CRx-026
Discovery and clinical development of CRx-026, a synthetic anti-mitotic agent with significant anti-cancer activity
Peter J. Elliott, Margaret S. Lee, Mitchell Keegan, Yanzen Zhang, M. James Nichols, Alexis A. Borisy, Curtis T. Keith. CombinatoRx Inc., Boston, MA 02118, USA

Introduction
A 'synthetic' drug comprises multiple biologically active compounds that interact synergistically to provide an optimal therapeutic effect with the potential to minimize undesired side effects. CRx-026, a novel synthetic anti-cancer agent, exerts a dual action in mitosis by selectively inhibiting hEg5/KSP, a mitotic kinesin essential for centrosome separation, and PRL phosphatases, which play an important role in regulating mitotic progression and proper chromosome separation. The two components of CRx-026 have been integrated into a pharmaceutical composition, and this new anti-cancer drug has been advanced into Phase II trials.

Mechanism of Action

A. Dual Mitotic Action
1. Inhibition of the mitotic kinesin, hEg5/KSP, at a molecular motor essential for centrosome separation
2. Inhibition of PRL phosphatases, putative regulators of mitotic progression and proper chromosome separation

B. Synergistic inhibition of cancer cell proliferation

Pre-Clinical Profile

Robust anti-tumor synergy vs. component agents
Favorable preclinical safety profile—minimal effect on body weight
Broad spectrum anti-cancer activity in both in vitro and xenograft
Synergy with taxanes and vinca alkaloids in vitro and in xenograft

Clinical Status

- Two Phase III trials underway to explore safety and pharmacokinetics.
- Both studies recruiting patients with solid tumors who have previously failed at least one treatment regimen.
- CRx-026 administered as a 2 h infusion at a fixed ratio.
- Standard '3 + 3' dose escalation format.
- Preliminary pharmacokinetic analysis suggests no drug-drug interactions between components of CRx-026.

Methods

Combination High Throughput Screen
- Combination high throughput screen of ~105 drug pairs.
- Screening tested in 36-point dose matrix format.
- Hundreds of leads identified
- CRx-026 the leading drug candidate

Pre-Clinical Profile

CRx-026 Synergizes With Paclitaxel

CRx-026 Synergizes With Vinorelbine

Figures 1-5: In vitro and in vivo efficacy of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 6: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 7: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 8: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 9: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 10: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.

Figure 11: In vitro and in vivo antitumor activity of CRx-026 and its components against established tumors (~500 mm3) in AA8 LLC xenograft models. Compounds administered IP at 33 µM.