Abstract:
The Riverside High School SMART Team (Students Modeling A Research Topic) created a 3D physical model of a farnesyltransferase (FTase)-inhibitor complex and discussed its significance in the development of a novel therapy for Hutchinson-Guilford Progeria. Farnesyltransferase inhibitors (FTIs) were originally designed as anti-cancer drugs, but recently have been shown to slow premature aging resulting from Progeria. This premature aging syndrome is caused by a mutation that affects processing of the Lamin A protein, a component of the nuclear lamina. A farnesylated prelamin intermediate accumulates, which in turn interferes with the assembly of a functional nuclear lamina. Farnesylation of prelamin A occurs on a CaaX box motif by the FTase. One class of FTIs structurally mimics the CaaX motif thereby inhibiting the enzyme. Inhibition of Lamin A farnesylation prevents the accumulation of farnesyl-prelamin A and inhibition of lamina assembly. This surprising discovery has given clinicians the first drug to treat this rare, but deadly premature aging syndrome. By studying the structure of FTIs bound to FTase, more new specific drugs might be found.

Normal Farnesylation of Pre-Lamin A
Pre lamin A is normally farnesylated at its C-terminal CaaX box. In a second processing step, this farnesylated C-terminus is cleaved from the protein, releasing mature Lamin A to assemble a functional nuclear lamina.

Cause of Progeria
Progeria is a premature aging disease in children. The molecular basis of this disease is a 50 amino acid deletion in the Pre-Lamin A protein. This deletion allows the initial farnesylation of the Pre-Lamin A protein, but interferes with the subsequent cleavage to generate the mature Lamin A protein. In progeria, the farnesylated Pre-Lamin A protein builds up in the nucleus and leads to nuclear instability.

The Model
A physical model of the ternary complex of (1) FTase, (2) the Jan3 inhibitor (colored green) and (3) the farnesyl pyrophosphate substrate was designed and built of plaster using a ZCorp 3D Color printer. The model was based on 1SA4.pdb. The alpha helices of the A subunit are colored blue. The alpha helices of the B subunit are colored red. Beta sheets are colored yellow.

Farnesyltransferase Inhibitors (FTIs)
Inhibitors have been found that block the binding of the CaaX box motif to FTase. By inhibiting the farnesylation of the Pre-Lamin A protein, it is mislocalized away from the nucleus. These inhibitors have recently been shown to prevent the formation of misshapen nuclei in mouse fibroblasts containing a targeted progeria syndrome mutation.

Future Research
Farnesyltransferase Inhibitors (FTIs) may be an effective treatment for progeria. However, this wouldn't be considered a cure because it would interfere with other reactions that require farnesylation within the cell. Farnesylation functions in normal phenotypes to establish a functioning nuclear lamina. If farnesylation is interfered with, then necessary proteins will not be made available.