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Screening for compounds to treat obesity and metabolic disease by generating brown fat

Researchers in Prof. Brian Feldman's laboratory have developed a patented drug screen to identify compounds that could potentially treat obesity and metabolic disease by converting cells to calorie-burning brown fat. This screen identifies individual agents that inhibit the hormone nuclear receptor vitamin D receptor (VDR) and thereby program either adipose precursor cells or other cells (including fibroblasts) to become brown fat. Brown fat is a thermogenic tissue that increases energy expenditure, burning calories and altering systemic metabolism to improve insulin sensitivity. VDR is a critical regulatory component to determine whether fat cells become the brown tissue that expends energy or the white tissue that stores it. VDR inhibitors identified by this screen could offer a first-in-class approach for treating for patients with obesity, diabetes and other metabolic diseases by altering the composition of adipose tissue.

Stage of Development
Initial studies validated VDR as a target that determines the type of fat produced and that it can be regulated separately from the systemic environment. The inventors established a luciferase reporter system, containing the critical regulatory elements for this process, which enables systematic screening of biologics or small molecules that are competent to target this activity. In addition, the inventors have completed the first round of screening with this method and are performing functional tests on the top hits from the assay.

Applications

- **Drug development for obesity and metabolic disease** - cellular assay to screen for VDR inhibitor agents that generate brown fat

Advantages

- **First in class approach** - to treat obesity and metabolic syndrome by altering the composition of adipose tissue to generate more thermogenic brown fat cells
- **Identifies single agents** - compounds identified by this screen can generate brown fat independently, without genetic modifications or a combination of drugs
- **Minimize side effects** of therapy by identifying compounds that activate brown fat in a context-specific way

Publications

- Ji, L., Gupta, M., & Feldman, B. J. (2016). Vitamin D regulates fatty acid composition in subcutaneous adipose tissue through Elovl3. *Endocrinology*, 157(1), 91-97
- Researchers discover switch for controlling fat cells, *Stanford Medicine News Center* Aug. 1, 2013
- Malloy, P. J., & Feldman, B. J. (2013). Cell-autonomous regulation of brown fat identity gene UCP1 by unliganded vitamin D receptor. *Molecular endocrinology*, 27(10), 1632-1642

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