PLX038 PEG~SN-38

We have a novel, slow-releasing PEGylated SN-38 (PEG~SN-38) that has entered Phase 1 clinical trials at MD Anderson as an anti-cancer agent. SN-38 is the active metabolite of the anti-cancer agent irinotecan (CPT-11) and is a potent inhibitor of topoisomerase I. In animal models, the ProLynx PEG~SN-38 conjugate PLX038 shows a unique combination of the most desirable features of a topo I inhibitor: (i) it has a very long half-life and very low C_{max}; (ii) it does not require liver metabolism and thus has minimal intestinal toxicity; (iii) it accumulates in solid tumors; and (iv) it shows high therapeutic efficacy. In contrast, none of the competing SN-38 or CPT-11 prodrugs provide delivery of SN-38 that maintains the drug over the target threshold for protracted periods, nor are they able to since their residence times are limited by the short cleavage half-lives of the ester linkage used (~12 to 24 h); further, C_{max} and the peak-to-trough excursions of such drugs are high. We believe these characteristics of PLX038 will translate into higher efficacy rates combined with an improved safety profile in cancer patients.

ProLynx retains world-wide rights to this PEG~SN-38 conjugate. We are seeking pharma partners or investors who share our conviction that this drug is superior to the alternatives, and will take initiative in moving it forward aggressively in Phase 2 and pivotal clinical trials.

PLX039 Once-Monthly GLP-1 Agonist

Agonists of the glucagon like-1 (GLP-1) receptor are an important treatment for type 2 diabetes and potentially useful anti-obesity agents. In 2013, GLP-1 agonists achieved sales of $3.2 billion and sales are expected to reach >$12 billion by 2024. Since the first twice-daily agonist Byetta was approved in 2005, a number of once-daily or once-weekly administered agonists have been developed and approved by the FDA. A current challenge is the development of even longer acting GLP-1 agonists.

We have developed an ultra-long acting delivery system for a GLP-1 agonist that is suitable for once-monthly administration. The agonist is covalently attached to 40μm hydrogel microspheres by a self-cleaving β-eliminative linker; upon subcutaneous injection the linker slowly cleaves and releases the drug. The serum half-lives for released GLP-1 agonist is ~30 days. Simulations indicate that this conjugate will support monthly administration in the human, thus representing the first viable once-monthly GLP-1 agonists. The ProLynx once-monthly GLP-1 agonist being readied for preclinical toxicology studies.

PLX040 Subcutaneous Long-Acting Octreotide

Octreotide is a cyclic octapeptide that is used to treat acromegaly and neuroendocrine tumors. It is commercially available as a thrice-daily subcutaneous (s.c.) immediate release injectable, and a long acting release formulation (Sandostatin LAR ®) that is injected intramuscularly (i.m.) each month. Yearly sales of Sandostatin LAR are currently about $1.5 billion.

There are several shortcomings of Sandostatin LAR. First, the PLGA formulation requires dry storage and a multi-step reconstitution at the time of injection. Second, the 2.5 mL deep intra-gluteal injection requires a large 1½ inch 20 gauge needle and must be administered monthly by a health care professional; not surprisingly, significant discomfort occurs at the injection site. Certainly, a considerable number of patients and physicians would welcome a patient-administered, relatively painless s.c. injection of a long-acting octreotide.

We have attached octreotide to 40μm hydrogel microspheres via our -eliminative linkers that can be administered s.c. through a small-bore 27 gauge needle. In an animal model, we can increase the half-life of octreotide to over 350 hours and maintain drug concentrations above therapeutic levels for prolonged periods. Pharmacokinetic simulations indicate that the hydrogel-octreotide microspheres will easily support weekly subcutaneous dosing in humans. Our data indicates that our hydrogel-octreotide conjugate should have the pharmacokinetic benefits of Sandostatin LAR, without its shortcomings. The ProLynx once-weekly s.c. octreotide is being readied for preclinical toxicology studies.