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Silencing Innovation: The Patent Eligibility of siRNA Therapeutics

Alexander M. Walker, PhD

Small interfering ribonucleic acids (siRNAs) are a type of nucleic acid capable of initiating the ribonucleic acid interference (RNAi) pathway.¹ siRNA-induced RNAi creates a gene-silencing effect that can be used to affect the function of difficult-to-treat diseases and may be especially useful for the treatment of certain cancers.² The silencing effect is created by complementary recognition of the siRNA sequence and the messenger RNA sequence (mRNA) of the target gene.³ Several siRNA-based therapeutics have received approval from the U.S. Food and Drug Administration (FDA) to begin clinical trials and one siRNA therapeutic has recently received FDA marketing authorization.⁴

Whether an invention represents a subject matter eligible for patenting is determined by 35 U.S.C. § 101,⁵ which also lists

1. *RNA Interference (RNAi)*, NAT'L CENTER FOR BIOTECH. INFO., <https://www.ncbi.nlm.nih.gov/probe/docs/technai/> (last visited Oct. 27, 2018).

2. See Sherry Y. Wu et al., *Targeting the Undruggable: Advances and Obstacles in Current RNAi Therapy*, SCI. TRANSLATIONAL MED., June 2014, at 1, 1 (“[An siRNA] approach has attracted particular interest within oncology, where many important targets have proven undruggable.”).

3. See Ashley J. Pratt & Ian J. MacRae, *The RNA-Induced Silencing Complex: A Versatile Gene-Silencing Machine*, 284 J. BIOLOGICAL CHEMISTRY 17897, at 17899 (2009) (“[T]he [siRNA] guide strand form[s] a Watson-Crick-paired, A-form double helix with a complementary region of the target RNA.”); see also discussion of complementary binding *infra* Section I.A.

4. See Chiranjib Chakraborty et al., *Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine*, 8 MOLECULAR THERAPY NUCLEIC ACIDS 132, 132 (2017); *FDA Approves First-Of-Its Kind Targeted RNA-Based Therapy to Treat a Rare Disease*, U.S. FOOD & DRUG ADMIN. (Aug. 10, 2018), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-targeted-rna-based-therapy-treat-rare-disease> [hereinafter *RNA-Based Therapy*] (“To date, approximately 20 clinical trials have been initiated using miRNA- and siRNA-based therapeutics.”).

5. See, e.g., *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013).

the statutory categories available to patentees.⁶ Patent eligibility has traditionally foreclosed certain subject matter called “judicial exceptions,”⁷ which includes laws of nature, natural phenomena, and abstract ideas.⁸ The patenting of deoxyribonucleic acids (DNA) began in force following the Supreme Court’s decision in *Diamond v. Chakrabarty*.⁹ Following this decision, DNA sequences (including genomic DNA) were routinely patented¹⁰ until key court rulings held many types of DNA patents ineligible for patenting.¹¹ However, no case law has directly addressed the patent eligibility of DNA or ribonucleic acid (RNA) therapeutics.¹²

The goal of this note is to explore the patent eligibility of siRNA therapeutics. Part I of this note discusses the molecular mechanism of siRNA, the judicial exceptions to 35 U.S.C. § 101, relevant case law on the patent eligibility of DNA molecules, and the general economic effects of patent protection. Though there is no case law directly addressing the patent eligibility of RNA molecules, applying holdings on DNA molecules to siRNA suggests that it has limited patent eligibility, potentially only as part of a “method of treatment” claim,¹³ as discussed in Part II

6. 35 U.S.C. § 101 (1952).

7. *CLS Bank Int’l v. Alice Corp. Pty. Ltd.*, 717 F.3d 1269, 1277 (Fed. Cir. 2013), *aff’d*, 573 U.S. 208 (2014) (“If the invention falls within one of the statutory categories, we must then determine whether any of the three judicial exceptions nonetheless bars such a claim.”).

8. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

9. See Aaron S. Kesselheim, *Gene Patenting—The Supreme Court Finally Speaks*, 369 NEW ENG. J. MED. 869, 871 (2013) (Discussing “[t]he landmark 1980 case of *Diamond v. Chakrabarty*, which ushered in the modern explosion in biotechnology patents.”).

10. See, e.g., Vincent Y. Ling, *Patently Ours? Constitutional Challenges to DNA Patents*, 14 U. PA. J. CONST. L. 813, 813 (2012) (“Since [1980], the PTO has granted over 40,000 patents on DNA.”).

11. See, e.g., *Myriad*, 569 U.S. at 577.

12. See *Roche Molecular Sys., Inc. v. CEPHEID*, 905 F.3d 1363, 1373 n.6 (Fed. Cir. 2018) (“We express no opinion on subject matter eligibility of method claims that exploit DNA or RNA for drug-like new applications.”); see also Robert W. Esmond & Alex Kwan-Ho Chung, *The Patent Landscape of siRNA Nanoparticle Delivery*, 11 NANOTECH. L. & BUS. 15, 26–27 (2014) (describing litigation of siRNA as dealing with inventorship, patent malpractice, and trade secret disputes).

13. See, e.g., *Vanda Pharm. Inc. v. W.-Ward Pharm. Int’l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018), *petition for cert. filed*, 87 U.S.LW. 3279 (U.S. Jan. 17, 2019) (No. 18-817).

of this note. However, siRNA represents a significant area of potential biopharmaceutical investment¹⁴ and offers numerous medical advantages over conventional therapeutics.¹⁵ Therefore, Part III of this note offers an alternative interpretation of DNA case law that could expand the statutory categories available to potential siRNA patents as well as a legislative solution capable of offering non-patent market exclusivity.

I. BACKGROUND

Part I of this note will begin by giving a brief primer on the scientific principles underlying siRNA before transitioning into an overview of patentable subject matter. It will then explore case law interpreting 35 U.S.C. § 101 with a focus on holdings related to nucleotide technologies.¹⁶ Further, this section will provide context on the patent landscape of siRNA therapeutics and the forecasted economy of siRNA technologies.

A. A BRIEF PRIMER ON NUCLEOTIDES

Structurally, DNA generally possesses four types of nucleotide bases: adenine, thymine, guanine, and cytosine.¹⁷ RNA, a closely related biological macromolecule, contains uracil in lieu of thymine, but otherwise shares the same bases as DNA.¹⁸ The sequence of nucleotide bases possessed by a given DNA or RNA molecule is generally referred to as its “sequence.”¹⁹ Further, nucleotides have directionality imparted by the presence of a phosphate group at one end (referred to as the 5’ end) and a free hydroxyl group at the other (referred to as the 3’ end) of each

14. Chakraborty et al., *supra* note 4, at 134 (“[B]iopharma companies are investing in the development of miRNA- and siRNA-based therapeutic molecules. However, there is a challenge for small biotechnology companies because there is some financial volatility in this area.”).

15. Cf. *Novartis and UC Berkeley Take on “Undruggable” Proteins in New Collaboration*, NOVARTIS: STORIES (Sept. 28, 2017), <https://www.novartis.com/stories/discovery/novartis-and-uc-berkeley-take-undruggable-proteins-new-collaboration> (Explaining that most proteins, and thus most disease targets, are undruggable) [hereinafter *Novartis*] (internal quotation marks omitted).

16. See, e.g., *Myriad*, 569 U.S. at 594–95 (holding that cDNA is patent-eligible subject matter and that genomic DNA is not).

17. E.g., *DNA and RNA*, JEFFERSON, <https://cm.jefferson.edu/learn/dna-and-rna/> (last visited Feb. 13, 2019).

18. E.g., *id.*

19. E.g., *id.* (“It is the sequence of these four bases along the backbone that encodes information.”).

nucleic acid molecule.²⁰ Because longer nucleotide strands are polymers formed of repeating nucleotide units, they also have 5' and 3' ends.²¹

DNA is generally double-stranded, while RNA is often (but not always) single-stranded.²² Two DNA or RNA strands interact with one another through hydrogen bonds formed between their respective bases. Double-stranded DNA or RNA molecules generally have an anti-parallel structure, wherein the individual strands run parallel but in opposite directions.²³ The process by which two nucleotide bases bond is generally referred to as “complementary base-pairing.”²⁴ Moreover, base-pairing tends to occur in a predictable regime—adenine base-pairs with thymine (or uracil, in the case of RNA) and guanine base-pairs with cytosine.²⁵ When all of the bases of two DNA or RNA strands are able to base-pair, those two sequences are also said to be “complementary” or “fully complementary.”²⁶ Strands that are not fully complementary but still have some bases engaging in complementary base-pairing are said to be “partially” complementary.²⁷

Notably, not all of the DNA within a given genome codes for a protein or another functional gene product.²⁸ Following RNA transcription, in which an RNA strand is synthesized from a template DNA strand, a process called “RNA splicing” removes

20. *E.g.*, DNA, UNL. OF QUEENSL.: DIAMANTINA INST., <https://di.uq.edu.au/community-and-alumni/sparq-ed/sparq-ed-services/dna> (last visited Feb. 13, 2019).

21. *See id.*

22. *See DNA and RNA, supra* note 17.

23. *E.g., id.*

24. *E.g., id.*

25. *E.g., id.*

26. *See, e.g., id.; see also, e.g.*, Akira Shimizu et al., *Characterisation of Cytoplasmic DNA Complementary to Non-Retroviral RNA Viruses in Human Cells*, NATURE SCI. REP., May 30, 2014, at 1, 2 (describing an RNA-DNA binding interaction as “fully complementary”).

27. *See, e.g.*, Susanna Monti et al., *Complementary and Partially Complementary DNA Duplexes Tethered to a Functionalized Substrate: A Molecular Dynamics Approach to Biosensing*, 13 PHYSICAL CHEMISTRY CHEM. PHYSICS 12479, 12478 (2011) (describing mismatched DNA sequences as “partially complementary”).

28. *See, e.g.*, *Transcription, Translation and Replication*, ATDBIO, [https://www.atdbio.com/content/14/Transcription Translation-and-Replication](https://www.atdbio.com/content/14/Transcription%20Translation-and-Replication) (last visited Feb. 13, 2019).

the noncoding regions, called “introns,” from the coding regions, called “exons.”²⁹

B. THE TECHNOLOGY ITSELF: HOW DOES siRNA WORK?

Though RNAs are perhaps best known by the role that mRNA³⁰ plays in gene expression as an intermediary between DNA and protein,³¹ other forms of RNA molecules have a wide range of functional and regulatory roles.³² RNA interference (RNAi) is a natural mechanism of regulating gene expression that utilizes small RNA sequences³³ and may have an “important role in pathogen resistance.”³⁴ Generally, the process of using RNAi to affect gene expression is known as “silencing.”³⁵ The RNAi pathway is sensitive to “trigger RNA” molecules, most commonly either pri-microRNA (pri-miRNA)³⁶ or double-stranded RNA (dsRNA).³⁷ The pre-miRNAs are expressed naturally in mammalian cells, typically have a short-hairpin structure, and are processed by the cell into pre-miRNA that is then processed into miRNA.³⁸ Unlike pre-miRNA, dsRNA precursors

29. See, e.g., *id.*

30. See, e.g., *What is RNA?*, THE RNA SOCIETY, <https://www.rnasociety.org/about/> (last visited Nov. 18, 2018) (“A central tenet of molecular biology states that the flow of genetic information in a cell is from DNA through RNA to proteins . . .”).

31. See, e.g., *Gene Expression*, NAT’L CANCER INST.: DICTIONARY OF CANCER TERMS, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/gene-expression> (last visited Nov. 27, 2018) (Defining “gene expression” as “[t]he process by which a gene gets turned on in a cell to make RNA and proteins.”).

32. See, e.g., THE RNA SOCIETY, *supra* note 30 (“In recent years, however, we have begun to realize that the roles adopted by RNA are much broader and much more interesting.”).

33. *RNA Interference (RNAi)*, *supra* note 1.

34. *Id.*

35. *Id.*

36. See generally Louise Adams, *Pri-miRNA Processing: Structure Is Key*, 18 NATURE REVS. GENETICS 145, 145 (2017) (explaining that pri-miRNA is processed into pre-miRNA, which is transported and processed into mature miRNA); see also generally Lin He and Gregory J. Hannon, *microRNAs: Small RNAs with a Big Role in Gene Regulation*, 5 NATURE REVS. GENETICS 522, 524–25 (2004) (explaining the biogenesis of miRNA).

37. See *RNA Interference (RNAi)*, *supra* note 1.

38. See, e.g., *Precursor miRNAs for Successful miRNA Functional Studies*, THERMOFISHER SCI., <https://www.thermofisher.com/us/en/home/references/ambion-tech-support/microrna-studies/tech-notes/precursor-mirnas-for-successful-mirna-functional-studies.html> (last visited Jan. 23, 2019).

can be derived from endogenous or exogenous³⁹ sources and are processed by the cell into siRNAs.⁴⁰

Once processed, miRNA and siRNA are loaded into Argonaute (Ago) proteins to form an RNA-induced silencing complex (RISC)⁴¹ capable of targeting one or more mRNA sequences for silencing.⁴² The sequence of the miRNA or siRNA controls which mRNA is recognized as the target mRNA through complementary interaction.⁴³ Once the RISC complex has bound the target sequence, it performs its gene-silencing function through one of four major mechanisms: by “slicing” or chemically breaking the target RNA, by preventing translation of it into a protein (either by blocking access to the target RNA or by targeting the RNA for degradation by other enzymes), by modifying the histones associated with the locus of the gene encoding the RNA target and thereby altering the rate at which the gene is transcribed, or by eliminating the DNA encoding the RNA from the genome altogether.⁴⁴

There are a number of important differences between miRNA and siRNA molecules beyond their structural dissimilarity.⁴⁵ An miRNA can bind to sequences with which it is only partially complementary, allowing it to target a broad range of sequences.⁴⁶ Conversely, an siRNA *must* be “fully complementary

39. “Endogenous” refers to molecules “[a]rising within the organism or cell.” *E.g.*, *Endogenous*, GENSCRIPT: MOLECULAR BIOLOGY GLOSSARY, <https://www.genscript.com/molecular-biology-glossary/935/endogenous> (last visited Feb. 13, 2019). “Exogenous” refers to molecules “[a]rising from a source outside the organism or cell.” *E.g.*, *Exogenous*, GENSCRIPT: MOLECULAR BIOLOGY GLOSSARY, <https://www.genscript.com/molecular-biology-glossary/1013/exogenous> (last visited Feb. 13, 2019).

40. Pratt & MacRae, *supra* note 3 at 17898 (“Silencing RNA can be derived from exogenous or intracellular origins . . .”).

41. *See RNA Interference (RNAi)*, *supra* note 1.

42. *See* Pratt & MacRae, *supra* note 3, at 17899 (“The core architecture of Argonaute and guide RNA allows RISC to efficiently locate specific targets within the vast pool of cellular RNAs.”).

43. *Id.* (“[T]he [miRNA or siRNA] guide strand form[s] a Watson-Crick-paired, A-form double helix with a complementary region of the target RNA.”).

44. *See id.* at 17989–90.

45. Even among experts in the field, these differences are sometimes unnoticed because “the distinction [between miRNA and siRNA] has been obscured because they are associated with common enzymes . . . and their functions overlap with each other to a certain extent.” Jenny K.W. Lam et al., *siRNA Versus miRNA as Therapeutics for Gene Silencing*, 4 MOLECULAR THERAPY NUCLEIC ACIDS 252, 253 (2015).

46. *Id.* at 254–55.

to its target mRNA,” thereby making siRNA-based RNAi highly specific.⁴⁷ Moreover, introducing synthetic siRNA directly to mammalian cells (rather than the longer dsRNA precursors) has been shown to further increase the specificity of the resulting RNAi response.⁴⁸ Because siRNA is fully complementary to its target sequence, it also is able to activate the “slicing” function of the siRNA-RISC complex.⁴⁹ Conversely, miRNA-mediated silencing usually “occurs through translation repression, or degradation by deadenylation, decapping or exonuclease action.”⁵⁰ At least for these reasons, siRNAs have been favored over miRNA for therapeutic applications of RNAi-based gene silencing.⁵¹

Further, siRNA-mediated RNAi offers a major improvement to conventional therapeutics, especially in the treatment of certain cancers.⁵² This is in part due to the ability of siRNA to target any given mRNA sequence and *only* that sequence.⁵³ Moreover, siRNA technologies have the capability to affect the expression (and thereby the function) of a broad range of genes as compared to traditional small molecule drugs—conventional therapeutics can only target certain classes of proteins, leaving “some diseases untreatable.”⁵⁴ By contrast, siRNAs “can downregulate the expression of virtually all genes and their mRNA transcripts,” significantly broadening the range of treatable targets “[s]ince

47. *Id.* at 253.

48. *See id.* (“[D]irect introduction of synthetic siRNAs, instead of the long dsRNAs (thus skipping the step of Dicer processing), leads to effective RNAi without the complication of activating the IFN response.”).

49. *See id.* at 253–55 (“[T]he guide strand guides the active RISC to its target mRNA for cleavage by AGO2. As the guide strand only binds to mRNA that is fully complementary to it, siRNA causes specific gene silencing.”).

50. *Id.* at 255.

51. *See id.* at 255–56, 264 (describing siRNAs as “extremely useful for targeting single gene disorders” and as having been favored by researchers as potential therapeutics due to the uncertainty surrounding miRNA “mechanism of action and specificity”).

52. *See, e.g.,* Kevin Bullis, *Gene-Silencing Drugs Finally Show Promise*, MIT TECH. REV. (Sep. 14, 2014), <https://www.technologyreview.com/s/530631/gene-silencing-drugs-finally-show-promise/> (“Treating cancer is one area where RNAi’s particular advantages are expected to shine.”).

53. *See id.* (“RNAi can be extremely precise, potentially shutting down only proteins found in cancer cells.”).

54. *Novartis, supra* note 15 (internal quotation marks omitted) (quoting Dan Nomura, director of the Novartis-Berkeley Center for Proteomics and Chemistry Technologies).

many diseases result from the expression of undesired or mutated genes, or from overexpression of certain normal genes.”⁵⁵ Despite the relative advantages of siRNA therapeutics, delivery of siRNA into the cell remains a major challenge.⁵⁶

Conventional siRNA therapeutics contain roughly nineteen to twenty-one nucleotides identical in sequence to the target gene as well as “two nucleotide overhangs at the 3’ end . . . which are important for recognition by the RNAi machinery.”⁵⁷ However, at least one study has shown that dsRNAs up to twenty-seven nucleotides in length are significantly “more potent inducers of RNAi than conventional siRNAs.”⁵⁸ Using dsRNAs with thirty or more nucleotides is thought to be undesirable because those dsRNAs can “activate[] . . . the interferon pathway,”⁵⁹ an immune system response to pathogen infection.⁶⁰

C. THE JUDICIAL EXCEPTIONS TO 35 U.S.C § 101 LIMIT PATENT ELIGIBILITY

Section 101 of the Patent Act establishes the four statutory categories of patentable subject matter: processes, machines, articles of manufacture, and compositions of matter.⁶¹ However, merely reciting subject matter directed to one of the four statutory categories does not guarantee patent eligibility.⁶² Rather, “laws of nature, natural phenomena, and abstract ideas” are

55. Lam et al., *supra* note 45, at 255.

56. Hassan Dana et al., *Molecular Mechanisms and Biological Functions of siRNA*, INT. J. BIOMED. SCI., June 2017, at 48, 50 (“The fantastic potential of siRNA to silence important genes in disease pathways comes with noteworthy challenges and barriers in its delivery.”).

57. Lam et al., *supra* note 45, at 255 (citing S. Patrick Walton et al., *Designing Highly Active siRNAs for Therapeutic Applications*, 277 FEBS J. 4806, 4807 (2010)).

58. Dong-Ho Kim et al., *Synthetic dsRNA Dicer Substrates Enhance RNAi Potency and Efficacy*, 23 NATURE BIOTECH. 222, 225 (2005).

59. *Id.* at 222.

60. See generally *Interferon (IFN) Cell Signaling Pathway*, THERMOFISHER, <https://www.thermofisher.com/us/en/home/life-science/cell-analysis/signaling-pathways/interferon/interferon-overview.html> (last visited Mar. 5, 2019) (“The interferon . . . pathway plays a critical role in the human immune response.”).

61. See 35 U.S.C. § 101 (1952) (listing, in general terms, subject matter eligible for patent).

62. See generally U.S. PAT. & TRADEMARK OFF., MPEP § 2104 (9th ed., Rev. 8, Jan. 2018) (describing four requirements, in addition to inclusion in one of these four statutory categories, for a patent application to be valid).

generally not patentable.⁶³ These exceptions to are often referred to as “judicial exceptions” to § 101’s broad statutory categories⁶⁴ and are designated as such because they are rooted in the common law rather than the statutory language of 35 U.S.C. § 101.⁶⁵ The judicial exceptions were developed to prevent the patenting of “basic tools of scientific and technological work”⁶⁶ and concepts that are “part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.”⁶⁷ From a policy perspective, the judicial exceptions are targeted to prevent patents from “reach[ing] too far and claim[ing] too much, on balance obstructing rather than catalyzing innovation.”⁶⁸ Thus, patents that simply recite “an instruction to ‘apply the natural law’ . . . foreclose[] more future invention than the underlying discovery could reasonably justify.”⁶⁹ However, courts have recognized that interpreting the judicial exceptions too broadly could seriously undermine the purpose of patent law because “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.”⁷⁰

In order to balance these competing policy interests, the Supreme Court has provided a two-step framework, articulated in *Alice Corp. v. CLS Bank International*, to determine if a claim that recites subject matter directed to one of the judicial exceptions is nonetheless eligible for patenting.⁷¹ If a court determines

63. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (“Excluded from . . . patent protection are laws of nature, natural phenomena, and abstract ideas.”).

64. *CLS Bank Int’l v. Alice Corp. Pty. Ltd.*, 717 F.3d 1269, 1277 (Fed. Cir. 2013), *aff’d*, 573 U.S. 208 (2014) (“If the invention falls within one of the statutory categories, we must then determine whether any of the three judicial exceptions nonetheless bars such a claim.”); U.S. PAT. & TRADEMARK OFF., *supra* note 62 (“[A] claimed invention must be directed to patent-eligible subject matter and not a judicial exception . . .”).

65. *Bilski v. Kappos*, 561 U.S. 593, 601 (2010) (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)) (“The Court’s precedents *provide three specific exceptions* to § 101’s broad patent-eligibility principles: ‘laws of nature, physical phenomena, and abstract ideas.’”) (emphasis added).

66. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

67. *Bilski*, 561 U.S. at 602 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)) (internal quotation marks omitted).

68. *CLS Bank*, 717 F.3d at 1277.

69. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 86 (2012).

70. *Id.* at 71.

71. *See Alice Corp. Pty. v. CLS Bank Int’l*, 573 U.S. 208, 216 (2014) (quoting *Mayo*, 566 U.S. at 84) (“First, we determine whether the claims at issue are

that a particular claim or set of claims are directed to one of the judicial exceptions, it must examine the elements of the claim to determine if there are “additional elements that ‘transform the nature of the claim’ into a patent-eligible application.”⁷² An additional element or a combination of additional elements amounting to “well-understood, routine, conventional activity,” as recognized by a court or a person of ordinary skill in the art, is not sufficient to transform a claim directed to a judicial exception into patent-eligible subject matter.⁷³ Further, claim elements are considered as a whole, meaning that even where individual steps may be well understood, routine, or conventional, the combination may “transform the nature of the claim’ into a patent-eligible application.”⁷⁴ If the additional element or combination of elements “amounts to significantly more than a patent upon the [judicial exception] itself,” then the claim is eligible for patenting.⁷⁵

Therapeutics and therapeutic strategies have posed special problems for courts interpreting 35 U.S.C. § 101. Methods of diagnosis have generally been regarded by both the Supreme Court and the Federal Circuit as reciting patent-ineligible subject matter insofar as such methods often are difficult to distinguish from the natural law they are applying.⁷⁶ However, the Federal Circuit recently held that a method of treating schizophrenia using the anti-psychotic drug iloperidone was patent-

directed to one of those patent-ineligible concepts. If so, we then ask, ‘What else is there in the claims before us?’”).

72. *Id.* at 216.

73. *Mayo*, 566 U.S. at 68 (citing *Parker v. Flook*, 437 U.S. 584, 590 (1978)) (“[Well-understood, routine, or conventional] activity is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law.”).

74. *Alice*, 573 U.S. at 211 (quoting *Mayo*, 566 U.S. at 74); *see also* *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1051 (Fed. Cir. 2016) (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)) (“[A] new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.”) (internal quotation marks omitted).

75. *Mayo*, 566 U.S. at 73.

76. *E.g.*, *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015) (holding a method of diagnosis based on “detecting” amplified DNA as patent ineligible on the grounds that the method used conventional steps to apply a natural law).

eligible.⁷⁷ Because the method at issue recited “using a specific compound at specific doses to achieve a specific outcome,” it was found to contain “more than the natural relationship” between iloperidone and schizophrenia.⁷⁸

D. THE *MYRIAD GENETICS* SAGA: DEFINING PATENT ELIGIBILITY OF NUCLEOTIDES

Nucleotide technologies present a difficult case for patent eligibility because of the close relationship between biotechnology and the natural properties of DNA.⁷⁹ The Supreme Court ruled on the patent eligibility of nucleotide sequences generally in *Association for Molecular Pathology v. Myriad Genetics*.⁸⁰ Myriad determined the chromosomal coordinates for the BRCA1 and BRCA2, which are commonly implicated in breast and ovarian cancer.⁸¹ At issue in *Myriad* were nine claims from three patents, though the holding focused in particular on four claims directed to different DNA formulations: the full-length BRCA1 gene sequence, the BRCA1 complementary DNA (cDNA) sequence,⁸² any DNA molecule of at least fifteen nucleotides having the identical sequence to any portion of the full-length BRCA1 sequence, and any DNA molecule of at least fifteen nucleotides having the identical sequence to any portion of the BRCA1 cDNA sequence.⁸³ In effect, Myriad’s patents gave it “the exclusive right to isolate and individual’s BRCA1 and BRCA2 genes (or any strand of 15 or more nucleotides within the genes)

77. *Vanda Pharm. Inc. v. W.-Ward Pharm. Int’l Ltd.*, 887 F.3d 1117, 1121, 1136 (Fed. Cir. 2018), *petition for cert. filed*, 87 U.S.LW. 3279 (U.S. Jan. 17, 2019) (No. 18-817).

78. *Id.*

79. *Cf.* Diane Gershon, *Recombinant DNA Technology*, 348 NATURE 92, 92–93 (1990) (describing the commercialization of recombinant DNA technology, which exploits natural properties of DNA, including hybridization, polymerization, mRNA structure, and restriction enzyme-based DNA modification).

80. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580 (2013) (“This case . . . requires us to resolve whether a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U.S.C. § 101 by virtue of its isolation from the rest of the human genome.”).

81. *See id.* at 582–83 (“Mutations in these genes can dramatically increase an individual’s risk of developing breast and ovarian cancer.”).

82. A “cDNA” molecule is created by using an mRNA molecule as a template to synthesize DNA “complementary” in sequence to the mRNA molecule. *See id.* at 582 (describing a laboratory method by which DNA can be created synthetically from “an mRNA molecule”).

83. *See id.* at 584 (describing each claim at issue).

. . . [and] to synthetically create BRCA cDNA.”⁸⁴ Because “isolation is necessary to conduct genetic testing,” Myriad’s patents also gave it a monopoly over diagnostic applications of the BRCA1 and BRCA2 genes.⁸⁵ The case arose on an action for declaratory judgment seeking a declaration that Myriad’s patents were directed to ineligible subject matter and therefore invalid under 35 U.S.C. § 101.⁸⁶

The Court found that Myriad’s claims to full-length gene sequences were invalid under 35 U.S.C. § 101 because they represent naturally occurring DNA sequences and that neither discovering the chromosomal location of a gene nor “separating the gene from its surrounding genetic material . . . is an act of invention.”⁸⁷ However, recognizing that naturally occurring genomic DNA sequences contain subsections known as “introns” and “exons,” the Court ruled that claims for cDNA sequences were patent-eligible because those sequences contain only exons and therefore represent a DNA sequence that is not naturally occurring.⁸⁸ The Court further recognized that there may be a sequence of cDNA that is sufficiently short so that it has an identical sequence to a genomic DNA sequence, and that such a cDNA would not be patent-eligible under 35 U.S.C. § 101.⁸⁹ Importantly, the Court did not address method claims directed to or involving DNA sequences,⁹⁰ though it did suggest that the techniques for isolating DNA described in Myriad’s patents were “well understood, widely used, and fairly uniform,”⁹¹ suggesting that they would likely be patent ineligible. Further, the Court did not directly address the patent eligibility of a DNA molecule having an unusual or non-natural composition, as Myriad’s

84. *Id.* at 585.

85. *Id.*

86. *Id.* at 589 n.3.

87. *Id.* at 592.

88. *Id.* at 594–95 (“cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a ‘product of nature’ and is patent eligible under § 101 . . .”).

89. *Id.* at 595 (“[A cDNA sequence is patent eligible] except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA.”).

90. *Id.* (“[T]here are no method claims before this Court.”).

91. *Id.* at 595–96 (internal quotation marks omitted) (quoting *Ass’n for Molecular Pathology v. U.S. Pat. & Trademark Office*, 702 F. Supp. 2d 181, 202–03 (S.D.N.Y. 2010)).

claims were primarily directed to nucleotide sequences rather than chemical compositions.⁹²

In *University of Utah Research Foundation v. Ambry Genetics*, a case related to *Myriad Genetics*, Myriad filed suit against Ambry Genetics for infringing three of its patents, including two of the patents at issue in *Myriad*.⁹³ Myriad alleged that Ambry sold kits to detect susceptibility to certain breast and ovarian cancers—Ambry counterclaimed that the relevant patents were invalid under 35 U.S.C. § 101.⁹⁴ Specifically, Ambry alleged that four composition of matter claims directed to DNA primers (“short, synthetic, single-stranded DNA molecules” that are complementary to a specific nucleotide sequence⁹⁵ and are capable of initiating DNA replication)⁹⁶ and two method claims “involv[ing] comparisons between the wild-type BRCA sequences with the patient’s BRCA sequences” were invalid.⁹⁷

Citing *Myriad*’s proposition that claims to DNA sequences—including those that do not occur naturally, like the synthetic DNA primers claimed in Myriad’s patents—as short as 15 nucleotides (the length of the primers in Myriad’s claims) could be held invalid if they have identical sequences to DNA molecules found in nature, the Federal Circuit held Myriad’s claims to DNA primers invalid under 35 U.S.C. § 101. Despite the fact that the primers themselves were not naturally occurring and, in fact, no DNA molecule having a single-stranded structure naturally occurs within the human body, the Court held the claims invalid because they had an identical *sequence* to a portion of naturally occurring DNA⁹⁸ and therefore did not have a “unique *structure*.”⁹⁹ Moreover, the Federal Circuit found the fact that

92. *Id.* at 593 (“[Myriad’s] claim is concerned primarily with the information contained in the genetic *sequence*, not with the specific chemical composition of a particular molecule.”).

93. *Univ. of Utah Research Found. v. Ambry Genetics*, 774 F.3d 755, 757 (Fed. Cir. 2014). *Ambry Genetics* was decided by the Federal Circuit one year after the Supreme Court’s ruling in *Myriad*.

94. *Id.* at 758.

95. *Id.* (internal quotation marks omitted) (citation omitted).

96. *Primers*, NATURE EDUC.: SCITABLE, <https://www.nature.com/scitable/definition/primer-305> (last visited Nov. 12, 2018).

97. *Ambry*, 774 F.3d at 759.

98. *Id.* at 760.

99. *Id.* at 761 (emphasis added). The Federal Circuit’s holding is unclear as to whether a nucleotide sequence is generally its “structure” for the purposes of 35 U.S.C. § 101 analysis or whether that is the case only for DNA primers. See discussion *infra* Section III.B. (“[T]he Federal Circuit has used a nebulous, and

DNA primers are able to serve as a starting material for DNA polymerization irrelevant, holding that the primers did not “perform a significantly new function”¹⁰⁰ despite the fact that naturally occurring DNA replication utilizes RNA primers rather than DNA primers.¹⁰¹ Instead, the Federal Circuit identified the function of DNA primers as the ability of “complementary nucleotide sequences [to] bind to each other,” which is an “innate ability of DNA.”¹⁰² Further, because the two method claims at issue involved “comparison steps,” the Federal Circuit found that the claims recited abstract ideas and subjected them to analysis under *Alice*.¹⁰³ Under the second step of *Alice*, the Court found that the “non-patent-ineligible elements” of the claims were “well-understood, routine, and conventional,” and therefore did not “make the claims as a whole patent-eligible.”¹⁰⁴

E. A RECENT CASE ELABORATES ON NUCLEOTIDE PATENT ELIGIBILITY

A recent Federal Circuit case, *Roche Molecular Systems, Inc. v. CEPHEID*, offers additional guidance on the patent eligibility of nucleotide sequences.¹⁰⁵ Primarily at issue in *Roche* were two families of claims in a patent related to the detection *rpoB*, a gene associated with drug-resistant strains of the pathogen *Mycobacterium tuberculosis*.¹⁰⁶ The first claim family was directed to a primer for use with polymerase chain reaction (PCR) tech-

perhaps counter-intuitive, definition of ‘nucleotide structure.’”); cf. *Ambry*, 774 F.3d at 761 (“Primers do not have [a unique] structure and are patent ineligible.”).

100. *Ambry*, 774 F.3d at 761.

101. See Appellants’ Opening Brief at 7, *Ambry*, 774 F.3d 755 (2014) (Nos. 14-1361, 14-1366) (“There are no short, single strands of DNA with a free 3’-OH group in nature that can serve as primers. In natural DNA replication, RNA primers are used as the starting material.”).

102. *Ambry*, 774 F.3d at 761.

103. *Id.* at 764.

104. *Id.*

105. *Roche Molecular Sys., Inc. v. CEPHEID*, 905 F.3d 1363, 1366 (Fed. Cir. 2018) (“[T]he [patent at issue] involves subjecting DNA extracted from a biological sample taken from a patient (e.g., a tissue or fluid sample) to amplification by polymerase chain reaction (‘PCR’) using a short, single-stranded nucleotide sequence (a ‘primer’).”).

106. See *id.* (“The [patent at issue] provides two types of claims: (1) composition-of-matter claims [of which there is one independent claim] . . . and (2) process claims for methods [of which there is one independent claim] . . .”).

niques capable of “hybridizing” to *rpoB* and having “14–50 nucleotides.”¹⁰⁷ The second claim family was directed to a process for “amplifying” *rpoB* using a “plurality of primers” capable of hybridizing to a “site comprising at least one position-specific [*M. tuberculosis*] signature nucleotide” and “detecting” the amplified gene product.¹⁰⁸

In a panel decision, a two-judge majority held that *Ambry* dictated that the primers were patent ineligible because they contained an identical sequence to naturally occurring DNA.¹⁰⁹ The majority opinion rejected Roche’s arguments that the primers were chemically and structurally distinct from any naturally occurring DNA molecule, relying on the *Ambry* court’s rejection of similar arguments.¹¹⁰ Roche further argued that the structure of its primers was more distinct from their relevant *M. tuberculosis* DNA counterparts than was the case with the primer/gene pairs at issue in *Ambry* because *M. tuberculosis* has a circular chromosome that lacks the 3’ end present in the primer sequences. The majority opinion also rejected this argument,¹¹¹ as well as Roche’s contentions about the “specificity” of the primers described in the patent.¹¹² Therefore, the majority found that Roche’s primer claims were patent ineligible.¹¹³

As to the method claims at issue, the majority found that the claims were directed to “a relationship between the . . . naturally occurring position-specific signature nucleotides and the presence of [*M. tuberculosis*] in a sample.”¹¹⁴ Applying *Alice*, the majority looked to the rest of the claim to see if there was an “inventive concept that transforms [the claim] into patent-eligible subject matter.”¹¹⁵ It found that the “amplification” step was

107. *Id.* at 1367 (citing U.S. Patent No. 5,643,723 col. 28 ll. 14–31 (filed May 26, 1994)).

108. *Id.* (citing U.S. Patent No. 5,643,723 col. 25 l. 57–col. 27 l. 6 (filed May 26, 1994)).

109. *Id.* at 1371 (“[Roche’s primers] are indistinguishable from their corresponding nucleotide sequences on the naturally occurring DNA, and . . . therefore, are patent-ineligible within the meaning of § 101.”).

110. *Id.* at 1369–70 (citing *Ambry*, 774 F.3d at 761).

111. *Id.* at 1370.

112. *Id.*

113. *Id.* at 1371.

114. *Id.*

115. *Id.* at 1372.

“routine’ when the patent application was filed”¹¹⁶ and that the “detecting” step was “devoid of an inventive concept because it involves a simple mental determination.”¹¹⁷ The majority further distinguished Roche’s method from a method for treating a disease with a new drug because Roche’s claims relied on the ability of their primers to hybridize to complementary nucleotide sequences.¹¹⁸ The opinion classified the hybridization of complementary nucleotides as a patent-ineligible “law of nature.”¹¹⁹ However, the majority stated in a footnote that they “express[ed] no opinion on the subject matter eligibility of method claims that exploit DNA or RNA for drug-like new applications.”¹²⁰

Writing separately in a concurring opinion, Judge O’Malley agreed that *Ambry* required that the claim be held invalid, but felt that the court should “revisit [the] holding in [*Ambry*] at least with respect to the primer claims.”¹²¹ O’Malley argued that the validity of claims directed to DNA primer was not the question at issue in *Ambry*—rather, she characterized the question before the *Ambry* court as whether the district court had abused its discretion in denying a preliminary injunction.¹²² Moreover, she suggested that the Federal Circuit’s decision in *Ambry* suffered from a lack of record evidence and that Roche’s DNA primer may have a unique, non-naturally occurring structure, and further “challenge[d] the conclusion that th[e] entire class of [DNA primer] molecules is ineligible under § 101.”¹²³ O’Malley distinguished the structure of DNA primers from their nucleotide sequence and therefore challenged the court’s determination of nucleotide structure based on only nucleotide sequence.¹²⁴ Further, O’Malley found unclear how primers “are structurally

116. *Id.* (quoting *Roche Molecular Sys., Inc. v. CEPHEID*, No.14-CV-03228-EDL, 2017 WL 6311568, at *15 (N.D. Cal. 2017)).

117. *Id.*

118. *Id.* at 1373.

119. *Id.*

120. *Id.* at 1373 n.6.

121. *Id.* at 1375 (O’Malley, J., concurring).

122. *Id.* (O’Malley, J., concurring).

123. *Id.* at 1377 (O’Malley, J., concurring).

124. *Id.* (O’Malley, J., concurring) (“[A] finding that the two [primers] have identical *sequences* does not entirely resolve the question of whether they are *structurally* identical because structure is not defined solely by nucleotide sequence.”).

identical to the ends of DNA strands found in nature.”¹²⁵ Likewise, O’Malley found that the record before the court also suggested that the primers at issue have a unique *function* as compared to naturally occurring DNA.¹²⁶ Ultimately, she found that Roche had submitted “evidence . . . that, at the very least, raises genuine issues of material fact as to whether there exists anything in nature that both has the structure and performs the function of the claimed primers.”¹²⁷

F. THERE ARE NO EXISTING INTERPRETATIONS OF § 101 AS APPLIED TO siRNA

There are virtually no adjudications of the patent eligibility of claims directed to siRNA technologies.¹²⁸ As discussed in Section I.E. of this note,¹²⁹ the Federal Circuit has expressly declined to comment on the patent eligibility of claims directed to RNA therapeutics.¹³⁰ The Patent Trial and Appeal Board (PTAB) found in *Ex parte Khvorova* that “the ability of siRNA sequences to silence genes is ‘directed to naturally occurring phenomena.’”¹³¹ However, the patent at issue in *Khvorova* was specifically directed to an algorithm for “determining . . . whether a particular siRNA sequence will result in gene silencing.”¹³² To that extent, the PTAB did not decide on the patent eligibility of RNA therapeutics. The PTAB ultimately found that the claim at issue “does not recite a specific algorithm . . . [and] preempts any algorithm for designing siRNA sequences,” and therefore was patent ineligible under 35 U.S.C. § 101.¹³³

125. *Id.* (O’Malley, J., concurring) (quoting *Ambry*, 774 F.3d at 760) (internal quotation marks omitted).

126. *Id.* at 1380 (O’Malley, J., concurring).

127. *Id.* at 1381 (O’Malley, J., concurring).

128. See Esmond & Chung, *supra* note 12, at 26–27 (describing litigation of siRNA as dealing with inventorship, patent malpractice, and trade secret disputes).

129. See discussion *supra* Section I.E.

130. *Roche Molecular Sys.*, 905 F.3d at 1373 n.6.

131. *Ex parte Khvorova*, No. 2012-010359, 2015 WL 4267897, at *4 (P.T.A.B. July 10, 2015) (quoting *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015)).

132. *Id.* at *3 (citing U.S. Pub. No. 10/940,892, claim 85 (filed Nov. 17, 2005)).

133. *Id.* at *5.

G. THE PATENT LANDSCAPE OF siRNA TECHNOLOGIES

A search of the Patent Full-Text Database for claims that contain the term “siRNA” returns over 2,200 patents.¹³⁴ Further, a survey of siRNA patent families by Robert W. Esmond and Alex Kwan-Ho Chung identified three main patent families of siRNA technologies: the “Carnegie” patents, broadly directed to double-stranded RNA (dsRNA) inhibition, the “Tuschl I” patents, directed to short (twenty-one to twenty-three nucleotide) dsRNAs and methods of inhibition using short dsRNAs, and the “Tuschl II” patents, claiming dsRNAs with nineteen to twenty-five nucleotides and 3' overhangs as well as a method of preparing such dsRNAs.¹³⁵ The Carnegie patents expired at the end of 2018, and therefore are not likely to prevent “generic” manufacture of siRNA therapeutics.¹³⁶ However, both the Tuschl patent families are set to expire in 2021, and therefore have the potential to “block companies from marketing [their own] siRNA therapeutics.”¹³⁷ Esmond and Chung postulate that infringement litigation or inter partes review (IPR) may occur with regard to these patents if a claimed siRNA therapeutic receives FDA approval prior to the expiry of their patent term.¹³⁸ However, if no therapeutic receives FDA approval by that time, any litigation or IPR will likely concern a patent having a more specific claim scope.¹³⁹ As of September 15, 2017, there were 20 clinical trials of miRNA- and siRNA-based therapeutics.¹⁴⁰ More recently, the FDA has for the first time granted marketing approval to an siRNA-based therapy,¹⁴¹ indicating that there may soon be litigation concerning these foundational siRNA patents.¹⁴² RNA-

134. *Patent Full-Text Database*, U.S. PAT. TRADEMARK OFF., <http://patft.uspto.gov/> (last visited Nov. 19, 2018) (follow “Advanced Search” hyperlink; then search for “ALCM/siRNA”).

135. Esmond & Chung, *supra* note 12, at 17–18.

136. *Id.* at 18.

137. *Id.*

138. *See id.* at 27 (describing the likelihood of litigation as compared to IPR of a patented technology that achieves FDA approval prior to the expiry of its relevant patent term).

139. *Cf. id.* (“After 2021, litigation concerning [the Carnegie, Tuschl I, and Tuschl II] siRNA and nanoparticle patents will be unlikely, as no company will have a dominating position.”).

140. Chakraborty et al., *supra* note 4, at 132.

141. *RNA-Based Therapy*, *supra* note 4.

142. *But Cf.* Esmond & Chung, *supra* note 12, at 27 (“After 2021, litigation concerning siRNA and nanoparticle patents will be unlikely, as no company will have a dominating position.”).

based therapeutics more generally are expected to have significant economic growth within the next decade and at least one organization has suggested that RNAi technologies could represent a \$1.81 billion market by 2025.¹⁴³

H. PATENT PROTECTION ENCOURAGES INVESTMENT

Because of the high cost of both developing and performing clinical trials on a new drug, “pharmaceutical companies are rarely willing to develop drugs without patent protection.”¹⁴⁴ A developer of a new drug may spend “hundreds of millions of dollars on clinical trials” while the drugs manufactured by a generic competitor are “exempted from [safety and efficacy standards] and enter the market at minimal cost[.]”¹⁴⁵ making patent protection arguably more important to pharmaceutical developers than other industries.¹⁴⁶ To this end, pharmaceutical manufacturers “regularly screen their drugs in R&D and discard ones with weak patent protection.”¹⁴⁷ Like conventional therapeutics, siRNA-based drugs also require FDA approval,¹⁴⁸ and will therefore encounter similar financial hurdles as conventional therapeutics. Some commentators have expressed fears that recent interpretations of 35 U.S.C. § 101 (including *Mayo* and *Myriad*) could “curtail further research and investment in areas broader” than the subject matter covered by the judicial exceptions.¹⁴⁹ Though at least one decision from the Federal Circuit seems to have utilized economic investment as justification that a tech-

143. See *Antisense & RNAi Therapeutics Market Size Worth \$1.81 Billion By 2025*, GRAND VIEW RESEARCH (Mar. 2018), <https://www.grandviewresearch.com/press-release/antisense-rnai-therapeutics-market> [hereinafter *Antisense & RNAi*].

144. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 505 (2009).

145. *Id.*

146. *Cf. id.* (“At a time when many scholars believe that patents often do more harm than good, the pharmaceutical industry is widely thought to showcase the benefits of patents.”).

147. *Id.*

148. See *RNA-Based Therapy*, *supra* note 4 (announcing the first FDA-approved siRNA-based drug).

149. See, e.g., Robert L. Stoll, *Are Patent Decisions Strangling Our Economy?*, HILL (May 13, 2016, 11:30 AM), <https://thehill.com/blogs/pundits-blog/technology/279830-are-patent-decisions-strangling-our-economy> (“This spate of decisions is clouding the validity of patents in everything from diagnostic methods to personalized medicine to business methods and gaming.”).

nology is not “conventional, routine, and well-understood” at *Alice* step two,¹⁵⁰ “labor” or “investment” in developing a technology is generally insufficient to overcome challenges under 35 U.S.C. § 101.¹⁵¹

II. ANALYSIS

The potential 35 U.S.C. § 101 eligibility of siRNA patent claims will be discussed by applying Supreme Court and Federal Circuit precedent on DNA patents. In particular, siRNA will be analyzed because of its utility in medical applications.¹⁵² Since the vast majority of siRNA patents are claimed as compositions of matter or processes,¹⁵³ each of these statutory classes will be addressed separately. Moreover, the major patent families identified by Esmond and Chung will be utilized as relevant examples of siRNA claim formulation.¹⁵⁴

A. siRNA IS LIKELY INELIGIBLE AS A COMPOSITION OF MATTER

Claims to siRNA formulated as a composition of matter may likely be patent-ineligible under the rulings in *Myriad*¹⁵⁵ and

150. *Cf. Exergen Corp. v. Kaz USA, Inc.*, 725 F. App'x 959, 966 (Fed. Cir. 2018) (“Following years and millions of dollars of testing and development, the inventor determined for the first time the coefficient representing the relationship between temporal-arterial temperature and core body temperature and incorporated that discovery into an *unconventional* method of temperature measurement.”) (emphasis added).

151. *See, e.g., Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 577 (2013) (“[E]xtensive effort alone is insufficient to satisfy § 101's demands.”).

152. *See Lam et al., supra* note 45, at 255 (describing siRNAs as “extremely useful for targeting single gene disorders” and as having been favored by researchers as potential therapeutics due to the uncertainty surrounding miRNA “mechanism of action and specificity”).

153. *See, e.g., U.S. Patent No. 8,552,171* (filed Oct. 10, 2004) (claiming siRNA as a composition of matter); *see, e.g., U.S. Patent No. 6,506,559* (filed Dec. 18, 1998) (claiming siRNA as a process). *See generally* Esmond & Chung, *supra* note 12, at 17–18 (detailing three fundamental families of siRNA patents as claiming compositions of matter or processes).

154. *See* Esmond & Chung, *supra* note 12, at 17–18.

155. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013).

Ambry.¹⁵⁶ Generally, siRNAs function by complementary interaction with a target mRNA.¹⁵⁷ In *Myriad*, the Court held that cDNA was patent-eligible insofar as it does not contain intron sequences that would otherwise be present in the corresponding genomic DNA sequence.¹⁵⁸ The Federal Circuit restated this holding in *Ambry* as generally prohibiting composition of matter claims directed to nucleotide sequences having a utility based on complementary binding.¹⁵⁹ Under the holding in *Myriad*, patents directed to siRNA molecules would likely not be patent-eligible if they claimed sequences identical to a naturally occurring mRNA molecule.¹⁶⁰ Patents that claim siRNA that is “perfectly complementary to an mRNA”¹⁶¹ are likely to be found patent ineligible in view of *Myriad* because there are no “intron sequences” to remove when designing siRNA molecules. Since siRNA must have perfect identity with a target mRNA in order to induce a silencing effect,¹⁶² this is likely to be problematic for claims to siRNA as a composition of matter. Neither the therapeutic function of the siRNA¹⁶³ nor the specificity of an siRNA to any particular mRNA¹⁶⁴ is likely to improve the patent eligibility of a perfectly complementary siRNA sequence in view of *Ambry*’s

156. Univ. of Utah Research Found. v. Ambry Genetics, 774 F.3d 775 (Fed. Cir. 2014).

157. See Pratt & MacRae, *supra* note 3, at 17899 (“[T]he [miRNA or siRNA] guide strand form[s] a Watson-Crick-paired, A-form double helix with a complementary region of the target RNA.”).

158. *Myriad*, 569 U.S. at 595.

159. *Ambry*, 774 F.3d at 761.

160. Cf. *Myriad*, 569 U.S. at 595 (“As a result, cDNA is not a ‘product of nature’ and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA.”).

161. See, e.g., U.S. Patent No. 8,552,171 (filed Oct. 10, 2004) (claiming siRNA that is “perfectly complementary to an mRNA.”).

162. See Lam et al., *supra* note 45, at 253 (“To elicit RNAi, the siRNA must be fully complementary to its target mRNA.”).

163. See *Ambry*, 774 F.3d at 760–61 (holding that the primary function for the purposes of patent eligibility of a complementary nucleotide is the ability of one complementary nucleotide sequence to bind to another even where the nucleotide sequence performs other functions).

164. See Roche Molecular Sys., Inc. v. CEPHEID, 905 F.3d 1363, 1370 (Fed. Cir. 2018) (holding that nucleotide sequences that are bind to natural sequences with high specificity are patent ineligible if they have an identical sequence to a naturally occurring sequence).

prohibition on the patenting of nucleotides having a utility based on complementary binding.¹⁶⁵

However, many siRNA sequences contain additional nucleotides or other alterations that could be a “chemical modification” sufficient to render the sequence patent-eligible.¹⁶⁶ For example, the Tuschl II family of patents claim siRNA therapeutics that contain a 3’ overhang of one to three nucleotides.¹⁶⁷ The Federal Circuit has indicated that mutations can render otherwise ineligible sequences patent-eligible.¹⁶⁸ Though the Federal Circuit has not provided guidance as to how many mutations are required for patent eligibility of such a sequence, its emphasis on disallowing DNA having “identical nucleotide sequences as naturally occurring DNA” suggests that even a single altered nucleotide may be sufficient to make a sequence patent-eligible.¹⁶⁹ Adding nucleotides should be treated by the courts as equivalent to mutating nucleotides because either process makes the relevant nucleotide sequence “different from those found in nature.”¹⁷⁰ Likewise, claims to siRNA that contain non-naturally occurring nucleotides¹⁷¹ may be patent-eligible because naturally occurring sequences inherently do not contain non-naturally occurring nucleotides. However, would-be patentees cannot simply add “conventional” 3’ nucleotide overhangs¹⁷² in order to bring their claims into patent eligibility,¹⁷³ likely limiting this strategy of patent claiming to overhangs or modifications that

165. See *Ambry*, 774 F.3d at 761 (holding that the ability of DNA primers to selectively bind a target DNA sequence is not a “significantly new function”).

166. See *Roche Molecular Sys.*, 905 F.3d at 1370 (“[A] primer having an identical nucleotide sequence to naturally occurring DNA without further chemical modification is a natural phenomenon.”).

167. See, e.g., U.S. Patent No. 8,362,231 (filed Mar. 24, 2011) (claiming an RNA molecule wherein “at least one RNA strand forms a single-stranded 3’-overhang from 1 to 3 nucleotides”).

168. See *Roche Molecular Sys.*, 905 F.3d at 1369 (“Nothing in the ’723 patent suggests that the Roche inventors introduced any mutations that would have made the primers’ nucleotide sequences different from those found in nature.”).

169. See, e.g., *id.* at 1370 n.5 (“We do not address the subject matter eligibility of primers that have been altered.”).

170. *Id.* at 1369.

171. See, e.g., U.S. Patent No. 8,552,171 (filed Oct. 10, 2004).

172. See, e.g., Lam et al., *supra* note 45, at 255 (citing Walton et al., *supra* note 57, at 4807) (describing conventional siRNA overhangs).

173. See *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, at 79 (2012) (holding that “well-understood, routine, conventional activity previously engaged in by scientists in the field” is not sufficient to bring patent ineligible subject matter into § 101 eligibility).

themselves are novel.¹⁷⁴ Because the common overhangs of siRNA are conventionally limited to a small pool of sequences,¹⁷⁵ they are likely insufficient to improve the patent eligibility of siRNA composition of matter claims.¹⁷⁶

Further, any argument that claims to explicitly double-stranded siRNA should be patent-eligible for the reason that a complementary mRNA is single-stranded as it exists in nature is likely to be rejected. Because the Federal Circuit held in *Ambry* that “separating DNA from its surrounding genetic material [is] not an act of invention,”¹⁷⁷ the argument would draw strength from the fact that the second strand of a double-stranded siRNA does not serve to “separate” it from its surrounding environment. Rather, the second strand can be described as “added” over the single-strand present in the complementary mRNA.¹⁷⁸ However, because the Federal Circuit has indicated that nucleotides deriving utility from complementary binding are generally patent ineligible, an argument that an RNA is patent-eligible by reason of a two-stranded, complementary structure is likely to be rejected (even if that structure does not exist in nature) because complementarity is “[o]ne of the primary functions of [nucleotide] structure in nature.”¹⁷⁹

B. siRNA METHOD CLAIMS HAVE LIMITED PATENT ELIGIBILITY

Only the Federal Circuit has provided guidance on patent eligibility of methods involving nucleotide sequences,¹⁸⁰ doing so in *Ambry* and *Roche*.¹⁸¹ However, *Ambry* dealt with method

174. *Cf. id.*

175. *See, e.g.,* Lam et al., *supra* note 45, at 255 (citing Walton et al., *supra* note 57, at 4807) (“A conventional siRNA consists of 19–21 nucleotides with two nucleotide overhangs at the 3’ end, usually TT and UU, which are important for recognition by the RNAi machinery.”).

176. *Cf. Mayo*, 566 U.S. at 79 (holding that “conventional activity previously engaged in by scientists in the field” is insufficient to cure patent ineligibility).

177. *Id.* (citing *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 591) (internal quotation marks omitted).

178. *See, e.g.,* Lam et al., *supra* note 45, at 252.

179. *Univ. of Utah Research Found. v. Ambry Genetics*, 774 F.3d 775, 761 (Fed. Cir. 2014).

180. *Id.* at 761 (citing *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595) (“While we addressed some of the method claims of the ‘441 patent in our *Myriad* decision, the Supreme Court did not address any method claims.”).

181. *Id.* at 764; *Roche Molecular Sys., Inc. v. CEPHEID*, 905 F.3d 1363, 1366 (Fed. Cir. 2018).

claims directed to the detection of mutations following routine DNA amplification or probe hybridization.¹⁸² Likewise, the method claims contested in *Roche* were directed to a method of detecting a gene product based on amplification by polymerase chain reaction (PCR).¹⁸³

Of the major siRNA patent families identified by Esmond and Chung as examples, only U.S. 8,420,391 (the ‘391 patent) of the Tuschl I claims a method for using siRNA sequences.¹⁸⁴ The ‘391 patent recites a method for “introducing” siRNA into cells, “maintaining” the resulting cells under conditions suitable for RNA interference, and “thereby producing” a knockdown effect, reducing the expression of a particular gene.¹⁸⁵ Unlike the claims contested in *Ambry* and *Roche*, these claims do not recite the abstract idea of “comparing,”¹⁸⁶ but nonetheless likely recite a patent-ineligible natural phenomena. The steps recited by the ‘391 patent are similar to those recited by the patent at issue in *Mayo*—that is, the knockdown effect recited by the ‘391 patent is produced by interaction of the siRNA with the RNAi pathway, which exists in nature.¹⁸⁷ To that extent, “producing” a knockdown effect by using that natural phenomena is also patent-ineligible subject matter.¹⁸⁸ Though there is no caselaw from article III courts on point, the PTAB has ruled consistently with this analysis.¹⁸⁹ The question then is whether the remainder of the

182. *Ambry*, 774 F.3d at 764.

183. *Roche Molecular Sys.*, 905 F.3d at 1366.

184. See, e.g., U.S. Patent No. 8,420,391 (filed Nov. 24, 2011); see also Esmond & Chung, *supra* note 12, at 17–18.

185. U.S. Patent No. 8,420,391 (filed Nov. 24, 2011) (reciting four independent claims containing only “introducing,” “maintaining,” and “producing” steps).

186. *Ambry*, 774 F.3d at 764; *Roche Molecular Sys.*, 905 F.3d at 1369.

187. Cf. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 77 (2012) (“Prometheus’ patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.”). See generally *RNA Interference (RNAi)*, *supra* note 1.

188. Cf. *Mayo*, 566 U.S. at 77 (“If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.”).

189. See *ex parte Khvorova*, No. 2012-010359, 2015 WL 4267897, at *4 (P.T.A.B. July 10, 2015) (quoting *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015)).

claims “add ‘enough’ to make the claims as a whole patent-eligible.”¹⁹⁰ The other steps recited by the ‘391 patent are “introducing” and “maintaining.”¹⁹¹ It is likely that these steps do not add enough to make the claims as a whole patent-eligible.

Looking to *Ambry*, “techniques that a scientist would have thought of” are insufficient to cure patent-ineligible subject matter.¹⁹² Likewise, *Mayo* held that even a combination of steps is ineligible where “the combination amounts to nothing significantly more than an instruction to [the relevant audience] to apply the applicable laws [of nature].”¹⁹³ The ‘391 patent appears to fail both formulations. Expert testimony notwithstanding, it is obvious that a scientist would have thought of “introducing” RNAi-capable RNA and “maintaining” cells in conditions suitable for RNAi in order to produce an RNAi-mediated knockdown.¹⁹⁴ Likewise, these steps are effectively an instruction on how to apply the law of nature, because producing an RNAi-mediated knockdown requires RNAi-capable RNA and “conditions under which RNA . . . interference occurs.”¹⁹⁵ Therefore, siRNA patents should avoid the formulation used by the ‘391 patent in order to avoid invalidity for failing to recite patent-eligible subject matter. Further, *Ambry* expressly forecloses the patenting of a DNA sequence based on its ability to “hybridize,” meaning a claiming strategy focused on the initial siRNA/mRNA hybridization event is just as likely to fail for failing to recite patent-eligible subject matter as claims focused on the later knockdown event.¹⁹⁶

Two patents from the Tuschl II family offer a different approach to siRNA method claims by reciting methods of producing siRNA molecules.¹⁹⁷ Both U.S. Patent No. 7,056,704 and U.S. Patent No. 7,078,196 recite “synthesizing” two RNA strands and

190. *Ambry*, 774 F.3d at 764.

191. U.S. Patent No. 8,420,391 (filed Nov. 24, 2011).

192. *Ambry*, 774 F.3d at 764.

193. *Mayo*, 566 U.S. at 79.

194. *Cf.* Lam et al., *supra* note 45, at 255–56 (summarizing existing best-practices for RNA interfering techniques).

195. *Compare id.*, with U.S. Patent No. 8,420,391 (filed Nov. 24, 2011).

196. *See Ambry*, 774 F.3d at 761 (finding that the ability of DNA primers to hybridize to other DNA strands is simply a manifestation of “the innate ability of DNA to bind to itself”).

197. U.S. Patent No. 7,056,704 (filed Dec. 23, 2004); U.S. Patent No. 7,078,196 (filed Nov. 11, 2004); *see* Esmond & Chung, *supra* note 12, at 17–18.

“combining” the synthesized strands.¹⁹⁸ Insofar as the claims cannot be construed to cover unpatentable siRNA sequences (as discussed in section II.A of this note),¹⁹⁹ this type of method claim may be patent-eligible. However, because synthesizing and combining are “routine” and “conventional,” this type of claiming strategy likely does not function as a workaround to the validity of a corresponding composition of matter claim,²⁰⁰ and may therefore have extremely limited practical utility to patent drafters.

C. CLAIMING A METHOD OF TREATMENT REMAINS AN OPTION TO OVERCOME § 101 HURDLES

Instead of patenting methods of administering siRNA to trigger the RNAi biological pathway, would-be siRNA patentees might be able to overcome § 101 challenges by following the patent held subject-matter eligible in *Vanda* and formulating their claims as a method of *treating* a disease or disorder.²⁰¹ Though the treatment in that case utilized a small molecule, the court’s holding did not rest on the small molecule’s structure, but rather that the patent at issue recited “a novel method of treating a disease.”²⁰² Further, the *Vanda* court distinguished the patent eligibility of a natural law applied to “treating a disease” from the same natural law applied to “administering a drug,” holding that using a natural law to treat a disease is patent-eligible subject matter.²⁰³ Therefore, the Federal Circuit’s holding in *Vanda* very likely opens up the door for the patenting of methods of treating diseases with siRNA, even where the siRNA itself is

198. U.S. Patent No. 7,056,704 (filed Dec. 23, 2004); U.S. Patent No. 7,078,196 (filed Nov. 11, 2004).

199. See discussion of the patentability of siRNA as a composition of matter *supra* Section II.A.

200. See *Ambry*, 774 F.3d at 760 (“[A]s the district court in the earlier *Myriad* case and our opinion in *Myriad* made clear, isolated DNA is routinely synthetically created.”).

201. Cf. *Vanda Pharm., Inc. v. W.-Ward Pharm. Int’l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018), *petition for cert. filed*, 87 U.S.LW. 3279 (Jan. 17, 2019) (No. 18-817) (holding a method of treating schizophrenia to be patent-eligible subject matter).

202. *Id.* at 1134.

203. *Id.* (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 74 (2012)) (“Although the representative claim in *Mayo* recited administering a thiopurine drug to a patient, the claim as a whole was not directed to the application of a drug to treat a particular disease.”).

otherwise patent ineligible.²⁰⁴ However, the court's holding seems to indicate that such a method claim would need to identify both "specific doses" and a "specific disease" to be treated,²⁰⁵ which may pose a challenge for siRNA researchers trying to patent their technology without performing clinical studies. A petition for certiorari has been filed but has not yet been granted, potentially subjecting this approach to an opportunity for reversal by the Supreme Court.²⁰⁶

III. ALTERNATIVE INTERPRETATIONS AND LEGISLATIVE SOLUTIONS

A lack of patent protection could seriously impact future development of siRNA therapeutics, which are forecasted to have significant market growth in the next few years.²⁰⁷ Part III of this note will explore alternative interpretations of 35 U.S.C. § 101 that may confer patent eligibility onto siRNA therapeutics as well as the role that sections of the Patent Act outside of § 101 can have to constrain overly broad nucleotide patents under a more open interpretation of 35 U.S.C. § 101. Further, it will explore legislative solutions to incentivize siRNA therapeutic development through non-patent market protections.

A. A LACK OF PATENT PROTECTION MAY STIFLE DEVELOPMENT OF SIRNA THERAPEUTICS

Because pharmaceutical firms tend to discard conventional drugs with "weak patent protection" during the drug development process,²⁰⁸ limiting the range of patents available to siRNA therapeutics could significantly impact their development by private research organizations. Private research investment is likely critical to rapid development and deployment of any therapeutic compound as pharmaceutical firms currently carry out

204. *Cf. id.* at 1135 (holding that "treating a disease" is a patent eligible application of a natural law).

205. *See id.* at 1136 ("[T]he [patent-eligible] claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome.").

206. *See generally id.*

207. *See, e.g., Antisense & RNAi, supra* note 143.

208. *See Roin, supra* note 144, at 505.

the majority of drug development in the United States.²⁰⁹ As contrasted with the diagnostic methods found ineligible in *Mayo* and *Roche*,²¹⁰ the development of therapeutic products benefit from exclusive licensing.²¹¹ Unless an interpretation of *Ambry* that is favorable to siRNA patenting is adopted by the courts²¹² or a legislative solution ensuring siRNA therapeutic market exclusivity is adopted by Congress,²¹³ it is likely that the primary route to patent protection for these compounds exists using the limited “method of treatment” approach as outlined in Section II.C.²¹⁴

Federal Circuit precedent states that infringement of a method patent can occur only where a single party performs all steps of the claimed method.²¹⁵ Thus, only a physician administering the siRNA could be liable for direct infringement of claims directed to a method of treatment using siRNA.²¹⁶ Generally, physician liability is severely limited by 35 U.S.C. § 287(c),

209. See generally Henry G. Grabowski et al., *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFF. 302, 303 (describing the role of patents in biopharmaceutical innovation as “essential”); cf. Ashley J. Stevens et al., *The Role of Public-Sector Research in the Discovery of Drugs and Vaccines*, 364 NEW ENG. J. MED. 535, 539–40 (2011) (finding that only 13.6%–21.1% of new drug applications originated from public sector research institutes).

210. *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. 66, 87–88 (2012) (finding a diagnostic test based on a metabolite level to be a patent-ineligible law of nature); *Roche Molecular Sys. Inc. v. CEPHEID*, 905 F.3d 1363, 1370–71 (Fed. Cir. 2018) (finding a method of diagnosis using DNA amplification and associated DNA primers to both be patent ineligible).

211. Cf. Julia Carbone et al., *DNA Patents and Diagnostics: Not a Pretty Picture*, 28 NATURE BIOTECH. 784, 785 (2011) (“[T]here is no evidence to suggest that exclusive licensing is as important in the field of *diagnostic testing* as in *therapeutics* in creating products that would not otherwise exist.”) (emphasis added).

212. See, e.g., discussion *infra* Section III.C.

213. See, e.g., discussion *infra* Section III.E.

214. See discussion of method of treatment patents *supra* Section II.C.

215. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 919 (2014) (citing *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1329 (Fed. Cir. 2008)).

216. Cf. *id.* at 921–22 (“The Federal Circuit held in *Muniauction* that a method’s steps have not all been performed as claimed by the patent unless they are all attributable to the same defendant, either because the defendant actually performed those steps or because he directed or controlled others who performed them.”).

which gives immunity for violations of some medical activity patents to licensed medical practitioners,²¹⁷ though § 287(c)(2)(A)(iii) specifically limits this immunity to allow liability for “the practice of a process in violation of a biotechnology patent.”²¹⁸ There is no statutory definition of what constitutes a “biotechnology patent,” but the section’s legislative history indicates that the provision likely would allow a physician to be liable for infringement of an siRNA-based patented method of treatment.²¹⁹ However, patentees may be reluctant to sue physicians given that lawsuits against doctors for infringing method of treatment patents have historically prompted extremely negative reactions from the public.²²⁰ At least to this extent, patentees may likely prefer to sue generic manufacturers for indirect infringement under §§ 271(b)–(c) rather than for direct infringement under § 271(a).²²¹

Liability under § 271(b) requires actual knowledge of the infringed patent.²²² Moreover, under § 271(b), the *patentee* has the burden of proving that the alleged infringer “possessed specific intent to encourage another’s infringement.”²²³ The specific intent for inducement liability “require[s] more than just intent to cause the acts that produce direct infringement.”²²⁴ Likewise,

217. See 35 U.S.C. § 287(c) (1999).

218. 35 U.S.C. § 287(c)(2)(A)(iii) (2011).

219. Cf. H.R. REP. NO. 104-863, at 854 (1996) (Conf. Rep.) (“For the purposes of [§ 287(c)(2)(iii)], the definition of the term ‘biotechnology patent’ includes a patent on a ‘biotechnological process’ as defined in 35 U.S.C. § 103(b), as well as a patent on a process of making or using biological materials, including treatment using those materials, where those materials have been manipulated *ex vivo* at the cellular or molecular level.”).

220. See Sally Squires, *AMA Condemns Patents for Medical Procedures*, WASH. POST (June 20, 1995), <https://www.washingtonpost.com/archive/politics/1995/06/20/ama-condemns-patents-for-medical-procedures/b339653c-e4fa-4991-ad41-e762edc52b16/>; see also Katherine J. Strandburg, *Legal but Unacceptable: Pallin v. Singer and Physician Patenting Norms* 1, 16 (NYU Ctr. for L., Econ. & Org., Working Paper No. 14-42, 2014) (describing the passage of § 287(c) as in response to *Pallin v. Singer*, a well-publicized suit concerning the violation of a medical procedure patent).

221. See generally 35 U.S.C. § 271.

222. *Glob.-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 765–66 (2011).

223. *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (citing *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990)).

224. *Id.* at 1306.

deliberate indifference cannot prompt liability for indirect infringement.²²⁵ Reasonable belief of non-infringement has also defeated inducement liability.²²⁶ The Federal Circuit has limited inducement liability for the prescription of a generic compound for infringing off-label uses.²²⁷ The District Court for the District of Delaware has expanded on the intent requirement specifically in regard to a “method of treatment” patent, holding that inducement liability can be avoided if a generic manufacturer does not list the infringing use on the label of the drug.²²⁸ The court further held that even where the relevant generic label indicated that it could be used to treat a disease identified in a patented method of treatment, inducement liability cannot be found where the direct infringer did not read the label.²²⁹ Because of these hurdles, § 271(b) may not present a realistic opportunity for siRNA patentees to collect damages from generic manufacturers of the compounds used in patented methods of treatment.

However, there is a possibility that an siRNA patentee could successfully sue a generic manufacturer for contributory infringement under § 271(c). Like § 271(b), liability under § 271(c)

225. See *Glob.-Tech Appliances, Inc.*, 563 U.S. at 770 (“[I]n demanding only ‘deliberate indifference’ to that risk, the Federal Circuit’s test does not require active efforts by an inducer to avoid knowing about the infringing nature of the activities.”).

226. *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1351 (Fed. Cir.), *amended on reh’g in part*, 366 F. App’x 154 (Fed. Cir. 2009) (holding that a jury could permissibly conclude that the defendant “reasonably believed” they were not infringing the patent at issue).

227. *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 633 (Fed. Cir. 2015) (holding that “speculation or even proof that some, or even many, doctors would prescribe” a generic drug in a way that infringes a method of treatment patent is likely insufficient for § 271(b) liability).

228. *GlaxoSmithKline LLC v. Teva Pharm. USA, Inc.*, 313 F. Supp. 3d 582, 592 (D. Del. 2018) (holding that there cannot be inducement liability for selling a drug used to infringe a method of treatment, because the generic’s “label omitted from its label the language contained on [the non-generic’s] label concerning the use” of the drug to perform the patented method of treatment); see also *Takeda Pharm. U.S.A., Inc.*, 785 F.3d at 633.

229. See *GlaxoSmithKline LLC*, 313 F. Supp. 3d at 591 (“As Dr. McCullough concedes that he did not read Teva’s label, he cannot state, for instance, that he noticed or otherwise knew what (if anything) that label said about using carvedilol to treat CHF.”); *but see AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (holding that a generic label that provides specific treatment instructions, such as how many times a day to use the relevant drug or what type of doses to utilize, may be sufficient evidence of intent for inducement liability).

requires actual knowledge of the infringed patent.²³⁰ The patentee's burden of proof for liability under § 271(c) includes showing that "the accused products are not staple articles of commerce suitable for no substantial non-infringing uses."²³¹ Presumably, an siRNA used in a patented method of treatment would not be a "staple article of commerce" and would have no real use outside of the patented method due to the specificity of siRNA-mediated gene silencing.²³² Though contributory infringement is generally not recommended as a primary method of patent enforcement,²³³ this remains a potential avenue of recovery against a generic manufacturer.

In short, siRNA therapeutics are likely restricted to a class of patents enforceable for direct infringement only against physicians, with any theory of liability for generic manufacturers instead relying on contributory infringement. Because pharmaceutical companies value strong patent protection when determining which products to develop,²³⁴ the limited enforcement strategies available to patentees could discourage the development of novel siRNA therapeutics.

B. THE FEDERAL CIRCUIT'S STANDARD MAY BE A SOURCE OF CONFUSION

Compounding the aforementioned problems facing siRNA patentees (as well as nucleotide patentees more generally), the Federal Circuit has used a nebulous, and perhaps counter-intuitive, definition of "nucleotide structure." *Ambry* rejected DNA primers in spite of evidence that primers are single-stranded and "single-stranded DNA cannot be found in the human

230. *Glob.-Tech Appliances, Inc.*, 563 U.S. at 764 (citing *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488 (1964)).

231. *See, e.g., In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1331 (Fed. Cir. 2012).

232. *Cf. Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006) (finding contributory infringement for sale of a fireplace burner that was not a "staple article of commerce and was especially made" for use with the plaintiff's patented invention); *see Lam et al., supra* note 45, at 255 (describing siRNAs as "extremely useful for targeting single gene disorders").

233. *Cf. James Yang, Claim Drafting Tip: Focus on Direct, Not Indirect Infringement*, OC PATENT L. (Sept. 14, 2015), <https://ocpatentlawyer.com/claim-drafting-tip-focus-on-direct-not-indirect-infringement/> (discouraging the use of claims that only capture indirect infringement).

234. *See Roin, supra* note 144, at 514 ("Moreover, it is well known that pharmaceutical companies generally refuse to develop new drugs unless they have strong patent protection over them.").

body.”²³⁵ *Ambry* cites *Myriad* for the proposition that “separating [DNA] from its surrounding genetic material is not an act of invention,” but does not explain how single-stranded primers are analogous to isolating a gene.²³⁶ Further, *Ambry* held that primers do not have a “unique structure, different from anything found in nature” potentially on that basis that the primers at issue have an identical *sequence* to a gene found in nature.²³⁷

Likewise, the Federal Circuit in *Roche* rejected arguments that Roche’s primers were structurally unique on the basis of 3’ hydroxyl groups that are not present in *M. tuberculosis* DNA.²³⁸ The court held that “distinction unavailing” and further that the appropriate “subject matter inquiry of primer claims hinges on comparing a claimed primer to its corresponding DNA *segment* on the chromosome—not the whole chromosome,” citing a passage from *Ambry* “emphasizing the appropriate comparison being” that of nucleotide *sequences*.²³⁹ Ultimately, the Federal Circuit has left the meaning of “nucleotide structure” indeterminate and uncertain.

Two potential working definitions of “nucleotide structure” arise from a survey of Federal Circuit precedent. It is possible that the Federal Circuit’s definition of “nucleotide structure” includes some, but not all, elements of nucleotide structure in the patent eligibility analysis.²⁴⁰ If that is the case, the court has failed to specifically enumerate *which* elements are useful to the determination of patent eligibility, likely creating a recurring

235. Univ. of Utah Research Found. v. Ambry Genetics, 774 F.3d 775, 760 (Fed. Cir. 2014).

236. *Id.* at 759 (quoting Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 590 (2013)) (internal quotation marks omitted).

237. *Cf. id.* at 761 (citing *Myriad Genetics*, 569 U.S. at 589) (“A DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found in nature . . . [p]rimers do not have such a different structure and are patent ineligible.”).

238. See *Roche Molecular Sys., Inc. v. CEPHEID*, 905 F.3d 1363, 1369–70 (Fed. Cir. 2018) (“Roche’s primers are indistinguishable from their corresponding nucleotide sequences on the naturally occurring MTB *rpoB* gene.”).

239. *Id.* at 1370 (citing *Ambry*, 774 F.3d at 760–61).

240. *Cf., e.g., Ambry*, 774 F.3d at 760 (“*Myriad* argues that primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body. But, as the Supreme Court made clear, ‘separating [DNA] from its surrounding genetic material is not an act of invention.’”).

source of uncertainty for patentees.²⁴¹ Alternatively, it is possible that the Federal Circuit treats “nucleotide structure” as meaning “nucleotide sequence.”²⁴² This definition is divorced from the conventional scientific understanding of DNA structure as the molecular structure of a DNA molecule²⁴³ and seems particularly insensible in view of the Supreme Court’s scientifically-nuanced handling of nucleotide patenting in *Myriad*.²⁴⁴ Hopefully, future holdings on the subject will clarify which definition of “nucleotide structure” the Federal Circuit uses for patent eligibility analysis.

C. RE-THINKING *AMBRY GENETICS*

One way to bring siRNA therapeutics further into patent eligibility would be to revise the holding of *Ambry*, as has been suggested by Judge O’Malley of the Federal Circuit.²⁴⁵ Specifically, Judge O’Malley has postulated that the Federal Circuit erred in treating a nucleotide sequence as its structure for the purposes of patent eligibility.²⁴⁶ Allowing unique chemical structures not found in nature, like the free 3’ hydroxyl groups of *Ambry* and *Roche*, to cure patent ineligibility of some nucleotide sequences may also carve out a space for the patenting of siRNA as compositions of matter. As discussed in Part I of this note, siRNA can have a number of structural features that are not

241. *Cf., e.g., Roche Molecular Sys.*, 905 F.3d at 1370 (emphasizing that the appropriate subject matter comparison for DNA primers is between the primers and the naturally occurring *sequence*).

242. *See id.* at 1377 (O’Malley, J., concurring) (implying the majority conflated sequence with structure); *cf., e.g., id.* at 1371 (Fed. Cir. 2018) (“We hold that the primers before us are indistinguishable from their corresponding nucleotide sequences on the naturally occurring DNA, and that the primer claims, therefore, are patent-ineligible . . .”).

243. *See, e.g., The Structure of DNA*, BOISE ST. U., <http://cs.boisestate.edu/~amit/teaching/342/lab/structure.html> (last visited Mar. 5, 2019) (describing the structure of DNA in terms of its molecular structure).

244. *Cf. Myriad Genetics*, 569 U.S. at 594–95 (distinguishing genomic DNA from cDNA for the purposes of patent eligibility).

245. *See Roche Molecular Sys.*, 905 F.3d at 1381 (O’Malley, J., concurring) (“I believe, accordingly, that we should revisit our conclusion in *BRCA1* en banc.”).

246. *See id.* (“[A]s the record in this case reveals, a finding that the two [DNA molecules] have identical *sequences* does not entirely resolve the question of whether they are *structurally* identical because structure is not defined solely by nucleotide sequence.”).

present in naturally occurring mRNA sequences, such as being double-stranded or having single-strand overhangs.²⁴⁷

D. THE REST OF THE PATENT ACT IS CAPABLE OF PREVENTING OVERBROAD CLAIMS

In adopting restrictive interpretations of 35 U.S.C. § 101, the courts have expressed a concern about the patenting of “basic tools of scientific and technological work.”²⁴⁸ In fact, this principle was cited in both *Myriad*²⁴⁹ and *Ambry*.²⁵⁰ However, a number of alternatives exist within the Patent Act to prevent overbroad patents that extend to basic tools of scientific research. 35 U.S.C. § 112, for instance, acts to prevent “pure functional claiming” that can extend a patent’s scope to an idea or a basic research tool.²⁵¹ Likewise, 35 U.S.C. § 102 incorporates the doctrine of “inherency” which “allows determination of whether subject matter that is not taught in the single reference was nonetheless known in the field of the invention.”²⁵² Modern interpretations of the doctrine are able to broadly exclude claim elements present in the prior art from patenting, including those that may not have been recognized by persons of ordinary

247. See generally Lam et al., *supra* note 45, at 254 (comparing siRNA design with miRNA design as a therapeutic gene agent); see also discussion of siRNA structure *supra* Section I.B

248. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

249. See *Ass’n of Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 71 (2012)) (“We have long held that [§ 101] contains an important implicit exception: Laws of nature, natural phenomena, and abstract ideas are not patentable. Rather, they are the basic tools of scientific and technological work that lie beyond the domain of patent protection.”) (quotations and citations omitted).

250. See *Univ. of Utah Research Found. v. Ambry Genetics*, 774 F.3d 775, 764 (Fed. Cir. 2014) (citing *Myriad Genetics*, 569 U.S. at 589) (“[I]t is antithetical to the patent laws to allow these basic building blocks of scientific research to be monopolized.”).

251. See, e.g., *Aristocrat Techs. Australia Pty Ltd. v. Int’l Game Tech.*, 521 F.3d 1328, 1333 (Fed. Cir. 2008) (“The point of [§§ 112(a)–(b)] is to avoid pure functional claiming.”); cf. *Med. Instrumentation & Diagnostics Corp. v. Elekta AB*, 344 F.3d 1205, 1211 (Fed. Cir. 2003) (“If the specification is not clear as to the structure that the patentee intends to correspond to the claimed function, then the patentee has not paid that price but is rather attempting to claim in functional terms unbounded by any reference to structure in the specification.”).

252. *Schering Corp. v. Geneva Pharm., Inc.*, 348 F.3d 992, 995 (Fed. Cir. 2003) (“The analytic tool of ‘inherency’ allows determination of whether subject matter that is not taught in the single reference was nonetheless known in the field of the invention [and therefore anticipated].”).

skill.²⁵³ Further, some scholars have argued that the second step of the *Alice* framework²⁵⁴ overlaps with the obviousness inquiry under § 103,²⁵⁵ thereby implying that patents on “basic tools of scientific and technological work” can be prevented through § 103 instead of § 101.²⁵⁶ Effectively, there are several alternatives to § 101 within the Patent Act available to prevent the patenting of basic tools of scientific and technological work under a more “relaxed” interpretation of *Ambry* that would allow for siRNA to be patent eligible as a composition of matter.

E. NON-PATENT siRNA MARKET EXCLUSIVITY COULD INCENTIVIZE INVESTMENT

In lieu of patent protection, Congress could extend an alternative form of limited market exclusivity to siRNA therapeutics. In theory, such a grant of exclusivity could resemble the already existing grant supplied to so-called “orphan drugs” (those that treat rare diseases).²⁵⁷ Historically, pharmaceutical companies have viewed orphan drugs as unprofitable and avoided investing in their development.²⁵⁸ Congress successfully incentivized the development of orphan drugs²⁵⁹ by conferring on them a seven-

253. *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (quoting *MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)) (“Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art.”) (internal quotation marks omitted).

254. That is, whether the claim elements are “well-understood, routine, or conventional.” *Alice Corp. Pty. v. CLS Bank Int’l*, 573 U.S. 208, 225 (2014) (quoting *Mayo*, 566 U.S. at 73) (internal quotation marks omitted).

255. See Paxton M. Lewis, *The Conflation of Patent Eligibility and Obviousness: Alice’s Substitution of Section 103*, 2017 UTAH ONLAW: THE UTAH L. REV. ONLINE SUPPLEMENT 13, 14 (2017) (“[Step two of the *Alice* framework] already takes place under section 103 for obviousness . . .”).

256. *Cf. id.* at 27 (illustrating how some Federal Circuit judges have used obviousness and patent eligibility interchangeably).

257. OFFICE OF INSPECTOR GEN., DEP’T OF HEALTH & HUMAN SERVS., OEI-09-00-00380, THE ORPHAN DRUG ACT IMPLEMENTATION AND IMPACT (2001), at 1 (defining orphan drugs in the U.S. as those that treat “a disease that affects fewer than 200,000 people”).

258. See *id.* at 4 (finding the drugs used to treat for small patient populations unprofitable).

259. See *id.* at 7 (“The Orphan Drug Act’s incentives . . . motivate[s] companies to develop orphan products.”).

year period of exclusive marketing rights.²⁶⁰ In the same way, conferring a limited term of market exclusivity onto siRNA therapeutics could serve to incentivize their development in place of patent rights.²⁶¹ Congress has more recently passed the Biologics Price Competition Innovation Act (“BPCIA”), which grants a twelve-year term of non-patent marketing exclusivity to certain protein-based therapeutics.²⁶² The text of the BPCIA does not extend exclusivity to nucleotides, but given that the act does grant exclusivity to other biomolecular therapeutics,²⁶³ legislation granting non-patent exclusivity to siRNA therapeutics would likely be uncontroversial.²⁶⁴

260. See *id.* at 4 (providing three incentives including 7-year market exclusivity to sponsors of approved orphan products); see generally CTR. FOR DRUG EVALUATION & RES., U.S. FOOD & DRUG ADMIN., PATENTS AND EXCLUSIVITY (2015), at 2, <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf> (describing the statutory requirements for orphan drug exclusivity).

261. Cf. ORPHAN DRUG ACT IMPLEMENTATION AND IMPACT, *supra* note 257, at 7 (describing the positive effect of market exclusivity on orphan drug development); cf. Angélique McCall & Gene Quinn, *The FDA Process, Patents and Market Exclusivity*, IP WATCHDOG (Mar. 12, 2017), <http://www.ipwatchdog.com/2017/03/12/fda-process-patents-market-exclusivity/id=79305/> (“A patent is not the only path to exclusivity. In fact, the FDA characterizes patents and ‘exclusivity’ separately.”).

262. See 42 U.S.C. § 262(k)(7)(A)(2019); see also U.S. FOOD & DRUG ADMIN., NEW AND REVISED DRAFT Q&AS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT (REVISION 2), at 12 [hereinafter NEW AND REVISED DRAFT Q&AS] (describing the BPCIA as amending the definition of “biological product” at § 262(i) to include certain protein-based therapeutics).

263. See 42 U.S.C. § 262(i)(1); see also NEW AND REVISED DRAFT Q&AS, *supra* note 262, at 12 (interpreting “protein” as used in the BPCIA “to mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size”).

264. Because the BPCIA was passed as a component of the Patient Protection and Affordable Care Act, at least one commentator has expressed concern about its continued viability in light of the recent *Texas v. United States* decision. See Kyle Faget, *ACA Strike-Down: Salvaging the BPCIA via Severability*, FOLEY & LARDNER LLP: HEALTH CARE LAW TODAY (Jan. 2, 2019), <https://www.healthcarelawtoday.com/2019/01/02/aca-strike-down-salvaging-the-bpcia-via-severability/>; see also *Texas v. United States*, 340 F. Supp. 3d 579, 614 (N.D. Tex. 2018) (finding the individual mandate of the Patient Protection and Affordable Care Act unconstitutional in light of the Tax Cuts and Jobs Act and further finding the individual mandate inseparable). To the extent that Congress may have to create new legislation if they want to maintain a system of limited market exclusivity for protein therapeutics, they would have an opportunity to include related protections for siRNA therapeutics. See *id.* at 614.

CONCLUSION

This note has illustrated the problems of patent eligibility that both would-be and current siRNA patentees may face. Like traditional therapeutics, siRNA therapeutics have a costly research and development cycle, as well as a costly FDA-approval process.²⁶⁵ Therefore, limiting the patent protection available to siRNAs could seriously stifle their development.²⁶⁶ Further, siRNA therapeutics could represent a \$1.81 billion market by 2025,²⁶⁷ and have numerous advantages over conventional therapeutics,²⁶⁸ illustrating both the economic and medical needs to encourage would-be patentees to invest in their development. In fact, many diseases are likely to remain untreatable without some kind of nucleotide-based therapy option.²⁶⁹

Under the dual holdings of *Ambry* and *Myriad*, it seems likely that siRNA therapeutics will only be patent eligible as methods of treatment, unless that option is foreclosed by potential Supreme Court review.²⁷⁰ As discussed in Part III of this note,²⁷¹ limiting the patent eligibility of siRNA therapeutics to methods of treatment may limit enforcement options against generic manufacturers and thereby may discourage development of siRNA therapeutics.²⁷² This note has identified two options to provide a form of market exclusivity to siRNA therapeutics in order to incentivize their private development: adopting an alternative interpretation of *Ambry* that relaxes current § 101 standards to allow patenting of siRNA as compositions of matter,

265. See discussion of the FDA-approval process, pharmaceutical investment, and siRNA, *supra* Section I.H.

266. Roin, *supra* note 144, at 505 (“[P]harmaceutical companies are rarely willing to develop drugs without patent protection.”).

267. *Antisense & RNAi*, *supra* note 143.

268. See, e.g., Bullis, *supra* note 52.

269. See, e.g., *Novartis*, *supra* note 15 (“[M]ost of the proteome is . . . undruggable.”).

270. See *Vanda Pharm., Inc. v. W.-Ward Pharm. Int’l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018), *petition for cert. filed*, 87 U.S.LW. 3279 (U.S. Jan. 17, 2019) (No. 18-817).

271. See *generally* discussion of the role of effective market exclusivity in driving investment in pharmaceutical-sector products *supra* Sections I.H, III.A, and III.E.

272. Cf. Yang, *supra* note 233 (describing reasons for avoiding claims that only capture indirect infringement).

as discussed in Section III.C,²⁷³ and extending non-patent market exclusivity rights to siRNA therapeutics, as discussed in Section III.E.²⁷⁴

273. See discussion *supra* Section III.C.

274. See discussion *supra* Section III.E.