

Feeding the World through Sustainable Agriculture

Robert H. Smith Faculty of Agriculture, Food and Environment
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Nature-Inspired Drug Design

Despite the enormous investment of time and resources devoted to drug discovery by the global scientific community, the productivity of this field has steadily declined over the decades. One of the challenges facing disease-control experts is to develop inhibitors that are highly selective for particular disease-related signal transduction pathways and have minimal side effects for patients.

Recently, Dr. Masha Niv, an outstanding young scientist at Hebrew University, established the first Computational Biology and Structural Bioinformatics laboratory at the Robert H. Smith Faculty of Agriculture, Food and Environment. A major research direction of Dr. Niv's laboratory is to develop computational tools suited to discovering and optimizing innovative compounds that will form the basis of new modulators of signal transduction and novel drugs.

Dr. Niv and her team work with nature-inspired templates that enable a highly selective protein-protein interface; the laboratory replicates parts of these interfaces, creating short, synthetic protein-like molecules (peptides and peptidomimetics). These nature-inspired highly selective molecules are being designed for the purpose of creating new drugs for the treatment of cancer and diabetes. This groundbreaking research has been patented and study results published in leading scientific journals (e.g. Mack et al. *Diabetes/Metabolism Research and Reviews*, 2008; Rubinstein and Niv, *Biopolymers* 2009).

A Better Understanding of Bitter Taste

Diabetes and obesity are world-wide pandemics. Along with developing new drugs for metabolic disorders, diet and life-style changes are key for treatment and prevention. Food taste is a major parameter determining food choice. For example, while some bitter compounds are toxic, others are beneficial, but not widely consumed due to their bitterness. Understanding the properties of food compounds that determine its taste is of great importance. Dr. Niv's lab is studying the molecular basis for taste perception, currently focusing on bitterness.

There are only 25 receptors for bitter taste; even so, they are able to recognize hundreds of compounds, many of them with strikingly dissimilar chemical features. The scientists are examining the nature of this phenomenon, and are trying to determine how different receptors bind these diverse bitter molecules. Among the questions being posed: Can one cavity in a receptor accommodate dissimilar compounds? What are the interrelations between different receptors? Can such receptors be rationally designed?

In order to answer these questions, Dr. Niv's team is using state-of-the-art computer modeling tools to construct three dimensional models of the receptors, and to identify potential binding modes of the bitter molecules. This research, launched in collaboration with an experimental laboratory, has enabled Dr. Niv to identify key positions responsible for binding bitter molecules. These exciting new findings have been published in the Proceedings of the National Academy of Science (Brockoff 2010).

Dr. Niv and her team are also constructing a database of bitter molecules. Their efforts to identify the characteristics of these molecules and the binding sites in their receptors will help the scientists to develop an *in-silico* predictor of bitterness. Such computational approaches are routinely used in drug discovery, but are just beginning to be applied to molecular recognition by the human senses.

One of the anticipated outcomes of Dr. Niv's research is the prediction of bitterness through use of a computer. The development of a "computerized tongue" will allow scientists to have a powerful new tool at their disposal when they engage in perception research and work on the rational design of new, tempting foods with health and medicinal benefits. Another important application is designing a selective inhibitor for individual receptors, in order to elucidate the role of that particular receptor in overall bitterness perception.

About Dr. Masha Niv

Dr. Masha Niv is a senior lecturer in the Institute of Biochemistry, Food Science and Nutrition at the Robert H. Smith Faculty. She joined The Hebrew University of Jerusalem in 2007 after having led a team of researchers at Keryx Biopharmaceuticals and spending several years as a post-doctoral research fellow and instructor at the Weill Medical College of Medicine at Cornell University.

Head of the first Computational Biology and Structural Bioinformatics laboratory at the Smith Faculty, Dr. Niv is leading a research group focused on the development and application of simulation methods for the study of the structure, interactions and dynamics of key signaling proteins. Accomplishments include the rational design of anti-diabetes peptides and computer-aided studies of the molecular basis for bitter taste perception. In 2010, Dr. Niv was awarded a Krill Prize for Excellence in Scientific Research.

