

BGSU takes lead role in international RNA project

Research into ribonucleic acids (RNA)—the building blocks of life—has exploded worldwide over the past several years as scientists are discovering RNA's roles in genetics, health, disease and the development of organisms. The rapidly growing body of knowledge has presented a need for scientists to develop a shared vocabulary and system for describing, cataloging and comparing their findings.

Last summer, Dr. Neocles Leontis, chemistry, was selected by the RNA Society to lead an international team of RNA scientists, the RNA Ontology Consortium, to create an RNA Ontology.

“The consortium will develop a common vocabulary and scientific concepts relating RNA structure and function to allow RNA scientists worldwide to communicate with one another and to integrate different kinds of information they obtain about RNA molecules.” Leontis said. “This will make it easier to turn molecular information into useful knowledge that can help us to understand how different cells grow and develop as they do. This knowledge is key to curing hereditary diseases,” he added.

The National Science Foundation will provide \$500,000 for the five-year project as one of its Research Coordination Networks, whose goals are to “encourage and foster interaction among scientists” and to facilitate “innovative ideas for implementing novel networking strategies.” This is the first time BGSU has received Research Coordination Network grant.

As principal Investigator on the grant, Leontis will serve as coordinator of the consortium, which includes scientists from the United States, Great Britain, France, Canada and Australia. Leading researchers from Stanford, Duke, Yale, Rutgers and Georgia Tech universities, the University of California-Berkeley, the University of North Carolina, the University of Rochester, the University of Montréal, Lawrence Berkeley National Laboratory, the Institut de Biologie Moléculaire et Cellulaire in France, and the Scripps Research Institute will participate.

Creating the RNA Ontology will require incorporating the methods and vocabularies of chemists, molecular biologists, genomicists, information scientists and structural biologists. To help sort out the difficult conceptual issues, the consortium will organize frequent face-to-face meetings of RNA scientists. Members will also report their progress at the annual RNA Society meetings and receive feedback from the wider community of researchers.

The ontology team will collaborate to identify all RNA motifs, or repeated patterns, mentioned in the literature or appearing in databases, to agree upon a definition for each motif and to write the definition in a structured manner. The consortium will make its work accessible on the Web to the various RNA communities using servers hosted at BGSU.

While some researchers focus on the sequences of RNA molecules, for example, others study their 3-dimensional structures. A major focus of the project will be to integrate the databases of RNA sequences and 3D structure.

Leontis has experience in both areas. He is affiliated with the BGSU Center for Biomolecular Sciences and the Northwest Ohio Bioinformatics Consortium, and is known internationally for his work on RNA structural bioinformatics (the field of science in which biology, computer science, and information technology merge). Methods he has developed for analyzing and classifying RNA structures have been adopted internationally to advance RNA structure prediction and simulation and RNA sequence analysis. His work is supported by the National Institutes for Health and the American Chemical Society.

The grant proposal was met with enthusiasm by the NSF, said Joanne Tornow, NSF program director. She wrote to Leontis that the “proposal was reviewed by two panels—the Gene Expression panel . . . and the Biological Databases and Infrastructure panel . . . Seven panelists were assigned to your proposal between these two panels, all of whom rated the proposal as Excellent, and both panels rated the proposal in the Outstanding category. This really is a beautiful proposal, and I am happy that we will be recommending it for funding of the NSF.”

The continuous discovery of new RNA molecules with novel biological functions is beginning to show that RNA plays far more roles than originally believed.

Unlike DNA, which never leaves the nucleus, RNA molecules can diffuse out of the nucleus as copies of the genes. Leontis describes them as “the software controlling how the genes are expressed to make proteins.” While DNA is double-stranded, they are in single strands, which makes them more flexible and adaptable but also less stable and shorter-lived.

The RNA molecules are twisted and folded in specific ways. Scientists look for recurring motifs, or sequences, like the letters that spell out words, and for folds, the overall architecture of the molecule. So far, using X-ray technology, researchers have determined the complete crystal structure of many different RNAs including several ribosomes, and have come up with blueprints for tens of thousands of sequences. “The sequence database is growing exponentially,” Leontis said. “We can now use the structure information to get much more information out of the sequence databases.”

RNA molecules are unique in being able to store and transmit information as well as process that information. For example, RNA molecules form ribosomes. “Think of ribosomes as molecular machines that read information stored in your DNA to make you and everything in your body,” said Leontis. Ribosomes are found in not only humans and animals but in every living thing on earth and can be used to track the evolution and interrelatedness of life forms.

Some startling discoveries have been made just in the last year, Leontis pointed out. For example, while genomicists had previously determined that humans and chimpanzees share 99 percent of the same protein genes, it has now been discovered that so do mice. “The hardware (proteins) for mice and humans is practically the same—but clearly mice and humans are different. Since the hardware is the same, the difference between mice and humans must be at the software level—which determines *how the hardware is used*. We are beginning to see that RNA is that software,” Leontis said.

The possibilities for applications of RNA knowledge are tremendous, he added. RNAs, especially ribosomal RNAs, have served as valuable tools to trace the evolutionary

history of life on earth, while the discoveries of catalytic RNAs have fueled research into plausible models for the origin of life itself. By observing how things changed and what solutions worked in nature, Leontis said, we may be able to design new therapies when things go genetically awry.

RNA science is also playing an important role in understanding normal and abnormal metabolism and physiology and in designing new strategies for intervention in the form of gene therapy. RNA also holds promise for important pharmaceutical uses and the development of new drugs.