DBPR114,
Multi-targeted Kinase Inhibitor for Solid Tumors

作用於多靶點激酶之抗癌候選發展藥物

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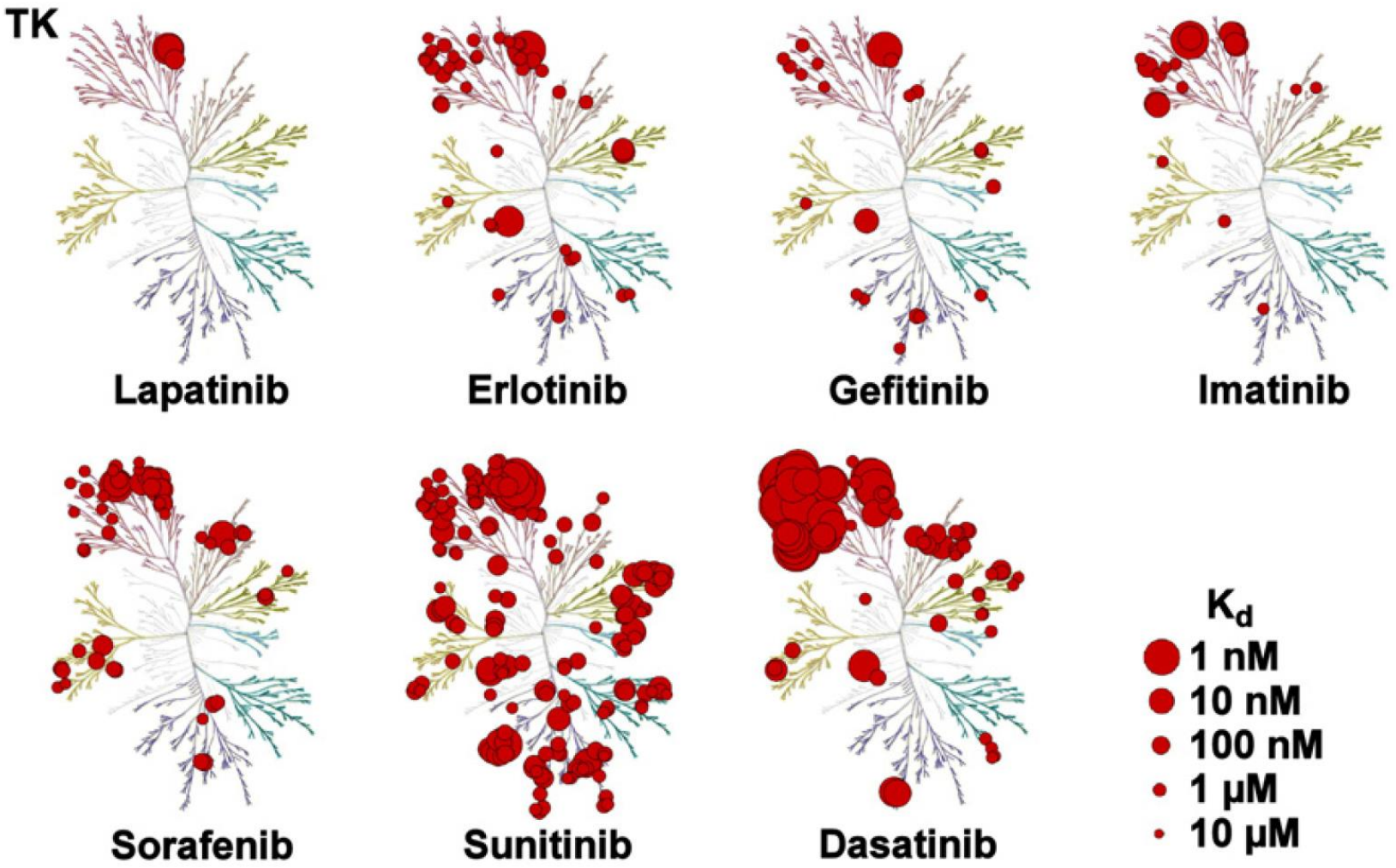
Multi-targeted Kinase Inhibitors



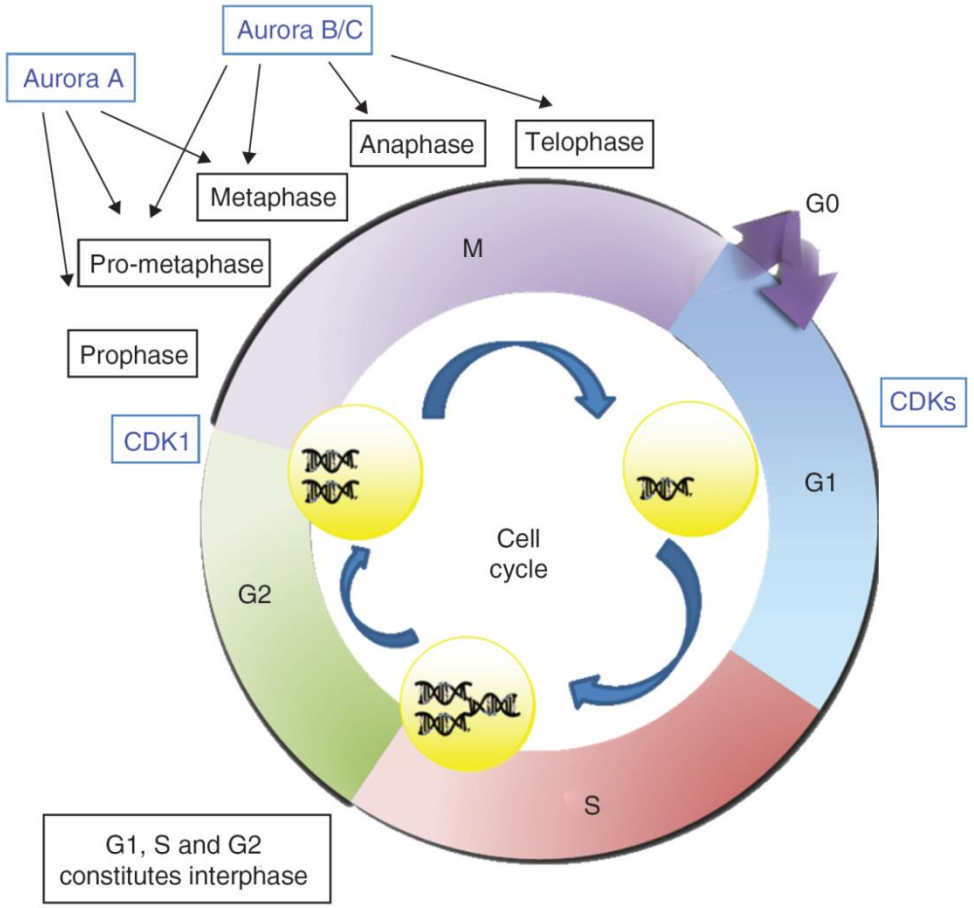
Toxicology and Applied Pharmacology, 2010, 244, 190–195.

Approved Multi-kinase Inhibitors for Different Indications

- ✓ **Sorafenib** (Nexavar, Bayer and Onyx Pharmaceuticals) —advanced renal cell carcinoma in December 2005, advanced hepatocellular carcinoma in November 2007, metastatic differentiated thyroid cancer in November 2013. **($ 1.03 billion in 2013)**
- ✓ **Sunitinib** (Sutent, Pfizer, SU11248) is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) — renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor on January 26, 2006 and pancreatic *Neuroendocrine tumor* in May 2011. **($ 1.19 billion in 2011)**
- ✓ **Pazopanib** (Votrient, GlaxoSmithKline) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor — renal cell carcinoma In October 2009, and soft tissue sarcoma in April 2012**. ($520 million in 2013)**
- ✓ **Regorafenib** (Stivarga, Bayer/Onyx, BAY 73-4506) is an oral multi-kinase inhibitor developed by Bayer which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK). — metastatic colorectal cancer on September 27, 2012 and advanced gastrointestinal stromal tumors on February 25, 2013. **($ 116.6 million in the first half of 2013)**

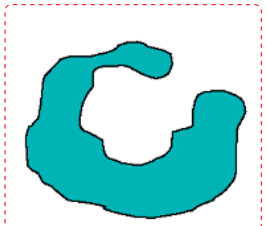
Biological Roles of Aurora Kinases

- The Aurora kinases are mitotic kinases for cell division and are overexpressed in a number of human cancers.
- Three isoforms A, B and C are known.
- Aurora A essential for centrosome maturation & bi-polar spindle assembly.
- Aurora B essential for accurate chromosome segregation and cytokinesis.

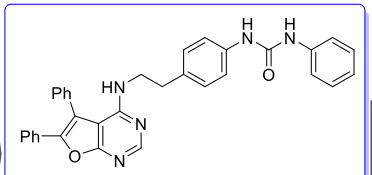


Hsieh, H. P.; Chang, J. Y. et al. *Expert Opin. Ther. Pat.* **2009**, *19*, 321-356.
Hsieh, H. P.; Chang, J. Y. et al. *Expert Opin. Investig. Drugs* **2009**, *18*, 379-398.
Hsieh, H. P.; Chang, J. Y. et al. *Expert Opin. Ther. Pat.* **2011**, *21*, 857-884.

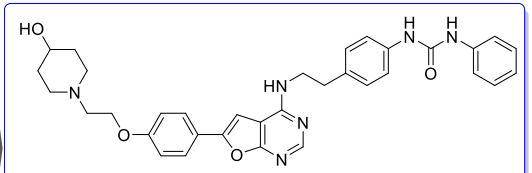
Identification of DBPR114, A Novel Multi-targeted Kinase Inhibitor



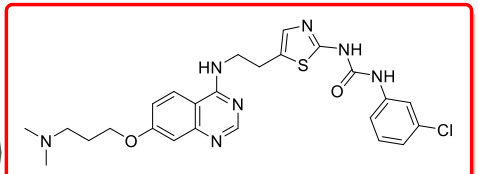
Aurora A Protein



BPR1K0432S0
1st generation Lead
Aurora-A IC_{50} = 41 nM
HCT-116 IC_{50} = 394 nM



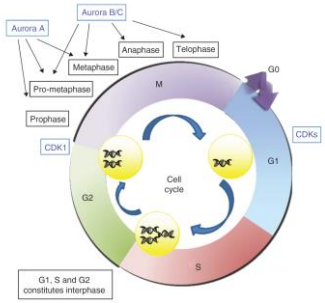
BPR1K0724S0
2nd generation Lead
Aurora-A IC_{50} = 7 nM
Aurora-B IC_{50} = 5 nM
HCT-116 IC_{50} = 185 nM

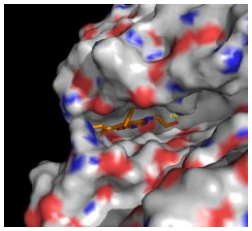


DBPR114
3rd generation Lead
Aurora-A IC_{50} = 6 nM
Aurora-B IC_{50} = 13 nM
HCT-116 EC_{50} = 141 nM

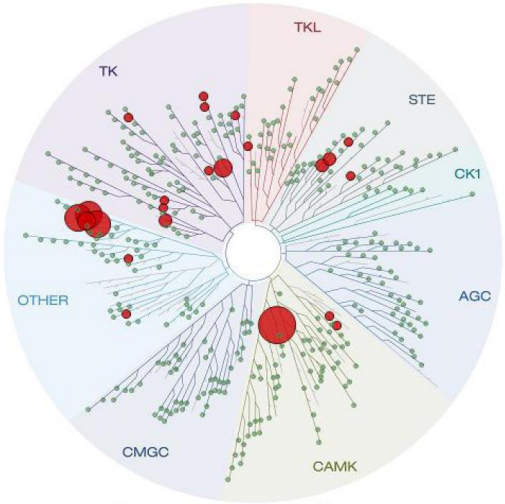
Knowledge Base Screening → **H.T.P.S.** → **Rationale Design & Lead Optimization** → **Scaffold Hopping**

J. Med. Chem. (2010) *J. Med. Chem. (2013) / PNAS (2013)* *Oncotarget (2016)*

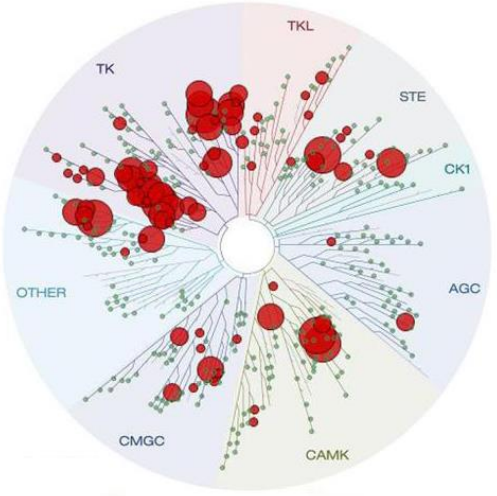




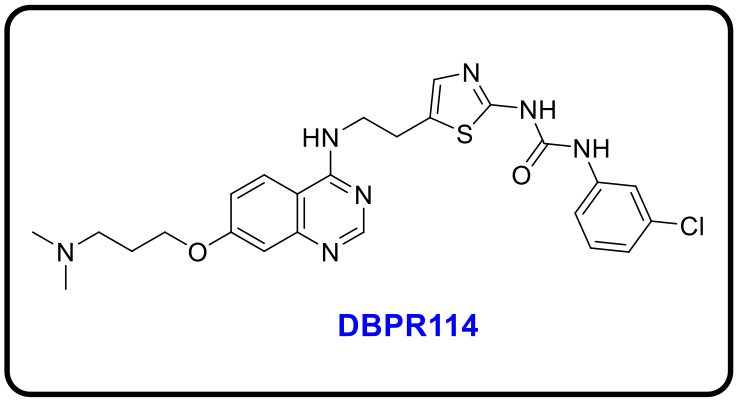
BPR1K0724S0 @ 1000nM



DBPR114 @ 1000 nM



DBPR114 Activity Profiles



DBPR114

Kinase	IC_{50} (nM)
Aurora-A	0.674
TRKA	0.988
FLT3	2.24
TYORS	5.36
TEK	5.61
CHK2	7.64
FLT1 (VEGFR1)	17.5
c-Met	33.4
PTK2B	58.5
EPHA4	58.9
RPS6KA2(RSK3)	95.9

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

Discovery of BPR1K871, a quinazoline based, multi-kinase inhibitor for the treatment of AML and solid tumors: Rational design, synthesis, *in vitro* and *in vivo* evaluation

Yung Chang Hsu[1,*], Mohane Selvaraj Coumar[2,*], Wen-Chieh Wang[1,*], Hui-Yi Shiao[1,*], Yi-Yu Ke[1], Wen-Hsing Lin[1], Ching-Chuan Kuo[1], Chun-Wei Chang[1], Fu-Ming Kuo[1], Pei-Yi Chen[1], Sing-Yi Wang[1], An-Siou Li[1], Chun-Hwa Chen[1], Po-Chu Kuo[1], Ching-Ping Chen[1], Ming-Hsine Wu[1], Chen-Lung Huang[1], Kuei-Jung Yen[1], Yun-I Chang[1], John T.-A. Hsu[1], Chiung-Tong Chen[1], Teng-Kuang Yeh[1], Jen-Shin Song[1], Chuan Shih[1], Hsing-Pang Hsieh[1,3]

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Keywords: *acute myeloid leukemia, aurora kinase, FLT3, quinazoline, multi-kinase inhibitor*

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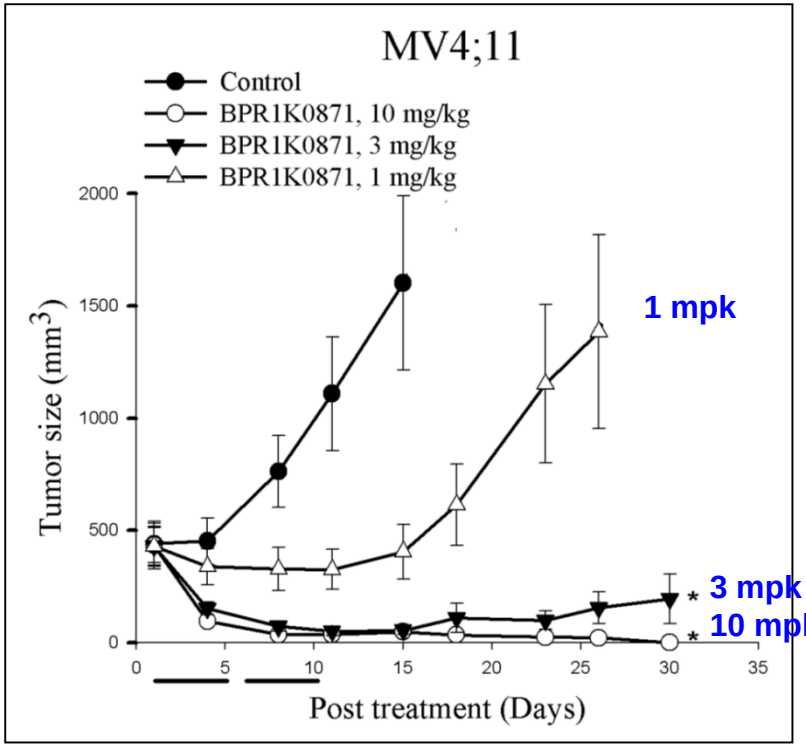
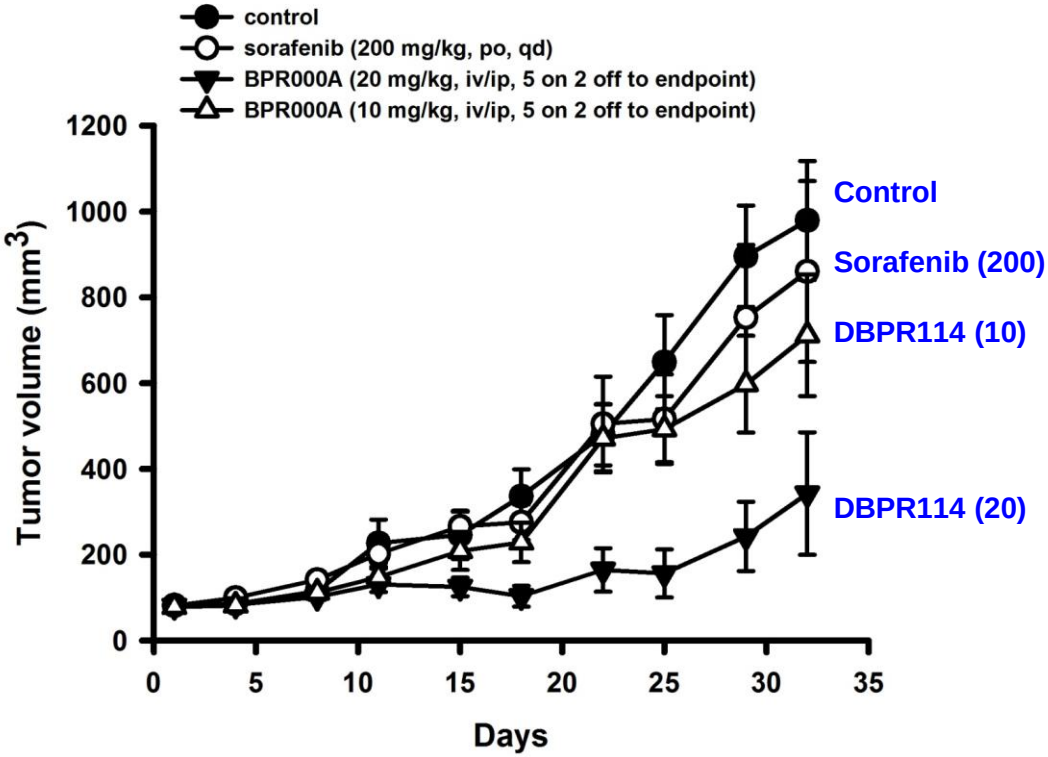
ABSTRACT

The design and synthesis of a quinazoline-based, multi-kinase inhibitor for the treatment of acute myeloid leukemia (AML) and other malignancies is reported. Based on the previously reported furanopyrimidine 3, quinazoline core containing lead 4 was synthesized and found to impart dual FLT3/AURKA inhibition (IC_{50} = 127/5 nM), as well as improved physicochemical properties. A detailed structure-activity relationship study of the lead 4 allowed FLT3 and AURKA inhibition to be finely tuned, resulting in AURKA selective (5 and 7; 100-fold selective over FLT3), FLT3 selective (13; 30-fold selective over AURKA) and dual FLT3/AURKA selective (BPR1K871; IC_{50} = 19/22 nM) agents. BPR1K871 showed potent anti-proliferative activities in MOLM-13 and MV4-11 AML cells (EC_{50} ~ 5 nM). Moreover, kinase profiling and cell-line profiling revealed BPR1K871 to be a potential multi-kinase inhibitor. Functional studies using western blot and DNA content analysis in MV4-11 and HCT-116 cell lines revealed FLT3 and AURKA/B target modulation inside the cells. *In vivo* efficacy in AML xenograft models (MOLM-13 and MV4-11), as well as in solid tumor models (COLO205 and Mia-PaCa2), led to the selection of BPR1K871 as a preclinical development candidate for anti-cancer therapy. Further detailed studies could help to investigate the full potential of BPR1K871 as a multi-kinase inhibitor.

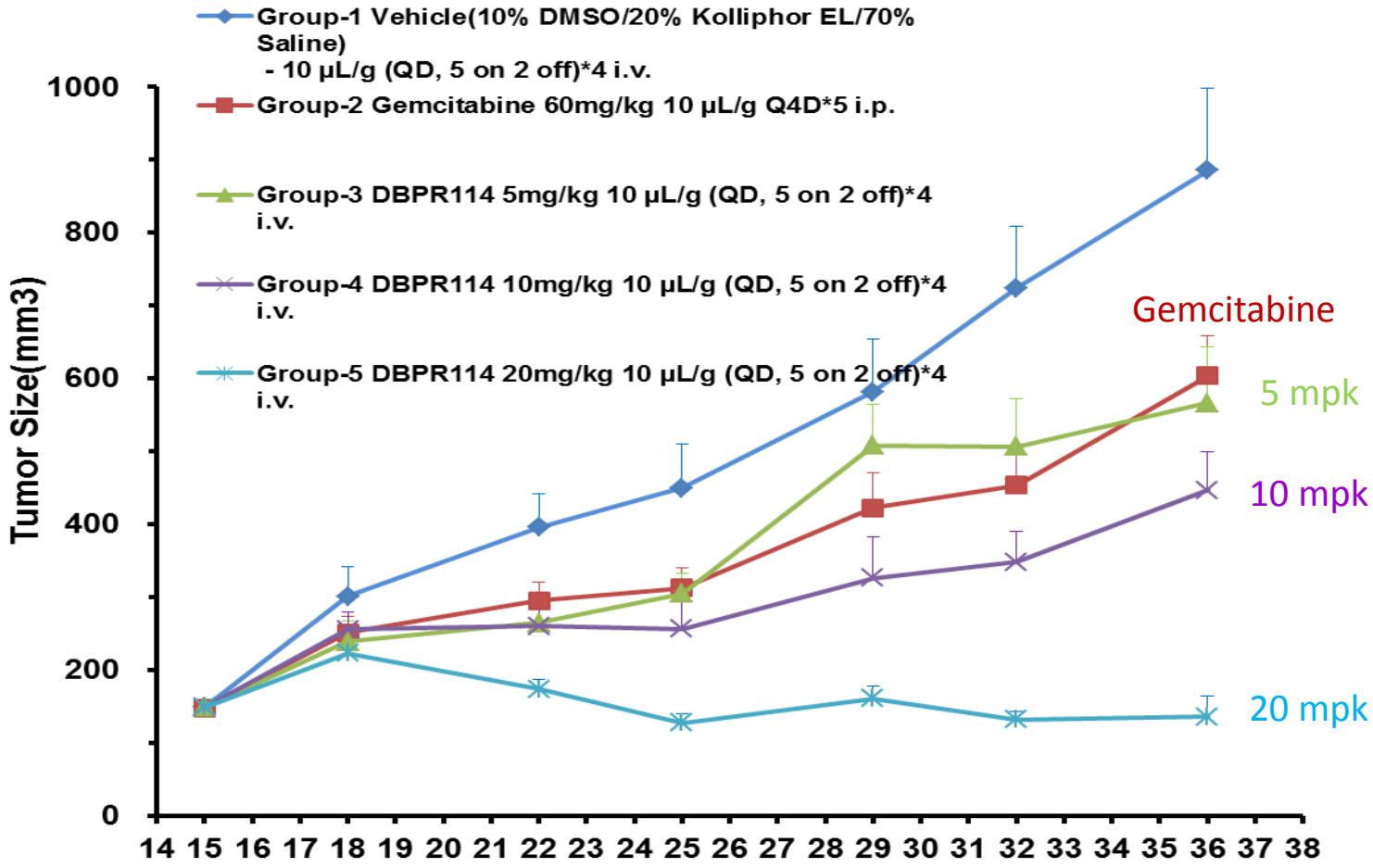
Oncotarget. 2016, 7, 86239-86256

DBPR114
in MV4-11 and in Hepatoma Hep3B Xenograft Model





DBPR114
in MIA-Paca 2 Xenograft Model



*DBPR114為S1

Dosing day: 15-19, 22-26, 29-33, 36-40

DBPR114 - Development Plan towards IND Application

2014

Grant approval (NRPB program)

- Process development (API)
- Pre-formulation, polymorphism
- Salt selection, crystalline evaluation
- 50g-scale synthesis

- API (Non-GMP 300 g and 3 kg)
- *In vitro* & *in vivo* pharmacology
- Tox. formulation study
- Analytical & bioanalytical methods development

2015

- In-house DRF in rat
- Clinical formulation study
- PK/ADME
- PDX

- Tox. DRF in rats and dogs

- GMP API production for clinical use (1 kg)
- 28-day tox studies in rats and dogs

2016

- DP production with stability studies
- Preparation for IND package
  - ✓ Investigational Brochure
  - ✓ Modules 2.4/2.6
  - ✓ Modules 3.2.S/3.2.P
  - ✓ Study reports
  - ✓ Clinical protocol

Planned US IND submission：May, 2017
Planned TW IND submission：July, 2017

2017

2016年王民寧獎

Major Advantages and Differentiation of DBPR114

- Multi-target kinase inhibition MOA (Aurora A/B/TrkA/Flt-3/c-Met) may translate to better efficacy for tough to treat solid tumors
- Novel inhibition of CSF1R which may lead to additional benefit on immune system activation (built in IO therapeutic advantages)
- Less prone to develop drug resistance phenotypes in clinical setting
- Broadly active *in vivo* in various solid tumor xenograft (mostly to GI tract cancers) and leukemia models (8 models)
- Excellent anti-tumor efficacy observed on intermittent schedules (Day 1, 4, 8, 11 and weekly/Day 1, 8)
- Acceptable DMPK (CYP, metabolic stability) profile
- Easy parental administration (i.v.) with acceptable/manageable toxicity profile
- Readily scale up and developable process (6 steps/14.7% yield)
- Potential First-in-Class asset for GI cancers (gastric, liver, pancreas and colon) and acute myeloid leukemia (AML)