

Non-Technical Abstract

We propose to use gene therapy to treat a rare inherited disease, called familial hypercholesterolemia (FH). This disease is caused by an abnormality in a liver protein, called the LDL receptor, that is responsible for breaking down the form of cholesterol that is associated with hardening of the arteries (atherosclerosis). Because LDL receptor protein is absent in patients with FH the level of cholesterol accumulates to very high levels and leads to death in childhood due to heart attacks. Most forms of therapy are not effective in lowering cholesterol in FH. We have used an animal model of FH, called the Watanabe Heritable Hyperlipidemic (WHHL) rabbit, to develop a gene therapy for this disease. The basic approach developed in the rabbit is described below. A small piece of liver tissue was removed from the rabbit and the individual cells, called hepatocytes, were isolated and grown in petri dishes in the laboratory for several days. During this time the hepatocytes were exposed to a harmless mouse virus that is capable of shuttling a gene into the cell that produces a normal LDL receptor protein. The genetically corrected cells were harvested and transplanted into the rabbit from which they were originally derived. This therapy was associated with a prolonged and possibly permanent improvement in hypercholesterolemia in the rabbits. We propose to use this same strategy to treat patients who inherit two abnormal LDL receptor genes and have severe hypercholesterolemia (so called FH homozygotes).