One minute response

- Q: If random samples are inefficient for coalescent analysis, why not collect carefully targeted ones?
- A: We don't know how to do the math
  - Fairly easy to relate random samples to expectations
  - Brutally hard if samples were picked strategically

Overview

- Cancer as an evolutionary process
- Mutations involved in cancer:

  - Tumor suppressor genes
  - Oncogenes

- Case study: Barrett's Esophagus

- Peto's Paradox

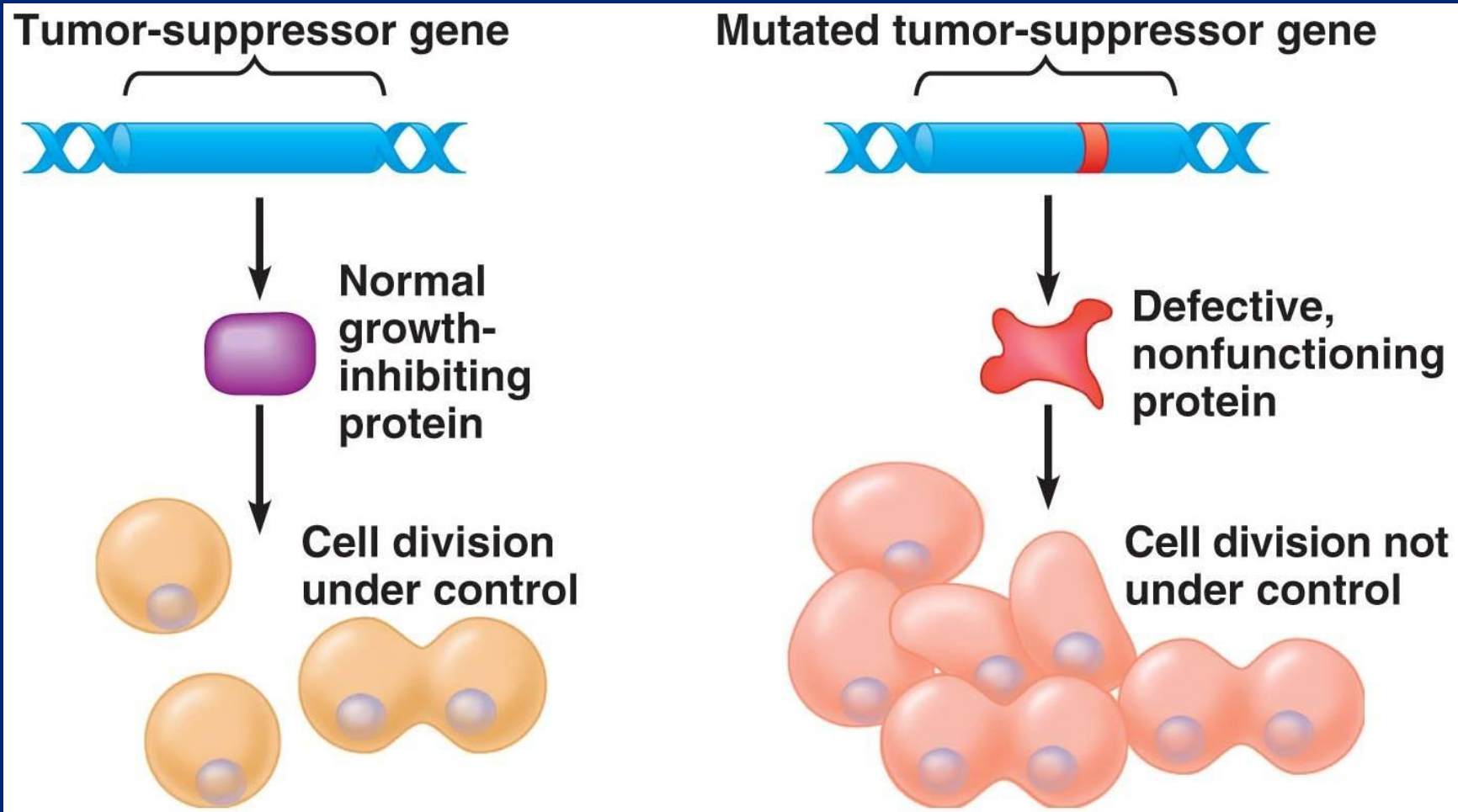
- Transmissable cancers

Cancer is an evolutionary process

- Normal somatic cells are kin-selected to work with the organism
- Somatic mutations or epigenetic changes can promote direct selection:
  - Cell gains a growth advantage
  - More and more copies of its genome produced
  - Further selection for growth and metastasis
  - Host death kills the cancer off (but see end of lecture)
- Anti-cancer genes evolve by kin selection (cells who do not murder their germ-line siblings get their genes into later generations)

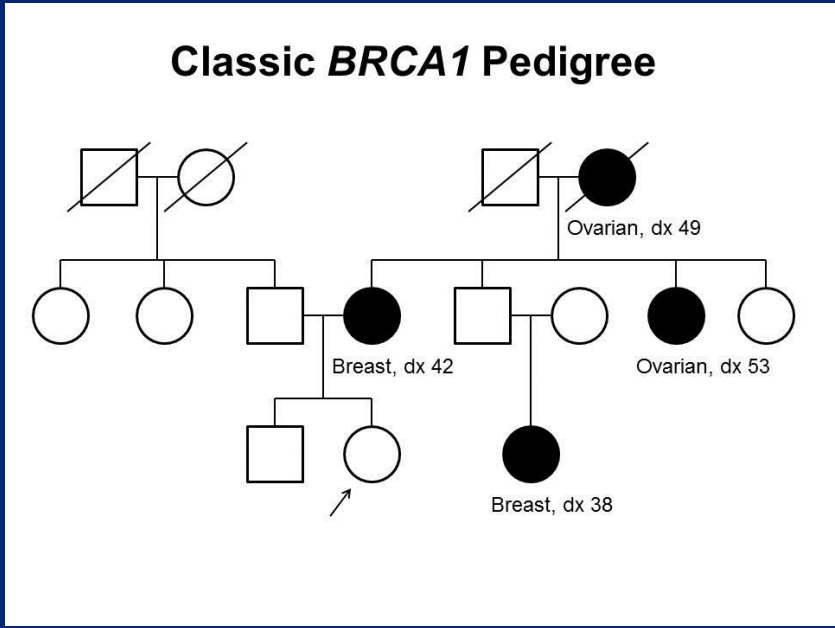
Tumor suppressor genes

- Involved in preventing or suppressing cancer:
  - DNA repair mechanisms
  - Cell-cycle checkpoints
  - Apoptosis
  - Immune system surveillance
- Cancer-causing behavior usually recessive
- First hit can be inherited; second usually somatic



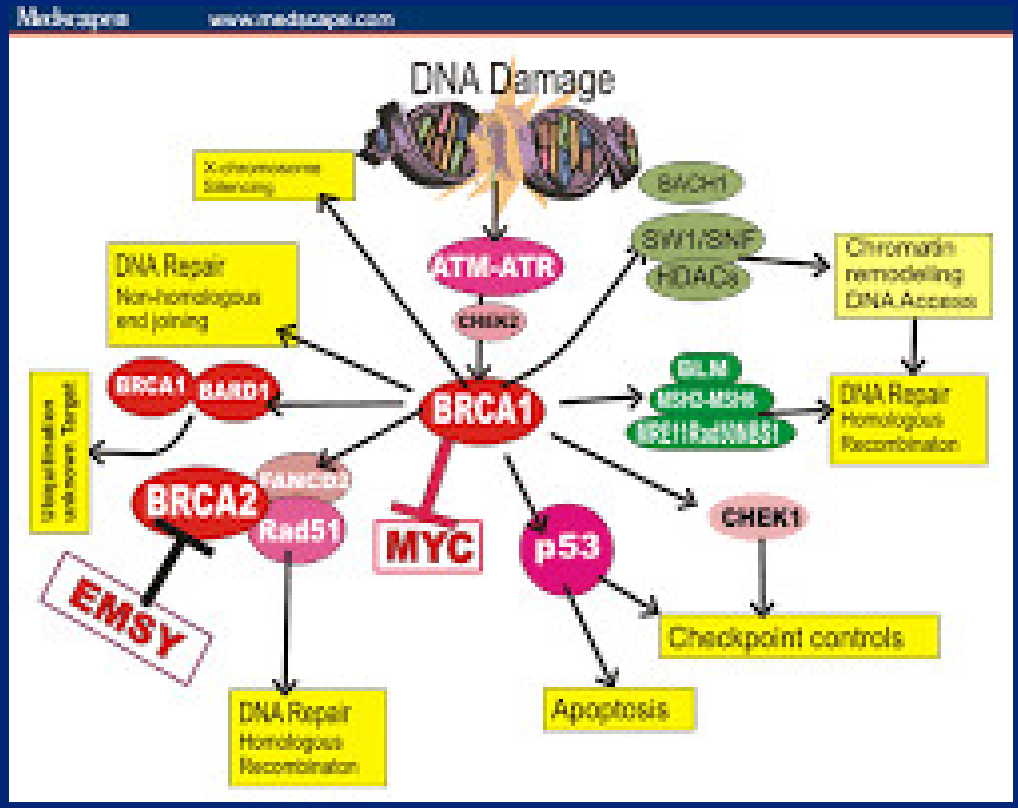
Familial versus sporadic breast cancer

- Women who inherit one BRCA1 mutation at 80% lifetime risk of breast cancer
- This mutation is probably recessive (little phenotype in cell culture)
- Why is it predisposing?



Familial versus sporadic breast cancer

- BRCA1 involved in DNA repair, recombination, checkpoints
- Normally 2 mutations needed to break it
- With a germ-line BRCA1 mutation only 1 hit is needed



BRCA1 puzzle

- BRCA1 (and BRCA2) involved in most familial breast cancer
- Risk to carriers is very high
- Most sporadic (non-familial) breast cancers do NOT have mutations in these genes
- Why not?

BRCA1 puzzle

- Single hit to BRCA1 has no growth advantage
- Chance of two hits to the same cell line low in an adult
- Having one hit in germ line is a huge head start
- Most sporadic cancers mutate genes that can give a growth advantage *in a heterozygous/hemizygous cell*
- Opposite case: familial and sporadic retinoblastoma both arise from mutations in RB gene

General puzzle about cancer

- Tumor suppressors are often involved in very basic cell functions:
  - DNA repair
  - Replication
  - Cell division
  - Programmed cell death
- BRCA1 is involved in DNA repair, which all cells need
- Why do mutations in BRCA1 cause breast and ovarian cancer–not colon, liver, or brain cancer?

General puzzle about cancer

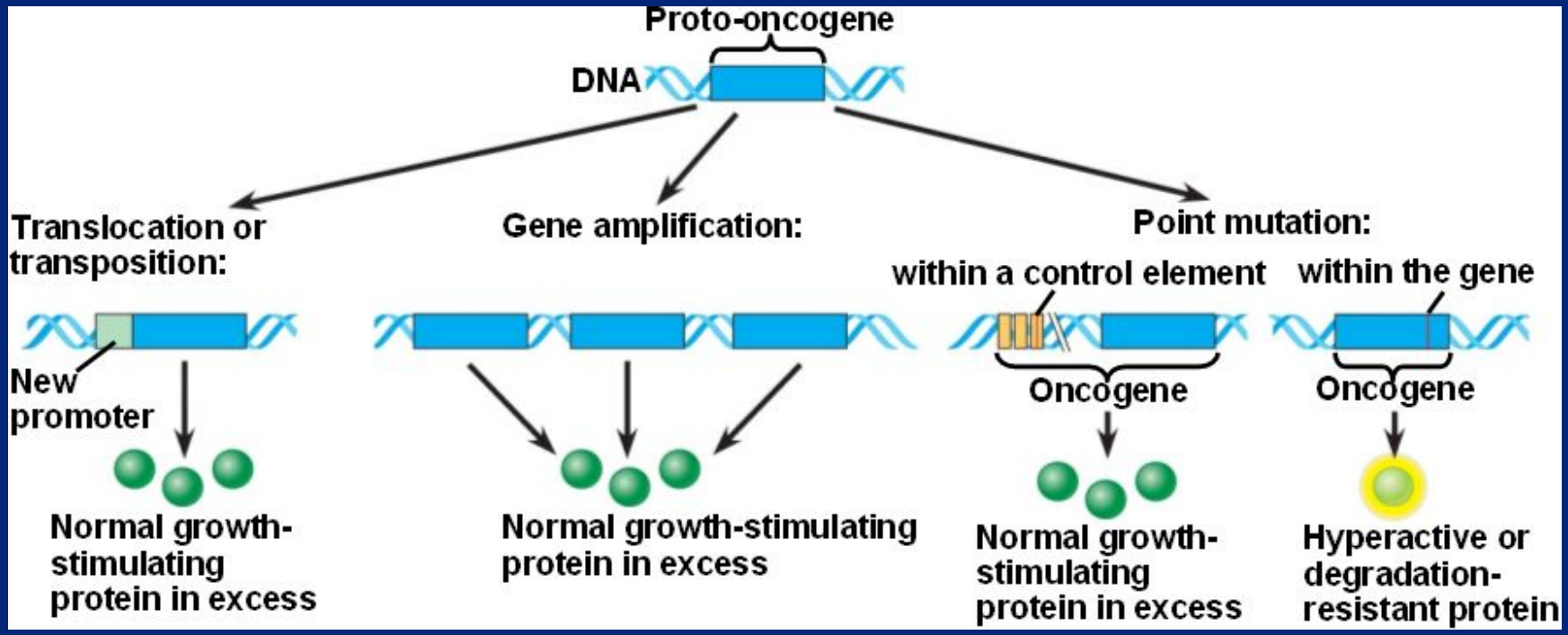
Some possible explanations:

- Different ability of mutant cells to spread in different tissues (different selection)
- Different timing of cell growth in different tissues
- Interacting genes turned on/off in different tissues
- Redundant systems in some tissues but not others

Oncogenes

- Mutant gene copies actively cause cancer:
  - Too much expression
  - Expression in the wrong place or time
  - Unregulated expression
  - Mutant protein can't be controlled (always active, overactive)
  - Mutant protein has a new function
- Often dominant
- Pathways often involved: cell growth, proliferation, blood vessel formation

Oncogenes

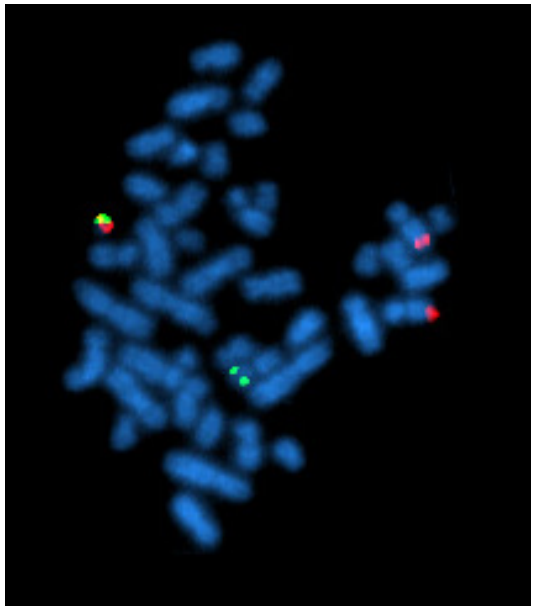

Proto-oncogene
DNA
Translocation or transposition:
Gene amplification:
Point mutation:
within a control element
within the gene
New promoter
Oncogene
Oncogene
Normal growth-stimulating protein in excess
Normal growth-stimulating protein in excess
Normal growth-stimulating protein in excess
Hyperactive or degradation-resistant protein

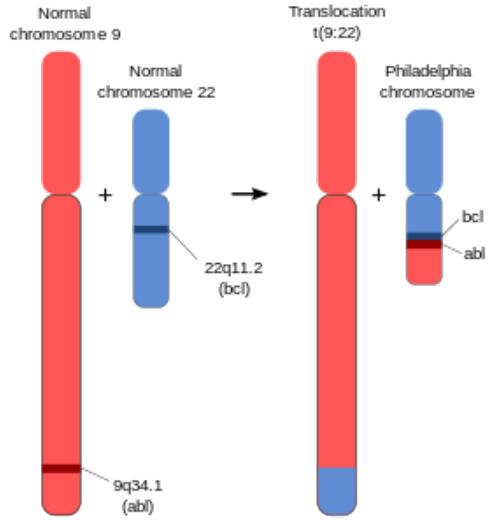
Cancers caused by viruses

- Several pathways:
  - Virus proteins shut down tumor suppressor genes (HPV)
  - Virus carries a copy of a host oncogene (HTLV-1)
  - Virus causes non-specific inflammation which damages DNA (Hepatitis C)
- About 18% of human cancers are viral, mainly due to:
  - Hepatitis B and C (hepatocarcinoma)
  - HTLV (adult T-cell leukemia)
  - HPV (reproductive tract cancers)
  - HHV-8 (Kaposi's sarcoma)

Cancer due to translocation

- Chromosomes 9 and 22 exchange ends ("Philadelphia chromosome")
- Fusion between $ABL1$ (chrom 9) and BCR (chrom 22)
- New gene is uncontrollably expressed
- This shortens the cell cycle and inhibits DNA repair
- Alu repeats in $ABL1$ and BCR may be involved





An evolutionary vulnerability

- Many recurrant translocations involve chr. 14
- The vulnerable site is the IgH locus, which is normally rearranged during development to produce diverse antibodies
- Many others involve Alu transposons
- Self-rearranging DNA is a risky thing....

Barrett's Esophagus (BE)

- Lower esophagus is damaged by gastric acid
- Abnormal tissue layer forms
- 5% go on to develop cancer of the esophagus

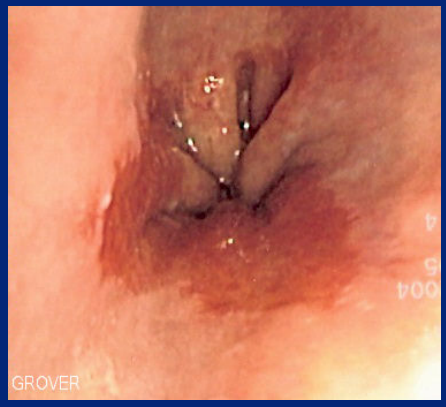
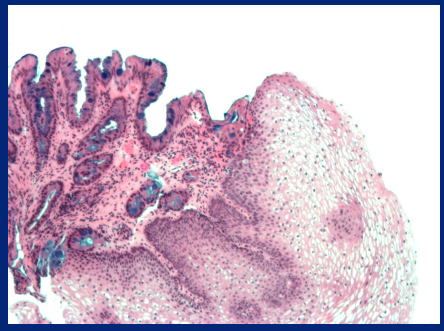


image by Samir, from Wikipedia

BE might be protective

- Normal esophageal lining is smooth flat layer
- BE has pockets ("crypts") like intestinal lining
- Each crypt has its own stem cells
- A dangerous mutation in one crypt can't easily spread to others



Barrett's Esophagus (left) and normal esophageal lining (right)
image by Nephron, from Wikipedia

Barrett's Esophagus mysteries

- Most people with BE never get cancer
- When cancer does develop it is usually quick (soon after BE diagnosis)
- Rate of this cancer is climbing rapidly in the Western world
- It is associated with obesity but started to climb before obesity did

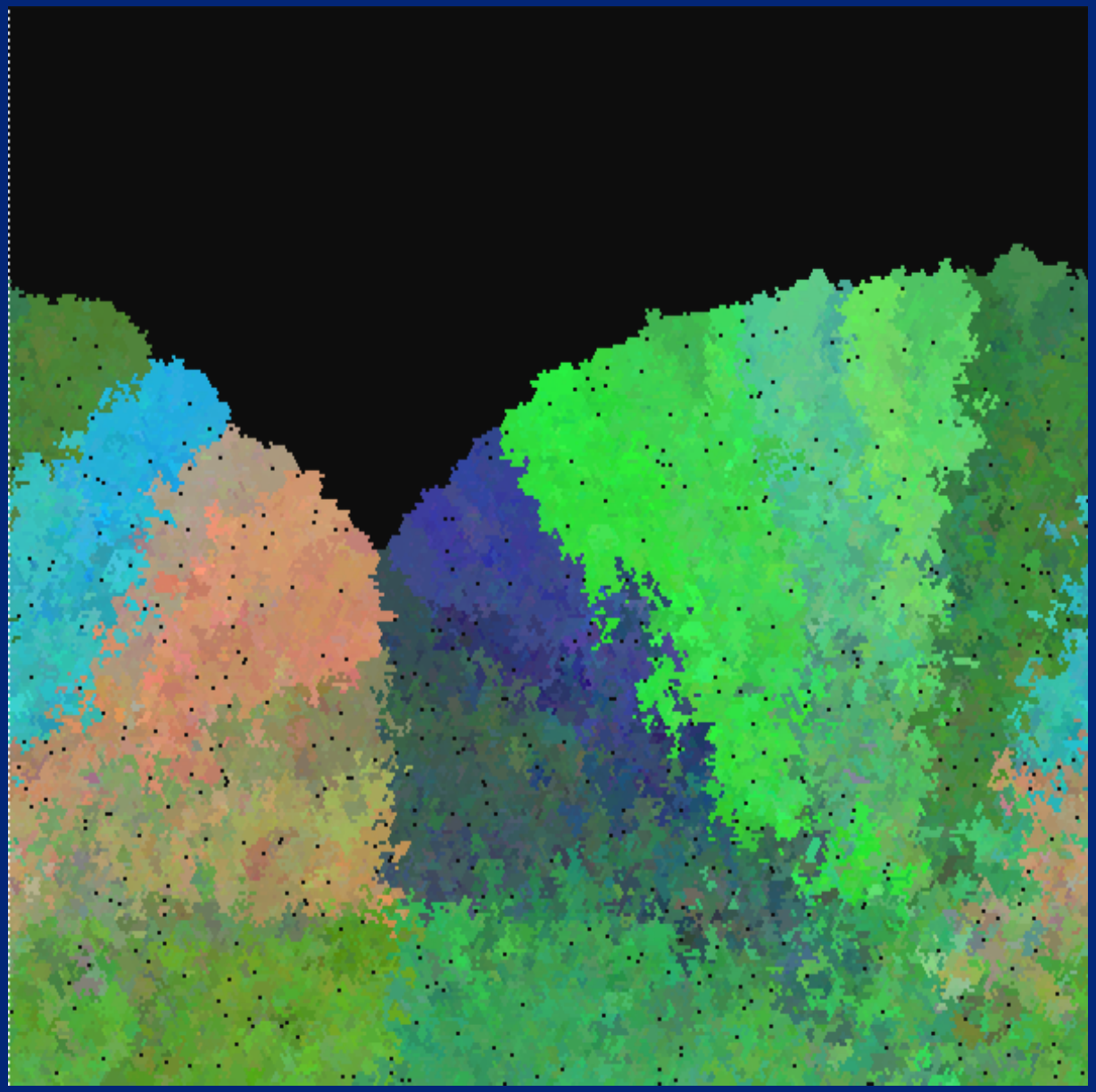
How does a tissue like this behave?

- Rumen Kostadinov and I simulated growth of an esophagus in the computer
- Crypts arose, divided, died out, and had mutations
- No natural selection–all cells equally good

Rumen Kostadinov, Johns Hopkins

How does a tissue like this behave?

- If we started with a non-mutant field of crypts, nothing much happened:
  - Cells did develop mutations
  - They hardly spread at all–BE does its job!
- The story is very different if we start with a few crypts at one end of the esophagus and let them colonize:
  - Mutant cells on the leading edge spread
  - Striking patterns were produced



Where have we seen this before?

- This resembles "gene surfing" in plant and animal populations
- When a population is spreading rapidly across the land, mutations on the leading edge can "surf" to high frequency
- Studied in expansion of French-Canadian population across Quebec
- Also observed in bacterial colonies on Petri plates
- This is a form of intense genetic drift

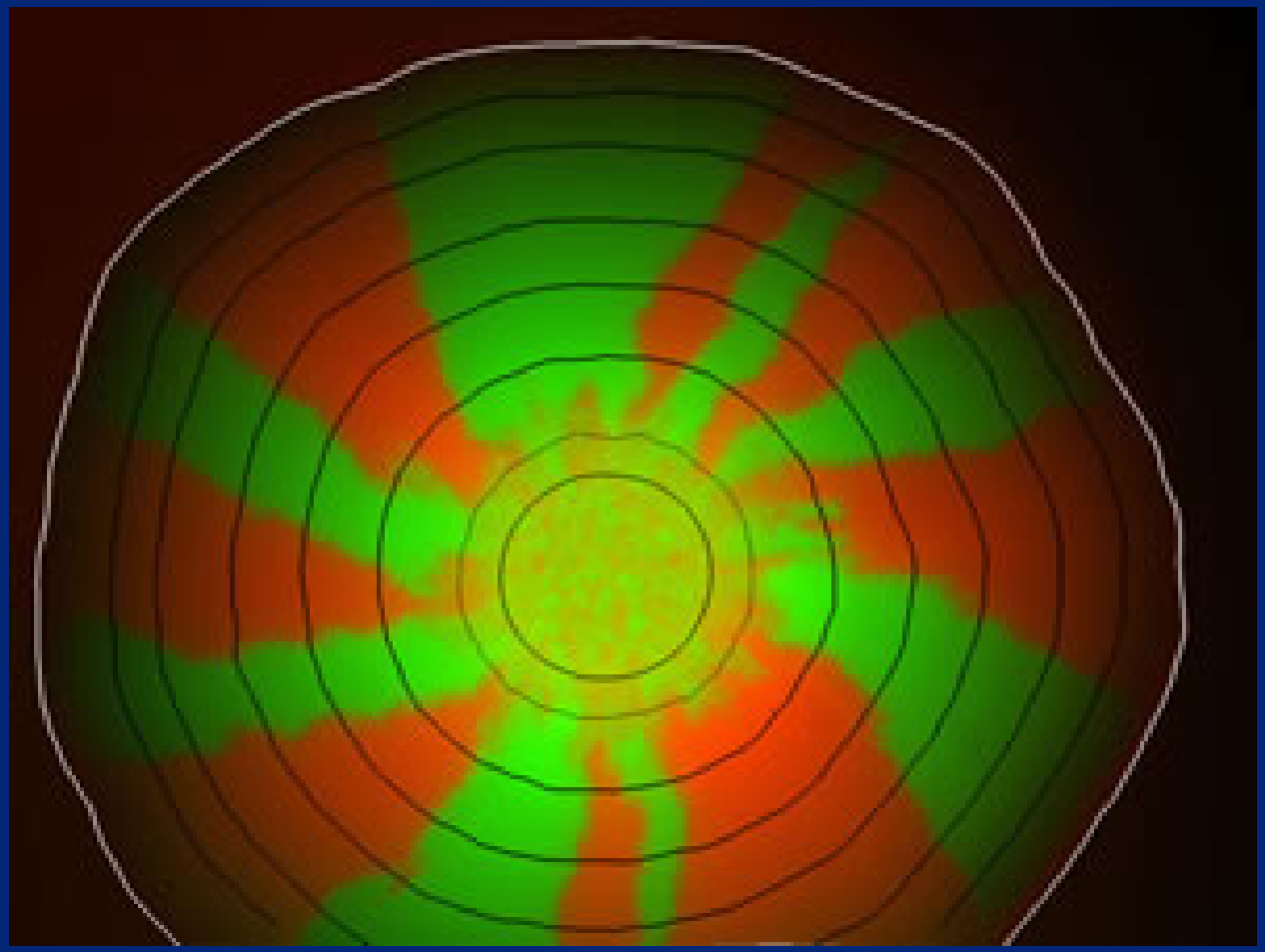


Plate was inoculated with a mix of red and green $E.\ coli$ at the center. Sectors arise due to gene surfing. Image courtesy of Dr. Oskar Hallatschek, UC Berkeley.

Multi-hit theory of cancer

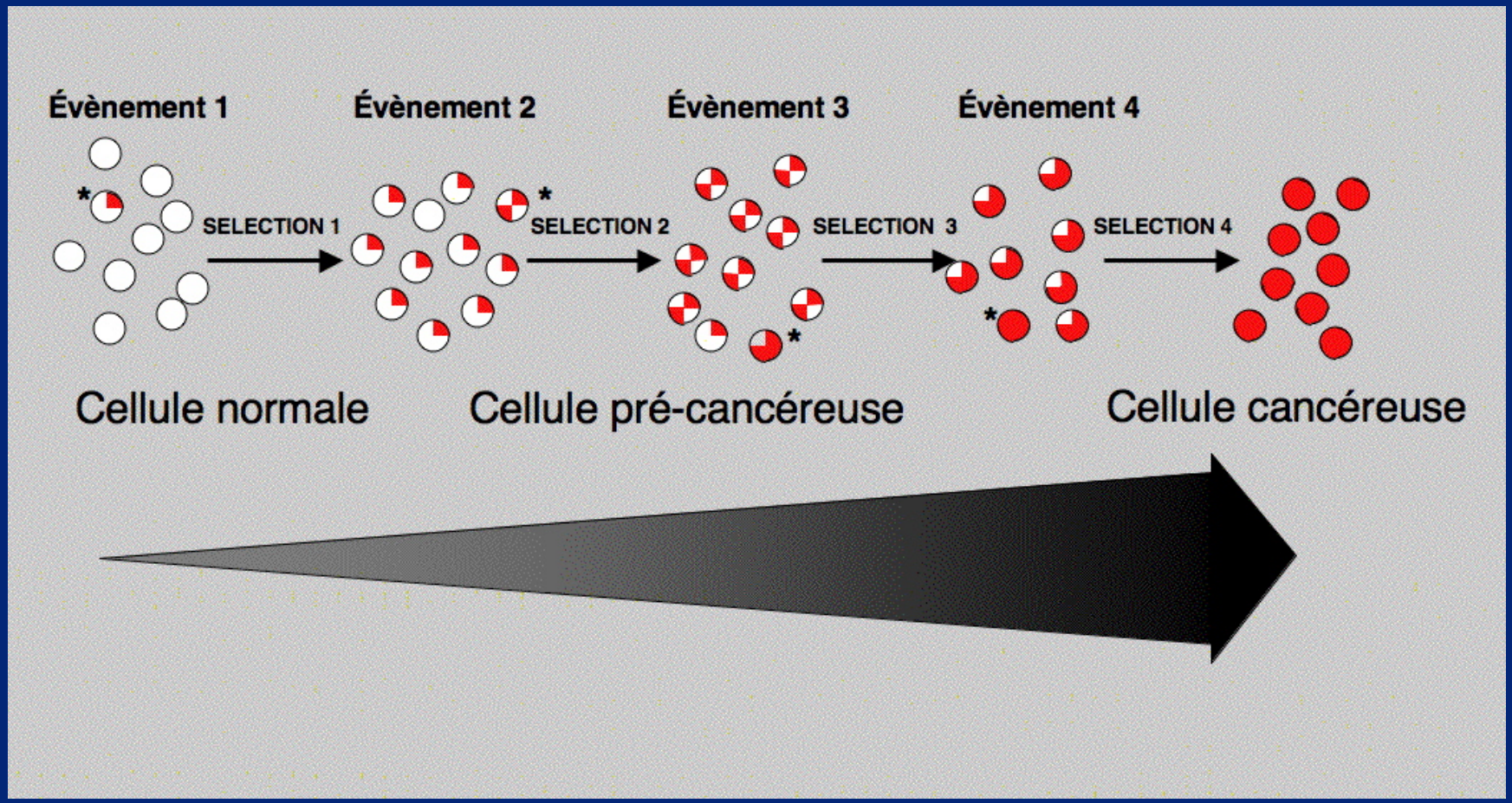


Image by Thierry Soussi, from Wikipedia

Multi-hit theory of cancer

- An advantageous pre-cancer mutation arises
- Its descendants grow due to the advantage
- They are now targets for additional mutations
- Several successive mutations needed for full-blown cancer

Doesn't fit BE particularly well

Theory:

- Predicts most cancers at bottom of esophagus where mutagens are concentrated
- Predicts gradual accumulation of cancers
- Predicts selective sweeps of esophagus

Observation:

- Cancers are most frequent midway up
- Cancer happens quickly or not at all in most people with BE
- Samples from BE don't show full sweeps

Alternative theory with gene surfing

- In most people with BE:
  - BE segment grows without any bad mutations
  - Once it has grown, it stops mutations from spreading
  - Mutant cells may have a small advantage but it's not enough to let them spread far
  - These individuals seldom get cancer
- In a few people with BE:
  - Carcinogenic mutations arise as BE is spreading
  - Gene surfing creates large mutant patches
  - Later mutations drive them on to cancer

Explanatory power

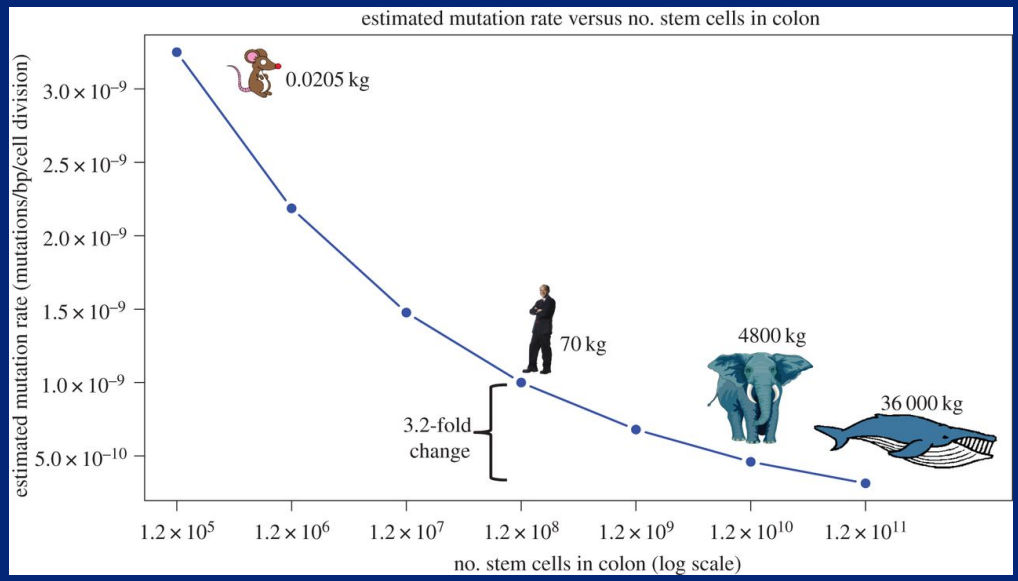
- Cancers arise toward the middle because gene surfing pushes mutations in the direction of growth
- Cancers arise quickly or not at all because they rely on an early surfing event
- We don't observe selective sweeps during surveillance because the mutations are not strongly advantageous
- I am currently trying to get funding for a detailed spatial map of BE within a patient

Peto's Paradox

- Mutations accumulate with number of cells and time
- This predicts that the larger and older an organism, the more cancer it should have
- Prediction is false:
  - Humans have more cancers than whales
  - In general cancer frequency does not scale with size or lifespan in mammals
- Why don't whales all get cancer? (10^{17} cells compared with 10^9 in mice)

Peto's Paradox – ideas

- More tumor suppressors? (Elephants have 20+ copies of $TP53$)
- Better tumor suppressors?
- Lower metabolic rate?
- Tumor must be bigger to endanger life, so more time to stop it?



Ultimate cancer evolution

Tasmanian Devil Facial Tumor Disease (DFTD)

- First detected in 1996
- 70% decrease in wild population
- Transmitted by biting, especially during sex
- Next slide is an unpleasant picture–feel free to look away

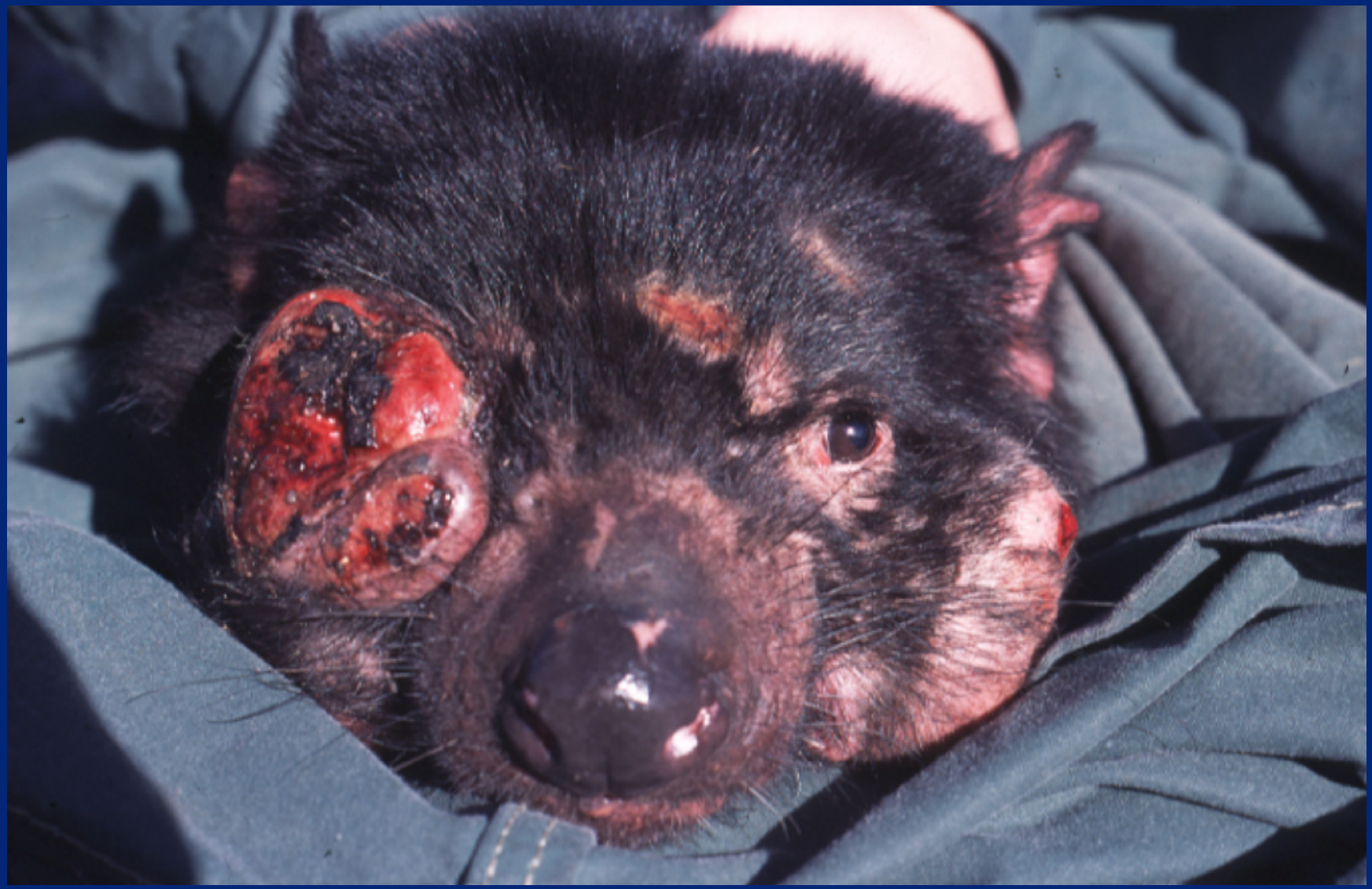


Photo: Menna Jones, from McCallum and Jones (2006) PLoS Biol

DFTD origins

- Initially attributed to an oncovirus
- DNA sequencing of animals and tumors:
  - Tumors more similar to each other than to their hosts
  - Single recent origin of tumor DNA
- Conclusion: the cancer itself is contageous

Evolution in action

- Host (Tasmanian devil) evolution
  - Females breed at younger age
- Parasite (DFTD) evolution
  - Evolution of multiple strains
  - Increase in tetraploid tumors which grow more slowly
  - Slow growth helps evade human projects to remove affected animals

Canine transmissible venereal tumor

- Worldwide distribution in domestic dogs
- Transmitted sexually
- Evolutionary history:
  - Based on microsatellites, diverged from canids >6000 years ago
  - Common ancestor only a few hundred years ago (severe bottleneck)
- May be becoming less virulent over time

Cancer's road to independent life

- Other known examples:
  - Contagious reticulum cell sarcoma in Syrian hamster
  - Kaposi's sarcoma in humans occasionally transmitted during transplantation
  - Arguably, HeLa cells ("host" is lab cell cultures)

Why aren't such diseases more common?

- Multicellular organism poor starting material for single-celled parasite?
- Asexual, non-recombining lifestyle often evolutionary dead end?
- Needs a vulnerable host species?
  - Devils, hamsters, domestic dogs all went through bottlenecks
- Could be more examples we haven't detected

Some last thoughts

- Please come with questions/problems for Friday review session
- Final is Wed Dec 13 2:30-4:20 – bring calculator
- Thank you for your active participation and involvement!