predicted to have the specified molecular function. The idea and its power relative to local sequence pattern searches were illustrated by searching for proteins with a disulfide oxidoreductase active site in three bacterial genomes.

Impact of structural genomics

Suggestions about how best to proceed with the structural genomics project were discussed. Ideas ranging from continuing 'research as usual' to establishing large centers for structural genomics were explored. The pilot projects will help shape the full scale effort. It is likely that relatively large centers will provide the infrastructure for X-ray crystallography and NMR spectroscopy, allow the economy of scale, foster collaboration, and also ensure that the technical and repetitive jobs are not performed by students and postdocs in the academic laboratories. Centers will make it possible for academic and pharmaceutical researchers to obtain protein samples and research information, such as purification protocols and crystallization conditions. Such an infrastructure will enable the individual laboratories to focus on more challenging research problems, including functional characterization of their favorite proteins, structure determination of disease targets, large proteins and protein complexes, study of post-translational modifications, and systemic questions involving networks of proteins. Structural biologists in the pharmaceutical industry will increase their impact on the drug discovery process because they will be in a position to determine the structures of many more protein–ligand complexes, at a lower cost and faster, using the structures, samples and protocols from the high-throughput structure determination. The impact of structural genomics on the structural and functional characterization of proteins, as well as on our understanding of the machinery of life and its evolution, will surely result in profusion of new drug targets and better drugs. Structural genomics will refocus biology, just as the advent of of high throughput DNA sequencing machines freed researchers to focus on more elaborate experiments rather than on accumulating sequence data.

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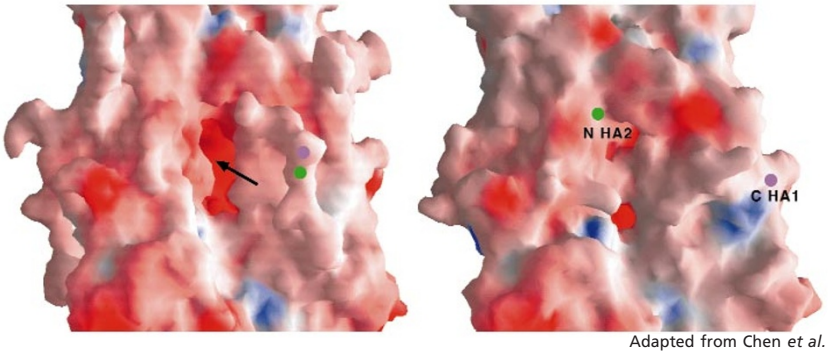
1. Structure-based functional genomics, October 4–7, Avalon, New Jersey (1998). http://lion.cabm.rutgers.edu/bioinformatics_meeting/. The meeting was organized by Gaetano Montelione, Stephen Anderson, Edward Arnold, and Ann Stock of the Center for Advanced Biotechnology and Medicine at Rutgers University (CABM), with the backing of the New Jersey Commission on Science and Technology, CABM, the Merck Genome Research Institute, and the Burroughs Wellcome Fund.
2. Synchrotron supplement. *Nature Struct. Biol.* **5**, 614–656 (1998).
3. Editorial, *Nature Struct. Biol.* **5**, 925–926 (1998).

Fight the flu



Adapted from Chen *et al.*

Every year, we are reminded of the power of the influenza virus, especially when severe and deadly outbreaks occur — such as last season's Hong Kong 'bird flu' in which 6 of the 18 confirmed cases in humans were fatal. What makes one influenza virus more virulent than another? In the case of the Hong Kong virus, one factor was probably a variation in its hemagglutinin (HA) precursor protein, which had a five residue insertion. Hemagglutinin, a glycoprotein that is held in the viral membrane by a C-terminal transmembrane sequence, is required for viral membrane fusion during infection. Two events must occur for hemagglutinin to become active: (i) the precursor protein, HA0, must be cleaved to create two disulfide linked subunits HA1 and HA2 and (ii) cleaved HA must undergo a low pH-induced conformational change in endosomes. The new N-terminus of HA2 is the fusion peptide that becomes embedded in the target membrane, leading to infection. The pH-induced conformational change projects the fusion peptide to the end of a long coiled coil, placing it close to the HA C-terminal transmembrane domain and thus bringing the viral and the target membranes into close proximity. The five-residue insertion in the Hong Kong HA0 hemagglutinin variant occurred at the HA0 cleavage site. Why would such a mutant lead to higher virulence? Researchers have found that HA0 variants with insertions in this region are more susceptible to proteases, leading to a greater proportion of cleaved HA molecules and hence a higher infectivity.

Hemagglutinin is a logical drug target because of its key role in the success of an infection. Researchers could aim to develop drugs that would block the cleavage step or prevent the conformational change. Useful information for such endeavors is provided by a recent structure of the HA0 precursor (Chen, J. *et al. Cell* **95**, 409-417; 1998), which shows the conformation of the intact cleavage site. A comparison with the previously determined cleaved HA structure suggests that proteolysis may be playing a direct role in setting the low pH trigger for the conformational change — in addition to playing more obvious roles in exposing the fusion peptide and giving conformational flexibility to the protein. In the HA0 precursor, the cleavage site (left image, between the dots) is exposed on a surface loop. After proteolysis, the new N-terminus of HA2 fills a hole in the protein (arrow), burying several ionizable Asp and His residues that were previously exposed in the cavity (right image). In theory, this could set a sensitive trigger: protonation of the His residue at low pH could severely destabilize the structure and lead to the dramatic conformational change that is necessary for infection. TS