The type I interferon (IFN-I) family of cytokines are well known for their antiproliferative and antiviral properties and utilized as therapies in some oncologic and infectious disease indications. Despite these beneficial properties, IFN-I is thought to be a central mediator of pathogenesis in many patients with Systemic Lupus Erythematosus (SLE). IFN-I exhibits profound immunomodulatory effects on both innate and adaptive responses of the immune system and chronic overexpression of this pathway may promote a break in peripheral tolerance in susceptible individuals. SLE is an autoimmune disease that can affect multiple organ systems and despite several interventional clinical trials only one drug has been approved by the FDA in over 50 years arguably due to the heterogeneous nature of this disease. During my talk I will discuss data supporting a causal role of IFN-I in SLE and review emerging therapeutic approaches to neutralize these molecules. I will further discuss methodologies to enable precision medicine in SLE in conjunction with inhibitors of this pathway.