

## WHAT IS CLAIMED IS:

1. An IL1RAP binding protein which competes for binding to human IL1RAP ~~proteins~~ with ~~an anti-any one of the~~ IL1RAP antibody~~s~~ having heavy and light chain variable regions comprising:

SEQ ID NOs:51 and 52,

~~respective heavy and light variable sequences of:~~ SEQ ID NOs: 2 and 7;

SEQ ID NOs:12 and 17;

SEQ ID NOs:22 and 27;

SEQ ID NOs:32 and 37;

SEQ ID NOs:42 and 47; ~~51 and 52;~~ or

SEQ ID NOs:63 and 68, respectively.

2. ~~An~~The IL1RAP binding protein of claim 1, further having the ability to directly kill IL1RAP expressing tumor cells via ADCC and/or CDC, inhibit the growth promoting effect of IL-1 on cancer cells, and/or promote an enhanced tumor-directed immune response by inhibiting the ~~MDSC-~~ promoting effects of IL-1 on myeloid-derived suppressor cells (MDSCs).

3. An IL1RAP binding protein which binds to ~~human IL1RAP at~~ one or both of amino acids at Gln1865 and Asn1866 of human IL1RAP (numbering according to ~~of~~ SEQ ID NO: 59) as determined by X-ray crystallography.

4. An IL1RAP binding protein, wherein the IL1RAP binding protein is a monoclonal antibody having comprising ~~one or more of:~~

CDRH1 as set forth in SEQ ID NO:33;

CDRH2 as set forth in SEQ ID NO:34;

CDRH3 as set forth in SEQ ID NO:35;

CDRL1 as set forth in SEQ ID NO:38;

CDRL2 as set forth in SEQ ID NO:39 and ~~or~~

CDRL3 as set forth in SEQ ID NO:40, or

a direct equivalent of each CDR wherein a direct equivalent has no more than two amino acid substitutions in said CDR.

5. The IL1RAP binding protein of claim 4, wherein said IL1RAP binding protein is a monoclonal antibody comprising

heavy chain CDR1-3 comprising SEQ ID NOs:33, 34, and 35, respectively, and  
light chain CDR1-3 comprising SEQ ID NOs:38, 39, and 40, respectively.

~~56. An~~ The IL1RAP binding protein of claim 5~~which binds to human IL1RAP protein,~~  
wherein said ~~IL1RAP binding protein monoclonal antibody~~ is a humanized antibody that  
comprises

a heavy chain variable ( $V_H$ ) domain comprising an amino acid sequence at least 85, 90,  
95, 98, or 99% identical to ~~the amino acid sequence set forth in~~ SEQ ID NO:51 and/or

a light chain variable ( $V_L$ ) domain comprising an amino acid sequence at least 85, 90,  
95, 98, or 99% identical to ~~the amino acid sequence set forth in~~ SEQ ID NO:52.

~~6. An humanized monoclonal antibodies having heavy chain CDRs having the amino acid~~  
~~sequences set forth in SEQ ID NO:33; SEQ ID NO:34; and SEQ ID NO:35, and light chain~~  
~~CDRs having the amino acid sequences set forth in SEQ ID NO:38; SEQ ID NO:39; and SEQ~~  
~~ID NO:40.~~

7. The IL1RAP binding protein of claim 6, wherein the ~~An humanized monoclonal~~  
~~antibodies having a~~  $V_H$  domain comprising ~~an amino acid sequence set forth in~~ SEQ ID  
NO:51; and ~~a the~~  $V_L$  domain comprising ~~an amino acid sequence set forth in~~ SEQ ID NO:52.

8. The IL1RAP binding protein of any one of claims 1-7, wherein the IL1RAP binding  
protein is a monoclonal antibody of human ~~monoclonal antibody~~  $IgG_1$  subtype.

~~89. The IL1RAP binding protein of claim 8, wherein the~~ ~~An humanized monoclonal~~  
~~antibodies antibody comprises a~~ having full length heavy chain ~~comprising an~~ amino acid  
sequence set forth in SEQ ID NO:55; and a full length light chain ~~comprising an~~ amino acid  
sequence set forth in SEQ ID NO:56.

10. The ILRAP binding protein of claim 8, wherein the monoclonal antibody comprises

a heavy chain encoded by a nucleotide sequence at least 85, 90, 95, 98, or 99% identical to SEQ ID NO:57 and

a light chain encoded by a nucleotide sequence at least 85, 90, 95, 98, or 99% identical to SEQ ID NO:58.

911. The IL1RAP binding proteinantibody of claim 8 or claim 7any one of the preceding claims, wherein the IL1RAP binding proteinwhich is afucosylated.

12. The IL1RAP binding protein of claim 11, wherein the IL1RAP binding protein is expressed from ~~POTELLIGENT~~an  $\alpha$ -1,6-fucosyltransferase (FUT8)-knockout CHO cell line, optionally a POTELLIGENT® cell line.

130. A pharmaceutical composition comprising ~~any one ofthe~~ IL1RAP ~~antigen-binding protein or antibodies~~of any one of claims 1-~~9~~12.

141. Use of the IL1RAP binding protein of any one of claims 1-12, for the manufacture of a medicament for ~~A method of~~treating acute myeloid leukemia (AML), chronic myeloid leukemia (CML), ~~and/or~~ myelodysplastic syndrome (MDS); ~~and/or a~~ solid tumor cancers selected from ~~the~~ group consisting of prostate, breast, lung, colon, melanoma, bladder, brain, cervical, ~~oesoph~~ageal, gastric, head/neck, kidney, liver, ovarian, lymphoma, pancreatic, and sarcomas in a human~~comprising administering a therapeutically effective amount of IL1RAP antigen-binding protein or antibody of any one of claims 1-10.~~

~~12~~15. One or more Ppolynucleotides encoding ~~the~~ IL1RAP binding proteins ~~of any one of claims 1-12~~having one or more of: CDRH1 as set forth in SEQ ID NO:33; CDRH2 as set forth in SEQ ID NO:34; CDRH3 as set forth in SEQ ID NO:35; CDRL1 as set forth in SEQ ID NO:38; CDRL2 as set forth in SEQ ID NO:39 and/or CDRL3 as set forth in SEQ ID NO:40 or a direct equivalent of each CDR wherein a direct equivalent has no more than two amino acid substitutions in said CDR.

13. ~~Polynucleotides encoding IL1RAP binding proteins which specifically bind to human IL1RAP protein, and wherein said ILrap binding protein comprises a V<sub>H</sub> domain comprising an amino acid sequence at least 85, 90, 95, 98, or 99% identical to the amino acid sequence set~~

forth in SEQ ID NO:51 and/or a V<sub>L</sub>-domain comprising an amino acid sequence at least 85, 90, 95, 98, or 99% identical to the amino acid sequence set forth in SEQ ID NO:52.

14. — ~~Polynucleotides encoding humanized monoclonal antibodies comprising heavy chain CDRs having the amino acid sequences set forth in SEQ ID NO:33; SEQ ID NO:34; and SEQ ID NO:35 and light chain CDRs having the amino acid sequences set forth in SEQ ID NO:38; SEQ ID NO:39; and SEQ ID NO:40.~~

15. — ~~Polynucleotides encoding humanized monoclonal antibodies comprising a V<sub>H</sub>-domain having an amino acid sequence set forth in SEQ ID NO:51; and a V<sub>L</sub>-domain having an amino acid sequence set forth in SEQ ID NO:52.~~

16. — ~~Polynucleotides encoding humanized monoclonal antibodies comprising full length heavy chain having an amino acid sequence as set forth in SEQ ID NO:55; and full length light chain having an amino acid sequence set forth in SEQ ID NO:56.~~

~~1716.~~ The P~~polynucleotide(s) of claim 15, comprising polynucleotides~~ having ~~identity~~ at least 85, 90, 95, 98, or 99% identity to ~~polynucleotide sequence of~~ SEQ ID NO:53, 54, 57, 58, or 72.

18. The A-P~~polynucleotide(s)~~ of claim ~~167,~~ comprising ~~a polynucleotide sequence of~~ SEQ ID NO:53, 54, 55, 56 or 72.

19. One or more expression A-vectors ~~and host cell~~ containing ~~any of~~ the polynucleotide(s) of any one of ~~claims 15-18~~17 or 18.

20. A host cell comprising the one or more expression vectors of claim 19.

21. A method of producing an IL1RAP binding protein, comprising  
culturing the host cell of claim 20 under conditions that allow expression of the IL1RAP  
binding protein, and  
isolating the IL1RAP binding protein from the cell culture.