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## Silstatins 1-8 and Structural Modifications: Antineoplastic Agents

The promise of marine derived microorganisms as productive sources of new anticancer and antiproliferative drugs continues to expand. Previously, Dr. Pettit and his team isolated and determined the structures of two very potent cancer cell growth inhibitors, cyclodepsipeptides from *Bacillus silvestris*, carried by a South Pacific crab. Subsequently, they completed the total synthesis of bacillistatin 2. Structurally, the bacillistatins are similar to valinomycin, a well-known antibiotic and cytotoxic cyclodepsipeptide that acts as a carrier-type potassium ionophore. With the recent advent in the antibody-drug conjugate (ADC) technology, there is a renewed interest in natural products as a source of potent payload for ADCs.

Dr. Pettit and his team at Arizona State University have expanded upon their earlier discovery of the remarkable anticancer bacillistatins from *Bacillus silvestris* and conducted SAR and other structural modifications such as availability of a free hydroxyl group for ADC and other prodrug linkage. This has resulted in seven structural modifications designated Silstatins 1-8 where the exceptional cancer cell growth inhibition of some of them ranges from GI50 10<sup>-3</sup>-10<sup>-4</sup> µg/mL. Silstatin 7 was converted to a glucuronic conjugate that has a potential application as a pro-drug.

These potent cancer cell growth inhibitors have a long patent life and are highly amenable to conjugation to further increase their utility and selectivity as well as reduce potential side effects.

### Potential Applications

- Cancer cell growth inhibitors
  - Suitable as payloads for ADCs
  - Glucuronide derivative of Silstatin 7 (prodrug; releases Silstatin 7 in vivo)
  - Potential application as a free drug

### Benefits and Advantages

- Highly potent inhibitors of cancer cell growth
- Suitable as payloads for ADCs
- Hydroxyl group for convenient conjugation to antibodies through a linker
- Glucuronide derivative of Silstatin 7 as a pro-drug
- Potential application as a free drug
- Intrinsic tumor targeting property
- Mechanism of action - Likely to act as K<sup>+</sup> ionophore
- Total synthesis achieved

### State of Development

Total Synthesis achieved. Glucuronide derivative of Silstatin 7 - prodrug created

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which releases Silstatin 7 in vivo.

Dr. Pettit's departmental webpage