When breast cancer cells spread outside the primary tumor to form metastases, sometimes decades after the initial diagnosis, the disease becomes refractory to therapies and generally incurable. Traditionally, most cancer treatments were designed to target cancer cells directly, a strategy that achieves initial responses in patients. However, since cancer cells accumulate mutations under therapeutic pressure, they eventually evolve and develop therapeutic resistance.

During the last two decades, the introduction of immune checkpoint (ICP) inhibitors in some metastatic cancers has created a paradigm shift in clinical oncology, demonstrating the unparalleled potential of the immune system to eradicate tumor cells completely. ***Unfortunately, the clinical responses in breast cancer patients are remarkably low, emphasizing a critical unmet need that lies at the heart of this proposal.*** Immunotherapy drugs restore the immune system's capacity to "seek and destroy" cancerous cells through a process of immune surveillance. This process is executed primarily by a subset of professional killer cells called T-cells. Together with another type of immune cells called macrophages, they form the first line of an informed, specific defense against pathogens and cancer. In the context of malignancy (e.g., breast cancer), T-cells will activate their killing machinery in response to foreign proteins expressed by tumor cells, called neoantigens.

Rationale: Macrophages are critical regulators of T cell activity, ***operating through two mutually exclusive and reversible activation states called M1 vs. M2***. While M1 macrophages stimulate T cells upon threat, the same cells will convert to the M2 state and suppress T cell activities once danger signals are cleared, preventing excessive tissue damage. In breast cancer, this plasticity is hijacked by tumor cells that "lock" macrophages in the M2 state through poorly understood mechanisms to gain protection from T-cell killing. Indeed, immune suppression by tumor-associated macrophages (TAMs) is considered one of the key processes driving immune evasion and resistance to immunotherapies. While M2 TAMs represent a major clinical hurdle, they expose a major vulnerability and an opportunity for intervention.

Dr. Ben-Chetrit is a new faculty member who developed strategies to "unlock" the M2 state in TAMs. He has pioneered a novel genetic screen in breast cancer TAMs to discover regulatory genes that control the M1/M2 phenotypic switch. He identified gene targets that, upon inhibition, force a full conversion of immunosuppressive TAMs (M2) back into immunostimulatory (M1) macrophages ("reprogramming"). Preliminary data from TAM reprogramming in breast and ovarian cancer mouse models provide encouraging results ***in late-stage, established tumors and liver metastases***. Treated mice demonstrate a substantial growth reduction with enhanced activation of T-cells, highlighting a potential synergism between macrophage reprogramming, immunotherapies, and treatments that expose neoantigens, such as radiotherapy. He has converged efforts with Dr. Silvia Formenti (co-investigator), the chair of the Radiation Oncology Department, and Michele Rakoff, an experienced consumer advocate, to tackle this challenge. Dr. Formenti is a prolific physician-scientist and an ideal research partner. She has pioneered the strategy of using focal radiotherapy (RT) with immunotherapy to convert breast cancer into an individual in situ vaccine. She also found evidence that M2 macrophages pose significant efficacy barriers to radio and immunotherapy in a clinical trial she is conducting in patients with invasive breast cancer.

Research goal: through this proposal, the partnering P.I.s seek to combine this powerful immune modulation in macrophages with focal RT, a standard care procedure to increase neoantigen exposure in cancer patients. RT can expose the neoantigens required for T cell activation against cancer, while macrophage reprogramming will create a more favorable environment for T cells to operate against cancer cells. Once the combination is optimized in terms of sequences, frequencies, and RT doses, this approach will be tested in combination with ICP to sustain an immune response and overcome T-cell exhaustion.

Impact: Combining these innovative experimental approaches, led by the unique expertise of the PIs and their team, including consumer advocate Michell Rakoff, ***will generate an effective therapeutic intervention to overcome immune evasion of breast cancer in established tumor and metastases***, responding to METAvivor overarching challenges to:

1) Identify what drives breast cancer growth and metastasis; determine how to stop it; 2) Revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival.