

Alexandra Grote

EDUCATION

Ph.D. New York University	2013- 2019 GPA: 4.0
B.A. University of California Berkeley Major: Integrative Biology	2007-2011 GPA: 3.8

RESEARCH EXPERIENCE

Postdoctoral Fellow **August 2019 – Current**
Earl Lab, Bacterial Genomics Group, Infectious Disease and Microbiome Program, Broad Institute of MIT and Harvard

Salmonella Persistence- Many bacterial pathogens including *Salmonella enterica* can establish persistent infections, evading the host immune system and killing by antibiotics, yet little is understood about the underlying mechanism. I used whole genome sequencing of *S. enterica* isolates from patients at early and late stages of chronic infection to identify genetic variants arising during infection and found that genes encoding global transcriptional regulators were most commonly mutated over time in the patient, with the *barA/sirA* two-component system, a global regulator of virulence genes, the most consistently affected. I then used RNA-Seq to identify the regulatory pathways affected by these variants, finding that late isolates with *barA* or *sirA* mutations led to significant downregulation of genes in the *Salmonella* Pathogenicity Island (SPI) 1, encoding the type III secretion system that delivers effector proteins necessary for intestinal invasion and the production of enteritis. Lastly, testing these mutations in *barA* and *sirA* using the *in vivo* mouse model revealed attenuated virulence in the late isolates.

Antibiotic Resistance- Multidrug resistant gram-negative bacteria are a rapidly growing threat, and the development of novel antimicrobials has failed to keep pace. Synergistic combinations of individually ineffective drugs present a potential solution, yet little is understood about the mechanisms of such combinations. With Thea Brennan-Krohn at BIDMC, I found that the combination of colistin and minocycline has a high rate of synergy against colistin-resistant and minocycline-resistant strains of *Klebsiella pneumoniae*. Using RNA-Seq, we characterized the transcriptional profiles of these strains when treated with the drugs individually and in combination, finding that the synergistic activity of this combination against bacteria resistant to each drug alone likely involves sublethal outer membrane disruption by colistin, which permits increased intracellular accumulation of minocycline.

Graduate Student **June 2014 – July 2019**
Ghedini Lab, Department of Biology, New York University

Filarial nematode / Wolbachia Symbiosis- I pioneered a method of Dual RNA-Seq to profile the transcriptomes of *Brugia malayi*, a nematode that parasitizes humans, and its obligate endosymbiotic bacteria, *Wolbachia*, over the lifecycle of the worm. This allowed me to pinpoint

functional pathways that are involved in this essential symbiotic relationship and provided by the developmentally regulated co-expression of nematode and bacterial genes.

Metabolomics and Drug Target Discovery- I measured the metabolome over the lifecycle of *Brugia malayi*. I combined these data with transcriptomic data to perform Flux Balance Analysis to identify essential reactions, or choke points, that could be exploited for therapy. I recently finished validating some of these predicted choke points using drugs developed against other pathogens.

Comparative Genomics- I analyzed the newly sequenced genome and transcriptome of *Onchocerca volvulus*, the causative agent of river blindness. I focused on determining what gene families were expanded in filarial nematodes. I also took an immunomics approach to vaccine candidate discovery, using the genome and transcriptome to predict proteins that could act as potential antigens or adjuvants in a vaccine. I identified several promising protein targets, one of which is currently under development. Additionally, I worked on a project where I identified the evolution of neo- X and neo- Y chromosomes in *Brugia malayi* using a comparative genomics approach of filarial nematode genomes.

Research Assistant/ Lab Manager

September 2011 - July 2013

Bhaya Lab, Department of Plant Biology, The Carnegie Institution for Science, Stanford, CA
Huang Lab, Department of Bioengineering, Stanford University, Stanford, CA

Phototaxis Project- I analyzed photoreception and phototaxis in photosynthetic cyanobacteria with Dr. Devaki Bhaya. I characterized and quantified the phototactic response of *Synechococcus OSB'*, an environmentally isolated thermophilic cyanobacteria, to light intensity as well as wavelength.

Polyphosphate Kinase Project- This project involved the study of how *Synechococcus OSB'* synthesizes and breaks down polyphosphate, a key storage compound in many prokaryotes. I confirmed the creation of a mutant in the polyphosphate kinase (*ppk*), an enzyme responsible for the synthesis of polyphosphate, and characterized its phenotype with respect to *ppk* expression.

Chiral Expansion in E. coli Project- I studied the molecular and cellular basis for bacterial colony organization with Professor K.C. Huang, developing an assay with which to visualize the difference in chiral growth and colony formation with respect to certain types of mutations in cell wall synthesis machinery.

Research Technician

January 2009 - September 2011

Bruns Lab, Department of Plant and Microbial Biology, University of California Berkeley

Point Reyes National Seashore Mycoblitz- I worked with Professor Thomas Bruns to characterize the fungal diversity as part of the Point Reyes Mycoblitz. I extracted DNA from fungal samples and sequenced the ITS-1 region of DNA, making use of the high degree of variation in this sequence to create phylogenetic trees of the major genera present. I was also in charge of curating fungal specimens for the Jepson Herbarium.

Ectomycorrhizal Associations- I assisted in a study on the associations between the wildflower *Pyrola aphylla* and ectomycorrhizal fungi, performing stable isotope analysis using mass spectrometry to track the transfer of carbon and nitrogen between plant roots and fungi.

AWARDS AND FELLOWSHIPS

Jane Coffin Childs Fellow Jane Coffin Childs Memorial Fund for Medical Research	2020-Current
F31 Ruth L. Kirschstein Pre-doctoral Individual NRSA National Institute of Allergy and Infectious Disease, National Institutes of Health	2018-2019
Dean's Dissertation Fellowship Graduate School of Arts and Sciences, New York University	2018-2019
T32 Ruth L. Kirschstein Institutional National Research Service Award National Institute of Allergy and Infectious Disease, National Institutes of Health	2016-2018
ASP Mark Dresden Student Travel Award American Society for Parasitology	2018
Young Investigator Award American Society of Tropical Medicine and Hygiene (ASTMH)	2017
Gladys Mateyko Research Award New York University, Department of Biology	2017
Outstanding Teaching Award College of Arts and Science, New York University	2017
Eugene Bell Research Award for Distinction in the Thesis Proposal Exam Biology Department, New York University	2015
Dean's List University of California, Berkeley	2009

PUBLICATIONS

Grote A, Piscon B, Manson A, Livny J, Earl A, Gal-Mor O. Persistent *Salmonella* infections in humans are associated with mutations in the SirA/BarA regulatory pathway. Under review at Cell Host & Microbe, 2022.

Grote A and Earl A. Within-host evolution of bacterial pathogens during persistent infection of humans. Current Opinion in Microbiology. 2022 Sept 1; 70:102197.

Zheng E, Andrews I, **Grote A**, Manson A, Earl A and Collins J. Modulating the evolutionary trajectory of tolerance using antibiotics with different metabolic dependencies. Nature Communications. 2022 May 9; 13(1): 1-11.

Brennan-Krohn T* and **Grote A***, Rodriguez S, Kirby JE, Earl A. Transcriptomics reveals how minocycline-colistin synergy overcomes antibiotic resistance in multidrug-resistant *Klebsiella pneumoniae*. *Antimicrobial Agents and Chemotherapy*. 2022 March 15; 66 (3), e01969-21

* *co-first authors*

van Dijk L, Walker B, Straub T, Worby C, **Grote A**, Schreiber A, Anyansi C, Pickering A, Hultgren S, Manson A, Abeel T, Earl A. StrainGE: A toolkit to track and characterize low-abundance strains in complex microbial communities. *Genome Biology*. 2022 March 7; 23(1): 1-27.

Aranda-Díaz A, Rodrigues C, **Grote A**, Sun J, Schreck C, Hallatschek O, Souslov A, Möbius W, Huang K. Bacterial Filamentation Drives Colony Chirality. *mBio*. 2021 November 2; 12 (6): e01542-21.

Chung M, Basting P, Patkus R, **Grote A**, Luck A, Ghedin E, Slatko B, Michalski M, Foster J, Bergman C, Dunning Hotopp J. A Meta-Analysis of Transcriptomics Reveals a Stage-Specific Transcriptional Response Shared Across Different Hosts. *G3: Genes, Genomes, Genetics*. 2020 September 2; 10 (9): 3243-3260.

Liu C, **Grote A**, Ghedin E, Unnasch T. CRISPR-mediated Transfection of *Brugia malayi*. *PLoS Neglected Tropical Diseases*. 2020 August 31; 14 (8): e0008627.

Curran DM* and **Grote A***, Nurisimulu N, Geber A, Voronin D, Jones D, Ghedin E, Parkinson J. Modeling the metabolic interplay between a parasitic worm and its bacterial endosymbiont allows the identification of novel drug targets. *Elife*. 2020 August 11; 9: e51850 * *co-first authors*

Grote A* and Li Y*, Liu C, Voronin D, Geber A, Lustigman S, Unnasch T, Welch L, Elodie G. Prediction pipeline for discovery of regulatory motifs associated with *Brugia malayi* molting. *PLoS Neglected Tropical Diseases*. 2020 June 23; 14(6): e0008275. * *co-first authors*

Tracey A, Foster J, Paulini M, **Grote A**, Mattick J, Libro S, Lustigman S, Michalski M, Rogers M, Twaddle A, Dunning Hotopp J, Berriman M, and Ghedin E. The Nearly Complete Genome of *Brugia malayi* strain FR3. *Microbiology Resource Announcements*. 2020 June 11; 9 (24): e00154-20.

Foster JM* and **Grote A***, Mattick J, Tracey A, Tsai Y-C, Brookes K, Chung M, Cotton JA, Clark TA, Geber A, Holroyd N, Kurlach J, Libro S, Lomax J, Lustigman S, Michalski ML, Paulini M, Rogers MB, Twaddle A, Berriman M, Dunning Hotopp JC, Ghedin E. Sex Chromosome Evolution in Parasitic Nematodes of Humans. *Nature Communications*. 2020 April 4; 11 (1): 1-12 * *co-first authors*

Voronin D, Schnall E, **Grote A**, Jawahar S, Ali W, Unnasch TR, Ghedin E, Lustigman S. Pyruvate produced by *Brugia* spp. Via glycolysis is essential for maintaining the mutualistic association between the parasite and its endosymbiont, *Wolbachia*. *PLoS Pathog*. 2019 Sept 30; 15 (9): e1008085.

Grote A, Caffrey CR, Rebello KM, Smith D, Dalton JP, Lustigman S. Cysteine proteases during larval migration and development of helminths in their final host. *PLoS Negl Trop Dis*. 2018 Aug 23; 12 (8): e0005919.

Lustigman S, **Grote A**, Ghedin E. The role of 'omics' in the quest to eliminate human filariasis. *PLoS Neglected Tropical Diseases*. 2017 Apr 20; 11 (4): e0005464.

Grote A, Voronin D, Ding T, Twaddle A, Unnasch TR, Lustigman S, Ghedin E. Defining *Brugia malayi* and *Wolbachia* symbiosis by stage-specific dual RNA-seq. *PLoS Neglected Tropical Diseases*. 2017 Mar 30; 1(3): e0005357.

Grote A, Lustigman S, Ghedin E. Lessons from the genomes and transcriptomes of filarial nematodes. *Molecular and Biochemical Parasitology*. 2017 Jul; 215: 23-29.

Bennuru S, Cotton JA, Ribeiro JM, **Grote A**, Harsha B, Holroyd N, Mhashilkar A, Molina DM, Randall AZ, Shandling AD, Unnasch TR, Ghedin E, Berriman M, Lustigman S, Nutman TB. Stage-Specific Transcriptome and Proteome Analyses of the Filarial Parasite *Onchocerca volvulus* and Its *Wolbachia* Endosymbiont. *MBio*. 2016 Nov 23; 7(6): e02028-16.

Cotton JA, Bennuru S, **Grote A**, Harsha B, Tracey A, Beech R, Doyle SR, Dunn M, Hotopp JC, Holroyd N, Kikuchi T, Lambert O, Mhashilkar A, Mutowo P, Nursimulu N, Ribeiro JM, Rogers MB, Stanley E, Swapna LS, Tsai IJ, Unnasch TR, Voronin D, Parkinson J, Nutman TB, Ghedin E, Berriman M, Lustigman S. The genome of *Onchocerca volvulus*, agent of river blindness. *Nature Microbiology*. 2016 Nov 21; 2:16216.

Gomez-Garcia MR, Fazeli F, **Grote A**, Grossman AR, Bhaya D. Role of polyphosphate in thermophilic *Synechococcus* sp. from microbial mats. *Journal of Bacteriology*. 2013 Aug; 195 (15): 3309-19.

CONTRIBUTIONS TO CONFERENCES

Oral Presentations:

“Understanding the mechanism of symbiosis between parasitic worms and *Wolbachia*.” Anthelmintics IV: From Discovery to resistance, Santa Monica, CA. February 2020. (Invited Talk)

"Sex Chromosome Evolution in Parasitic Nematodes of Humans." NYC Parasitology meeting, New York, NY. December 2019

“Using metabolic networks to probe the symbiosis between *Wolbachia* and filarial nematodes.” *Wolbachia* Meeting 2018, Salem, MA. June 2018.

“Using metabolic networks to probe the symbiosis between *Wolbachia* and filarial nematodes, and identify novel drug targets.” American Society for Parasitology, Cancun, Mexico. July 2018.

“Understanding the symbiosis between parasitic worms and bacteria.” Metropolitan Society for Natural Historians, New York, NY. February 2018. (Invited Talk)

“Determining the mechanisms of endosymbiosis between filarial nematodes and *Wolbachia*.” American Society for Tropical Medicine and Hygiene Annual Meeting, Baltimore, MD. November 2017.

“Searching for metabolic choke points to disrupt the *Brugia malayi* / *Wolbachia* symbiosis” NYC Parasitology Meeting II, New York, NY. October 2017.

“Defining metabolic choke points involved in the *Brugia malayi*/ *Wolbachia* symbiosis.” Molecular and Cellular Biology of Helminths XI, Hydra, Greece, September 2017.

“Defining *Brugia malayi* and *Wolbachia* symbiosis by stage-specific dual RNA-seq.” Molecular Helminthology, Cape Cod, MA. March 2017.

“Filarial genomes and transcriptomes: lessons and opportunities.” NYC Parasitology Meeting, New York, NY. September 2016.

“Molecular mechanisms of filarial endosymbiosis.” New York Area Worm Meeting, New York, NY. January 2015.

Poster Presentations:

Grote A, Gabso B, Gabso B, Livny J, Earl A, Gal-mor O. “Persistent Salmonella infections in humans are facilitated by mutations in key virulence regulators.” 17th Annual Broad Retreat, Cambridge, MA. December 2021.

Grote A, Lustigman S, Ghedin E. “Investigating mechanisms of filarial endosymbiosis.” Society for Microbiology and Evolution Annual Meeting, Austin, TX. June 2017.

Grote A, Lustigman S, Ghedin E. Sex chromosome evolution in filarial nematodes.” Evolutionary Genomics of Sex Conference, Tempe, AZ. November 2016.

Grote A, Lustigman S, Ghedin E. “Investigating mechanisms of filarial endosymbiosis.” Anthelmintics: from Discovery to Resistance in San Diego, CA. February 2016.

Grote A, Lustigman S, Ghedin E. “First look into the newly sequenced *Onchocerca volvulus* transcriptome.” Gordon Conference on Tropical Infectious Disease in Galveston, TX. March 2015.

Grote A, Voronin D, Lustigman S, Ghedin E. “Molecular mechanisms of filarial endosymbiosis.” American Society of Tropical Medicine and Hygiene Annual Meeting in New Orleans, Louisiana. November 2014.

Grote A, Sedivy E, Chau R, Huang KC, Bhaya D. "Characterizing Phototaxis of Thermophilic *Synechococcus sp.*" American Society of Microbiology Annual meeting, 2012.

TEACHING EXPERIENCE

Guest Lecturer, Mechanisms of Microbial Pathogenesis, Harvard Medical School

2022

Guest Lecturer, Essentials of Public Health Biology, NYU	2018
Head Teaching Assistant and Course Administrator, Molecular and Cellular Biology, NYU	2017
Teaching Assistant, Molecular and Cellular Biology, NYU	2015, 2016, 2017
Teaching Assistant, Principles of Biology, NYU	2014

SCIENTIFIC OUTREACH

Broad Summer Research Program, Selection Committee Volunteer	2022
Science Education Partner, The Harvard Museums of Science and Culture	2021
Speaker, Metropolitan Society for Natural Historians	2018
Contributing Author, The Cooper Square Review	2017-2018
Organizer, Ada Lovelace Day at New York University	2014-2017
Finalist, Imagine Science Film Festival Symbiosis Competition	2017
Mentor, Research Experiences for Teachers, National Science Foundation	2013
Mentor, Summer Internship Program, The Carnegie Institute for Science	2012