SMALL MOLECULE INHIBITORS OF THE HUMAN UREA TRANSPORTER ('UREARETICS') FOR USE AS A NOVEL DIURETIC

Tech ID: 19063 / UC Case 2007-004-0

BACKGROUND

Volume over-load conditions, such as congestive heart failure, cirrhosis, nephrotic syndrome, and volume-sensitive hypertension are often treated with a battery of different types of diuretics, such as loop diuretics, thiazides, and K-sparing diuretics that affect different functions of the kidney. However, some of these diuretics, particularly thiazides, cause unwanted side-effects, such as potassium imbalance or acid-base disorders. Diuretics also have limited efficacy in some conditions (e.g., diuretic-refractory edema in congestive heart failure).

Recent studies suggest that drugs designed to inhibit urea transporters (a.k.a. "urearetics") in the kidney could be used to treat water and salt imbalance disorders. Urea transporters play a role in concentrating urea in the urine and thus affect water and salt concentrations. One potential advantage of urearetics is that they are unlikely to cause secondary potassium imbalance or acid-base disorders. Unfortunately, potent and specific urea transporter inhibitors have not been available.

DESCRIPTION

Using a high-throughput, phenotypic screening assay, UCSF investigators have identified and optimized high-affinity small-molecule inhibitors of the human urea transporter, UT-B. The inhibitors belong to several chemical classes and alter the transport activity of UT-B with low nanomolar potency.

Based on these results, and previous genetic analyses in mice, the researchers conclude that the compounds could be used to regulate water excretion in the kidney and treat conditions such as heart failure. Proof of this concept has been recently validated in an in vivo rodent model in which compound administration under conditions producing therapeutics concentration in kidney disrupt unrinary concentrating ability to the same extent as UT-B knockout.

ADVANTAGES

- First in its class agent; novel mechanism of diuretic action

CONTACT

Todd M. Pazdera

todd.pazdera@ucsf.edu

tel: 415-502-1636.

OTHER INFORMATION

KEYWORDS

heart failure, UT-B, urea, potassium imbalance, diuretic

CATEGORIZED AS

- Medical
  - Disease: Cardiovascular and Circulatory System
  - Therapeutics

RELATED CASES

2007-004-0

- Unlikely to cause secondary potassium imbalance or acid-base disorders that are common with certain diuretics
- An SAR analysis performed by the researchers provide the basis for future optimization of ADME properties

APPLICATIONS

- Could be used for volume overload in congestive heart failure, cirrhosis, nephrotic syndrome, and volume-sensitive hypertension
- Can be used to conduct chemical knock-out studies in animal tissues
- Could be used in combination with existing diuretics to limit side-effects

PUBLICATIONS

Levin MH, de la Fuente R, Verkman AS. (2007) Urearetics: a small molecule screen yields nanomolar potency inhibitors of urea transporter UT-B. FASEB J. Feb;21(2):551-63.

Yao, C. et al. (2011) In preparation.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,316,633	04/19/2016	2007-004

ADDRESS

UCSF

Innovation Ventures

600 16th St, Genentech Hall, S-272,

San Francisco,CA 94158

CONTACT

Tel:

innovation@ucsf.edu

https://innovation.ucsf.edu

Fax: