

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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*Ex parte*

KARL L. WOMER, SIHONG SONG, TERENCE R. FLOTTE, SCOTT A. LOILER, MARK A. ATKINSON, MICHAEL CLARE-SALZLER, JUDE SAMULSKI, and CHENGWIN LI

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Appeal 2008-5268  
Application 10/427,165  
Technology Center 1600

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Decided: November 25, 2008

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Before DEMETRA J. MILLS, ERIC GRIMES, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

**DECISION ON APPEAL**

This is an appeal under 35 U.S.C. § 134 involving claims to a method of expressing an exogenous gene in an immature dendritic cell. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## BACKGROUND

“DCs [dendritic cells] are potent antigen presenting cells that play an important role in regulating immune responses.” (Specification 1.) Vectors derived from adeno-associated virus (AAV) “have been used to introduce and express an exogenous nucleic acid in a eukaryotic cell” (*id.*).

The Specification discloses that recombinant AAV serotype 1 (rAAV1) “was clearly superior to rAAV serotype 2 (rAAV2) at transferring genes into DC” and that “rAAV serotypes 3, 4, and 5 (rAAV3, rAAV4, and rAAV5) were capable of transferring genes into DC” (*id.* at 2).

## DISCUSSION

### 1. CLAIMS

Claims 1-3, 6-8, 10-12, 15-17, 19, and 20 are pending and on appeal. Claim 1 reads as follows:

Claim 1: A method of expressing an exogenous gene in an immature dendritic cell comprising a step of infecting an immature dendritic cell with a rAAV virion comprising capsid proteins of a single AAV serotype wherein the serotype is selected from the group consisting of any one of 1, 3, 4 and 5.

### 2. OBVIOUSNESS

Claims 1-3, 6-8, 10-12, 15-17, 19, and 20 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Zhang<sup>1</sup> and Xiao.<sup>2</sup> The claims have

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<sup>1</sup> Yi Zhang et al., *CD40 Ligand-Dependent Activation of Cytotoxic T Lymphocytes by Adeno-Associated Virus Vectors In Vivo: Role of Immature Dendritic Cells*, 74 J. VIROL. 8003-8010 (2000).

<sup>2</sup> Weidong Xiao et al., *Gene Therapy Vectors Based on Adeno-Associated Virus Type 1*, 73 J. VIROL. 3994-4003 (1999).

not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Zhang discloses “an in vitro method of infecting immature dendritic cells with a rAAV virion comprising an AAV serotype 2 capsid protein” that comprises an exogenous gene (Answer 3). The Examiner further finds that “Zhang does not teach a method of expressing an exogenous gene in an immature dendritic cell wherein the rAAV serotype is selected from the group consisting of any of 1, 3, 4, and 5” (*id.* at 3-4).

The Examiner relies on Xiao as disclosing “a comprehensive review of the AAV Type 1 adenovirus” and that “AAV-1 vectors could be used in patients who develop anti-AAV2 neutralizing antibodies due to a naturally acquired infection or previous treatment with AAV-2 vectors” (*id.* at 4).

The Examiner concludes that the combined references would have suggested the method of claim 1 because “Zhang provides the core practice of the claimed method with relation to immature dendritic cells,” while Xiao would have “motivate[d] the ordinary artisan to use AAV-1 in the case a patient mounts an immune response to AAV-2” (*id.*).

We conclude that the Examiner has set forth a *prima facie* case that claim 1 would have been obvious to the ordinary artisan. Zhang discloses that “[a]deno-associated virus type 2 (AAV) has become an attractive tool for gene therapy due to its broad host range, excellent safety profile and durable transgene expression in infected hosts” (Zhang 8003). Zhang also discloses infection of immature dendritic cells with an rAAV virion encoding the exogenous lacZ gene (*id.* at 8004, left-hand column

(“Recombinant AAV (rAAV) expressing *lacZ* (AAV-*lacZ*) . . . were generated.”) and 8004, right-hand column (“DCs were . . . infected separately with AAV-*lacZ*.”).)

Zhang concludes that the “findings demonstrate . . . that immature DCs can take up AAV-*lacZ* and induce a . . . T-cell immune response” (*id.* at 8006). Zhang also discloses that “[p]revious studies showed that immunization with antigen-bearing DCs efficiently primes both CD4<sup>+</sup> helper and CD8<sup>+</sup> CTL immunity and leads to protective immunity to infectious agents and tumors” (*id.*).

Xiao discloses gene therapy vectors based on AAV type 1 (Xiao at 3994). Xiao teaches that “AAV-1 vectors could be used in patients who develop anti-AAV-2 neutralizing antibodies (NAB)” (*id.*). Xiao also discloses that AAV-1 vectors were “evaluated with immunodeficient mice . . . injected intramuscularly or in the portal circulation to target the liver” and that “AAV-1 outperformed AAV-2 in muscle when equivalent titers based on genomes were administered” (*id.* at 4000). Xiao also discloses that “transduced genomes of AAV have been shown to confer long-term gene expression in a number of tissues, including muscle, liver, brain, and retina” (*id.* at 3994).

We agree with the Examiner that it would have been *prima facie* obvious to one of skill in the art to combine the teachings of Zhang and Xiao and thereby arrive at the invention of claim 1. Zhang discloses that dendritic cells infected with an AAV-2 virus that carries a heterologous target gene generates an immune response to the transduced gene and that immunization with antigen-bearing DCs leads to protective immunity to infectious agents

and tumors. Xiao discloses that AAV-1 vectors are more efficient than AAV-2 vectors in transducing certain cell types and may be useful in patients who have developed antibodies to AAV-2. Thus, it would have been obvious to one of skill in the art to express an exogenous gene in immature dendritic cells using an AAV-1 vector because such cells would be expected to be useful to generate protective immunity to infectious agents or tumors in patients who have antibodies to AAV-2.

Appellants argue that the combination of references does not suggest the invention of claim 1 because “Zhang requires **coinfection using wild type Adenovirus (not AAV)** and AAV-lacZ” (Appeal Br. 11). Thus, Appellants argue that Zhang “does not provide motivation or suggestion to infect immature dendritic cells with AAV serotypes other than serotype 2. Not only does Zhang fail to mention other AAV serotypes, but the method disclosed in Zhang required coinfecting dendritic cells with Adenovirus (Ad) to observe more than minimal expression of the transgene” (*id.* at 12).

We are not persuaded by this argument. Although Zhang indicates that the transduction efficiency of AAV-lacZ was substantially enhanced by coinfection with wild type adenovirus, Zhang also discloses, as discussed above, that the population of cells infected by AAV-lacZ alone was effective *in vivo* in generating a T-cell immune response. Thus, given that the transduction efficiency was sufficient to stimulate a T-cell immune response *in vivo*, one of skill in the art would have appreciated that the transduced cells could be used for that purpose. Further the claims are not limited to the use of the AAV virus alone, but also encompass the use of the AAV virus with adenovirus.

Appellants further argue that the Examiner’s rationale “that Xiao et al. ‘motivates the ordinary artisan to use AAV-1 in the case a patient mounts an immune response to AAV-2 . . .’ is flawed because the immune response discussed in Xiao is not relevant to the immune modulation achieved through genetic modification of dendritic cells” (Appeal Br. 11-12). Appellants further argue that Xiao “actually *teaches away* from using AAV-1 virions in the case a patient mounts an immune response to AAV-2 . . . [because] Xiao et al. states ‘initial treatment with AAV-2 **diminished retreatment with AAV-1 approximately 20-fold . . .**’” (*id.* at 13-14).

We are not persuaded by this argument. Although Xiao and Zhang may disclose generating different types of immune responses, Appellants have pointed to no evidence in the record to show that dendritic cells transduced with AAV do not lead to antibodies to AAV, as discussed by Xiao. Thus, the evidence of record does not support Appellants’ position that the immune response discussed in Xiao is irrelevant to immune modulation via dendritic cells.

Appellants’ teaching away argument is also unpersuasive. Xiao teaches that “AAV-2 and AAV-1 completely blocked readministration of the same serotype” (Xiao at 4002). Thus, those skilled in the art would have recognized that AAV-1 would allow retreatment after AAV-2 treatment, even though the efficacy the AAV-1 treatment would be somewhat reduced.

Finally, Appellants argue that “[b]ecause different AAV serotypes infect different types of cells with differing efficiencies, Xiao et al. provides no reasonable expectation of success of using rAAV1 virions to infect

immature dendritic cells resulting in expression of the transgene in the immature dendritic cells” (Appeal Br. 13).

We are not persuaded by this argument. As discussed above, Zhang discloses that AAV-2 infects immature dendritic cells and Xiao discloses that both AAV-2 and AAV-1 serotypes infected both muscle and liver cells, albeit with differing efficiencies. Thus, given the disclosure that both serotypes infect muscle and liver cells, and AAV-2 was demonstrated to infect immature dendritic cells, one of skill in the art would have a reasonable expectation that AAV-1 would infect immature dendritic cells. “Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Appellants have presented no evidence to rebut the Examiner’s reasoned finding, and attorney argument does not take the place of evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

#### SUMMARY

The Examiner’s rejection is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 1-3, 6-8, 10-12, 15-17, and 19-20 under 35 U.S.C. § 103(a).

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

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