

Sickle Selections

a quarterly newsletter from the University of Rochester Sickle Cell Program

January 2002

Sickle Cell Disease Cured in Mice By Gene Therapy

By inserting a modified version of the beta-globin gene into mouse stem cells and then transferring these cells into the mice, researchers from Harvard Medical School and MIT led by Philippe Leboulch* were successful in curing sickle cell disease in mice.

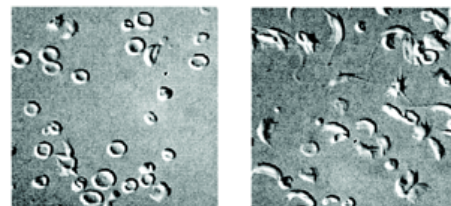
Because the manifestations of sickle cell disease (SCD) are caused by the polymerization of sickle hemoglobin, attempts to cure the disease have focused on methods of inhibiting this polymerization. Since γ -globin is a strong inhibitor of HbS polymerization, these researchers altered the gene that codes for β^A globin to include part of the γ -globin gene. Specifically they changed codon 87 of the β -globin gene which normally codes for threonine to code instead for glutamine which is the amino acid residue responsible for most of the antisickling activity of γ -globin. They called their new gene β^{A-T87Q} -globin.

To test the antisickling capacity of their new gene they generated transgenic mice to express both human β^{A-T87Q} -globin and human α -globin but neither mouse α - nor mouse β -globin. They then extracted the β^{A-T87Q} -globin from the red blood cells of these mice and found that it was almost as potent an inhibitor of HbS polymerization as γ -globin itself.

The next problem was to get their mutant β^{A-T87Q} -globin gene into the stem cells of the mouse bone marrow. To do so they packaged their gene with a small piece of genetic material (vector) found in the human immunodeficiency virus (HIV). They then added this modified gene/vector combination to bone marrow extracted from a mouse with sickle cell disease. To healthy mice whose bone marrow had been destroyed by irradiation, they added the marrow of the sickle disease mouse containing the modified gene/vector. These mice did

not develop sickle cell disease. To other healthy mice whose bone marrow was also destroyed they added the disease marrow without the modified gene. These mice did develop sickle cell disease.

They then inserted this same modified gene/vector into two different sickle cell disease transgenic mouse models (SAD and BERK). They showed that 99% of the red cells in the mice were making the beta globin encoded by the mutant



Rbc's from mice 3 months after transplantation with marrow from a SCD mouse. Left: healthy disc shaped cells produced by mouse receiving marrow first treated with β^{A-T87Q} -globin/vector. Right: sickled cells from mouse receiving untreated marrow.

gene. After 10 months these mice showed no signs of sickling, splenomegaly or the urine concentration defect found in sickle cell anemia.

Although the technique involves marrow transplantation which is a high risk procedure and the safety of coupling the gene with an HIV vector needs to be assured, these results are a very promising development in the search for a cure for sickle cell disease using gene therapy.

Camp KOPE will take place July 8-11, 2002 at the Camp Good Days & Special Times facility in Branchport, NY.

Please encourage your families to take advantage of this beneficial program. They may attend the camp information and registration night on Wednesday, March 20, 2002 at 6 PM at Strong Children's Hospital.

For more information regarding Camp KOPE or other programs call their office at 585-524-5555 or visit their web site at www.campgooddays.org.

*P. Leboulch et al., *Science* 494, 2368 (2001)

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