PURSUING the POTENTIAL for RNA BIOLOGY

RNA IS ESSENTIAL FOR THE PROCESS OF TURNING GENES' DNA instructions into the proteins that actually drive cellular functions. The field of RNA biology is dynamic and growing, as researchers discover the functions of a dizzying array of types of RNA. Jefferson's RNA biology program is multifaceted and rich with potential for both understanding human biology and developing ways to treat or prevent disease.

For example, **Ya-Ming Hou, PhD**, professor of biochemistry, guides a basic science research program addressing RNA's roles in a range of biomedical challenges, from cancer to antibiotic resistance. Recently, she may have identified an RNA-based vulnerability in gram-negative bacteria such as E.coli and Salmonella—which are antibiotic-resistant because their cells have two membranes and numerous toxin pumps that expel antibiotic molecules. Dr. Hou's group has shown that creating a defect in a specific transfer RNA (tRNA) undermines those defenses. This finding holds promise as a path for pursuing new, more effective antibiotics.

tRNA molecules are not a typical antibiotic target; they are part of the protein-building machinery cells need to function. But Dr. Hou's team found that to function properly, bacteria require the addition of a methyl group to one particular location on the spine of several tRNAs. When these tRNAs were deficient in methylation, the cells were more likely to have protein-building defects. Next, Hou's team created bacteria genetically deficient in tRNA methylation, and showed that the bacteria had more-permeable membranes and were less effective at pumping out chemicals, compared to normal bacteria. Finally, when the bacteria with defective tRNAs were exposed to antibiotics, they died faster and were less capable of developing drug resistance. The team is now screening molecules that could drive the same de-methylation effect as the genetic engineering; and, because the target in bacterial tRNAs is absent from human cells, the resulting drug could be less likely to have off-target effect on human cells.

Dr. Hou and colleague **Davide Trotti, PhD**, professor of neuroscience, have also been studying the role of specific tRNAs in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS)—pursuing investigations of a particular tRNA's role in the disease and whether it could be a therapeutic target. In that context, Drs. Trotti and Hou have undertaken an NIH-funded study on the most common cause of inherited ALS: a mutation resulting in patients having hundreds or even thousands copies of GGGGCC sequence in the gene C9orf72.

Ya-Ming Hou, PhD
Professor of Biochemistry

Davide Trotti, PhD
Professor of Neuroscience

Recent work by Dr. Trotti's group—in collaboration with **Aaron Haeusler, PhD**, assistant professor of neuroscience, and **Piera Pasinelli, PhD**, Frances and Joseph Weinberg Professor of Neuroscience and Director of the Jefferson Weinberg ALS Center—looked at what triggers these repeated sequences in the C9orf72 gene to eventually produce the toxic proteins associated with ALS (as well as with frontotemporal dementia and other neurodegenerative diseases in patients carrying the mutation). Suspecting that stressors may be a trigger, the investigators tested a number of agents that cause neurons to turn on the stress responses. Indeed, many of these also initiated production of toxic protein. The investigations also showed that neuronal over-excitation—similar to what happens during a seizure—also triggered the protein production.

Once the integrated stress response is activated, it is difficult to stop the production of the toxic proteins. But, by honing in on this over-arching cellular mechanism, the researchers gained insights on specific methods that might block the neuron-damaging response. The drug trazodone, which is approved for the treatment of depression, is known to act on parts of the integrated stress response. The researchers tested it in their repeat-mutation cellular model of the disease and found that it could block toxic protein-production. Now, they are screening for other molecules that might be even more effective at blocking the process. ■