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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANASTASIA KHVOROVA, ANGELA REYNOLDS, DEVIN LEAKE, WILLIAM MARSHALL, STEVEN READ, and STEPHEN SCARINGE

Appeal 2017-006246
Application 10/940,892
Technology Center 1600

Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method for obtaining a siRNA sequence for a target gene, wherein said siRNA sequence comprises 19–30 nucleotide bases. The Examiner rejected the claims under 35 U.S.C § 101 as directed to non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as Thermo Fisher Scientific Inc. (*see* App. Br. 1).

[2] We note that there was a prior decision affirming the Examiner, Appeal 2012-010359.

Statement of the Case

Background

"[R]esearchers observed that double stranded RNA ('dsRNA') could be used to inhibit protein expression. This ability to silence a gene has broad potential for treating human diseases, and many researchers and commercial entities are currently investing considerable resources in developing therapies based on this technology" (Spec. 1:21–25). "More recently it has been shown that when short (18–30 bp) RNA duplexes are introduced into mammalian cells in culture, sequence-specific inhibition of target mRNA can be realized without inducing an interferon response" (*id.* at 2:6–8). "Successful siRNA-dependent gene silencing depends on a number of factors. One of the most contentious issues in RNAi is the question of the necessity of siRNA design, *i.e.*, considering the sequence of the siRNA used" (*id.* at 3:15–17). "Unfortunately, none of the reported methods have provided a satisfactory scheme for reliably selecting siRNA with acceptable levels of functionality" (*id.* at 3:33 to 4:1). "Accordingly, there is a need to develop rational criteria by which to select siRNA with an acceptable level of functionality, and to identify siRNA that have this improved level of functionality, as well as to identify siRNAs that are hyper functional" (*id.* at 4:1–4).

The Claims

Claims 67–69, 73–78, 90 and 91[3] are on appeal. Independent claim 90 is representative and reads as follows:

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[3] We note that while claims 67–69, 73–79, 81–85, and 89–91 were rejected in the Final Rejection (*See* Final Act.5/5/2016 at 2), only claims 67–69, 73–78, and 90–91 were appealed (*see* App. Br. 6).

> 90. A method for selecting and generating a hyperfunctional siRNA for a target gene, said method comprising the steps:
>
> (a) selecting a target gene;
>
> (b) generating a set of candidate siRNA sequences that are between 19 and 30 bases in length, and that comprises a plurality of candidate siRNA sequences, wherein each candidate siRNA sequence comprises a sense region of 19–30 bases, wherein said sense region comprises a sense sequence of 19 bases that is at least 79% similar to a region of the target gene;
>
> (c) determining a functionality score for each candidate siRNA sequence within the set of candidate siRNA sequences, wherein said functionality score is determined by applying selection criteria, wherein the selection criteria comprise at least four non-target specific criteria and wherein the functionality score for an siRNA corresponds to its relative predicted functionality;
>
> (d) selecting fewer than all candidate siRNA sequences in said set of candidate siRNA sequences to form a set of selected siRNA sequences, wherein said selecting is based on said functionality scores of each candidate siRNA sequence;
>
> (e) for each siRNA sequence within the set of selected siRNA sequences, introducing an siRNA molecule that corresponds to the selected siRNA sequence into a test cell of a test cell line;
>
> (f) assessing the ability of each siRNA molecule in vitro to degrade the target mRNA, wherein an siRNA molecule that induces 80% silencing or greater at subnanomolar concentrations for greater than 120 hours is a hyperfunctional siRNA; and
>
> (g) generating the hyperfunctional siRNA *in vitro* or *in vivo*.

The Issue

The Examiner rejected claims 67–69, 73–78, 90 and 91 under 35 U.S.C. § 101 as being directed to non-statutory subject matter (Final Act. 2–4).

The Examiner finds that the claims are directed to "an abstract idea" and a "law of nature describing the relationship between siRNA sequence data and gene silencing" (Final Act. 3). The Examiner also finds that the claims "are directed to an algorithm for generating data of an siRNA sequence that will function to silence expression of a target gene, which is similar to the abstract idea of organizing information through mathematical correlations at issue in *Digitech Image Techs., LLC v. Electronics for Imaging, Inc.* 758 F.3d 1344 (Fed. Cir. 2014)" (Ans. 2) (italics added).

The Examiner also finds the claims "have additional elements that constitute conventional steps appended to the judicial exception" (Final Act. 3). The Examiner supports this position by relying on Elbashir,[4] who teaches

> a conventional process of designing siRNA molecules with a likelihood of inhibiting gene expression at pages 200–202. In vitro assay of siRNA degradation of mRNA is shown on page 200 and pages 203–209. The commercial availability of prior art custom synthesis of siRNA molecules that target a desired mRNA are shown on pages 202–203. The additional elements do not comprise an inventive concept when considered individually or as an ordered combination that transforms the claimed judicial exception into a patent-eligible application of the judicial exception.

(Final Act. 4).

The Examiner reached these conclusions by applying the test set out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S.

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[4] Elbashir et al., Analysis of gene function in somatic mammalian cells using small interfering RNAs, 26 Methods 199–213 (2002).

66 (2012) (Final Act. 2–6) based on the two-step *Alice* framework. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014).

Analysis

To determine whether a claim is invalid under § 101, we employ the two-step *Alice* framework. In *Alice* step one, we ask whether the claims are directed to a patent ineligible concept, such as an abstract idea or law of nature. *Alice*, 134 S.Ct. at 2355; *Mayo*, 566 U.S. at 75–77; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015). While method claims are generally eligible subject matter, method claims that are directed only to abstract ideas and/or natural phenomena are directed to a patent ineligible concept. *Ariosa*, 788 F.3d at 1376. In *Alice* step two, we examine the elements of the claims to determine whether they contain an inventive concept sufficient to transform the claimed naturally occurring phenomena into a patent-eligible application. *Mayo*, 566 U.S. at 71–72 (quoting *Alice*, 134 S.Ct. at 2355).

Alice Step One

Claims 67 and 90 of the instant application are directed to methods for obtaining a siRNA sequence for a target gene, wherein said siRNA sequence comprises 19–30 nucleotide bases. That process is directed to both a law of nature and an abstract idea. In particular, the law of nature/natural phenomenon is the correlation between siRNA sequences and gene silencing. Appellants' claims purport to apply natural laws describing the relationship between siRNA sequence data and gene silencing to predict the likelihood that a particular siRNA sequence will result in gene silencing. *Cf. Mayo*, 566 U.S. at 77 ("[L]aws 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"). That the relationship is obtained by accessing a generic computer and causing the computer to apply a computer program does not change the fact that the relationship between siRNA sequence data and gene silencing "exists in principle apart from any human action" *Mayo*, 566 U.S. at 77.

In addition, the recited steps of "accessing a computer and causing said computer to apply a computer program product being embodied in a computer readable storage medium", "determining a predicted relative functionality of at least two siRNA sequences within said set of candidate siRNA sequences . . . algorithm", and "generating an output comprising said siRNA sequence for gene silencing that is selected . . . siRNA sequence for gene silencing" all involve categorizing and/or analyzing information. The Federal Circuit has explained that "[i]nformation as such is an intangible" and "that collecting information, including when limited to particular content (which does not change its character as information)," analyzing it, and presenting the results of the collection and analysis are patent ineligible abstract concepts. *See, e.g*, *Electric Power Group, LLC v. Alstom S.A.*, 830 F.3d 1350, 1353–54 (Fed. Cir. 2016).

> This case is similar to *Digitech Image Technologies, LLC v. Electronics for Imaging, Inc.*, 758 F.3d 1344 (Fed. Cir. 2014). There, the claims of the challenged patent were directed to the abstract idea of organizing information through mathematical correlations. *Id.* at 1350–51. . . . A process that started with data, added an algorithm, and ended with a new form of data was directed to an abstract idea. *Id.*

RecogniCorp LLC v. Nintendo Co., Ltd, 855 F.3d 1322, 1327 (Fed. Cir. 2017). Additionally, in *Digitech*, the Federal Circuit stated that "[w]ithout additional limitations, a process that employs mathematical algorithms to

manipulate existing information to generate additional information is not patent eligible. 'If a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory'" *Digitech Image Technologies, LLC v. Electronics for Imaging, Inc.*, 758 F.3d 1344, 1351 (Fed. Cir. 2014). Here, the process employs mathematical algorithms to manipulate existing information to generate additional information, here an siRNA sequence, and therefore is not patent eligible.

Additionally, the steps of selecting a target gene and generating a set of candidate siRNA sequences can be performed mentally and therefore are abstract ideas. As the Federal Circuit explained, "methods which can be performed mentally, or which are the equivalent of human mental work, are unpatentable abstract ideas--the 'basic tools of scientific and technological work' that are open to all'" *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1361, 1372, (Fed. Cir. 2011) (*citing Gottschalk v. Benson*, 409 U.S. 63 (1972)).

Because the claims are directed to an abstract idea/natural law, we turn to the second step of the *Alice* framework.

Alice Step Two

In *Alice* step two, we examine the elements of the claims to determine whether they contain an inventive concept sufficient to transform the claimed naturally occurring phenomena into a patent-eligible application. *Mayo*, 566 U.S. at 71–72 (quoting *Alice*, 134 S.Ct. at 2355). We must consider the elements of the claims both individually and as an ordered combination to determine whether the additional elements transform the nature of the claims into a patent-eligible concept. *Ariosa*, 788 F.3d at 1375.

The Specification acknowledges that it was known that inserting "short (18–30 bp) RNA duplexes" into mammalian cells causes "sequence-specific inhibition of target mRNA" (Spec. 2:6–8).

The Examiner finds, and Appellants do not dispute, that Elbashir shows "a conventional process of designing siRNA molecules with a likelihood of inhibiting gene expression", and that "custom synthesis of siRNA molecules that target a desired mRNA" was "commercially available" (Ans. 4; *cf.* Elbashir 202 "selection of siRNA sequences" and "siRNAs are obtained from commercial RNA oligonucleotide synthesis suppliers"). Moreover, Elbashir performs an *in vitro* assay of siRNA degradation of mRNA (Ans. 4; *cf.* Elbashir 207 "Detection of siRNA-mediated specific gene silencing"). Elbashir also gives criteria for selecting the target gene and generating a set of siRNA sequences (Elbashir 199, Fig. 2, 201–202). Additionally, Elbashir teaches that siRNA sequences should be less than 30 bp and teaches synthesizing sense siRNA sequences that are 21–24 bp long (e.g. AA(N19)UU or 5'-(N19)TT) using the target sequence (*id.*). Therefore, Elbashir teaches that the sense region comprises a sense sequence of 19 bases that is at least 79% similar to a region of the target gene, because one selects sense sequences from the target gene that meets the criteria (e.g. AA(N19)UU or 5'-(N19)TT) of Elbashir.

Therefore, the instant facts are similar to those confronted in *Electric Power*, where the court held that "[n]othing in the claims, understood in light of the specification, requires anything other than off-the-shelf, conventional computer, network, and display technology for gathering, sending, and presenting the desired information" *Electric Power Group, LLC v. Alstom S.A.*, 830 F.3d 1350, 1355 (Fed. Cir. 2016). Here, the step of

generating an output requires nothing other than "off-the-shelf, conventional computer, network, and display technology for gathering, sending, and presenting the desired information".

The Examiner finds that "additional elements do not comprise an inventive concept when considered individually or as an ordered combination that transforms the claimed judicial exception into a patent-eligible application of the judicial exception" (Ans. 3). Appellants provide no evidence rebutting this position (*see* App. Br. 10–11).

In sum, the evidence of record supports the Examiner's position that the claims do not add something "significantly more" to the abstract idea and/or law of nature. Instead, each of the steps in the "claims (e.g., selecting the target gene, generating a set of siRNA sequences, and generating an output) are conventional, routine, and well-known. The generating step involves the normal, basic functions of a computer" *Versata Development Group, Inc. v. SAP America, Inc.*, 793 F.3d 1306, 1335 (Fed. Cir. 2015). "In order for the addition of a machine to impose a meaningful limit on the scope of a claim, it must play a significant part in permitting the claimed method to be performed, rather than function solely as an obvious mechanism for permitting a solution to be achieved more quickly, i.e., through the utilization of a computer for performing calculations" *SiRF Tech., Inc. v. Int'l Trade Comm'n*, 601 F.3d 1319, 1333 (Fed. Cir. 2010).

We conclude that the method claims does not result in an inventive concept that transforms the abstract idea/natural phenomena described above into a patentable invention. *Mayo* and *Ariosa* make clear that transforming claims that are directed to a law of nature requires more than simply stating

the law of nature while adding the words "apply it." *Mayo*, 566 U.S. at 72; *Ariosa*, 788 F.3d at 1377.

Appellants argue that in the prior decision, the "PTAB emphasized the following elements as being absent from appealed claim 85: (1) the claim provided no particular coefficient for the algorithm; and (2) the claim provided no specific metric by which to identify improved gene silencing" (App. Br. 8). Appellants contend that the "PTAB implied that the presence of either of these features could provide the basis for a determination of patentable subject matter" and that these issues are addressed in the current claims (*id.*).

We are not persuaded. We stated:

> Claim 85 does not recite a specific algorithm, and preempts any algorithm for designing siRNA sequences. The claim limitation recited by Appellants regarding the four asserted "variables" can simply represents the presence or absence of the four alternative bases possible in siRNA, adenine, guanine, cytosine, and uracil (FF 5). The claim requires no particular coefficient for the algorithm, nor does the claim impose any specific metric to identify improved gene silencing. *Ariosa* notes that "patent claims should not prevent the use of the basic building blocks of technology-abstract ideas, naturally occurring phenomena, and natural laws." *Ariosa* at 7. Instant claim 85, by failing to recite any specific elements of the claimed algorithm, specifically attempts to fully preempt any process for designing siRNA.

(*Ex parte Khvorova*, 2015 WL 4267897 at *5 (PTAB 2015)). While preemption is the concern underlying the judicial exceptions, it is not a stand-alone test for determining eligibility. *Rapid Litig. Mgmt. v. CellzDirect, Inc.,* 827 F.3d 1042, 1052, (Fed. Cir. 2016). Simply reducing concerns regarding preemption does not render the claims patent eligible.

We find Appellants' reliance on *McRO, Inc. v. Bandai Namco Games America Inc.*, 837 F.3d 1299 (Fed. Cir. 2016) unavailing (*see* App. Br. 8–9). Appellants contend that the claims in *McRO* were "'limited to rules with specific characteristics', and they required one to apply those rules to sub-sequences" *(id.* at 9). Appellants further contend that "claim 67 recites specific rules in step (c) and applies those rules to determine a predicted relative functionality in step (d)" (*id.* at 9).

The claims in *McRO* were drawn to improvements in the operation of a computer itself at a task, rather than applying a computer to perform known tasks. *See McRO*, 837 F.3d at 1314. Here, Appellants have not demonstrated such an improvement in the operation of the computer itself, but at best suggest an improvement in the application of an algorithm for siRNA design. Therefore, *McRO* does not persuades us that Appellants' claims relying on correlations using known computer components and known prior art mathematical algorithms as discussed above are patentable subject matter.

Appellants contend that:

> In *Mayo*, the Court emphasized that the critical focus should be on whether the process contains an inventive concept sufficient to ensure that the patent in practice amounts to significantly more than a patent upon life itself. In *Mayo*, the purported invention was the recognition of the precise correlation between metabolic levels of 6-TG and 6-MMP with the likelihood that a particular dosage of a thiopurine drug would cause harm or be ineffective. Significantly, scientists already knew that the levels of certain metabolites were correlated with effectiveness and deleterious effects; the only things that they did not know were the precise correlations. By contrast, with respect to the applicant's claim 67, there is no suggestion that at the time of

> the applicant's invention, there was recognition of either: (1) the fact that the examination of a plurality non-target specific criteria that are each determined based on the presence or absence of a base at a position would be helpful in predicting functionality; or (2) that different criteria could be weighted differently. Therefore, the presently claimed invention is not directed to a law of nature under Mayo.

(App. Br. 9–10)(internal citations omitted).

We find this argument unpersuasive. *Mayo* explicitly states "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field", thereby indicating that the law of nature does not have to be known in order for it to be a law of nature. *Mayo Collaborative Services v. Prometheus Labs, Inc.*, 132 S.C.C. 1289, 1294 (2012). The issue is not whether the abstract idea or law of nature itself is in the prior art, but rather whether the claim as a whole is drawn to a patent eligible application of the abstract idea or law of nature. Here, for the reasons already given, we conclude that the claimed method is not.

Appellants content that

> [w]ith respect to the issue of whether claim 67 is directed to a law of nature, *Rapid Litigation Management Ltd. v. Cellz Direct, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016) is instructive. In that case, the CAFC contrasted the claimed invention, which was directed to a method of preserving hepatocytes, with a hypothetical method that merely detected or observed the ability of hepatocytes to survive multiple freeze-thaw cycles. The CAFC emphasized that the inventors had achieved a better way of preserving the hepatocytes. *Id.* Similarly, in the present case, the applicant achieved a better way of discriminating among candidate siRNA and did not claim a method that merely observes that different siRNA may be differentiated based on functionality.

(App. Br. 10).

We are also not persuaded by these arguments. The claims in *Rapid Litigation Management* were directed to a method with specific laboratory steps for processing and cryopreserving hepatocytes (*Rapid Litigation Management,* 827 F.3d at 1046) and did not contain steps that were laws of nature or abstract ideas. Here, the inquiry is different as the claims contain abstract ideas (such as using a generic computer to computing an algorithm, determining, and selecting) as well as a law of nature (the relationship between siRNA sequence data and gene silencing) (*see* Claims 67, 90).

Appellants contend that "contained within the methods of claims 90 and 91 is a two-step screening process, first by a bioinformatics technique (steps (a) –(c) of claim 90), and then by empirical testing under a specific metric (steps (e)–(g) of claim 90)" and that we stated that "the presence of a specific metric [is] suggestive of patentable subject matter" (App. Br. 10).

We are also not persuaded by these arguments, because, as explained above, our prior decision stated that by failing to recite any specific elements of the claimed algorithm, the claim specifically attempts to fully preempt any process for designing siRNA. We did not state that the presence of a specific metric is suggestive of patentable subject matter. While preemption is the concern underlying the judicial exceptions, it is not a stand alone test for determining eligibility. *Rapid Litig. Mgmt,* 827 F.3d *at* 1052. Simply eliminating concerns regarding preemption does not render the claims patent eligible.

We are also not persuaded by these arguments, because steps (a), (c), (d), and (e) can be performed mentally and are therefore abstract ideas. As the Federal Circuit explained, "methods which can be performed mentally,

or which are the equivalent of human mental work, are unpatentable abstract ideas--the 'basic tools of scientific and technological work' that are open to all" *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1361, 1372, (Fed. Cir. 2011) (citing Gottschalk v. Benson, 409 U.S. 63, 175 USPQ 673 (1972)). Moreover, Elbashir shows that steps (b), (f), and (g) are routine and conventional (*see* Elbashir 199–203, 207) as discussed above.

Finally, Appellants contend that steps (e)–(g) are post-solution steps that are not insignificant, because the steps are "critical for moving from the set of candidate siRNA that are predicted to be functional to a subset that is hyperfunctional", "are concrete steps that apply a specific standard in order to determine which candidate siRNAs are able to effect a desired level of functionality" and "improve on . . . the earlier steps" (App. Br. 10–11). However, as explained above, Elbashir demonstrates, and Appellants do not rebut with evidence, that these steps are routine and conventional. Thus, we are not persuaded by Appellants' arguments.

We therefore conclude that all of the claims on appeal are directed to patent-ineligible subject matter.

SUMMARY

In summary, we affirm the rejection of claims 67–69, 73–78, 90, and 91 under 35 U.S.C. § 101, as being directed to non-statutory subject matter.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED