

Sickle Selections

a quarterly newsletter from the University of Rochester Sickle Cell Program

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RNA Repair - An Alternative Genetic Approach to Sickle Cell Disease Therapy

Using gene therapy to develop curative treatments for hemoglobinopathies is difficult because globin gene expression is highly regulated and may be imbalanced by gene transfer. A recent paper in *Science* by Dr. Bruce Sullenger of Duke University reported an alternative method of genetic therapy based on RNA repair using splicing ribozymes. Since fetal hemoglobin ($\alpha_2\gamma_2$) impedes polymerization of sickle hemoglobin², it was reasoned that replacing the messenger RNA for sickle β -globin with that for gamma globin could produce fetal hemoglobin at the expense of sickle hemoglobin and offer a new therapy for sickle cell disease.

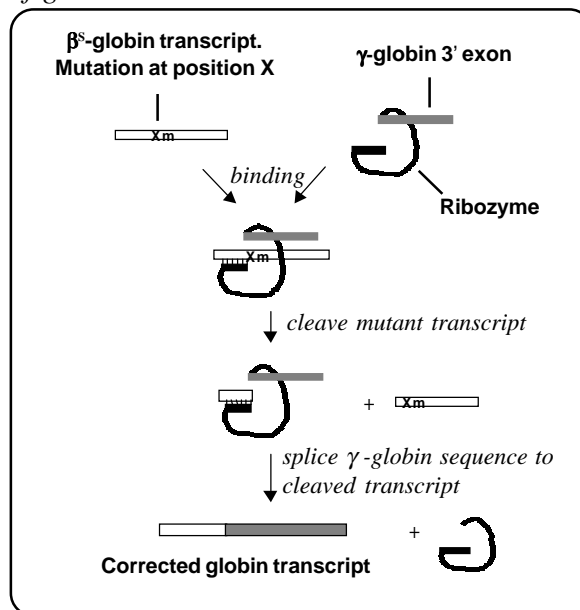
A ribozyme is an RNA molecule that can cleave another RNA molecule, e.g. messenger RNA. Some ribozymes can also splice the cleaved RNA molecule to another RNA molecule. A ribozyme was made that recognizes the sickle β -globin transcript by base pairing to an accessible region of the RNA upstream of the mutant nucleotide (Xm on figure 1), cleaves it, releases the mutation-containing cleavage product, and splices onto the remaining normal fragment the corresponding portion of the γ globin transcript (*see figure 1*).

The reaction was carried out on erythrocyte precursors derived from sickle cell patients. Sequence analysis demonstrated that in each case the ribozyme had correctly spliced the γ -globin 3' exon onto the β -globin target transcript.

The efficiency of β -globin RNA repair probably does not have to be 100% because levels of HbF at 10-20% have been shown to improve outcome.³ The authors state that whether this level of β -globin conversion can be achieved is currently unclear.

1. N. Lan et al., *Science* **280**, p. 1593 (5 June 1998)
2. H. R. Sunshine, J. Hofrichter, W. A. Eaton, *Nature* **275**, 619 (1994);
M. J. Behe and S. W. Englander, *J. Mol. Biol.* **133**, 137 (1979)
3. D.R. Powars et al, *Blood* **63**, 921 (1984)

figure 1



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Regarding treatment contact:

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Regarding laboratory diagnosis, newborn screening and genetic counseling, contact:

Dr. Peter Rowley, Sandra LaBella or Starlene Loader, Division of Genetics 275-4602

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