TPH1 inhibition for a non-cytotoxic leukemia treatment

Technology #cu12100

Leukemia is a rapidly proliferative cancer of the bone marrow, commonly found in children, and is difficult to cure. Current treatment protocols rely on multiple rounds of chemotherapy, bone marrow transplantation, and experimental drugs whose efficacy varies depending upon the type of leukemia involved. This technology targets serotonin production in the bone, where serotonin acts as a key suppressant of hematopoiesis, by inhibiting its synthesizing enzyme TPH1. By releasing hematopoiesis from its biological break, the population of normal osteoblasts greatly increases and leukemic blasts must compete for space and nutrients within the bone marrow. This eliminates their ability to expand and metastasize without the use of cytotoxic agents. As such, this technology provides a safe, efficacious method of treating leukemia and other hematopoietic diseases.

Serotonin suppression for efficacious, safe, and comprehensive leukemic blast reduction

This technology achieves the difficult task of targeting a specific type of cancer without the use of cytotoxic agents. In the bone marrow, leukemic blasts proliferate by competing with normal osteoblasts for nutrients and physically crowding out all other cell types. Further, those few osteoblasts that survive are likely to have mutated and can become leukemic themselves. The small molecule LP533401 inhibits the serotonin-synthesizing enzyme TPH1 and reduces serotonin production. As serotonin suppresses hematopoiesis in bone marrow, this allows new osteoblasts to form. The population of normal osteoblasts, therefore, increases, preventing both leukemic proliferation and the production of additional leukemic cells from mutated osteoblasts.

This technology efficiently treats both potential sources of leukemic cells at once, greatly reducing tumor burden. Trials conducted with similar molecules have demonstrated low toxicity and versatility, treating diseases ranging from osteoporosis to irritable bowel syndrome. Importantly, this compound does not cross the blood-brain barrier, as evidenced by unaffected levels of neuronal serotonin, thus preventing mood destabilization and behavioral side effects.

The inhibitor described in this technology has been tested in mice and found to eliminate leukemic blast cells, prevent bone loss, and curb secondary hind-limb paralysis.
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Applications:
- Potential leukemia therapeutic
- Reagent for basic serotonin research
- Therapy for diseases involving non-neural serotonin (irritable bowel syndrome, etc.)
- Compound described has potential to slow bone loss in osteoporosis, treat other blood cell production abnormalities

Advantages:
- Uses well tolerated compound
- Restores bone marrow homeostasis, which greatly reduces leukemic blast counts and allows normal blood cell production to resume
- Does not cross the blood-brain barrier
- Safer and more precise than traditional chemotherapy drugs
- Can be combined with other cancer therapies

Patent Information:
Patent Pending (WO2013074889)
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Related Publications:

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