# COTI-2 PRODUCT INFORMATION

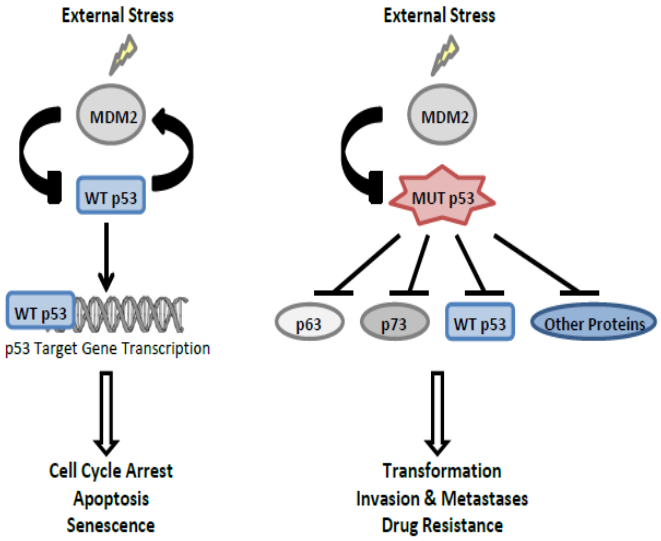
## What is COTI-2?

- 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 is likely to be effective against solid tumors with p53 mutations and/or AKT over-expression.

## What is p53?

- p53 is a multifunctional tumor suppressor protein that mediates 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 transformation to cancer cells, metastasis (spread of tumors to new sites) and drug resistance[2].
- The simplified representation in Figure 1 highlights the differences between wildtype (normal p53) and mutant p53[2].
  - Wildtype p53 is maintained at low levels in normal cells due to the tightly regulated negative feedback loop it forms with MDM2.
  - Mutant p53 in cancer cells, on the other hand, is stable and often accumulates in tumor cells because it cannot engage in the negative feedback mechanism.

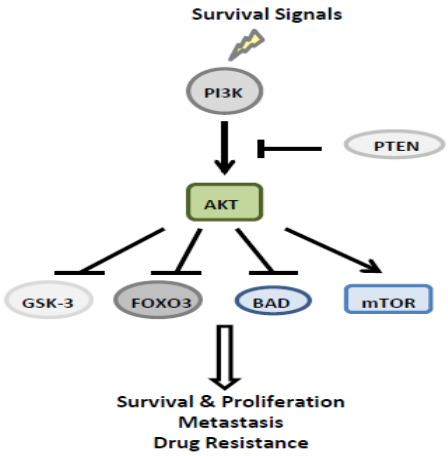
**Figure 1.** Simplified representation of p53 pathway.




## What is AKT?

- AKT is a key component of the PI3K/AKT/mTOR signaling pathway (Figure 2) and is involved in cell proliferation, survival, motility, and metabolism[3].
- The increased expression or activation of AKT typically found in many cancerous cells leads to abnormal downstream events, such as tumor proliferation, survival, metastasis, and drug resistance[4].

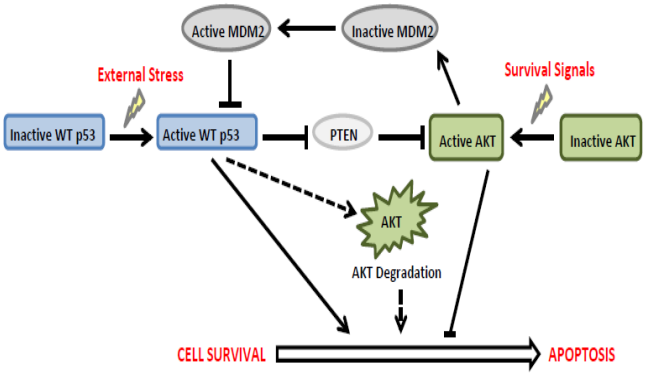
**Figure 2.** The PI3K/AKT/mTOR pathway simplified.




## Interconnection between p53 and AKT

- An intricate cross-talk exists between AKT and p53 (Figure 3)[5].
- Under conditions of stress activated p53 inhibits AKT through activation of PTEN and degradation of the AKT protein.
- Survival signals, on the other hand, activate AKT which in turn inhibits p53 through MDM2.

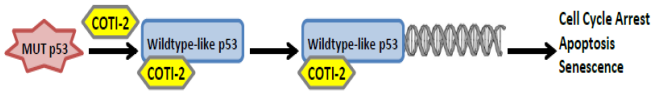
**Figure 3.** Model of cross-talk between p53 & AKT.



## How does COTI-2 work?

- Data indicates that COTI-2 normalizes mutant p53 structure and function to wildtype-like conformation to promote apoptosis (Figure 4).
- 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 and pancreatic cell lines.
  3. COTI-2 significantly reduces p53 mutant protein levels and significantly increases wildtype p53 protein levels.

**Figure 4.** Proposed action of COTI-2.




- COTI-2 negatively modulates the PI3K/AKT/mTOR pathway thus promoting apoptosis.
- Experimental evidence indicates that COTI-2 inhibits AKT in two ways:
  1. It up-regulates PIK3IP1, which is a direct inhibitor of PI3K (an AKT activator).
  2. It down-regulates (degrades) the total AKT protein levels, thereby reducing the high levels of protein expression found in cancer cells likely through its action on p53.

## What cancers is COTI-2 suitable for?

- Tumors with mutant p53 and/or abnormally high levels of AKT are suitable for COTI-2 therapy.
- Approximately 50% of human cancers are characterized by mutant p53[1]. Similarly, high levels of AKT have been reported in a broad range of human cancers, including breast, pancreatic, colorectal, ovarian, endometrial, SCLC, NSCLC, brain, and leukemia[6].
- Initial data indicates that COTI-2 has significant *in vitro* efficacy in multiple stem cell assays.

## Biomarkers for COTI-2 therapy

- The identification of biomarkers relevant in oncology allows for personalized treatment[7].
- Potential biomarkers for COTI-2 therapy are cancers with mutant p53 and/or high AKT protein levels.

## Highlights of the COTI-2 development program

- COTI-2 is highly effective *in vitro* against many 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

- Complete the pre-IND toxicology program in a rodent and non-rodent species.
- Complete the balance of FDA enabling research for the first-in-man multicentre United States based Phase 1 Clinical Trial.

## 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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3. Blume-Jensen P. & Hunter T. *Nature* 2001; 411: 355-365.
4. Vivanco I & Sawyers CL. *Nat Rev Cancer* 2002; 2: 489-501.
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7. Franke R & Hargreaves R. *Nat Rev Drug Discov* 2003; 2: 566-580.