L024, a Promising Candidate for the Prevention and Interception of Triple-Negative Breast Cancer and Its Metastasis to the Brain

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BACKGROUND

- In patients with TNBC, adjuvant therapy aims to eliminate residual disease and halt metastasis, however, metastases in brain are unaffected, due to the limited penetrance of adjuvant treatments into the brain.
- The mainstays of treatment after brain metastasis detection are stereotactic radio-surgery and brain radiation which carry debilitating side effects without improving survival.
- **Novel systemic strategies with sufficient efficacy and reduced toxicity are needed.**
- We have shown that L024, a proprietary formulation of licochalcone A reduces SREBP-1dependent lipogenesis and the activity of PI3K-AKT-mTOR signaling, essential for the growth and metastasis of brain-tropic TNBC.

OBJECTIVES

1. **Does L024 block TNBC and its metastatic cascade to the brain?**
2. **Pharmacokinetics: Does L024 cross the BBB?**

METHODS

RNA sequencing was conducted in high-risk women's breast microstructures treated with L024 (5 μM, 24 h) *ex vivo*. **Xenografts** were established in female athymic nude mice by inoculation with luminal or triple negative breast cancer cells, treated with LicA or vehicle for 28 days at a dose of 80 mg/kg.day and the rate of tumor growth evaluated. Publicly available data on brain-tropic 4T1-BM2 cells was analyzed using Enrichr. **Proliferation** of brain-tropic TNBC cells was monitored in incuCyte as a function of single and repeated dosing of L024. **Migration** of brain-tropic TNBC cells was evaluated using the Transwell assay. **Western blots** were conducted on brain-tropic TNBC cells to confirm the involvement of the PI3K-AKT pathway. **Pharmacokinetics** of L024 was evaluated in CD-1 mice after quantification of L024 in plasma and brain using LC-MS/MS and SAMII.

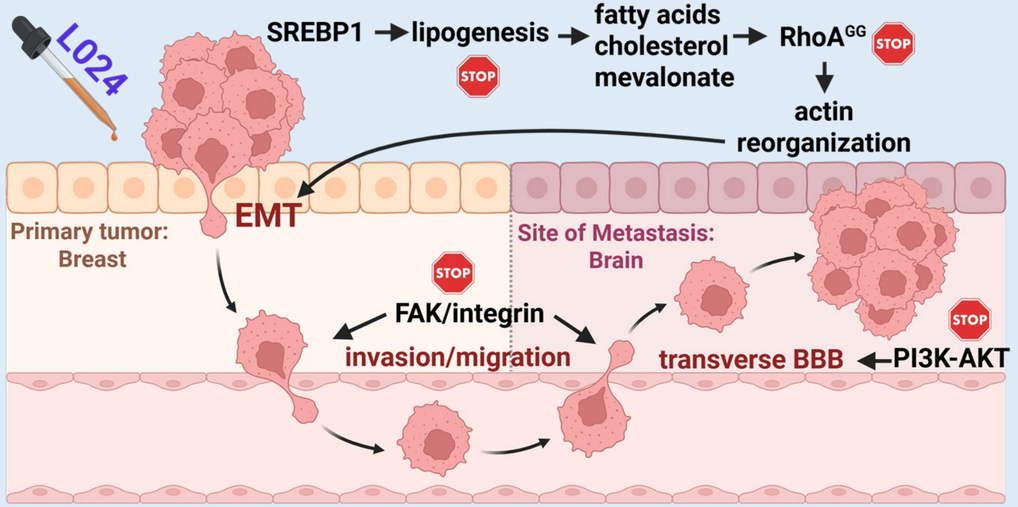
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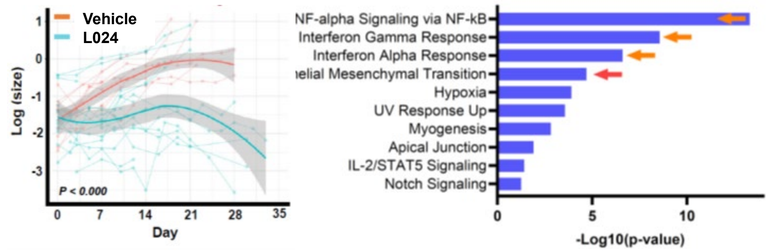
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L024: metabolic prevention & interception of TNBC & brain metastasis

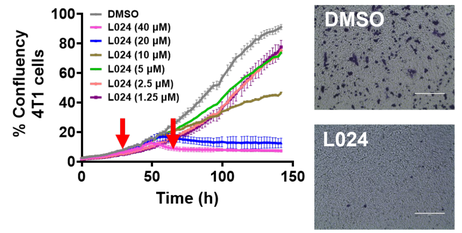


L024 is the **first-in-its class** candidate therapeutic with promising **BBB penetrance**, retention, and clearance. It arrests proliferation, migration, and several steps in **metastatic cascade** → **TRANSLATIONAL PROMISE**

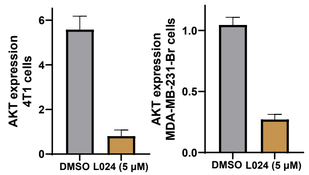
L024 blocks TNBC growth in animals and downregulates EMT in tumors

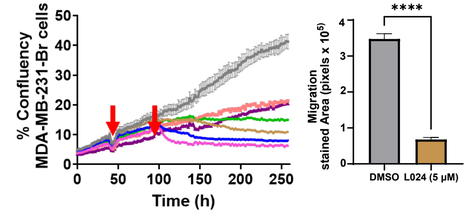


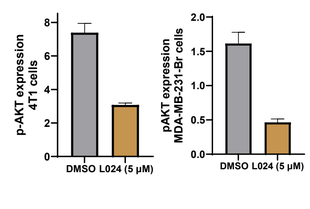
L024 reduces proliferation and migration of brain-tropic TNBC cells



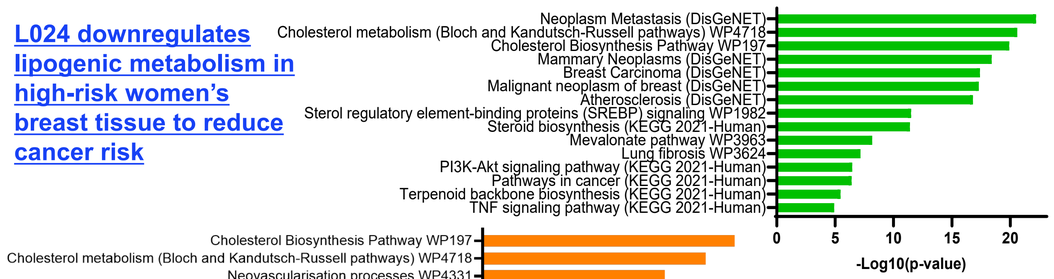
L024 blocks PI3K-AKT pathway

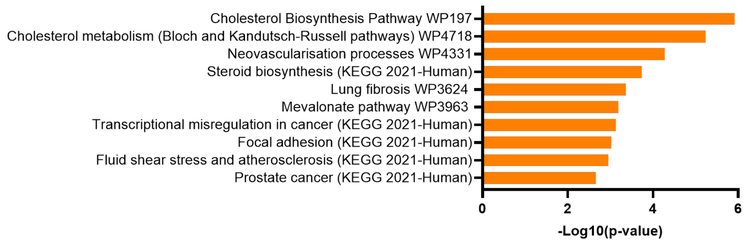






L024 downregulates lipogenic metabolism in high-risk women's breast tissue to reduce cancer risk





Brain-tropism of TNBC cells is associated with their upregulated lipid metabolism.

L024 crosses the BBB and has favorable PK in mice

