**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**

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