Role of tissue factor in a mouse model of thrombotic microangiopathy induced by antiphospholipid (aPL) antibodies. Surya V. Seshan¹, Claus Franzke², Patricia Redecha², Marc Monestier³, Nigel Mackman⁴ and Guillermina Girardi². ¹ Department of Pathology, Weill Cornell Medical College, New York, NY 10021, USA. ² Hospital for Special Surgery – Department of Medicine, Weill Cornell Medical College, New York, NY 10021, USA. ³ Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA 19140, USA. ⁴ Department of Medicine, University of North Carolina, Chapel Hill, NC, USA.

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SUMMARY
We developed a new animal model of TMA induced by antiphospholipid (aPL) antibodies, an invaluable tool to understand the molecular and cellular events that determine glomerular endothelial injury. Using this model we found more than one mechanism/signaling pathway is involved in glomerular injury induced by aPL-
antibodies. Both complement dependent and complement-independent pathways were identified that lead to glomerular endothelial cell damage and renal function impairment. We also found that C5a-C5aR interaction is a crucial step for the activation of the coagulation cascade and glomerular injury induced by complement activating antibodies. In addition, our studies demonstrated complement independent mechanisms in which reactivity with β2 glycoprotein I (β2GPI) plays an important role in aPL-induced glomerular damage and renal failure. Independently of the mechanism responsible for aPL-induced TMA, mice that express low levels of tissue factor (TF) were protected from glomerular injury. That genetic reduction of TF prevents TMA induced by different aPL antibodies indicates that TF is a common mediator of glomerular damage and a possible target for selective pharmacological intervention. Treatment with pravastatin, that downregulates glomerular TF synthesis prevents aPL-induced TMA in this mouse model, thus emphasizing that targeting TF might be a good therapeutic intervention in patients with TMA.