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## Following Important Leads

## Cancer and Aging

Cancer and aging are inextricably linked, so the study of specific aging syndromes has the potential to lead to clues about various aspects of cancer. Recent research by the laboratories of Paola Scaffidi, Ph.D., and Thomas Misteli, Ph.D., show that cells affected by Hutchinson-Gilford Progeria Syndrome (HGPS), a disease associated with premature aging, can be made healthy again. Using specially modified segments of DNA, the scientists reversed the abnormalities seen in HGPS cells by correcting defects associated with a key protein.

HGPS is a rare inherited disease affecting about one in eight million children. While appearing normal at birth, infants with HGPS age rapidly after their first 18 months, and physical symptoms include stunted growth, loss of hair and body fat, joint stiffness, osteoporosis, and heart problems.

The genetic basis for HGPS is a single mutation in the gene encoding lamin A, a critical structural protein in the cell's nucleus. Without lamin A, the nuclei of progeria cells become wrinkled, misshapen, and unable to function normally. Experiments showed that "in order to achieve a potential therapeutic effect, we needed to completely eliminate the mutant protein," said Dr. Scaffidi.

Misteli and Scaffidi designed a chemically stable DNA sequence that the cell wouldn't be able to degrade, which would bind to the mutant gene splice site in RNA transcribed from the defective gene. The resulting DNA-RNA complex prevents the splicing machinery from cutting the RNA in the wrong place. "You can think of it as a molecular Band-Aid®," said Misteli. The researchers inserted their bandage into the progeria cells and observed that after four days almost all the mutant lamin A RNA had been eliminated and replaced with the properly spliced counterpart.

"It's amazing that we could take a cell that looked about ready to die, and a few days later it was healthy and ready to divide again," said Dr. Misteli.

One of the unique features of HGPS is the absence of tumors; most other premature aging diseases are characterized by high tumor volume. Consequently, the researchers are currently exploring whether HGPS will be a useful model system for finding the molecular links between aging and

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tumor formation.



Tom Misteli, Ph.D., Head, Cell Biology of Genomes Group, NCI

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