

## Solution key -7.012 Recitation 19 - 2010

### Question

You are investigating a method of gene therapy directed to the liver of a patient with familial hypercholesterolemia (FH). The patient, who is homozygous for the FH alleles, is a human recipient for FH gene therapy. She suffered a massive heart attack with permanent damage at the age of 16, revealing the severity of her disease. The procedure for her treatment is as follows. Fifteen percent of the patient's liver was removed. The liver tissue sample was then dissociated into individual hepatocytes (liver cells) and cultured in dishes. The cultured cells were provided with a wild-type copy of the gene that is mutated in this patient. The genetically altered hepatocytes were injected back into the patient via a vein entering the liver. After some time, the patient was given bile acid binding resins.

a) Why are the patient's liver cells specifically being targeted?

*75% of the cholesterol is absorbed by the LDL-receptors located on the surface of the liver cells. Since the FH patients have homozygous recessive mutations of the LDL-receptor gene (LDL-R - / LDL-R-) they cannot absorb any cholesterol. Therefore these cell are being targeted by gene therapy.*

b) What is the significance of giving the patient bile acid binding resins?

*These resins can bind to and eliminate the bile and also the cholesterol bound to the bile as a part of the feces.*

c) Shown below is a measurement of the LDL concentration in the bloodstream of the patient before and after the gene therapy. The average, normal LDL level in an adult is 125 milligrams per deciliter (mg/dl). A sample of the patient's liver, removed 18 months after the procedure, contained cells which expressed the introduced gene in the ratio of 1 expressing cell per 1,000 to 10,000 total hepatocytes.

#### LDL concentration in the bloodstream:

<u>Pre-Gene Therapy</u>	<u>Post-Gene Therapy</u>	
<u>minus resins</u>	<u>minus resins</u>	<u>plus resins</u>
482 mg/dl	404 mg/dl	356 mg/dl

Which gene is being introduced into the hepatocytes of the patient?

*The genes that encodes LDL -receptor protein.*

d) Before the treatment, the patient was unresponsive to conventional therapy for heterozygous FH patients (such as bile acid-binding resins) to reduce LDL in the blood.

i. Why is this patient responsive to conventional treatment after the gene therapy?

*Now some of the liver cells in patients are expressing the LDL- receptors, although at a lower concentration. Therefore the patient behaves more like a carrier and responds to conventional therapy.*

ii. After some time, the patient was given the drug Lovastatin, an enzymatic inhibitor of HMG coA reductase. What is the significance of inhibiting HMG coA reductase?

*This is the rate- limiting enzyme for cholesterol biosynthesis. Therefore the inhibition of this enzyme will reduce the synthesis of cholesterol thus helping the patients.*