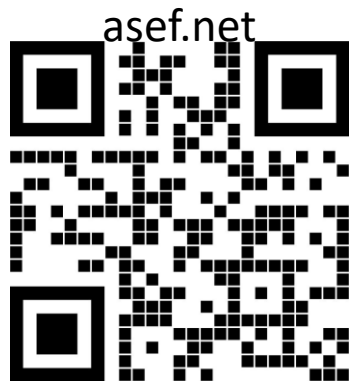




ASEF
SPEAKER SERIES

Predavanje bomo pričeli ob 19:03



- ASEF štipendijski program:
 - 10 tedenski raziskovalni obisk v tujini
 - ASEF tutorstvo
 - Delavnice, predavanja
 - Team building, izleti, ostali dogodki...
- ASEF Speaker Series



Retrotranspozoni: 'Trojanski konji' naših genov



prof. dr. Jernej Ule

Kemijski inštitut Ljubljana | Francis Crick Institute London | Dementia Research Institute at King's College London

Torek, 14. marec ob 19:00 (CET)

Prešernova dvorana SAZU (Novi trg 4, 1000 LJ) | Zoom



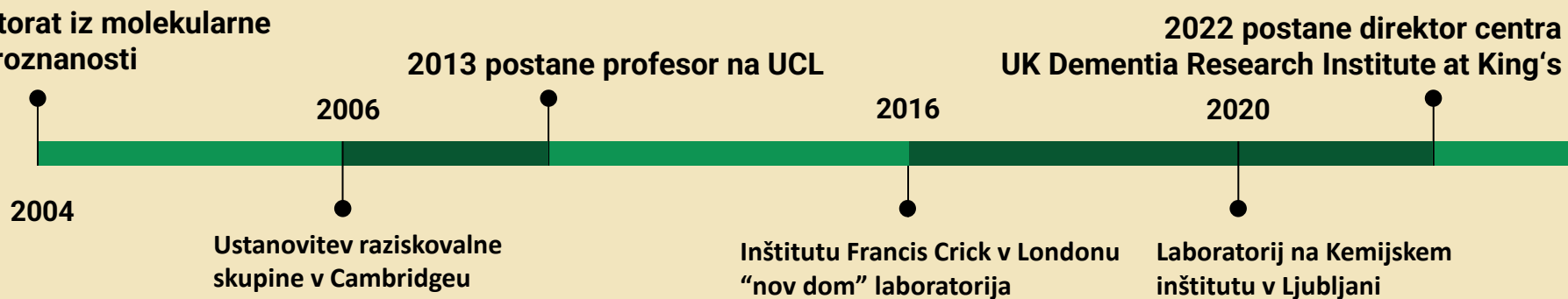
ASEF

AMERICAN SLOVENIAN
EDUCATION FOUNDATION

Prof. Dr. Jernej Ule



Doktorat iz molekularne
nevroznanosti



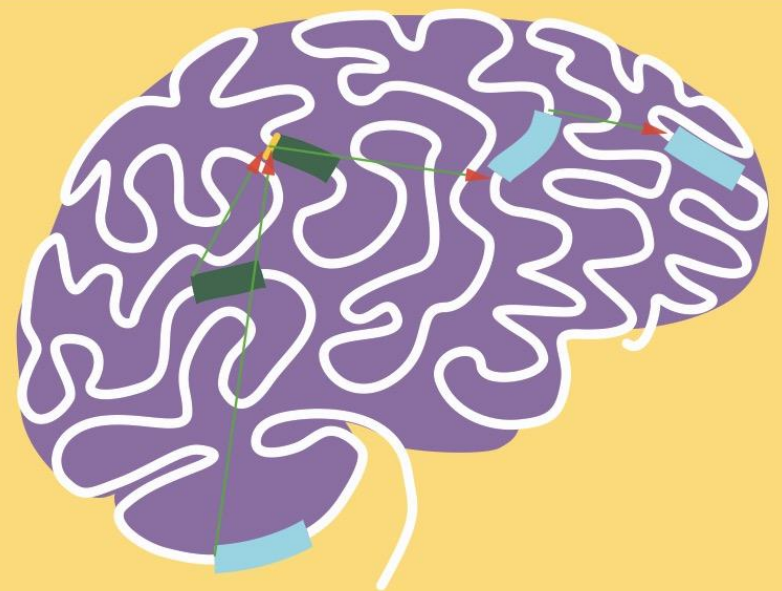
Vprašanja

- **KDAJ?** Na koncu predavanja
- **KAKO?** Vprašanja zastavite na www.sli.do s kodo `ΔSFFSneakerSeries`

Joining as a participant?

Enter code here



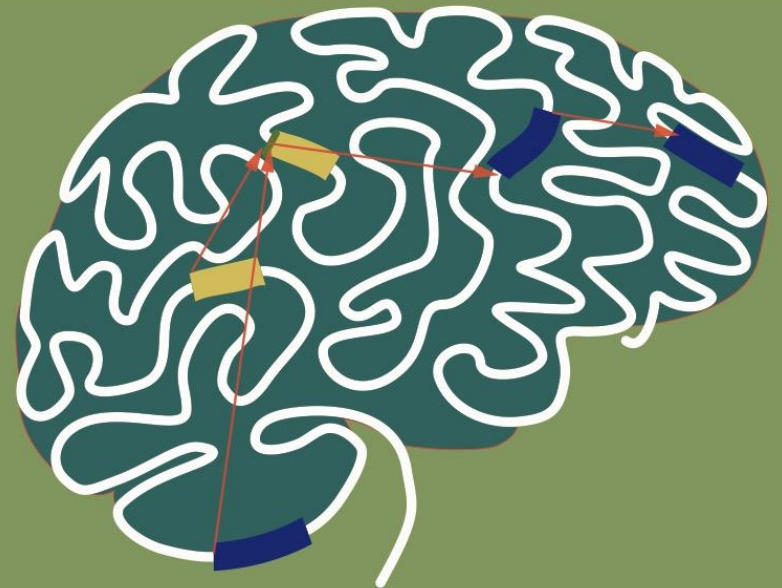


Retrotranspozoni: 'Trojanski konji' naših genov

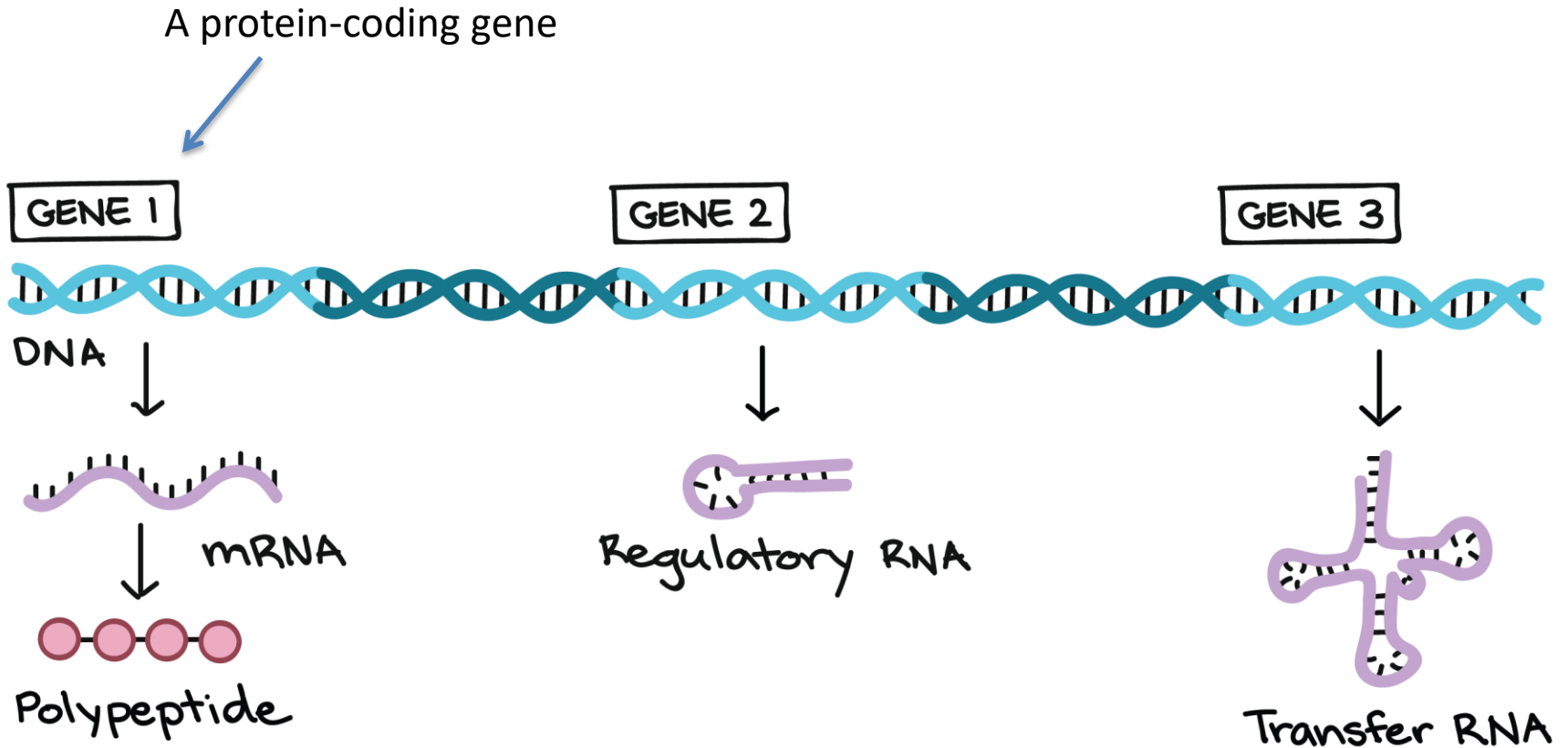
Jernej Ule

www.ulelab.info

Dementia Research Institute at King's, The Francis Crick Institute, Slovenian Institute of Chemistry



If DNA is a cookbook, RNAs are the recipes



Each gene is first dutifully transcribed into a nascent RNA

DNA



nascent RNA



Each gene is first dutifully transcribed into a nascent RNA

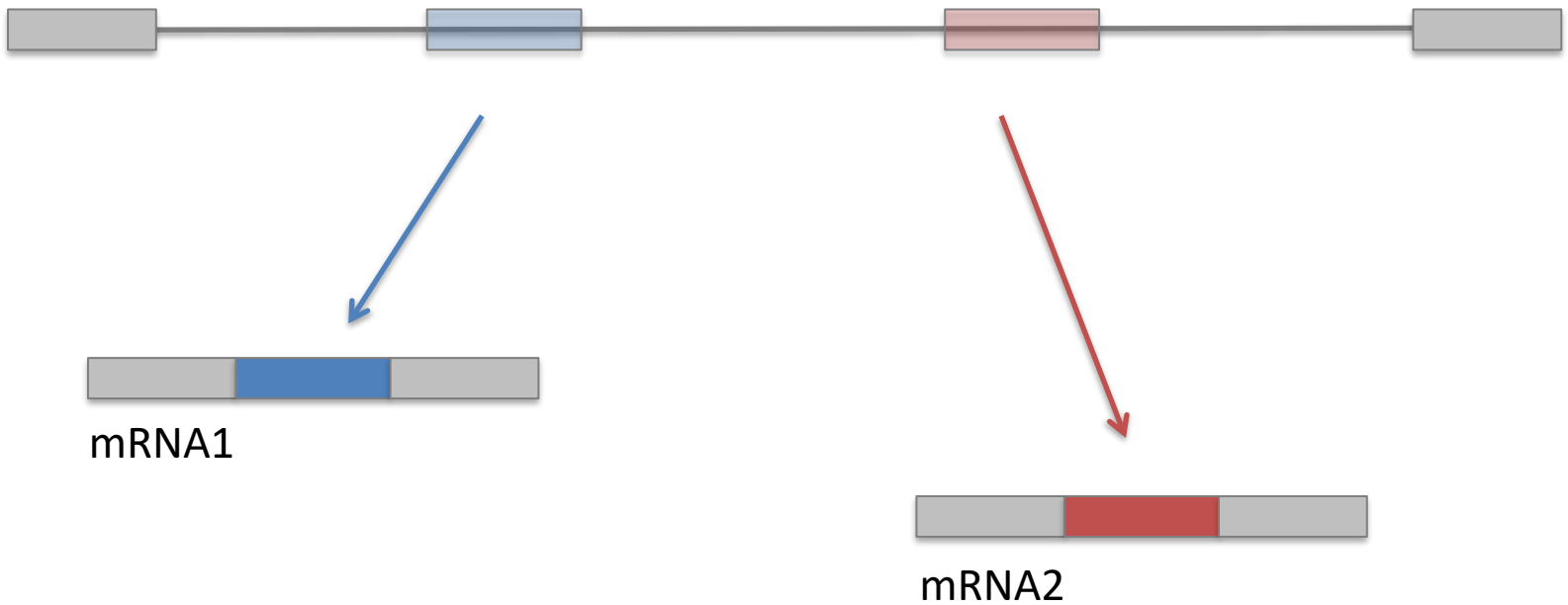
nascent RNA

Only exons are used to make the final recipe, the 'mRNA'

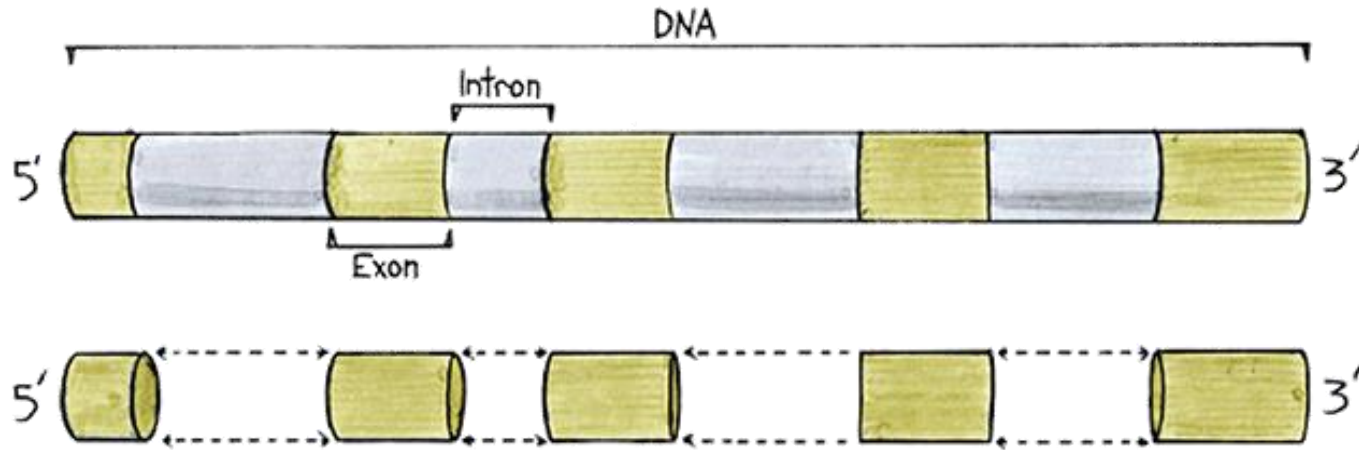


Most genes can produce variant mRNA recipes

Alternative splicing



Only a tiny part of human genome makes the mRNA recipes!



Whole genome

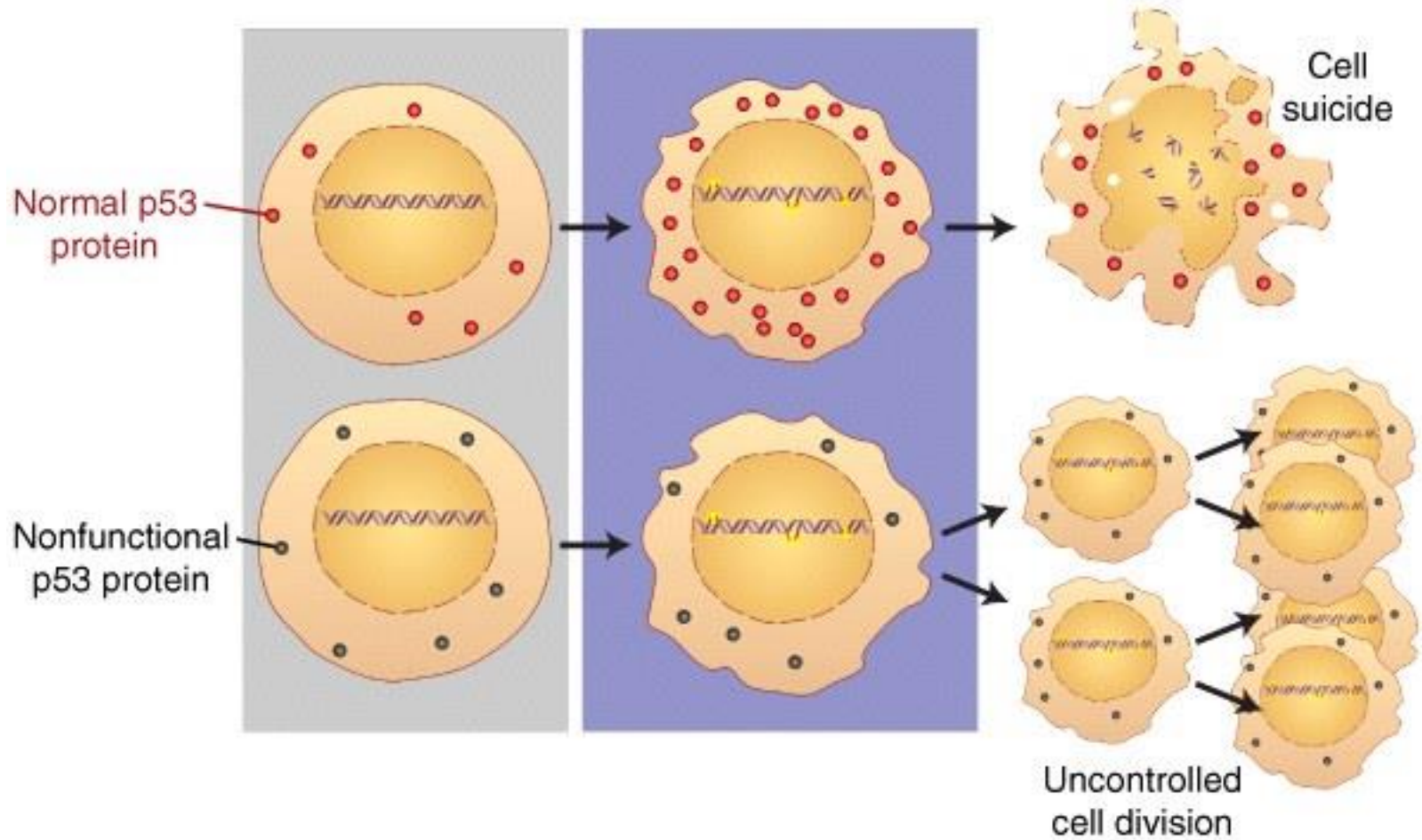
The exons make the mRNA recipes.

Exome = 1%



This contains instructions for when and how the recipes are made.

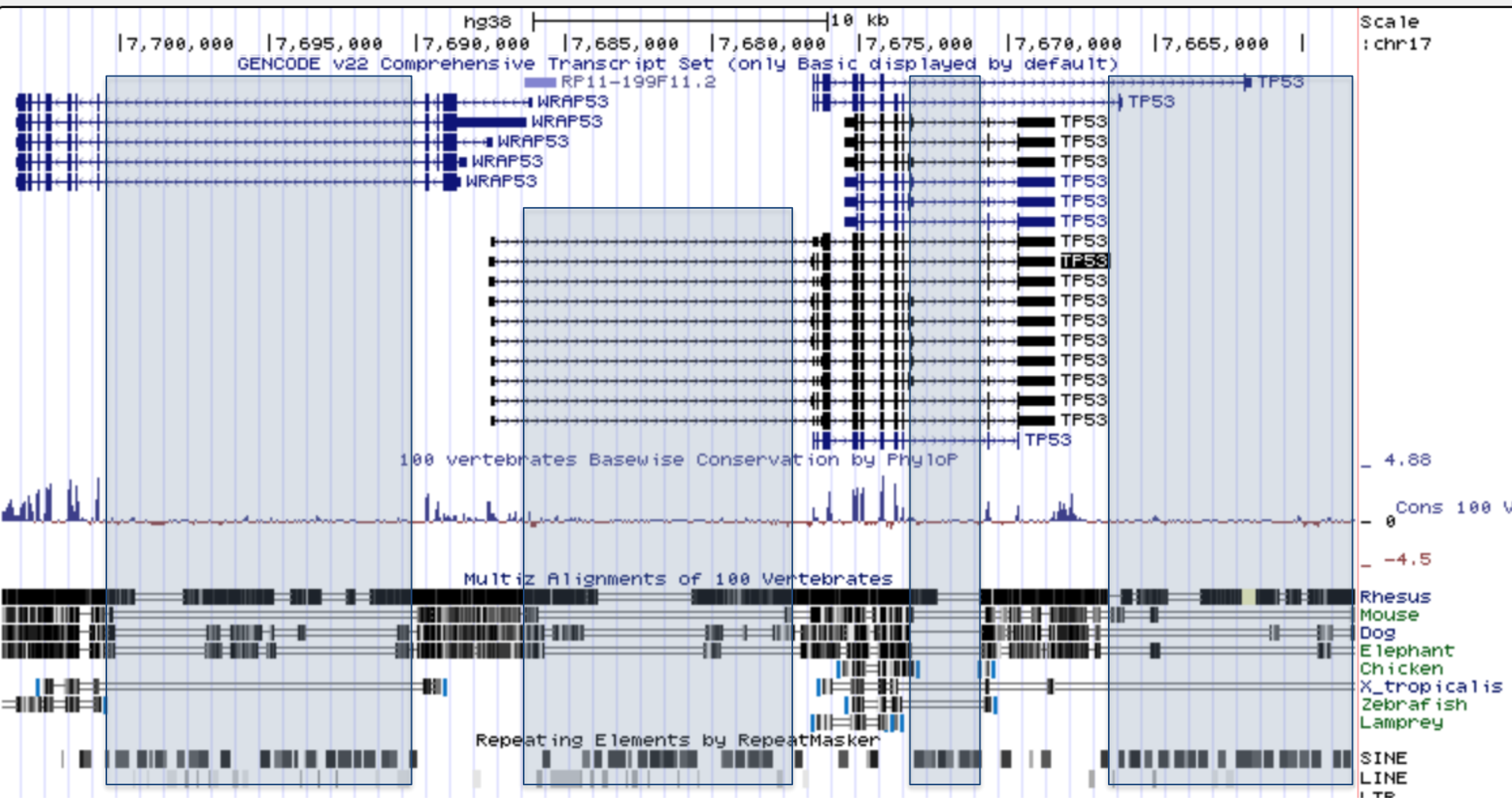
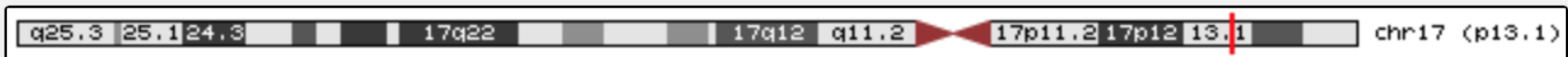
P53: a protein protecting us from cancer



P53 gene in the human genome

chr17:7,658,253-7,704,023 45,771 bp.

enter position, gene symbol or search terms

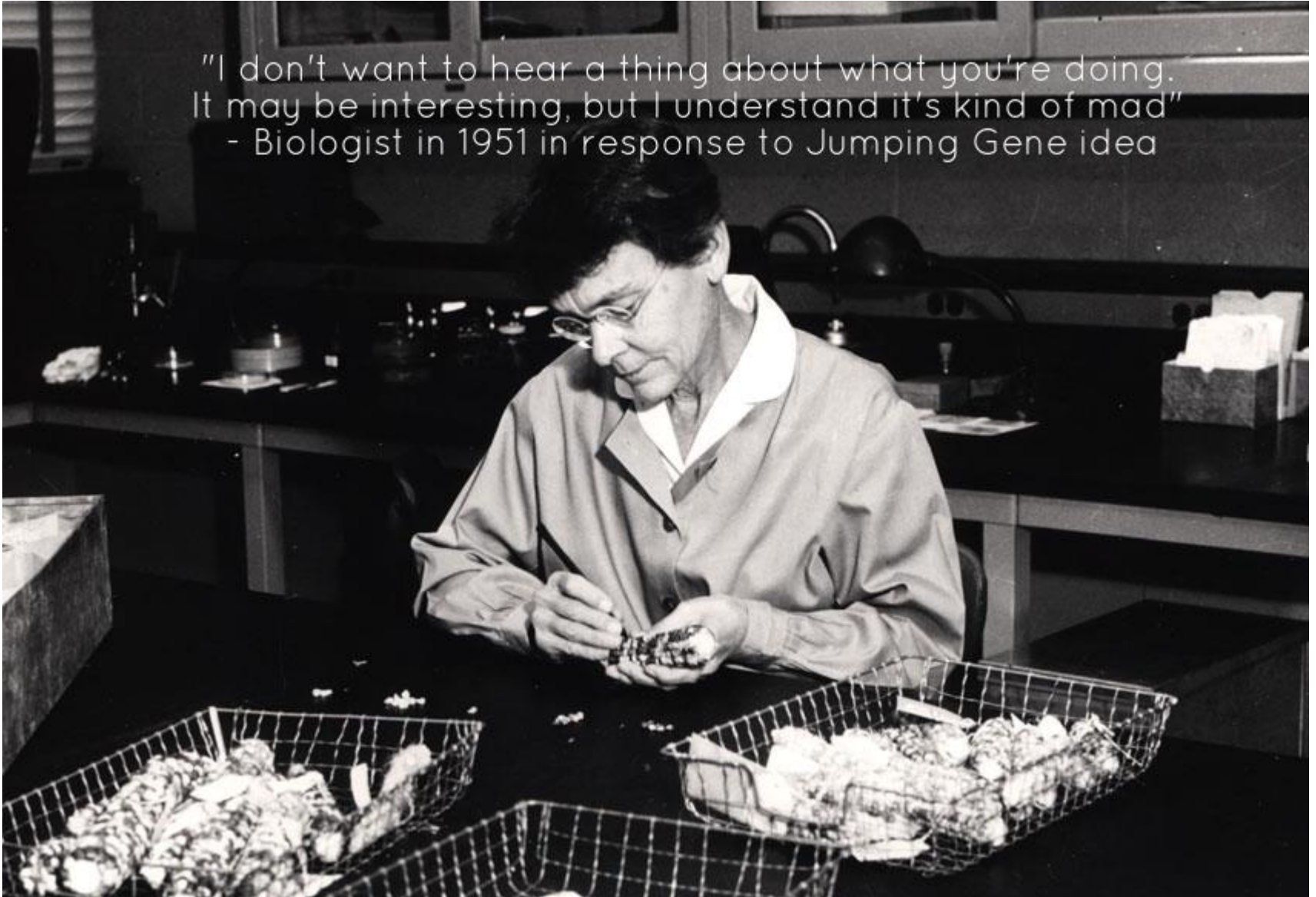


Barbara McClintock

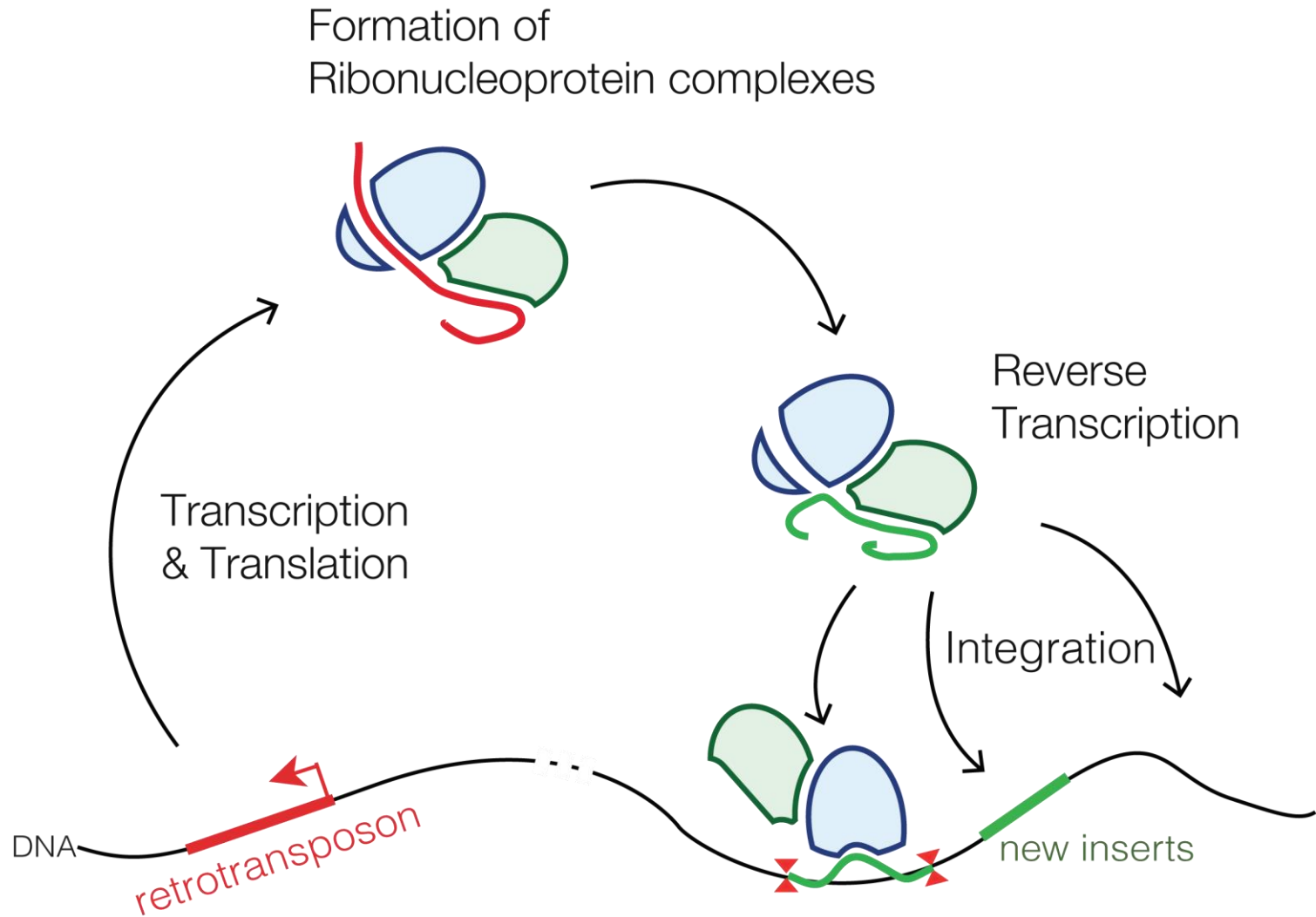


Barbara McClintock

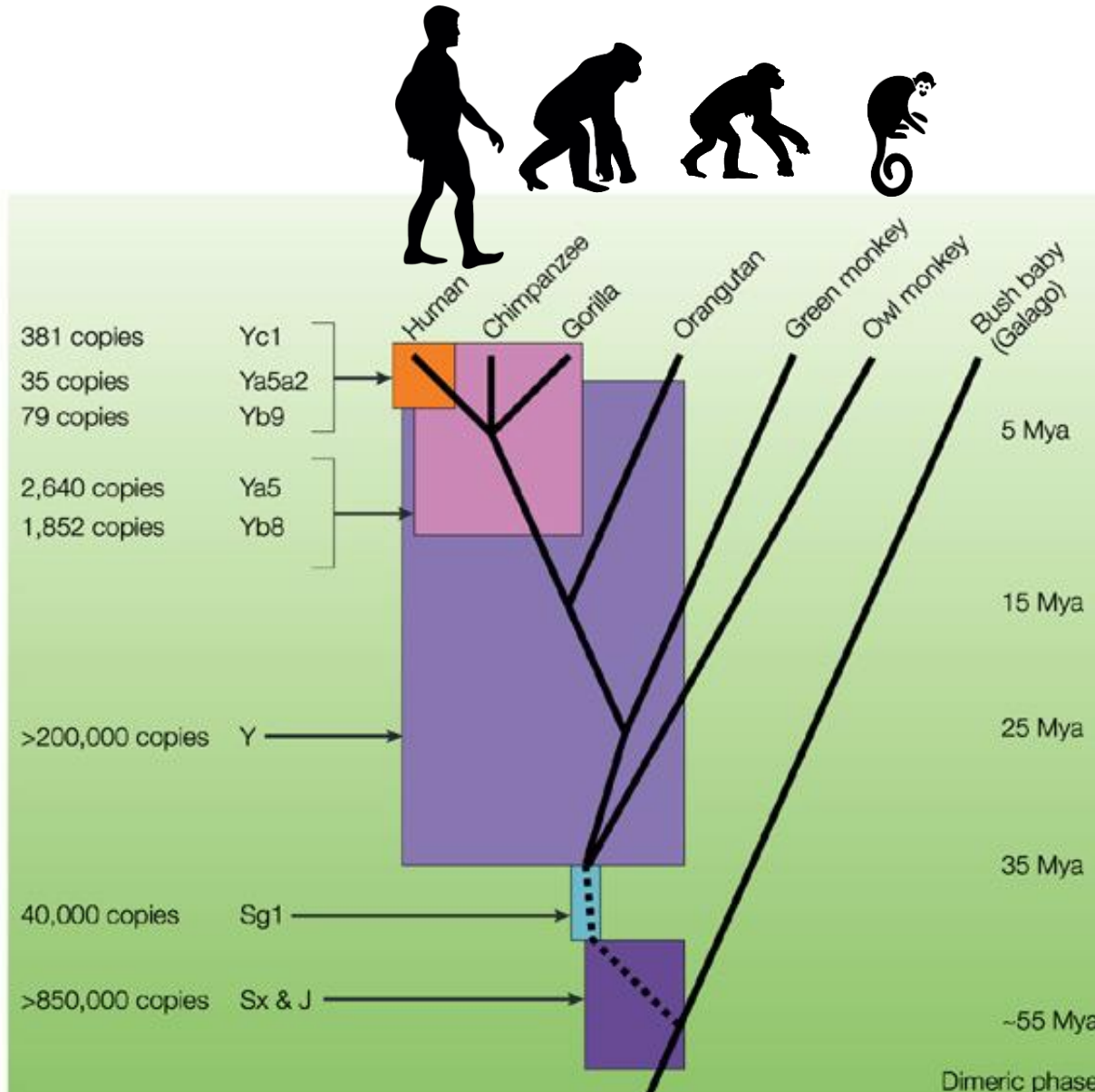
"I don't want to hear a thing about what you're doing.
It may be interesting, but I understand it's kind of mad"
- Biologist in 1951 in response to Jumping Gene idea



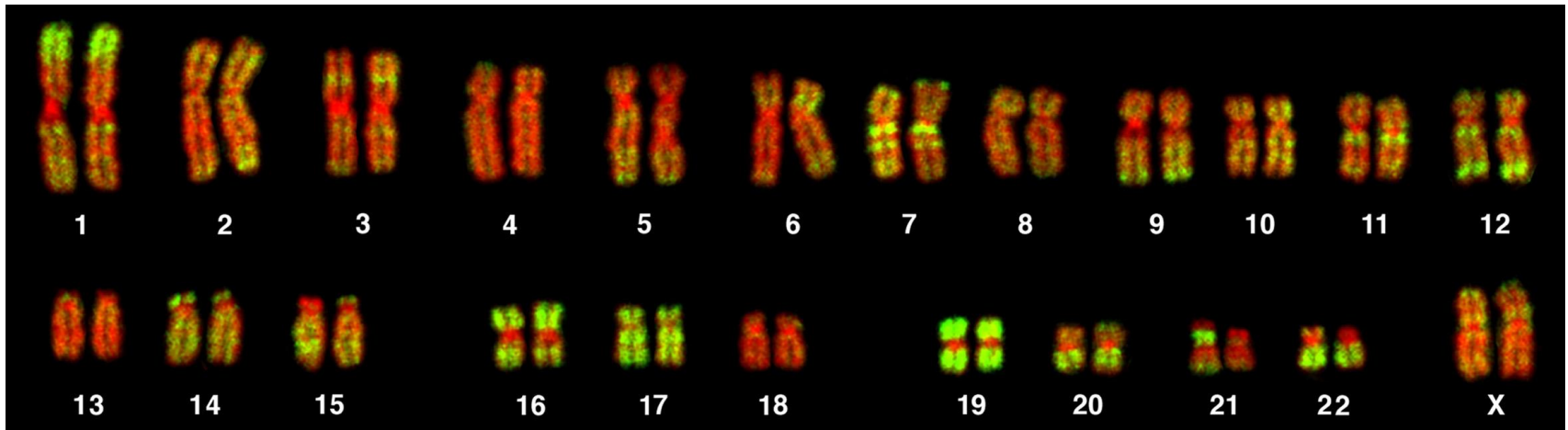
Retrotransposons are a common source of repetitive sequences



Alus are primate-specific retrotransposons



Alu elements in the human genome



Alu elements are stained in green

Many thousands of Alus contain sequences that can make exons



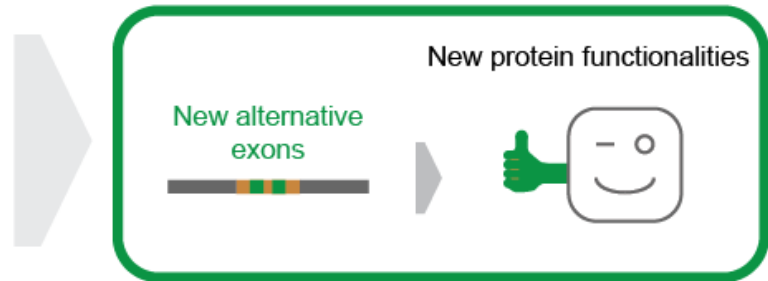
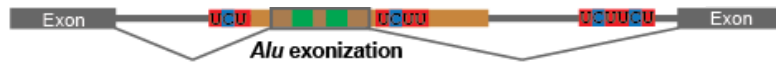
Kathi Zarnack
Frankfurt U.



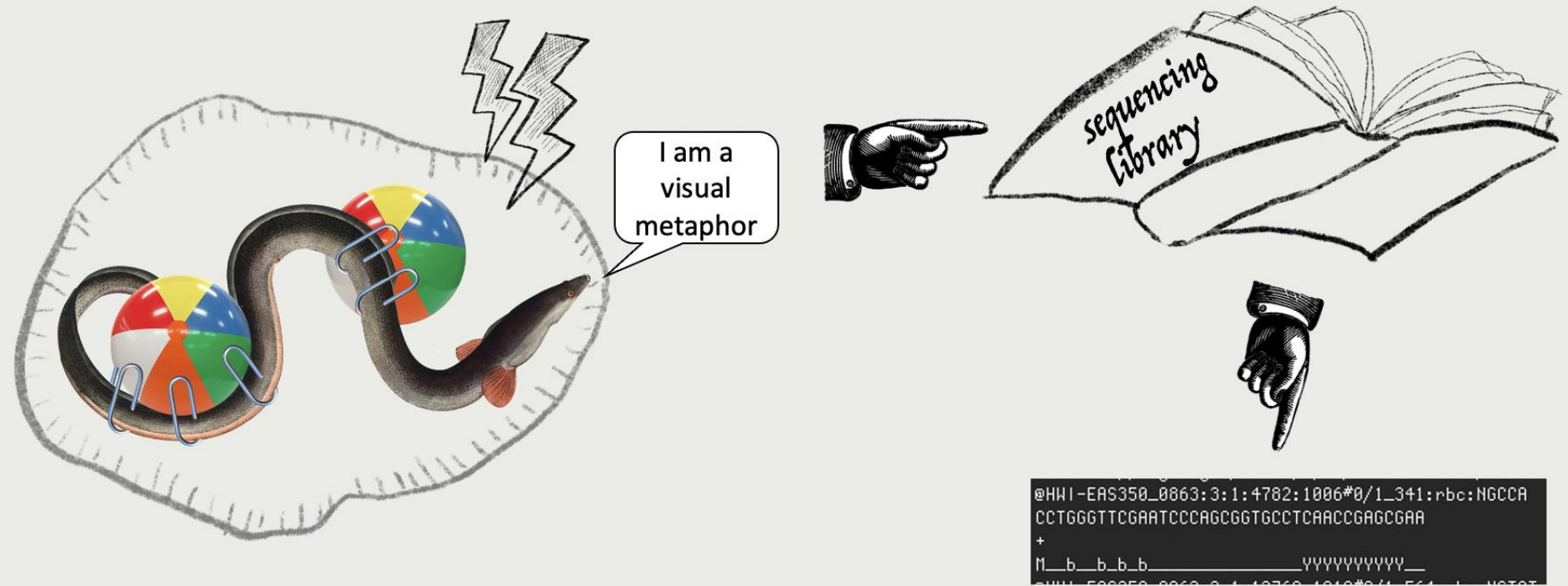
Julian König,
IMB Mainz



Nick Luscombe
Crick Institute



We use crosslinking and immunoprecipitation (CLIP) to identify protein-RNA interactions

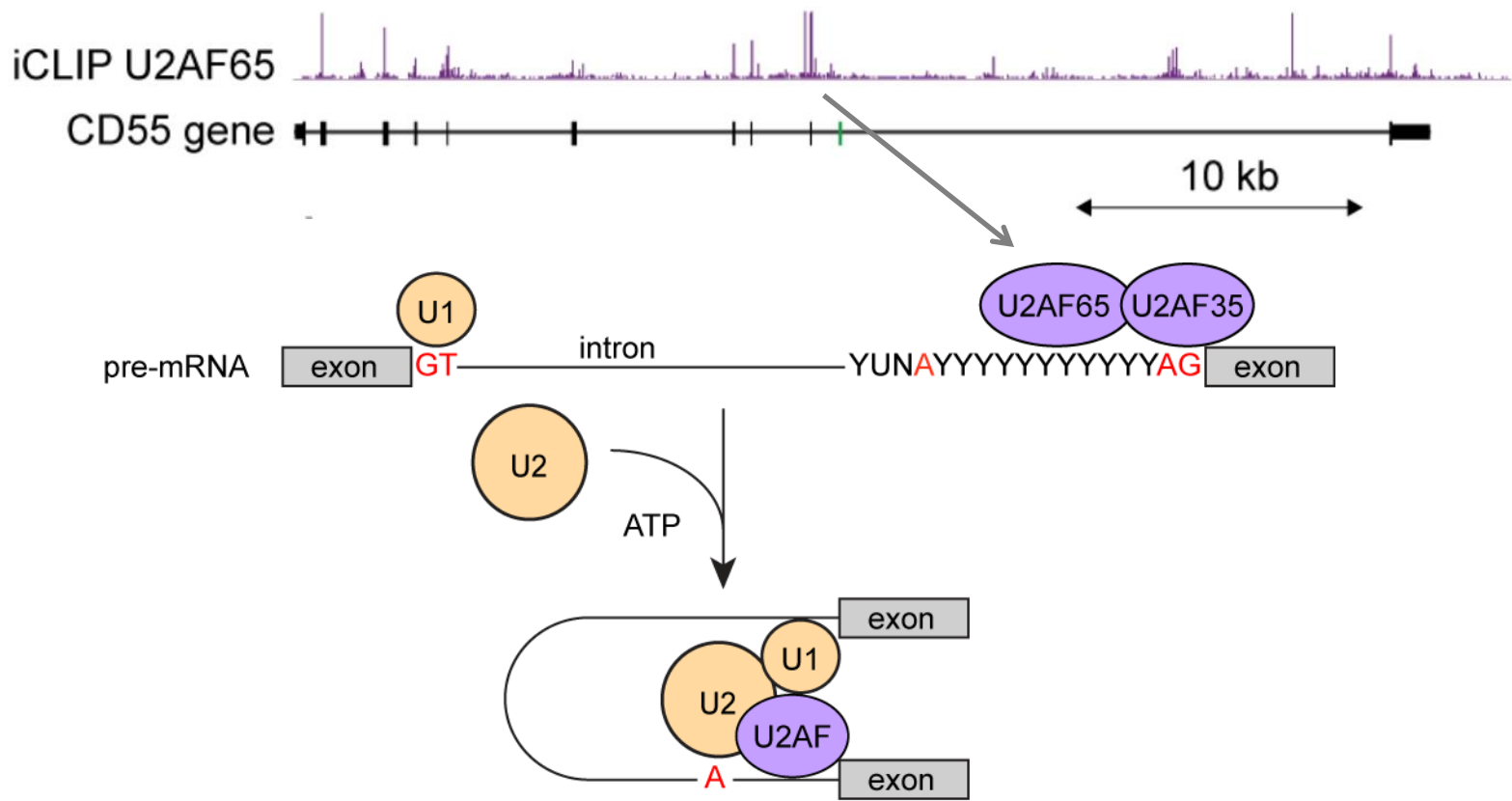


Lee et al, 'An improved iCLIP protocol', bioRxiv 2021

Also reports a protocol for input iCLIP control: Input-SP3



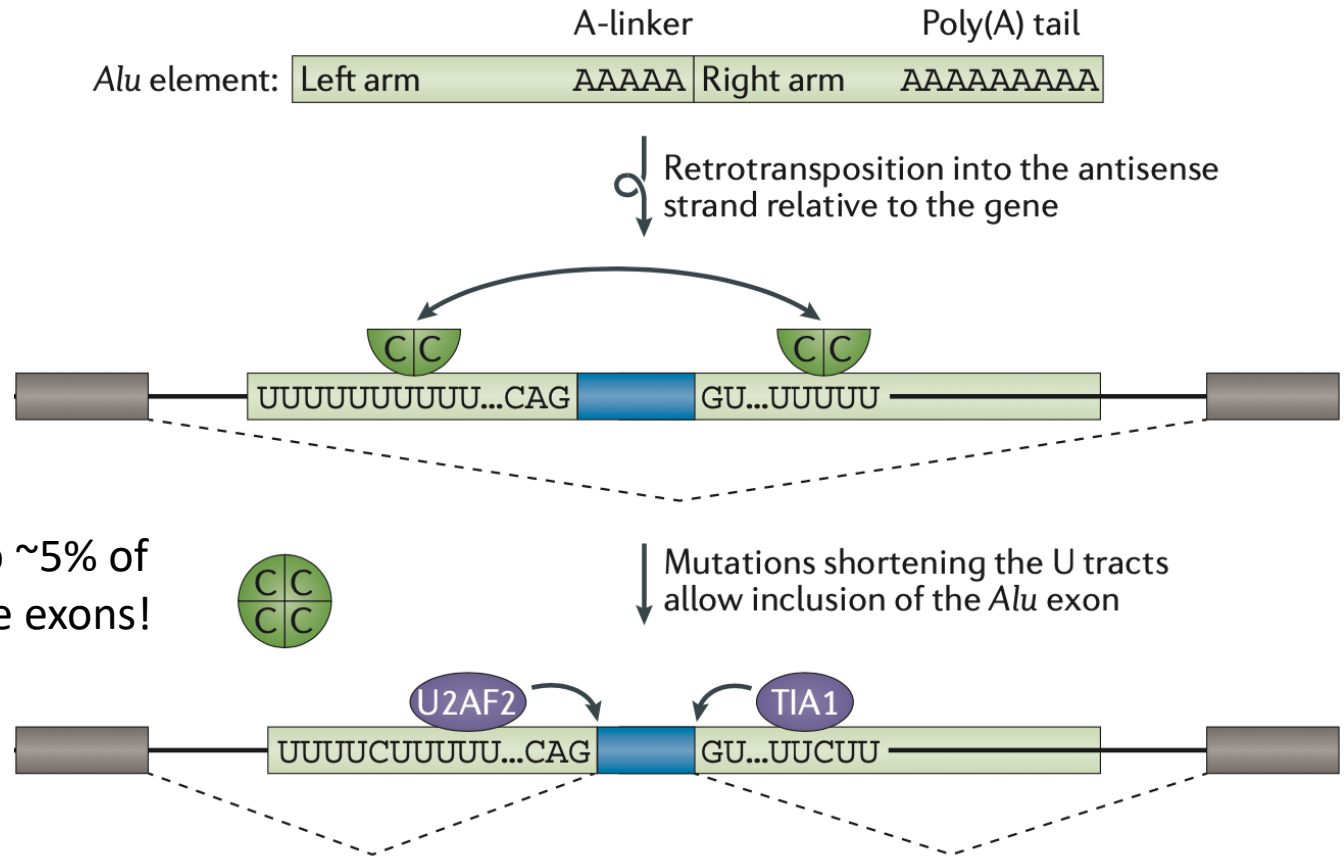
hnRNP C displaces U2AF65 from introns



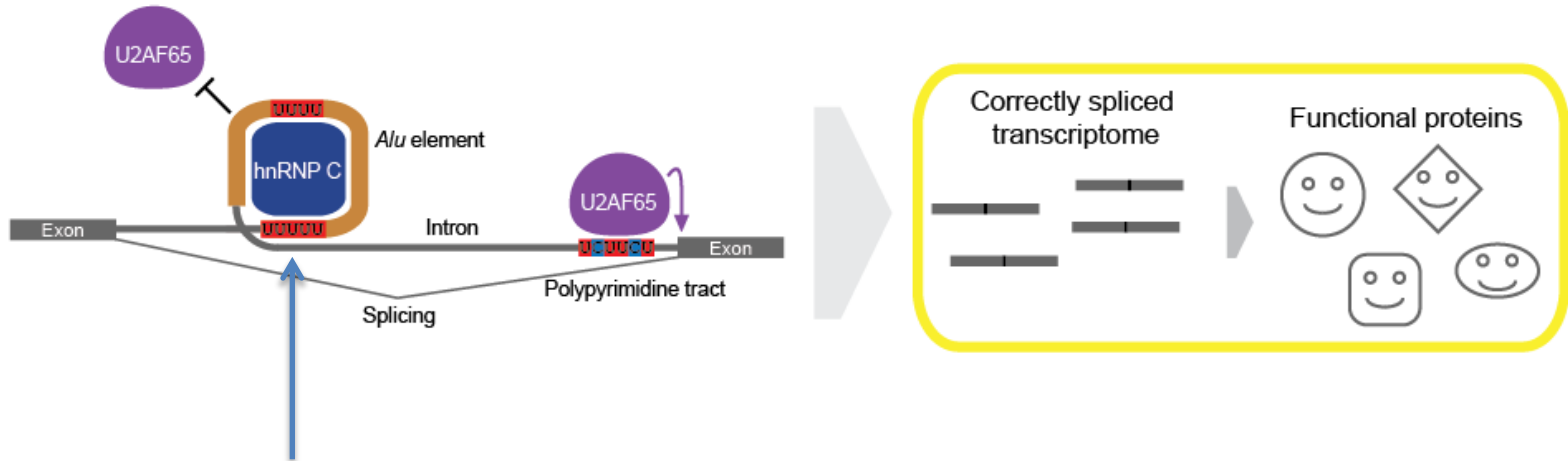
Alu elements are a source of new exons in primate

Alus resemble exons when in antisense orientation in introns

- cryptic 5' and 3' splice sites
- poly-U tracts

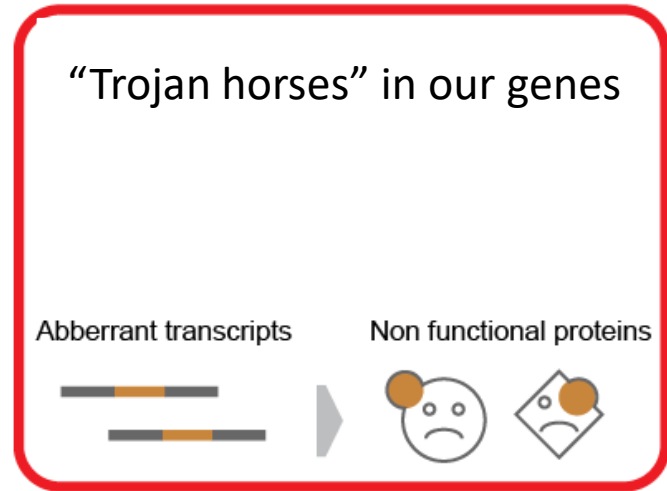
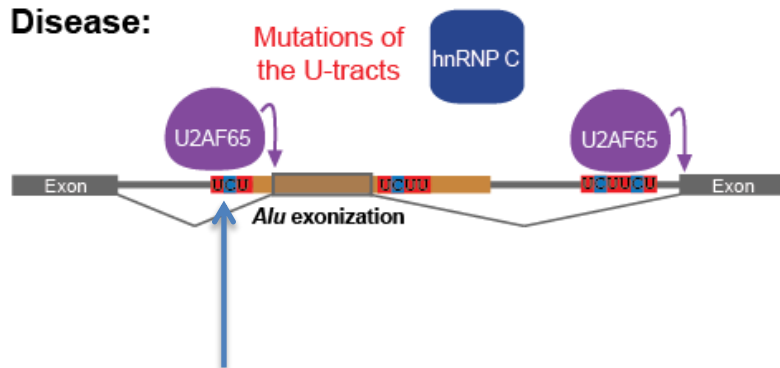
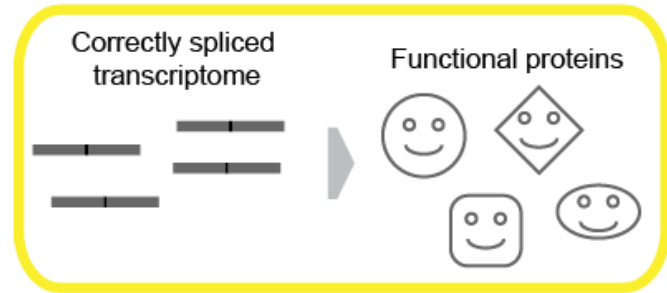
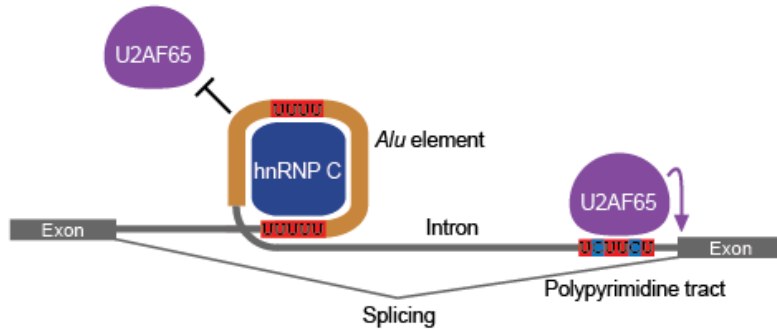


We discovered a protein that masks the Alu-exons



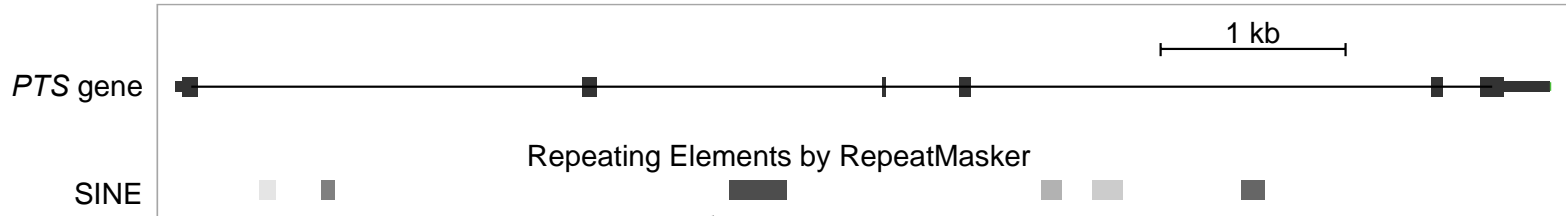
The 'mask' is attached to the U-tracts (such as UUUUUUUU) inside Alus

Mutations can shorten U-tracts to unmask the Alu-exons

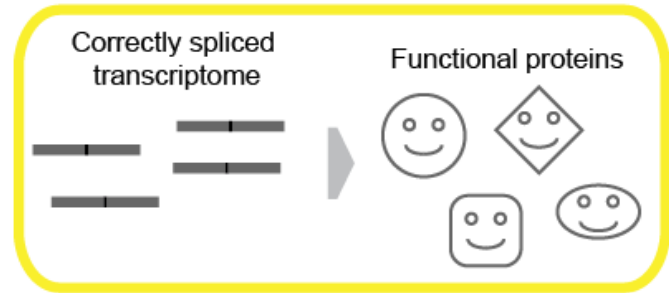
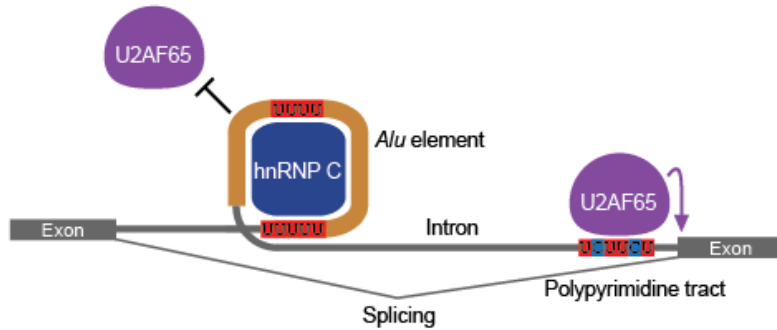


Mutations in U-tract unmask the Alu-exon, and thereby change the mRNA recipe

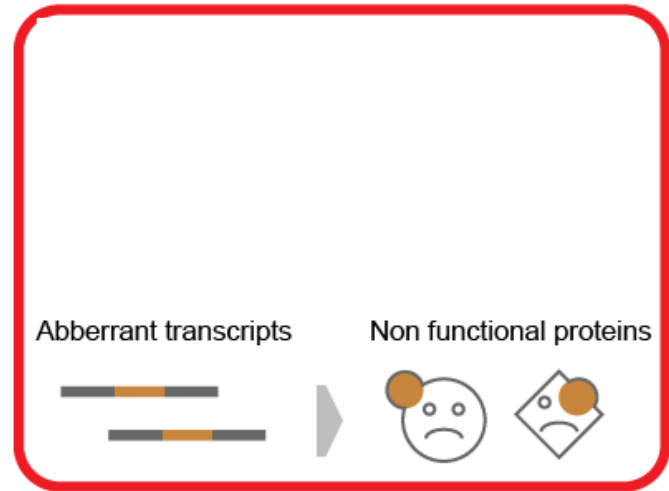
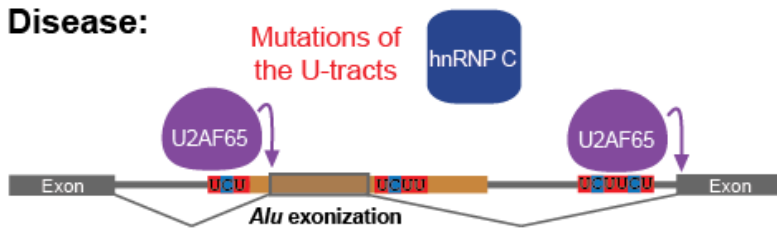
A mutation in the hnRNP C binding site leads to neurologic disease



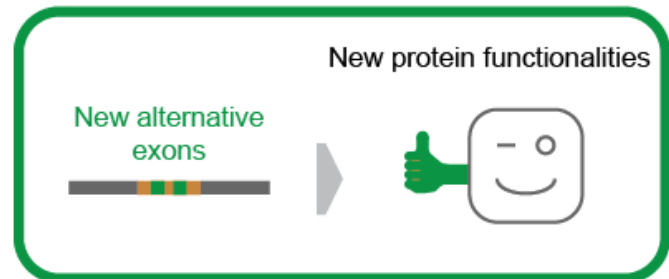
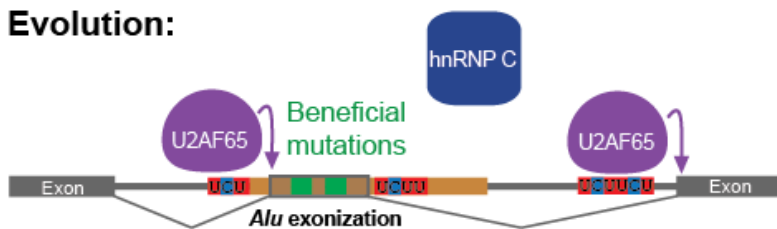
With additional mutations, beneficial Alu-exons can evolve



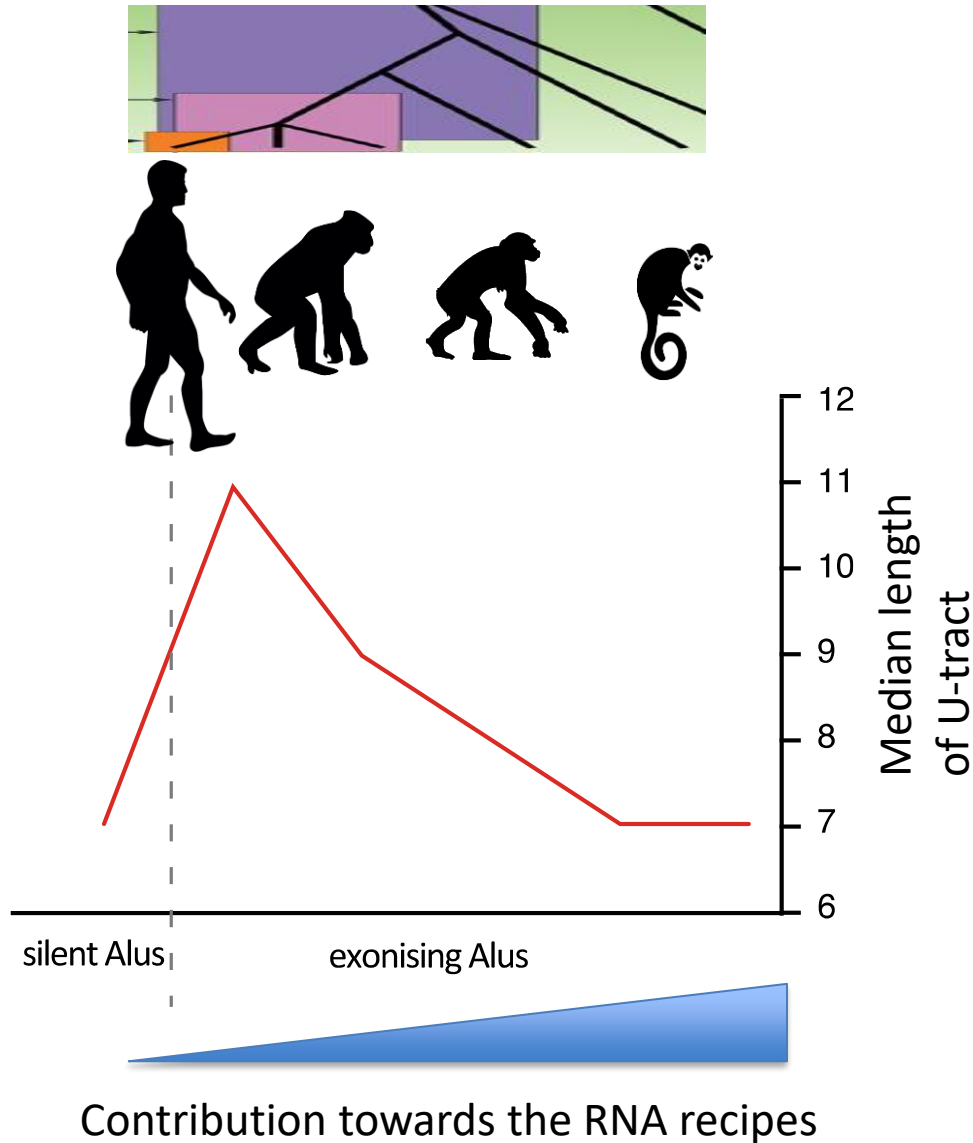
Disease:



Evolution:



Alu U-tracts are like a tunable dimmer controls for graduate evolution.



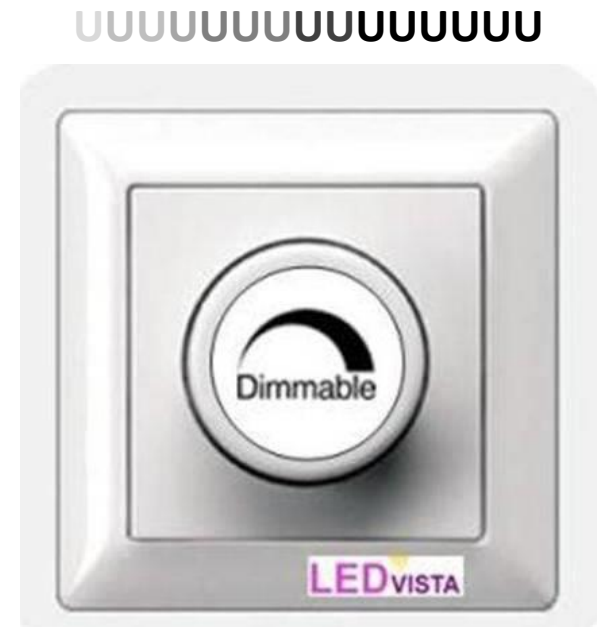
Jan Attig



Nejc Haberman



Aarti Singh





Klara Kuret

<https://github.com/uclalab/peka>

“Positional motif analysis reveals the extent of specificity of protein-RNA interactions observed by CLIP” Kuret et al., Genome biology, 2022

QuickTime Player File Edit View Window Help

iMaps - PEKA

imaps.goodwright.com/apps/peka/

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each belongs to.

Positionally-enriched k-mer analysis (PEKA) is a software package for identifying enriched protein-RNA binding motifs from CLIP datasets. PEKA compares k-mer enrichment in proximity of high-confidence crosslink sites (tXn - thresholded crosslinks), located within crosslinking peaks and having a high cDNA count, relative to low-count crosslink sites located outside of peaks (oXn - outside crosslinks). This approach reduces the effects of technical biases, such as uridine-preference of UV crosslinking. Each k-mer is assigned a PEKA score, which is used to rank the k-mers from the most to the least enriched. Additionally, PEKA provides comprehensive visualisations of motif enrichment profiles around the high-confidence crosslink sites and clusters the motifs that display similar profiles. PEKA also enables motif discovery within specific transcriptomic regions, including or excluding repetitive elements. PEKA code is available from [Ulelab github](#).

[Download Data](#)

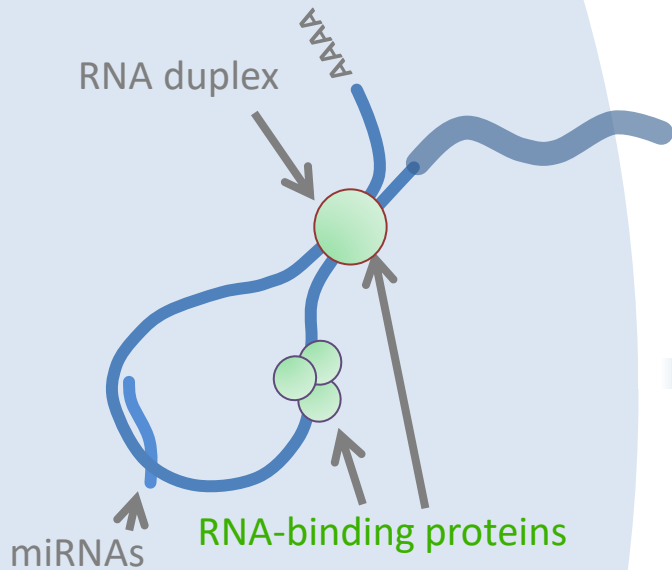
Heatmap

Heatmap visualises the relative occurrence of 40 5-mers with the highest PEKA score around the high-confidence crosslink sites (tXn). 5-mers are clustered based on sequence similarity, the clusters are separated by white lines and arranged from top to bottom by descending maximal value of PEKA score within the cluster. Grayscale heatmap on the right shows the PEKA score of each k-mer.

Supplementary data is shown in heatmaps below:

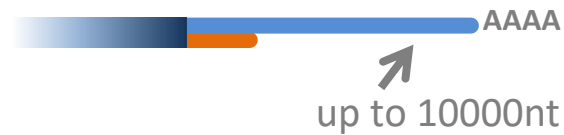
- **Similarity** score reports how much the top motif ranks of a specific dataset match those of all other datasets.
- **Recall** measures the overlap of top motifs in each eCLIP dataset to its orthogonal in vitro dataset (RNA Bind-N-Seq or RNAcompete).
- **log2FC eRIC** shows the log2-fold change in crosslinked over non-crosslinked samples of the proteins identified by enhanced RNA Interactome Capture (eRIC) in proliferating Jurkat cells ([Perez-Perri et al. 2018](#)).
- **tXn per region (%)** shows the percentage of high-confidence crosslink sites (tXn) for each RBP within introns, 3' UTRs and other exonic regions of protein-coding genes (coding+5'UTRs).
- **% noncoding peaks** shows the proportion of IDR (irreproducible discovery rate) peaks (as available for eCLIP datasets from ([Van Nostrand et al. 2020](#))) in non-coding regions of the transcriptome (noncoding_exon, noncoding_5ss, noncoding_3ss, noncoding_proxintron, noncoding_distintron).
- **total number of peaks** shows the total number of IDR peaks available for each dataset.

Protein-RNA complexes

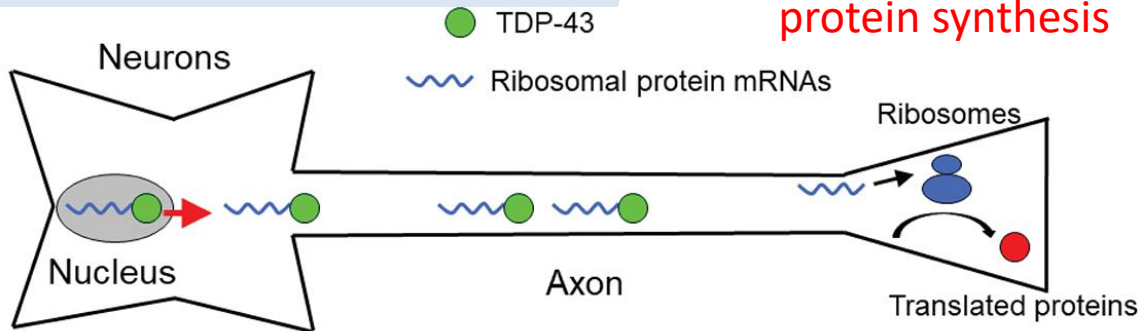


Neuronal regulatory functions

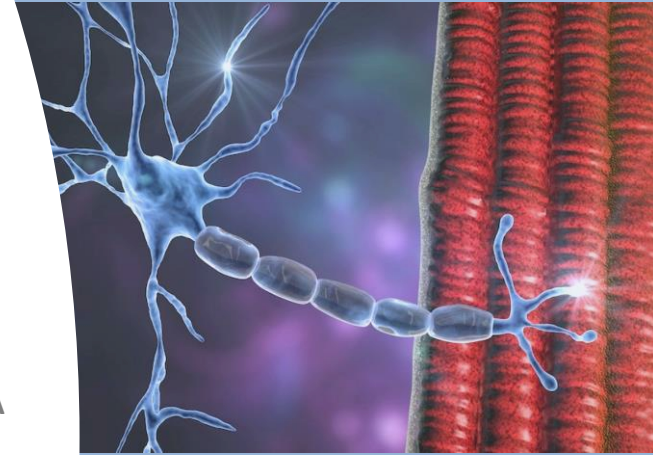
Long 3'UTRs of neuronal mRNAs



mRNAs are transported to allow **localised protein synthesis**



Amyotrophic lateral sclerosis (ALS)

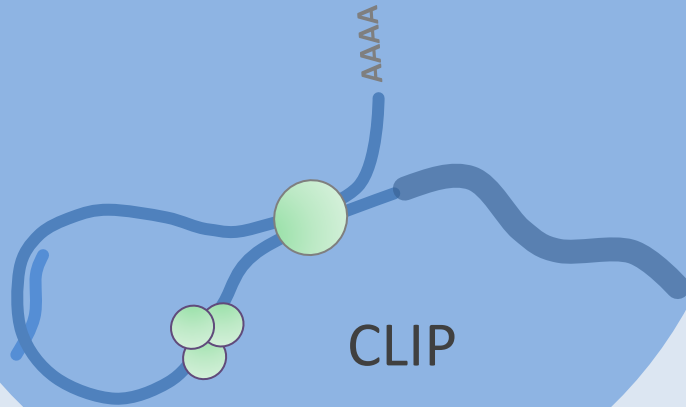


No cure available
Lifetime risk $\pm 1/400$ in UK

Mutations in >10 genes encoding **RNA-binding proteins** can cause ALS

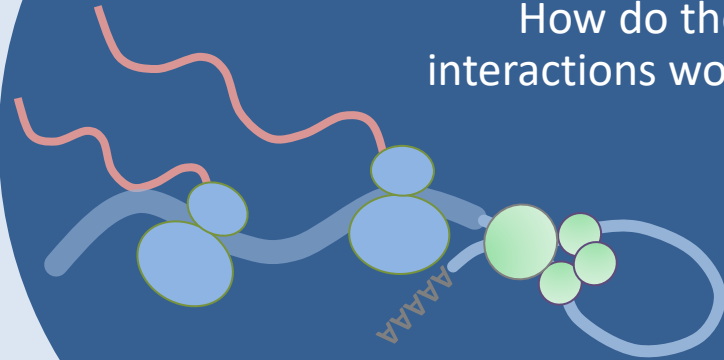
Measure interactions

Which interactions drive the assembly of protein-RNA complexes?



Integrate layers of data

How do these interactions work?

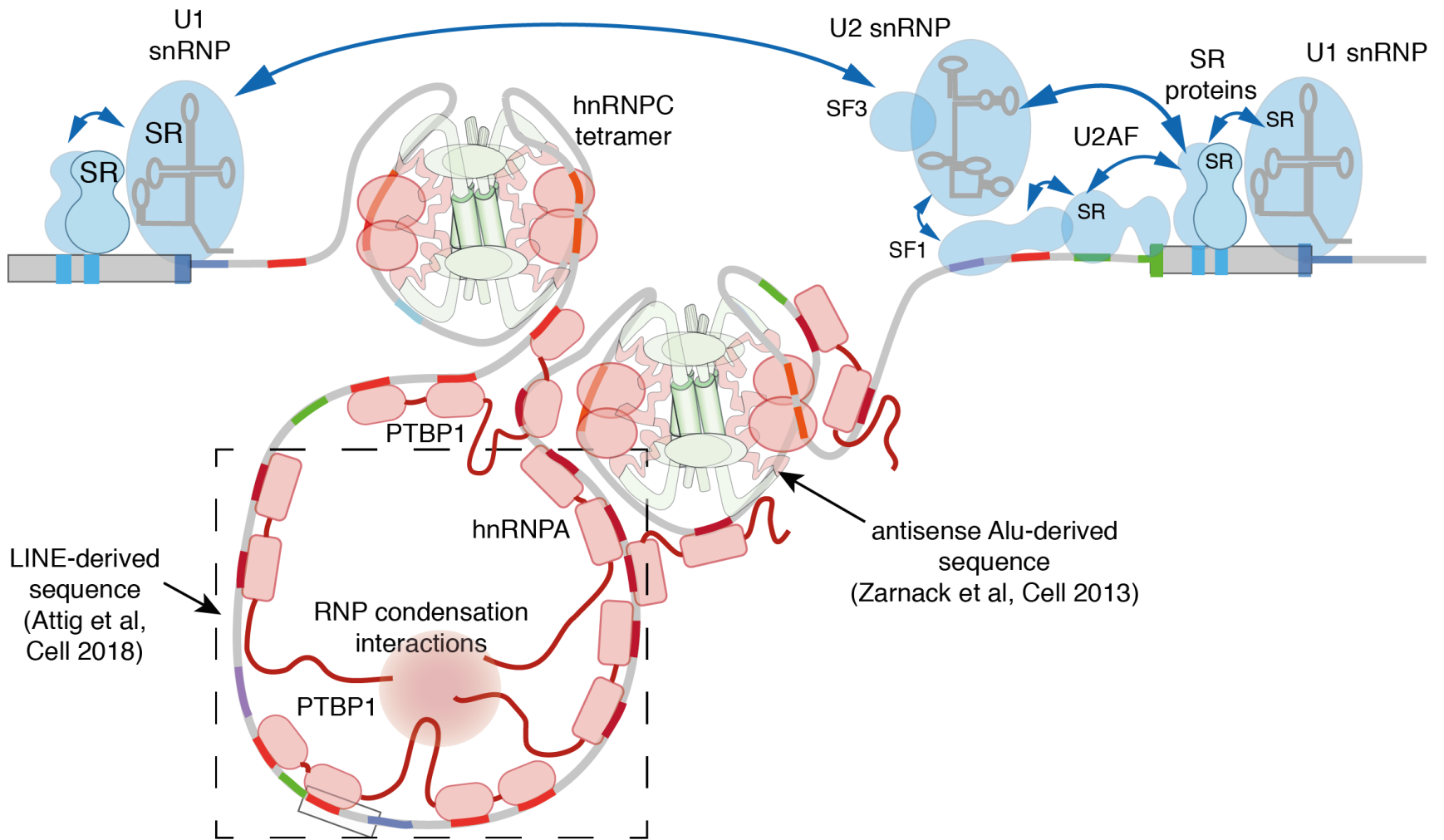


<https://flow.bio/>

Interpret mutations

How do mutations disrupt protein-RNA complex assembly?





Attig et al, Cell, 2018

Ule & Blencowe, Mol Cell, 2019

Ljubljana Lab



Klara Kuret



Tajda Klobučar



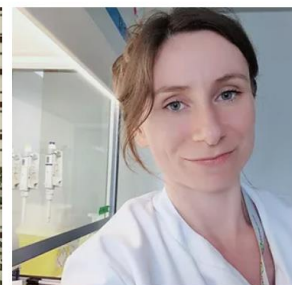
Urška Janjoš



Anja Trupej



Žiga Vičič



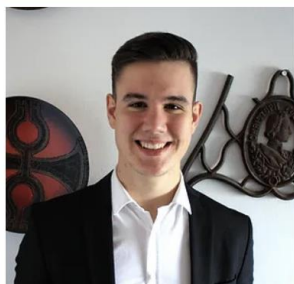
Aniela Skrzypczyk



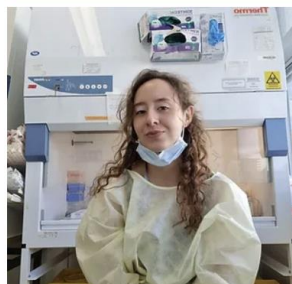
Maksimiljan Adamek



Jure Rebselj



Jona Novljan



Taja Valovec

Klara Kuret, visiting student since November 2019 and started PhD in 2020, works on computational studies of nuclear RNP condensates.

Tajda Klobučar, PhD student since 2020, studies protein-RNA and RNA-RNA interactions that assemble nuclear RNP condensates, mentored by Miha Modic.

Urška Janjoš, Research assistant since December 2020 and PhD student since 2021, studies the functions of nuclear RNPs that form on retained introns.

Anja Trupej, visiting student since 2020, and then starting PhD in October 2022, works on proximity-based studies of RNP condensates.

Žiga Vičič, Research assistant since October 2021, works on iCLIP, ribosome profiling and molecular biology.

Aniela Skrzypczyk, postdoc since April 2022, studies mechanisms of RNA condensates in neuronal differentiation.

Maksimiljan Adamek, PhD student since 2022, works on biochemistry and structural studies of protein-RNA complexes.

Jure Rebselj, visiting student since Sept 2022, focusing on computational biology.

Jona Novljan, visiting student since Dec 2022, focusing on high-throughput studies of RNP assembly and function on specific RNAs.

Taja Valovec, visiting student Jan-Apr 2023, working with Urška on retained introns.

Thank you!



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European Research Council
Established by the European Commission

This project has received funding from the European Research Council (ERC) under the European Union's Seventh Framework Programme (617837-Translate) and Horizon 2020 research and innovation programme (835300-RNPdynamics)



Donirajte del dohodnine ASEFu

- **1% dohodnine** za financiranje upravičencev do donacij.
- Donacija dela dohodnine vas **ne stane nič**.
- Zadnji rok je **31. december 2023**.

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1. **Elektronsko** prek portala eDavki.
 - Vloga "Zahteva za namenitev dela dohodnine za donacije (Doh-Don)".
 - V vlogi vpišite naziv organizacije (Inštitut ASEF),
 - davčno številko (84740175) in
 - višino odstotka, ki ga namenjate (0,1 %, 0,2 %, ... 1%).
2. Osebno ali po pošti pri pristojnem finančnem uradu z izpolnjevanjem **fizične kopije dokumenta**. Dokument lahko dobite danes pri nas.



Z vašo donacijo bo ASEF lahko še dalje omogočal nove priložnosti za mlade talente in povezoval Slovenijo s svetom.