

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* DIDIER TRONO and MACIEJ WIZNEROWICZ

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Appeal 2007-4320<sup>1</sup>  
Application 10/720,987  
Technology Center 1600

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Decided: May 7, 2008

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Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and  
FRANCISCO C. PRATS, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-7, 9-11, 13, 41, 46, and 47, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

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<sup>1</sup> Oral hearing held April 8, 2008.

## INTRODUCTION

The claims are directed to a polynucleotide construct (claims 1-7, 9-11, and 13) and a mammalian cell comprising the polynucleotide construct (claim 41, 46, and 47). Claims 1 and 41 are illustrative:

1. A polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain.

41. A mammalian cell comprising a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain, said polypeptide regulator being encoded by said cell.

The Examiner relies on the following prior art references to show unpatentability:

Verma	US 6,013,516	Jan. 11, 2000
Giordano	EP 1 229 134 A2	Aug. 7, 2002

Ulrich Deuschle et al., "Tetracycline-Reversible Silencing of Eukaryotic Promoters," 15(4) *Mol. and Cell. Biol.* 1907-1914 (1995).

Sayda M. Elbashir et al., (Elbashir I), "Functional anatomy of siRNAs for mediating efficient RNAi in *Drosophila melanogaster* embryo lysate," 20 *EMBO* 6877-6888 (2001).

Sayda M. Elbashir et al., (Elbashir II), "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells," 411 *Nature* 494-498 (2001).

We recognize that after the oral hearing Appellants filed an unsolicited communication that included the Moosmann reference<sup>2</sup> (*See* Communication filed April 11, 2008). Apparently, Appellants filed this communication in response to a discussion at the oral hearing wherein the following statements were made with reference to Deuschle's statement "data not shown" (Deuschle 1910: col. 1, l. 9):

MR. PARKER: . . . one would think that if a scientist wanted to support a point . . . that scientist would have put that information in this paper . . . .

JUDGE ADAMS: Maybe there's a whole variety of reasons scientists don't do that, in fact. That could be such a surprising discovery that it's another paper. Right?

MR. PARKER: Right.

(Oral Hearing Transcript 12: 26 - 13:7). According to Appellants the Moosmann reference was identified after this discussion at the oral hearing (Communication filed April 11, 2008). Appellants' correspondence, however, fails to comply with the rules regarding the submission of an information disclosure statement (*see* 37 C.F.R. § 1.97). Accordingly, Appellant's correspondence was placed in the administrative file, but the Moosmann reference was not entered or considered by this Merits Panel.

The rejections as presented by the Examiner are as follows:

1. Claims 41, 46, and 47 stand rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter.
2. Claims 1-7, 9-11, 13, 41, 46, and 47 stand rejected under 35 U.S.C.

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<sup>2</sup> Peter Moosman et al., "Silencing of RNA Polymerases II and III-Dependent Transcription by the KRAB Protein Domain of KOX1, a Krüppel-Type Zinc Finger Factor," 378 Biol. Chem. 669-677 (1997).

§ 103(a) as unpatentable over the combination of Giordano, Elbashir I, Elbashir II, Deuschle, and Verma.

We affirm.

## DISCUSSION

### *Statutory Subject Matter:*

Claim 41 is drawn to a mammalian cell. The claimed cell comprises a polynucleotide construct. The polynucleotide construct comprises a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain, said polypeptide regulator being encoded by said cell. Claims 46 and 47 depend from claim 41 and define the scope of the mammalian cell to include “an undifferentiated cell” (claim 46) and “an oocyte or fertilized oocyte” (claim 47). As Appellants’ Specification makes clear an oocyte and fertilized oocyte are undifferentiated cells (Spec. 19: 4-5). Accordingly the cells identified in claim 47 are species of the genus encompassed by the undifferentiated cell set forth in claim 46.

A fertilized oocyte is an art recognized term for an animal at an embryonic stage. *See e.g.*, Leder<sup>3</sup>, col. 1, ll. 27-32 (“the invention features a transgenic non-human eukaryotic animal . . . at an embryonic stage (preferably the one-cell, or fertilized oocyte, stage . . .)”). Appellants’ Specification expressly discloses that “[h]umans, are specifically contemplated to be organisms for which the methods and compositions of

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<sup>3</sup> Leder

US 4,736,866

Apr. 12, 1988

the invention are applicable” (Spec. 19: 2-3). Accordingly, claims 41, 46 and 47 read on a human embryo.

As the Examiner points out a human is non-statutory subject matter (Ans. 5; *See also* the Manual of Patent Examining Procedure § 2105 stating “[i]f the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter”). Accordingly, a human embryo is also non-statutory subject matter.

We disagree with the Examiner’s assertion “that this rejection could be overcome by amendment to recite an isolated mammalian cell” (*id.*). Absent evidence to the contrary, of which there is none, whether *in vitro* (e.g., isolated from a human body) or *in vivo* - a fertilized oocyte is recognized in the art to read on a human embryo. *See Leder*. Since Appellants have defined their “mammalian cell” to encompass a human embryo, the rejection cannot be overcome by simply amending the claims to read “an isolated mammalian cell” since they would still cover a human embryo (*i.e.*, an isolated human embryo).

We recognize Appellants’ assertion that the claims “may well cover a cell in the future that has been *placed into* a human, but it does not *cover* the human. In order to ‘cover’ the human, the claims would be required to read ‘a human comprising the cell of claim 41’ or something of that nature. This type of claim is not at issue here” (Reply Br. 6). For the foregoing reasons we disagree with Appellants’ unsupported assertion that the claims, which encompass a human embryo, do not read on a human. In this regard, we note Appellants’ assertion that the claims “could potentially cover some

future transgenic human” (App. Br. 12). We are not persuaded by Appellants’ intimation that because the claim does not expressly state “a transgenic human”, “the claims are not ‘directed to’ a transgenic human” (*id.*).

We also disagree with Appellants’ assertion that “[t]here is no way that . . . a human can be made out of stem cells or oocyte cells” (Reply Br. 6). To assert that oocyte cells (female gametocytes - eggs) are not involved in human reproduction is contrary to even the most fundamental of biological principles. Nevertheless, as discussed above, the claims read on a fertilized oocyte – a human embryo. Accordingly, we are not persuaded by Appellants’ assertion.

In sum, Appellants failed to (1) provide an evidentiary basis to support their position, (2) identify any legal precedent to support their position that a fertilized oocyte (a human embryo) is patentable subject matter, or (3) provide a persuasive argument in support of their position.

For the foregoing reasons, we affirm the rejection of claims 41, 46, and 47 under 35 U.S.C. § 101 as directed to non-statutory subject matter.

*Obviousness:*

Claims 1-7, 9-11, 13, 41, 46, and 47 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Giordano, Elbashir I, Elbashir II, Deuschle, and Verma. Appellants have presented separate arguments for two groups of claims: I. claims 1-7, 9-11, 13, and 41; and II. claims 46 and 47. Therefore, we limit our discussion to representative claims 1 and 47. Claim 1 is drawn to a polynucleotide construct. The claimed polynucleotide construct comprises a region encoding a siRNA

(small interfering RNA molecule<sup>4</sup>) operably linked to an externally controllable RNA polymerase III promoter. In addition, claim 1 requires that the expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain. Claim 47 is drawn to a mammalian cell comprising a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain, said polypeptide regulator being encoded by said cell, wherein the cell is an oocyte or fertilized oocyte.

*Findings of Fact (FF):*

1. Giordano teaches nucleic acid contained in a vector (Giordano, col. 3, l. 26).
2. The Examiner finds and Appellants do not dispute that Giordano teaches siRNAs within the scope of Appellant's claimed invention (Ans. 6; Reply Br. 2).
3. Giordano teaches that the vector may “be transformed such that it is stably integrated into a chromosome of the cell” (Giordano, col. 3, ll. 28-31).
4. Giordano teaches that the vector “contains a promoter operably linked to a nucleic acid” (Giordano, col. 3, ll. 31-33).
5. Giordano teaches that “the double stranded RNA expression vector comprises at least one RNA polymerase II promoter, for example, a human CMV-immediate early promoter (HCMV-IE) . . . , at least one

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<sup>4</sup> See Spec. 1: 20.

- RNA polymerase I promoter, or at least one RNA polymerase III promoter” (Giordano, col. 3, ll. 40-45; Ans. 6).
6. Giordano teaches that the cell may be a mammalian cell, a gamete or a stem cell (Giordano, col. 5, ll. 14-17; Ans. 6).
  7. The Examiner finds and Appellants do not dispute that oocytes are included within the term “gamete” (Ans. 6).
  8. The Examiner finds that Giordano does “not teach the use of an inducible or repressible promoter that includes both a DNA binding domain and a repressor domain” as in instant claim 1 (Ans. 6-7).
  9. Deuschle teaches “[a] tetracycline-controlled transrepressor protein [TetR-KRAB] . . . to silence transcriptional activities of eukaryotic promoters that are stably integrated into the chromatin of human cells” (Deuschle 1907, Abstract).
  10. Deuschle teaches that TetR-KRAB “exerts its silencing activity by binding to several *cis-acting tetO* sites placed at a distance from the transcriptional initiation site of a eukaryotic promoter” (Deuschle 1907, col. 2, ll. 3-6).
  11. Deuschle teaches that “[p]romoter activity is restored upon administration of tetracycline, which prevents binding of TetR-KRAB to the *tetO* sequences” (Deuschle 1907, col. 2, ll. 6-8).
  12. Deuschle teaches that “[t]he TetR-Krab silencing system should be useful as a genetic switch for regulating the expression of chromosomally integrated heterologous and endogenous genes present in mammalian genomes” (Deuschle 1907, Abstract; Ans. 7-8).
  13. Deuschle’s “rationale is to generate a fusion protein TetR-KRAB that binds in *cis* to *tetO* sequences upstream of the transcriptional initiation

site of the CMV promoter . . . or to any other promoter” (Deuschle 1908, col. 2, ll. 56-59).

14. Deuschle teaches that “[a]ll of the many different promoters tested so far in this system were found to respond to TetR-KRAB-mediated silencing equally well” (Deuschle 1910, col. 1, ll. 7-10).
15. The Examiner finds and Appellants do not dispute that Deuschle’s TetR-KRAB fusion protein “is reasonably considered to be a polypeptide regulator that comprises a DNA binding domain and a repressor domain” (Ans. 7; Reply Br. 3).
16. The Examiner finds and Appellants do not dispute that Elbashir I teaches “that siRNAs are valuable reagents for inactivation of gene expression . . . in mammalian cells, with great potential for therapeutic application” (Ans. 7; Reply Br. 2).
17. The Examiner finds and Appellants do not dispute that Elbashir II teaches “that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments” (*id.*; Reply Br. 3).
18. The Examiner finds, and Appellants do not dispute that Verma teaches “lentiviral vectors that express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be a promoter and that a wide range of promoters, including suitable viral and mammalian promoters are known in the art” (Ans. 8; Reply Br. 3).

Based on this evidence the Examiner concludes that

[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to formulate a polynucleotide construct comprising a region encoding a siRNA (as taught by Elbashir et al.) operably linked to an externally controllable promoter that was a lentiviral vector construct wherein expression of the siRNA was regulated by a TetR-KRAB operator/repressor system (as taught by Giordano et al., Verma et al. and Deuschle et al.) wherein the externally controllable promoter was repressible by means of an externally applied agent that is an externally applied drug, wherein the repressible promoter was regulated by a Tet repressor and comprises at least one *tetO* sequence and is from the TeT<sup>R</sup> gene wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue, in order to transducer mammalian cells . . . (as taught by Giordano et al.) for the purposes of studying gene function . . . by down regulating the expression of cellular genes on top of their normal regulation (as taught by Giordano et al., Elbashir et al. and Deuschle et al.).

(Ans. 8-9.)

In response, Appellants assert “that the Examiner has failed to provide, or adequately provide, an ‘apparent reason’ why one of skill would seek to use the pol II controllable expression system of Deu[s]chle in the pol III siRNA construct of Giordano” (Reply Br. 3). Appellants do not dispute that Giordano relates “to the controlled expression of siRNA” (Reply Br. 4), instead Appellants argue that Giordano “fails to teach the special type of controlled expression involving the use of both a DNA binding domain and a repressor domain” (*id.* at 3). However, we do not interpret claim 1 to require that expression is controlled by a polypeptide regulator that *involves* “the use of both a DNA binding domain and a repressor domain” (*id.*). Claim 1 states that the repressor has both a DNA binding domain and a

repressor domain, but there is no language in the claim that would require both domains to have the stated regulatory function.

Nevertheless, Appellants assert that Giordano does not “teach a polypeptide regulator having **both** a DNA binding domain and a repressor domain. In fact, it teaches to instead use a regulator having only a DNA binding domain. (col. 34, line 3-4; ‘tet ON/OFF’)” (Reply Br. 2). We are not persuaded by this argument as the Examiner’s rationale is the combination of Giordano with Deuschle. As Appellants recognize, Deuschle teaches “that externally controllable systems of gene expression having both a DNA binding domain and a repressor domain are known” (Reply Br. 3). Thus, even under Appellants’ interpretation, the claimed element would be obvious.

Regarding Deuschle, Appellants assert that “Deuschle is silent on the use of such a control element in the context of siRNA and instead employs the control element in the context of ‘genes’” (Reply Br. 3). In addition, Appellants assert that “Deuschle is silent on the use of such a control element in the context of a pol III promoter. Indeed, Deuschle implicitly instructs the reader to use the control element only in the context of the very different pol II promoter” (*id.*). We are not persuaded.

Deuschle teaches that “[a]ll of the many different promoters tested so far in this system were found to respond to TetR-KRAB-mediated silencing equally well” (FF 14). Thus, while Deuschle exemplifies a pol II promoter, Deuschle provides a reasonable expectation of success for other promoters, including the use of a pol III promoter as taught by Giordano. In this regard, we note that Deuschle’s “rationale is to generate a fusion protein TetR-KRAB that binds in *cis* to *tetO* sequences upstream of the transcriptional

initiation site of the CMV [(pol II)] promoter . . . or to any other promoter” (FF 13). There is no evidence on this record to suggest that Deuschle’s reference to “any other promoter” (FF 13) excludes a pol III promoter. Additionally, there is no evidence on this record that the TetR-KRAB regulatory element is restricted to pol II promoters. Further, there is no evidence that the expression product (*e.g.*, siRNA) plays any role in TetR-KRAB’s ability to regulate a promoter. Accordingly, we are not persuaded by Appellants’ assertion that there was no “reasonable expectation that combining the Deuschle pol II related gene control expression system would be successful in controlling *i) siRNA expression* from *ii) a pol III promoter*” (Reply Br. 4).

In addition, because claim 1 does not require that expression be controlled by a process that involves the use of both a DNA binding domain and a repressor domain, we are not persuaded by Appellants’ assertion that Giordano’s teaching that ““these factors carry protein domains that transactivate or transrepress **the RNA polymerase II.**” Col 33, line[s] 19-21” (App. Br. 17) teaches away from using TetR-KRAB in the context of RNA pol III. Claim 1 only requires that the repressor has both a DNA binding domain and a repressor domain. As discussed above, Deuschle teaches that TetR-KRAB “exerts its silencing activity by binding to several *cis-acting tetO* sites placed at a distance from the transcriptional initiation site of a eukaryotic promoter” (FF 10). Appellants have not provided any evidence that these sites placed upstream of a pol III promoter would not have been expected to work.

As stated in *KSR Int 'I Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740 (2007) “when a patent claims a structure already known in the prior art that

is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” In expressly rejecting the "obvious to try" argument in support of patentability, KSR states:

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” . . . When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

*KSR*, 127 S. Ct. at 1742.

On this record, Giordano teaches a polynucleotide construct, and a mammalian cell (e.g., an oocyte) comprising such a construct, comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter (FF 1-7). Giordano does not teach the regulation of siRNA expression by a polypeptide regulator having both a DNA binding domain and a repressor domain (FF 8). Deuschle, however, makes up for this deficiency in Giordano by teaching a polypeptide regulator having both a DNA binding domain and a repressor domain that is operable with a variety of different promoters (FF 9-14).

Accordingly, we are not persuaded by Appellants’ unsupported assertion that there is “no reasoning as to why one of skill would expect that TetR-KRAB would work with siRNA as opposed to a gene” or “whether [T]etR-KRAB could work with a [ ] pol III promoter instead of a pol II

promoter in the context of siRNA expression” (Reply Br. 5). To the contrary, the combination of references relied upon by the Examiner teaches a person of ordinary skill in the art that a TetR-KRAB fusion protein “binds in *cis* to *tetO* sequences upstream of the transcriptional initiation site of the CMV [pol II] promoter . . . or to any other promoter” e.g., a pol III promoter (FF 13). Giordano teaches a vector comprising a siRNA operably linked to an externally controllable RNA polymerase III promoter (FF 1-7). Notwithstanding Appellants’ unsupported assertions to the contrary, there is no evidence on this record to suggest that the a TetR-KRAB fusion protein would not bind to *tetO* sequences placed upstream of the transcriptional initiation site of a pol III promoter which is operably linked to a polynucleotide region encoding siRNA just as it would upstream of the transcriptional initiation site of a pol II promoter operably linked to a polynucleotide region encoding siRNA.

Accordingly, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Giordano, Elbashir I, Elbashir II, Deuschle, and Verma. Claims 2-7, 9-11, 13, and 41 fall together with claim 1.

As to claim 47 Appellants assert that “the Deuschle reference says nothing about gametes . . . so we know nothing about the ability of the TetR-KRAB construct to function in those cells, or the ability of such a construct to function in those cells to regulate siRNA from a pol III promoter” (Reply Br. 5-6). There is, however, no evidence on this record that TetR-KRAB or a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter would function any differently in an oocyte than in any other mammalian cell.

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Accordingly, we affirm the rejection of claim 47 over the combination of Giordano, Elbashir I, Elbashir II, Deuschle, and Verma. Claim 46 falls together with claim 47.

#### CONCLUSION

In summary, we affirm the rejections of record.

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

AFFIRMED

Ssc:

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