4849

Abstract #3617

YPN-005, an oral CDK7 inhibitor, shows a significant antitumor activity in Myc amplified solid tumors and MCL-1 overexpressed blood cancers

Jakyung Yoo, Jun Hee Lee, Mi Jung Lee, Kang Woo Lee, Ji Eun Min, Jinhwan Kim, Ki-Nam Min, Da-Hye Jeon, Dae Seong Lim, Kwang-Ok Lee*

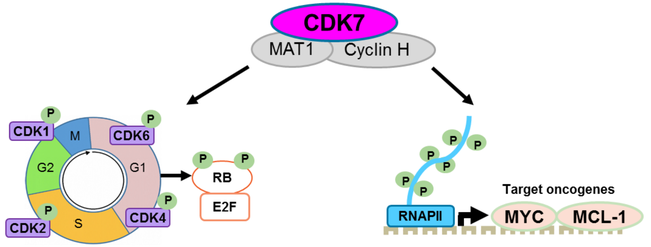
R&D Institute, Yungjin Pharmaceutical Co., Ltd, 109, Gwanggyo-Ro, Yeongtong-Gu, Gyeonggi-do 16229, Republic of Korea

Introduction

- CDK7 as a promising anti-cancer target regulates cell cycle progression through the regulation of cell-cycle proteins, and gene transcription through the regulation of RNA polymerase II (RNAPII)
- CDK7 causes transcriptional activation of oncogenes Myc and MCL-1
- Myc amplification in solid tumors is correlated with tumor aggression and poor therapeutic outcome
- MCL-1 is shown to be critical to the development and maintenance of hematological cancers
- YPN-005 shows potential as a therapeutic agent across both solid tumor cells as well as hematological cancer cells via Myc and MCL-1 downregulation and cell cycle arrest
- YPN-005 is currently being evaluated in treatment for hematological cancers via the intravenous route and closely followed in development for solid cancers via the oral route

CDK7 pathway plays a key role in cancer

CDK7 regulates cell cycle progression and gene transcription:



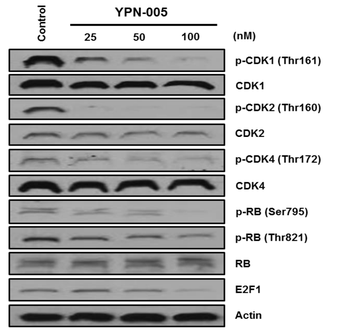
I. Cell-cycle regulation
- Via activation of downstream CDKs (CDK 1, 2, 4, and 6)

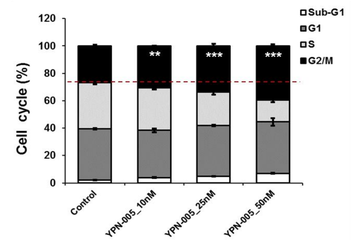
II. Transcriptional activation of oncogenes
- Via RNA polymerase II phosphorylation

YPN-005 inhibits cell cycle signaling leading to the induction of apoptosis and the disruption of Myc and MCL-1 expression

TNBC (MDA-MB-231)

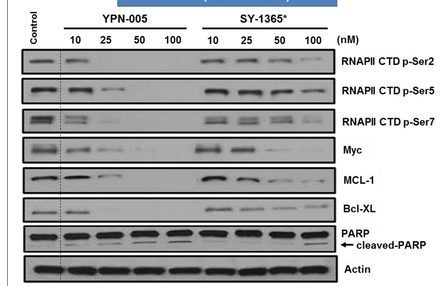
YPN-005 causes the inhibition of phosphorylation of cell-cycle proteins





Note: Cells were treated with YPN-005 for 20 hours.
Cell cycle was measured by flow cytometry (PI staining).
N=3, Data means ± SD.
** P<0.01, ***P<0.001 vs Control group (G2/M phase).

TNBC (MDA-MB-231)

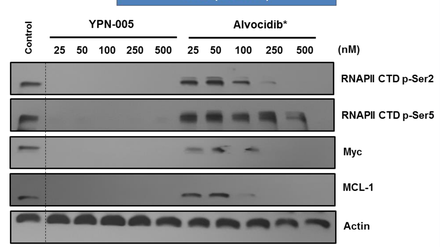


Note: Cells were treated with YPN-005 and SY-1365 for 24 hours

Compound	GI_{50} (nM)	GI_{90} (nM)
YPN-005	7.4	66.6
SY-1365*	21.7	195.3

Note: YPN-005 and SY-1365 treatment for 72 hours

AML (MV-4-11)



Note: Cells were treated with YPN-005 and Alvocidib for 4 hours
* Comparative compound

Compound	GI_{50} (nM)	GI_{90} (nM)
YPN-005	2.8	25.2
Alvocidib*	124.2	1117.8

Note: YPN-005 and Alvocidib treatment for 72 hours

YPN-005 inhibits Myc/MCL-1 expressing cancer cell growth

Myc (+) solid tumor cells

Cell line	GI_{50} (nM)	GI_{90} (nM)	Origin
MDA-MB-468	11.2	100.8	Breast (TNBC)
MDA-MB-231	7.4	66.6	Breast (TNBC)
HCC70	11.2	100.8	Breast (TNBC)
MCF-7	15.1	135.9	Breast (ER+/Her-)
HepG2	4.4	39.6	Liver (HCC)
Hep3B	6.4	57.6	Liver (HCC)
Huh7	11.6	104.4	Liver (HCC)
OVCAR-3	4.8	43.2	Ovary
SKOV-3	9.6	86.4	Ovary
BxPC-3	6.7	60.3	Pancreas
LNCaP	8.0	72	Prostate
DU145	11.5	103.5	Prostate

Note: YPN-005 treatment for 72 hours

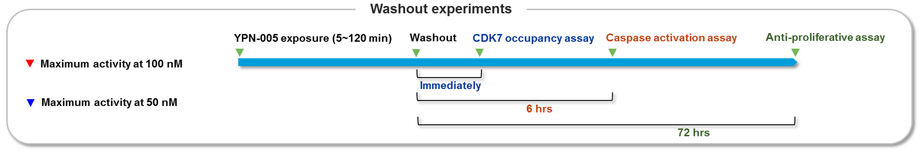
MCL-1 (+) hematological cancer cells

Cell line	GI_{50} (nM)	GI_{90} (nM)	Cell line	GI_{50} (nM)	GI_{90} (nM)
MOLM-13	19.0	170.9	CCRF-CEM	15.6	140.7
MOLM-14	2.8	24.9	JURKAT	17.5	157.2
MV4-11	11.8	106.4	MOLT4	4.5	40.6
OCI-AML2	7.7	69.7	DAUDI	9.2	82.4
THP-1	2.0	17.6	SR	5.8	52.5
U937	2.4	21.9	K562	18.9	170.1
KG-1	29.0	261.4	MEG-01	4.0	36
SKM-1	25.0	225.4	KU-812	3.6	32.8
BDCM	2.7	24.1	RPMI-8226	16.4	147.9
NB4	12.9	116.4	MOLM/AZA-1	13.2	118.7
RCH-ACV	4.1	36.9	MOLM/DEC-5	14.9	134.2
TOM-1	4.4	39.2	THP/DEC-2	3.6	32.4
NALM-20	18.6	167	MOLM/CYT	0.9	8.5
KASUMI-2	6.3	56.3			

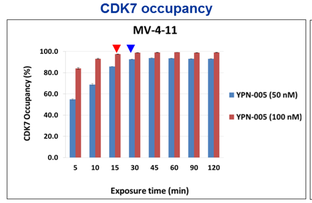
Note: YPN-005 treatment for 72 hours

CDK7 occupancy is correlated with antitumor activities

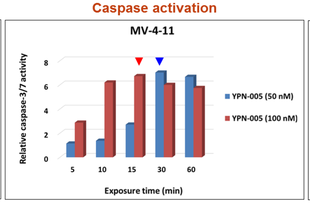
15 - 30 minutes exposure of YPN-005 was sufficient to achieve the maximal in vitro activities including CDK7 occupancy, caspase activation and anti-proliferative activity



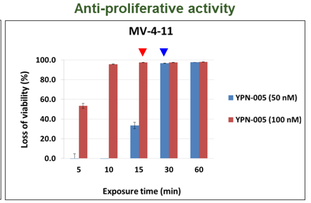
CDK7 occupancy



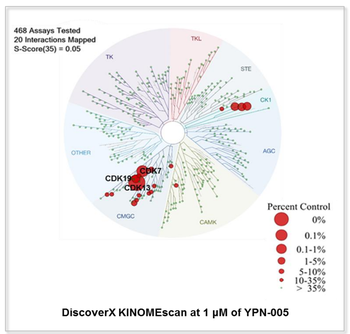
Caspase activation



Anti-proliferative activity



YPN-005 is a potent and selective CDK7 inhibitor



DiscoverX KINOMEscan at 1 μM of YPN-005

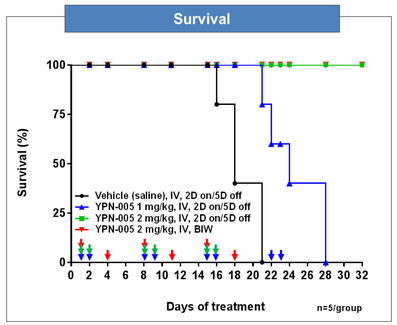
CDK	[1] %Control at 1 μM	[1] Kd (nM)	[2] IC_{50} (nM)
CDK1	100	[3] NC	NC
CDK2	80	NC	NC
CDK3	95	NC	NC
CDK4	97	NC	NC
CDK5	70	NC	NC
CDK6	100	NC	NC
CDK7	**0.25** *	**5.1** *	**31** **
CDK8	21	570	NC
CDK9	82	NC	NC
CDK10	63	NC	NC
CDK11B	100	NC	NC
CDK12	11	9.7	> 1,000
CDK13	0	2.1	> 1,000
CDK14	73	NC	NC
CDK15	30	180	NC
CDK16	16	91	NC
CDK17	52	NC	NC
CDK18	60	NC	NC
CDK19	1.4	170	NC

[1] KINOMEscan™ (DiscoverX); [2] KinaseProfiler™ (eurofins); [3] NC: Not calculated

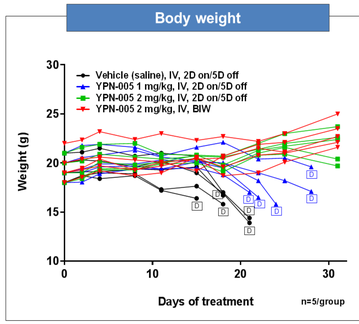
* CDK7 only (Binding assay)
** CDK7/cyclinH/MAT1, Km ATP (Radiometric assay)

YPN-005 shows antitumor efficacy in MOLM-13 orthotopic AML model

Survival



Body weight



NSG mice (Jackson Laboratory) were injected (I.V.) via the tail vein with MOLM-13-GFP cells. The day after mice were treated with YPN-005 at 1 mg/kg (2 days on/5 days off for 4 cycles) and 2 mg/kg (2 days on/5 days off or biweekly for 3 cycles). Survival durations observation is ongoing. (D: dead animals)

Conclusions

- **YPN-005: Novel oncology product candidate for multiple solid and hematological cancer indications**
- **A potent, selective, irreversible, and orally available CDK7 inhibitor**
- **Myc and MCL-1 downregulation and cell cycle arrest**
- **Rapid induction of apoptosis and subsequent cell death**
- **Dose dependent antitumor responses without weight loss in AML orthotopic models**

Contacts:

YUNGJIN PHARM

Business Development:
Ms. Sun Young JUNG.
T. +82-2-2041-8227
E. syjung@yungjin.co.kr

Research and Development:
Ms. Jakyung YOO, Ph.D.
T. +82-31-546-6970
E. jyoo76@yungjin.co.kr

Author Disclosures **All Authors:** Employees in Yungjin Pharmaceutical Co., Ltd.

AACR Annual Meeting, June 2020