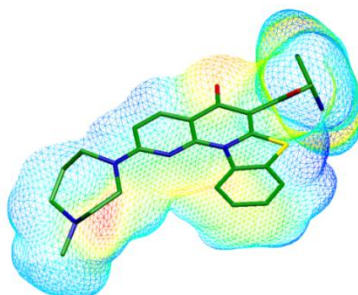


CX-5461

Non-Genotoxic Activator of p53 through Selective Inhibition of RNA Polymerase I for the Treatment of Hematologic Malignancies



Substantial Market Potential

Hematologic and select solid tumor indications

Targeted Cancer Agent

- Exploits newly validated Pol I target
- Ideal path to activate p53 - no DNA damage
- Acts through well understood MOA
- Highly differentiated from other therapies

Attractive Clinical Qualities

- Rapid and straightforward path to approval
- Clearly defined sensitive patient population
- Addresses large unmet medical needs

Development Stage

- IND enabling studies in progress
- Robust activity in multiple animal models
- Small molecule with ease of synthesis
- cGMP manufacture completed
- Suitable for Oral or IV administration

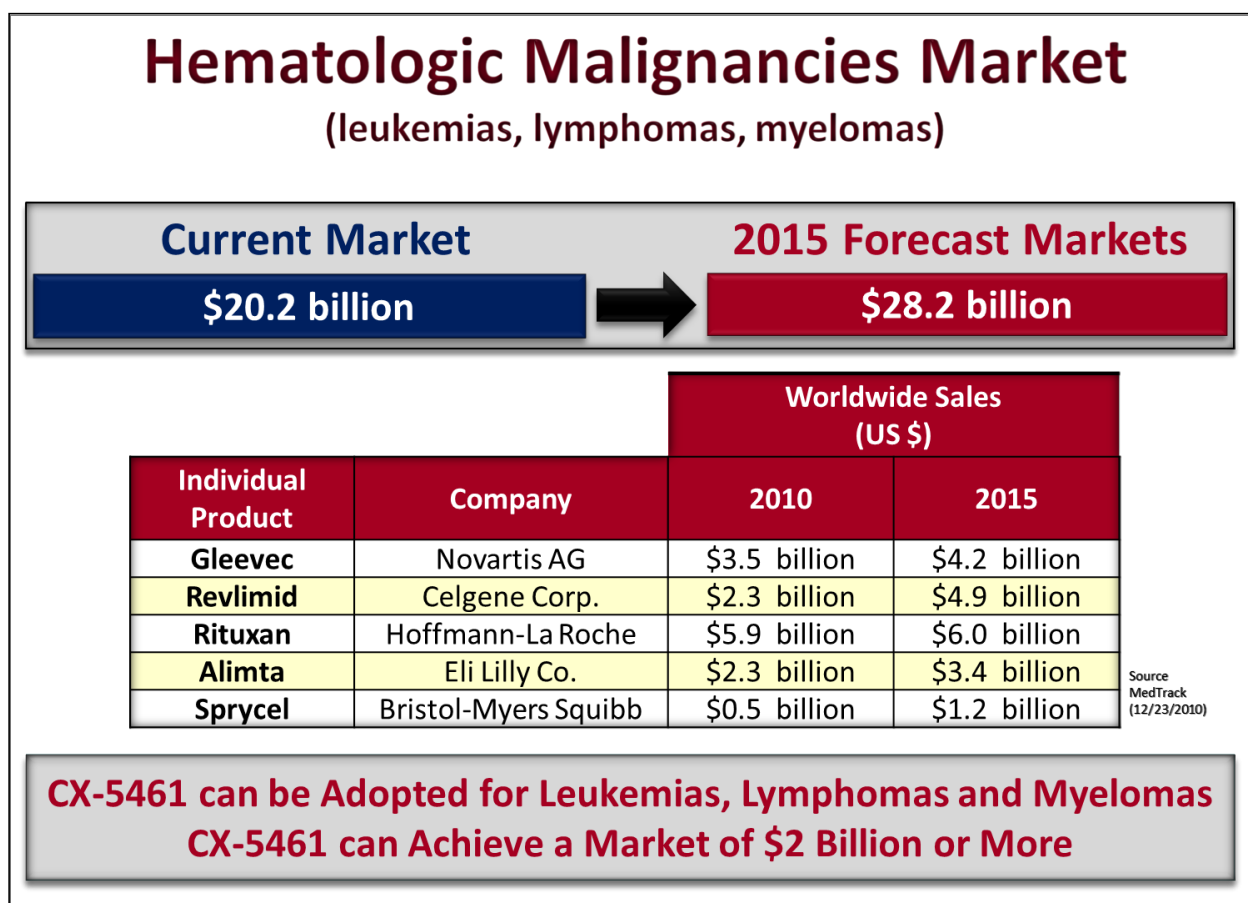
Robust IP Position

- Patent granted by USPTO
- Extensive library of analogues for next generation molecules

Market and Needs for Hematological Malignancies

The considerable success of some of the major marketed products in hematological malignancies has captured the interest of many drug developers. Biogen Idec/Genentech/Roche's Rituxan (rituximab) and Novartis's Gleevec (imatinib) have achieved blockbuster status, despite initial approval in small, niche indications. As such, the pharmaceutical and biotech industries are keen to replicate the commercial and clinical successes of such revolutionary drugs.

Despite these advances, the treatment of hematological malignancies continues to have areas of considerable unmet medical need. Additionally, the incidence of blood cancers will continue to rise due to the aging population and factors such as increased disease awareness and better diagnosis. These facts point to an expansion of the hematologic market (Table below) for years to come and highlight the need for innovative and effective therapies.



Cylene's small molecule agent, CX-5461, exploits newly validated target yet acts through a highly desired and well validated mechanism for killing cancer cells (p53 activation) that has particular relevance to hematological cancers. It is targeted against RNA Polymerase I (Pol I) which provides the ideal, non-genotoxic path for p53 activation. CX-5461 demonstrates a favorable preclinical profile, potently and selectively kills cancer cells, demonstrates robust *in vivo* efficacy in multiple models, and has demonstrated oral bioavailability in multiple species. CX-5461 is expected to deliver substantial market potential in hematologic cancers as well as select solid tumor indications.

Targeted Inhibition of RNA Polymerase I is the Ideal Path to Activate p53

The tumor suppressor protein p53, known as “the guardian of the genome”, orchestrates cellular responses to diverse stress factors. Activation of this protein can lead to cell cycle arrest or cell death (apoptosis or autophagy) and it is pivotal in determining whether cancer cells proliferate or die. Activation of p53 has long been an attractive approach to treating cancers, yet it has not been successfully clinically exploited due to difficulties in targeting p53 and its pathways. Activation of p53 is especially relevant for hematologic malignancies, in which the vast majority of cancers have wild-type (wt) p53 status. Moreover, basic research studies have demonstrated that forced increases in p53 levels results in rapid induction of apoptotic cell death in hematologic cancer cells and senescence and autophagy in solid tumor cells. Thus, patients having wt p53 hematologic cancers represent a sensitive population for the treatment of cancers through p53 activation and an ideal opportunity to demonstrate clinical proof of concept with CX-5461.

Control of p53 activation is regulated through Nucleolar Stress Signaling Pathway or the Oncogenic/Genotoxic Stress Pathways (Figure 1). Many chemotherapeutic agents effectively activate p53 through genotoxic insult, but such agents also damage DNA in normal cells, resulting in significant toxicities. **Activation of p53 through the Nucleolar Stress Signaling Pathway can be accomplished by small molecule inhibition of the RNA Polymerase I (Pol I) enzyme in the nucleolus without damaging DNA, thereby representing the ideal, non-genotoxic path to activate p53 and selectively kill cancer cells.**

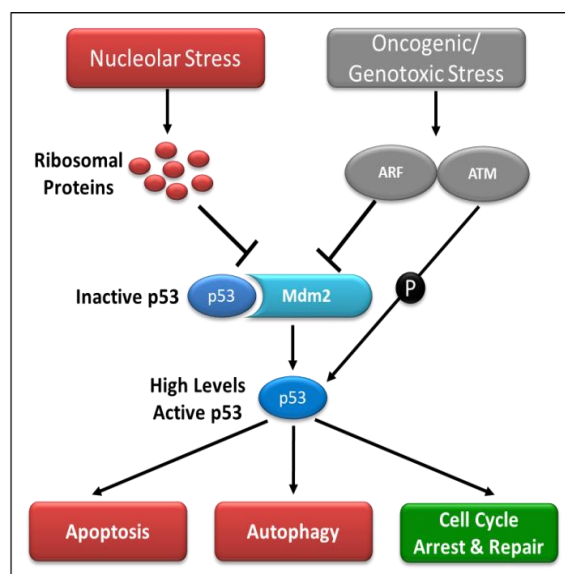


Figure 1. Signaling Pathways for p53 Activation

Cancer is characterized by deregulated cell growth and excessive proliferation which requires heightened levels of ribosome biosynthesis to meet the demands for increased protein synthesis. Ribosome biosynthesis is regulated within the nucleolus by Pol I that produces ribosomal RNA (rRNA), the key building block of ribosomes. In cancer cells, the increased need for ribosomes and rRNA is satisfied by increasing the rate of Pol I transcription (typically 3 fold). Inhibition of Pol I transcription in cancer cells by even 35% causes nucleolar stress that leads to the release of ribosomal proteins (RP) from the nucleolus. The released RP then sequester the p53 inhibitory protein Mdm2, thereby activating the p53 stress response. This increases the level of p53 which then induces apoptotic or autophagic death in cancer cells. **Thus, non-genotoxic agents that target Pol I lead to activation of p53 and selectively trigger death in tumor cells, and in particular induce apoptotic cell death in hematologic cancer cells.**

CX-5461 is a Potent and Selective Inhibitor of RNA Polymerase I

CX-5461 is a small molecule that was designed to selectively inhibit rRNA synthesis by RNA Polymerase I (Pol I), but not to inhibit mRNA synthesis by RNA Polymerase II (Pol II) (Figure 2A). Additionally, CX-5461 does not inhibit DNA replication or protein synthesis. The inhibition of Pol I results in nucleolar stress, which causes the release of ribosomal proteins (RP) from the nucleolus (Figure 2B and C) and subsequent activation of p53, resulting in apoptosis as seen in Figure 2D.

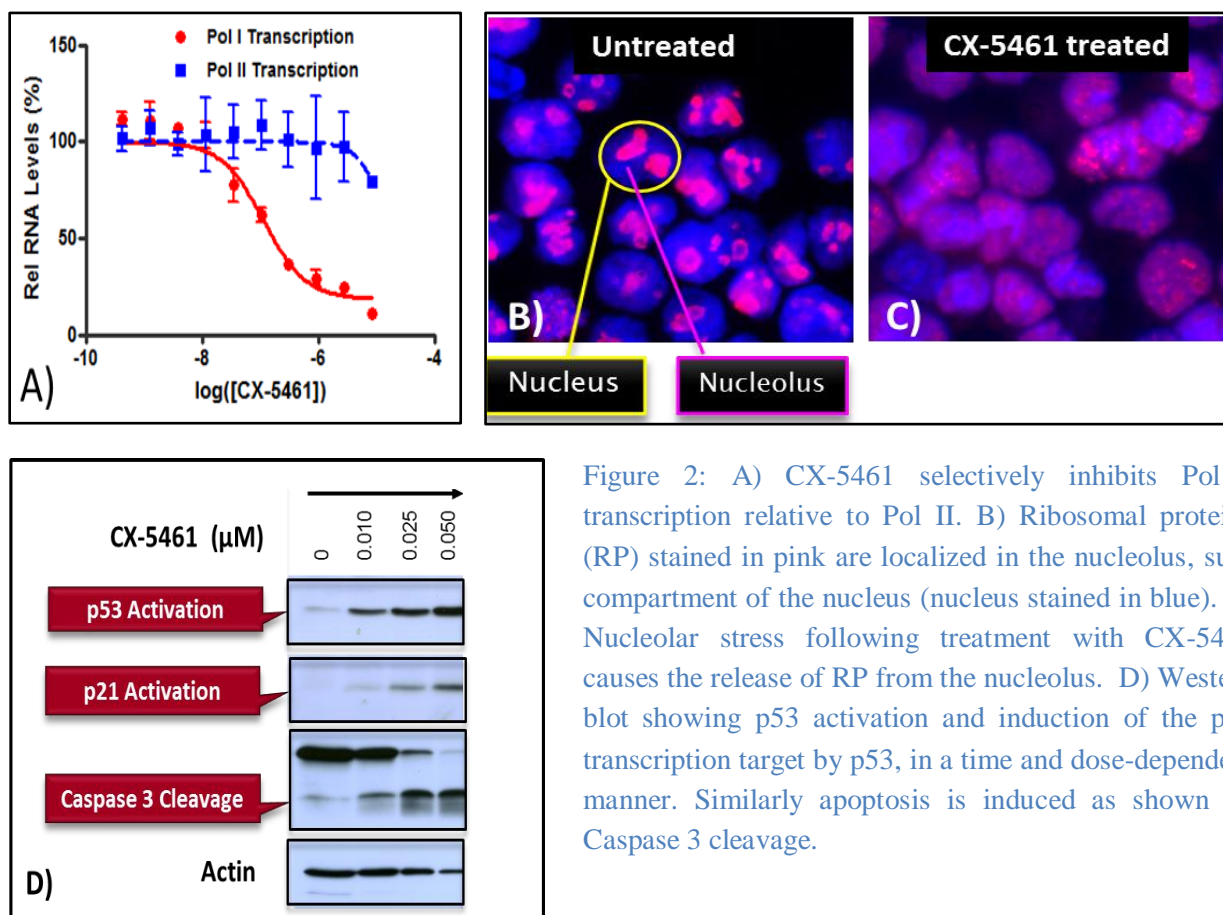


Figure 2: A) CX-5461 selectively inhibits Pol I transcription relative to Pol II. B) Ribosomal proteins (RP) stained in pink are localized in the nucleolus, sub-compartment of the nucleus (nucleus stained in blue). C) Nucleolar stress following treatment with CX-5461 causes the release of RP from the nucleolus. D) Western blot showing p53 activation and induction of the p21 transcription target by p53, in a time and dose-dependent manner. Similarly apoptosis is induced as shown by Caspase 3 cleavage.

p53 Wild Type Hematologic Cell Lines are Highly Sensitive to CX-5461

CX-5461 exhibits a broad range of antiproliferative activity, with wild-type (wt) p53 cells derived from hematological malignancies being the most sensitive. Figure 3 illustrates the ability of CX-5461 to selectively kill cancer cells relative to normal cells. The median IC_{50} in normal cells is 5,000 η M. We previously demonstrated that CX-5461 triggers autophagic cell death in solid tumor cell lines and exhibits antitumor activity in xenograft models (Drygin et al. Cancer

Res. 2010). CX-5461 has antiproliferative activity against p53 wt solid tumors with median IC_{50} s of 164 nM. More impressively though, hematologic cancers were highly sensitive to the antiproliferative activity of CX-5461, with p53 wt cells being the most sensitive (median IC_{50} of 25 nM). In the clinical setting, the vast majority of hematologic malignancies have p53 wt status and represent a sensitive population for the rapid clinical development of RNA Polymerase I inhibitors.

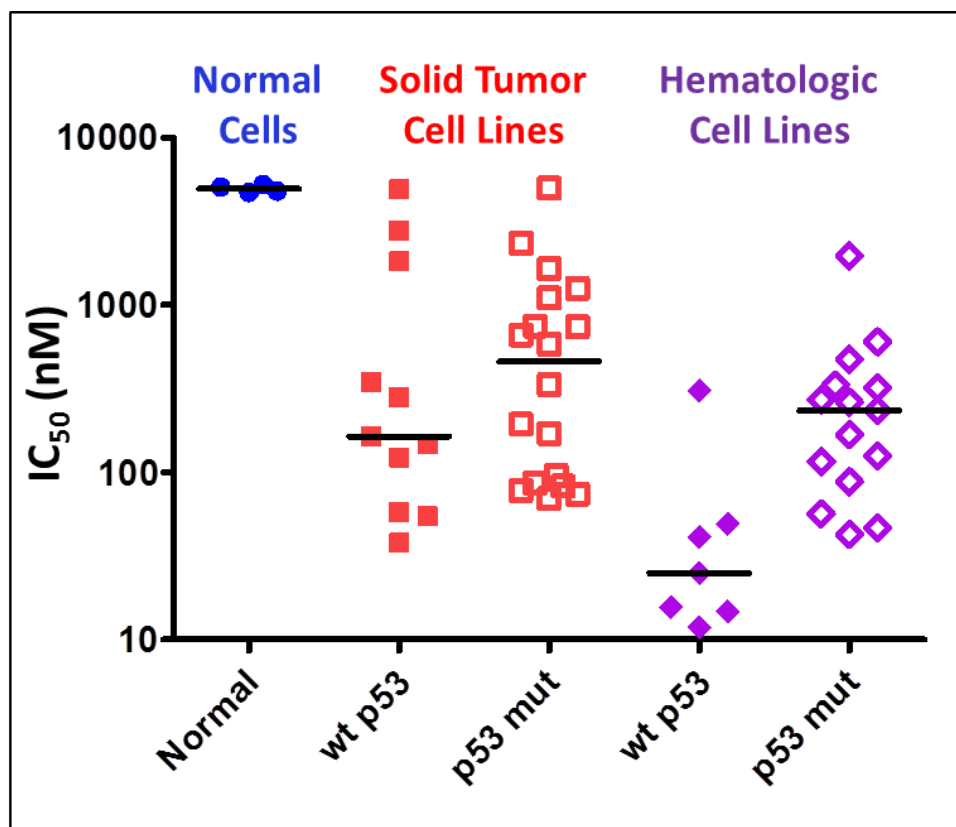


Figure 3. Antiproliferative activity of CX-5461 against normal cells, p53 wild type and mutated solid tumor cell lines, and p53 wild type and mutated hematologic cancers. Each point represents the nanomolar IC_{50} in a cell viability assay for CX-5461 against a cell line in each category.

CX-5461 Exhibits Potent In Vivo Antitumor Activity in Animal Models of Leukemia and Lymphoma

In separate p53 wt murine lymphoma and leukemia models, CX-5461 displayed dramatic anticancer activity upon administration of either a single dose or multiple doses. In the lymphoma model a major reduction in circulating tumor burden was observed within 24 hours (Figure 3A) and in a survival study (Figure 3B), resulted in 100% remissions in CX-5461 treated animals compared to untreated group (untreated subjects succumbed to disease by day 15). A similarly dramatic antitumor effect was observed in the leukemia model as monitored by luciferase imaging of tagged cancer cells (Figure 3C).

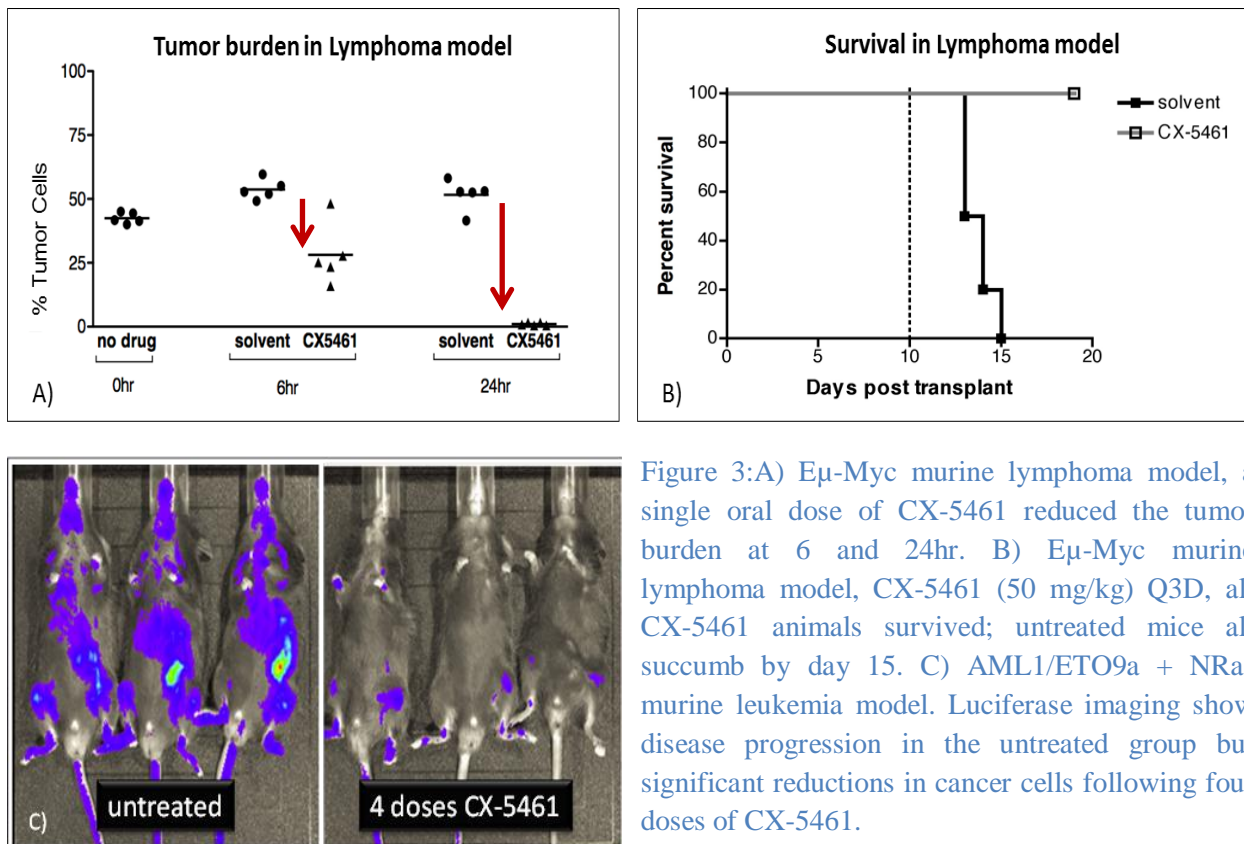


Figure 3:A) E μ -Myc murine lymphoma model, a single oral dose of CX-5461 reduced the tumor burden at 6 and 24hr. B) E μ -Myc murine lymphoma model, CX-5461 (50 mg/kg) Q3D, all CX-5461 animals survived; untreated mice all succumb by day 15. C) AML1/ETO9a + NRas murine leukemia model. Luciferase imaging show disease progression in the untreated group but significant reductions in cancer cells following four doses of CX-5461.

Personalized Treatment of Leukemias, Lymphomas and Myelomas

CX-5461 acts through the newly validated Pol I target to trigger non-genotoxic, nucleolar stress and activate p53 to induce apoptotic cell death in hematologic cancer cells. The RNA Polymerase I program represents a novel approach to exploiting a highly desirable anticancer strategy. CX-5461 demonstrates a favorable preclinical profile, potently and selectively kills cancer cells, demonstrates robust *in vivo* efficacy in multiple models, and has demonstrated oral bioavailability in multiple species. Cylene has completed cGMP manufacture and the molecule is being advanced to the clinic.

The hematologic cancer market includes considerable areas of unmet medical need and the incidence of these malignancies will continue to rise. CX-5461 is expected to deliver substantial market potential in target hematologic cancer indications as well as select solid tumor indications.

Contact Information

Sean E. O'Brien Ph.D.
 Dir. Research and Business Development
 Cylene Pharmaceuticals
 +1 858-875-5103
sobrien@cylenepharma.com

Kelly Lisbakken
 Vice President - Investment Banking
 Wedbush Morgan Securities, Inc.
 +1 415-263-6655
kelly.lisbakken@wedbush.com