EXHIBIT 16

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE, LTD., ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE, INC. Defendants.	Civil Action No. 05-CV-12237 WGY **CONTAINS CONFIDENTIAL INFORMATION SUBJECT TO PROTECTIVE ORDER**

EXPERT REPORT OF DR. WILLIAM L. JORGENSEN

What is not known about CERA, however, is its three-dimensional structure, or "conformation" -- the overall shape of the molecule. Dr. Lodish's graphics and animations are not instructive as to this three-dimensional structure.

125. According to Dr. Lodish's report, his graphics were generated using "standard computer modeling tools" and modified coordinates from the ones reported in the Syed publication. (*See* Lodish, p. 29). Based on my extensive experience with computer modeling programs, however, it is my opinion that these illustrations reflect little more than imagination and the programmer's preferred depiction. The structures and interactions of CERA have never been directly elucidated experimentally, e.g., via x-ray crystallography or nuclear magnetic resonance (NMR). In fact, the detailed structure of CERA cannot be determined with these, or any other known methods. In the most basic terms, the molecule is constantly moving, and does not stay still long enough for a clear image to be captured. As a result, no experimentally determined coordinates have been reported for CERA and no modeling tools are available to provide reliable images of such large, complex structures.

126. The computer graphics software used to generate Dr. Lodish's CERA cartoons is PyMOL. (*See* Lodish, p. 29). This one of many computer programs that are available for making graphical images ("pretty pictures" and animations) of molecular systems. PyMOL does not (and is not intended to) validate the chemical accuracy of any of the images it generates. It is purely a visualization tool; it allows a user to input three-dimensional (x, y, z) coordinate data for atoms and then generate graphical representations of these atoms in space. If the data are not accurate, the image generated is meaningless. No accurate coordinate data for CERA are available or can be generated with current computational methods. However, one can contrive

coordinate data, generate images and make them move, just as a cartoon animator can create images and make them move.

127. I have not been provided with a description of how the initial x, y, z-coordinates for CERA were obtained for Dr. Lodish's illustrations and animations, and I understand from counsel that Amgen is unable to cite any data on which these figures are based. *See* April 6, 2007 Expert Report of Harvey Lodish, ¶¶102-103. My expectation is that the cartoonist started with x-ray or NMR-based coordinates for EPO or an EPO mutant[26] and then attached and grew a representation of a polyethylene glycol chain using an arbitrary (Monte Carlo) procedure. In such a procedure the cartoonist would add one carbon or oxygen atom of the polyethylene glycol at a time. The position of a new atom, "D", in an A-B-C-D sequence is determined by the bond length C-D, the bond angle B-C-D, and dihedral angle A-B-C-D (see illustration, below).[27]

[26] As noted in Dr. Lodish's report, these coordinates are publicly available online, through the Protein Data Bank.

[27] It is also possible that the cartoonist grew the "PEG" by itself to yield the "spaghetti ball" structure that was then attached to the EPO structure. This would also account for the appearance of the illustrations, and it would be an entirely invalid procedure.

molecular dynamics was run to generate the snake-like oscillations of the "PEG moiety." The simulation has undoubtedly not been run long enough to equilibrate, i.e., remove the biases from the initial structural choice. In any event, the inadequate time scale, the description of the energetics used for the simulations, and lack of essential details such as explicit representation of the aqueous environment (which, as mentioned above, includes thousands of water molecules and ions), have resulted in illustrations and animations that have no scientific value and bear no relationship to the reality of a CERA molecule.

129. To illustrate the point that one can create alternative images for CERA, I provide the attached example (Ex. D) that resulted from work with my biomolecular modeling program MCPRO [Molecular Modeling of Organic and Biomolecular Systems Using BOSS and MCPRO. Jorgensen, W. L.; Tirado-Rives, J. J. Comput. Chem. 2005, 26, 1689-1700.] The starting point was an NMR structure for EPO, which was retrieved from the Protein Data Bank. About 680 ethyleneoxy units were then added around the EPO in a similar manner to adding solvent molecules; they were relaxed in a Monte Carlo statistical mechanics simulation, and then they were linked to form the polyethyleneoxy chain attached to the EPO N-terminus. The energetics of the system are described by my OPLS energy functions, which are one of the standards in biomolecular modeling. The system is not fully equilibrated and it contains no water or ions. However, in my opinion, the illustrated structure is reasonable and is consistent with the observed properties of CERA including the reduced antigenicity, longer half-life, and reduced binding affinity for the EPO-receptor in comparison to EPO. Concerning the latter, the illustrated structure is consistent with a greater reorganization penalty for CERA than EPO to achieve a binding geometry for the EPO-receptor.

"A Likely Ro50-3821 Structure (static)"