Hydrocarbon Stapled Peptides that Inhibit the Linear Ubiquitin Chain Assembly Complex (LUBAC) for the Therapy of the Activated B Cell-like (ABC) Subtype of Diffuse Large B Bell Lymphoma (A Type of Non-Hodgkin's Lymphoma)

Summary (1024-character limit)

Researchers at the National Cancer Institute (NCI) have developed an invention consisting of hydrocarbon stapled peptides that disrupt the linear ubiquitin-chain assembly complex (LUBAC), which is involved in NF-□B signaling. These peptides can be used as a therapeutic in the treatment of the activated B cell-like (ABC) subtype of diffuse large B cell lymphoma (DLBCL), a type of non-Hodgkin's lymphoma, as well as inflammatory diseases. The NCI seeks licensing and/or co-development research collaborations for inhibitors of NF-□B signaling and/or treatment of ABC DLBCL, as well as inflammatory diseases.

NIH Reference Number

E-035-2013

Product Type

- Therapeutics

Keywords

- Linear Ubiquitin-chain Assembly Complex, LUBAC, NF-□B, Activated B Cell-like, Diffuse Large B Cell Lymphoma, ABC DLBCL, Non-Hodgkin's Lymphoma, Peptide Inhibitor, Cancer, Inflammatory, Autoimmune, Therapeutic, Staudt, Bernal

Collaboration Opportunity

This invention is available for licensing and co-development.

Contact

- John D. Hewes
  NCI - National Cancer Institute

  240-276-5515

  John.Hewes@nih.gov

Description of Technology

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma and consists of three subtypes: activated B-cell (ABC), germinal center B-cell (GBC), and primary mediastinal B-cell (PMB). Despite advances in the front-line therapy for DLBCL, approximately one-third of patients will relapse. Substantially worse outcomes have been reported for patients diagnosed with ABC DLBCL

and treated with standard chemoimmunotherapy, suggesting the need for novel strategies that improve treatment outcomes.

ABC DLBCL cell survival depends largely upon NF-□B signaling being constitutively active. The linear ubiquitin chain assembly complex (LUBAC) participates in NF-□B signaling, consists of three proteins (HOIP, HOIL-1L, and SHARPIN), and protects against apoptosis. Inhibiting LUBAC using HOIP and/or SHARPIN peptide inhibitors attenuates LUBAC activity and promotes ABC DLBCL cell death.

LUBAC peptide inhibitors present a new therapeutic strategy for the treatment of ABC DLBCL and could be combined with radiation, chemotherapy, or CAR-T therapy for ABC DLBCL or other cancers. Researchers at the National Cancer Institute (NCI) have developed HOIP and SHARPIN peptides that inhibit HOIP/HOIL-IL (E-035-2013) and SHARPIN/HOIL-IL (E-019-2017) interactions, respectively. Additionally, these peptides could be applied to treat rheumatoid arthritis, chronic autoinflammation, systemic lupus erythematosus, Crohn's inflammatory bowel disease, polyglucosan body myopathy, or psoriasis. The NCI is seeking statements of capability or interest from parties interested in licensing or in collaborative research to co-develop technologies that disrupt NF-□B signaling and present new therapeutic strategies for ABC DLBCL and inflammatory disease treatment.

Potential Commercial Applications

- Targeted therapies of ABC DLBCL
- Combination cytotoxic chemotherapies for ABC DLBCL treatment
- Treatment of inflammatory diseases, such as polyglucosan body myopathy, rheumatoid arthritis, chronic autoinflammation, systemic lupus erythematosus, Crohn's inflammatory bowel disease, and psoriasis

Competitive Advantages

- Novel composition of inhibitors for advanced stage ABC DLBCL
- Effective therapies targeting the NF-□B pathway
- Novel therapeutic for ABC DLBCL not responsive to R-CHOP or EPOCH therapies
- In HeLa cells, SHARPIN-LTM peptides (E-019-2017) reduce Human Papilloma Virus-E6 and E7 expression at a dose of 10 µM, 5 times lower as curcumin, does to have the same effect;, and also, in half theof time thatof standard treatment needsed to reach a 50% decrease in viability (24h for LTM compared to 48 h for curcumin) (Molecules. 2015; 20:11830-60). Importantly thise SHARPIN peptide (E-019-2017) synergizes with Nutlin (currently in clinical trials) to reactivate p53 and decrease viability on HeLa cells at a 1:1 molar ratio (20 □M final concentration), which is lower than the 80 µM Nutlin dose needed to reach a similar effect.

Inventor(s)

Louis M. Staudt (NCI), Yibin Yang (NCI), Federico Bernal (NCI), Amanda Whiting (NCI)

Development Stage

- Discovery (Lead Identification)

Publications

Yang Y et al. Essential role of the linear ubiquitin chain assembly complex in lymphoma revealed by rare germline polymorphisms. [PMID: 24491438]

Fujita, H, et al. Cooperative Domain Formation by Homologous Motifs in HOIL-1L and SHARPIN Plays a Crucial Role in LUBAC Stabilization. [PMID: 29694895]

Patent Status

- **U.S. Patent Filed:** U.S. Patent Application Number 61/789,064, Filed 15 Mar 2013
- **PCT:** PCT Application Number PCT/US2014/023006 , Filed 10 Mar 2014
- **U.S. Patent Issued:** U.S. Patent Number 9,783,586 , Issued 10 Oct 2017

Related Technologies

- E-019-2017

Therapeutic Area

- Cancer/Neoplasm
- Immune System and Inflammation