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Parallel creative domains – Arts, Science, Nature

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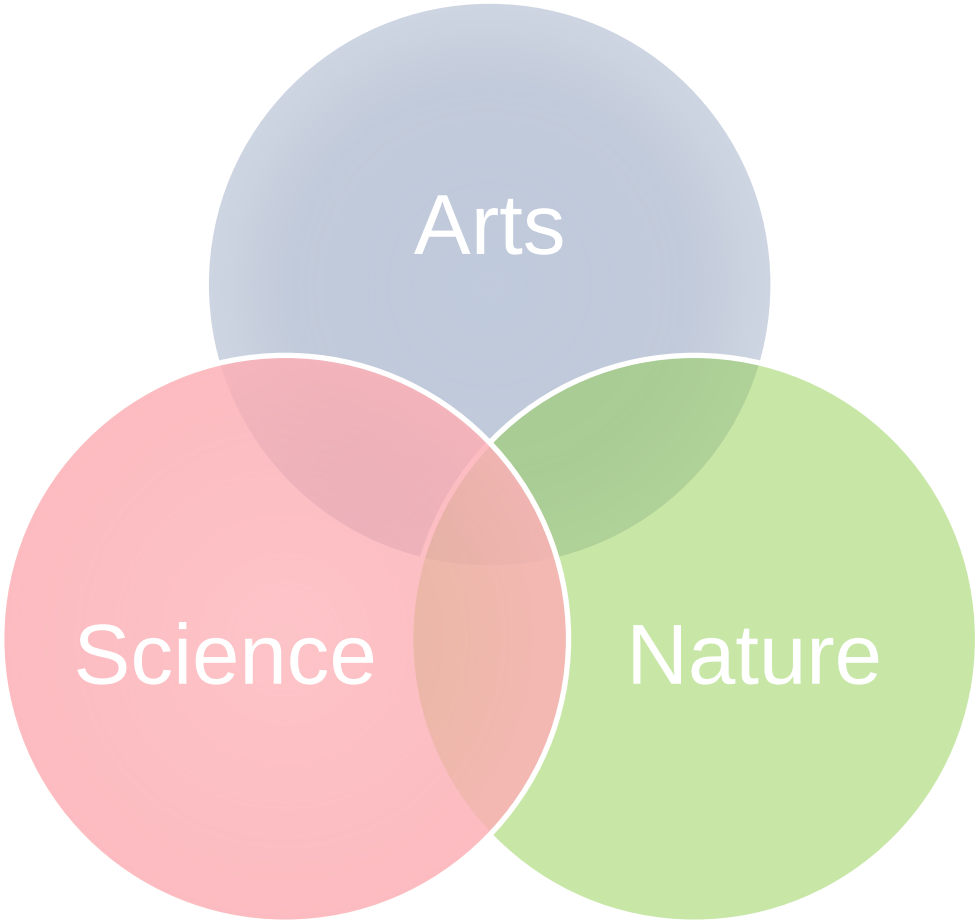
Is creativity involved in all these fields?



Scientific epistemiology
(How do we gain knowledge?)

Inductionism (Bacon ...)
gather & interpret data

Positivism
"prove" your theory

Hypothesis-driven research
(Popper ....)
falsify your hypothesis

Positive results are easier to publish than negative ones

Scientific epistemiology
(How do we gain knowledge?)

> Hypothesis-driven research (Popper a.o.) - the myth of the "critical experiment"

- formulate hypothesis
- make prediction(s), based on your hypothesis
- design and perform a critical experiment to test prediction(s)
- if predictions are not fulfilled, the hypothesis is false
- if predictions are fulfilled, you're no wiser than before
- important: remain unbiased throughout the process

Positive results are easier to publish than negative ones

Scientific epistemiology
(How do we gain knowledge?)

> Types of scientific activity

- literature studies
- reflection (including grant writing & hypothesis formulation)
- method development ("make things work")
- observations and measurements
- reflection & interpretation
- writing up results

where is the "critical experiment"?
where the falsified hypothesis?
is this an unbiased approach?

Scientific epistemiology
(How do we gain knowledge?)

> Types of scientific activity

- literature studies
- reflection (including grant writing & hypothesis formulation)
- ≥ 50% — method development ("make things work")
- observations and measurements
- reflection & interpretation
- writing up results

how much time do you spend on each of these activities?

Scientific epistemiology
(How do we gain knowledge?)

> Types of scientific activity

- literature studies
- reflection (including grant writing & hypothesis formulation)
- ≥ 50% — method development ("make things work")
- observations and measurements
- reflection & interpretation
- writing up results

which of these activities are creative?

Method development ("make things work")

- Proven protocols
- Instructions by experienced scientists
- Educated guesses
- Systematic variations
- "Tinkering"
- Keep on trying ...

which of these activities are creative?

Natural creativity (not creation or creationism)

Nature

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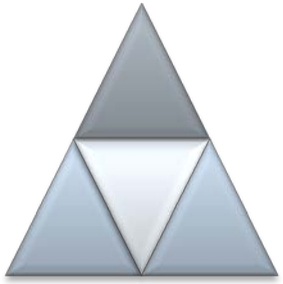
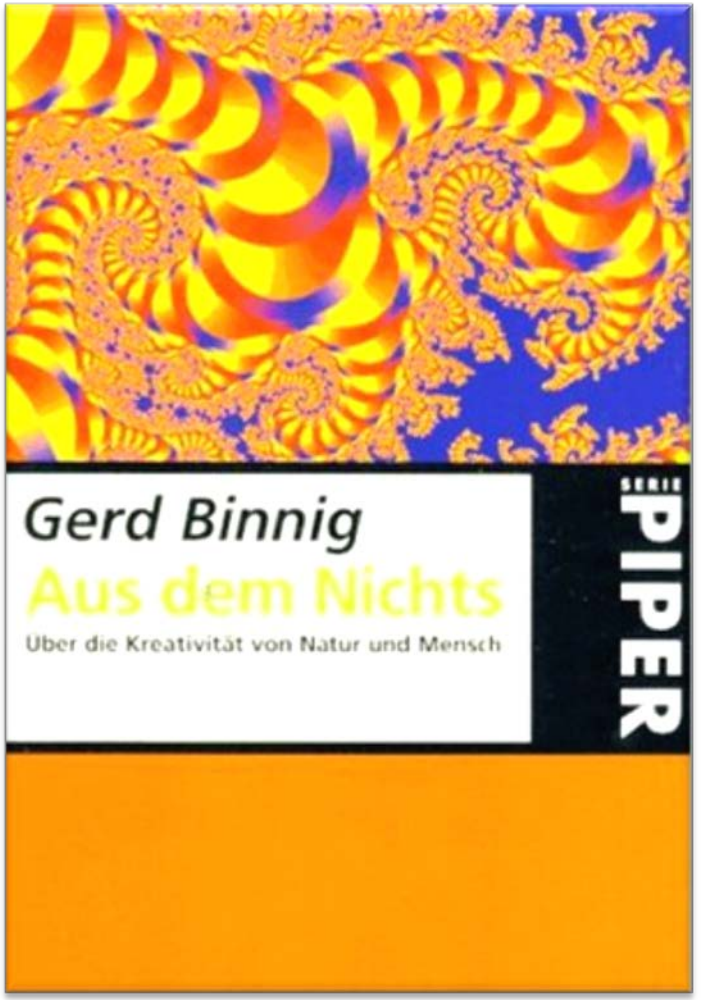
- The physical world:
  - modular
  - pyramidal
  - multi-scale
  - fractal
  - the composite is more than the sum of its building blocks



Gerd Binnig (born 20 July 1947)
1986 Nobel Prize in Physics
with Heinrich Rohrer
"for their design of the scanning tunneling microscope"



Natural creativity (not creation or creationism)

Nature

- The living world is:
  - everything the physical world is
  - **evolution**
    - chance and necessity
    - rule and variation
    - selection

Jacques Monod
(9 February 1910 – 31 May 1976)
1965 Nobel Prize in Physiology or Medicine
with François Jacob and André Lwoff
"for their discoveries concerning genetic control of enzyme and virus synthesis"

Is creativity similar in all these fields?

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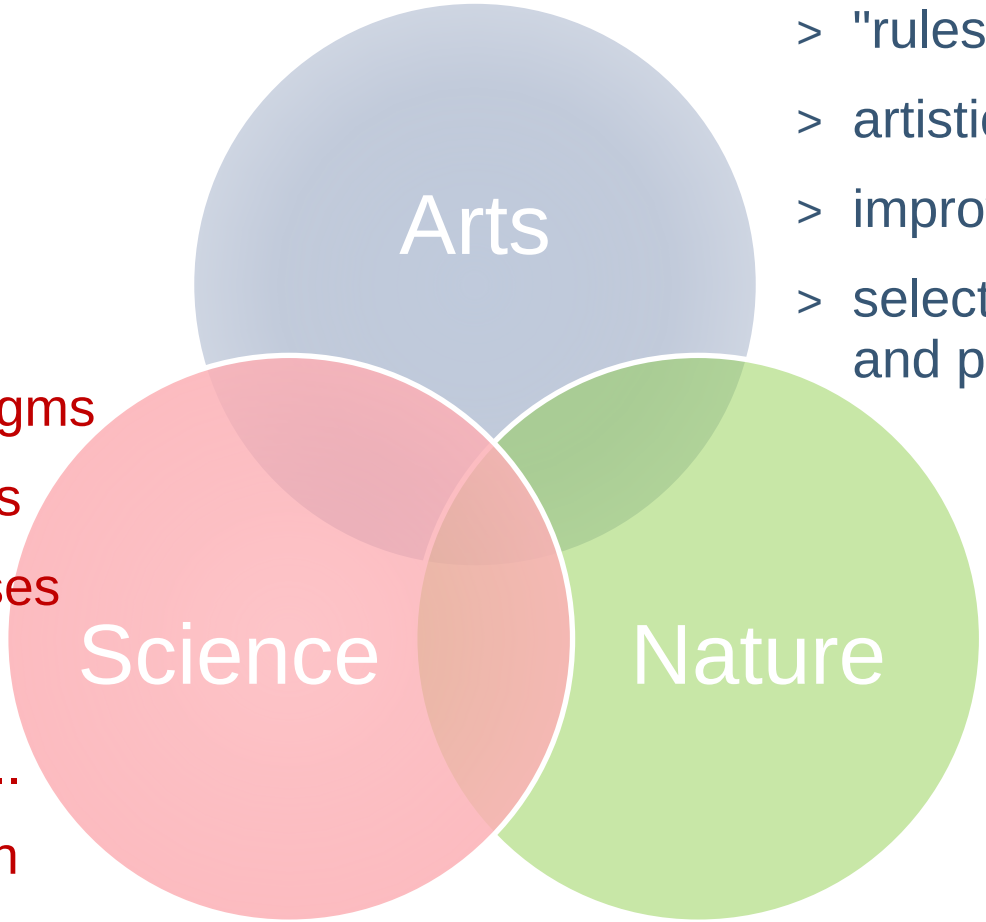

- "rules"
- artistic freedom
- improvisation
- selection by artist and public

- scientific paradigms
- proven protocols
- educated guesses
- "Tinkering"
- keep on trying ...
- publish or perish

- modularity
- rule
- variation
- selection

Other parallels between Arts and Science

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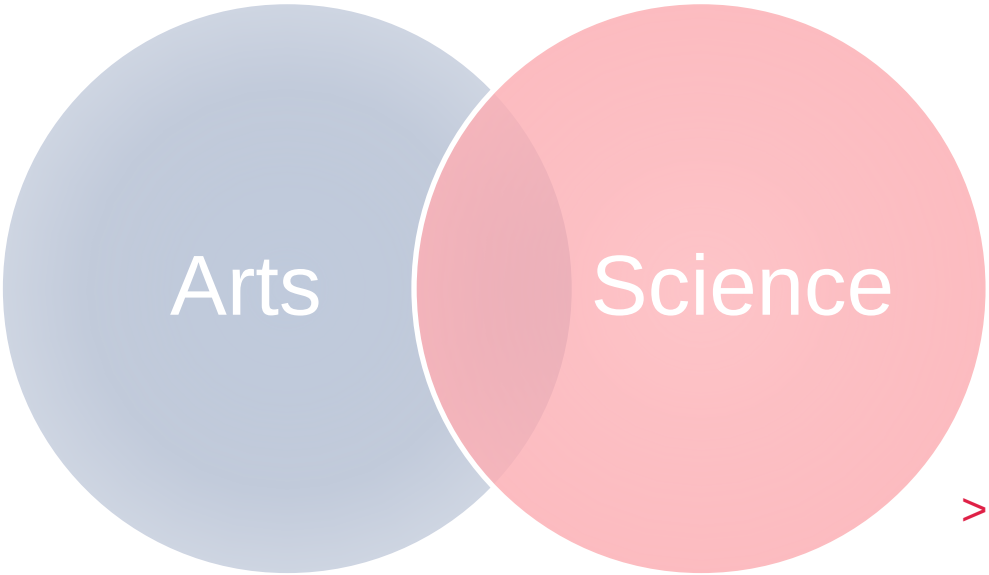
- paradigmatic arts stand in the limelight
- most artistic activities are barely noticed by society
- some artistic activities are team efforts

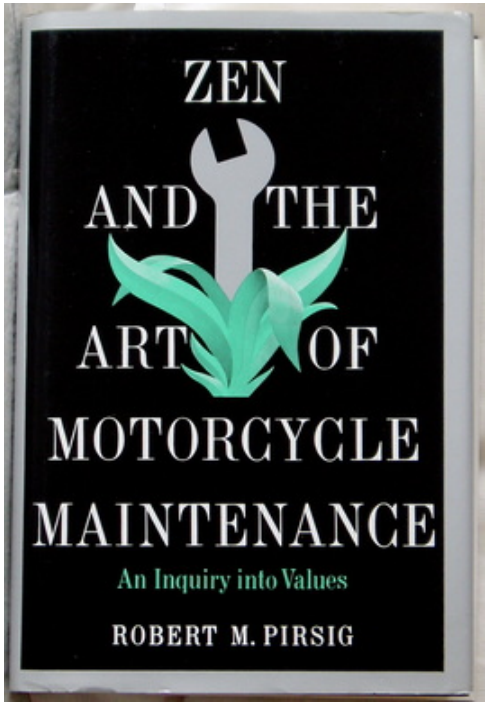


- paradigmatic science stands in the limelight
- most scientific activities are barely noticed by society
- most scientific activities are team efforts

Team creativity

The term QUALITY in Pirsig's ZAMM

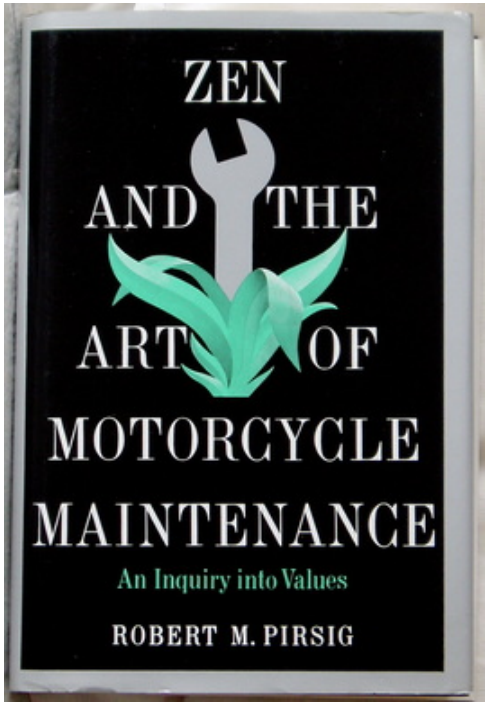
- Some people look at the world in a romantic way (what feels good is good, technology is bad and ugly)
- others use a rational approach. They can analyse problems and solve them, like fixing a motorcycle
- Often the "rationals" and the "romantics" encounter each other with suspicion



1974

The term QUALITY in Pirsig's ZAMM

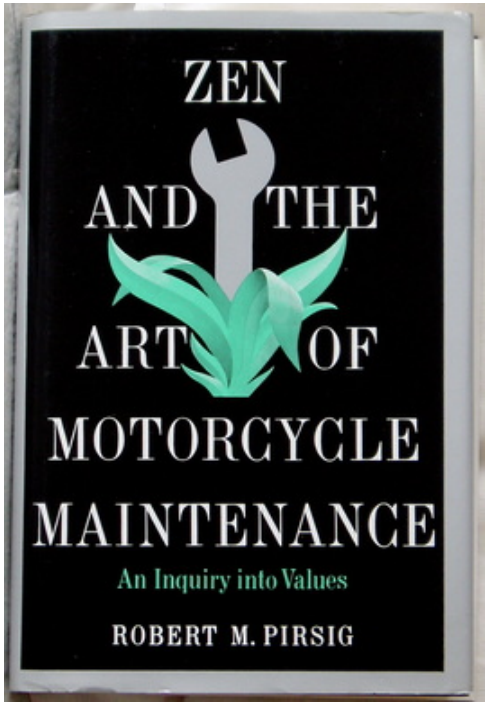
- Pirsig aims towards a perception of the world that embraces the rational and the romantic. This means encompassing "irrational" sources of wisdom and understanding as well as science, reason and technology.
- In particular, this must include bursts of creativity and intuition that seemingly come from nowhere and are not (in his view) rationally explicable (**e.g. TINKERING**).
  Pirsig seeks to demonstrate that rationality and Zen-like "being in the moment" can harmoniously coexist.



The term QUALITY in Pirsig's ZAMM

- He suggests such a combination of rationality and romanticism can potentially bring a higher **QUALITY** of life.

- **QUALITY** makes divisions obsolete
  - **TRUE** vs. **GOOD**, or **BEAUTIFUL**
  - **SUBJECT** vs. **OBJECT**



Creativity requires freedom and peace of mind

"I expect you all to be independent, innovative, critical thinkers who will do exactly as I say!"

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RNA processing and gene therapy

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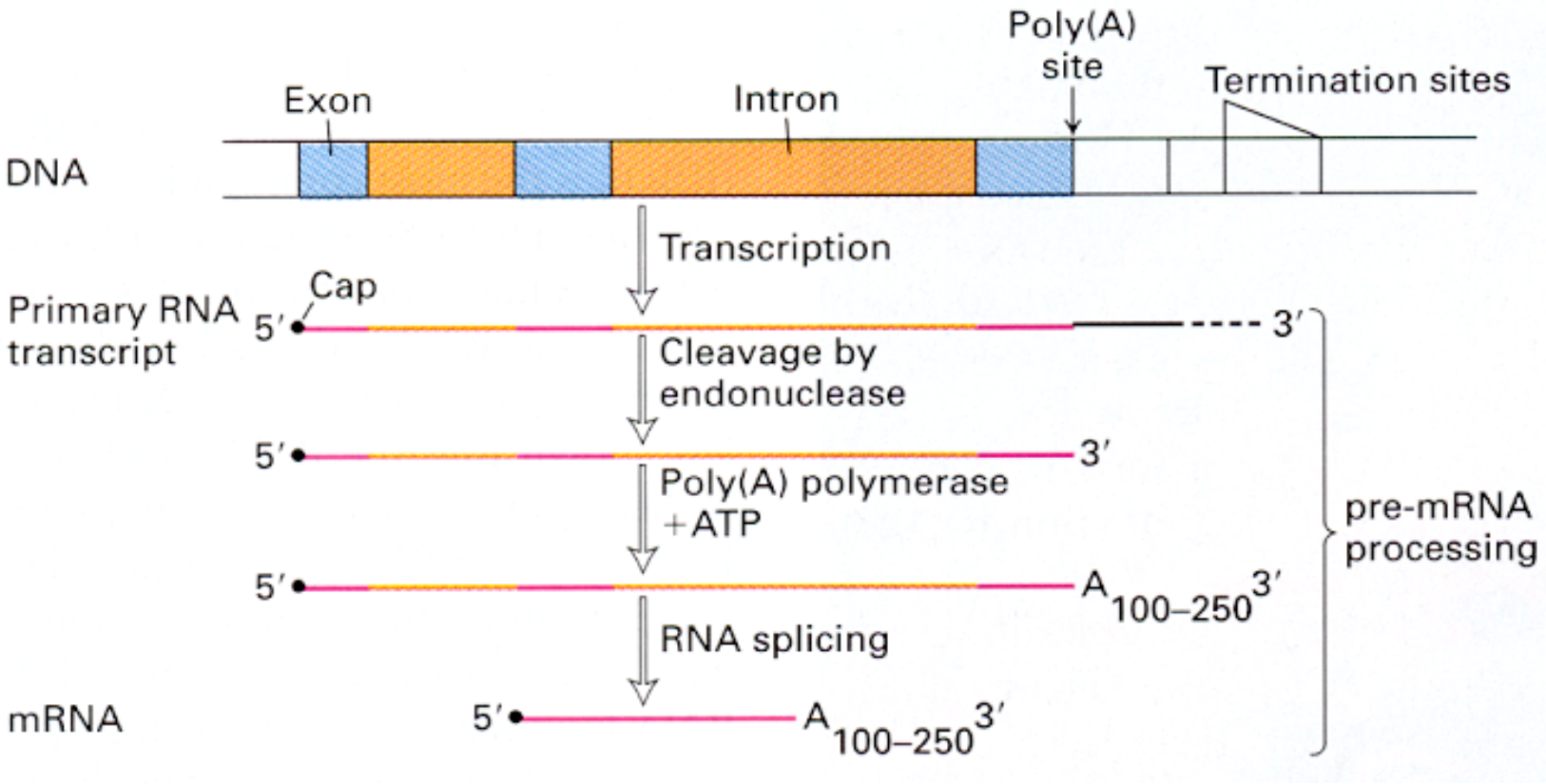
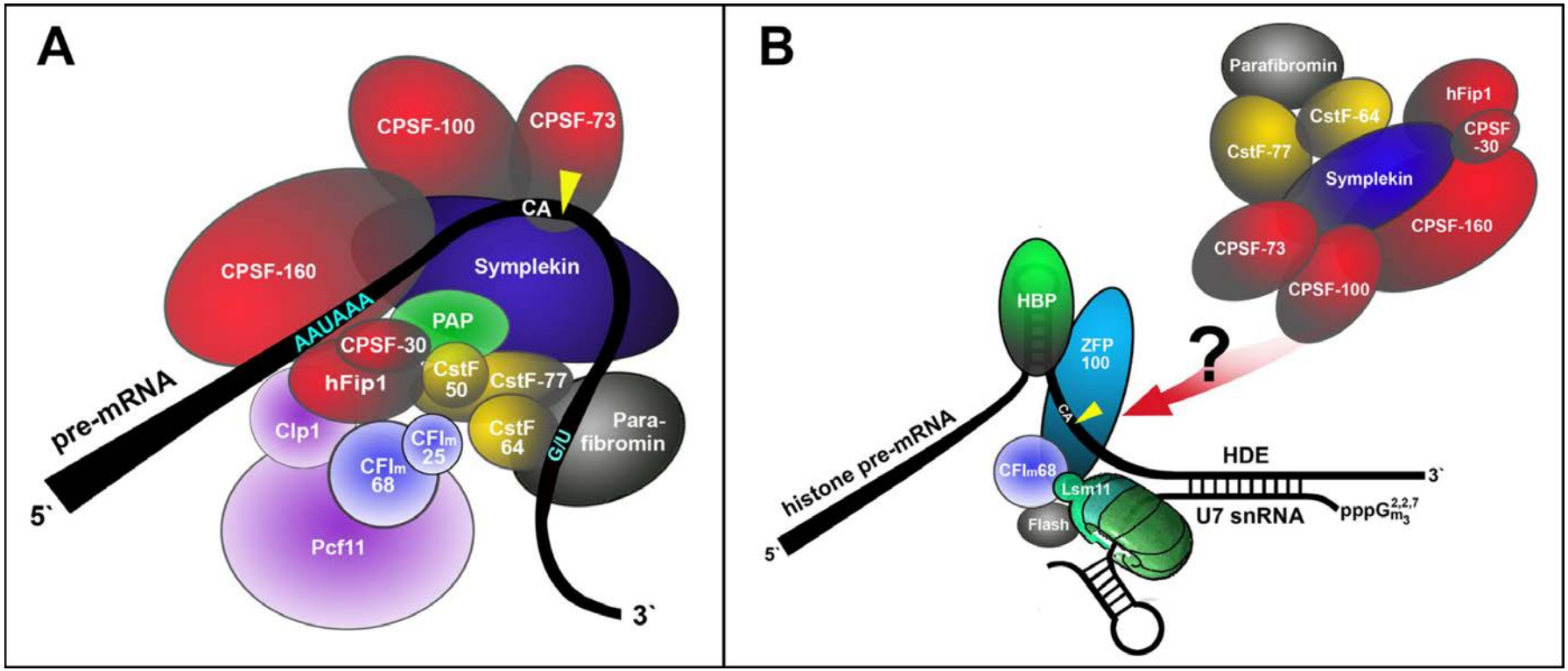
mRNA processing in eucaryotes



mRNA 3' end processing



Gene therapy: the birth of U7 Sm OPT as a splicing modulation tool

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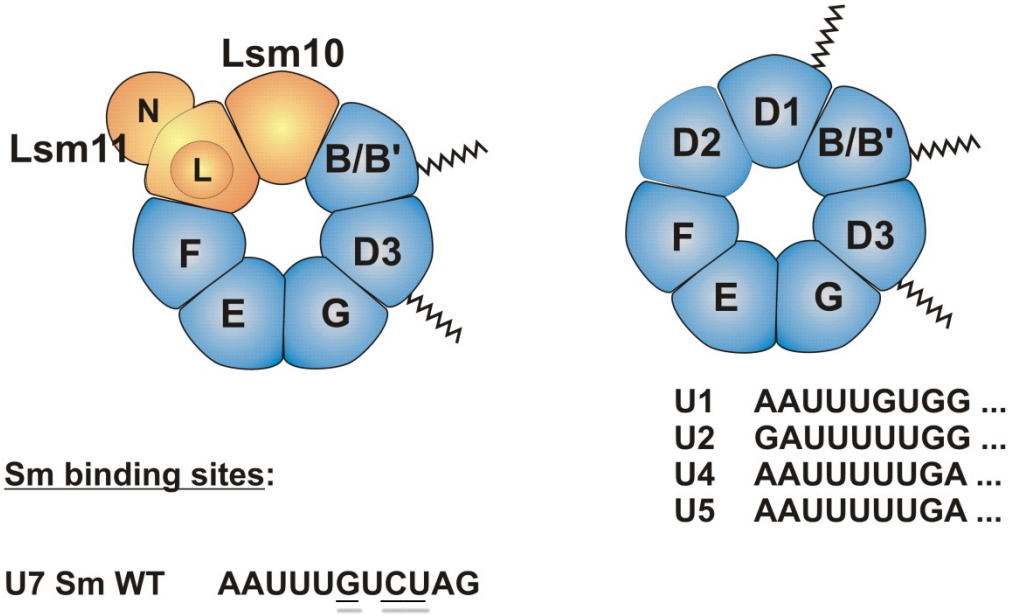
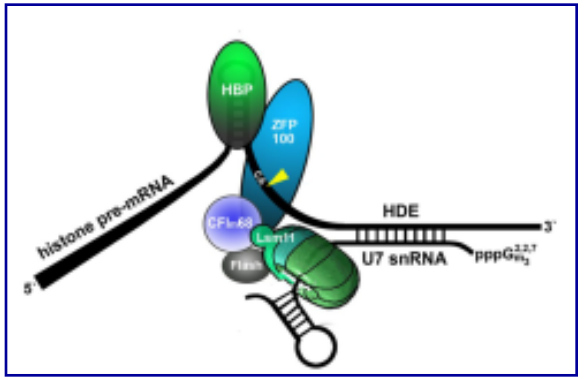


Grimm et al. (1993) EMBO J. 12, 1229-1238
Stefanovic et al. (1995) Nucl. Acids Res. 23, 3141-3151
Pillai et al. (2001) EMBO J. 20, 5470-5479
Pillai et al. (2003) Genes Dev. 17, 2321-2333

> can U7 Sm OPT RNA derivatives be used to modulate splicing?

Properties of U7 Sm OPT RNA:

- three nucleotides changed in Sm binding site
- binds Sm D1/D2 instead of Lsm10/11
- accumulates 3x more efficiently in the nucleus
- non-functional in histone RNA processing
- masks HDE >> inhibits histone RNA processing by wt U7 snRNPs



An altered base pairing region changes the specificity of U7 snRNP targeting

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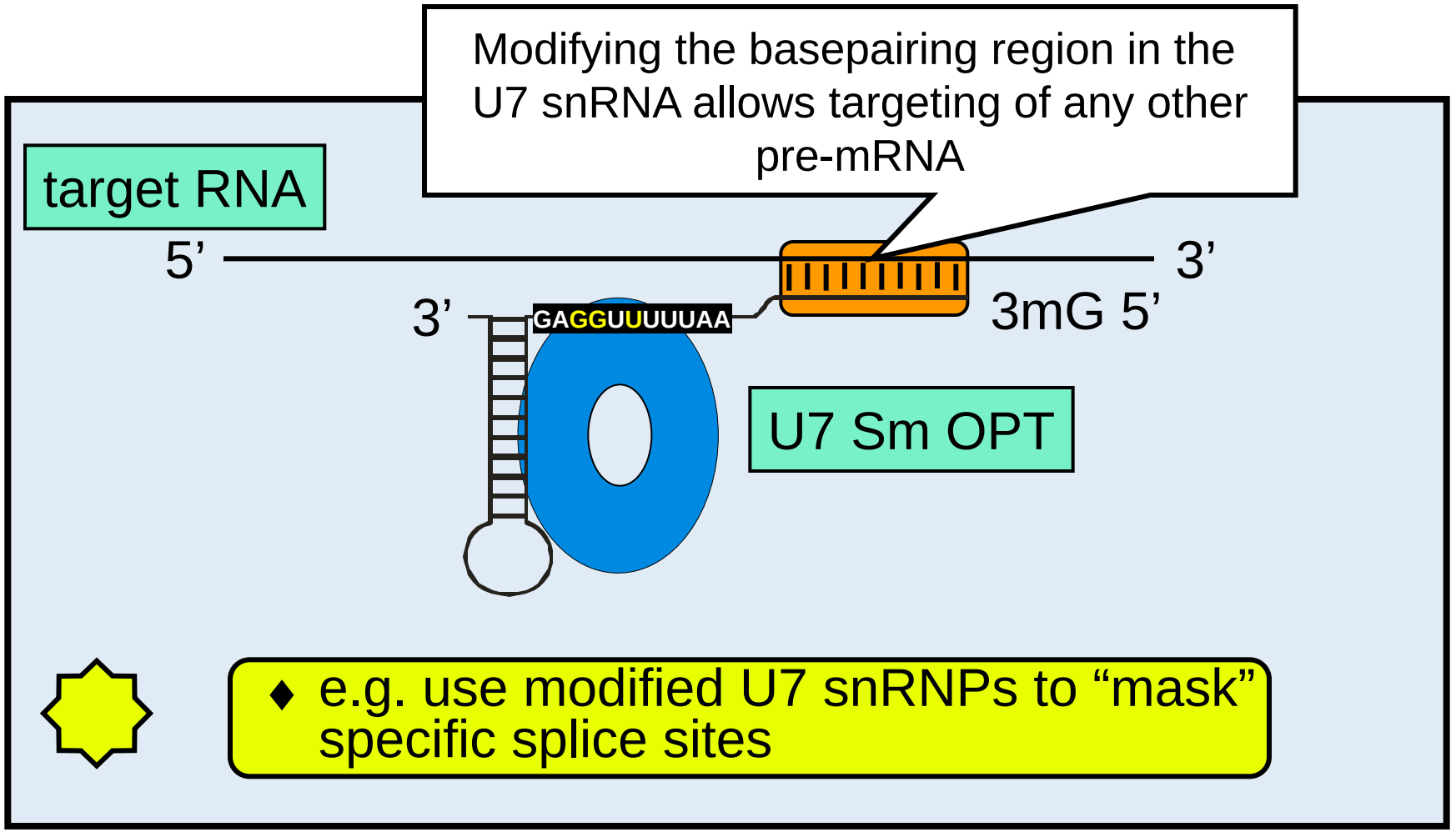
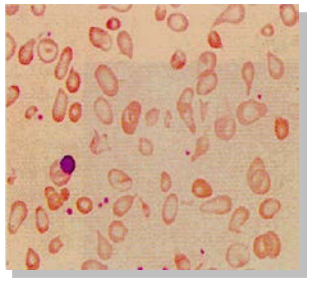
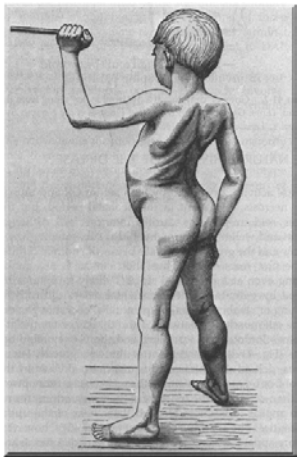


- e.g. use modified U7 snRNPs to “mask” specific splice sites

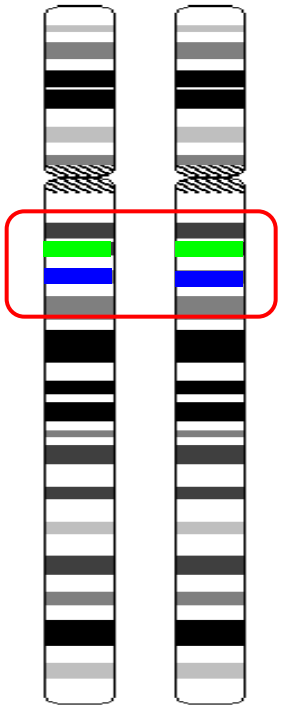
U7-based exon skipping





- Restoration of splicing defects
  (e.g. β-thalassemias)
- Restoration of defective reading frames
  (e.g. Duchenne muscular dystrophy)
- Interfering with alternative splicing decisions in infectious agents
  (e.g. HIV-1)

Genetics of SMA



Chromosome 5

SMN1 = 1 or 2 copies
SMN2 = not important

➔ normal phenotype

SMN1 = 0 copies
SMN2 = 1-2 copies

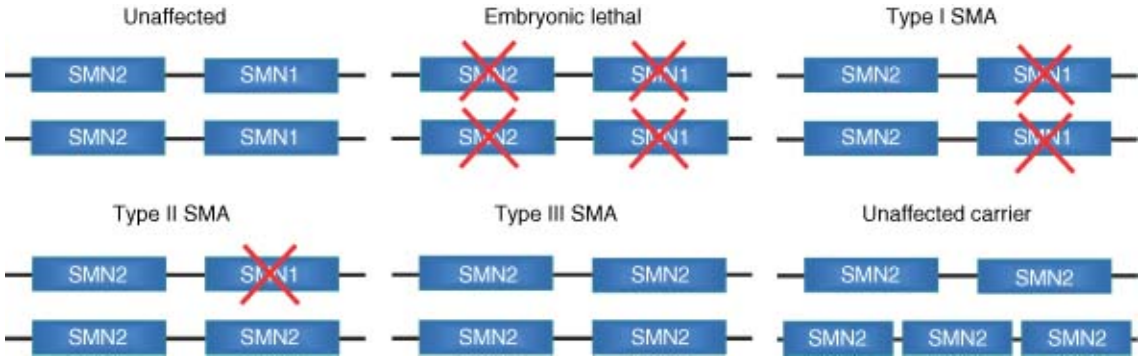
➔ SMA Type I

SMN1 = 0 copies
SMN2 = 3 - 4 copies

➔ SMA Type II - III

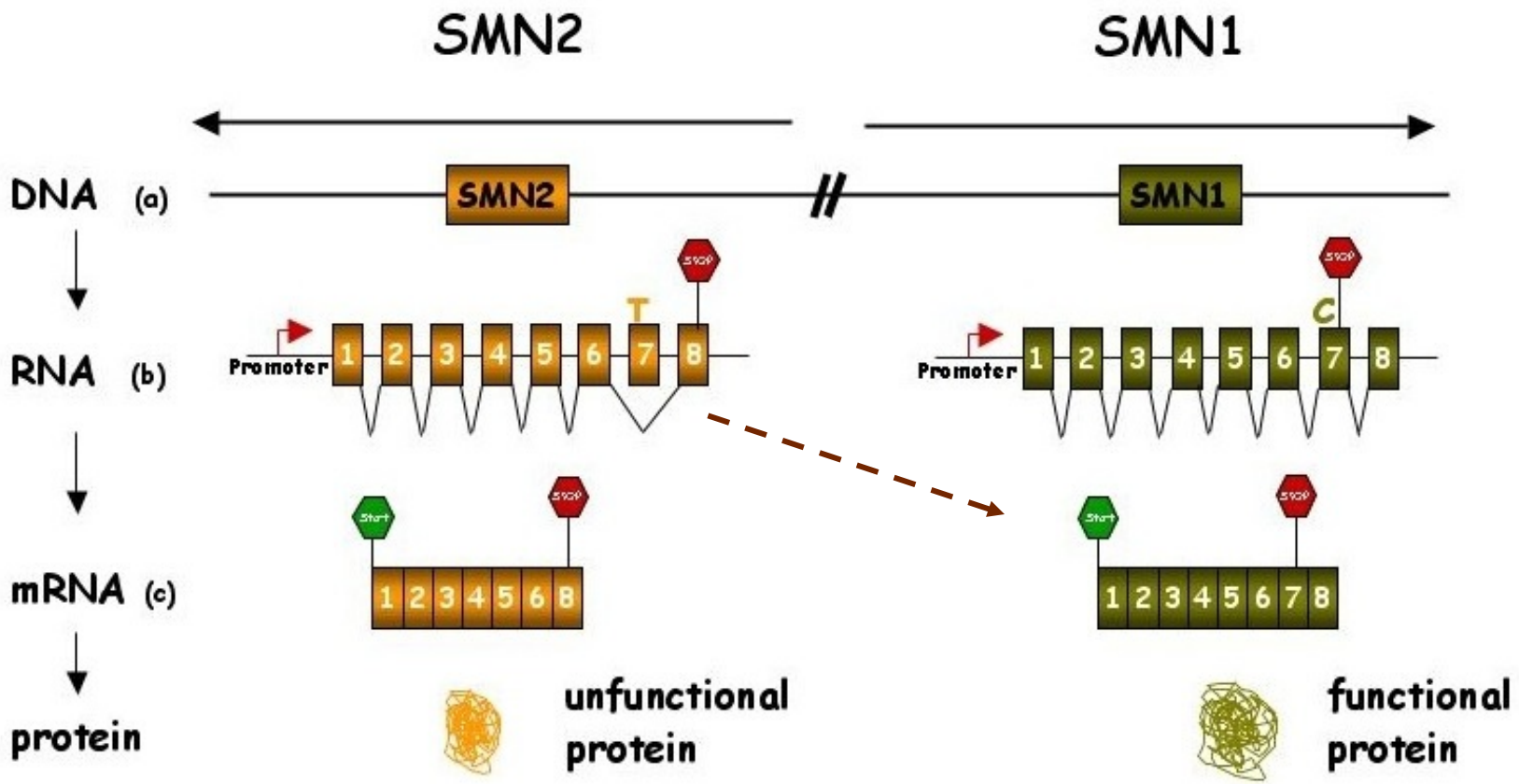
SMN1 = 0 copies
SMN2 = 0 copies

➔ early embryonic lethal

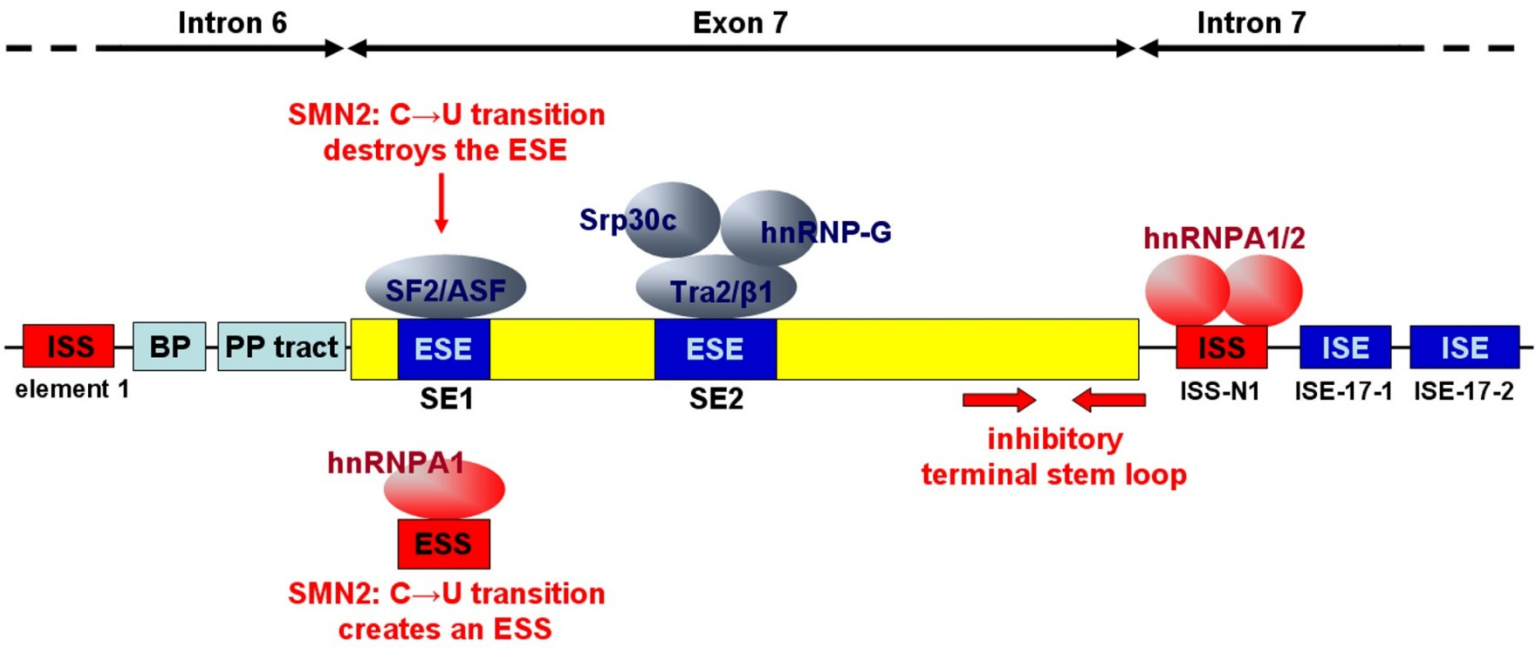


SMN = survival of motoneurons

SMA is due to a splicing defect in *SMN2* exon 7



Explanation for the splicing problem of *SMN2* exon 7



SMN1:
mainly FL mRNA
functional Protein

SMN2:
mainly Δ exon7 mRNA
unstable truncated Protein

Results with *SMN2*-Luc minigene in transiently transfected HeLa cells

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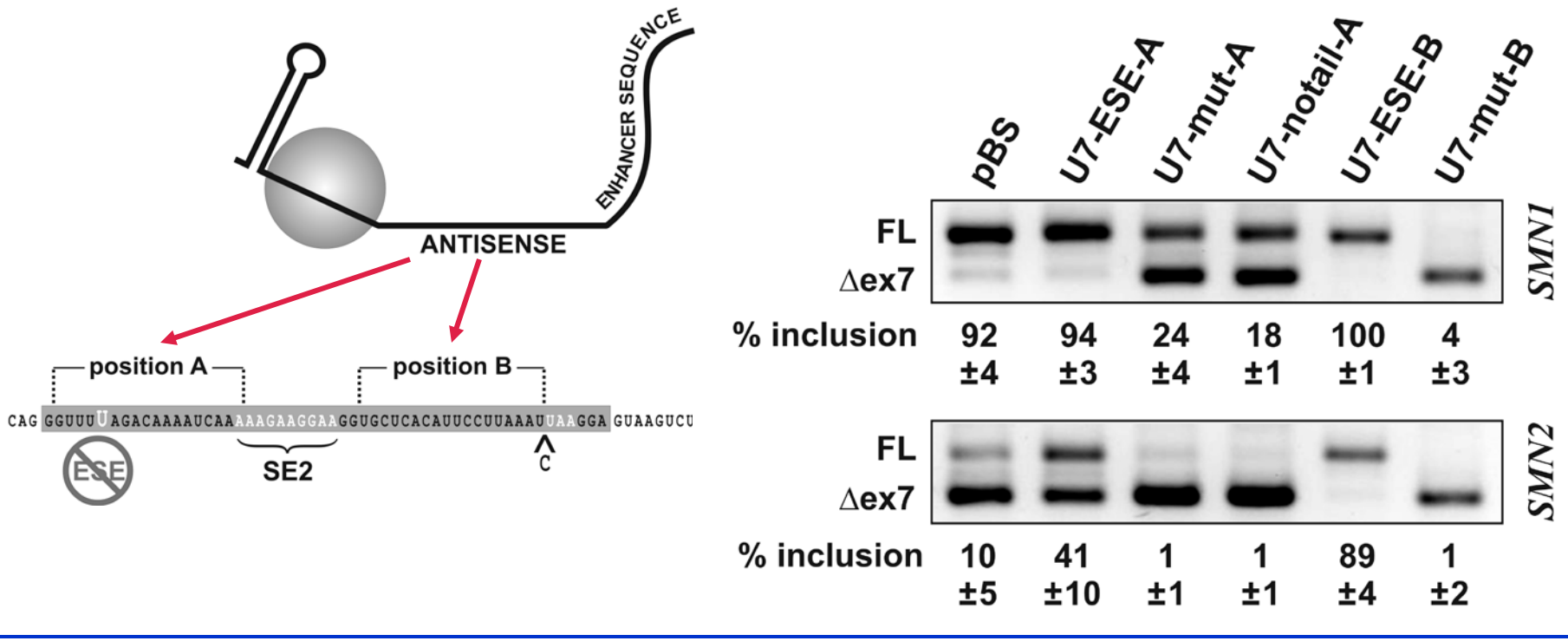


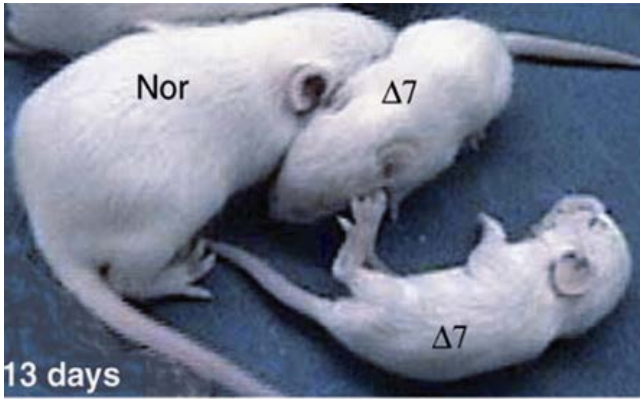
Marquis et al. (2007) Mol. Ther. 15: 1479-1486

Mouse models for SMA

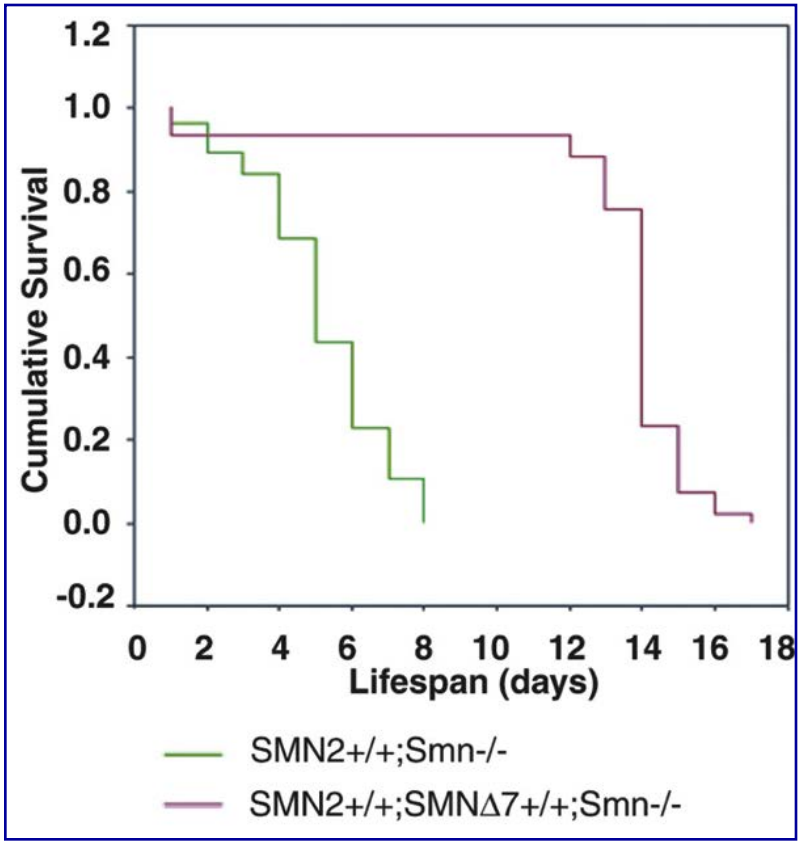
Monani et al. (2000) Hum Mol Genet, 9, 333-339.

"severe"

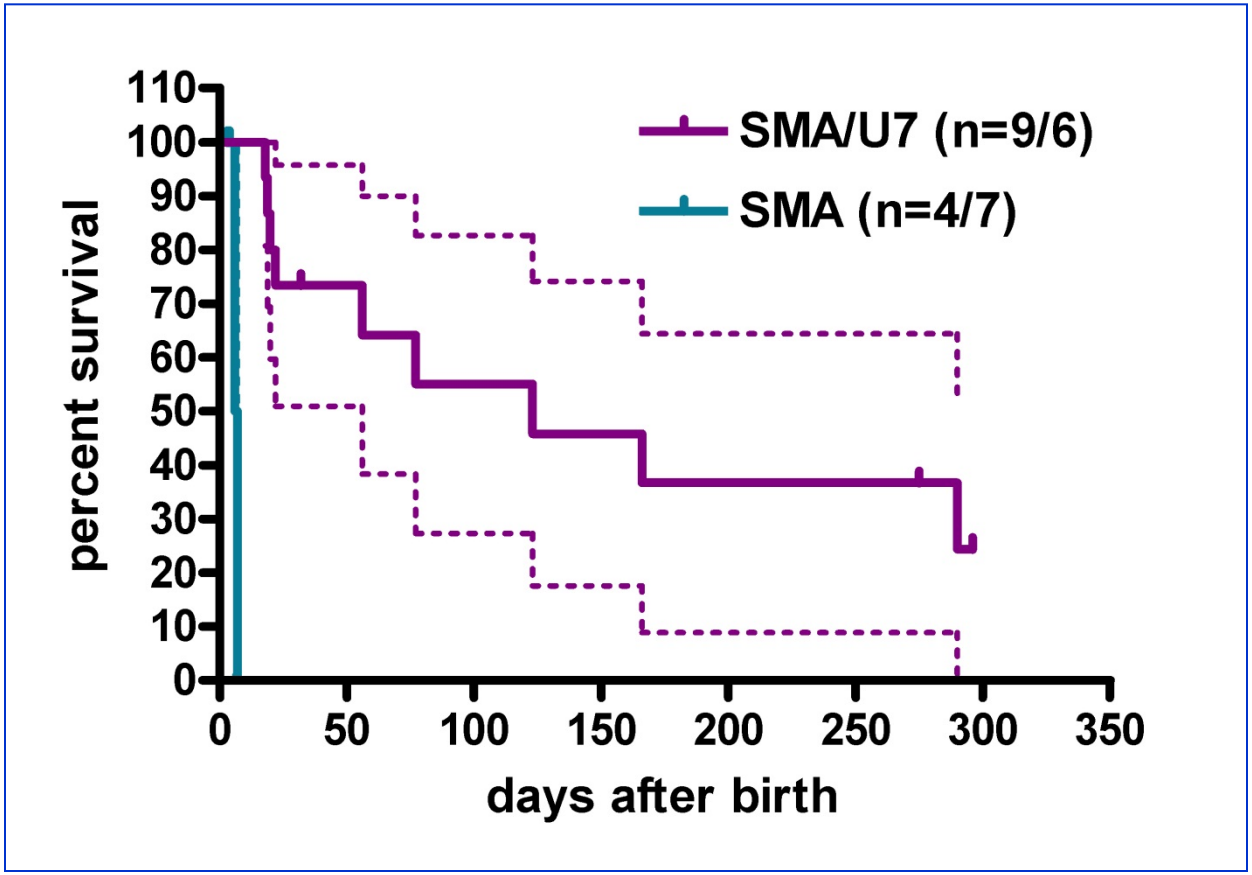
Le et al. (2005) Hum Mol Genet, 14, 845-857



"Δ7"

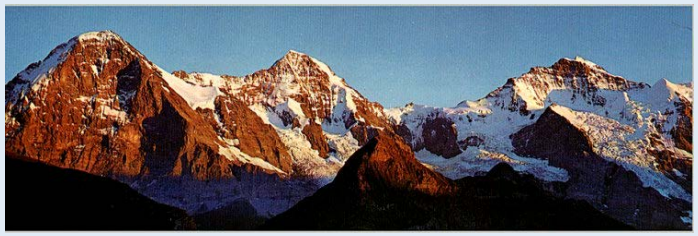


SMA mice with U7 transgene survive for > 4 months



Meyer et al. (2009) Hum Mol Genet 18, 546-555. Epub 2008

Acknowledgements



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3' Processing:

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fondation suisse de recherche sur les maladies musculaires