



Auristatin 15-PE: New Modifications to Dolastatin 15

AzTE Case # 96-002

Inventors

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Invention Description

Auristatin 15-PE is a seven subunit depsipeptide that has exceptional anticancer activity. The compound is uniquely active in pancreatic cancer, a disease marked by a high mortality rate and few treatment options. Preliminary studies show auristatin 15-PE to inhibit tubulin polymerization, IC_{50} 15 μ M. However, other evidence suggests a second cellular target is likely, based on CRI's experience with two other compounds in clinical development (dolastatin 10 and auristatin PE), it is believed that auristatin 15-PE has tremendous potential for clinical development.

Auristatin 15-PE has been evaluated against a variety of murine and human cancer cell lines. Inhibitory effects in mouse leukemia P388, ED_{50} .26 ng/ml, mouse leukemia L1210, IC_{50} 2 nM, and human CA46 Burkitt lymphoma, IC_{50} .3 nM, are illustrative of the *in vitro* data results. In the Burkitt cells, the 15-PE causes a marked rise in the mitotic index. Repetitive testing in the NCI's 60 cell human tumor primary system consistently yielded a mean panel GI_{50} value very similar to that of the parent compound, dolastatin 15. However, based on structure-activity studies of analogues of dolastatin 10, CRI expects the behavior of auristatin 15-PE *in vivo* to differ from that of dolastatin 15, both in the dose and eventual clinical response, as has been the experience with dolastatin 10 and its 2-phenylethylamine counterpart auristatin PE, how in human clinical trials.

The *in vivo* preclinical anticancer results, especially against pancreatic carcinoma and in combination with Gemcitabine, have been quite dramatic (70% cure rate). There has been recent evidence in unpublished work of exceptional *in vivo* activity in a mouse model for a combination of auristatin 15-PE with bryostatin 1 in ALL, where complete cures were seen. Further promising results were obtained with pancreatic cancer in the mouse model with the same combination, where three out of five mice were completely cured.

Stage of Development: Auristatin 15-PE may be prepared in quantity by a synthetic process described by Pettit et al. (Anti-Cancer Drug Design 1998, 13, 47-66). CRI has demonstrated consistently high yields and the process requires fewer steps than the synthesis of the parent compound. Overall, this synthesis gives ready access to supplies of auristatin 15-PE.

Intellectual Property

Status:

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Potential Applications

- Anticancer therapeutic agents – particularly pancreatic cancer

Benefits and Advantages

- These new modifications to dolastatin 15 exhibit significant inhibition of cancer cell growth