237 Antisense-based Cancer Therapeutic

Asset Overview

Product Type	Nucleic acid
Indication	Oncology
Current Stage	Lead Identification/optimization
Target(MoA)	Morpholino-modified antisense oligonucleotide to E2F8
Brief Description	• KDM5A/B histone demethylases are amplified and overexpression in multiple solid tumors, making these enzymes ideal targets for cancer therapy • KDM5B loss/inhibition induced robust antitumor immune response, leading to prolong survival of tumor bearing mice in multiple models (Figure below) • Specific inhibitors of KDM5 inhibitors (IC50s of ~20 nM) have been identified. 35 high-resolution crystal structures (1.22-2.29 Å) of KDM5A with various inhibitors are available to support further medicinal chemistry optimization
Organization	Yale University

Differentiation

□ **Unmet need of current targeted therapy for lung cancer**

- Lung cancer (LC) is the most frequent cause of cancer deaths worldwide with limited treatments for patients
- Even though LC development is largely associated with mutations in oncogenic Kras or in the tumor suppressor p53, there are no clinically effective drugs for these patients
- Targeted inhibitors against receptor tyrosine kinases (RTKs) or epidermal growth factor receptor (EGFR) have shown some efficacy but a majority of patients develop therapeutic resistance

□ **E2F8 (atypical repressors) have a role in cell cycle promotion**

- The E2F family is a core transcriptional axis crucial for cell cycle transitions by regulating gene expression, including expression of cyclins and CDKs
- E2Fs are categorized into three groups based on their transcriptional activity: activators (E2F1-E2F3), canonical repressors (E2F4-E2F6), and atypical repressors (E2F7-E2F8)
- Upon mitogenic stimulation, activated E2F1-E2F3 will accumulate in the late G1 phase and initiate a transcriptional program that drives cells into S phase. The G1/S-specific transcriptome is then attenuated by the action of E2F7 and E2F8
- Expression of E2F7 and E2F8 is tightly correlated with expression of proliferative marker Ki-67 and associated with hepatocyte proliferation
- Upregulation of E2F8 promotes cell proliferation and tumorigenicity in breast, hepatocellular, and lung cancer
- E2F8 accelerates the S-phase transition by transcriptionally upregulating cyclin E1 and cyclin E2 in breast cancer cells and cyclin D1 in hepatocellular cellular carcinoma through interactions with regulatory elements in their promoters
- E2F7 and E2F8 form homodimers (E2F7-E2F7 and E2F8-E2F8) or heterodimers (E2F7-E2F8) to control transcription of cell cycle-related genes, and both atypical (E2F7, E2F8) and typical (E2F1-E2F3) E2Fs bind to similar DNA sequences

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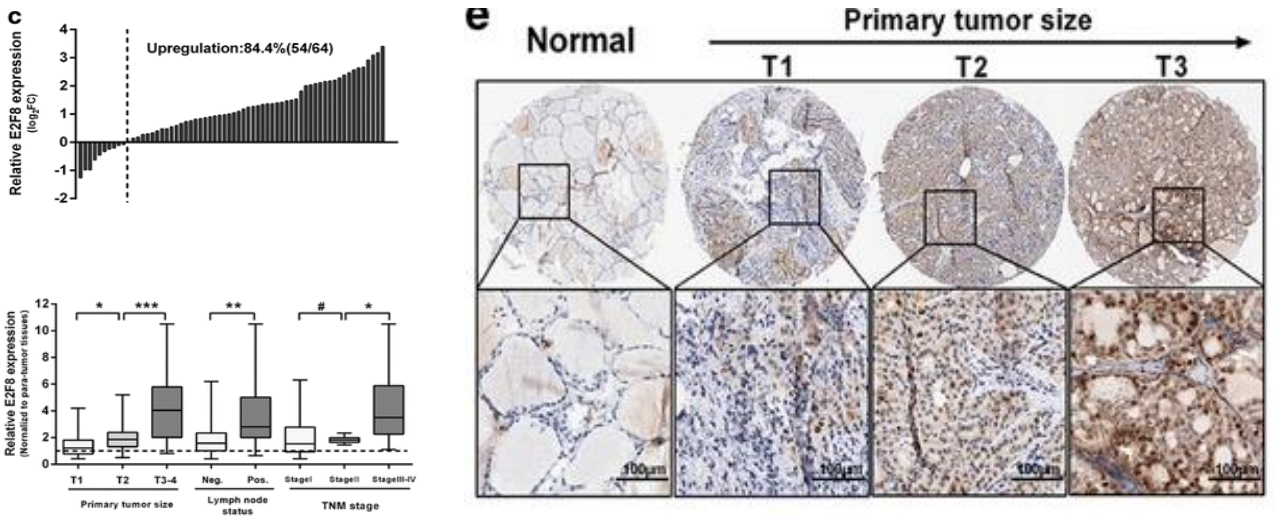
Key Data

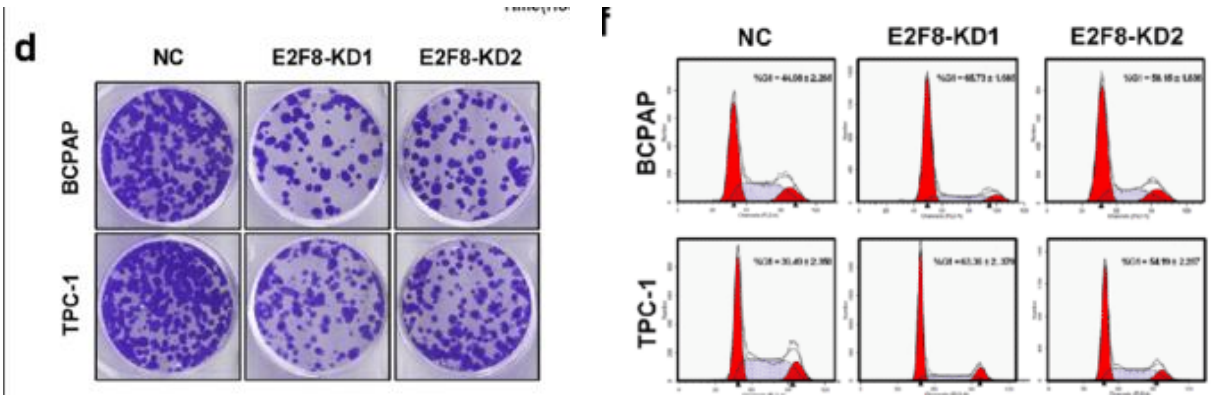
E2F8 is widely upregulated in tumor tissues and correlates with more aggressive clinicopathological features



c qRT-PCR analysis showed that E2F8 was upregulated in 84.4% of 64 PTC patients (Normalized to adjacent normal tissues). d E2F8 mRNA fold change in different T stages, N stages and TNM stages. e Representative TMA IHC analysis of E2F8 in normal thyroid tissue and PTC tissues in different T stages.

J Exp Clin Cancer Res. 2017 Mar 7;36(1):40. doi: 10.1186/s13046-017-0504-6

Knockdown of E2F8 inhibits cells proliferation



BCPAP and TPC-1 cells transfected with siRNA-E2F8 exhibited more arrest at G1 phase than those transfected with siRNA-NC.

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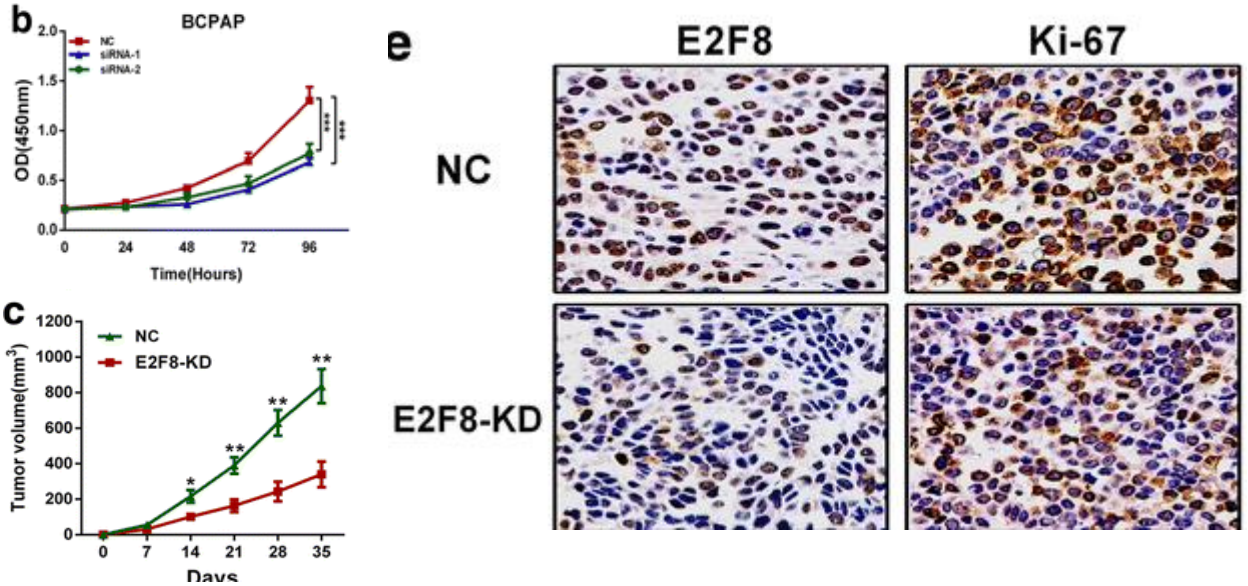
Anti-tumor effect of Antisense-based Cancer Therapeutic



b Nodules harvested from shRNA-NC group and E2F8-KD group. c and d Tumor nodules derived from shRNA-E2F8-transfected TPC-1 cells are significantly smaller than those in shRNA-NC group. e IHC analysis of xenograft tumors showed that Ki-67 staining was weaker in shRNA-E2F8 group. *p < 0.05, **p < 0.01, ***p < 0.001

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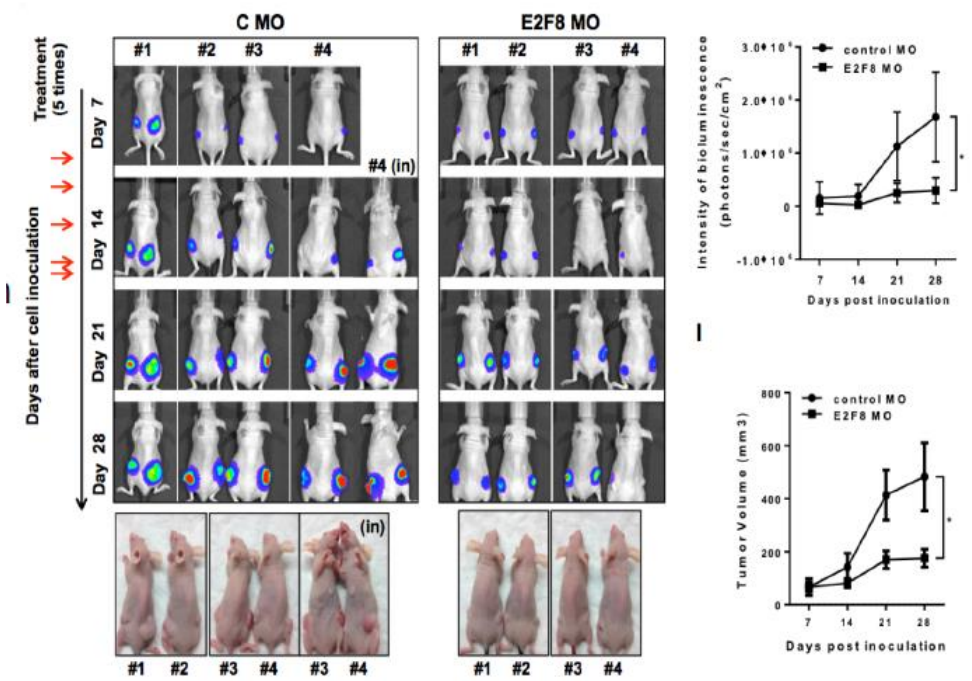

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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