296. Discovery of New Class of Trypanocidal Compounds Targeting the Energy Metabolism of African Trypanosomes
Emmanuel Oluwadare Balogun, PhD;1 Daniel Ken Inoaka, PhD;2 Tomoo Shiba, PhD;2 Yoshi-Tchi Watanabe, PhD;2 Anthony Moore, PhD;2 Shigeharu Harada, PhD;2 and Kiyoshi Kita, PhD;3 Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria;1,2 Nigela School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan,1 Department of Applied Biology, Kyoto Institute of Technology, Kyoto, Japan,2 Department of Biomedical Chemistry, The University of Tokyo, Tokyo, Japan,2 Department of Biochemistry and Molecular Biology, University of Sussex, Sussex, United Kingdom

Session: 50. Global Infections
Thursday, October 5, 2017: 12:30 PM

Background. African trypanosomes are the pathogens that cause sleeping sickness in humans and Nagana in animals. These diseases are fatal, endemic in sub-Saharan Africa and attributed to the underdevelopment of the subregion. Not less than 25,000 human lives and animals worth $1.5 billion are lost annually to the diseases. There is no vaccine and the available therapeutic options are few and with limited efficacy, prompting the search for new drug candidates. The unique energy metabolism pathway of African trypanosomes is considered a validated rational strategy towards the development of new drugs. Our previous results show that the simultaneous inhibition of the parasites' glycerol kinase (TGK) and alternative oxidase (TAO), two key enzymes for ATP synthesis in the parasites' resulted in trypanosomes death. However, while ascorfuranone (AF) is an established TAO inhibitor, there is no known inhibitor for any TGG. The present study was aimed at the discovery of novel TGG inhibitors for co-administration with AF.

Methods. Protein X-ray crystallography, computational medicinal chemistry, and enzyme assay approaches was used to conduct large-scale screening of a chemical library.

Results. The resulting hits were compounds possessing different structural scaffolds, which potently inhibited TGG up to 50 nM IC50 values. Interestingly, a number of the inhibitors caused the expected improvement in the potency of AF against trypanosome cells, causing a shift in trypanocidal activity of AF (IC50) from nanomolar to picomolar concentrations (P < 0.05). Remarkably, one of the inhibitors was identified as a dual inhibitor of TGG and TAO. The complete structures of both inhibitors have been determined, providing a platform for further refinement of the trypanocidal potencies by structure-activity relationship studies.

Conclusion. We have utilized rational design approach to identify novel trypanocidal compounds that may be used for the design of new class of anti-trypanosomal drugs for African trypanosomiasis.

Disclosures. All authors: No reported disclosures.

297. Serial Multiplex PCR May Help Differentiate Causal Pathogens from Colonizing Organisms in Children with Acute Diarrhea in Guatemala
Satoshi Kida, MD;1 Mario Melgar, MD;2 Diva M Calvinsmontes, MD;3 Edwin Asturias, MD;4 Ingrid Contreras-Roldan, MD;5 Samuel Dominguez, MD, PhD;6 Christine C. Robinson, PhD;7 Molly Lamb, PhD;7 Stephen Berman, MD;1,3 and James Gaensbauer, MD, MScPH;1,3 Children’s Hospital Colorado and University of Colorado School of Medicine, Aurora, Colorado;2 Hospital Roosevelt, Guatemala City, Guatemala;3 Children’s Hospital Colorado at Aurora, Colorado

Session: 50. Global Infections
Thursday, October 5, 2017: 12:30 PM

Background. Determination of the cause of childhood diarrhea in low- and middle-income countries is complicated by the presence of multiple potential pathogens in stool at the time of illness. Serial multiplex PCR may offer a method to characterize pathogens more likely to clear over time (suggesting a higher likelihood of causality) vs. those that are more typically persistent (suggesting higher likelihood of nonpathogenic colonization). Such determination may have both clinical and epidemiologic utility.

Methods. Children 6–35 months old with acute non-bloody diarrhea (duration <72 hours) were enrolled in a clinical trial between 3/2015 and 1/2016 in three sites (one rural, two urban) in Guatemala. Stool collected at enrollment and 31 days later were analyzed by multiplex PCR (BioFire, USA) that allows simultaneous identification of 22 viral, parasitic and bacterial diarrheal pathogens. Rates of prevalence (positive day 1), persistence (positive both day 1 and 31), and acquisition (negative day 1 and positive day 31) of each pathogen were evaluated.

Results. We analyzed 298 subjects with a median age of 17 (range 6–35) months, 54% male and 57% residence in rural areas with poor sanitation. Persistence rates by pathogen are shown in Figure 1. 56% of pathogens on day 1 were persistently positive. Viruses tended to clear from stools over the 31-day period, while parasites and E. coli other than O157:H7 and Shiga toxin-producing E. coli tended to be persistent. New acquisition of at least one pathogen occurred in 80% of children (mean new pathogens 1.7/subject, range 0–7). Day 1 prevalence rates of each pathogen were strongly correlated with acquisition rates in other subjects (R2 = 0.818, P < 0.001), suggesting that these pathogens are efficiently transmitted throughout the community (Figure 2). Similar correlations were observed in both rural and urban populations.

Conclusion. Serial multiplex PCR suggests viruses and select bacteria (e.g., E. coli O157:H7) may be more likely causes of acute diarrhea than parasites or certain bacteria (especially less virulent E. coli pathotypes) in Guatemalan children. In addition, pathogens identified by multiplex PCR with high frequency at one time point may enable prediction of future pathogen acquisition in communities.

Disclosures. All authors: No reported disclosures.

298. Clinical Features of PCR Confirmed Human Ehrlichiosis and Anaplasmosis in an Endemic Area of the Northeast United States
Zachary Fleischner, MD;1 Teresa Koo, MD;2 Mehtap Haktanir Abdul, MD;3 and Luis A. Marcos, MD, MPH;2 1Internal Medicine, Stony Brook University Hospital, Stony Brook, New York; 2Infectious Diseases, Stony Brook University Hospital, Stony Brook, New York; 3Department of Tropical Medicine, Ahmadu Bello University, Zaria, Nigeria; 4Department of Biomedical Chemistry, The University of Tokyo, Tokyo, Japan; 5Department of Biochemistry and Molecular Biology, University of Sussex, Sussex, United Kingdom

Session: 50. Global Infections
Thursday, October 5, 2017: 12:30 PM

Background. The clinical manifestations for Ehrlichiosis and Anaplasmosis, two tick-borne diseases, can be indistinguishable in endemic areas. The antibody-capture serological tests for these infections have low sensitivity in acute illness and the follow-up convaleseant titer needed to confirm the diagnosis are rarely checked in clinical practice. Now, blood PCR testing for Ehrlichia and Anaplasma is increasingly more available to aid in accurate diagnosis. The aim of this study was to characterize and compare the clinical features of Ehrlichiosis and Anaplasmosis by using PCR as the gold standard for case definition in an endemic area of the Northeast United States.

Methods. A retrospective chart review was performed in all patients with ICD-9 or ICD-10 diagnostic codes for Ehrlichiosis or Anaplasmosis between 2014 and 2016 at Southampton Hospital (a major community hospital for the rural east end of Suffolk County, Long Island, New York) and Stony Brook University Hospital (the only tertiary medical center in Suffolk County). Inclusion criteria consisted of a positive blood PCR for either Anaplasma phagocytophilum or Ehrlichia spp. (caiffensis, canis, muris-like, or ewingii). Demographics, clinical, and laboratory variables were collected and compared with distinguish characteristics of these two different infections. Cases with three or more previously defined markers of severe disease (acute kidney injury (AKI), leukopenia, thrombocytopenia, elevated transaminases) were defined as severe cases.