

## 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 adrenocorticotrophic 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” adrenocorticotrophic 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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### INVENTORS

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### OTHER INFORMATION

#### KEYWORDS

Cushing disease, adrenocorticotrophic 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

#### RELATED CASES

2019-621-0

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