



Hamar Péter RNS világ

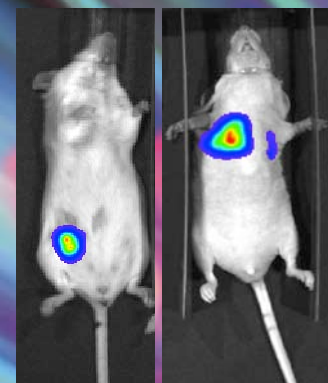
Lánczos Kornél Gimnázium,
Székesfehérvár, 2014. október 21.

www.meetthescientist.hu

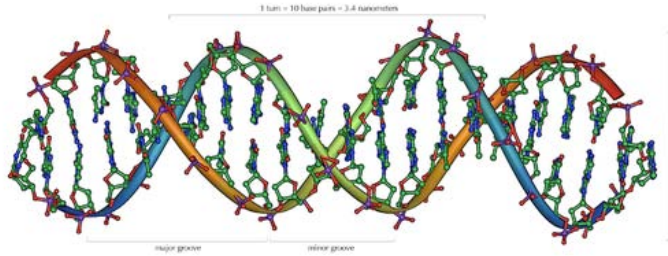
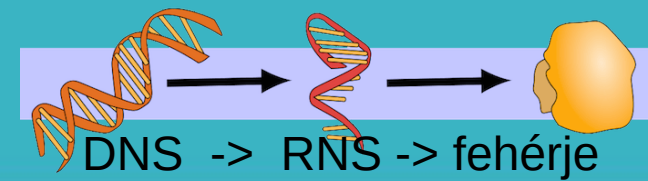


ORSZÁGOS TUDOMÁNYOS KUTATÁSI ALAPPROGRAMOK

OTKA



Főszereplők:

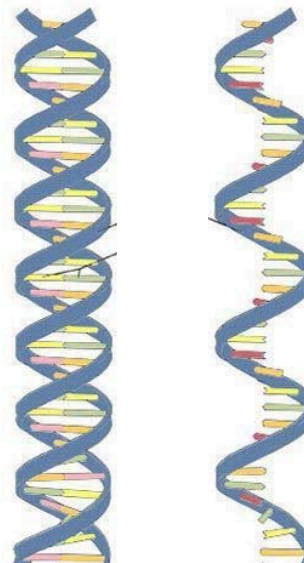


Deoxy-ribo-**N**uklein-**S**av:
DNS az élet kódja

megkettződés
(replikáció)

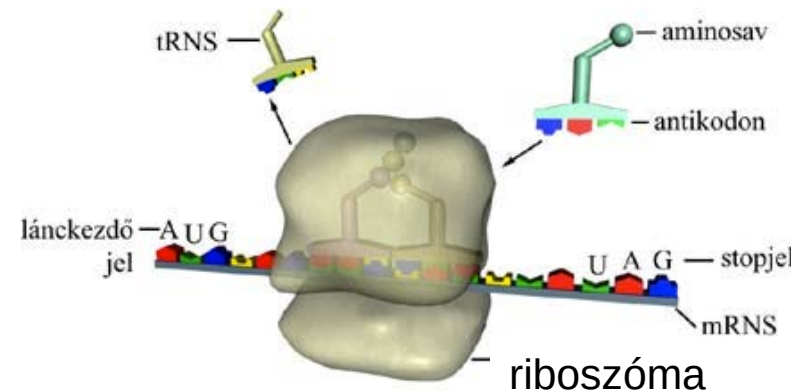
átírás
(transzkripció)

A kód lefordítása



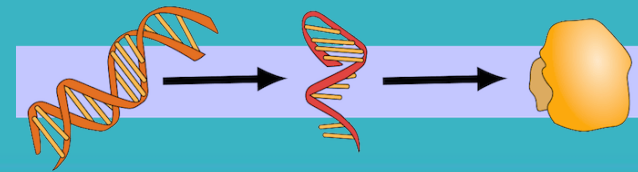
DNS -> RNS: a hírvivő
(messenger: mRNS)
Ribo-**N**uklein-**S**av

fehérje szintézis
(transzláció)



Fehérje: építő-elem

Az örökítő anyag felfedezése

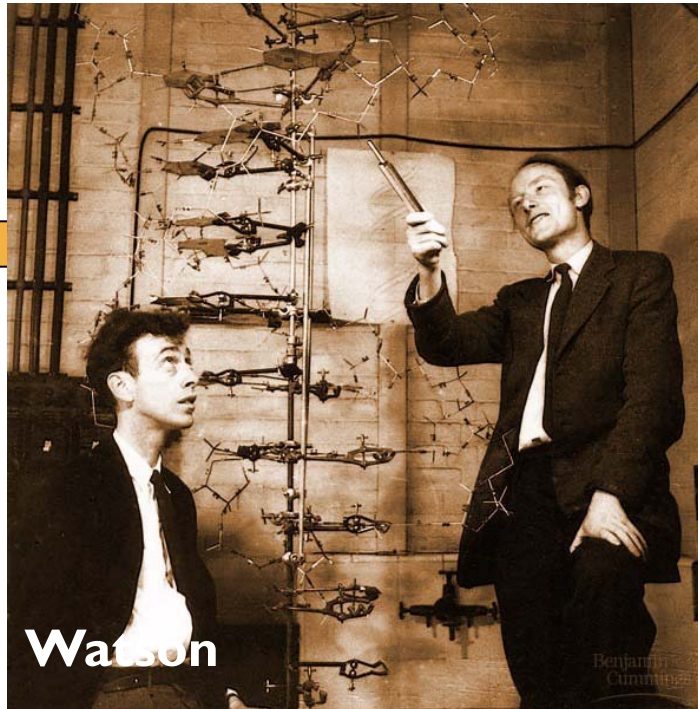


“központi dogma”

Francis Crick

1953

1958



Watson

Benjamin
Cummings

No. 4356 April 25, 1953

NATURE
737

MOLECULAR STRUCTURE OF NUCLEIC ACIDS A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons:

(1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions.

Each chain loosely resembles Furberg's² model No. 1: that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's standard configuration³, the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3.4 Å, in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so

that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain, does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain, is given, then the sequence on the other chain is automatically determined.

It has been found experimentally^{4,5} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data^{6,7} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until a has been checked against more exact results. Some of these are given in time following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereo-chemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J.D.W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J.D. WATSON
F.H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

¹ Pauling, L., and Corey, R. B. *Nature*, 171, 366 (1953); *Proc. U.S. Nat. Acad. Sci.*, 39, 84 (1953).

² Furberg, S. *Acta Chem. Scand.*, 6, 634 (1952).

³ Chargaff, E., for references see Zamecnik, S., Elzermann, G., and Chargaff, E., *Biochim. et Biophys. Acta*, 9, 402 (1952).

⁴ Wyatt, G.R. *J. Gen. Physiol.*, 34, 201 (1952).

⁵ Astbury, W.T., *Proc. Roy. Soc. (London)*, 1, *Nucleic Acid*, 66 (*Cambridge Univ. Press*, 1947).

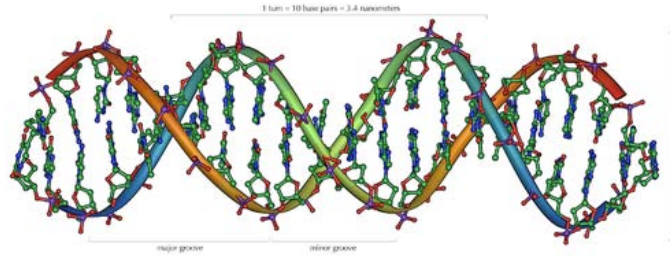
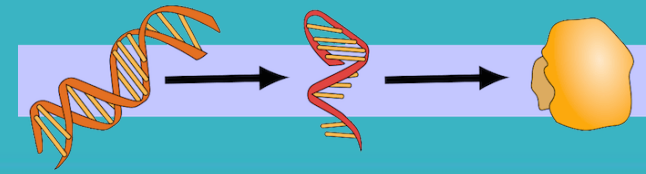
⁶ Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, 10, 102 (1953).

This figure is purely diagrammatic. The two ribbons represent the two phosphates—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.



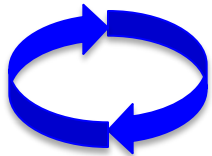
1962

A (molekuláris) biológia alap tézise: központi (centrális) dogma



A sejten belüli információátadás

DNS az élet kódja



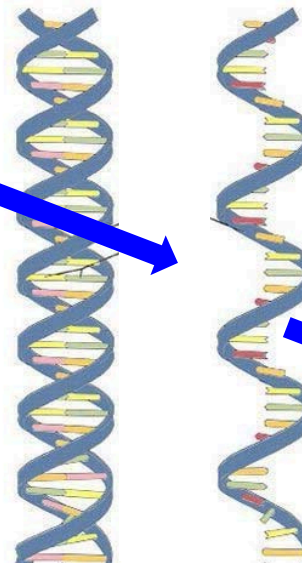
megkettőződés
(replikáció)

átírás

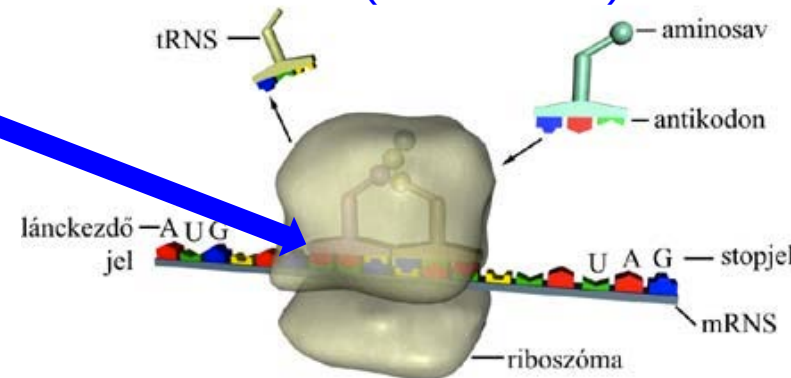
DNS-polimeráz

(transzkripció)

RNS-polimeráz



fehérje szintézis
(transzláció)



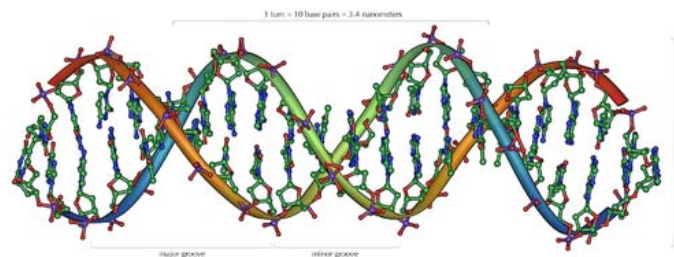
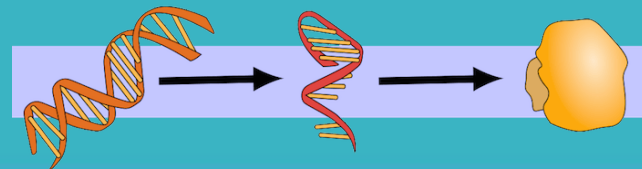
DNS -> RNS: a hírvivő

Fehérje: építő-elem

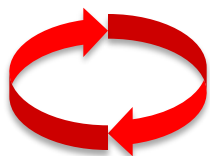
Riboszóma



Központi (centrális) dogma - jelenleg



DNS az élet kódja



megkettőződés
(replikáció)

Reverz
transzkripció

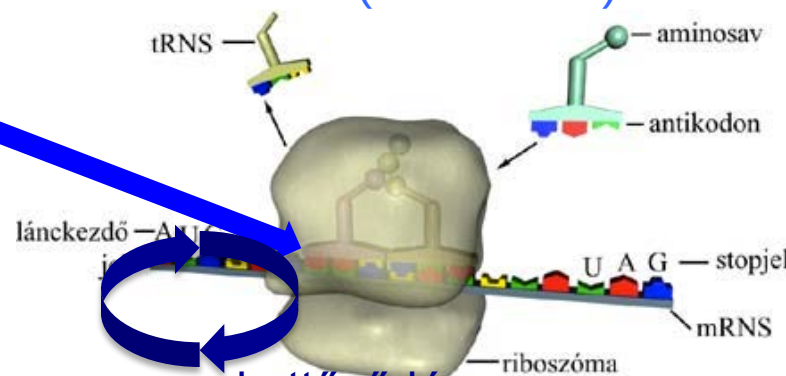
Retro vírus:
RNS alapú DNS
polimeráz

átírás

(transzkripció) DNS -> RNS: a hírvivő

RNS vírus: RNS alapú RNS polimeráz
megkettőződés
(replikáció)

fehérje szintézis
(transzláció)



megkettőződés
(replikáció)

Fehérje

Prion

szabályozás



Szabályozott mRNS lebontás: RNS interferencia

Belső RNS interferencia = mikro RNS (miRNS)

hosszú
dsRNS
(vírus)

citoplazma

Dicer

sejtmag

RNS indukálta
csendesítő komplex
(RISC) aktivációja

miRNS
(Endogén)

Cél mRNS kötése,
feldarabolása

transzláció

siRNS
(szintetikus)

RNS interferencia

siRNS=siRNA



Az RNS interferencia felfedezése

Co-szuppresszió

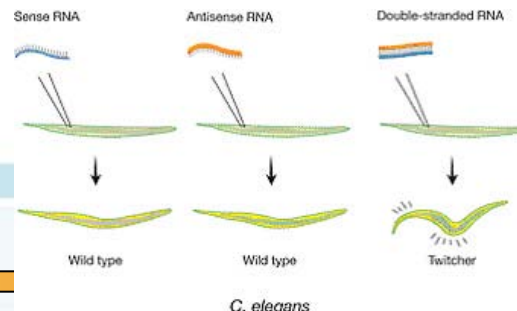
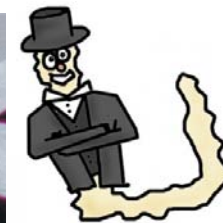
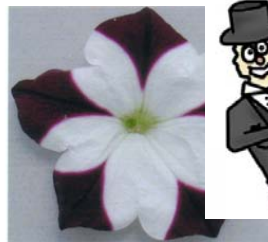
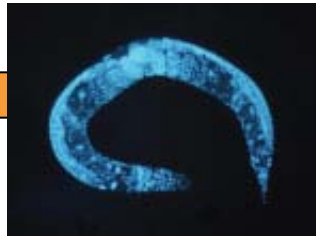
Richard Jörgensen
1990

RNS interferencia
eukaryota szervezetben (*C. elegans*)

RNS interferencia = Géncsendesítés
Kettős szálú RNS-el

1998

Andrew Z. Fire and Craig C. Mello



2006



Akut vese károsodás (AVK)

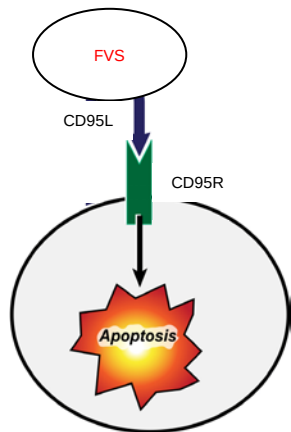
→ akut veseelégtelenség

- Intenzív terápiás betegek akár 67%-a
 - Magas **halálozási arány**
 - **Szövődmények** (krónikus veseelégtelenség, dialízis)
- A terápia **korai** alkalmazása növeli **gyógyulást** és a **túlélést**

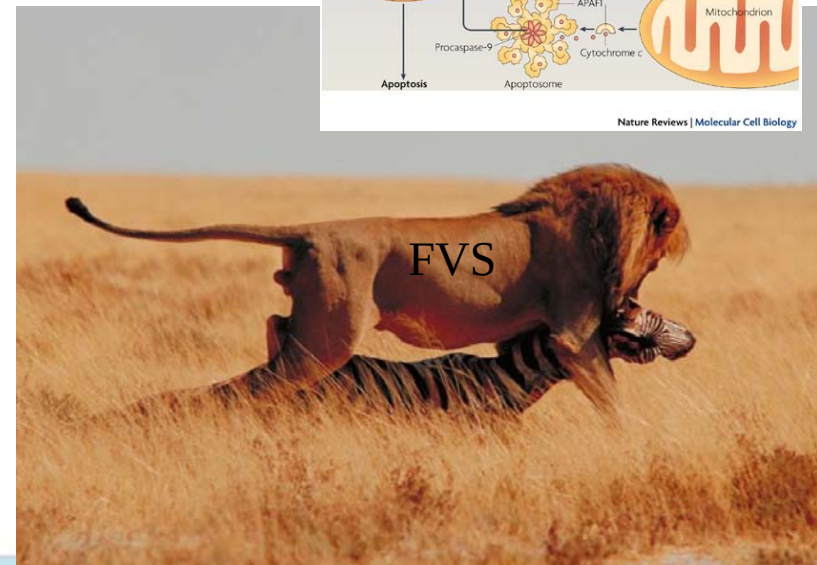
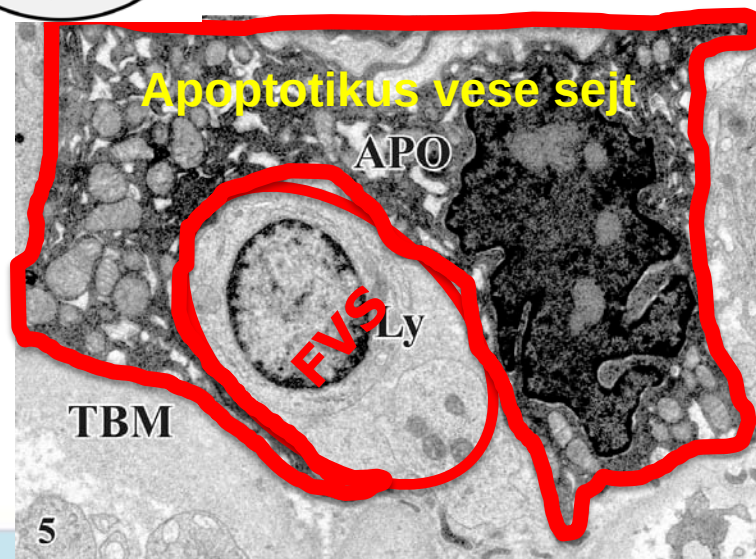
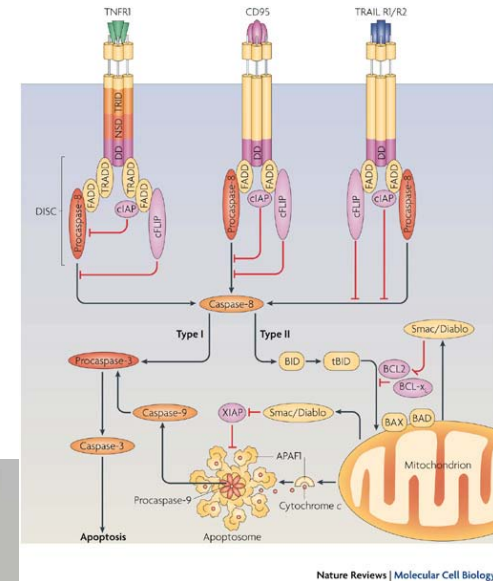


Apoptózis: falevél hullás - programozott sejthalál

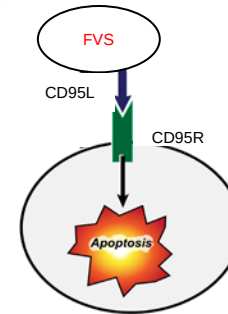
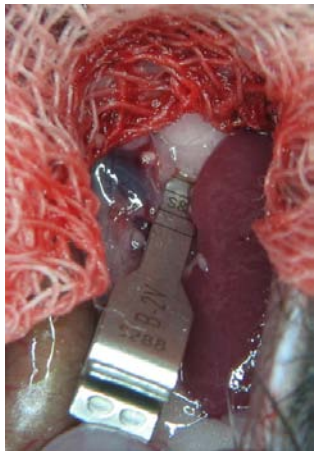
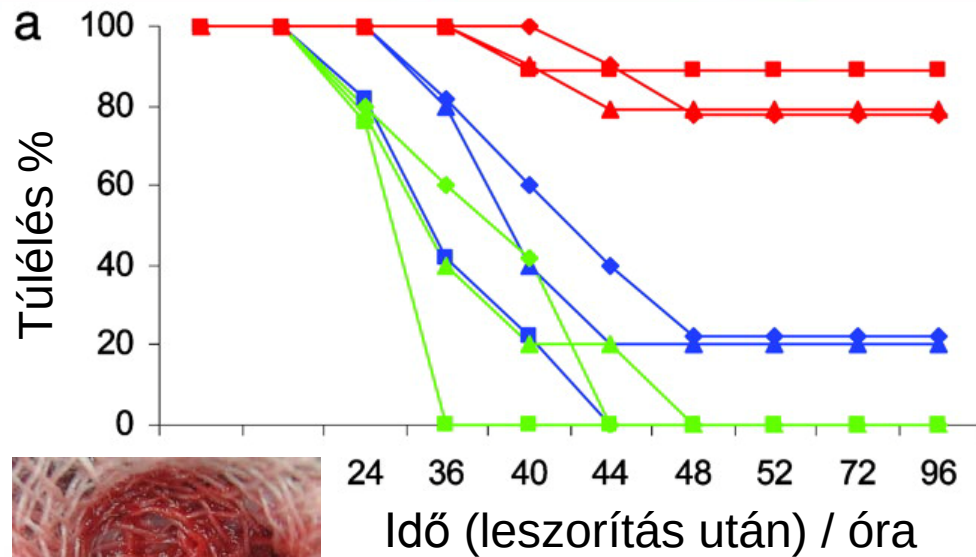
Apoptózis receptor – a halálos csók



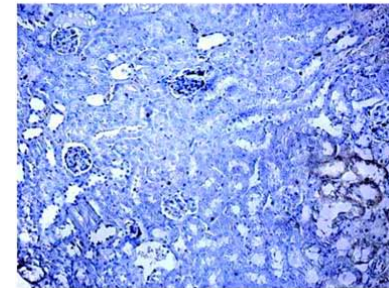
Halál receptorok



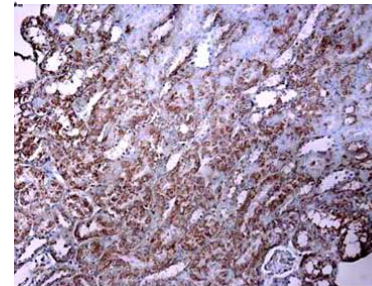
CD95 csendesítés védő hatása oxigénhiány okozta akut vese elégtelenségben



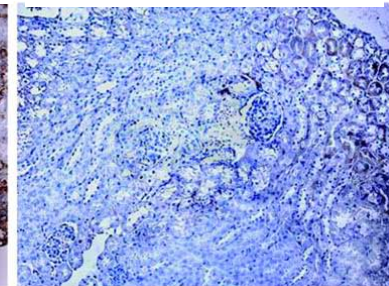
- Nem ischémiás



Ischemia – kezelés nélkül



Ischemia + CD95 siRNS



Vértelenség -> oxigén-hiány = ischemia

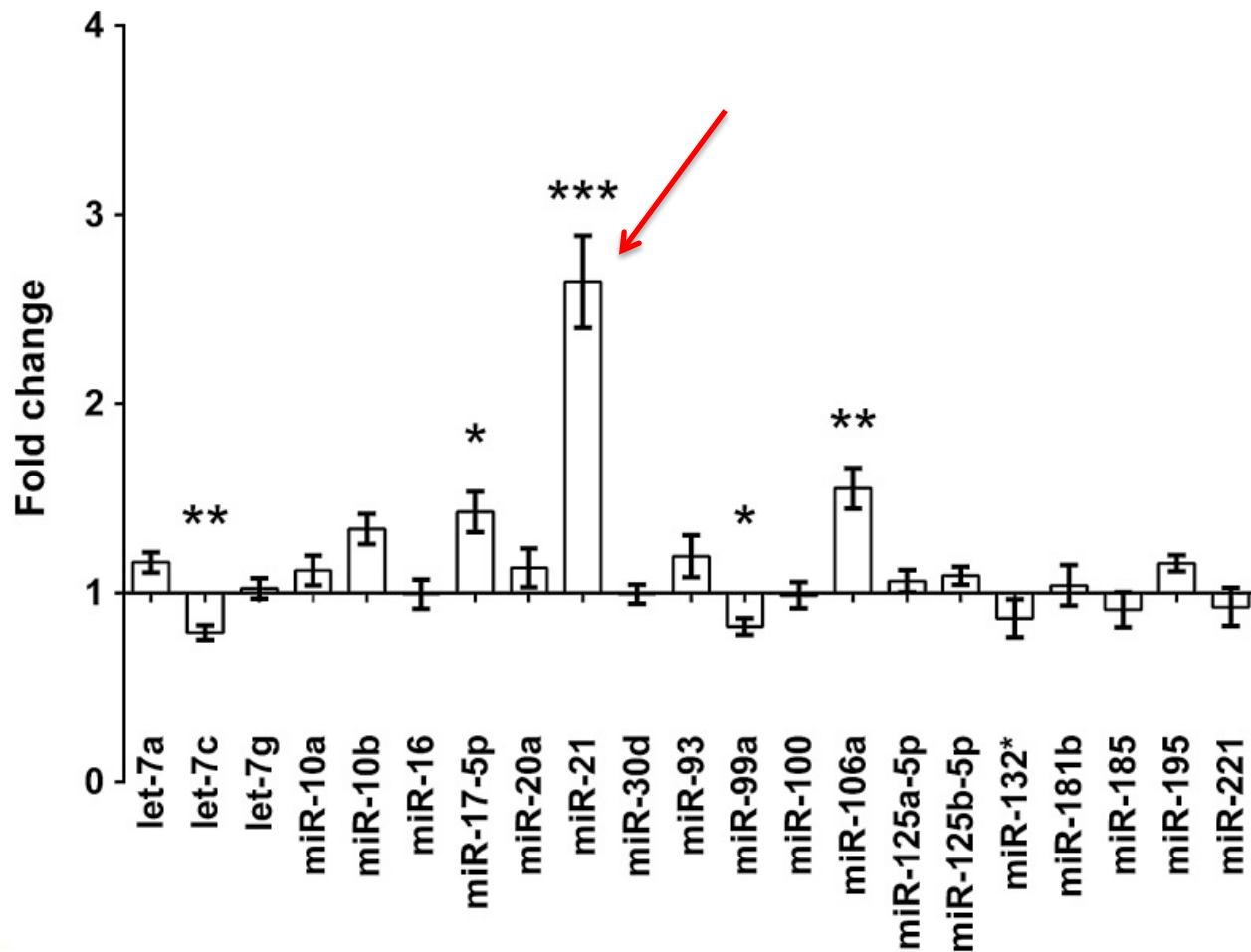
CD95 immunfestés

Hamar P et al. Proc Natl Acad Sci 2004;101:14883-14888

©2004 by National Academy of Sciences

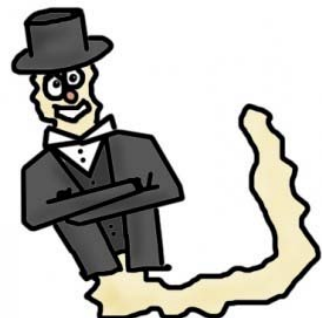
PNAS

miR-21 akut vese hipoxiát követő reperfúzióban



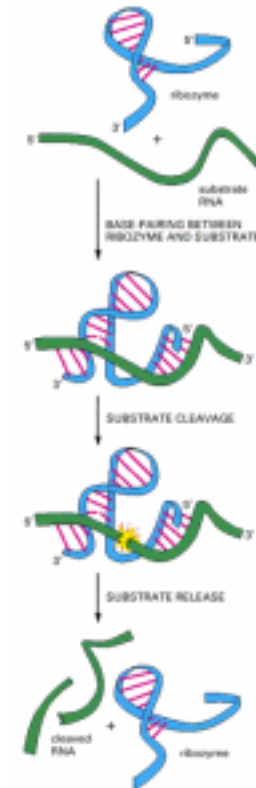
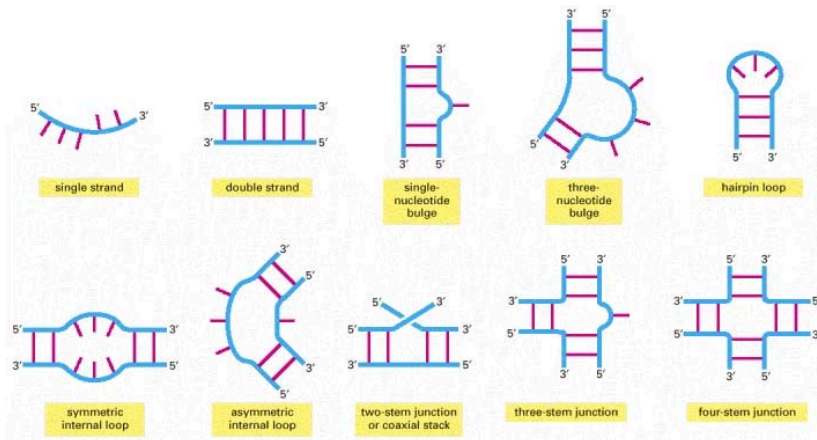
Humán genom projekt legfontosabb következtetései (2004)

- 20,500 génünk van
 - Ember – csimpánz: ~ 95% azonos genom, 99% azonos kódoló gének
 - ~ kb. 2x kerek féreg
 - ~ a genom 1.1% - 1.4%-a kódol fehérjét
 - 85–90% ‘szemét’ DNS: nem gén, nem kódol fehérjét
 - A nem kódoló szakaszoknak részben lehet szabályozó szerepe

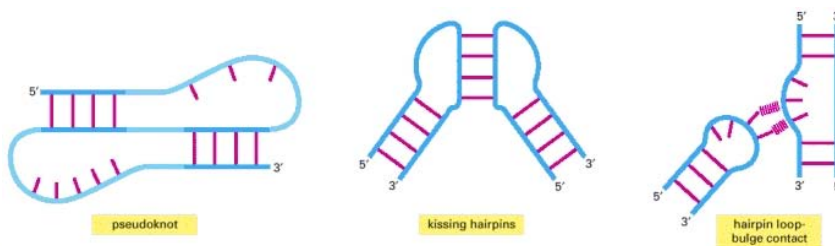


RNS térszerkezet és funkció

Az RNS is lehet 1 vagy 2 szálú

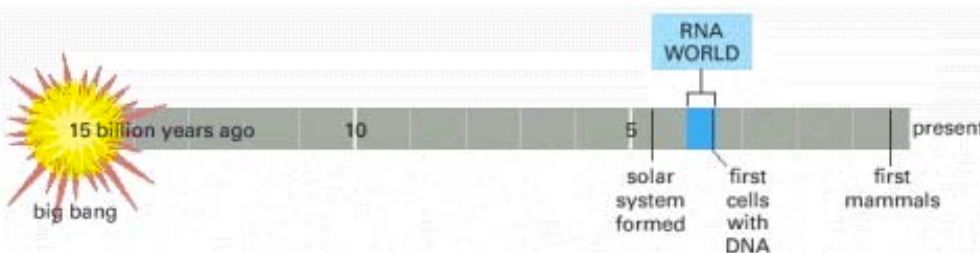


RNS: 2. és 3.lagos térszerkezeti struktúrák



Ribonukleinsav (RNS) - enzim:
Ribozim (ribozyme)

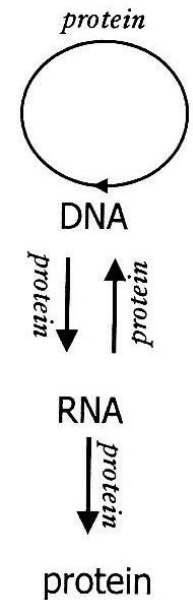
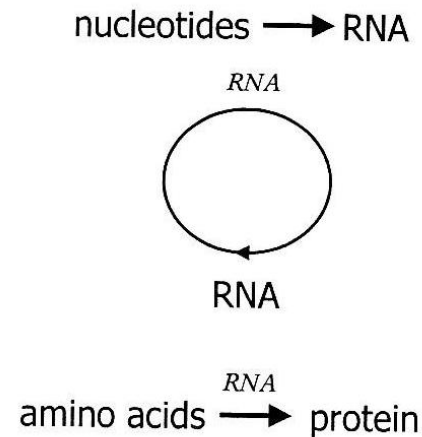
Az RNS világ hipotézis



The RNA World

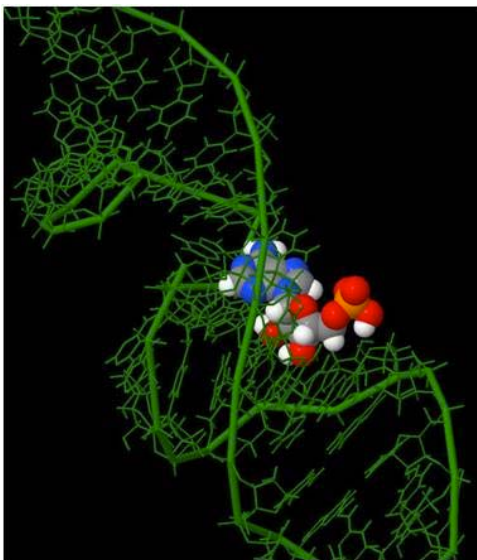
The Transitional Period

Világunk jelenleg



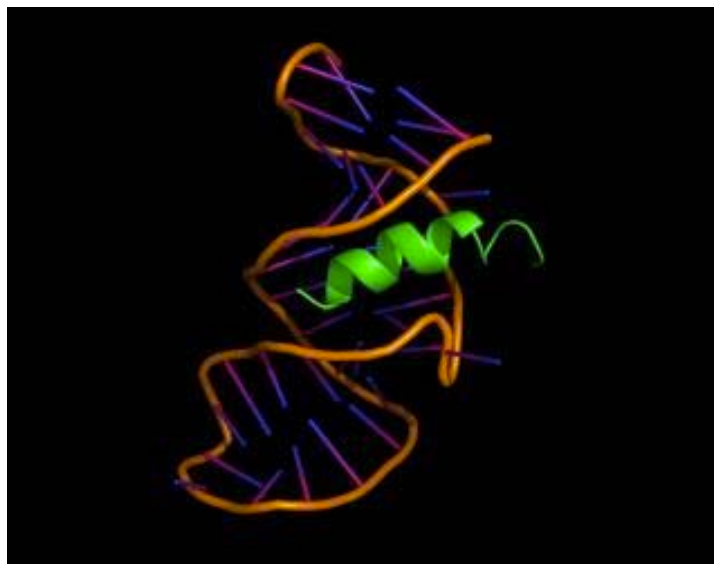
Aptamer

Aptus <lat.>: helyes
Meros <Gr.>: rész



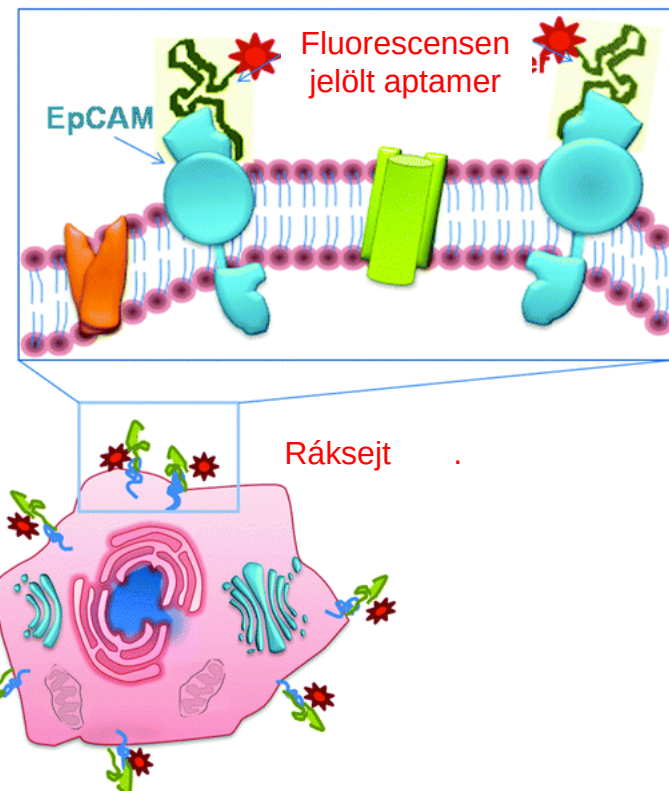
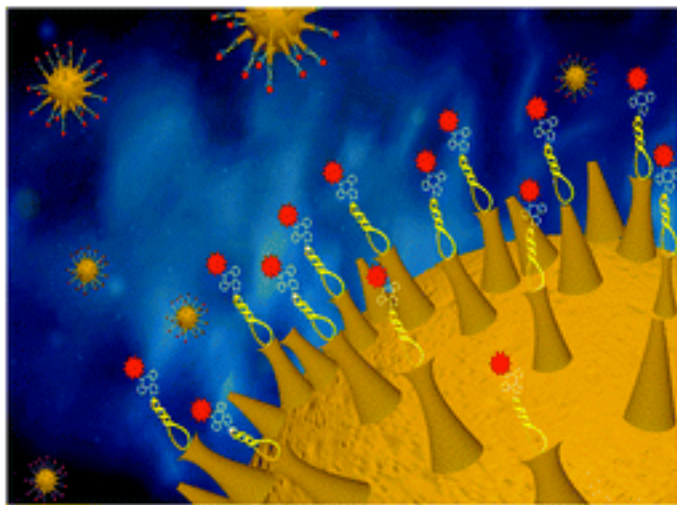
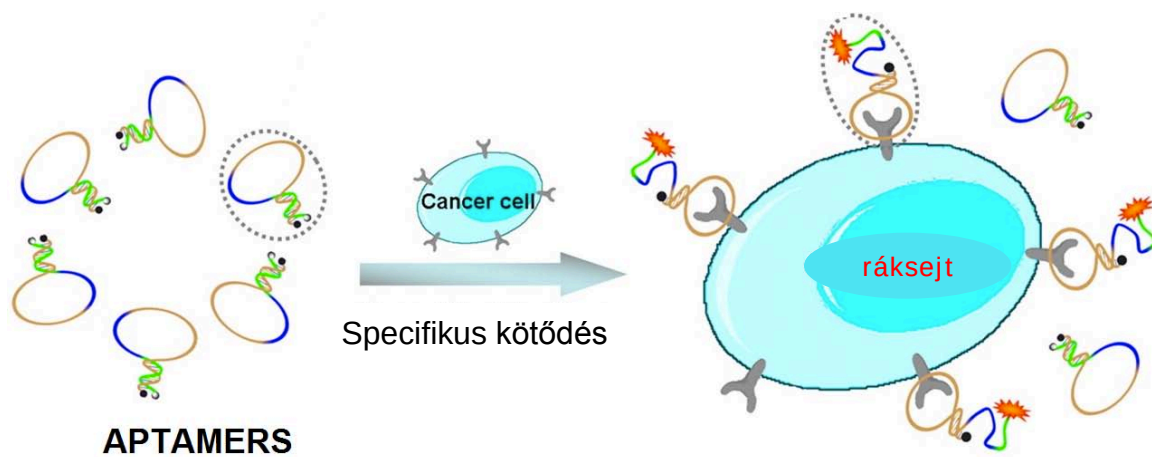
20-80 nucleotid (NT)

Akár egyszálú RNS molekulák
képesek komplex térszerkezet
kialakítására

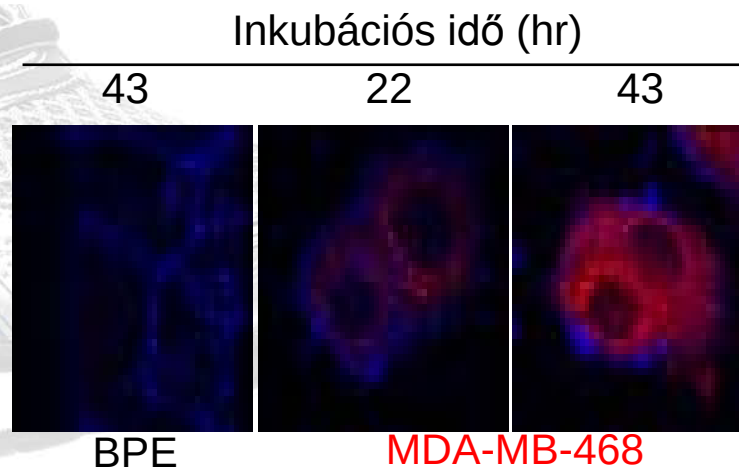
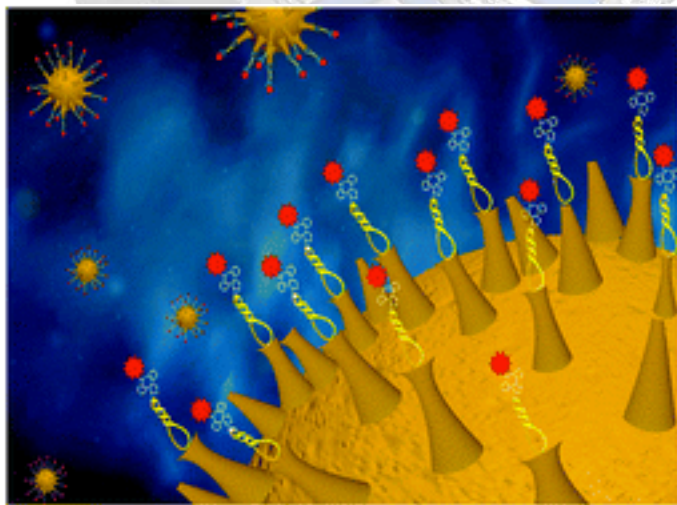
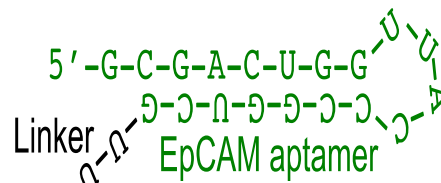
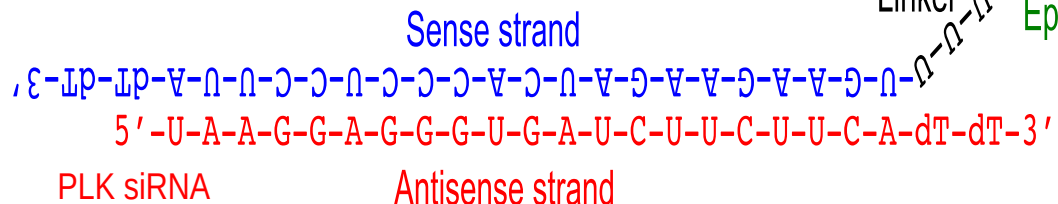


Fehérjét kötő RNS aptamer

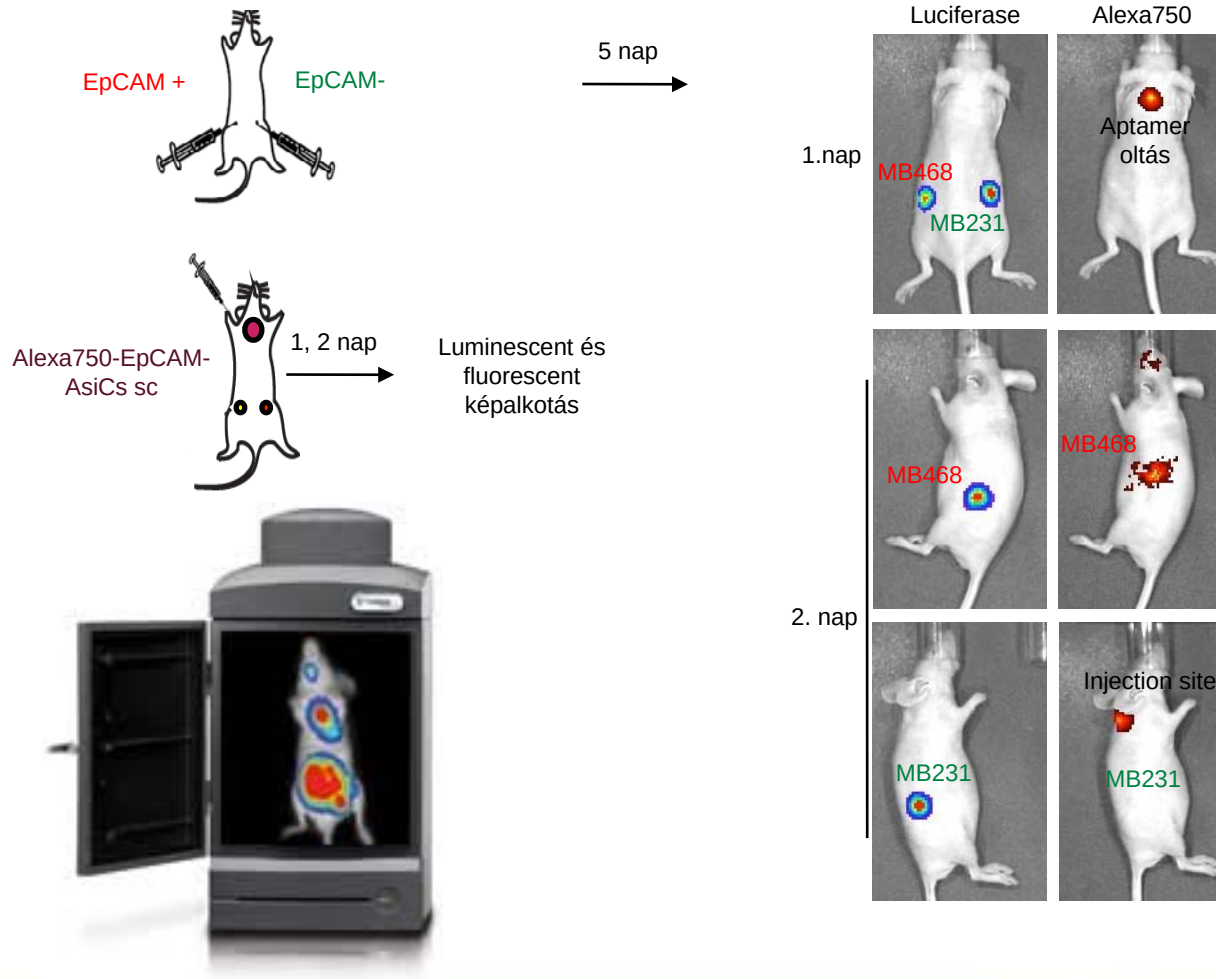
Epcam Aptamer



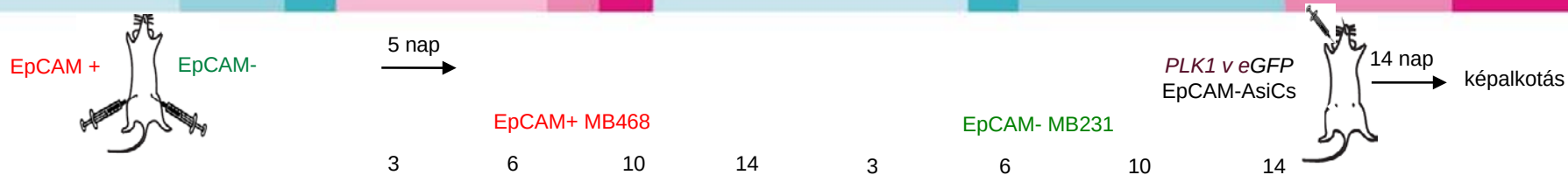
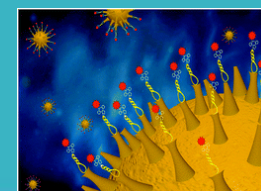
Aptamer siRNS complex(es)



Fluorescences jelölt EpCam-Asic a tumorba vándorol

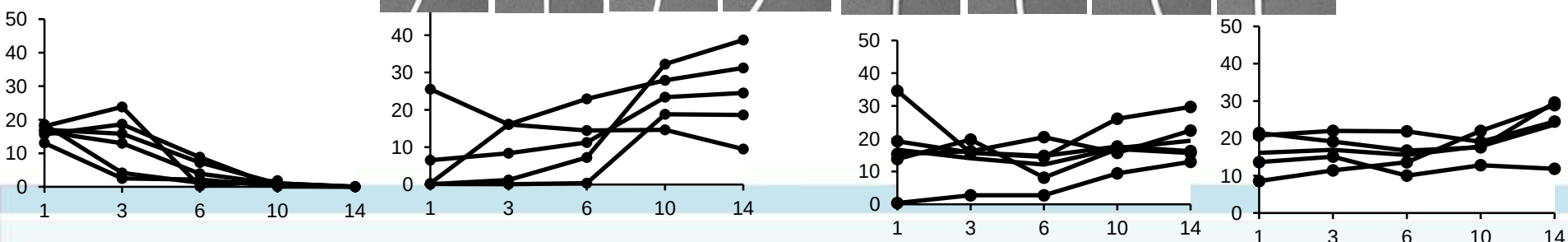
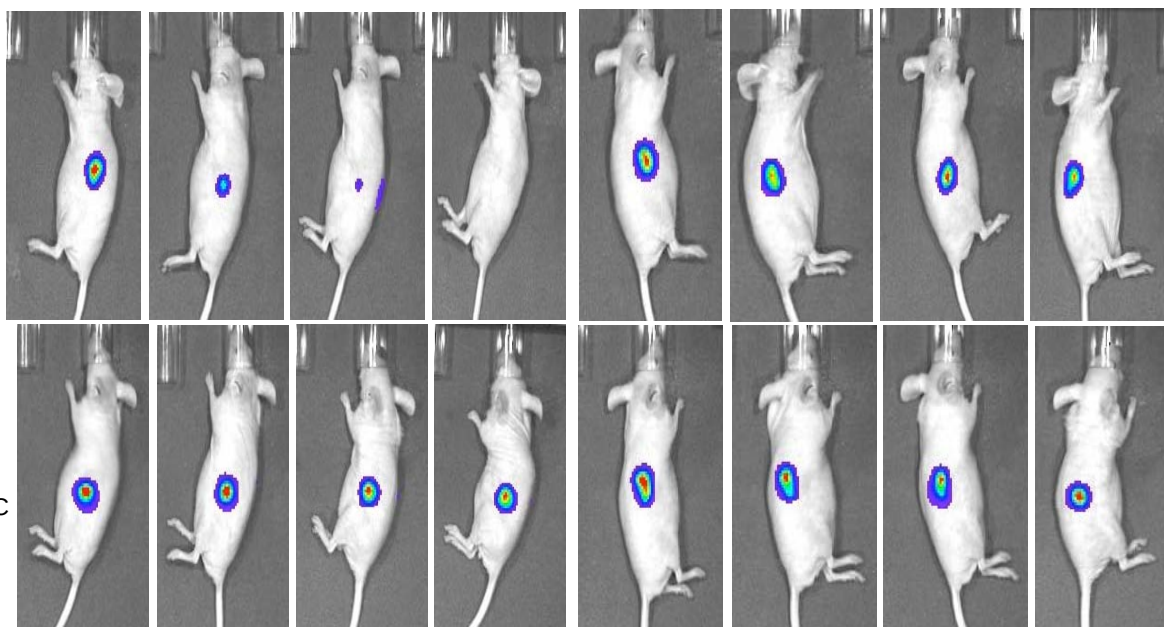


EpCAM-PLK-Asic elpusztítja a fluoreszcensen jelölt rákot



PLK1 AsiC

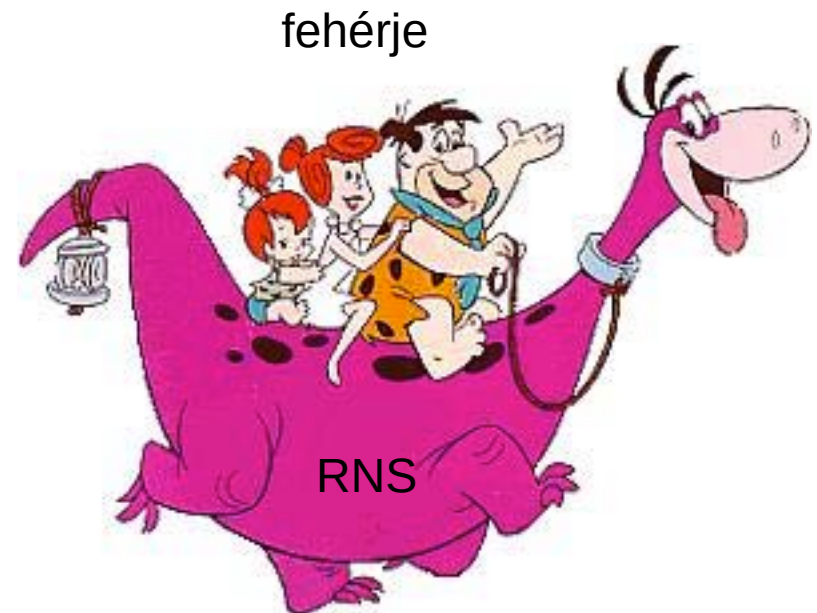
eGFP AsiC



RNS és fehérje

RNS funkciói:

- mRNS: a hírvivő (póstás)
= A kódolt információ továbbítása
- tRNS: transfer (fehérje szintézis)
- Katalízis: enzim (ribozyme)
- Génexpresszió szabályozás:
 - siRNS
 - miRNS
- További RNS-ek:
 - lncRNS
 - piRNS
 - snRNS



Javasolt olvasni való

- A DNS szerkezetének felfedezéséről:
 - James Watson: A kettős spirál
 - In Pictures: The story behind DNA's double helix
(<http://www.bbc.co.uk/science/0/22270604>)
- Az RNS világról:
 - The RNA World and the Origins of Life
In: Alberts B, Johnson A, Lewis J, et al. - Molecular Biology of the Cell. 4th edition.
New York: Garland Science; 2002. (<http://www.ncbi.nlm.nih.gov/books/NBK26876/>)
 - Pesthy Gábor, Simon Tamás: Újabb lépések az élet kialakulásának megértéséhez. Origo:
<http://www.origo.hu/tudomany/20090107-rnsvilag-enzimek-nelkul-szintetizaltak-hosszabb-rnst.html>
 - Csermely Péter: Az élet születésének biokémiája. Természet Világa, 128. évf. 1. sz.
1997. január, 10–14. o., <http://www.termeszetvilaga.hu/tv9701/csermely.html>
- Génexpresszióról:
 - mRNS.hu: <http://www.mrns.hu/fogalomtar/G/genexpresszio>
- RNS interferenciáról:
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