What the past says about the future

New research is unravelling the secrets of many serious diseases

By Dr. Ford Doolittle

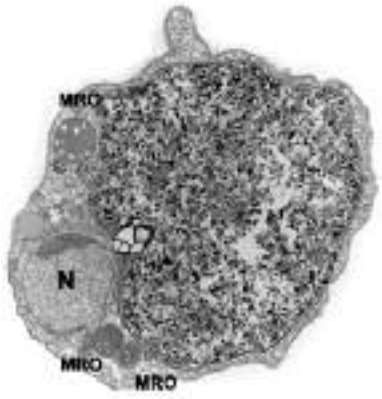
A team of world-renowned evolution researchers embedded in Dalhousie's Medical School is changing the way we study disease. In addition to researchers from medicine, the Centre for Comparative Genomics and Evolutionary Bioinformatics (CGEB; www.cgeb.dal.ca) has members from science (biology, mathematics and statistics) and computer science. However, its largest contingent and its Director, Dr. Andrew Roger, who holds a Canada Research Chair (CRC) award, work out of the Department of Biochemistry and Molecular Biology within the Dalhousie Medical School.

Dr. Roger, along with Drs. John Archibald and Claudio Slamovits and two Professors Emeritus (both former holders of CRC positions), Mike Gray and Ford Doolittle, aim to bring advances in genomics and bioinformatics to bear on the biology and disease-causing nature of an enormously important but under-investigated group of microbes called protists.

Among such "bugs" are causative agents of malaria, toxoplasmosis, African sleeping sickness and "beaver fever" (giardiasis), plus many less harmful or free-living relatives. Studying these microbes allows CGEB members to identify, through comparative genomics, key steps in processes by which an organism that can live harmlessly with humans can become a killer.

Often, the process that allows organisms to cause disease entails an overall loss of genetic information in the form of genes. Of particular interest to the CGEB group is the fate of tiny structures within the microbe called mitochondria and chloroplasts. These are the energy-generating structures that originated as engulfed and enslaved bacteria, an event that took place some two billion years ago.

These engulfed microbes (so called endosymbionts) now represent a major feature for many types of cells, including human cells. Astonishingly, the malaria parasite (*Plasmodium*) and its relatives (i.e. *Toxoplasma* and *Cryptosporidium*) are actually highly degenerate free-living plant cells that no longer have photosynthetic capacity due to loss of chloroplast genes but remain vulnerable to herbicides by virtue of residual plant functions.



Electron micrograph provided by Grant Stevens, showing hydrogen-generating mitochondrion-related organelles (MRO) of *Blastocystis*, an anaerobic pathogen (N designates nucleus).

One lab overseen by Dr. Slamovits studies mechanisms, reasons and consequences of gene loss, not only in organisms related to the malaria parasite but also in infectious marine organisms that impact fisheries and can indirectly poison us. Dr. Archibald's group focuses on novel "secondary endosymbionts." These are ancient cells that had engulfed bacteria as chloroplasts that were in turn swallowed whole and enslaved by new hosts to create more complex organisms.

Understanding the natural history and evolution of cells provides new and unexpected insights into how best to deal with these organisms for improved human health. For further information, contact Andrew Roger (aroger@dal.ca).

Mitochondria (the other energy-generating structure found in all cells) also have suffered evolutionary vicissitudes. Many pathogens that infect humans and animals do not need to use mitochondria for energy but these pathogens still retain mitochondria-related structures that carry out a subset of mitochondrial functions, plus novel activities, like producing hydrogen.

Dr. Roger's lab studies these microbes and has developed sophisticated methods for inferring the novel biochemistry and potential drug sensitivities of many organisms that have maintained these vestigial mitochondria. Through analyses of evolutionary data involving genomics and gene expression, Dr. Roger has been able to target *Blastocystis*, a human pathogen.

CGEB's members have pioneered the application of whole-genome sequencing and analysis of all the products (or transcripts) of the genome to protist biology. They have been remarkably successful at recruiting various U.S. sequencing centres to do the sequencing for free, allowing CGEB's 10 principal investigators and about 50 research trainees (including 12 post-doctoral fellows) to concentrate on high-end experimental and computational investigations. In the last 12 months, the group brought in $2 million in research funding from the Canadian Institutes of Health Research and other agencies, and have produced 75 peer-reviewed publications. This represents a remarkable level of research productivity and has huge impact internationally.

The TULA Foundation has provided an eight-year grant of $3 million for the support primarily of post-doctoral researchers. These young people, the next generation of researchers, have visited Halifax from all over the world: New Zealand, Japan, China, Kazakhstan, the Czech Republic, Norway, Sweden, Germany, France, Spain, Britain, Canada and the U.S . They are drawn by the reputation Dalhousie (and in particular researchers in its medical school) has built in microbial genomics and bioinformatics and its unique critical mass in the application of these methods to a great range of experimental and theoretical questions in microbial biology, ecology, evolution and human health.

Metagenomics and microbiomics: new approaches in microbial health

Expanding knowledge about the microbes inhabiting our bodies

By Dr. Ford Doolittle

As part of its new Canadian microbiome initiative, the Institute of Infection and Immunity within the Canadian Institutes for Health Research recently chose to fund seven emerging team grants. Ranked first in the country among these awards was a multi-disciplinary, multi-institutional bioinformatics project linking biochemistry and molecular biology within the Dalhousie Medical School (Ford Doolittle), computer science (Rob Beiko), biology, mathematics and statistics (Joe Bielawski) in a unique three-faculty research collaboration at Dalhousie University.

The Human Microbiome Project, a global effort Canada is supporting, offers unique intellectual challenges and opportunities. The goal of this program is to create comprehensive knowledge about the microbes inhabiting the interior and exterior of the human body and to understand how these microbes vary in and influence health and disease. The group will determine how diet, geography and lifestyle might impact the behaviour of these microbes.

This knowledge will come through "metagenomics," a massive high-throughput sequencing of all the constituent parts of the information system contained within all cells, the DNA, RNA and protein isolated from specific sites. Ultra-sophisticated computational analyses will convert the enormous data sets obtained into an understanding of which microbes occupy which parts of the body, what they are doing or what they could potentially do.

One might think that generations of microbiologists culturing bugs from sick and healthy people would have already figured this out. But our knowledge remains woefully incomplete. There are simply too many different kinds of microbes, too many of which have not been and perhaps cannot be cultured, and too much variation in their numbers and activities.

Indeed the very notion that we might count the number of bacterial species in the typical gut or on the typical fingernail is belied by the fact that different isolates of the same species can vary by about 40 per cent in the genes they carry. Indeed, through the application of sophisticated molecular technologies we now appreciate that genes can actually be gained by one species though direct transfer of genes from other member of the same species or by transfer from members of a completely different species.

Likewise, genes can be lost. This plasticity of gene composition is now recognized to be sufficiently frequent as to render the notion of species highly problematic philosophically. This is why the research team also includes the world's leading philosopher concerned with species definitions and classification, Marc Ereshefsky in Calgary.

Dalhousie's microbiome team. From left: Joe Bielawski, Rob Beiko and Ford Doolittle.

Still there is detectable and exploitable order and predictability in the living world and many intriguing discoveries are emerging daily. For example, obesity is associated with shifts in the taxonomic composition, diversity and gene repertoires of the microorganisms living in the human gut so that these organisms have increased capacity for nutrient utilization. Recently in the news was the discovery that the gut microflora of nori-eating Japanese people carries genes for digestion of this seaweed's carbohydrates—genes obtained by transfer from marine bacteria.

Making sense of metagenomic data produced by the Human Microbiome Project will demand more sophisticated assessments of community compositions and distributions, and more holistic, process-based approaches to understanding community functions. The Dalhousie team aims to develop and implement a new generation of bioinformatic tools to meet this demand. Its unique combination of bioinformatics experience, computational sophistication, evolutionary and population genetic orientation and philosophical rigor will help make microbiomics into a predictive health science with great therapeutic potential. Our deliverables will be widely-applicable software based on advances in understanding how microbial genomes evolve in communities. An invaluable byproduct will be a cadre of interdisciplinary trained graduate students and post-doctoral fellows. Ultimately, this type of information will provide much of the basis for decisions concerning the health care of individuals and health policies for our population.

For more information, contact Dr. Ford Doolittle at ford@dal.ca.

"We are witnessing staggering advances in our understanding of genetics and genomics, approaches that were more akin to science fiction only a decade ago. Researchers within the Medical School are leading this world-wide effort to understand the fundamental nature of life itself."
—Dr. Gerald Johnston, Associate Dean, Research, Faculty of Medicine.
Email: g.c.johnston@dal.ca