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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTOPHER STROH
and ANJA VON HEYDEBRECK

Appeal 2017-011384[1]
Application 13/378,711
Technology Center 1600

Before RICHARD M. LEBOVITZ, TAWEN CHANG, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to methods for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer will respond to treatment with an anti-EGFR antibody. The Examiner rejected the claims under 35 U.S.C. § 101 as patent-ineligible because they are directed to a natural law or natural phenomenon. Pursuant to 35 U.S.C. § 134, Appellants appeal the Examiner's determination that the claims are unpatentable. We have

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[1] The Appeal Brief ("Appeal Br.") identified Merck Patent Gesellschaft mit beschränkter Haftung as the real-party-in-interest.

jurisdiction under 35 U.S.C. § 6(b). The Examiner's decision is AFFIRMED.

STATEMENT OF THE CASE

Claims 1–3, 6, 9–15, 22–28, and 46–53 stand rejected by the Examiner under 35 U.S.C. § 101 as directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea). Final Act. 6. The Examiner states that the claims are "directed to the natural correlation between expression levels of prognostic genes or gene expression products, including VAV3 and TGFA[,] and responsiveness to treatment to EGFR antibody," without reciting "additional elements that amount to significantly more" than the correlation. *Id.*

Claim 1, which is illustrative of the claimed subject matter, is reproduced below (additional indenting added for clarity). All Appellants' arguments are focused on this claim. Consequently, claims 2, 3, 6, 9–15, 22–28, and 46–53 stand or fall with claim 1.

> 1. An in vitro method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing tumor, who is a candidate for treatment with an anti-EGFR antibody, will respond to the treatment with said anti-EGFR antibody, the method comprising
>
> measuring the expression level of VAV3 and TGFA in a KRAS wild type EGFR expressing colorectal cancer (CRC) or metastatic colorectal cancer (mCRC) tumor tissue sample obtained from said patient by subjecting a nucleic acid sample from the tumor sample from the patient to PCR or an RNA or DNA array,
>
> wherein (i) higher expression of VAV3, compared to a reference value, indicates that the patient is likely to respond to said treatment, and (ii) lower expression of TGFA, compared to a reference

> value, indicates that the patient is likely to respond to said treatment,
>
> wherein the reference value is the mean expression level of VAV3 and the mean expression level of TGFA, respectively, obtained from a reference patient or a patient group, and
>
> wherein said anti-EGFR antibody is administered to said patient upon a finding that said patient will likely respond to the treatment with said anti-EGFR antibody, wherein the anti-EGFR antibody is c225 (cetuximab).

CLAIM 1

The claims are directed to predicting the likelihood that a patient suffering from a KRAS wild type EGFR (epidermal growth factor receptor) expressing colorectal cancer will respond to treatment with an anti-EGFR antibody.

KRAS is a gene which makes the k-ras protein, a signaling protein involved in signaling pathways in human cells.[2] K-ras is specifically is involved in the EGFR signaling cascade. Spec. 14:8–10. Mutated KRAS has been identified in several different cancers.[3] The claims, however, are drawn to the class of patients having colorectal cancer expressing the "wild-type" or normal form of the KRAS gene and EGFR on the cell surface.

Cetuximab is an example of an "anti-EGFR antibody," as claimed, which had been used prior to the invention to treat cancer tumors which express EGFR. Spec. 2:25–27.

EGFR expression on cancer cells "has proved to be a disappointing biomarker for the efficacy of EGFR-targeted treatment in CRC." *Id.* at

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[2] *See* https://ghr.nlm.nih.gov/gene/KRAS (last visited November 16, 2018).
[3] *See* https://www.cancer.gov/publications/dictionaries/cancer-terms/def/kras-gene (last accessed November 16, 2018).

14:5–7. A cancer tumor may express EGFR on its surface, but not respond to anti-EGFR antibody therapy. As a result, scientists have looked for other biomarkers which predict the response to anti-EGFR antibody therapy.[4] The Specification discloses that the "mutation status of KRAS" has been found "to be a powerful predictive biomarker for cetuximab activity in CRC, allowing the exclusion from treatment of a subpopulation unlikely to derive a significant benefit." Spec. 14:17–19.

Tumors in which KRAS is wild-type also do not always respond to cetuximab. Spec. 14:20–23. The Specification states that therefore "there is a need for the identification and use of further biomarkers that can be used in addition to the KRAS mutation status to better predict the clinical outcome of cetuximab treatment in CRC patients." *Id.* at 14:24–26. The inventors found that the expression of the biomarkers called VAV3 and TGFa can be used to predict the response to anti-EGFR antibodies in patients with colorectal cancer expressing wild-type KRAS. *Id.* at 6:17–20. VAV3 is the abbreviation for Vav Guanine Nucleotide Exchange Factor 3 which has a role in cell signaling pathways.[5] TGFa is a growth factor that is a ligand for the epidermal growth factor receptor which is encoded by the TGFA gene.[6] The inventors found that VAV3 is predictive for a positive response and TGFa is predictive for a negative or negligible response. Spec. 6:17–20.

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[4] Khambata-Ford et al., 2007, *J. Clin. Oncol.*, 25(22):3230-3237 (listed on IDS provided by Appellants on Jan. 25, 2016).
[5] *See* https://www.ncbi.nlm.nih.gov/gene/10451 (last accessed November 16, 2018).
[6] *See* https://www.ncbi.nlm.nih.gov/gene/7039 (last accessed November 16, 2018).

Claim 1 comprises measuring the expression levels of VAV3 and TGFA in a KRAS wild type EGFR expressing colorectal cancer (CRC) or metastatic colorectal cancer (mCRC) tumor tissue sample. The levels are measured using PCR or an RNA or DNA array. As indicated above, (i) higher expression of VAV3, compared to a reference value, indicates that the patient is likely to respond to anti-EGFR antibody treatment, and (ii) lower expression of TGFA, compared to a reference value, indicates that the patient is likely to respond to the antibody treatment. The reference values are the mean expression values obtained from a reference patient or patient group. The antibody is administered to a patient upon finding that the patient will likely respond to the antibody treatment. Thus, the claim does not require anti-EGFR antibody administration in all cases in which VAV3 and TGFa are measured. Furthermore, it does not require treatment of the patient with a therapeutic amount of anti-EGFR antibody even if an increased likelihood of a patient response is determined based on TGF and VAV3 levels. The claim also requires the antibody to be cetuximab.

ISSUE

The Examiner rejected all of the claims in this appeal on the basis of the claims being directed to a law of nature or natural phenomenon which are judicial exceptions to eligibility for patenting under 35 U.S.C. § 101. Final Act. 6. The Examiner found that the claims are directed to the "natural correlation" between expression levels of VAV2 and TGFA and the cancer's responsiveness to treatment with an EGFR antibody, which the Examiner characterized as a natural law or natural phenomenon. *Id.* The Examiner further found that the claim does not include additional elements that are

significantly more than the judicial exception. *Id.* Rather, the Examiner found that the additional steps in the claims were routine and conventional at the time of the invention. As evidence of this, the Examiner cited the disclosure in the patent publication by Ford.[7] The Examiner found that Ford describes using genetic biomarkers to determine whether a patient having colorectal cancer will be responsive to an anti-EGFR antibody. Final Act. 10.

Appellants argue that "the additional elements amount to a claim *as a whole* that adds meaningful limits on the use of the exception (the correlation and critical thinking step)." Appeal Br. 4. Appellants contend that the rejected claims "do not foreclose the public from taking advantage of the correlation between VAV3 and TGFA expression levels [following exposure] of a KRAS wild-type EGFR expressing CRC or mCRC tumor [to an anti-EGFR antibody and the] responsiveness to treatment of the tumor with" that anti-EGFR antibody. *Id.* at 6. Appellants explain that the claims require a "a particular technique for measuring the expression of VAV3 and TGFA" and "a very specific therapy targeted to the individual subpopulation of patients with KRAS wild-type expressing CRC or mCRC tumors." *Id.*

DISCUSSION

We have considered Appellants arguments, but are not persuaded that the Examiner erred in concluding that, under the two-step test of *Alice Corp.*

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[7] Ford et al., WO 2007/025044 A2, published March 1, 2007 (hereinafter "Ford").

Pty. Ltd. v. CLS Bank Int'l, 134 S.Ct. 2347 (2014), claim 1 is directed to patent-ineligible subject matter.

The *Alice* Court stated that "[i]n *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* [132 S.Ct 1289 (2012)] we set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp.,* 134 S.Ct. at 2355. The *Alice* Court described the *Mayo* test as follows:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "'inventive concept'" – i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Id. (citations omitted).

The *Mayo* Court applied its test to claims that are similar to the rejected claims in this appeal. In *Mayo,* the claimed invention was a "method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising administering a thiopurine drug to a patient and then determining the subsequent level of 6-thioguanine (6-TG). *Mayo,* 132 S.Ct at 1295. 6-TG was a known metabolite of the drug. *Id.* at 1295. The claim recited that the level of 6-TG below or above certain amounts indicated a need to increase or decrease the drug dosage.

Rejected claim 1 is similar to the *Mayo* claim in that biomarkers produced by the body through a natural process are used to inform a doctor about treatment considerations. Specifically, the level of a biomarker is used to tell the doctor whether to administer cetuximab to the patient. For this reason, the *Mayo* Court's conclusion that the claims at issue in that case "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" — are applicable here. *Mayo*, 132 S.Ct. at 1296. That is, rejected claim 1 sets forth a law of nature, namely, a natural relationship or natural correlation between the levels of a biomarker in a patient expressed by colorectal cancer tissue and the likelihood that the patient responds to treatment with the anti-EGFR antibody. The fact that the rejected claims involve measurement of the biomarkers in a tissue sample outside the body, while the *Mayo* claims involved the *in vivo* production of the biomarker inside the body does not change the analysis because in both cases a biomarker is being used for the same diagnostic purpose to determine parameters of drug administration to a patient. For this reason, we conclude that under the first step of the *Alice/Mayo* test, claim 1 on appeal is directed to a law of nature or natural phenomenon.

The *Mayo* Court next turned to the question of "[w]hat else is there in the claims before us?" *Mayo*, 132 S.Ct. at 1297. The claims in *Mayo* included an "administering" step, a "determining" step, and a "wherein" clause. *Id.* The Court found that "the 'determining' step tells the doctor" to determine the level of the relevant metabolites in the blood, through whatever process the doctor or the laboratory wishes to use, which the Court

determined in their case to be "well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1297–1298. Relying on earlier case law, the Court stated that "conventional or obvious" activity "is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Id.* at 1298.[8]

The Court considered all three steps as an "ordered combination" and found that "the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Mayo*, 132 S.Ct. at 1298. The Court stated:

> The upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations. To put the matter more succinctly, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.

Id. at 1298. The Court concluded that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Id.*

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[8] We note that claim 1 is not directed to a method of treatment. The claim preamble does not recite a method of treatment. Moreover, the wherein clause concerning administration of anti-EGFR after determining the expression levels of VAV3 and TGFa does not recite that a therapeutically effective amount of anti-EGFR is administered, nor does it recite administration of a particular amount or dosage range of anti-EGFR to administer. Thus, we do not find claim 1 to be like the claims found patent eligible in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals*, 887 F.3d 1117 (Fed. Cir. 2018).

The rejected claims in this appeal stand on similar footing. The step of measuring the expression levels of the VAV3 and TGFA biomarkers is analogous to the "determining the level of 6-TG" step of the *Mayo* claim, because both are directed to measuring a biomarker from a biological sample for the same purpose of informing the doctor of the appropriate therapy to administer to the patient. As in *Mayo*, the measuring step "simply tell[s] doctors to gather data from which they may draw an inference in light of the correlations," which in this case is whether or not to administer the anti-EGFR antibody. *See Mayo*, 132 S.Ct. at 1298.

The method by which the VAV3 and TGFA levels were determined in the patient's tissue was found by the Examiner to be disclosed in Ford, providing evidence that the activity was "well-understood, routine, conventional activity already engaged in by the scientific community." *Mayo*, 132 S.Ct. at 1297–1298; *see also* Final Act. 4, 8. Thus, the Examiner had basis to conclude that they added "nothing significant beyond the sum of their parts taken separately." *Mayo*, 132 S.Ct. at 1298.

Appellants contend that "when viewed 'as a combination' it is clear that the claims are not 'directed to' the natural correlation, but integrate the correlations into a method of measuring and treatment that adds significantly more to the natural correlation." Appeal Br. 5. Appellants argue that the "significantly more" test in *Mayo* "aims to ensure that patent claims recite meaningful limitations such that the public is not foreclosed *(i.e.,* preempted) from taking advantage of what exists in nature." *Id.* at 5. Appellants state that the "instant claims do not foreclose the public from taking advantage of the correlation between VAV3 and TGFA expression levels following exposure of a KRAS wild-type EGFR expressing" colorectal cancer tumor

to an anti-EGFR antibody and the responsiveness to treatment of the tumor with that anti-EGFR antibody. *Id.* at 6. The reason, Appellants explain, is that they use a specific technique to measure the VAV3 and TGFA, namely "PCR or a DNA or RNA array," and a narrowly tailored therapy. *Id.*[9]

This argument does not persuade us that the Examiner erred.

The claim covers RNA and DNA *arrays* and PCR for measuring expression levels of VAV3 and TGFA. Ford discloses that microarray technologies had been used in the prior art to identify molecular markers to predict patient outcome. Ford 2:9–27. Ford also describes the use of arrays in its own work. *Id.* at 6:25, 10:17–20, 43:4–23. The Specification cites prior art publications which used microarrays to measure expression of biomarkers in CRC tumors. Spec. 18:13–19. Ford also describes using PCR technology to measure biomarkers. Ford 6:25, 7:16, 11:26–30. The Specification also describes prior art publications using PCR technology to measure biomarker levels in KRAS wild-type tumors. Spec. 18:17–18. Ford also discloses measuring both VAV3 and TGFA expression levels utilizing commercially available arrays. *Id.* at 47:1–11, 48–49 (Table 2), 57 (Table 4), 49:10–11. Thus, the evidence establishes that arrays and PCR, the same techniques which are claimed, were routinely used prior to the invention to identify and determine levels of a biomarker in a cancer.

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[9] Notably absent from Appellants' argument regarding "a narrowly tailored therapy" is any assertion that the claims require a therapeutically effective amount of the specific anti-EGFR antibody be administered or that a particular dosage range of the specific anti-EGFR antibody be administered to treat the cancer.

Despite this explicit disclosure, Appellants contend that the "Office has not provided any evidence that it was routine in the art to measure the VAV3 and TGFA expression of EGFR-expressing CRC or mCRC tumors in order to determine responsiveness to treatment" with the anti-EGFR antibody. Appeal Br. 9. However, as discussed above, a preponderance of the evidence before us shows that it was routine in the art to measure expression levels of biomarkers in cancerous tumors using arrays and PCR. Appellants have not provided objective evidence to the contrary. Indeed, Ford actually measured the levels of VAV3 and TGFA in colorectal tumor tissues using arrays. Ford 48–49 (Table 2), 57 (Table 4), 49:10–11.

With regard to whether the colorectal cancer expresses EGFR as required by claim 1, Ford teaches that EGFR expression is detected in colorectal cancer. Ford 3:15–27. Thus, the technique described by Ford is applicable to CRC in which EGFR is detected.

Appellants state that "the use of markers for predicting treatment responsiveness was *not actually routinely or conventionally used* by clinicians." Appeal Br. 9. Appellants also contend that Ford's technique, described in one patent publication, is not sufficient to establish it as "conventional activity" already engaged in by the scientific community (*Mayo*), citing guidance materials provided by the USPTO. Appeal Br. 10–11.

This argument is not persuasive. Both Ford and the Specification in their descriptions of the prior art provide evidence that gene expression levels are routinely utilized in the prior art to identify biomarkers associated with cancer and to predict drug responses. Spec. 1:31–2:7; Ford 2:5–27, 4:25–27, 47:1–11, 48–49 (Table 2), 57 (Table 4), 49:10–11. This evidence

has been discussed above. Furthermore, as also discussed above, the claimed PCR and array techniques for measuring gene expression were also well-known in the art and Ford actually measured the levels of VAV3 and TGFA in colorectal tumor tissues using arrays. Ford 48–49 (Table 2), 57 (Table 4), 49:10–11. The point is that claim 1 has not added anything significantly more than what was already available in the prior art to one who sought to measure VAV3 and TGFA levels as an indicator of responsiveness to anti-EGFR antibody. *Mayo* did not strictly limit what is "significantly more" to transform an ineligible claim to anything that is not *conventional* or *routine*, but rather considered factual scenarios where steps that were "obvious" or "already in use" could be insufficient, as well. *Mayo*, 132 S.Ct. at 1299. As explained in *Mayo*, a process of using a mathematical equation was found to be patent eligible in *Diamond v. Diehr*, 450 U.S. 175 (1981) because it "nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." *Mayo*, 132 S.Ct. at 1299. In sum, claim 1 uses arrays in exactly the same way as described by Ford, namely to predict a response to an anti-EGFR antibody by measuring levels of VAV3 and TGFA.

We considered Appellants' argument that "the use of gene expression markers for tumor diagnosis was still gaining acceptance and approval, both in the medical community and within government agencies at the time the application was filed," but are not persuaded by it. Appeal Br. 10.

First, Appellants did not direct us to evidence that government approval is necessary to establish that a technique is conventional. Second, Appellants have not provided evidence that measuring biomarkers as described in Ford and the Specification had not gained acceptance in the

industry as a useful tool to predict a response to a drug. Indeed, the Specification discloses that one such marker, HER2, had been used clinically to select patients for antibody treatment. Spec. 2:3–4. An argument made by counsel in a brief does not substitute for evidence lacking in the record. *Estee Lauder, Inc. v. L'Oréal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997).

Ford specifically teaches array and PCR technologies address the need for "[n]ew prognostic and predictive markers [to] facilitate an individualization of therapy for each patient, []to accurately predict patient response to treatments, such as small molecule or biological molecule drugs, in the clinic." Ford 1:23–26; 2:9–27. Thus, the same gene expression technologies which are claimed were "already in use" to measure levels of biomarkers in cancerous tumors and thus do not add "significantly more" to the claimed natural correlation. *Mayo*, 132 S.Ct. at 1298–1299. Appellants have not provided evidence that actual clinical use is necessary to establish that the steps in a claim do not add significantly more to an otherwise ineligible natural law.

Appellants also attempt to distinguish claim 1 on the basis of the anti-EGFR antibody administration. Appellants argue:

> Ford *et al.* does not demonstrate routine administration of an anti-EGFR antibody to a subpopulation of CRC or mCRC tumors having increased expression of VAV3 and decreased expression of TGFA. In fact, Ford *et al.* does not teach administration of an anti-EGFR antibody at all. Instead, the reference is directed solely to predicting the likelihood of response to any EGFR modulator.

Appeal Br. 10–11.

Appellants contend that the market approval in 2004[10] does not provide an indication for KRAS wild type colorectal tumors and thus cannot be evidence of routine use. Reply Br. 3. Appellants provided an FDA label from 2012 in which they assert establishes this fact. *Id.*

Claim 1 does not require that an antibody be administered to a patient. The claim specifies that the anti-EGFR antibody is administered "upon a finding" of higher VAV3 expression and lower TGFA expression as compared to reference values indicating "that said patient will likely respond to the treatment with said anti-EGFR antibody." The claim, however, does not require administering antibody when the recited reference values are not met. Appellants' attempt to distinguish the claim based on antibody administration is not persuasive because the claim as a whole does not require an antibody to be administered. Consistently, the claim preamble recites that it is "[a]n *in vitro* method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing tumor . . . will respond to the treatment with said anti-EGFR antibody." The "likelihood" of a response is a reflection of the natural levels of the VAV3 and TGFA biomarker in the specific cancer type and therefore the claim as a whole is directed to a natural law. For this reason, while we reviewed Appellants' arguments regarding antibody administration, we do not find it necessary to address them.

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[10] Appellants don't explain the inconsistency with statement in the Specification that approval was obtained in 2004.

Appellants' contention that Ford does not teach anti-EGFR antibody administration to CRC tumors is not persuasive because, as discussed above, claim 1 does not require antibody administration, but rather is a method of predicting the likelihood of a response to the anti-EGFR antibody: When certain biomarker parameters are not met, the antibody is not administered.

Because the claim is neither directed to administration of a therapeutic amount of antibody nor requires such administration, the issue before us is whether the claim is directed to a natural law, namely, the *natural correlation* between VAV3 and TGFA levels and anti-EGFR response and its predictive value in determining whether to administer the antibody to a patient suffering from KRAS wild type EGFR expressing tumor. The additional step of measuring the levels of the VAV3 and TGFA is not significantly more than the natural law, itself, because this step merely informs the doctor to apply the correlation to the patient when determining whether to administer antibody. The claimed techniques to do so were the routinely used in the industry to measure biomarkers expressed in tumors as established by the disclosures in Ford and the Specification.

Appellants cite *Rapid Litigation Management Ltd and In Vitro, Inc. v. CellzDirect, Inc.* as holding that claims which "merely 'involved' a natural phenomenon" are patent eligible. Appeal Br. 6. Appellants argue that such analysis applies here since claim 1 does not just measure a metabolite, but utilizes a particular procedure with several manipulative steps. *Id.* at 7.

This argument does not persuade us that the Examiner erred. In *CellzDirect*, the claims were directed to a method of producing cryopreserved hepatocytes comprising steps of subjecting the cells to density gradient fractionation, recovering the viable cells, and cryopreserving them.

CellzDirect, 827 F.3d at 1046. In contrast, rejected claim 1 is directed to a "method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer (mCRC) will respond therapeutically to the treatment with an anti-EGFR antibody"; no cell based product is produced.

In *CellzDirect*, the claims were found eligible for a patent because the "end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells." *CellzDirect*, 827 F.3d at 1048. In claim 1, the so-called manipulative steps recited in the claim are carried out to measure the VAV3 and TGFA levels which are used to determine whether to administer the antibody. The end result is an "observation" about the levels of the biomarker. Claim 1 does not even require antibody administration if the expression levels of VAV3 and TGFA do meet the recited reference values. Rather, the claim is an in vitro method for predicting the likelihood of a response to anti-EGFR antibody.

For the foregoing reasons, the rejection of claim 1 under 35 U.S.C. § 101 is affirmed. Claims 2, 3, 6, 9–15, 22–28, and 46–53 were not argued separately and fall with claim 1.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED