Learning From Nature: New Antibiotics Found In Our Body

Oct. 25, 2016 by Andrii Buvailo

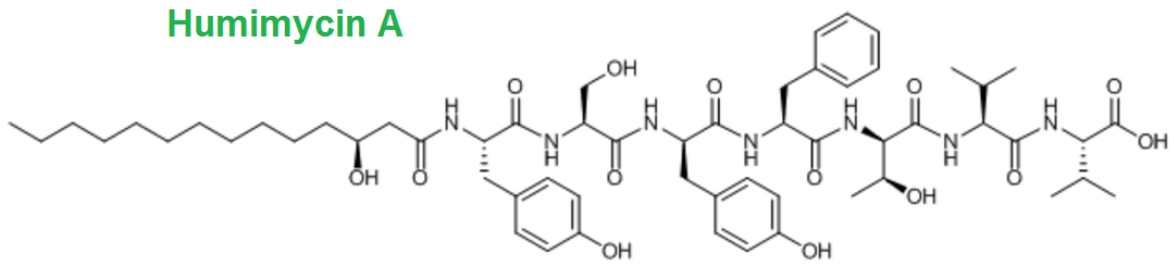
To date, nature has been the best teacher for drug discovery scientists, especially for those who develop antimicrobial drugs. Lately, a new example proving this notion emerged in press - a recent publication in a prestigious research journal Nature describing a new powerful method of identifying yet unknown classes of antibiotics by learning from bacteria living in our body - microbiota.

It is known that all bacteria produce, among other things, small molecule chemicals, metabolites, as products of their living. Those products range in properties and biological activity, for example, some of them appear to be powerful antibiotics helping bacteria protect themselves from other microbes. The characterization of such products is a powerful tool, if not the most successful one, for identifying new small-molecule therapeutics. This is how we learn from nature.

In a typical experimental flow using this approach, scientists have to culture bacteria in labs and analyze metabolites to identify novel bioactive compounds. The limitation, however, arises from our inability to culture a majority of bacteria in the laboratory and from the fact that most biosynthetic gene clusters are not active under laboratory conditions, meaning they do not produce compounds they would do in a natural environment.

On the other hand, extensive sequencing of bacterial genomes and metagenomes has shown that the natural potential of the bacterial biosynthetic diversity is huge, compared to that small fraction that we can access in a lab.

In a recent study, scientists from The Rockefeller University, together with their colleagues from Rutgers University, experimentally validated a way for the discovery of bioactive small molecules that circumvents the need for either bacterial culture or gene cluster expression. In the reported approach, bioinformatic computer algorithms were used to predict natural product structures based on primary sequence data. Next, the structures predicted this way were chemically synthesized and tested for antibacterial properties showing astounding results: several new MRSA active antibiotics have been identified, humimycin A and humimycin B.



The primary sequence is an order of amino-acids in a protein or enzyme, also called the primary structure. The current level of technology offers an easy way of “reading” the primary sequence of any protein of interest. Over the past two decades, scientists learned also how to predict the identity, order and modification of the amino acids comprising so-called nonribosomal peptides (NRPs) from solely the primary sequence data of NRP megasynthetases - enzymes that produce them.

In other words, computer models can now predict the result of this biochemical process without actually doing a costly and technologically difficult laboratory experiment of gene expression.

In validating the above approach to drug discovery, the authors focused on the exploration of human microbiota stems. Myriads of various bacteria co-exist with our body, literally occupying a space inside ourselves. This community of bacteria is called microbiota and the collective genomes represented by those microorganisms are called microbiome. Bacteria in our body are perfectly used to deal with all the versatility of external intruders threatening the human’s body. So, for instance, the antibiotics which are produced by microbiota bacteria might be the best drug candidates for our medical needs. Our own bacteria know better than anything else what our body needs to protect against other species, so to speak.

Authors named the bioinformatically inspired compounds they discovered syn-BNPs. The novel antibiotics, humimycins, discovered in the reported work, validate bioinformatics approach as a strategy for identifying bioactive metabolites and highlights the unique state of the field of natural product chemistry today.

The future of drug discovery

It is clear that advanced computer modeling techniques become valuable tools for identifying novel drug candidates. The above report describes just one example of using computers for data mining from biological systems. The next possible move would be to implement advanced computational algorithms, such as machine learning or even artificial intelligence, for a more accurate and insightful analysis of the obtained datasets. A number of startups developing such computational technologies have recently

emerged, focusing on drug discovery and giving hope for new drug discovery breakthroughs.