

Inventions In Unpredictable Fields — Not Always Unobvious

Law360, New York (November 07, 2012, 1:24 PM ET) -- On Sept. 21, 2012, a three-judge panel of the Federal Circuit in *In re Droge* (2011-1600) held that the claims in U.S. patent application serial no. 10/082,772 (the '772 application"), directed to a method of recombining DNA in eukaryotic cells, were unpatentable for obviousness. The Federal Circuit affirmed the decision of the Board of Patent Appeals and Interferences, affirming the patent examiner's rejection for obviousness despite an expert opinion from the applicant that the prior art failed to provide an expectation of success in the claimed combination.

The declaration failed to specifically rebut the examiner's allegations and support from the scientific literature by using either scientific reasoning or by citation to contrary scientific literature or data. The field of biotechnology is viewed by the U.S. Patent and Trademark Office as generally unpredictable and biotechnology inventions are often found to be nonobvious because of this general unpredictability. *In re Droge* demonstrates that the prior art may establish enough predictability, which, if unrebutted by equally convincing evidence to the contrary, may be sufficient to sustain an obviousness rejection even in unpredictable fields.

The rejected claims in *In re Droge* are directed to a method for recombining (i.e., splicing) segments of DNA inside of a eukaryotic cell by application of particular DNA recombining enzymes (i.e., a recombinases) derived from the integrase family ("Int") of DNA recombinases. By way of background, a eukaryotic cell (e.g., a mammalian cell) contains nonsupercoiled chromosomal DNA within a specialized subcellular structure; the nucleus. This contrasts with prokaryotic cells (e.g., a bacterial cell), in which chromosomal DNA is negatively supercoiled and found free within the cytoplasm of the cell. The specific recombinases used by the '772 application, known as Int-h and Int-h/218, are mutated of the naturally-occurring Int recombinases.

The U.S. Patent Office rejected the claims as being obvious over two references, an issued U.S. Patent No. 6,143,530 to Crouzet and an article by Christ and Droge, who are two of the three inventors identified on the '772 patent application.

The patent examiner argued that Crouzet teaches recombining DNA in both eukaryotic and prokaryotic cells in the manner claimed except that the recombining enzyme was a naturally-occurring form of the Int recombinase. The examiner further argued that Christ and Droge describes the Int-h and Int-h/218 mutant recombinases and their use for site specific recombination in prokaryotic cells lack co-factors (i.e, enzyme-assisting molecules) normally present in eukaryotic cells.

Christ and Droge attribute this finding to the enhanced affinity of the mutant recombinases for core sites and an increased ability to function as Int family recombinases. Based on these findings, the examiner concluded that the mutant family recombinases reasonably should be expected to work in eukaryotic cells, a cell type in which the naturally occurring Int recombinase works.

The patent applicant filed a declaration by inventor Droge arguing that the skilled artisan would not have had a reasonable expectation that the mutant Int recombinases would work in eukaryotic cells. The Droge declaration argued that the success of the mutant recombinases in prokaryotic cells may have been based on two factors, (1) the presence of specific co-factors (e.g. IHF) and (2) that DNA in prokaryotic cells is negatively supercoiled. Droge cited to no scientific evidence to back up either assertion of unpredictability.

The patent examiner concluded that Droge's arguments were rebutted by several scientific publications, including "Lange-Gustofson." According to the examiner, Lange-Gustofson reported that the mutant recombinases worked better with nonsupercoiled DNA than with supercoiled DNA in the presence of the IHF co-factor but worked equivalently with both DNA forms when the IHF co-factors was absent. The patent applicant did not dispute this fact by citation of any scientific reasoning or contrary scientific literature but attempted to undercut the reference by arguing that Lange-Gustofson's experiments were performed in vitro under conditions not akin to the interior of a living eukaryotic cell.

The Federal Circuit affirmed the decision of the Board of Patent Appeals and Interferences which sustained the rejection of the '772 application claims for being obvious over the prior art. The court found that the Droge declaration, in view of Lange-Gustofson, failed to establish substantial evidence against the examiner's finding that there was a reasonable expectation for the mutant recombinases to work in eukaryotic cells which lack co-factors and have nonsupercoiled DNA. In affirming the position of the Board of Patent Appeals, the Federal Circuit cited to *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)) to emphasize that a finding of obviousness does not require absolute predictability of success but instead requires only a reasonable expectation of success.

The chemical and biological arts are generally considered to have a relatively high degree of unpredictability. Therefore, it is not uncommon for patent applicants to provide declaration evidence from inventors or other experts in the field to counter arguments that the prior art provided a motivation to combine certain teachings or that, as in the present case, such a combination gave rise to a reasonable expectation that the combination would be successful for its intended use. In *re Droge* demonstrates that, even for the relatively unpredictable arts, the use of a declaration that merely asserts unpredictability, without providing experimental evidence or a scientific reasoning, may be insufficient to overcome an obviousness rejection for which the declarant's assertions are contradicted by the scientific literature.

--By Barry Wilson and Anthony Kuhlmann, Sheppard Mullin Richter & Hampton LLP

Barry Wilson and Anthony Kuhlmann are special counsel in Sheppard Mullin's Del Mar, Calif., office.

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