SUMMARY OF THE DISCLOSURE

The present disclosure is directed to methods and compositions that modulate the multiple effects of hIL-12 binding so that desired therapeutic signaling occurs, particularly in a desired cellular or tissue subtype, while minimizing undesired activity and/or intracellular signaling in other cellular or tissue subtypes. In some embodiments, the present disclosure provides heterodimeric hIL12Fc muteins having an extended duration of action *in vivo* in a mammalian subject.

In one aspect, provided herein is the use of a pharmaceutically acceptable formulation comprising as an active ingredient a heterodimeric hIL12Fc mutein in the manufacture of medicament for treating a mammal suffering from a neoplastic disease, wherein the heterodimeric hIL12Fc mutein comprises a first polypeptide having the sequence of any one of SEQ ID NOs: 80, 83, 85, 86, 88, 90, 92, 121, 129, 132, 135, 138, 141, 144, 147, 150, and 153; and

a second polypeptide having the sequence of any one of SEQ ID NOs: 81, 82, 84, 87, 89, 91, 93, and 124; and

wherein the mammal is to be contacted with the pharmaceutically acceptable formulation.

In some embodiments the present disclosure provides heterodimeric hIL12Fc muteins comprising a heterodimeric protein comprising first and second fusion proteins, the first fusion protein comprising a human p35 polypeptide having 90% or greater, alternatively 91% or greater, alternatively 92% or greater, alternatively 93% or greater, alternatively 94% or greater alternatively 95% or greater, alternatively 96% or greater, alternatively 97% or greater, alternatively 98% or greater, alternatively 99% or greater, alternatively 100% sequence identity to the SEQ ID NO: 2 (wild type mature hP35), a first upper hinge region of a human immunoglobulin molecule, and a first Fc domain of a human immunoglobulin molecule ("hP35Fc") and the second fusion protein comprising a human p40 mutein ("hP40M") polypeptide having 90% or greater, alternatively 91% or greater, alternatively 92% or greater, alternatively 93% or greater, alternatively 94% or greater alternatively 95% or greater, alternatively 96% or greater, alternatively 97% or greater, alternatively 98% or greater, alternatively 99% or greater, sequence identity to the SEQ ID NO: 4 (wild type mature hP40), the human p40 mutein comprising one or more amino acid substitutions at one or more positions selected from the group consisting of W37, P39, D40, A41, K80, E81, F82,

K106, E108, D115, H216, K217, L218, and K219 (numbered in accordance with SEQ ID NO: 3), a second upper hinge region of a human immunoglobulin molecule, and a second Fc domain of a human immunoglobulin molecule ("hP40MFc") wherein the first and second Fc domains are modified to promote heterodimerization.

In some embodiments the present disclosure provides heterodimeric hIL12Fc muteins comprising a human p40 mutein ("hP40M") polypeptide comprising one or more amino acid substitutions at one or more positions selected from the group consisting of W37, P39, D40, A41, K80, E81, F82, K106, E108, D115, H216, K217, L218, K219 and K282 (numbered in accordance with SEQ ID NO: 3). In some embodiments the present disclosure provides heterodimeric hIL12Fc muteins comprising a human p40 mutein ("hP40M")