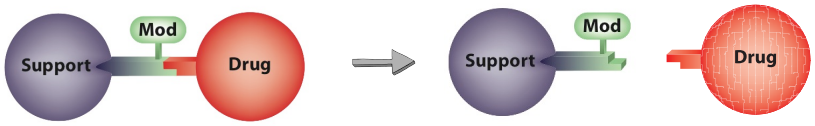
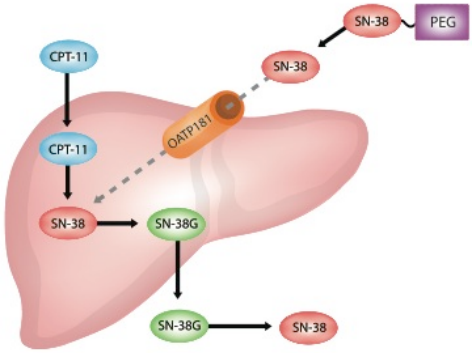
EXECUTIVE SUMMARY – PLX038: PROLYNX'S PEG~SN-38

Company. Prolynx has a technology platform for half-life extension that involves chemical conjugation of drugs to macromolecular carriers with releasable β-eliminative linkers. Our novel linkers release the native, active drug at predictable and adjustable rates, and do not require enzymes. Using linkers with slow release rates, we can deliver drugs for extended periods of time – days to months – with a very low C_{max} and keeping the released drug above a target threshold concentration for long periods



PEG~SN-38 program overview. We have a novel, slow-releasing PEGylated SN-38, PLX038, in Phase 1 clinical trials at MD Anderson as an anti-cancer agent. The SN-38 released from PEG~SN-38 has a very low C_{max}, low liver exposure and gastrointestinal (GI) toxicity, and a very long half-life.

SN-38 is the active metabolite of the anti-cancer agent irinotecan (CPT-11) and is one of the most potent inhibitors of topoisomerase I (topo I). Inhibition of topo I results in time-dependent DNA damage and consequent apoptosis. Topo I inhibition also prevents accumulation of HIF-1α needed for tumor survival in low-oxygen conditions and responsible for production of survival proteins such as VEGF. CPT-11 is primarily used to treat colon cancer, usually in combination with other agents. It is also effective in cancers such as pancreas, breast and lung.



While highly effective, the SN-38 pro-drug CPT-11 has many undesirable features: (i) it is extensively metabolized and shows high inter-patient variability in its pharmacokinetics and pharmacodynamics; (ii) it shows a high C_{max} and short time-over-threshold; (iii) it requires activation to SN-38 in the liver, is glucuronidated and transported through the bile and frequently shows intestinal toxicity.

In contrast, the SN-38 released from PLX038 (i) is not further metabolized, so should not show inter-patient variability; (ii) shows a low C_{max} and a very long time-over-threshold; (iii) does not require activation so it has low liver exposure and low GI toxicity; and (iv) shows high accumulation in solid tumors by the enhanced permeability and retention (EPR) effect. *Thus, our PEG~SN-38 has a unique set of advantageous properties that qualifies it as an exciting new anti-cancer agent.*

Combination Chemotherapy with PLX038. The nano-particle size and long half-life of PEG~SN-38 promotes its accumulation in vasculature of solid tumors by the EPR effect. Indeed, both PEG~SN-38 and free SN-38 are present in high concentrations in tumors for up to two weeks after administration and after most systemic drug has cleared. Based on the above, we posit that the EPR effect of PLX038 could be exploited in combination chemotherapy. Specifically, if a tumor is first loaded with PLX038 via the EPR effect, and the systemic PLX038 allowed to clear, a second drug that is synergistic with SN-38 but has overlapping toxicity could be administered without toxic combination effects on normal tissue. Here, the tumor would be exposed to both drugs — the PEG~SN-38 and

SN-38 accumulated by EPR, and the second administered systemically — whereas normal tissue would only be exposed to the second drug administered. We believe that the high accumulation of PLX038 in solid tumors may enable the effective use of synergistic drug combinations such as PARP inhibitors, vincristine, FU, oxaliplat, and others with lower systemic toxicities.

Competition and Competitive Advantage. Three PEGylated analogs with cleavable ester linkers are yielding promising results in clinical trials: 1) NKTR-102 (Nektar) is a PEGylated CPT-11 which after esterase cleavage of the linker releases CPT-11; 2) CRLX101 (Cerulean) is an analogous ester-containing PEGylated camptothecin; and 3) NK-012 is a soluble PEG-Glu micelle (Kashiwa/Nippon Kayaku) again linked by an ester to SN-38. In addition, a liposomal formulation of CPT-11 (MM-398; Merrimack) that achieves sustained delivery of CPT-11 has recently been approved for treatment of pancreatic cancer.

None of the current PEGylated CPT-11 or SN-38 conjugates maintain the concentration of free SN-38 over the target threshold for protracted periods; nor are they able to because they are limited by the relatively short half-lives of ≤30 hours for spontaneous hydrolysis of their ester linkages. Also, unlike PLX038, all of the current prodrugs show high C_{max} values of SN-38 that likely contributes to toxicities.

Intellectual Property. PLX038 and our linker technology are covered in numerous issued and pending U.S. and international patent applications.

Potential market. There are ~95,000 colorectal cancer (CRC) patients/year in the US and Europe. Since CPT-11 is a component of FOLFIRI, and since FOLFIRI is used as either first- or second-line therapy in CRC, most of these patients will be treated with CPT-11. It has also been projected that ~40,000 patients with pancreatic cancer will be treated with a form of CPT-11. Based on scientific rationale and preclinical studies we expect PLX038 will show significantly improved safety and efficacy over CPT-11 by maintaining a low C_{max} and keeping SN-38 levels for long periods of time-over-threshold. Pursuit of other indications for our PEG~SN-38 in combination with other anti-cancer agents could achieve significant additional sales; for example, exploitation of the EPR effect in combination with drugs such as the PARP inhibitors could be useful in treatment of ovarian and breast cancers. We believe that a premium-priced product with superior efficacy and less side effects could again command the sales that CPT-11 had before going generic; a similar scenario was realized when Abraxane was introduced as a superior alternative to generic Paclitaxel.

Proposition. Prolynx owns non-Asian rights to the PEG~SN-38 conjugate. Assuming favorable results in ongoing Phase 1 trials, we are seeking a partner to advance PLX038 alone and in combinations through Phase 2/3 clinical trials. We envision an experienced collaborator who shares our conviction that this drug will be superior, and will take the initiative in moving it forward in well-designed science-based trials.

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