

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* ERIC N. OLSON

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Appeal 2007-4153  
Application 10/043,658  
Technology Center 1600

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Decided: May 22, 2008

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Before DEMETRA J. MILLS, LORA M. GREEN, and  
RICHARD M. LEOVITZ, *Administrative Patent Judges*.

LEOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 1, 4, and 9. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

“Cardiac hypertrophy is an adaptive response of the heart to virtually all forms of cardiac disease, including those arising from hypertension,

mechanical load, myocardial infarction, cardiac arrhythmias, endocrine disorders and genetic mutations in cardiac contractile protein genes. While the hypertrophic response is initially a compensatory mechanism that augments cardiac output, sustained hypertrophy can lead to dilated cardiomyopathy, heart failure, and sudden death. In the United States, approximately half a million individuals are diagnosed with heart failure each year, with a mortality rate approaching 50%” (Spec. 2).

Myocyte enhancer factor-2 (MEF2) is a transcription factor expressed in cardiac tissue which is described in the Specification as having an important role in the control of cardiac hypertrophy (Spec. 4-5). The Specification states that inhibiting the function of MEF2 can be used to treat cardiac hypertrophy (Spec. 6-7). The claims in this appeal are directed to methods of treating hypertrophy in a cardiomyocyte by inhibiting the function of MEF2.

Claims 1, 4, and 9 are pending, stand rejected, and are appealed (App. Br. 4). There is one rejection at issue: Claims 1, 4, and 9 under 35 U.S.C. § 112, first paragraph, for lack of enabling disclosure (App. Br. 4; Ans. 4). Claims 1 and 9, which read as follows, are representative of the claimed subject matter.

1. A method of treating hypertrophy in a cardiomyocyte cell comprising the step of inhibiting the function of MEF2.
  
9. The method of [claim 1 further comprising inhibiting the upregulation of a gene upregulated by MEF2] 4, wherein the agent that inhibits the function of said genes is an antisense construct.

### ISSUE ON APPEAL

The Examiner contends that claims contain subject matter which is “not described in the specification in such a way as to enable one skilled in the art . . . to make and/or use the invention” (Ans. 4). The Examiner finds the following deficiencies in the Specification:

1) MEF2 is a class of transcription factors which include the MEF2A, MEF2B, MEF2C, and MEF2D isoforms (Spec. 4: 1-4; 16-17). The Specification, however, only provides evidence that MEF2C is involved in cardiac hypertrophy, but not the other members of the MEF2 family (Ans. 5-6);

2) The Specification shows a correlation between cardiac hypertrophy and up-regulation of MEF2, but no direct evidence that MEF2 is a causative factor of hypertrophy (Ans. 5);

3) The Specification is not enabled for the claimed method because “no specific compounds are provided in the specification” (Ans. 12) to achieve the claimed method of “treating hypertrophy in a cardiomyocyte comprising the steps of . . . inhibiting the function of MEF2.”

### DISCUSSION

*No evidence that all MEF2 isoforms are involved in cardiac hypertrophy*

The MEF2 family of transcription factors includes four different isoforms, MEF2A, MEF2B, MEF2C, and MEF2D (Spec. 4: 1-4; 16-17). Claim 1 is directed to treating cardiac hypertrophy by “inhibiting the function of MEF2” and thus covers inhibition of any one (or all) of the four known isoforms. The Examiner asserts that the Specification provides evidence that only one of these isoforms, MEF2C, is involved in cardiac

hypertrophy and thus concludes that the Specification is not enabled for the full scope of the claim (Ans. 5).

In response to the Examiner's objection, Appellant provides several lines of evidence which he asserts establishes "that the extrapolation from MEF2C to other isoforms is indeed warranted, and . . . that simply alleging unpredictability . . . cannot shift the burden to appellant to provide clinical evidence of efficacy" (App. Br. 5). That evidence, which is discussed in more detail below, includes pre- and post-filing publications, and a declaration by Dr. Tim Kinsey, an employee of the licensee of the instant application.

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling." *Wright*, 999 F.2d at 1561-1562. In making our determination, we apply the preponderance of the evidence standard. *See Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

We agree with the Examiner there would have been reasonable basis at the time of filing to doubt that all the identified MEF2 isoforms are involved in cardiac hypertrophy. *Wright*, 999 F.2d at 1561-1562. The Specification states that “[o]f the four mammalian MEF2 genes, three (MEF2A, MEF2B and MEF2C) can be alternatively spliced, which have significant functional differences” (Spec. 16-17). Thus, Appellant admits that there are “significant functional differences” between the different isoforms (*id.*). This statement is consistent with experiments described in the Specification showing that “a subset of cardiac genes is dependent on MEF2C” for expression, while certain other cardiac genes which “also contain essential MEF2 binding sites in their promoters” are “MEF2C-independent” (Spec. 74). Based on these experiments, the Specification concluded that “it is likely that another member of the MEF2 family can support . . . expression [of the MEF2C-independent genes] in the absence of MEF2C” (*id.*). Thus, direct evidence is provided in the Specification that not all members of the MEF2 family have the same function. In our opinion, these facts establish a reasonable basis to doubt that each of MEF2A, MEF2B, and MEF2D would have the same functional role as MEF2C in cardiac hypertrophy.

Appellant provides several lines of evidence to rebut the Examiner’s finding of reasonable doubt, none of which we conclude is sufficient to overcome the rejection.

Appellant relies on two post-filing publications – Xu<sup>1</sup> and Mora<sup>2</sup> – to show “that extrapolation from MEF2C to other isoforms is indeed warranted” (App. Br. 5).

He characterizes Xu as reporting “that MEF2A behaves [as] much as does MEF2C in terms of sarcomeric disorganization, focal elongation, altered gene expression, extracellular matrix remodeling, and ion handling.” Appellant concludes “[t]hus, there is indeed evidence to indicate that MEF2A, like MEF2C, is involved in hypertrophic signaling” (App. Br. 6).

This evidence is not convincing. Appellant does not explain how the disclosure that MEF2A’s behavior is like that of MEF2C in certain cellular processes establishes that MEF2A is also a player in hypertrophic signaling (App. Br. 6). In particular, Appellant does not state how these cellular processes predict that MEF2A, like MEF2C, would have a role in cardiac hypertrophy.

Mora, Appellant states, shows that “MEF2A and MEF2D form a heterodimer, further suggesting a common role for these two proteins” (App. Br. 6). Once again, Appellant has not explained how this activity would compel persons of skill in the art to believe that MEF2A and MEF2D function similarly to MEF2C – making it reasonable to extrapolate that they would have the same function in hypertrophy as does MEF2C. For example, Mora does not state that the heterodimer occurs in hypertrophy; rather, Mora

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<sup>1</sup> Xu et al., “MEF2A and MEF2C Induce Dilated Cardiomyopathy in Transgenic Mice”, *J. Biol. Chem.*, M5:10217, Feb. 6, 2006.

<sup>2</sup> Mora and Pessin, “The MEF2A Isoform is Required for Striated Muscle-specific Expression of the Insulin-responsive GLUT4 Glucose Transporter”, *J. Biol. Chem.*, 275(21): 16323-328, 2000.

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describes the occurrence of MEF2A and MEF2D in insulin-stimulated glucose uptake (Mora, at 16323, Abstract; *see* Ans. 9).

There is an additional reason why we find this evidence insufficient. Enablement is determined as of the application filing date. *In re Hogan*, 559 F.2d 595, 604 (CCPA 1977). Xu was published in 2006; Mora was published in 2000. The instant application claims the benefit of an application having a filing date of Nov. 10, 1999 and provisional applications filed Nov. 10, 1998 and Nov. 12, 1998 (Bibliographic Data Sheet). Thus, it appears that both scientific articles were published *after* the filing date of the instant application.

[A] later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. . . . [However, a later publication can be used] as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative. *Compare In re Hogan*, 559 F.2d 595, 605 (CCPA 1977) ('This court has approved use of later publications as evidence of the state of the art existing on the filing date of an application.' (footnotes omitted) (emphasis in original)) with *In re Glass*, 492 F.2d 1228, 1232 (CCPA 1974) (later publications which add to the knowledge of the art cannot be used to supplement an insufficient disclosure).

*Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

In this case, there is no evidence that the facts disclosed about MEF2A and MEF2D as described in Xu and Mora were available to those skilled in the art ("existing on the filing date") as of the filing date of the instant application. Thus, under *Gould*, the later dated publications cannot be used to supplement the disclosure.

Our analysis is consistent with *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005). Rasmusson had filed a chain of nine

patent applications, each claiming a method of treating prostate cancer by administering finasteride. The Board found that there would have been reason to doubt as of the application filing dates of the first eight applications that finasteride could be used to treat prostate cancer. It wasn't until the ninth application was filed that evidence became available that finasteride was effective to treat prostate cancer.

[N]one of the applications filed before the ninth application “would have enabled a person of ordinary skill in the art as of each of the respective filing date[s] to treat human prostate cancer by administering a therapeutically effective amount of finasteride to a human in need thereof without undue experimentation.” The Board based that finding on its determination that a person of ordinary skill in the art would have had no basis as of the filing date of the eighth application for believing that finasteride could be used to treat prostate cancer [as required by the claims] in light of the state of the art and in light of Rasmusson's failure to provide any data to demonstrate the effects of finasteride in treating prostate cancer.

*Rasmusson*, 413 F.3d at 1322.

Although Rasmusson provided post-filing evidence that the finasteride actually worked in treating prostate cancer, the Federal Circuit concurred with the Board that this evidence was only effective to establish enablement as of the date when the evidence became known to persons of skill in the art – at which time it would have become effective to dispel the reasonable doubt about the adequacy of the enabling disclosure.

Black,<sup>3</sup> however, was available prior to the application filing date. Appellant states that this reference provides “additional studies indicating

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<sup>3</sup> Black et al., “Cooperative transcriptional activation by the neurogenic basic helix-loop-helix protein MASH1 and members of the myocyte enhancer factor-2 (MEF2) family”, *J. Biol. Chem.*, 271(43): 26659-26663, 1996.

that MEF2A, MEF2C and MEF2D have similar functions with respect to interactions with MASH1 and E12” (App. Br. 6). This argument is not convincing. According to Black, each of MEF2A, MEF2C, and MEF2D interact with the MASH1/E12 heterodimer (Black, at 26663, col. 1). Appellant has not explained why the ability to interact with MASH1/E12 would predict that these isoforms would have the same functional involvement with cardiac hypertrophy as does MEF2C.

As acknowledged by Appellant, the different MEF2 isoforms are “alternatively spliced” and have “significant functional differences” between them (Spec. 16-17). Figure 1 of the Specification shows the isoforms to share the same DNA binding domain, but to vary in the regions involving transactivation. The Specification explicitly states that the transcription activation domain (“transactivation”) of MEF2C “is a nuclear target for hypertrophic signaling pathways” (Spec. 23). Thus, we find that persons of ordinary skill in the art would have had reason to believe that differences between the various isoforms in their transcription activation domains could lead to functional differences in their role in cardiomyocyte hypertrophy.

A declaration under 37 C.F.R. § 1.132 (dated Sept. 14, 2006) by Dr. Tim McKinsey (“McKinsey II Dec.”) was provided during prosecution in which he described experiments using one-month old MEF2D knockout mice (McKinsey II Dec. ¶ 3). The results showed that thoracic aortic banding (TAB) produced cardiac hypertrophy in wild-type mice, but not in animals lacking a functional MEF2D gene (*id.*)

This evidence does not persuade us that the Examiner erred in rejecting the claims as non-enabled. First, Appellant does not identify support in the Specification for making and using the MEF2D knockout

mice (Ans. 10). Although the Specification describes methods of making transgenic knockout mice (see Spec. 19-23), there is no explicit statement in the Declaration that these methods were followed; consequently, it is not clear that the experiments described in the McKinsey II Declaration were enabled as of the application filing date.

In addition to this, there is a discrepancy between the function of MEF2C and MEF2D in the knockout mice. According to the Specification, mice lacking MEF2C (“knockout”) die at the embryonic stage from severe cardiovascular defects (Spec. 73-74). However, MEF2D knockout mice apparently do not die as embryos, but live at least one month after birth (McKinsey II Dec. ¶ 3). These results hardly support Appellant’s contention that the results for MEF2C can be extrapolated to MEF2D; in fact, MEF2C appears to be an embryonic lethal, whereas MEF2D is not.

We also note that Appellant has not made arguments regarding the reasonableness of extrapolating from MEF2C to MEF2B. This issue was not addressed in the Appeal Brief nor in the McKinsey II Declaration.

For the foregoing reasons, we conclude that the preponderance of the evidence supports the Examiner’s conclusion that claim 1 is not enabled for its full scope, i.e., for treating cardiac hypertrophy by inhibiting all isoforms of the MFE2 family.

*No evidence that inhibiting MEF2 would be effective to treat hypertrophy in cardiomyocytes*

The Examiner acknowledges that “there is evidence that MEF2C plays a role in the signal transduction pathway that is activated during conditions that cause hypertrophy” in cardiac cells, but argues that there is

no direct evidence that MEF2 is a causative factor (Ans. 5, 7). The Examiner finds that cardiac “hypertrophy is a complex process of signal transduction” suggesting that “simply inhibiting MEF2 will have no effect (*id.* at 5). As evidence of this, the Examiner relies on two post-filing references, Olson and Prassier.<sup>4</sup> The Examiner also cites the Specification for its statement on page 82 that “[c]ardiac hypertrophy has been shown to be controlled by a signaling pathway involving calcineurin and the transcription factor NFAT3, but there is evidence for alternate pathway” involving “activation of MEF2 by CaMK-dissociation of HDAC” as evidence that multiple pathways control cardiac hypertrophy.

Appellant contends that the Examiner erred. “The only specific attack on MEF2 gene therapy is that inhibiting MEF2 generally would not be believed to inhibit cardiac hypertrophy. . . . [A]ppellants have submitted an expert declaration (McKinsey Declaration A; Exhibit 4) and a recently published paper on this precise point (Xu et al., 2006; Exhibit 1), both documents **supporting** the position that down-regulating MEF2 would indeed be therapeutic of cardiac hypertrophy” (App. Br. 8).

The Examiner bears the initial burden of setting forth a reasonable explanation as to why the claims are not adequately enabled by the Specification. A number of factors may be considered in making this determination, including: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior

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<sup>4</sup> Both are post-filing publications. The Examiner has not established that the facts in Olson and Prassier were available as of the instant application filing date. *See Gould supra*. Thus, we have not considered them in our analysis.

art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Here, the Examiner states that the absence of working examples, the lack of a direct link between MEF2 inhibition and treatment of hypertrophy, and the finding that multiple pathways are involved cardiac hypertrophy (generally, “unpredictability”) together constitute a reasonable basis for doubting that the invention could be carried out as claimed (*see* Ans. 4). As we find no defect in the Examiner’s reasoning, we turn to Appellant’s response.

To rebut the Examiner’s conclusion, Appellant relies on additional evidence (App. Br. 7-9): Xu and a declaration by Dr. McKinsey dated Apr. 4, 2005 (“McKinsey I Dec.”). However, Xu, as discussed previously, was published after the application’s filing date and is therefore relevant only as to those facts known on the application’s filing date. Likewise, Dr. McKinsey bases his opinion on post-published references: Zhang<sup>5</sup> in 2002 and his own post-filing reference<sup>6</sup> (McKinsey, 2002).

As we stated previously, enablement is determined as of the application filing date. *Hogan*, 559 F.2d at 604. Appellant has not addressed the pivotal issue: whether persons of ordinary skill in the art would have reasonably believed *at the time of filing* that the claimed method was enabled in light of the evidence in the Specification coupled with the

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<sup>5</sup> Zhang et al., “Class II Histone Deacetylases act as signal-responsive repressors of cardiac hypertrophy”, *Cell*, 110: 479-88, 2002.

<sup>6</sup> Dr. McKinsey provided only the abstract of his publication. The abstract was incomplete: the right-hand margin was cut off, deleting the last few letters and words of every line. Because of the defect in the abstract and the failure to provide the complete publication, we have not considered it in our analysis.

knowledge of the ordinary skilled artisan. What is lacking is evidence from Appellant that the information disclosed in the Specification would have led persons of ordinary skill in the art to reasonably believe that the claimed method of inhibiting MEF would work to treat cardiac hypertrophy. The evidence provide by Appellant is all post-filing (*see* Ans. 9; *see supra.* at p. 7) and thus does not address the sufficiency of the Specification.

In reaching this determination, we note that the Specification provides explicit evidence for a role of MEF2 in cardiac hypertrophy (*see* Specification; Examples 2, 3, 4, and 7). The Specification also provides evidence that CaMK and calcineurin pathways “synergize to active MEF2” (Spec. 8; *see* Fig. 2), in contrast to the Examiner’s assertion to the contrary. The Specification also describes experiments involving several MEF2 isoforms which show their interaction with HDAC (Spec. 79-81). However, Appellant does not explain how this information would have been sufficient to enable the full scope of claim 1, which is drawn to inhibiting the function of MEF2—including all of its isoforms—to treat hypertrophy in a cardiomyocyte cell, but instead rely only post-filing evidence. Appellant also does not clarify how their results concerning the effects of CaMK and calcineurin on MEF2 are consistent with other statements in the Specification indicating the pathways are alternatives to each other (Spec. 82).

*The Specification does not disclose specific compounds to be used in the claimed method*

The Examiner contends that at the time of filing the Specification was not enabled for decreasing expression of MEF2 to achieve treatment of

hypertrophy in cardiomyocytes (Ans. 12). The Examiner states that “no specific compounds” are disclosed in the Specification to treat hypertrophy (*id.*). The Examiner also states that antisense as a therapeutic agent “is not a routine art accepted method” (*id.* at 13).

Appellant contends that the Specification provides “a detailed explanation of **how** one can achieve inhibition of MEF2 signaling” (App. Br. 9), as well as disclosing specific compounds useful for this purpose, such as antisense polynucleotides and antibodies (*id.* at 10).

With respect to antisense technology, we find there is sufficient guidance in the Specification to utilized antisense polynucleotides to treat hypertrophy in a cardiomyocyte. *See* instant claim 9. The Specification provides detailed guidance on how to design antisense polynucleotides (Spec. 24-37), as well as methods of introducing the polynucleotides into cells (Spec. 36-52). The Examiner states that antisense technology “is not a routine art accepted method” (Ans. 13), but does not identify a specific defect in the Specification disclosure. Nor does the Examiner explain why it would involve undue experimentation to utilize antisense polynucleotides in view of the guidance in the Specification.

We do not find this same level of disclosure for antibodies. The Specification states that antibodies can be used “to block the function of an MEF2 polypeptide” (Spec. 27-28), but does not explain how antibodies would be introduced into a cardiomyocyte to treat hypertrophy as required by claim 1. Thus, the enabling disclosure is not commensurate with the full scope of claim 1. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

### CONCLUSION

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. Claims 4 and 9 fall with claim 1 because they were not separately argued. *See* 37 C.F.R. § 41.37(c)(vii)(1).

### TIME PERIOD

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)(2006).

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