

siRNA Delivery for Cancer-specific Therapy

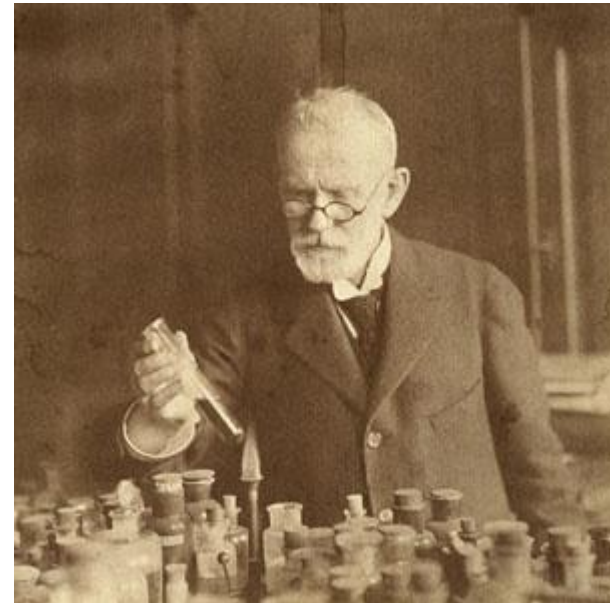
Olaf Heidenreich

nanoLAB Lunchtime Seminar
Newcastle University
June 28th, 2017

Magic Bullets

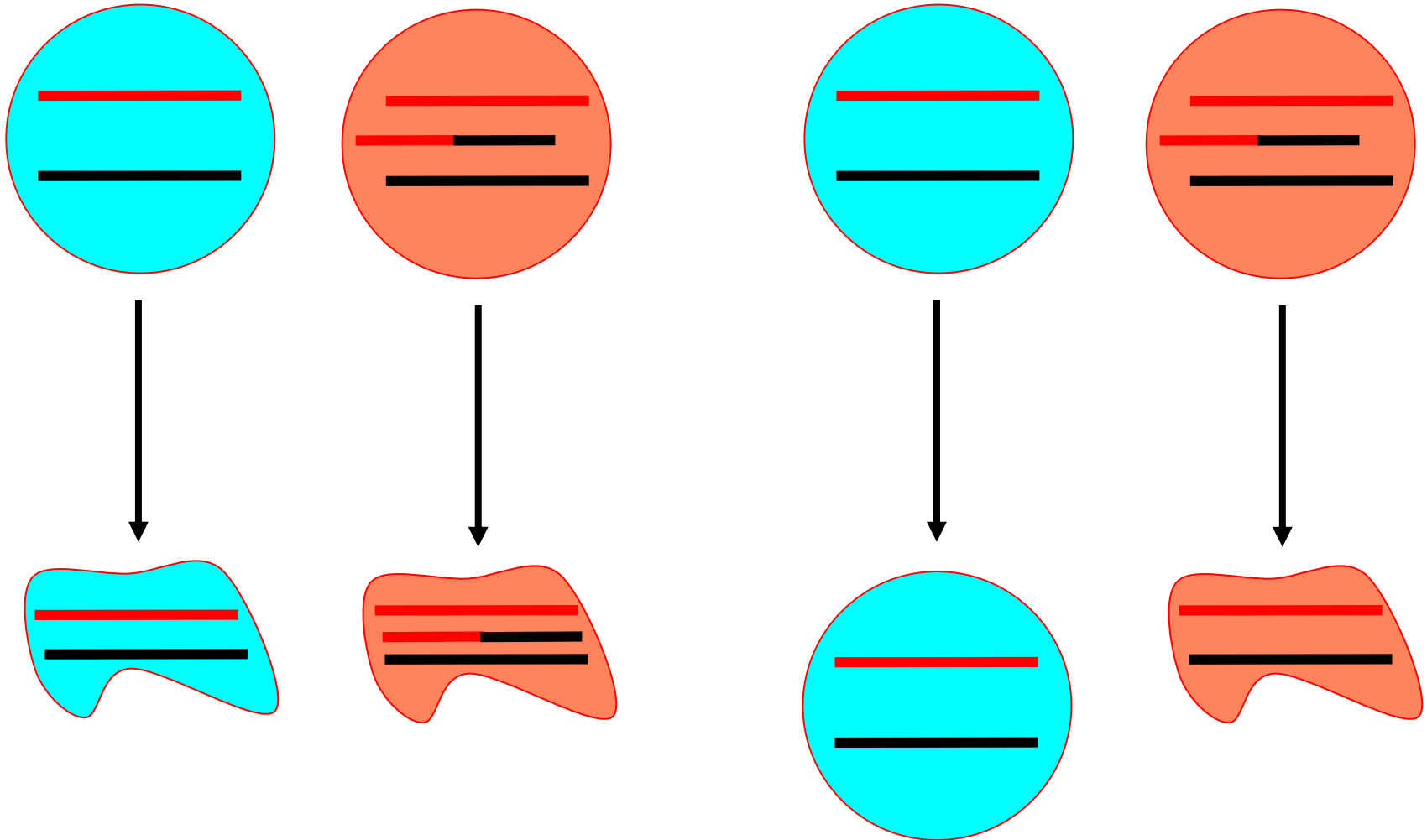


"Wir müssen lernen, magische Kugeln zu gießen, die gleichsam wie Zauberkugeln des Freischützen - nur die Krankheitserreger treffen."



Paul Ehrlich (1854 – 1915)

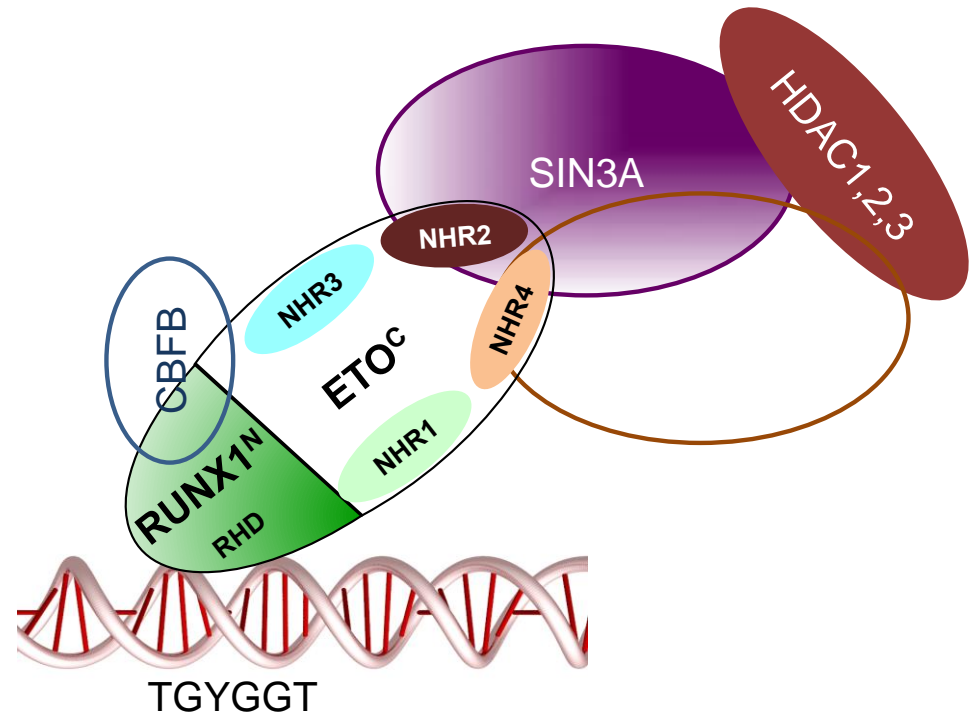
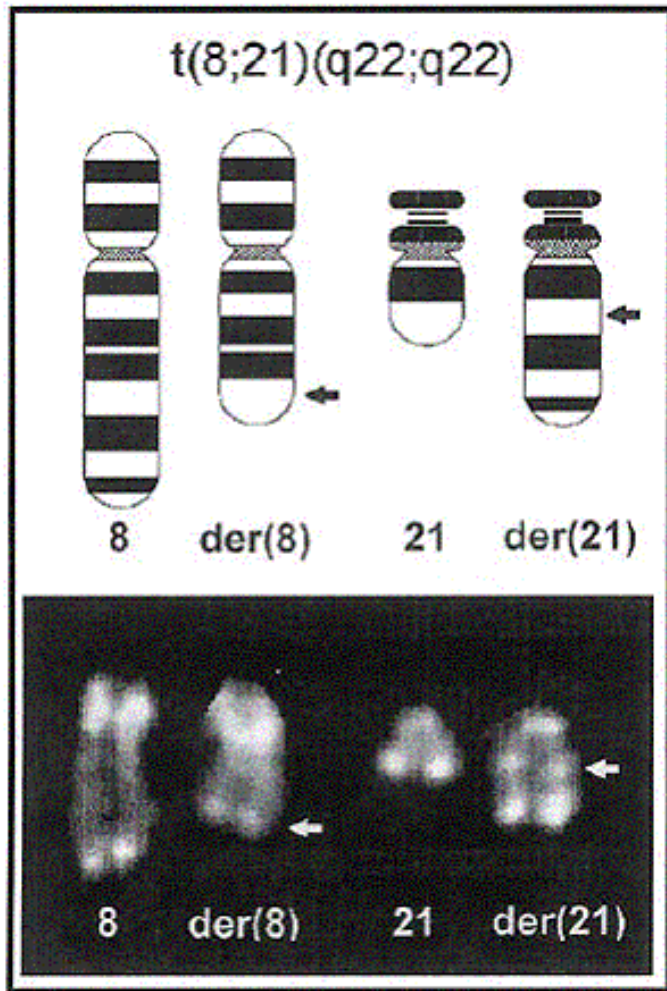
The Optimal Treatment



t(8;21) Acute Myeloid Leukaemia

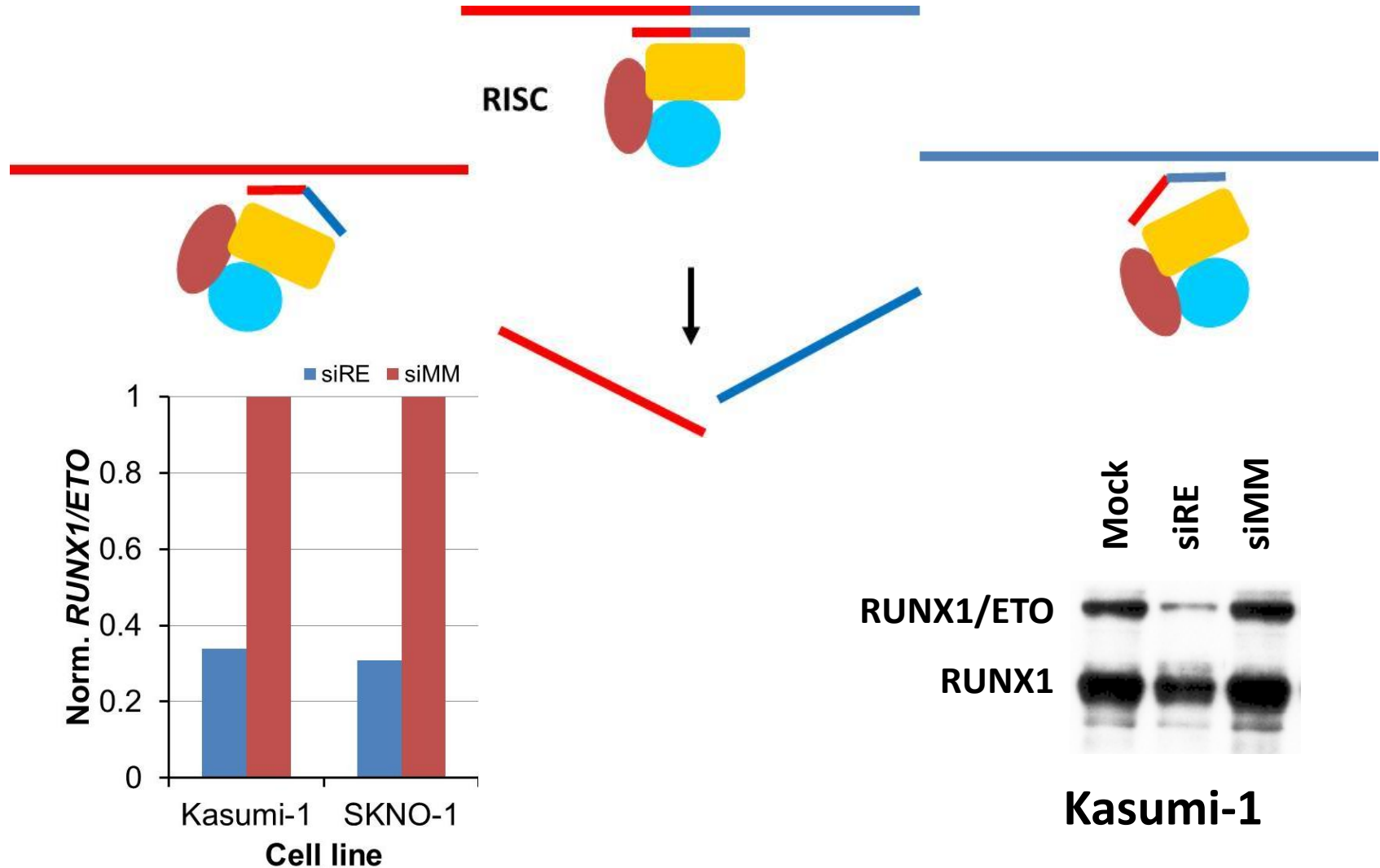
t(8;21)(q22;q22)

- 12% of all paediatric AMLs
- Prominent in adolescents
- Intensive genotoxic therapy
- RUNX1/ETO



Rowley, J. D. *Annales de génétique* 16, 109–12 (1973)

RUNX1/ETO Knockdown

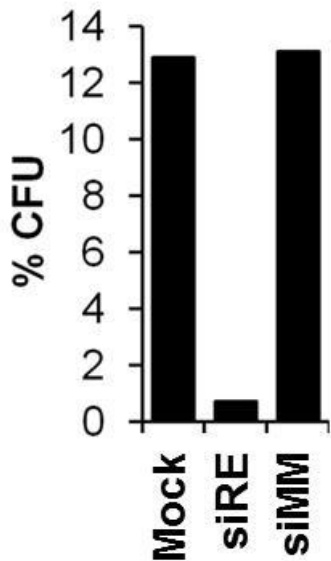
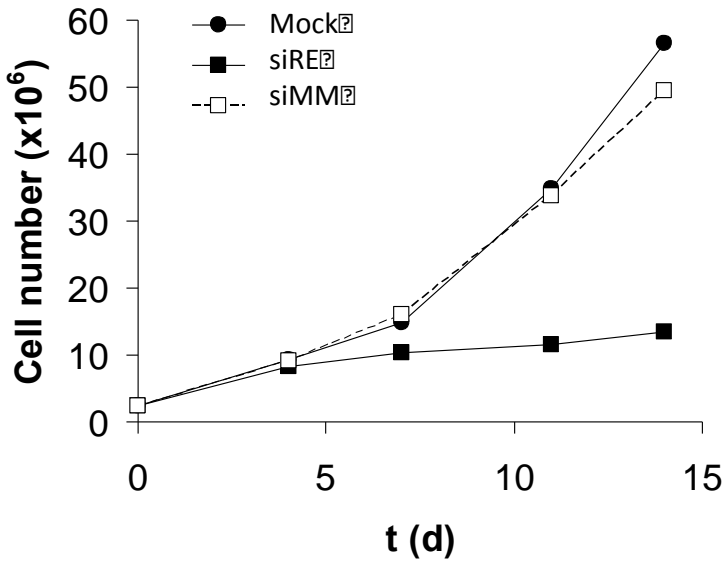


Heidenreich (2004)
Curr. Pharm. Biotech. 5, 349 ff.

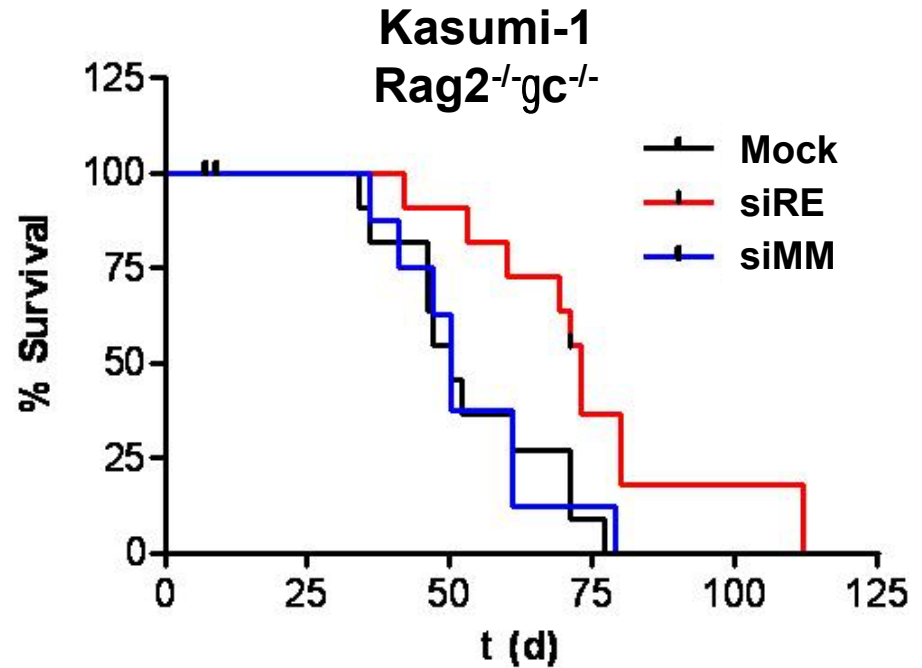
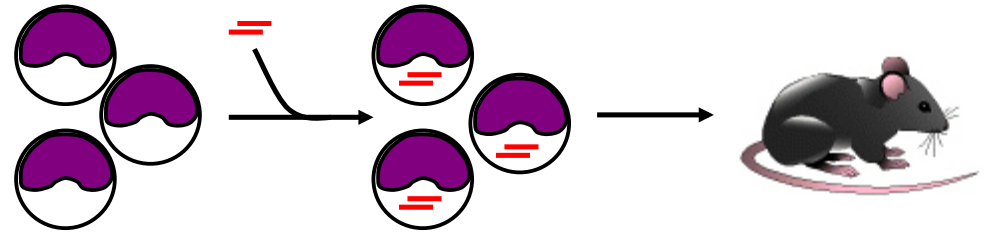
Heidenreich et al. (2003)
Blood 101, 3157 ff.

Martinez et al. (2004)
BMC Cancer 4; 44

RUNX1/ETO Drives Leukaemic Propagation

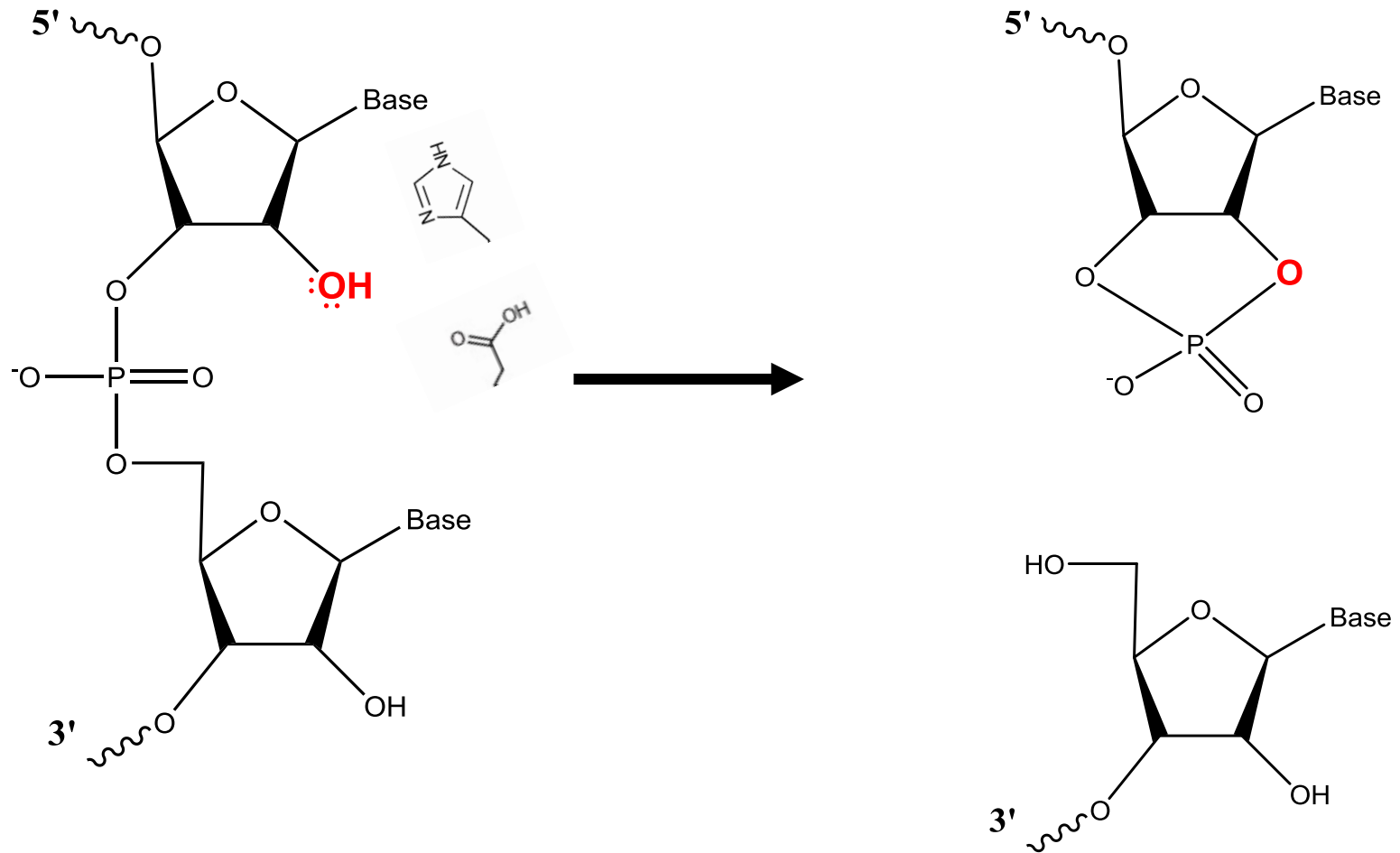


Martinez et al. (2004)
BMC Cancer 4; 44

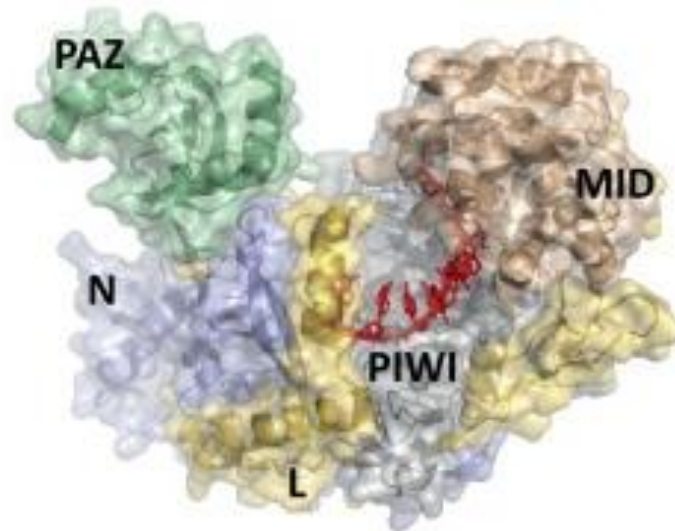
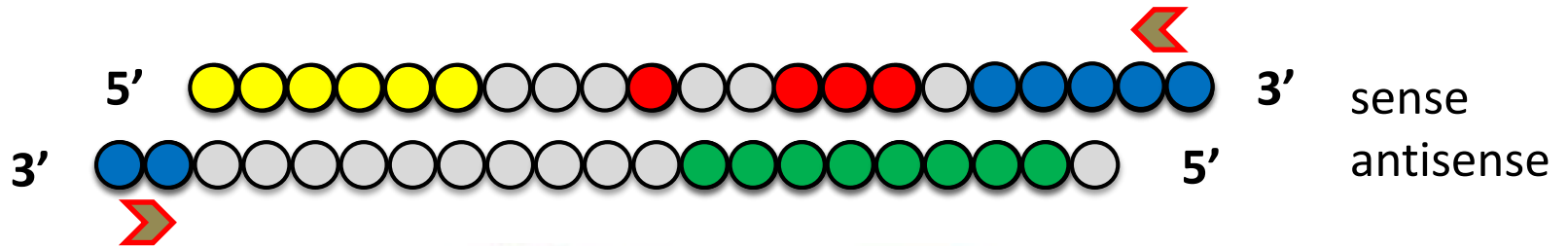
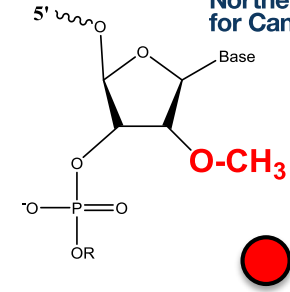
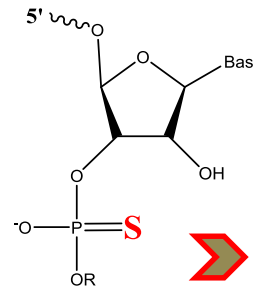
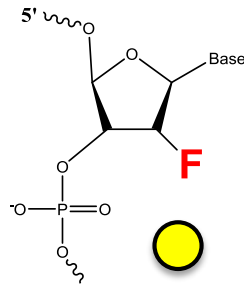
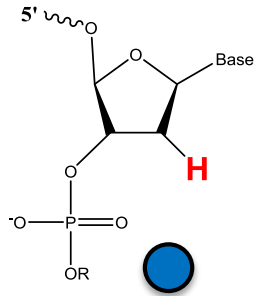


Martinez Soria et al. (2009)
Leukemia 23, 188 ff.

RNA hydrolysis

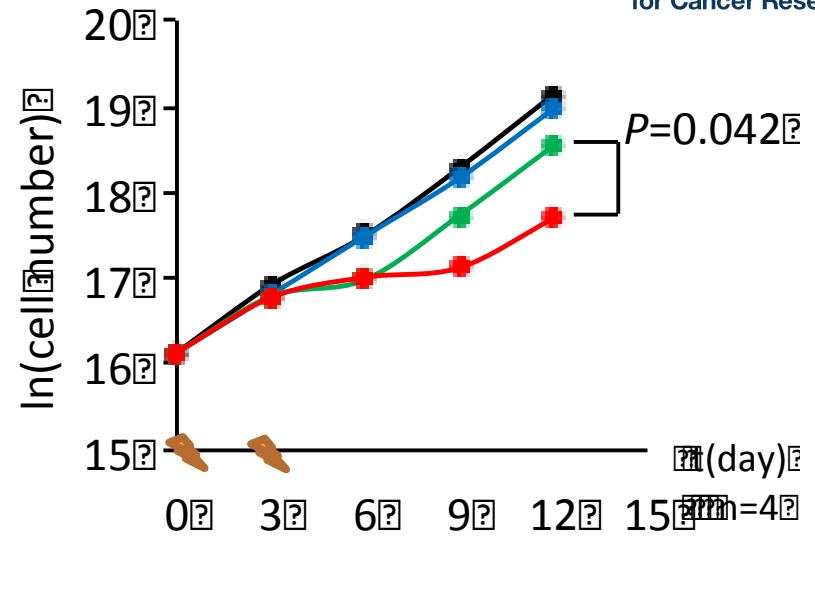
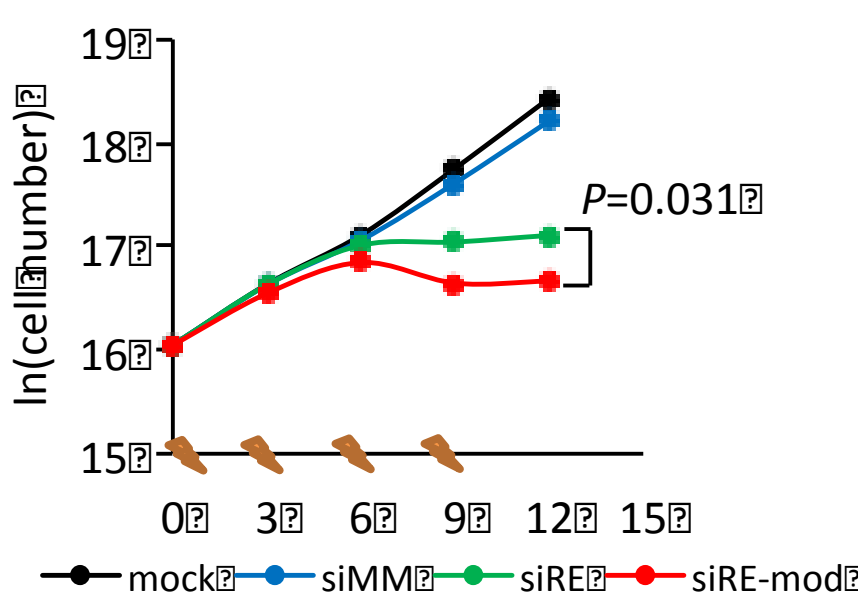


siRNA Modifications

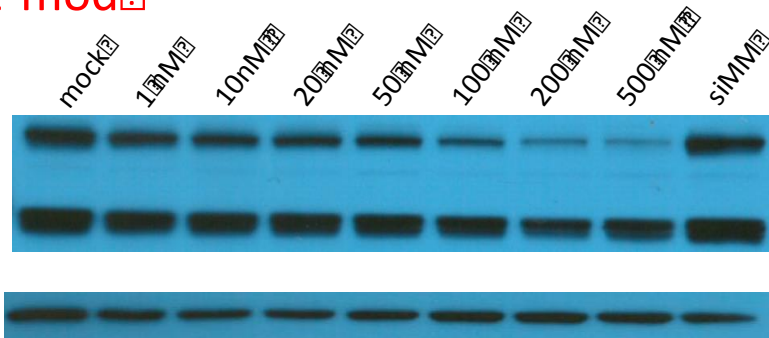


Modified siRNA Efficacy *in vitro*

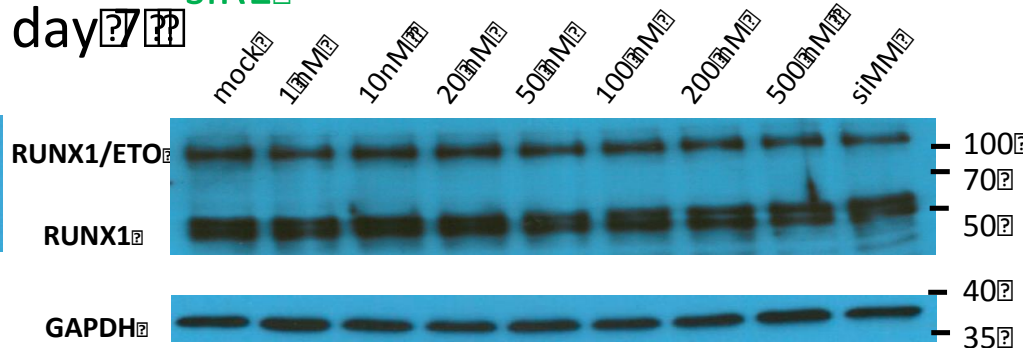
100 nM siRNA mediated RUNX1/ETO knockdown effect on SKNO-1 proliferation



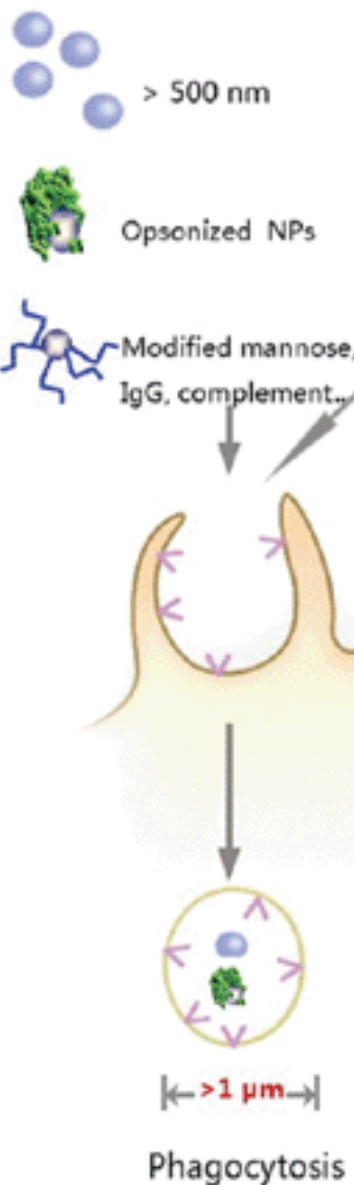
siRE-mod



siRE



Phagocytic pathways

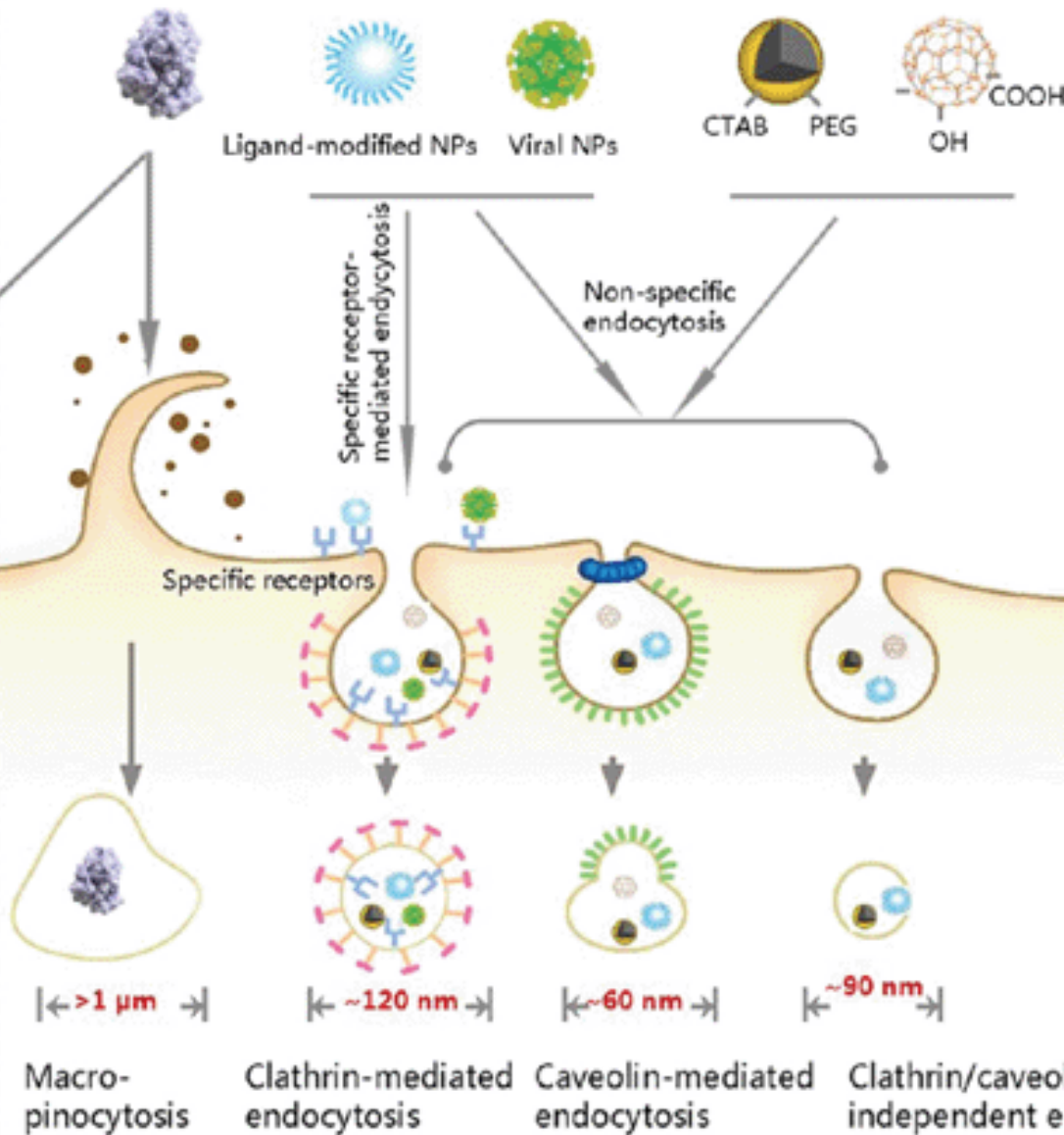


Pinocytotic pathways

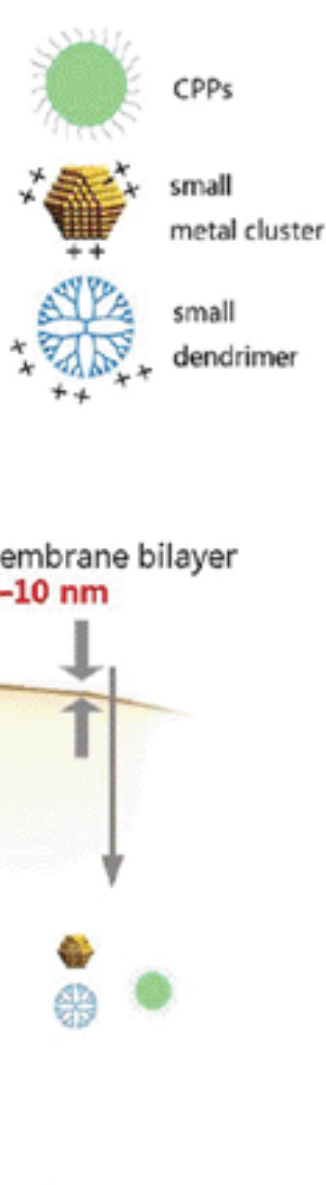
Agglomerates

Functionalized NPs

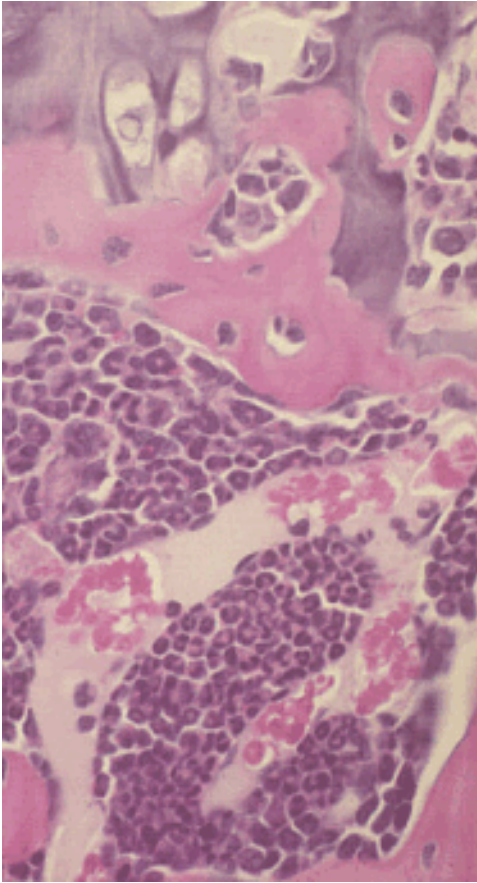
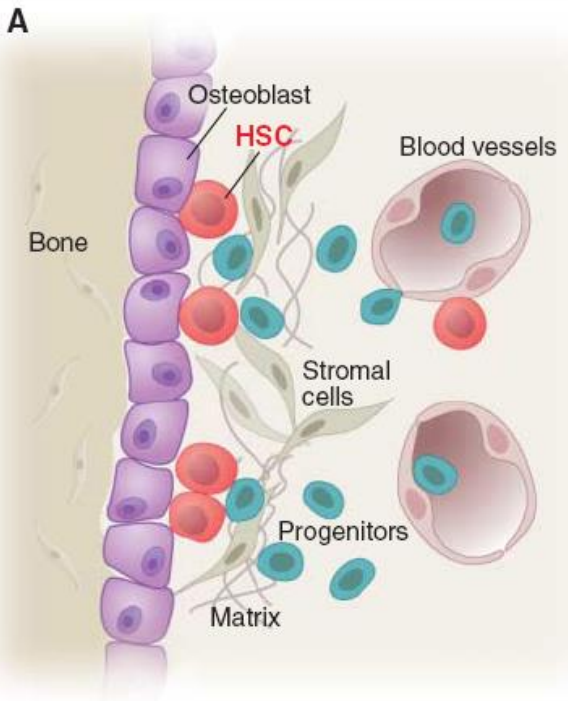
Nonfunctionalized NPs



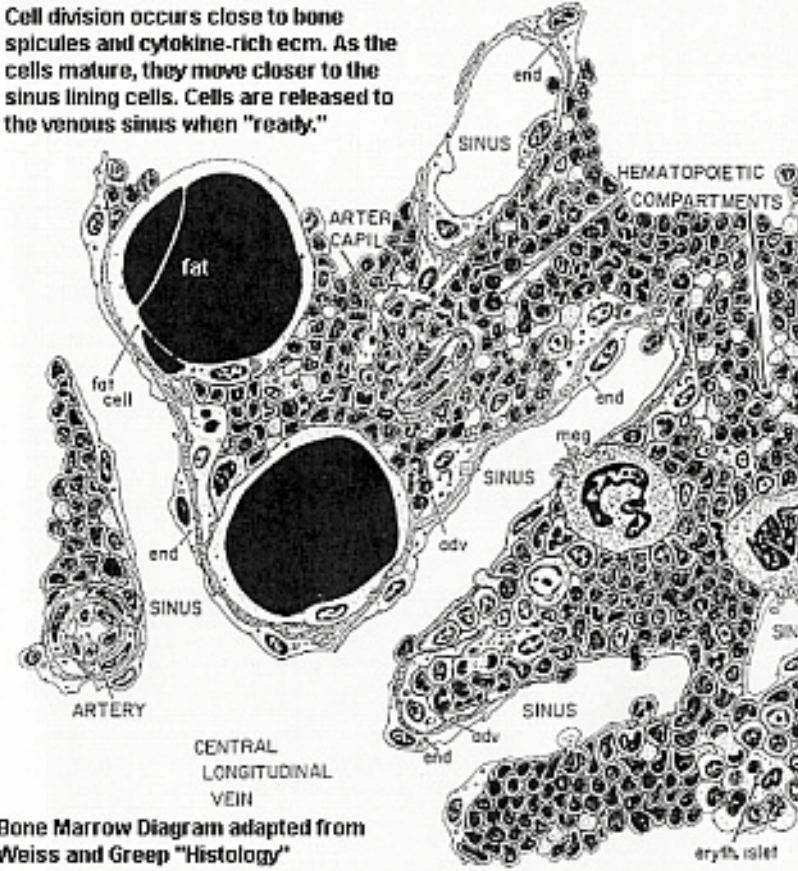
Direct penetration



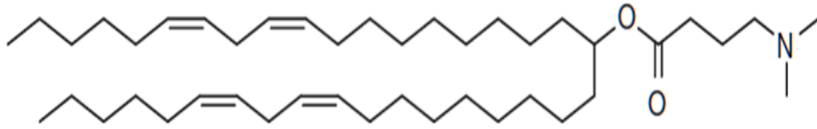
Human Bone Marrow



Cell division occurs close to bone spicules and cytokine-rich ecm. As the cells mature, they move closer to the sinus lining cells. Cells are released to the venous sinus when "ready."

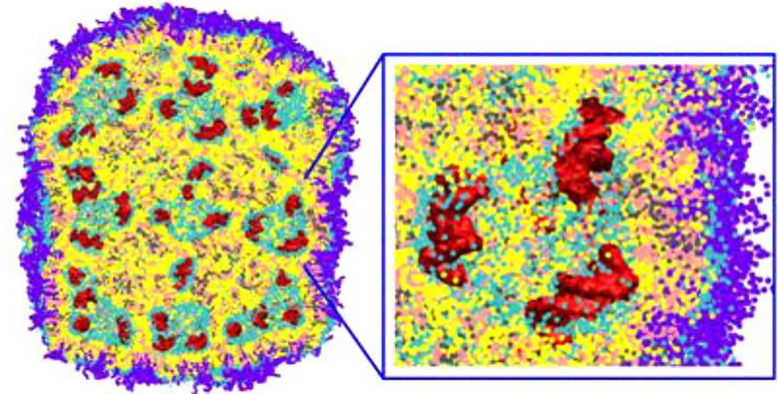
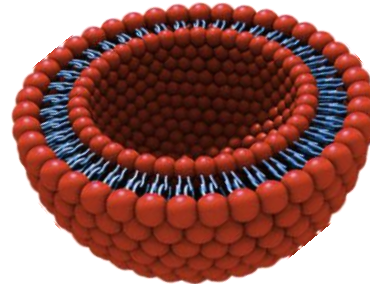
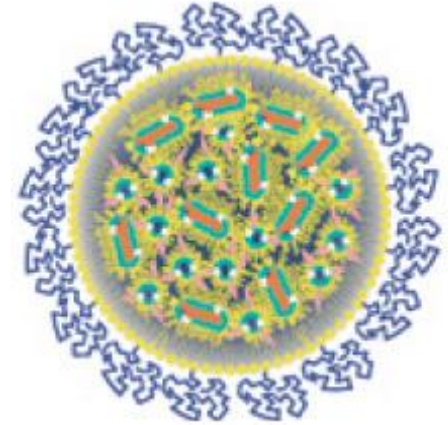


Lipid-based siRNA Delivery System



Dlin-MC3-DMA

Diameter = 70 nm
Charge = -5 mV



Composition	Ratio %
DLin-MC3-DMA	50
DSPC	10
Cholesterol	38.5
PEG-DMG	1.5

High siRNA encapsulation efficiency

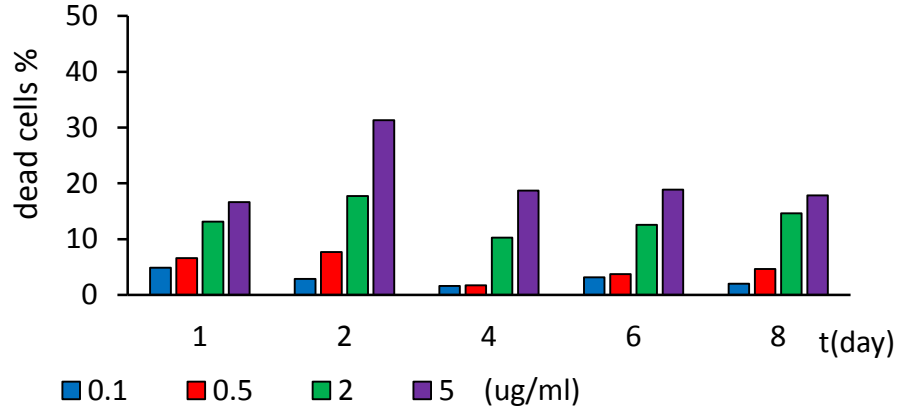
High stability over time

Low toxicity in vivo (mice, rats, hamsters, monkeys) – clinical trial

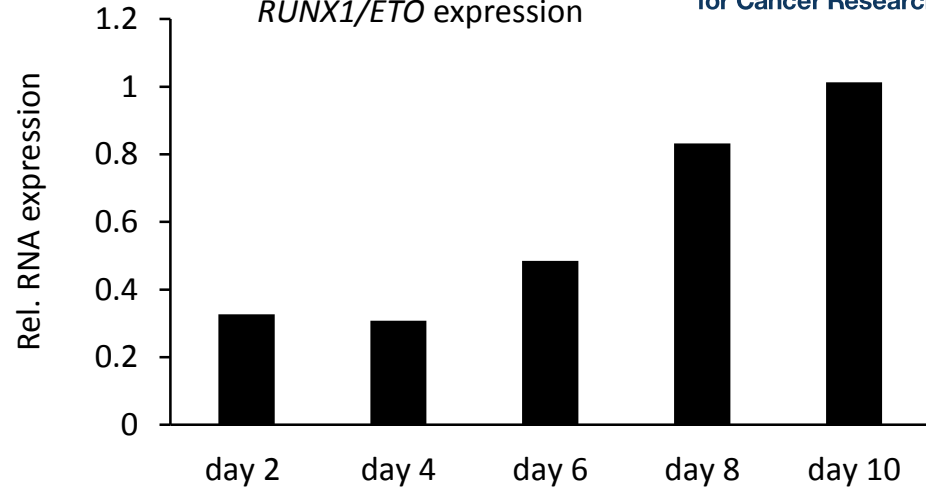
Produced via controlled microfluidic system

LNP-siRNA Efficacy *in vitro*

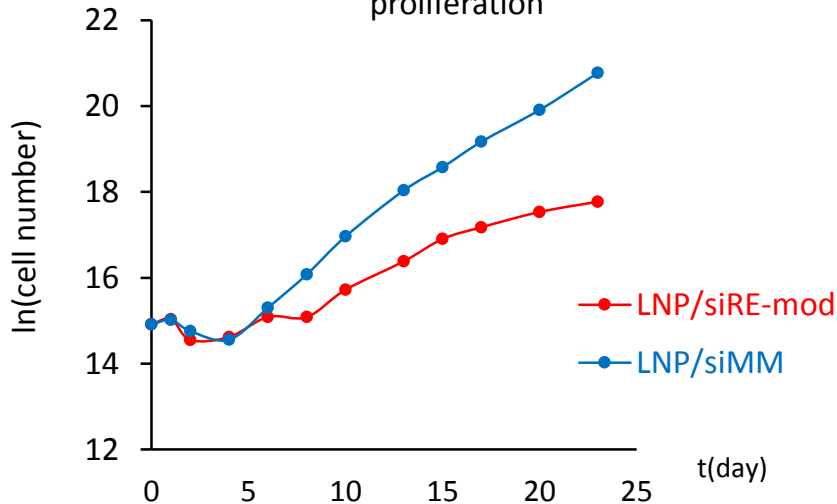
LNP/siRE-mod toxicity in Kasumi-1



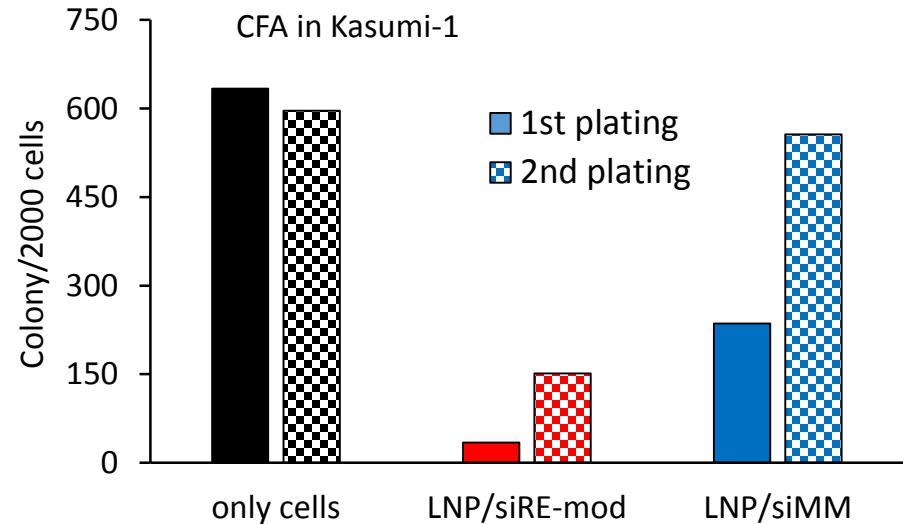
RUNX1/ETO expression



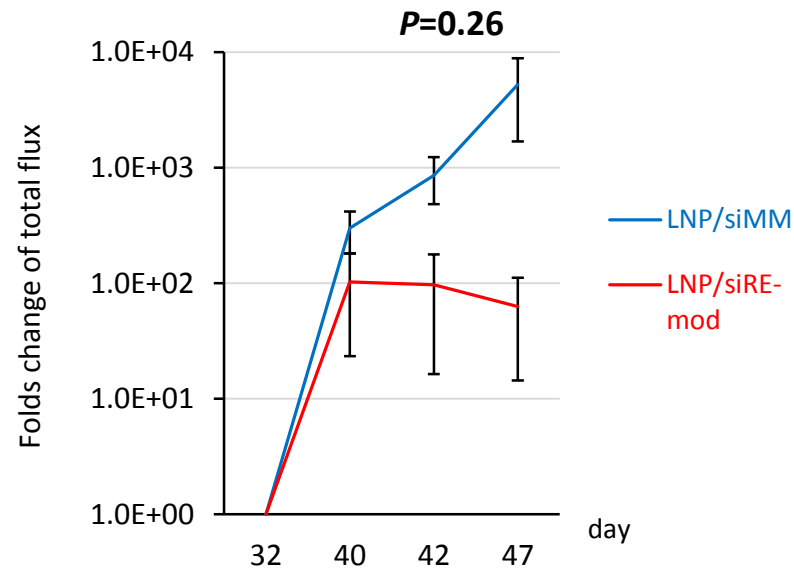
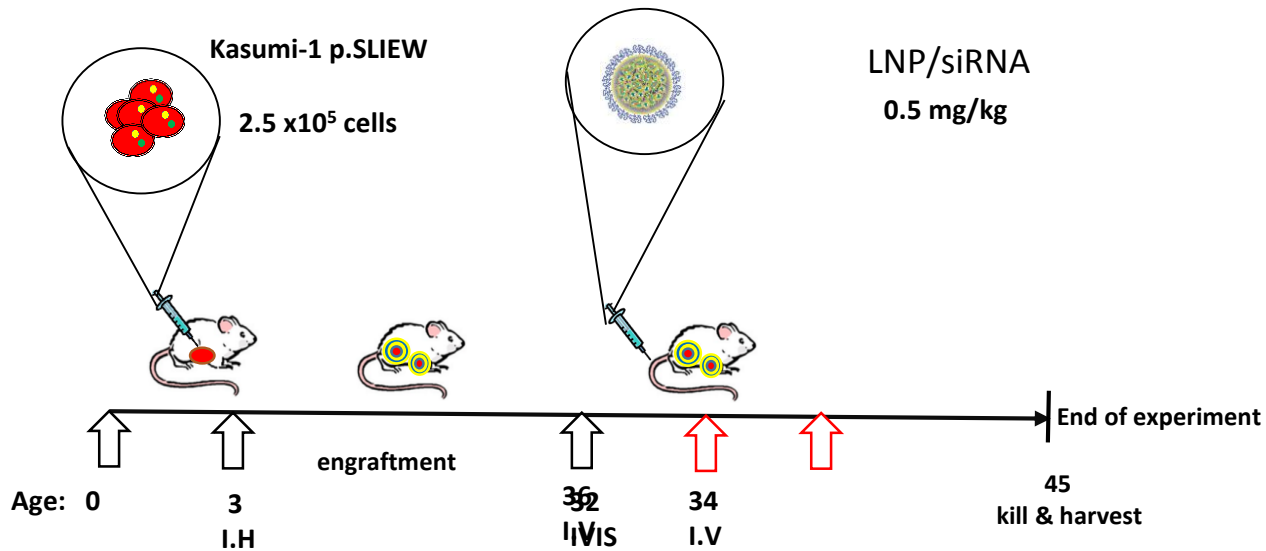
LNP mediated *RUNX1/ETO* effect on Kasumi-1 proliferation



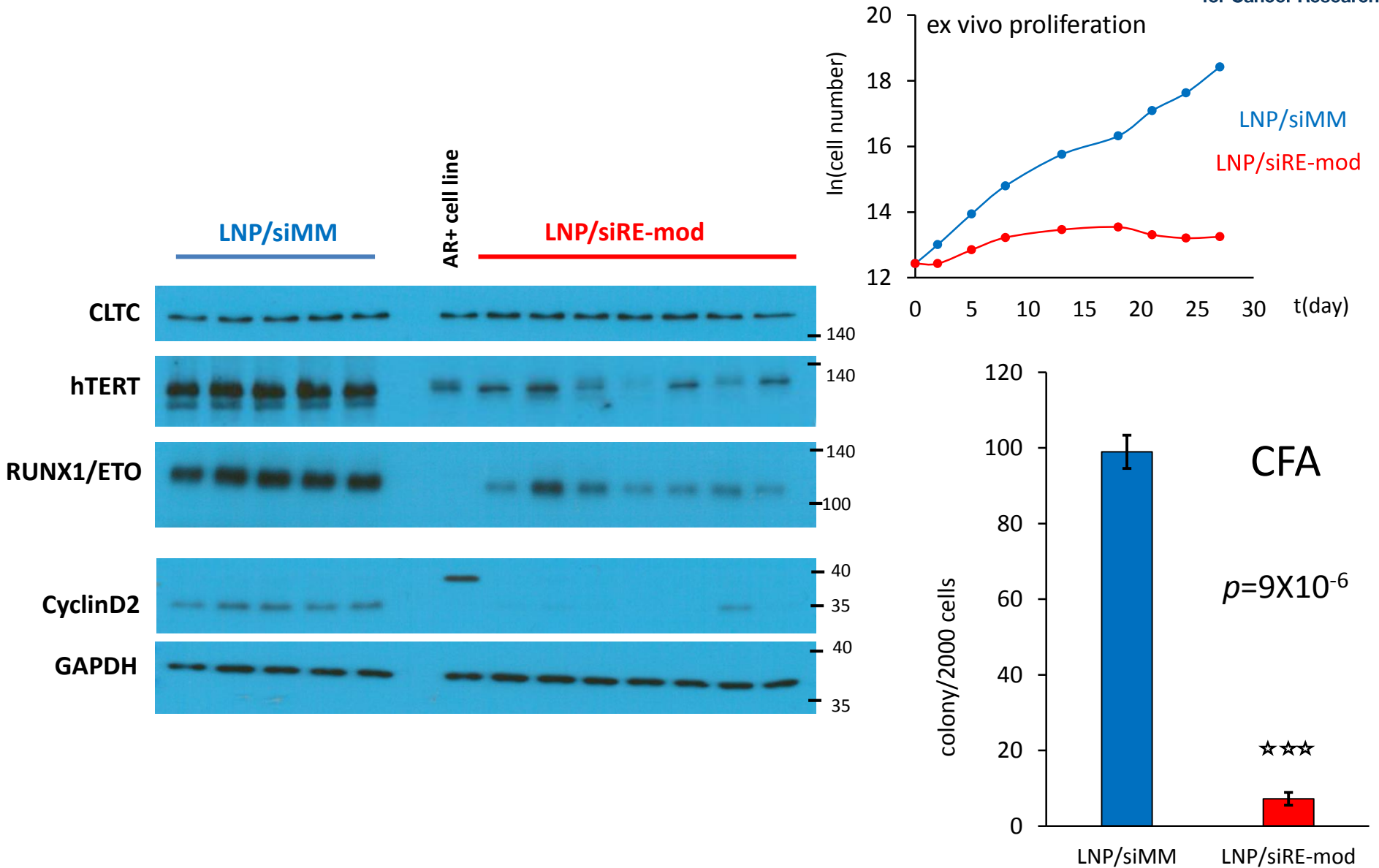
CFA in Kasumi-1



LNP-siRNA efficacy *in vivo*

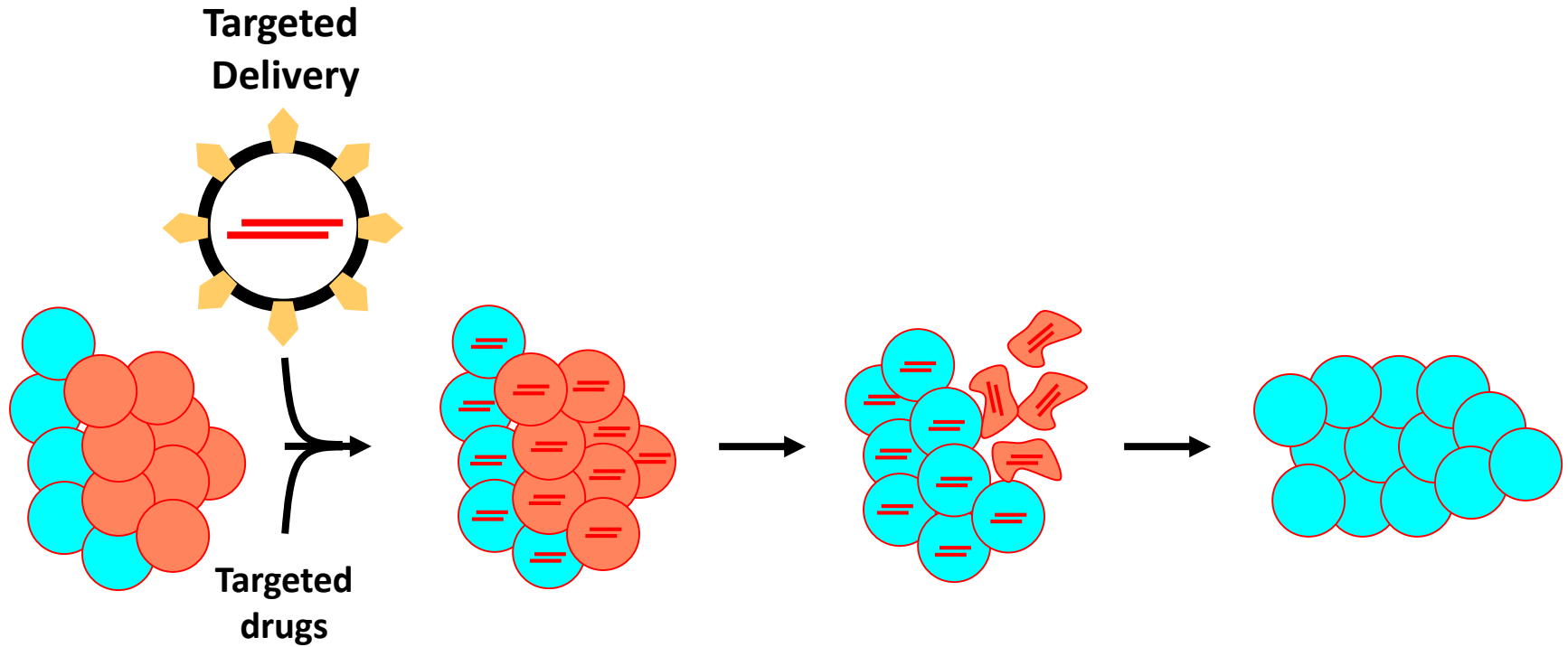


RUNX1/ETO knockdown in Rag2^{-/-} γ c^{-/-}



- Chromosomal rearrangements create cancer-specific targets.
- siRNA-mediated knockdown of RUNX1/ETO compromises malignant self-renewal.
- Liposome-mediated siRNA delivery reduces RUNX1/ETO levels and impairs leukaemic propagation *in vitro* and *in vivo*.
- Targeted delivery using ligands and antibody fragments

Cancer-specific Treatment



Sola dosis facit venenum

Philippus Aureolus Theophrastus Bombastus von Hohenheim
(1493 – 1541)



Acknowledgements

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Thank you

LNP Formulation with Nanoassembler

