United States Court of Appeals for the Federal Circuit

06-1154
(Interference No. 104, 776)

IAN FRAZER and JIAN ZHOU,

Appellants,

v.

C. RICHARD SCHLEGEL
and A. BENNETT JENSON,

Appellees.

Beth A. Burrous, Foley & Lardner, LLP, of Washington, DC, argued for appellants. With her on the brief was Courtenay C. Brinckerhoff.

Elliot M. Olstein, Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, of Roseland, NJ, argued for appellees. With him on the brief were Raymond J. Lillie, Alan J. Grant, and Kenneth L. Winters.

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

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(Interference No. 104,776)

IAN FRAZER and JIAN ZHOU,

Appellants,

v.

C. RICHARD SCHLEGEL
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Appellees.

DECIDED: August 20, 2007

Before NEWMAN, Circuit Judge, FRIEDMAN, Senior Circuit Judge, and RADER, Circuit Judge.

NEWMAN, Circuit Judge.

Dr. Ian Frazer and Dr. Jian Zhou (together the interference party "Frazer") appeal the decision of the United States Patent and Trademark Office, Board of Patent Appeals and Interferences ("the Board") awarding priority to Dr. C. Richard Schlegel and Dr. A. Bennett Jenson (together the interference party "Schlegel").[1] The interference is between

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1 Frazer v. Schlegel, Interference No. 104,776 (Bd. Pat. App.& Inter. Sept. 20, 2005).

Frazer's United States patent application Serial No. 08/185,928 entitled "Papilloma Virus Vaccine," which claims priority from Australian and Patent Cooperation Treaty ("PCT") applications, and Schlegel's United States application Serial No. 08/216,506 entitled "Papillomavirus Vaccine."

DISCUSSION

Vaccines in general work by a mechanism whereby a person potentially at risk is deliberately exposed to a disease-causing organism that has been modified or weakened so that it is not capable of producing the disease but that nonetheless causes the immune system to produce antibodies to the disease; then, if that live disease-causing organism should enter the body, the immune system already has the antibodies needed to fight the disease. The invention here contested relates to a vaccine for use against human papillomaviruses ("HPVs"), a class of viruses that can cause cervical cancer and other diseases. All HPVs have a similar structure: they have a core of disease-causing viral DNA, surrounded by an outer protein coat called a "capsid" that has an icosahedral, or twenty-sided, shape.

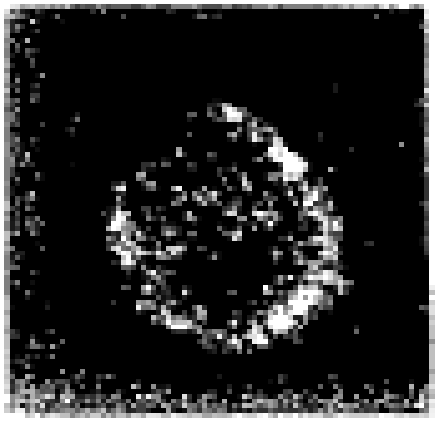
The facts are generally undisputed, although their significance is disputed. Dr. Frazer and Dr. Zhou, working at the University of Queensland in Australia and using procedures derived from recombinant DNA technology, succeeded in preparing what they call "papilloma virus (or virion)-like particles" that have the external icosahedral shape of the virus capsid and thereby mimic the papilloma virus, but lack the disease-causing genetic material. Their idea was to create a vaccine from such a virus-like particle, and thereby to stimulate the immune system to make antibodies that would deactivate any authentic papillomavirus that might enter the body. They first reported this work in a

scientific article that was received by the journal Virology in California on May 21, 1991, entitled "Expression of Vaccinia Recombinant HPV 16 L1 and L2 ORF Proteins in Epithelial Cells Is Sufficient for Assembly of HPV Virion-like Particles," published at 185 Virology 251 (1991). The article included experimental details of the production of these virus-like particles, including photomicrographs of the products; the Introduction included the following text:

> A recombinant vaccinia virus . . . was designed to coexpress the L1 and L2 late genes of human papillomavirus type (HPV16) . . . . The production of HPV-like particles using recombinant vaccinia virus should be useful for biochemical studies and could provide a safe source of material for the development of a vaccine . . . . Infection of the human cervix with human papillomavirus (HPV) types 16 of 18 is strongly associated with cervical cancer.

185 Virology at 251.

The text and experimental data from the article were included in a patent application filed in Australia on July 19, 1991, including electron micrographs of HPV virus-like particles, as shown in Fig. 5, Australian application PK 7322:



In the Australian patent application, the statement of objects of the invention included the following:

> [I]t is an object of the invention to provide a vaccine for use with papilloma virus infections which is effective in use. The invention therefore in one aspect includes a method for production of a vaccine which includes the steps of:
>
> (i) constructing one or more recombinant DNA molecules encoding the L1 and L2 proteins;
>
> (ii) transfecting a suitable host cell with said one or more recombinant DNA molecules so that virus like particles (VLPs) are produced within the cell after expression of the L1 and L2 proteins; and
>
> (iii) obtaining the VLPs from the transfected cells and incorporating the VLPs in a vaccine.

Frazer Australian application, p.6, l.19 - p.7, l.4. The Australian application describes the recombinant DNA encoding the L1 and L2 proteins, and explains that the L1 and L2 genes may be included in the same or different DNA recombinant molecules. The application describes the amplification of the HPV-16 L1 and L2 genes using the polymerase chain reaction, identifies the two primers used, indicates the codons, and provides the procedures of extraction, purification, digestion, and subcloning. The application discusses sequencing of the resulting plasmid, its use to prepare the desired gene fragments, and its cloning into the specified site of the vaccinia vector. The purification and separation and identification of these virus-like particles are described.

Frazer's procedures for electron microscopy of the capsid particles, and analysis by immunoprecipitation and immunoblot, are also described in the Australian application, as are the methods of confirmation of L1 protein by autoradiography, and L2 transcription by northern blot of RNA extracted from infected CV-1 cells. The Australian application contains illustrations and electron micrographs showing approximately 40nm diameter virus-like particles in cell nuclei. The application discusses the fifty-six known human

papillomavirus types and the diseases they cause, as well as immunotherapies and potential vaccines for papillomavirus infections. The application reports combinations of proteins that were and were not successful, and places the results in the context of the scientific knowledge then available, including citations to scientific articles and discussion of the advances made.

Drs. Frazer and Zhou presented this research on July 22, 1991 at the Papillomavirus Workshop, a scientific conference held in Seattle, Washington. The lecture by Dr. Frazer included the method of preparation of the virus-like particles, electron micrographs of the synthetic capsid, and a discussion of vaccine use of these VLPs. A written abstract by Dr. Zhou was distributed at the Workshop.

A PCT application was filed on July 20, 1992, claiming priority from the Australian application with additional text and experimental data; the PCT application contained the following summary:

> A method of providing papilloma virus-like particles which may be used for diagnostic purposes or for incorporation in a vaccine for use in relation to infections caused by the papilloma virus. The method includes an initial step of constructing one or more recombinant DNA molecules which each encode papilloma virus L1 protein or a combination of papilloma virus L1 protein and papilloma virus L2 protein followed by a further step of transfecting a suitable host cell with one or more of the recombinant DNA molecules so that virus like particles (VLPs) are produced within the cell after expression of the L1 or combination of L1 and L2 proteins. The VLPS are also claimed per se as well as vaccines incorporating the VLPs.

Frazer's United States patent application, claiming the priorities of the PCT and Australian applications in accordance with statute, see 35 U.S.C. §§119, 363, was filed on January 19, 1994. This application was placed in interference with the Schlegel application and two other applications not here relevant.

Dr. Schlegel and Dr. Jenson of Georgetown University Medical Center on June 25, 1992 filed the United States patent application that is involved in the interference. It is not here disputed that the Schlegel and the Frazer applications are directed to the same subject matter. Schlegel was declared senior party, having the earlier United States filing date. Frazer was then granted the benefit of the Australian filing date, but that benefit was withdrawn by the patent examiner during the interference. This appeal turns on whether Frazer is entitled to rely on the filing date of the Australian application to show possession of the subject matter in interference.

The Interference

The examiner established the following interference count, designated Count 2 and based on claims from Frazer's United States application, as follows:

> Count 2. A composition of matter according to claim 67 of Frazer or a method according to either claims 65 or 97 of Frazer.
> Frazer Claim 65: A method of making a papillomavirus virus-like particle, which method comprises: constructing a recombinant DNA molecule that contains a sequence encoding a papillomavirus L1 protein; transfecting a host cell with the recombinant DNA molecule; expressing papillomavirus virus-like particles from the transfected host cell; wherein the papillomavirus is not HPV 16.
> Frazer Claim 67. A papillomavirus virus-like particle made by the method of claim 65.
> Frazer Claim 97. A method of producing anti-papillomavirus antibodies in an animal comprising administration of a papillomavirus virus-like particle to the animal.

The Board held that Frazer is not entitled to the benefit of the Australian application's filing date, holding that the application's disclosure was inadequate. The Board also held that even if Frazer were found to have established conception in the United States based on the submission to the Virology journal or the presentation at the Seattle Papillomavirus

Workshop, Frazer could not establish diligence to reduction to practice because all of Frazer's experimental work was done in Australia. The Board observed that since "all of Frazer's actual reductions to practice occurred outside of the United States, Frazer must rely either on the filing dates of its Australian and PCT applications for inter alia conception and constructive reductions to practice, or on disclosures within the United States of such activities," citing 35 U.S.C. §104(a). Board op. at 35. Thus the Board declared Schlegel the first inventor based on Schlegel's United States filing date.

We conclude that Frazer was entitled to the priority date of the Australian patent application. Since the Australian filing date antedates any date alleged by Schlegel, priority must be awarded to Frazer. We thus do not reach Frazer's assertion that Schlegel derived the subject matter of the count from Frazer's presentation at the Seattle Workshop, at which Schlegel was present.

DISCUSSION

In accordance with United States law, when the priority claim is based on subject matter disclosed in a foreign patent application whose filing date is properly claimed, 35 U.S.C. §119(a), the foreign application has the same effect as if filed in the United States. §119(a), (e)(1). The invention must be "disclosed in the manner provided by the first paragraph of section 112." §119(e)(1); see Schur v. Muller, 372 F.2d 546, 551 (CCPA 1967) (it is a "general principle" in interference proceedings that a party may claim the benefit of a foreign-filed priority document provided that it discloses all of the limitations of the count).

Constructive reduction to practice does not invoke different standards whether the priority document is foreign or domestic. When interference priority is at issue, constructive

reduction to practice of a count may be established by disclosure of an embodiment within the count. See Fontijn v. Okamoto, 518 F.2d 610, 617 (CCPA 1975) (foreign application disclosing one embodiment of the invention that meets the count as broadly construed, and that meets the requirements of 35 U.S.C. §112, is sufficient to establish constructive reduction to practice); Yasuko Kawai v. Metlesics, 480 F.2d 880 (CCPA 1973) ("the written specification in the application is the evidence proving the invention of that which is reduced to practice"); see generally In re Zletz, 893 F.2d 319, 323 (Fed. Cir. 1989) (in an interference, "[p]riority as to a genus may be indeed shown by prior invention of a single species . . . but the genus will not be patentable to an applicant unless he has generic support therefor"); Oka v. Youssefyeh, 849 F.2d 581, 584 (Fed. Cir. 1988) (in an interference, it is a correct principle that the "conception of a species within a genus may constitute conception of the genus").

Although the Board analyzed the Australian application in terms of "conception," when reliance is on a patent document already filed, the question is whether the document discloses the invention of the count by meeting the written description and enablement requirements of 35 U.S.C. §112 ¶1, for a filed application serves as a constructive reduction to practice of its content.

The Board held that Frazer's Australian application "did not provide a described and enabled anticipation under 35 U.S.C. §102(g) of the subject matter of the count," Board op. at 43-44, because at the time the Australian application was filed "Frazer believed that both the L1 and L2 genes had to be expressed together from the same plasmid," whereas his "later work shows that only L1 protein was necessary." Id. at 53. Although the Board acknowledged that "[t]he work reported in the Zhou manuscript [in Virology] and in the

[Australian] application appears to be the first reports of particles comprised of coat protein from a papillomavirus obtained by recombinant techniques," id. at 51, the Board ruled that this did not show "conception" because Frazer stated in these documents that both the L1 and L2 genes were expressed, whereas Frazer later discovered, and reported in the PCT application, that expression of either the L1 gene alone, or the L1 and L2 genes together, form the virus-like particle. The Board also referred to an "unexplained" difference in particle size and shape between Frazer's initial and later observed VLP conformational epitope formation.

The Board acknowledged the uncertainties in the science at the time this work was done, stating that:

> Recombinant protein technology for vaccines was an extremely complex art. In 1991, the art was nascent, evidenced by the perhaps understandable incorrect conclusions noted supra, which were based on experimental evidence, even as to such relatively "simple" matters as which proteins were necessary to form virus-like particles, and whether baculovirus was a suitable system for papillomavirus coat protein expression.

Board op. at 62. The Board stated that "[r]evising hypotheses in the face of evidence is a hallmark of well-conducted research," id. at 62-63, and ruled that Frazer was not entitled to any date of disclosure until he accurately and fully understood the mechanism. The Board referred to Dr. Frazer's "admission" that "it was impossible to determine, in 1991, whether the particles they produced had conformational epitopes of the native virions: 'at that time, the reagents that would be needed to do that work were not available.'" Id. at 55 (quoting Dr. Frazer's testimony). The Board ruled that neither the PCT application nor the ensuing United States application was entitled to the priority date of the Australian application.

We conclude that the Board erred in denying Frazer's entitlement to the date of the Australian patent application. The Australian application contained complete details of the method that is the subject of the interference count, and depicts the papillomavirus-like particle of the count with full disclosure of how to produce it. The specification also includes the DNA sequences encoding the papillomavirus L1 and L2 proteins. While Frazer in the Australian application reported the expression of both the papillomavirus L1 protein and the papillomavirus L2 protein, and he testified that at that time he believed both proteins were involved, his later discovery that either the L1 protein or both the L1 and L2 proteins led to capsid formation does not negate or contradict his disclosure and constructive reduction to practice of the method of the count that produced the papillomavirus-like particle of the count. Frazer correctly argues that the Australian application describes and enables the formation of the papilloma virus-like particles. The filing of a patent application is a constructive reduction to practice of the invention disclosed therein. Hyatt v. Boone, 146 F.3d 1348, 1352 (Fed. Cir. 1998); see, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986) ("constructive reduction to practice occurs when a patent application on the claimed invention is filed").

It is not disputed that Frazer's Australian application described virus-like particles and their production from recombinant vaccinia virus. Dr. Frazer testified concerning the uncertainties in the science:

> We drew the conclusion, first of all, because HPV virions of HPV-16 type had not been seen or purified, suggesting a problem with their -- with their assembly and secondly, because the virus-like particles that we had produced were not identical to -- morphologically identical, in other words identical in appearance, to papillomaviruses from BPV-1 or HPV-1, which were, if you like, the types available for -- that you could derive tissue and look at.

Quoted in Board op. at 31. The Board cited this testimony as supporting the Board's ruling that the Australian application did not show "conception." Indeed, Dr. Frazer pointed out that this was new science, but acknowledgment of the complexities of the science does not negate the disclosure of the production of these virus-like particles. In Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1367-68 (Fed. Cir. 1997), the court explained that "[w]here, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching," recognizing the stage of development of the technology. The Australian application was not "merely proposing an unproved hypothesis" or guess, Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005); it was an enabling disclosure.

On this appeal Frazer points out that "The Board never determined that Frazer failed to teach any essential step required to make VLPs of non-HPV-16 papillomavirus types. In fact, the Board acknowledged that 'VLPs having the same shape and much more nearly the size of native virions could be made following the general procedure disclosed by the Australian application.'" Appellants' br. at 71. There was no evidence contradicting Frazer's production of the virus-like particles shown in the Australian application and the method shown therein of producing these particles.

The Board ruled that the Australian application was not a constructive reduction to practice, explaining in a decision on motions: "We have held that the Australian application does not provide an enabling disclosure with respect to VLPs from the prototype HPV 16 . . . . [S]ufficient doubt had been raised, and evidence to the contrary offered by Frazer was

not sufficient to outweigh doubts of enablement." However, it was not disputed that the procedures set forth in the Australian application produce the papillomavirus-like particles shown in the Australian application and in the PCT and United States applications. The evolving state of the scientific study of papillomaviruses was recognized by the Board, which apparently believed that Frazer was not entitled to rely on the Australian application because Frazer had not appreciated that they were working with the wildtype virus. However, the description of the procedures used, and the successful production of the virus-like particles there achieved and reported, disclose and enable a species within the count. The Board erred in ruling "that Frazer has failed to prove legal conception of an embodiment within the scope of the Count on the basis of the Australian application." Board op. at 36.

Based on the constructive reduction to practice of an invention whose disclosure is in compliance with the requirements of §112, Frazer is entitled to the priority benefit of the Australian filing date. That date predates Schlegel's earliest date. The award of priority to Schlegel is reversed, and priority is awarded to Frazer.

We remand to the PTO for appropriate further proceedings.

REVERSED and REMANDED