

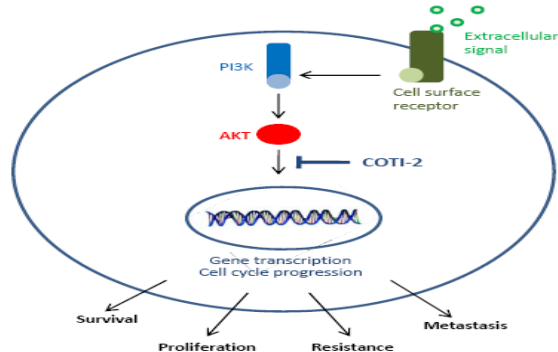
What is COTI-2?

- COTI-2 is a small molecule designed for the oral treatment of susceptible cancers.
- Specifically, COTI-2 is likely to be highly effective against human cancers that express high levels of the protein Akt2 such as endometrial, ovarian, and pancreatic cancers.
- Novel, potential first-in-class MOA: non-ATP competitive Allosteric inhibitor of Akt2.
- Demonstrates greater selectivity, improved safety profile and pharmacokinetics versus other Akt inhibitors, including MK-2206.

What is Akt2?

- Cells are able to sense their external environment and respond through a complex network of cell surface and intracellular proteins that communicate over signaling pathways¹.
- Cells become cancerous when controlled regulation of proteins involved in these signaling pathways is lost due to mutations or abnormal expression/activity¹.
- Akt is a key component of the PI3K/Akt/mTOR signaling pathway (Fig. 1) and is involved in cell proliferation, survival, motility, morphology and metabolism². Akt is comprised of a family of 3 proteins, Akt1, Akt2, and Akt3.
- The increased expression or activation of Akt2 typically found in many cancerous cells leads to abnormal downstream events³.
- These events result in cancer promoting activities such as tumor proliferation, survival, metastasis (spread of tumors to new sites) and resistance.

Fig.1 The PI3K/Akt/mTOR pathway



How does COTI-2 work?

- COTI-2 promotes tumor cell death by interfering with Akt2 in the PI3K/Akt/mTOR pathway.
- Experimental evidence indicates that COTI-2 prevents the activation of Akt2, thereby preventing its cancer promoting activities.
 - Human cancer cells exposed to COTI-2 exhibit reduced levels of activated Akt2 compared to untreated cells.
 - COTI-2 did not exhibit any activity towards cells in which Akt2 activity was removed by silencing RNA. Therefore, in the absence of its target (Akt2) COTI-2 was unable to promote death in cancer cells. This indicates that Akt2 is the specific target of COTI-2.

How does COTI-2 differ from other cancer treatments?

- Treatment by conventional cancer chemotherapy involves the killing of all growing and dividing cells in the body. This often leads to significant toxic side effects in patients.
- Unlike conventional chemotherapy, COTI-2 specifically targets and destroys tumor cells.
 - COTI-2 targets tumor cells with abnormally high levels of active Akt2.
 - COTI-2 has demonstrated very low toxicity in normal human cells compared to human cancer cells.
 - COTI-2 has demonstrated very low toxicity in rodents.
 - Many studies have shown that the activation of Akt2 causes tumor cells to become resistant to chemotherapeutic drugs and signal molecule inhibitors (e.g., Gleevec[®], Iressa[®], and Herceptin[®])^{4, 5}.
 - Unlike the conventional therapeutic agents, paclitaxel and cisplatin, COTI-2 did not induce resistance in cancer cells. COTI-2 was actually highly effective against paclitaxel and cisplatin resistant cancer cells.
- The combined scientific evidence indicates that COTI-2 is an ideal agent for combination therapy with current standard agents.

What cancers is COTI-2 suitable for?

- Tumors that express abnormally high levels of active Akt2 are suitable for COTI-2 therapy.
- Frequent activation of Akt2 has been reported in a broad range of human cancers, including breast, pancreatic, colorectal, ovarian, endometrial, SCLC, NSCLC brain cancer and leukemia⁶.
- The percent of tumors with active Akt2 range from 20% to 100% depending on the cancer type.

Akt2 as a biomarker and testing for Akt2

- A biomarker provides a measurable indication of the biological state of cells. The identification of biomarkers relevant in oncology allows for the personalization of treatment and thus brings new medicines to the right patients faster.
- High levels of active Akt2 in tumor cells used as a biomarker may provide evidence that an appropriate therapy would involve the use of a drug like COTI-2.
- Testing of tumors for high levels of active Akt2 will identify those patients that are most likely to benefit from treatment with COTI-2. The levels of active Akt2 in tumors can be determined by simple testing of tumor biopsies from patients.

Highlights of the COTI-2 development program

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

Projected developmental activities for the next 6-to 12 months

- Finalize the optimal oral formulation for completing pre-IND studies and the subsequent Phase 1 clinical trial.
- Complete an *in vivo* study on the pharmacodynamics of Akt
- Complete an *in vivo* 28 day acute toxicity study using the optimal oral formulation
- 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 chemotherapeutic agents and potential for longer term outpatient therapy as an oral agent support a dramatic change in the treatment of susceptible cancers.

References

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