

Potentiating Melphalan in Multiple Myeloma by Targeting the Fanconi Anemia/BRCA Resistance Pathway



Multiple myeloma (MM), a plasma cell malignancy, affects approximately 24,000 people per year. There are also currently approximately 80,000 patients living with multiple myeloma, and the 5-year survival rate is only 45%. First line treatment with melphalan is initially effective, but importantly, will eventually fail and patients will become resistant to melphalan treatment. This technology is a method of overcoming resistance by silencing key DNA damage response proteins and re-sensitizing multiple myeloma cells to melphalan treatment.

COMMERCIAL OPPORTUNITY

- Multiple myeloma (MM) patients who are not candidates for autologous stem cell transplants receive melphalan as a standard of care, in combination with other therapies.
- Only 25% of MM patients receive transplants, meaning 18,000 multiple myeloma patients a year will be treated with melphalan. Treatment with melphalan is initially effective, but all patients will eventually become resistant to therapy.
- Our studies have shown that FANCF siRNA potentiates the effect of melphalan and overcomes resistance to melphalan in cell lines.
- siRNA therapeutic technology for various oncology indications is actively being pursued by several companies including, Alnylam, Isis Pharmaceuticals, Marina Biotech, Silence Therapeutics, and Tekmira, indicating the attractiveness of this novel biologic therapeutic strategy.
- Alnylam Pharmaceuticals is developing liposomes to encapsulate siRNA for delivery to bone marrow, which has been successful in monkeys and mice (Molecular Therapy-Nucleic Acids (2012) 1, e4), suggesting that it may eventually be feasible to successfully target siRNA therapies in MM patients.

TECHNOLOGY

Our technology is a patent-protected method to treat multiple myeloma patients with FANCF siRNA in combination with melphalan or cisplatin. Fanconi anemia (FA) proteins interact with BRCA to repair DNA cross-links, UV-induced dimers and double strand breaks through homologous recombination. The FA/BRCA DNA damage pathway repairs melphalan-induced DNA interstrand cross-links, rendering melphalan therapy ineffective. Knockdown of FANCF in melphalan-resistant 8226 cells with FANCF siRNA resulted in a two-fold increase in apoptosis upon treatment with melphalan ($P < 0.05$). Disruption of the FA/BRCA pathway by silencing FANCF successfully inhibited DNA repair ($P < 0.05$). Our data show that our patent-protected method of treating multiple myeloma patients with FANCF siRNA successfully resensitizes cells to melphalan-induced DNA damage.

PUBLICATION/PATENT

- Chen et al. Blood 2005; 106:698. Yarde et al. Cancer Res 2009; 69:9367.
- US Patent 8,227,434 granted July 24, 2012 to Moffitt on behalf of Drs. Dalton, Hazlehurst and Chen

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LICENSING OPPORTUNITY



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