Stichting Oncowijs

Epigenetics and Cancer

Hoe controle mechanismen van invloed zijn op tumor ontwikkeling.

Riëtte Ruijten – Driessen
MANP, verpleegkundig specialist oncologie
Laurentius ziekenhuis

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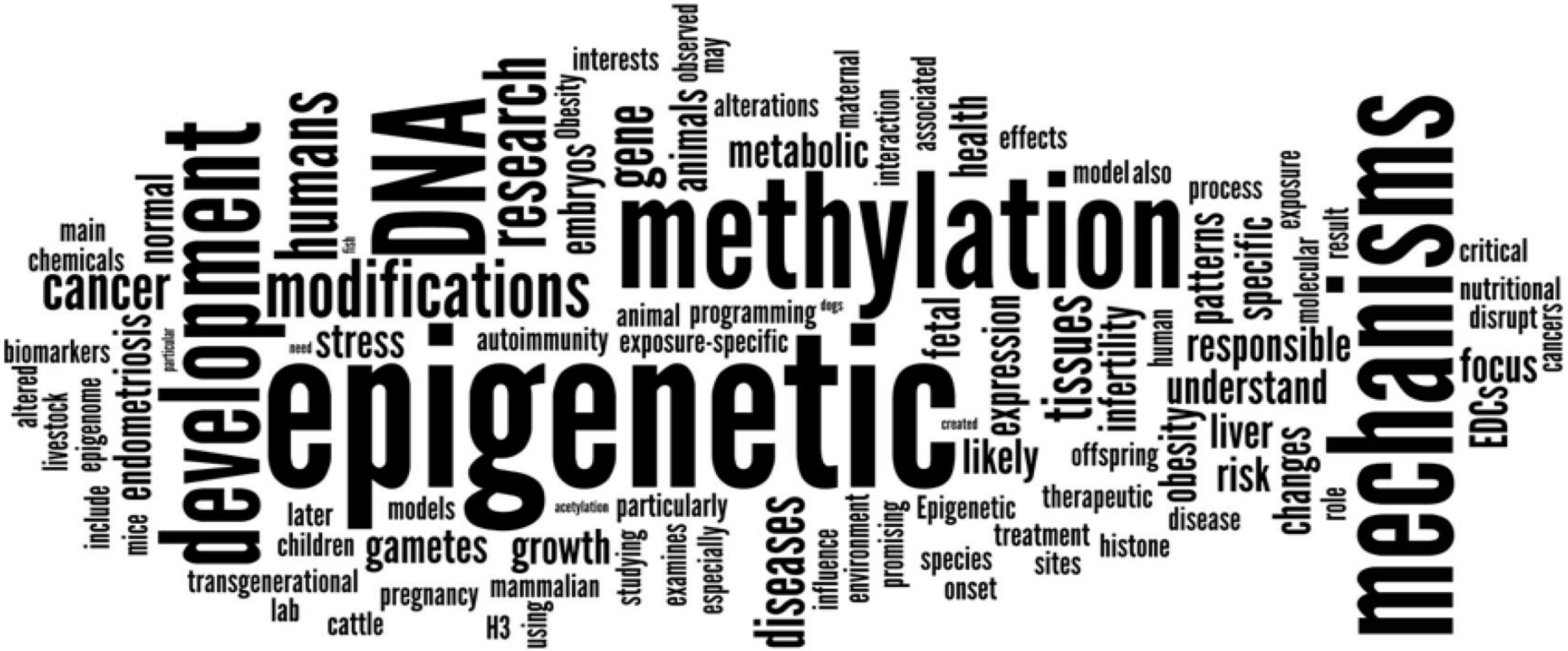

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Inhoud

Stichting Oncowijs

- Ontwikkeling epigenetica
- Verschil genetica en epigenetica
- Wat is epigenetica?
- Ontstaan van kanker
- Epigenetisch effect behandeling
- Medicatie resistentie
- Take home message

Van Kanker genomics naar epigenomics

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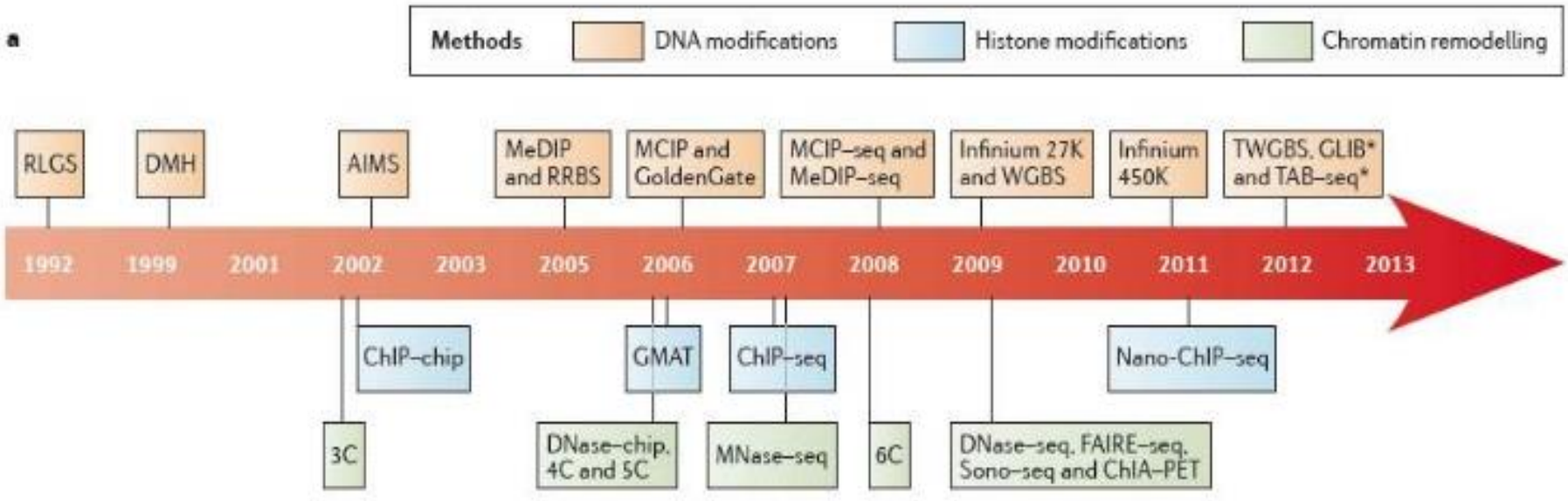

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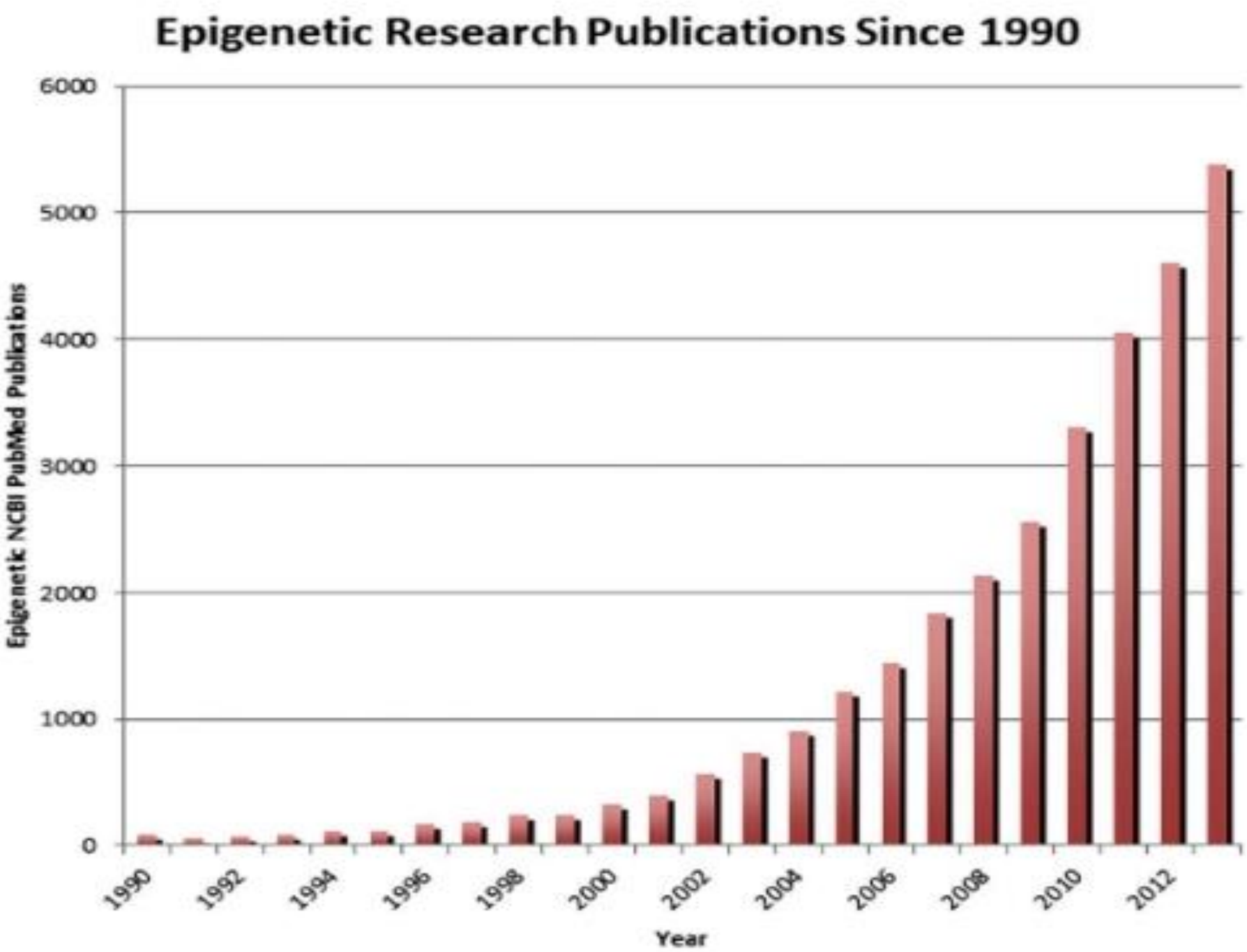

Fig. 1. Growing number of publications in the epigenetics field.

Biologie van kanker

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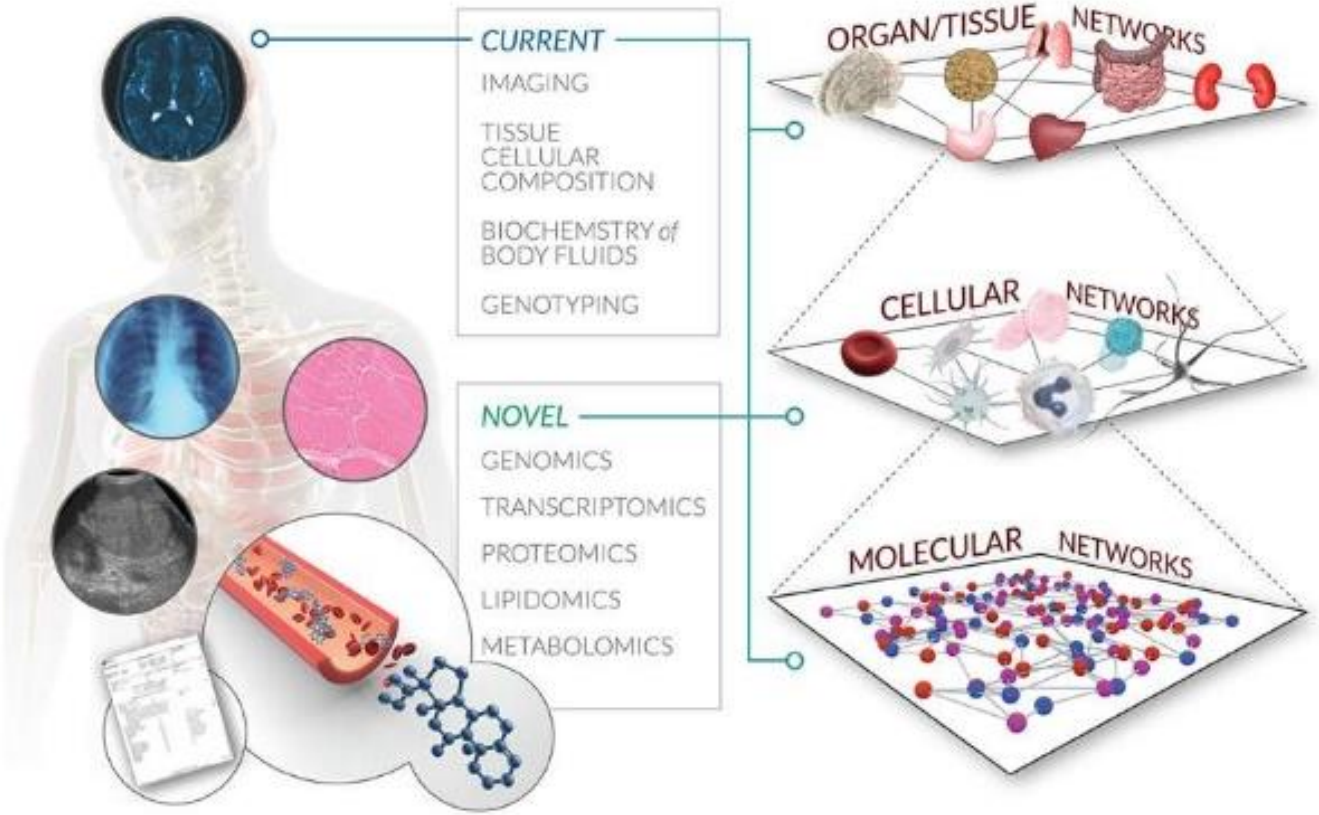

Understanding complex biological systems using computational and mathematical modeling

Van genomics naar epigenomics van kanker

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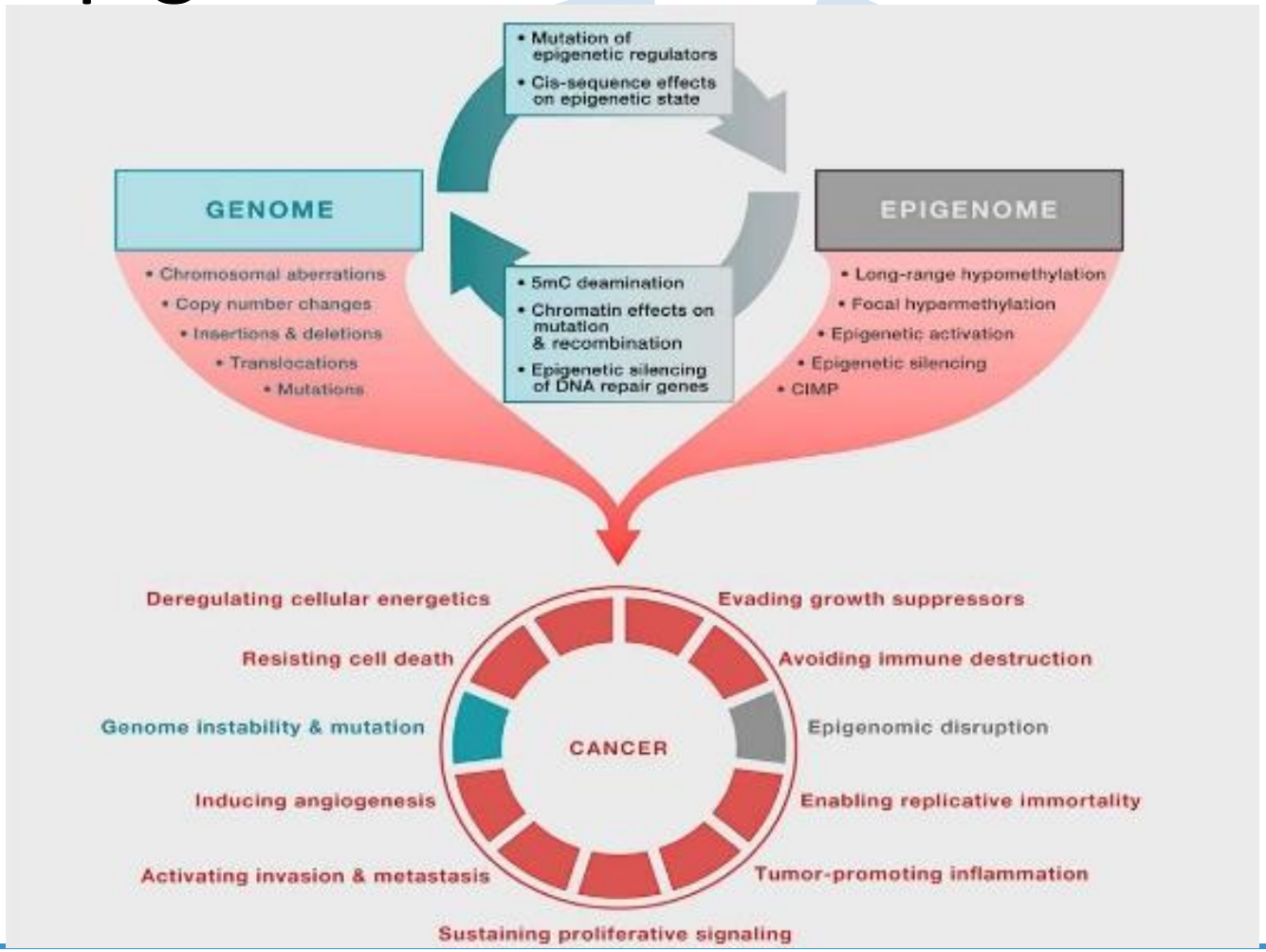

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Het verschil tussen genetica en epigenetica

Stichting Oncowijs

Het verschil tussen genetica en epigenetica

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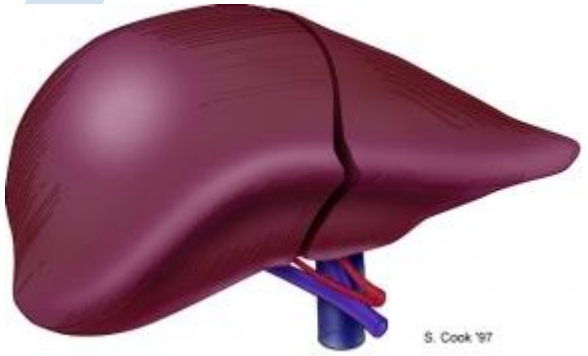

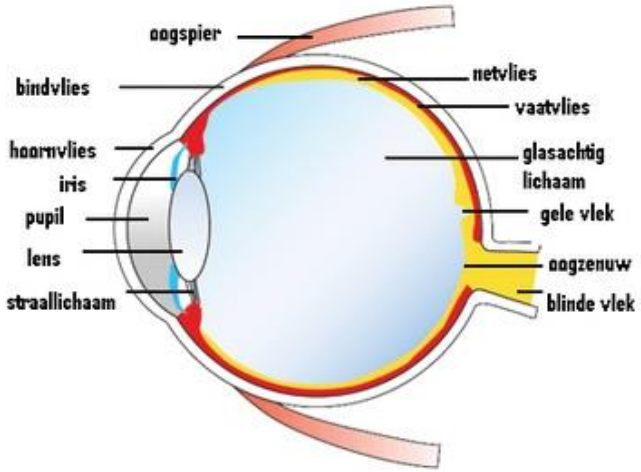

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Het verschil tussen genetica en epigenetica

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- Tweelingen kunnen genetisch en phenotyperend gelijk zijn.

Het verschil tussen genetica en epigenetica

Stichting Oncowijs

- Er is steeds meer begrip hoe dingen fout kunnen gaan.
- Genetische en epigenetische processen bepalen samen de proliferatie van een cel

Wat is epigenetica?

Stichting Oncowijs

- De studie van omkeerbare (erfelijke) veranderingen, zoals histonmodificaties en DNA – methylering, op de functie van genen.
- Dit uit zich in expressie van specifieke mRNA's en eiwitten, en uiteindelijk in het fenotype van een cel of organisme.

Wat is epigenetica?

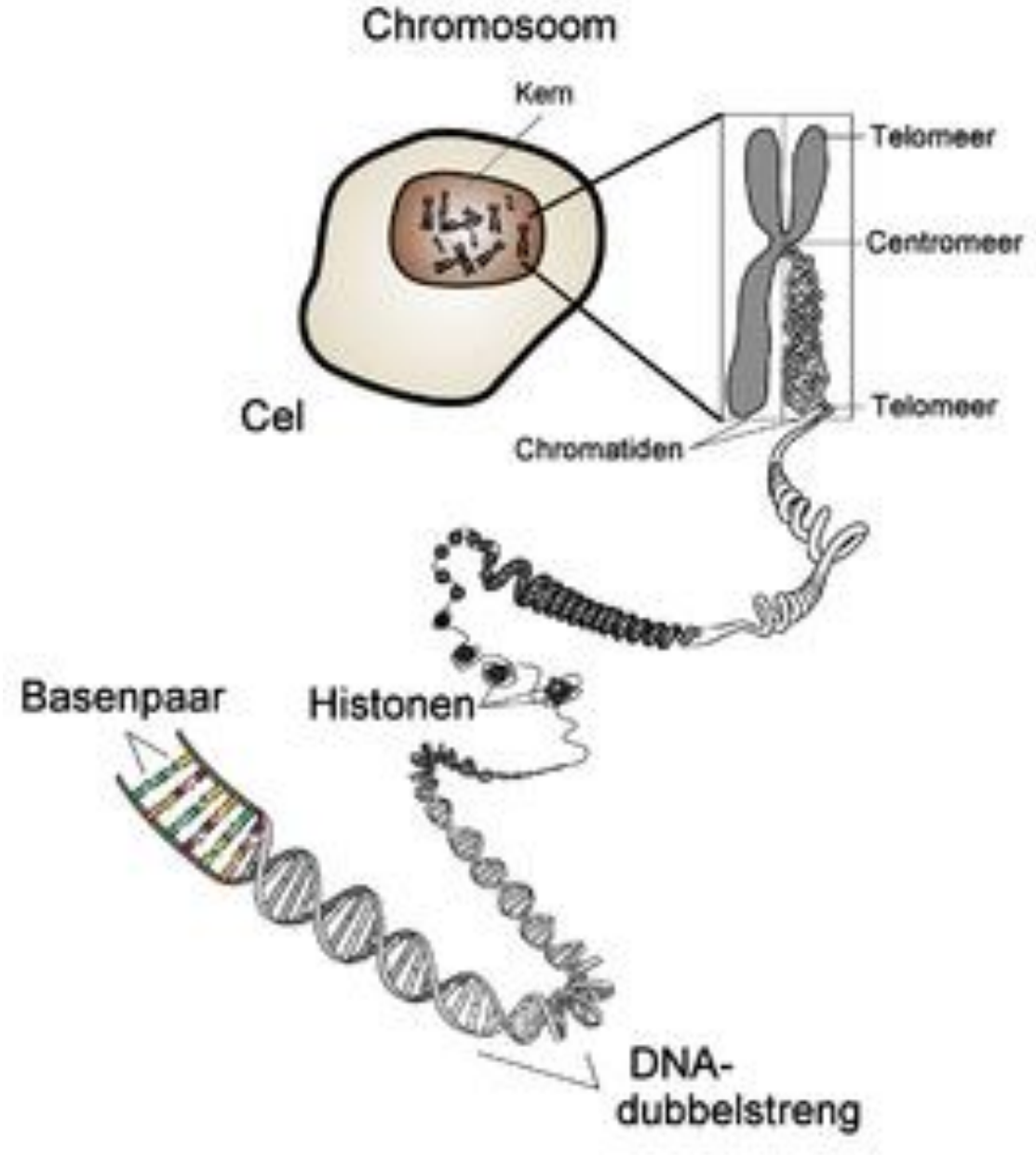
Stichting Oncowijs

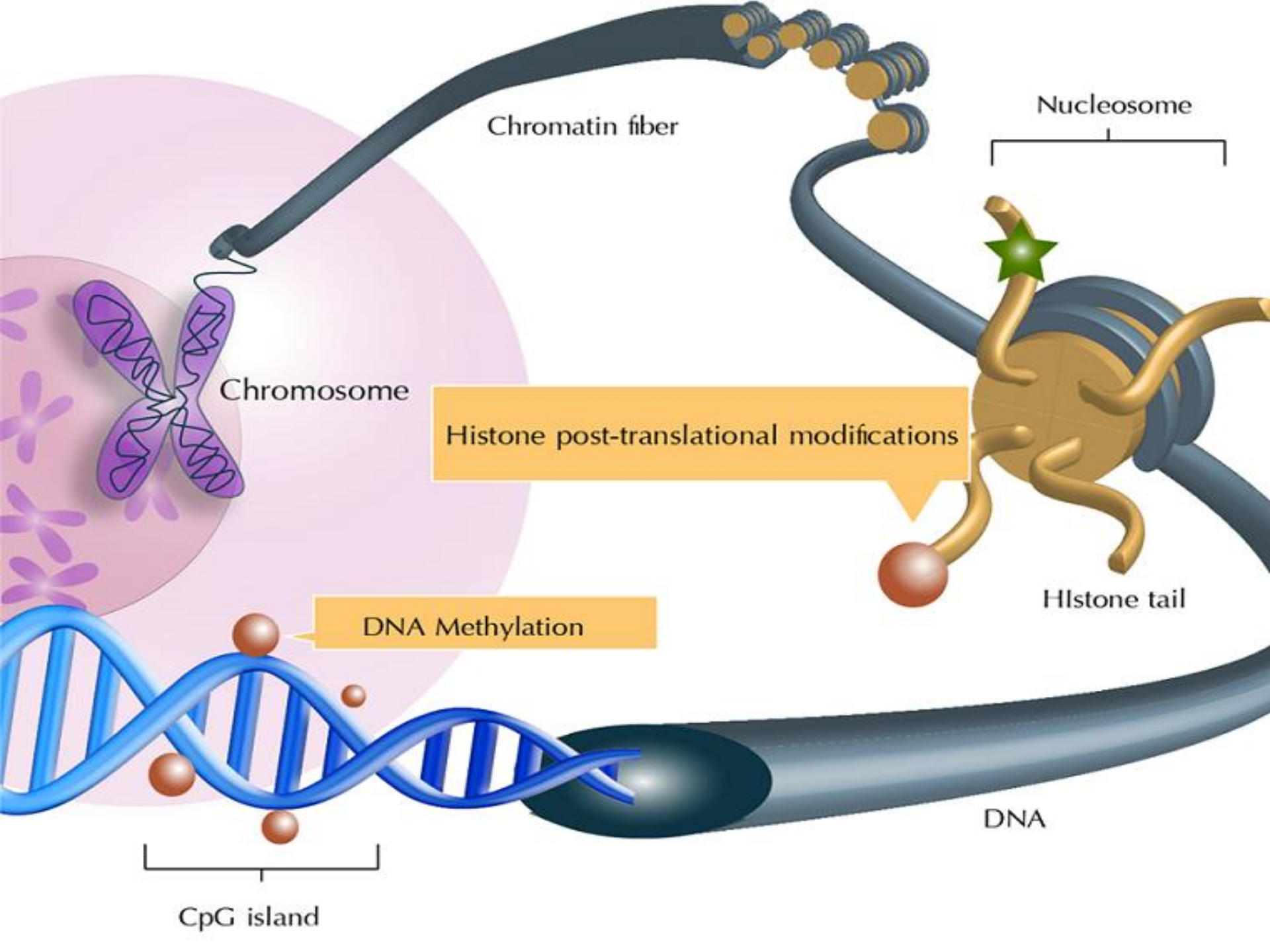
- Term 'Epi' in het woord epigenetica, = 'boven op' de genetica, of 'toegevoegd aan het DNA'.
- Toegevoegd aan DNA:
  - 1) de chemisch modificatie van de DNA basen;
  - 2) de eiwitten die direct of indirect aan DNA gebonden zijn en de chemische modificatie van deze eiwitten.

Wat is epigenetica?

Stichting Oncowijs

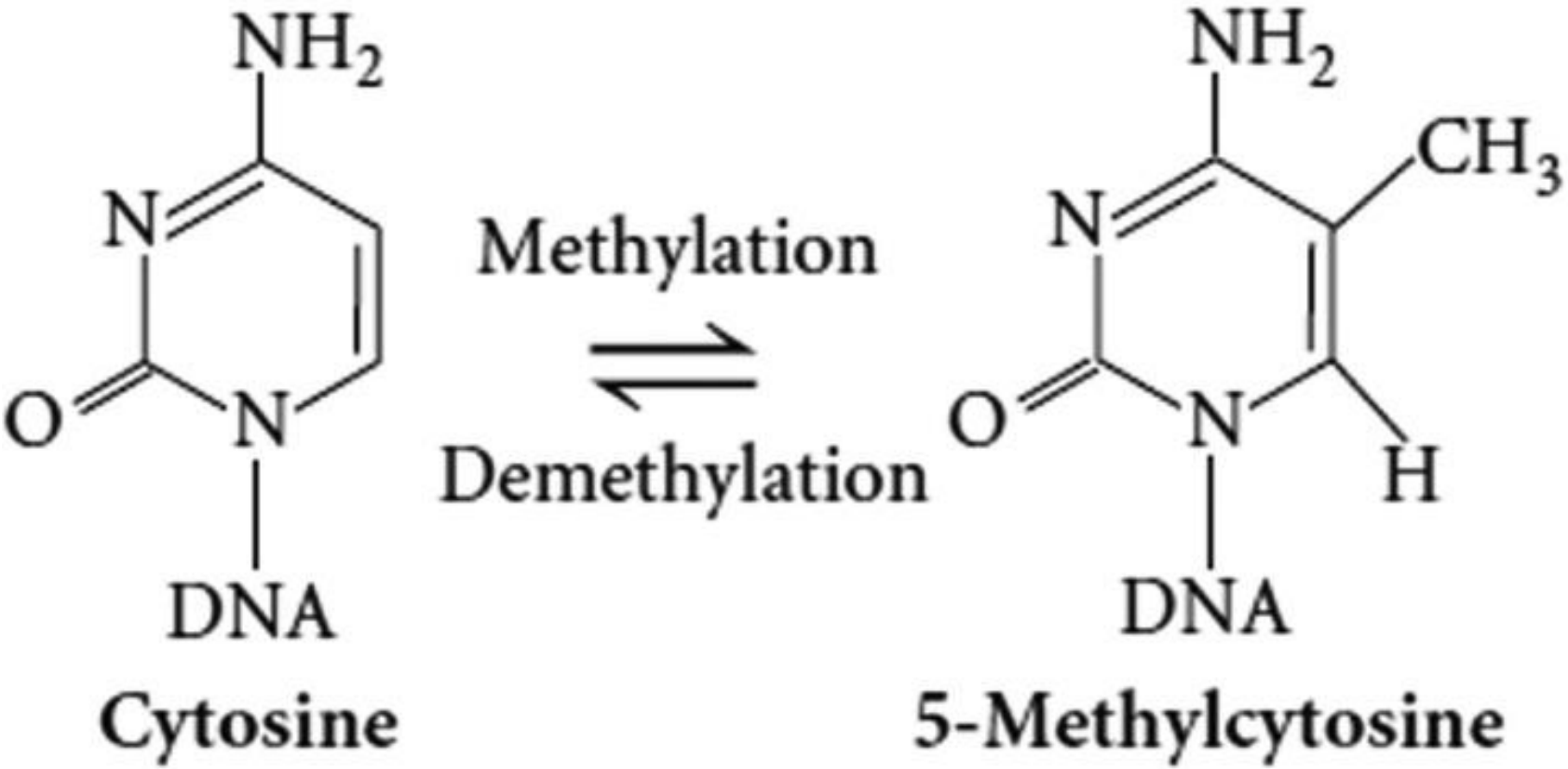
- Epigenetica houdt zich bezig met chromatinestructuur en de veranderingen daarin die optreden bij het reguleren van genexpressie.

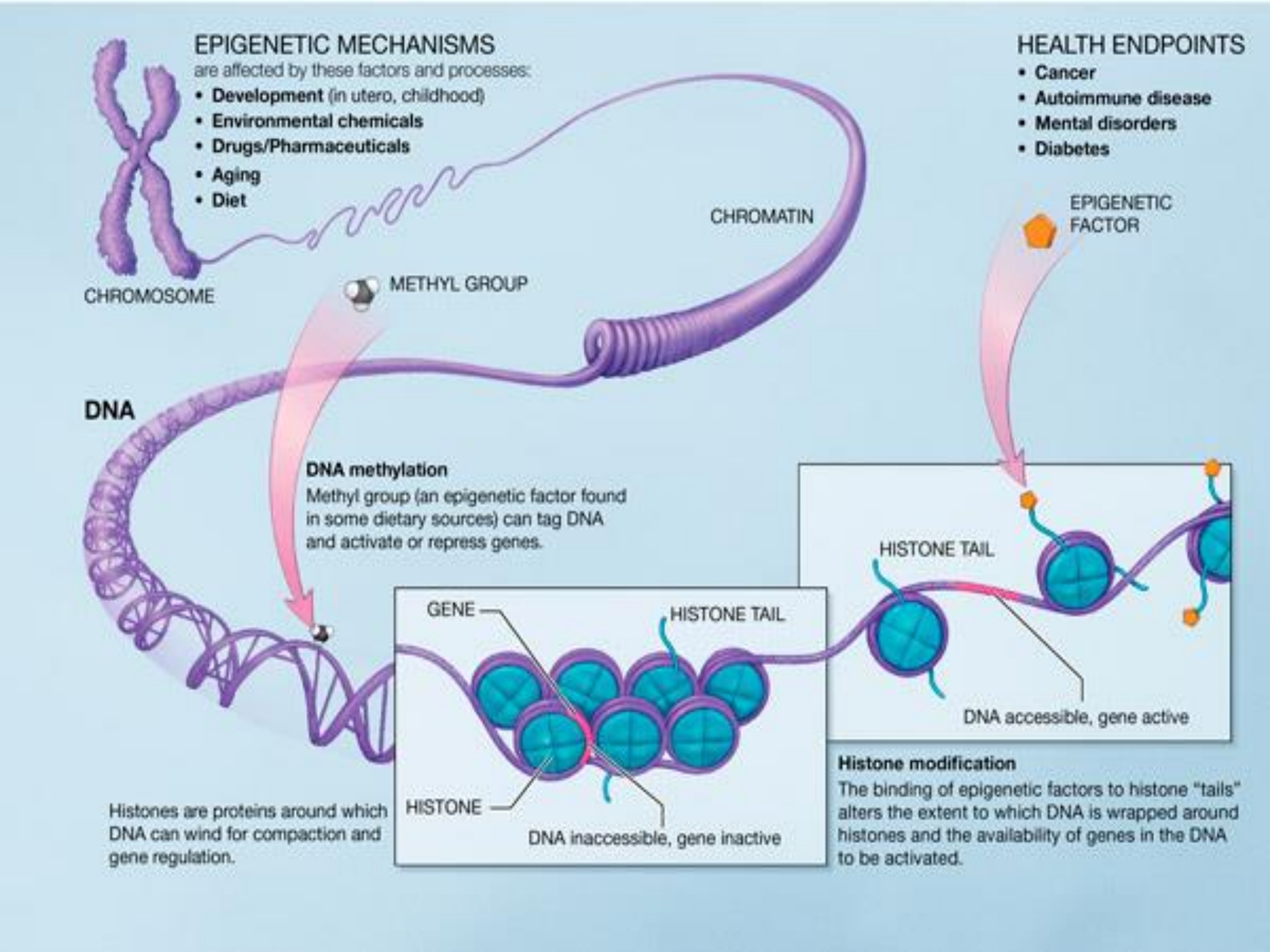



Chromatin fiber
Nucleosome
Chromosome
Histone post-translational modifications
HIstone tail
DNA Methylation
DNA
CpG island

DNA methylering

Stichting Oncowijs




EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

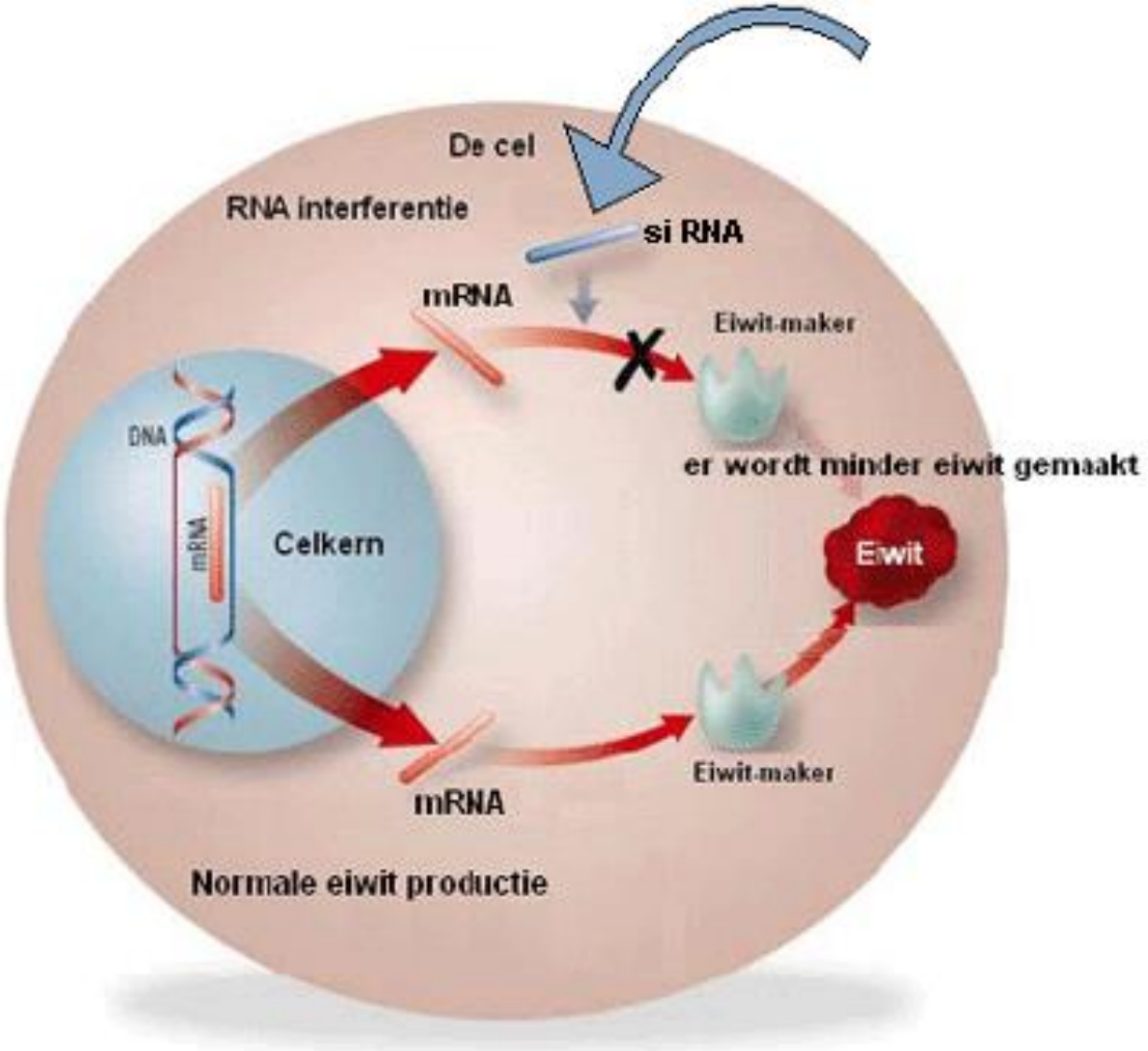
Methylering

Stichting Oncowijs

- Gedurende het leven meer afwijkingen in methylering
- Methyleringstoename in tumoren
- Methyleringstoename in gebieden rondom de tumoren
- Samenhang met dieetfactoren, alcoholgebruik, roken en virale factoren (niet bewezen)

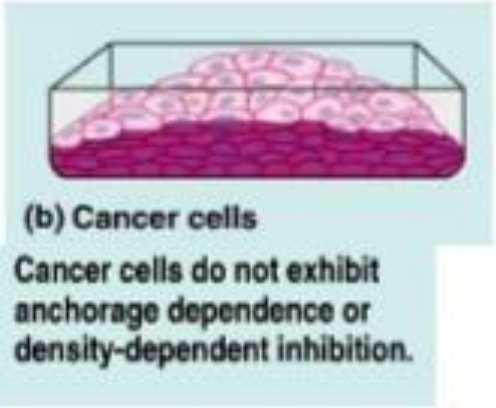
RNA-interferentie

Stichting Oncowijs



Development of Cancer

- Cancer develops only after a cell experiences ~6 key mutations ("hits")
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes (p53)
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
    - turn on chromosome maintenance genes
  - promotes blood vessel growth
    - turn on blood vessel growth genes
  - overcome anchor & density dependence
    - turn off touch-sensor gene



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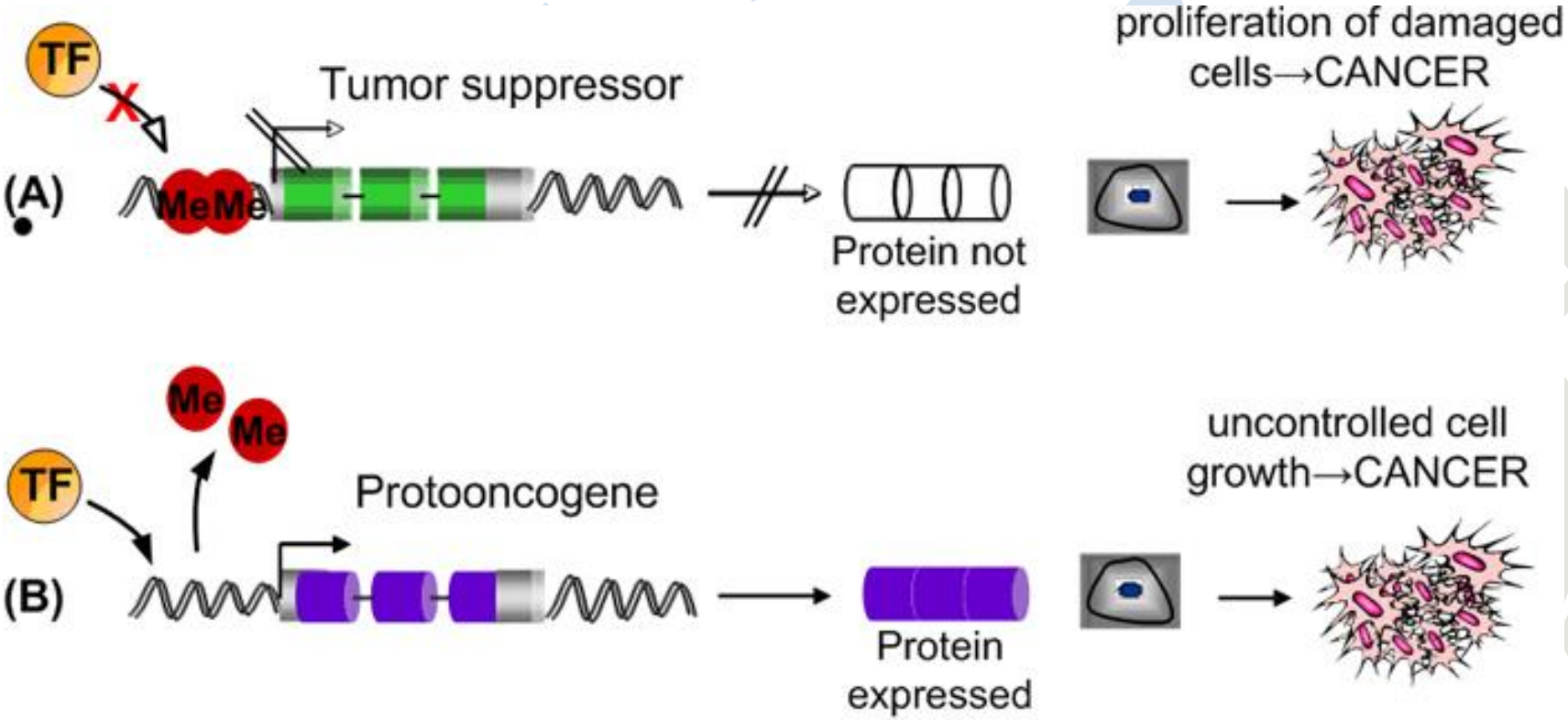
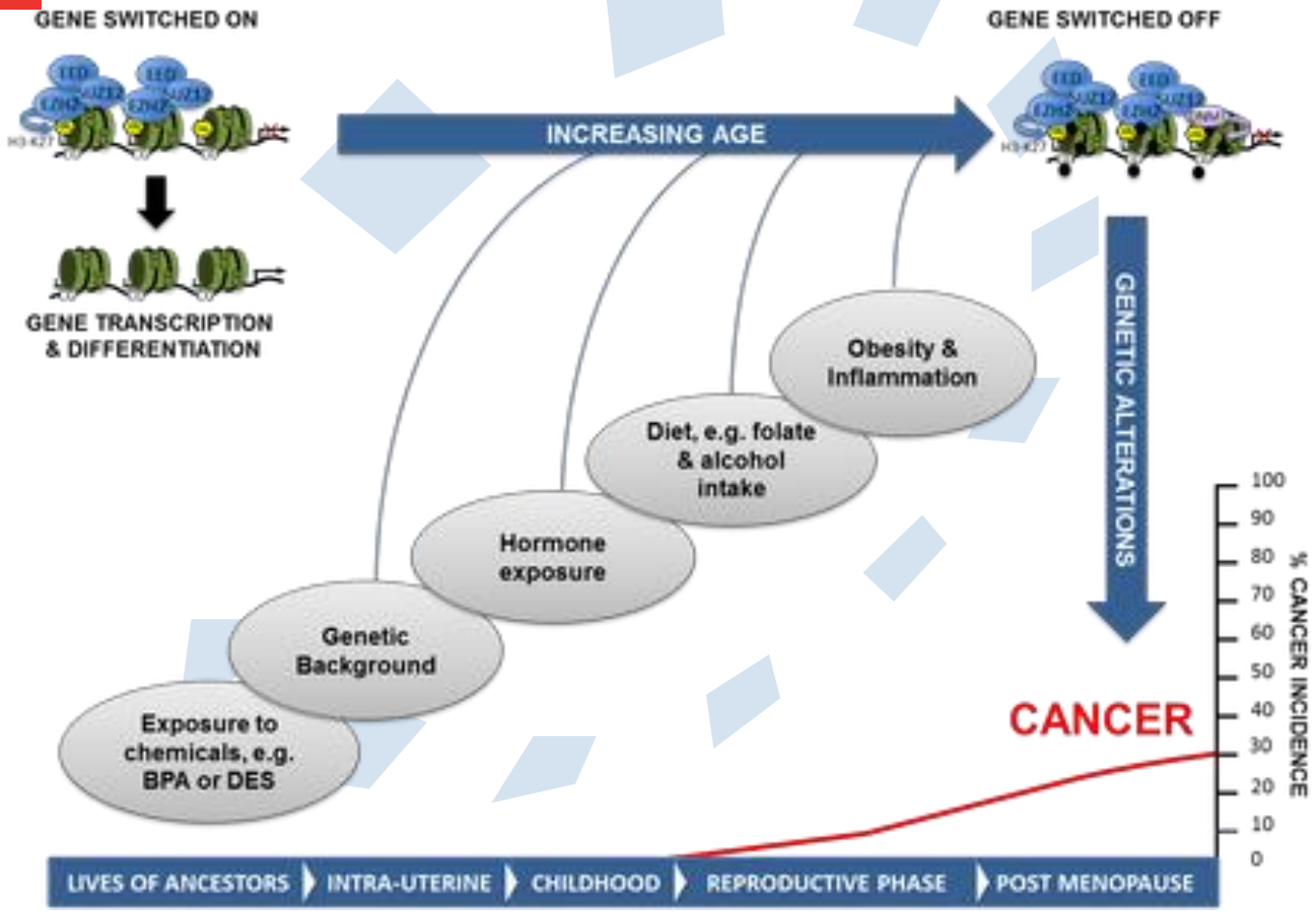


Epigenetica tijdens het leven

Stichting Oncowijs

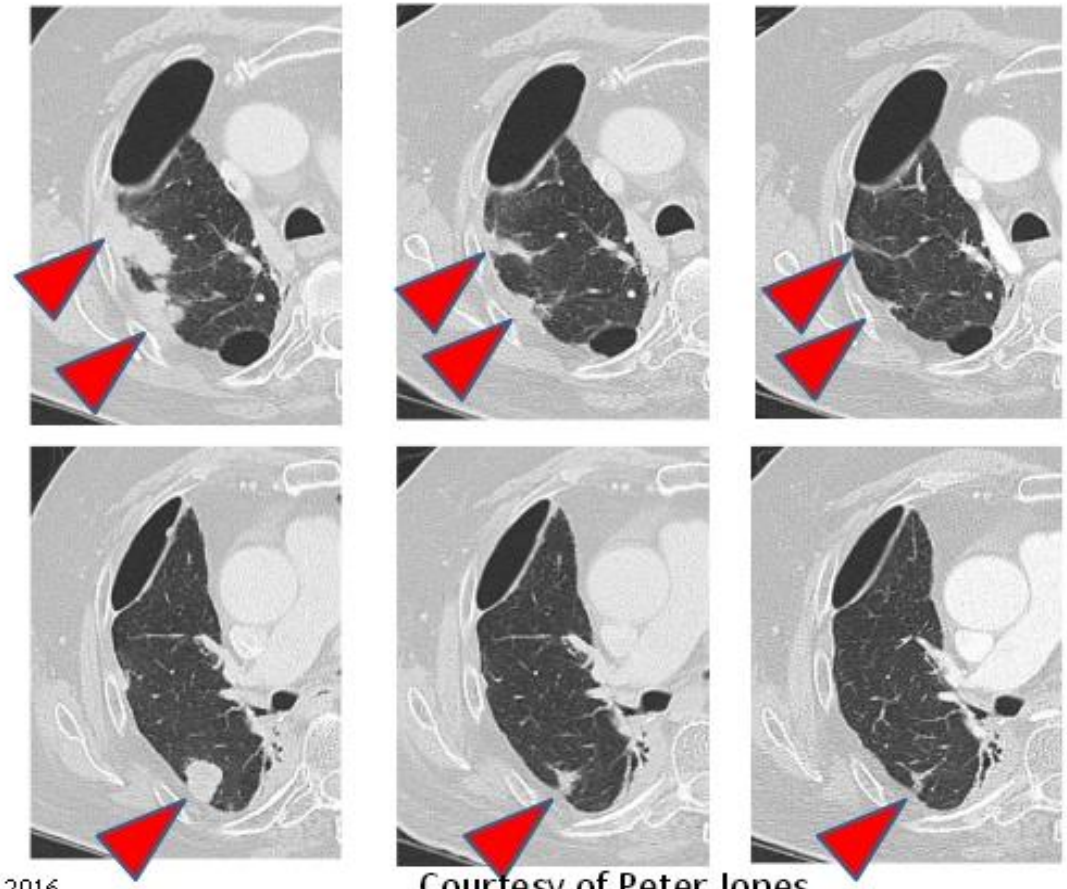


Gregory, 2005

Gene	Function	Reference
BHLHB4	Transcriptional regulator, differentiation	(23)
BLU	Transcription repressor	(17, 23)
CDKN2A	Inhibitor cyclin-dependent kinase; cell cycle arrest	(15, 16)
CDH1	Cell adhesion/metastasis	(16)
CDH13	Cell adhesion	(16)
CXCL14	Pro-apoptosis, cell cycle arrest	(24)
DAPK1	Apoptosis	(16)
DKK3	Wnt pathway antagonist	(21)
DCL1	Cell growth, apoptosis, cell adhesion	(15)
HOXA genes	Homeobox transcriptions factors; differentiation	(22)
MGMT	DNA repair	(16, 23)
MMP2	Degradation extracellular matrix	(23)
RARß	Retinoic acid receptor ß; differentiation	(16)
RASSF1A	Cell cycle control	(16, 17, 25)
Reprimo	Mediator of p53-mediated cell cycle arrest	(20)
RUNX3	Transcription factor target TGF-ßpathway	(25)
SFRP1	Antagonist of Wnt pathway	(26)
TCF1	Differentiation	(19)
TIMP3	Tissue inhibitor of metalloproteinase 3; metastasis	(15)
WIF1	Antagonist of WNT pathway	(18)

Oncowijs

Response of a "non-immunogenic" tumor to anti-PD-1: Stage IV Non-Small Cell Lung Cancer with prior epigenetic therapy



Courtesy of Peter Jones

Pt. 001-0605

History: 61 y.o. male with stage IV NSCLC refractory to multiple surgeries, RT, two multidrug chemotherapy regimens, 5-AZA and entinostat (HDACi).

E. Heard, 2016

COLLÈGE DE FRANCE 1530

DNMT inhibitors

Stichting Oncowijs

Epigenetic effects of DNMT inhibition by azacitidine (AZA) or decitabine (DAC).

5-azacitidine and entinostat, which alter the epigenome, may prime patients' immune systems to respond to the checkpoint inhibitor.

Pairing these drugs may radically improve patient outcomes. Large clinical trials ongoing

Werking 5-AZA

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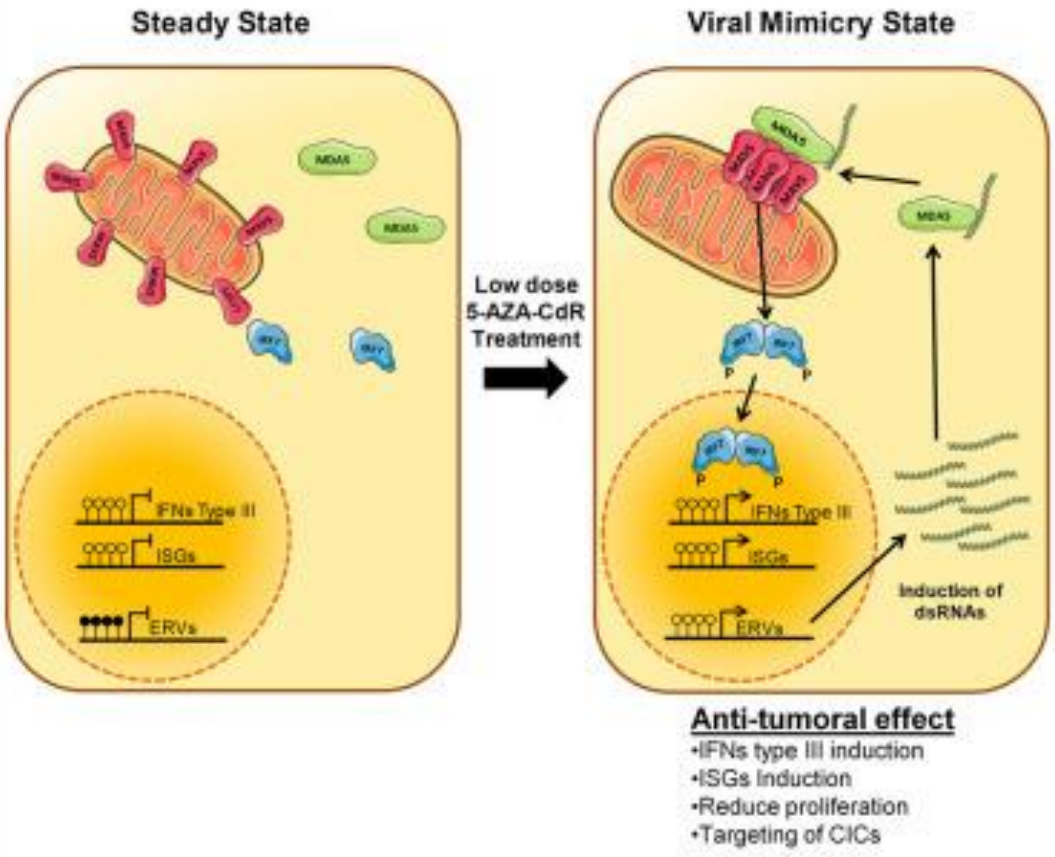

Genetische en epigenetische medicatie resistentie

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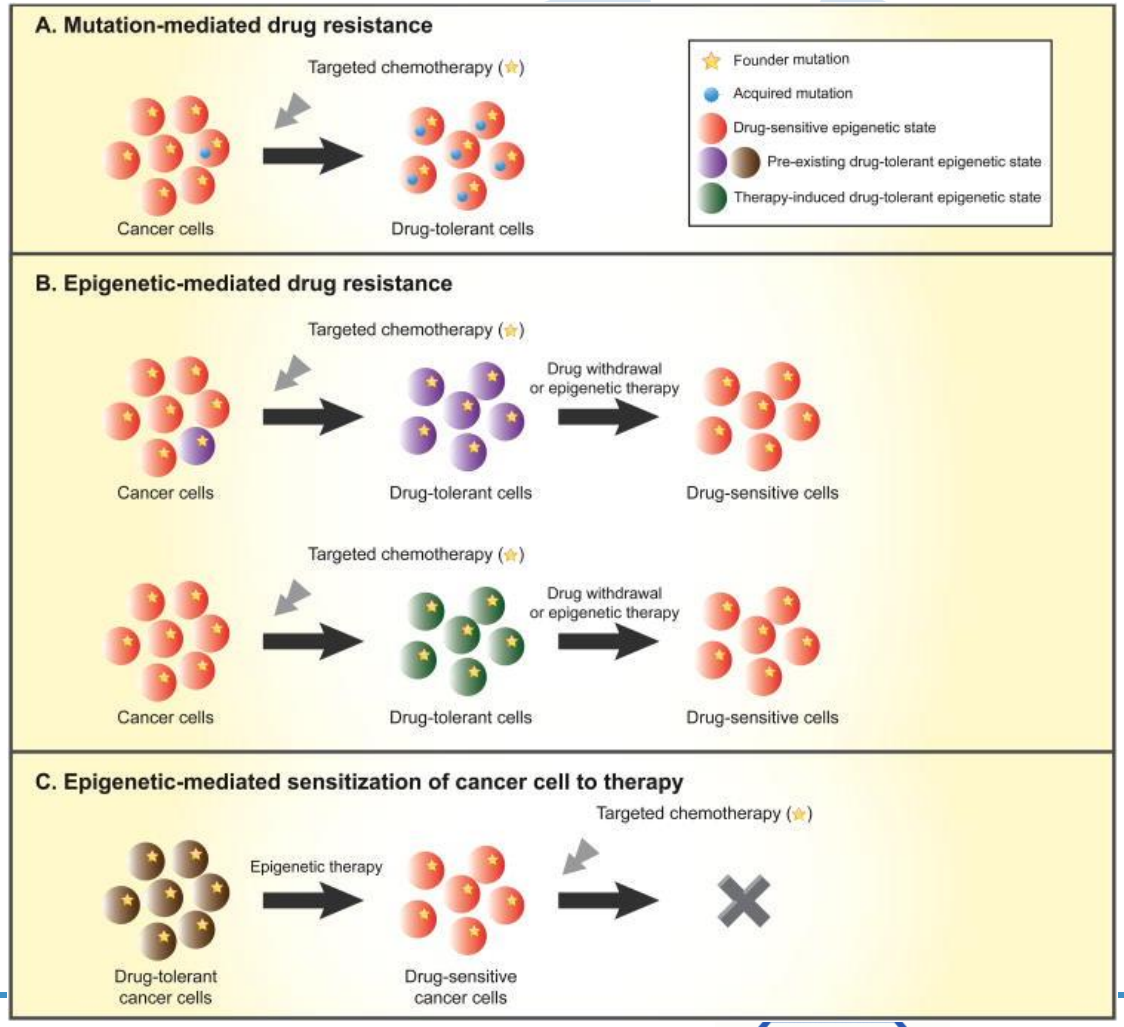
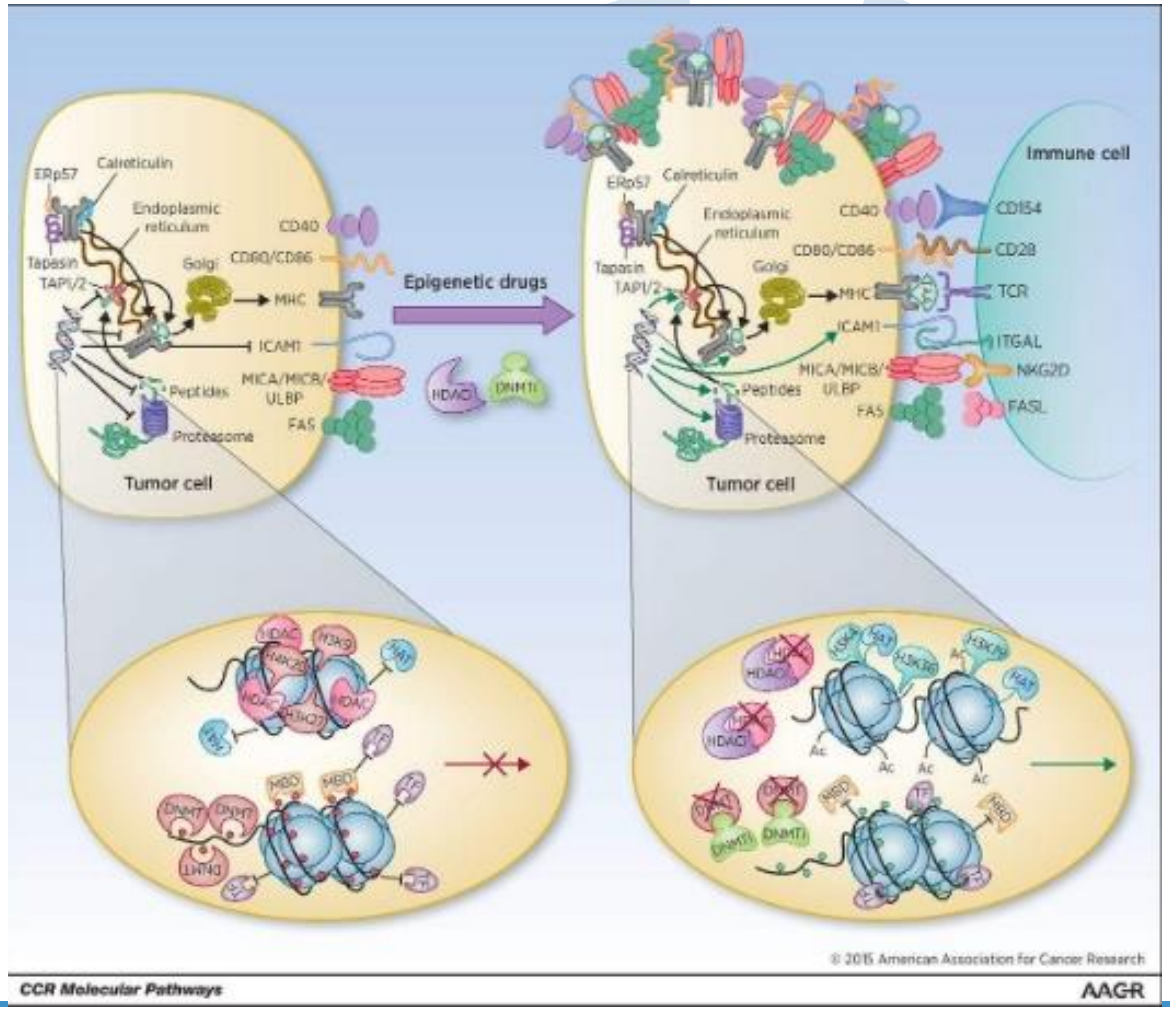


Easwaran e.a. 2014

Medicatie resistente kankercellen



Heard, 2016

Van mechanisme naar therapie

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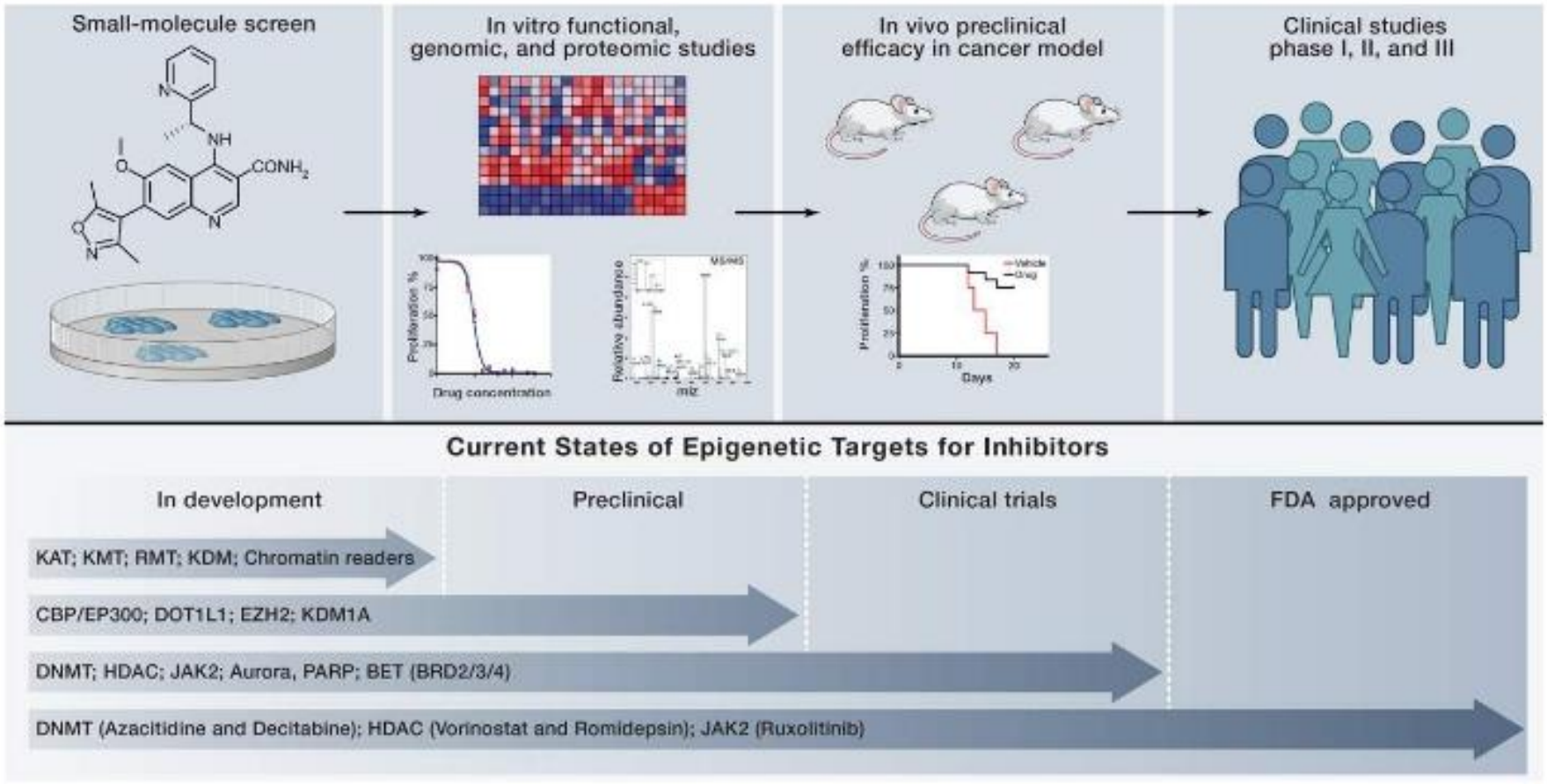

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Take home message

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- Fouten in DNA spelen cruciale rol in ontstaan maligniteiten.
- Methylering speelt substantiële rol in vroege fase tumorontwikkeling
- Methylering gaat mogelijk vooraf aan morfologische veranderingen (biomarker).
- Methylering als doelwit antikankerbehandeling veelbelovend


BIG
CHANGE
STARTS HERE.

Stichting Oncowijs

Vragen ?

Bedankt voor jullie aandacht !

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