Drug Repurposing To Explore Novel Treatment For Cushing Disease

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SUMMARY

UCLA researchers in the Department of Medicine and the Department of Molecular and Medicinal Pharmacology have identified several small molecule reagents to treat Cushing disease.

BACKGROUND

Cushing disease is a rare disease characterized by excessive adrenal-derived cortisol production, primarily as a result of adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. Cushing disease patients have greater propensity to develop osteoporosis, diabetes, cardiovascular disease, and other metabolic diseases. The first-line treatment of Cushing disease is surgical resection of ACTH-secreting pituitary adenoma, but is limited to microadenomas with <1cm diameter. Disease recurrence is usually treated with repeated pituitary surgery with <50% success rate, or pituitary-directed radiation therapy that causes hypopituitarism in ~40% patients. Alternatively, bilateral adrenalectomy resolves hypercortisolism but requires lifelong gluco- and mineralo-corticoid replacement, and may spur rapid pituitary tumor growth in 25% patients. Thus, there is an unmet medical need in developing treatment for Cushing disease.

INNOVATION

Researchers at UCLA have developed a unique highly sensitive and specific “gain of signal” adrenocorticotropic hormone (ACTH) AlphaLISA assay in a rigorous high-throughput screen evaluation. Using this ACTH AlphaLISA assay in combination with nuclei staining, researchers have identified several compounds that exhibit anti-proliferation effects with IC50 at nanomolar range. One particular molecule, which belongs to the phosphoinositide 3-kinase (PI3K)/histone deacetylase (HDAC) inhibitor family has demonstrated outstanding performance to block tumor growth and ACTH secretion in both human corticotroph tumor primary cell culture and a Cushing disease xenograft mouse model.

APPLICATIONS

- Treatment for Cushing disease

ADVANTAGES

- Both inhibit ACTH secretion to attain eucortisolemia, and block tumor growth
- The identified compound is deemed non-toxic and well tolerated in humans, as it is being studied in phase II clinical trials for other disease indications
- Known action mechanism
- Orally bioavailable

STATE OF DEVELOPMENT

The efficacy has been demonstrated in in vitro and in vivo models of Cushing disease.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Published Application	2022-018408	06/16/2022	2019-621

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OTHER INFORMATION

KEYWORDS

Cushing disease, adrenocorticotropic hormone, ACTH, pituitary adenoma, phosphoinositide 3-kinase inhibitor, histone deacetylase inhibitor, high-throughput screen

CATEGORIZED AS

- **Medical**
  - Disease: Metabolic/Endocrinology
  - New Chemical Entities, Drug Leads
  - Research Tools
  - Screening
  - Therapeutics
- **Research Tools**
  - Reagents
  - Screening Assays

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