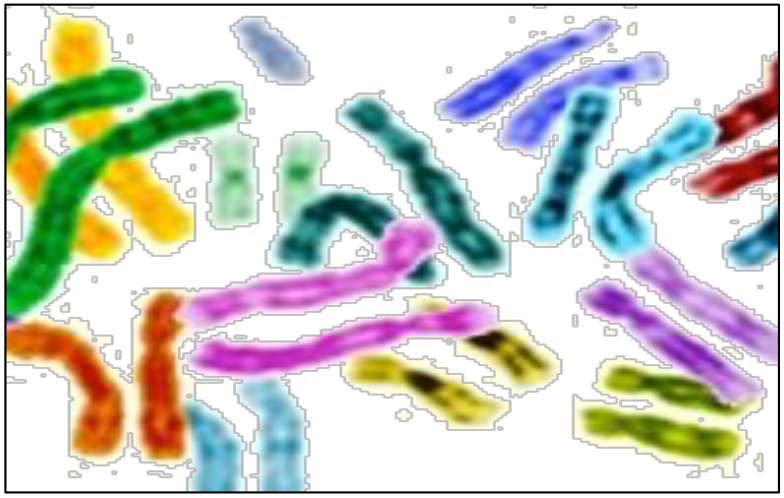
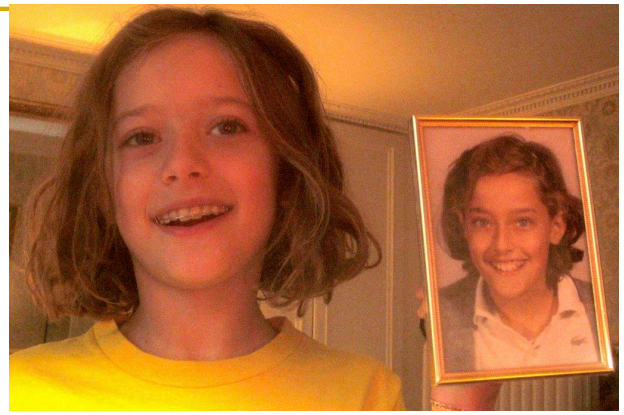
Révolutions et évolutions en Génétique au 21ème siècle

Alexandra Henrion-Caude – Institut Imagine, Inserm, Paris, France

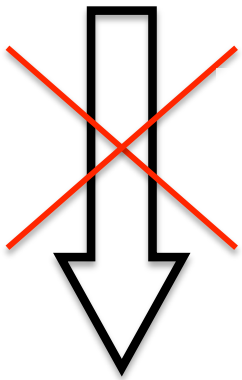


What is life?

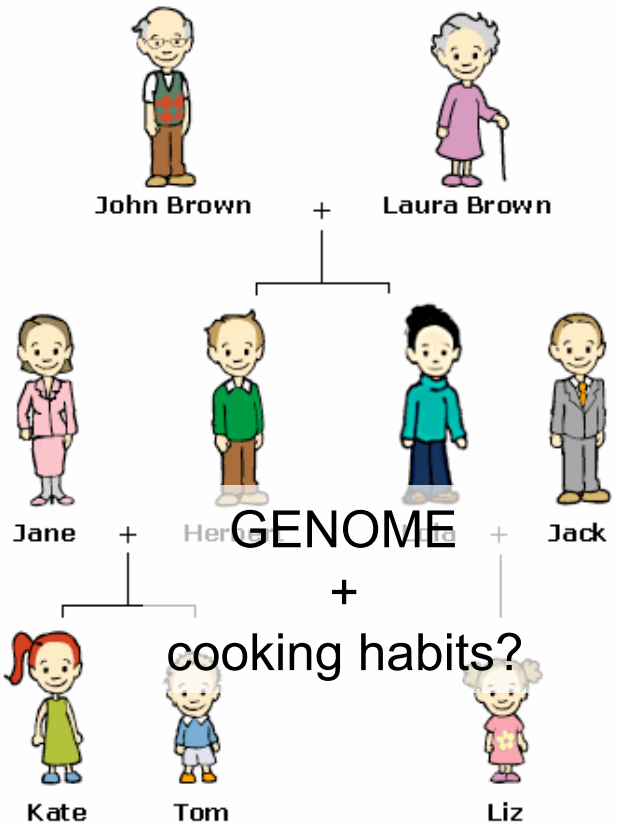


SAME ATOMS

SAME PHYSICOCHEMICAL PRINCIPLES



HEREDITY&
FUNCTIONS



Qui sommes-nous ?

- Des **atomes**, comme les cailloux…
- Une **conscience…** d'avoir eu un(e) grand-p(m)ère
- Un **génome** qui n'a de cesse d'évoluer (gènes sauteurs, mutations/remaniements de novo, information épigénétique)
- Une histoire **imprégnée dans nos molécules** (*in utero*, partenaire, saut de génération, microchimérisme…): **DOHaD**

  Developmental Origin of Health and Disease

Genetics: a Young Science in Evolution

Heredity is transmitted in discrete units (Gregor Mendel, 1865)

A physical unit - Living elementary particle (Weisman-de Vries,1880)

A measurement unit - Unit for calculation (Johannsen,1905)

A physical location - A locus on a chromosome (Morgan,1915/Mc Clintock)

The gene : considered as « nominal »

A segment of DNA:

① 1st breakthrough: Schrödinger (program) / Avery (heredity). 

=> A genetic information (1944).

① 2nd breakthrough: Description of DNA structure (Watson&Crick,1953).  

=> A functional segment of DNA?

bearing some discontinuity in the coding part: the introns (Sharp & Robert 1977).  

The gene : Open Reading Frame to keep up with the prediction era

Societal Perception on Genetics

- **the most intimate of our molecules**
- **a source of fear**

  ...as well as hope
- **a response to an old quest of humanity for eternity**
- **a sense of power...**

23andMe Adaptation Admixture Agriculture Anthropology Archaeogenetics Behavior Genetics Blog Creationism Culture Daily

phylogenetics Politics Population Genetics Psychology Race Religion Science Select Post Technology

- Greek closest equivalent for "inherited diseases" was *"family diseases"*.
- Greek etymology of *"genetics"* : "genesis", birth, or "genos", origin.
- Latin etymology of *"heredity"* : "hereditas, i.e what you receive after your parents' death.


SPECIAL SECTION
TIME
The New Genetics: Man Into Superman
1971
INSIDE
A Day With Jimmy Carter
+10
Shaping Life in the Lab
The Boom In Genetic
Prince Charles Picks a Bride
+20
LOTT'S IMPEACHMENT PLAN
SPECIAL ISSUE
THE FUTURE OF
EDICINE
How genetic engineering will
1990
Infidelity
It may be in our genes
1994
SPECIAL REPORT
Genetics
THE FUTURE IS NOW
New breakthroughs can cure diseases and save lives,
1994
SOLVING TH
MYSTERIES
OF HEREDIT
1999
: EVEN BADDER THAN YOU THOUGHT
2003
IRAQ'S POWER BROKER
PIXAR'S INCREDIBLE NEW MOVIE
Does our DNA compel us to seek a higher power? Believe it or not, some scientists say yes
PLUS: A quiz—How spiritual are you?
THE GOD GENE
2004
TIME
HAPPY COUPLE
Listing your suitable marital partners
016
INSIDE THIS ISSUE: A 43-PAGE SPECIAL SECTION
THE BEST INVENTIONS OF 2006
GOD VS. SCIENCE
A spirited debate between atheist biologist Richard Dawkins and Christian geneticist Francis Collins
2006
SOLVING THE MYSTERIES OF
DNA
The 50th Anniversary: Reliving Watson and Crick's historic discovery
How gene science has changed our lives
2009
uncovered about
HOW MEMORY WORKS and how to improve it
THE I.Q. GENE?
2009
Yemen: The New Center Of Terror
Why the Recession Hasn't Been Cool To Teens
WHY YOUR DNA ISN'T YOUR DESTINY
The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids
BY JOHN CLOUD
2010
Egypt Divided / Pot's Big Moment / Best of 2012
Want to Know My Future?
Alzheimer's
Dementia
Asthma
Diabetes
Cancer
Hemochromatosis
Cystic fibrosis
Colon cancer
Breast cancer
Tay-Sachs disease
Huntington's disease
Epilepsy
Burkitt's lymphoma
Parkinson's
Malignant melanoma
Glaucoma
Prostate cancer
Obesity
New genetic tests can p
but not always
BY BONNIE ROCHM
2012

Une connaissance parallèlement à des progrès techniques/technologiques

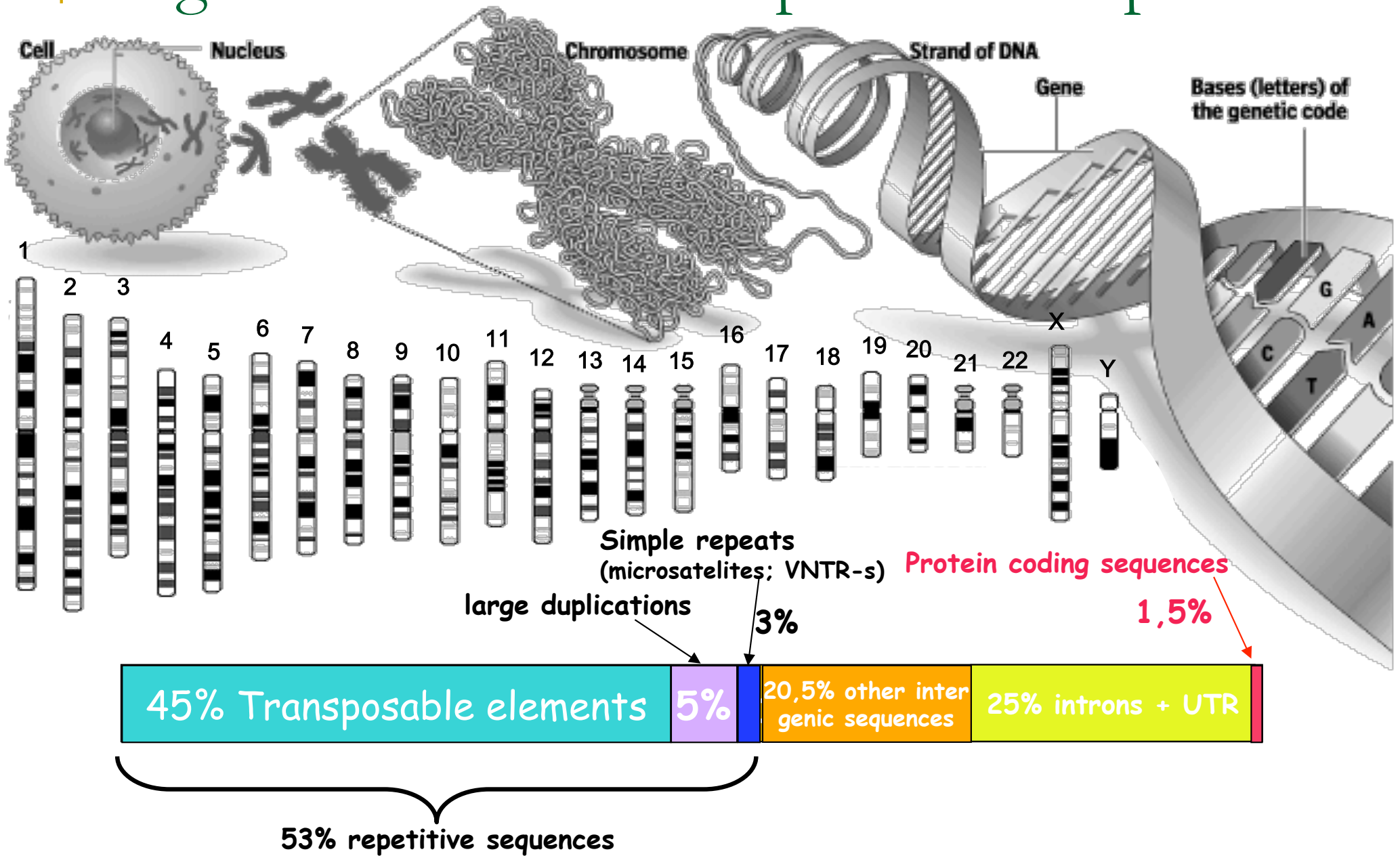
- Séquençage du tout génome
- Tests génétiques
- Manipulations génétiques

Le livre vivant des génome(s)

- **60** genomes séquencés.
- Le vôtre ~3Mb (3 300 000 000 pb) pou

- Avec une immense **variation interindividuelle** : toutes les 1000 bases versus le génome de référence.
- Effort considérable pour assigner une **fonction**.

Le génome nucléaire humain: une pochette-surprise



Adapted from Hein, The Washington Post, 2004
& from Gregory, T.R. *Nature Reviews Genetics* 2005

L'essor des tests génétiques d'ADN nucléaire

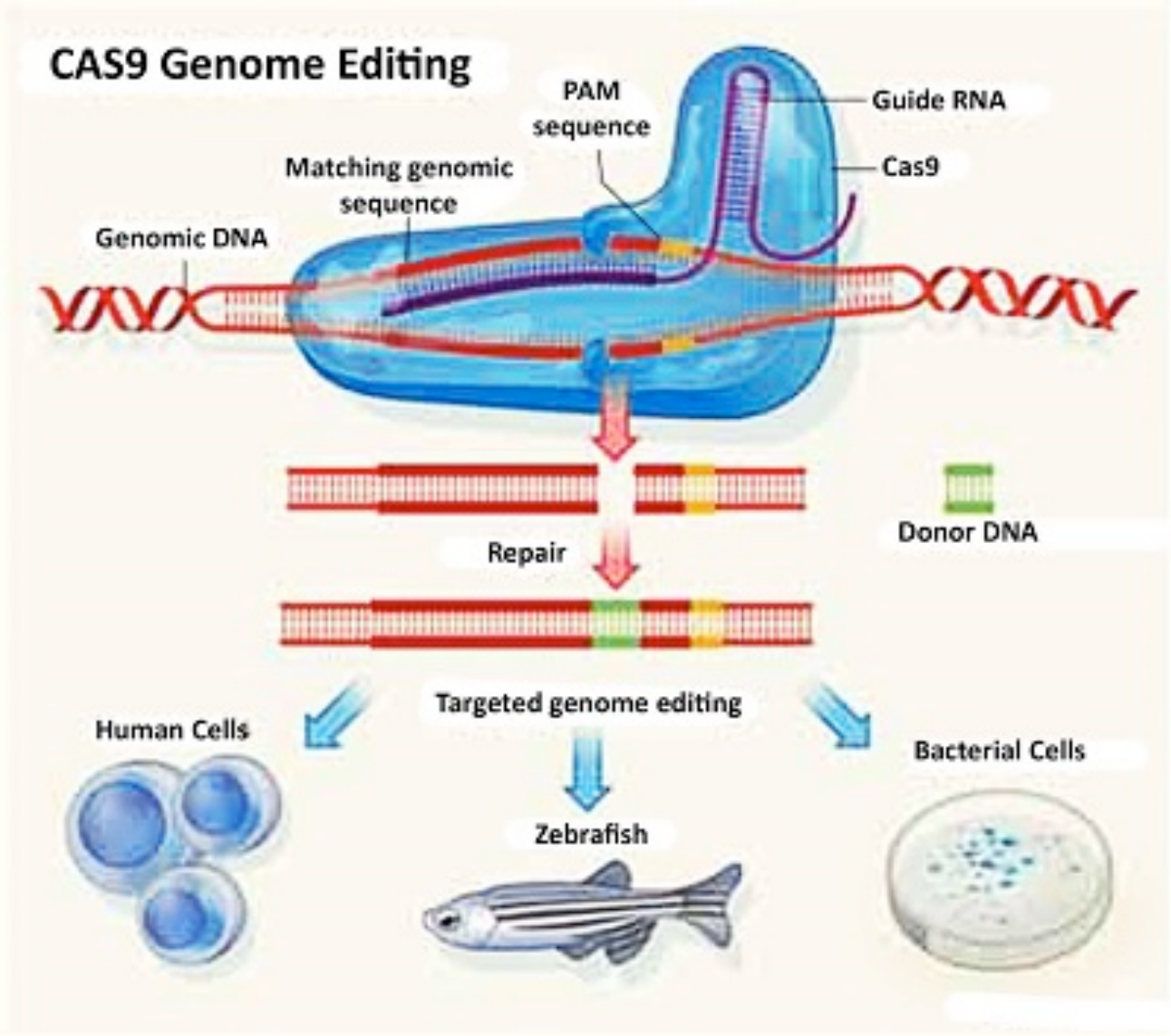
Tests génétiques en vente libre aux Etats-Unis, au Canada et dans certains pays européens

Psychomédia | Publié le 26 octobre 2015

Deux ans après avoir été forcée par la *Food and Drug Administration* (FDA), l'agence américaine des médicaments, à cesser la commercialisation de kits d'analyse d'ADN déterminant des risques de maladies, la société *23andMe* vient d'obtenir l'autorisation de vendre de nouveaux tests génétiques au public.

Pour l'instant, indique le site internet de *23andme*, les nouveaux kits offrent de l'information sur plus de conditions héréditaires qui pourraient être [illegible]ance, 10 façons dont l'ADN [illegible]ux médicaments, [illegible] au lactose.

Manipulations génétiques: fines et facilitées



Progrès techniques/technologiques

- 1970's: la taille de l'ADN est trop important pour que l'on puisse un jour modifier le génome humain (Jacques Monod)…
- 1975: premières manipulations génétiques (Asilomar) => Re: 2015.
- 1990: séquençage du génome humain impossible (*dixit un consensus de généticiens…*)
- 2003: le génome humain est séquencé
- Prix du séquençage passe de 3 milliards à 1000 $
- 2014: *Illumina* classée l'entreprise « la plus intelligente » par le MIT
- Investissements concentrés sur la santé numérique: Big Data et la science analytique.

Qui en sourit?

Sept, 2013

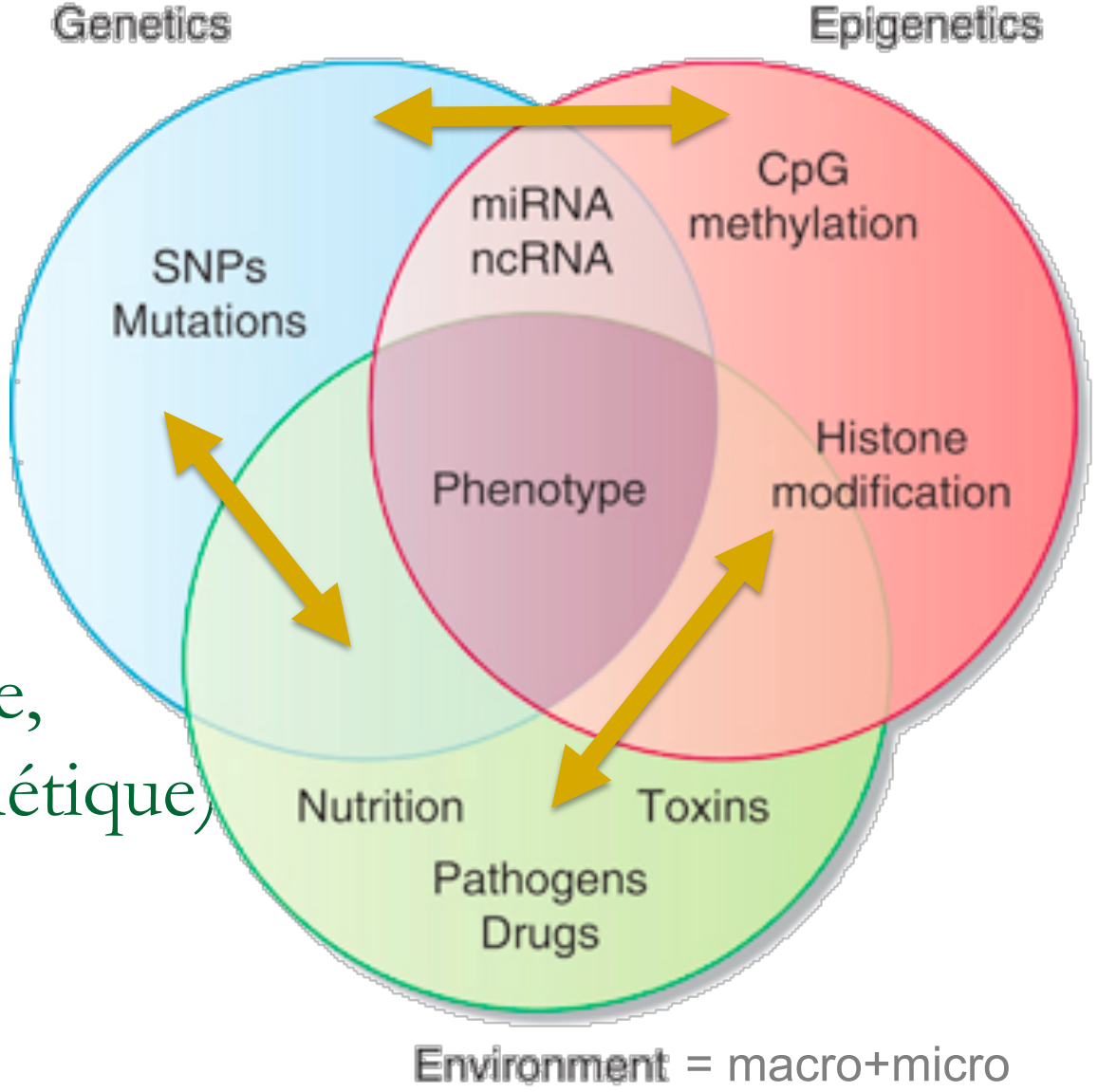
Du réel au virtuel

Danger du fossé d'une technique qui dépasse la connaissance

- La connaissance que nous acquérons de *ce que nous sommes* augmente nos responsabilités.
- Nécessité d'exercer ces responsabilités *intelligemment*.
- De nouvelles responsabilités génératrices d'angoisse comme si nous comprenions le souci de l'application de ces techniques sans en connaître les conséquences sur… *l'Humanité*.

Et pourtant, selon notre connaissance

Phénotype=*f*(Génétique, Environnement,Epigénétique)



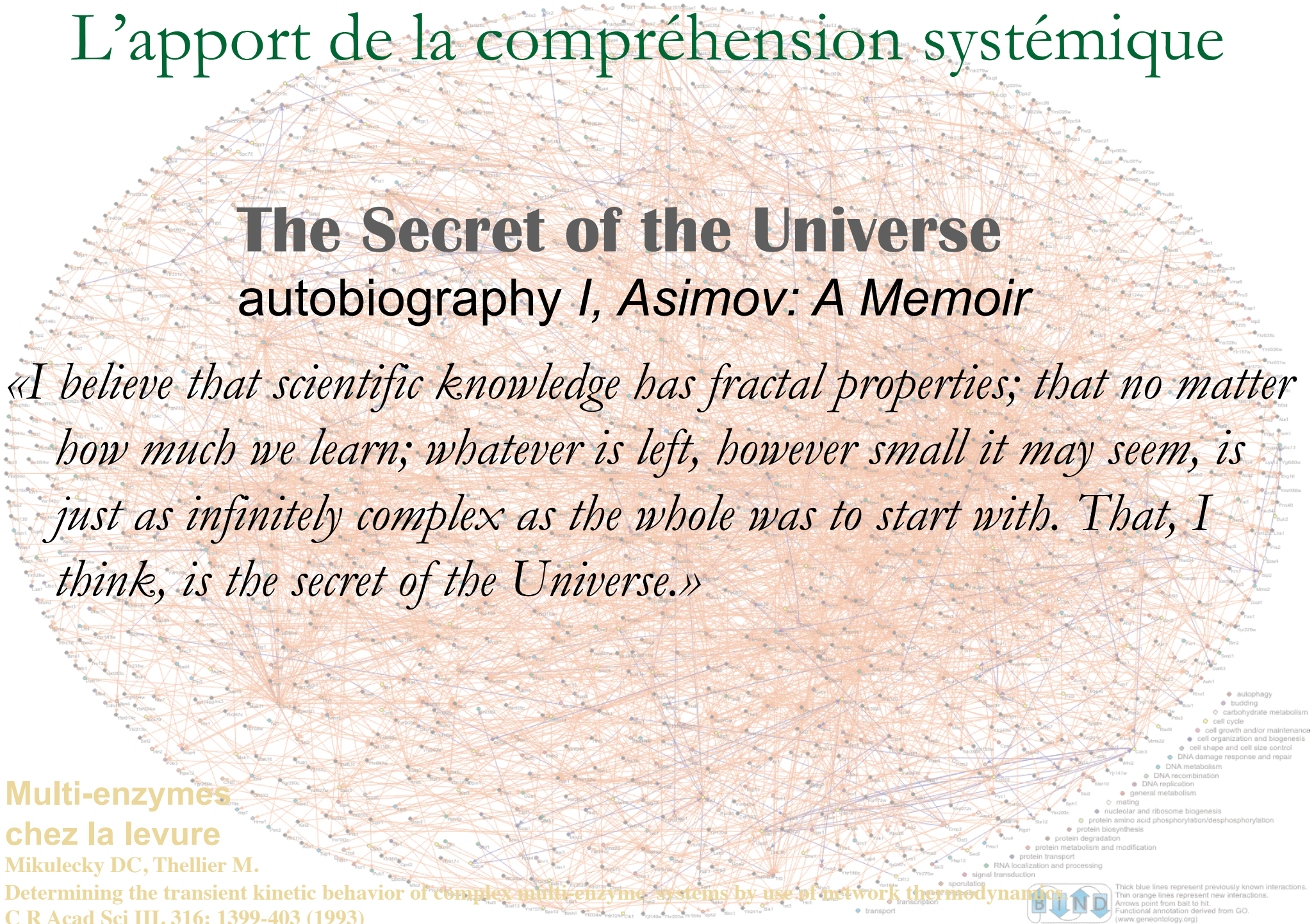
From Dwivedi et al, Kidney International 2011

L'apport de la compréhension systémique

The Secret of the Universe

autobiography *I, Asimov: A Memoir*

«I believe that scientific knowledge has fractal properties; that no matter how much we learn; whatever is left, however small it may seem, is just as infinitely complex as the whole was to start with. That, I think, is the secret of the Universe.»



Multi-enzymes chez la levure

Mikulecky DC, Thellier M.

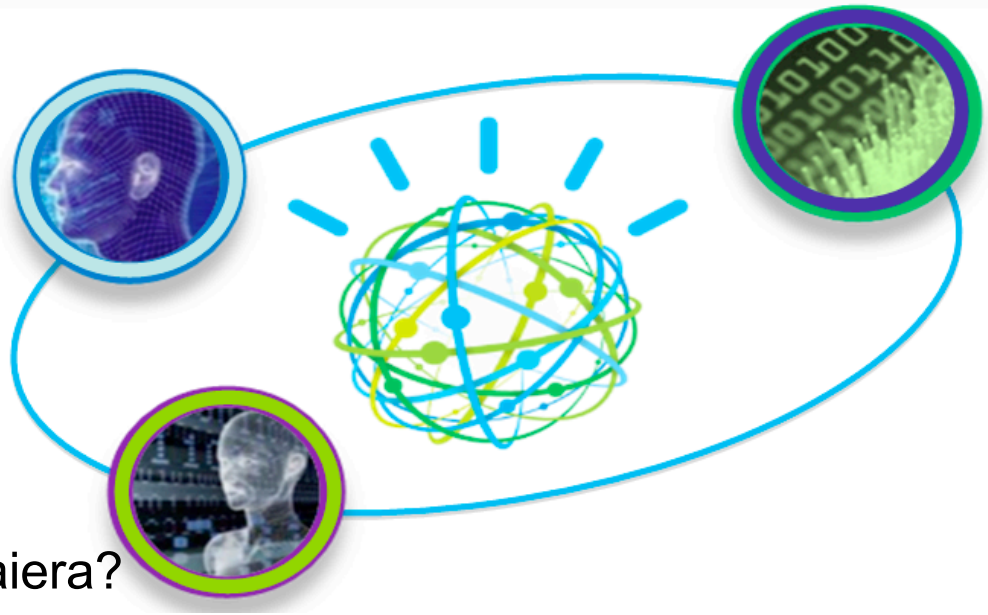
Determining the transient kinetic behavior of complex multi-enzyme systems by use of network thermodynamics.

C R Acad Sci III. 316: 1399-403 (1993)

Quel bénéfice patient par rapport aux promesses de Watson?

Qui est propriétaire des données sur sa santé? Chacun?! Non!
L'Islande a vendu les données génétiques de sa population.

IBM WATSON

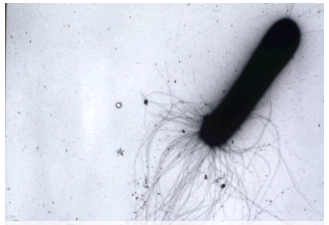


Qui re-traitera périodiquement l'information?

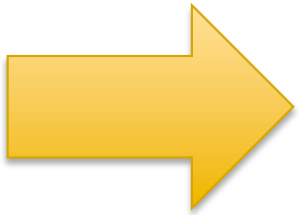
Qui informera la patient? Quand?

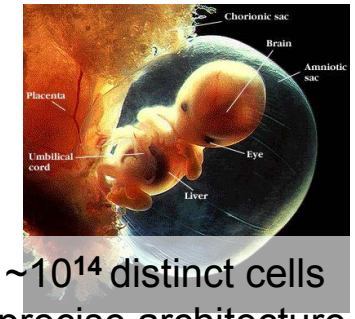
Quelle capacité de stockage? Qui paiera?
Quel coût sur l'environnement?

~~Taille du génome~~
~~Nombre de chromosomes~~
~~Nombre de gènes~~



Unicellular > colony
Limited differentiation



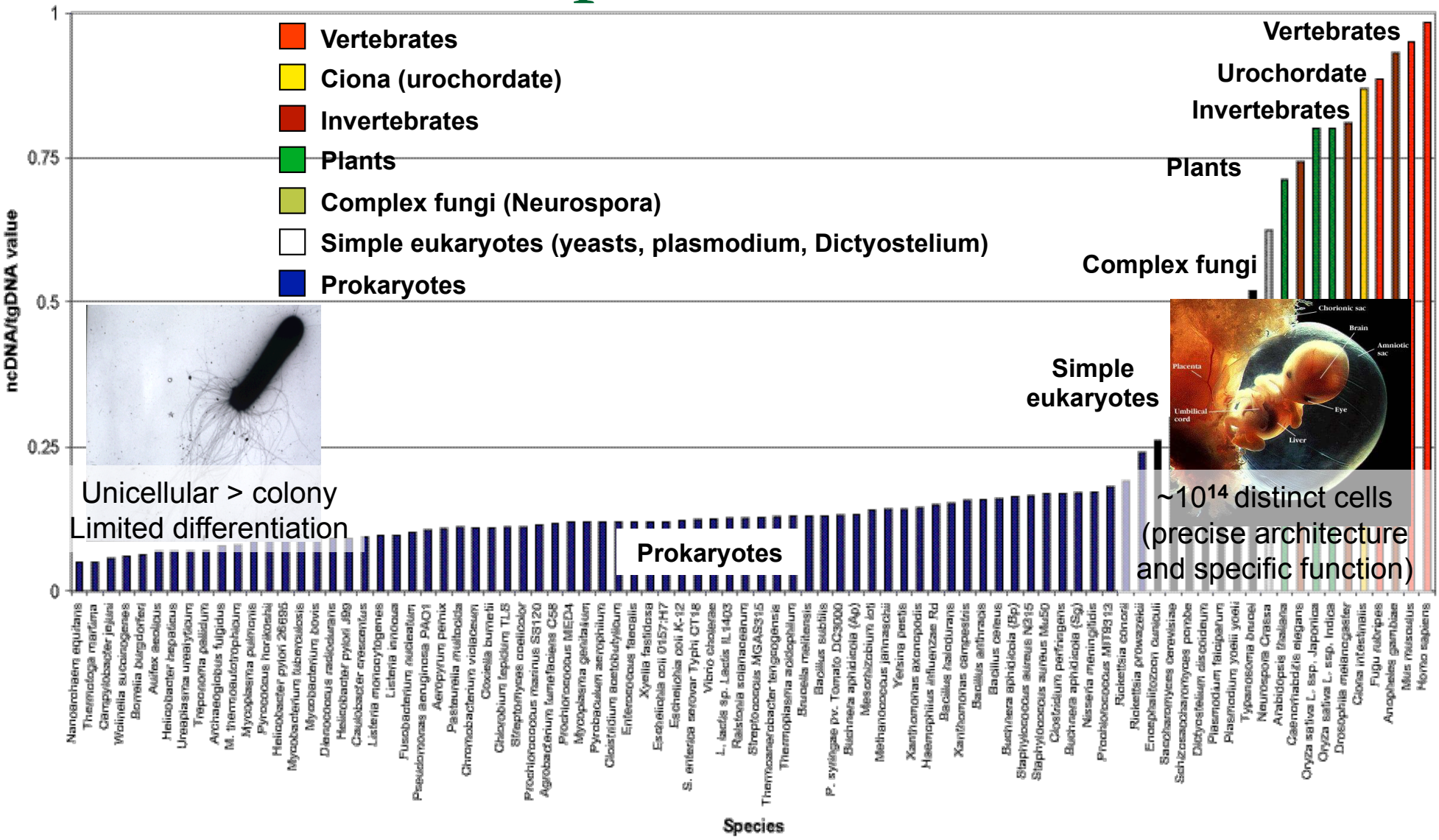


~10^{14} distinct cells
(precise architecture
and specific function)

No correlation with the size of the nuclear genome

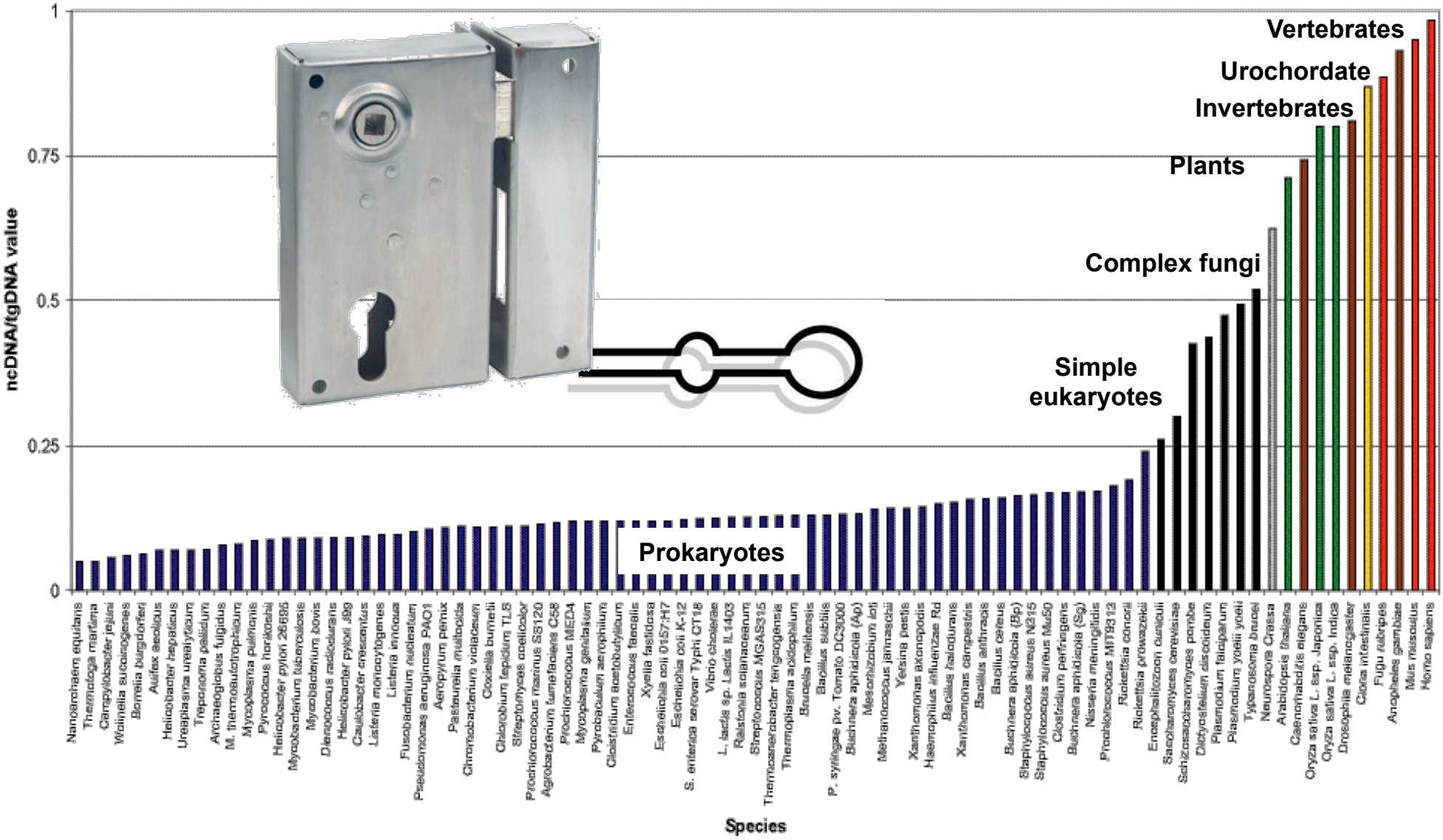
	Mitochondrial genome	Nuclear genome
Saccharomyces cerevisiae	85,779 bp	1.2×10^7 bp
Homo sapiens	16,554 bp	2.9×10^9 bp

Une clé dans la poubelle: le non-codant



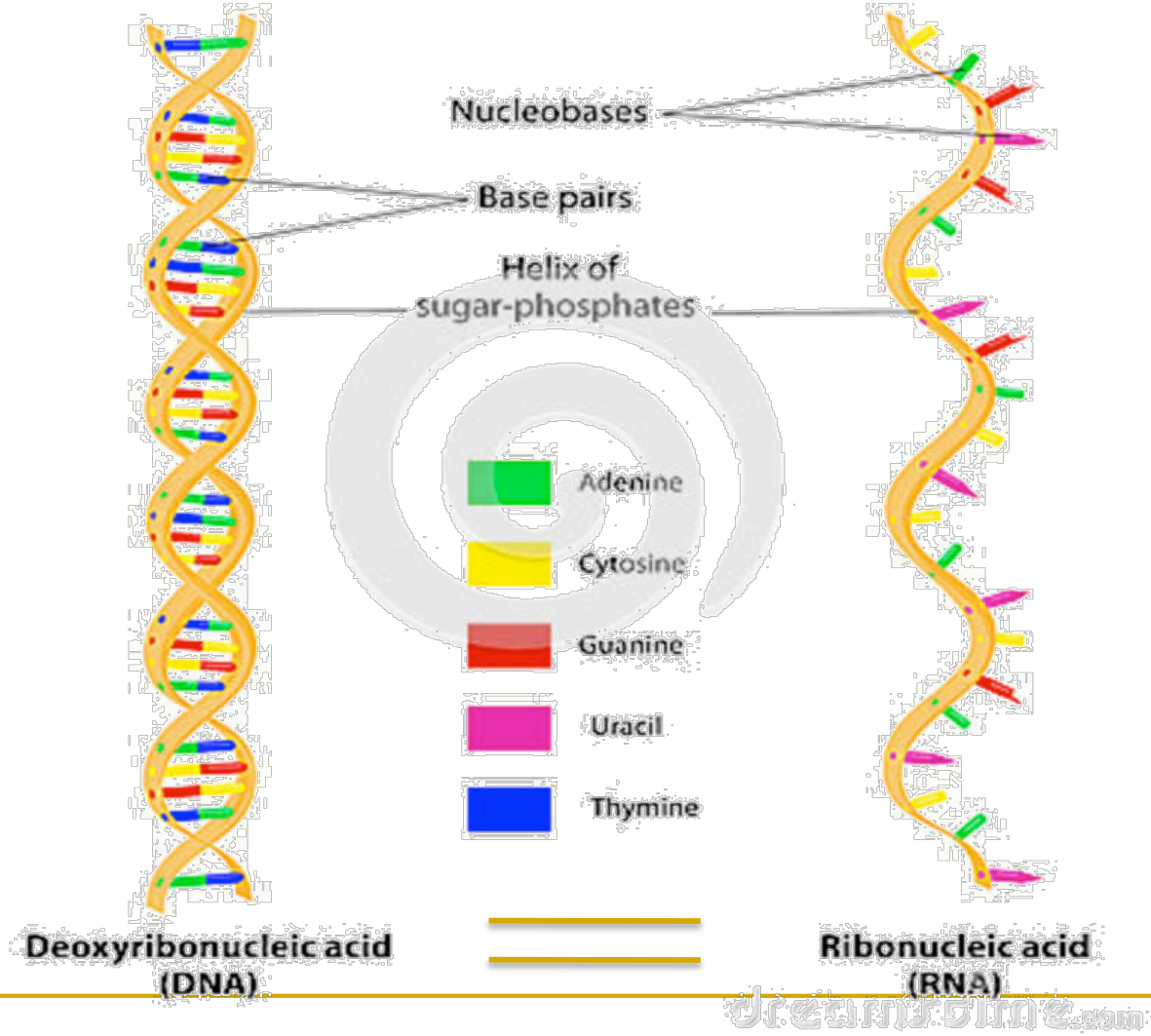
Taft and Mattick, Bioessays 2007

Le non-codant: clé innovante de l'évolution



Taft and Mattick, Bioessays 2007

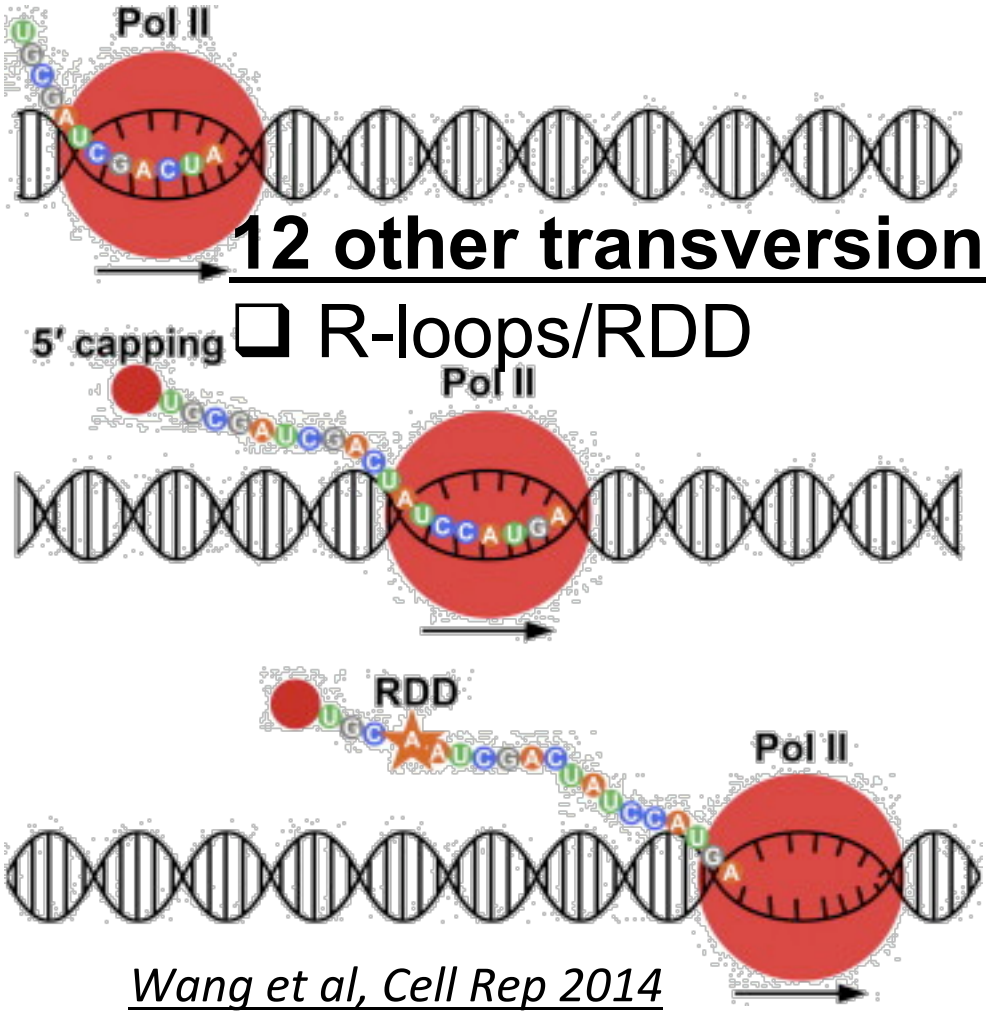
Les limites de notre compréhension: l'ADN copié en ARN…



RNA-DNA sequence differences (RDDs)

RNA editing (1986)

- ❑ C>U, APOBEC
  apolipoprotein B mRNA editing enzymes
- ❑ A>I (G), ADAR
  adenosine deaminases



Wang et al, Cell Rep 2014

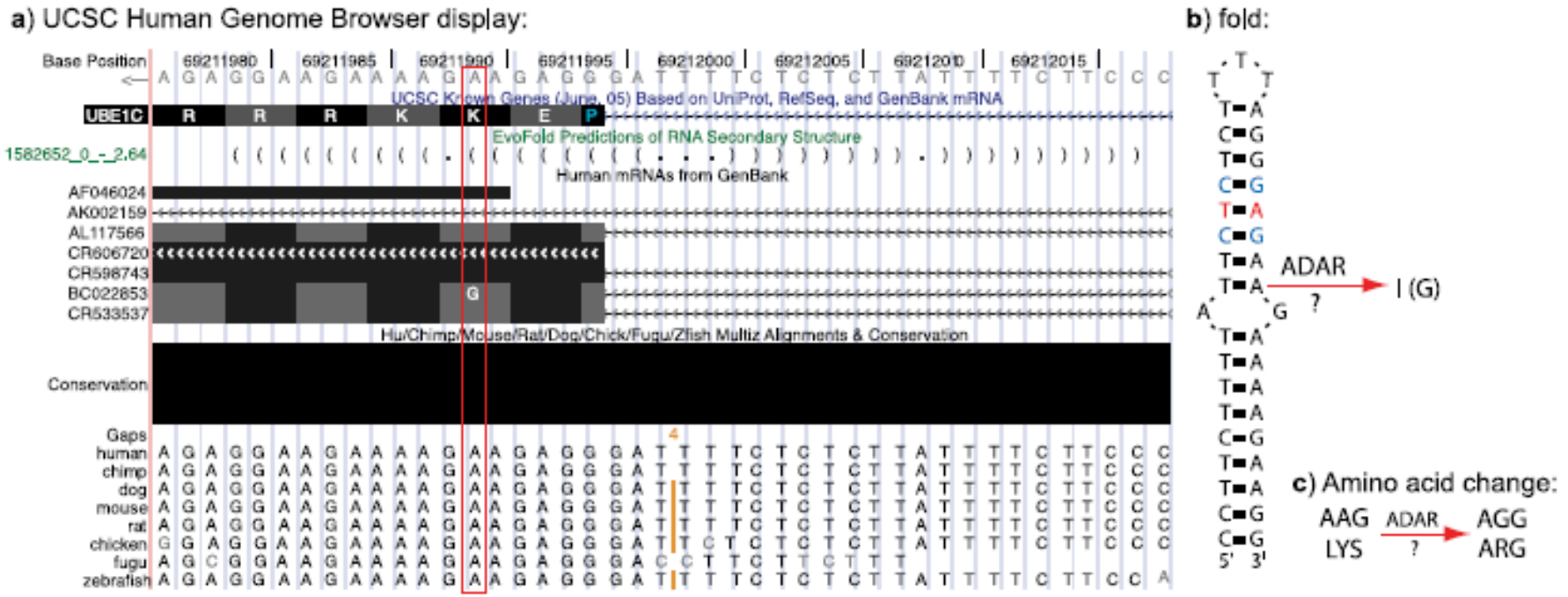


Figure 4. Candidate Substrate for A-to-I Editing

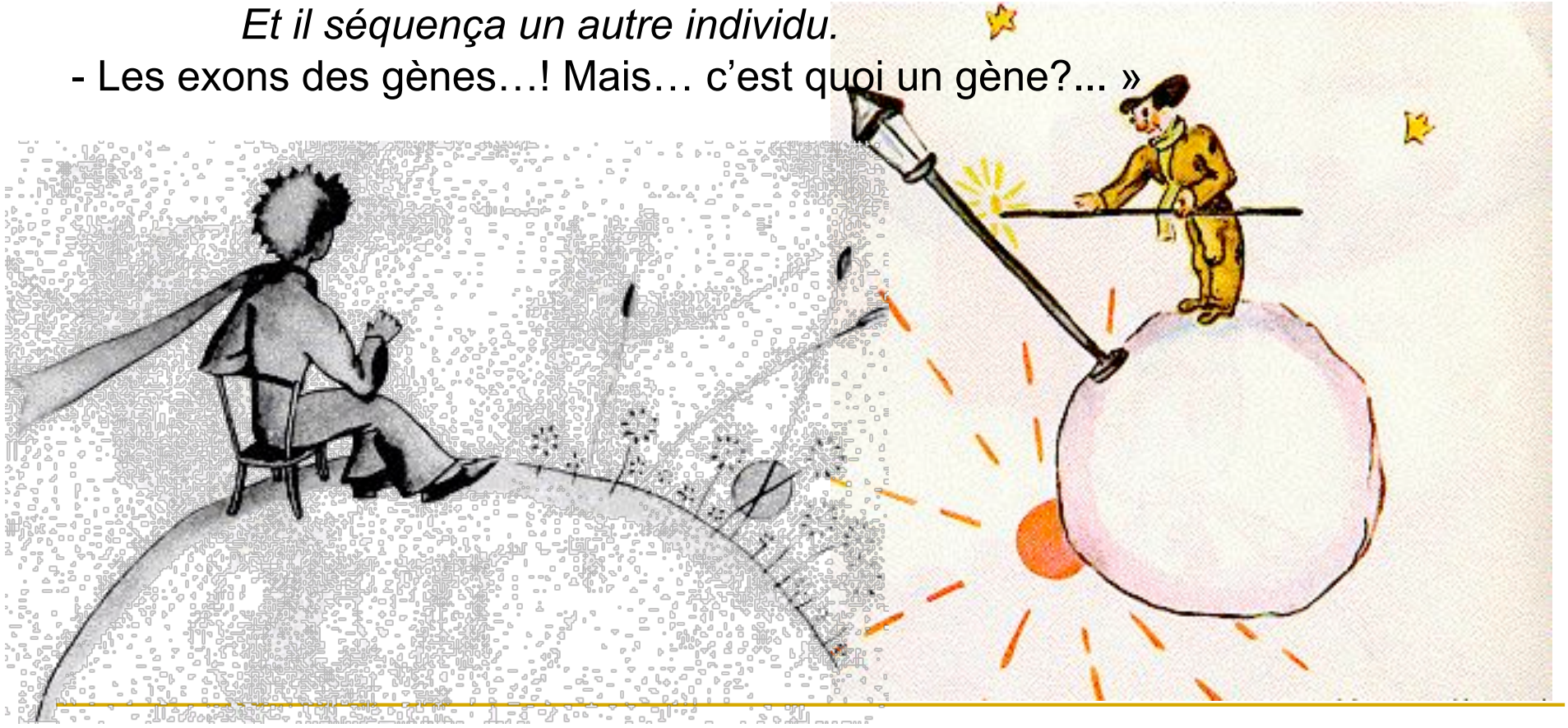
(A) Gene structure, EvoFold predictions, cDNAs, conservation, and eight-way alignment are shown at the start of the second exon of the *UBE1C* gene. The predicted hairpin is shown in parenthesis format and can be seen to overlap the intron–exon boundary. The red box highlights a position where the genomic sequence contains an A and a cDNA contains a G. The orange bar and label "4" indicate that up to four extra bases are present in this loop location in the indicated species.

(B) Depiction of hairpin (see Figure 3B for color legend) with indication of the potential site of ADAR editing (A-to-I).

(C) Which would lead to a lysine to arginine amino acid change.

Pendant ce temps, une nouvelle réalité clinique

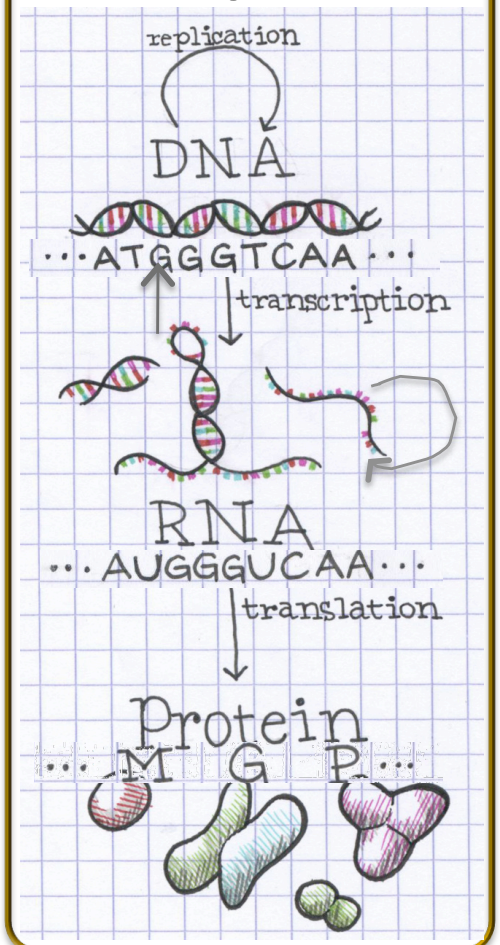
Et si le Petit Prince se rendait à l'hôpital:
« Bonjour. Pourquoi viens-tu de séquencer les exons?
- C'est la consigne, répondit le généticien.
- Qu'est-ce « la consigne »?
- C'est de séquencer les exons des gènes.
Et il séquença un autre individu.
- Les exons des gènes…! Mais… c'est quoi un gène?... »



Open to debate - What is a gene?

LATELY

Molecular Biology Dogma



CURRENTLY

An expanding family WITH 1 protein-coding only

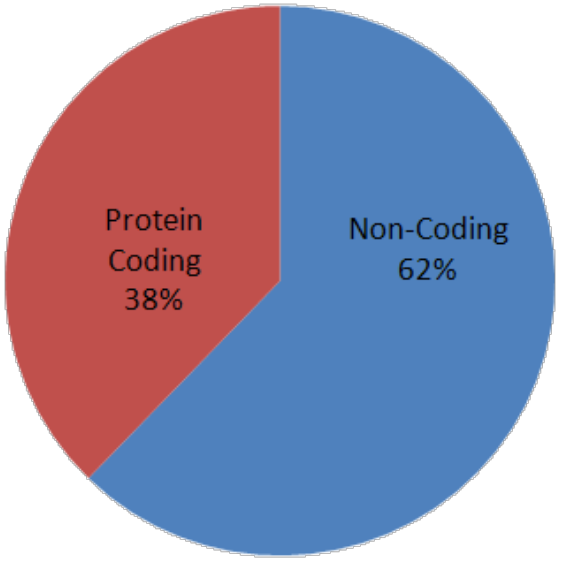
known for decades:
- rRNA
- snoRNA
- snRNA
- rRNA
- tRNA
- mRNA

recently discovered:
- piRNA
- siRNA
- miRNA (Fire-Mello)
- lncRNA (Blackburn)

and TODAY ??

Tom Gingeras, ENCODE

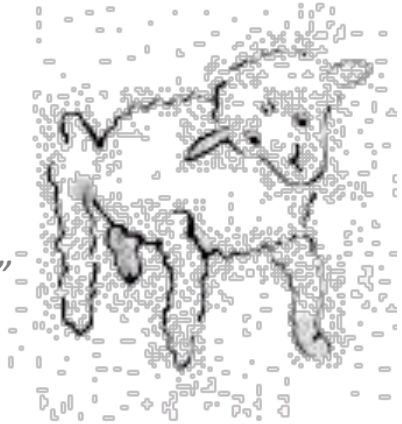
There's no such thing as a gene… Every base of the genome is transcribed in both directions, sense and antisense… But, if you really HAVE to count genes:



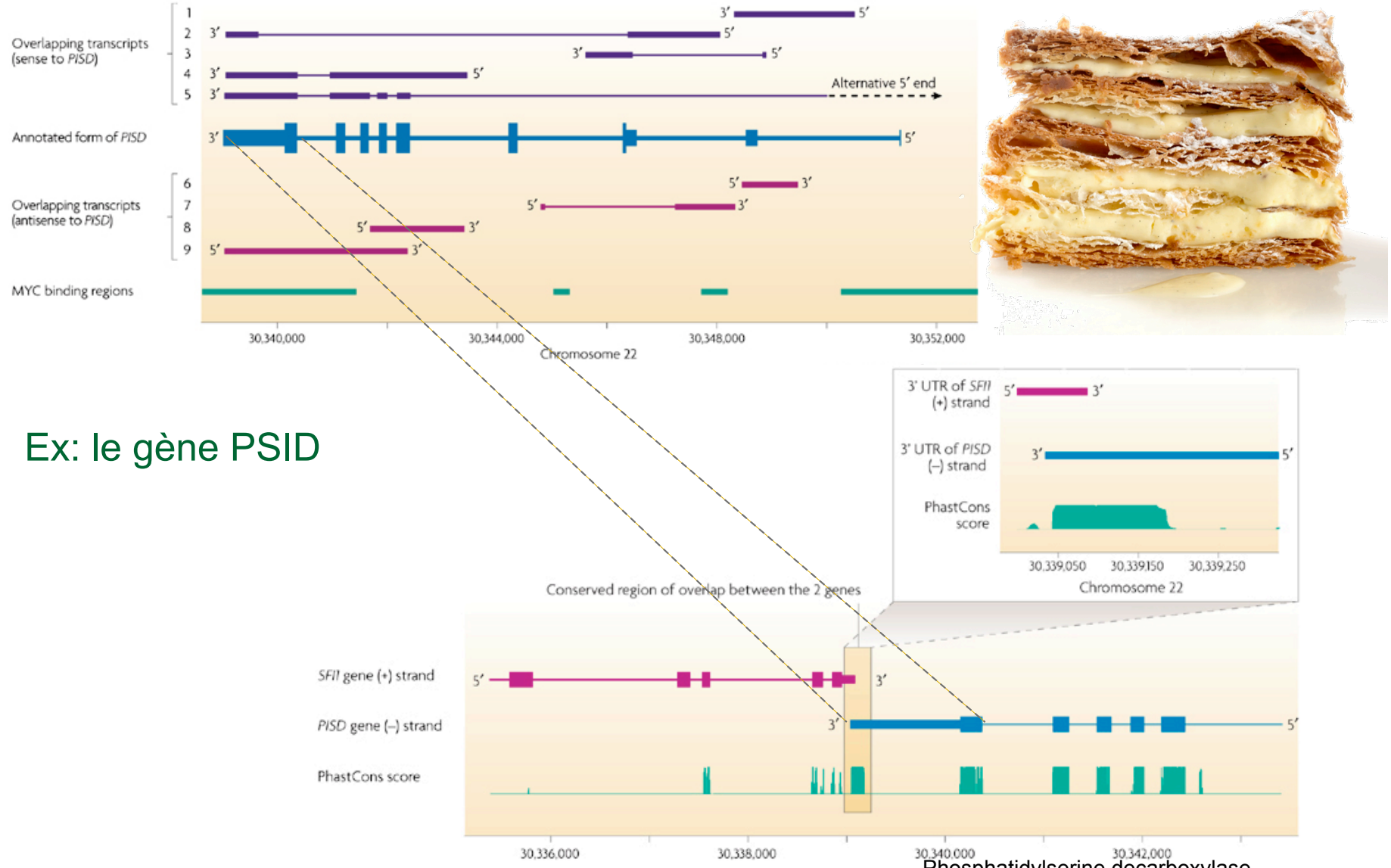
Harrow et al 2012, *Genome Research*

S'il te plait…

dessine-moi un "gène"



Le génome: un millefeuille transcriptomique

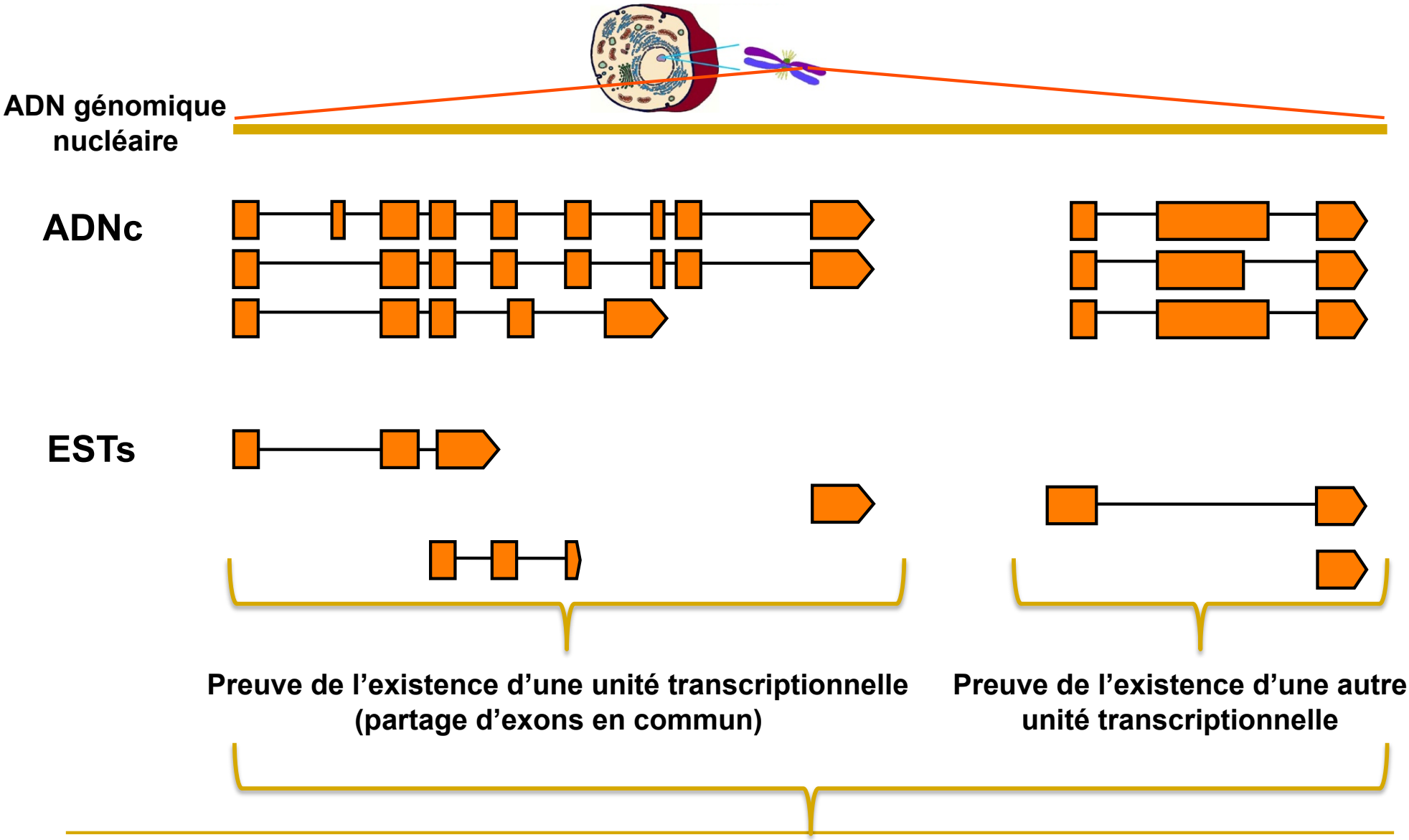


Ex: le gène PSID

Phosphatidylserine decarboxylase

Kapranov, Nat Rev Genet 2007

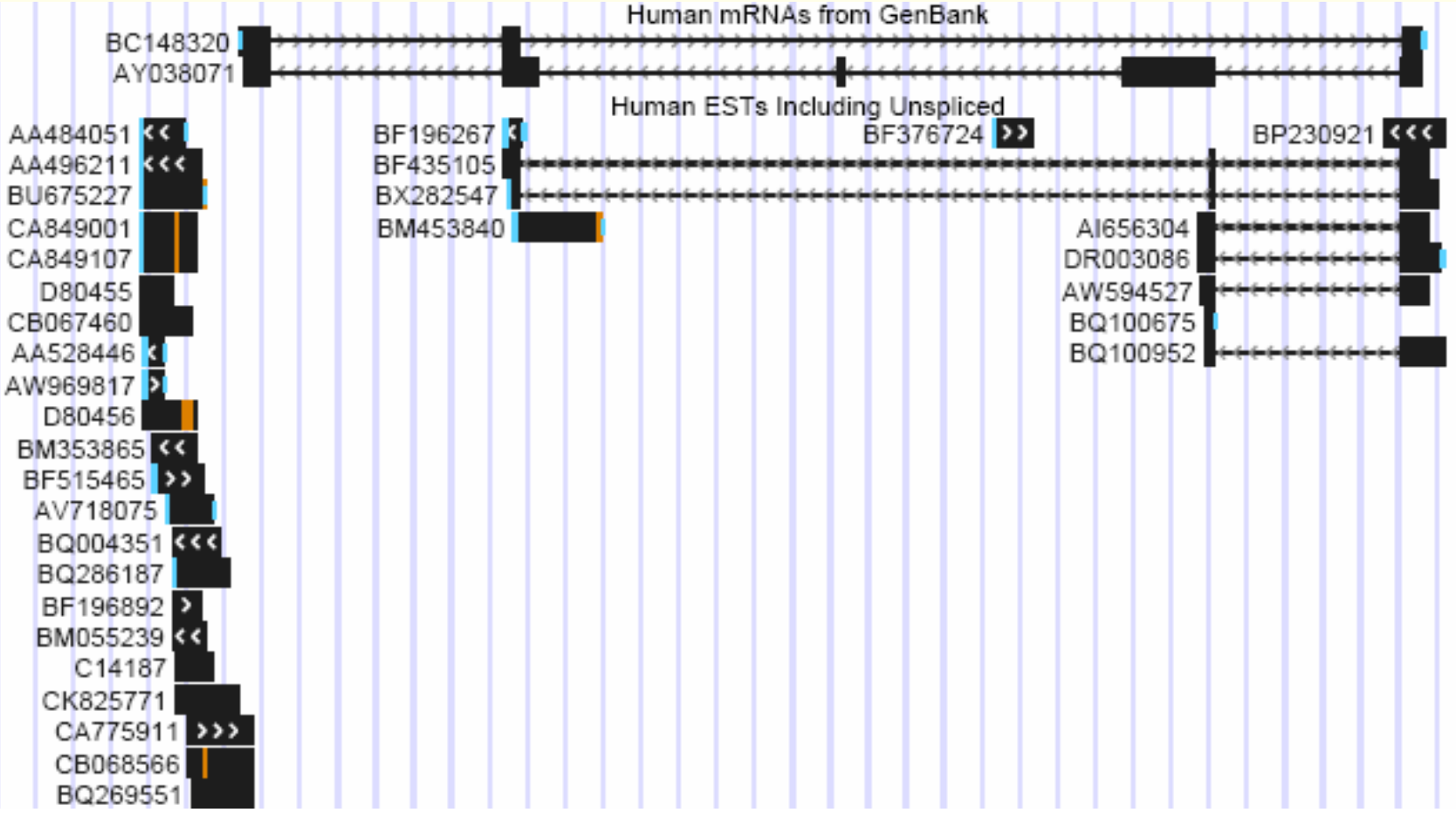
La difficulté de délimiter un gène



L'apport des ESTs

Methods

GenBank human mRNAs were aligned against the genome using the blat program. When a single mRNA aligned in multiple places, the alignment having the highest base identity was found. Only alignments having a base identity level within 0.5% of the best and at least 96% base identity with the genomic sequence were kept.



Annotation fonctionnelle en ébullition

2013 ENCODE stats + add-ons

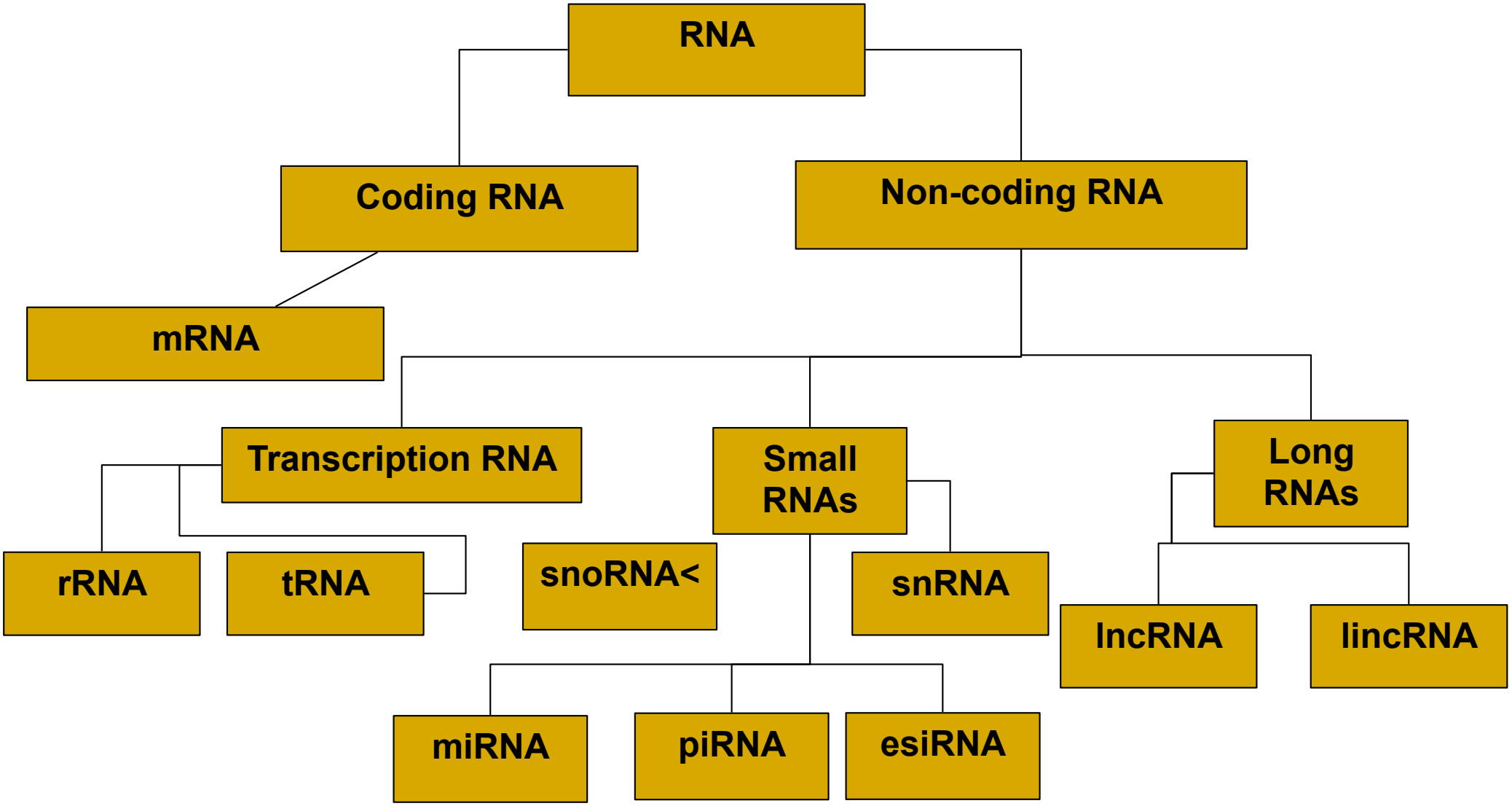
Total No of Genes	57281
Protein-coding genes	20330
Introns	**>100,000**
Long non-coding RNA genes	13333
Small non-coding RNA genes	9078
Pseudogenes	14154
Mobile elements	**>1,100,000**

FANTOM
FUNCTIONAL ANNOTATION OF THE MAMMALIAN GENOME

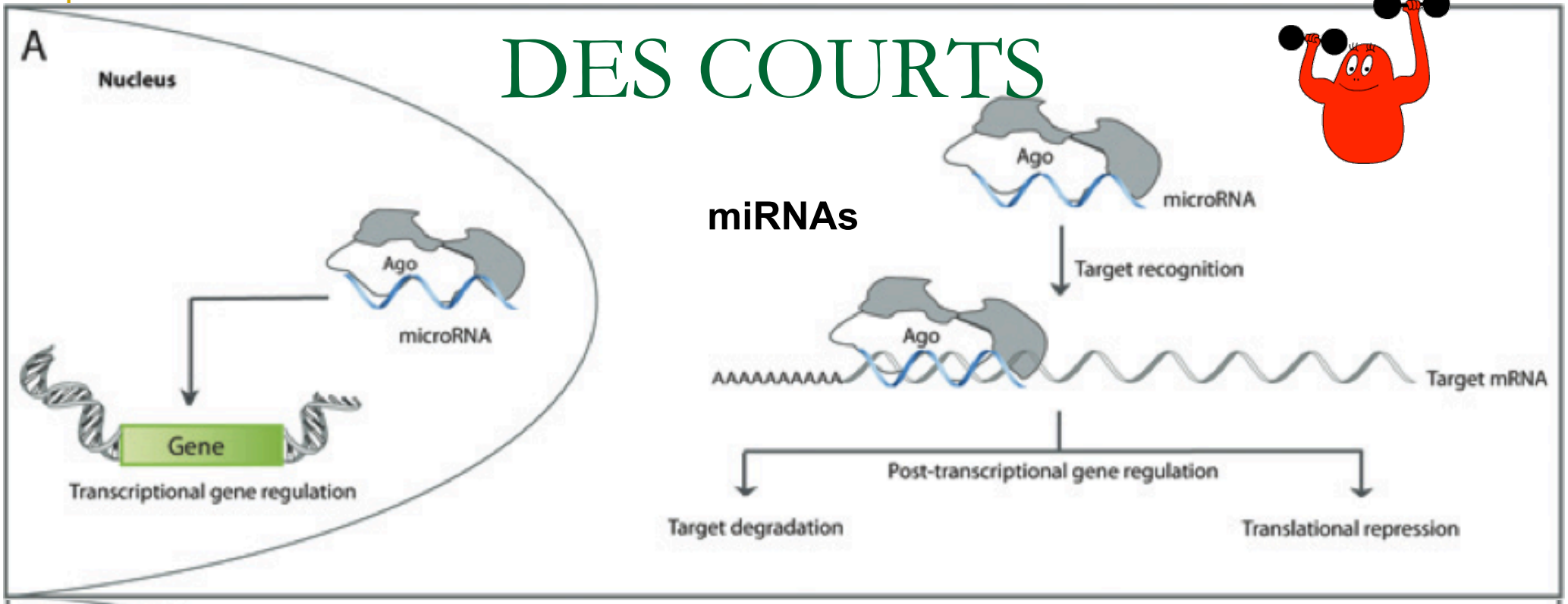
GENCODE

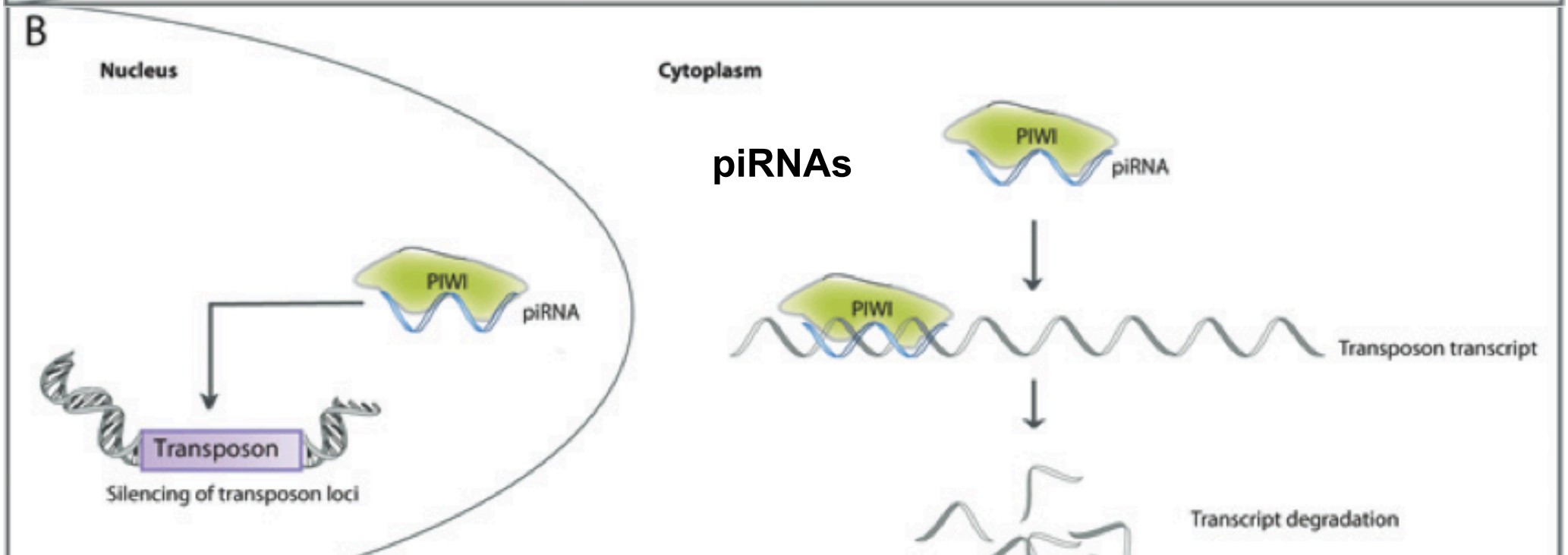
Encode-July 10, 2013
Version 17 (February 2013 freeze, GRCh37)-Ensembl 72

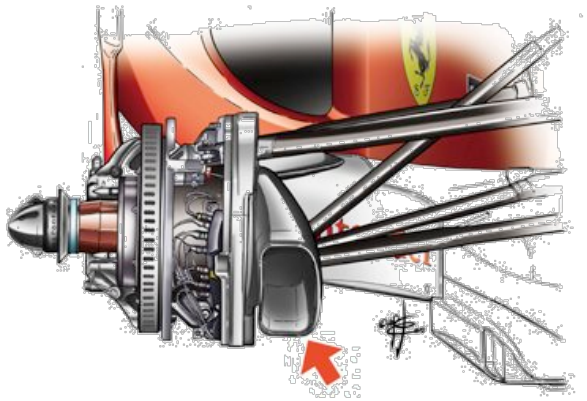
L'arbre florissant des ARN

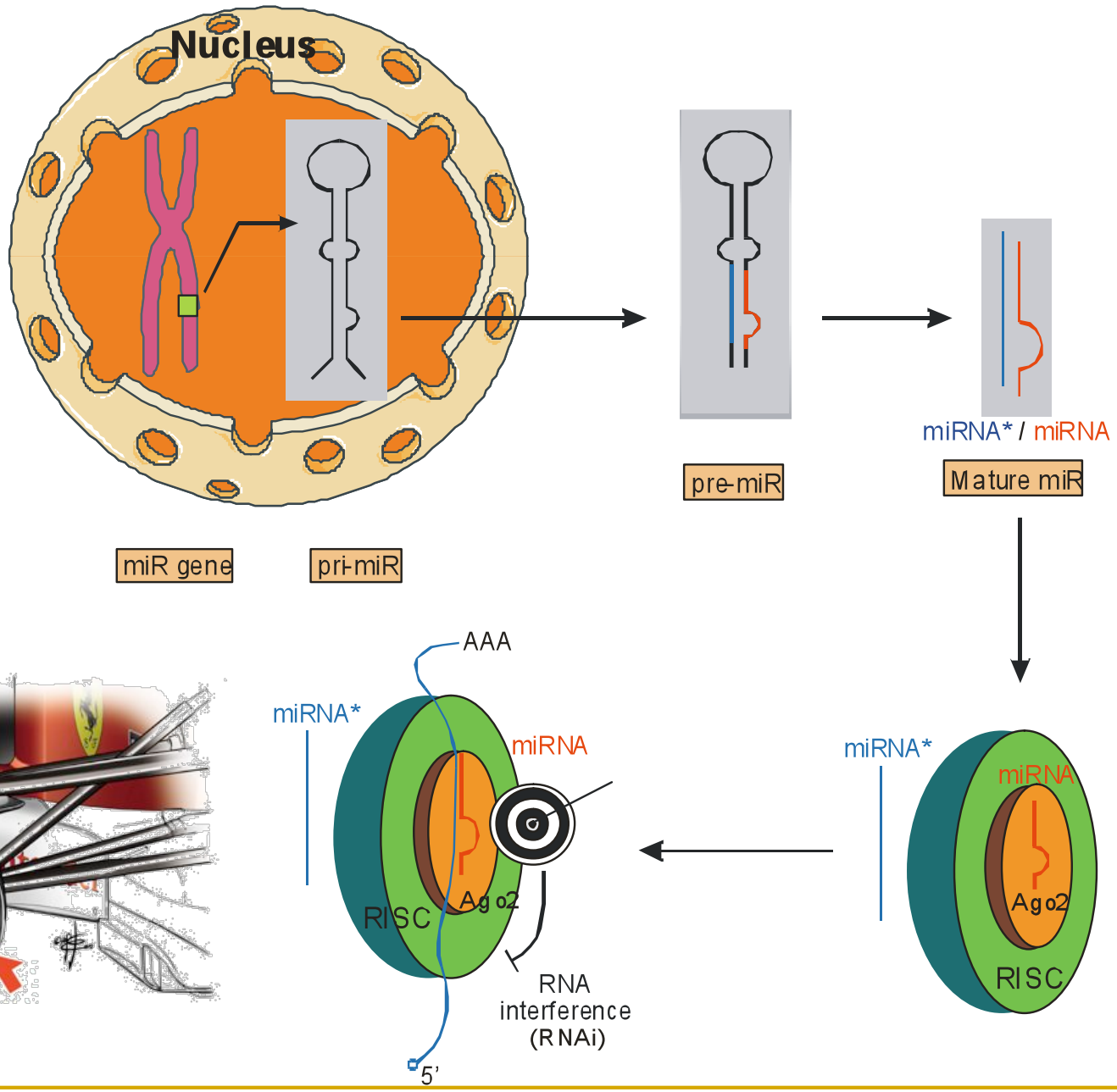


DES COURTS

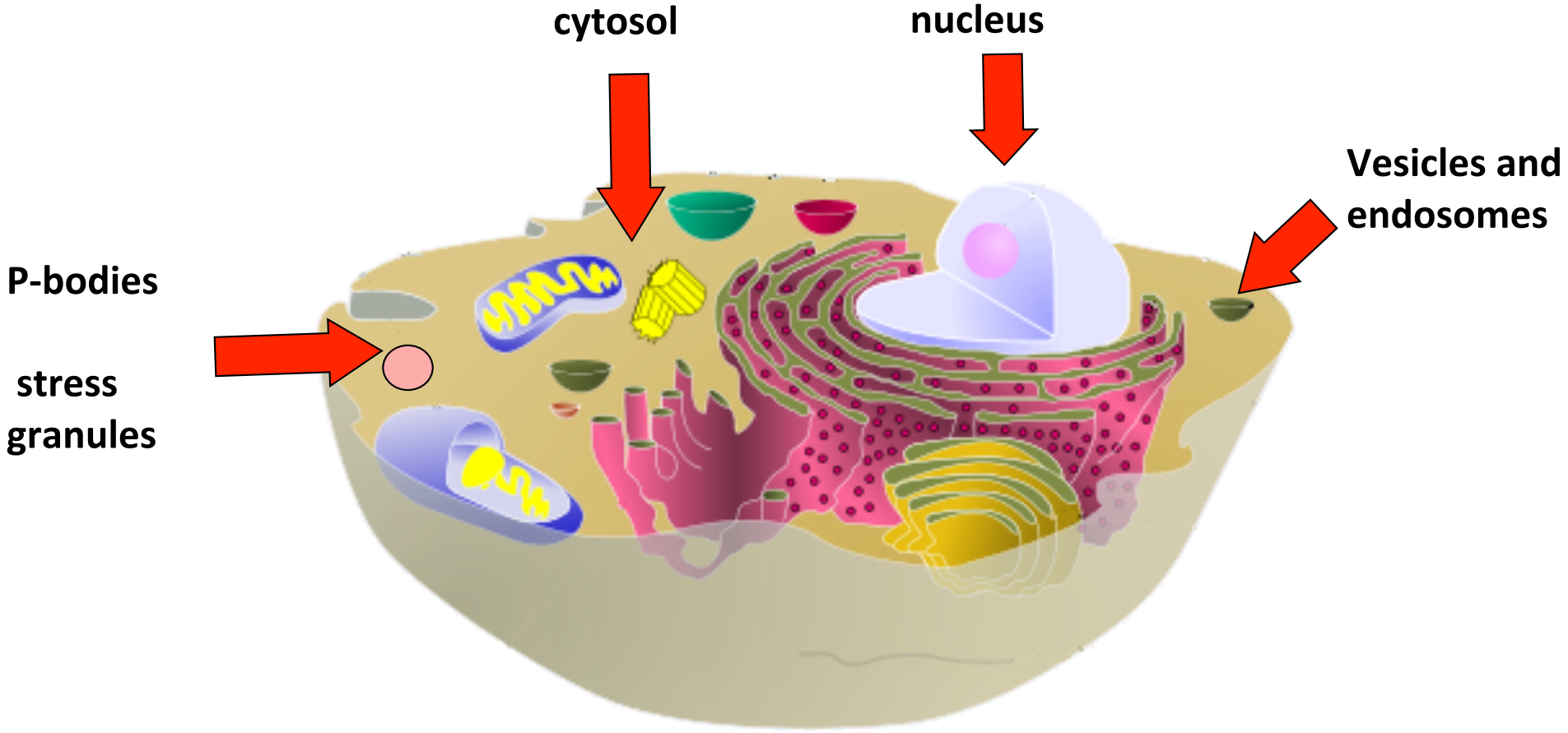

A
Nucleus
Ago
microRNA
Gene
Transcriptional gene regulation
miRNAs
Ago
microRNA
Target recognition
Ago
Target mRNA
Post-transcriptional gene regulation
Target degradation
Translational repression


B
Nucleus
PIWI
piRNA
Transposon
Silencing of transposon loci
Cytoplasm
piRNAs
PIWI
piRNA
PIWI
Transposon transcript
Transcript degradation




Nucleus
miR gene
pri-miR
pre-miR
miRNA* / miRNA
Mature miR
miRNA*
miRNA
Ago2
RISC
RNA
interference
(RNAi)
AAA
5'

-1- Intracellular miRNAs: Compartmentalization of Ago2 and miRNAs



Assembly of RISC at the level of :

-the nucleus *(Hwang, 2007; Liao, 2010; Park 2011; Jeffries 2011)*

-microvesicles and endosomes *(Valadi, 2007; Hunter, 2008; Gibbings 2009)*

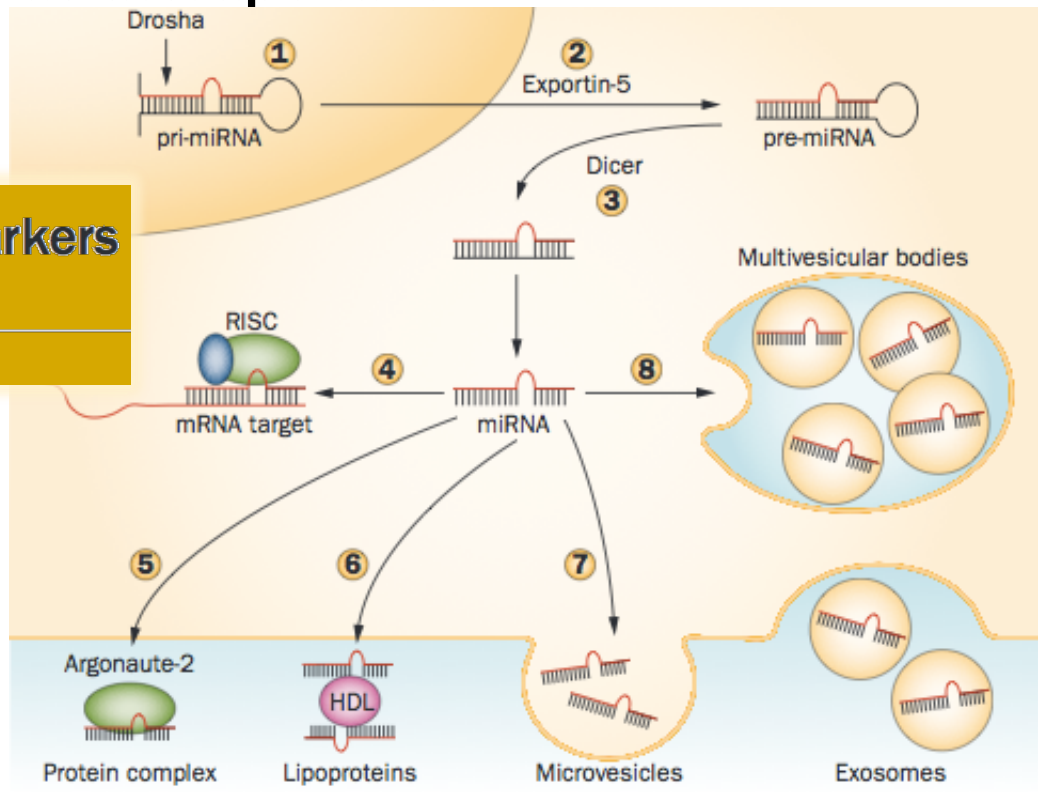
-2- Extra-cellular miRNAs: Complex with Ago1-2, HDL

- Discovery of circulating nucleic acids (Mendel and Metais, 1948)
- miRNA in blood, serum, urine, saliva, tears, breast milk, CSF (2008)
- Correlations with human disease, e.g T1D (40 miRNAs dont 2 tissulaires)
- Usefulness as biomarkers and as therapeutics

Circulating microRNAs as novel biomarkers for diabetes mellitus

Claudiane Guay and Romano Regazzi

Guay and Regazzi, Nat Rev Endoc 2013



-3- Exogenous miRNAs: cellular activity / intercellular communication

- **Exogenous RNA taken up from the environment:**
  - from fungi, bacteria, viruses
  - from food: detection of the plant miR-168 in human circulation (Zhang, 2012)

- **The field is just beginning to be explored, and is so far limited by the approaches for quantification**

Exogenous plant MIR168a specifically targets mammalian

Effective detection and quantification of *dietetically* absorbed plant microRNAs in human plasma

Liang et al, J Nutr Biochem 2015

Zhang et al, Cell Research 2012

Hongwei Liang[1], Suyang Zhang[1], Zheng Fu[1], Yanbo Wang, Nan Wang, Yanqing Liu, Chihao Zhao, Jinhui Wu, [illegible]m[1], Yiqiao Hu, Junfeng Zhang, Xi Chen*, Ke Zen*, Chen-Yu Zhang* [illegible]u[1], [illegible]hang[1],

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Food Science & Nutrition

Open Access

ORIGINAL RESEARCH

Assessing the survival of exogenous plant microRNA in mice

Witwer and Hirschl, BioEssays 2014

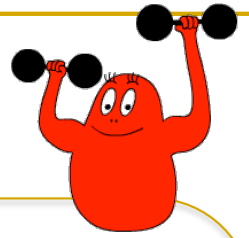
Negative result
and regulate ge

GaoFeng Liang[1,2], YanLiang Zhu[1], Bo Sun[1], YouHua Shao[1], AiHua Jing[2], JunHua Wang[1] & ZhongDang Xiao[1]

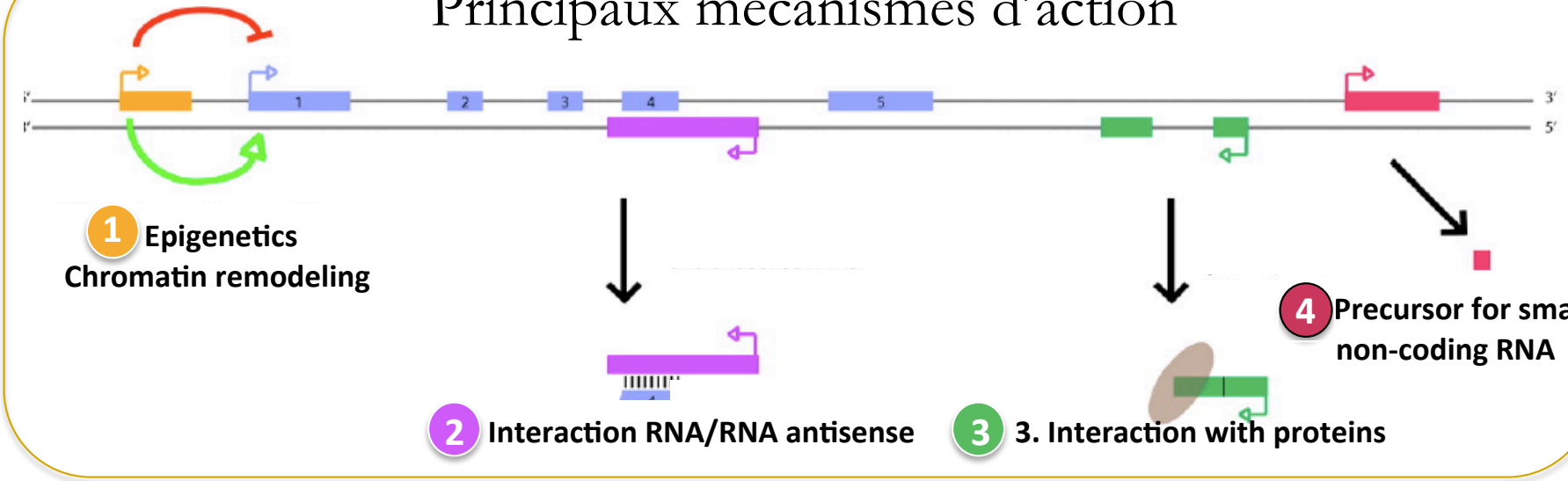
Kenneth W. Witw

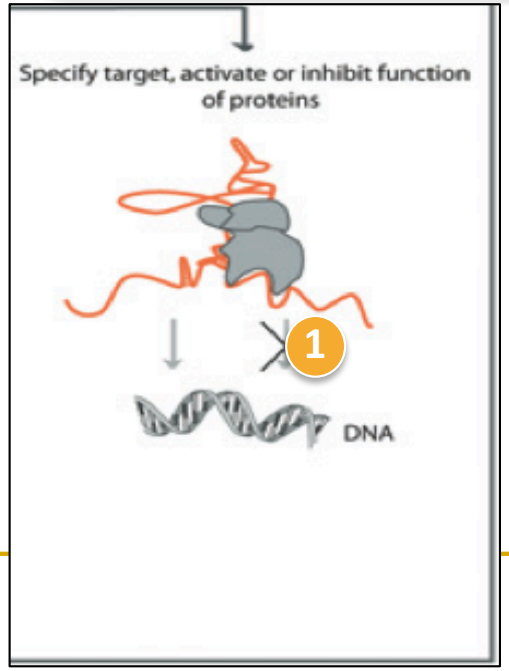
[1]State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, China
[2]School of Medical Technology and Engineering, Henan University of Science and Technology, Luo Yang 471003, Henan, China

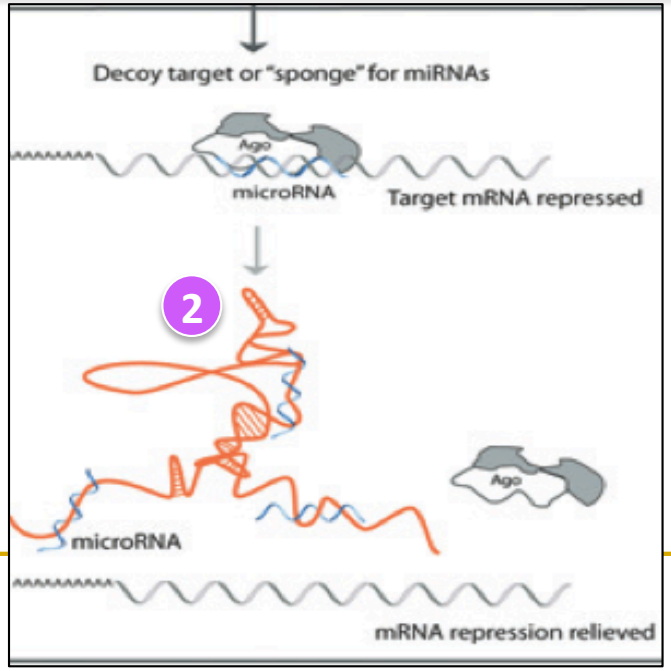
DES LONGS

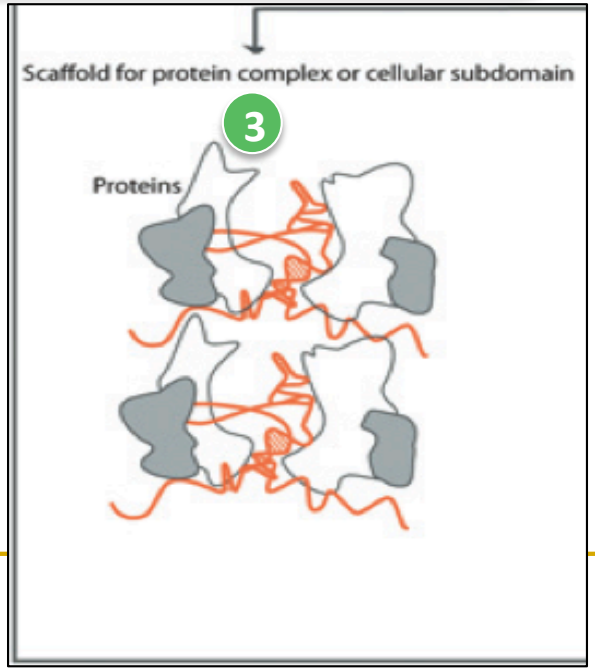


Principaux mécanismes d'action

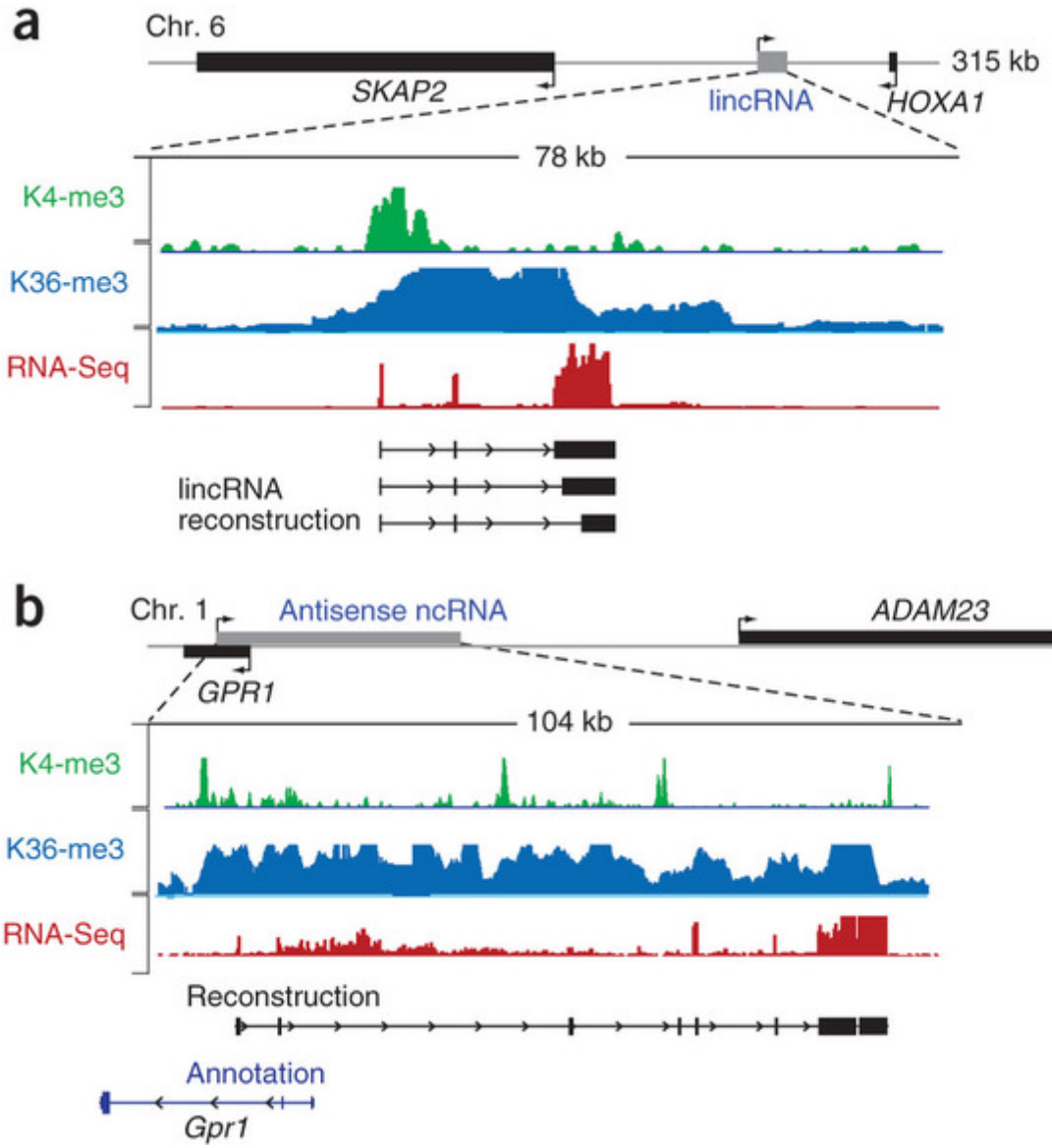


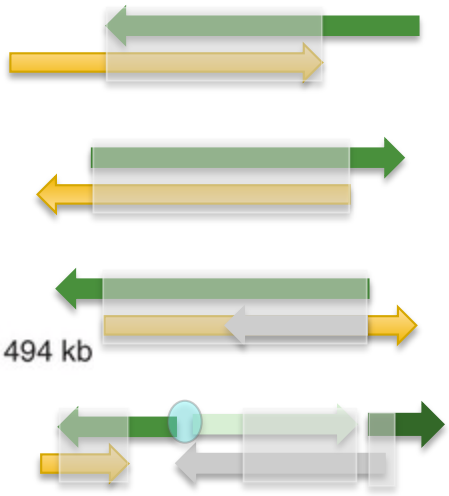






lincRNAs (long intergenic non coding RNAs)





Organisation

Convergente (3'/3' sens-antisens)

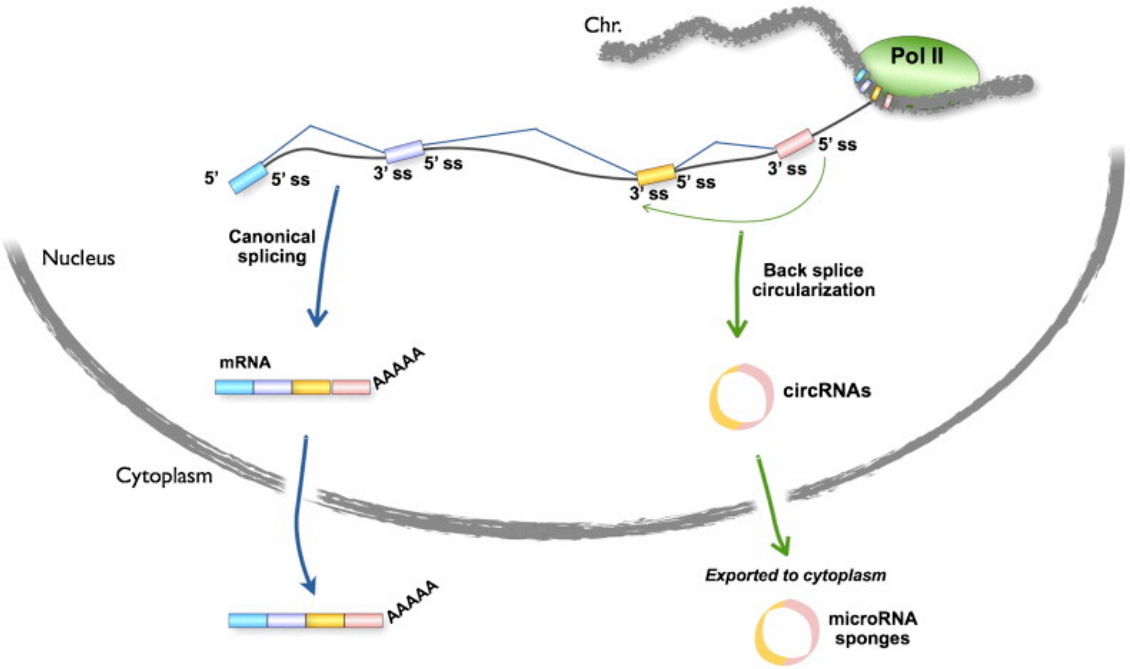
Divergente (5'/5' sens-antisens)

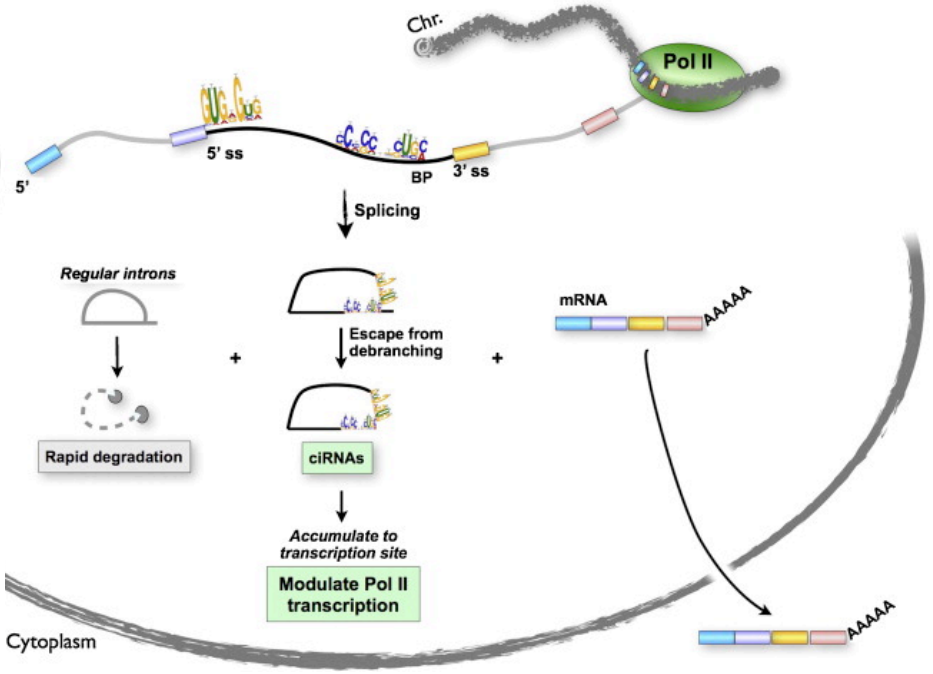
Complexe (gène niché)

Imbrication de gènes (convergent, divergent, promoteur bi-directionnel)

DES RONDS

Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types

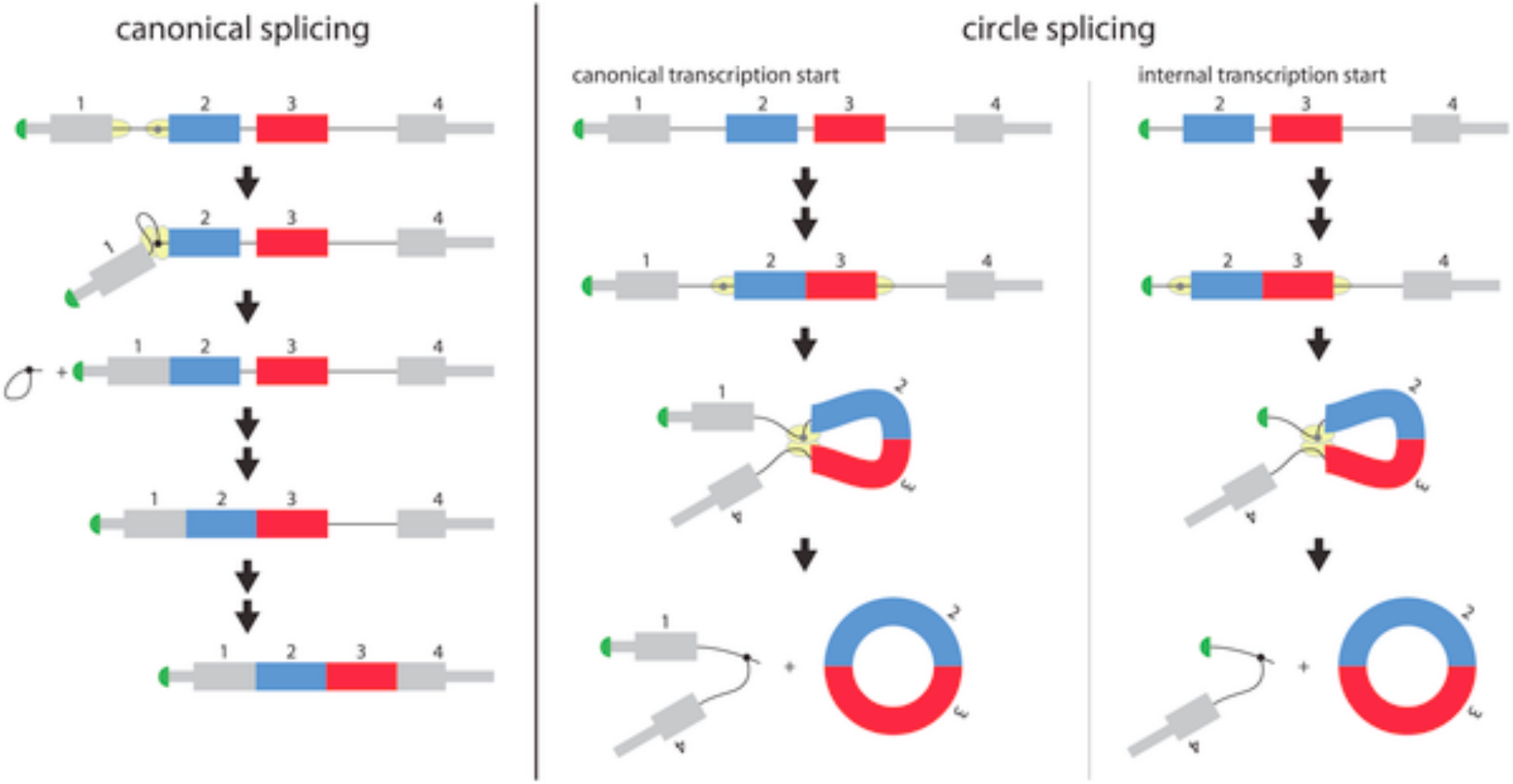




Human fibroblasts: 25,000 unique circular RNA species that arise from 14.4% of expressed genes.

Salzman et al. PLoS ONE, 2012

When it comes to RNA, assume nothing



Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types

Julia Salzman[1☯], Charles Gawad[1,3☯], Peter Lincoln Wang[1], Norman Lacayo[3], Patrick O. Brown[1,2*]

1 Department of Biochemistry, Stanford University School of Medicine, Stanford, California, United States of America, **2** Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California, United States of America, **3** Department of Pediatric Hematology/Oncology, Stanford University School of Medicine, Stanford, California, United States of America

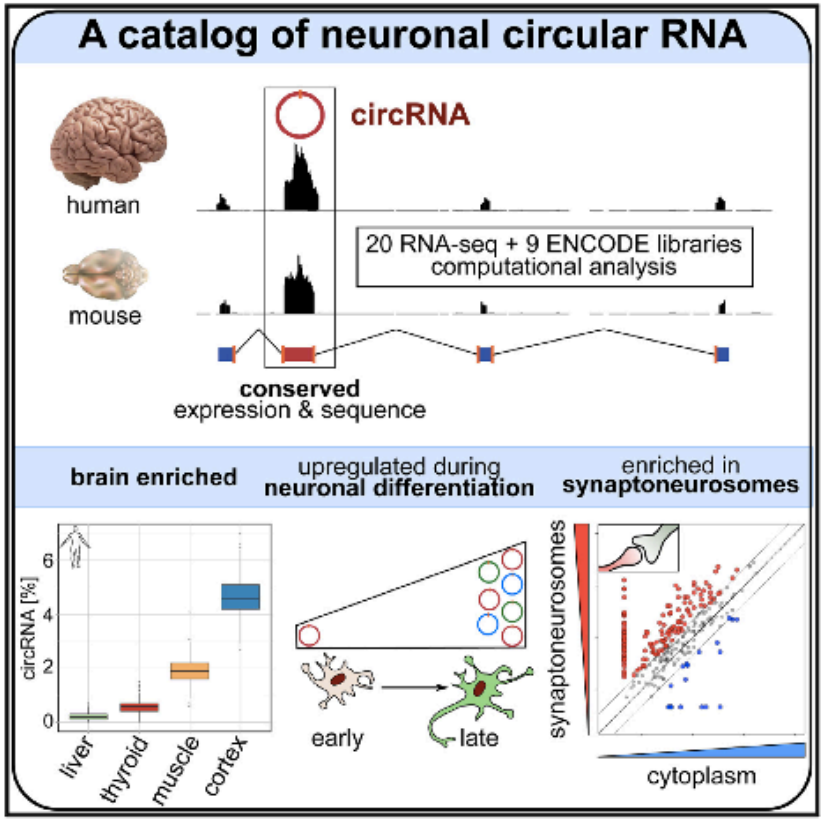
Salzman et al- PLoS ONE (2012)

Rybak-Wolf et al., 2015, Molecular Cell 58, 1–16
June 4, 2015

Molecular Cell

Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed

Graphical Abstract



Authors

Agnieszka Rybak-Wolf,
Christin Stottmeister, ...,
Sebastian Kadener, Nikolaus Rajewsky

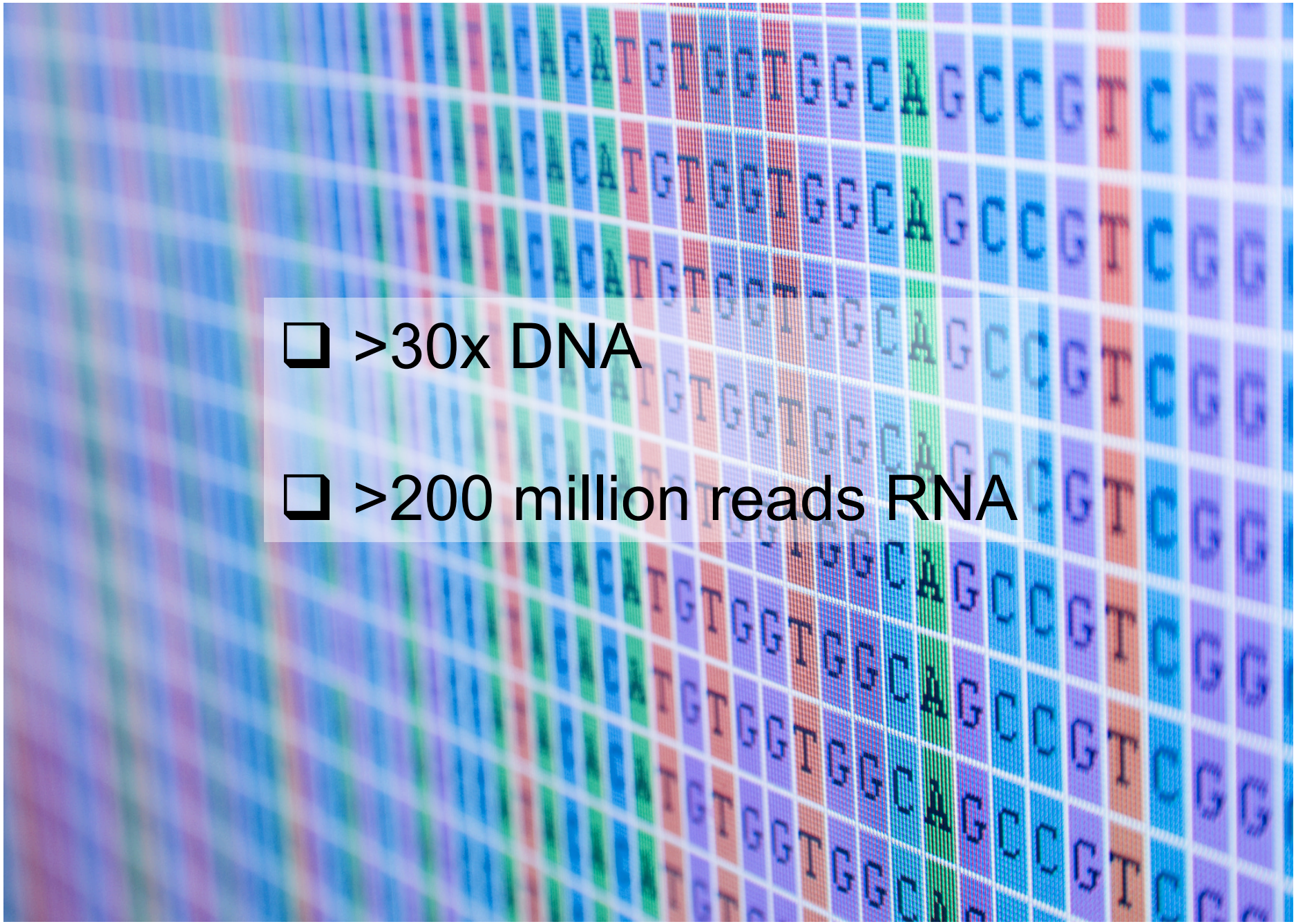
Correspondence

rajewsky@mdc-berlin.de

In Brief

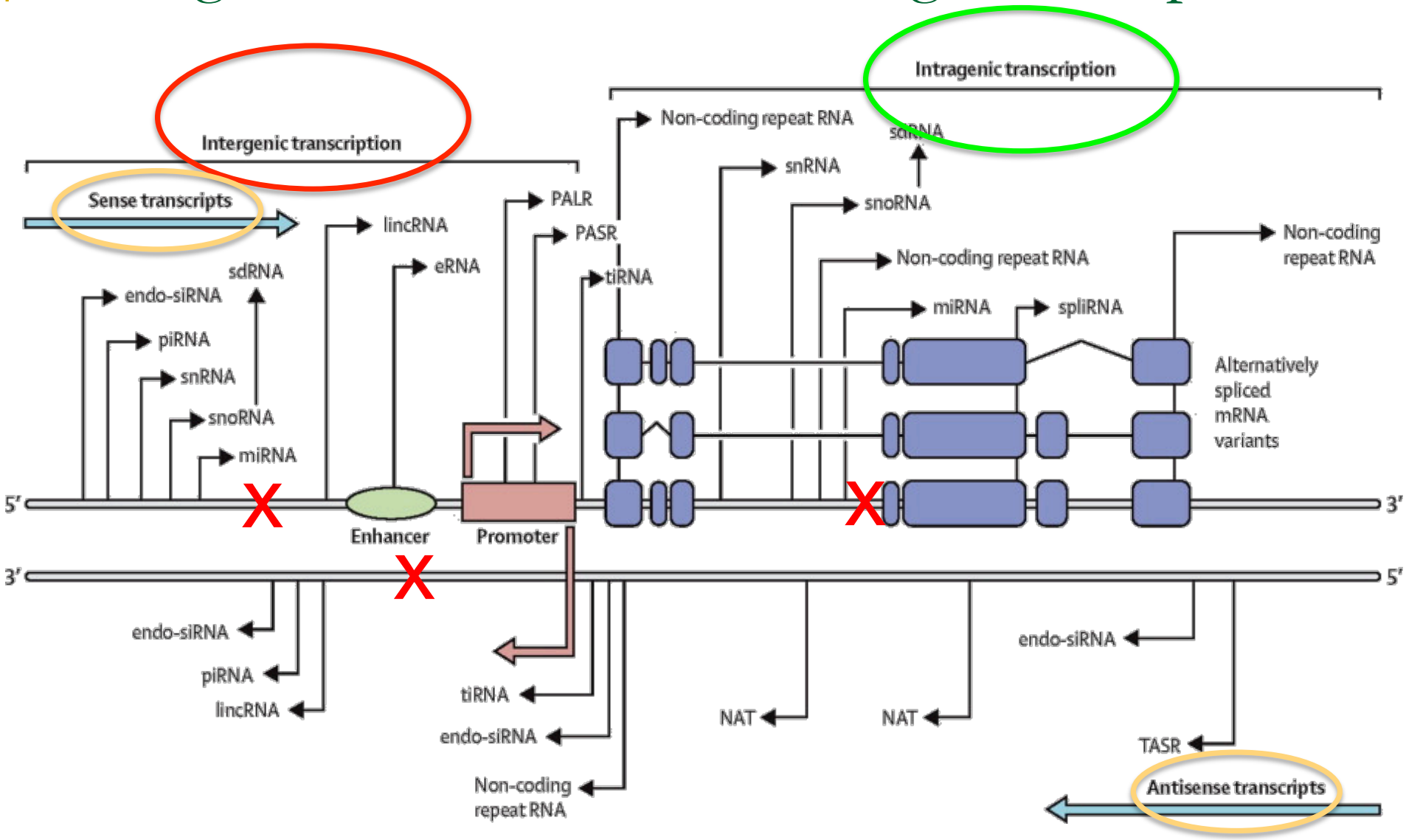
Rybak-Wolf et al. combined computation and experiment to compile a catalog of circRNA expression in the brain. circRNAs are highly enriched in the mammalian brain, with specific and dynamic expression during neuronal differentiation, often independent of linear transcripts. Brain-expressed circRNAs are often conserved in expression and display elevated sequence conservation.

L'ARN: une nouvelle dimension au NGS



- >30x DNA
- >200 million reads RNA

Adding technical and methodological complexities



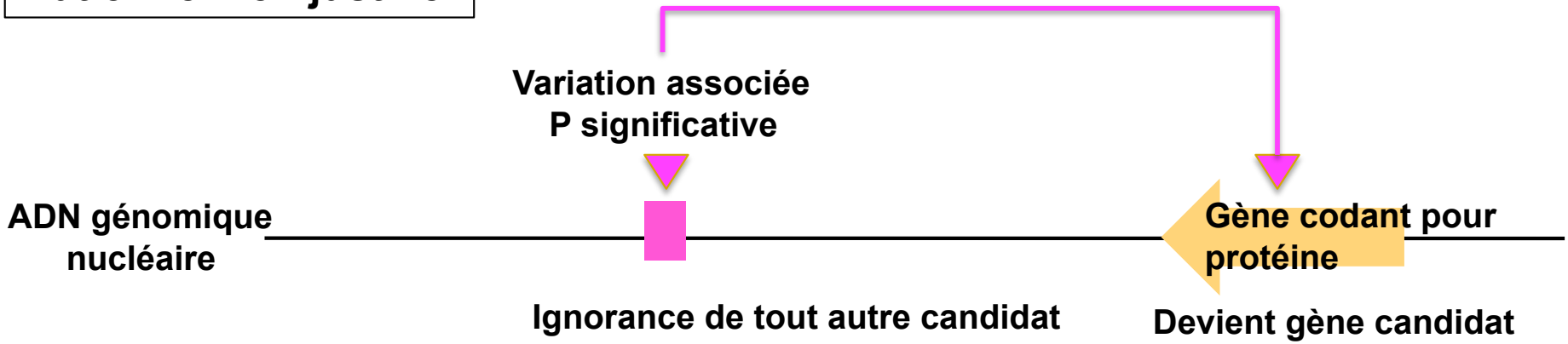
Salta and De Trooper, Lancet Neurol 2012

Une autre réalité pour les GWAS

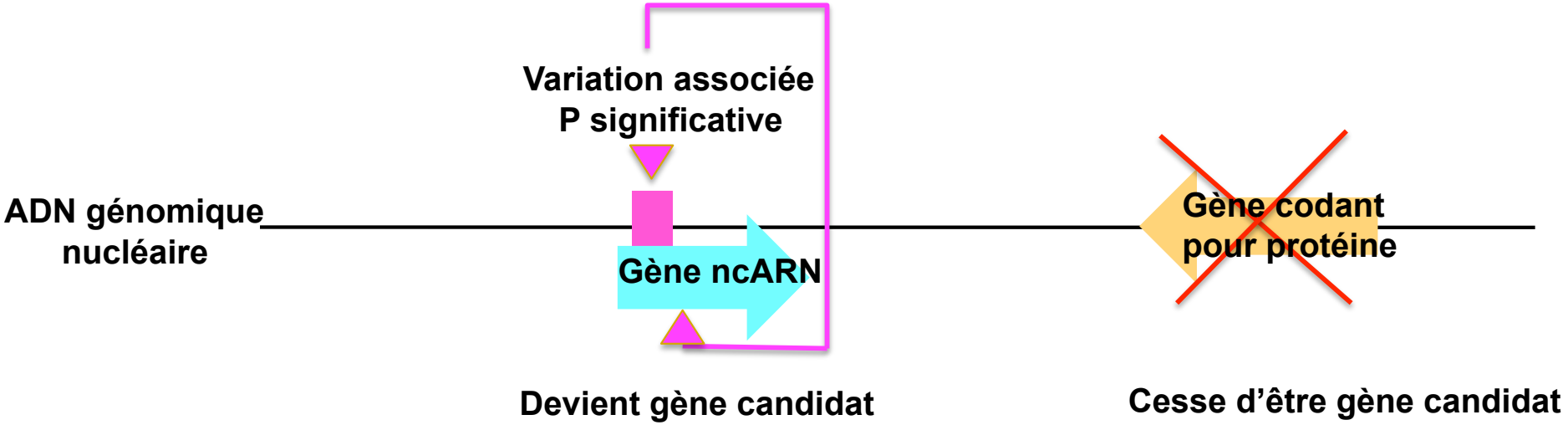
- 1,200 GWAS ont identifié près de 6 500 SNPs de maladies ou de prédisposition à un trait.
- Seulement 7% de ces SNPs sont localisés dans des régions de gènes codant pour des protéines. Les 93% restant sont dans des régions… non-codantes.

Pennisi-Science 2011
Kumar et al-Semin Immunol 2012
Hindorff et al, PNAS 2009

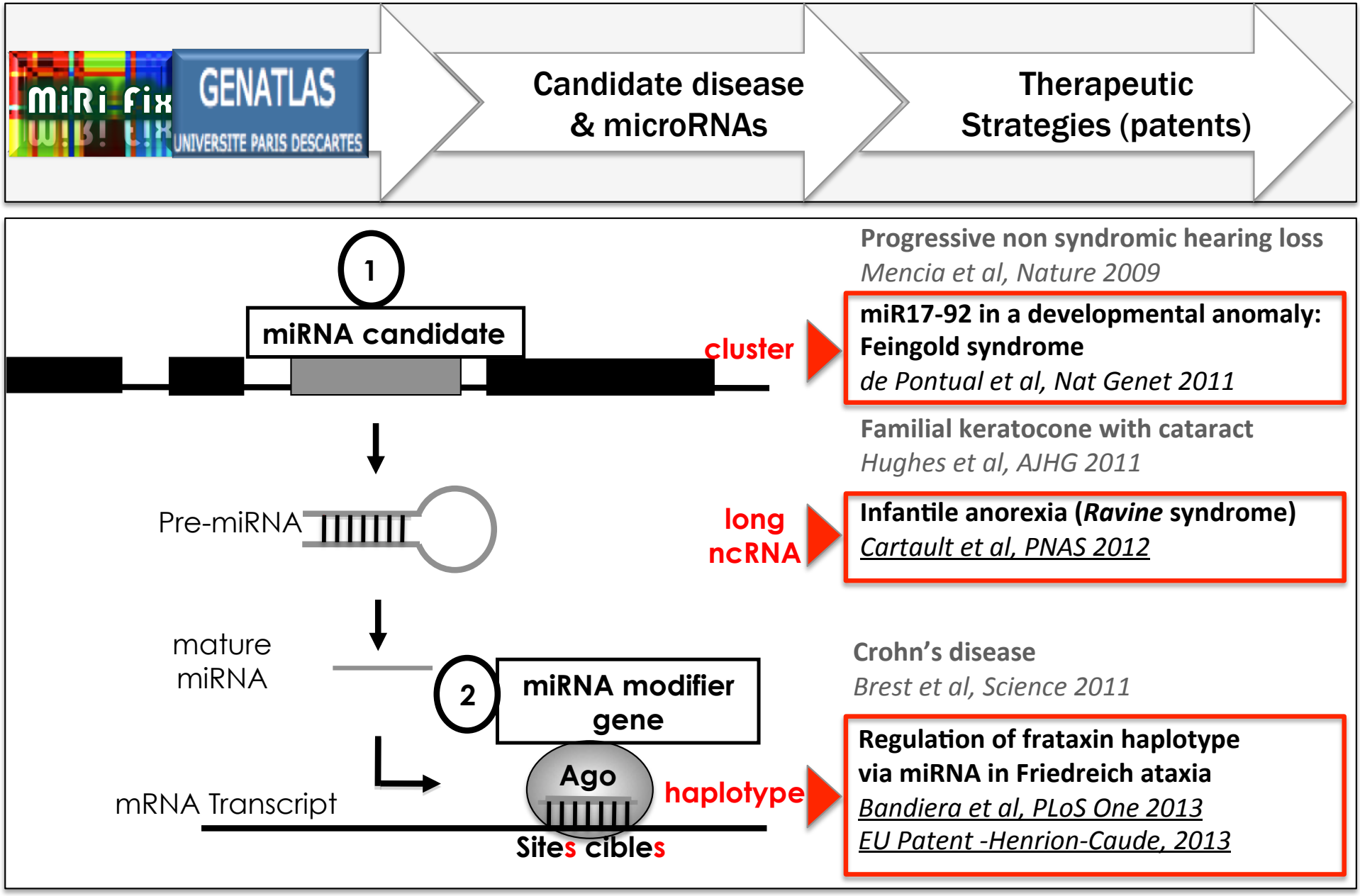
Rationnel non justifié



Rationnel justifié – Prise en compte des ncARNs



Maladies rares: source de variation fonctionnelle

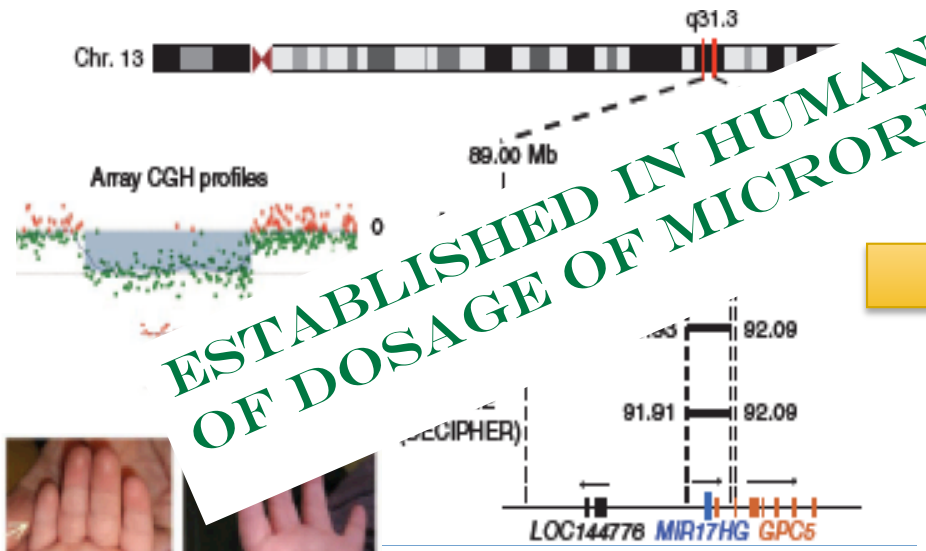


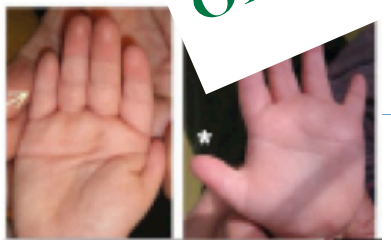
nature genetics LETTERS

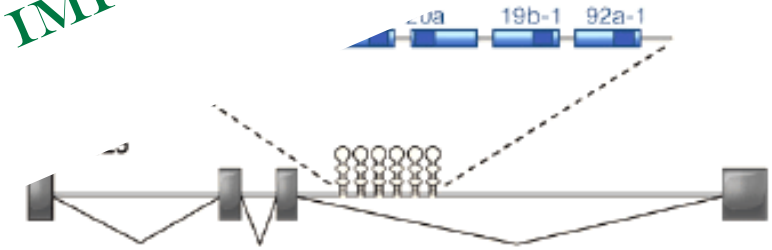
Germline deletion of the miR-17~92 cluster causes skeletal and growth defects in humans

Loïc de Pontual[1,2,10], Evelyn Yao[3,10], Patrick Callier[4], Laurence Faivre[4], Valérie Drouin[5], Sandra Cariou[1], Arie Van Haeringen[6], David Geneviève[7], Alice Goldenberg[5], Myriam Oufadem[1], Sylvi… nouvrier[8], Arnold Munnich[1,9], Joana Alves Vidigal[3], Michel Vekemans[1], Stanislas Lyonnet[1,9] …a Henrion-Caude[1], Andrea Ventura[3,10] & Jeanne Amiel[1,9,10]

ESTABLISHED IN HUMAN THE IMPORTANCE OF DOSAGE OF MICRORNAS

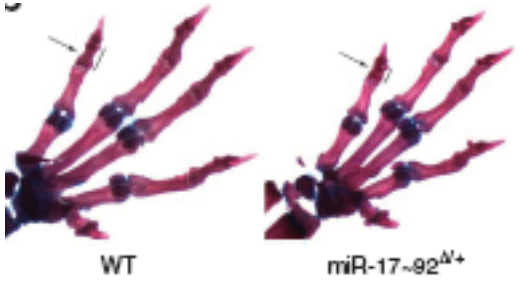






OncomiR-1

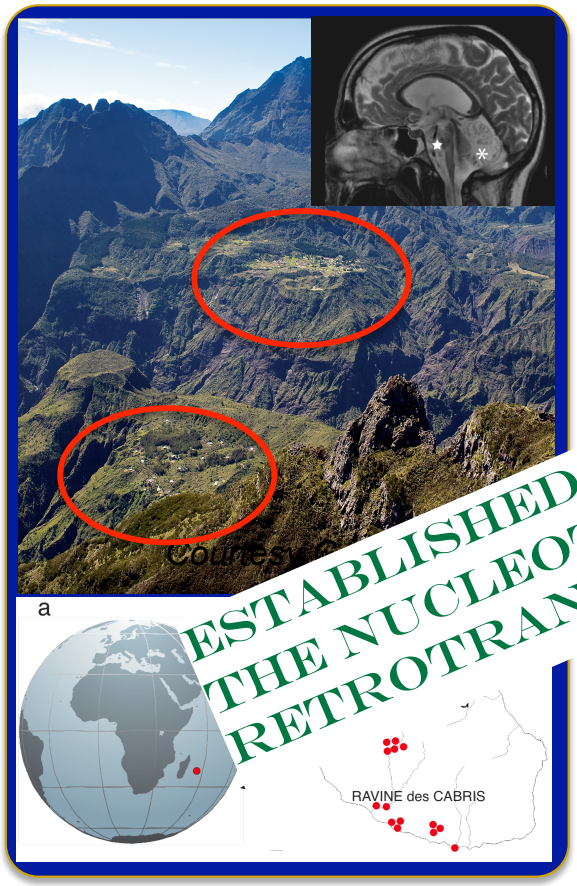
DevmiR

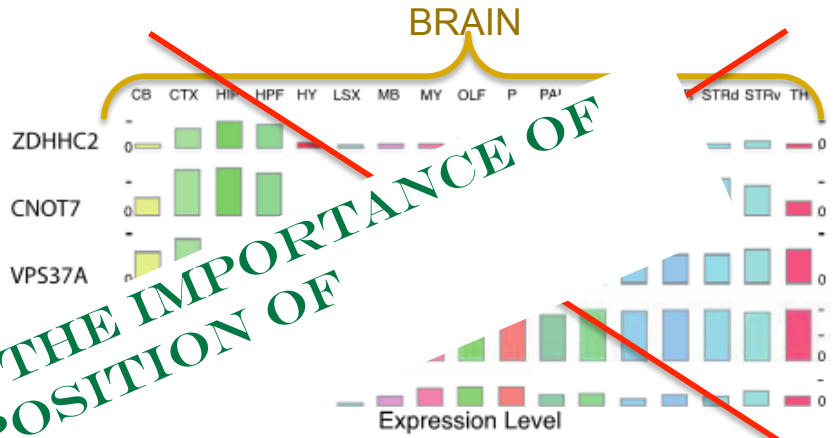


de Pontual et al, Nat Genet 2011

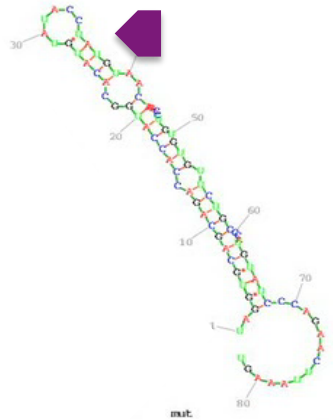
Mutation in a primate-conserved retrotransposon reveals a noncoding RNA as a mediator of infantile encephalopathy

François Cartault[a,b,1], Patrick Munier[a], Edgar Benko[c], Isabelle Desguerre[d], Sylvain Hanein[b], Nathalie Boddaert[e], Simonetta Bandiera[b], Jeanine Vellayoudom[a], Pascale Krejbich-Trotot[f], Marc Bintner[g], Jean-Jacques Hoarau[f], Muriel Girard[b], Emmanuelle Génin[h], Pascale de Lonlay[b], Alain Fourmaintraux[a,i], Magali Naville[j], Diana Rodriguez[k], Josué Feingold[b], Michel Renouil[i], Arnold Munnich[b,l], Eric Westhof[m], Michael Fähling[c,2], Stanislas Lyonnet[b,l,2], and Alexandra Henrion-Caude[b,1]



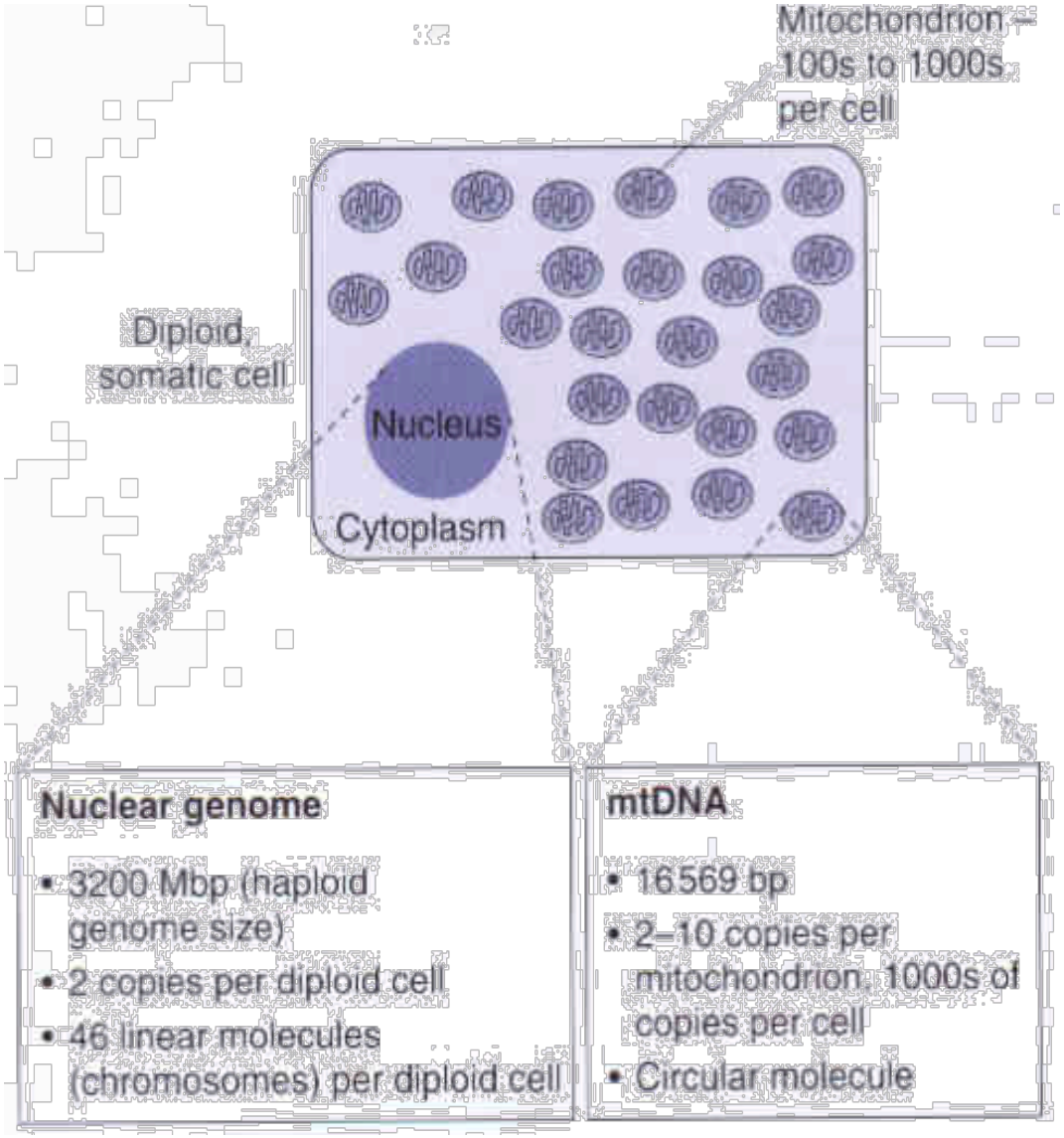


ESTABLISHED IN HUMAN THE IMPORTANCE OF THE NUCLEOTIDIC COMPOSITION OF RETROTRANSPOSONS

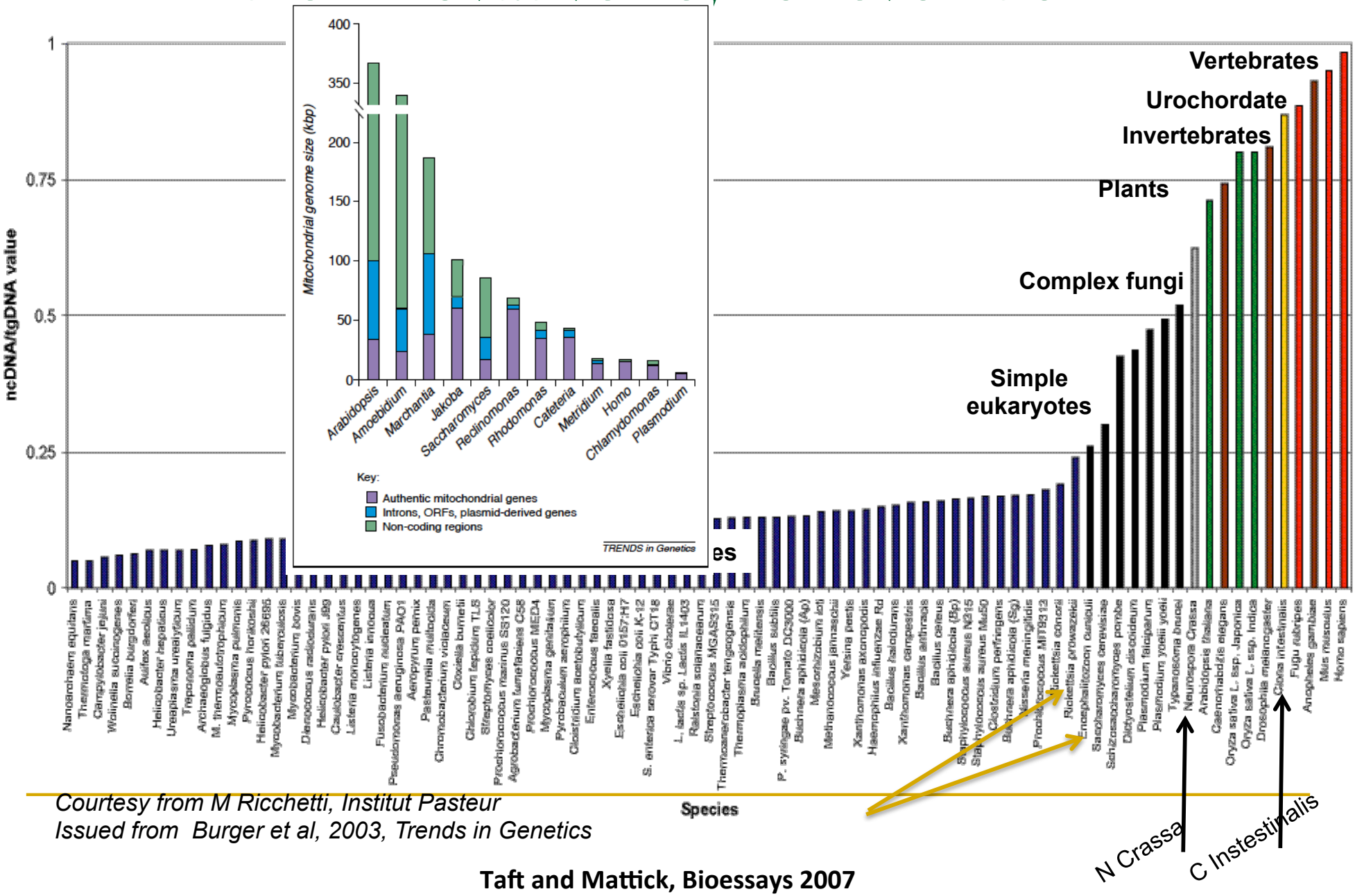


Cartault et al, PNAS 2012

Sans oublier notre autre génome



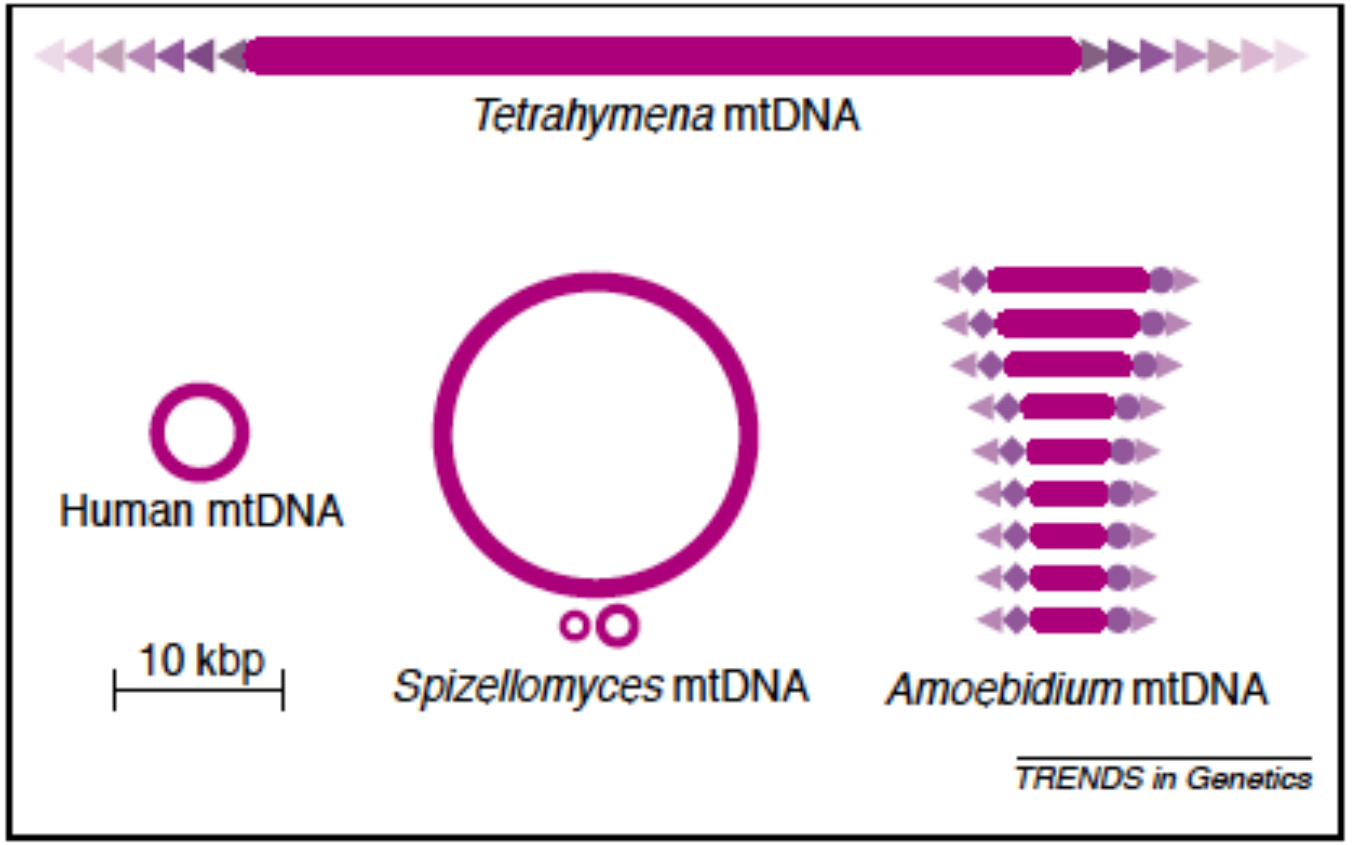
NON-CODING
-the innovative key for evolution-



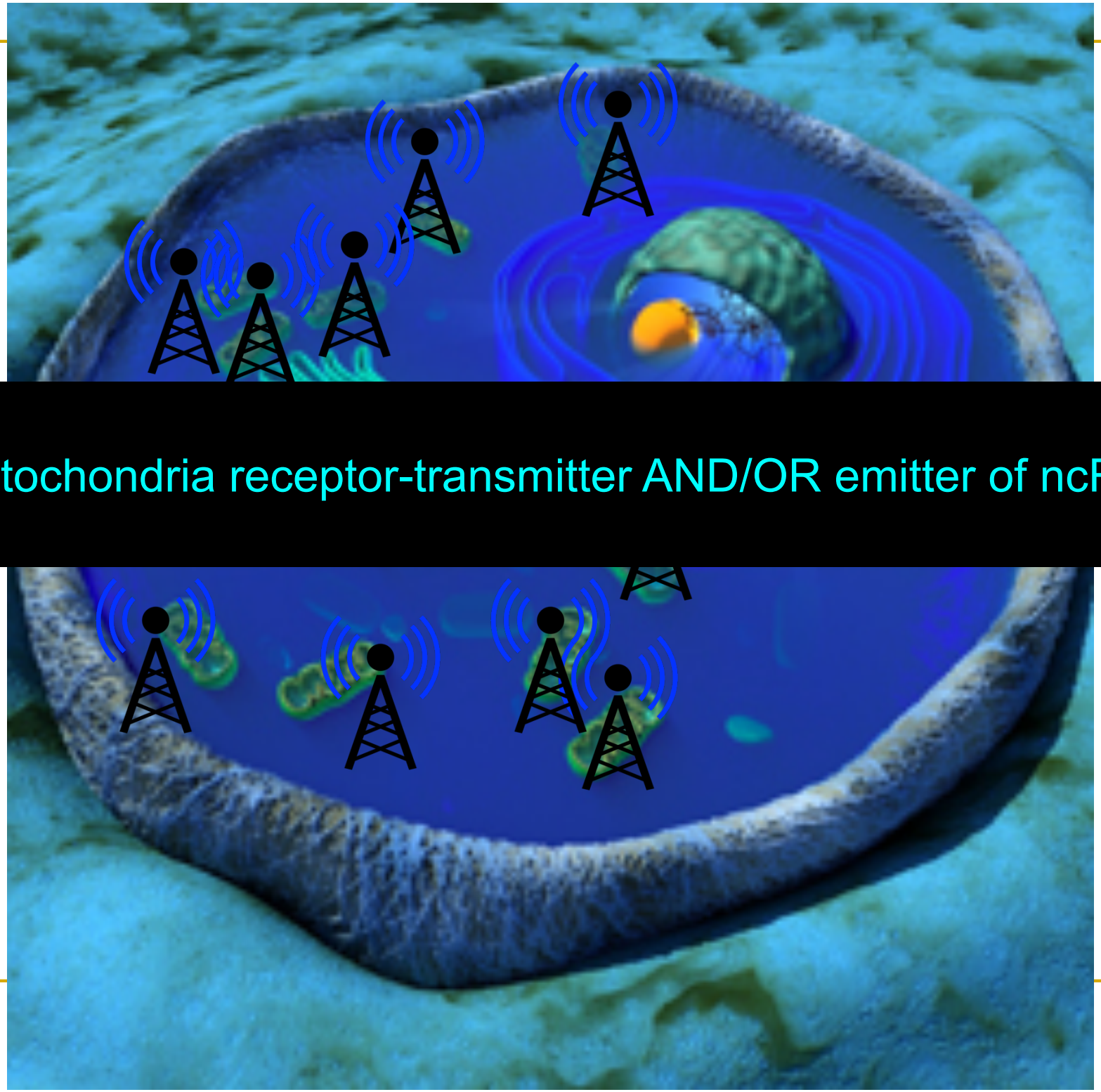
Courtesy from M Ricchetti, Institut Pasteur
Issued from Burger et al, 2003, Trends in Genetics

Taft and Mattick, Bioessays 2007

Mt genome architecture

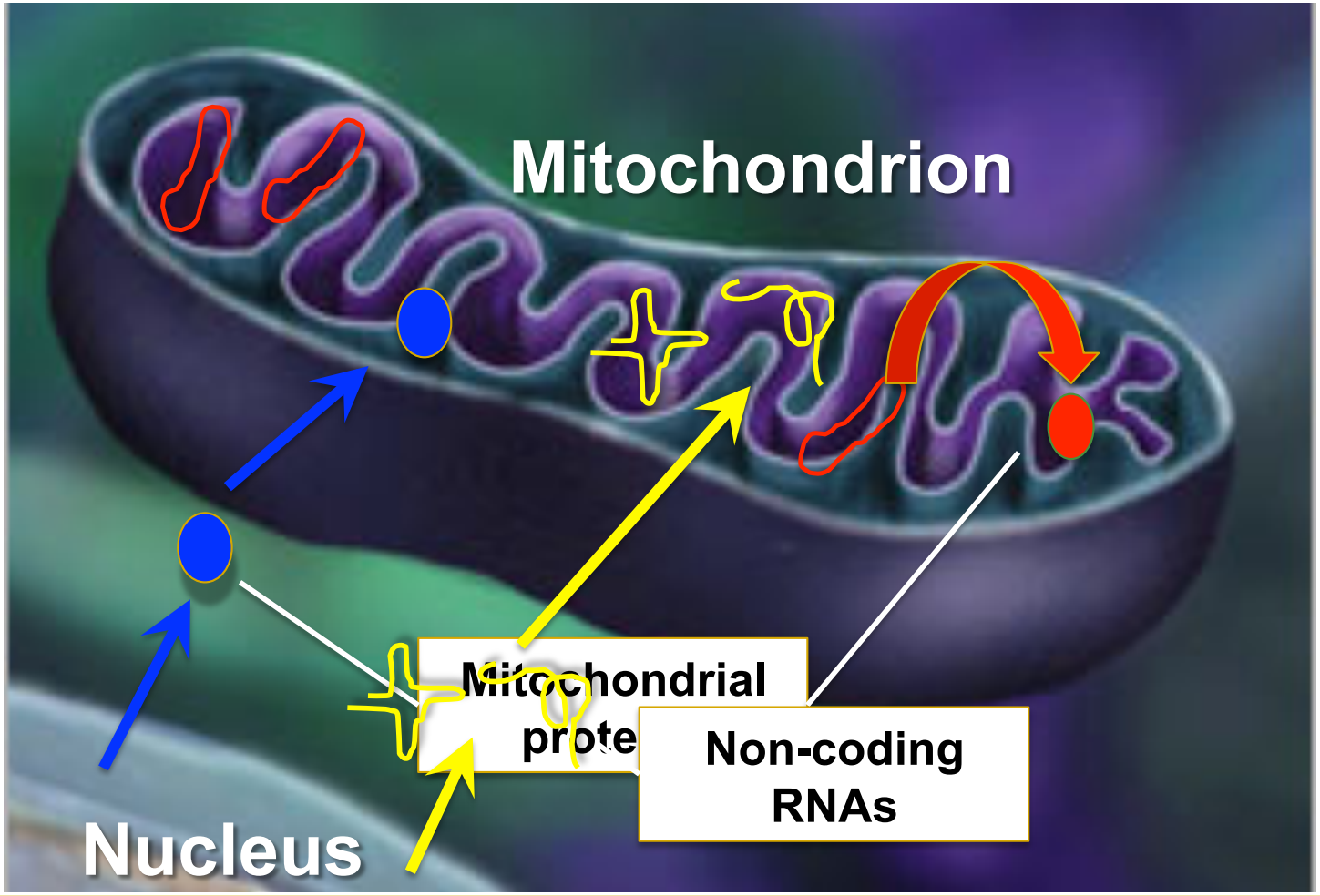


from Burger et al, 2003, Trends in Genetics 19



Are mitochondria receptor-transmitter AND/OR emitter of ncRNAs?

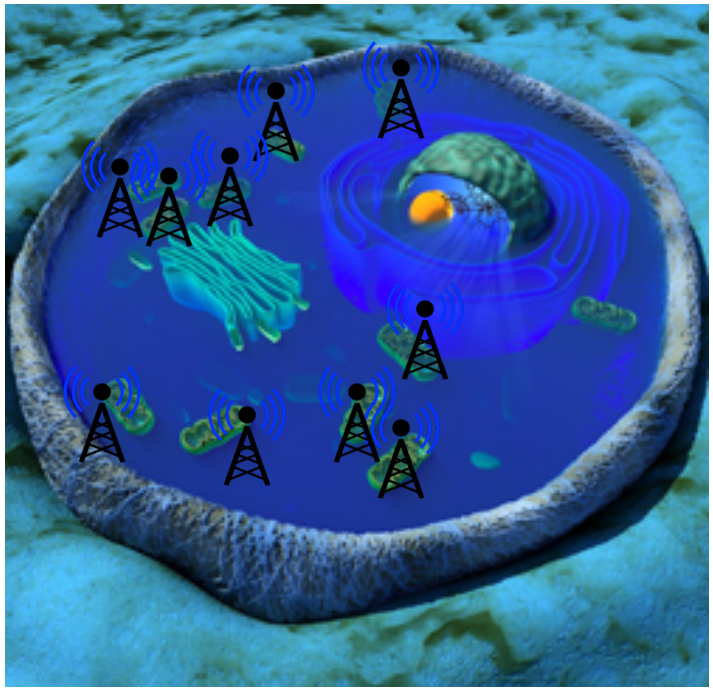
Traffick of non-coding RNA was known

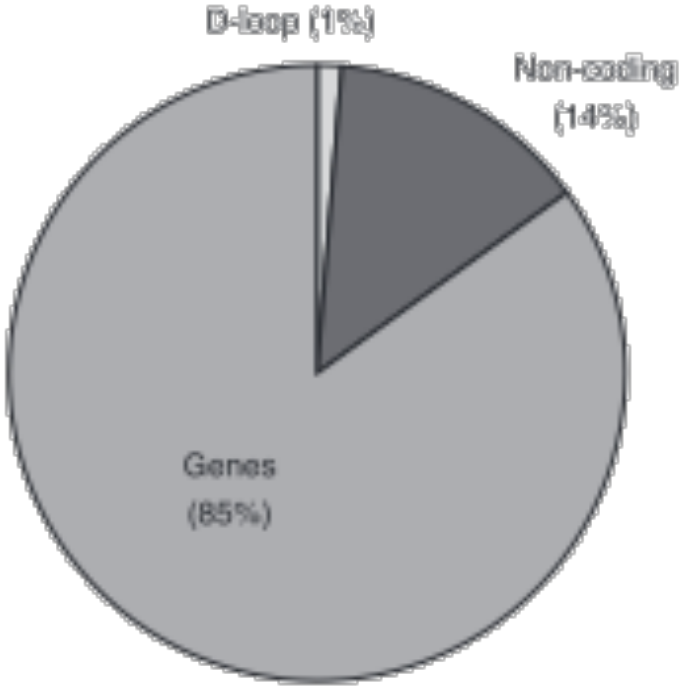


- *5S rRNA*
- RNA moieties of RNase MRP and RNase P
- 2 cytosolic $tRNA^{Gln}$

(Topper and Clayton, 1990; Entelis et al, 2001; Puranam and Attardi, 2001; Rubio et al, 2008)

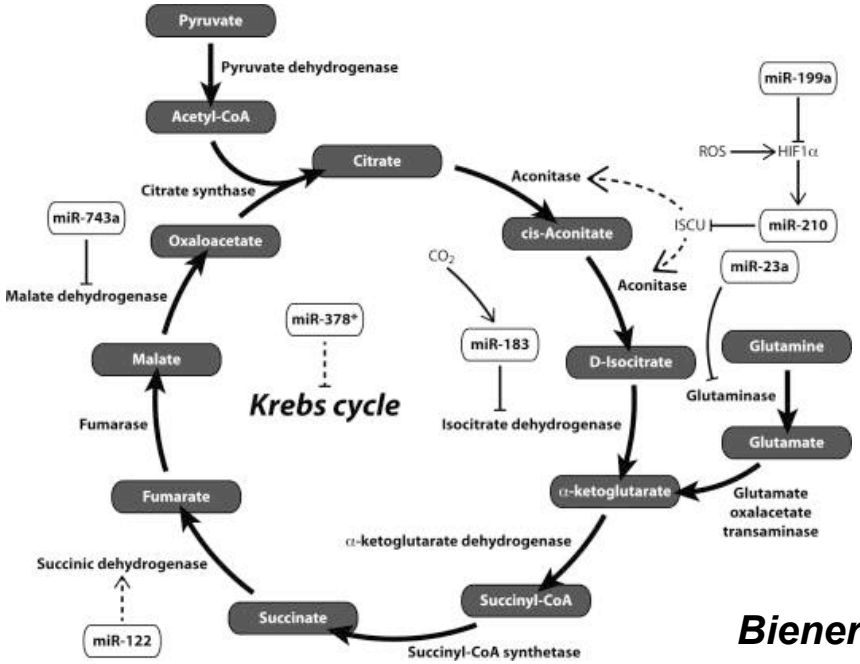
Mitochondrion: emitter of small AND long ncRNAs

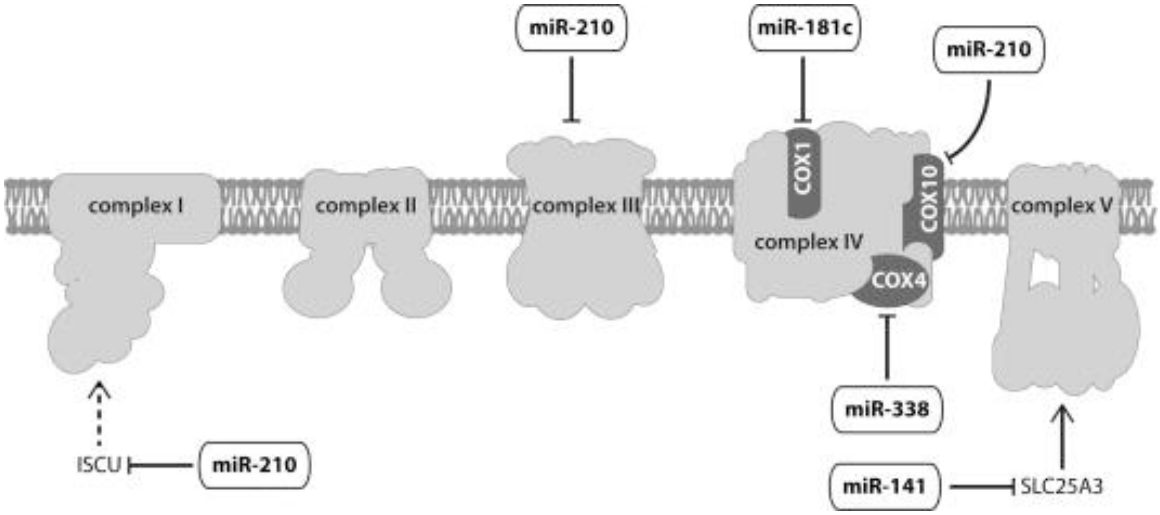




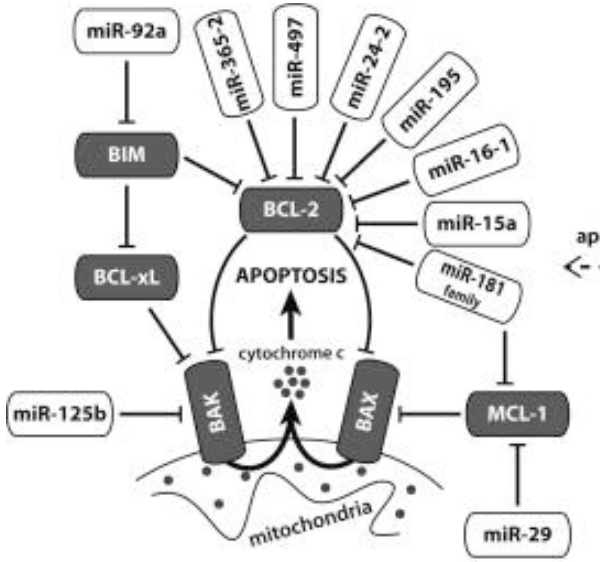
Rackham et al, RNA 2011

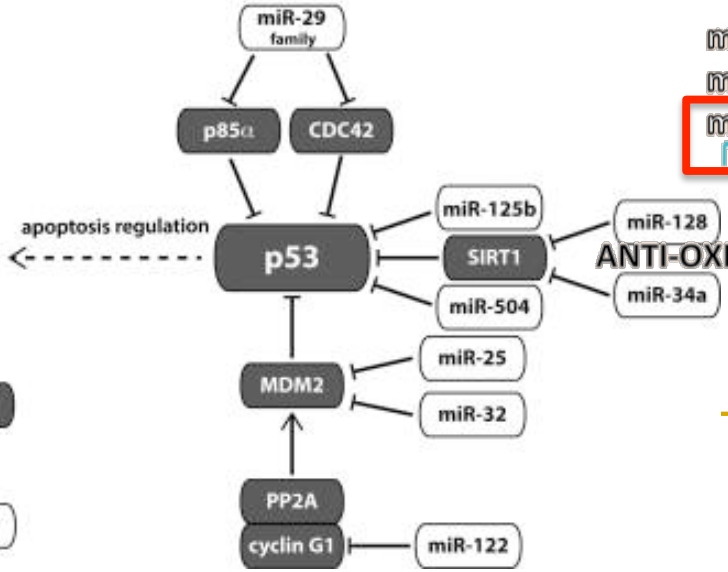
Mitochondrial regulation *via microRNA*

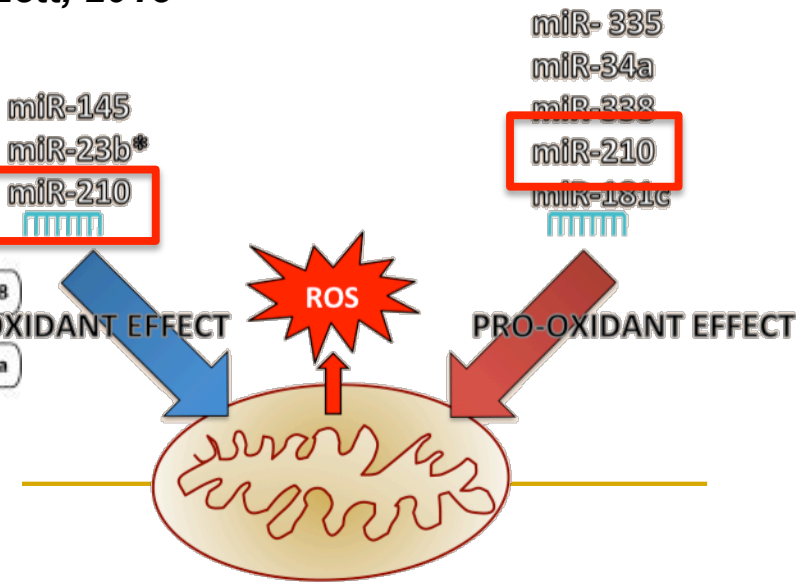




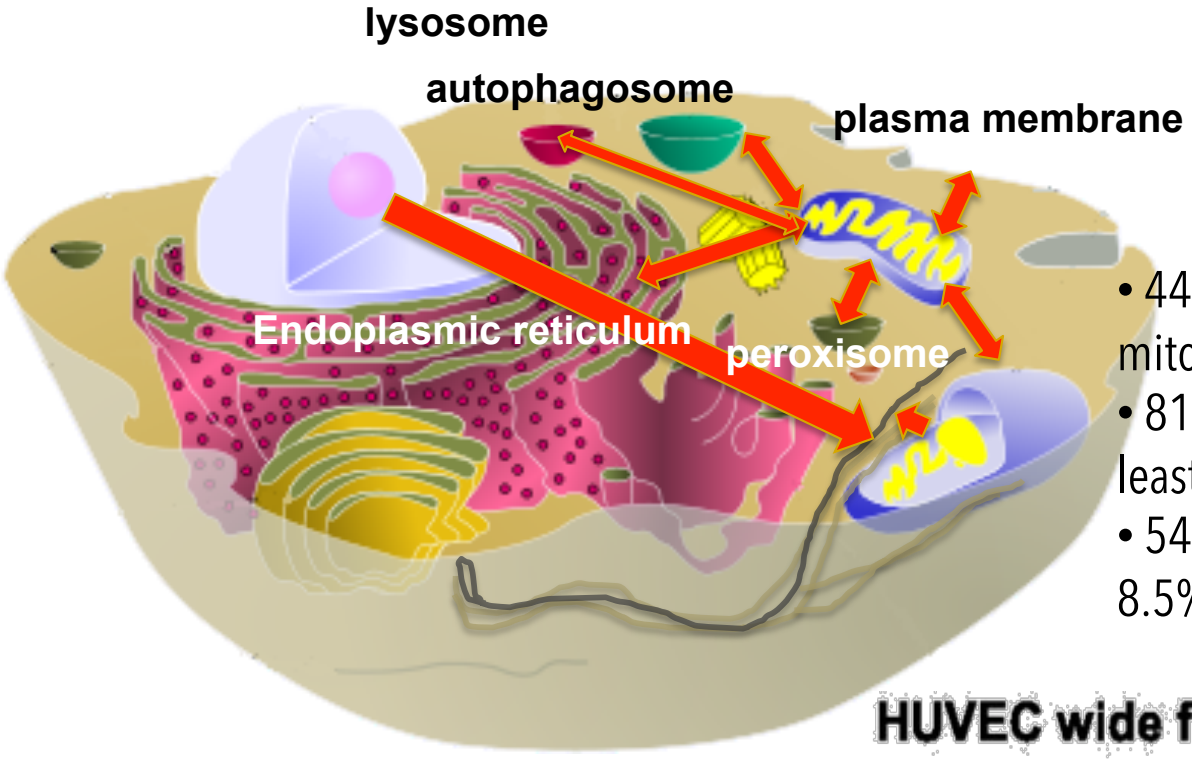
Bienertova-Vasku, Cancer Lett, 2013





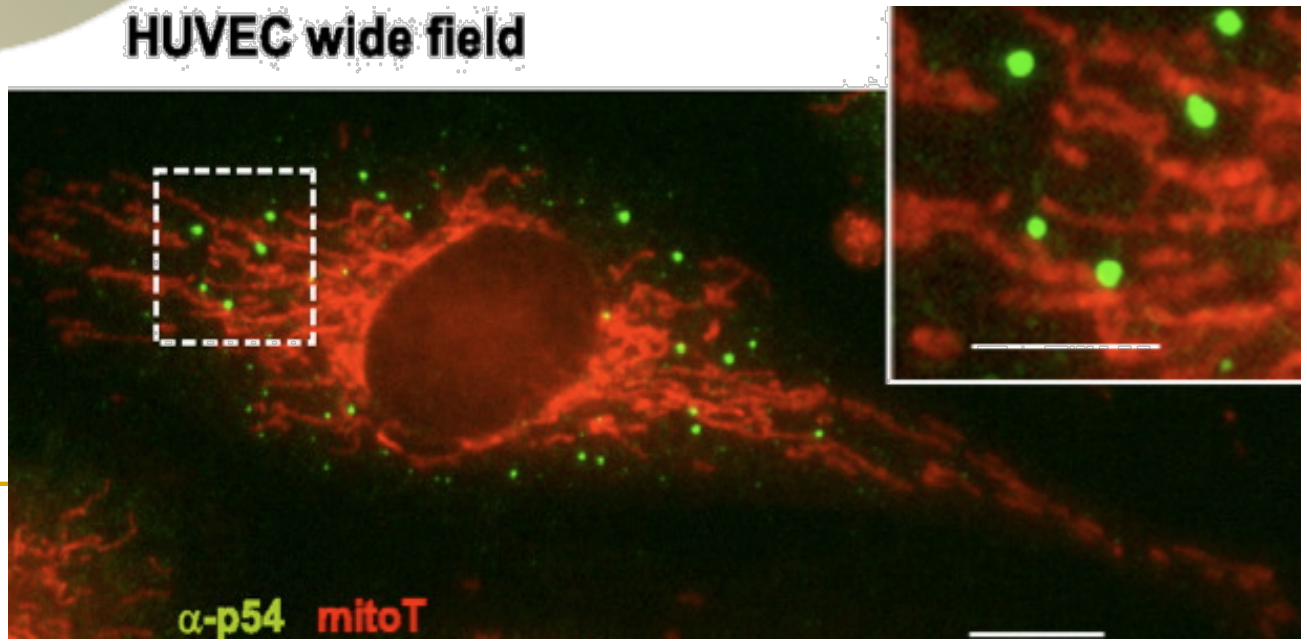


Mitochondria, P-bodies and RNAi



and P-bodies…

- 44% of the P-bodies were associated with mitochondria (time 0).
- 81% of the P-bodies contacted a mitochondrion at least once during the 3-min movie.
- 54.5% of the contacts lasted more than 12 s, and 8.5% more than 3 min.



Huang, JBC, 2011

Functional evidences of mitomiRs

miR-181c in heart

IN VITRO

Nuclear miRNA Regulates the Mitochondrial Genome in the Heart

Samarjit Das, Marcella Ferlito, Oliver A. Kent, Karen Fox-Talbot, Richard Wang, Delong Liu, Nalini Raghavachari, Yanqin Yang, Sarah J. Wheelan, Elizabeth Murphy, Charles Steenbergen

Das et al, Circ Res 2012

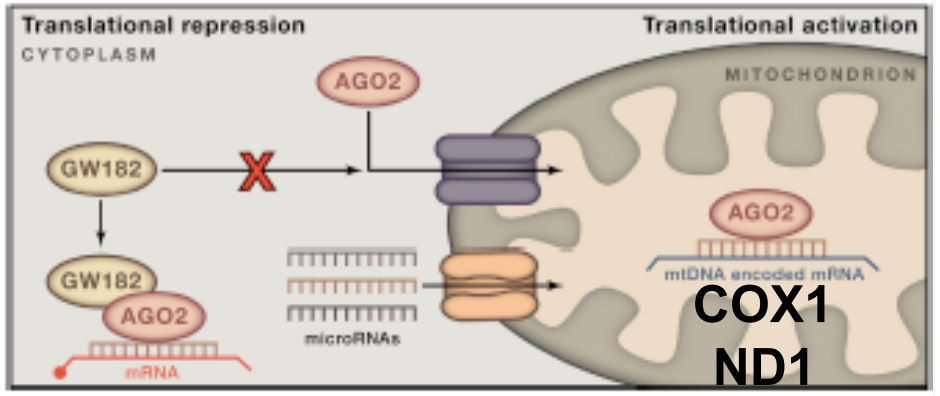
IN VIVO

miR-181c Regulates the Mitochondrial Genome, Bioenergetics, and Propensity for Heart Failure *In Vivo*

Samarjit Das, Djahida Bedja, Nathaniel Campbell, Brittany Dunkerly, Venugopal Chenna, Anirban Maitra, Charles Steenbergen

Das et al, PLoS One 2014

miR-1 in myogenesis



Zhang et al, Cell 2014

miR-378 in diabetic heart

AGO2
FXR1
ATP6

Circ Cardiovasc Genet. 2015 Sep 16. pii: CIRCGENETICS.115.001067. [Epub ahead of print]

Translational Regulation of the Mitochondrial Genome Following Redistribution of Mitochondrial MicroRNA (MitomiR) in the Diabetic Heart.

miR-378

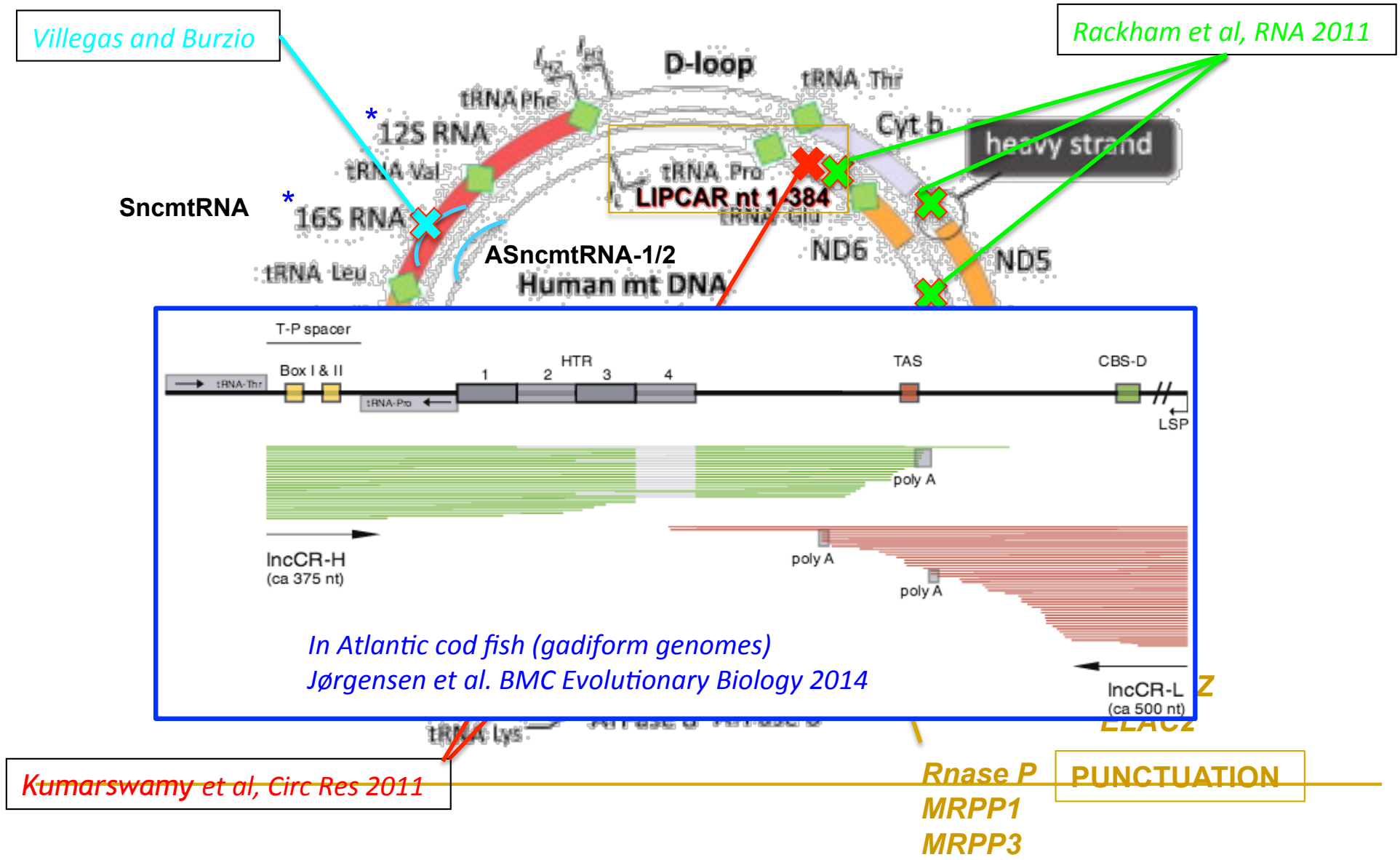
Jagannathan R[1], Thapa D[1], Nichols CE[1], Shepherd DL[1], Stricker JC[2], Croston TL[1], Baseler WA[1], Lewis SE[1], Martinez I[3], Hollander JM[4].

Jagannathan et al, Circ Genet 2015

Mitochondrial regulation *via lncRNA*

lncRNA	Illustrative cases	References
HIF1A-AS1 (antisense HIF1A)	Apoptosis inhibitor	Wang et al. *Mol Cell Biochem* 2015
HOTAIR (antisense HOXC)	Mitochondrial homeostasis in cancer cells	Zheng et al. *Mol Cell Proteom* 2015
CARL (Cardiac Apoptosis-Related lncRNA)	Inhibits anoxia-induced fission (via PHB2) Apoptosis inhibitor Sponges miR-539	Wang et al. *Nat Commun* 2014
MDRL (Mitochondrial Dynamic Related lncRNA)	Mitochondrial network Sponges mir-361 & promotes processing of miR-484	Wang et al. *PLoS Genet* 2014

Map of long noncoding RNAs (lncRNAs) on the human mitochondrial genome



Adapted from Sadakierska-Chudy et al, Pharm & Ther, 2014

En résumé:

Leading Edge
Review

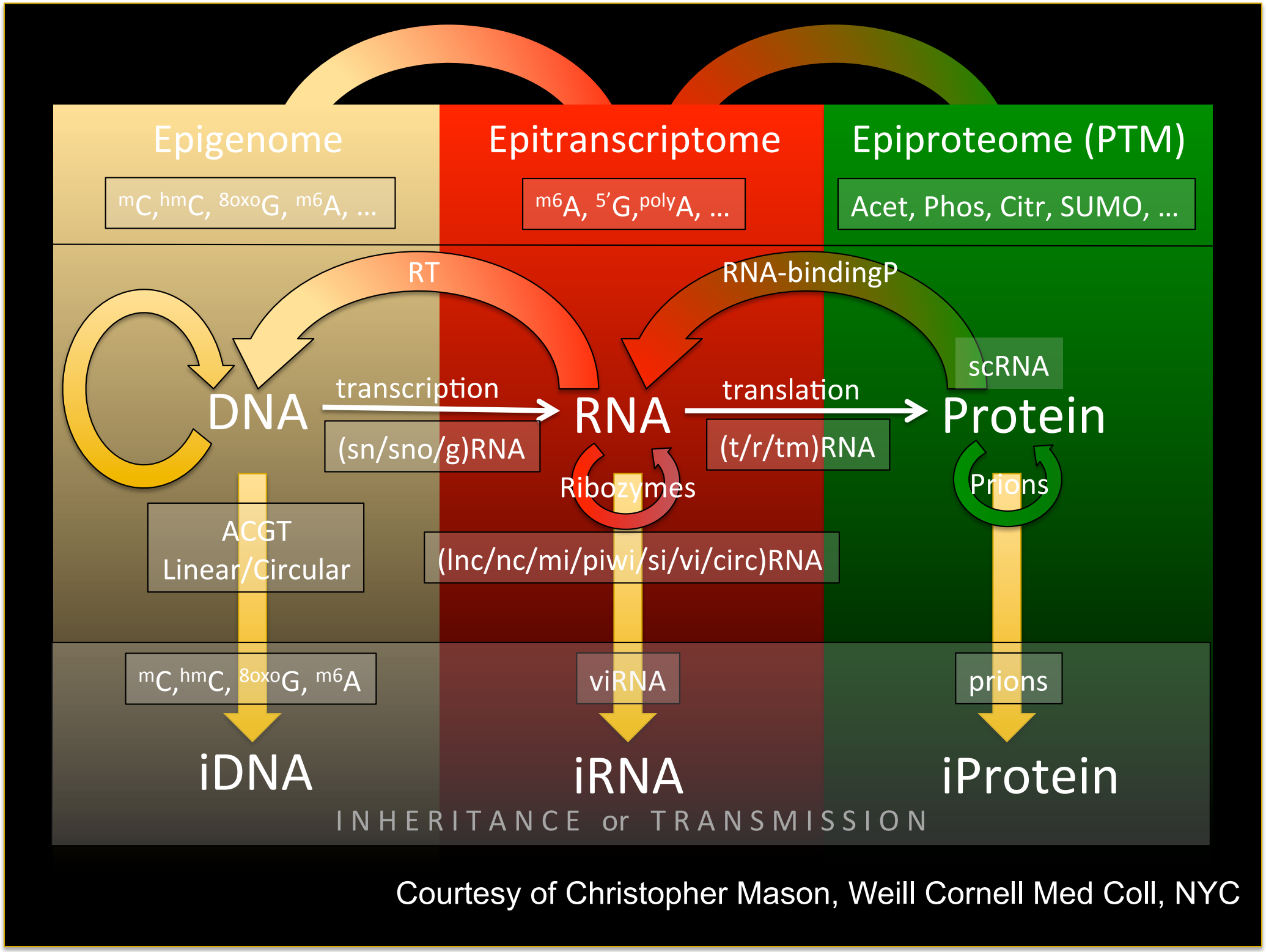
Cell

The Noncoding RNA Revolution—Trashing Old Rules to Forge New Ones

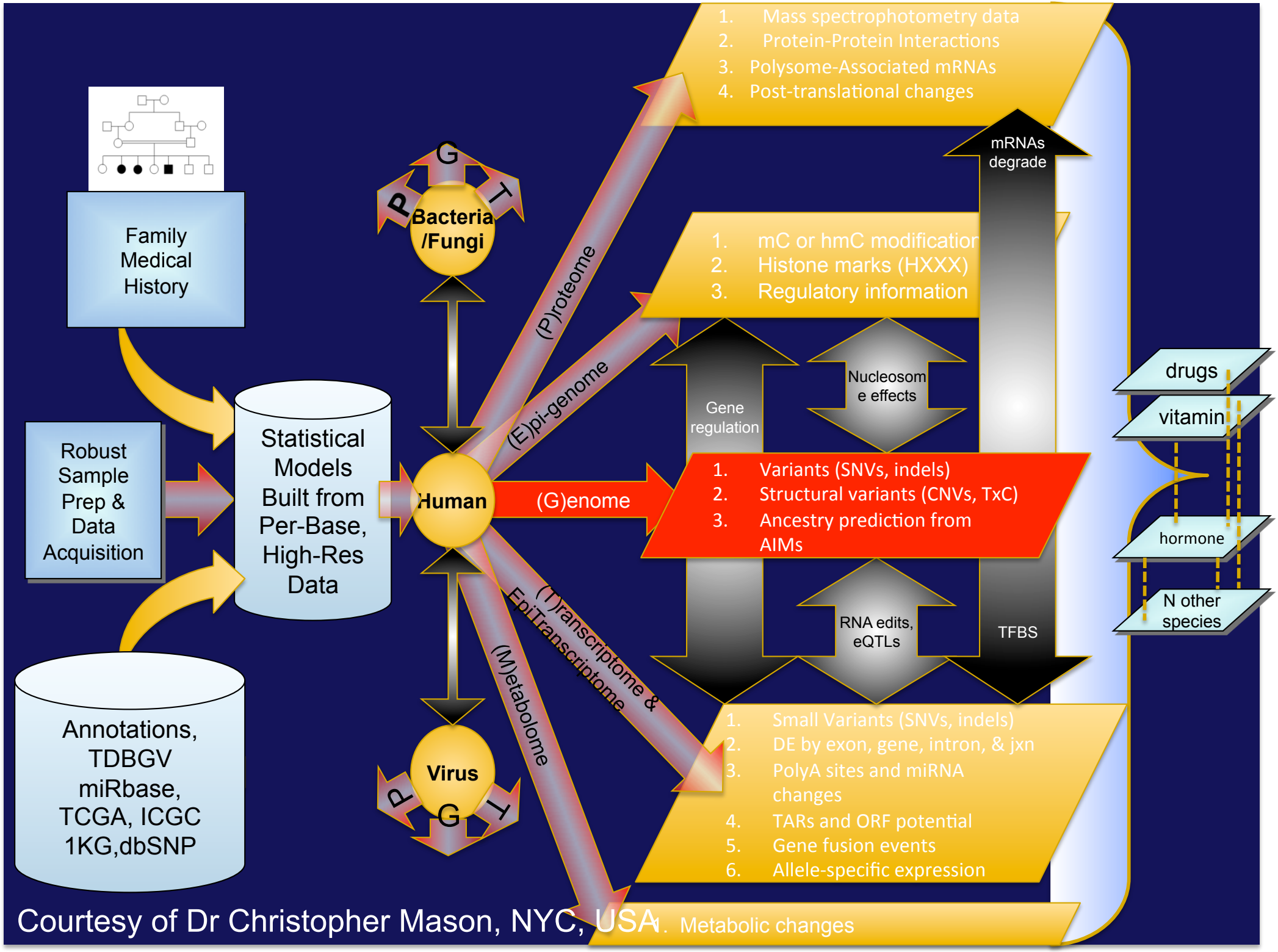
Thomas R. Cech[1,2,*] and Joan A. Steitz[1,3]
[1]Howard Hughes Medical Institute
[2]Department of Chemistry & Biochemistry, BioFrontiers Institute, University of Colorado Boulder, Boulder, CO 80309, USA
[3]Department of Molecular Biophysics and Biochemistry, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT 06536, USA
*Correspondence: thomas.cech@colorado.edu
http://dx.doi.org/10.1016/j.cell.2014.03.008

En résumé

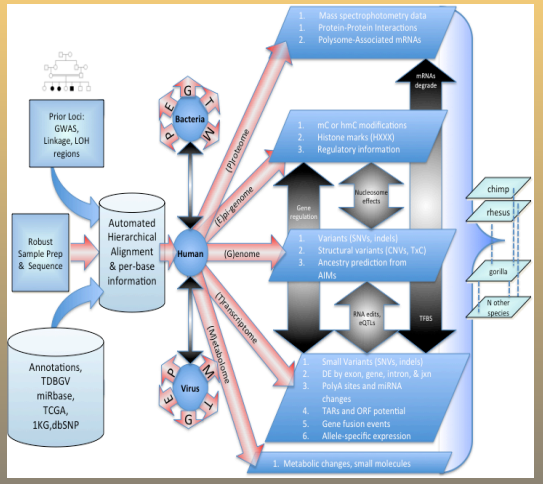
- Les ARNnc sont **divers dans leurs structures**, avec une taille qui varie de 20 nt à 100 kb.
- Les ARNnc, longs ou courts, jouent un rôle essentiel dans de nombreux processus biologiques et sont cruciaux pour le **développement** et dans les **maladies**, et interviennent probablement dans **l'évolution** des organismes.
- La plupart des ARNnc dont la fonction a été caractérisée participe à la **régulation de l'expression**.
- Leurs propriétés leur permettent de fonctionner:
  - soit par **complémentarité de séquence** nucléotidique ARN/ADN, ARN/ARN
  - soit en **formant des structures** avec des protéines et/ou des acides nucléiques.
- Les sous-classes de **petits ARN non-codants** sont relativement bien définies et déterminent des modes de fonctionnement semblables. Ce qui n'est pas le cas des **longs ARN non-codants**.
- Tous **sont mis en jeu dans la mitochondrie,** issus ou non du génome mitochondrial. Avec des spécificités mécanistiques.



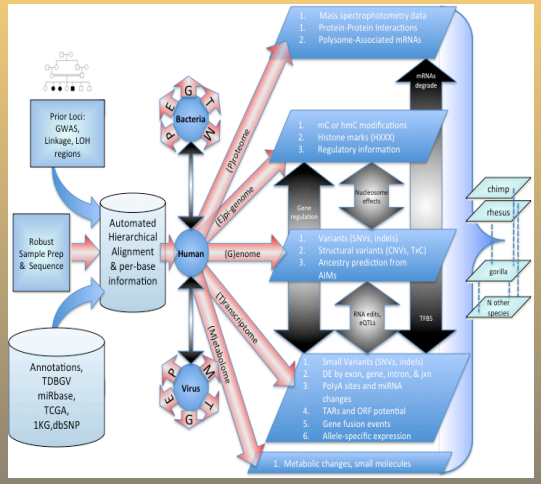
Courtesy of Christopher Mason, Weill Cornell Med Coll, NYC


Family Medical History
Robust Sample Prep & Data Acquisition
Statistical Models Built from Per-Base, High-Res Data
Annotations, TDBGV miRbase, TCGA, ICGC 1KG,dbSNP
Bacteria /Fungi
Virus
Human
(P)roteome
(E)pi-genome
(G)enome
(T)ranscriptome & EpiTranscriptome
(M)etabolome
1. Mass spectrophotometry data
2. Protein-Protein Interactions
3. Polysome-Associated mRNAs
4. Post-translational changes
mRNAs degrade
1. mC or hmC modification
2. Histone marks (HXXX)
3. Regulatory information
Gene regulation
Nucleosome effects
1. Variants (SNVs, indels)
2. Structural variants (CNVs, TxC)
3. Ancestry prediction from AIMs
RNA edits, eQTLs
TFBS
1. Small Variants (SNVs, indels)
2. DE by exon, gene, intron, & jxn
3. PolyA sites and miRNA changes
4. TARs and ORF potential
5. Gene fusion events
6. Allele-specific expression
1. Metabolic changes
drugs
vitamin
hormone
N other species
Courtesy of Dr Christopher Mason, NYC, USA

Environment



T=0



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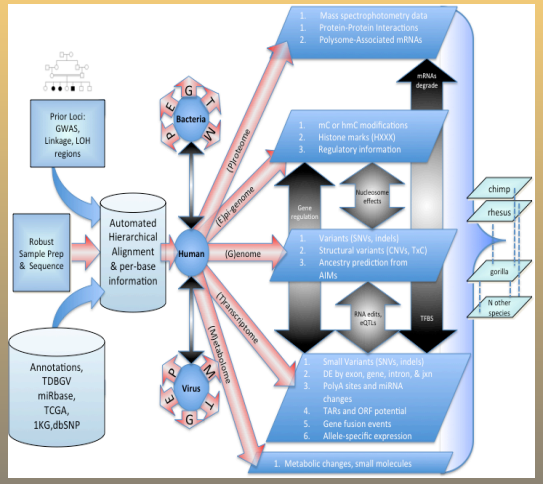
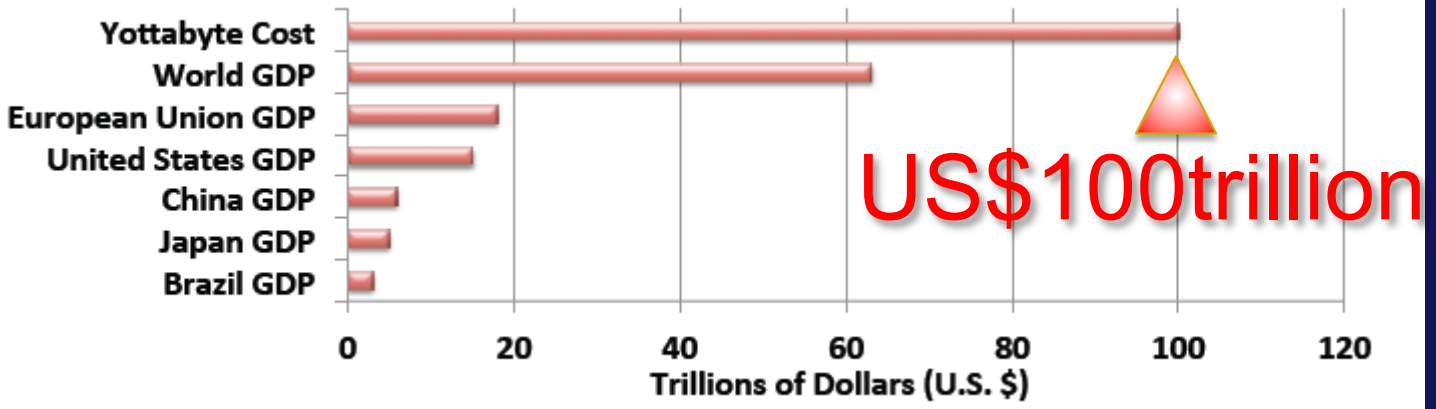


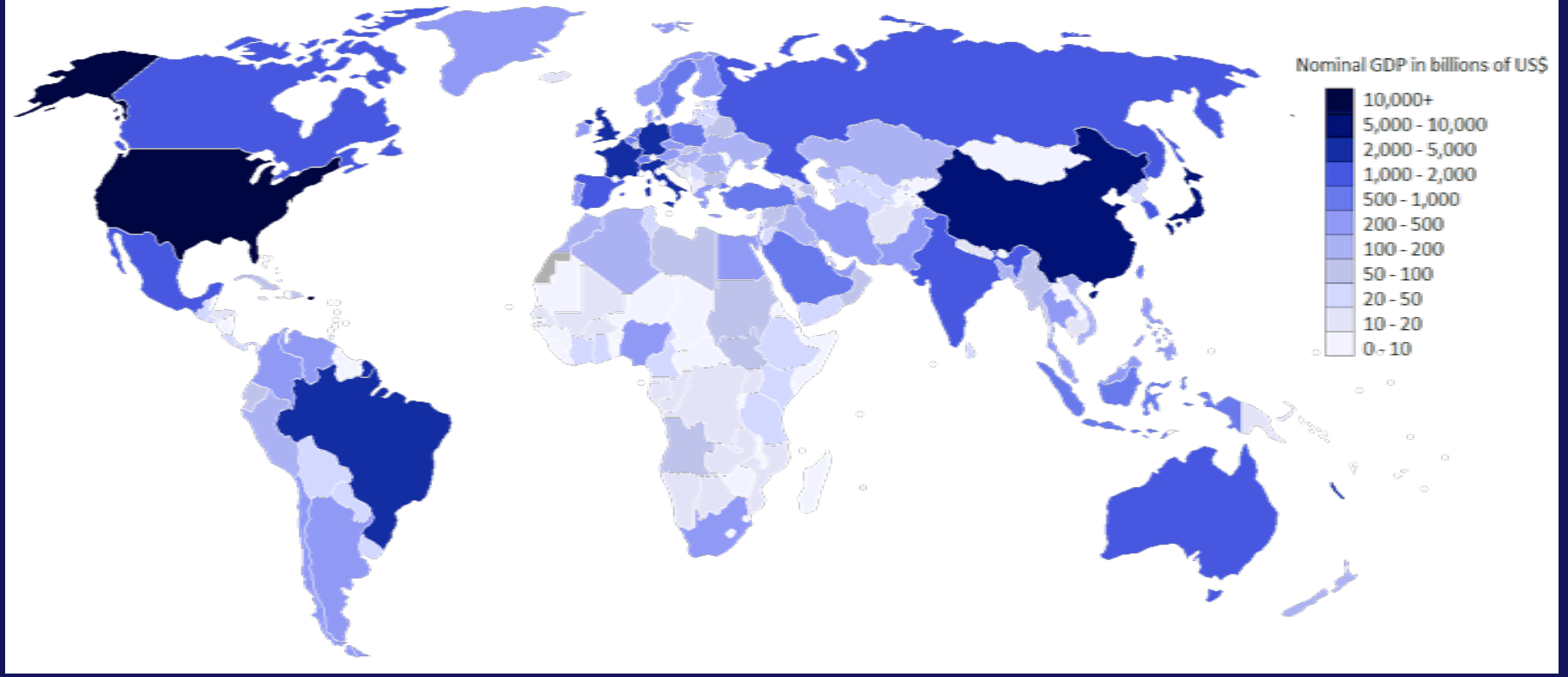
T=N

Environment

Courtesy of Christopher Mason, Weill Cornell Med Coll, NYC

WANTED 1 Yottabyte = 1 trillion Terrabyte





Courtesy of Christopher Mason, Weill Cornell Med Coll, NYC

Construire une recherche et une santé durable

Soigner l'humain
Manifeste pour un juste soin au juste coût

17 décembre 2015
Hôpital Saint-Louis, Paris

- Homme-Plantes: une relation symbiotique méconnue (le baobab, arbre des palabres / le chêne, dans nos contrées)

Ameenah Gurib-Fakim, présidente de l'ile Maurice, lauréate Oreal-Unesco : La chimiste décode les vertus thérapeutiques d'une centaine de plantes

LAST UPDATED ON MONDAY, 16 NOVEMBER 2015 11:51 | WRITTEN BY AMA
MONDAY, 16 NOVEMBER 2015 11:18

- 80 % de la population mondiale dépendent de ces plantes médicinales (d'après l'OMS)

- Plantes médicinales ont une valeur marchande chiffrée

≥ 60 milliards de dollars

Acknowledgements

Inserm UMR1163– Institut Imagine, Paris

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Platforme d'imagerie cellulaire IFR 94

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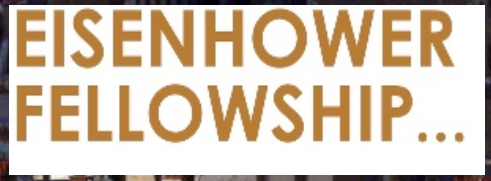


« Toute vérité franchit trois étapes. D'abord elle est ridiculisée. Ensuite, elle subit une forte opposition. Puis, elle est considérée comme ayant toujours été une évidence. » A. Schöpenhauer

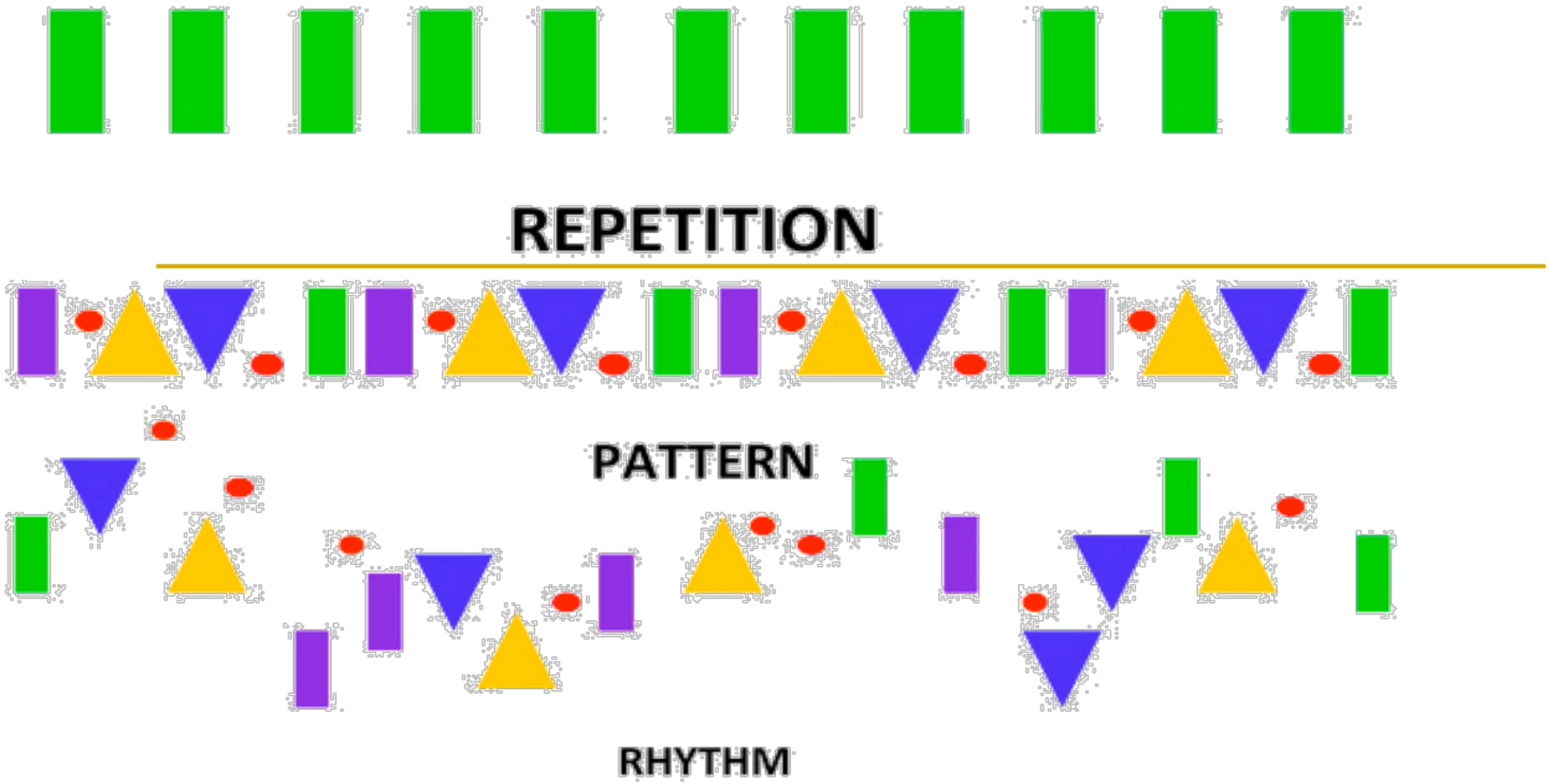
Traitement du SCORBUT	Soigner l'humain *Manifeste pour un juste soin au juste coût*	**Traitement du PALUDISME**
Découvertes empiriques: Fraîcheur des agrumes?	**QUALITÉ DE L'OBSERVATION** (temps, échange)	*Découvertes empiriques: Éparses Sous le sceau du secret*
A l'encontre de… la compréhension médicale de l'époque	**OBSTACLES** (transmission, mode du moment)	*A l'encontre de… la volonté de comprendre de l'époque (OMS)*
Importance du mode d'administration (fraîcheur)	**UN DESIGN DURABLE** (galénique, intérêt économique)	*Importance du mode d'extraction (sans bouillir)*

Reaching beyond ignorance: what is repetition?

Repetition refers to one object or shape repeated (disappointing: junk!).

Pattern is a combination of elements or shapes repeated in a recurring and regular arrangement.

Rhythm is a combination of elements repeated, but with variations.



What is the best analogy?

A combinatorial view of "Plug and Play" RNA motifs

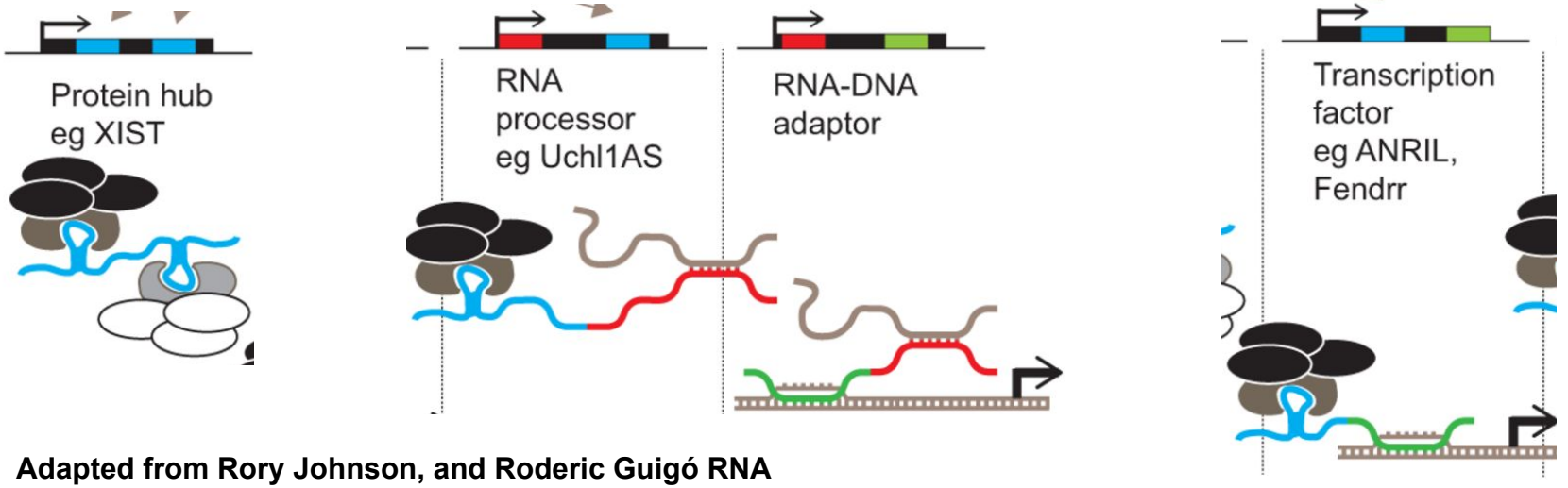
@Chang's lab
icChIPed by any chance, Howard?

In Mathematics: - If the order does not matter, it is a **Combination.**
- If the order does matter, it is a **Permutation (i.e. ordered combination).**

In Poetry: Repetition is a basic unifying device.
It may reinforce, supplement, or even substitute for meter.

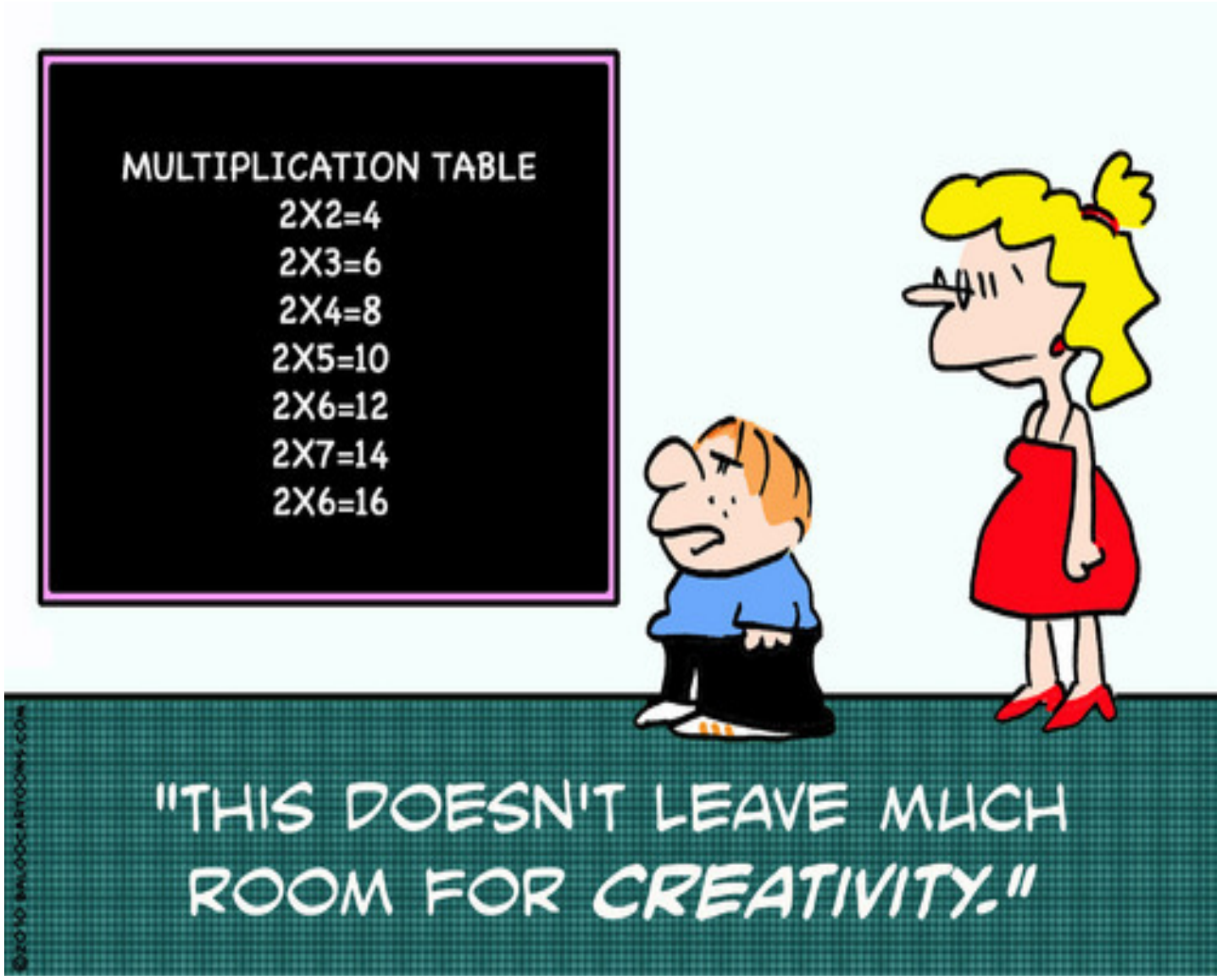
The RePeat Insertion Domains of LncRNAs hypothesis
(Johnson&Guigo, 2014)
PLUG-AND-PLAY

1. RNA/Protein
2. RNA/RNA
3. RNA/DNA



Adapted from Rory Johnson, and Roderic Guigó RNA 2014;20:959-976

Repetition is learning



A core principle of music is repetition

FAMILIARITY

INSTRUCTIVITY

MEMORY

EFFECT

CUES

TRANCE

Why do we listen to our favourite music over and over again? Because repeated sounds work **magic** in our brains

Repetition is so powerfully linked with **musicality** that its application can dramatically **transform:** non-musical materials => song

This takes place by shifting our **perceptual circuitry** such that the segment of sound is heard as music.

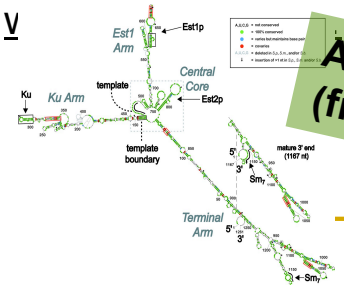
Music originates from « noise »… (free adaptation from Mattick's talk)

Alu RBP: STAU1, SRP14, p68… (free adaptation from Maquat's talk)

Repetition serves as a **handprint of human intent**. A phrase that might have sounded arbitrary the first time might come to sound purposefully « shaped and communicative » the second.

Can you make anything into music just by repeating it?

Yes! No matter the constituent material, whether it's strings of syllables or strings of pitches, it seems that the brute force of repetition can work to musicalise sequences of sounds, triggering a profound shift in the v



An arm in your back, on your leg… (free adaptation from Cech's talk)

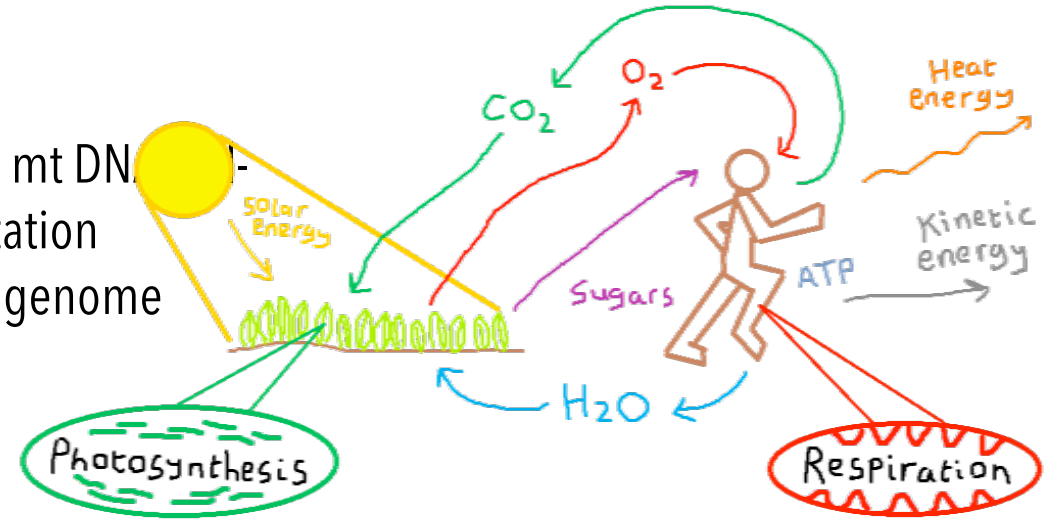
No, there seems to be something special about sound. The few studies that have transferred musical devices, such as rhythm, repetition, and periodicity, to non-auditory domains – flashing lights, for example – suggest that the distinctive kinds of mental processing associated with music are harder to elicit when the basic material isn't sonic

L'intérêt d'un génome modèle: la mitochondrie?

- closed-circular
- double-stranded
- ternal inheritance
- reduced model but abundant -approx 1000 mt DN[illegible]-

heteroplasmyexceptional economy of organization

- much smaller (16,500 bp) than the nuclear genome
- normally does not undergo recombination
- relatively rapid sequence evolution
- inter-relates with other genome



- haploid genome
- ma