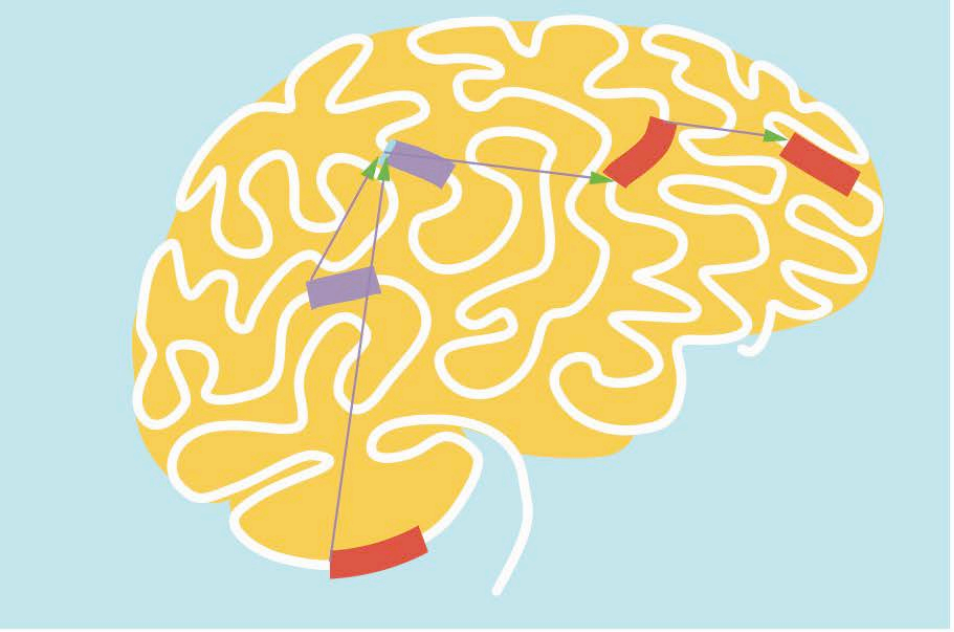
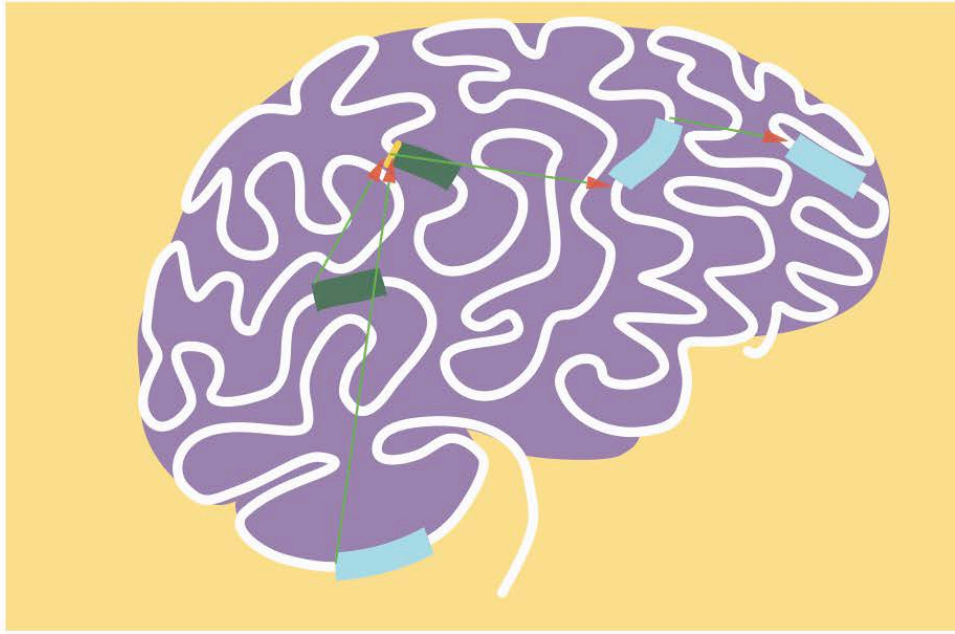
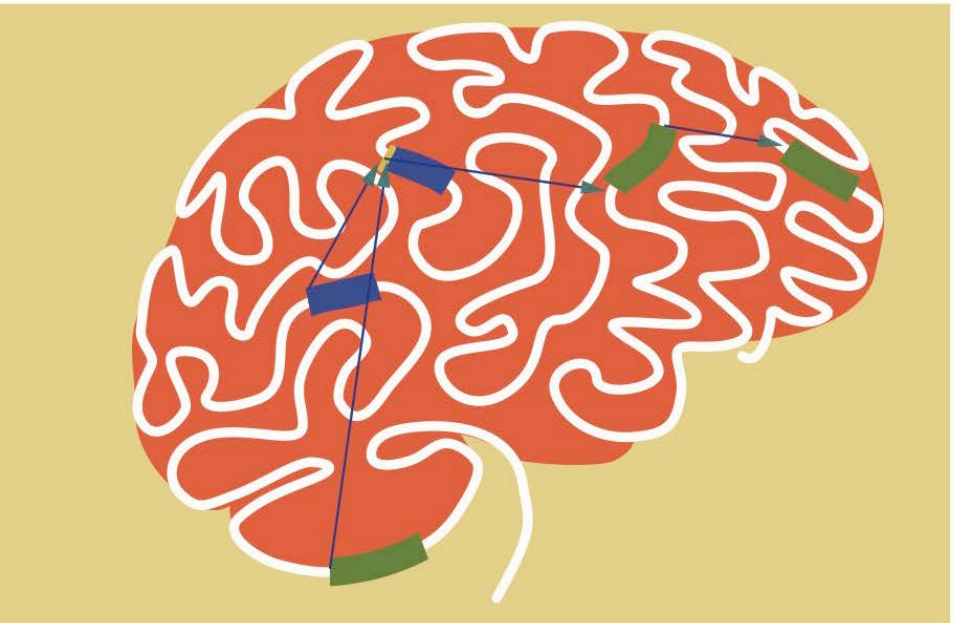
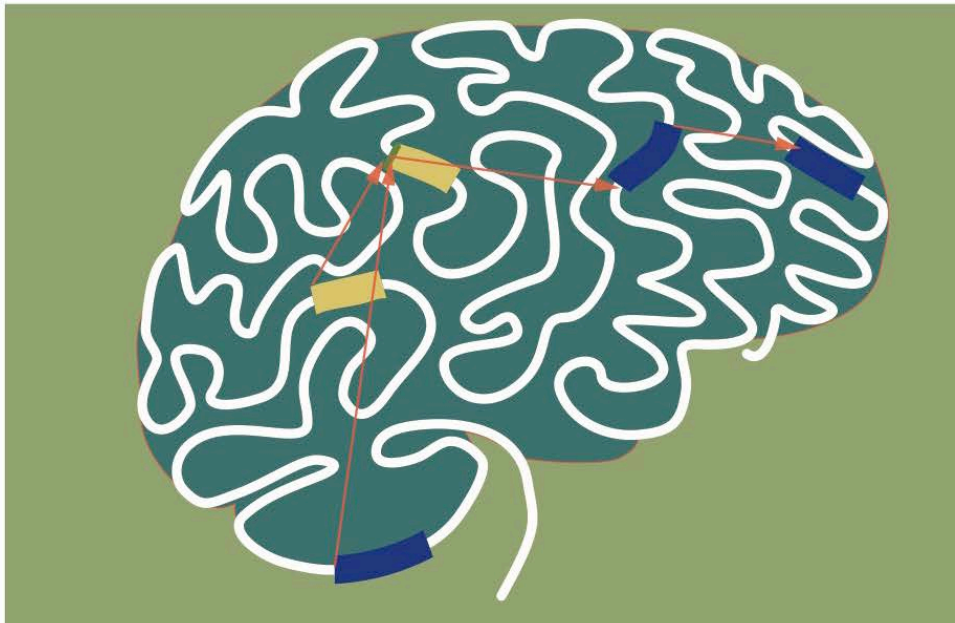




The tricks neurons use to express their genes: jumping genes, zero-length exons and RNA loops

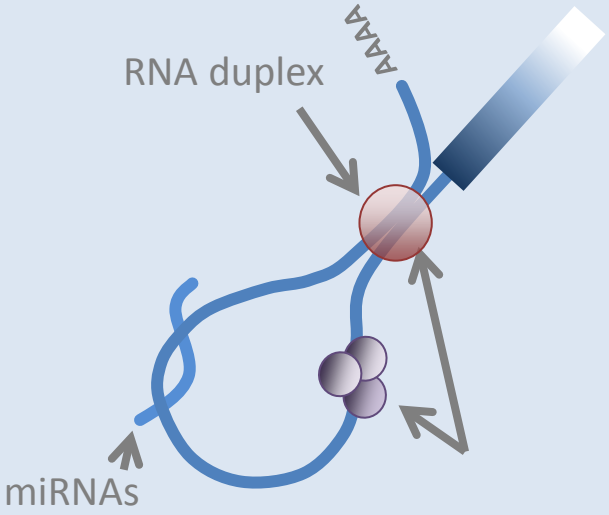
Jernej Ule, UCL Institute of Neurology, ulelab.info





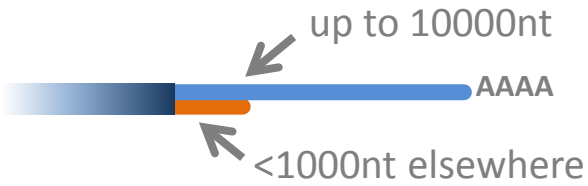
How are RNAs important for gene expression in neurons?

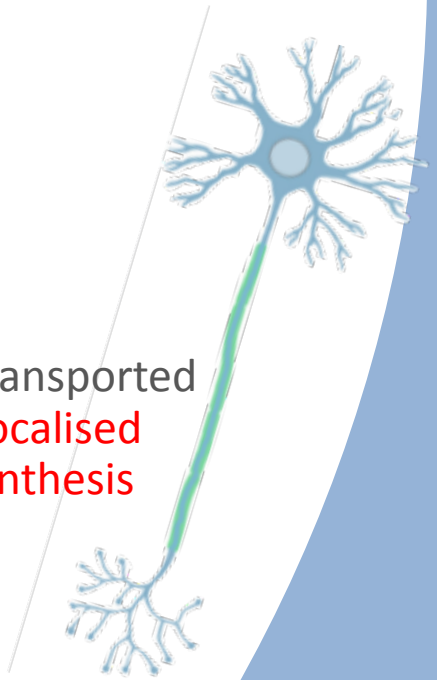
mRNA



neurons

Longer mRNAs in neurons





mRNAs are transported to allow localised protein synthesis

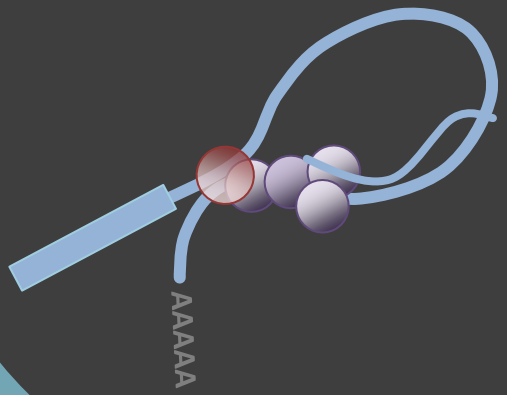
motor neuron disease

No cure available
1/232 deaths in 2012

Mutations in six
RNA-binding proteins

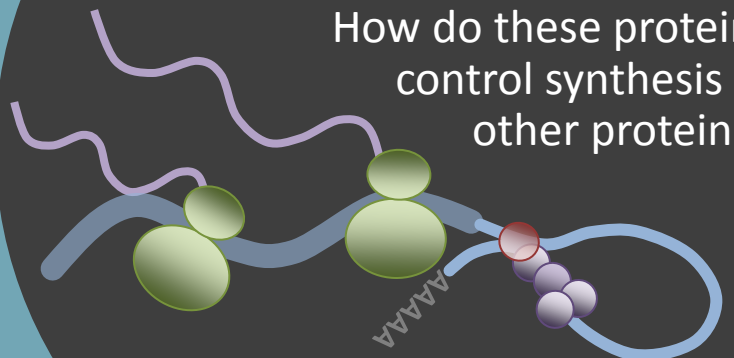
Measure interactions

What proteins bind to an RNA?



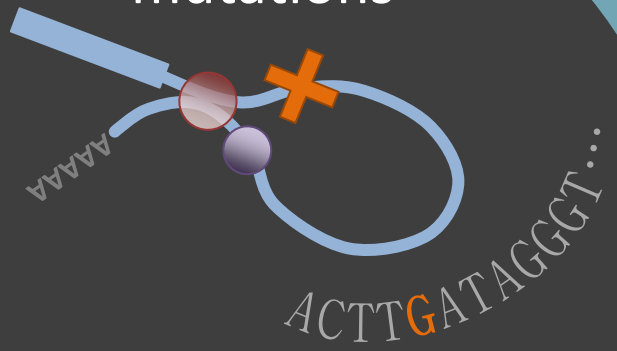
Integrate regulation

How do these proteins control synthesis of other proteins?



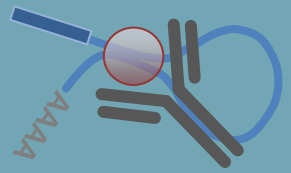
RNA splicing, stability, translation

Interpret mutations



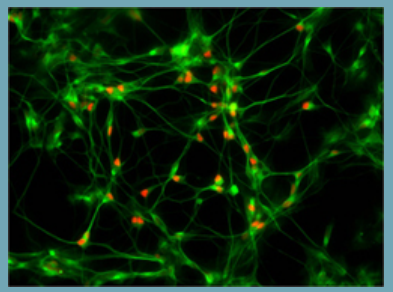
How mutations disrupt protein-RNA interactions.

New techniques



hiCLIP & iCLIP

Disease models



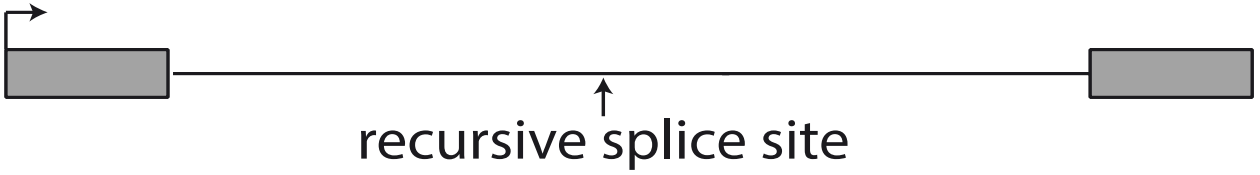
iPS-derived motor neurons

Zero-length exons

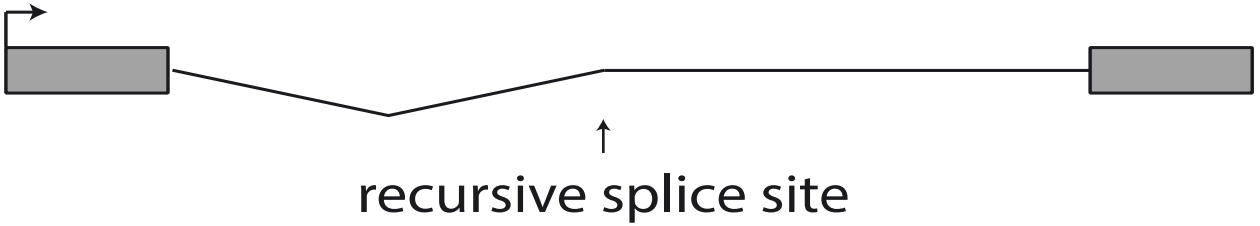
Splicing makes an mRNA

Splicing makes an mRNA

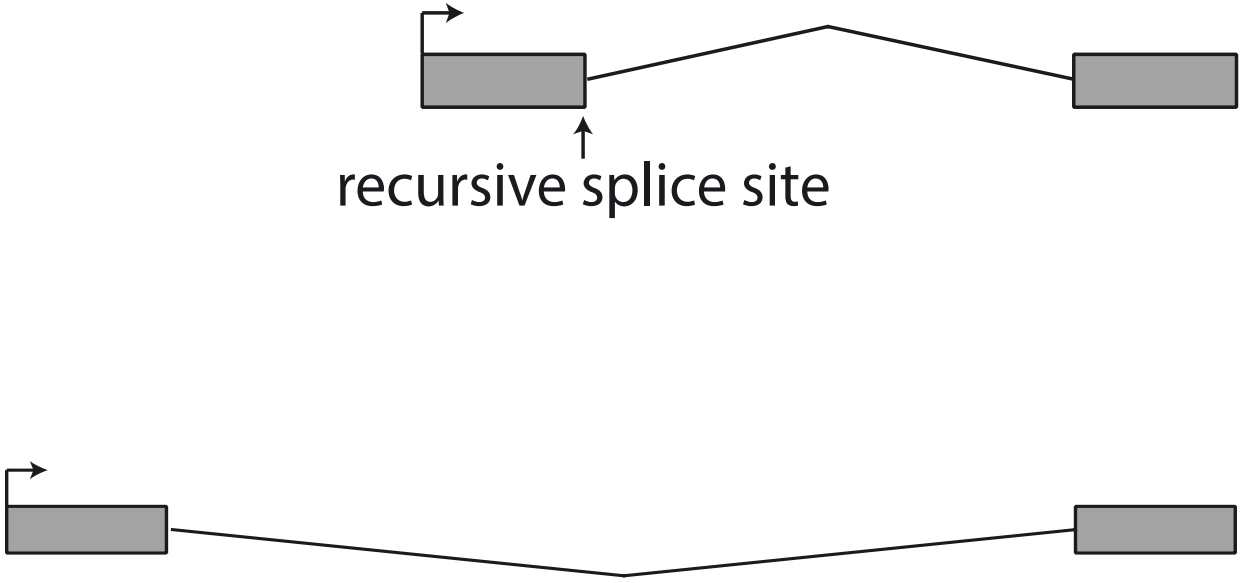
Recursive splicing makes same mRNA



Recursive splicing makes same mRNA

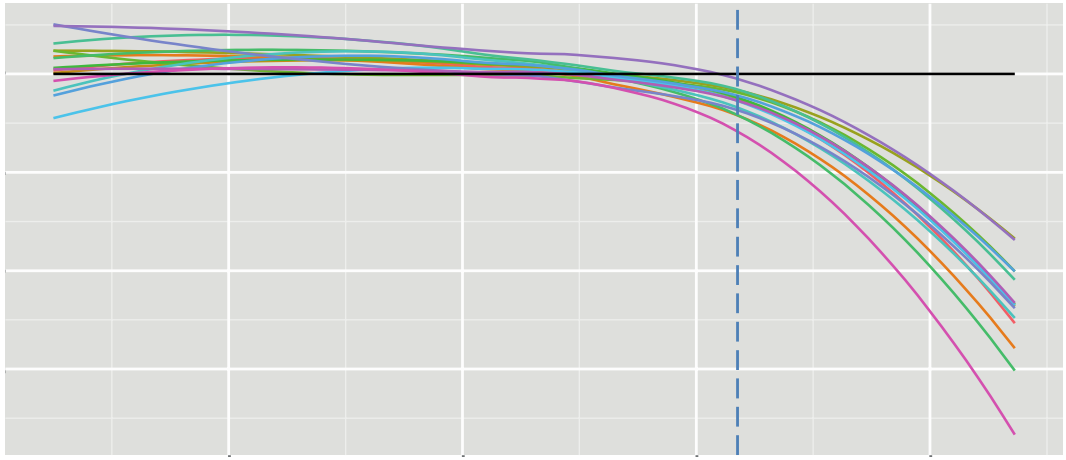


Recursive splicing makes same mRNA



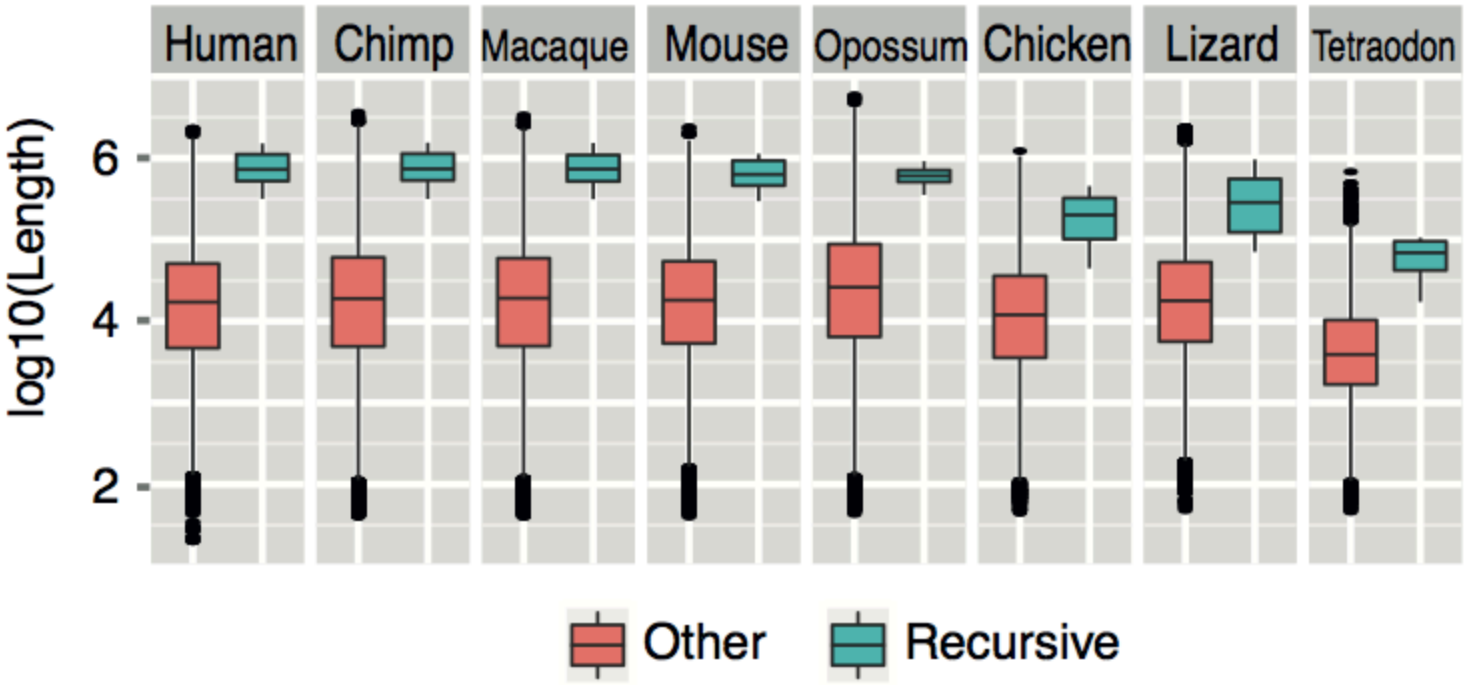
Recursive splicing makes same mRNA

Genes expressed in the brain are extremely long



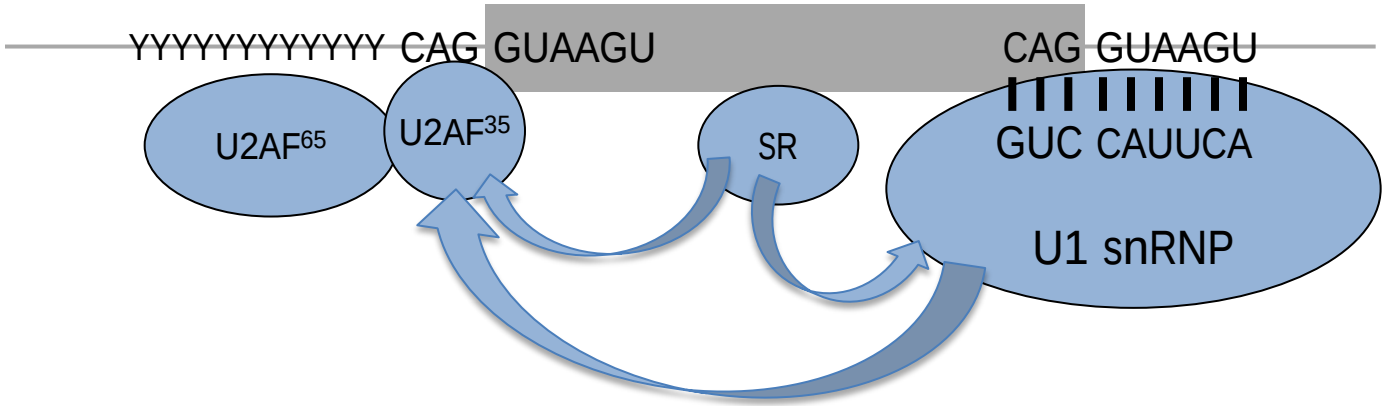
Sibley et al, Nature, 2015

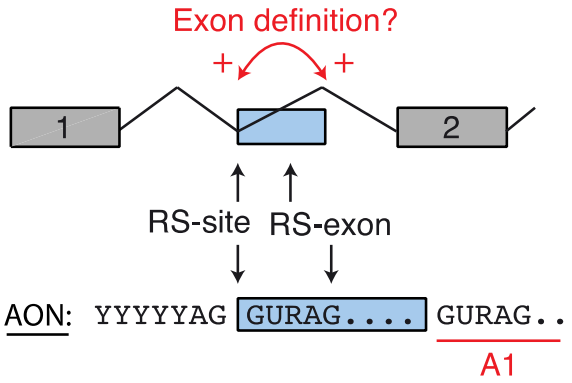
Recursive splice sites are present within some of the longest genes

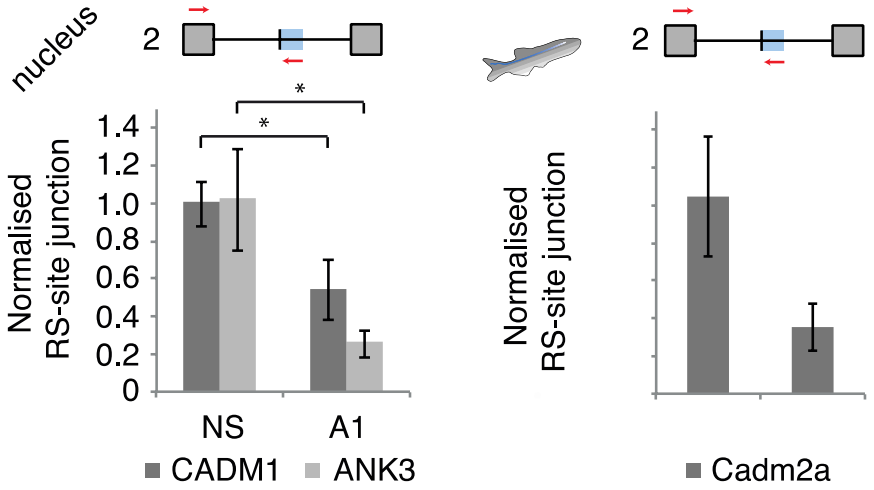


Sibley et al, Nature, 2015

Definition of the cryptic exon is required for recursive splicing

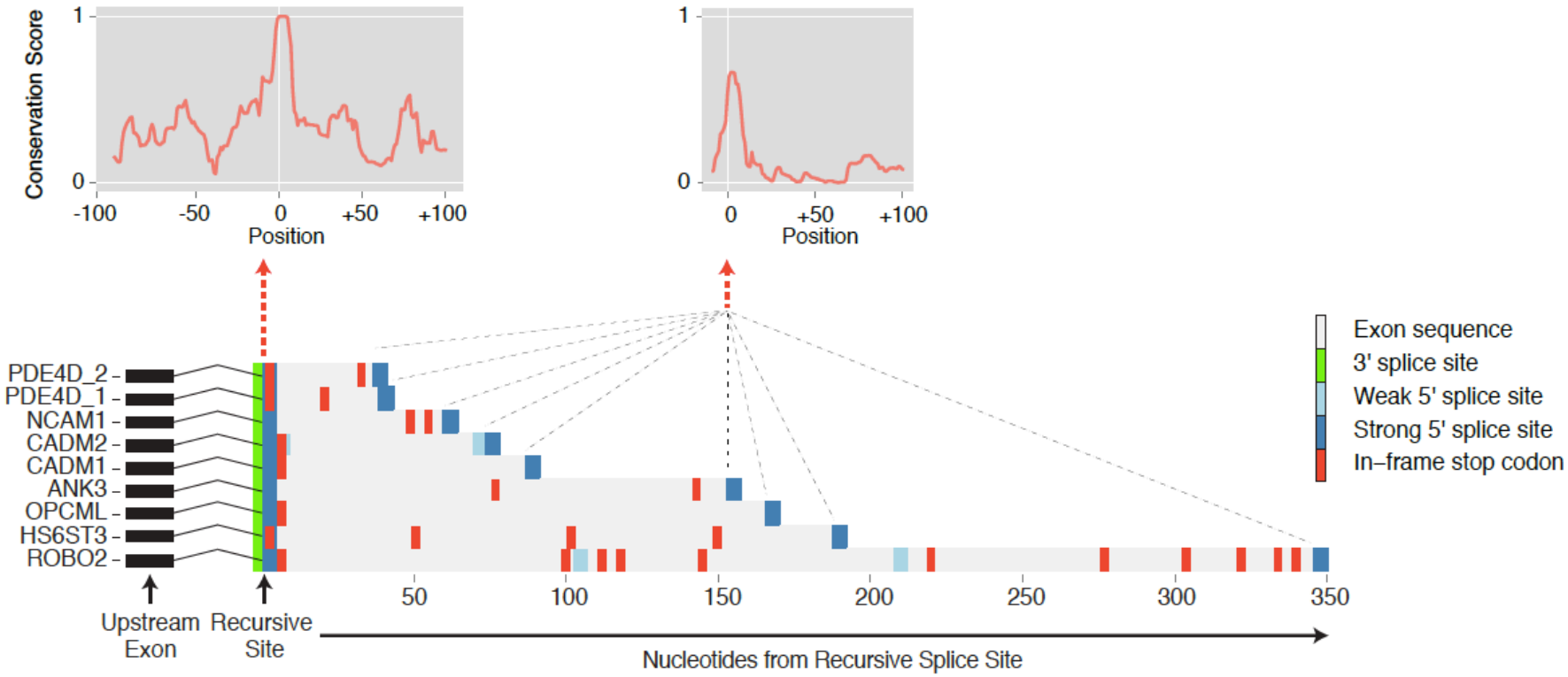






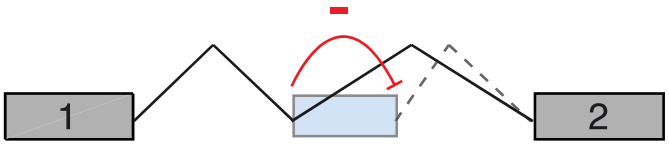
Sibley et al, Nature, 2015

Recursive sites are followed by cryptic poison exons



Sibley et al, Nature, 2015

Recursive site prevents inclusion of the cryptic exon



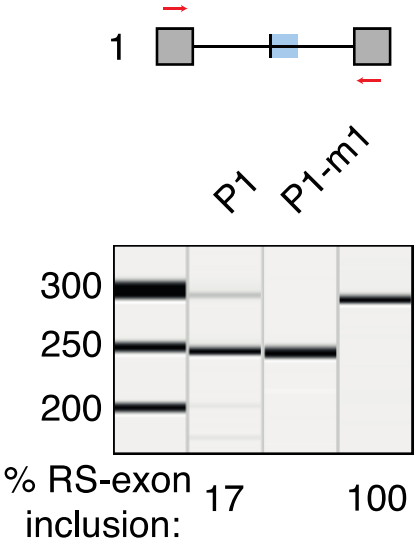
RS-site RS-exon

MG:

P1: YYYYYAG GTAAGC... GTAAA..

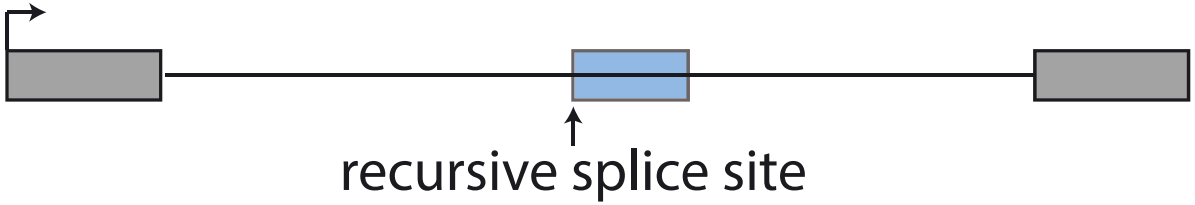
P1-m1: YYYYYAG GTAAGC... ATAAA..

P1-m2: YYYYYAG GCAGCC... GTAAA..

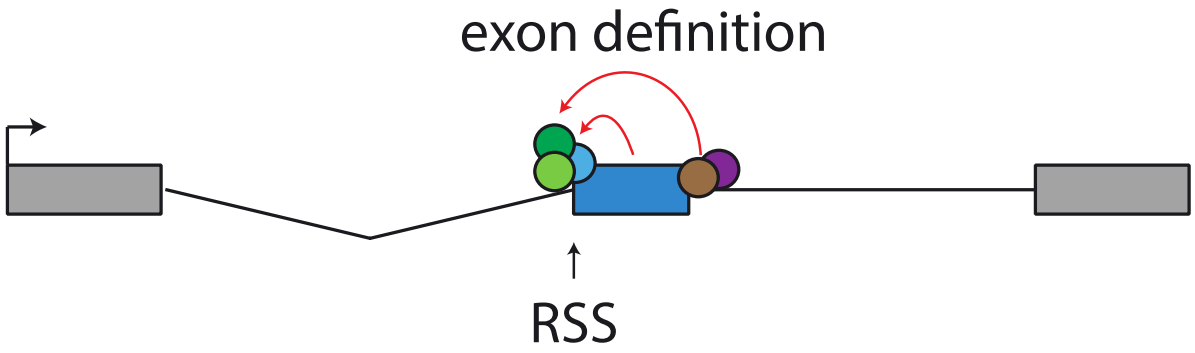


Sibley et al, Nature, 2015

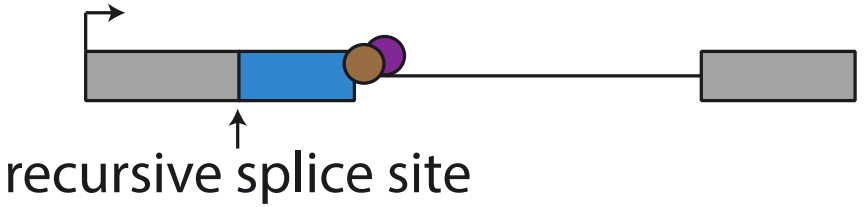
Suggested model for the mechanism of recursive splicing in vertebrates



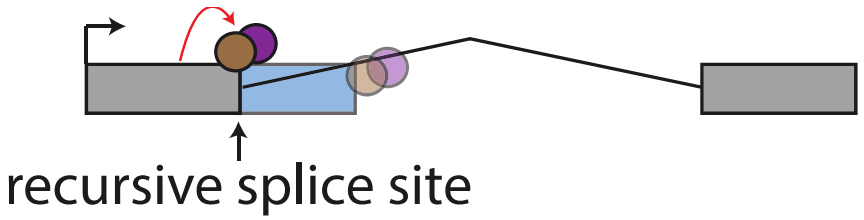
Suggested model for the mechanism of recursive splicing in vertebrates



Suggested model for the mechanism of recursive splicing in vertebrates

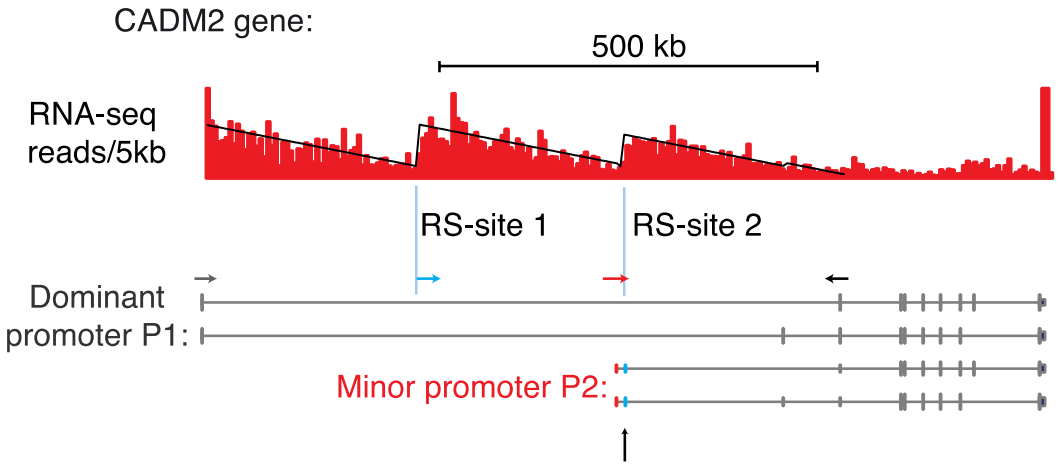


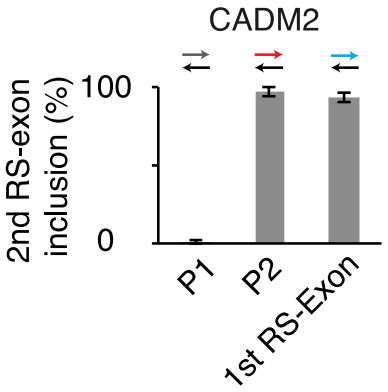
Suggested model for the mechanism of recursive splicing in vertebrates



Suggested model for the mechanism of recursive splicing in vertebrates

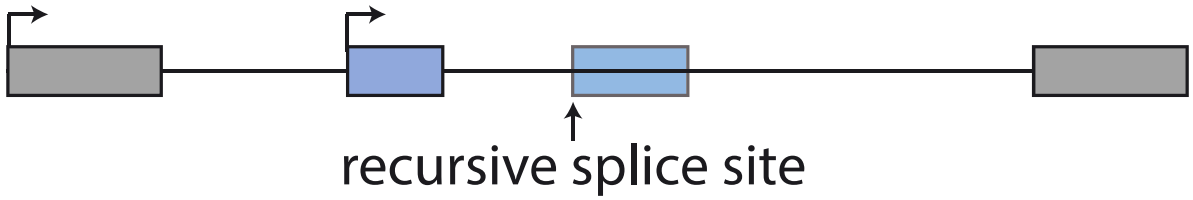
The cryptic exon is included if preceded by another cryptic exon

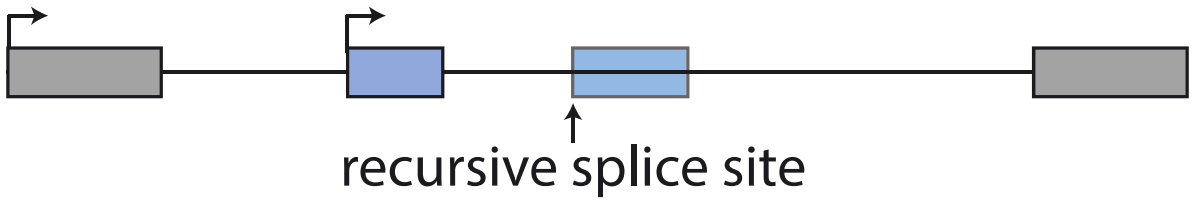




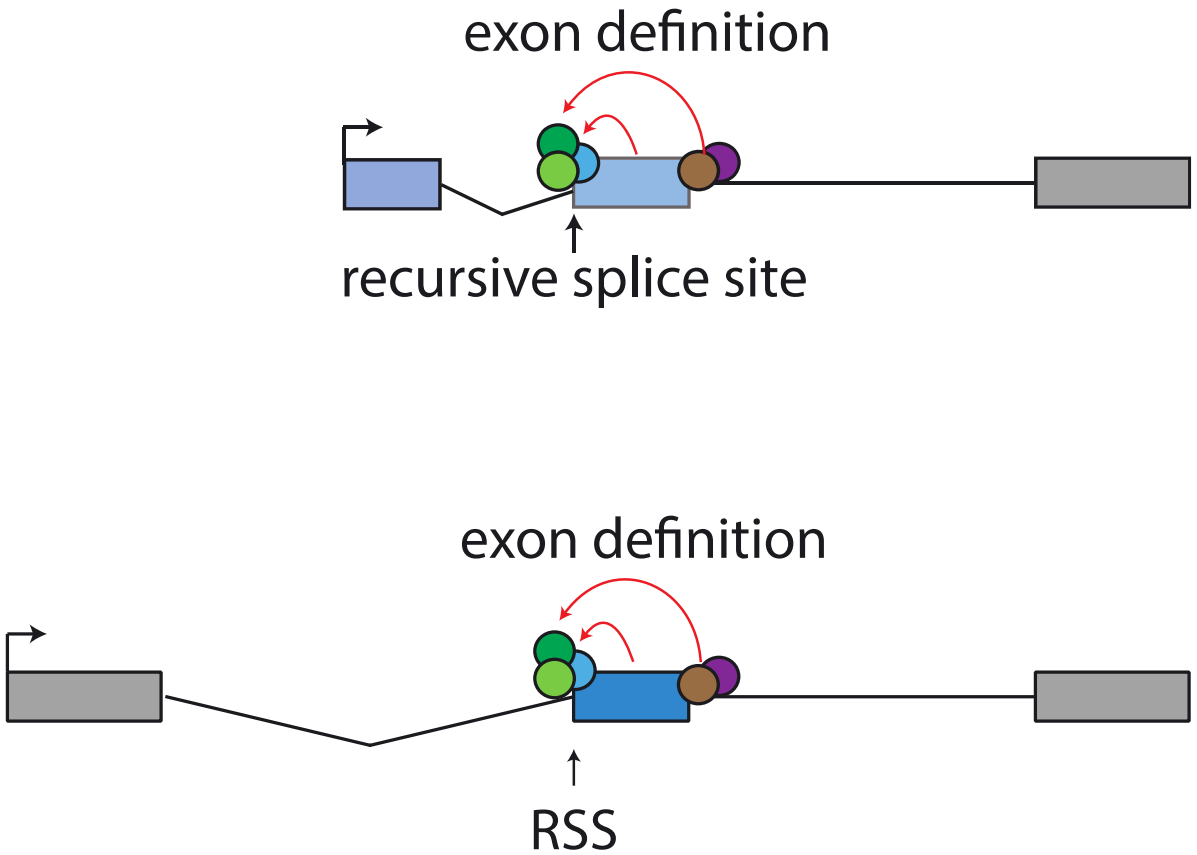
Sibley et al, Nature, 2015

Recursive splicing detects upstream cryptic exons

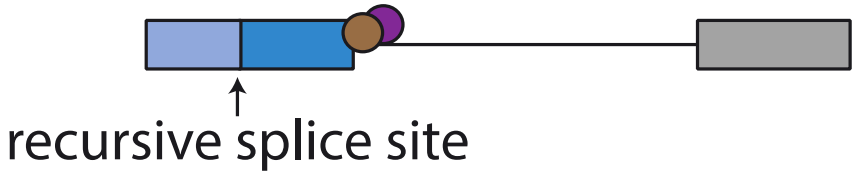


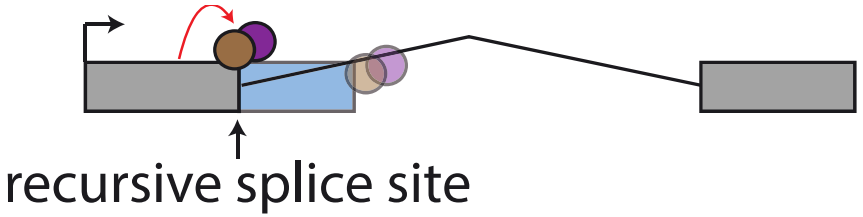


Recursive splicing detects upstream cryptic exons

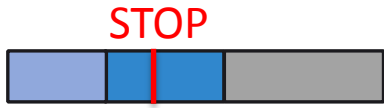


Recursive splicing detects upstream cryptic exons

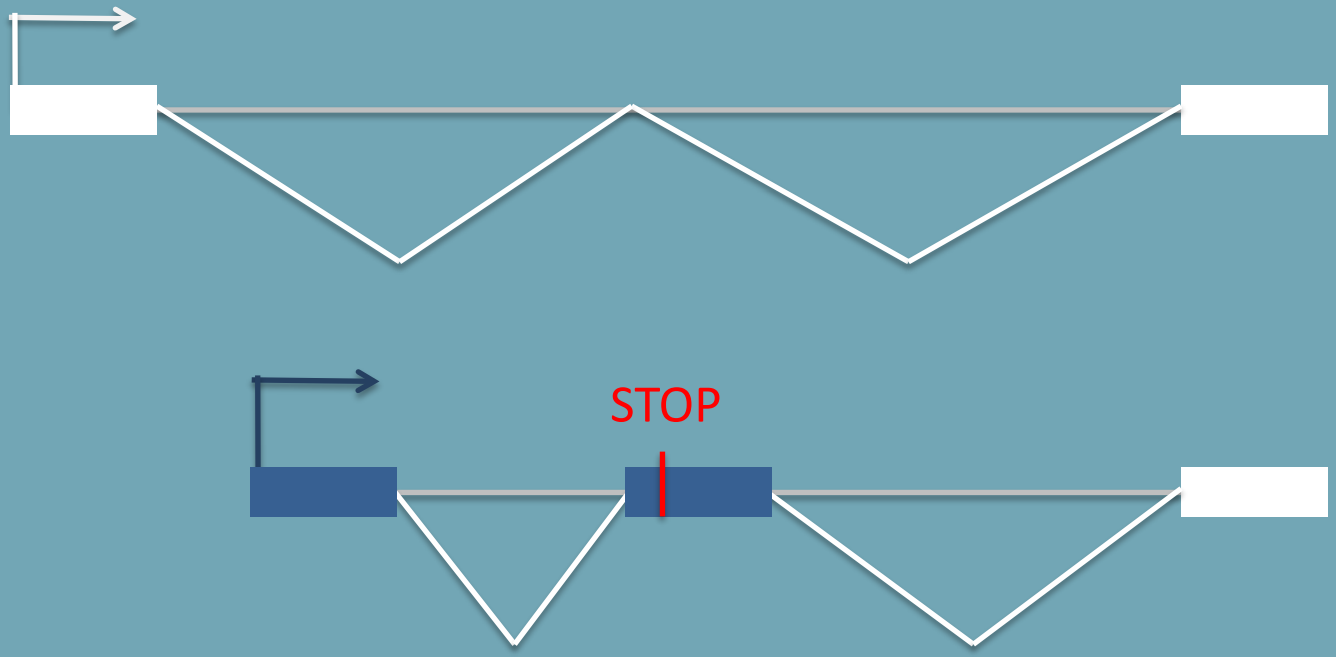




Recursive splicing detects upstream cryptic exons



Cryptic exon detects other cryptic exons due to recursive splicing

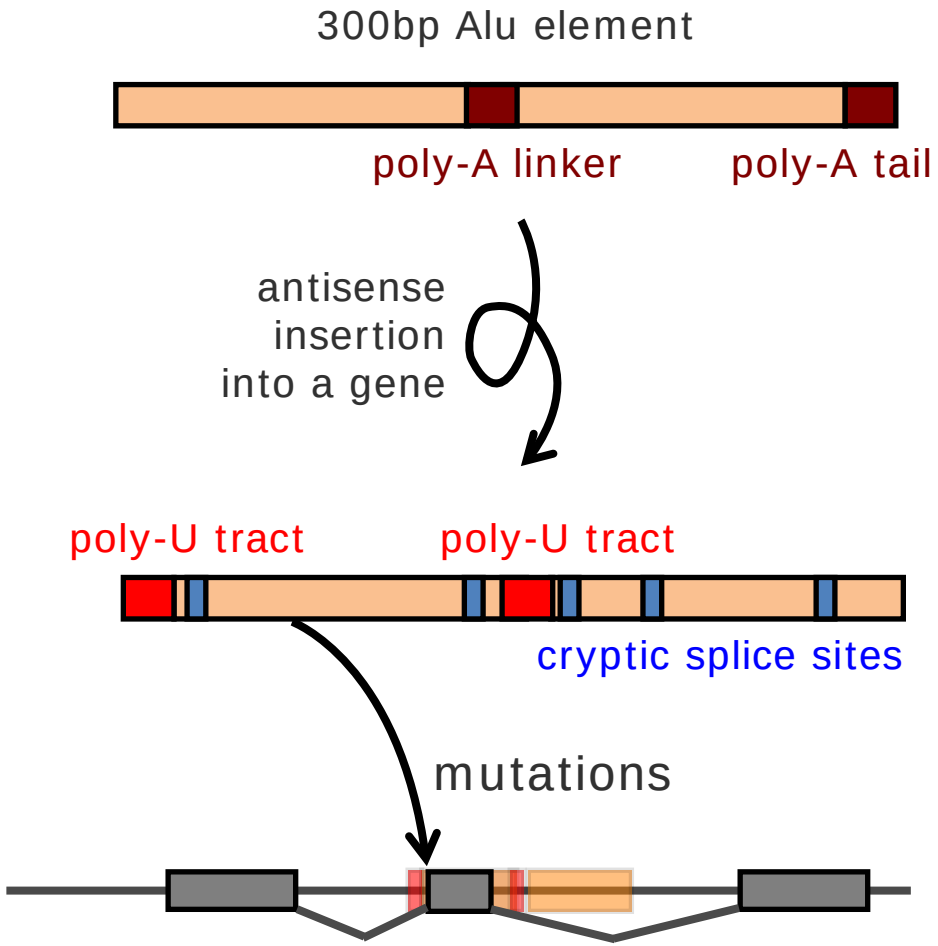


designed by Petra Kokol

Jumping genes

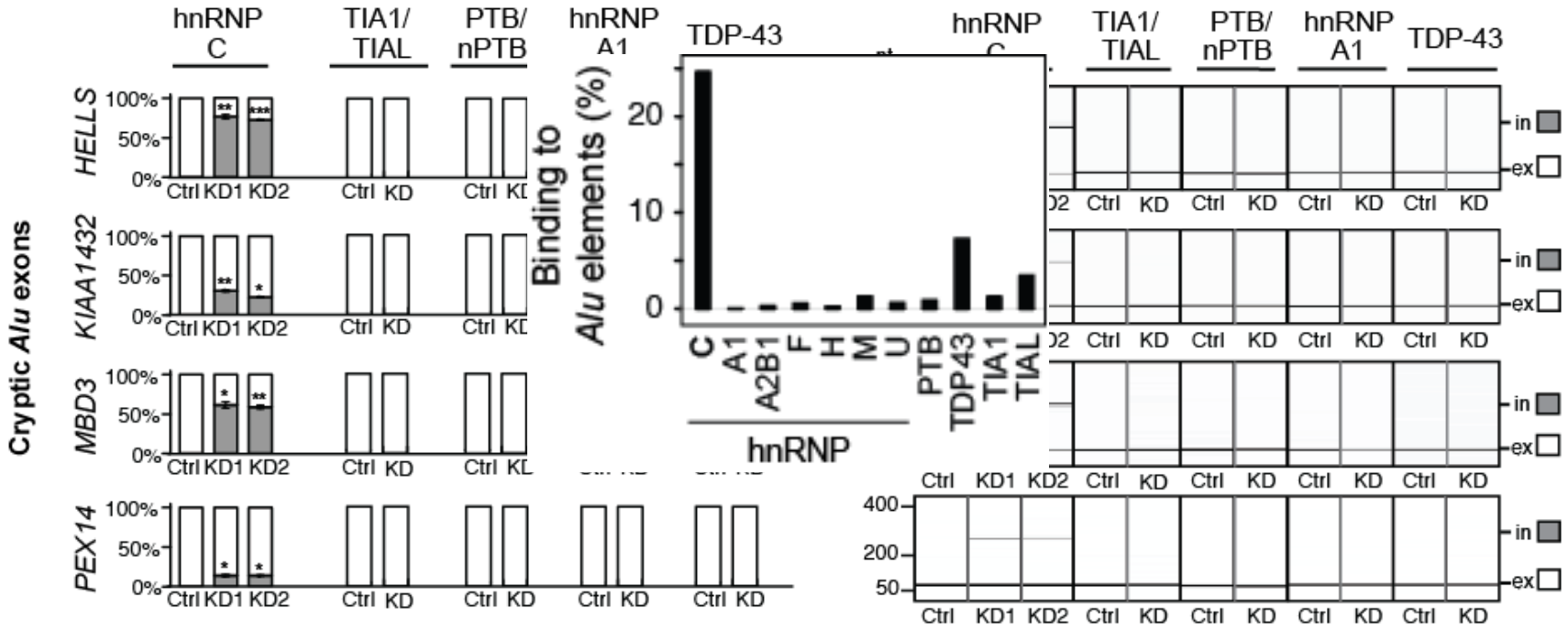
Formation of exons from antisense *Alu* elements

- Alus are transposable elements
  - 10% of human genome
  - 650k in introns
- Alus resemble exons when in antisense
  - Cryptic splice sites
  - poly-U tracts
- Alus are an important source of new exons in primates
  - ~5% of human alternative exons



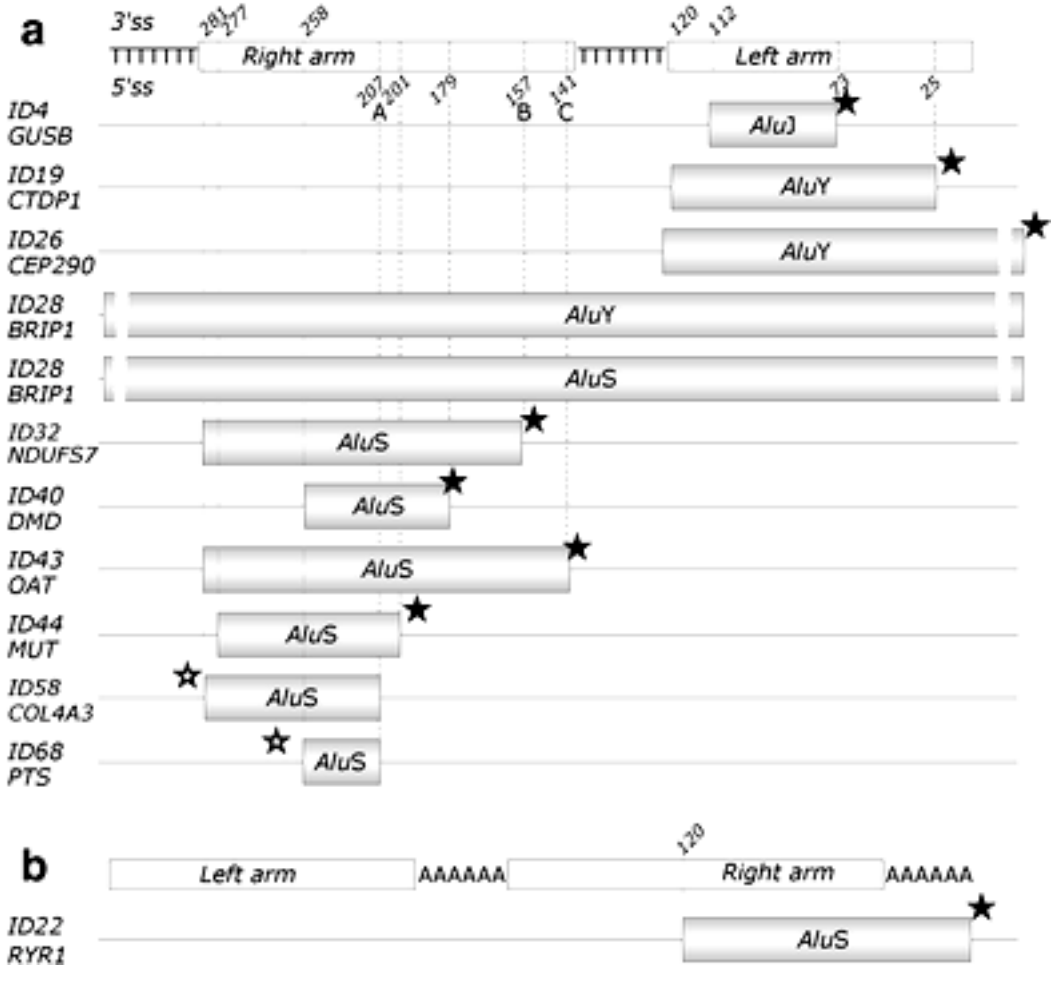
Keren et al, *Nat Rev Gen* 2010

hnRNP C represses splicing of *Alu* exons



Zarnack et al, Cell, 2013

Alu exons can cause human diseases

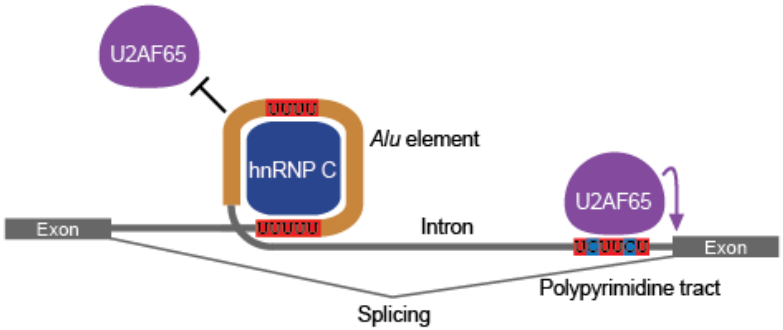


Antisense Alus

Sense Alu

Vorechovsky et al., Human Genetics 2010

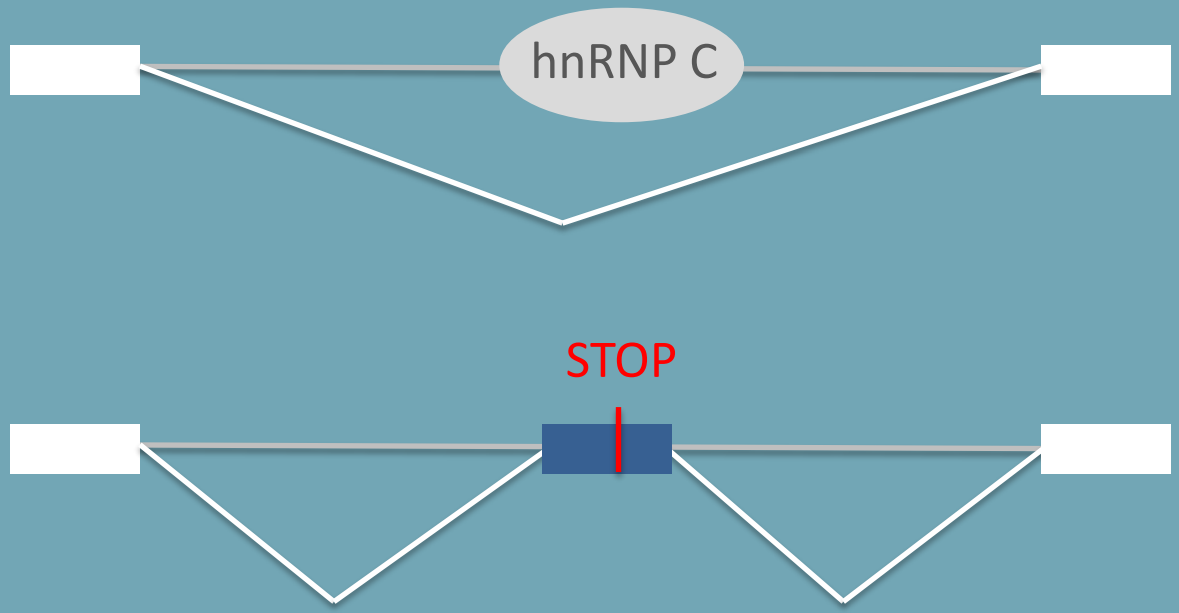
hnRNP C controls the emergence of *Alu*-derived cryptic exons

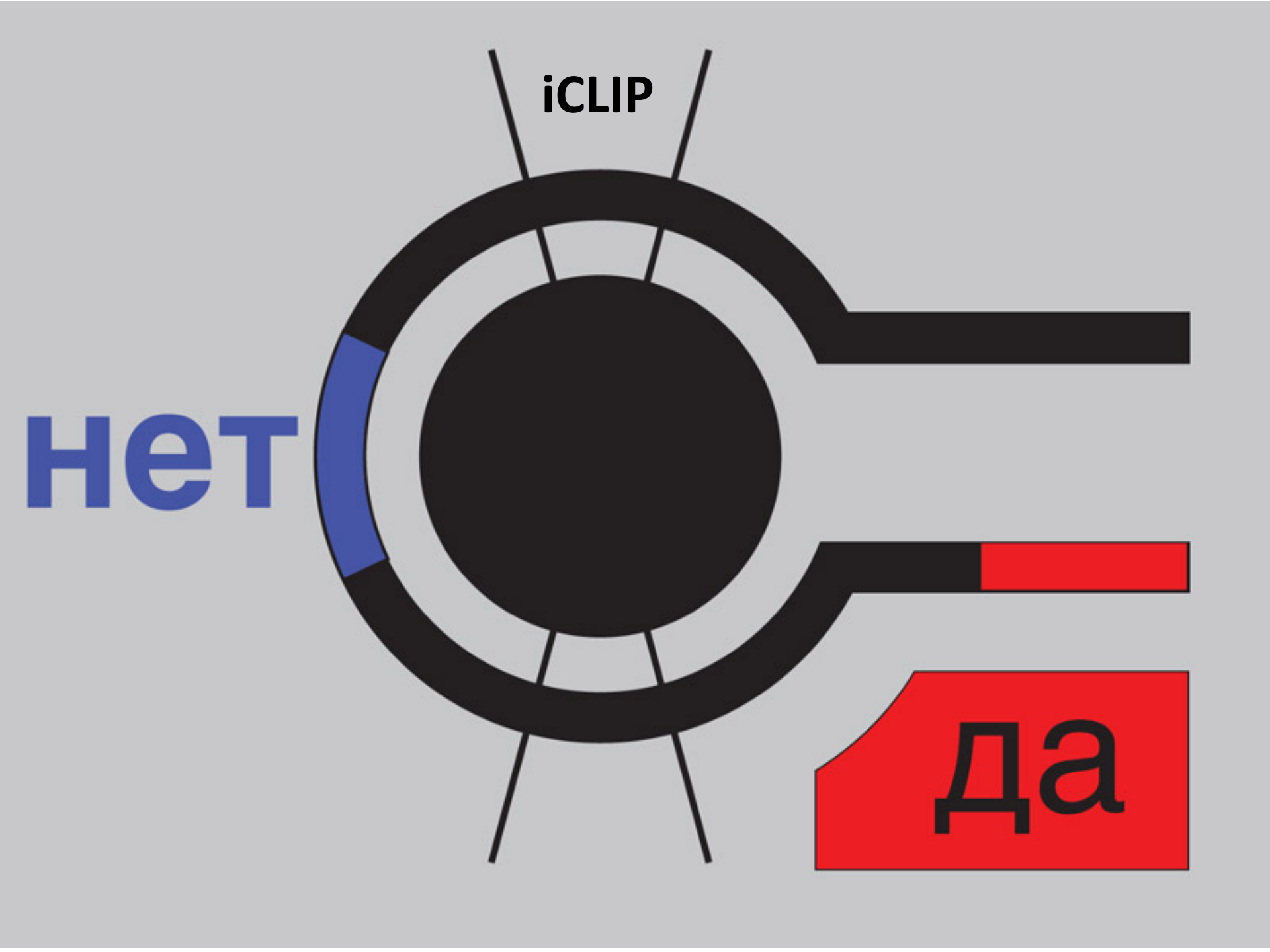


Alu exon repressed

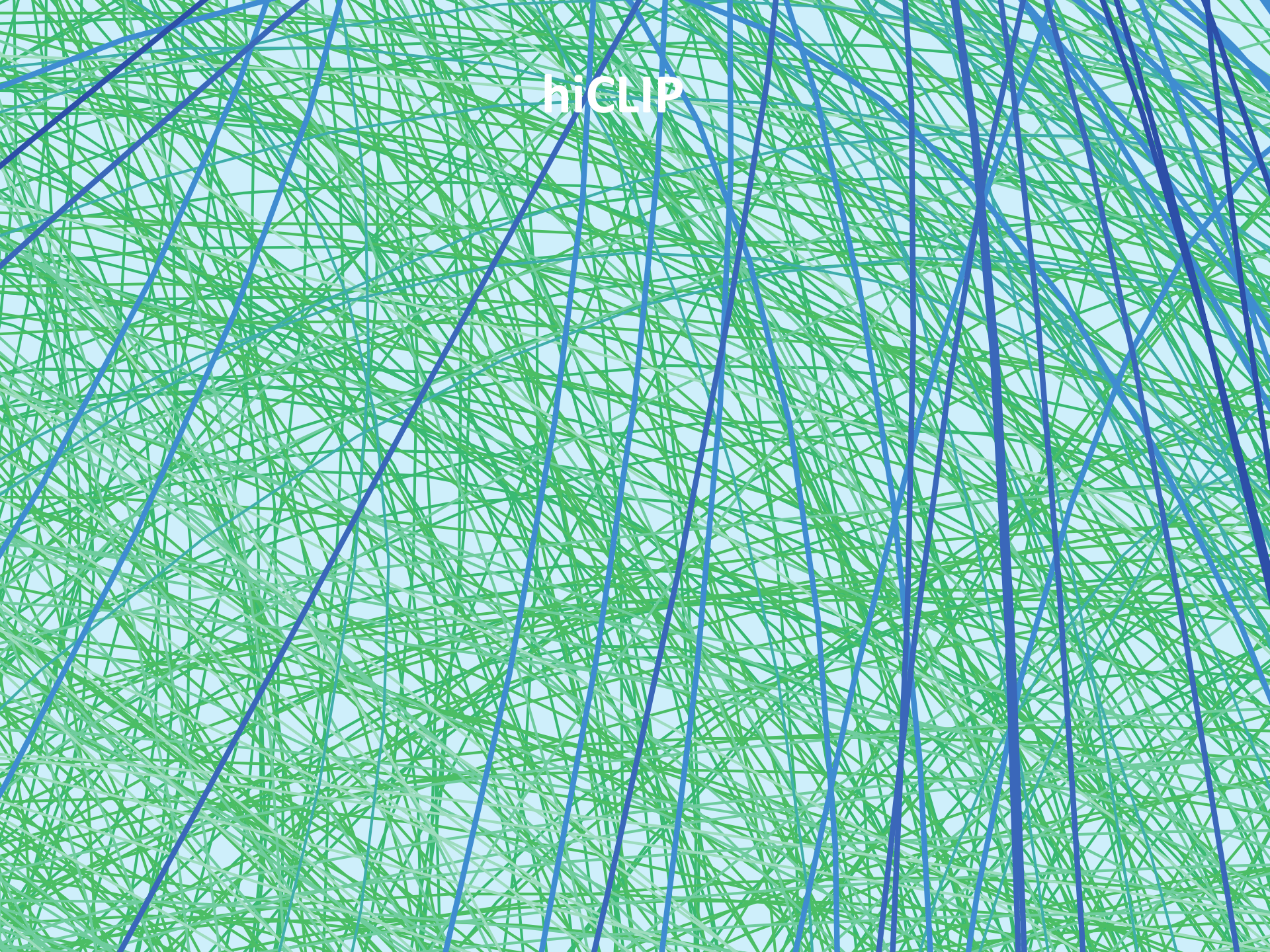
Zarnack et al, Cell, 2013

hnRNP C represses damaging cryptic *Alu* exons

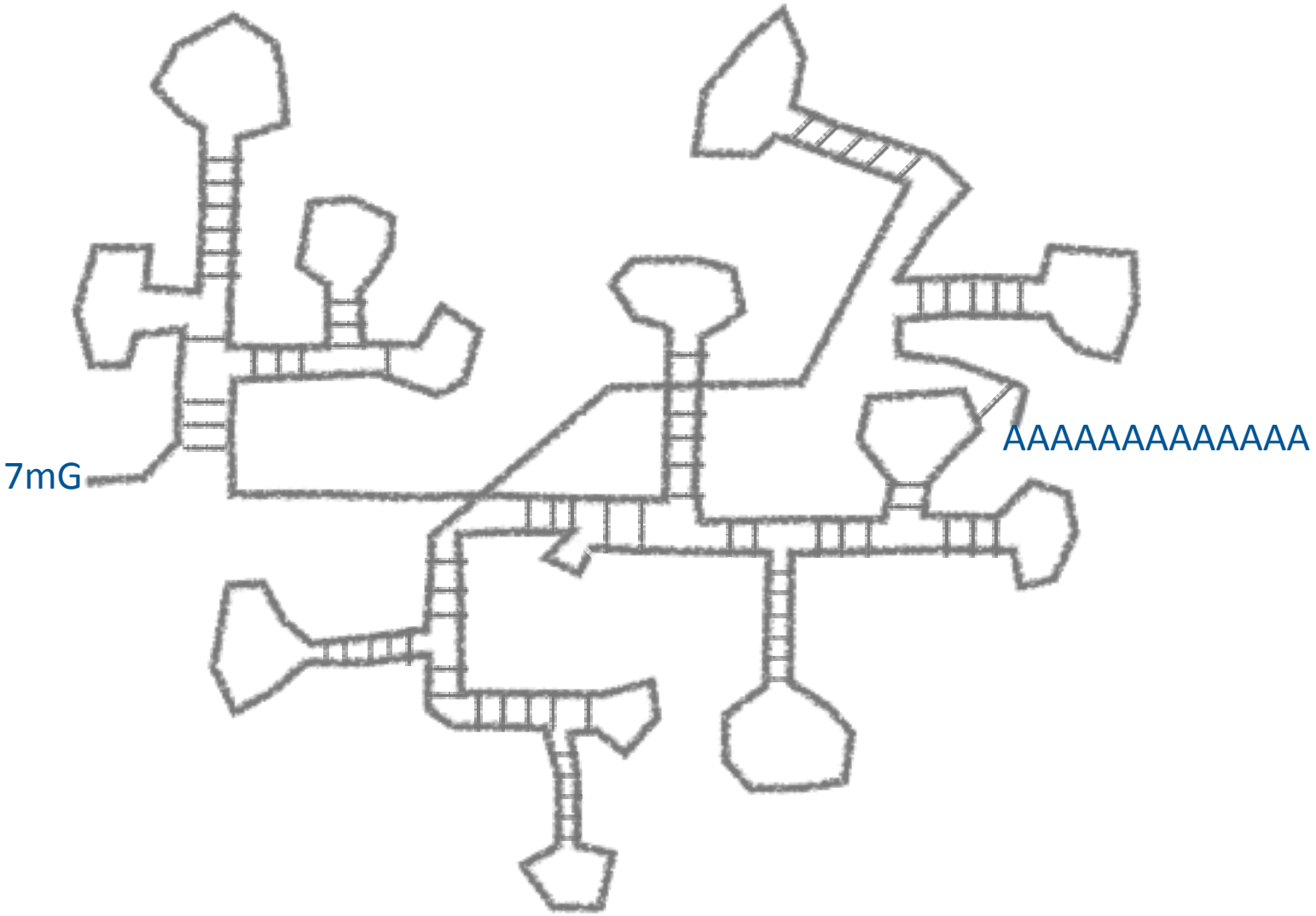



iCLIP
нет
да

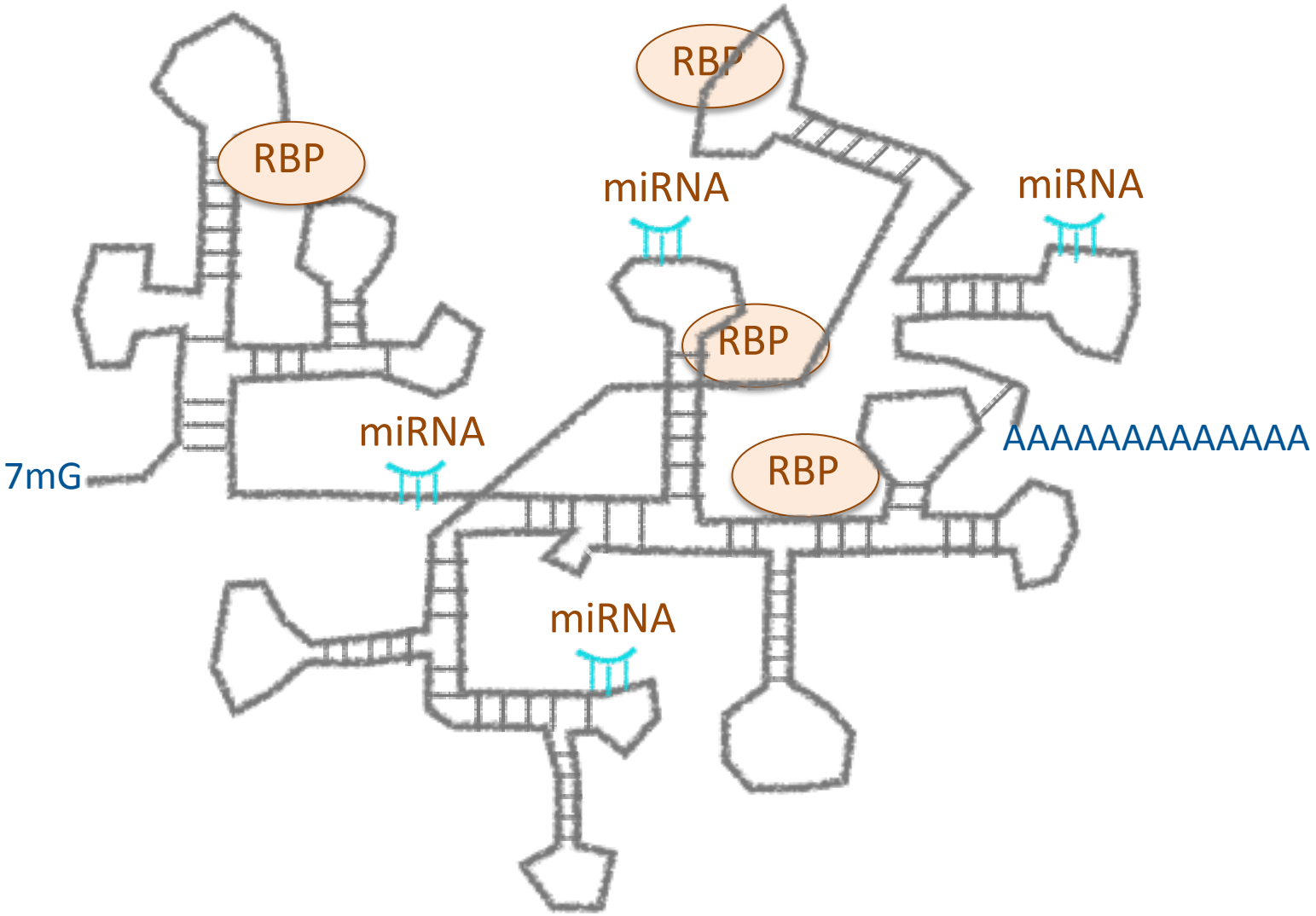
RNA loops


hiCLIP

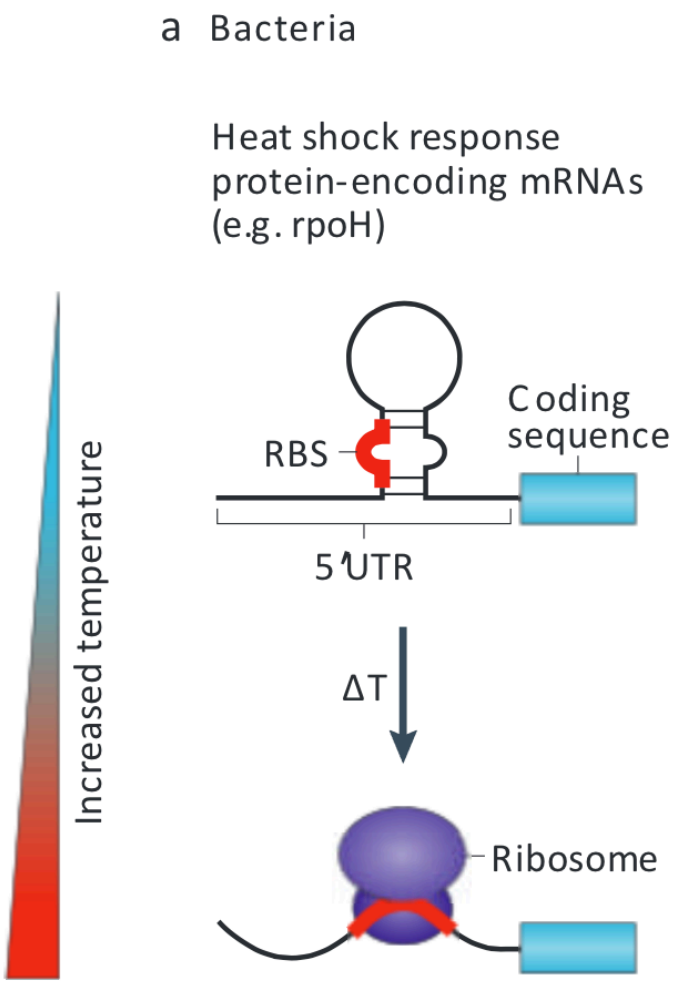
mRNAs have a structure



…to form mRNPs

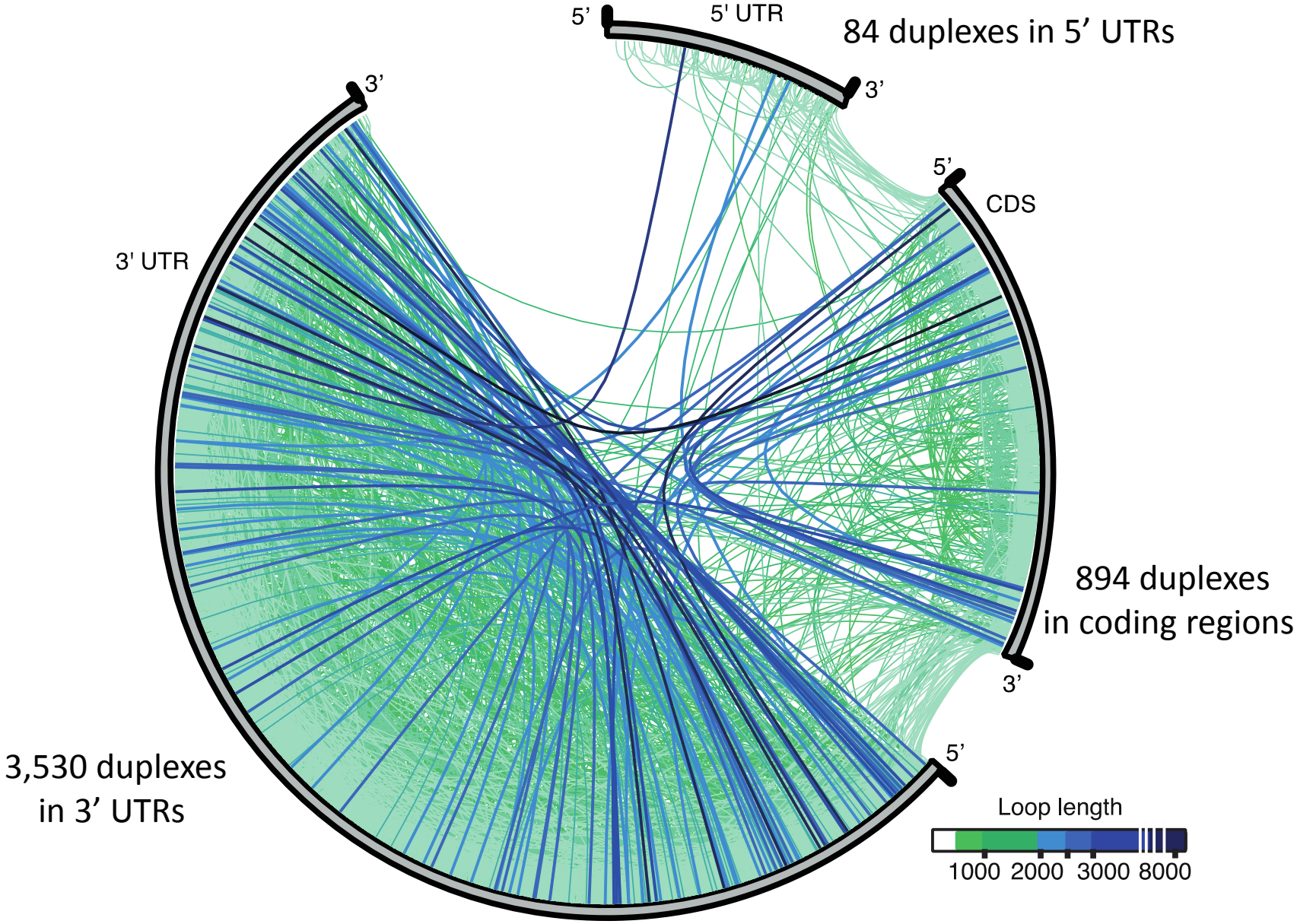


Example 1: RNA structures can act as thermometers

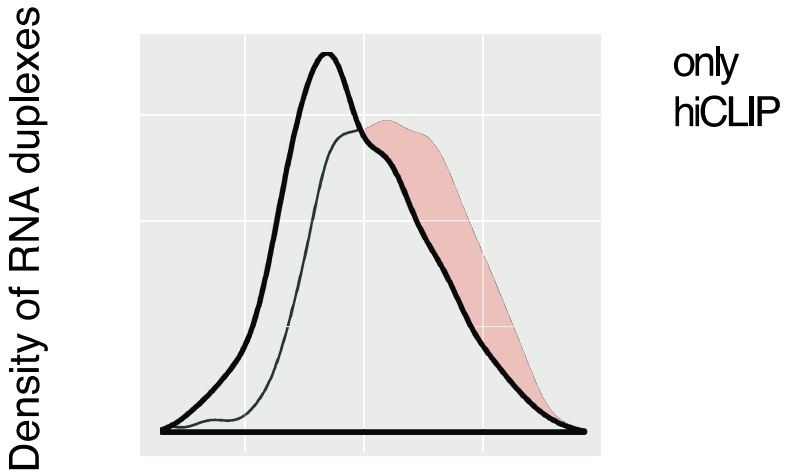


Mortimer et al, Nat Rev Gen, 2014

RNA duplexes in 3’ UTR lead to formation of long RNA loops

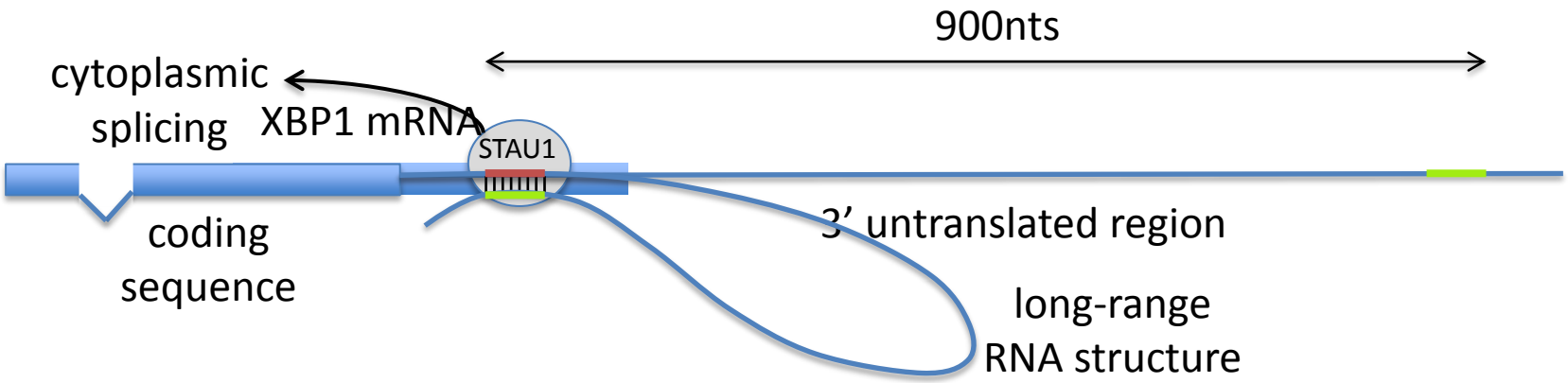


Long-range RNA duplexes are not computationally predicted



Sugimoto et al, Nature 2015

STAU1 regulates cytoplasmic splicing of the XBP1 mRNA



We identified an RNA duplex in the XBP1 3'UTR

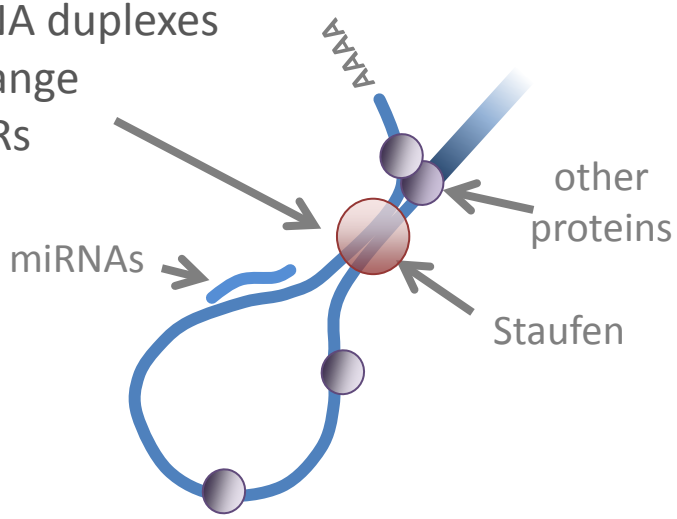
The RNA duplex is required for STAU1 binding to XBP1 mRNA

STAU1 is required for efficient cytoplasmic splicing
of XBP1 mRNA during UPR

Sugimoto et al, Nature 2015

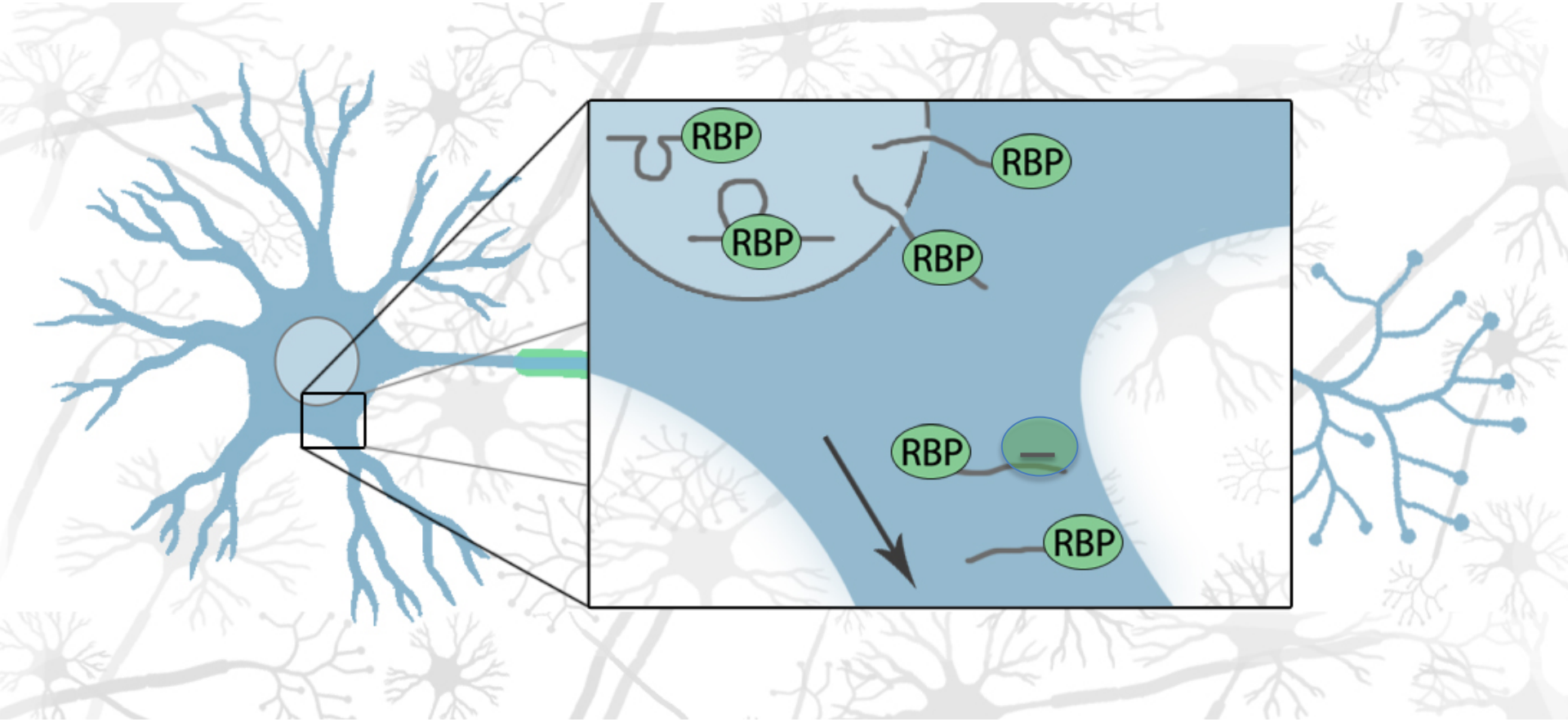
summary

Staufen binds RNA duplexes that form long-range contacts in 3'UTRs



Sugimoto et al, Nature 2015

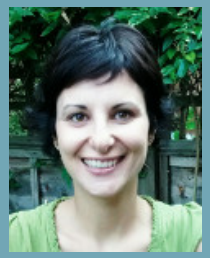
RBPs regulate the time and space of neuronal gene expression



Thanks to…

Recursive splicing


Chris Sibley


Lorea Blazquez


Nejc Haberman


Warren Emmett


Miha Modic

iCLIP, Alu exons


Julian König


Kathi Zarnack

hiCLIP, Staufen


Yoichiro Sugimoto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UCL Institute of Genetics

HFSP

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MRC Medical Research Council

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