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The Instrument Pilot Handbook Courtney L. Flatau, Jerome F. Mitchell, 1980 **Tailoring NK Cell Receptor-Ligand Interactions: an Art in Evolution, 2nd Edition** Ulrike Koehl, Antoine Toubert, Gianfranco Pittari, 2018-11-13 Recognition and killing of aberrant infected or tumor targets by Natural Killer NK cells is mediated by positive signals transduced by activating receptors upon engagement of ligands on target surface These stimulatory pathways are counterbalanced by inhibitory receptors that raise NK cell activation threshold through negative antagonist signals While regulatory effects are necessary for physiologic control of autoimmune aggression they may restrain the ability of NK cells to activate against disease Overcoming this barrier to immune surveillance multiple approaches to enhance NK mediated responses are being investigated since two decades Propelled by considerable advances in the understanding of NK cell biology these studies are critical for effective translation of NK based immunotherapy principles into the clinic In humans dominant inhibitory signals are transduced by Killer Immunoglobulin Like Receptors KIR recognizing cognate HLA class I on target cells Conversely KIR recognition of missing self HLA due to HLA loss or HLA KIR mismatch triggers NK mediated tumor rejection Initially observed in murine transplant models these antitumor effects were later found to have important implications for the clinical outcome of haplotype mismatched stemcell transplantation Here donor NK subsets protect against acute myeloid leukemia AML relapse through missing self recognition of donor HLA C allele groups C1 or C2 and or Bw4 epitope These studies were subsequently extended by trials investigating the antileukemia effects of adoptively transferred haplotype mismatched NK cells in non transplant settings Other mechanisms have been found to induce clinically relevant NK cell alloreactivity in transplantation e g post reconstitution functional reversal of anergic NK cells More recently activating KIR came into the spotlight for their potential ability to directly activate donor NK cells through in vivo recognition of HLA or other ligands Novel therapeutic monoclonal antibodies mAb may optimize NK mediated effects Examples include obinutuzumab GA101 a glyco engineered anti CD20 mAb with increased affinity for the Fc RIIIA receptor enhancing antibody dependent cellular cytotoxicity lirilumab IPH2102 a first in class NK specific checkpoint inhibitor blocking the interaction between the major

KIR and cognate HLA C antigens and elotuzumab HuLuc63 a humanized monoclonal antibody specific for SLAMF7 whose anti myeloma therapeutic effects are partly due to direct activation of SLAMF7 expressing NK cells In addition to conventional antibodies NK cell targeted bispecific BiKEs and trispecific TriKEs killer engagers have also been developed These proteins elicit potent effector functions by binding target ligands e g CD19 CD22 CD30 CD133 HLA class II EGFR on one arm and NK receptors on the other An additional innovative approach to direct NK cell activity is genetic reprogramming with chimeric antigen receptors CAR To date primary NK cells and the NK92 cell line have been engineered with CAR specific for antigens expressed on multiple tumors Encouraging preclinical results warrant further development of this approach This Research Topic welcomes contributions addressing mechanisms of NK mediated activation in response to disease as well as past and contemporary strategies to enhance NK mediated reactivity through control of the interactions between NK receptors and their ligands

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