Profile of Ian A. Wilson

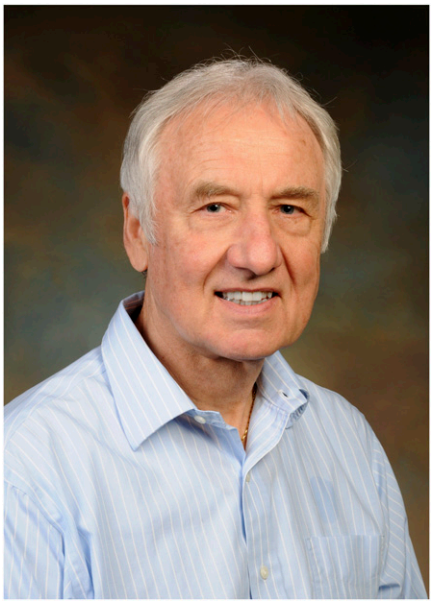
Leigh Cooper, *Science Writer*

Viewed up close, antibodies, cellular receptors, and viral proteins may look like sloppy piles of spaghetti, fettucine, and fusilli to the untrained eye, but that's not what Ian Wilson sees. "Protein structures are things of beauty, with their complex web of intricately positioned and interlocking elements that fold up precisely to generate a particular biological function," says Ian Wilson, a professor of structural biology at The Scripps Research Institute in La Jolla, California.

Wilson, who was elected a member of the National Academy of Sciences in 2016, has dedicated his career to solving the structures of immune system proteins. He hopes that these structures will provide insights into how the immune system interacts with and neutralizes human pathogens and, thus, how improved vaccines and therapies can be designed.

Soccer Journalism to Structural Biology

Wilson grew up in Perth, Scotland, with his parents and sister. His father, who was a journalist, enlisted Wilson to help cover the major soccer matches in his home town. During live matches, Wilson would take his father's copy covering the game and, every few minutes, dictate it by telephone to the local newspaper for evening publication. "He would also send me to local soccer matches, and I would have to write up 50 words and send it in within 10 minutes of the match finishing," says Wilson. He adds that this practice was excellent training for his career, which can include impromptu speaking events and writing abstracts, grants, and papers.



Ian Wilson. Image courtesy of BioMedical Graphics, The Scripps Research Institute.

After earning a degree in biochemistry from the University of Edinburgh in 1971, "I wanted to understand how enzymes worked and evolved," says Wilson. Although only a handful of protein structures had been solved at the time, Wilson decided that the best way to study enzymes was to examine the proteins' 3D structures. So he joined molecular biophysicist David Phillips' laboratory at the University of Oxford.

Wilson says Phillips suggested he join the team to study triosephosphate isomerase, an enzyme involved in the glycolytic pathway, which helps cells generate energy. Wilson turned to X-ray crystallography to determine the enzyme's molecular and atomic structure. In X-ray crystallography, a crystal diffracts X-ray beams in different directions; the pattern of the diffracted beams can be analyzed to generate the crystal's 3D structure. Wilson needed to make hundreds of thousands of measurements to complete the 3D structure of the enzyme.

Wilson and his colleagues unraveled the triosephosphate isomerase structure in 1976 (1). "When we first determined the structure, we built a physical atomic model. The structure at that time was very unusual: a highly organized and very regular beta-barrel–type structure," Wilson says, describing the complex elongated doughnut arrangement of eight β-strands and α-helices. "But that turned out to be one of the more common folds that we have seen over the past 30 or 40 years."

Unveiling Influenza

After graduating with a doctorate in molecular biophysics in 1976, Wilson joined structural biologist Don Wiley's laboratory at Harvard University, where he began studying hemagglutinin in collaboration with Sir John Skehel at the National Institute for Medical Research in Mill Hill, outside of London. Hemagglutinin is the principal surface glycoprotein of influenza that enables the virus to bind to host cell receptors and gain entry into the host cell. During an immune response, host antibodies bind to the hemagglutinin to neutralize the virus. Specifically, Wilson worked on the 1968 H3N2 Hong Kong pandemic strain; H3 refers to hemagglutinin that is one of the 18 known subtypes, H1–18, of hemagglutinin proteins (2), which trigger the host's humoral immune response.

For Wilson, the hardest part of the project was finding a suitable heavy atom, such as mercury or platinum, to solve the structure. Wilson needed to compare diffraction from heavy atom–protein complexes with those from the native protein crystal to deduce the phases. Molecular replacement, which uses information from previously

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article, on page 206 in issue 2 of volume 114.

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solved structures to determine unknown structures, and multiwavelength anomalous diffraction methods, have together largely displaced this process for solving structures.

In 1981, Wilson and his colleagues reported their hemagglutinin structure (3). A companion paper illustrated how influenza is recognized by the human immune system (4). By studying the evolution of the hemagglutinin from year to year, Wilson and his colleagues predicted sites on hemagglutinin that were likely targeted by antibodies as well as the number of mutations that hemagglutinin would need to undergo to evade preexisting human immunity. The latter information could help predict when a new seasonal vaccine would be required.

Structural Biology Catches a Wave

When he was offered a position at The Scripps Research Institute, which was then primarily focused on immunology, Wilson traveled to La Jolla, California, to help construct a structural biology unit within the new molecular biology department under the leadership of molecular biologist Richard Lerner. Since joining Scripps in 1982, Wilson's interests have crisscrossed the fields of virology, immunology, and structural biology. He and his laboratory members have solved more than 500 structures, including structures of major histocompatibility complexes, T-cell receptors, erythropoietin receptors, Toll-like receptors, variable lymphocyte receptors, and more than 250 antibody structures and complexes with antigens.

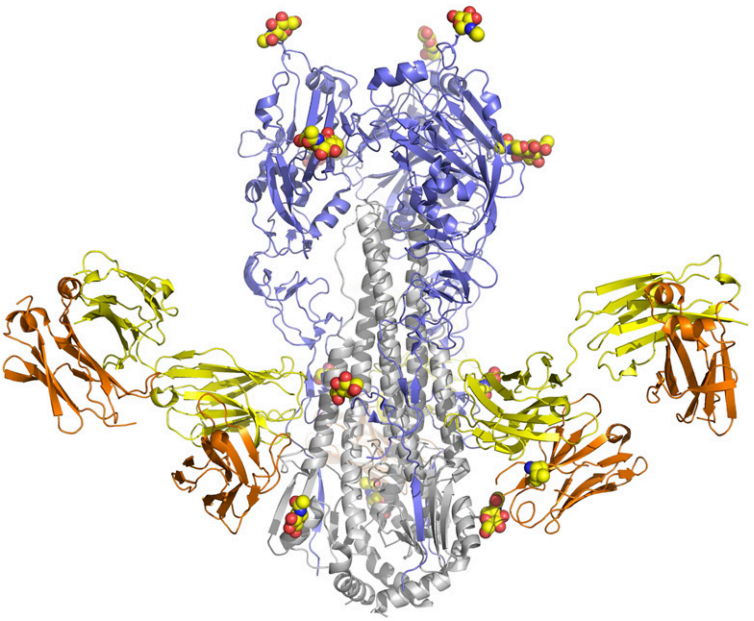
In the late 1980s, Wilson's laboratory began investigating HIV, which lacks an effective vaccine. Wilson's group determined structures of antibodies that can neutralize HIV, but Wilson knew that researchers needed to visualize the exact shape of HIV's envelope protein (Env) to design a vaccine, a challenge complicated by the fact that Env evolves quickly.

In 2013, Wilson's X-ray team, in conjunction with Andrew Ward's cryo-electron microcopy group at Scripps and John Moore and Rogier Sanders at Weill Cornell Medical College, generated atomic-level structures of Env (5, 6). They found that the Env structure consists of three identical prongs that fold up to form the receptor binding site and fusion machinery that are required for viral entry. Wilson also studies how broadly neutralizing antibodies can block HIV, work that might aid the structure-based design of a potential HIV vaccine.

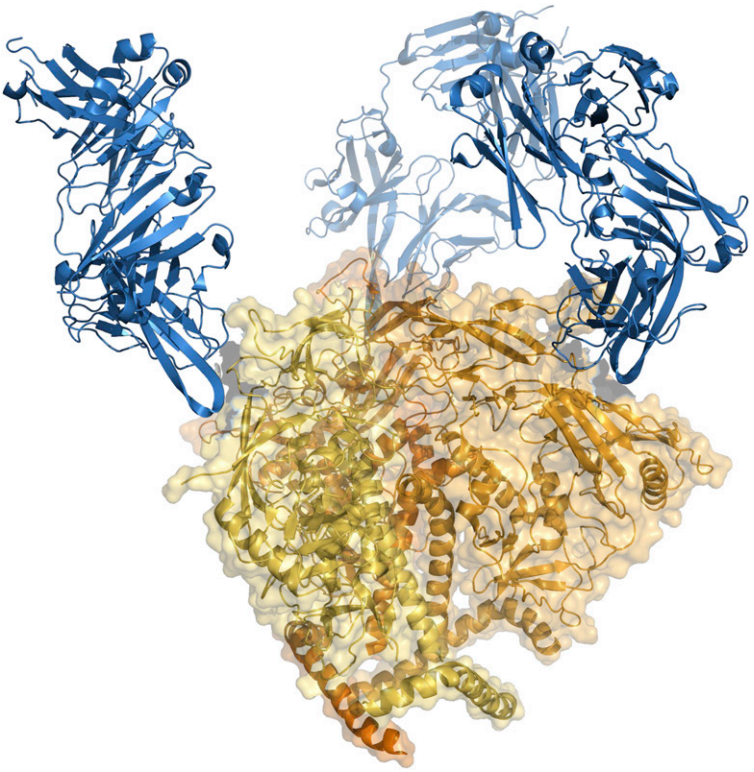
Flu's Many Faces

Working with long-time collaborator Jim Paulson from Scripps, Wilson also continued his studies on influenza. "We have been very interested in how avian flu or swine flu can jump into humans," says Wilson. Together, they showed that it was not easy to mutate the hemagglutinin of the 2004 Vietnam H5N1 bird flu to enable it to become a human pathogen (7).

Wilson says that in other pandemic viruses, such as 1918 H1N1, 1957 H2N2, and 1968 H3N2, only two mutations were necessary for influenza to jump species. Despite the existence of 16 hemagglutinin subtypes of avian flu, only viruses with three of these subtypes—H1, H2, H3—have successfully become human viruses, says Wilson. "It seems to be quite difficult for avian viruses to cross the species barrier," says Wilson. "We don't get that many pandemics." Wilson has continued solving the structures of hemagglutinin from different emerging strains and subtypes of influenza virus.



Broadly neutralizing antibody CR6261 bound to a hemagglutinin stem. Image courtesy of Marc-André Elsliger (The Scripps Research Institute, La Jolla, CA).



Soluble HIV-1 envelope in complex with broadly neutralizing antibody PGT122. Image courtesy of Marc-André Elsliger (The Scripps Research Institute, La Jolla, CA).

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Wilson has also generated structures for antibodies that can block influenza and, in 2009 his laboratory—in collaboration with biotechnology company Crucell Holland, now a subsidiary of Janssen Vaccines—solved the structure of CR6261, a broadly neutralizing antibody, in complex with hemagglutinins of the 1918 H1N1 Spanish flu and the 2004 Vietnam H5N1 bird flu (8). Until then, researchers had only found human antibodies that bound to the cap of the hemagglutinin's mushroom shape, but CR6261 attached to the hemagglutinin stalk, which is harder to reach but less apt to evolve, says Wilson. "Seeing that structure led us and others to focus on the stem region as a place to target with antibodies for a universal flu vaccine" (9), says Wilson. Wilson continues to characterize broadly neutralizing antibodies to multiple viruses, such as influenza, HIV, and hepatitis C, as he works toward universal vaccines for these viruses.

In his Inaugural Article, Wilson and postdoctoral researcher Rameshwar Kadam describe the structure of Arbidol, an unapproved broad-spectrum antiviral that appears to be effective against influenza, in complex with hemagglutinin from the 1968 H3N2 Hong Kong pandemic strain and the 2013 H7N9 bird flu (10). The researchers found that Arbidol anchors in a cavity in the hemagglutinin stem, stabilizing the hemagglutinin subunits and limiting its ability to enter human cells. "It makes you think about how one might design other molecules or modify existing molecules to bind in that site to prevent viral fusion," says Wilson.

Evolution of Structural Biology

Although the general process of determining molecular structures has remained constant throughout Wilson's career, the technology he uses has evolved greatly. For example, when Wilson worked on triosephosphate isomerase for his doctorate, he had to isolate the enzyme on his own. "We would go down to the local market and buy some chicken breast, grind it up, and extract the enzymes," says Wilson. "Nowadays, because we're choosing targets of interest rather than what's readily available, we spend a lot more time trying to express and purify proteins [for crystallization]." Wilson says that crystallization was mystifyingly difficult in its early days, but has now largely become a sophisticated, streamlined, and scientific process.

Wilson emphasizes that huge improvements in X-ray diffraction technologies, computation, and equipment, as well as breakthroughs in cryo-electron microcopy, have greatly reduced the time spent on solving a structure. In fact, the Joint Center for Structural Genomics, a multi-institute consortium based at The Scripps Research Institute and directed by Wilson since 2000, has determined more than 1,600 structures over the last 16 years. "We can solve structures much faster now," says Wilson. "Instead of spending a lot of time on the mechanics of solving a protein structure, we can now focus on thinking more about the biological implications of the structures and how we can use that information to combat human pathogens and design new vaccines and therapeutics."

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