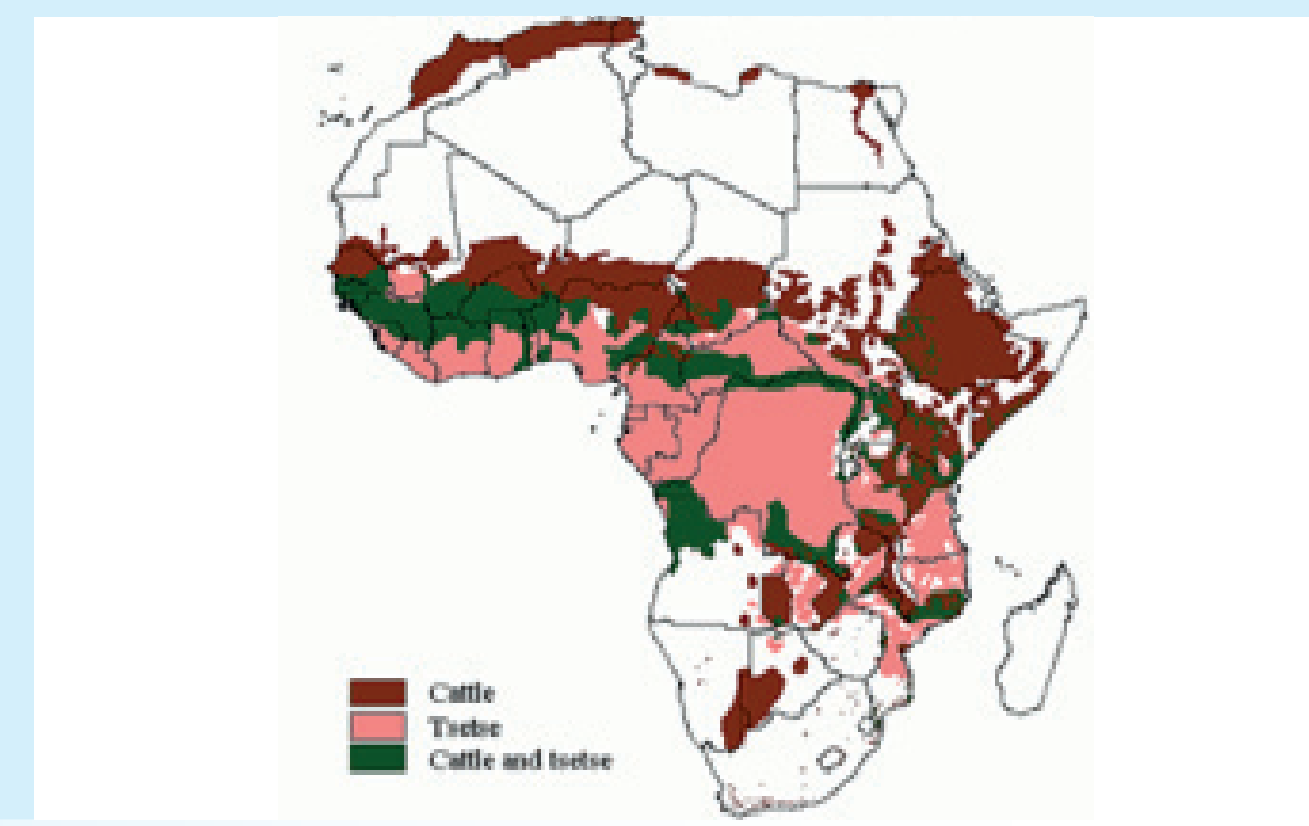


# Mzima Cow Project

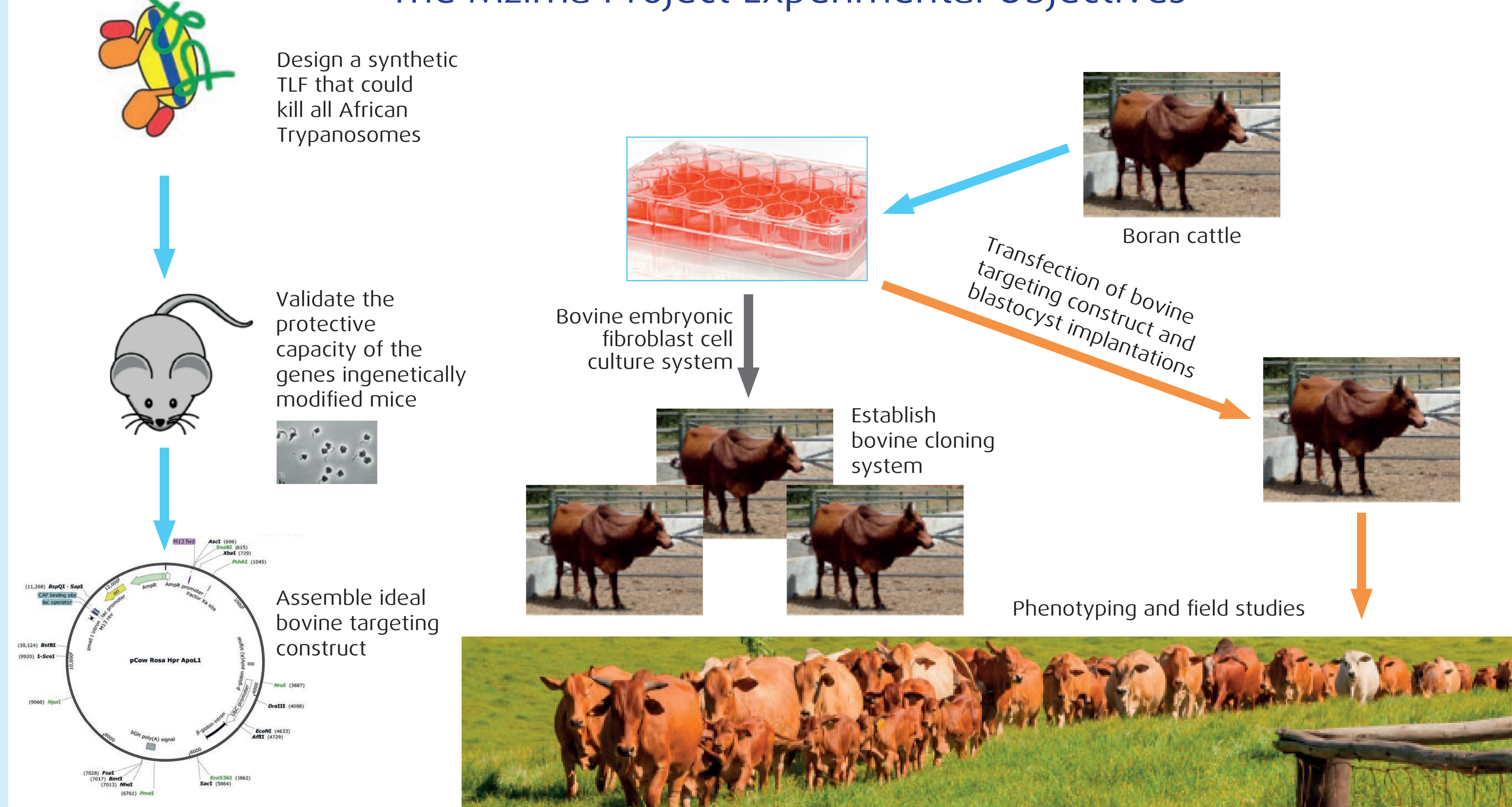
A transgenics approach to the basic mechanisms underlying trypanosome resistance

## The Challenge

We are developing transgenic cattle resistant to an important disease, trypanosomiasis, that could have a major impact across Africa. Our long-term aim is to generate genetically modified cattle, which carry a gene that imparts resistance to African trypanosomes. The gene, APOL1, encodes for the pore forming protein component apolipoprotein L-I of trypanosome lytic factors (TLFs).



## The Mzima Project Experimental Objectives

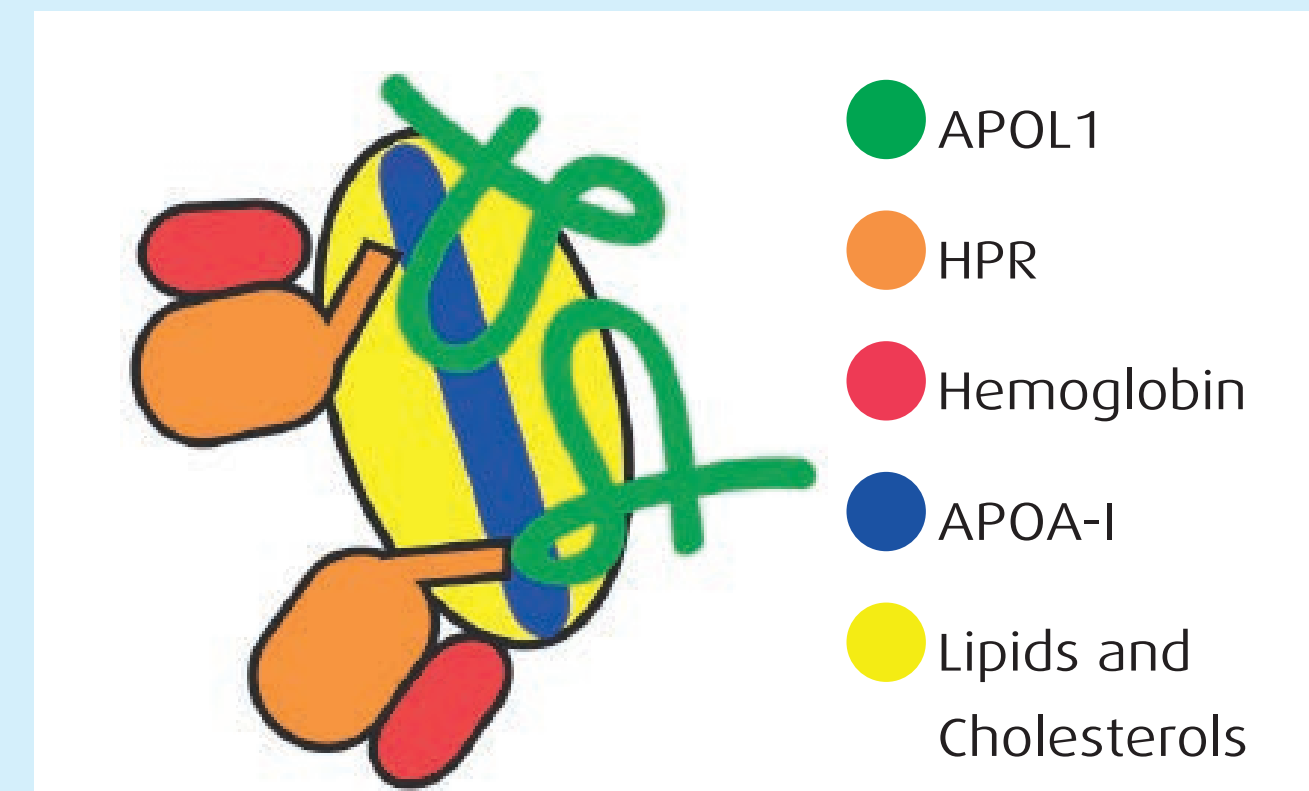


## Broader Impacts

- Trypanosome resistant cattle will survive in the tsetse belt -10 million square miles
- The women who till the land by hand (90% of sub-Saharan Africa) can use cattle for:
  - Haulage, traction and soil fertility -crop production could increase 10-fold
  - Have milk and meat products -less vulnerable to critical harvest time imposed by plants
  - Have a store of wealth for future investments

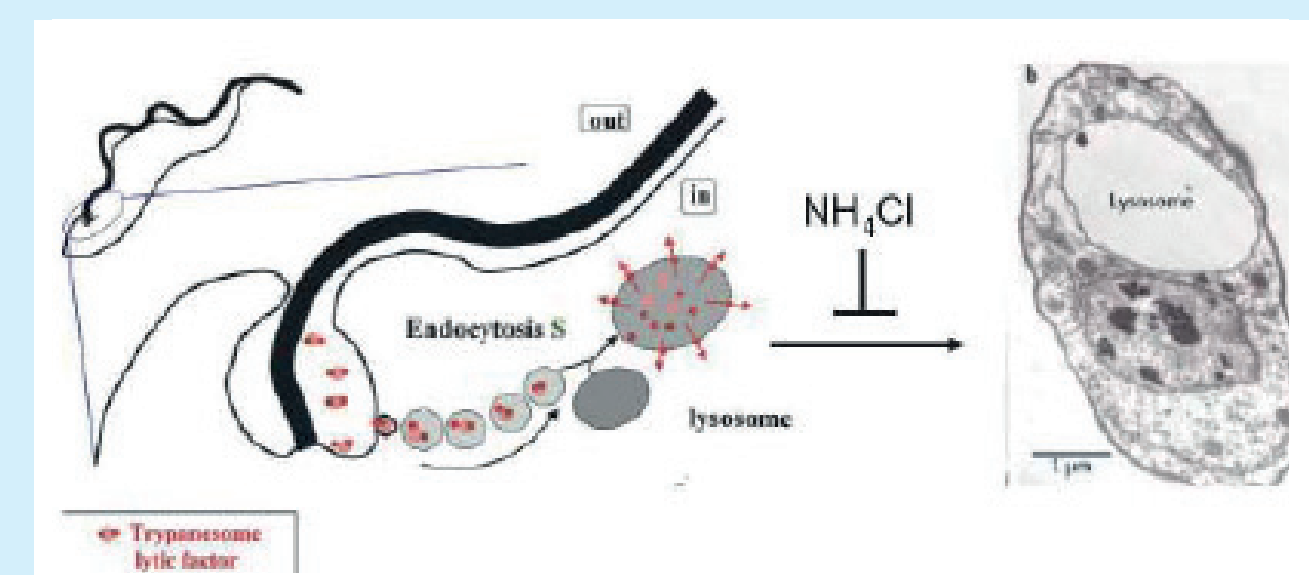
## Trypanosome Lytic Factor

Trypanosome lytic factor is a high-density lipoprotein (HDL) (the good cholesterol) that circulates in the blood of some primates. It is composed of lipids and three proteins, apolipoprotein A-I (APOA-I), haptoglobin related protein (HPR), and the pore forming apolipoprotein L-I (APOL1).

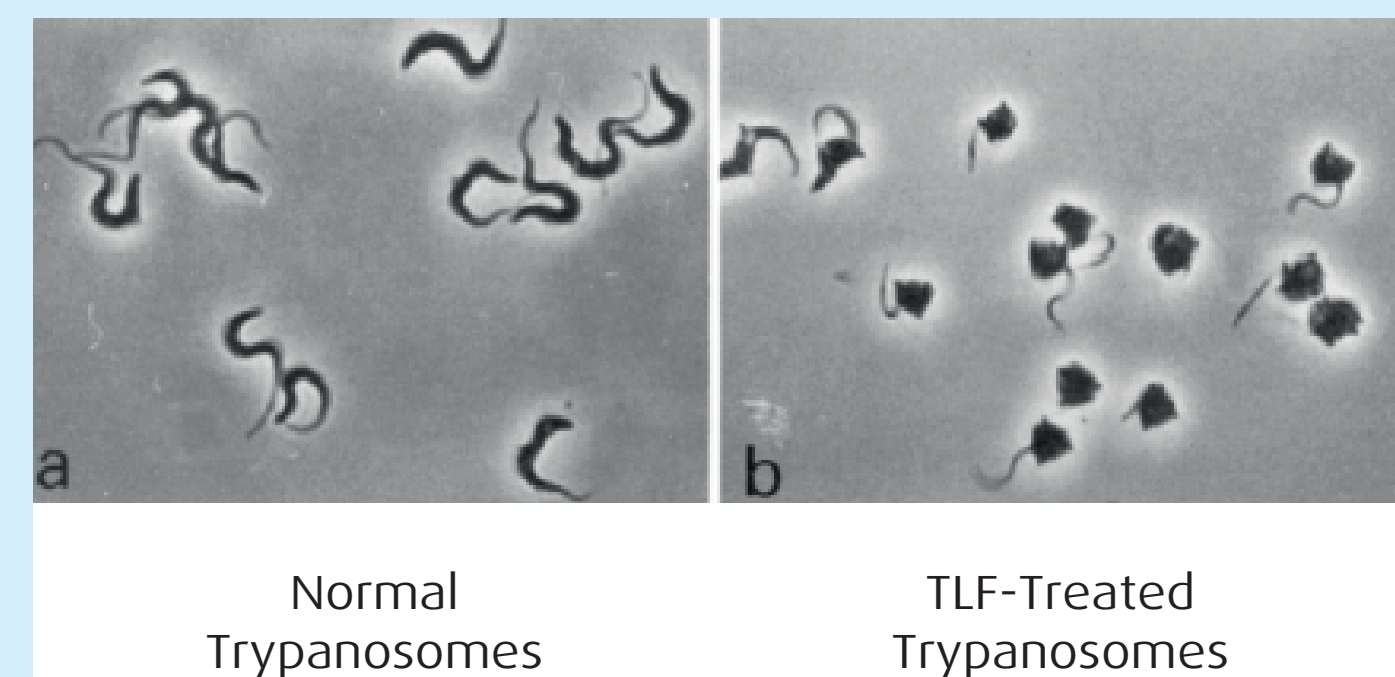


## Mechanism of Action of Trypanosome Lytic Factor

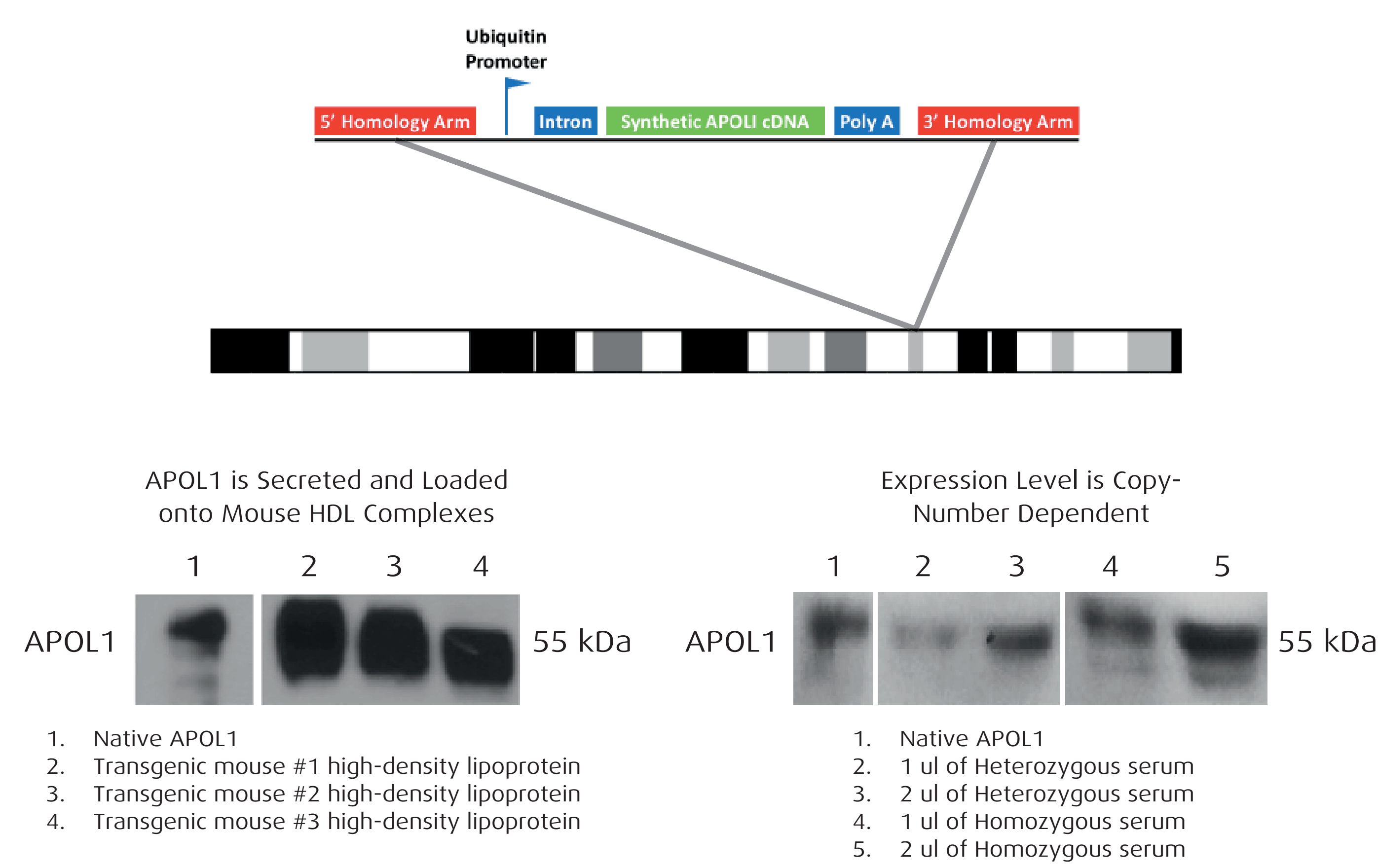
TLF binds in the flagellar pocket to a receptor (mediated by HPR) and is endocytosed by the parasite. TLF is activated in the acidic endosome and APOL1 is released from the particle and inserts into the membrane forming a monovalent ionic pore.



The activation can be blocked by the weak base ammonium chloride (NH<sub>4</sub>Cl), which neutralizes the endolysosomal system. The pore allows the equilibration of ions down their concentration gradients, leading to the dissipation of the membrane potential and the influx of water, such that the parasite swells and bursts.

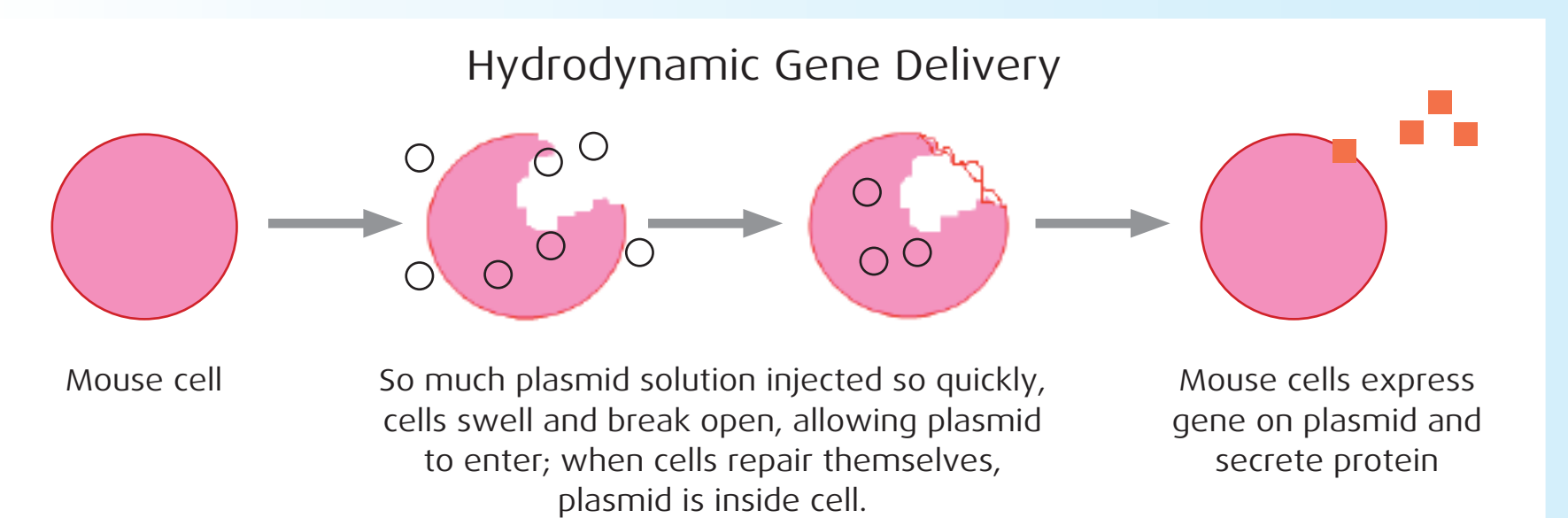
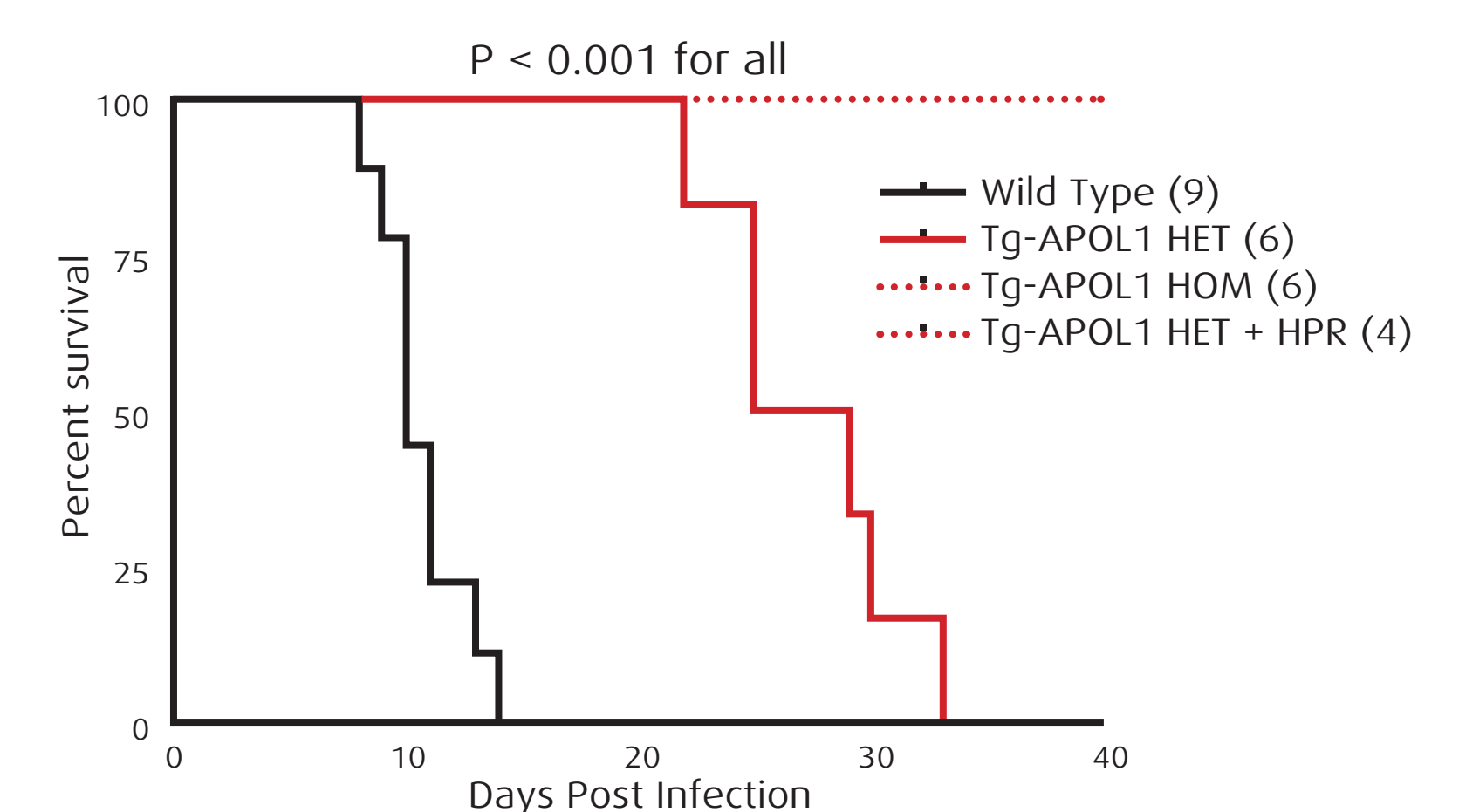


## Expressing APOL1 in Mice



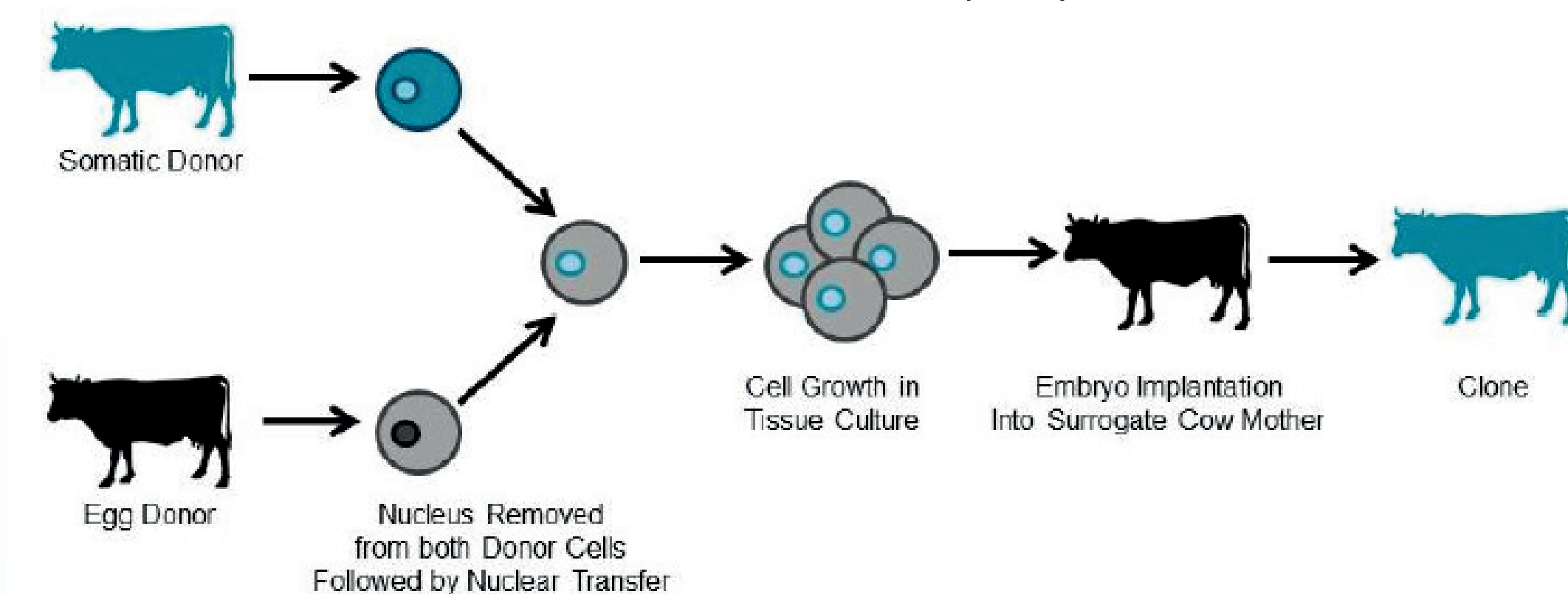
## APOL1 Protects Against Trypanosome Infection

Human and Cattle-Infective *T. b. rhodesiense*

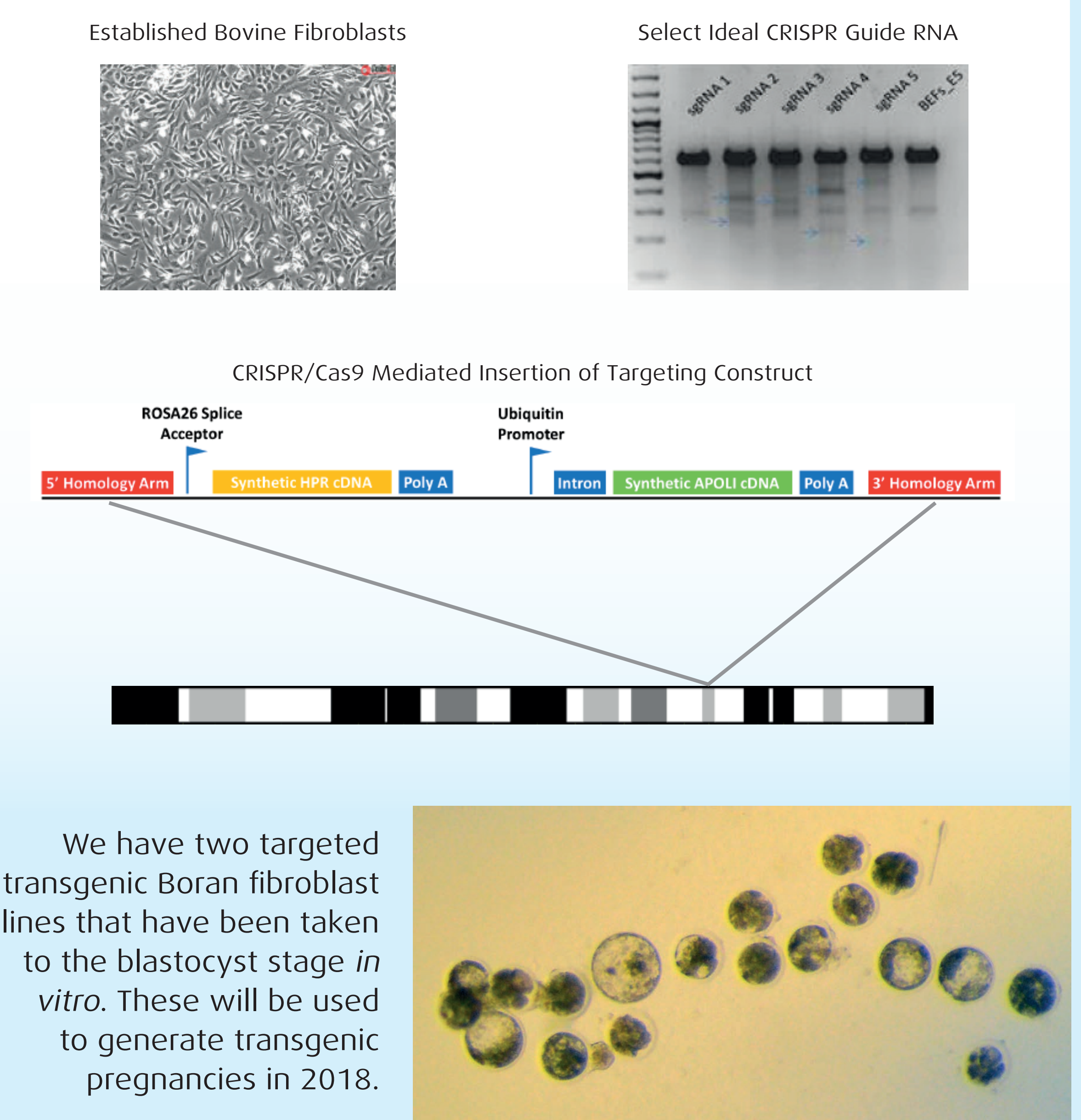


## Cloning the First Boran Bull Tumaini at ILRI

- African Bos indicus breed
- High resistance to ticks and heat
- Can endure scarcity of water
- Can live on low quality feed



## Generating APOL1 and HPR Knock-In Bovine Cells



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