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 in Case No. 1:20-cv-01226, Judge Richard G. Andrews

BRIEF OF AMICI CURIAE PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY, THE J. DAVID GLADSTONE INSTITUTES, AND DANA-FARBER CANCER INSTITUTE IN SUPPORT OF APPELLANTS AND IN SUPPORT OF REVERSAL

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May 15, 2024

CERTIFICATE OF INTEREST

Counsel for *amici curiae* certifies the following:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1). Provide the full names of all entities represented by undersigned counsel in this case.

Parker Institute for Cancer Immunotherapy and

The J. David Gladstone Institutes

Dana-Farber Cancer Institute

2. Real Party in Interest. Fed. Cir. R. 47.4(a)(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.

None.

3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(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.

None.

4. Legal Representatives. 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).

All counsel are entering appearances contemporaneously with the filing of this brief.

5. Related Cases. 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)?

☐ Yes (file separate notice; see below) ☐ No ☒ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). Please do not duplicate information. This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

None.

6. Organizational Victims and Bankruptcy Cases. 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).

None.

Dated: May 15, 2024

/s/ Kevin A. Marks

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TABLE OF CONTENTS

Page

CERTIFICATE OF INTEREST i

TABLE OF AUTHORITIES v

STATEMENT OF INTEREST OF *AMICI CURIAE* 1

INTRODUCTION 4

FACTUAL BACKGROUND 5

I. GENE THERAPY 6

II. CELL THERAPY 7

III. IMMUNO-ONCOLOGY 8

IV. RELEVANT LABORATORY TECHNIQUES 11

A. Recombination 11

B. cDNA 13

C. Transformed Cells 14

D. Cell Culture 17

V. DEVELOPMENT COSTS 18

ARGUMENT 20

I. APPELLANTS' CLAIMS ARE PATENT ELIGIBLE 20

A. The Claimed Invention Has Markedly Different Characteristics From Any Natural Product 21

1. A "Recombinant Nucleic Acid Molecule" Is Patent Eligible 21

2. A "Host Cell Containing a Recombinant Nucleic Acid" Is Patent Eligible 22

3. A "Host Cell Containing a Recombinant Nucleic Acid Molecule … Further Compris[ing] a Heterologous Non-AAV Sequence" Is Patent Eligible 26

4. "A Cultured Host Cell Containing a Recombinant Nucleic Acid Molecule … Further Compris[ing] a Heterologous Non-AAV Sequence" Is Patent Eligible 26

B. The Claimed Invention Has Potential For Significant Utility 27

C. The District Court Erred in Applying the *Alice* Two-Step Framework, But Even if *Alice* Applied, the Claims Are Patent Eligible 29

II. IF NOT REVERSED, THE LOWER COURT'S DECISION WILL HINDER CRITICAL INNOVATION IN IMMUNO-ONCOLOGY 30

A. Patents Provide Crucial Incentives To Invest In Immuno-Oncology 31

B. Patent Protection Is Critical To Moving The Inventions Supported By Non-Profit Organizations Like *Amici* From Bench To Bedside 35

CONCLUSION 38

CERTIFICATE OF COMPLIANCE

TABLE OF AUTHORITIES

CASES

Page(s)

AMP v. USPTO, 689 F.3d 1303 (Fed. Cir. 2012) 4, 24

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Rule 29 1

81 Fed. Reg. 42,328 (June 29, 2016) 32

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amici curiae are non-profit biomedical research organizations and pioneers in the development of immuno-oncology therapies that have the potential to make cancer a curable disease.

The Parker Institute for Cancer Immunotherapy ("PICI") is radically changing how cancer research is done. Founded in 2016 through a $250 million gift from Silicon Valley entrepreneur and philanthropist Sean Parker, the San Francisco-based non-profit is an unprecedented collaboration between the country's leading immunotherapy researchers and cancer centers. PICI's network of research institutions include Stanford Medicine; the University of California, Los Angeles; the University of California, San Francisco; the University of Pennsylvania; Dana-Farber Cancer Institute; The J. David Gladstone Institutes; and Weill Cornell Medicine. PICI also supports top researchers at other institutions, including The University of Texas MD Anderson Cancer Center; Memorial Sloan Kettering Cancer Center; City of Hope; Fred Hutchinson Cancer Research Center; Icahn School of Medicine at Mount Sinai; Institute for Systems Biology; and Washington University School of Medicine in St. Louis. By forging alliances with

[1] No counsel for any party authored this brief in whole or in part, and no person or entity other than amici and their counsel made a monetary contribution intended to fund the preparation or submission of this brief. Pursuant to Fed. R. App. P. 29(a)(2), all Parties have consented to the filing of this brief.

academic, industry and non-profit partners, PICI makes big bets on bold research to fulfill its mission: to accelerate the development of breakthrough immunotherapies to turn all cancers into curable diseases. PICI facilitates collaboration between top cancer and immunology researchers, helps its partners focus solely on the science, and provides its members with access to critical research tools including intellectual property, advanced bioinformatics, cell manufacturing, sequencing, immune monitoring, industry-owned drugs, genetic engineering, and clinical trial management.

The J. David Gladstone Institutes ("Gladstone") is one of PICI's partner institutions. Gladstone explores the power of genomics to fight cancer by creating a community of experts in immunology, synthetic biology, human genetics, and CRISPR genome engineering. For example, Gladstone researchers are using CRISPR/Cas9 gene-editing to investigate how genetic changes lead to improved immune cell response; mapping the genome, epigenome, and transcriptome of immune cells to determine how genome variants increase the risk of autoimmune disease; and creating improved CAR T-cell treatments using genome engineering and synthetic biology.

Since its founding in 1947, Dana-Farber Cancer Institute ("DFCI") has been committed to providing adults and children with cancer with the best treatment available today while developing tomorrow's cures through cutting-edge research.

Placing an equal emphasis and commitment on providing excellent patient care, the research is informed by patient care, and patient care relies on the research – including research directed to immunotherapies, often using gene-based or cell-based therapeutic technologies. The deep expertise in both research and clinical care uniquely positions DFCI to develop, test, and gain FDA approval for new cancer therapies, which has resulted in DFCI researcher contributions to the development of 35 of 75 cancer drugs recently FDA approved for use in cancer patients.

Amici have a significant interest in ensuring that engineered biologics remain eligible for patent protection. *Amici* conduct and support critical research in immuno-oncology, a field that is already revolutionizing how we treat cancer. Unlike conventional cancer treatments, which target cancer cells only while they are administered, immunotherapy offers the chance to help our bodies learn to combat reoccurrence and turn remission into a lasting cure. Further, immuno-oncology has the potential to allow precise targeting of cancer cells while sparing healthy tissue, in contrast to other existing cancer therapies. This has the potential to revolutionize the treatment of cancer by dramatically reducing side effects and complications for patients.

These groundbreaking treatments employ human-made biologics such as engineered T cells and antibodies to train a patient's immune system. The district

court's improper expansion of § 101 threatens patent protection for these innovations, which hampers the ability of non-profits like *amici* to attract the partners needed to build on such non-profits' breakthroughs and bring new treatments to patients quickly and at scale.

INTRODUCTION

There are few clear lines in the § 101 case law. But since 1980, it has been well-established that non-naturally occurring human-made organisms are eligible for patent protection. *See Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980). As this Court determined in 2012, this principle extends to "transformed … host cell[s]." *AMP v. USPTO*, 689 F.3d 1303, 1310, 1333-1334 (Fed. Cir. 2012), *rev'd on other grounds*, *AMP v. Myriad*, 569 U.S. 576 (2013). Further, since 2013, it has been clear that human-made nucleic acids with a "unique" structure not found in nature are patent eligible. *Myriad*, 569 U.S. at 593. Thus, with respect to these categories of invention, the §101 jurisprudence provides clear direction for human-made organisms and non-natural nucleic acid sequences.

The district court ignored these principles and injected significant uncertainty into well-settled law. Appellants' claims recite both a human-made organism and a non-natural nucleic acid sequence. Appx384(437:55-63) ("A ***cultured host cell*** containing a ***recombinant nucleic acid molecule*** … [that] further comprises a ***heterologous non-AAV sequence***"); *see also* Appx725-

726(195:25-196:4) (Sarepta's expert agreeing that the claimed "cultured host cells" do not "exist in nature"); Appx744-747(250:24-253:1) (Sarepta's expert agreeing "that a recombinant nucleic acid molecule that contains an AAV sequence and a heterologous non-AAV sequence is not naturally occurring").[2] Either of these features should have been enough to satisfy *Chakrabarty* and *Myriad*'s "markedly different characteristics" test.

Further, while the two-step *Alice* framework does not apply to composition claims, *infra* pp. 29-30, the claims at issue are not directed to patent ineligible subject matter at *Alice* Step 1 even if that test applied because they claim a new and useful composition that is not found in nature.

The district court's decision is particularly troubling because this is not an edge case that tests the boundaries of § 101. Rather, it involves a biotechnology invention that falls squarely within the heartland of patent-eligible subject matter. If affirmed, the district court's decision would therefore seriously hinder critical advances in biotechnology, including the lifesaving immuno-oncology work done by non-profit research organizations like *amici*.

FACTUAL BACKGROUND

The legal principles that govern this case are straightforward and simple to apply, but because they are critical to encouraging cutting-edge inventions in

[2] All emphasis added unless otherwise indicated.

complex fields, it is helpful to start with some background on gene therapy, cell therapy, and immuno-oncology, as well as related laboratory techniques, to illustrate why human-made organisms and non-natural nucleic acid sequences are—and need to be—eligible for patent protection.

I. GENE THERAPY

Gene therapy seeks to treat or prevent disease by modifying a patient's DNA. *What Is Gene Therapy?*, FDA (July 25, 2018).[3] Gene transfer typically involves adding a new gene to a cell in order to "restore the missing function of a faulty or missing gene." *What are Genetic Therapies?*, NIH (March 2022).[4] Genome editing changes the cell's existing DNA to, for example, knock-in a desirable sequence or knockout an undesirable sequence. *Id.*

Many gene therapy applications require vectors to deliver genetic material or gene-editing tools to the patient's cells. *See How Does Gene Therapy Work*, MedlinePlus (Feb. 28, 2022).[5] "Adeno-associated virus (AAV) vectors are the leading platform for gene delivery for the treatment of human diseases." Wang et al., *Adeno-associated Virus Vector as a Platform for Gene Therapy Delivery*, 18

[3] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.

[4] https://www.nhlbi.nih.gov/health/genetic-therapies.

[5] https://medlineplus.gov/genetics/understanding/therapy/procedures/.

Nature Reviews Drug Discovery 358, 3558 (2019).[6] They are also known to be among the safest vectors for gene delivery. *See Vectors 101*, Am. Soc'y Gene & Cell Therapy (Jan. 30, 2024).[7] AAV comprises a protein shell called a capsid that surrounds a single-stranded DNA genome containing three genes: *Rep* (Replication), *Cap* (Capsid), and *App* (Assembly). *See* Naso et al., *Adeno-Associated Virus (AAV) as a Vector for Gene Therapy*, 31 BioDrugs 317, 318 (2017).[8]

To date, many different AAV subtypes or "serotypes" have been identified. U.S. Patent No. 10,526,617 (the "'617 Patent") claims cultured host cells that can be used to create gene therapy vectors based on AAV serotype 10 (AAVrh.10). "[V]ectors based on rh.10 (44-2) capsids of the invention are particularly well suited for use in [the] lung." Appx178(26:48-54).

II. CELL THERAPY

Cell therapy uses cells to treat disease. *See* El-Kadiry et al., *Cell Therapy*, 8 Front Med. (Nov. 22, 2021).[9] A patient's cells can be genetically modified or replaced with cells that have a desired function or benefit. *See Cell Therapies*,

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6927556/pdf/nihms-1061308.pdf.

[7] https://tinyurl.com/mty67t27.

[8] https://link.springer.com/article/10.1007/s40259-017-0234-5.

[9] https://www.frontiersin.org/articles/10.3389/fmed.2021.756029/full.

Harvard Stem Cell Institute (2024).[10] For example, synthetic biology can enhance a cell's therapeutic function "through precision control over therapeutic transgene expression or delivery of secreted therapeutic factors, or by programming cells to sense biomolecular species associated with a specific tissue compartment or disease state and respond via altered cell behaviour." Bashor et al., *Engineering the Next Generation of Cell-Based Therapeutics*, 21 Nature Rev. Drug. Discovery 655, 663-664 (2022).[11]

III. IMMUNO-ONCOLOGY

Cancer immunotherapy or "immuno-oncology" leverages a patient's own immune system to fight cancer. *See Immunotherapy to Treat Cancer*, NCI (Sept. 24, 2019).[12] Immune checkpoint therapy ("ICT") inhibits immune checkpoint regulators to allow T cells to kill cancer cells using normal immune processes. ICT is now the standard of care for several different cancer types. *See* Gubin & Vesely*, Cancer Immunoediting in the Era of Immuno-Oncology*, 28 Clin. Cancer Res. 3917 (2022).[13]

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[10] https://hsci.harvard.edu/translation/what-are-drugs-5-cell-therapies.

[11] https://www.nature.com/articles/s41573-022-00476-6.

[12] https://www.cancer.gov/about-cancer/treatment/types/immunotherapy.

[13] https://aacrjournals.org/clincancerres/article/28/18/3917/709011/Cancer-Immunoediting-in-the-Era-of-Immuno. PICI Director James Allison won the Nobel Prize for his work on immune checkpoint regulators. *See* Merville, *Immunotherapy Innovator Jim Allison's Nobel Purpose*, MD Anderson Cancer Center (2018)*,*

Adoptive cellular therapy ("ACT") uses T cells to fight disease and is a powerful treatment for several types of cancer. *Adoptive Cell Therapy*, NIH.[14] For example, chimeric antigen receptor T cell ("CAR-T") therapy is a highly personalized approach that modifies a patient's T cells with surface proteins called chimeric antigen receptors, or CARs, which bind to specific proteins on the surface of that patient's cancer cells. *See CAR T-Cells*, NCI (March 2022).[15] Scientists are investigating whether other types of immune cells can be similarly engineered to create "cancer-killing machines." *CAR-T and Cell Therapy*, PICI.[16]

https://www.mdanderson.org/publications/conquest/immunotherapy-innovator-jim-allisons-nobel-purpose.h36-1592202.html.

[14] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adoptive-cell-therapy.

[15] https://www.cancer.gov/about-cancer/treatment/research/car-t-cells.

[16] https://www.parkerici.org/research-focus/car-t-and-cell-therapy-the-next-wave/.

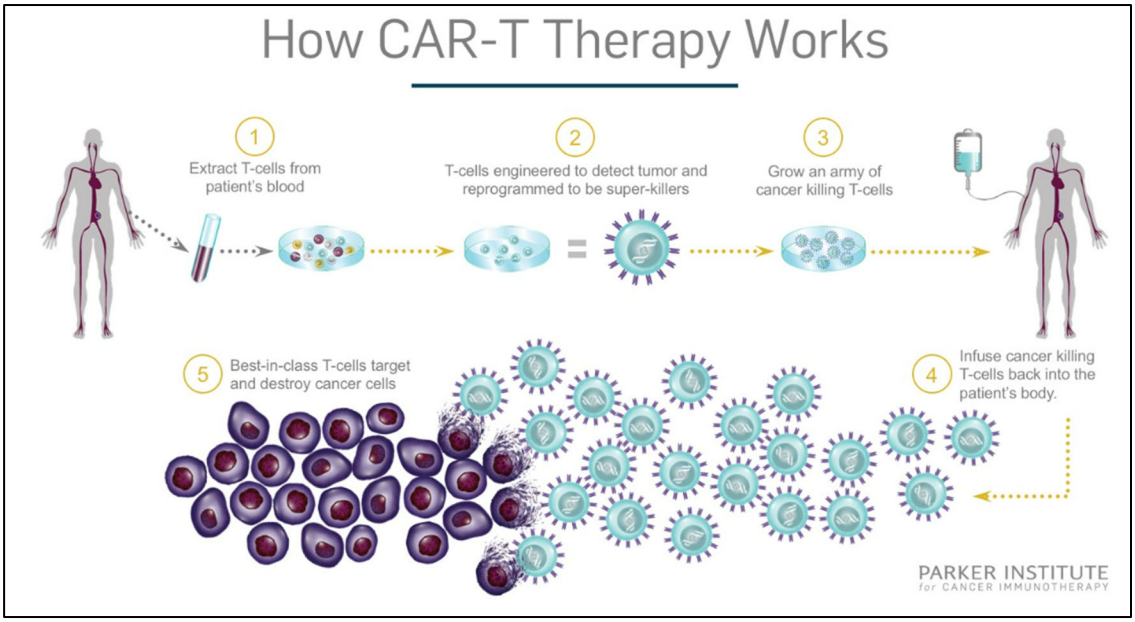

Figure 1. Overview of CAR-T Treatment.[17]

In another example of ACT, tumor-infiltrating lymphocyte ("TIL") therapy leverages a patient's own lymphocytes (white blood cells) that penetrate solid tumors. *See* Boldt, *TIL Therapy*, MD Anderson Cancer Center (April 15, 2021).[18] TILs naturally recognize a patient's tumor as abnormal, but human intervention is needed to transform TILs into effective cancer therapeutics. The FDA recently approved Iovance's AMTAGVI, which "expand[s] a patient's unique T cells" to amplify the patient's anti-tumor immune response. *See* Press Release, Iovance Biotherapeutics, *Iovance AMTAGVI™ (lifileucel) Receives U.S. FDA Accelerated*

[17] *From Leukemia to Cancer-Free: How CAR-T Immunotherapy Saved Emily Whitehead*, PICI (Aug. 30, 2017), https://www.parkerici.org/the-latest/from-leukemia-to-cancer-free-how-car-t-immunotherapy-saved-emily-whitehead/.

[18] https://www.mdanderson.org/cancerwise/what-is-tumor-infiltrating-lymphocyte-til-therapy--6-things-to-know.h00-159460056.html.

Approval for Advanced Melanoma (Feb. 16, 2024).[19] Another approach modifies a patient's TILs to enhance their antitumor efficacy. *See* Warner et al., *Tumor-Infiltrating Lymphocyte Therapy in Melanoma*, 29 Clin. Cancer Res. 1835, 1849 (2023).[20]

IV. RELEVANT LABORATORY TECHNIQUES

A. Recombination

Several gene therapy, cell therapy, and immuno-oncology technologies utilize recombinant nucleic acids—i.e., nucleic acids "combining genetic material from two different sources"—to create new, human-made sequences. *Recombinant*, NCI Dictionary of Cancer Terms.[21]

Recombination frequently involves modifying a nucleic acid sequence with a heterologous sequence—i.e., genetic material from another species. *See Heterologous*, Merriam-Webster Online.[22] For example, recombinant AAV vectors (rAAVs) are commonly used in gene therapy. Appx1166(¶47). rAAVs generally have the same capsid sequence as non-modified AAVs, but are typically engineered to include coding information from a non-AAV gene of interest. *Id*.

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[19] https://ir.iovance.com/news-releases/news-release-details/iovances-amtagvitm-lifileucel-receives-us-fda-accelerated.

[20] https://aacrjournals.org/clincancerres/article/29/10/1835/726243.

[21] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/recombinant.

[22] https://www.merriam-webster.com/dictionary/heterologous.

Creating recombinant DNA is a multi-step process that employs different enzymes and laboratory techniques. *Recombinant DNA Technology*, NIH (Mar. 2024) ("*NIH Recombinant DNA Technology*").[23] First, fragments of DNA are typically created by digestion with restriction enzymes (or nucleases) that cleave the DNA at specific sites. Cooper, *The Cell: A Molecular Approach*, NIH (2nd ed. 2000) (Recombinant DNA).[24] Restriction enzymes must be carefully chosen to yield the desired DNA fragments while limiting off-target cleavage. Second, the DNA fragments are joined together by DNA ligases. Once the fragments are paired, the bond can be covalently sealed in a process known as ligation. *Id*. Third, the recombinant nucleic acid sequence is propagated. For example, a DNA fragment can be ligated to a plasmid that has also been modified to confer antibiotic resistance. Cooper, *Recombinant DNA*. The resulting recombinant plasmid can then be used to transform *E.coli* (bacteria) host cells. *Id.* When the *E.coli* cells are cultured in the presence of antibiotics, the antibiotic-resistant colonies containing the engineered plasmid DNA can be selected. The plasmid can then be amplified by growing these selected colonies. *Id.* Finally, the recombinant DNA must be extracted from the bacterial chromosomal DNA to yield a purified plasmid DNA. *Id.*

[23] https://www.genome.gov/genetics-glossary/Recombinant-DNA-Technology.

[24] https://www.ncbi.nlm.nih.gov/books/NBK9950/.

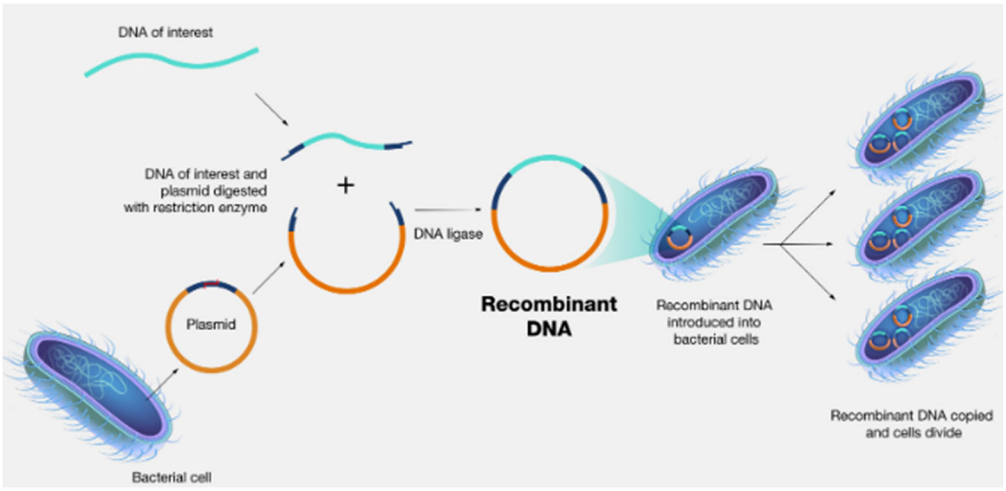

Figure 2. Sample protocol for creating recombinant DNA.[25]

B. cDNA

"Creation of proteins from DNA involves two principal steps, known as transcription and translation." *Myriad*, 569 U.S. at 581. During transcription, "pre-RNA" containing nucleotides corresponding to both coding ("exon") and non-coding ("intron") segments is generated from DNA. *Id.* at 581-582. The pre-RNA is then "naturally 'spliced' by the physical removal of the introns," resulting in an exon-only messenger RNA ("mRNA"). *Id.* cDNA is DNA synthesized from an RNA template. *Reverse Transcription Reaction Setup–Seven Important Considerations*, ThermoFisher Scientific.[26] cDNA created using an mRNA template results in a synthetic, exon-only DNA molecule.

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[25] *See NIH Recombinant DNA Technology*.

[26] https://www.thermofisher.com/us/en/home/life-science/cloning/cloning-learning-center/invitrogen-school-of-molecular-biology/rt-education/reverse-transcription-setup.html#rt_a6.

cDNA is created using a process called reverse transcription. *Reverse Transcription Reaction Setup–Seven Important Considerations.* First, the template RNA is combined with primers and deoxynucleotide triphosphates corresponding to each of the nucleotide bases. *Id.* Second, an enzyme called "reverse transcriptase" is used to "extend[] the primer by adding complementary nucleotides in a 5' to 3' direction to synthesize cDNA." *Id.* Third, the reaction is stopped, typically by heating the reaction mixture to inactivate the enzyme. *Id.* Finally, after first-strand synthesis is complete, a DNA polymerase enzyme can be used to produce a complementary strand of the first cDNA strand. *Id.*

C. Transformed Cells

Cells that are modified or transformed to contain exogenous nucleic acids are used in many gene therapy, cell therapy, and immuno-oncology applications. Early genetic engineering took advantage of conjugation, a natural process by which DNA is transferred "between bacteria in cellular contact." *Conjugation*, Merriam-Webster Online.[27] During conjugation, the donor bacterium "produce[s] a thin, tubelike structure called a pilus" that "draws the two bacteria together," allowing the donor to transfer its genetic material to the recipient. Scitable by Nature Education (2014) (defining "conjugation (prokaryotes)").[28]

[27] https://www.merriam-webster.com/dictionary/conjugation.

[28] https://www.nature.com/scitable/definition/conjugation-prokaryotes-290/.

Cells can also be modified through transfection, "the process of artificially introducing nucleic acids (DNA or RNA) into cells." *Introduction to Transfection*, ThermoFisher Scientific.[29] There are many different transfection methods, including chemical, physical, and biological approaches. *Overview of Transfection Methods*, ThermoFisher Scientific.[30]

"Chemical gene delivery methods use carrier molecules that neutralize or impart a positive charge onto nucleic acids." *Overview of Transfection Methods.* For example, calcium phosphate precipitation causes DNA to bind to the cell surface, which allows for uptake of DNA by endocytosis. *Id.*

[29] https://www.thermofisher.com/us/en/home/references/gibco-cell-culture-basics/transfection-basics/introduction-to-transfection.html.

[30] https://www.thermofisher.com/us/en/home/life-science/cell-culture/transfection/methods.html.

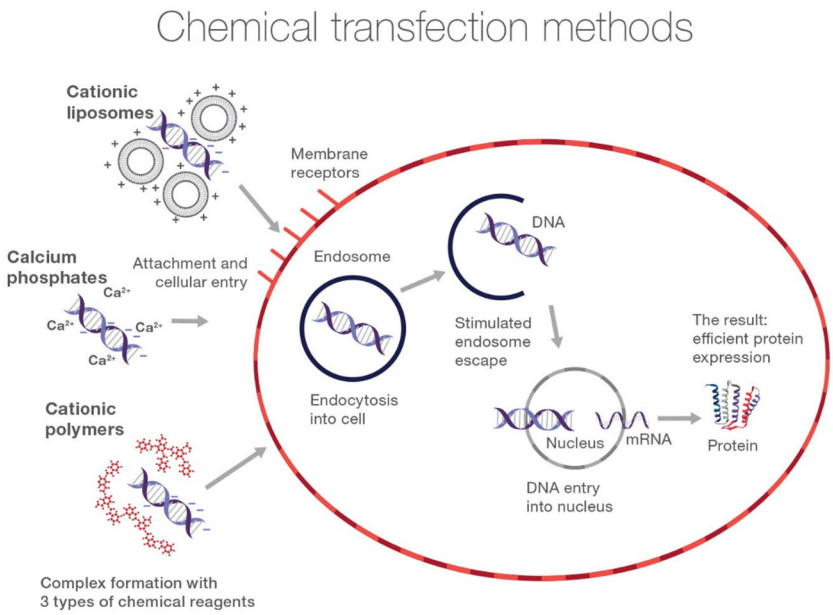

Figure 3. Examples of chemical transfection methods.[31]

By contrast, physical gene delivery methods do not require the use of chemical agents. For example, electroporation "uses an electrical pulse to create temporary pores in cell membranes through which nucleic acids can pass." *Id.*

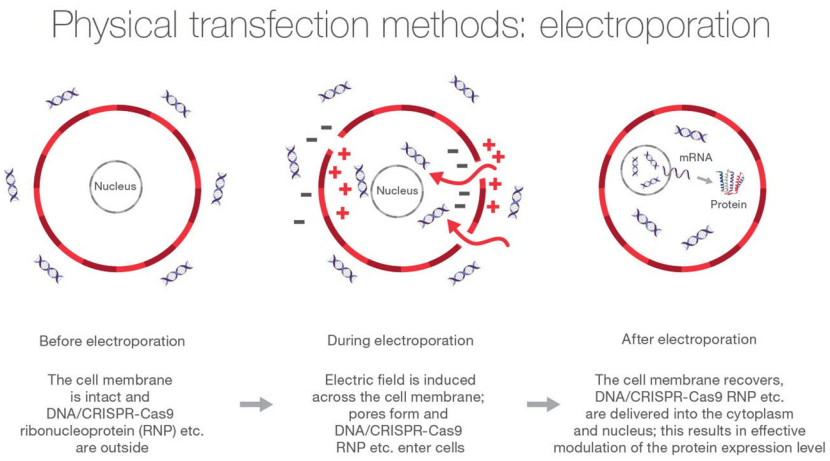

Figure 4. Examples of physical transfection methods.[32]

[31] *Id.*

[32] *Id.*

Finally, biological transfection, called transduction, uses genetically engineered viruses to transport nucleic acids of interest into the target cell. *Id*.

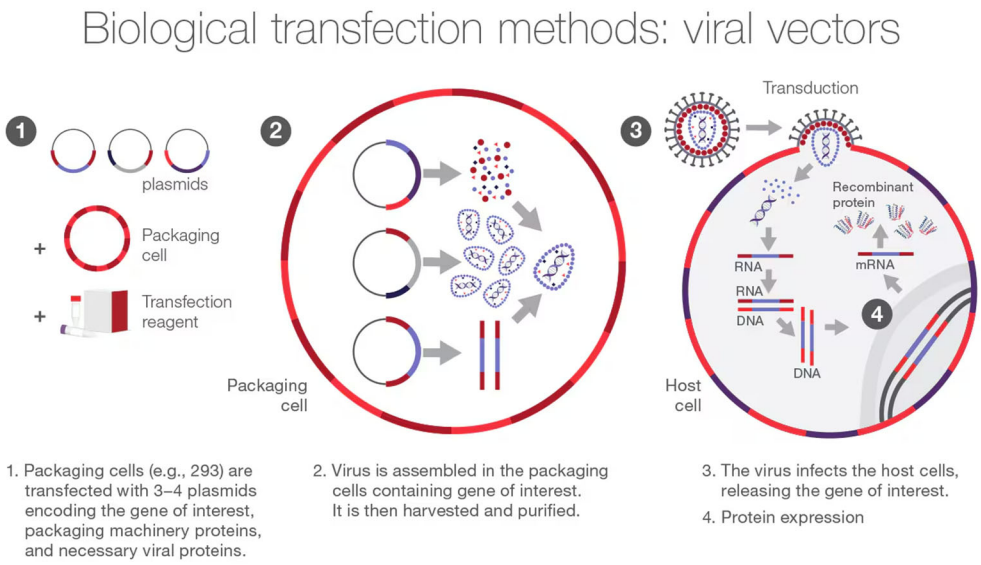

Figure 5. Example of transduction.[33]

D. Cell Culture

Cell culture techniques allow researchers to artificially control for genetic and environmental variables that arise in naturally occurring cell populations. Cell culture is a critical component of gene therapy, cell therapy, and immuno-oncology, which utilize cultured cells to study biological phenomena and to create and deliver therapeutic agents. *Supra* pp. 6-11.

Cell culture systems generally require specific culture media, temperature, pH, and CO_2 and O_2 levels to allow for growth and replication under unnatural *in vitro* conditions. *See* Arango et al., *Chapter 45: Cell Culture and Cell Analysis*,

[33] *Id.*

741, 742, in *Autoimmunity: From Bench to Bedside* (1st ed. 2013);[34] Segeritz & Vallier, *Cell Culture*, in Basic Sciences Methods for Clinical Researchers at 161-162 (2017).[35] Further, the format of cell growth is also a key consideration because cells grown in suspension exhibit different characteristics than those grown in plated form. Segeritz & Vallier, at 160-161.

The choice of cell line depends on the specific application and the capabilities of the laboratory doing the culturing. *See* Segeritz & Vallier, at 160. Primary cells are directly isolated from human tissues, are typically "finite," and "rely on a continuous supply of stocks since their proliferation ceases after a limited amount of cell divisions." *Id.* Transformed cells can be genetically manipulated to facilitate culture. For example, immortalized cell lines permit "fast growth rates and stable conditions for maintenance and cloning." *Id.* Finally, self-renewing cells can differentiate into other cell types and can be maintained for a significant time *in vitro*.

V. DEVELOPMENT COSTS

There are many hurdles that make developing an immuno-oncology therapeutic unpredictable and incredibly expensive. For example, the interplay between a patient's tumor and immune system is complicated and variable. Atkins

[34] https://www.ncbi.nlm.nih.gov/books/NBK459447/pdf/Bookshelf_NBK459447.pdf.
[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7149418/pdf/main.pdf.

et al., *Maximizing the Value of Phase III Trials in Immuno-Oncology*, 10 J. ImmunoTherapy of Cancer (2022) ("Atkins").[36]

Even after a successful treatment is developed, immuno-oncology remains expensive and difficult due to the complexity of making and delivering therapies. Peter Marks, Head of the FDA's Center for Biologics Evaluation and Research, has explained "that better characterization of [the] manufacturing process must go hand-in-hand with [work in immuno-oncology] as the field grows." Oakes, *White Paper Addresses Immuno-oncology's Growing Pains*, Regulatory Focus (Feb. 2021).[37] This is because immuno-oncology relies heavily on modified cells that can be difficult to produce in any significant quantity or with the necessary reliability. *Supra* pp. 8-11.

In addition, many immuno-oncology treatments are tailored to an individual or relatively small groups of patients. *Supra* pp. 8-11. The cost to bring these kinds of precision treatments to market has been estimated at $3.5 billion, although the actual costs can vary significantly. *See* Henderson et al., *Delivering the Precision Oncology Paradigm*, 16 J. Pharm. Policy & Practice (2023).[38] This high cost reflects both the special challenges inherent in creating such customized

[36] https://jitc.bmj.com/content/jitc/10/9/e005413.full.pdf.

[37] https://www.raps.org/news-and-articles/news-articles/2021/2/white-paper-addresses-immuno-oncologys-growing-pai.

[38] https://joppp.biomedcentral.com/articles/10.1186/s40545-023-00590-9.

treatments, as well as the expense associated with development of all oncology products. *See* Atkins at 2.[39]

ARGUMENT

I. APPELLANTS' CLAIMS ARE PATENT ELIGIBLE

The district court's decision misapplied § 101. Engineered biologics like Appellants' cultured host cells are patent eligible under the "markedly different characteristics" test. *See Chakrabarty*, 447 U.S. at 310. In *Chakrabarty*, the Supreme Court determined that a bacterium modified to contain two or more naturally occurring plasmids was patent eligible because it had "***markedly different characteristics*** from any found in nature and … the ***potential for significant utility***." 447 U.S. at 310.

Here, the challenged claims recite multiple elements that have "markedly different characteristics" from anything "found in nature." *See* '617 Patent, claim 1 ("A **cultured host** cell containing a **recombinant** nucleic acid molecule … wherein the **recombinant** nucleic acid molecule further comprises a **heterologous** non-AAV sequence."). Further, the claimed cultured host cell indisputably has the potential for significant utility because, at minimum, it can be used to create vectors for gene therapy. Appellants' claims are therefore patent eligible. Further, while this Court has suggested that the *Alice* two-step inquiry does not apply to

[39] *Supra* note 36.

composition claims, the challenged claims are not directed to patent ineligible subject matter under *Alice* Step 1 because they recite a new and useful composition not found in nature.

The district court's contrary determination rested on a series of errors and threatens the development of engineered biologics, which the FDA has recognized have the potential to "offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available." *What Are "Biologics" Questions and Answers*, FDA (Feb. 6, 2018).[40]

A. The Claimed Invention Has Markedly Different Characteristics From Any Natural Product

1. A "Recombinant Nucleic Acid Molecule" Is Patent Eligible

In *Myriad*, the Supreme Court held that cDNA was patent eligible because it was "an exons-only molecule that is not naturally occurring." *Myriad*, 569 U.S. at 594. Here, claim 1 of the '617 Patent recites "a recombinant nucleic acid molecule." Appx384(437:55-63). Recombinant nucleic acids combine genetic material from different sources to create entirely ***new, human-made sequences***. *Supra* pp. 11-13. Further, the complex, multi-step recombination process involves at least as much human intervention as the reverse transcription process used to create cDNA. *Compare supra* pp. 11-13 *with* pp. 13-14. A recombinant nucleic

[40] https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.

acid is therefore indisputably patent eligible as "distinct" from the sequences from which it was "derived." 569 U.S. at 595. The district court missed this clear off-ramp established by *Chakrabarty* and *Myriad* that should have ended its drive toward concluding that the claims of the '617 Patent were directed to unpatentable subject matter.

The district court's decision rested on its erroneous determination that the claimed invention was "similar to the ineligible claims in *Funk Brothers*" because "[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. But recombination creates a single, unified nucleic acid using sophisticated genetic engineering techniques and does not merely "mix[]" nucleic acids "together" like the bacteria at issue in *Funk Brothers*. *Supra* pp. 11-13. For this reason alone, the district court's decision should be reversed.

2. A "Host Cell Containing a Recombinant Nucleic Acid" Is Patent Eligible

Claim 1's "recombinant nucleic acid sequence" is enough standing alone to render the claim patent-eligible, but here there is even more: claim 1 additionally recites a non-naturally occurring human-made organism, i.e., a "host cell containing a recombinant nucleic acid." '617 Patent, claim 1. This use of a ***transformed host cell*** also renders claim 1 patent eligible under *Chakrabarty*. *See* 447 U.S. at 310; *supra* pp. 14-17.

Indeed, the transformed host cells at issue here are even more clearly patent eligible than *Chakrabarty*'s bacterium. In *Chakrabarty*, the inventors "utilized a process of ***natural*** conjugation" to modify *Pseudomonas* bacterium with ***naturally occurring*** plasmids. Brief for Petitioner, 1980 WL 339757, at n.3; *supra* p. 14 (discussing conjugation). Here, by contrast, the host cells are ***artificially*** transformed using ***human-made*** nucleic acids in a process that requires substantial human intervention. *E.g.*, Appx176-178(21:62-26:54); *supra* pp. 11-17 (discussing transformation and recombination). Accordingly, even after ignoring the off-ramp provided by "recombinant nucleic acid sequence," the district court's analysis should have stopped at the additional off-ramp provided by "***host cell*** containing a ***recombinant*** nucleic acid molecule."

Rather than address the claimed host cell, the district court improperly focused on the recited nucleic acid sequences in isolation. *See* Appx10. But *Chakrabarty* made clear that a microorganism genetically engineered to include an exogenous nucleic acid sequence is not "directed to" that nucleic acid sequence. Indeed, *Chakrabarty* involved *Pseudomonas* bacteria that were modified to contain a combination of ***naturally occurring*** plasmids. 447 U.S. at 305 n.1 (explaining that Chakrabarty "discovered plasmids capable of degrading camphor and octane" and developed "a process by which four [such] plasmids … could be transferred to and maintained stably in a single *Pseudomonas* bacterium"). The Supreme Court

found that the claims were patent eligible because ***the bacterium*** had "markedly different characteristics from any found in nature," not because the plasmids had been altered in any way. *Id.* at 310.

Moreover, this Court has previously confirmed the patentability of a "transformed … host cell containing an altered … gene." *AMP*, 689 F.3d at 1310. In *AMP*, this Court held Myriad Genetics' claim 20 patentable because "at the heart [of the claim] is a transformed cell, which is made by man, in contrast to a natural material." *Id.*at 1333-1334. Notably, this Court's analysis did not focus on whether the "altered … gene" was itself naturally occurring. *Id* at 1336.[41] The transformation of the host cell was sufficient by itself.

The district court failed to substantively address *AMP* and its undeniable relevance to the transformed host cells at issue here. *See* Appx10(n.3). Instead, the district court asserted without explanation that "[t]he claims at issue also differ from claim 20 in *AMP*." *Id.* A side-by-side comparison makes clear that the claims are strikingly similar for purposes of patent eligibility:

[41] Unlike the human-made recombinant nucleic acid at issue here, the "altered … gene" in *AMP* referred to a naturally-occurring mutant BRCA1 gene known to increase the risk of cancer. *See* U.S. Patent No. 5,747,282, 16:61-65 ("Thus, the presence of an altered (or a mutant) BRCA1 gene … directly correlates to an increased risk of cancer.")

AMP Claim 20 (U.S. Patent No. 5,747,282)	'617 Patent, Claim 1
A method for screening potential cancer therapeutics which comprises: growing a ***transformed eukaryotic host cell containing an altered BRCA1 gene*** causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said ***transformed eukaryotic host cell*** in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.	A ***cultured host cell*** containing a ***recombinant nucleic acid molecule*** encoding an AAV vp 1 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***.

Finally, contrary to Sarepta's suggestion below, Appellants' claimed host cell is not merely a "container" for the recombinant nucleic acid. Appx449. Rather, the host cell is a critical part of the invention because it uses the recombinant nucleic acid to manufacture viral vectors for potential therapeutic use. *Supra* pp. 6-7, 11. Thus, the host cell has "entirely different characteristics, function, and use than the" individual nucleic acids that were spliced together to create the claimed recombinant nucleic acid sequence. Appx1240(¶80) ("The amino acid and nucleotide sequences on their own may be used for sequence analysis or potentially as primers, but they cannot be used on their own, without additional components, to manufacture gene therapy vectors."); *id.* at (¶81) ("[T]he

cultured host cells covered by the asserted claims are used as part of the triple transfection process to prepare rAAV vectors for gene therapy."); Appx786-790(125:9-129:13) (explaining that sequences alone cannot make viral vectors).

The "host cell containing a recombinant nucleic acid" limitation thus provides another reason the district court's decision should be reversed.

3. A "Host Cell Containing a Recombinant Nucleic Acid Molecule … Further Compris[ing] a Heterologous Non-AAV Sequence" Is Patent Eligible

Having already missed two clear off-ramps, the district court missed a third when it ignored that Appellants' claims are patent eligible because they additionally recite "wherein the recombinant nucleic acid further comprises a ***heterologous non-AAV sequence***." This nucleic acid indisputably does not exist in nature because it covalently combines an AAV sequence with a nucleic acid ***from another species***. *Supra* p. 11. Such an invention is patent eligible even under the narrowest permissible interpretation of *Chakrabarty* and *AMP*. Again, the district court erred in ignoring this claim language entirely and treating the claimed invention as a mere mixture of naturally occurring DNA. *Supra* p. 22.

4. "A Cultured Host Cell Containing a Recombinant Nucleic Acid Molecule … Further Compris[ing] a Heterologous Non-AAV Sequence" Is Patent Eligible

Finally, the claimed invention is patent eligible because it additionally requires a "***cultured*** host cell." As explained above, cultured host cells are

designed to be markedly different from natural cell populations, including by minimizing the variability in naturally occurring cells. *Supra* pp. 17-18. But the district court failed to consider the requirement that the claimed host cell be "cultured" and instead erroneously viewed the claimed invention as a mere mixture of different DNA sequences. *Supra* p. 22.

* * *

The district court thus missed four clear off-ramps that should have avoided a declaration of patent ineligibility. Moreover, claims must be read as a whole not analyzed limitation-by-limitation, and the collective impact of these errors amplifies the need for reversal.

B. The Claimed Invention Has Potential For Significant Utility

The claimed invention indisputably has the potential for significant utility. The '617 Patent explains that the claimed host cells can be used to make recombinant AAV vectors for gene therapy applications. *E.g.*, Appx166(1:41-42). rAAVs are one of the most important gene delivery tools, and one of the safest. *Supra* pp. 6-7. Further, the claimed cultured host cells allow for the efficient creation of bacterial cell banks for future use. Appx1167(¶¶50-54). This uncontroverted utility should have been enough.

The district court nevertheless concluded that the claims did not meet *Chakrabarty*'s utility standard because "Plaintiffs do not point to anything in the

claims or specification that ***requires*** utility for gene therapy" and "some of the claimed embodiments cannot even be used for gene therapy.'" Appx11. The district court therefore effectively required Appellants to show that every embodiment of the claimed invention had certain utility. That is not the standard and contradicts long-established precedent. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (Fed. Cir. 1983) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. 101 is clearly shown.").

In *Chakrabarty*, the Supreme Court required only the "***potential*** for significant utility." 447 U.S. at 310. Indeed, the Supreme Court's finding of utility was based only on the fact that "Chakrabarty's invention ***[wa]s believed*** to have significant value for the treatment of oil spills." *Id.* at 305-306. Thus, it should have been enough that Appellants' host cells are believed to have significant value for gene therapy applications.

Further, the claims at issue in *Chakrabarty* did not themselves require that the bacterium be successfully used to clean up oil spills, nor did they limit the bacterium to use in that application. *See* 447 U.S. at 305 ("[A] bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway." (quoting U.S. Patent No. 4,259,444, claim 1)). Thus, there is no support for the district court's determination that Appellants were required to prove certain

utility for every embodiment of the claimed invention. For this independent reason, the district court's decision should be reversed.

C. The District Court Erred in Applying the *Alice* Two-Step Framework, But Even if *Alice* Applied, the Claims Are Patent Eligible

The composition of matter claims here should be analyzed under the "markedly different characteristics" test rather than the two-step *Alice* framework. This Court has previously explained that the "Supreme Court in *Myriad* relied on *Chakrabarty's* 'markedly different characteristics' framework" and "never applied the *Alice/Mayo* two-step framework." *ChromaDex, Inc. v. Elysium Health, Inc.*, 59 F.4th 1280, 1285 (Fed. Cir. 2023). Further, neither *Chakrabarty* nor *Myriad* suggest that a non-naturally occurring composition must be made using non-conventional techniques in order to satisfy the requirements of Section 101. *See Myriad*, 569 U.S. at 594-595 (not discussing conventionality of techniques); *Chakrabarty*, 447 U.S. at 310 (same). Indeed, in *Myriad*, the specification expressly acknowledged that several aspects of the invention were performed using "conventional techniques." U.S. Patent No. 5,747,282, 25:13-20, 25:50-58, 30:32-35, 35:27-22.

In any event, even if the *Alice* two-step framework applied, the claims would still be patent eligible because they are not "directed to" any judicial exception to patent eligibility under *Alice* Step 1. As explained above, the claims recite new

and useful cultured host cells and recombinant nucleic acid sequences that indisputably do not exist in nature. *Supra* pp. 20-27; *see also, e.g.*, *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (Fed. Cir. 2016) (claims directed to a "new and improved way of preserving hepatocyte cells" were not "directed to" ineligible subject matter even though they recited naturally occurring cells).

* * *

Since *AMP*, this Court has primarily been confronted with edge cases testing the boundaries of the Supreme Court's § 101 jurisprudence, largely with respect to sample preparation and diagnostics. But transformed compositions of matter like Appellants' host cells and recombinant nucleic acids lie at the heart of efforts to improve upon the workings of nature through human ingenuity. This case is not remotely close to the line, and the district court's ruling should be reversed under a straightforward application of *Chakrabarty* and *AMP*.

II. IF NOT REVERSED, THE LOWER COURT'S DECISION WILL HINDER CRITICAL INNOVATION IN IMMUNO-ONCOLOGY

Immuno-oncology is a relatively new field, but it is already "leading to a transformational shift in treatment paradigms for patients with cancer." *Immuno-Oncology*, FDA (Feb. 1, 2018).[42] Many of the most successful immuno-oncology

[42] https://www.fda.gov/about-fda/oncology-center-excellence/immuno-oncology.

treatments like CAR-T and TIL therapy employ engineered biologics similar to the host cells at issue here. *Supra* pp. 9-11. By threatening the continued eligibility of these inventions, the district court's decision has the potential to stifle critical and lifesaving innovation and deprive patients of access to important discoveries.

A. Patents Provide Crucial Incentives To Invest In Immuno-Oncology

As explained above, immuno-oncology largely relies on engineered biologics that are directly threatened by the district court's decision. *Supra* pp. 8-11. The cost to develop these engineered biologics into commercial immuno-oncology treatments is immense. *Supra* pp. 18-20. Accordingly, the field relies heavily on patents to provide therapeutic developers with a chance of reasonable financial recovery. *See* Grabowski et al., *The Roles of Patents and Research and Development Incentives In Biopharmaceutical Innovation*, 34 Biomed. Innovation 302, 302 (2015) ("We conclude that patents and regulatory exclusivity are likely to remain the core approach to providing incentives for biopharmaceutical research and development.");[43] Pan & Chen, *Patent Trend and Competitive Analysis of Cancer Immunotherapy in the United States*, 13 Hum. Vaccin. Immunother. 2583, 2583 (2017) ("The growth of patent numbers in this field has outpaced the

[43] https://dukespace.lib.duke.edu/server/api/core/bitstreams/fea5afc7-2306-45ba-813b-dc313fd52948/content.

background rate ….");[44] Wild & Au, *Oncology Drives Major Pharma Deals While Immuno-Oncology Patent Activity Soars*, IAM (May 23, 2018) (noting "expansive" growth in immuno-oncology patents).[45]

The importance of patents to encourage immuno-oncology research and development was recognized by the White House, which implemented the Cancer Immunotherapy Pilot Program in 2016 as part of the National Cancer Moonshot initiative. As relevant here, this program provided for expedited review of patent applications directed toward immuno-oncology inventions to incentivize increased innovation in that space. *See* 81 Fed. Reg. 42,328 (June 29, 2016).[46] Analysis of the Moonshot initiative noted that "[p]rovision of comprehensive intellectual property portfolio development resources is … a necessity for the success of [Immuno-Oncology Translational Network] discoveries" because "secure intellectual property is a necessary component of IOTN discoveries that may be successfully translated to the clinic." Annapragada et al., *The Cancer Moonshot Immuno-Oncology Translational Network at 5*, 115 J. Nat'l Cancer Inst. 1262,

[44] https://www.tandfonline.com/doi/pdf/10.1080/21645515.2017.1361074.

[45] https://www.iam-media.com/article/oncology-drives-major-pharma-deals-while-immuno-oncology-patent-activity-soars.

[46] This program ended on January 31, 2023.

1267 (2023).[47] This is because of the sheer cost and unpredictability of bringing an immuno-therapeutic to market. *Supra* pp. 18-20.

If affirmed, the district court's decision could therefore have a sweeping effect on the development of these innovations by removing a critical incentive to pursue this life-saving work. To illustrate, a simple search of issued U.S. Patents from the last 24 years identified more than 25,000 patents reciting "recombinant" in the claims; more than 6,000 patents reciting both "host cell" and "recombinant" in the claims; more than 150 patents reciting a "cultured host cell" in the claims; more than 3,000 patents reciting "host cell" and "heterologous" in the claims; and more than 3,000 patents reciting "recombinant" and "heterologous" in the claims. Similarly, clinicatrials.gov lists more than 1,200 clinical trials involving gene therapy; more than 2,500 clinical trials involving cell therapy; more than 5,500 clinical trials involving a recombinant product; and more than 250 studies involving a heterologous product.

Consistent with this, a recent landscape analysis of ACT therapies in the development pipeline confirms the number of emerging therapies that could be impacted by the district court's decision. *See* Fig. 6.

[47] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10637038/pdf/djad151.pdf

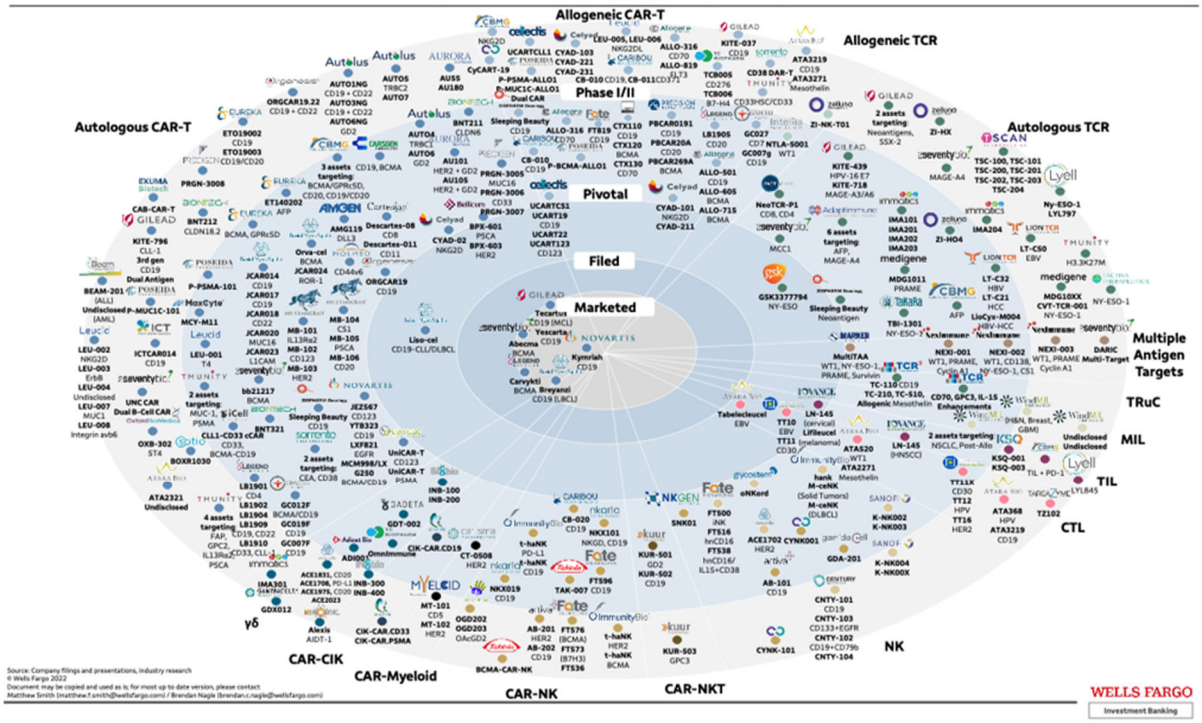

Figure 6. ACT Immuno-Oncology Landscape. ©Wells Fargo 2022

Further, affirming the district court decision could lead to a larger disparity between how human-made biologics are treated in the United States versus overseas. For example, the EPO permits patenting of "[a]n element isolated form the human body or otherwise produced by means of a technical process, including the sequence … of a gene" where the "industrial application" of the sequence is disclosed. Rule 29 EPC. Further, "biological material which is isolated from its natural environment or produced by means of a technical process" can also be patent eligible "even if it previously occurred in nature." Rule 27 EPC. Affirming the district court's decision would widen this patent eligibility divide and could ultimately hamper U.S. innovation.

B. Patent Protection Is Critical To Moving The Inventions Supported By Non-Profit Organizations Like *Amici* From Bench To Bedside

If the district court's decision is affirmed, the important work done by non-profit organizations like *amici* would be severely impacted, to the detriment of patients. Non-profit organizations like *amici* often focus on specific disease areas and/or treatment modalities, making them uniquely suited to perform and support the basic scientific research needed to identify promising treatments. *See* Giusti & Hamermesh, *How Nonprofit Foundations Can Sustainably Fund Disease Research*, Harvard Bus. Rev. (Sept. 30, 2020).[48] But basic scientific research is not enough to get treatments into the hands of patients. Rather, treating patients at scale requires overcoming substantial regulatory and logistical hurdles. *Supra* pp. 18-20. Moreover, the unpredictability of translating benchtop research into "human applications" results in a "valley of death" "between basic research (bench) and clinical research and patients (bed) who need their new treatments." Seyhan, *Lost in Translation*, Translational Med. Comms. (Nov. 18, 2019).[49]

Amici do critical work to narrow this "valley of death" and get treatments into the hands of patients by supporting translational research, investing in startups,

[48] https://hbr.org/2020/09/how-nonprofit-foundations-can-sustainably-fund-disease-research.

[49] https://transmedcomms.biomedcentral.com/articles/10.1186/s41231-019-0050-7.

developing patent strategies, and facilitating connections with the industry partners needed to shepherd a product through regulatory approval and commercial manufacturing and distribution. For example, PICI helped fund Tmunity Therapeutics, Inc., a biotherapeutics company focused on next generation CAR-T therapies. Tmunity's innovation is now being translated into real-world therapeutics following its acquisition by Kite, a global leader in cell therapy. *Kite Completes Acquisition of Tmunity*, Gilead (Feb. 22, 2023).[50]

Similarly, members of the PICI network founded ArsenalBio, a clinical stage, programmable cell therapy company focused on the treatment of solid tumors. Arsenal currently has six projects in the clinical development pipeline. *See Pipeline*, Arsenal Bio.[51] Arsenal's founders credit their success in part to PICI's unique model, which gave them "freedom to operate" and the ability to "invest in science." *See All the Right Ingredients*, PICI (June 24, 2021).[52]

Patents enable non-profits like *amici* to make these substantial investments and attract industry partners who can bring a product through regulatory approval and to market. Without the possibility of future revenue afforded by patents,

[50] https://www.gilead.com/news-and-press/press-room/press-releases/2023/2/kite-completes-acquisition-of-tmunity.

[51] https://arsenalbio.com/pipeline/.

[52] https://www.parkerici.org/the-latest/all-the-right-ingredients-a-qa-with-the-founders-of-arsenalbio/.

industry partners would be unwilling to undertake the significant investment necessary to transform basic science into bedside treatments. As a result, groundbreaking innovations would wither on the vine, or be restricted to isolated experimental uses.

A historical analogy helps illustrate the point. Before the Bayh-Dole Act encouraged commercial partners to invest the effort needed to transform government-funded basic research into practical advances, "hundreds of new compounds developed at university laboratories had not been tested and screened … because manufacturers were unwilling to undertake the expense without some possibility of obtaining exclusive rights to further development of a promising product." *The University and Small Business Patent Procedures Act: Hearing Before the S. Comm. on the Judiciary on S.414*, at 6 (May 16, 1979) (Statement of Elmer B. Staats, Comptroller General of the United States).[53] Non-profits like *amici* do critical work and invest in critical basic research, but they cannot do it all by themselves, and patents are critical to forging the partnerships and ecosystem necessary to ensure that the innovations *amici* support reach patients.

For this model to work, *amici* must shape their patent portfolios to withstand patentability challenges. Since their founding, *amici* have relied on the clear § 101

[53] https://www.gao.gov/assets/109391.pdf.

roadmap for transformed biological species and modified nucleic acid sequences. If the district court's decision is affirmed, an important fire wall will be breached, and *amici* and other immunotherapy researchers will face uncertainty regarding the patentability of their breakthrough inventions. In turn, this will chill investment and divert resources away from critical research in engineered biologics, including in the field of immuno-oncology.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be reversed.

Respectfully submitted,

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May 15, 2024

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May 15, 2024