Docket #: S00-021

Mouse Model for Hypertension and for Drug Screening of Antihypertensive Drugs

Completed Research:
· The invention is a genetically altered mouse that exhibits defects in regulation of smooth muscle contraction. The genetic alteration is a knockout (lesion) of the calcium-activated potassium channel beta subunit gene. The mouse serves several purposes:
· Serves in evaluating potential anti-hypertensive drugs for their specificity against the calcium activated potassium channel beta1 subunit.
· Serves as a mouse model for hypertension in evaluating drugs against other non-beta1 targets.
· In addition, may serve similar roles for drug design for asthma and incontinence.

Advantages

- The beta1 subunit is an accessory subunit of alpha subunit of the calcium-activated potassium channels. Calcium activated potassium channels alpha subunits are expressed quite ubiquitously, and in smooth muscle control tone and are likely to have an important role in blood pressure regulation. Currently, the beta1 subunit of calcium-activated potassium channels is the target of study for antihypertensive drugs. The reason for this is that it is specifically expressed in smooth muscle cells, and provides a means to modulate calcium activated potassium channels (and smooth muscle contraction) without affecting other tissues that also utilize alpha subunit (such as brain).
- Evaluation of drug specificity is a costly and time-consuming process. The beta1 knockout mouse may provide useful controls during pharmacological screens in evaluating drugs for specificity against the beta1 protein.

- Because beta1 knockout mice show an increased blood pressure but very little other pleitropic effects, the beta1 knockout mice would provide an excellent model to study anti-hypertensive drugs that target other proteins besides the beta1 subunit.
- The beta1 subunit is also expressed in bladder and airway smooth muscle. It could serve similar roles in drug screening against asthma and incontinence, respectively.
- The current mouse model for hypertension is renalectomy and requires feeding the mice excess salts. These mice have renal problems as well and other non-hypertensive problems. This new knockout mouse is more specific model for hypertension.

Publications

- Nature article in the Oct. 19, 2000 issue (Nature 407, 870 - 876 [2000]): "Vasoregulation by the 1 subunit of the calcium-activated potassium channel" http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v407/n6806/full/407870a0_fs.html
- Nature "News and Views" piece in Oct. 19, 2000 issue (Nature 407, 845 - 848 [2000]): "Cardiovascular biology: Tuning channels for blood pressure" http://www.nature.com/cgi-taf/dynapage.taf?file=/nature/journal/v407/n6806/index.html
- Howard Hughes Medical Institute website, related commentary: http://www.hhmi.org/news/aldrich.html, http://www.hhmi.org/science/neurosci/aldrich.htm

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