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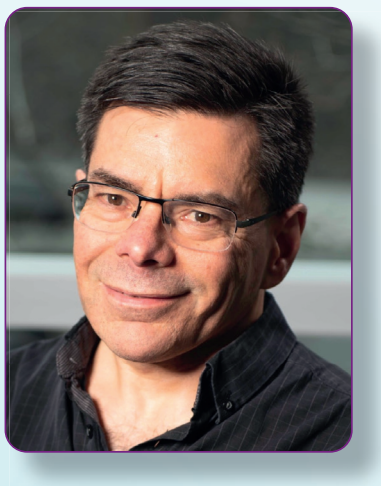
PAPER OF THE MONTH • FEBRUARY 2024

In tribute to Dr. Jerry Pelletier



We pay tribute to a remarkable scientist, colleague, mentor and friend who left an indelible mark for so many of us and by his very essence continues to challenge us to continue his legacy of passion, excellence, rigor and collaboration in scientific research.

PNAS

A second-generation eIF4A RNA helicase inhibitor exploits translational reprogramming as a vulnerability in triple-negative breast cancer

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Breast cancer is a heterogeneous disease that is classified into three main histological subtypes, which informs both patient outcome and treatment options for clinical management of the disease. These include estrogen/progesterone receptor (ER/PR)-positive (+) (~65% incidence), human epidermal growth factor receptor 2 (HER2)+ (~20% incidence), and triple-negative breast cancers (TNBC: ER-/PR-/HER2-) (~15% incidence). In comparison to other subtypes, TNBCs tend to be more aggressive and are more likely to be diagnosed in pre-menopausal women. Moreover, in contrast to ER+ and HER2+ breast cancers, effective targeted therapies for TNBC remain elusive, and chemotherapy remains the standard of care.

In this study, we aimed to address the current limitations of therapies for macro-metastatic triple-negative breast cancer (TNBC) and provide a therapeutic lead that overcomes the high degree of heterogeneity associated with this disease.

Specifically, we focused on well-documented but clinically underexploited cancer-fueling perturbations in mRNA translation as a potential therapeutic vulnerability. We therefore developed an orally bioavailable rocaglate-based molecule, MG-002, which hinders ribosome recruitment and scanning via unscheduled and non-productive RNA clamping by the eukaryotic translation initiation factor (eIF) 4A RNA helicase.

We demonstrate that MG-002 potently inhibits mRNA translation and primary TNBC tumor growth without causing overt toxicity in mice. Importantly, given that metastatic spread is a major cause of mortality in TNBC, we show that MG-002 attenuates metastasis in pre-clinical models. We report on MG-002, a rocaglate that shows superior properties relative to existing eIF4A inhibitors in pre-clinical models.

Our study also paves the way for future clinical trials exploring the potential of MG-002 in TNBC and other oncological indications.

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