[006] Another of these pathways is the WNT pathway, which is implicated in a variety of developmental and regenerative processes. Allen at 4340. The pathway is complex, however, and much about it and about how its components affect bone remains unclear. For example, it has been suggested that LRP-5, mutations of which are associated with increased bone mass in humans, and β-catenin, through which canonical WNT signaling occurs, "may not be linked directly via WNT signaling to the control of bone mass." *Id.*

[007] Recent analysis of gene expression data has led to the identification of new targets of WNT signaling. *See, e.g.,* Torisu, Y., et al., Cancer Sci., 99(6):1139-1146, 1143 (2008). One such target is Notum Pectinacetylesterase, also known as NOTUM and LOC174111.

3. SUMMARY

[007a] In one aspect, there is provided use of a monoclonal antibody that binds human notum pectinacetylesterase (NOTUM) and reduces human NOTUM activity in a trisodium 8-octanoyloxypyrene-1,3,6-trisulfonate (OPTS) assay *in vitro*, in the manufacture of a medicament for treating or preventing a disease or disorder characterized by bone loss in a patient.

[008] In some embodiments, a monoclonal antibody that binds human notum pectinacetylesterase (NOTUM) and neutralizes at least one activity of NOTUM is provided. In some embodiments, the antibody binds to a NOTUM selected from mouse NOTUM, guinea pig NOTUM, cynomolgus monkey NOTUM, and rhesus monkey NOTUM. In some embodiments, the antibody has at least one activity selected from reducing NOTUM activity in a trisodium 8-octanoyloxypyrene-1,3,6-trisulfonate (OPTS) assay *in vitro*, and reducing NOTUM activity in a Wnt signaling assay *in vitro*. In some embodiments, the antibody has at least one activity selected from increasing serum PINP levels *in vivo*, increasing bone mineral density *in vivo*, increasing midshaft femur cortical thickness *in vivo*, increasing midshaft femur bone area *in vivo*, increasing midshaft humerus cortical thickness *in vivo*, increasing endocortical bone formation *in vivo*, increasing the proportion of cortical bone volume in the LV5 vertebral body *in vivo*, and increasing the proportion of femoral neck bone volume to femoral neck total volume *in vivo*. In some embodiments, an antibody that binds NOTUM binds to a polypeptide having the amino acid sequence of SEQ ID NO: 1 with K_D of less than 50 nM, less than 20 nM, or less than 10 nM.

[009] In some embodiments, the antibody has at least one binding characteristic selected from: a) binds to a polypeptide having the amino acid sequence of SEQ ID NO: 83 with a binding affinity that is at least 5-fold stronger than the binding affinity of the antibody for a polypeptide having the amino acid sequence of SEQ ID NO: 84; b) binds to a polypeptide having the amino acid sequence of SEQ ID NO: 85 with a binding affinity that is at least 5-fold stronger than the binding affinity of the antibody for a polypeptide having the amino acid sequence of SEQ ID NO: 86; c) binds to a polypeptide having the amino acid sequence of SEQ ID NO: 1 with a binding affinity that is at least 5-fold stronger than the binding affinity of the antibody for a polypeptide having the amino acid sequence of SEQ ID NO: 94; d) binds to a polypeptide having the amino acid sequence of SEQ ID NO: 1 with a binding affinity that is at least 5-fold stronger than the binding affinity of the antibody for a polypeptide having the amino acid sequence of SEQ ID NO: 99; e) binds to a polypeptide

chain variable region comprises the amino acid sequence of SEQ ID NO: 79 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 81; or j) the heavy chain comprises the amino acid sequence of SEQ ID NO: 80 and the light chain comprises the amino acid sequence of SEQ ID NO: 82; or k) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 39 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 40; or l) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 67 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 69; or m) the heavy chain comprises the amino acid sequence of SEQ ID NO: 68 and the light chain comprises the amino acid sequence of SEQ ID NO: 70; or n) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 47 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 48; or o) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 55 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 56; or p) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 63 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 65; or q) the heavy chain comprises the amino acid sequence of SEQ ID NO: 64 and the light chain comprises the amino acid sequence of SEQ ID NO: 66.

[014a] In one aspect, there is provided a monoclonal antibody that binds human notum pectinacetylesterase (NOTUM) and that neutralizes at least one activity of NOTUM, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein:

a) the heavy chain variable region comprises a CDR1 having the amino acid sequence of SEQ ID NO: 41, a CDR2 having the amino acid sequence of SEQ ID NO: 42, and a CDR3 having the amino acid sequence of SEQ ID NO: 43, and wherein the light chain variable region comprises a CDR1 having the amino acid sequence of SEQ ID NO: 44, a CDR2 having the amino acid sequence of SEQ ID NO: 45, and a CDR3 having the amino acid sequence of SEQ ID NO: 46; or

b) the heavy chain variable region comprises a CDR1 having the amino acid sequence of SEQ ID NO: 57, a CDR2 having the amino acid sequence of SEQ ID NO: 58, and a CDR3 having the amino acid sequence of SEQ ID NO: 59, and wherein the light chain variable region comprises a CDR1 having the amino acid sequence of SEQ ID NO: 60, a CDR2 having the amino acid sequence of SEQ ID NO: 61, and a CDR3 having the amino acid sequence of SEQ ID NO: 62.

[015] In one aspect, there is provided a nucleic acid molecule comprising first and second polynucleotide sequences encoding the respective heavy and light chains of the antibody as described herein. In some embodiments, a nucleic acid molecule is provided that comprises a polynucleotide sequence that encodes a heavy chain or a light chain of an antibody that binds NOTUM and neutralizes at least one activity of NOTUM. In some embodiments, the nucleic acid molecule comprises a first polynucleotide sequence that encodes the heavy chain, and a second polynucleotide sequence that encodes the light chain. In some embodiments, the nucleic acid molecule is a vector. In one aspect, there is provided a host cell comprising the nucleic acid molecule as described herein. In some embodiments, a host cell comprising a nucleic acid molecule that comprises a polynucleotide sequence that encodes a heavy chain or a light chain of an antibody that binds NOTUM and neutralizes at least one activity of NOTUM is provided. In some embodiments, a host cell comprising a nucleic acid molecule that comprises a first polynucleotide sequence that encodes a heavy chain, and a second polynucleotide sequence that encodes a light chain, is provided. In some embodiments, a host cell comprises a first nucleic acid molecule comprising a polynucleotide sequence that encodes a heavy chain, and a second nucleic acid molecule comprising a polynucleotide sequence that encodes a light chain. In one aspect, there is provided a method of producing an antibody as described herein comprising incubating the host cell as described herein under conditions sufficient to express the antibody. In some embodiments, a method of producing an antibody that binds to NOTUM and neutralizes at least one activity of NOTUM is provided, comprising incubating a host cell under conditions sufficient to express the antibody.

[016] In one aspect, there is provided a pharmaceutical composition comprising the antibody as described herein. In some embodiments, a pharmaceutical composition comprising an antibody that binds NOTUM and neutralizes at least one activity of NOTUM is provided. In some embodiments, a method of stimulating endocortical bone formation in a patient, comprising administering an effective amount of the pharmaceutical composition is provided. In some embodiments, a method