METHODS OF USE AND COMPOSITIONS OF TETRANDRINE FOR THE TREATMENT OF MALIGNANCIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a U.S. Utility Patent application which claims the benefit of priority to both U.S. Provisional application No. 63/453,063, filed March 17, 2023, entitled "Methods of Use and Compositions of Bisbenzylisoquinolines such as 6,6',7,12-tetramethoxy-2,2'-dimethyl-berbaman or Analogs for the Treatment of Leukemic Stem Cells, Cancer Stem Cells and Precancerous Stem Cells" and U.S. Provisional application No. 63/453,068, filed March 18, 2023, entitled "Leukemic Stem Cell Treatment," each of which are hereby incorporated herein by reference in their entirety.

BACKGROUND

[0002] While both systemic and local toxicities of cancer chemotherapeutics can limit their utility, treatment failure and cancer relapse are also the result of drug resistance and self-renewal properties of a small population of tumor cells identified as cancer stem cells (CSCs). Some properties of CSCs, such as cell surface markers (CD44, CD24, and CD133) have been identified that can allow the development of therapies better suited toward eradicating these cellular populations. CSCs have a survival reliance on certain signaling pathways (e.g., Wnt/β-catenin, Notch, NF-kB, NLRP3 and Hedgehog that control CSCs properties. Normal stem cells do not. For CSCs, this reduces apoptotic signals and increases proliferative ones, and they over-express drug-efflux pumps that allow escape from toxic chemotherapeutic concentrations. Moreover, the influence of the bone marrow microenvironment interaction with leukemic stem cells through the Wnt/β-catenin pathway, NF-kB as well as the NLRP3 inflammatory pathway provides the opportunity for therapeutic intervention. Knowing the survival characteristics of CSCs allows for the identification and development of therapeutics especially suited toward their elimination. Cancers for which CSCs-enriched populations have been identified and include brain, head and neck, breast, pancreatic, lung, liver, gastric, colorectal, lymphomas and leukemias.

[0003] Tetrandrine (6,6',7,12-tetramethoxy-2,2'-dimethylberbam), also known as d-tetrandrine, TET, NSC#77037, and ES-3000 is a bis-benzylisoquinoline alkaloid, extracted from roots of the plant *Stephania tetrandra S. moore*. ES-3000 (Tetrandrine) is