

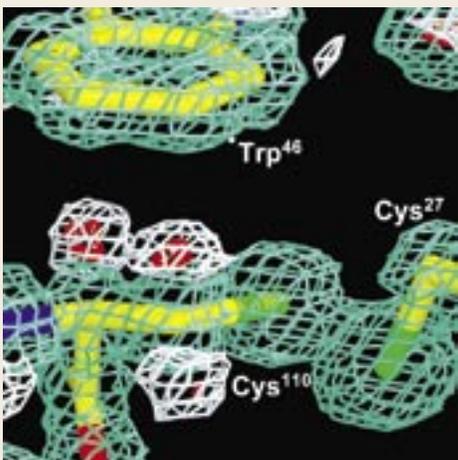
VISUALIZING THE IMMUNE SYSTEM'S MISSING LINK

Protecting us from diseases and infections, the immune system is traditionally divided into two parts: innate immunity, a nonspecific response to pathogens that cause disease; and adaptive immunity, which can specifically recognize a pathogen and to mount stronger attacks each time it is encountered. Some invertebrates only have innate immunity, which, at about one billion years old, is the more primitive of the two subsystems. It wasn't



Authors (from left) José Hernández Prada and David Ostrov

until many years later that adaptive immunity appeared along with innate immunity in jawed vertebrates. While much is known about the evolution of the immune system to the current two-part system found in lizards, humans, cats, and countless other



Non-canonical interactions in the core of VCBP3 V1 solved by MAD and refined to 1.15 Å. The side chain of Trp46 and the intrachain disulfide bond (Cys27-Cys110) are shown in the core of VCBP3 V1 (yellow for carbon, orange for sulfur, blue for nitrogen). Non-canonical interactions mediated by p electrons and H atoms apparent in the Fo-Fc electron density are shown at the 3s level (red), 2s level (white) and superimposed onto the final model (yellow for carbon, green for sulfur, blue for nitrogen, red for oxygen atoms). 2Fo-Fc electron density calculated from phases to 1.15 Å was contoured at the 2s level (colored in blue/green).

organisms, details of its origin remain unknown. At the NSLS, a team of researchers looked for this missing link and unveiled valuable information that could be used in the medical community.

“In order to find something that represents the transition between the innate and adaptive immune systems, we needed to study an organism that was just below the level of jawed vertebrates on the evolutionary scale,” said researcher David Ostrov, from the University of Florida College of Medicine.

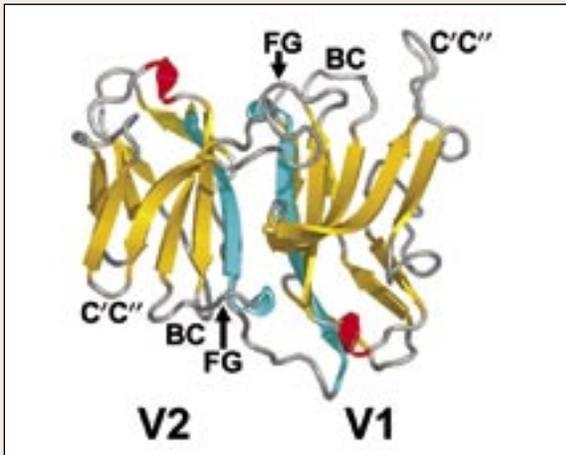
The organism chosen was amphioxus, a small, jawless, invertebrate marine animal. The researchers focused on specific amphioxus V-type immunoglobulin domains, which are proteins used by the immune system to identify and neutralize foreign objects. Also used in antibodies, these V-type domains were studied on the structural level using x-ray crystallography at beamline X6A.

“We tried to answer the question, ‘Does this protein resemble the types of proteins we use in our immune systems?’ Ostrov said. “And the answer is clearly ‘yes.’ Even though the primitive immune response protein and the one seen in humans have very different sequences, at the structural level they’re almost identical.”

During their research, which was published in the August 2006 edition of *Nature Immunology*, the scientists ended up with something much more revealing than a simple answer. Using the multi-wavelength anomalous dispersion method (MAD), the researchers solved the structure of the immunoglobulin protein down to atomic resolution – the first V-type immunoglobulin structure ever solved to that level. “We could see structural details at the core of the domain that no one has ever seen,” Ostrov said.

Learning the intricate details of this protein could allow scientists to generate more stable immune response proteins that might improve the treatment of cancers and immune diseases. “The problems with using antibodies as they exist is that they are susceptible to degradation,” Ostrov said. “If we could learn how to stabilize antibodies, they could last longer in the bloodstream and be more useful clinically.”

Other researchers involved in the study include José Hernández Prada, University of Florida College of Medicine; Robert Haire, University of South Florida College of Medicine; Marc Allaire, Jean Jankovic, and Vivian Stojanoff, NSLS; John Cannon, University of South Florida College of Medicine and H. Lee Moffitt Cancer Center and Research Institute; and Gary Litman, University of Florida



Crystal structure of VCBP3 V1V2 solved by SAD and refined to 1.85 Å. (a,b) Secondary structure is shown (Gold; β -strands, gray; loop regions, red; helices). The G strand and FG loop encoded by a joining gene segment-like element is shown in cyan. The loops corresponding to CDR regions in T-cell receptor and Ig: BC loop, CDR1; C'C'', CDR2; FG, CDR3.

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For more information, see: J. Prada, R. Haire, M. Allaire, J. Jakoncic, V. Stojanoff, J. Cannon, G. Litman, and D. Ostrov, "Ancient Evolutionary Origin of Diversified Variable Regions Demonstrated by Crystal Structures of an Immune-Type Receptor in Amphioxus," Nat. Immunol., 7, 875-882 (2006).

— Kendra Snyder