence from AAVrh10 (or a sequence at least 95% identical to it) and one that includes a

heterologous, non-AAV sequence. Independent claim 1 of the '617 patent recites:

> A cultured host cell containing a recombinant nucleic acid molecule
>
> > encoding an AAV vp1 capsid protein having a sequence comprising amino acids 1 to 738 of SEQ ID NO: 81 (AAVrh.10) or a sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 81, wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

Appx384.

Sarepta brushes aside every limitation in the claims of the '617 patent except one: "a sequence comprising amino acids 1 to 738 of SEQ ID NO: 81 (AAVrh.10) or a sequence at least 95% identical." But the claims require much more than that sequence alone.

Claim 1 requires "a cultured host cell containing a recombinant nucleic acid molecule." Appx384. As explained in Appellants' opening brief, "recombinant" refers to genetic material from multiple sources chemically spliced together, Appx1320; Appx1238-1239, ¶ 74, and "recombinant DNA" refers to "[s]egments of DNA from one organism artificially manipulated or inserted into the DNA of another organism through gene splicing." Appx1322; Appx1238-1239, ¶ 74. The claims further define the necessary elements of the recombinant DNA molecule: the recombinant DNA molecule must be

composed of AAVrh10 DNA spliced to a "heterologous non-AAV sequence"—a sequence from a species other than AAV. Appx384; Appx1239-1240, ¶¶ 76-78. Such a molecule could not occur in nature (*see* Appellants' Opening Brief ("OB") at 9, 21), a point that Sarepta fails to address.

The claims also require that this recombinant nucleic acid molecule composed of DNA from multiple species chemically spliced together be incorporated into a cultured host cell. As detailed previously, both by Appellants and amici supporting Appellants' position, no natural cell could contain such a DNA molecule. OB at 22-23; D22 at 5-7; D27 at 21-27; D33 at 8-11. Sarepta does not dispute that. *See infra* at Section I.D.

Sarepta justifies ignoring these limitations by asserting that each was "conventional." Sarepta Br. at 41-45. But it cites to no case that slices up a claimed composition to determine whether parts of that composition would have been conventional on their own, and Appellants are aware of none. And as Appellants explained in their opening brief, Sarepta's approach would be a dangerous one; all compositions of matter consist of natural elements. OB at 2. Moreover, despite relying on testimony from the inventors for its conventionality argument, Sarepta ignores inventor testimony that the claimed combination of elements was "the essence of this application or this patent." Appx1021, Gao at 353:4-14 ("Q. So the techniques for assembling

recombinant nucleic acid molecules were conventional according to the '617 patent, right? A. The method itself, yes, but the content to put different sequence together, it's the essence of this application or this patent."). And Sarepta never addresses whether the claimed cultured host cell—including ***all*** of the required claim limitations—was known or conventional; it was not. Sarepta's failure to meaningfully deal with these claim limitations is fatal to its argument.

B. Sarepta's Experts Admitted that the Claimed Invention as a Whole is Not Natural

Sarepta is forced to isolate a single piece of the claim because it has no argument that the claimed invention as a whole is a natural product. Sarepta does not address, or even acknowledge, that its experts admitted that the claimed cultured host cells are a non-natural product, even though Appellants relied on those admissions before the district court and in their opening brief here. OB at 9-10; Appx398-99; Appx493. Sarepta's failure to deal with these admissions is particularly striking given the space it spends detailing irrelevant facts or lobbing unwarranted slights at Appellants.[1]

[1] Appellants do not spend time here addressing facts that do not relate to the issues on appeal. Appellants do note that many of Sarepta's irrelevant statements are untrue. For example, Sarepta argues that Appellants filed the '617 patent in "an attempt to ensnare" Sarepta's sequence based on "the

When questioned at their depositions, Sarepta's experts freely admitted that both the recombinant nucleic acid molecules and cultured host cells described in the claims are not natural. Sarepta expert Dr. Gabor Rubanyi testified that the recombinant nucleic acid molecules of the asserted claims were not naturally occurring:

> Q. Would you agree that a recombinant nucleic acid molecule that contains an AAV sequence and a heterologous non-AAV sequence is not naturally occurring?
>
> THE WITNESS: Yes, I agree.

Appx746-747, 252:20-253:1 (objections omitted). Another Sarepta expert, Dr. Mark Kay, testified that the cultured host cells required by the claims are not found in nature:

> Q. Do the cultured host cells with the features required by the asserted claims exist in nature?
>
> THE WITNESS: No.

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inclusion of the 'at least 95% identical' element." Sarepta Br. at 14, n.4. But the '617 patent is a continuation application in a family of patents with priority dating to 2002, and the limitation requiring 95% identity to the AAVrh10 sequence had been included in patents in that family since at least February 2013, when U.S. Patent Application No. 2013/0045186 published containing that limitation.

Appx725-726, 195:25-196:4 (objections omitted). Dr. Rubanyi agreed. Appx744-745, 250:24-251:11.) These admissions are fatal to Sarepta's argument, and Sarepta does not even address them.

C. The Inventors' Work Was More than Just Isolating a Sequence

Failing to address its experts' admissions, Sarepta attempts to support its reading of the claims by relying on excerpts of inventor testimony, but it ignores the full scope of that testimony. It also ignores the portions of the '6017 patent specification that show the inventors did far more than isolate sequences.

The '617 patent discusses the newly-discovered sequences, and goes on to describe the inventors' work using those sequences to create cultured host cells. After isolating the AAV sequences, the inventors chemically spliced (created new chemical bonds between) the DNA encoding the AAVrh10 viral capsid proteins (the proteins that form the shell of the AAV virus) to DNA from organisms not naturally associated with AAVrh10 to create a recombinant DNA molecule. *See, e.g*., Appx174, 17:36-18:8; Appx1320. The University inventors then took that human-created recombinant DNA molecule and incorporated it through genetic engineering into a host cell grown in culture. *See, e.g.*, Appx174, 18:8-67.

Dr. Gao, one of the inventors of the patent, testified consistently. He repeatedly said that the invention of the '617 patent was not just the discovery and isolation of the rh10 sequence but the creation of a previously unknown cultured host cell. Specifically, Dr. Gao explained his understanding of the patent:

> But I think if I understand this patent correctly, it's not only the rhesus 10 sequence itself. It's recombination or engineering rhesus 10 cap sequence together with AAV2 sequence and other non-AAV sequence as well as use those in cells for engineering monoclonal cloning in bacteria and testing for packaging and formation of a variant in mammalian cells and testing its capability of transducing mammalian tissues.

Appx944-945, 54:22-55:11; *see also* Appx945, 55:12-19; Appx951, 75:3-13; Appx955, 79:5-12; Appx958, 93:7-20; Appx967, 102:9-17; *see also* Appx850-51, 22:24-23:8 (inventor Dr. Wilson testifying that "through the development of the vector there were a lot of manipulations to that [rh10] sequence that ultimately led to its use as a vector"). Moreover, Dr. Gao testified that the inventors' work developed a new recombinant nucleic acid construct that was used to create a new, never before known cultured host cell:

> Q. And when you talk about cells -- mammalian or bacteria cells that can be used to form a viral vector, mammalian and bacterial cells were known in the art at the time of the '617 patent that were used to make viral vectors; isn't that correct?
>
> A. That was -- those were used for cloning of recombinant DNA by bacteria and used mammalian cells for viral vector packaging.

> Those were common practice at the time but not before our work -- not used for this recombinant construct I just described. We are the first one doing so.

See, e.g., Appx941, 48:2-20; *see also* Appx942, 49:10-21. Sarepta's arguments that the inventors "conceded" that their invention was the isolation of a natural sequence is belied by both the '617 patent and inventor testimony.

D. The File History Supports Appellants' Arguments

Sarepta next attempts to justify ignoring certain claim limitations by mischaracterizing the file history, asserting that Appellants' arguments were rejected by the examiner. Sarepta is mistaken. The file history fully supports Appellants' position.

Sarepta's assertion that many of the claim limitations are just another way of saying an "isolated" AAVrh10 sequence conflicts with both the plain language of the claims and the file history. The file history shows that the examiner saw a difference between claims to "isolated" DNA, which were not patentable, and patent-eligible claims to recombinant DNA molecules composed of AAV and non-AAV DNA (such as a non-viral plasmid) or cultured host cells.

During prosecution, the examiner rejected a number of claims under 35 U.S.C. § 101 for reciting only "a recombinant nucleic acid molecule . . . encoding an AAVrh10 vp1 capsid protein" having a particular sequence, with

nothing more required in the claim. Appx650-653. In these claims, the examiner found that the word "recombinant" alone was insufficient to render the claims patentable because the claims only required DNA from AAV, and the word "recombinant" did not "distinguish the products [of the rejected claims] from naturally occurring nucleic acids or proteins." Appx654. However, claims specifying that the recombinant DNA molecule was composed of *both* AAV viral DNA and non-AAV DNA, such as non-viral plasmid DNA, were allowed because that molecule could not occur in nature. Appx655 (stating that "plasmid" was interpreted as a "non-viral vector" and objecting to claims specifying a "plasmid" only because they "depend[] on rejected claims").

The examiner rejected claims reciting only a "host cell" as unpatentable because they could read on a human organism. Appx650. But the examiner allowed the claims that required "isolated host cells" or "cultured host cells," like the asserted claims, because they did not cover natural products under section 101. *See* Appx650; Appx665-671. The file history does not support Sarepta's argument that the claims of the '617 patent recite unpatentable subject matter.

II. SAREPTA'S ARGUMENTS REWRITE THE LAW

The parties appear to agree that *Chakrabarty's* markedly different standard is the proper test for determining the eligibility of the '617 patent claims.[2] Both Sarepta and the district court, however, fail to properly apply that test in their analyses.

A. The '617 Patent Claims Have "Markedly Different" Structure under *Chakrabarty's* Test

Chakrabarty used the natural process of bacterial conjugation to develop "a new strain of bacteria by the incorporation in a single cell, by transmission thereinto of a plurality of compatible 'plasmids,' of a capacity for simultaneously degrading several different components of crude oil with the result that degradation occurs more rapidly." *In re Chakrabarty*, 571 F.2d 40, 41(C.C.P.A. 1978), *aff'd sub nom. Chakrabarty*, 447 U.S. 303 (1980). Essentially, Chakrabarty combined "four different plasmids," which were themselves natural but appeared in nature only in different bacteria, into a

[2] Sarepta continues to discuss step two of the *Mayo* framework, which is irrelevant because the claims are not directed to a natural product at step one. *See Core Wireless Licensing S.A.R.L. v. LG Elecs.*, 880 F.3d 1356, 1361 (Fed. Cir. 2018). And, while not necessary to decide this case, there is an open question as to whether the step two analysis is even applicable to product claims in light of *Chakrabarty's* markedly different framework. *See ChromaDex, Inc. v. Elysium Health, Inc.*, 59 F.4th 1280, 1285-86, 1286 n.5 (Fed. Cir. 2023) ("[I]n one prior case, we analyzed composition of matter claims under *Myriad* and *Chakrabarty* but analyzed method claims under *Mayo*.").

single bacterium. *Chakrabarty*, 447 U.S. at 305 & n.1. This new bacterium was markedly different from anything found in nature.

Chakrabarty's new bacteria, like the cultured host cells here, was "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity having a distinctive name, character, and use." *Id.* at 309-10 (cleaned up). Both claimed products have "markedly different" structural characteristics from any natural product (any natural bacteria in Chakrabarty or any natural DNA or cell here) and thus are patent eligible under section 101. *Id.* at 310.

Sarepta ignores the similarities between the claims here and the *Chakrabarty* claims, and ignores that the claimed cultured host cell containing a genetically engineered recombinant DNA molecule is even further removed from anything found in nature than the patent-eligible bacterium in *Chakrabarty* containing a mixture of natural plasmids. Instead, Sarepta focuses only on how the *Chakrabarty* claims recite "each of said plasmids providing a separate hydrocarbon degradative pathway.'" *Id.* at 305; Sarepta Br. at 35 n.6. While Sarepta suggests that this requirement claims a specific function, it is readily interpreted as simply specifying which bacterial plasmids to choose—those with separate, non-inhibitive pathways. And Sarepta cites no authority to suggest that the new structure that Chakrabarty

created by combining multiple plasmids into a single bacterium was not alone sufficient to impart eligibility. Indeed, the Supreme Court discussed both the structural and functional differences of the claimed product as compared to the natural bacteria. Those structural differences cannot simply be ignored.

B. Sarepta's Flawed Reading of the Claims Infects Its Analysis of the Case Law

Sarepta's misreading of the claims to isolate a single element infects its analysis of the case law. Because it does not address the claims as a whole, Sarepta's analogy to the isolated DNA claims in *Myriad* falls flat. Those claims merely covered "[a]n isolated DNA coding for a BRCA1 polypeptide," having a specified amino acid sequence. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 584 (quotation omitted). Finding that claim and others like it would give Myriad "the exclusive right to isolate an individual's BRCA1 and BRCA2 genes," the Supreme Court held the isolated DNA claims patent ineligible. *Id.* at 585. There is no dispute that, under *Myriad*, if the '617 patent's claims simply recited isolated AAVrh10 DNA, they would be ineligible. But that is not what the claims recite. Instead, they claim a cultured host cell that is genetically engineered to incorporate an artificial DNA molecule, wherein AAVrh10 DNA is chemically spliced to heterologous non-AAV DNA. The claims do not give anyone the "exclusive right to isolate" the

AAVrh10 DNA and do not raise the concern that led to the finding of ineligibility in *Myriad*.

Sarepta relies repeatedly on the Supreme Court's analysis in *Myriad* that the isolated DNA is "not rendered patentable simply because it has been separated from the 'surrounding genetic material,'" (Sarepta Br. at 27 (quoting *Myriad*, 569 U.S. at 596)), arguing that the additional claim limitations in the '617 patent claims merely relate to isolating naturally occurring rh10 sequences (Sarepta Br. at 28).

But Sarepta's argument is both irrelevant and without support. The '617 patent does not claim the AAVrh10 DNA separated from surrounding genetic material—the mere breaking of chemical bonds. *Myriad*, 569 U.S. at 593. Instead, the claims require the creation of *new* chemical bonds and a new molecule, by chemically splicing AAVrh10 DNA to heterologous non-AAV DNA —a composition that does not occur in nature—and incorporating that new molecule into a cultured host cell. *See supra* Section I.A. These additional elements result in the creation of an entirely new, non-naturally occurring DNA molecule, which is then incorporated into a new, non-naturally occurring cell, which is the product that the claims recite.

The Supreme Court's analysis of the cDNA claims in *Myriad* is closer to the situation here than the isolated DNA claims. Even though cDNA consists

entirely of natural DNA sequences, with intron segments removed, the Supreme Court held that it was patentable because "the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived." *Myriad*, 569 U.S. at 595. Sarepta cites to the Supreme Court's statement that a "very short series of DNA may have no intervening introns to remove" and thus "a short strand of cDNA may be indistinguishable from natural DNA." *Id.* at 595; Sarepta Br. at 30. But the claims *do not* recite short strands of AAV DNA that are indistinguishable from their natural state. Again, they recite cultured host cells that incorporate a recombinant DNA molecule that includes AAVrh10 DNA chemically spliced to heterologous non-AAV DNA. As Sarepta's experts admitted, those cultured host cells were originally created by University scientists, and undisputedly do not occur in nature. *See supra* Section I.D.

As with cDNA, "the lab technician unquestionably creates something new" in making the claimed cultured host cells, which are "distinct" from the various natural sequences they incorporate. *See Myriad*, 569 U.S. at 595. The Supreme Court's analysis of the cDNA claims also undermines Sarepta's argument that courts have never found the fact that a product is "non-natural," involves "human intervention," and is made "in the laboratory" to be

relevant to patent eligibility. Sarepta Br. at 24. Plainly, the fact that human intervention created a non-natural product in the laboratory was "relevant" to the eligibility analysis for the cDNA claims. Moreover, Sarepta's argument that "[m]erely combining two naturally occurring DNA sequences in the same 'cultured host cell' container, without more, does not result in any 'markedly different characteristics'" (Sarepta Br. at 20) is contradicted by the analysis of the cDNA claims in *Myriad*. Those claims, which "merely" combined two or more naturally occurring DNAs (i.e., two sections of DNA that originally surrounded an intron) into a single molecule, were found patentable even though the natural DNA sequences were unchanged. *See Myriad*, 569 U.S. at 594-95.

This Court's analysis of the eligible method claims in *AMP* is also more relevant to the claims at issue than the isolated DNA claims of *Myriad*. Claim 20 in *AMP* was a method claim requiring the use of a non-natural host cell, like the cultured host cells in the asserted claims, transformed with an altered *BRCA1* gene. Sarepta spends barely a paragraph dealing with this Court's analysis of that claim, which was not appealed to the Supreme Court. Sarepta argues that the use of the word "transformed" in the *AMP* claim instead of the word "contains" in the claims here makes all the difference. Sarepta Br. at 39. But as Sarepta itself argues, the section 101 analysis does not depend on the

"draftman's art." *Id.* at 7, 48. And its argument also ignores that the eligible claims of *Chakrabarty* also use the word "contain" to cover its transformed cells. *Chakrabarty*, 447 U.S. at 305 (quoting claims that recite "bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway"). Plainly, the claimed cultured host cells are "transformed" because they are engineered to incorporate DNAs that do not occur together in nature. The '617 patent's non-natural cultured host cells are just as "transformed" as the host cells that imparted patentability to AMP's claim 20 and should similarly lead to eligibility here. *Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Off.*, 689 F.3d 1303, 1336 ("The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent eligible.").

C. Sarepta's Arguments Brush Aside Markedly Different Functional Differences

Because the cultured host cells of the asserted claims are markedly different in structure from a natural product, there is no requirement that they *also* be markedly different in function to show eligibility. The analysis of the cDNA claims in *Myriad* demonstrates this. After finding that the claimed cDNA non-natural based on structural differences from natural DNA, the

Supreme Court did not go on to analyze whether it is also had functional differences. In *Myriad*, the markedly different structure alone rendered the claims eligible, as Sarepta concedes. Sarepta Br. at 32 (noting that *Myriad* "does not address functional differences because it was not necessary given the 'markedly different characteristics' already present in the structure of cDNA"). No function is recited in the patent-eligible cDNA claims in *Myriad*. *Myriad*, 569 U.S. at 584.

But as detailed in Appellants' opening brief (OB at 14, 35-37), the claimed cultured host cells of the '617 patent are also markedly different in function from any natural product, providing an additional reason why they are patent eligible. Bacterial host cells covered by the claims can make multiple copies of the recombinant plasmid containing the viral AAVrh10 capsid gene, and can proliferate to make more host bacterial cells and thus many copies of that plasmid. Appx1167, ¶¶ 50-53. No naturally occurring bacteria can perform that function. Appx1230-1231, ¶ 53.

Those plasmids can be collected, concentrated, and transfected into the mammalian cultured host cells, also covered by the claims, and used in a variety of ways. The mammalian host cells can be used to manufacture AAV gene therapies which contain the AAV viral shell (i.e., the AAV capsid) and a gene of interest, and are administered to a patient. Appx1231, ¶ 54;

Appx1240, ¶¶ 80-81. But beyond the gene therapy use, the only one that Sarepta addresses, the mammalian host cells can also be used to manufacture populations of empty AAV capsids that do not contain a gene of interest, which can be used for applications such as vaccination and serotyping. Appx1231-1233, ¶ 55. Additionally, the cultured host cells can be used to make isolated populations of capsid proteins that can be used in laboratory and research applications. Appx1233, ¶ 56; Appx1290, ¶ 393.

Faced with these undisputed facts, Sarepta takes two different approaches: (1) rewriting the legal test to require that the markedly different functional characteristics be the "defining feature" of the claimed invention; and (2) alleging that Appellants waived reliance on functions other than gene therapy. Sarepta is wrong on both counts.

1. Sarepta's "Defining Features" Test Is Unsupported by the Case Law and Was Not Used by the District Court

Sarepta relies upon its "defining features" test to assert the claims are not patent eligible, but that test is wholly unsupported in the law. Indeed, the words "defining features" neither appear in any case Sarepta cites nor in the district court's opinion. Sarepta's broad argument that "features that are not claimed are irrelevant" to the section 101 analysis cites to *American Axle*, which does not perform a markedly different analysis. The full quote from

American Axle states that "features that are not claimed are irrelevant as to step 1 or step 2 of the *Mayo/Alice* analysis" and cites to other cases in that same context. *Am. Axle & Mfg., Inc. v. Neapco Holdings LLC*, 967 F.3d 1285, 1293 (Fed. Cir. 2020). The relevant analysis here is the "markedly different" analysis discussed in *Chakrabarty* to determine whether a claimed composition is a natural product or not, by looking for such "markedly different" characteristics and the "potential for significant utility" of the claimed composition.[3]

Sarepta relies primarily on *Chromadex* as support for its argument that the markedly different functions have to be "defining features" of the claims, in other words, that the features must be specifically claimed. Sarepta Br. at 35. But the issue in *Chromadex* was that the increased bioavailability was the only alleged "marked" difference; there were *no* structural differences between the claimed composition and natural milk. As this Court explained, "[t]he claimed compositions remain indistinguishable from natural milk because, other than separation from some other components, the isolated NR is no different structurally or functionally from its natural counterpart in

[3] Sarepta criticizes Appellants for stating that the standard is whether a claimed composition has the "potential for significant utility." Sarepta Br. at 37. But that language is the Supreme Court's, not Appellants'. *Chakrabarty*, 447 U.S. at 310.

milk." *Chromadex*, 59 F.4th at 1284. In that situation, when the claim as written has no structural differences from natural milk, it is logical that there would have to be a particular function different from milk to make the claims patent eligible. But this is not that situation—the claims do not read on any natural product, contrary to the district court's unsupported conclusion. *See supra* Section I.D; Appx9-10, Appx12. Instead, as Sarepta's experts admitted, the claimed cultured host cells do *not* occur in nature. *See supra* Section I.D.

Relying upon its "defining features" test, Sarepta addresses only the gene therapy function, ignoring all the other markedly different potential functions for the claimed cultured host cells, arguing that because not all the claimed host cells are useful for gene therapy, that function is not relevant to the eligibility analysis. But Sarepta cites nothing that requires that every possible embodiment that falls within the claims must have the *same* markedly different function. The other functions for other embodiments of the claimed cultured host cells are also markedly different from the natural sequences on their own. *See* Appx1230-1233.

Moreover, Sarepta fails to recognize that functions that are properties of the claimed cultured host cells can be considered even if they are not specifically claimed because a composition and its properties are one and the same. *See In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) ("From the

standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."). And while it is true that the potential for use in gene therapy is not a property of *all* embodiments of the claims, Sarepta does not even address the other markedly different functions that Appellants raised, which are also properties of various embodiments of the claims.

Sarepta also cites to *In re Roslin*, a case not cited to or by the district court, as alleged support for its "defining features" test. But *Roslin* does not discuss functional differences at all. *Roslin*'s holding that the claimed composition—Dolly the cloned sheep—lacked any marked difference from the natural product—a natural sheep—rests on the fact that "Dolly herself is an exact genetic replica of another sheep and does not possess 'markedly different characteristics from any [farm animals] found in nature.'" *In re Roslin Inst. (Edinburgh)*, 750 F.3d 1333, 1337 (Fed. Cir. 2014). The marked differences argued by the patentee were structural, not functional—phenotypic characteristics and mitochondrial DNA. But unlike the present case, neither of those structural differences were claimed, *id.* at 1338, so the claim covered an organism that is "an exact genetic replica" of something natural. *Roslin* thus provides no support for Sarepta's requirement that a markedly different function must be an expressly recited, "defining feature" of the claim.

Finally, though Sarepta relies on the unsupported "defining features" test it created, Sarepta accuses Appellants of not applying the proper test for patent eligibility. Sarepta Br. at 24-26. In so doing, Sarepta ignores the three amicus briefs submitted in support of Appellants' view of the law, and instead dismisses the legal and policy arguments from amici in a footnote. *Id.* at 61 n.10. Sarepta fails to address the fact that amici, including the AIPLA, a former judge on this Court, and three non-profit biomedical research organizations agreed with Appellants', not Sarepta's, view of the law of patent eligibility. And notably, no amici entered briefs in support of Sarepta.

2. Sarepta's Waiver Argument Ignores the Record

In addition to its improper "defining features" test, Sarepta accuses Appellants of waiving reliance on functions other than gene therapy. Not so. During summary judgment proceedings, Appellants referred to gene therapy as an example of a function that is markedly different from natural products. *See* Appx400 (referring to the markedly different functions "including" gene therapy); Appx583 ("The claimed cultured host cells, on the other hand, have significant functions that the sequences alone do not, such as use in the triple transfection process that is critical to producing rAAV vectors for gene therapy."); Appx495 ("There is no dispute that the claimed cultured host cells have the potential for significant utility that the AAV sequences alone do not

have, for example, for use in making AAV gene therapy vectors."). Both Sarepta and Appellants referred the district court to the specific paragraphs of the expert report of Appellants' expert Dr. Leone that discuss uses of the claimed cultured host cells beyond gene therapy, such as making copies of recombinant nucleic acid molecules, making empty capsids that can be used in other applications, and research applications like determining molar ratios and ELISA assays. Appx1230-33, ¶¶ 53-56. The district court did not have to "hunt" for these other functions, as Sarepta wrongly suggests. Sarepta Br. at 33. The functions were referred to in paragraphs of an expert report that were cited in Appellants' argument on section 101. Sarepta has failed to show waiver.

D. *Funk* Is Inapposite

The district court's decision was based in large part on *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). Tellingly, Sarepta spends only five paragraphs addressing *Funk* on page 51 of its brief; that is because *Funk* is inapposite. *See also* OB at 29-33. The claims in *Funk* required only that two different, naturally occurring bacteria be placed together in a single package, to take advantage of the natural properties of those bacteria. *Id*. at 128-130. As the Supreme Court explained, the claims in *Funk* covered

something that was "hardly more than an advance in the packaging of the inoculants." *Id.* at 131.

Sarepta's attempts to analogize this case to *Funk*, asserting that the claimed cultured host cells are merely a "container" like the packaging in *Funk*, are wrong as a matter of fact and law. As a factual matter, Sarepta misconstrues the testimony of Appellants' FDA expert, Erika Lietzan. Contrary to Sarepta's assertions (Sarepta Br. at 15, 49), Ms. Lietzan never analogized cultured host cells to a sterile container. Instead, Ms. Lietzan opined on an issue not relevant to this appeal—whether Sarepta's cultured host cells themselves are "approved" by FDA. Appx1420-21 ¶ 51. In explaining her opinion that only Sarepta's final gene therapy receives FDA premarket approval, she also explained that many aspects of the manufacturing process are subject to FDA's regulatory authority, including Sarepta's cultured host cells. Appx1422 ¶¶ 53-54. In reaching that conclusion, Ms. Lietzan stated:

> It would not be consistent with the FDA framework to refer to a host cell substrate — described in the marketing application as *used to produce* SRP-9001 — as itself being the subject of premarket approval. The agency does not "approve" the cell substrates used in the manufacturing process any more than it "approves" the "sterile vessel" used to store the eluted plasma [sic] DNA during the process or the "high-salt buffer elution" used during Thiophilic Absorption Chromatography, both of which are discarded after use, much like the host cells.

Appx1424 ¶ 58. Sarepta is stretching to suggest Ms. Lietzan "analogized" cultured host cells to a sterile container for purposes of patent eligibility.

Sarepta's legal arguments are similarly flawed and ignore the subsequent Supreme Court decisions in *Chakrabarty* and *Myriad*. Indeed, *Chakrabarty* distinguished the claims in *Funk*, which covered merely the discovery of "some of the handiwork of nature," *Funk Bros.*, 333 U.S. at 131, from the claims at issue in *Chakrabarty*, which were "not nature's handiwork, but [the inventor's] own," *Chakrabarty*, 447 U.S. at 309-10. The Supreme Court's decision in *Myriad* is consistent, finding that cDNA claims, which require intervention by the lab technician to create something new, were patentable, while claims that simply covered an isolated natural DNA were not. *See supra* Section II.B. And, as discussed in detail above, the claims here fall on the *Chakrarbarty*/cDNA side of the eligibility line—they recite non-natural cultured host cells having a structure and function like nothing in nature.

E. There Is No Preemption Concern Here

The '617 claims do not improperly preempt the use of any natural product. The preemption analysis is concerned with ensuring that "patent law not inhibit further discovery by improperly tying up the future use of these

building blocks of human ingenuity." *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014) (quotation omitted). But the claims here do *not* claim a natural "building block of human ingenuity." They claim a non-natural cultured host cell that incorporates a genetically engineered recombinant nucleic acid molecule with an AAVrh10 sequence as just one component. They do not preempt all uses of the natural AAVrh10 sequence or sequences 95% identical to it. Those of skill in the art are free to use those sequences as they wish, in research applications, in diagnostics, as part of the AAVrh10 virus itself, or in many other applications. Appx384-385. Sarepta addresses none of these potential uses. It argues only that "complete preemption" is not required to demonstrate ineligibility. Sarepta Br. at 50 n.7. But Sarepta has to do *something* to show improper preemption other than to complain that Appellants obtained claims to cultured host cells that Sarepta would now like to use.

That the cultured host cells are an "important tool" for gene therapy and a "research tool" for purposes of the safe harbor analysis does not implicate the preemption analysis. Many inventions can be characterized as research tools, but that does not make them improperly preemptive. The claims reflect a specific application of the AAVrh10 sequence in a cultured host cell, which is the type of application of a discovery that courts have repeatedly found meets

section 101's requirements. *See Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1329 (Fed. Cir. 2020) (inventors used physical process step to selectively remove fragments of natural cell-free fetal DNA); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (Fed. Cir. 2016) ("The inventors certainly discovered the cells' ability to survive multiple freeze-thaw cycles, but that is not where they stopped, nor is it what they patented. Rather, as the first party with knowledge of the cells' ability, they were in an excellent position to claim applications of that knowledge." (quotations omitted)).

Sarepta wrongly claims that Appellants did nothing to build on their discovery of the AAVrh10 sequence because they supposedly only added "generic elements;" the claims are the epitome of the "application" of the inventors' discovery to a patentable invention. Indeed, Sarepta never addresses the fact that the claimed cultured host cells are undisputedly something new and non-natural that had not previously existed. *See supra* Section I.D. Nor does Sarepta address the portions of the patent or the inventor testimony regarding the invention and development of the claimed cultured host cells. *See supra* Section I.B.

III. THE DISTRICT COURT IMPROPERLY DREW FACTUAL INFERENCES AGAINST APPELLANTS

As explained in Appellants' opening brief, the district court made at least two erroneous and unsupported factual inferences in Sarepta's favor. First, the district court adopted Sarepta's unsupported conclusion that the cultured host cells are no more than a "container" for genetic material. Sarepta's only response is to say "that is exactly what the Asserted Claims say," without actually citing to those claims. As detailed herein, the cultured host cells are far more than a container, and the claims require far more than isolated DNA, contrary to Sarepta's arguments.

The district court also erred in ignoring the multiple potential utilities for the cultured host cells, focusing only on their potential utility for gene therapy. As discussed above, contrary to Sarepta's argument, Appellants did not waive this argument, and the evidence supporting these additional utilities was before the district court. Appx1230-1233, ¶¶ 53-55. It was error for the district court to ignore them. At least vacatur and remand is required.

IV. ALLOWING THE DISTRICT COURT DECISION TO STAND THREATENS IMPORTANT RESEARCH

Finally, Defendants' contention that the district court's decision here is "simply the application of well-established precedents" (Sarepta Br. at 59) that will not have serious consequences is belied by the facts. This decision is

a novel and dangerous expansion of section 101. *No case* has previously found ineligible a claim for a genetically engineered composition that undisputedly does not occur in nature. The amici supporting Appellants here, including organizations involved in cancer research, recognize the danger. Those amici have detailed the risks to cancer and biotechnology research, which often depends on genetically engineered cells, that would arise from allowing this decision to stand, as well as the uncertainty for thousands of patents that use terms similar to those at issue here. D22 at 13-17; D27 at 30-38; D33 at 3-7. The PTO also believes such claims are eligible, as evidenced by the section 101 guidance it has instructed examiners to apply for nearly a decade. And the PTO has issued countless patents to inventors who have relied on that interpretation. The district court's decision calls those patents into question and will have a chilling effect on research and development involving genetically engineered compositions with potentially important medical applications.

CONCLUSION

For the reasons described herein, Appellants respectfully ask this Court to reverse the grant of Sarepta's motion for summary judgment under section 101, reverse the denial of Appellants' motion for summary judgment, hold that the claims recite eligible subject matter under section 101, and remand to

the district court for further proceedings. In the alternative, Appellants respectfully ask this Court to vacate the district court's decision and remand this case for further proceedings.

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Respectfully submitted,

/s/ Julie S. Goldemberg
Julie S. Goldenberg
julie.goldemberg@morganlewis.com
MORGAN, LEWIS & BOCKIUS
1701 Market Street
Philadelphia, PA 19103
Telephone: (215) 963-5000

Amy M. Dudash
MORGAN, LEWIS & BOCKIUS LLP
1201 N. Market Street, Suite 2201
Wilmington, DE 19801
amy.dudash@morganlewis.com
Telephone: (302) 574-3000

Attorneys for Plaintiff-Appellant
THE TRUSTEES OF THE
UNIVERSITY OF PENNSYLVANIA

/s/ Susan E. Morrison
Susan E. Morrison
morrison@fr.com
FISH & RICHARDSON P.C.
222 Delaware Avenue, 17th Floor
Wilmington, DE 19801
Telephone: 302-652-5070

Deanna J. Reichel
reichel@fr.com
FISH & RICHARDSON P.C.
60 S. 6th St., Suite 3200
Minneapolis, MN 55402
Telephone: 612-335-5070

Attorneys for Plaintiff-Appellant
REGENXBIO INC.

CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(g) and Federal Circuit Rule 32(b)(3), the undersigned counsel hereby certifies that:

1. This brief complies with the type-volume limitations of Federal Circuit Rule 32(b)(1). This brief contains 6,982 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared using Microsoft Word 2016 in a proportionally spaced typeface: Cambria, font size 14 point.

Dated: August 29, 2024

/s/ Susan E. Morrison
Susan E. Morrison