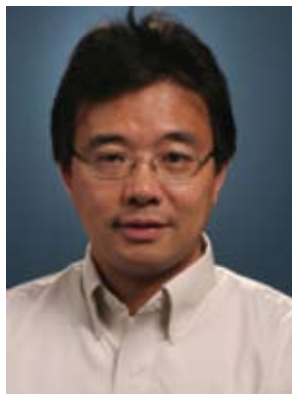


Discovery of Small Molecular Agonist for Glucagon-like Peptide 1 (GLP1) Receptor for Diabetes and Obesity Treatment

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Diabetes mellitus (type 1 and type 2) now affects >9% of the U.S. population, and totally about 250 millions people in the world. GLP-1 benefits glucose control by directly stimulating insulin release from pancreatic β cell, suppressing the release of glucagon from α cells, and slowing gastric emptying. GLP-1 suppresses appetite in animals and humans and over time reduces body weight. Most excitingly, GLP-1 increases β cell mass in rodents, reduces cell apoptosis, increases the glucose responsiveness of rodent and human islets in vitro, and stimulates the differentiation of rodent and human islet precursor cells into β cells. GLP-1 acutely and chronically normalizes glucose in diabetic patients, but its short half-life makes it less desirable as a drug than longer-acting peptides, such as exenatide and liraglutide. Clinical use of peptidic “incretin mimetics,” such as exenatide (BYETTA), for weight loss and near-normalization of hemoglobin A1c (HbA1c) levels may be limited by their need to be injected. Another strategy for developing orally available drugs is to inhibit a key enzyme, dipeptidyl peptidase IV, that degrades endogenous GLP-1. For example, Vildagliptin from Novartis and Sitagliptin from Merck have been developed and launched into clinic use. However, endogenous peptide exclusion may limit this approach.

To identify nonpeptidic small-molecule GLP-1R agonists, a sensitive high throughput screening was conducted to identify small molecular agonist for GLP-1 receptor through a collaboration effort with scientists in National Drug Screening Center in Shanghai. After screening 48,160 compounds, two synthetic compounds (SH14800 and SH17249) invoked luciferase reactions. However, freshly re-synthesized new batches did not repeat GLP-1 receptor agonist activity (Fig.1 Upper panel). Interestingly, after sitting on the shelf for a few months, these “re-synthesized compounds” did show GLP-1 receptor agonist activity. After a long time and careful analysis, we discovered that these compounds formed dimers of cyclobutane, which showed biological activities. Minor structural modifications of SH14800 yielded compounds NC133908 and NC133909 (Fig.1 Upper panel), and their dimers, S4P and Boc5 after photodimerization, respectively. These dimers have greater biological activity, such as elevation of cAMP and displace [125 I]GLP-1(7–36) amide from receptors in addition to reporter gene activation.

S4P and Boc5 induce dose-dependent luciferase responses in HEK293-rGLP-1R cells with similar potencies. S4P at concentrations up to 10 μ M maximally evoked only 37% of the GLP-1 response, but Boc5 appeared to be a full agonist of GLP-1R. We then investigated the effects of Boc5 in isolated rat pancreatic islets, which contain native GLP-1R. Insulin secretion increased 9.1-fold in control (vehicle-treated) islets when the superfusing glucose concentration was changed from 3.3 to 25 mM. This response was augmented by a factor of 2.6 after incubation with GLP-1 (100 nM). When incubated with Boc5 (up to 10 μ M),

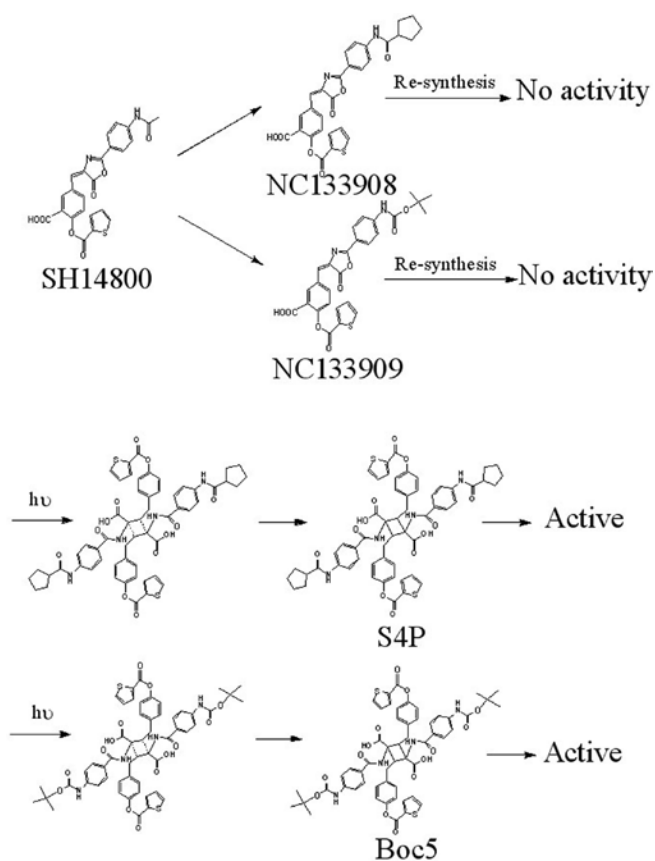


Figure 1. Discovery of small molecular agonists for the GLP1 receptor. Hit (SH14800) from high throughput screening and its derivatives cannot activate GLP1 receptor (Upper). After photodimerization under sun light, the dimmers act as agonist for GLP1 receptor (Lower).

glucose-stimulated insulin secretion was amplified by a factor of up to 4.5.

Chronic peripherally administered GLP-1R agonists reduce HbA1c and plasma lipid levels, restore β cell function, increases insulin sensitivity in models of type 2 diabetes, and induce β cell neogenesis and differentiation, which is beneficial for type 1 diabetes. Effects of chronically i.p. injected Boc5 and S4P were studied in C57BL/6J-m_l/l_l Lepr^{db} (db/db) mice, a rodent model of type 2 diabetes. HbA1c was robustly lowered with Boc5 administration and remained low throughout the experiment. After 4–6 weeks of dosing, it became indistinguishable from that of wild-type mice. After 6 weeks, HbA1c values for wild-type and Boc5-treated (1 mg and 2 mg) groups were similar but significantly less than values in pair-fed or ad libitum-fed db/db mice. Weight changes in pair-fed, Boc5 (2 mg)-treated and wild-type mice were indistinguishable during the 6 weeks of treatment, and all showed less weight gain than did ad libitum-fed db/db mice. An i.p. glucose tolerance test was done in half of the mice after 6 weeks of treatment and again 15 weeks after cessation of therapy. After 6 weeks of therapy, the area under the curve was higher for ad libitum- and pair-fed db/db mice than for wild-type mice. Mice treated with 2 mg of Boc5 had smaller glucose excursions than those in ad libitum- and pair-fed controls and indistinguishable from those in wild-type mice. Fasting insulin concentrations in ad libitum-fed and pair-fed db/db mice were markedly higher than those in wild-type mice, indicating impaired insulin sensitivity. Fasting insulin levels in mice treated with 1 and 2 mg of Boc5 were lower or trending lower, than in pair-fed controls.

Boc5 is the first proved small molecule as competitive agonist for GLP-1 receptor, and Class B GPCRs, which regulate hormones in many human physiological processes and are major targets for therapeutic development. Discovery of small molecular agonist for Class B GPCR has been a very challenging task for scientists in the past. This discovery opened new revenues to support research into small molecule interaction with Class B GPCRs in the future.

Shingles Vaccine, Seniors' Joy

Jon Mo



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Introduction

Shingles caused by the Varicella Zoster virus (VZV), the same virus that causes chickenpox. VZV infection is highly contagious, producing annual epidemics among susceptible individuals during winter and spring in temperate climates. The virus establishes latency in cells of the dorsal root ganglia during primary infection ¹. It can reappear many years later to cause a case of shingles, which is usually observed in elderly or immunocompromised patients. People can't catch shingles from another person with shingles. Only someone who has had a case of chickenpox or gotten chickenpox vaccine can get shingles. It is estimated that more than 500,000 cases of herpes zoster occur each year in the United States ⁵.

Symptoms

Shingles is a skin rash, often with blisters. It is also called Herpes Zoster. A shingles rash usually appears on one side of the face or body and lasts from 2 to 4 weeks (Fig. 1). Its main symptom is pain, which can be quite severe. Other



Fig. 1 Shingles rash (A) Neck ; (B) Upper back

symptoms of shingles can be fever, headache, chills and upset stomach. Very rarely, a shingles infection can lead to pneumonia, hearing problems, blindness, brain inflammation (encephalitis) or death. For about 1 person in 5, severe pain can continue even after the rash clears up. This is called Post-herpetic neuralgia (PHN) ¹.

Shingles vaccine

Zostavax vaccine (Fig. 2), the vaccine containing live, attenuated VZV (Oka/Merck strain), is indicated for the prevention of herpes zoster (shingles) ². The virus was originally obtained from a child with naturally-occurring varicella and then grown in the laboratory in human diploid cell cultures. Zostavax protects