Invest Dermatol has been shown for both In contrast to IV therapy, we believe that over 1 hour post with similar molecular weights (1736 and 1763, respectively) and with (J Invest Dermatol 140:1480 (P46) in the FN first type III repeat. P46, a 15 endopeptidase abundant in wounds beginning about 4 days post tissue injury (21.3µm) and of a similar maximal diameter terminal arcade (3.8µm). (JWMRP, W81XWH-2-2004). Using dose range, one log lower to one log higher than 0.01mg/kg, we confirmed that 0.01mg/kg of P12 is the optimal IV dose at 1h post-burn that spurs burn wound closure 14d afterburn (70% vs 20% control). These data were obtained in the IND (funded by JWMRP, W81XWH-2-15-C-0043). We found that vasodilation of the perivascular microvasculature is the mechanism of action for cP12 burn therapy (see Figures 5 and 6). A Phase 1 Clinical was successfully completed in 2019 (Military Burn Research Program, JWMRP, W81XWH-1-18-02085).

P12 milestones 1. Orphan Drug designation 2011 2. IND accepted 2017 3. Fast Track designation 2019 4. Successful completion of Phase 1 Clinical Trial 2019 5. Phase 2a Trial Synopsis to be submitted to the IND 2022 6. Posted to conduct a Phase 2a Clinical Trial P12 is extremely sensitive to human and porcine elastase (HNE), an endopeptidase abundant in wounds beginning about 4 days post tissue damage. Thus, P12 is minimally active as a topical therapy for 4 days post injury (funded by Joint Warrior Burn Research Program, JWMRP, W81XWH-1-14-01005).

Subsequently, NeoMatrix Therapeutics (NMT) discovered another peptide (P46) in the FN type III repeat. P46, an 15-residue peptide, is substantially related to elastase (J Invest Dermatol 138:2480-2483, 2013). NMT engineered several peptides from P46 to resist high concentrations of human neutrophil elastase during a 24 h incubation. After a cycle of biologically active, engineered peptide, designated cNP8 was chosen for further study. NP8 speeds healing, and reduces scarring when given IV at 0.001 mg/kg for 4h post-burn (J Invest Dermatol 140:1480-1483, 2020) (funded by JWMRP, W81XWH-1-15-C-0043). Given that cNP8 is 67% homologous to P12 with similar molecular weight (1736 and 1763, respectively) and similar isolectric points (-11.3), we assume that blood levels in pigs and humans are about the same for 0.01mg/kg doses, i.e 100µM to 1000µM over 1 hour post-injection (exclusively scaling). Since cNP8 contains an RWRPK sequence that strongly vasodilates the microvasculature at low levels, we post that this is also the mechanism of action for cNP8 IV therapy (see Figure 5). In contrast to IV therapy, we believe that topical cP12 and cNP8 promote wound healing through fibroblast stimulation and growth at 1µM - 100µM as has been shown for both P12 (J Invest Dermatol 134:1119-1127, 2014; J Invest Dermatol 134:1119-1127, 2014; J Invest Dermatol 138:2480-2483, 2013) and cNP8 (J Invest Dermatol 140:1480-1483, 2020). At µM doses cNP8 also promotes angiogenesis for P12 (Poster MSRS-22- 04958). Given the sequence similarities of cNP8 to cP12, we propose that cNP8 will also stimulate angiogenesis at µM doses.

cNP8 milestones 1. Preclinical safety and efficacy complete for IV therapy 2. Manufacturing cNP8 Drug Product complete 3. Stability of cNP8 Drug Product ongoing 4. cNP8 for IV therapy IND submission scheduled for late 2022. 5. cNP8 for topical therapy award 2022 by Joint Warrior Burn Research Program (JWMRP).