

Active immunization with IFN α Kinoid prevents the development of Systemic Lupus Erythematosus in an IFN α -induced murine model of lupus disease

Sophie Koutouzov¹, Géraldine Grouard-Vogel², Patrick Larcier², H el ene Le Buanec, Alexis Mathian³
Dominique Emilie¹, Daniel Zagury²

¹INSERM U 764 and Universit e Paris XI, 92140 Clamart, France

²NEOVACS SA, 75014 Paris, France

³INSERM U543, H opital Piti e-Salp etri re, 75013 Paris, France

Purpose: Recent studies have provided evidence that IFN α plays a critical role in the pathogenesis of systemic lupus erythematosus (SLE). We recently showed that prolonged expression of IFN α *in vivo* - achieved by adenovirus (Adv) delivery- rapidly induces a full-blown lupus with development of severe glomerulonephritis in young, pre-autoimmune, NZB/NZW F1 mice. Neovacs developed a vaccine IFN α Kinoid[®] - chemical conjugation of murine IFN α and Keyhole limpet hemocyanin (KLH) - that elicits high titers of neutralizing anti-IFN α antibodies *in vivo*. The goal of this work was to assess the ability of IFN α Kinoid to prevent IFN α -induced lupus in NZB/NZW F1 mice.

Methods: Female NZB/NZW F1 mice were immunized 4 times intramuscularly with either murine IFN α Kinoid, KLH, or PBS, in the presence of ISA51 adjuvant, prior to injection of mIFN α adenovirus. Mice were followed for proteinuria and survival at least twice weekly from Day 15 to Day 123 after IFN α Adv treatment. Blood samples were collected prior to, and after IFN α Adv challenge to assess anti-IFN α antibody titers and neutralizing capacity. Histopathology examination of the kidney was performed at sacrifice (Day 123).

Results: Immunization with IFN α Kinoid elicited high titres of neutralizing anti-mIFN α antibodies. Using the conventional antiviral cytopathic assay, sera inhibited 50% of mIFN α biological activity in the dilution range of 1/1,800. No toxicity related to IFN α Kinoid immunization was observed during the study period. IFN α Kinoid immunized animals showed striking amelioration of IFN α -induced lupus. At the end of the study (i.e., Day 123 following initiation of IFN α Adv treatment), IFN α Kinoid-treated mice showed lower levels of proteinuria ($p < 0.0001$ *vs* IFN α Adv control group, $p < 0.008$ *vs* KLH group). 50% of the kinoid immunized mice were still alive compared with only 8% of the animals in the KLH group ($p < 0.03$), whereas all animals in the control IFN α Adv group had died by Day 85 ($p < 0.001$). Clinical efficacy of the IFN α Kinoid vaccine was confirmed by kidney histopathology examination of the surviving mice: 50% showed only slight glomerular deposits while the remaining 50% showed no autoimmune changes indicating amelioration of the pathological process with IFN α Kinoid immunization.

Conclusions: This study shows that active immunization with IFN α Kinoid is safe and elicits neutralizing polyclonal anti-IFN α antibodies that prevent the development of IFN α inducible lupus. It may thus represent a novel therapeutic strategy for the treatment of lupus.