

TARGET RATIONALE

A common hallmark of cancer is the dysregulation of cell proliferation, and accordingly, a number of anticancer drugs approved for clinical use affect phases of the cell-division cycle. Among these drugs, those that interfere with mitosis have shown significant efficacy, as exemplified by taxanes and vinca alkaloids. However, these anti-mitotic drugs are often associated with serious side effects, underscoring a particular need for novel agents that would disrupt mitosis without the adverse effects seen with current anti-mitotic agents.

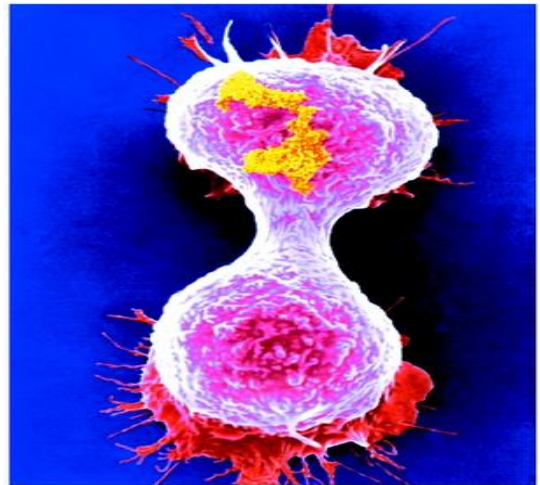


Fig. 1. Scanning electron micrograph of a breast cancer cell dividing.
From: www.biologyreference.com/Co-Dn/Cytokinesis.html

MITOTIC INHIBITORS DISCOVERED BY TRAP[®]

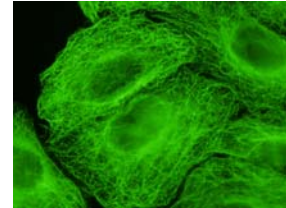
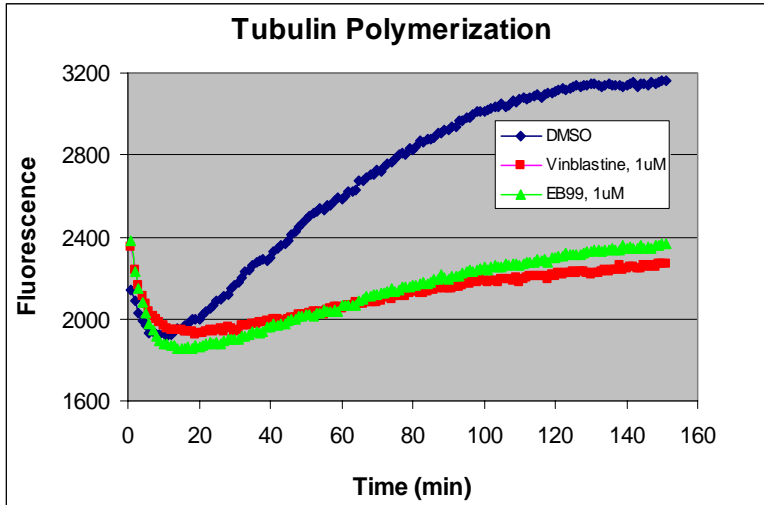
- Potent mitotic inhibitors were discovered using Telik's proprietary drug discovery technology TRAP[®].
- Compounds induced mitotic arrest and apoptosis in tumor cells at nanomolar concentrations.
- A correlation between mitotic arrest and cytotoxicity was observed.
- Immunostaining allowed us to detect disruption of microtubule assembly and confirm that anti-mitotic activity was due to inhibition of tubulin polymerization. (Fig. 2).
- We also confirmed that compounds are not substrates for P-glycoprotein.
- Significant tumor-growth inhibition was observed in xenograft models after oral administration.

ACTIVITY PROFILE OF REPRESENTATIVE COMPOUNDS

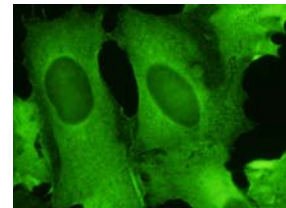
Representative compounds:

- Inhibit tubulin polymerization in A549 cells with IC₅₀ of 20 to 70 nM;
- Induce histone H3 phosphorylation with EC₅₀ of 15 to 200 nM;
- Induce cell cycle arrest at G2/M and appear to cause accumulation of the 4N population;
- Appear to be cytotoxic with CC₅₀ of 30 to 50 nM against several human cancer cell lines, including A549 (lung), HCT116 (colon), OVCAR3 (ovarian) and HL60 (leukemia).
- Show dose-dependent anti-tumor activity in the HL60 promyelocytic leukemia mouse xenograft model (Fig. 3). As much as 90% tumor-growth inhibition was observed after oral administration.

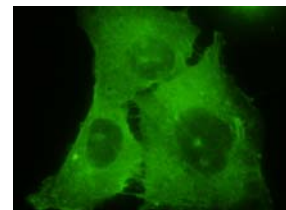
Fig. 2. Inhibition of Tubulin Polymerization by Compound EB99



DMSO

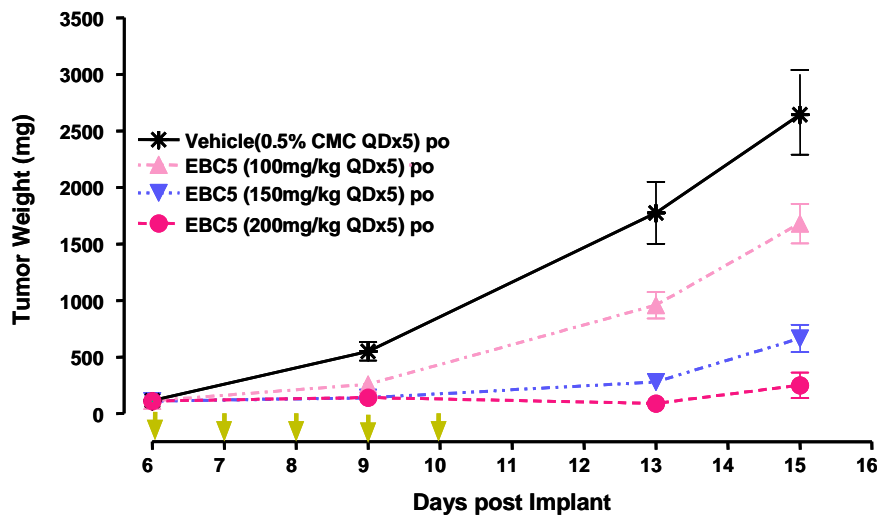


Vinblastine, 0.1uM



EB99, 0.5uM

Fig. 3. In Vivo Tumor Growth Inhibition by Compound EBC5



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