122. The teaching in Schreiber regarding the effector domain of rapamycin provides additional motivation for a person of ordinary skill in the art to view modifications at C28 as less favorable, because it was known to be proximal to the interaction of rapamycin with the unidentified biological target of the rapamycin/FKBP-12 complex. (*Id.*) Further, because the interaction between the rapamycin/FKBP-12 complex and this second target had not been fully characterized, a person of ordinary skill in the art would have been motivated to start with small modifications at the C40 position in order to avoid introducing modifications that interfered with this binding. (*Id.*)

123. Therefore, the teaching of Van Duyne regarding the interactions of rapamycin with FKBP-12 and its second biological target highlighted that the hydroxyl group at C40 was the best position to modify rapamycin without disrupting its biological activity. Further, because the interaction between rapamycin, FKBP-12, and the unknown target were not fully characterized, a person of ordinary skill in the art would have been motivated to start with small modifications at C40 so as to avoid unnecessarily disrupting binding to the unknown target as well as FKBP-12.

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6. Standard Assays to Test Immunosuppressive Activities and Properties of Rapamycin Derivatives Were Well-Known to Those of Ordinary Skill in the Art

124. A person of ordinary skill in the art making modifications to rapamycin in October 1992 would also be strongly motivated to consider the assays known in the prior art for evaluating a compound's immunosuppressive activity.

125. And, as reflected in the prior art references disclosing other modifications to rapamycin, after synthesizing a rapamycin derivative, it was routine by October 1992 for those of ordinary skill in the art to assess the compound's immunosuppressive activity in standard assays. For example, Hughes and Schiehser identify a number of derivatives of rapamycin and indicate that "[i]mmunosuppressive activity was evaluated in an in vitro ***standard*** pharmacological test procedure . . . and in two in vivo ***standard*** pharmacological test procedures." (Ex. 1009, Hughes at 2:62-65 (emphases added).) One of the *in vivo* procedures described in Hughes assesses the ability of the rapamycin derivatives to prevent the rejection of a skin graft transplant in mice. (*Id.* at 3:51-4:12.) Hughes indicates that "[b]ased on the results of these standard pharmacological test procedures, the compounds are useful in the treatment of transplantation rejection such as, heart, kidney, liver, bone marrow, and skin transplants; [and] autoimmune diseases." (*Id.* at 4:48-56.) These same types of

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standard biological assays for evaluating compounds for immunosuppressant activity was also disclosed in Schiehser. (Ex. 1011.) Further, as detailed in Morris, these are precisely the types of immunosuppressant activities, including allograft rejection, that had been widely reported for rapamycin. (Ex. 1005, Morris at 54-64.)

126. With respect to immunosuppressant compound candidates, those of ordinary skill in the art would routinely instruct technicians or collaborators to perform such standard assays to assess the activity of these candidates. Similarly, measurement of a compound's solubility in aqueous solution was well known to those of ordinary skill in the art long before October 1992, and such measurements were reported for the rapamycin derivatives disclosed in Stella. (Ex. 1010, Stella at Tables 2 and 3.) Those of ordinary skill in the art would routinely instruct technicians or collaborators to perform such standard measurements.

B. Prior Art Relevant to Obviousness Grounds 3 and 4

1. Computer Based Modeling Allowed for Rapid Screening of Possible Modifications

127. In addition to the rational structure based drug discovery process described above, those of ordinary skill in the art were also familiar with computer-aided drug design by October 1992. This included interactive display of

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protein-ligand complexes and the modeling of analogues of the ligand bound to the protein.

128. One particular advance aided by developments in computer technology was the use of molecular graphics to visualize and virtually manipulate drug compounds bound to their target receptors. (Ex. 1015, Silverman, *Drug Discovery, Design, and Development*, THE ORGANIC CHEMISTRY OF DRUG DESIGN & ACTION 11, 44-47 (1992) ("Silverman").) Such a three-dimensional representation allowed the operator to "visualize the interactions of small molecules with biologically important macromolecules," superimpose structures, and assemble new structures from known molecular fragments. (*Id.* at 45.) The applicability of this technique was best applied to ligand-receptor structures that had already been identified through crystallographic means. (*See id.*) Thus, for compounds whose structure in complex with its biological target had been characterized, the ability to use molecular graphics and modeling techniques provided a significant advantage to screen and evaluate potential modifications to identify those with favorable steric and electronic characteristics before undertaking the efforts to actually synthesize each of the potential new compounds. (*Id.* at 44-47.)

129. By obtaining the three-dimensional coordinates of the bound rapamycin/FKBP-12 molecule available from Van Duyne as described above, a

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person of ordinary skill in the art could use software that was available by October 1992 to produce computer models of complexes of rapamycin and derivatives with FKBP-12. Using such models allow those of skill in the art to investigate the complexes of various derivatives of rapamycin bound to FKBP-12. Software was specifically used for designing new potential drugs; key examples are the programs GROW (Ex. 1013, Joseph B. Moon & W. Jeffrey Howe, *Computer Design of Bioactive Molecules: A Method for Receptor-Based de Novo Ligand Design*, 11 PROTEINS: STRUCTURE, FUNCTION, & GENETICS 314 (1991)), LEGEND (Ex. 1028, Yoshihiko Nisibata *et al.*, *Automatic Creation of Drug Candidate Structures Based on Receptor Structure. Starting Point for Artificial Lead Generation.*, 47 TETRAHEDRON 8985 (1991)), and LUDI (Ex. 1014, Hans-Joachim Böhm, *LUDI: rule-based automatic design of new substituents for enzyme inhibitor leads*, 6 J. COMPUTER-AIDED MOLECULAR DESIGN 593 (1992)). These represent core activities of "structure-based drug design;" the computer programs allowed researchers to quickly build models of complexes of potential drugs with their protein targets.

X. CLAIMS 1-3 & 8-10 OF THE '772 PATENT WOULD HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART

130. I have reviewed the claims of the '772 Patent. I understand from counsel for Par that because the specific compound claimed in claim 10 of the '772

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