Smallest, fastest-known RNA switches provide new drug targets

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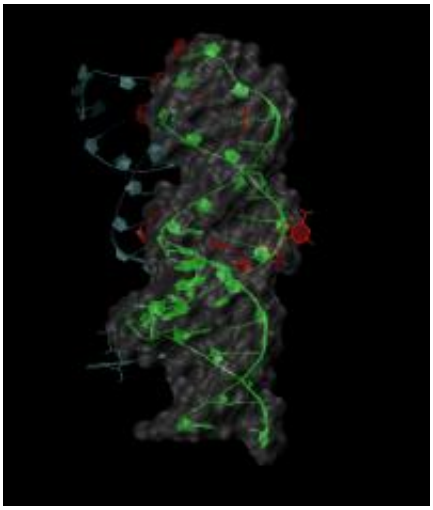

Credit: Hashim Al-Hashimi

(Phys.org)—A University of Michigan biophysical chemist and his colleagues have discovered the smallest and fastest-known molecular switches made of RNA, the chemical cousin of DNA. The researchers say these rare, fleeting structures are prime targets for the development of new antiviral and antibiotic drugs.

Once believed to merely store and relay genetic information, RNA is now known to be a cellular Swiss Army knife of sorts, performing a wide variety of tasks and morphing into myriad shapes.

Over the past decade, researchers have determined that most of the DNA in our cells is used to make RNA molecules, that RNA plays a central role in regulating gene expression, and that these macromolecules act as switches that detect cellular signals and then change shape to send an appropriate response to other biomolecules in the cell.

While RNA's switching function has been well-documented, Hashim Al-Hashimi and his U-M colleagues report online Oct. 7 in the journal *Nature* a new class of switches that are significantly smaller and orders of magnitude faster than the other known class of RNA switches.

Al-Hashimi calls these short-lived structures, which were detected using a new imaging technique developed in his laboratory, micro-switches.

"We're finally able to zoom in on these rare, alternative forms of RNA that exist for just a split second and then are gone," said Al-Hashimi, the Robert L. Kuczkowski Professor of Chemistry and Biophysics. "These things are so difficult to see because they exist for roughly 1 percent of the time and for only a microsecond to a millisecond."

In biology, a molecule's three-dimensional shape determines its properties and affects its function. RNA molecules are made of single chains that can remain stretched out as long threads or fold into complex loops with branching, ladder-like arms.

The micro-switches described by the U-M researchers involve temporary, localized changes of RNA structure into alternative forms called excited states. The structural change is the switch: the shape shift transmits biological signals to other parts of the cell.

"These excited states correspond to rare alternative forms that have biological functions," Al-Hashimi said. "These alternative forms have unique architectural and chemical features that could make them great

molecules for drugs to latch onto. In some sense, they provide a whole new layer of drug targets."

In their *Nature* report, the U-M researchers looked at transient structural changes in three types of RNA molecules. Two of the RNAs came from the HIV virus that causes AIDS and are known to play a key role in viral replication. The third is involved in quality control inside the ribosome, the cellular machine that assembles proteins.

The newly found excited states of all three of these RNAS provide potential targets for drug development: antiviral drugs that would disrupt HIV replication and antibiotics that would interfere with protein assembly in bacterial ribosomes.

Evidence for the existence of these tiny RNA switches has been mounting for years. But until now, they're evaded detection because they are simply too small and too short-lived to be captured by conventional imaging techniques, Al-Hashimi said.

To make their discovery, the team used a modified form of nuclear magnetic resonance spectroscopy, along with a strategy for trapping and capturing the transient RNA structures. In a finding reported last year in *Nature*, the researchers used similar NMR techniques to catch the rare instances when bases in the DNA double helix roll back and forth.

In recent years, Al-Hashimi and his co-workers have also used NMR to create "nanovideos" that revealed in three dimensions how RNA molecules change shape—twisting, bending and rotating about their structural joints.

In addition to Al-Hashimi, authors of the *Nature* report are U-M's Elizabeth Dethoff, Katja Petzold, Jeetender Chugh and Anette Casiano-Negroni. Al-Hashimi is an adviser to, and holds an ownership interest in,

Nymirum Inc., an RNA-based drug discovery company in Ann Arbor.

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