United States Court of Appeals for the Federal Circuit

01-1094
(Serial no. 07/945,865)

IN RE JAGANNADAHA K. SASTRY, RALPH B. ARLINGHAUS,
CHRIS D. PALTSOUCAS, and PRAMOD N. NEHETE

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Appealed from: United States Patent and Trademark Office
Board of Patent Appeals and Interferences

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DECIDED: April 5, 2002

Before RADER, SCHALL, and BRYSON, Circuit Judges.

BRYSON, Circuit Judge.

Jagannadha K. Sastry, Ralph B. Arlinghaus, Chris D. Platsoucas, and Pramod N. Nehete (collectively, "Sastry") filed U.S. patent application No. 07/945,865 ("the '865 application") on September 16, 1992. An examiner with the U.S. Patent and Trademark Office rejected all the claims of the application for obviousness and lack of enablement. The PTO's Board of Patent Appeals and Interferences reversed the enablement rejection but sustained the obviousness rejection. We affirm.

I

The appealed claims are directed to a composition for treating and preventing HIV, the name given to the group of closely related viruses that cause AIDS. HIV is deadly because it infects immune system cells—the very cells that are responsible for controlling and destroying pathogens such as HIV. In particular, HIV targets white

blood cells known as T helper cells, which help promote the proliferation, maturation, and immunological function of other types of immune system cells.

After an individual is infected with HIV, the virus may remain dormant for many years. At some point, however, the virus begins to replicate rapidly, reducing the number of T helper cells in the individual's body and thereby compromising the body's immune system. When the number of T helper cells is reduced below a certain level, the individual is said to have developed AIDS.

Research into anti-HIV drugs and vaccines has focused on bolstering the effectiveness of the body's immune response to the virus. The immune system has two ways of responding to viral infection. The first is the "antibody-mediated response," by which the immune system operates to prevent foreign particles, or antigens, from continuing to infect other cells. The second is the "cell-mediated" response, by which the immune system acts to destroy cells that have already been infected.

The cell-mediated response operates as follows: When a protein of an infectious particle (e.g., the outer membrane of HIV known as the "envelope protein") enters a cell, it is broken down into short chains of amino acids known as peptides. The cell then "presents" these cleaved peptides on its surface via a protein known as MHC, which stands for major histocompatibility complex. In this manner, the cell "marks" itself as infected. Special immune system cells known as cytotoxic T lymphocytes (CTLs) then recognize and destroy the marked cells. CTLs are antigen-specific; that is, the introduction of a particular antigen into the body activates specialized CTLs that recognize that antigen. The CTLs then target those cells whose surfaces are marked with a fragment of the activating antigen.

Researchers have found that certain regions of HIV proteins (i.e., peptides) produce a beneficial immune response to the virus. Once identified, those peptides can be synthetically produced and incorporated into anti-HIV compositions. Peptide-based compositions are particularly important in fighting HIV because there is a reluctance, given the deadly nature of the pathogen, to introduce even attenuated or inactive forms of HIV into the body as part of a vaccine or therapeutic formulation.

II

The ’865 application proposed a peptide-based composition designed to stimulate an effective immune response to HIV. Claim 1 is representative (formatting of the claim has been changed for clarity):

1. A composition comprising a first and second peptide,

(a) the first peptide being a CTL-inducing peptide having the ability to stimulate the formation or enhance the activity of cytotoxic T cells that are capable of killing MHC-matched target cells that have the peptide on their surfaces, and

(b) the second peptide is selected from the group of peptides consisting of

an HIV infection-inhibiting peptide derived from the V3 loop of an HIV envelope protein,

an HIV infection-inhibiting peptide derived from the N-terminal portion of an HIV envelope protein,

an HIV infection-inhibiting peptide derived from the CD4 binding region of an HIV envelope protein, and

a T helper cell-inducing peptide characterized as having an amphipathicity value of from about plus 10 to about plus 20, and an alpha helix turn of 100 ± 15 degrees, or a 3_{10} helix turn of 120 ± 15 degrees.

The composition of claim 1 recites a "first peptide" and a "second peptide." The first peptide is described as a "CTL-inducing peptide," which is defined in the '865 application as "a peptide . . . which is capable of stimulating the formation, or increasing the activity, of specific cytotoxic T cells." The inclusion of this peptide in the composition is designed to promote the development of CTLs that will destroy HIV-infected cells. The second peptide of claim 1 functions to assist the immune response elicited by the first peptide by ensuring that the body maintains a large population of uninfected T helper cells. Claim 1 recites that the second peptide is selected from a group of four peptides. Three of these peptides are described as "HIV infection-inhibiting peptide[s]," while the fourth is described as a "T helper cell-inducing peptide." The three HIV infection-inhibiting peptides each correspond to a different region of the HIV envelope protein. Those peptides are each intended to elicit an immune response that interferes with the process by which HIV particles infect T helper cells. The HIV infection-inhibiting peptides therefore achieve the stated aim of the second peptide of claim 1—ensuring a large number of healthy T helper cells—by preventing those cells from becoming infected. On the other hand, the T helper cell-inducing peptide that is identified as the fourth member of the group of "second peptides" of claim 1 ensures the maintenance of a large population of uninfected T helper cells not by preventing the

infection of the body's existing T helper cells, but by inducing the body to generate new T helper cells.

The examiner rejected claim 1 and all other pending claims for obviousness. The examiner found that U.S. Patent No. 5,128,319 to Arlinghaus taught the "first peptide" of claim 1. The examiner also found that a number of other references taught the "second peptide" of claim 1 and supplied the motivation to combine the two peptides into a composition within the scope of claim 1. On appeal to the Board, Sastry argued that the references did not contain the necessary motivation to combine. The Board sustained the examiner's rejection based on Arlinghaus and several other references, including a 1988 journal article by Takahashi et al., and a 1989 journal article by Javaherian et al. This appeal followed.

III

For purposes of this appeal, Sastry focuses on claim 1 of the '865 application. The rejected dependent claims stand or fall with claim 1, because Sastry has not separately argued the merits of those claims. In re Dance, 160 F.3d 1339, 1340 n.2, 48 USPQ2d 1635, 1636 n.2 (Fed. Cir. 1998). Because the other independent claims are not argued at all, we confine our analysis to claim 1.

Sastry concedes that both the "first" and "second" peptides of claim 1 of the '865 application are taught by the prior art. As the Board noted, Takahashi teaches a CTL-inducing peptide (Sastry's "first peptide"), while Javaherian and other references teach an HIV infection-inhibiting peptide (Sastry's "second peptide"). Sastry's argument is that claim 1 is patentable because the combination of those peptides was new, i.e., that

it was nonobvious to combine a "CTL-inducing peptide" with either an "HIV infection-inhibiting peptide" or a "T helper cell-inducing peptide" of the types recited in claim 1.

Sastry takes issue with the Board's reliance on Arlinghaus, which teaches a composition for treating and preventing HIV. Sastry asserts that Arlinghaus does not provide the motivation to combine the two types of peptides recited in claim 1. To the contrary, Sastry contends, Arlinghaus teaches away from combining peptides such as those discussed in Takahashi and Javaherian. According to Sastry, Arlinghaus teaches that CTL-inducing peptides should not be used if they induce a significant antibody-mediated response. Because, in Sastry's view, the HIV infection-inhibiting peptides taught by Javaherian and several of the other references induce a significant antibody response, Sastry contends that Arlinghaus would suggest that those peptides could not successfully be combined with the CTL-inducing peptides taught by Takahashi.

Contrary to Sastry's contention, Arlinghaus does not teach away from the combination of claim 1. In fact, Arlinghaus provides a roadmap for combining the peptides of Sastry's claim 1 by disclosing two peptide-based compositions that have CTL-inducing properties and that contain peptides that satisfy the requirements of Sastry's second peptide, including eliciting a low-level antibody-mediated response.

As the Board observed, Arlinghaus teaches a composition that "provides a suitable T cell response that produces cytotoxic T cells or other types of T cell responses that kill or otherwise neutralize target cells such as T lymphocytes." The Board further noted that Arlinghaus suggests using various peptides for such compositions and "including specific peptide sequences as part of the plurality of active peptides." Among the peptides explicitly suggested by Arlinghaus are two of the

specific peptide sequences included in the ’865 application. The Board noted this overlap, focusing on two dependent claims of Arlinghaus, which “provide limitations for including specific peptide sequences as part of the plurality of active peptides (see e.g., Arlinghaus claims 6 [sic: 5] and 22). These peptide sequences correspond to SEQ ID. NOs: 4 and 2, respectively, of the instant application.”

Independent claim 1 of Arlinghaus, and dependent claims 5 and 22, on which the Board relied, provide as follows:

> 1. A composition containing water having dispersed therein a peptide multimer comprising a plurality of active peptides each of which consists essentially of 7 to about 30 amino acid residues having a sequence that corresponds to a portion of a conserved domain of an HIV protein, said composition, when used to immunize an immunocompetent animal, having the capacity to induce cytotoxic T cell activation to the corresponding native HIV protein but being substantially free from inducing antibodies that immunoreact with said corresponding native HIV protein.
>
> 5. The composition of claim 1, wherein said peptide multimer includes an active peptide that includes an amino acid sequence of
> -EQLWVTVYYGVPV-.
>
> 22. The composition of claim 1, wherein said peptide multimer includes an active peptide that includes an amino acid sequence of
> -CRIKQIINMWQGVGKAMYA-.

By virtue of being dependent from claim 1, claim 5 of Arlinghaus recites a composition having both a "plurality of active peptides" and the "capacity to induce cytotoxic T cell activation to the corresponding native HIV protein." Those limitations are equivalent to the "first peptide" limitation of claim 1 of the '865 application. In addition, claim 5 of Arlinghaus recites that the claimed composition includes a peptide with the amino acid sequence EQLWVTVYYGVPV. Claim 20 of the '865 application, which depends from claim 1, characterizes the peptide having that same sequence as an "HIV infection-inhibiting peptide." The specification of the '865 application further describes that peptide, which it refers to as SEQ ID NO: 4, as derived from the "N-terminus" portion of the HIV envelope protein. Because claim 1 of the '865 application also recites that its "second peptide" may be an HIV infection-inhibiting peptide from the N-terminal region of the HIV envelope protein, the specific peptide recited in claim 5 of Arlinghaus reads on the "second peptide" limitation of claim 1 of the '865 application. By virtue of the incorporated limitations of claim 1 of Arlinghaus, claim 5 therefore reads on both the first and second peptides of claim 1 of the '865 application.

A parallel analysis applies to dependent claim 22 of Arlinghaus. Like dependent claim 5, claim 22 recites a composition having both a "plurality of active peptides" and the "capacity to induce cytotoxic T cell activation to the corresponding native HIV protein." As in the case of claim 5, those limitations read on the "first peptide" limitation of claim 1 of the '865 application. In addition, claim 22 of Arlinghaus recites that the claimed composition includes a peptide with the amino acid sequence CRIKQIINMWQGVGKAMYA. Claim 15 of the '865 application, which depends from claim 1, identifies that peptide as a "T helper cell-inducing peptide." Sastry's

specification characterizes that peptide in the same manner. Thus, claim 22 of Arlinghaus also reads on both peptides of claim 1 of the '865 application.

Sastry disputes this analysis and argues that claims 5 and 22 of Arlinghaus do not read on claim 1 of the '865 application. Sastry contends that the claims are different in scope because Arlinghaus discloses only multimers formed by repeating units of the same peptide, while the "first peptide" and "second peptide" limitations of claim 1 of the '865 application require a composition composed of at least two different types of peptides.

Sastry's characterization of Arlinghaus is clearly wrong. The Board noted that Arlinghaus suggests using "a mixture of relevant peptides," and the plain text confirms that Arlinghaus contemplates the use of more than one type of active peptide in a multimer-based composition. In the "Summary of the Invention," Arlinghaus describes compositions having "[t]wo specific classes of multimers," each of which "can contain one or a plurality of different peptide sequences." U.S. Patent No. 5,128,319, col. 3, ll. 43, 67-68. Arlinghaus repeats this characterization of the disclosed multimers in the "Description of the Preferred Embodiment":

> It should also be noted that a peptide multimer of a composition can contain more than one, active, T cell stimulating peptide as described previously. The inclusion of more than one such active peptide permits activation by more than a single T cell epitope to a single HIV protein, as well as to a plurality of HIV proteins.
>
> Id. at col. 22, ll. 34-39.

Accordingly, Sastry cannot credibly argue that Arlinghaus discloses only peptide multimer compositions having a single, repeating peptide unit. Claims 5 and 22 of Arlinghaus and claim 1 of the '865 application each contemplate anti-HIV compositions composed of different peptides.

In light of the overlap between claims 5 and 22 of Arlinghaus and claim 1 of the '865 application, the Board could have based its rejection on anticipation rather than obviousness. The Board's decision to base its determination on obviousness was not error, however. Because Arlinghaus discloses two compositions that induce CTL activation and include specific peptides within the scope of the "second peptide" of Sastry's claim 1, Arlinghaus can properly be viewed as providing the necessary motivation to combine the peptides of Takahashi and Javaherian.

Nor was Arlinghaus the only reference before the Board that provided a motivation to combine the prior art peptides. For example, prior art U.S. Patent No. 4,943,628, issued to Rosen, discusses classes of peptides corresponding to Sastry's first and second peptides and suggests that "[t]hese peptides provide a basis for a vaccine by combining effective T cell activating sites with neutralizing B cell [antibody-mediated] determinants to produce highly immunogenic molecules eliciting effective memory responses to the native virus." A journal article by Norley and Kurth also teaches the desirability of promoting both the cell-mediated and antibody-mediated responses simultaneously: "[I]t is likely that a vaccine will have to stimulate a cell-mediated immune (CMI) response in addition to neutralizing antibodies." Finally, Takahashi and other references more generally teach the benefits of combining multiple peptides to construct a useful vaccine. In light of the pertinent teachings of all

of those references, we hold that substantial evidence supports the Board's finding of a motivation to combine the CTL-inducing peptides of Takahashi with the HIV infection-inhibiting peptides of Javaherian to produce the composition of Sastry's claim 1.

AFFIRMED.