

Generation of a pig model carrying the KCNJ5G151R mutation, characterization and treatment with mutant KCNJ5 inhibitors

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Primary aldosteronism (PA), the excessive production of the adrenal steroid hormone aldosterone, is considered the most common cause of secondary hypertension. A main cause of PA are benign adrenal tumors, so-called aldosterone-producing adenomas (APAs). Two heterozygous somatic mutations in the KCNJ5 potassium channel (G151R, L168R) account for about 40% of APAs. Germline mutations in the same gene cause a subform of familial hyperaldosteronism. The diagnosis of APAs requires a difficult invasive testing procedure that is only available at select tertiary care centres; the standard therapy is unilateral adrenalectomy. A series of macrolide antibiotics was identified as specific inhibitors of mutant, but not WT KCNJ5 channels. Their inhibitory activity is independent of their antibiotic activity. Response to such compounds could potentially be used to diagnose APAs with KCNJ5 mutations; long-term treatment may lead to tumor shrinkage.

In this project, we propose to use the CRISPR/Cas9 system to generate a pig model carrying the KCNJ5G151R mutation. Mutagenesis of porcine fetal fibroblasts will be performed to use them as donor cells for somatic cell nuclear transfer. The characterization of the knock-in animals will be followed by short-term and long-term treatment with macrolides to assess their diagnostic and therapeutic potential in primary aldosteronism.

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