

were filtered at a False Discovery Rate (FDR) of < 5% and proteins were required to have two or more peptide forms observed to be considered. No rabies virus derived peptides were detected in any sample. In aggregate, the abundance of 180 proteins were statistically significant between patients and controls ($p < 0.05$) when corrected for multiple testing and 36 proteins were more than 2 fold increased in patients and 64 proteins were detected only in patients only. Some of the groups that these proteins were involved in innate and acquired immunity, complement, proteases, structural proteins, synaptic granules, energy metabolism, innate immunity and natriuresis.

CO.18

TH17 CELLS: COULD THEY BE THE LAST ATTEMPT OF THE HOST TO CLEAR THE RABIES VIRUS?

Fernandes ER¹, Guedes F¹, Martins JF², Pagliari C³, Duarte MIS³ – ¹Instituto Pasteur de São Paulo, ²Instituto de Infectologia Emílio Ribas – Departamento de Patologia, ³Faculdade de Medicina da Universidade de São Paulo – Departamento de Patologia

Introduction: following an antigenic stimulus *naive* CD4+ T lymphocytes become activated, expand and differentiate into T helper subtypes Th1 or Th2 lymphocytes. Recently, a new subtype named Th17 has been proposed. Similar to the other subtypes of immune response, Th17 cells require specific cytokines and transcription factors for their differentiation. TGF- β along with IL-6 are crucial cytokines in this process, while the IL-21 has a role in the amplification of the Th17 response and IL-23 is responsible for the maintenance of differentiated Th17 cells. Although the role of Th17 cells is not yet fully understood, data from the literature suggest that these cells have important role in host defense against microorganisms, in particular when the Th1 and Th2 type immunity is not efficient to clear the pathogen. **Aim:** to evaluate and quantify the cells expressing IL-6, IL-17 and TGF- β in specimens of central nervous system in human rabies cases transmitted by dogs. **Material and methods:** six fragments of central nervous system (cortex, hippocampus, basal ganglia, cerebellum, medulla oblongata and spinal cord) were selected from each specimen of the four human rabies cases transmitted by dogs. By immunohistochemical reaction with the use of Streptavidin-biotin-peroxidase method it was examined the expression of cytokines IL-6, IL-17 and TGF- β . All immunostained cells were quantified using a grid-scale in an area of 0.0625 mm² considering 40 fields in each fragment of the CNS (10 fields in meningeal and 30 fields in parenchyma). Results were expressed in number of cells per mm². **Results:** it was observed high expression of TGF- β (586.68 cells/mm²), followed by IL-6 (228.79 cells/mm²) mainly in the parenchymal region and the presence of cells expressing IL-17 primarily in meningeal (187.21 cells/mm²). **Discussion and conclusion:** considering that the cytokine microenvironment will direct the type of immune response against infection, if there is a predominance of cytokines such as IL-1 and IL-6, there is a proinflammatory profile, if there is an increased expression of TGF- β and IL-10, we can suggest an immunoregulatory profile; however, the combination of cytokines can generate other profiles of the immune response in an attempt to combat the infectious agent. The concomitant presence of cells expressing TGF- β , IL-6 and IL-17 suggest a Th17 pattern of immune response, which would be an attempt by the host to clear the rabies virus after the profiles of Th1 and Th2 immune response have failed viral elimination.

CO.19

ANIMAL MODELS AND BIOLOGICS EVALUATION: EXPERIMENTAL RABIES VIRUS INFECTION AND DOSE TITRATION OF CL184 MONOCLONAL ANTIBODY COMBINATION IN THE SYRIAN HAMSTER

Taylor ST¹, Ellison JA¹, Franka R¹, Marissen WE², Rupprecht C¹ – ¹Centers for Disease Control and Prevention, Atlanta, GA, USA – Division of High-Consequence Pathogens & Pathology, ²Cruce Holland BV, Leiden, The Netherlands

Rabies is an acute progressive encephalitis responsible for over 55,000 human fatalities each year. This zoonosis is preventable, if prompt medical intervention includes wound care and both active and passive immunization. Approximately 10 million people receive rabies post-exposure prophylaxis (PEP) annually. The World Health Organization recommends the administration of human and/or equine derived antirabies immune globulin (HRIG and ERIG) as well as cell culture vaccine for modern PEP in humans. However, in many developing regions where canine rabies is enzootic, alternative solutions for passive immunization are necessary due to the cost prohibitive, limited supply of HRIG and ERIG. Such disparities have prompted the development of anti-RABV monoclonal antibody (mAb) cocktails that can be produced on an industrial scale with consistent potency and decreased production costs in comparison to HRIG and ERIG. To assess the efficacy of a mAb combination in rabies PEP, we evaluated the use of CL184, a 1:1 protein mixture ratio of two human anti-RABV mAbs (CR57/CR4098) produced on the PER.C6[®] human cell line, in the Syrian hamster model. In separate experiments, female hamsters were divided into groups and inoculated on Day -1 into the gastrocnemius muscle with a lethal dose of a genetically distinct carnivore or bat RABV isolate (Asian dog or *Parastrellus hesperus*, respectively). On Day 0, HRIG at 20 IU/kg (n=21) or CL184 at 6 μ g/kg, 12 μ g/kg or 16 μ g/kg (n=21/group) was administered to groups at the site of inoculation. In each experiment, a control group (n=12) and a vaccine only group (n=21) received a placebo inoculation. On Days 0, 3, 7, 14, and 28, hamsters in experimental groups received a 50 μ l dose of commercially available RABV vaccine. High mortality was observed in both placebo and vaccine only groups by Day 40. Preliminary data from the Syrian hamster experiments demonstrate these animals are a suitable model and suggest that CL184 may be a non-inferior alternative for HRIG in rabies PEP scenarios.

CO.20

ANALYSIS OF RABIES VIRUS GLYCOPROTEIN SEQUENCES IN RELATION TO THE PROPOSED USE OF MONOCLONAL ANTIBODIES FOR POST-EXPOSURE PROPHYLAXIS

Kuzmina N¹, Ellison J¹, Orciari L¹, Marissen W², Kuzmin I¹, Rupprecht C¹ – ¹CDC, ²Cruce Holland

The demand for rabies immune globulin (RIG) for post-exposure prophylaxis (PEP) is significant. Unfortunately, the cost of RIG is prohibitive for many patients in developing countries. Several monoclonal antibodies (MAbs) which neutralize rabies virus (RABV) have been proposed as a replacement for conventional RIG due to the ability of their large-scale production at a reduced cost. In the present study, we generated 487 RABV glycoprotein (G) sequences from a variety of viral lineages, and supplemented the dataset with 154 complete and 115 partial G sequences available in GenBank. The objective was to evaluate variability of known MAb-binding epitopes on the G, which may preclude virus neutralization. The analysis demonstrated that binding site of MAb CR57 (amino acids 226-231 of the G ectodomain) is very conservative.