Drug Repurposing To Explore Novel Treatment For Cushing Disease
Tech ID: 30335 / UC Case 2019-621-0

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
<table>
<thead>
<tr>
<th>Country</th>
<th>Type</th>
<th>Number</th>
<th>Dated</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Of America</td>
<td>Published Application</td>
<td>2022-018408</td>
<td>06/16/2022</td>
<td>2019-621</td>
</tr>
</tbody>
</table>