ProLindac™ Fact Sheet

What is ProLindac™?

ProLindac™ (formerly AP5346) is Access Pharmaceutical's lead oncology drug in Phase 2 clinical development. ProLindac™ is a polymer therapeutic which utilizes a safe, water-soluble polymer to increase efficacy by delivering more DACH platinum (the active part of the currently-marketed drug, oxaliplatin) to tumors while lessening toxic side effects by reducing delivery of DACH platinum to normal tissues. Oxaliplatin had worldwide sales exceeding $2 billion in 2006.

ProLindac™ has been shown to be much more effective than oxaliplatin in a large number of murine tumor models.

In a Phase 1 clinical study:

- At least five times more platinum could be administered to patients with ProLindac™ than oxaliplatin before the onset of toxicity.
- In patients resistant to prior platinum treatment, ProLindac™ produced two partial responses and four cases of stable disease in an evaluable patient population of 16.
- A Phase 2 study to determine the efficacy and safety of ProLindac™ in patients with recurrent ovarian cancer is underway in Europe.

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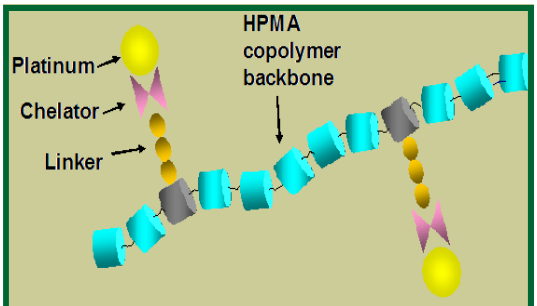
Chemistry of ProLindac™

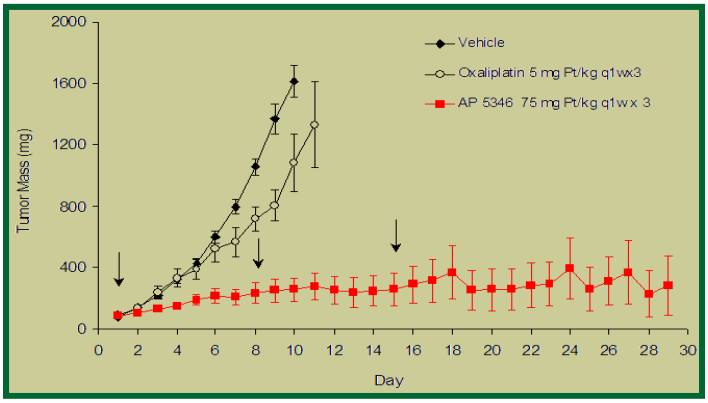
ProLindac™ is a prodrug of DACH platinum in which the cytotoxic agent is bound to a water-soluble biocompatible copolymer backbone, called hydroxypropylmethacrylamide (HPMA).

ProLindac™ is designed to be relatively non-toxic while in general circulation, and for the platinum drug to be released within the tumor environment. In ProLindac™, platinum is believed to be released by a mechanism which makes use of the fact that tumors are generally more acidic than surrounding normal tissue. ProLindac™ releases platinum much more rapidly in a slightly acidic environment compared with an environment at physiological pH.



ProLindac™ comprises a linear copolymer chain of HPMA (blue) and peptide (black) to which platinum is attached via a pH-sensitive chelator.

Preclinical Efficacy Data

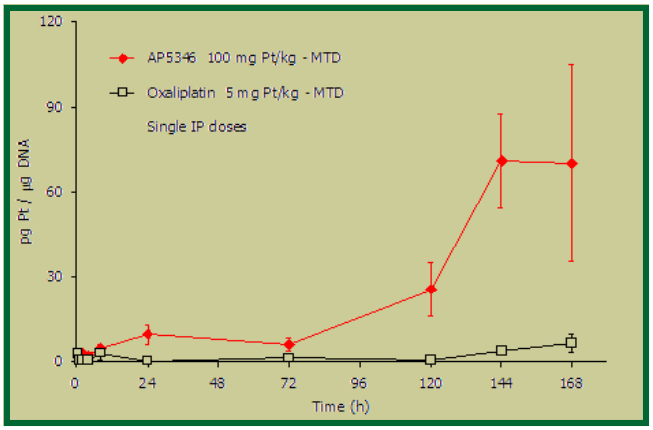


The above graph displays typical results for ProLindac™ in a mouse tumor model; in this case the B16 melanoma model. These tumors grow rapidly in mice that are not treated, as shown by the "vehicle" plot. When the mice were treated with oxaliplatin there was a slight reduction in the rate of growth of the tumor (open circles). However, ProLindac™ (red squares), when dosed at an equitoxic dose to that of oxaliplatin retarded tumor growth to a much greater extent than oxaliplatin. As shown in the table on the right, ProLindac™ has been studied 11 tumor models. It was never inferior to oxaliplatin and was markedly superior (as demonstrated in the B16 model) in three cases. It was also determined to be superior (no overlap of error bars at later time points) in an additional five models. These very promising data provided the impetus to advance ProLindac™ into clinical development.

Tumor Model	Efficacy compared to oxaliplatin
M5076 sarcoma (Pt-resistant)	Markedly Superior
B16 melanoma	Markedly Superior
2008 ovarian xenograft	Markedly Superior
Colo-26 colon	Superior
HT-29 colon xenograft	Superior
HCT-116 colon xenograft	Superior
L1210 leukemia	Superior
0157 Hybridoma	Superior
M5076 sarcoma	Similar
Lewis lung	Similar
P815 Mastocytoma	Similar

Enhanced Delivery of Platinum to Tumors

There is strong evidence that platinum chemotherapeutic agents kill tumor cells by forming adducts in DNA. The formation of platinum-DNA adducts is believed to trigger apoptosis in platinum-sensitive malignant cells. The extent of cell killing increases as more and more drug is delivered to the tumor. In the B16 melanoma mouse model, when administered at equally toxic doses, ProLindac™ delivered 16-fold more platinum to the tumor than oxaliplatin, and 14-fold more platinum-DNA adducts were formed in the nucleus of tumor cells, when ProLindac™ and oxaliplatin were administered at doses of equal toxicity. This striking result may help to explain why ProLindac™ is considerably more effective in many mouse tumor models than oxaliplatin.



ProLindac™ delivered 14-fold more platinum to the DNA of the tumor than oxaliplatin when both compounds were administered at their maximum tolerated doses (determined from the relative areas under the curves in this graph).

Phase 1 Clinical Study

A 26-patient dose-ranging open label Phase 1 study was conducted in Europe to:

- To determine the maximum tolerated dose.
- To establish a recommended dose for Phase 2 trials.
- To determine the toxic effects of ProLindac™
- To document possible anti-tumor activity.
- Determine the pharmacokinetic profile of ProLindac™

Patients were treated weekly for three weeks, then were rested for a week.

The investigators reached the following conclusions:

- The recommended dose for further assessment of ProLindac™ administered over 1 hour for 3 weeks out of every 4 weeks is 640 mg Pt/m^2.
- ProLindac™ was tolerated up to a dose of 640 mg Pt/m^2, with a toxicity profile characterized by frequent grade 1-2 nausea, vomiting, and creatinine elevations, with an absence of grade 3-4 hematotoxicity below 1280 mg Pt/m^2.
- Evidence of antitumor activity was observed in several patients. Partial responses achieved in 2 patients, one with melanoma and one with platinum-resistant ovarian cancer, and disease stabilizations in patients with melanoma, esophageal cancer, and ovarian cancer.
- Normalization of the CA 125 biomarker occurred in another ovarian cancer patient.
- Total and ultrafiltrate platinum C_{max} and area under the curve increased linearly with dose, and terminal half-life did not vary with dose.
- Phase 2 assessment of ProLindac™ is warranted in relapsed ovarian cancer patients.

In the Phase 1 study, responses were observed in patients with platinum-resistant ovarian cancer. A Phase 2 clinical study of ProLindac™ in patients with recurrent ovarian cancer commenced in 2006 at several sites in Europe.

Future ProLindac™ Development

Given the potential of ProLindac™ to treat a wide variety of cancers, several development pathways are available for this compound. A Phase 2 clinical study of ProLindac™ in patients with recurrent platinum-sensitive ovarian cancer is underway. The FDA has approved an IND for ProLindac™ for the first phase of a development program that will permit replacement of oxaliplatin by ProLindac™ in the FOLFOX regimen. In addition, the compelling preclinical and clinical results in melanoma indicate that ProLindac™ also has considerable potential for the treatment of this disease as well.

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