



OncoMutation Silence: **Mutation-Specific Epigenetic Therapy of** **Oncogenic KRAS Mutant in NSCLC**

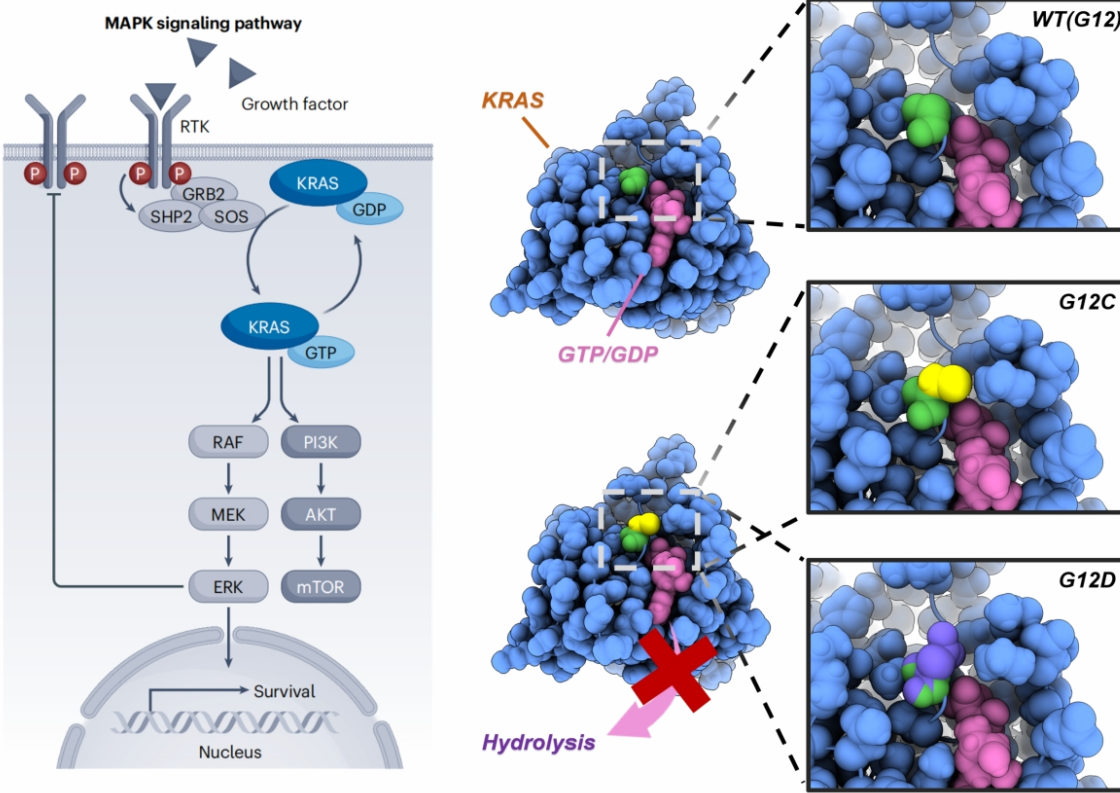
Yvan Guo, Jie Gu, Di Ge*

Zhongshan Hospital, Fudan University
Shanghai Geriatric Medical Center
Shanghai, China

Background

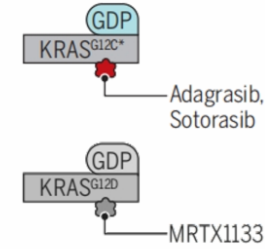
KRAS mutations: 'Model-target' for undruggable mutations

Oncogenic mechanism

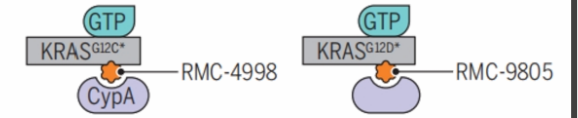


Recent advances

Mutant-selective off-state inhibitors



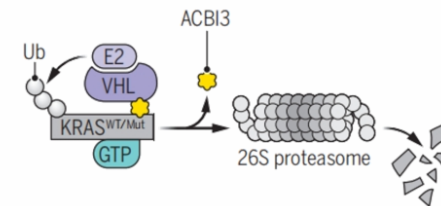
Tricomplex mutant-selective on-state inhibitors



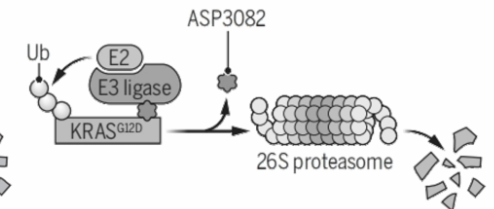
Tricomplex-RAS multi-on-state inhibitor



Pan-KRAS "off-state" degrader



Mutation-selective degrader



Challenges

- KRAS exhibits **picomolar (pM) affinity** for GTP
- **High intracellular GTP concentration (~500 nM)**
- **Lack of binding "pockets"** for small-molecule inhibitors
- Inhibitor resistance (KRAS G12C)
 - Primary resistance: 16–45%
 - **Co-mutations at the inhibitor binding site**

Background

Current targeted therapies are limited by binding pockets & permanent DNA damage

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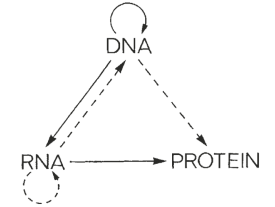


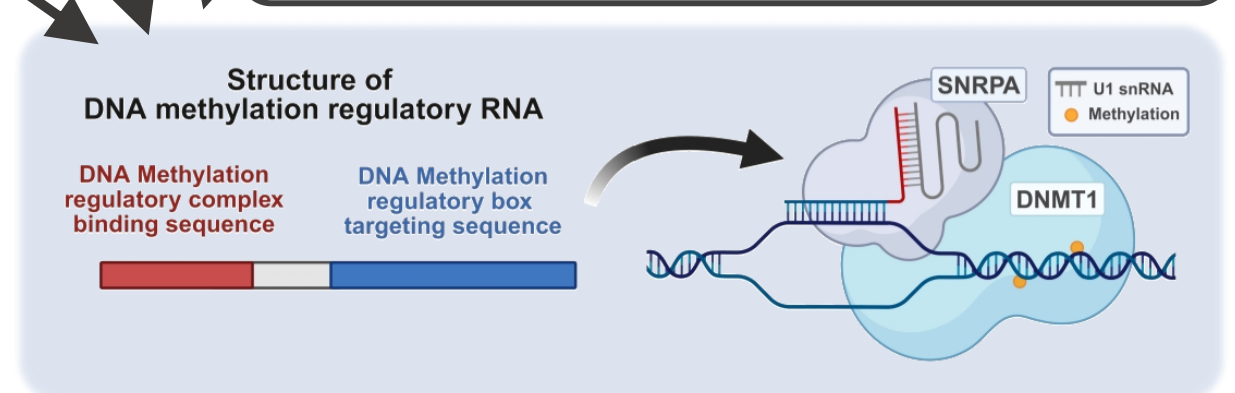
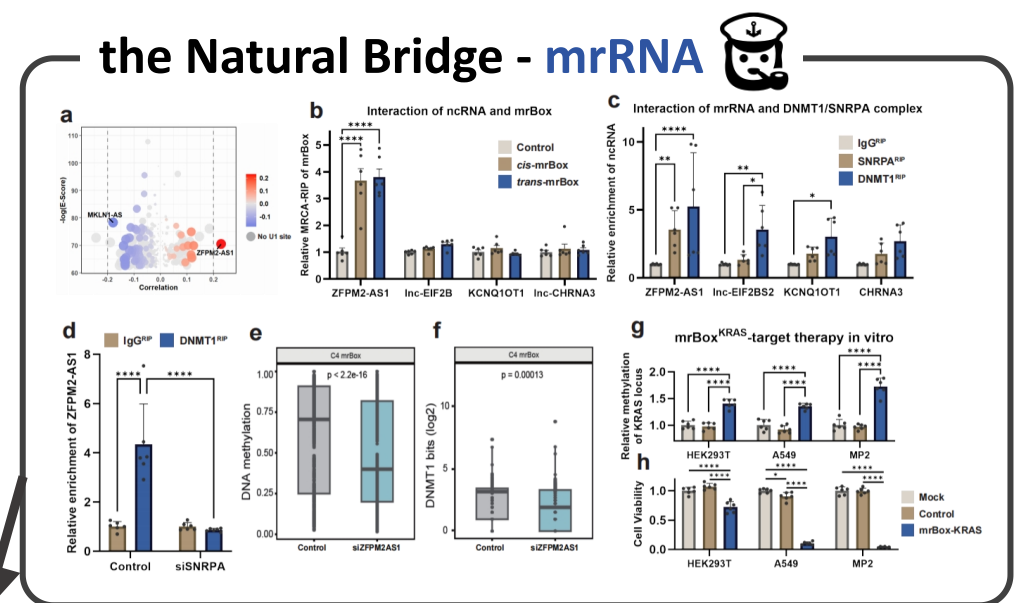
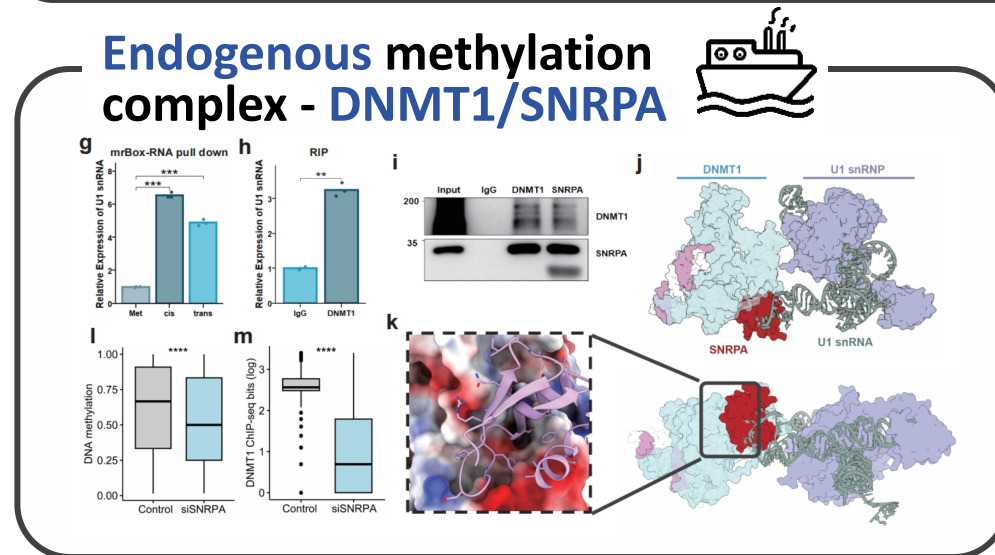
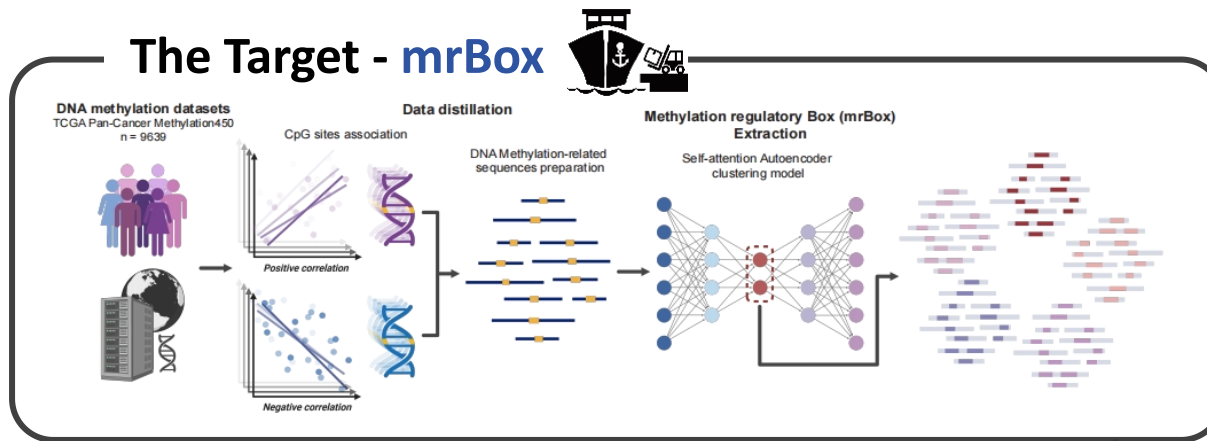
Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.

	Protein-level Inhibitors, PROTAC	Protein-level CRISPR	Epigenetic-level OncoMutation Silence
Avoid complicated binding pocket screen ?	✗	✓	✓
Avoids Exogenous proteins requirement ?	✓	✗	✓
Avoids irreversible primary DNA damage	✓	✗	✓

[1] CRICK, F. Central Dogma of Molecular Biology. Nature 227, 561–563 (1970).

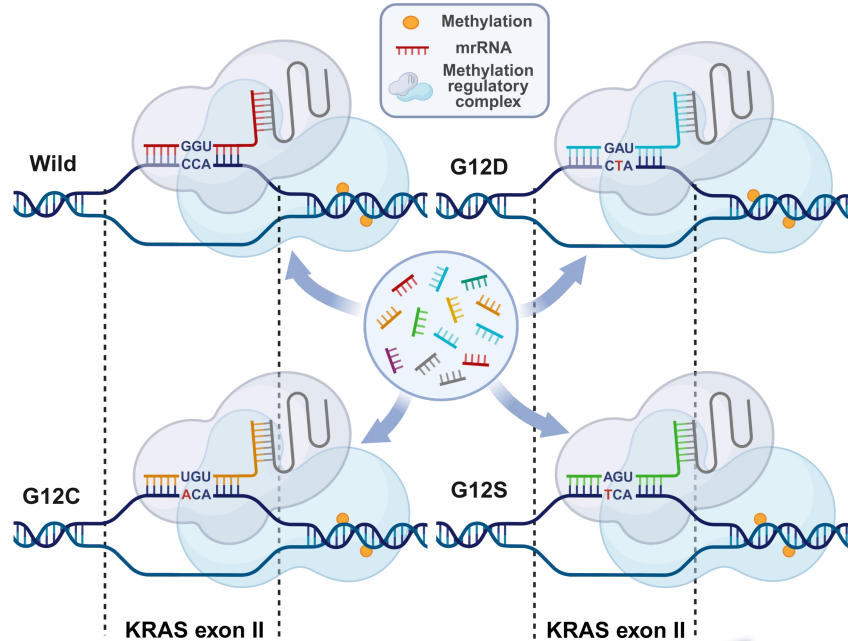
Insight

DNA methylation regulatory RNAs act as 'bridges' to direct precise DNA methylation



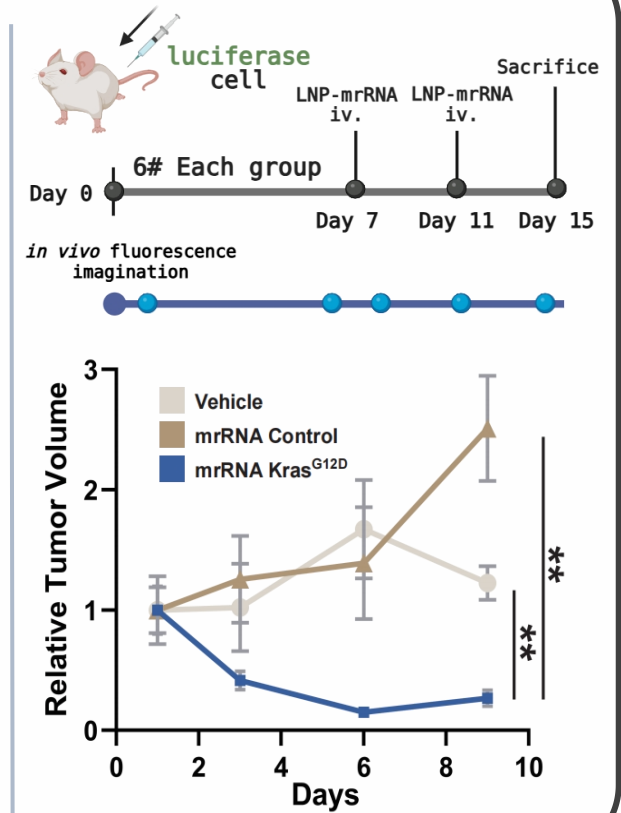
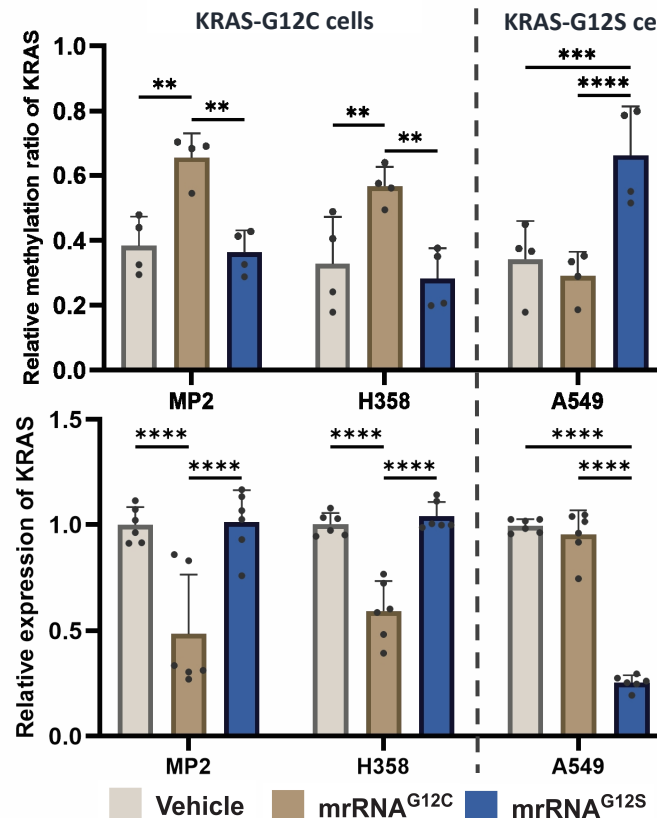
Invention

Engineered mrRNAs selectively direct methylation complex to silence oncogenic KRAS mutations



The synthetic mrRNA perfectly discriminates between *point mutations*, inducing targeted hypermethylation only at the precise oncogenic locus.

Precious Hypermethylation & Silence



Conclusion

Key Takeaways

- Elucidate a novel **lncRNA-SNRPA/DNMT1-guided precise DNA methylation mechanism**
- **OncoMutation Silence (OMS) Platform:**
 - A **mutation-specific epigenetic strategy** utilizing a customized regulatory RNA to selectively silence the oncogenic mutant via targeting DNA methylation
 - Distinguishing Potential of Point Mutations
 - **Zero**-exogenous protein

Thank You.

Disclosure

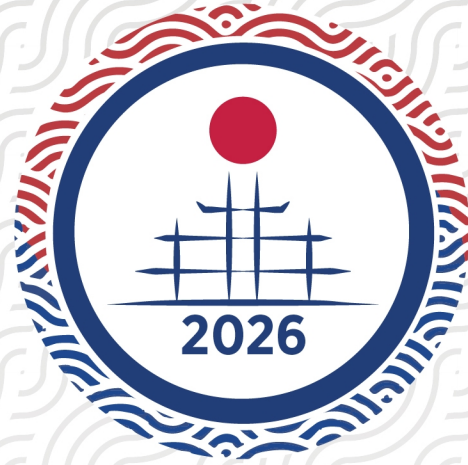
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Thank You.