Top 10 Exemplar Publications:

- (2001) Bordenstein, S.R., F.P. O'Hara, and J.H. Werren. *Wolbachia*-induced incompatibility precedes other hybrid incompatibilities in *Nasonia*. **Nature** 409: 707-710.

  This landmark paper demonstrated that endosymbionts are not just passengers or metabolic influencers; they are active drivers of speciation in the animal kingdom, appearing before the evolution of nuclear genetic incompatibilities. Specifically, the adaptation of *Wolbachia*-induced cytoplasmic incompatibility served as the primary barrier to gene flow between species of the *Nasonia* wasp genus. It established the first case system for endosymbionts contributing directly to incipient F1 hybrid inviability and thus speciation.

- (2013) Brucker, R.M. and S.R. Bordenstein. The hologenomic basis of speciation: Gut bacteria cause hybrid mortality in the genus *Nasonia*. **Science** 341(6146): 667-669.

  By showing that the gut microbiome—not just endosymbionts—cause lethality in F2 hybrid *Nasonia* wasps, this work provided the first definitive empirical proof for the gut microbiome's role in reproductive isolation and speciation. This paper also showed that hybrids of *Nasonia* have different microbiome structures than pure species of the genus, and the dominant gut microbial members directly underpin hybrid death. It historically coined the term 'phylosymbiosis', defined as the widespread pattern when gut microbiome relationships between host species mirror the phylogeny of the host species.

- (2014) Metcalf, J.A., L.J. Funkhouser-Jones, K. Brileya, A.L. Reysenbach, and S.R. Bordenstein. Antibacterial Gene Transfer Across the Tree of Life. **eLife** 3: e04266.

  This study revealed an astonishing breadth of horizontal gene transfer, showing that antibacterial genes that cut peptidoglycan have jumped across the Tree of Life from bacteria to eukaryotes and archaea multiple times. It underscores the deep evolutionary reliance of complex organisms on the metabolic and defensive innovations of the microbial world and was the first case of deciphering an anti-bacterial gene in the domain Archaea.

- (2017) LePage, D.P., J.A. Metcalf, S.R. Bordenstein. J. On, J.I. Perlmutter, J.D. Shropshire, E.M. Layton, L.J. Funkhouser-Jones, J.F. Beckmann, S.R. Bordenstein (2017) Prophage WO genes recapitulate and enhance *Wolbachia*-induced cytoplasmic incompatibility. **Nature** 543(7644): 243-247.

  This seminal work identified the *cifA* and *cifB* (*cytoplasmic incompatibility factor*) genes within prophage WO of the widespread insect endosymbiont *Wolbachia*, proving that viral genes are the actual effectors of *Wolbachia*-induced reproductive manipulation. By successfully recapitulating cytoplasmic incompatibility and rescue in *cifAB* transgenic flies, the study provided the simple genetic basis for how a bacterial endosymbiont controls sperm and egg compatibility, offering a powerful new genetic toolkit for using *Wolbachia* to curb the spread of mosquito-borne human diseases such as Zika and Dengue.

- (2016) Brooks, A.W., K.D. Kohl, R.M. Brucker, E.J. van Opstal, and S.R. Bordenstein. Phylosymbiosis: Relationships and functional effects of microbial communities across host evolutionary history. **PLOS Biology** 14(11): e2000225.

  This paper formalized the concept and statistical tools of phylosymbiosis, an eco-evolutionary-based rule that microbial community relationships frequently mirror the evolutionary history of their hosts across diverse taxa. It provided a robust statistical framework widely adopted in hundreds of studies to date, and it functionally established that phylosymbiosis patterns are not just widespread, but consequential to holobiont survival and performance.

- (2021) Perlmutter, J.I., J.E. Meyers[Ψ], and S.R. Bordenstein. A single synonymous nucleotide change impacts the male killing phenotype of prophage WO gene *wmk*. **eLife** 10: e67686

  This study was built from the candidate's discovery of the *Wolbachia* male-kiling gene, *wmk*, in 2019. Here, the work demonstrated that a single synonymous nucleotide change in the *wmk* gene determines the fate of whether male *Drosophila* embryos live or die. This work highlighted the extreme precision of symbiont, functional genetics and revealed how subtle (non-coding) molecular variations in killer genes dictate the survival and sex ratios of insect populations.

- (2022) Markowitz, R.H.G., A.L. LaBella, M. Shi, A. Rokas, J.A. Capra, J.F. Ferguson, J.D. Mosley, and S.R. Bordenstein. Microbiome-associated human genetic variants impact phenome-wide disease risk. **Proceedings of the National Academy of Sciences** 119(26): e2200551119.

  This paper investigated nearly 1000 human genetic variants associated with gut microbiome variation and linked a subset of the loci to a wide array of disease risks across the human phenome. From large clinical data across two databanks, it provided triadic evidence that human genetic diversity and microbial diversity are functionally coupled to various types of clinical health codes. Moreover, a selective sweep and population differentiation impacts some of the triadic relationships. In the context of precision diagnostics, it highlights the relevance of human genetic background for microbiome-related modulation or therapeutics.

- (2024) Kaur, R., A. McGarry, J.D. Shropshire, B.A. Leigh, and S.R. Bordenstein. Prophage proteins of an insect symbiont modulate sperm noncoding RNA and DNA to kill embryos. **Science** 383: 1111-1117

  This study elucidated the most detailed molecular crosstalk of symbiont-induced reproductive parasitism, showing how prophage proteins, CifA and CifB, from *Wolbachia* manipulate sperm noncoding RNA and DNA during spermiogenesis to induce embryo death. This discovery provides a biochemical bridge between viral genes, symbiotic bacteria, and animal development and establishes the mechanistic basis of a symbiont adaptation currently deployed worldwide in mosquito vector control.

- (2025) Vay Syoc, E.P., A. Gomez, E.R. Davenport, and S.R. Bordenstein. Gut fungal profiles reveal phylosymbiosis and codiversification across humans and nonhuman primates. **PLOS Biology** 23(9): e3003390

  Expanding the phylosymbiosis framework to the often-forgotten fungi of the intestinal tract, this work showed that gut fungal profiles exhibit phylosymbiosis across humans and nonhuman primate relatives. It revealed that select gut fungi are enriched in humans and remarkably can cospeciate in hominids. The findings originate a new view of the eco-evolutionary rules governing human-gut fungi relationships in a hominid context.

- (2025) Vay Syoc, E.P., E.R. Davenport, and S.R. Bordenstein. Gut fungi are associated with human genetic variation and disease risk. **PLOS Biology** 23(9): e3003339.

  This research established for the first time that human genetic variation significantly influences the gut mycobiome, which in turn correlates with specific disease risks. By integrating fungi into the GWAS foundations of traditional human gut microbiome studies, the study completed a more holistic picture of how the number and types of human genes influence gut fungal ecosystems and health. Notably, the gut fungi *Kazachstania* forms a causal relationship with cardiovascular disease risk in a mendelian randomization analysis, which in turn offers potential for gut fungi modulation of heart disease.