

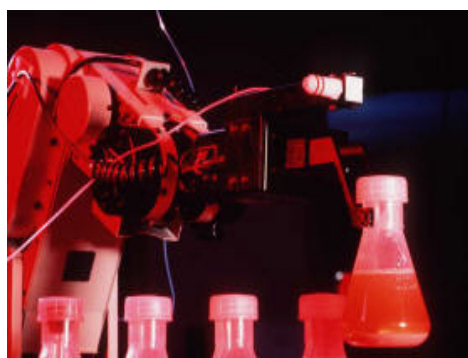


Novel Sansalvamide A Derivatives as Treatments for Colorectal and Pancreatic Cancer

Natural derivatives show efficacy against drug-resistant strains of cancer

Although many advances in the chemotherapeutic treatment of cancers have been made, several cancers have been identified that have few treatment options.

In 2004, ~150,000 people were diagnosed with colorectal cancer. About 10% of those cancers express a genetic mutation referred to as Microsatellite Instability (MSI). MSI colorectal cancers do not respond positively to existing chemotherapies. During the same period, 29,000 people were diagnosed with cancer of the pancreas. The five-year survival rate for advanced pancreatic cancer is <1% and mortality is equivalent to incidence. New antitumor agents are needed.



Often, the best source for novel compounds is Nature. However, Nature supplies a limited number of compounds, so it is imperative to modify compounds with known anti-tumor activity to optimize their potency and minimize toxicity. Cyclic peptides comprise a potent class of naturally occurring bioactive molecules, and they have several advantages as drug candidates. Cyclic peptides are more lipophilic and membrane permeable than linear peptides, meaning they can be taken up by cells *in vivo*. In addition, cyclic peptides are much more stable than linear peptides, and exhibit greater *in vivo* half-lives.

Sansalvamide A is a cyclic peptide produced by a marine fungus of the genus *Fusarium*, which is found on Little San Salvador Island in the Bahamas. This compound has been shown to have significant cancer cell cytotoxicity against the National Cancer Institute's 60-cell-line panel. Dr. Shelli McAlpine has generated over 60 novel compounds based on the structure of Sansalvamide A that show efficacy against colorectal cancer cells (both MSS and MSI

strains) and pancreatic cancer, as well as additional cancer cell lines.

The compounds are macrocyclic peptides that utilize novel arrangements of natural and unnatural amino acids and can inhibit the growth of cancer cell lines at IC_{50} better than natural Sansalvamide A, or existing chemotherapeutic agents (e.g., Mitomycin C)

These compounds will be screened against existing cancer drug targets, and will form the basis for the development of novel therapeutic agents that attack drug-resistant cancers

Benefits

- More potent than natural compounds
- Effective against drug-resistant cancer strains
- Wide range of efficacy against cancer cells

Applications

- Use in library screens against existing drug targets
- Drug development

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