The Netherlands Cancer Institute
Antoni van Leeuwenhoek

- What is the NKI-AVL?
- Cancer can be hereditary

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NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

The Netherlands cancer Institute/Antoni van Leeuwenhoek

1913

8-10
researchers

5 clinicans
17 patients

Specialized
Cancer hospital

and

Scientific
Research institute

2020

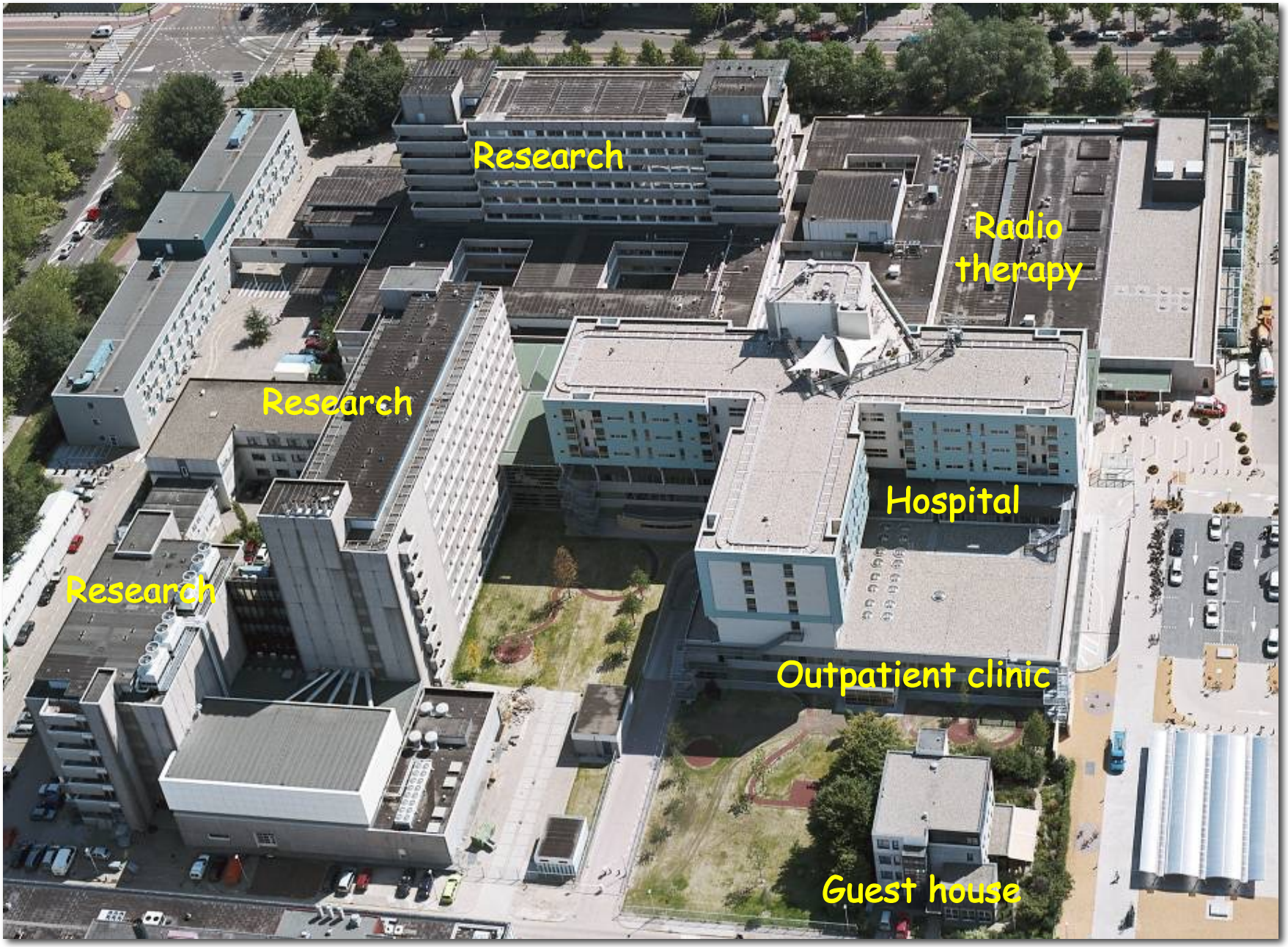
600
researchers

180 beds
1200 employees
53 medical doctors
24.000 pts/year

1913-Keizersgracht

1929-Sarphatistraat

1975-Plesmanlaan



Location Slotervaart Amsterdam

1975-Plesmanlaan

The mission of the NKI-AVL

- Patient care

  applying most recent treatment modalities

- Research

  scientific research

  improving diagnostics and treatment

- Education

  Training of **Clinicians/nurses**

  Training of **PhD students**

  Undergraduate students

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Research at the NKI-AVL

600 researchers

42 principal investigators basic research
30 principal investigators translational and clinical research
25 of 72 have a professorship at a Dutch university

88% is postdoc/PhD student/technician

PhD students (OIOs)	*365*
Postdocs	*150*
Technicians	*50*

Half is female!!
20% from outside NL

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A cancer researcher can look like this…

Dr. Kees Jalink, biofysicist

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…but most look like this!

Group Te Riele

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They work day and (sometimes) night in the laboratory

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Until one day…

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Until one day…graduation!!

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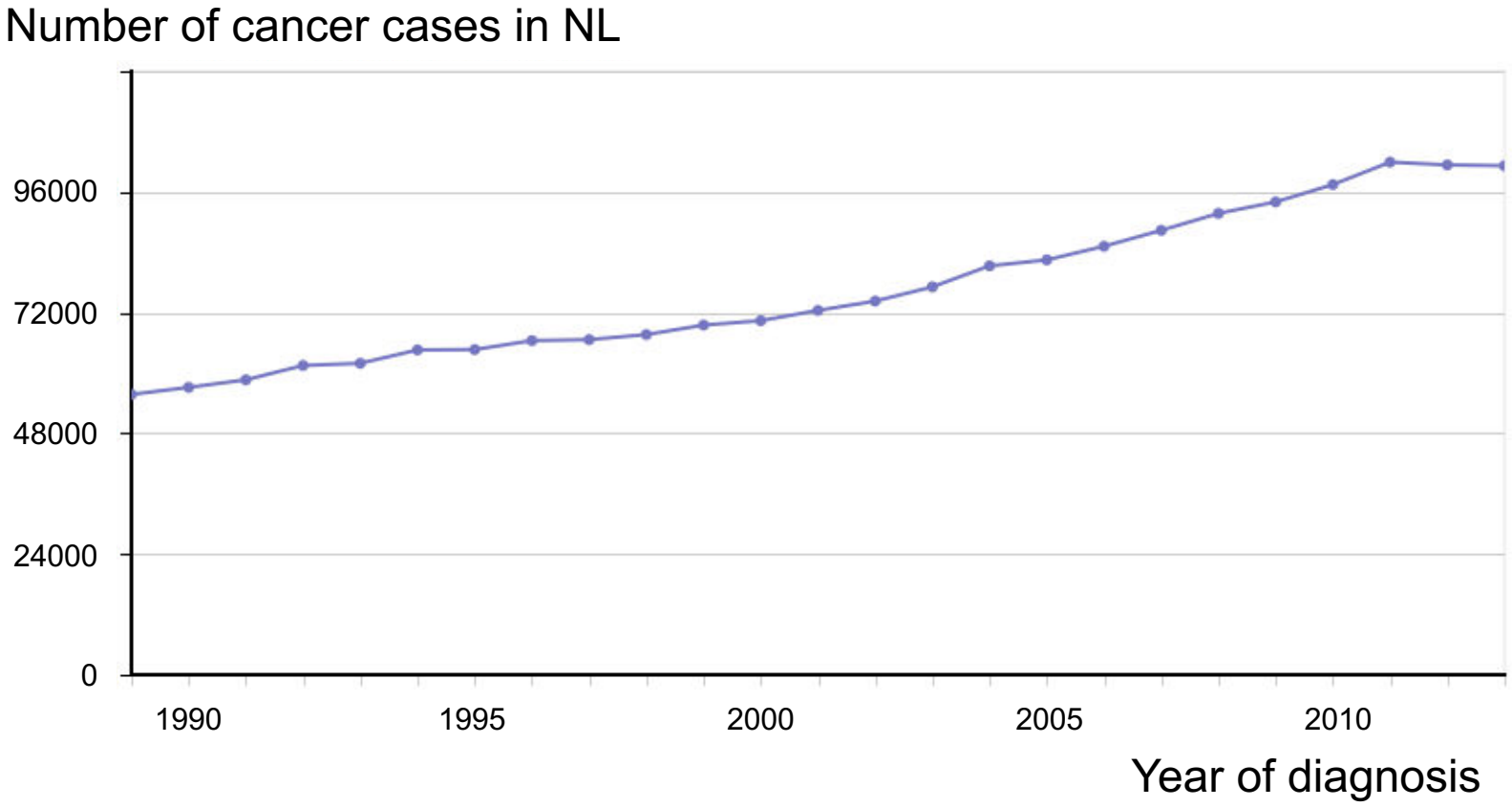
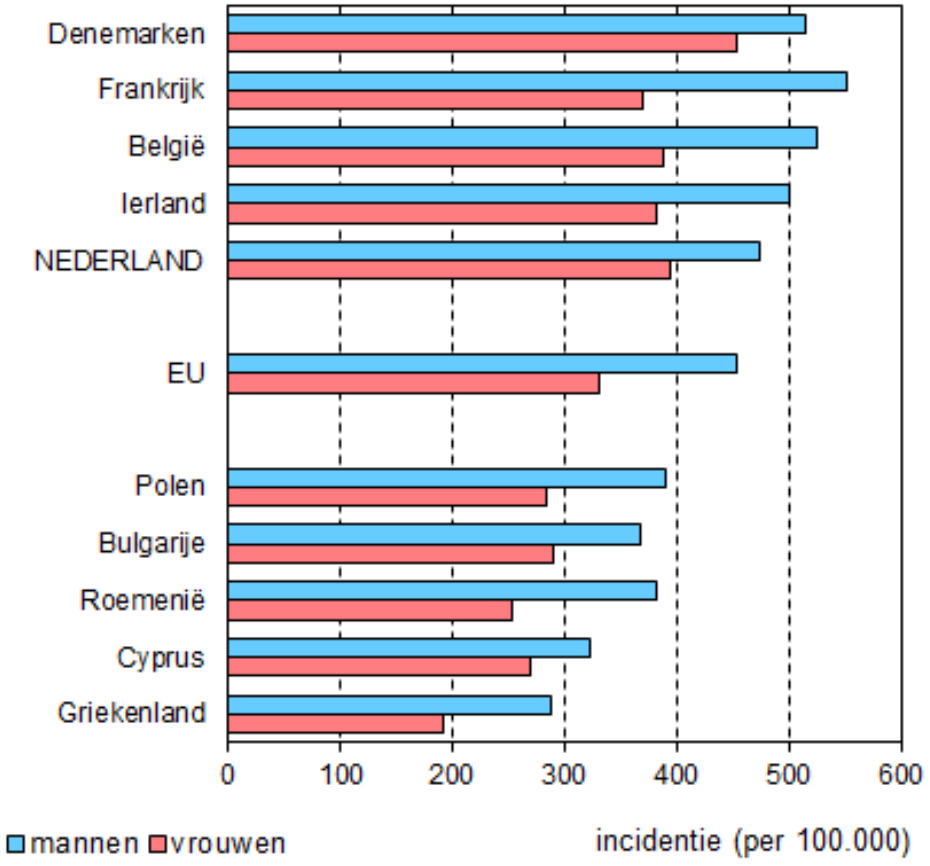
Why is cancer research still needed?

Cancer is cause of death #1
Cancer incidence is rising world wide
Also in the Netherlands



Why is cancer research still needed?

Cancer incidence in Europe



Men:
- Prostate
- Lung
- Colon

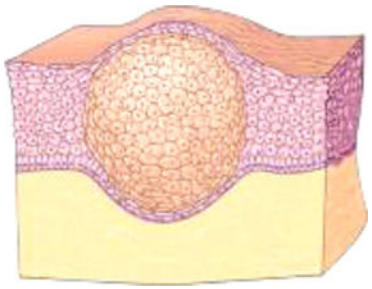
Women
- Colon
- Lung

What is cancer?

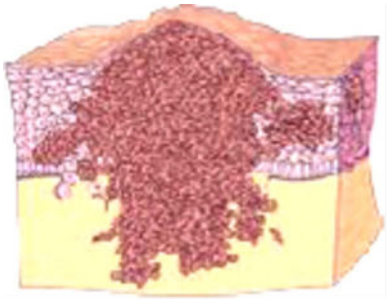
Asocial behavior of cells:

- Uncontrolled cell proliferation

  non-responsive to growth-inhibiting signals from their environment
- Invasion in surrounding tissue



Benign



Malignant

- Seeding to other parts of the body: metastases

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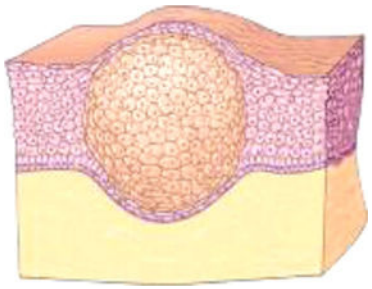

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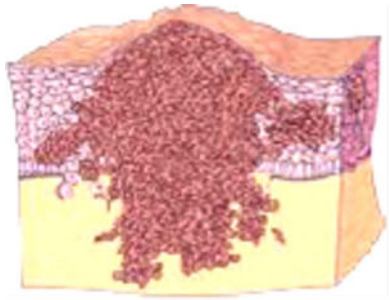


Malignant

- Seeding to other parts of the body: metastases

Cause: changes (mutations) in the DNA

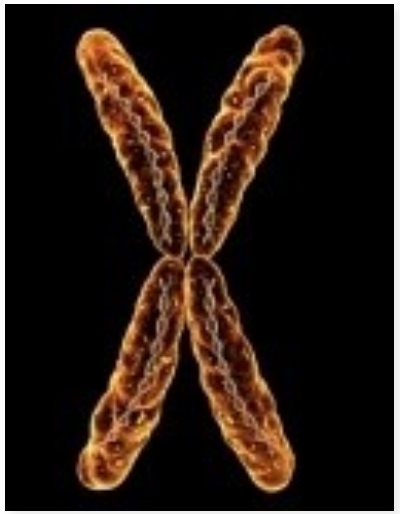
How do mutations arise in DNA?

Environmental and internal causes:

Chemical compounds

radiation

spontaneous



DNA damage

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DNA repair mechanisms

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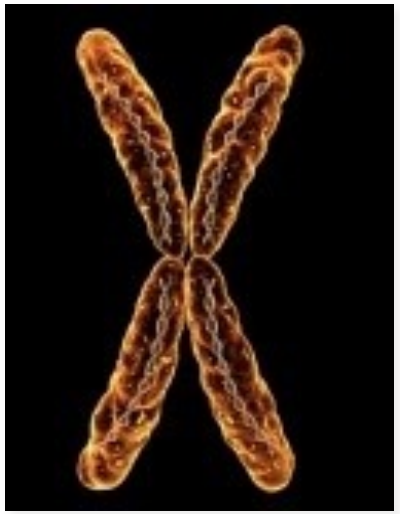

DNA damage

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Defective DNA repair mechanisms

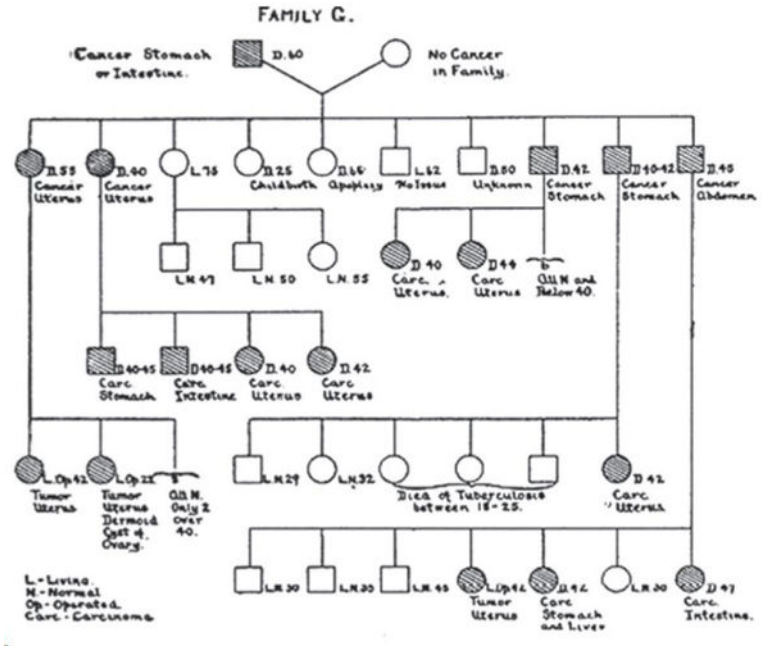
High exposure a/o defective repair => mutations => cancer

Hereditary cancer

Often due to inherited defect in DNA repair

Lynch syndrome

Inherited defect in DNA Mismatch Repair (MMR)



1913 – Family *G*
reported by A. Warthin

1966 – Families N and M
reported by Henry Lynch
hereditary nonpolyposis colorectal cancer (HNPCC) => Lynch syndrome

Lynch syndrome: cancer at early age

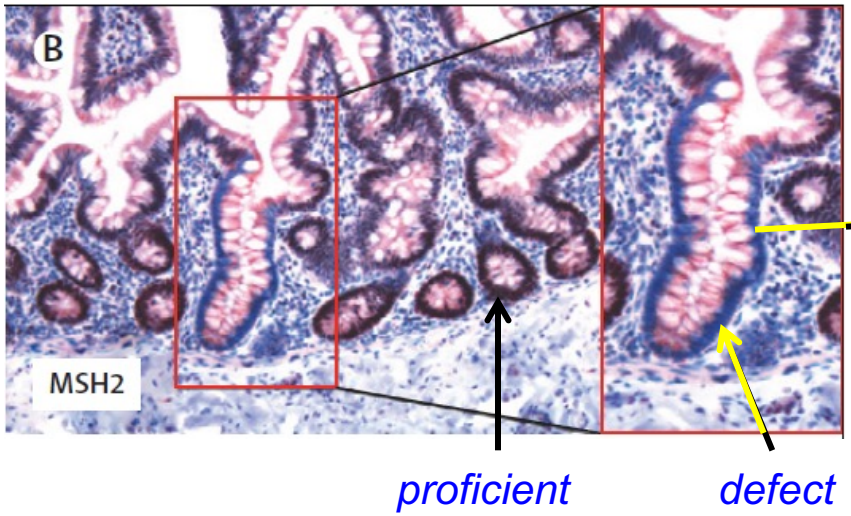
colon, **endometrium**, **small intestine**,
sebaceous gland *(Muir-Torre)*, ***glioblastoma*** *(Turcot)*

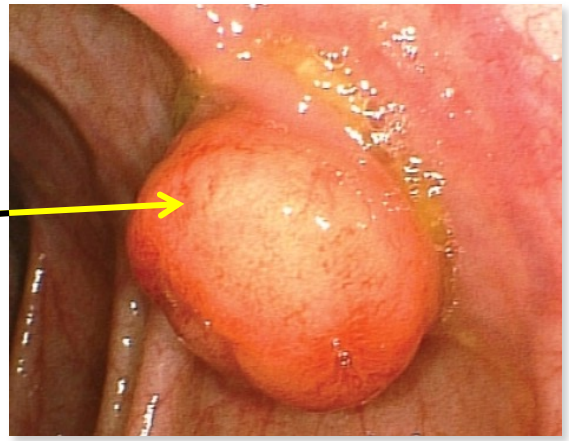
Lynch syndrome

Inherited defect in DNA Mismatch Repair (MMR)
Loss of repair capacity in part of the cells

Repair-defective cells

60-80% risk for colon cancer





Kloor et al. *Lancet Oncol* 2012;13:598

Lynch syndrome

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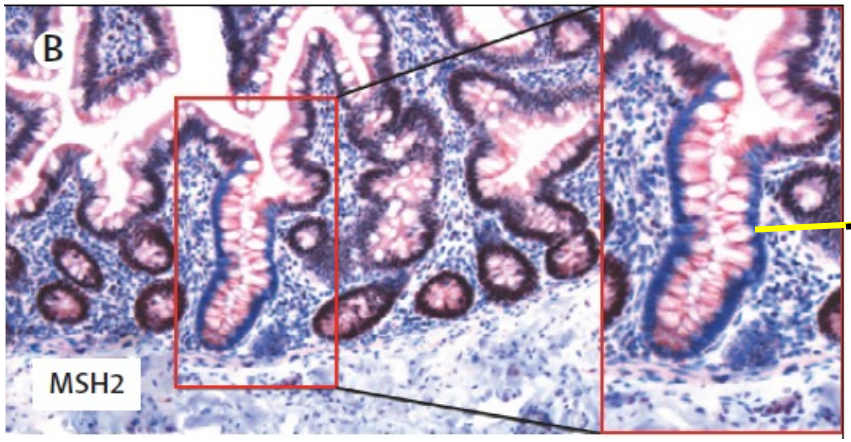
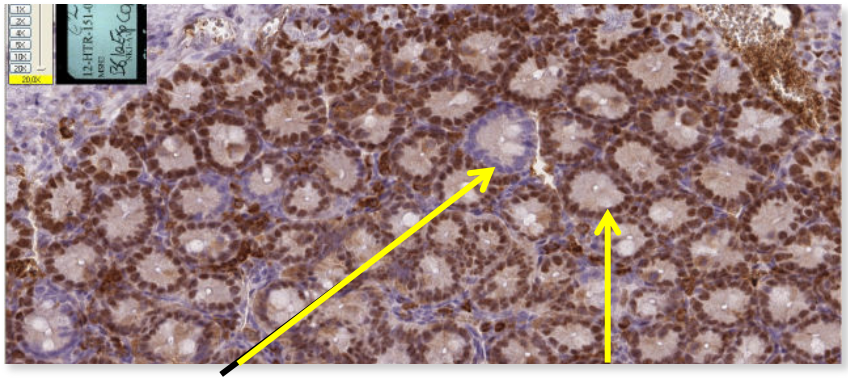
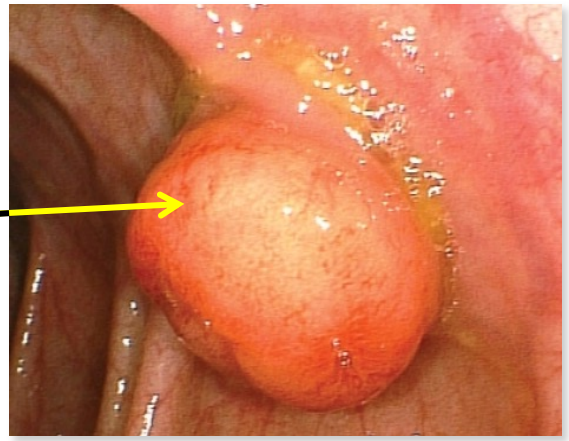




defect *proficient*

60-80% risk for colon cancer



Lynch syndrome in the mouse

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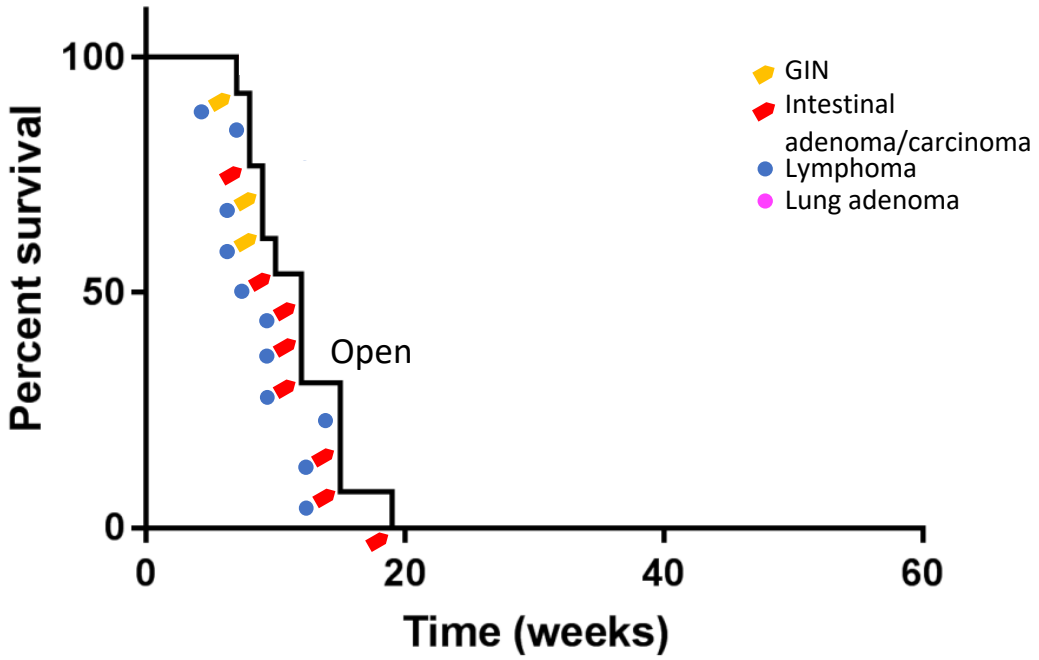
Intestinal tumors??

Wojciechowicz et al. *Gastroenterol* 2014;41:1064

Lynch syndrome in the mouse

Survival and tumor incidence



Open facility:

- lymphomas
- **92% intestinal tumors**

Wojciechowicz et al. *Gastroenterol* 2014;41:1064

Moving to a new animal facility

Different housing conditions: more clean

OLD

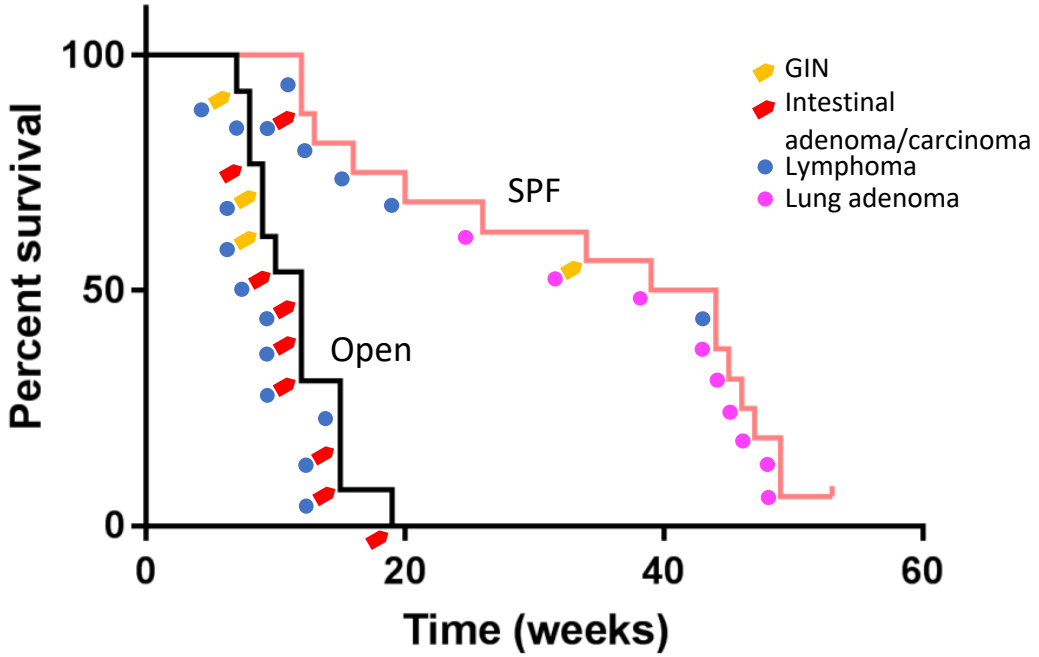
Open cages
“conventional”

NEW

Closed cages
“SPF”

Lynch syndrome in the mouse

Survival and tumor incidence
In a cleaner environment



Open facility:

- lymphomas
- **92% intestinal tumors**

SPF facility:

- lymphoma/lung tumors
- only ~**9% intestinal tumors**

Loss of intestinal tumor development in SPF mice!

Pieters et al. *Gut Microbes* 2022;14:e2035660

Lynch syndrome in the mouse

"Open" *versus* SPF conditions: what's the difference?

The intestinal flora (microbiota):

- Collection of micro-organisms in the colon
- Local and systemic effects
- A role in shaping (anti-tumor) immune responses

Old facility
"Conventional" facility

Open cages
Free exchange of microbes

New facility
SPF facility

Specific pathogen free
Closed environment

"Open" *versus* SPF conditions:
=> large differences in microbiota composition

Pieters et al. *Gut Microbes* 2022;14:e2035660

Lynch syndrome in the mouse

FMT: fecal microbiota transplantation

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“Conventional” facility

Open cages
Free exchange of microbes

New facility
SPF facility

Specific pathogen free
Closed environment

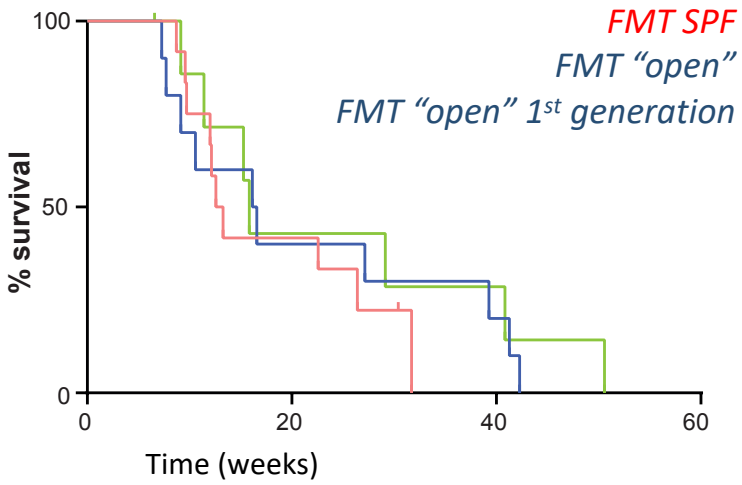
Poeh transplantation

-80 °C preserved feces from old facility

Impact of microbiota on tumorigenesis

FMT: fecal microbiota transplantation

Msh2-Lynch mice



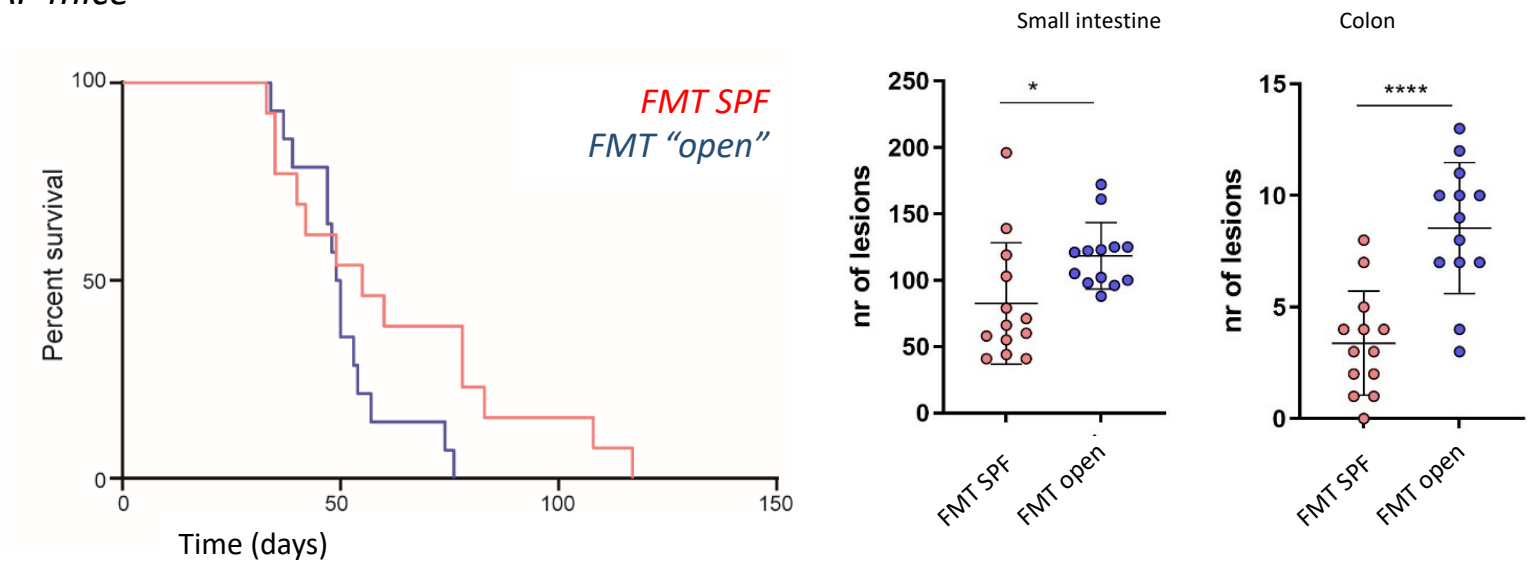
Still no intestinal cancer in LS mice, but

- *Many "new" bacteria*
- *in close contact with intestinal tissue*
- *Severe inflammation*
- *Increased cell division => more mutations in DNA!*

Impact of microbiota on tumorigenesis

FMT: fecal microbiota transplantation

APC FAP mice



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Increased tumorincidence in FAP mice!

Acknowledgements

MSH2-Lynch mouse

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