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Highly-selective clinical stage CDK2/9 inhibitor with targeted development potential in hematological malignancies and solid tumors.

Novel Phase 1 CDK Inhibitor

CYC065¹ is a highly-selective, orally-available, 2nd generation inhibitor of cyclin dependent kinases (CDK) 2 and 9 in Phase 1 clinical development. CDKs 2 and 9 play pivotal roles in cancer cell growth and DNA damage repair. CYC065 causes apoptotic cell death of cancer cells at submicromolar concentrations. Antitumor efficacy has been achieved *in vivo* with once a day oral dosing at well tolerated doses. Translational biology supports the development of CYC065 as a stratified medicine for solid tumors as well as orphan diseases including adult and pediatric leukemias.

The Function of Cyclin Dependent Kinases

CDKs are a family of enzymes first discovered as regulators of the cell cycle, but now understood to include proteins with pivotal functions in the control of proliferation such as the regulation of transcription, DNA repair and metastatic spread. The precise selectivity of an individual CDK inhibitor molecule for certain preferred CDKs is key to targeting particular tumor types and avoiding undesirable side effects through non-specific antiproliferative activity.

Mechanism of Action

Different CDKs are responsible for control of different aspects of proliferation, and when dysregulated can be drivers of particular cancer sub-sets. CYC065 targets:

- CDK2, which drives cell cycle transition and activates major DNA double-strand break repair pathways;
- CDK9, which regulates transcription of certain genes (incl. cyclins, MCL-1, DNA double-strand break repair pathway components) through phosphorylation of RNA polymerase II.

CYC065 Characteristics

CYC065 is mechanistically similar to Cyclacel's first generation CDK inhibitor, seliciclib, but with significantly improved metabolic stability, efficacy and potency *in vitro* and *in vivo*. CYC065 causes proportionally greater CDK9 inhibition, leading to improved efficacy in hematological malignancies. Physicochemical properties enable dosing by oral or intravenous routes.

In vitro potency and selectivity of CYC065

CDK	2	5	9	3	7	4	1
CYC065 IC ₅₀ (nM)	5	21	26	29	193	232	578
Ratio to CDK2		4	5	6	39	46	116

Competitive Positioning

As a highly selective CDK2/9 inhibitor, CYC065 offers an improved therapeutic window and lower myelosuppressive potential than pan-CDK inhibitors that, among other CDKs, also target CDK1. Six clinical stage CDK inhibitors inhibit multiple CDK targets, including CDK9. Except for seliciclib, all of these molecules inhibit CDK1 which is cytotoxic for all proliferating cells, whether malignant or not. CDK1 inhibition also counteracts the degradation of MCL-1, protecting cancer cells from anticancer agent activity.

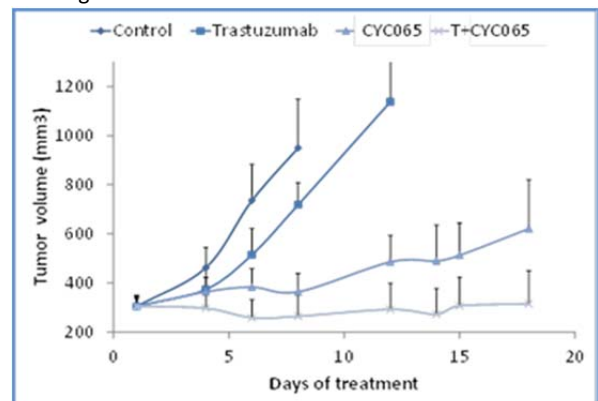
Approved and clinical stage CDK4/6 inhibitors e.g. palbociclib, provide an important therapeutic advance, causing prolonged cell cycle arrest in certain solid tumors. In contrast CDK9 inhibitors induce tumor cell death. CDK2 inhibitors can also enhance cell cycle arrest, and may overcome cyclin E dependent resistance to CDK4/6 inhibitors.²

Preclinical data on the molecular rationale and therapeutic potential of CYC065 in both hematologic and solid tumors show that CYC065:

- may reverse drug resistance associated with addiction of cancer cells to cyclin E, the partner protein of CDK2;³
- inhibits CDK9-dependent oncogenic and leukemogenic pathways, including malignancies driven by certain oncogene and MLL rearrangements. MLL gene status and levels of Bcl-2 family proteins correlate with sensitivity of AML cell lines to CYC065;⁴
- presents an opportunity for patient stratification and combinations with anti-leukemic agents;⁴
- was effective against uterine serous carcinomas with cyclin E amplified/overexpressed, and synergistic with PIK3CA inhibition *in vivo*, together a new therapeutic option;⁵
- could be active in triple-negative breast cancer;⁶
- prolongs survival in MYCN-addicted neuroblastoma.⁷

Solid Tumor Indications

Several sub-sets of drug-resistant breast cancer (BC) have been associated with overexpression of full-length and truncated cyclin E. These included trastuzumab-resistant BC,³ and triple negative breast cancers (TNBC).⁸ CYC065 resensitizes trastuzumab-resistant BC to apoptotic cell killing.



CYC065 in trastuzumab resistant HER2+ve BC

CDK2 has been shown to participate in DNA repair and to be a therapeutic target in BRCA-deficient cancers through inhibition of double strand break repair. CDK2 and CDK9 inhibition have also been shown to reduce expression of components of DNA double-strand break repair pathways including BRCA proteins. CDK2/9 inhibitor potentiation of DNA damaging agents is being explored in an early phase combination trial of seliciclib and sapacitabine.⁹

CYC065 also inhibits CDK5 with a similar potency to CDK9. CDK5 overexpression has been detected with high frequency in metastatic pancreatic and lung cancers and CDK5 is hyperactivated downstream of mutant K-RAS¹⁰. Pharmacological CDK5 inhibition in over-expressing cancer cell lines significantly reduces cell migration.¹¹ Separately it has been shown that K-RAS and N-RAS mutant NSCLC cell lines are sensitive to seliciclib.¹²

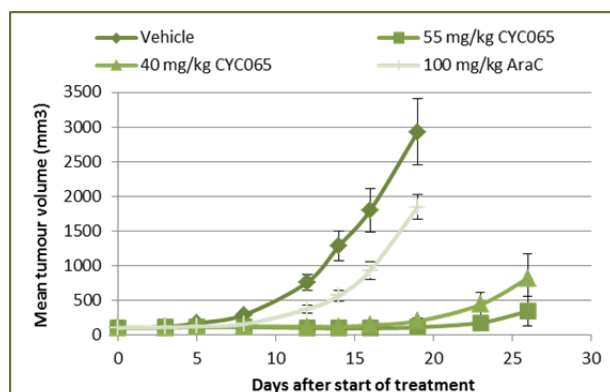
Hematological Indications

CYC065 has been shown to target key components of survival and leukemogenic pathways in acute leukemias including the Myeloid cell leukemia sequence-1 (MCL-1), an anti-apoptotic protein related to BCL-2, and transcription driven by the rearranged Mixed Lineage Leukemia gene (MLL).

Rearrangements involving the MLL gene at chromosome 11q23 are associated with the development of acute leukemia with an adverse prognosis. MLL abnormalities gene can be detected in *de novo* acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and acute lymphoblastic leukemia (ALL) in adults and children as well as in therapy related AML, particularly after treatment with DNA topoisomerase II inhibitors.

Rearranged MLL interacts with the transcription complex including CDK9 and upregulates genes which contribute to leukemic transformation.¹³ MCL-1 is overexpressed in leukemia with MLL rearrangements and is associated with resistance to prednisone.¹⁴ Targeting MCL-1 may be an additional therapeutic mechanism of CYC065 for MLL-induced leukemia, particularly in cases of steroid-resistance.

CYC065 is highly efficacious for MLL rearranged AML



CYC065 studies⁴ showed that AML cell lines with WT or rearranged MLL are highly sensitive to CYC065. Five to 8 hours treatment is sufficient to achieve maximum inhibition of cell proliferation and induction of cell death.

CYC065 upregulates p53, down-regulates MCL-1 and induces apoptosis. It also significantly inhibits the transcription of Meis1 and Hoxa1, MLL-regulated leukemogenic genes.

Importantly, Meis1 expression is a rate limiting determinant of the biology of MLL leukemia stem cells.

In separate studies^{15,16} cell death was induced in CLL and MIM cell lines after short exposures to CYC065 in the presence of stromal cells which confer protection from standard chemotherapies. MCL-1 and XIAP down-regulation was observed in these studies suggesting a major pro-apoptotic mechanism of CYC065.

Development Status

CYC065 entered first in human Phase 1 studies in October 2015 (NCT02552953). The pre-NDA development was partly supported by a grant award of approximately \$1.9 million from the UK Government's Biomedical Catalyst program.¹⁷ A key component of the grant funded project is a translational biology effort to validate patient stratification biomarkers, which may be used to inform clinical development and direct CYC065 administration to patient groups most likely to benefit from the drug's mechanism. Cyclacel discovered CYC065 and other novel CDK inhibitors in collaboration with the Cancer Research UK Centre for Cancer Therapeutics at The Institute of Cancer Research (ICR), London, UK.

Endnotes:

1. An experimental drug under clinical investigation. Not approved for human use.
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3. Scaltriti, et al, 2011 PNAS 108:3761
4. Zheleva, et al, *SOHO 2015 Abs 213*
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7. Poon, et al, *4th Neuroblastoma Society Symposium 2015, 26 – 27 November, Newcastle, UK*
8. Akli, et al, 2011 *Cancer Res* 71:3377
9. Shapiro, et al, 2013 *Proc AACR Ann Meet LB-202*
10. Lockwood, et al, 2008 *Oncogene* 27:4615
11. Eggers, et al 2011 *Clin Cancer Res*, 17 :6140
12. Galimberti, et al, 2010 *Clin Cancer Res* 16 :109–20
13. Dou & Hess, *Int J Haematol.*2008, 87:10
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17. *Cyclacel Press Release November 5, 2012.*

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