

THE AUTHOR FILE

Mihaela Zavolan

A better way to identify miRNA target sites

To some, RNA is king. A growing empire of RNAs with many functions is emerging from labs. When micro-RNAs (miRNAs), which belong to the family of non-coding RNAs, burst onto the scientific stage 12 years

ago, Mihaela Zavolan, a computational biologist who heads a research group at the University of Basel's Biozentrum, wondered how these molecular power brokers could have remained undiscovered for so long.

Although miRNAs tend to only modestly change the expression of individual genes, they generally trigger strong pheno-

Mihaela Zavolan with collaborator and paper coauthor Erik van Nimwegen.

types, Zavolan says. Removing miRNAs or expressing them in the wrong cells at the wrong time can, for example, turn cancer more aggressive. They are even able to return differentiated fibroblasts, the cells in connective tissue, to a pluripotent state from which they can redifferentiate. "This is amazing, if you think about it," she says. "Cell reprogramming is a complex process. How can these miRNAs that are normally expressed in a different cell type even find relevant targets to regulate in fibroblasts?"

These types of questions call for identification of miRNA targets, for which scientists have been using *ad hoc* rules, she says. "From the very beginning, it has been frustrating that we didn't have a quantitative model to study miRNA-target interactions."

She and her Biozentrum colleagues have now developed a quantitative biophysical model called MIRZA to improve the identification of miRNA target sites and which she has made available to other researchers on her lab's server. Mohsen Khorshid, who is first author on the paper and Zavolan's graduate student, suggested the name, which combines 'miRNA' with a term that describes Persian nobility.

MIRZA includes not only canonical target sites, in which the first seven or eight nucleotides on the miRNA match the target exactly, but also the noncanonical ones, which are rare and do not line up quite so well to the miRNA seed region. Current prediction methods either do not predict them at all or have low accuracy, she says. Examples to feed into computational models have been lacking, but recent experimental progress has let scientists isolate binding sites of the

miRNA-containing complex, which delivered data for the model.

These types of projects are easier now that big data showers on biologists. Zavolan remembers how underpowered the dearth of data left the models on immune response she built in medical school. "Being able to obtain large amounts of data in a short time has completely changed biological research," she says.

Two years in the works, MIRZA is the type of puzzle Zavolan enjoys. Originally intent on becoming a psychiatrist, she obtained her MD at the University of Medicine and Pharmacy of Timișoara, Romania. "Then I got interested in basic science along the way," she says, as she explored computational models of immune responses. To deepen those efforts, she decided to pursue a PhD in computer science.

From across the world in Romania, she sought out Alan Perelson, theoretical biologist at the Santa Fe Institute. "I visited in February and ended up having to drive a Buick rental car in a snowstorm," she says, adding that she got lost on the highways of a country she barely knew. She landed a research associate post in the Institute's theoretical immunology program and later one at Los Alamos National Laboratory's division of theoretical biology and biophysics, a position she held while completing her PhD at the University of New Mexico. She began working on miRNAs as a postdoctoral researcher at Rockefeller University.

Zavolan stays connected to her roots. Computational biologist Thomas Kepler from Boston University School of Medicine, who was a coadviser on her PhD thesis, accompanied her on a visit to her Romanian medical school. "It was extraordinary to see how much affection and appreciation Mihaela feels for her teachers, and how sympathetic she is to their plight," he says. Under Romanian dictator Nicolae Ceaușescu, Zavolan's mentors had been required to publish in Romanian and could not freely exchange information with scientists internationally. Despite his regime's fall, many barriers remain for researchers in Romania. Zavolan was determined to overcome the obstacles her mentors faced and to succeed on a larger stage, Kepler says. "She continues to push beyond boundaries of various types in pursuit of her scientific vision."

Vivien Marx

Khorshid, M., Hausser, J., Zavolan, M. & van Nimwegen, E. A biophysical miRNA-mRNA interaction model infers canonical and noncanonical targets. *Nat. Methods* **10**, 253–255 (2013).

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A. Roulier/Biozentrum