Probiotic studies of ASD children are in the early planning stages, according to Mazmanian. *B. fragilis* is not commercially available and is not approved for humans. Whether it proves safe or effective for children with ASD remains to be determined, he says. Although “parents of children with ASD are desperate for solutions,” he adds, “we don’t want to oversell our research and give people false hope.”

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Carol Potera is a freelance writer in Great Falls, Mont.

**RESEARCH ADVANCES**

**Drug Target Discovery Is Focus for ID Structural Genomics Centers**

John Otrompke

The Seattle Structural Genomics Center for Infectious Disease (SSGCID) and the Chicago-based Center for Structural Genomics of Infectious Diseases (CSGID) recently received renewal grants, worth $25 million over five years and dedicated to solving three-dimensional (3-D) structures of proteins or other macromolecules from microorganisms of biodefense and emerging infectious disease (ID) importance. Solving such structures is part of a broader effort toward discovery and early-stage drug development. Support for the centers comes from the National Institute of Allergy and Infectious Disease (NIAID), part of the National Institutes of Health.

X-ray crystallography is an important component of the work being done by the two consortia. The primary mission for SSGCID, for example, is to determine the structure of about 70 protein targets from the NIAID Category A-C agents, as well as emerging and re-emerging microorganisms responsible for infectious disease, each year for the next five years. Similarly, CSGID applies state-of-the-art, high-throughput structural biology technologies to characterize the 3-D atomic structure of similar proteins.

SSGCID has 5 to 10 structures that are in the early-to-mid stage of lead optimization for drug discovery, while others are very early-stage vaccine candidates, according to SSGCID director Peter Myler from the Department of Global Health at the University of Washington, Seattle. Tuberculosis and malaria are a major focus for the center, he adds. Additional microbial agents under study include the Middle East respiratory syndrome coronavirus (MERS-CoV), a SARS-like respiratory tract-infecting organism that was found in Saudi Arabia in 2012 and continues to circulate throughout the Middle East, and the Bas-Congo virus, which is a relative of the Ebola and rabies viruses.

Researchers affiliated with SSGCID solved about 650 structures in seven years, of which about 40 or 50 were collaborative projects with outside researchers, Myler continues. From 20 to 30 of those structures have been investigated for drug discovery, he says. “During the first five years of our existence, we selected most of our targets by ourselves, but since then, more than half of our targets have been requests by outside investigators.” The center has solved about 250 structures requested by about 160 different researchers from outside the consortium.

“It’s possible that some of the compounds we’re working on could get into phase 1 trials within the next year or two,” says CSGID director Wayne Anderson of Northwestern Feinberg School of Medicine in Chicago. One of the structures that researchers from CSGID and their collaborators are working on—protein PA4794 from the bacterial pathogen *Pseudomonas aeruginosa*—was selected as the NIAID “structure of the month” last January. PA4794 has N-acetyltransferase activity, and selectively acetylates peptides with C-terminal lysines, and this type of protein modifying activity has important “regulatory potential” and could prove to be a drug discovery target,” NIAID officials point out.

Meanwhile, investigators at SSGCID recently characterized several proteins from *Mycobacteria tuberculosis* (*Mtb*) and nontuberculosis (*TB*) mycobacteria. They succeeded in solving structures for 16 of the 179 *Mtb* targets, and...
MINITOPIC
Electrons Hop along Hemes of Proteins in Bacterial Nanowire

Electrons travel irregularly along the 10 hemes arranged along and within the MtrF nanowire protein from *Shewanella oneidensis*, according to geochemist Kevin Rosso of the Department of Energy Pacific Northwest National Laboratory in Richland, Wash., and his collaborators at University College London in the United Kingdom. Their calculated estimate of this heme-to-heme flux of electrons is “consistent with recently measured rates for the related multiheme protein complex MtrCAB,” they note. Their findings also “suggest that the [bacterial nanowire] protein evolved to harbor low-potential hemes without slowing down electron flow.” Details appeared 2 January 2014 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1316156111).

in 40 other cases, at least one structure was solved for a homolog. For example, researchers were unable to purify *M. abscessus* cytidylate kinase, a potential drug target, because it did not crystallize. However, the team solved structures for two homolog proteins from *M. smegmatis* and *M. abscessus*, which have 68 and 74% global sequence identity, respectively.

John Otrompke is a freelance writer in Chicago, Ill.

RESEARCH ADVANCES
Plant Virus That Infects Honeybees May Harm Colonies

Marcia Stone

Tobacco ringspot virus (TRSV), a plant pathogen, hopped kingdoms into honeybees, according to Yan Ping Chen at the Agricultural Research Service (ARS) Laboratory in Beltsville, Md., and her collaborators around the United States (US) and in Beijing, China. “Honeybees exposed to contaminated pollen can also be infected, [alerting] us to the risk of new viral diseases secondary to host shifting,” she says. Details appeared in the 21 January 2014 *mBio* (http://bit.ly/asmtip0114g).

“The serendipitous detection of TRSV during a routine screening for viruses in European honeybees, formally known as *Apis mellifera*, made us wonder if the virus was simply colonizing the arthropod host or if it was actively infecting it,” Chen says. Because TRSV is a positive-stranded RNA virus, the group began analyzing bee tissues for proof of its replication. Negative-stranded copies of the TRSV genome can be detected in most bee tissues, consistent with active replication, according to Chen’s collaborator Ji Lian Li of the Chinese Academy of Agricultural Science in Beijing.

RNA viruses such as TRSV can exist as genetically related variants, or “quasispecies,” that together infect their prey, a capacity that heightens suspicion that TRSV is linked to honeybee colony collapse disorder (CCD). Indeed, both TRSV and the Israel acute paralysis virus (IAPV) are found in bees from weak colonies but are absent from bees from strong ones. Meanwhile, the deformed wing virus (DWV) is the most commonly detected virus in weak bee colonies, followed in frequency by black queen cell virus (BQCV), IAPV, and TRSV.

Another complicating factor is that TRSV, like many other viruses, is seasonal—increasing from 7% of the viral load of bees in spring to 22.5% in winter, which is when colonies tend to collapse. Honeybee colonies suffering high levels of multiple viral infections fail rapidly beginning in the fall, whereas those with fewer viral assaults tend to survive through winter.

*Varroa* mites, the “vampire” parasites that transmit viruses between honeybees while feeding on their blood, are also colonized with, but not infected by, TRSV. Because the viruses remain in the gastric cecum of such mites, it “appears that they facilitate the horizontal spread of TRSV without becoming systemically invaded themselves,” note Li, Chen, and their collaborators.

“The discovery that a plant virus, TRSV in this case, replicates, spreads, and has [an] increased prevalence in weak honeybee colonies will lead to additional studies on the mechanisms of host-specific adaption and the role of cross-kingdom infections in the transmission of this and possibly other viruses,” says Michelle Flenniken at Montana State University in Bozeman. “It will be very interesting to compare the complete genome sequence of honeybee-associated TRSV to currently circulating plant TRSV sequences from diverse geographic regions.”

Some scientists insist that testing for viral replication in one of the recently developed honeybee cell lines is the only way to rule out any possibility of plant contamination. Chen agrees, but says that the limited availability of honeybee-derived cell lines makes it difficult to plan such investigations. However, cell lines derived from Lepidoptera insects such as butterflies are available, and she considers them very helpful for studying viral propagation and pathogenesis in these pollinators.

Marcia Stone is a science journalist based in New York City.

PUBLIC HEALTH
Aquavalens Project To Develop Tests To Improve European Water Safety

Barry E. DiGregorio

The year-old European Aquavalens Project, led by the University of East Anglia (UEA) in Norwich, England, is applying genetic techniques such as rRNA/rDNA fingerprinting combined with nanotechnology for detecting microorganisms in water as part of a...