New ASU worldwide resource for exploring genes' hidden messages

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Marco Mangone has devoted his career to looking at a peculiar region found at the ends of genes, called untranslated elements, or 3'UTRs. The are found on the end of messenger RNAs, but as the name suggests, they don't actually make protein. Stresses Mangone: "They have to be there for a reason." Mangone's goal is to understand the function of every UTR in the human body, called the h3'UTRome. Credit: Biodesign Institute at Arizona State University

After a decade-long $3 billion international effort, scientists heralded the 2001 completion of the human genome as a moon landing achievement for biology and the key to finally solving intractable diseases like cancer.

But it turns out this was only the end of the beginning, with a much greater complexity to life revealed by the roughly 20,000 genes found within the human genome. For one, most diseases are incredibly complex, with very few caused by a single gene mutation. Rather, the more accurate picture is many acting genes acting in concert, with the routes to disease looking like public transit or subway maps.

Since then, efforts such as the modENCODE project - a $57 million multi-center initiative funded by the National Human Genome Research Institute (NHGRI) - have been aimed at identifying all the genome elements that can turn on and off genes.

Now, an international scientific team, led by Arizona State University professor and Biodesign Institute researcher Marco Mangone, has added a new worldwide resource with the first library built for researchers to explore genes' deep and hidden messages. The paper was published in *BMC Genomics*, DOI: 10.1186/s12864-015-2238-1).

The end of the message

"If the genome is considered the blueprint of the cell, proteins are the really bricks and mortars," said Josh LaBaer, director of the Virginia Piper Center for Personalized Diagnostics, which aims to undercover the telltale early warning signs of disease from a systematic study of all of the proteins in the human body, a field called proteomics.

But to make proteins, first the DNA genomic information must be transcribed with complete fidelity, chemical letter by letter into an intermediary molecule, called messenger RNA, or mRNA. In what is

known as the central dogma of biology, DNA makes RNA, which makes protein.

Marco Mangone, a core faculty member in LaBaer's center, has devoted his career to looking at a peculiar region found at the ends of the mRNA sequence information, called untranslated elements, or UTRs. As the name suggests, these regions do not go on to make protein, but stresses Mangone: "They have to be there for a reason."

Mangone's raison d'etre is to understand the function of every UTR in the human body, called the 3'UTRome (3' indicates a location at the end of the mRNA).

And so he and his team have painstakingly put together the first and largest human 3'UTRome library in the world. It is made up of 1,461 human 3'UTRs to date (representing about 10 percent of genome), and freely available to the worldwide scientific community to explore all aspects of biology, gene regulation and disease.

Shooting the messenger

Sophocles first wrote in his Greek civil war play "Antigone": "no one loves the messenger who brings bad news." And when all roads led to ancient Rome, and messengers were sent about delivering the news, a revolutionary change occurred in communications tactics: killing the messenger to prevent the communication from taking place.

Mangone, a native Italian who did his doctoral studies in Rome, has harkened back to this strategy when examining the role of the 3'UTRome. His lab uses standard molecular biology and bioinformatics tools to study the production, function and disease contributions of UTRs and their role in governing gene expression. He pioneered this work in a simple animal, the worm *C. elegans*, and now, in the new BMC

paper, toward human genomics.

Why would this elaborate system be in place? Based on numerous studies, the role of the 3'UTRome is complicated, but one major theme that has emerged is to prevent the mRNA message from ever being delivered, or in biology terms, ever translated into protein.

Small RNAs, called micro RNAs (miRNAs), work to pair with a UTR to block translation, killing the message, and thus, silencing a gene. Uncovering the interplay between miRNA and their specific UTRs have become a hot area in biology, and big business.

Big pharma, big future

These gene silencers have become all the rage in the pharmaceutical industry. So much so, that the global miRNA research market was valued at nearly $295.1 million in 2011 and is expected to reach $763 million by 2017.

It's become big business because of their potential as therapeutics for the treatment of some severe diseases, including cancer and genetic disorders, by introducing specific miRNAs into diseased cells to silence the defective gene.

A broad portfolio of miRNA pathway drug candidates have been developed, some already in Phase II clinical trials, showing promising clinical data in different areas of medicine, such as cancer, HCV infection, and cardiovascular diseases.

Mangone's team, which involved an international collaboration with Dublin City University, demonstrated the feasibility and potential of their human 3'UTRome library by screening a panel of 87 3'UTRs for targeting by two miRNAs: let-7c, which is implicated in tumor

formation, and miR-221, implicated in atherosclerosis and heart disease.

After screening, the panel was enriched with genes involved in the RAS cancer signaling pathway, and the team identified many novel targets for the two miRNAs, as well as new genes implicated in tumor formation and heart disease.

Mangone ultimately seeks to map all the UTR targets for every miRNA, and to accelerate discovery, has made the first high-quality human 3'UTRome library available to researchers worldwide. "Once we have this in place, we will be able to build the framework for understanding the underlying commonalities between gene networks," said Mangone.

More information: Kasuen Kotagama et al. A human 3′UTR clone collection to study post-transcriptional gene regulation, *BMC Genomics* (2015). DOI: 10.1186/s12864-015-2238-1

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