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Abstract Submission Form

Poster Title: **Sepiapterin-induced trained immunity prevents breast cancer by MAMPs**

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Category: **Cancer Biology**

HER2-positve breast tumor has an immune-suppressive tumor microenvironment (TME) and is refractory to most chemotherapies and immunotherapeutic agents. Thus, there is an urgent need to develop an effective treatment to improve the patients' outcomes. It has been demonstrated that adjuvant use of fecal microbiota transplantation (FMT) from treatment responders significantly improves the clinical outcome of patients with HER2+ breast tumors. However, the mechanisms by which FMT exerts anti-cancer effects have not been fully understood. Recent studies unveiled that gut microbes indirectly interact with host immune cells through specialized postbiotics, microbe-associated molecular patterns (MAMPs), to promote immunogenicity. Importantly, certain MAMPs could induce long-term sensitization of immune cells, termed 'trained immunity' against broad types of pathogens. Trained immunity, in facts, plays critical roles in prevention of different diseases, including cancer. Given the tremendous therapeutic potentials of MAMPs, further studies would be needed to identify and characterize them extensively. We previously isolated lipid fractions of fecal bacteria from animals which had been well protected from mammary tumor incidence after treatment with L-sepiapterin (SEP), an endogenous precursor of tetrahydrobiopterin, the cofactor of nitric oxide synthase. We applied these fractions, in comparison to fractions from tumor-susceptible animals to natural killer cells and macrophages. We found long-term sensitization of innate immune cells against cancer cells after treatment with SEP fractions. We hypothesize that these fractions of SEP-treated animals contain specific MAMPs capable of inducing trained immunity against breast cancer cells. In the present study, we aim to chemically characterize MAMPs from SEP-treated animals and determine the mechanisms by which MAMPs induce long-term sensitization of innate immune cells against HER2+ breast cancer cells. We found that the bacterial lipopeptides can activate the innate immune cells through TLR2/6 using a TLR assay and we found that lipopeptide analysis is possible in *B. subtilis* because of the prototype analysis. Therefore, we will perform lipidomics to determine their chemical properties of these MAMPs. We will then test their presence in the circulation of SEP-treated animals to verify their functionalities as MAMPs. The findings of this study will help design new cancer therapies based on MAMPs that can prevent HER2+ breast cancer.