RAID Projects with Dr. Samuel Danishefsky, Memorial Sloan-Kettering Cancer Center

The Epothilones

Fermentation Products Known Since the 1990s to Have Anticancer Activity

DTP provided the following:

- First confirmation of microtubule-based mechanism of action of epothilones, with epothilone B being especially active.
- First kinetic demonstration that epothilones A and B are competitive inhibitors of paclitaxel binding to tubulin.
- First demonstration that a paclitaxel-resistant cell line with a tubulin mutation retains sensitivity to epothilones and first confirmation that MDR cells retain sensitivity to epothilones.
- First demonstration that tubulin assembly induced by epothilone B is inhibited by drugs that inhibit tubulin assembly.

First RAID Application Received from Dr. Danishefsky 02/1999

Applicant prepared a number of analogs related to the epothilones A and B. Included in these analogs was 12,13-desoxyepothilone B, which was found to be much less toxic than epothilone B itself. In in vivo studies, the desoxy compound was well tolerated and virtually curative against a variety of tumors, including some resistant to paclitaxel.

RAID Application Approved and Initiated 06/1999

- A 5 g pilot batch of material was produced and analyzed.
- A 40- to 50-step synthesis was required.
- Material was returned to Dr. Danishefsky for testing.

First RAID Application Completed and Second Application Received 02/2000

Pharmacology Studies Initiated 07/2000

- Species-dependent in vitro metabolism with plasma from various species: rat > mouse >> dog >> human.
- Similar pattern with liver S9 fractions.
- In vitro data predictive of in vivo half-life: mouse = 3.6 minutes, rat = 19 minutes, dog = 476–2634 minutes

KOSAN Biosciences Licenses and Collaborates with DTP 03/2001

Two Different Formulations Studied 03/2001

Two proposed clinical formulations are:

1. 10 mg/mL epothilone D in Diluent 12.
2. 10 mg/mL epothilone D in cremophor: propylene glycol (PG): ethanol (20:30:50) by volume.

Material Made Available for Clinical Trials

- DTP contractor produced 25 g of material.
- KOSAN developed a biological production system.

12,13-Desoxyepothilone First Tested in Man 10/2001

Currently Entering Phase II Clinical Trials

In Vitro Half-Life of Epothilone D in Plasma From Various Species

Range-Finding and IND-Directed Toxicology Studies Conducted 09/2000

- Toxicology studies were conducted in dogs given a 4-hour continuous i.v. infusion.
- The maximum tolerated dose (MTD) in the dog when given as a 4-hour continuous i.v. infusion is 110 mg/m² as a single dose and >110 mg/m²/dose weekly x 3.
- Gastrointestinal and bone marrow toxicity were dose limiting.
- The recommended clinical starting dose was 11 mg/m²/dose weekly x 3 (i.e., one-tenth the maximum tolerated dose given weekly x 3 in the dog).