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**Yuan Li, Laura A.L. Dillon, Kacey L. Caradonna, V. Keith Hughitt, Cecilia F. Dupecher, Kwame Okrah, Hector Corrada Bravo, Barbara A. Burleigh and Najib M. El-Sayed\*** (elsayed@umd.edu). *Simultaneous interrogation of the transcriptomes of pathogens and their host cells*. Preliminary report.

We have adopted a novel approach aimed at characterizing host-pathogen infectomes. We define the infectome as the component of the pathogen's genome/transcriptome/proteome that allows it to subvert the functions of host cell molecular machineries, receptors, and signaling proteins, as well as the portion of the host cell's -omes that play a role in the infection process. Our screens include the use of a combination of 1) bioinformatic tools aimed at predicting surface and secreted components, 2) simultaneous interrogation of the host and pathogen transcriptomes during infection and intracellular survival and 3) high-throughput protein-protein interaction screens between a selection of host and pathogen proteins informed by the first two steps. The application of this approach to *Trypanosoma cruzi* and *Leishmania major*, two intracellular pathogens that parasitize mammalian cells is yielding significant biological insights into host-pathogen interactions. The identification and quantification of co-regulated genes has provided evidence regarding the mechanisms used by each of the two parasites to elude host defenses. We have also gained novel insights into host-pathogen interactions that influence establishment and maintenance of intracellular infection in mammalian host cells. (Received January 19, 2015)