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LAB

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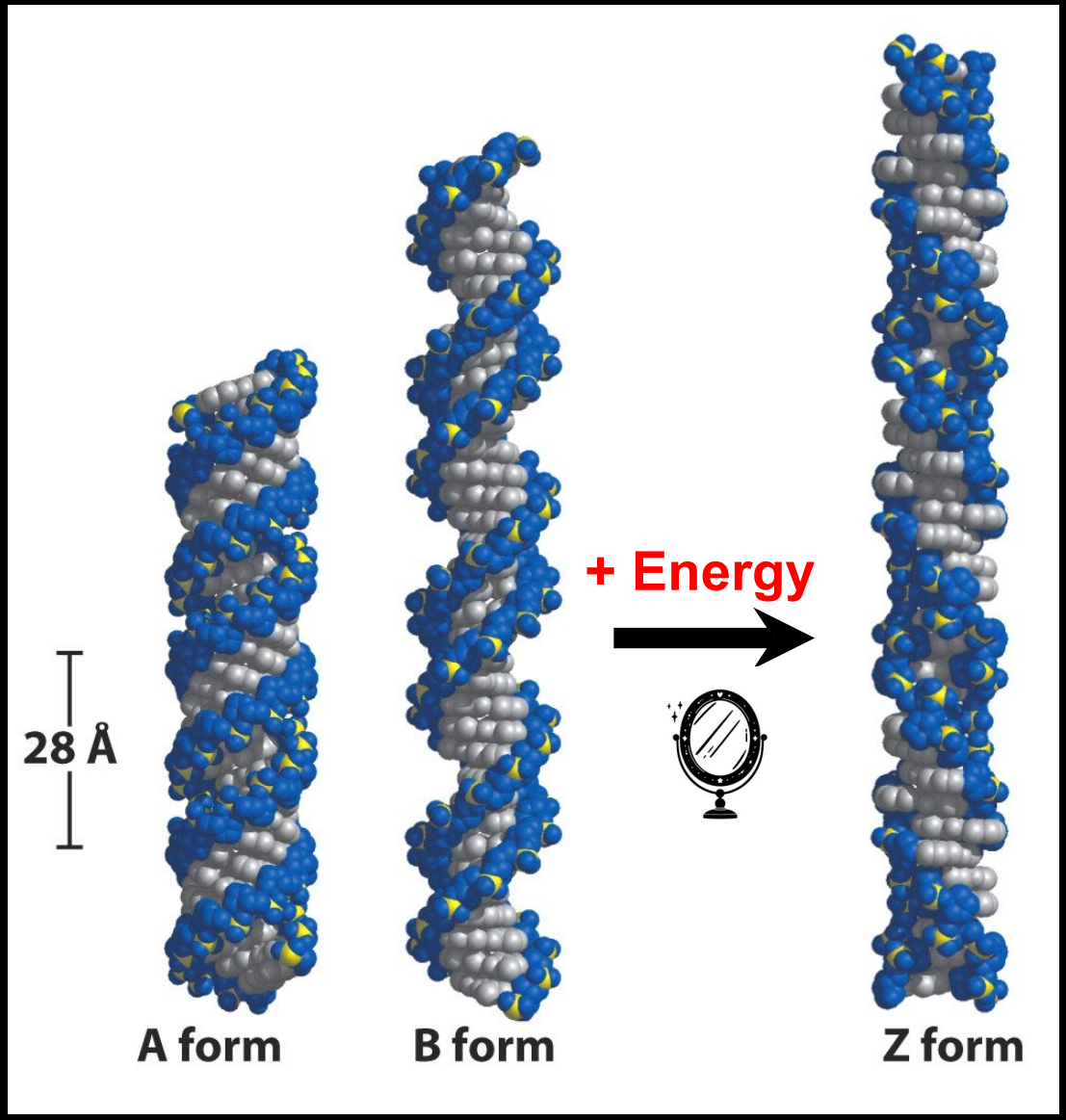
Mirror image nucleic acids -- The Z-form

Mirror Image Biology: Pushing the Envelope in Designing Biological Systems – A Workshop

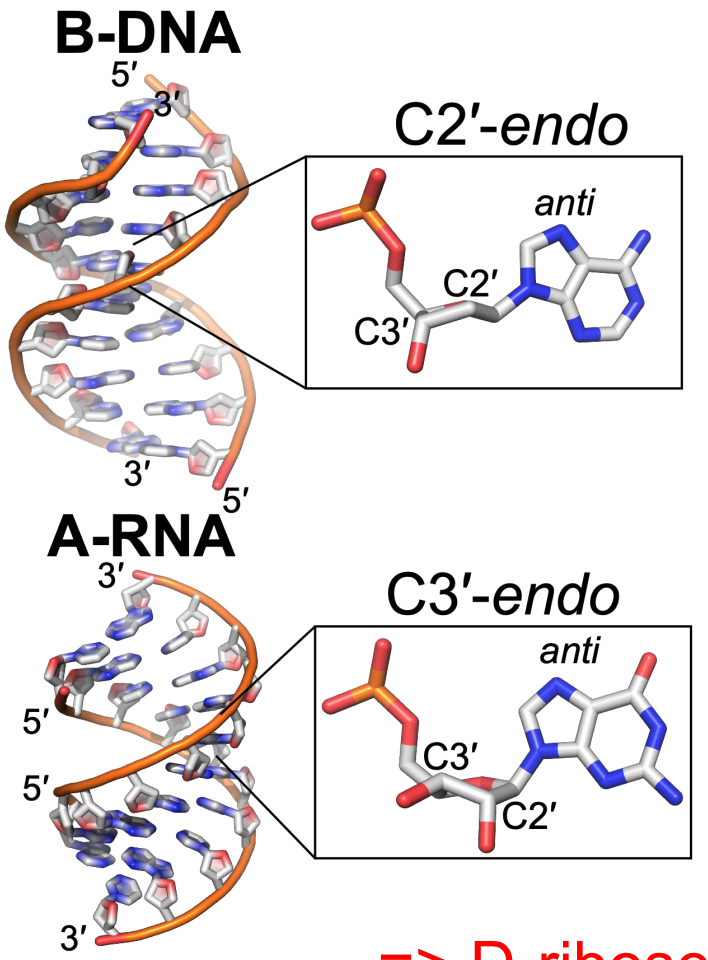
National Academies of Sciences, Washington DC, Sept 29-30, 2025

What are mirror image DNA and RNA?

Z-DNA and Z-RNA

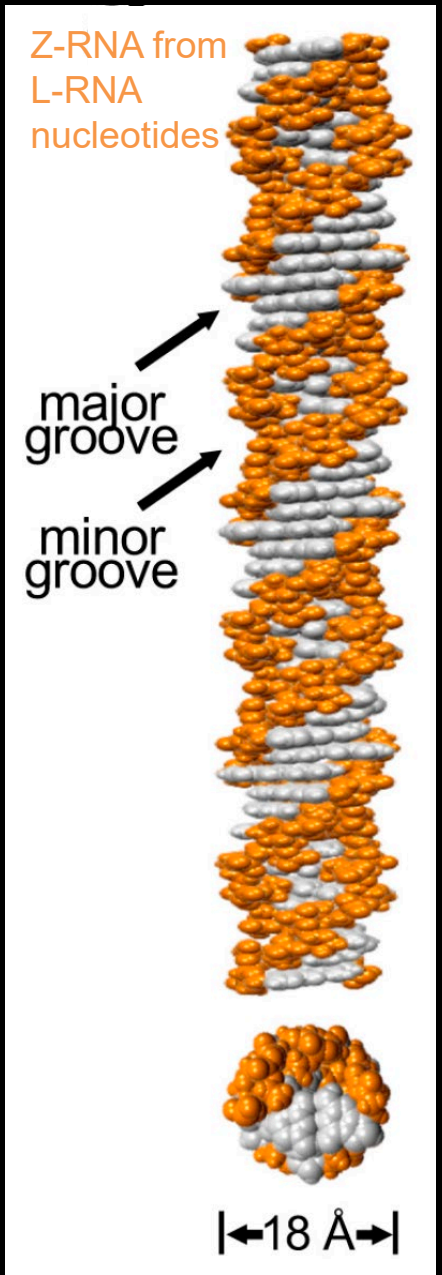


Z-DNA and Z-RNA



=> D-riboses => They are natural

Two different mirrors



We deal with two different levels of “chirality” in nucleic acids

=> The prospects and dangers emanating from Z-RNA/Z-DNA are very different from those from L-RNA/L-DNA.

Song – Wang – Xu, 2024, *Molecules*

What happens in the Z-mirror world?

Z-DNA functions

- Forms under supercoiling stress in nucleus
- Implicated in cellular processes that depend on recombination, deletion, and translocation, such as:

➢ transcriptional regulation (torsional buffer, structural switch for gene expression)

➢ genome stability (chromatin remodeling, instability promotor)

➢ immune signaling (viral infection detector, interferon signaling)

Z-RNA functions

- Form mostly in cytoplasm, induced by specific proteins and chemical modifications

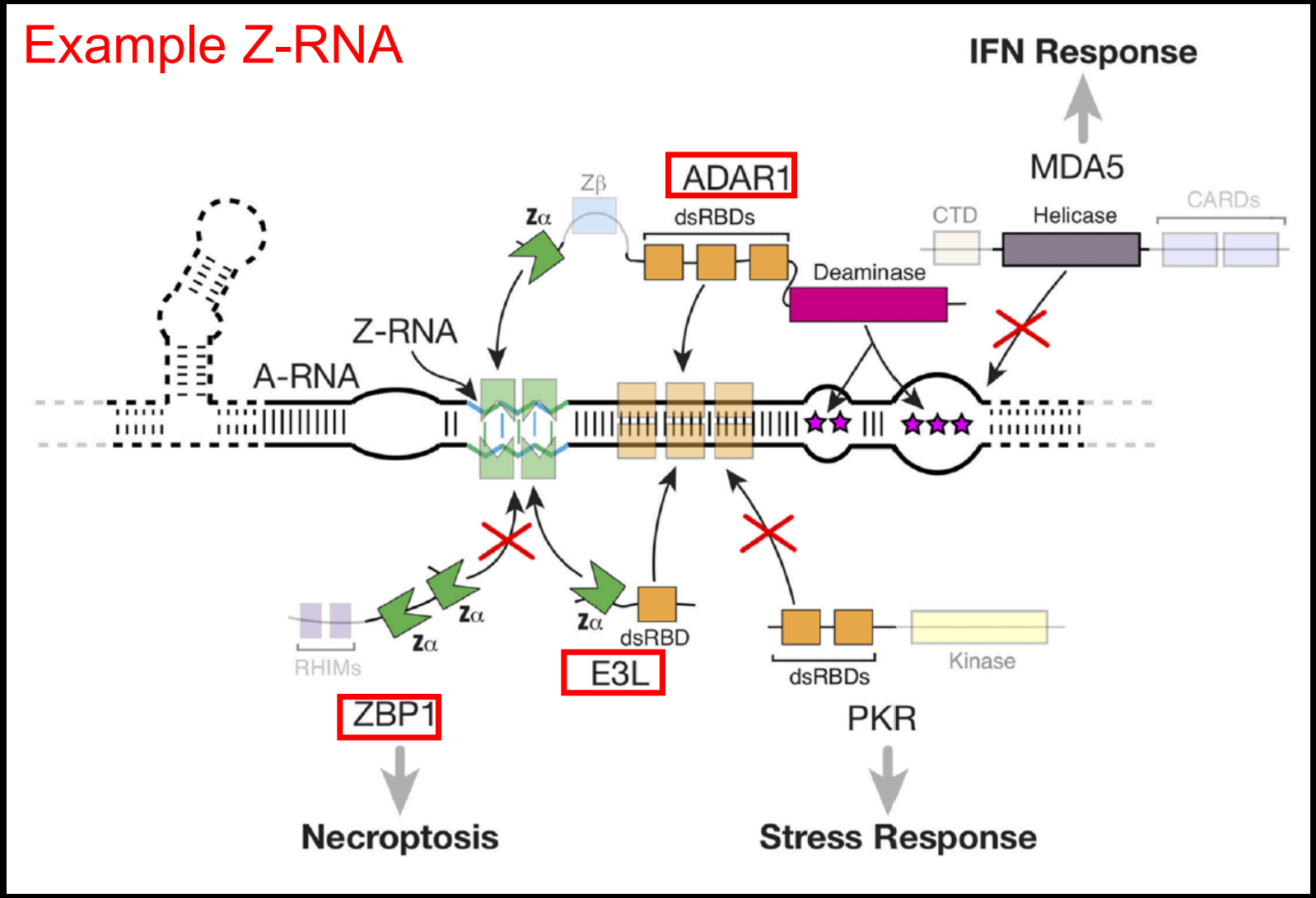
➢ Innate immune activation/stress response: Z-RNA as a viral or damage-associated molecular pattern; triggers PANoptosis, inflammasome activation

➢ Regulator of RNA editing: Attract proteins to modulate A-to-I RNA editing, potentially altering immune tolerance and viral response

➢ Viral countermeasures: Some viruses have evolved mechanisms to avoid or suppress Z-RNA formation to evade immune detection

➢ Role in cancer and autoimmune disease: Aberrant Z-RNA recognition may contribute to inflammation, autoimmunity (e.g., Aicardi-Goutières syndrome), or tumorigenesis

Zα domains bridge the two worlds



Nichols – Krall – Henen – Vögeli – Vicens, 2023, *RNA*

Applications/prospects

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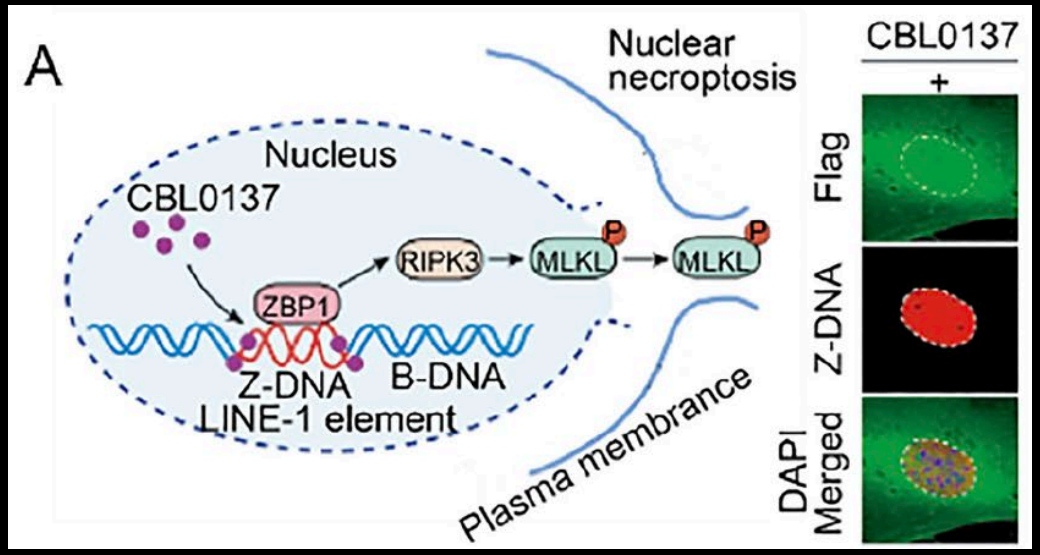
A nascent but ‘hot’ field

Cancer

- The promise: depletion of ADAR1 causes cell death in ~half of cancer cells as IFN response can overcome resistance to immune checkpoint blockade
- Currently no FDA-approved ADAR1 inhibitors
- Similar considerations for ZBP1
- Where we are at:



Zhang - … - Herbert - Balachandran, 2022, *Nature*

C) Targeting Zα domains: e.g. selectively targeting Zα domain of ADAR1, but not its other domains (Vicens/Vögeli labs, other labs/companies)

Further ideas

A) Immunomodulatory strategies?

Autoimmune Regulator (AIRE)-induced gene expression modulated by manipulating Z-DNA formation
(Mathis lab, 2024, *Nature*)

B) Memory?

Z-DNA bound to ADAR1 reduces Z-DNA levels in fear extinction learning in mice, Zα domain necessary for memory flexibility
(Bredy lab, 2020, *Nat Neurosci*)

C) Recoding specific RNA by editing? (Maybe not Z-mirror world)

Use small RNAs to target ADAR1 for recoding specific RNAs by A-to-I editing; ideal for diseases caused by single base changes; like CRISPR approach without rewriting the DNA sequence

D) Alzheimer's disease?

DNA in the hippocampus of brains affected by Alzheimer's is found in the left-handed Z-DNA conformation (Rao lab, 2015, *NeuroMol Medicine*)

Challenges

- Difficult to target Z-DNA, Z-RNA, ADAR1, or ZBP1 (even inhibitors of protein domains other than Zα are controversial)

- Z-RNA/Z-DNA are involved in many pathways and interlinked

- Pathways not entirely understood

However:

Unlike truly chiral molecules, Z-RNA/Z-DNA biology poses no danger due to bio-orthogonality!