Critical Outcome Technologies Inc.

COTI-2
PRODUCT INFORMATION

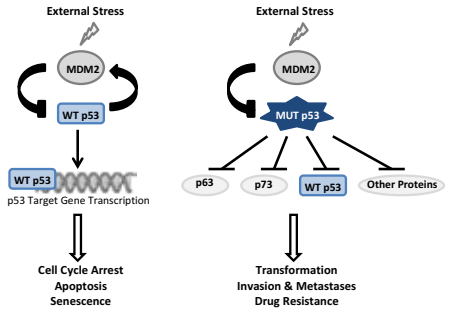
WHAT IS COTI-2?

- COTI-2 is a novel small molecule discovered using our proprietary CHEMSAS® discovery engine.
- COTI-2 is a 3rd generation thiosemicarbazone engineered for low toxicity and designed as an oral treatment of susceptible cancers.
- COTI-2 restores p53 function to a wide range of common p53 mutations and acts as a negative modulator of the PI3K/AKT/mTOR pathway.

WHAT IS p53?

- p53 is a multifunctional tumor suppressor protein that regulates many important cellular responses, such as cell growth arrest and apoptosis, to environmental/external stress[1].
- Mutant p53 proteins are often found at high levels in cancers and contribute to the transformation of cancer cells, metastasis (the spread of tumors to new sites) and drug resistance[2].
- TP53 is the most frequently mutated gene in human cancer with mutation frequencies ranging from 38 to 96%[3].
- The simplified representation in Figure 1 highlights the differences between wildtype (normal p53) and mutant p53[2].
- In normal cells, wildtype p53 is maintained at low levels due to the tightly regulated negative feedback loop it forms with MDM[2].
- In cancerous cells, on the other hand, mutant p53 is stable and often accumulates in tumor cells because it cannot engage in the negative feedback mechanism.

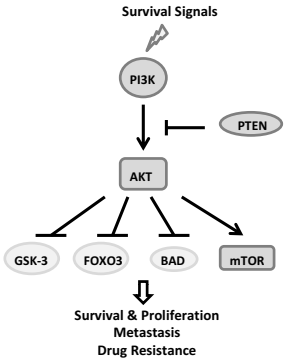
Figure 1. A simplified representation of p53 pathway.



WHAT IS THE PI3K/AKT/mTOR PATHWAY?

- The PI3K/AKT/mTOR signaling pathway is involved in cell proliferation, survival, motility, and metabolism (Figure 2)[4].
- Abnormalities or mutations in this pathway are typically found in many cancerous cells, which lead to tumor proliferation, survival, metastasis, and drug resistance[5].
- Frequent activation of the PI3K/AKT/mTOR pathway has been reported in a broad range of human cancers at frequencies of up to 50%[6].

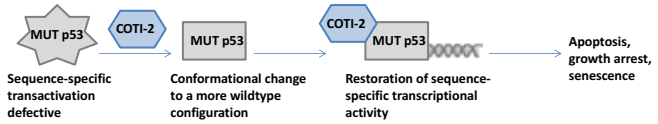
Figure 2. The PI3K/AKT/mTOR pathway simplified.



COTI-2 AND p53

- Data indicates that COTI-2 normalizes mutant p53 to wildtype-like conformation to promote apoptosis/cell death (Figure 3).
- Experimental evidence to support this:
  1. COTI-2 IC_{50} and p53 mutational status are strongly correlated.
  2. COTI-2 induces a 'wildtype-like' conformational change in mutant p53 in ovarian, pancreatic, and other cancer cells.
  3. COTI-2 significantly reduces p53 mutant protein levels and significantly increases wildtype p53 protein levels.
  4. COTI-2 is also highly effective in animal tumor models with p53 mutations.

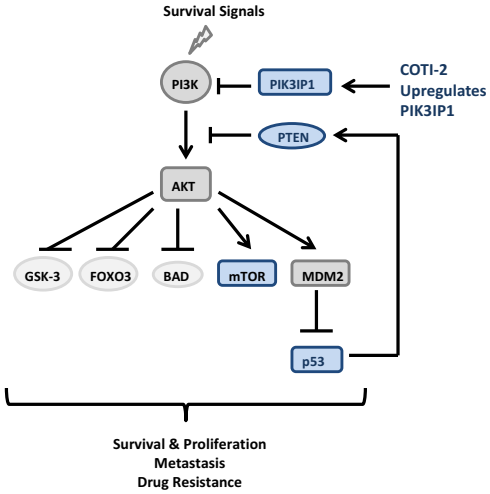
Figure 3. The proposed action of COTI-2 on p53.



COTI-2 AND THE PI3K/AKT/mTOR PATHWAY

- COTI-2 negatively modulates the PI3K/AKT/mTOR pathway thus promoting apoptosis (Figure 4).
- Experimental evidence indicates that COTI-2 inhibits this pathway in three ways:
  1. It upregulates PIK3IP1, which is a direct inhibitor of PI3K.
  2. The restoration of p53 function also stimulates PTEN activity and promotes AKT protein degradation.
  3. Early evidence also suggests that COTI-2 negatively modulates mTOR.

Figure 4. The proposed action of COTI-2 on the PI3K/AKT/mTOR pathway.



WHAT CANCERS IS COTI-2 SUITABLE FOR?

- Tumors with mutant p53 and/or abnormal PI3K/AKT/mTOR pathway are suitable for COTI-2 therapy.
  - TP53 is the most frequently mutated gene in human cancer with mutation frequencies ranging from 38 to 96%[3].
  - Frequent activation of the PI3K/AKT/mTOR pathway has been reported in a broad range of human cancers at frequencies of up to 50%[6].
- Initial data also indicates that COTI-2 has significant *in vitro* efficacy in multiple cancer stem cell assays.

HIGHLIGHTS OF THE COTI-2 DEVELOPMENT PROGRAM

- COTI-2 is highly effective *in vitro* against multiple human cancer cell lines.
- COTI-2 is also highly effective against human colon cancer cell lines with abnormal/mutated KRAS, which were otherwise not sensitive to current therapy with Erbitux®.
- COTI-2 has demonstrated a good pharmacokinetic profile and low toxicity.
- COTI-2 is highly effective as a single or combination agent in animal models of human cancers, including SCLC, colon, brain, endometrial, ovarian, pancreatic, and leukemia.

ONGOING DEVELOPMENTAL ACTIVITIES

- IND was granted by the FDA on May 2015.
- Phase I trial currently underway for gynecological cancers at multiple sites in the US.

WHY SHOULD YOU CARE ABOUT COTI-2?

- Drugs like COTI-2 have the potential to revolutionize outpatient cancer therapy.
- Its specific protein target, low toxicity, combination effectiveness with standard agents and potential for longer term outpatient therapy as an oral agent support a dramatic change in the treatment of susceptible cancers.
- Just as protease inhibitors became part of Highly Affective Anti-Retroviral Therapy (HAART) and dramatically altered the course of HIV infection, drugs like COTI-2, as part of Highly Active Anti-Neoplastic Longer Term (HAALT™), therapy may significantly alter the course of some cancers from potential death sentences to more chronic and manageable out-patient diseases.

REFERENCES

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5. Vivanco I & Sawyers CL. *Nat Rev Cancer* 2002; 2: 489-501.
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