We use molecular biology, immunology, virology and genetics to tackle intractable immunodeficiencies, be they the bare lymphocyte syndrome or AIDS. These approaches also find resonance in autoimmunity and cancer. In the process, these diseases and their pathogens educate us about human biology and evolution. Indeed, new paradigms in genomic stability, transcription, transport and intracellular traffic have been forthcoming from these studies. Our ultimate goals are to use this knowledge of basic molecular mechanisms to cure human diseases.