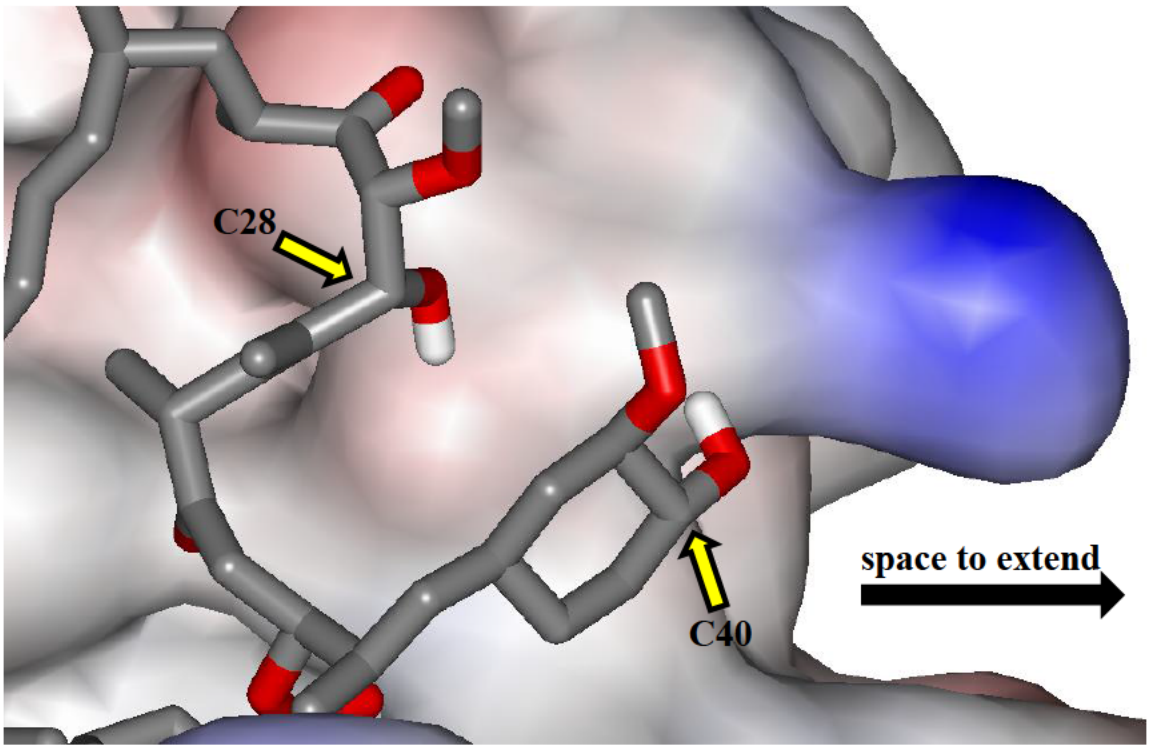
art would be guided by the structure to avoid modifying the hydroxyl group on C28 to avoid disrupting interactions with FKBP-12 and thus the immunosuppressant activity.

177. In contrast to these other two hydroxyl groups, the bound structure shows that the hydroxyl group on C40 is a substituent that could be modified to improve the solubility of the rapamycin molecule. As shown in the figure below, the FKBP-12 protein when bound to rapamycin is positioned in such a way that the C40 hydroxyl group resides on the periphery of the complex and could accommodate modifications.



178. From this information based on the structure, a person of ordinary skill in the art in October 1992 would have been motivated to make modifications to rapamycin at the C40 position.

179. Further, because coordinates of Van Duyne structure could be obtained and because computer-aided drug design software was available and widely in use, a person of ordinary skill in the art would have been able to model substitutions in detail at C40 in order to determine which substitutions would be structurally promising and permissible sterically. (*See* § IX.A.5.b.) In addition, the structure of FKBP-12 in solution had been published, providing further information valuable for modeling the interactions with rapamycin using these computer programs. (Ex. 1029, Stephen W. Michnick *et al.*, Solution Structure of FKBP, a Rotamase Enzyme and Receptor for FK506 and Rapamycin, 252 SCI. 836 (1991).) Such modeling would have allowed a person of ordinary skill in the art to filter out substitutions that would be sterically unfavorable. Thus, a person of ordinary skill in the art would have been motivated to evaluate substitutions at C40 using molecular modeling tools.

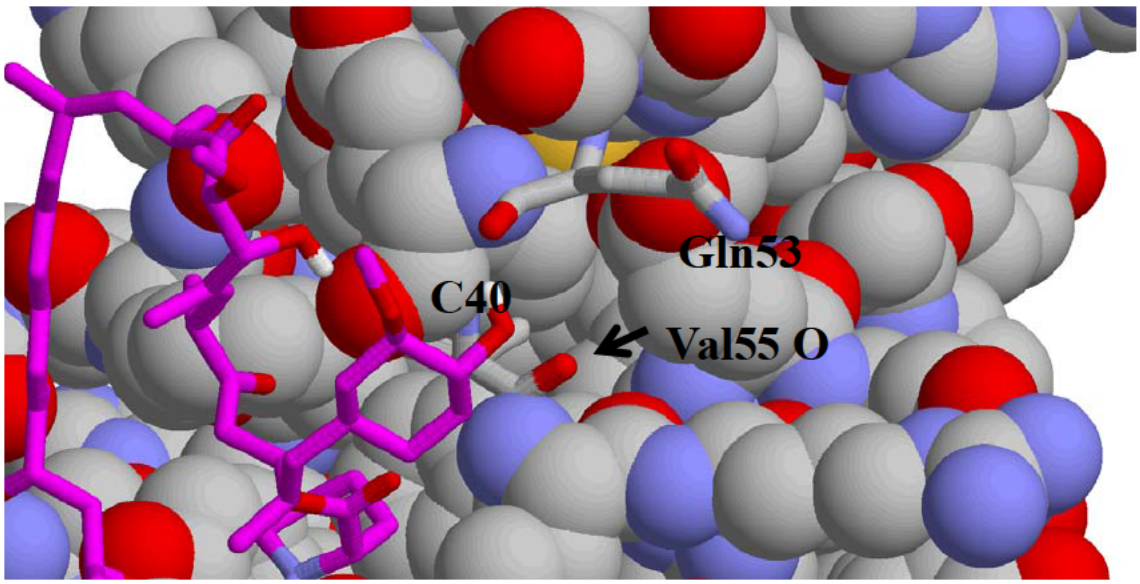
180. Additionally, as discussed above, a person of ordinary skill in the art would have been motivated to screen modifications to rapamycin that would improve rapamycin's known poor solubility. (*See*, § IX.A.2, above.) Based on the (1) teachings from Lemke, (2) the knowledge that introducing side chains with

flexible and rotatable bonds provides a free energy driving force toward dissolution from Yalkowsky, and (3) the underlying principle of drug design that modifications should be as small as possible to avoid disrupting the target biological behavior or introducing off-target metabolic or toxicity problems (*see* § IX.A.3, above), a person of ordinary skill in the art would model potential substitutions to rapamycin at the C40 position.

181. With these general concepts in mind, a person of ordinary skill in the art in October 1992 would screen a number of potential modifications to rapamycin at the C40 position. Among these modifications, one of skill in the art would model (1) a 2-hydroxyethoxy group (OCH_2CH_2OH); (2) a 2-aminoethoxy group ($OCH_2CH_2NH_2$); and (3) a carboxymethoxy group (OCH_2COOH). Each of these possible substitutions would have resulted in a small modification to rapamycin that would have reasonably been expected to improve solubility without disrupting binding to FKBP-12.

182. Additionally, each of the 2-hydroxyethoxy group (OCH_2CH_2OH), the 2-aminoethoxy group ($OCH_2CH_2NH_2$), and the carboxymethoxy group (OCH_2COOH) substitutions would be accommodated in the model of the rapamycin backbone bound to FKBP-12. These groups could project into the solvent and benefit from hydrogen bonds with water molecules and/or possibly make hydrogen bonds, for example, with the side chain amide group of the Gln53

or backbone carbonyl group of Val55 of FKBP-12, as show in the Figure below. The substitutions at C40 would cause loss of the hydrogen bond between the C40 hydroxyl group and the carbonyl oxygen of Gln53 that is present in the Van Duyne crystal structure. (Ex. 1006, Van Duyne at 7434.) However, a person of ordinary skill in the art would recognize that in aqueous solution, the water structure in this region could adjust to accommodate a hydrogen bond between a water molecule and the carbonyl oxygen of Gln53



183. A person of ordinary skill in the art would have recognized that modifications at C40 could be made and retain immunosuppressant activity, as shown by the results of Hughes, which modified the C40 hydroxyl of rapamycin and showed that the resulting derivatives maintained immunosuppressant activity. (*See* § IX.A.4, above.)

184. Given these ultimately favorable indications from the model, a person of ordinary skill in the art in October 1992 would have been motivated to synthesize rapamycin derivatives with these substitutions to evaluate their biological and physiochemical properties using standard and routine techniques. (*See* IX.A.6, above.) Further, because of the model, a person of ordinary skill in the art in October 1992 would have a reasonable expectation that, when synthesized, these derivatives would result in a compound that has immunosuppressant activity and improved solubility.

185. Therefore, it is my opinion that based on (1) the structure of the rapamycin/FKBP-12 complex, (2) the available modeling software for three-dimensional drug-protein interactions, and (3) the teachings of Lemke and Yalkowsky on improving solubility, a person of ordinary skill in the art would have been motivated to synthesize at least the $–OCH_2CH_2OH$, $-OCH_2CH_2NH_2$, and –OCHCOOH derivatives at the C40 hydroxyl of rapamycin.

186. Claim 1 of the ’772 Patent claims a compound of the formula:

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