

Parasitic Nematode Group at Washington University Receives over \$1.5 Million NIH/NIAID Grant to Study Parasites that Infect Nearly 3 Billion People

Scientists at the Genome Center (GC) at Washington University School of Medicine in St. Louis have received a five-year National Institutes of Health (NIH) grant to study the genetics of the main groups of human parasitic roundworms (nematodes). The most important parasites of this group include hookworms, *Ascaris* and whipworm (>1 billion infections each) and the filarial worms that cause elephantiasis and African riverblindness. Infections of humans by nematodes result in substantial human mortality and morbidity, especially in the tropical regions of Africa, Asia, and the Americas.

“Roundworms belong to a highly diverse group of organisms that belong to the phylum Nematoda, occupy diverse ecological niches and comprise one of the most successful groups of metazoan parasites”, says Makedonka Mitreva, Ph.D., faculty member and assistant director of the GC, and principal investigator for the grant. A recent study of mostly urban Peruvian women found 65 percent had *Ascaris* and 48 percent had hookworm. In the Phillipines, a sample of 333 school-age children revealed 75 percent had *Ascaris* and 45 percent had hookworm. “One major effect of hookworm is anemia — the worms sit in the intestine and feed on the host’s blood,” explains Dr. Mitreva. “In children, this can lead to stunted growth and detrimental effects on cognitive development. *Ascaris* lives in the small intestine and can grow to 12 inches in length, causing diarrhea and, in certain cases, a potentially life-threatening impairment of the bile duct”.

As other parasites nematodes undergo reductive evolution, relying on host metabolism and homeostatic buffering. However, many parasitic nematodes spend time outside the hosts or have multiple hosts. Therefore, they may instead maintain or expand metabolic and regulatory functions. “Our focus will be on biochemical pathways conserved and/or taxonomically restricted, including proteins that may prove useful as drug targets”, says Dr. Mitreva.

Dr. Mitreva is leading the world's largest effort aimed at sequencing human, animal, and plant parasitic nematodes, since 2002. In previous research, funded for seven years by the NIH/NIAID and the National Science Foundation, the GC researchers studied a broader range of roundworms that infect humans, animals and plants, identified and made publicly available over 120,000 genes from 28 parasitic species, averaging 20% of total genes per species. The information they produce are made publicly available through Nematode.net, an online database of roundworm genetics created by GC researchers. They also began integrating Nematode.net and Wormbase, a genetics database dedicated to the nematode *C. elegans*, which was the first multicellular organism to have its entire genome sequenced. “The value of *C. elegans* as a model organism for understanding human health and disease has long been recognized. The genomes of four other *Caenorhabditis* spp. are completed. However, decoding the genomes of the most closely related parasitic nematodes represents an extraordinary and unique resource for comparative evolutionary developmental studies, offering power to identify genes and regulatory sequences by ‘phylogenetic footprinting’, better defining of proteins involved in nematode parasitism, expanding the understanding of both conserved and divergent aspects of nematode biology which will enhance the value of *Caenorhabditis* spp. as a model for understanding health and disease, host-parasite relationships, and basic biological processes”, says Dr. Mitreva.

Researchers at the Genome Center and the Sanger Center in the United Kingdom completed the *C. elegans* genome in 1998. Today this collaboration continues, and in the coming five years, projects at the GC and the Sanger Institute will increase available parasitic nematode sequences by another order of magnitude, adding 25 draft parasitic nematode genomes. “The initiative for decoding the genomes of 10 parasitic nematodes at the Genome Center is supported by the NIH/NHGRI (<http://www.genome.gov/10002154>). We are producing the data scientists need to develop new treatments that interfere with the activities of key genes in parasites that are of human and veterinary importance,” says Dr. Mitreva, Ph.D. “We’re also going to investigate unusual aspects of their biology, hoping to identify unique molecular features that are archetypical to the phylum Nematoda” adds Dr. Mitreva.

Among the nematode-derived proteins, there are two intriguing groups that provide potent new avenues of attack for pharmaceutical researchers, Mitreva notes. “In the first group are proteins that are specific to the pathogen and can be good targets for drugs with low toxicity to the host or for environmentally safe pesticides. In the second are the conserved essential proteins within a pathogen that are more resistant to evolutionary change, since compromising their function may be lethal. Targeting these proteins with drugs is attractive because of their essential function but problematic because of the likelihood of target-based toxicity to the host. Our recent discoveries have shown that highly homologous and essential pathogen proteins may contain potentially targetable insertions and deletions when compared to human homolog(s), and have sufficiently diverged in the host as to be functionally absent or altered. Our pan-phylum studies have focused on identification and characterization of these 2 groups of proteins, because they can be good targets for drugs with low toxicity to the host or for environmentally safe pesticides”, says Dr. Mitreva.

“Our next step is to get collaborators who can work on characterizing the functions of these genes,” Mitreva says. The nematode genome project at the GC has substantial support from the parasitic nematode scientific community, resulting in established collaborations with over 30 investigators, 22 of whom provided material used for NIAID/NHGRI-funded sequencing and many of whom are now involved in analyzing the resulting data.

“Washington University continues to be a leader in applying genomic approaches that revolutionize parasitology. We believe that we have advanced the field by providing fundamental molecular information about these parasites accelerating basic research and development of new diagnostics and therapeutics”, says Dr. Mitreva.