

# Pancreatic Neuroendocrine Neoplasms

From Genetics to Everolimus Resistance

Timon Vandamme



Van paarden...

Als je hoe  
denk



rd...



...tot kanker

DE STANDAARD  
DINSDAG 27 JANUARI 2015

wetenschap | D9

SIGARETTEN EISEN HUN TOL

# Longkanker steekt borstkanker voorbij

...tot kanker

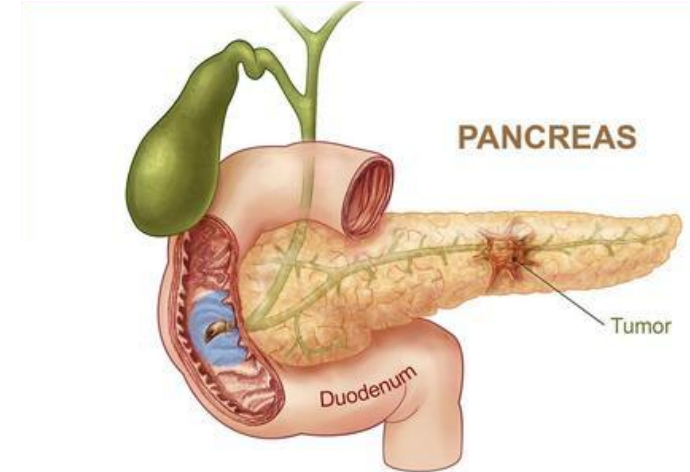


**23% van alle kankerpatiënten in Europa lijden aan een zeldzame vorm van kanker**

# Pancreatische neuro-endocriene neoplasiën

- Pancreas

- Orgaan met dubbele functie
  - Vertering
  - Hormoonproductie



- Pancreatische neuroendocriene neoplasiën (pNEN)

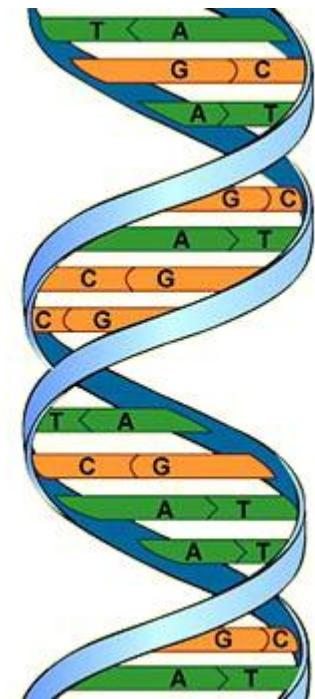
- Tumoren van hormoonproducerende cellen
- Tumoren ontstaan door cellen die “op hol” slaan
- Soms symptomen door overproductie hormonen



# DNA

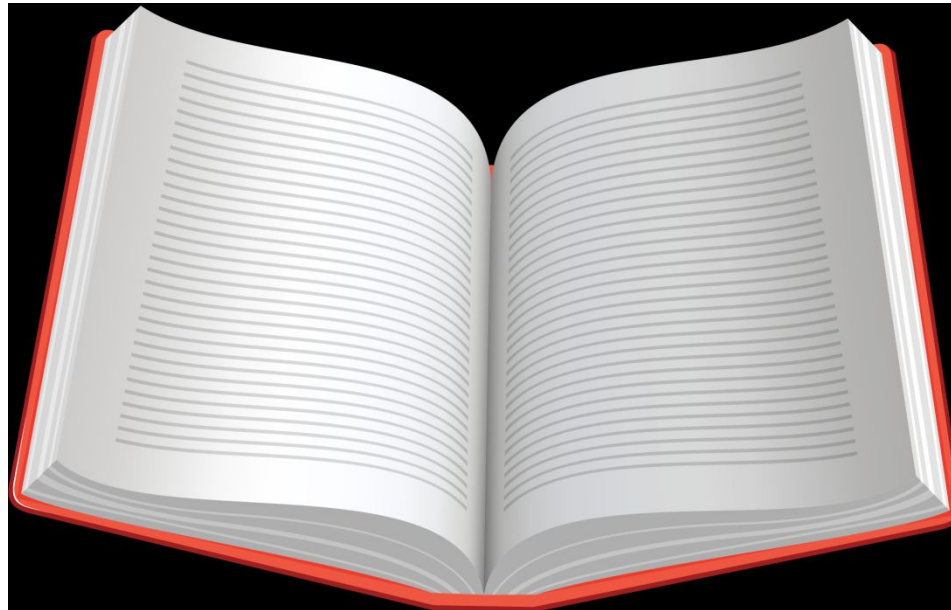
Erfelijk materiaal= DNA

Handleiding die ons lichaam vertelt wat het moet doen en wanneer



# DNA

Alle boeken zijn opgebouwd uit slechts 4 letters: A, T, C en G



```
...AATCGCTAAAGGGGCCTGACTGCCTTTTTGAACGTCCCGGG  
ATCGCAGTCGATTAGCCCCGCTACTGCTGTGTCAACTAGCTGC  
ATGCGCAAATGCGCTATCGTCAGTCATGCTGCATGAAATATGC  
CGCATCGACTAGCTAGGCTTTAAAAGCATCGCGACTG...
```

# DNA

Soms zitten er fouten in het DNA:

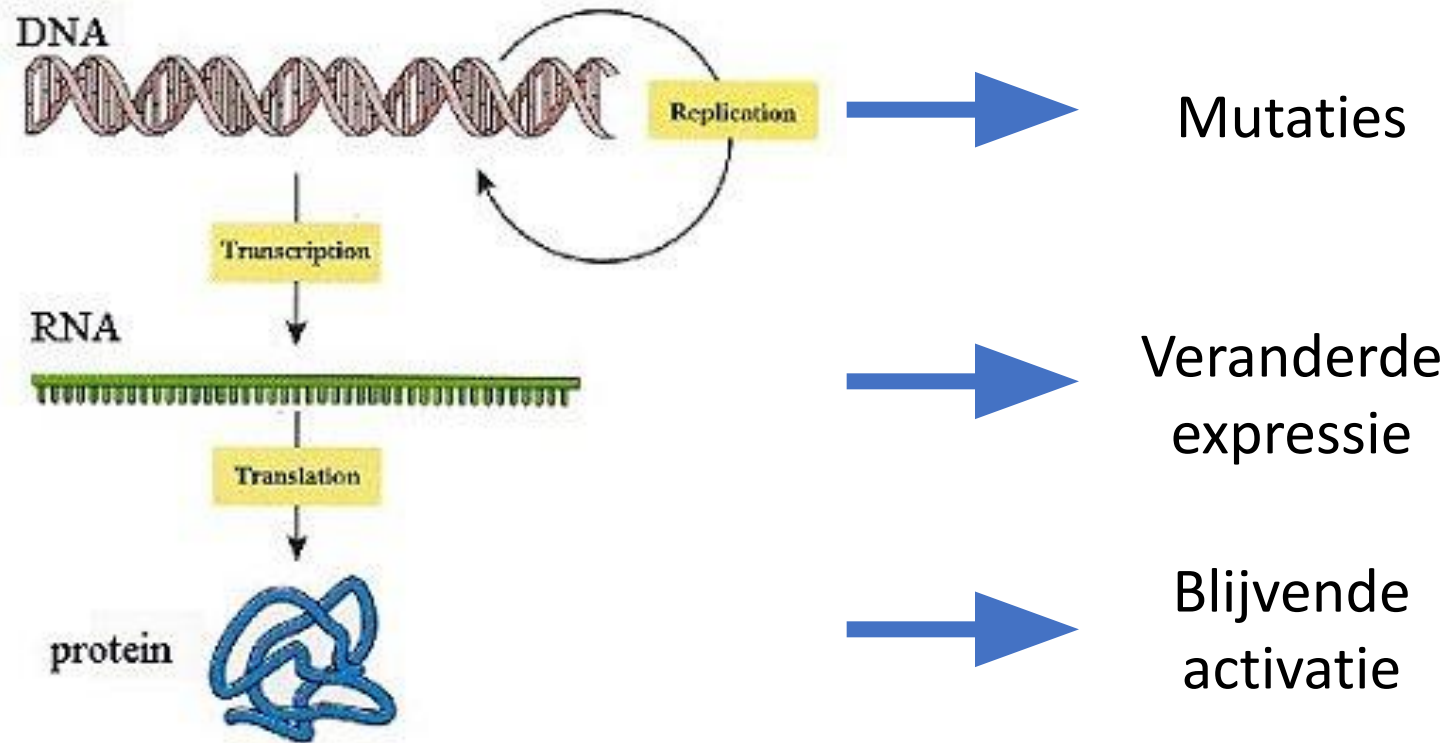
```
...AATCGCTAAAGGGGCCTGACTGCCTTTTTGAACGTCCCGGG  
ATCGCAGTCGATTAGCCCCCGCTGAGCTACTGCTGTGTCAACTA  
GCTGCATGCGCAAATGCGCTATCGTCAGTCATGCTGCATGAAA  
TATGCCGCATCGACTAGCTAGGCTTTAAAAGCATCGCGACTG...
```

Grote fouten = mutatie

Ons lichaam weet niet meer wat het moet doen  
=> Er kan een kanker ontstaan



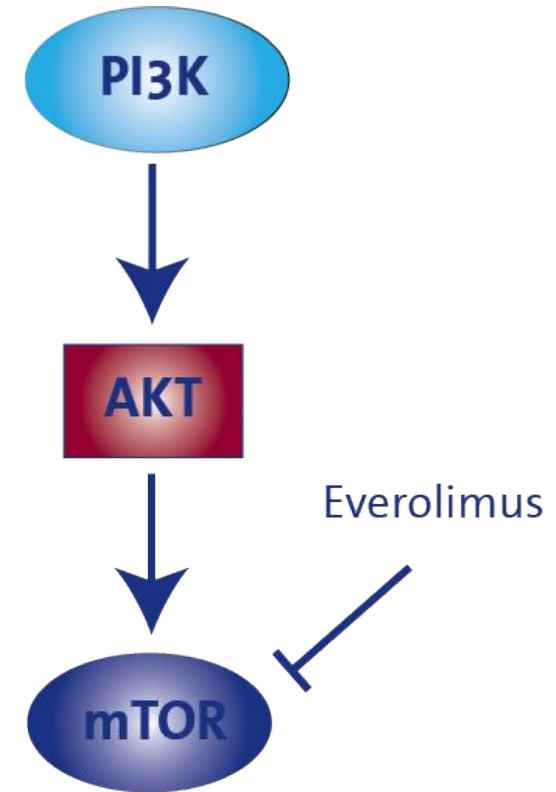
# DNA – RNA – eiwitten



- Veranderingen zorgen voor ongecontroleerde celgroei

# PI3K-AKT-mTOR in kanker

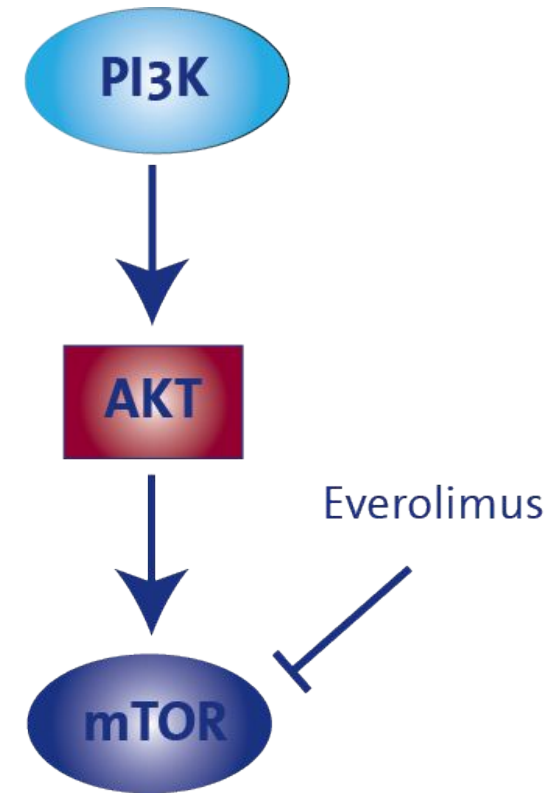
- Ongecontroleerde celgroei = kanker
- PI3K-AKT-mTOR signaaltransductieweg
  - Centrale speler voor celgroei
- Bij ontregeling
  - Ontstaan pNEN



PI3K-Akt-mTOR signaaltransductieweg

# pNEN remmen met everolimus

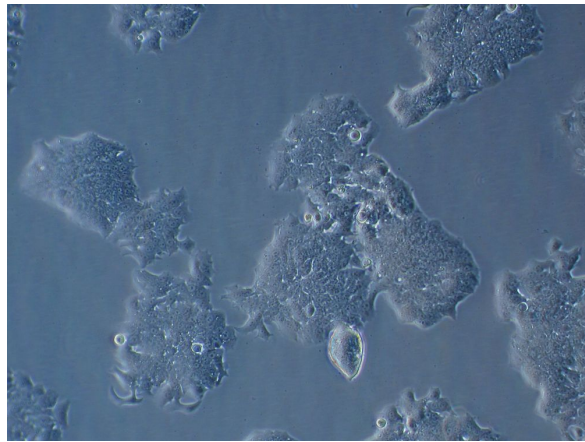
- Everolimus
  - In pilvorm
- Blokkeert mTOR en remt kankergroei
- Beperkt effect in klinische studies
  - Ontsnappen van kanker aan behandeling
  - = resistentie



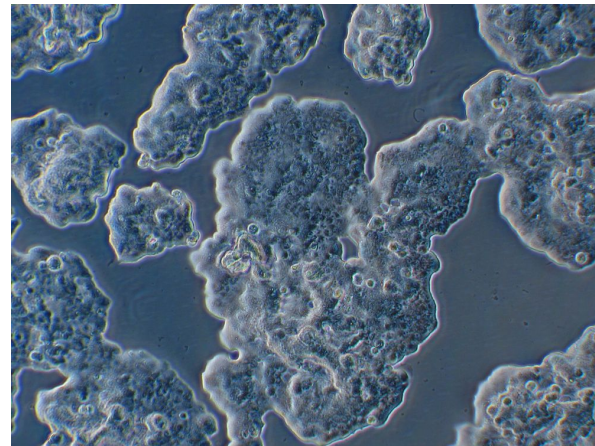
PI3K-Akt-mTOR signaaltransductieweg

# pNEN cellijnen

- Cellijnen van pNEN patiënten als onderzoeksmodel
  - BON-1
  - QGP-1

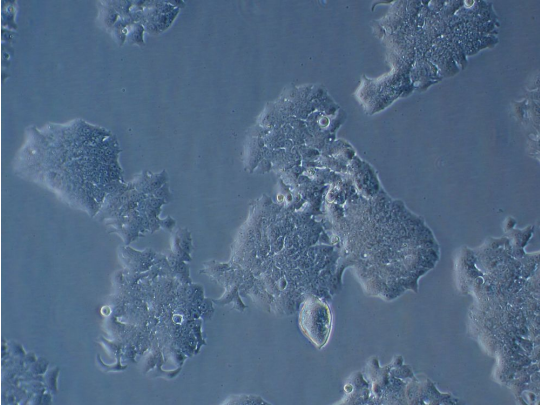


BON-1 cellen in kweek

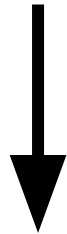
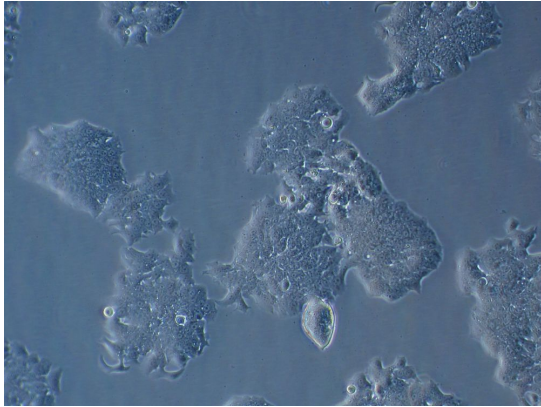


QGP-1 cellen in kweek

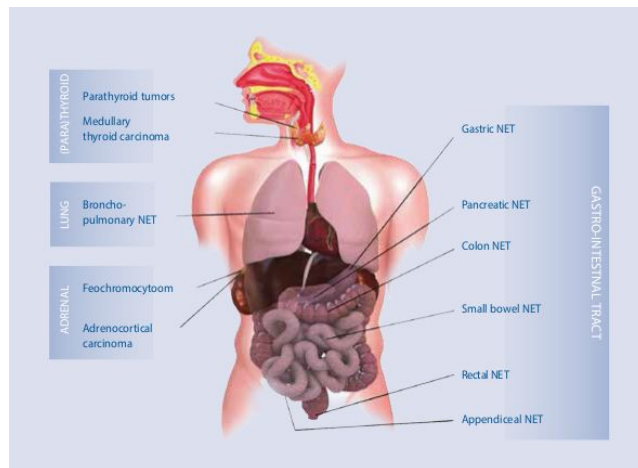
# Doelen



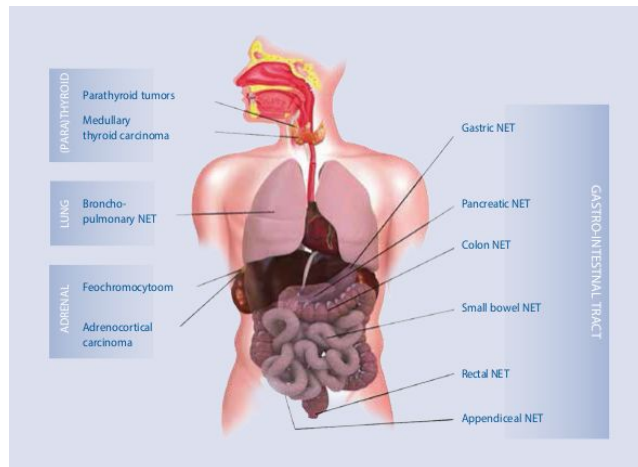
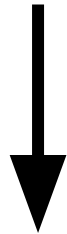
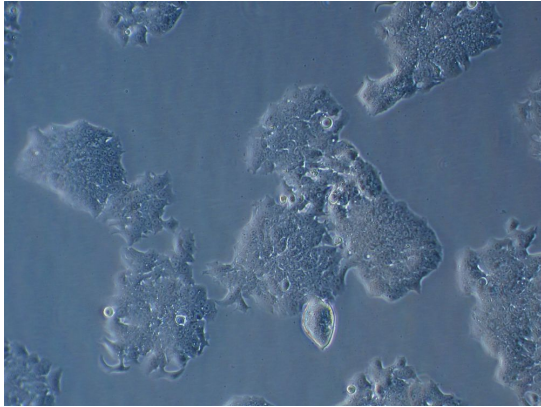
# Doelen



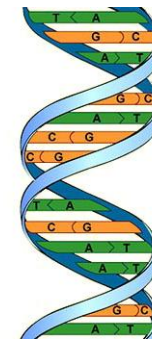
## Hoofdstuk 2: Karakterisatie pNEN cellijnen



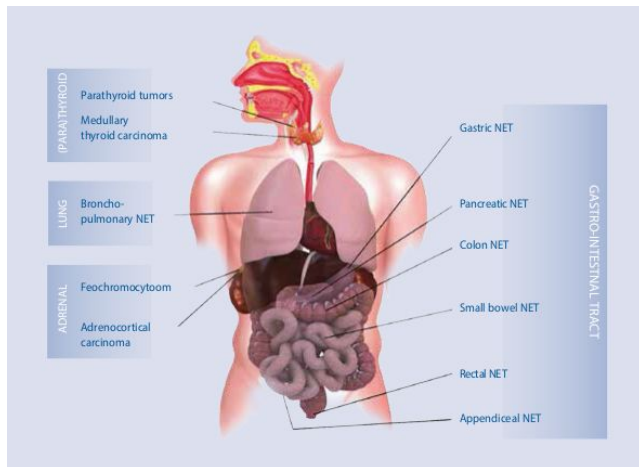
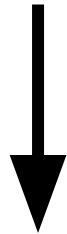
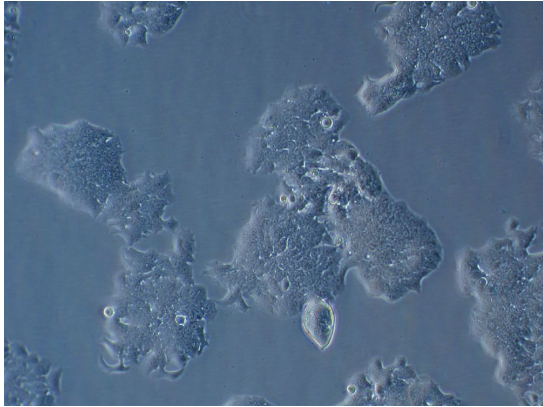
# Doelen



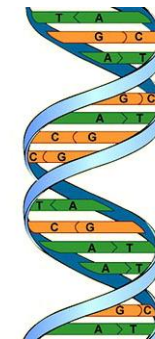
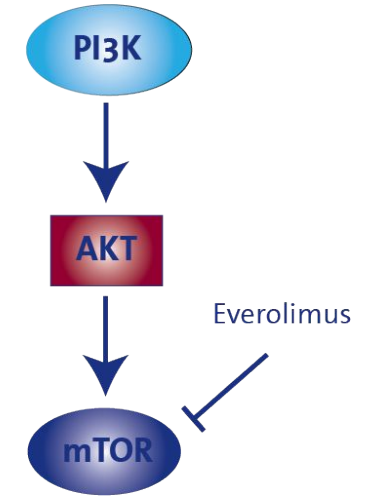
## Hoofdstuk 3: Hotspot mutaties in pNEN patiënten



# Doelen

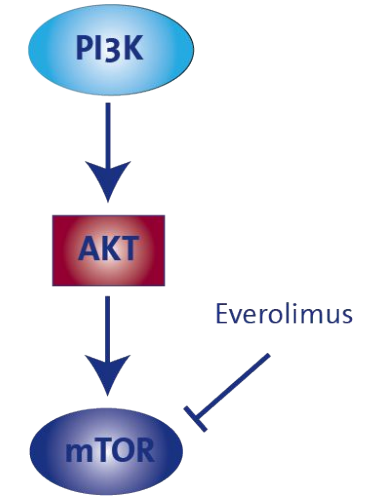
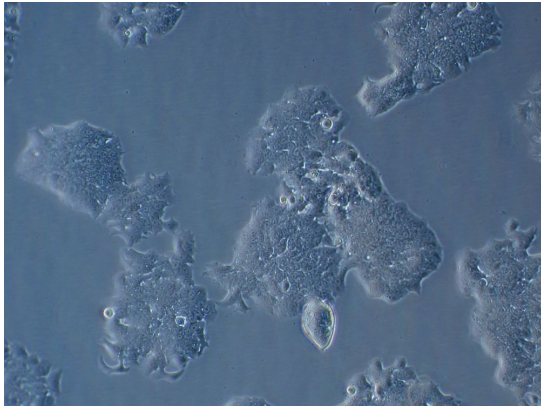


## Hoofdstuk 4: Everolimusresistentie induceren

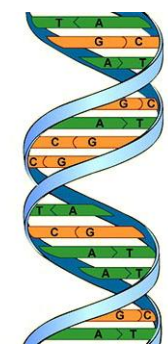
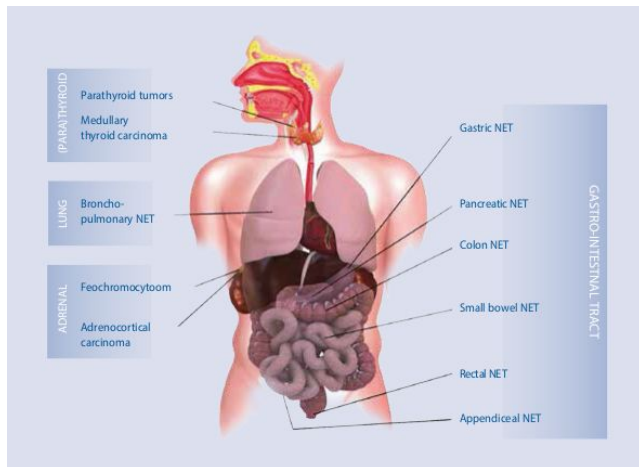




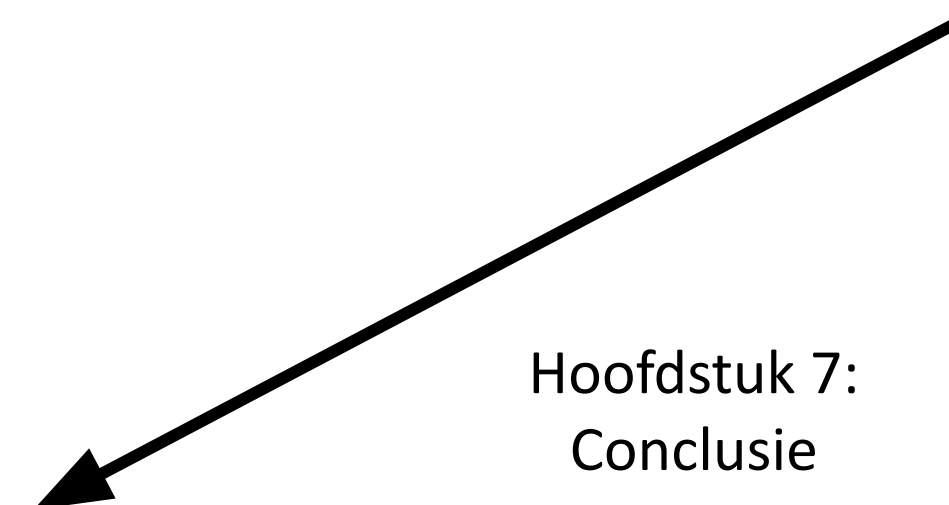
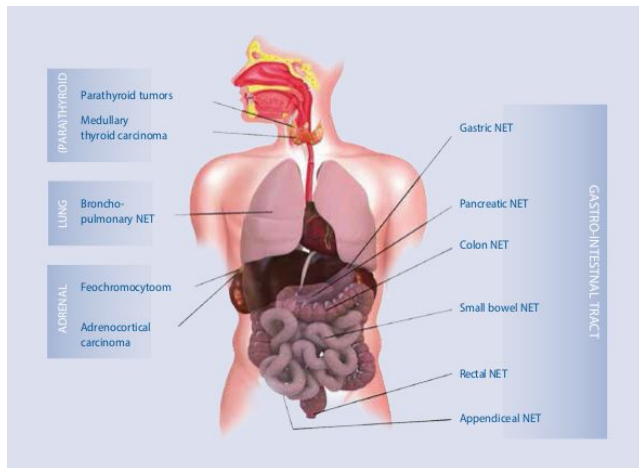
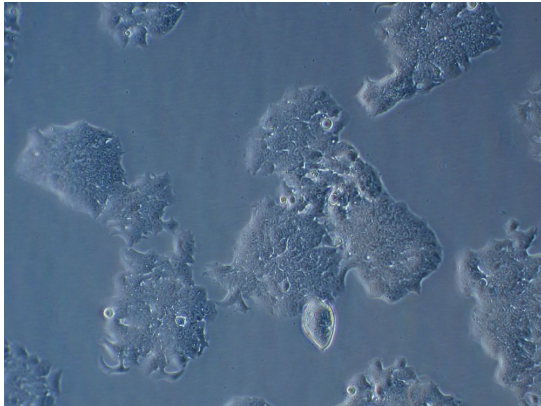
# Doelen



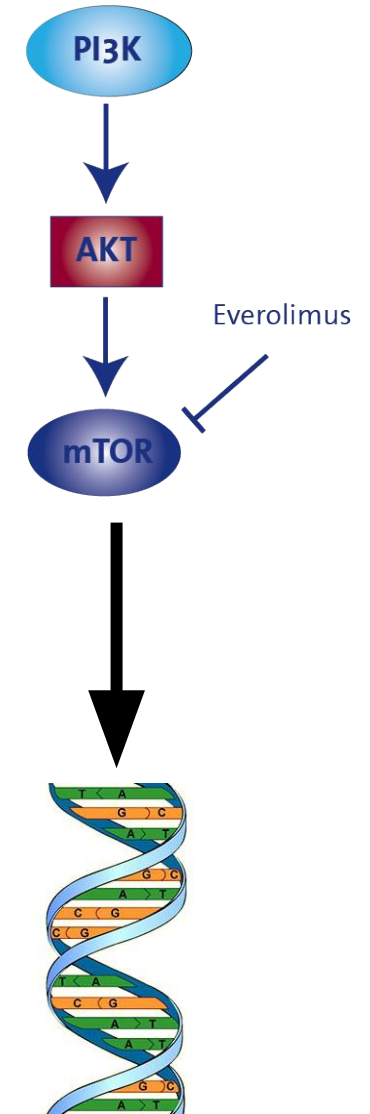
Hoofdstuk 5-6: Everolimusresistentie begrijpen



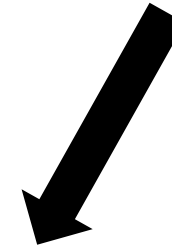
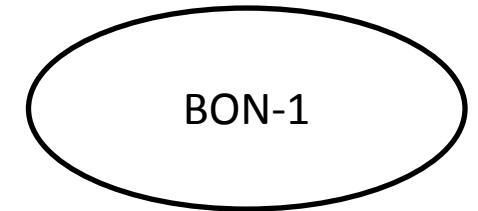
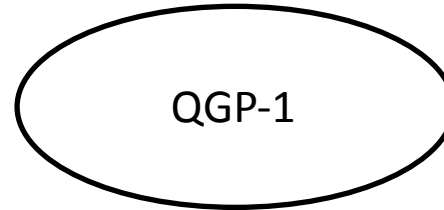
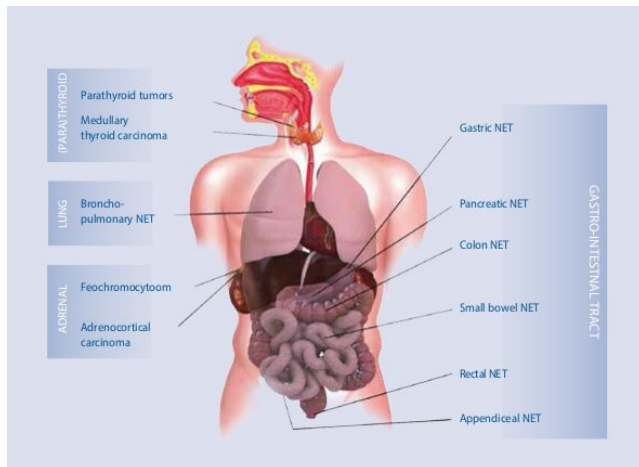
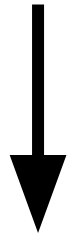
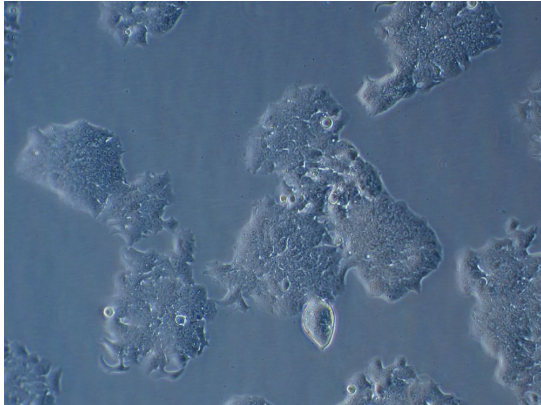
# Doelen



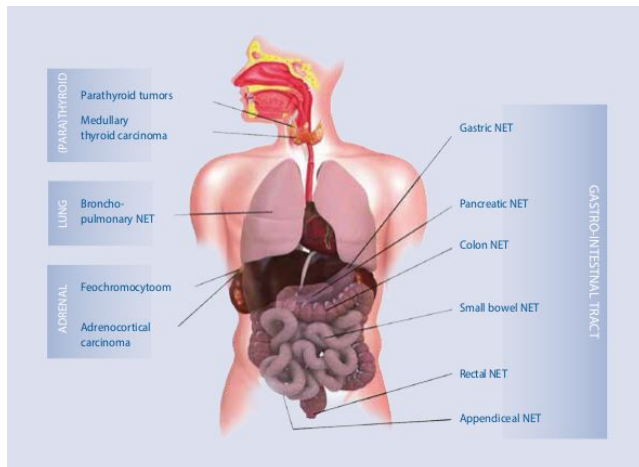
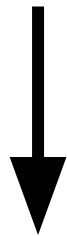
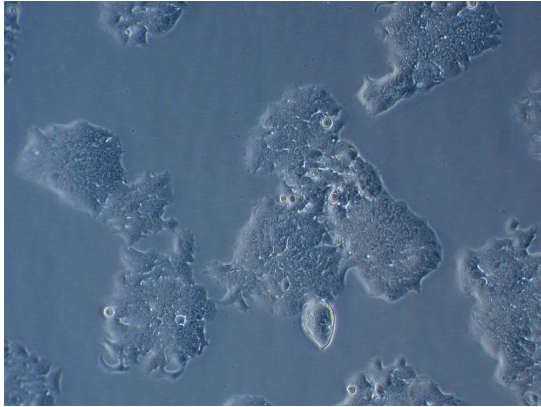
Hoofdstuk 7:  
Conclusie



# Hoofdstuk 2: Karakterisatie pNEN cellijnen

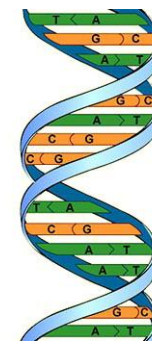
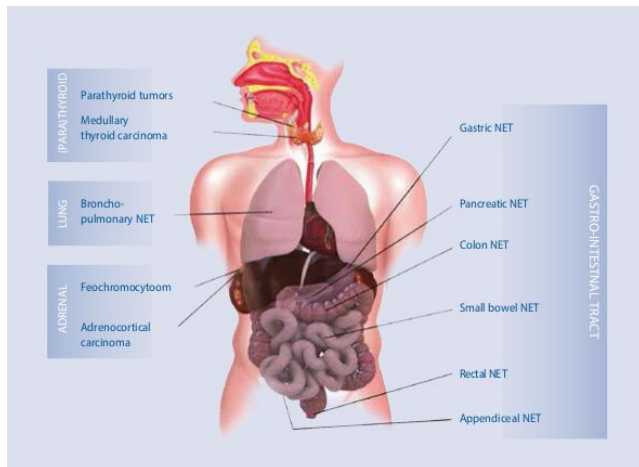
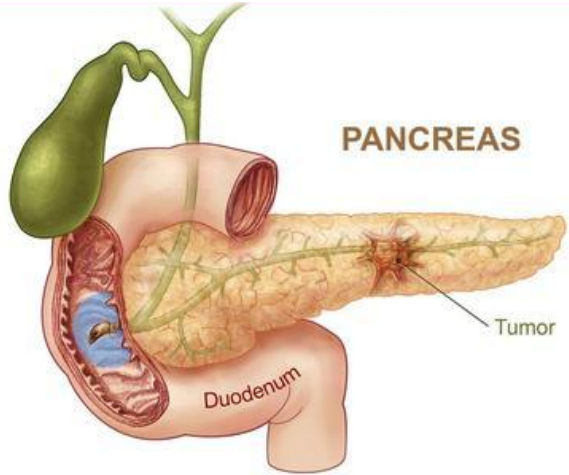


# Hoofdstuk 2: Karakterisatie pNEN cellijnen

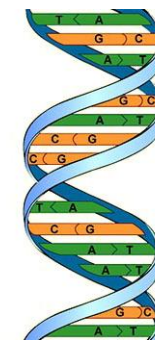
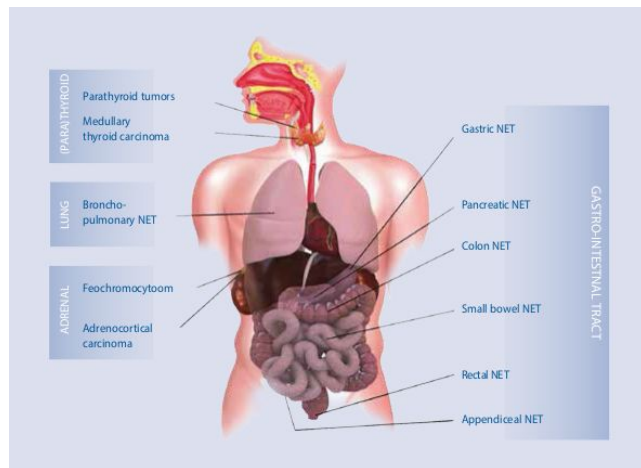
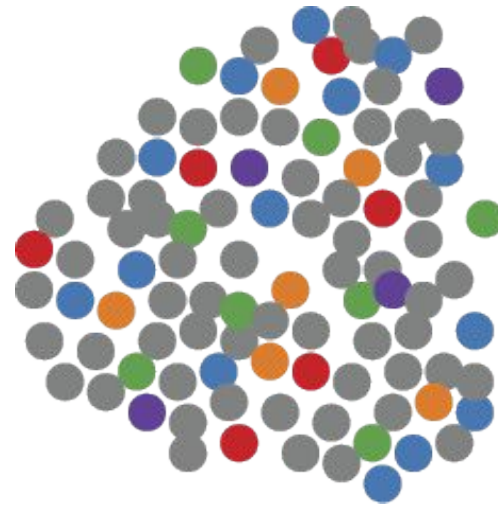
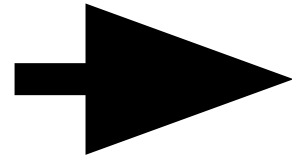
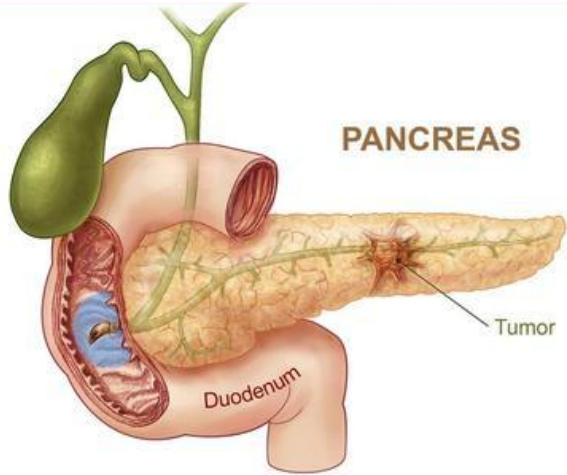


- Veel genetische veranderingen in BDNF-1 en QGP-1
- Zelfde mutaties in cellijnen als patiënten
- Ongekende mutaties als aangrijpingspunt

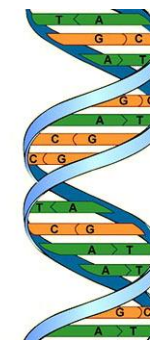
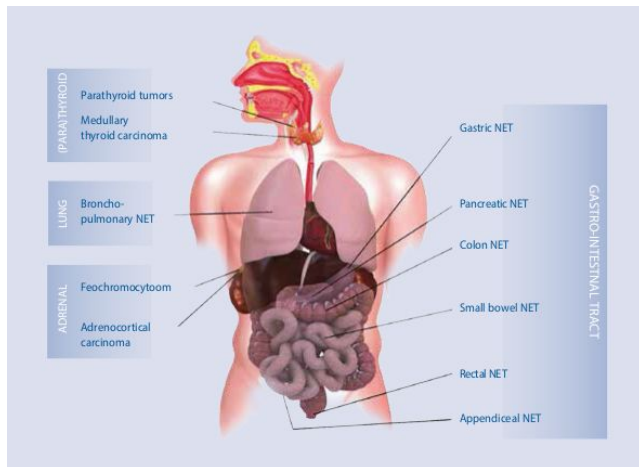
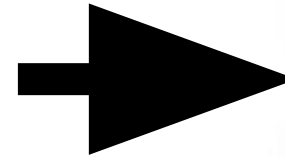
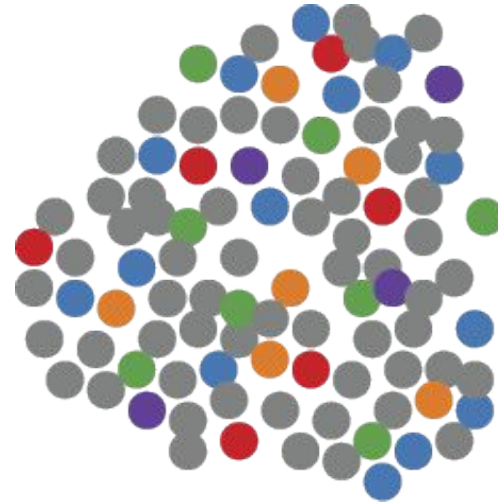
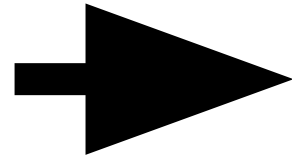
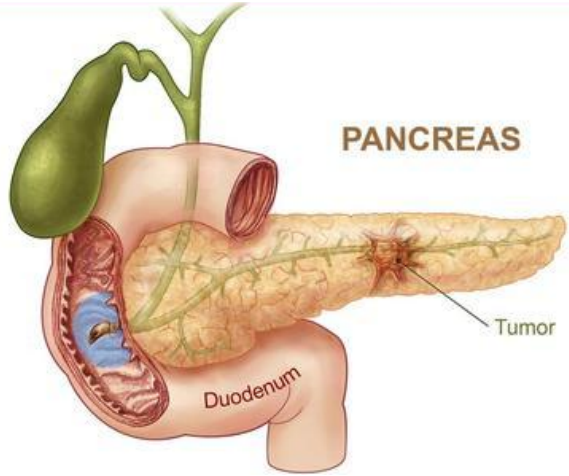
# Hoofdstuk 3: Hotspot mutaties



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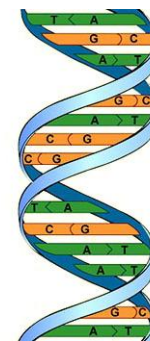
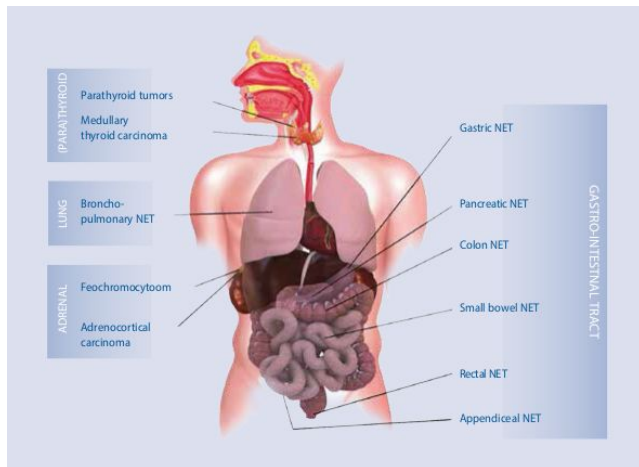


# Hoofdstuk 3: Hotspot mutaties



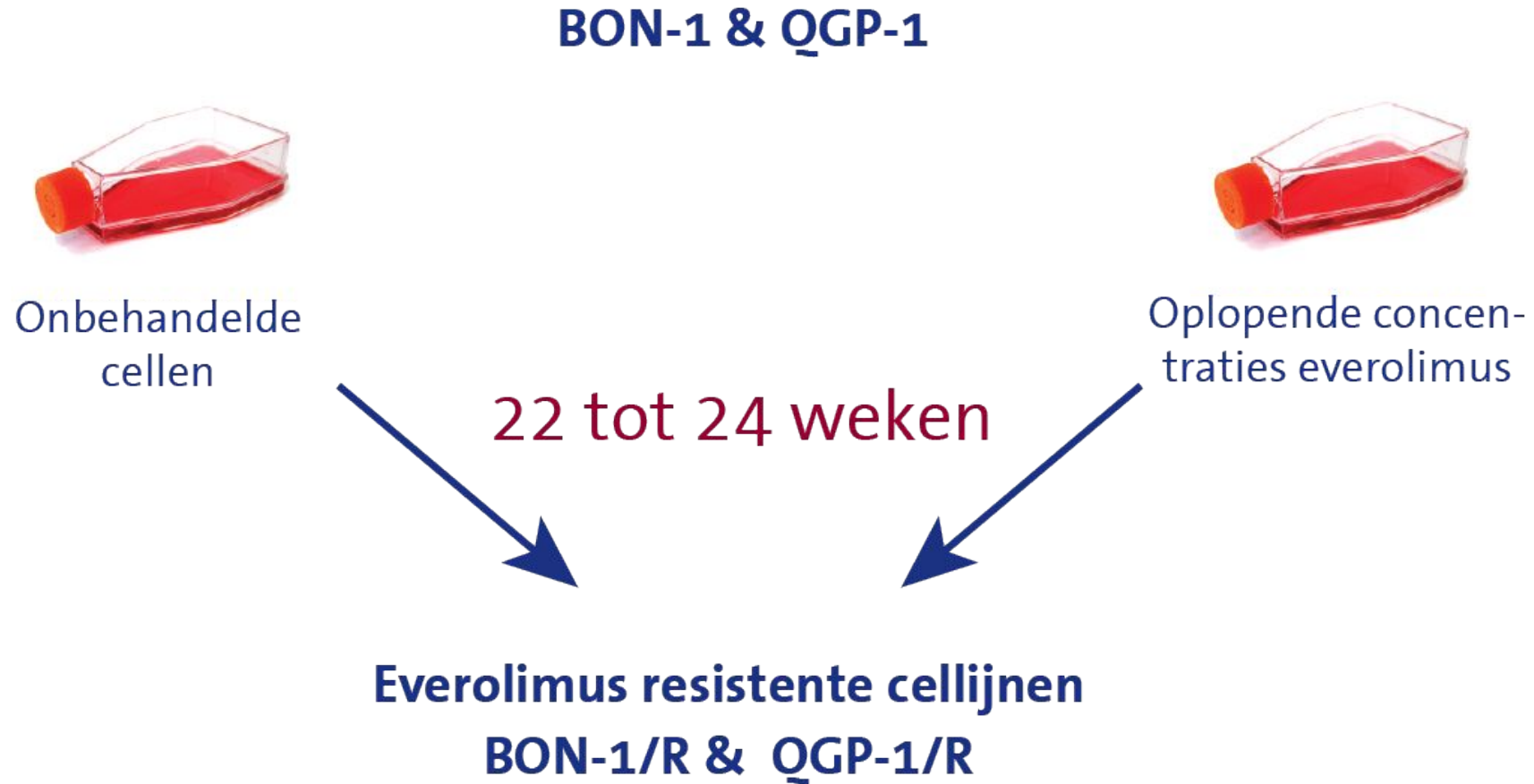
# Hoofdstuk 3: Hotspot mutaties

- Aparte celgroepjes in de tumor hebben unieke mutaties
- Mutaties in de PI3K-Akt-mTOR in 1/3de van alle patiënten
- Eerste terugkerende mutaties in "hotspots" in het DNA

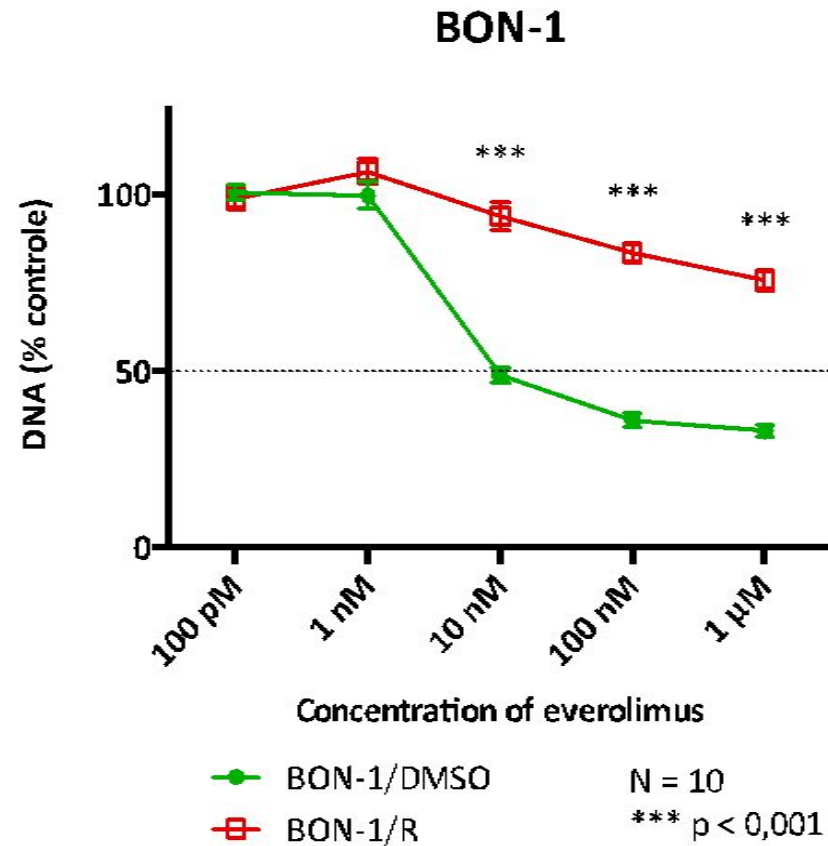




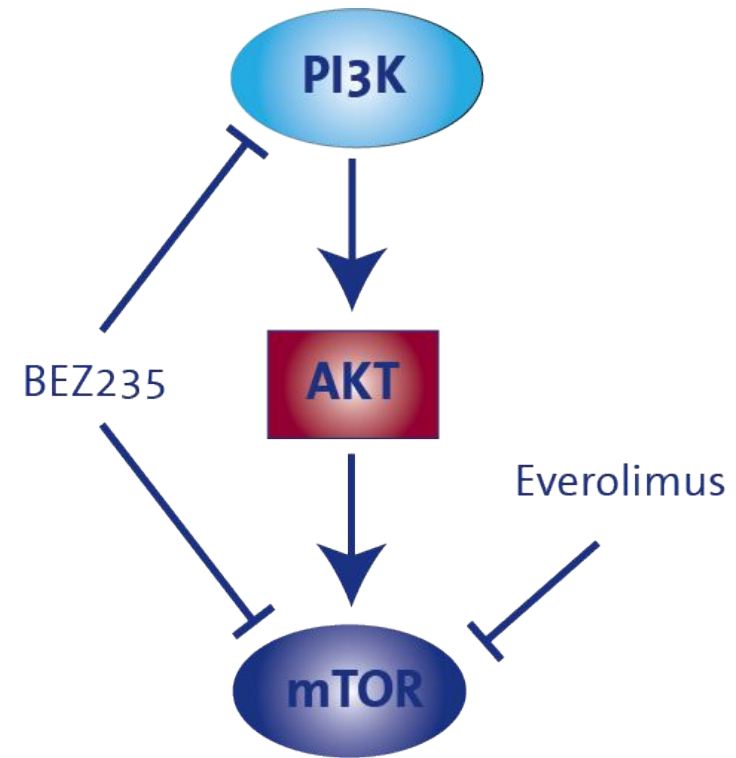
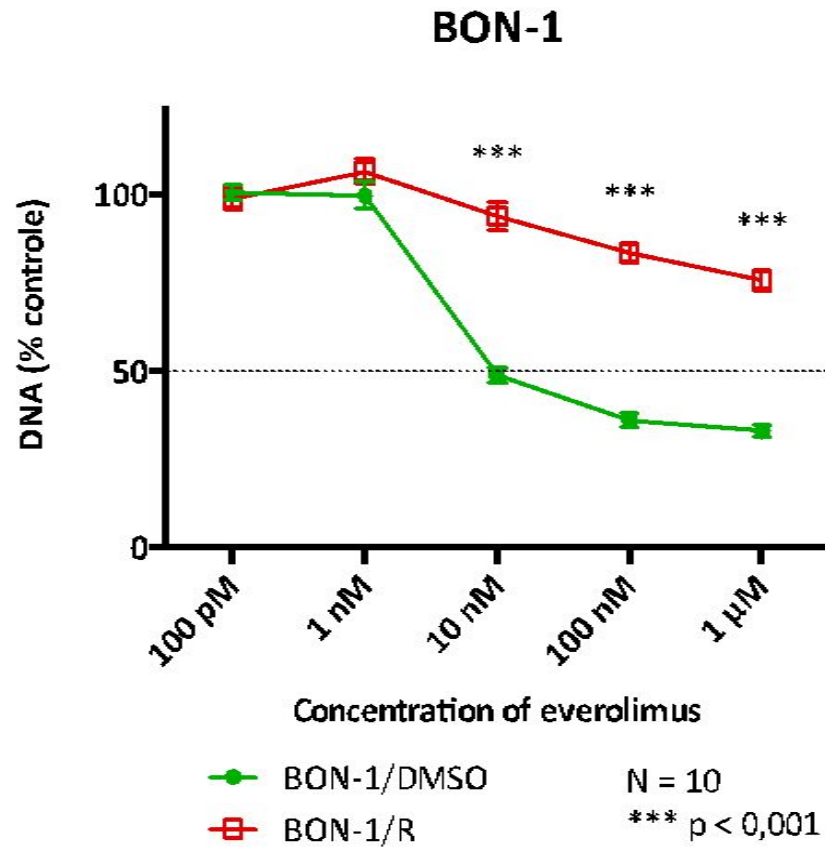
# Hoofdstuk 4: Resistentie-inductie



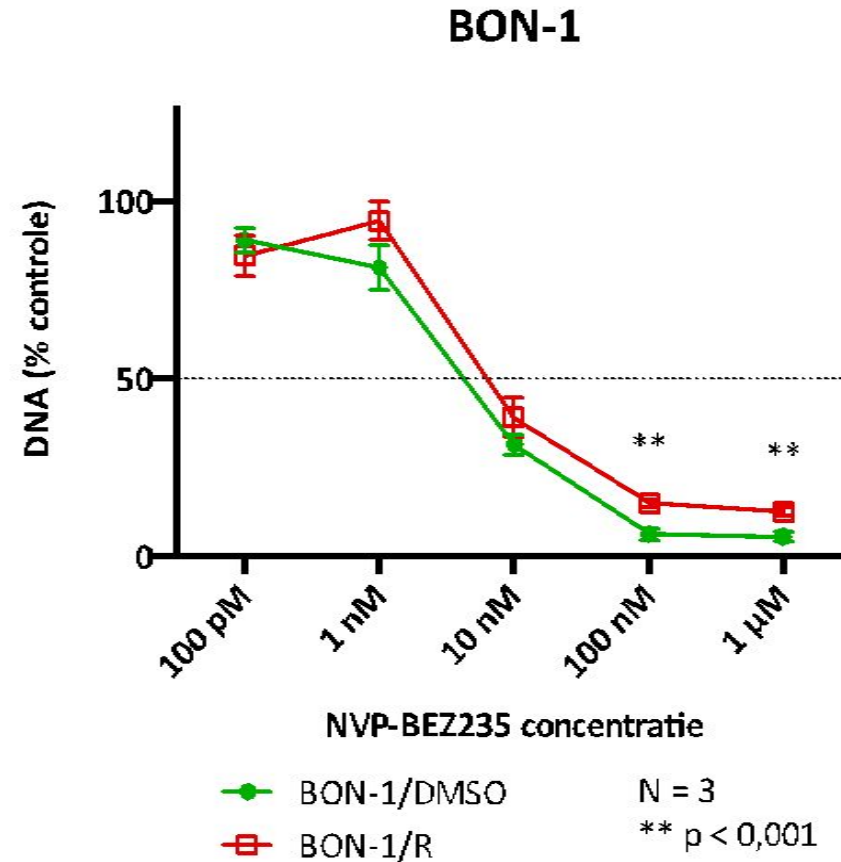
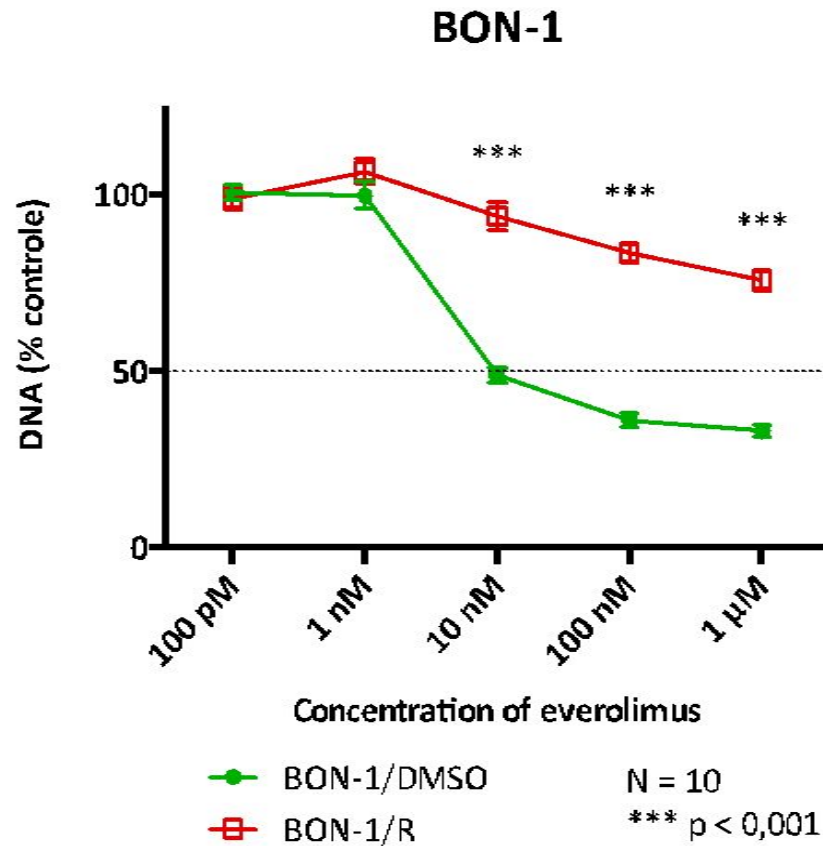
# Hoofdstuk 4: Resistentie vaststellen



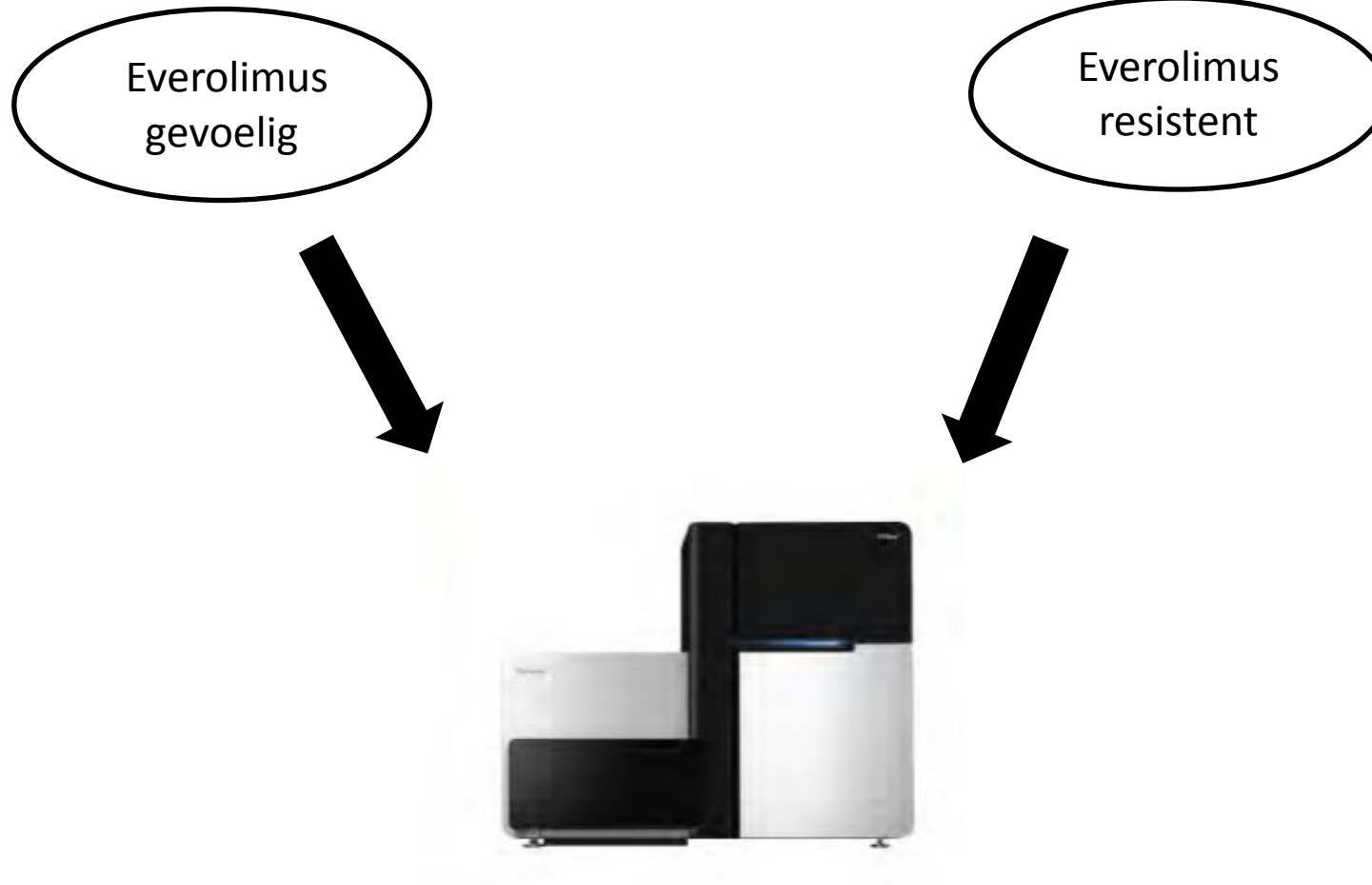
# Hoofdstuk 4: Resistentie overwinnen



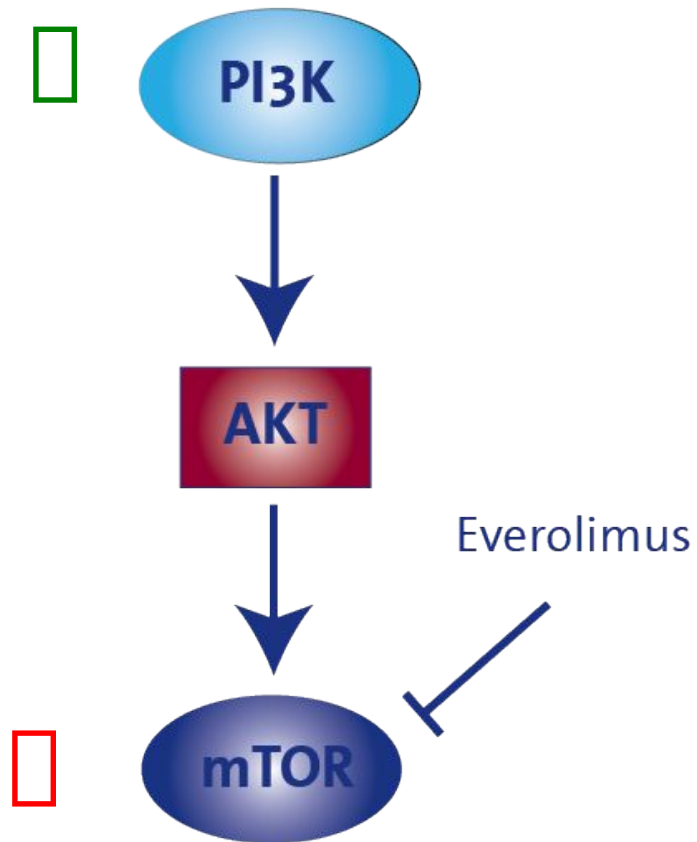
# Hoofdstuk 4: Resistentie overwinnen



# Hoofdstuk 5-6: Resistentie begrijpen



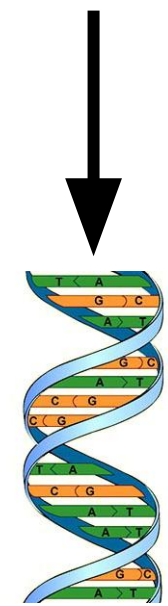
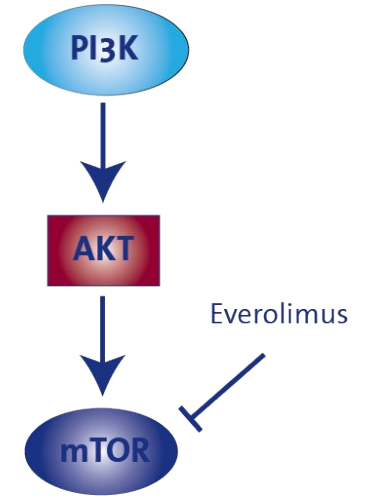
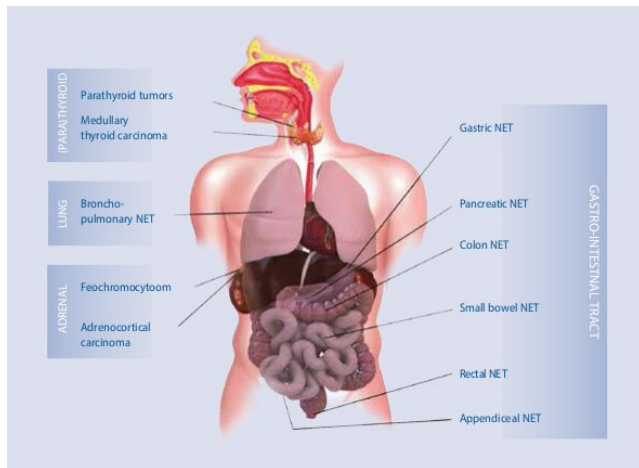
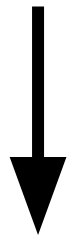
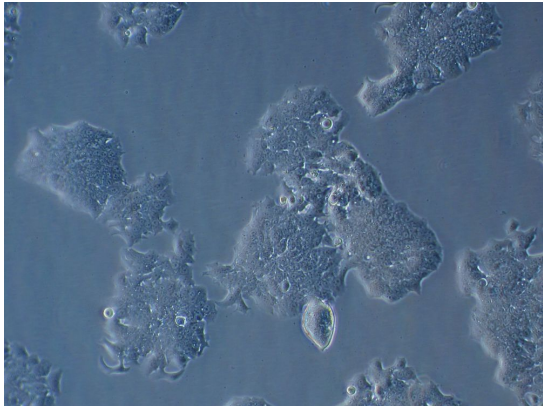
# Hoofdstuk 5-6: Resistentie begrijpen



# Hoofdstuk 7: Conclusie

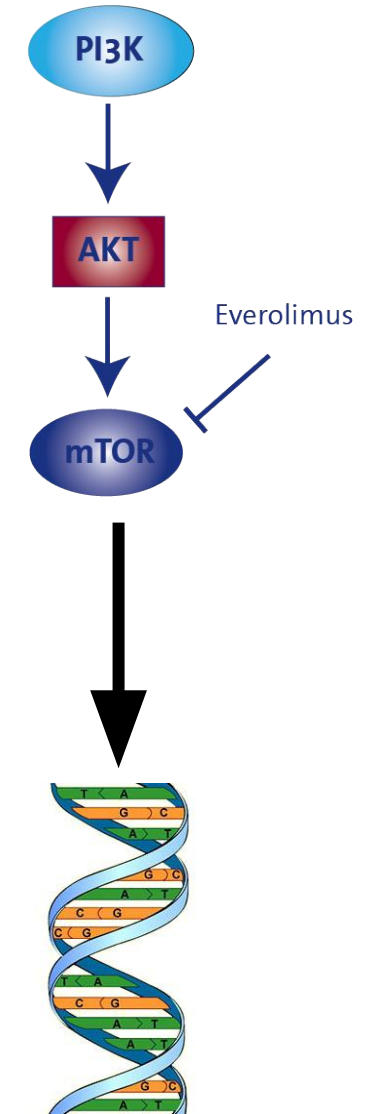
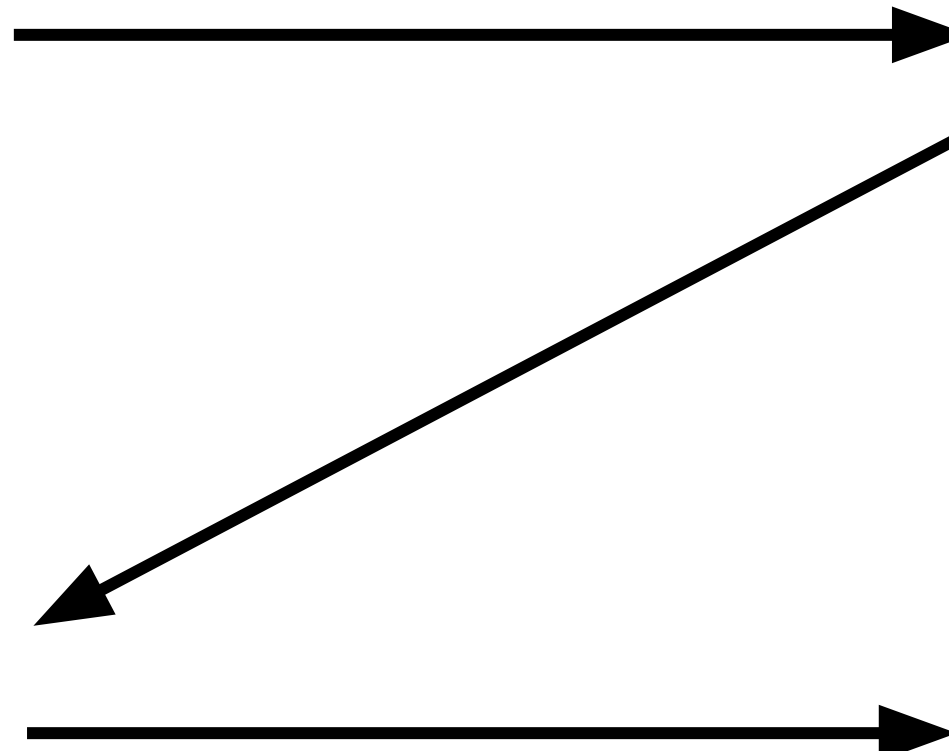
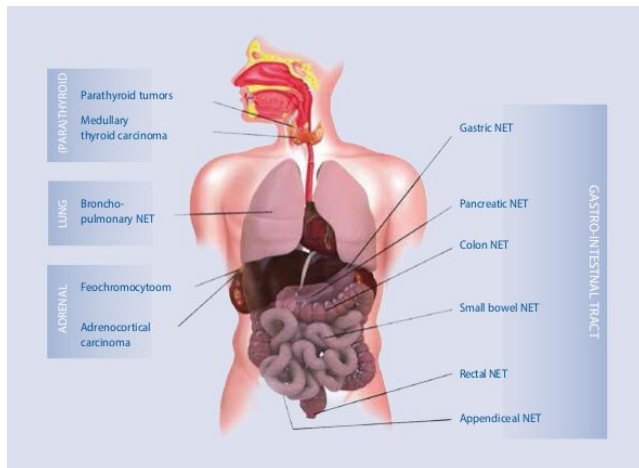
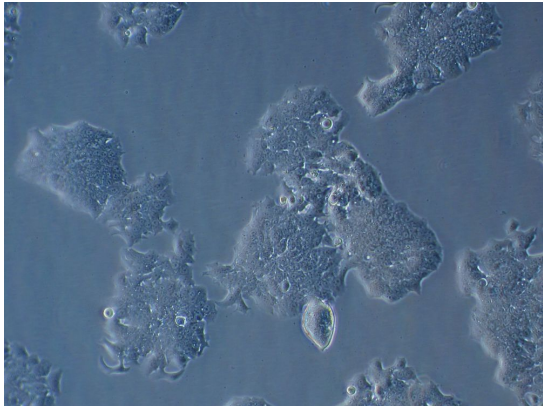
- Cellijnen zijn goede genetische modellen voor patiënten
- Niet elke tumorcel in patiënten is genetisch hetzelfde
- Everolimus-resistentie geïnduceerd, overwonnen en gekarakteriseerd

# Hoofdstuk 7: Conclusie

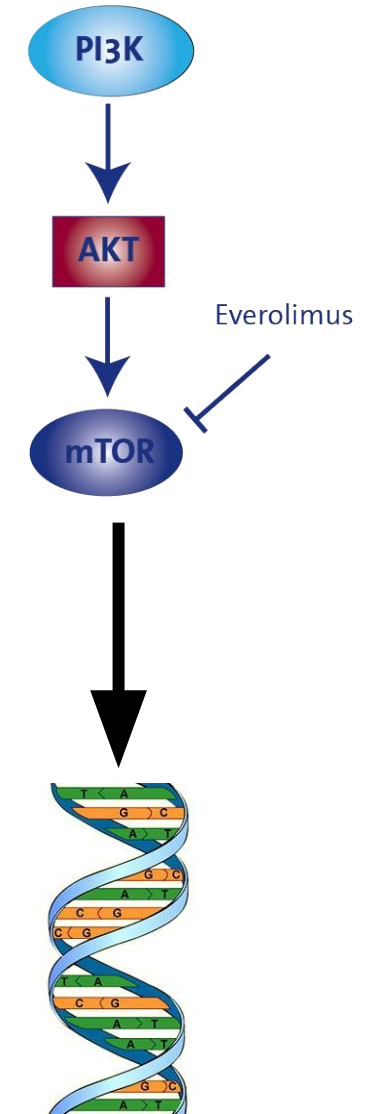
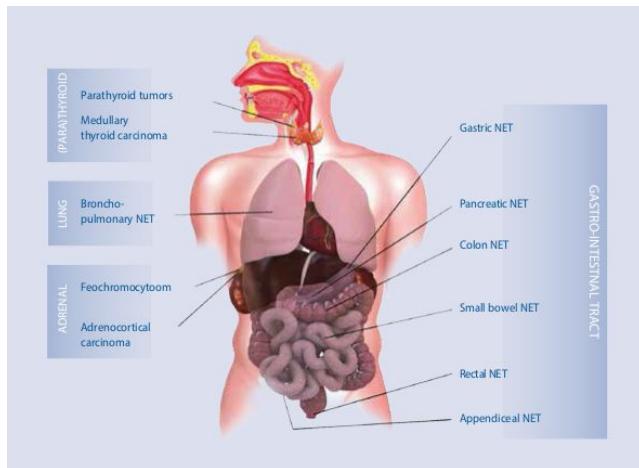
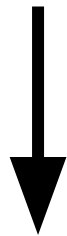
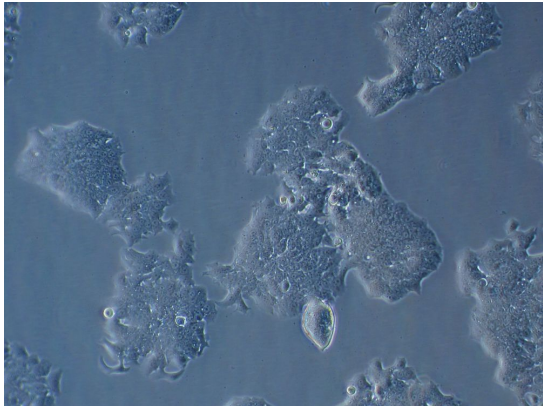




# Hoofdstuk 7: Conclusie



# Hoofdstuk 7: Conclusie



# Blik op de toekomst

- Belangrijke rol veranderingen in vertaalslag van DNA naar eiwit ?
- Van cellijnen naar patiëntenweefsel in kweekschaal?
- Tumor-DNA in bloed volgen om everolimusresistentie te bestuderen?

# Pancreatic Neuroendocrine Neoplasms

From Genetics to Everolimus Resistance

Timon Vandamme