Alexandra R Lucas et al., Med Chem 2014, 4:12
http://dx.doi.org/10.4172/2161-0444.S1.013

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
December 08-10, 2014 DoubleTree by Hilton Hotel San Francisco Airport, USA

Serine protease inhibitor (serpin) reactive site loop peptides as therapy for acute viral sepsis with inflammatory vascuits and hemorrhage

Alexandra R Lucas, Donghang Zheng, Sriram Ambadapadi and **Ganesh Munaswamy- Ramanujam**
University of Florida, USA

Background: Serine protease inhibitors (Serpins) have critical regulatory roles in coagulation and inflammation, representing a large percentage of circulating blood proteins. Serpins regulate normal homeostasis in vascular disease and sepsis with disseminated intravascular coagulation. Modification of serpin activity is used for treating clinical disorders, i.e. heparin decreases clotting through activation of anti-thrombin (SERPINC1). Prior studies report the use of N terminal serpin peptides for treatment in sepsis and HIV. Myxomavirus Serp-1 significantly reduced vascular disease after balloon angioplasty or after transplants in rodent models. Serp-1 further improved mortality in a lethal Mouse gamma herpes virus (MHV68) infection in interferon gamma receptor (IFNγ) knockout mice and mouse adapted Zaire Ebola infection with marked reduction in vasculitis, pulmonary hemorrhage, and congestion.

Methods: We have assessed the capacity of Reactive Site Loop (RSL) peptides derived as projected metabolites, 4 Serp-1 RSL peptides and 4 neuroserpin (NSP) peptides, to reduce vascular inflammation. Forty mice had aortic allograft transplant with a single IV injection of each individual peptide. Twenty four IFN KO mice had MHV68 infection and were treated for 30 days with either saline, S-2 ($_{360}$ISRMAV$_{365}$) or S-7 ($_{305}$GTTASSDTAITLIPR$_{319}$) peptides.

Results: RSL peptides with R or RN sequences, but not RM, and with 0-+1 charge (S-1, S-3, S-7 and S-8), significantly reduced vascular inflammatory cell invasion and plaque growth after aortic allograft transplant in mice (5-6 transplants per peptide tested) ($P<0.01$). Hydrophobic and -4 charge caused increased thrombosis. One S-7 peptide significantly improved survival in a MHV68 infection lethal vascultic model (150 days survival; $P<0.02$), while an inactive S-2 peptide had no effect (P=NS; 40 days).

Conclusions: Serpin RSL peptides expand regulatory function. Viral and mammalian serpin peptides with R or RN sequences and 0-+1 charge reduce aortic allograft vasculopathy and improve survival in lethal MHV68 mouse vasculitis models.

alexandra.lucas@medicine.ufl.edu