FRESNO STATE
Chemistry

Chemistry Department
Seminar Series

Molecular Basis For The Cross-species Specificity of The Anti-serum Albumin VHH M79

by

Mike Jian

Thesis Presentation
Tuesday, April 21, 2020
10 - 10:50 A.M. | Via Zoom

Abstract

VHHs are single domain antibodies derived from heavy chain antibodies found in camelid species. VHHs are attractive therapeutics as they are easy to produce, are stable, and can bind targets inaccessible to traditional antibody formats. However, one potential disadvantage associated with VHHs is rapid renal clearance resulting in a short serum half-life. One innovative solution to increase the serum half-life of VHH is to make use of multivalent VHH. In this format, a therapeutic VHH is genetically fused to a second VHH specific for the abundant plasma protein, serum albumin. Such multi-specific VHH targeting serum albumin increase the half-life of therapeutic VHHs. The use of a VHH that cross react with research animal albumin is particularly desirable, as the bispecific VHH could be used in pre-clinical animal trials. Previously, a panel of VHHs which cross-react with serum albumins from human, macaques, mouse, and rat were generated. To determine the basis of VHH cross-species specificity, the structure of VHH M79 in complex with human serum albumin (HSA) was obtained through X-ray crystallography. The structure revealed that only two of three CDR loops (CDR2 and CDR3) formed polar contacts with HSA. M79 bound to the apex of HSA domain II, specifically forming polar contacts with residues Asp308, Asp314, Asn318, and Glu321 on HSA. Comparison of serum albumin sequences from human, macaques, mouse, and rat show that the interacting residues are highly conserved across the four species. Molecular docking of M79 with serum albumin from macaques, rats, and mice shows that the VHH also binds to domain II of these proteins. Finally, competitive binding experiments revealed that two other VHHs (R11 and R28) compete with M79, suggesting they also bind albumin domain II. This work gives insights into the cross-species specificity of M79, R11, and R28 towards serum albumin and can bolster the use of the VHHs in animal model experiments.