

Selected amino acid variations in humanized VH frameworks

| Sequence | SEQ. ID NO. 1 |   |   |   |   |   |   |   |   |    | SEQ. ID NO. 2 |    |    |    |    |    |    |    |    |    |
|----------|---------------|---|---|---|---|---|---|---|---|----|---------------|----|----|----|----|----|----|----|----|----|
|          | 1             | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11            | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Human    | L             | F | L | L | L | L | L | L | L | L  | L             | L  | L  | L  | L  | L  | L  | L  | L  | L  |
| Human    | L             | F | L | L | L | L | L | L | L | L  | L             | L  | L  | L  | L  | L  | L  | L  | L  | L  |

| Sequence | SEQ. ID NO. 3 |   |   |   |   |   |   |   |   |    | SEQ. ID NO. 4 |    |    |    |    |    |    |    |    |    |
|----------|---------------|---|---|---|---|---|---|---|---|----|---------------|----|----|----|----|----|----|----|----|----|
|          | 1             | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11            | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Human    | L             | F | L | L | L | L | L | L | L | L  | L             | L  | L  | L  | L  | L  | L  | L  | L  | L  |
| Human    | L             | F | L | L | L | L | L | L | L | L  | L             | L  | L  | L  | L  | L  | L  | L  | L  | L  |

Fig.1

## Selected amino acid variations in humanized VL frameworks

|          | FR1 |   |   |   | FR2 |   |   |   | FR3 |   |    |    | FR4 |    |    |    |
|----------|-----|---|---|---|-----|---|---|---|-----|---|----|----|-----|----|----|----|
|          | FR1 |   |   |   | FR2 |   |   |   | FR3 |   |    |    | FR4 |    |    |    |
| 00000000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00000111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00001111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00010111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00011111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00100111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00101111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00110111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 00111111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01000111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01001111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01010111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01011111 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100000 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100001 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100010 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100011 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100100 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100101 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100110 | 0   | 1 | 2 | 3 | 4   | 5 | 6 | 7 | 8   | 9 | 10 | 11 | 12  | 13 | 14 | 15 |
| 01100111 | 0   | 1 |   |   |     |   |   |   |     |   |    |    |     |    |    |    |

Fig. 2

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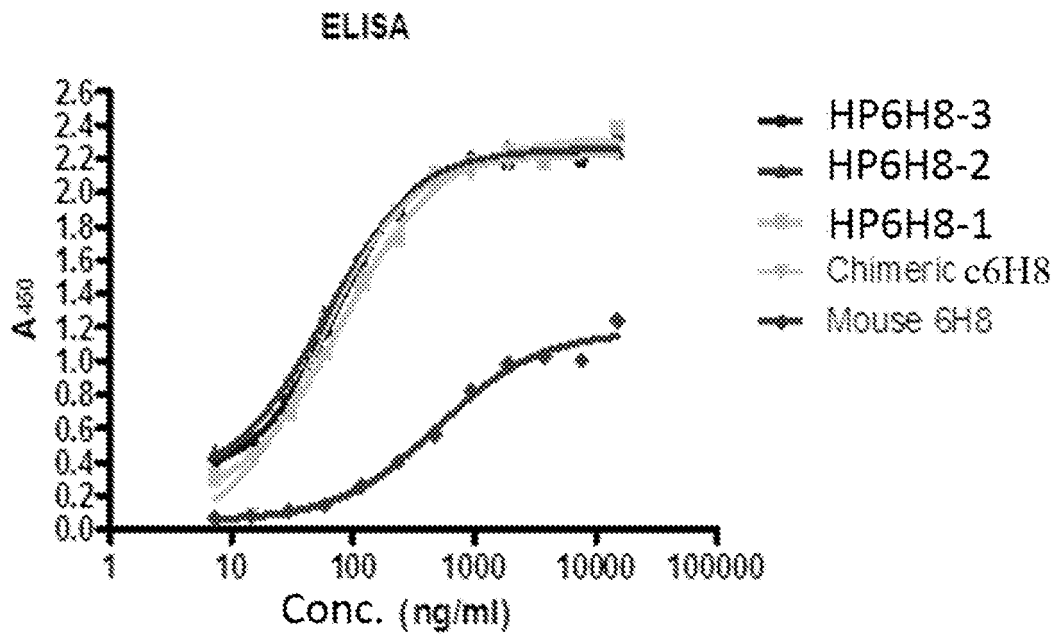


Fig. 3

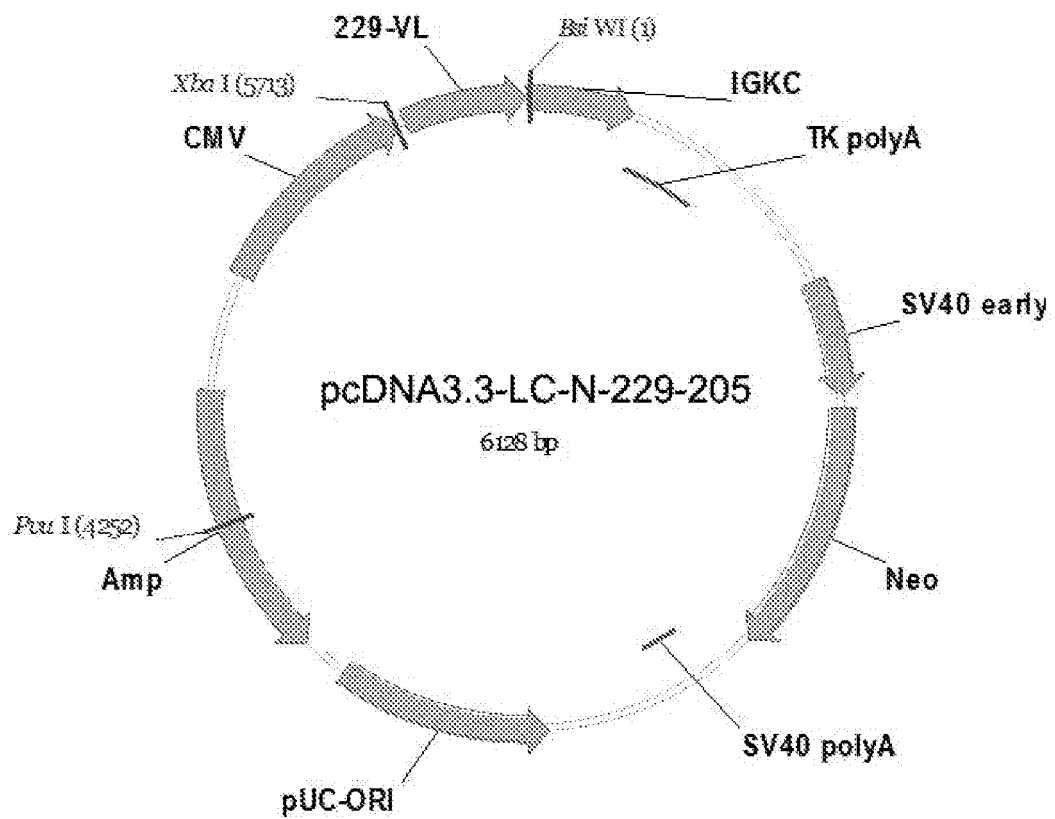


Fig. 4

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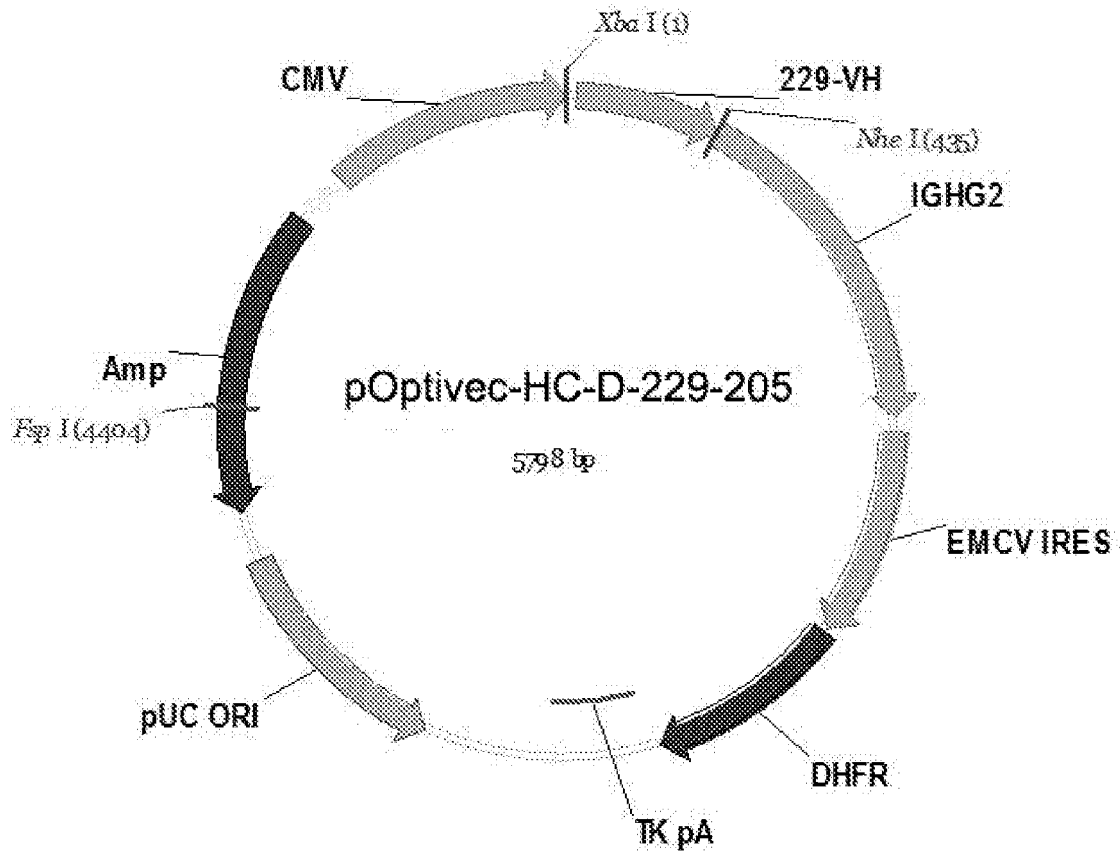


Fig. 5

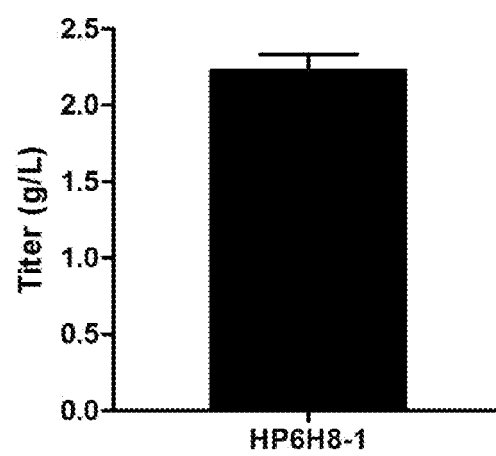


Fig. 6

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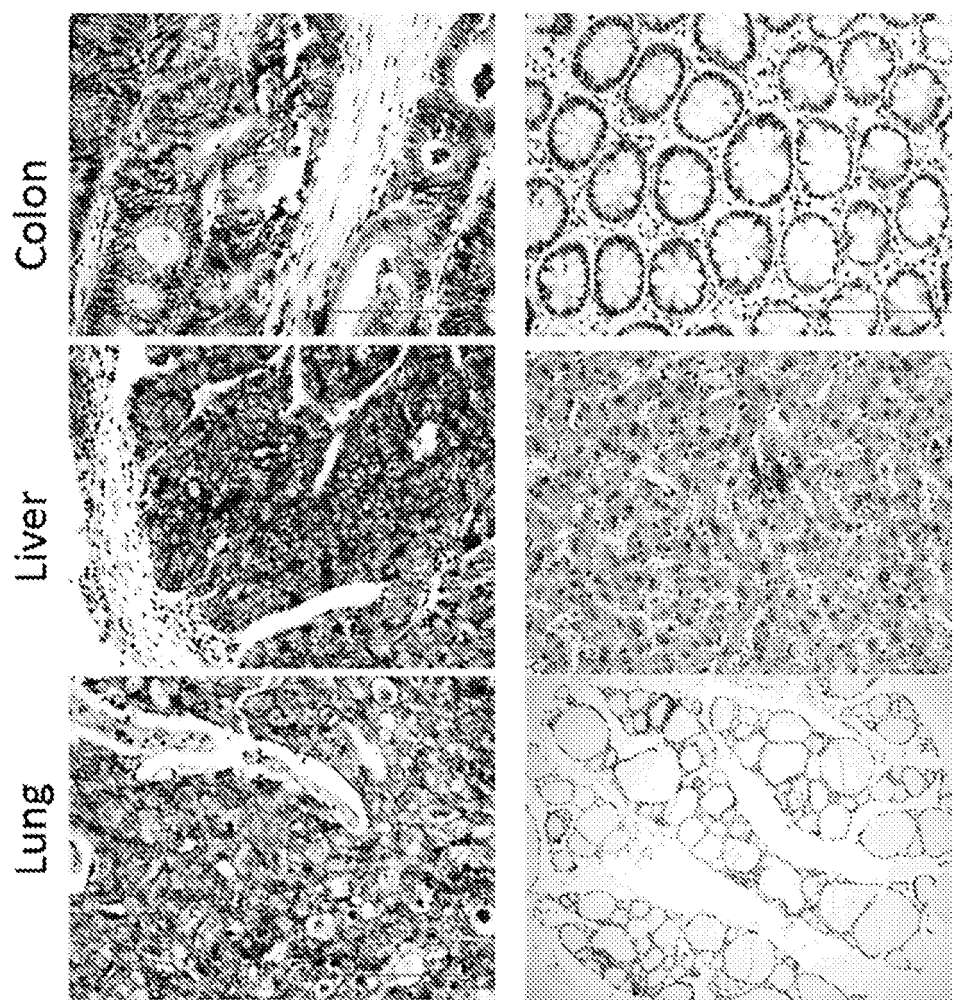


Fig. 7

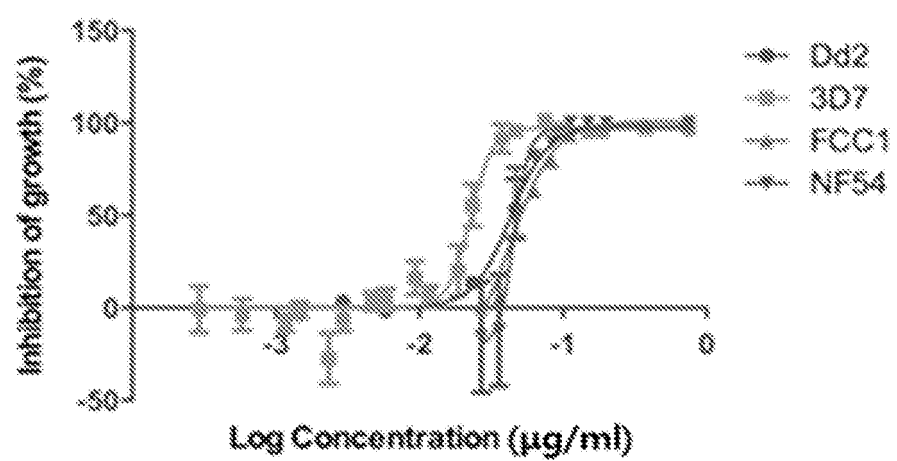


Fig. 8