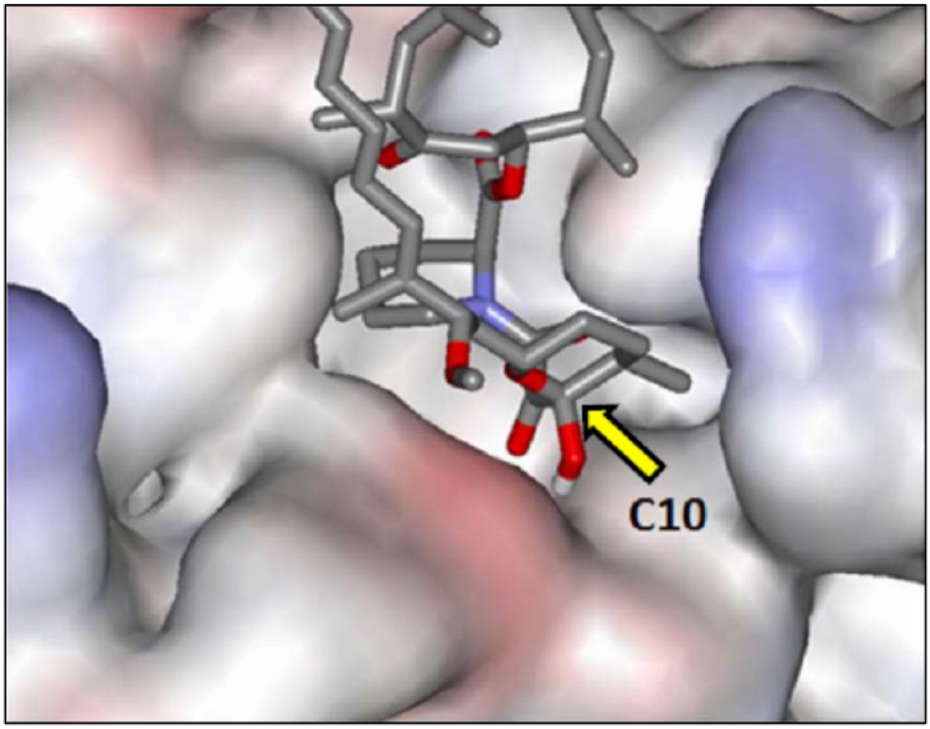
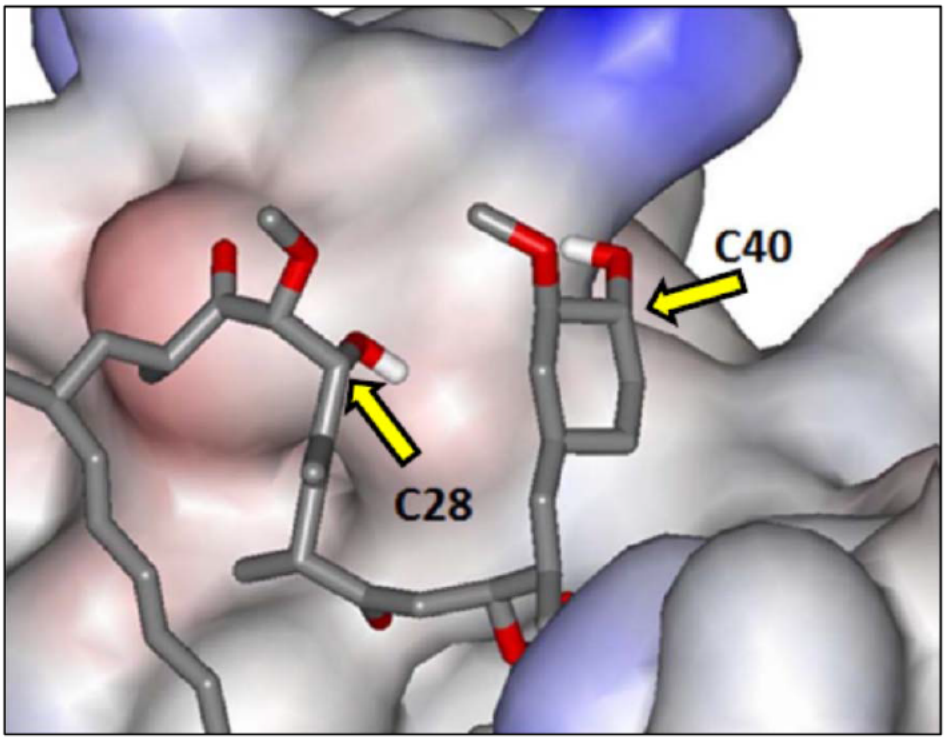


117. This portion of the structure informs a person of ordinary skill in the art that the carbon at rapamycin's C10 position lies in a "pocket" in the FKBP-12 protein. A person of ordinary skill in the art therefore understands from the structure that the C10 position is a poor candidate for molecular modification, because any substituents added to the carbon at the C10 position (which will be larger than the hydroxyl group) are likely to interfere with rapamycin's ability to bind to FKBP-12 and therefore interfere with rapamycin's immunosuppressive activity. The C10 hydroxyl group is also part of an acetal, ROCHR′OH. Making ketal (ROCHR′OR″) derivatives of acetals is generally undesirable as they may be easily hydrolyzed back to the acetal.

118. In the next figure below, the local environments of the hydroxyl groups attached to the carbons at rapamycin's C28 and C40 positions are depicted.



119. Like the carbon at rapamycin's C10 position, a person of ordinary skill in the art would understand from the structure that the carbon at rapamycin's C28 position is a poor candidate for molecular modification, because any substituents added to the carbon at the C28 position (which will be larger than the hydroxyl group) are likely to interfere with rapamycin's ability to bind to FKBP-12.

120. The carbon at rapamycin's C40 position, by contrast, is farther from the core of the FKBP-12 and adjacent to empty space (the white space in the Figure above, which is only filled with water). A person of ordinary skill in the art

would recognize that substituents could be attached to the C40 oxygen atom that would extend into this water-filled space without interfering with rapamycin's binding to FKBP-12. As such, the structure directs a person of ordinary skill in the art that the C40 hydroxyl group is the optimal position for modifying rapamycin to avoid disrupting binding with FKBP-12 and thus its immunosuppressive activity.

c. Rapamycin Was Further Known to Bind to Another Unidentified Biological Target

121. By October 1992, as noted above, it was further known that the rapamycin/FKBP-12 complex interacted with a second unknown biological target that was essential for the immunosuppressant activity of rapamycin. (*See, e.g.*, Ex. 1012, Schreiber at 286.) Although, the biological target had not yet been identified, the effector domain, the portion of rapamycin that interacted with this second target, had been identified, as shown in the figure below. (*Id.* at Fig. 5(B).)