

2008 TAIWAN INTERNATIONAL SCIENCE FAIR

CATEGORY : Chemistry

**PROJECT : Synthetic Analogs of Smoothened
Intracellular Loop as Potent Inhibitors of
Cancer Cells Growth**

AWARDS : Chemistry First Award

SCHOOL : Middletown Senior High School

FINALISTS : Jarrett Renn Remsberg

COUNTRY : United States

Chemistry

Synthetic Analogs of Smoothened Intracellular Loop as Potent Inhibitors of Cancer Cells Growth

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Smoothened (SMO) is a critical component of Hedgehog (HH) pathway that is essential for stem cell renewal and is dysregulated in many cancer types. SMO is a seven transmembrane domain protein with three intracellular loops. Primary structures of SMO intracellular loops are unique and very much conserved among the species, which is indicative of significant and unique roles in intermolecular or intramolecular interactions. The hypothesis was that synthetic analogs of SMO intracellular loops may function as HH pathway inhibitors.

Derivatives of second intracellular loop were synthesized utilizing automated solid phase peptide synthesis based on Fmoc chemistry. Peptides were purified by HPLC and their anti-proliferative activity tested on melanoma cells by MTT assay.

Targeted libraries of second loop derivatives of varying length helped to identify compounds that inhibited the growth of melanoma cells *in vitro* with IC_{50} in nanomolar range. The most potent of antagonists obtained is the palmitoyl derivative of the N-terminal half of the loop, and is 12 residues long. Lipidation proved to be critical for the activity. Remarkably, retro-inverso versions of the peptide, in which all amino acids are in D-configuration, are even more potent and have IC_{50} in subnanomolar range. Circular dichroism studies proved that the peptides are folded both in aqueous solutions and in the presence of lipids mimicking the membrane environment. They also suggested that retro-inverso analogs have a different fold, which may contribute to higher activity. The new compounds are promising drug candidates and present convenient tools for solving the mechanisms of hedgehog signaling.

評語

- 1) 題目有趣，成果亦有相當的實用價值。
- 2) 實驗過程嚴謹，研究人員對數據的解讀完整且有依據。