COMMENTARY: BRCA1/2 Mutations, Vulnerability to Breast/Ovarian Cancer, and Current and Future Treatment Modalities

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It is now well-recognized that both men and women can inherit BRCA1 and BRCA2 mutations from their parents, making them vulnerable to the development of breast and ovarian (prostate in case of males) cancer. Such cancers can occur at an early or late stage of life, depending on various factors, and such incidences of cancer run in families. The mutations occur in tumor suppressor genes such as BRCA1 which encodes the 1863 amino acid protein BRCA1. This protein constitutes macromolecular complexes with other proteins involved in DNA damage repair and cell cycle checkpoints. The highly interactive nature of BRCA1 protein helps maintain genomic stability which is lost due to some mutations in the genome encoding DNA repair functions, thus accelerating the incidence of cancer [1, 2]. The germline transfer of BRCA1 or BRCA2 mutant genes to women with family history of breast or ovarian cancer thus creates the feelings of anxiety and frustrations in women, particularly young women, who remain at edge not knowing when the cancer will strike.

If or when the cancer strikes, the usual response is to have surgical removal of the tumor, or the organ itself, followed by radiation and chemotherapy. Aside surgery, particularly radical mastectomy for breast cancer which is highly controversial, the hardest part is to go through radiation and chemotherapy because of the associated toxicities such as nausea, diarrhea, skin rash, interstitial lung disease, cardiotoxicity, anemia and others [3]. Fortunately, there appears to be on the horizon potential new drugs, proteins and peptides of bacterial origin, that appear to have very little toxicity but significant cancer regressing effect. An example of such a protein drug is azurin, a 14 kDa protein elaborated by *Pseudomonas aeruginosa* that gets secreted on contact with cancer cells when the bacteria sense the presence of such cells in their vicinity. Once released, azurin can preferentially enter cancer cells, but not normal cells, and exert strong inhibitory effect on cancer cell growth through interference in multiple steps of cancer growth [3, 4]. In xeno-transplanted tumor-bearing mice harboring human melanoma and breast cancer, intravenous injections of azurin elicited 60 to 80% regression of the tumors without any apparent toxicity [3, 4], thus demonstrating azurin's potential effectiveness as an anticancer agent without toxicity in mice.

To help bring bacterial proteins such as azurin to the bedside, a company CDG Therapeutics Inc. (www.cdgti.com) applied to the USFDA seeking approval for conducting a phase I clinical trial to determine its toxicity. The FDA, however, advised the company that as a protein to be isolated from bacteria with possible LPS (cell wall Lipopolysaccharide) contamination, azurin will have to go through stringent regulation (BLA) as a Biologic. A chemically-synthesized fragment of azurin would have quicker FDA approval if it is found to be nontoxic in animals. Accordingly, the company CDGTI developed a 28 amino acid peptide fragment from azurin, termed p28 that was found to have no toxicity in animals, including monkeys. On approval from the FDA, p28 was tested in 15 stage IV cancer patients in five escalating doses through intravenous injections. These patients had multiple drug-resistant tumors and they had a life expectancy of about 6 months. P28 exhibited very little toxicity even at the highest concentration, but showed significant beneficial effect including stabilization of tumor growth in 6 patients, partial regression in 3 patients and complete regression in 1 patient with 3 patients alive beyond 2 to 3 years after the trial with 1 patient demonstrating no tumor [5]. Encouraged by such results, the National Cancer Institute (NCI) and the Pediatric Brain Tumor Consortium (PBTC) started a second phase I trial with p28 in October, 2013, using the adult dose of p28 used in the first trial. The trial was

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conducted in 11 hospitals in the US with 18 patients aged 3-21 with brain tumors. When starting the trial, the sponsors stipulated that if p28 would prove to be toxic to the kids or lack efficacy, allowing the tumors to keep on growing, they would stop the trial. The trial has been ongoing for more than 2 years now, again suggesting that p28 appears to have acceptable toxicity, if any, but significant efficacy in the treatment of some pediatric brain tumor patients (http://clinicaltrials.gov/ct2/show/NCT01975116). Indeed, p28 has recently been approved for designation as an orphan drug by the USFDA for the treatment of glioma.

What do the above observations portray? It appears that some pathogenic bacteria with long term residence in the human body consider the human body as their habitat and try to defend it by producing a weapon such as azurin that has not only anticancer and cancer preventive activity but also anti-viral (HIV-1), and anti-parasitic activities against the malarial parasite or *Toxoplasma gondii* by interfering in their ability to bind host cell receptors and cause infections [3]. As a protein, azurin needs to be administered via intravenous injections to allow it to enter the blood stream, since proteins are too large in size to be effective orally for passing through the tight junctions in the intestinal epithelial cells. The technologies are, however, evolving, as exemplified by the recent attempts to develop oral insulin or similar somewhat smaller sized peptides for oral administration in diabetic patients. Although not yet fully developed, such small protein/peptide drugs are likely to reach the market for the benefit of many patients. To promote such new approaches, as well as to encourage new types of drug development, particularly for cancers in susceptible young girls with family history of cancer, we have written a book, a science fiction, entitled 'Three Daughters: Three Journeys'. This book depicts how three young girls, each inheriting BRCA1/BRCA2 type of mutations from their parents, became victims of cancer but eventually took three different avenues including traditional surgery/radiation/chemotherapy for one, and two new innovative approaches for using a bacterial protein drug that was fully functional during oral consumption, either as pills or as part of food. We believe that a book like 'Three Daughters: Three Journeys' will raise interesting questions and thought-provoking arguments among the readers about the future of the ways we treat cancer.

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