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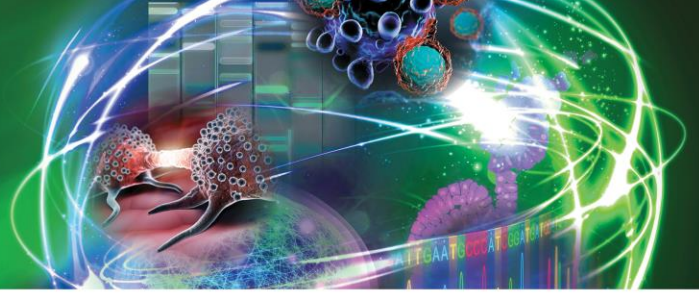

# PC14586: The First Orally Bioavailable Small Molecule Reactivator of Y220C Mutant p53 in Clinical Development

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# Disclosure Information



## Melissa Dumble, PhD

I have the following financial relationships to disclose:
Stockholder in: PMV Pharma
Employee of: PMV Pharma

I will not discuss off label use and/or investigational use in my presentation.

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# PMV's First in Class Y220C Lead Program is Focused on the Reactivation of p53

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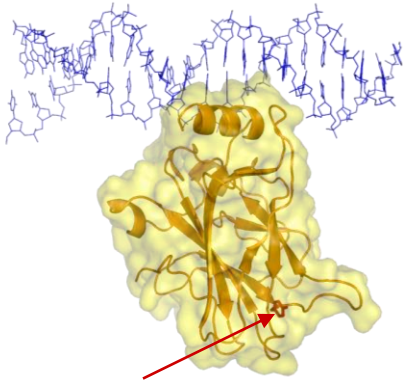

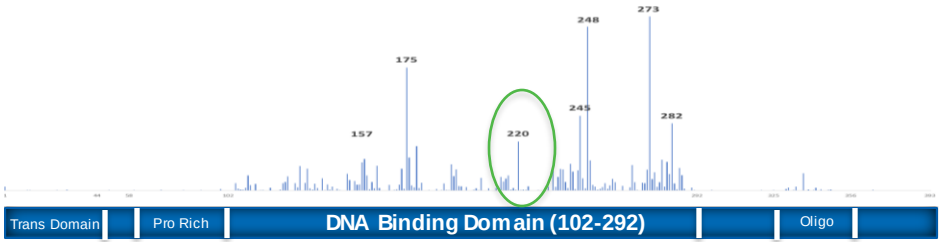


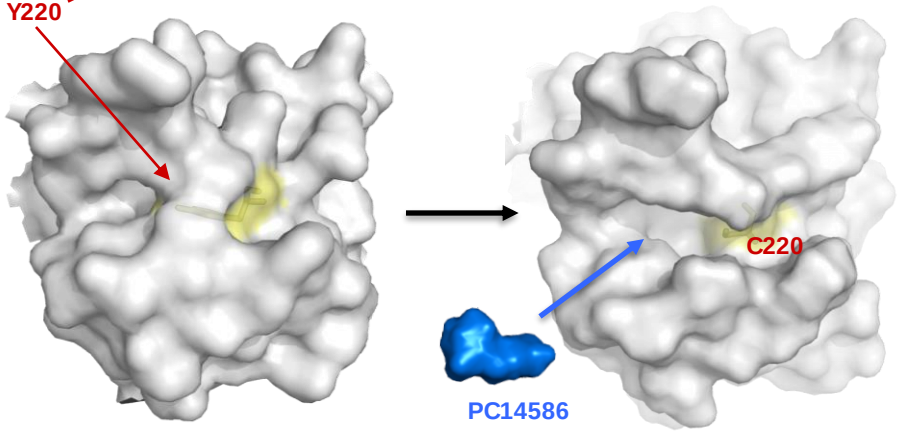


**Y220C-SM Complex Thermally Stable**

↓

**p53 Transcriptional Activity Restored**

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# PC14586 Converts p53 Y220C to Wild Type and Selectively Initiates p53 Transcription

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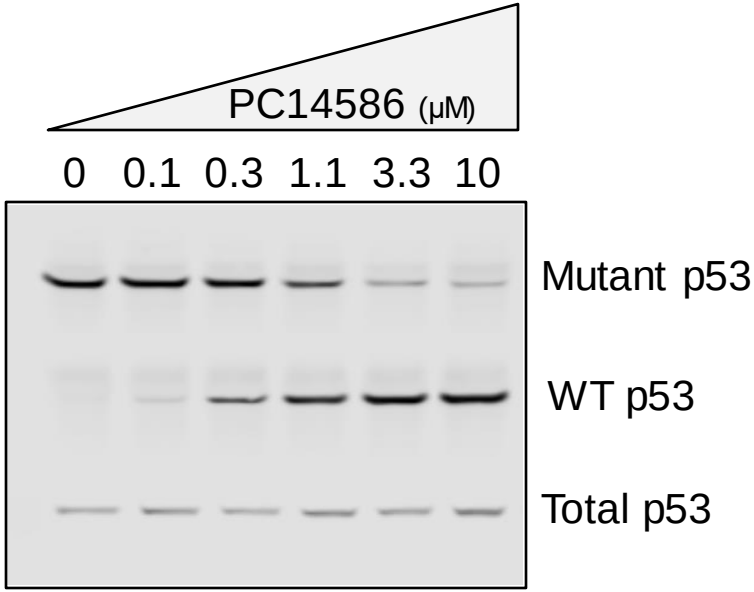
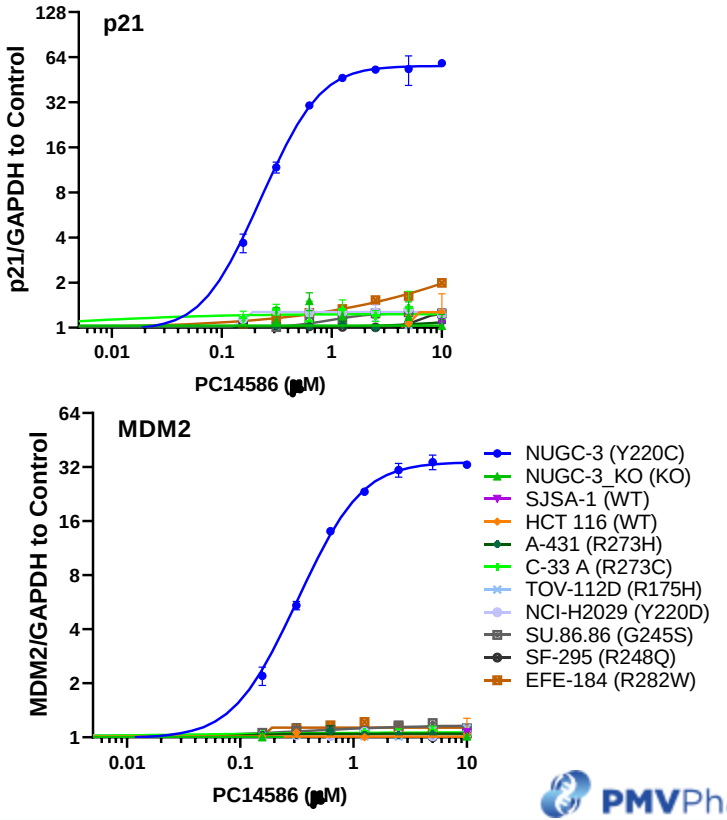



2 h treatment of NUGC3 cells followed by IP with indicated Ab

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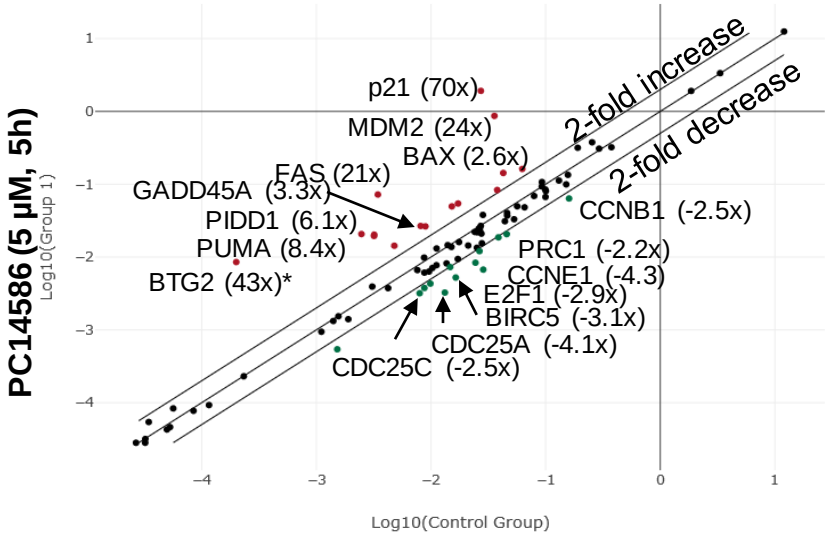
# PC14586 Leads to Effective Reactivation of the p53 Transcriptional Pathway

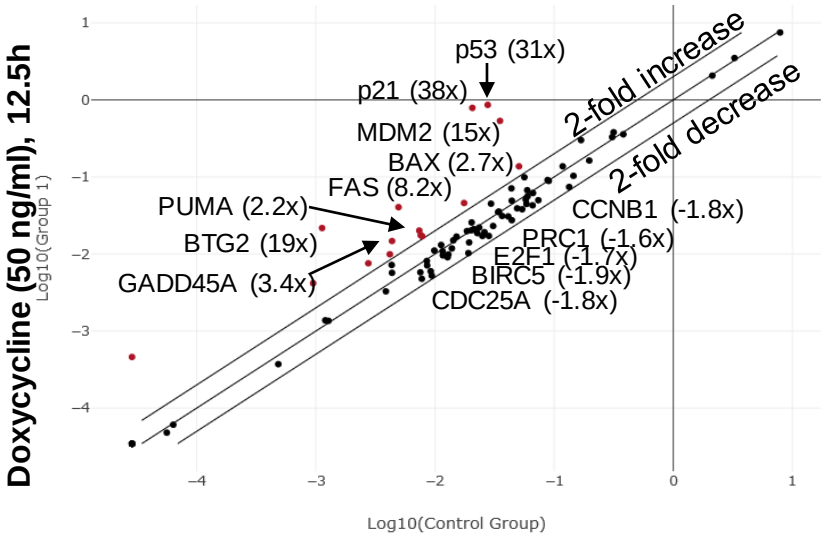


Parental NUGC3 (Y220C)




DMSO Control

NUGC3_KO w/ Inducible WT p53




DMSO Control

- No activity in NUGC3-KO, other p53 mutants and WT p53 expressing cells

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# PC14586 Inhibits Proliferation Across All p53 Y220C Cell Lines Tested

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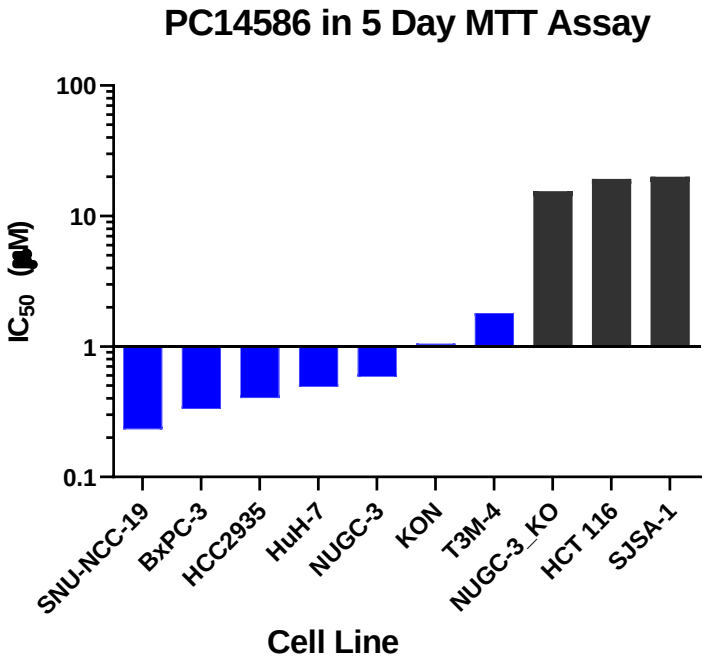


| Cell Line | Tumor | Mutations | $IC_{50}$ (uM) |
|---|---|---|---|
| SNU-NCC-19 | intestinal adenocarcinoma | Y220C | 0.23 |
| BxPC-3 | pancreatic adenocarcinoma | Y220C | 0.33 |
| HCC2935 | lung adenocarcinoma | Y220C | 0.40 |
| HuH-7 | hepato cellular carcinoma | Y220C | 0.49 |
| NUGC-3 | gastric adenocarcinoma | Y220C | 0.59 |
| KON | oral squamous carcinoma | Y220C | 1.05 |
| T3M-4 | pancreatic adenocarcinoma | Y220C | 1.81 |
| NUGC-3_KO | gastric adenocarcinoma | KO | 15.5 |
| HCT 116 | colorectal carcinoma | WT | 19.3 |
| SJSA-1 | osteosarcoma | WT | >20 |

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# Oral Administration of PC14586 in NUGC3 Xenografts Results in Robust Tumor Regression

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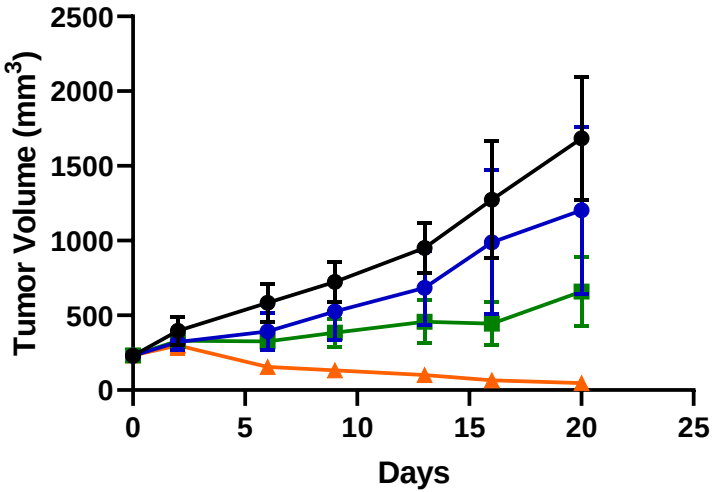
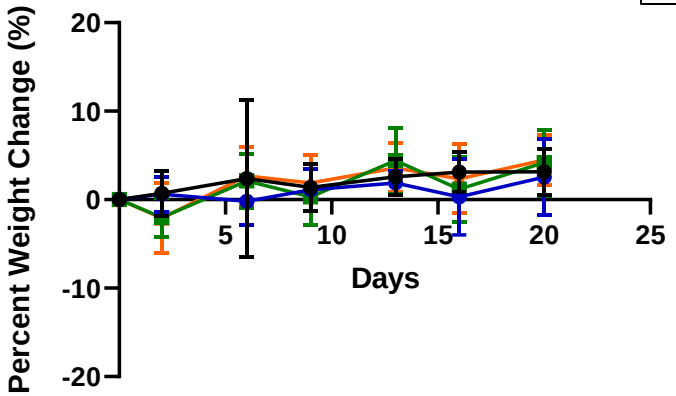
NUGC3 Model




N = 10 per group
Vehicle = 2% HPMC, 0.5% Tween 80

- Vehicle, QDx21
- PC14586, 25 mg/kg, QDx21
- PC14586, 50 mg/kg, QDx21
- PC14586, 100 mg/kg, QDx21

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# Robust Pharmacodynamic Changes Following Oral Administration of PC14586

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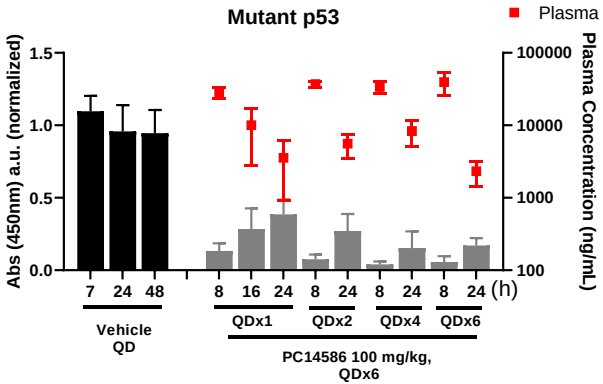
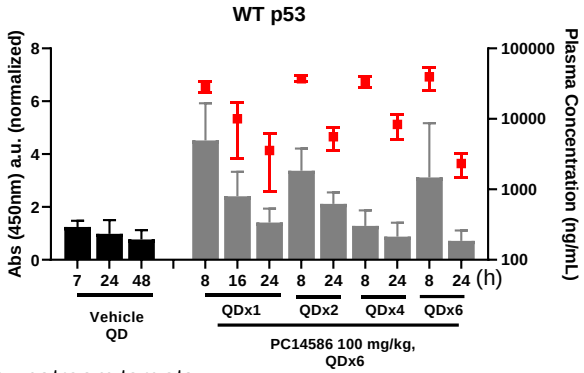
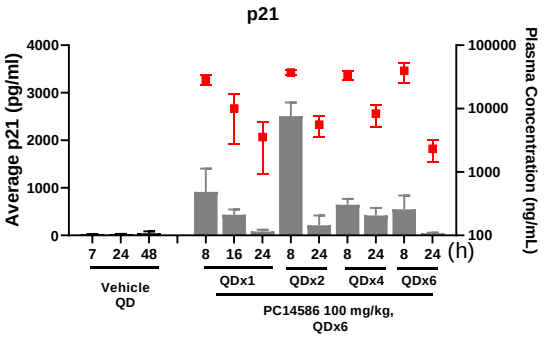
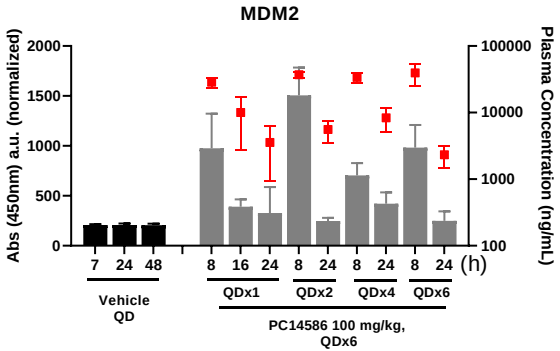
NUGC3 Model

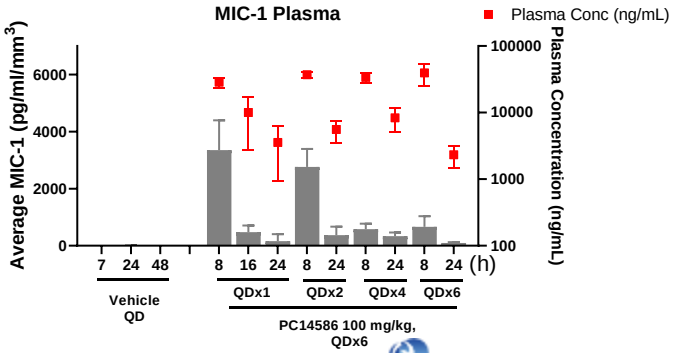



Downstream targets

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# Gene Expression Changes In vivo Following PC14586 Daily Administration

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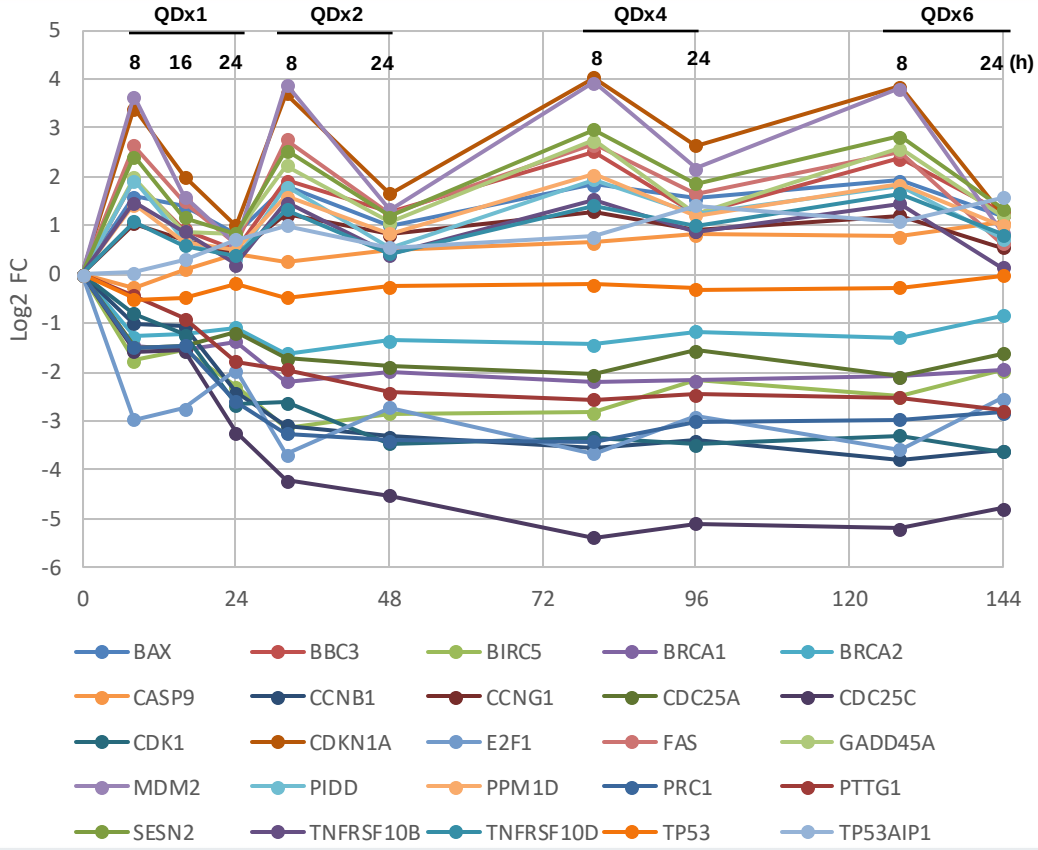


NUGC3 Model

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# Phase 1/2 Clinical Trial Ongoing in Advanced Solid Tumors that Have a p53 Y220C Mutation



- p53 Y220C present in ~1% of solid cancers, predicted top tumor types listed below

| Histology<br>FMI, Nov 2019 | Frequency (%) |
|---|---|
| Ovarian | **2.77** |
| Pancreatic | **1.42** |
| Gastric/Esophageal | **1.08** |
| Breast | **1.02** |
| Non-small cell lung cancer | **0.88** |
| Colorectal | 0.62 |
| Prostate | 0.49 |

- PC14586 is currently being evaluated for safety and efficacy in a seamless Phase 1/2 clinical study (NCT study identifier NCT04585750)
  - solid tumor agnostic trial, patients selected by Y220C *TP53* mutation

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# PC14586 Reactivates p53 Y220C Function



- PC14586 is a first-in-class small molecule reactivator of p53 Y220C
  - Non-covalently binds Y220C p53 and stabilizes the mutant protein in the wildtype conformation
  - Selectively reactivates p53 dependent transcription resulting in cell-cycle arrest and apoptosis
  - In mice, oral daily delivery results in robust tumor regression and is well tolerated
  - Several pharmacodynamic biomarkers of p53 reactivation have been developed and modelled for clinical implementation (e.g. target gene expression, p21, MDM2 and MIC-1 protein expression)
- PC14586 is being tested in a Phase 1/2 clinical trial in advanced cancer patients whose tumor harbors a *TP53* Y220C mutation (NCT study identifier NCT04585750)

# PMV Team

Kuo-Sen Huang (Cepter Biopartners)
Binbin Liu (WuXi AppTec)