



Massachusetts
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Technology



Cancer as an evolutionary process

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Theory

PNAS

Impact of deleterious passenger mutations on cancer progression

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PNAS

Tug-of-war between driver and passenger mutations in cancer and other adaptive processes

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Experiments

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Molecular and Cellular Pathobiology

Cancer Research

The Damaging Effect of Passenger Mutations on Cancer Progression

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<https://cancerres.aacrjournals.org/content/77/18/4763.long>

Main points

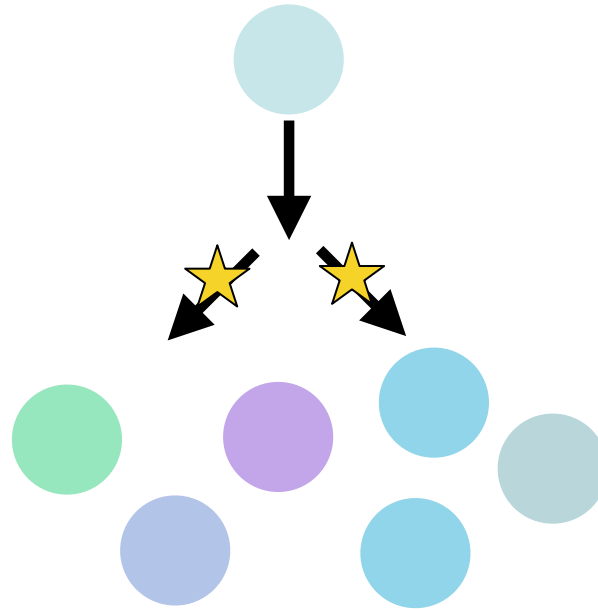
1. Cancer is an evolutionary process
2. Cancer genomics allows to look under the hood of this process
3. Treating cancer using its own evolutionary mechanisms

Evolution

mutations

diversity

selection

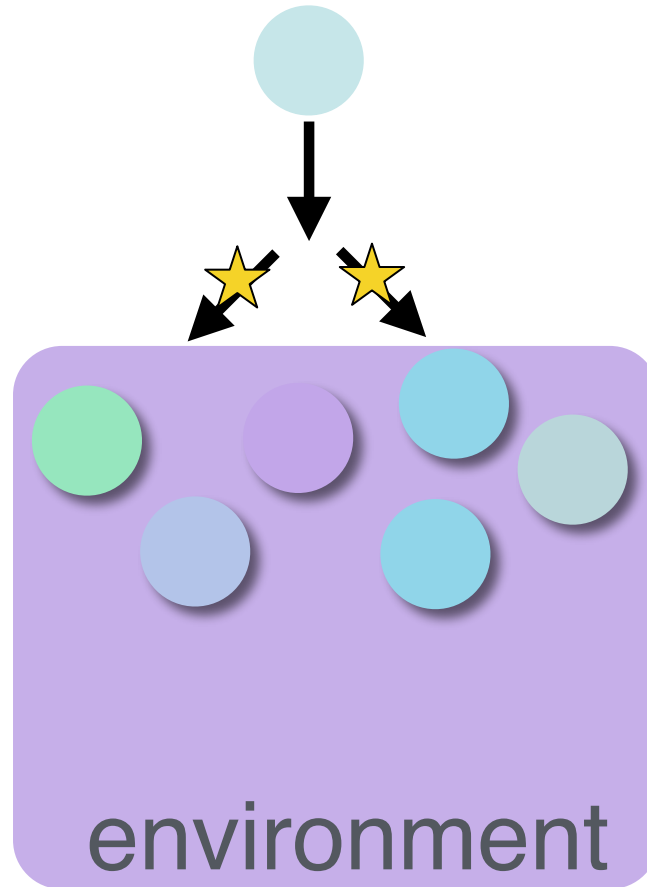


Evolution

mutations

diversity

selection

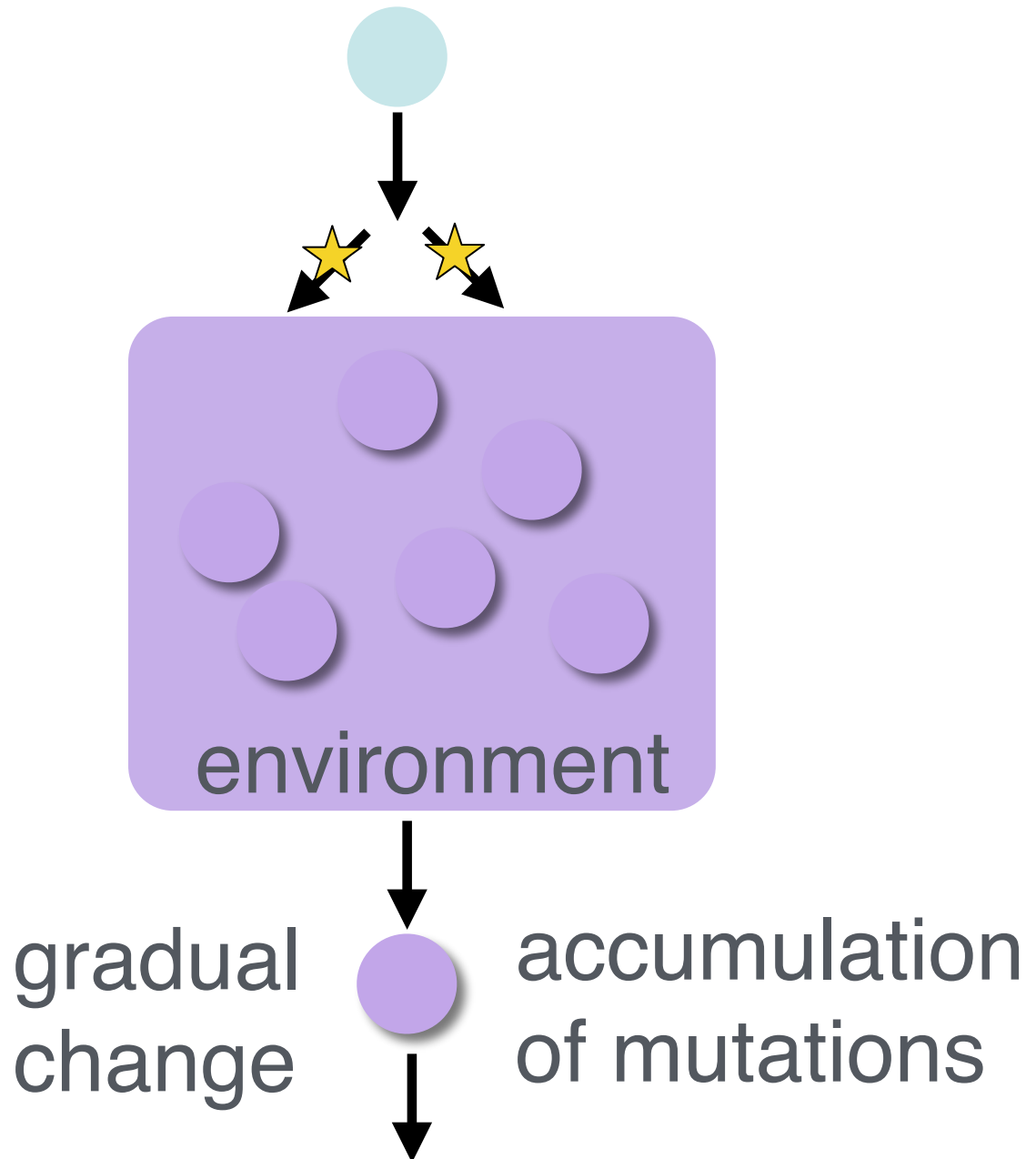


Evolution

mutations

diversity

selection



Mutant is new normal

mutations

 new phenotype
↓
is acquired

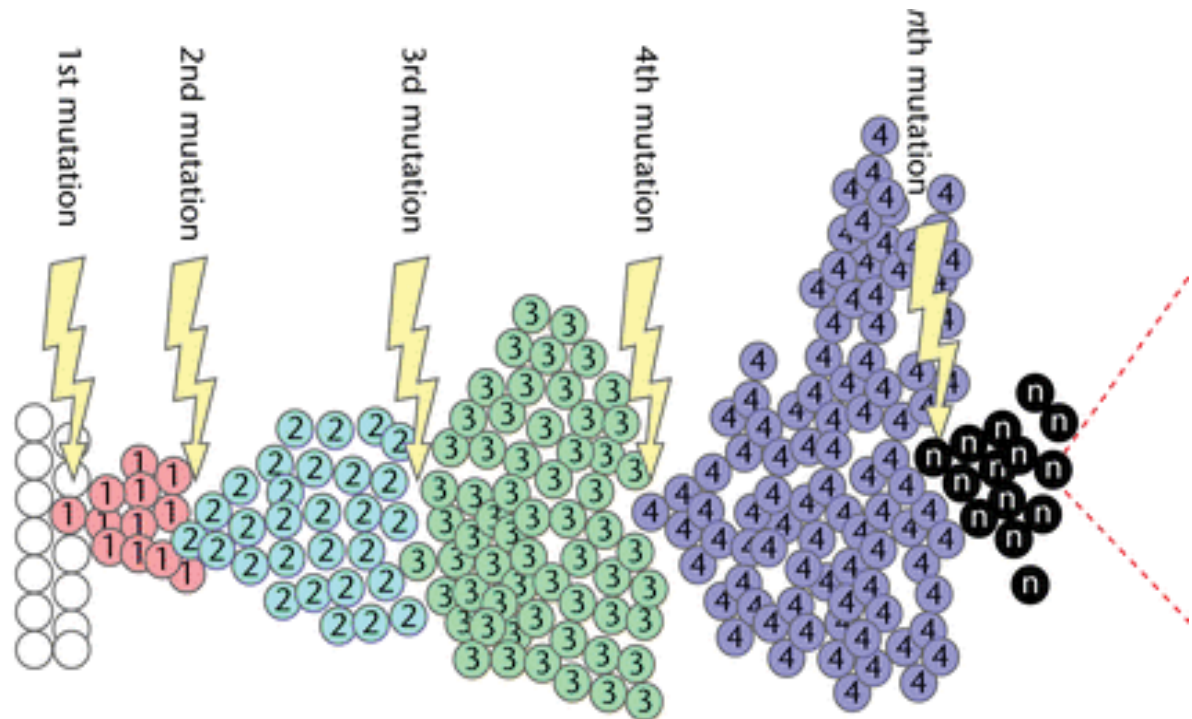
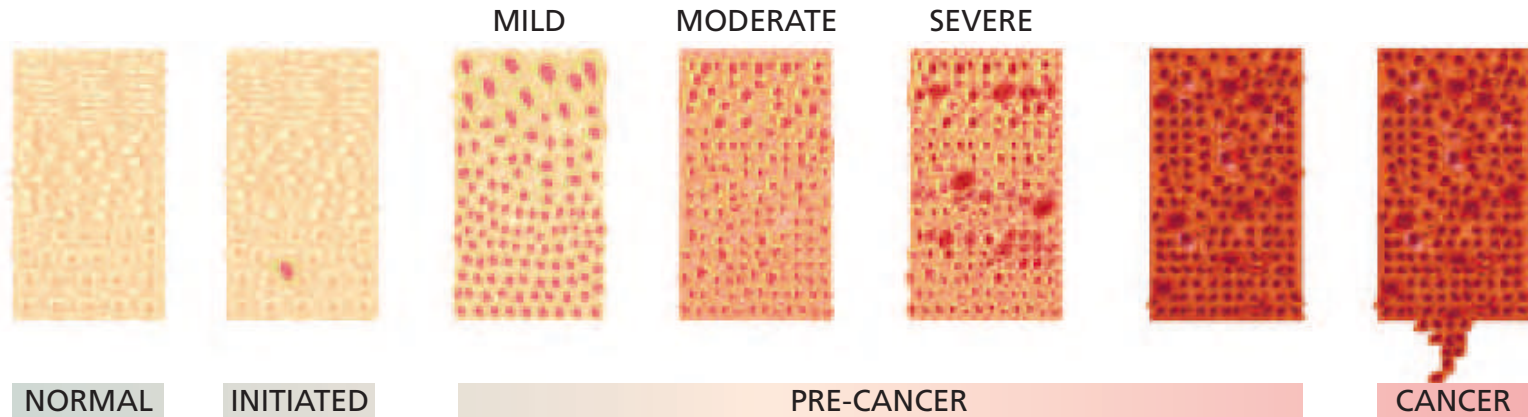
diversity

selection

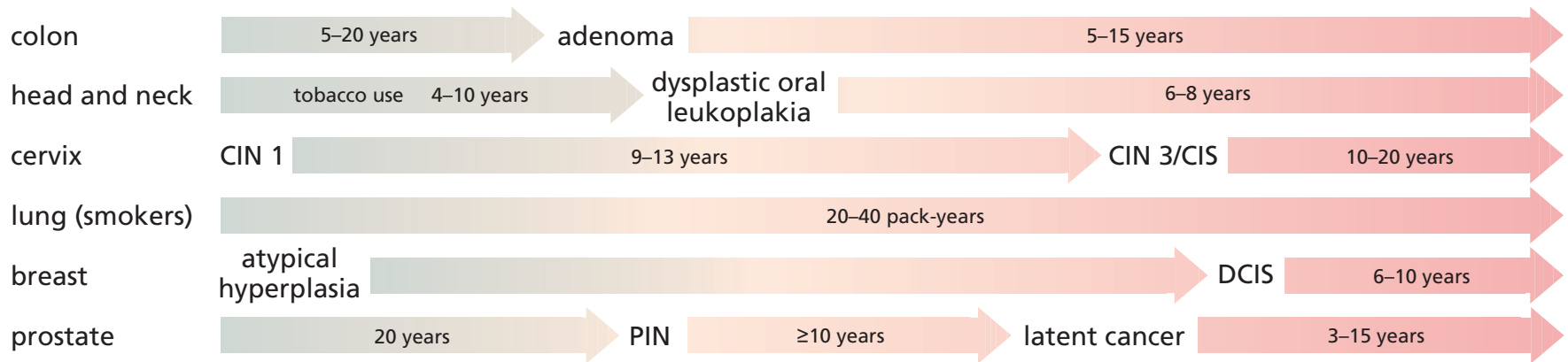
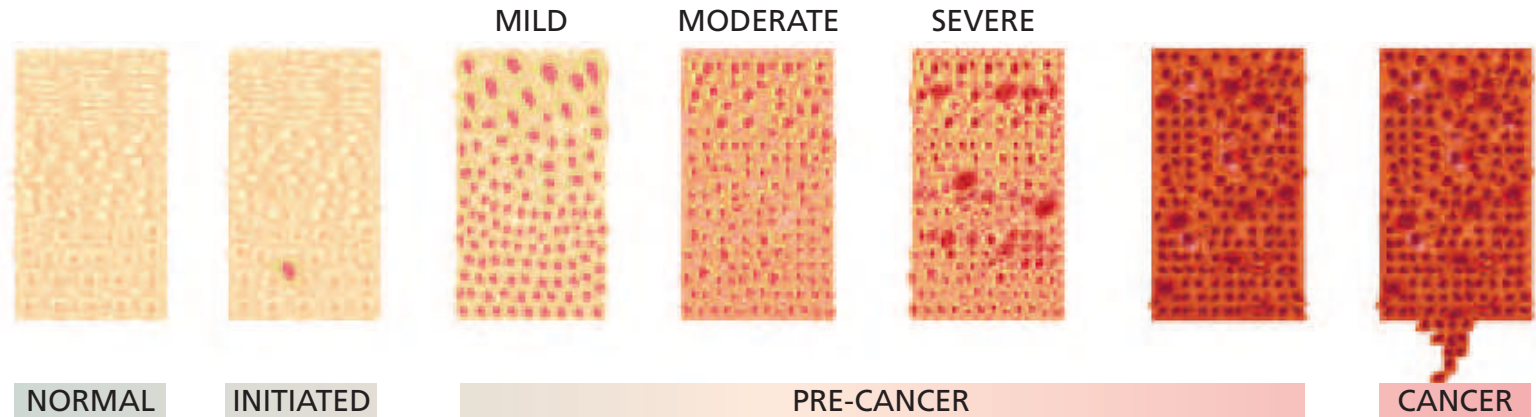
gradual
change

accumulation
of mutations

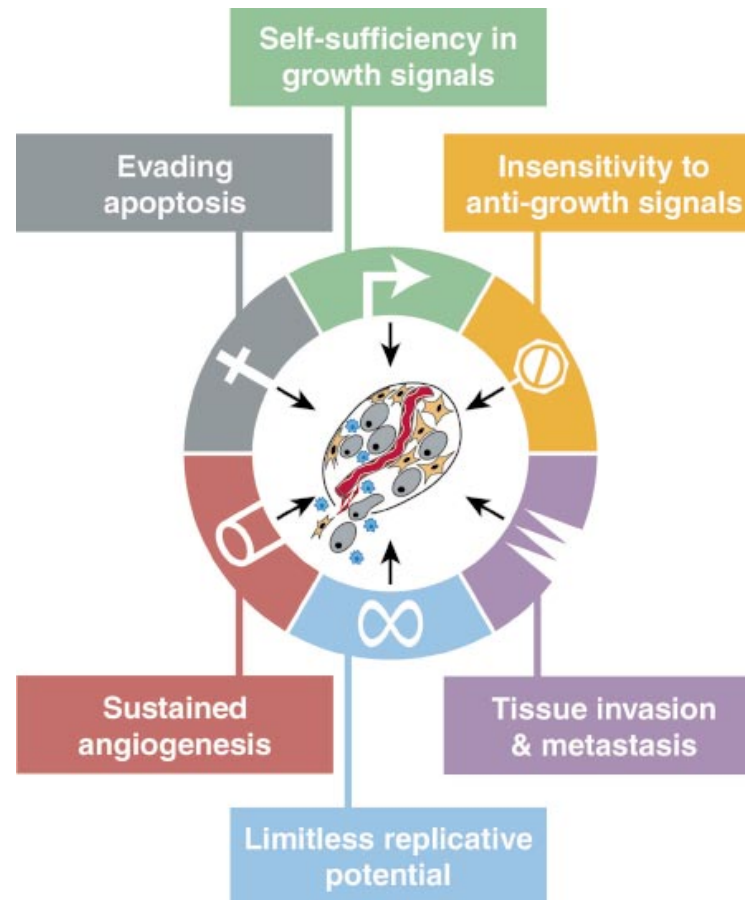
Cancer = evolution



Cancer = evolution



Acquired phenotypes of cancer



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

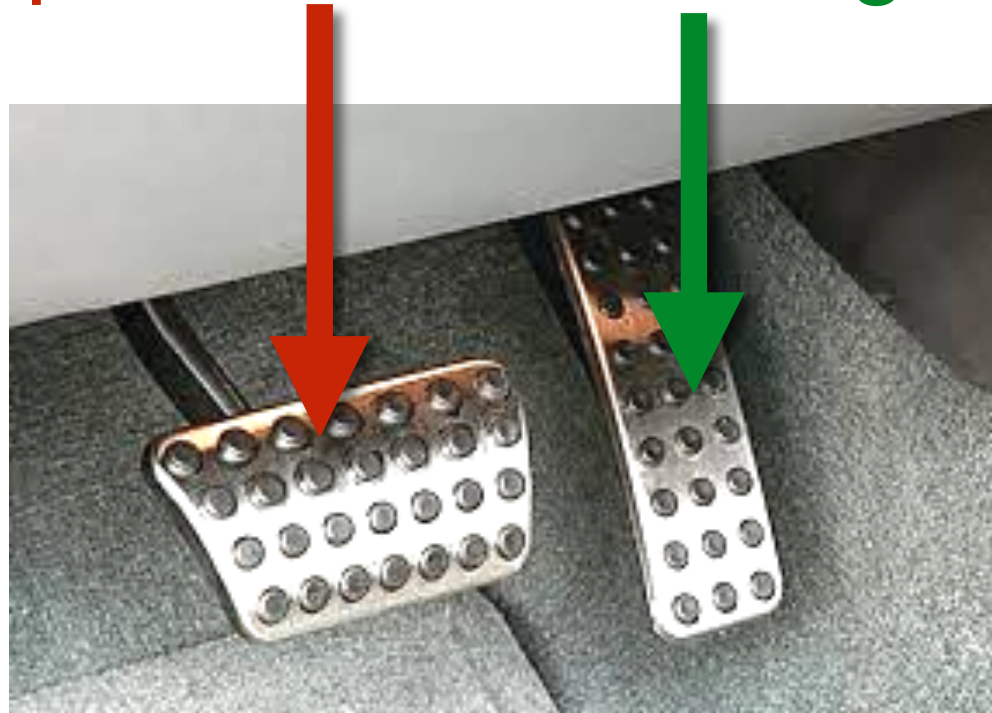
Douglas Hanahan* and Robert A. Weinberg†

Acquired phenotypes of cancer acquired *mutations*

Mutation targets
tumor suppressors and oncogenes

Acquired phenotypes of cancer acquired *mutations*

Mutation targets
tumor suppressors and **oncogenes**



Acquired phenotypes of cancer acquired *mutations*

Mutation targets
tumor suppressors and **oncogenes**



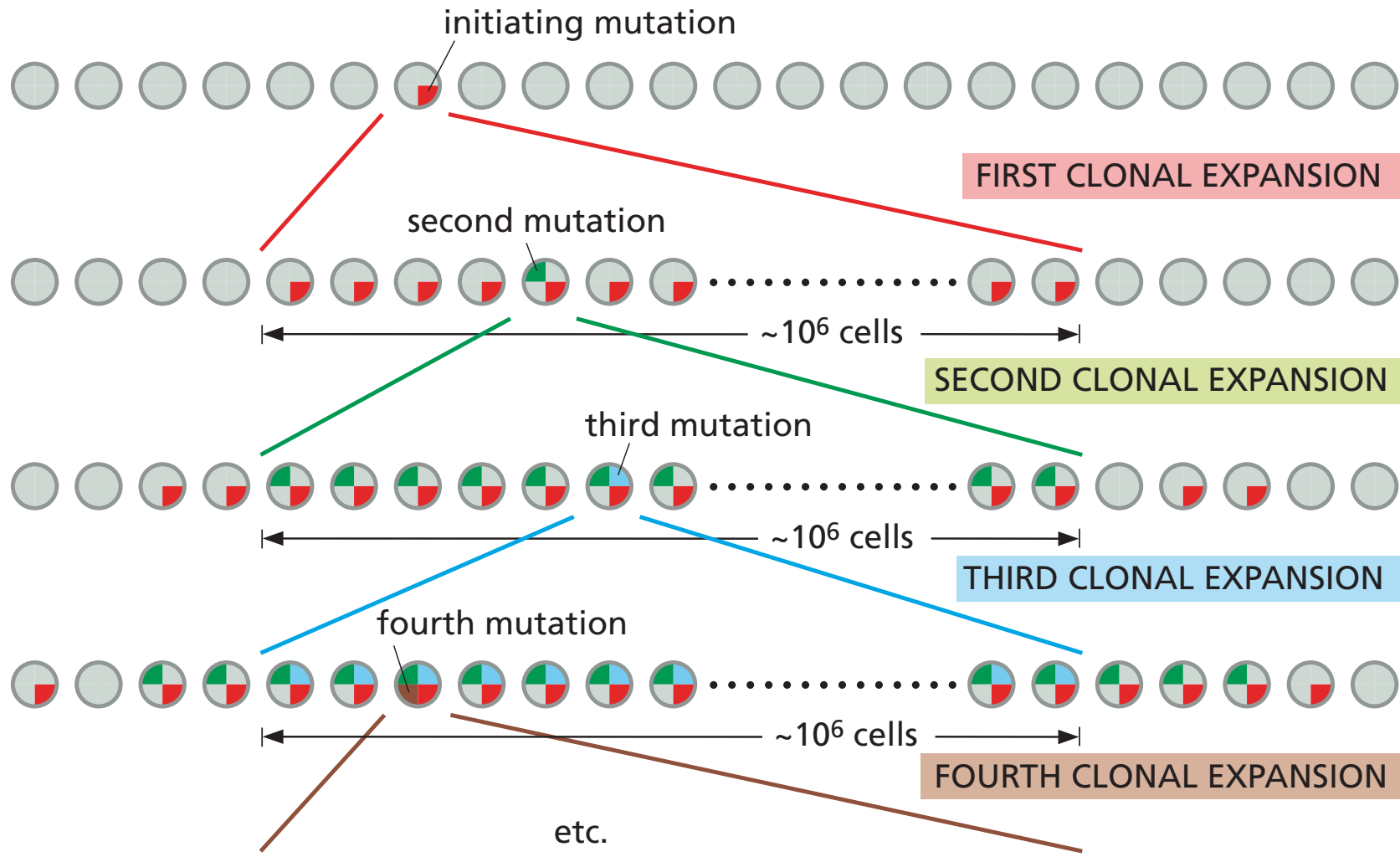
Mutation targets
tumor suppressors and oncogenes
[drivers]

Oncogenes and tumor suppressors

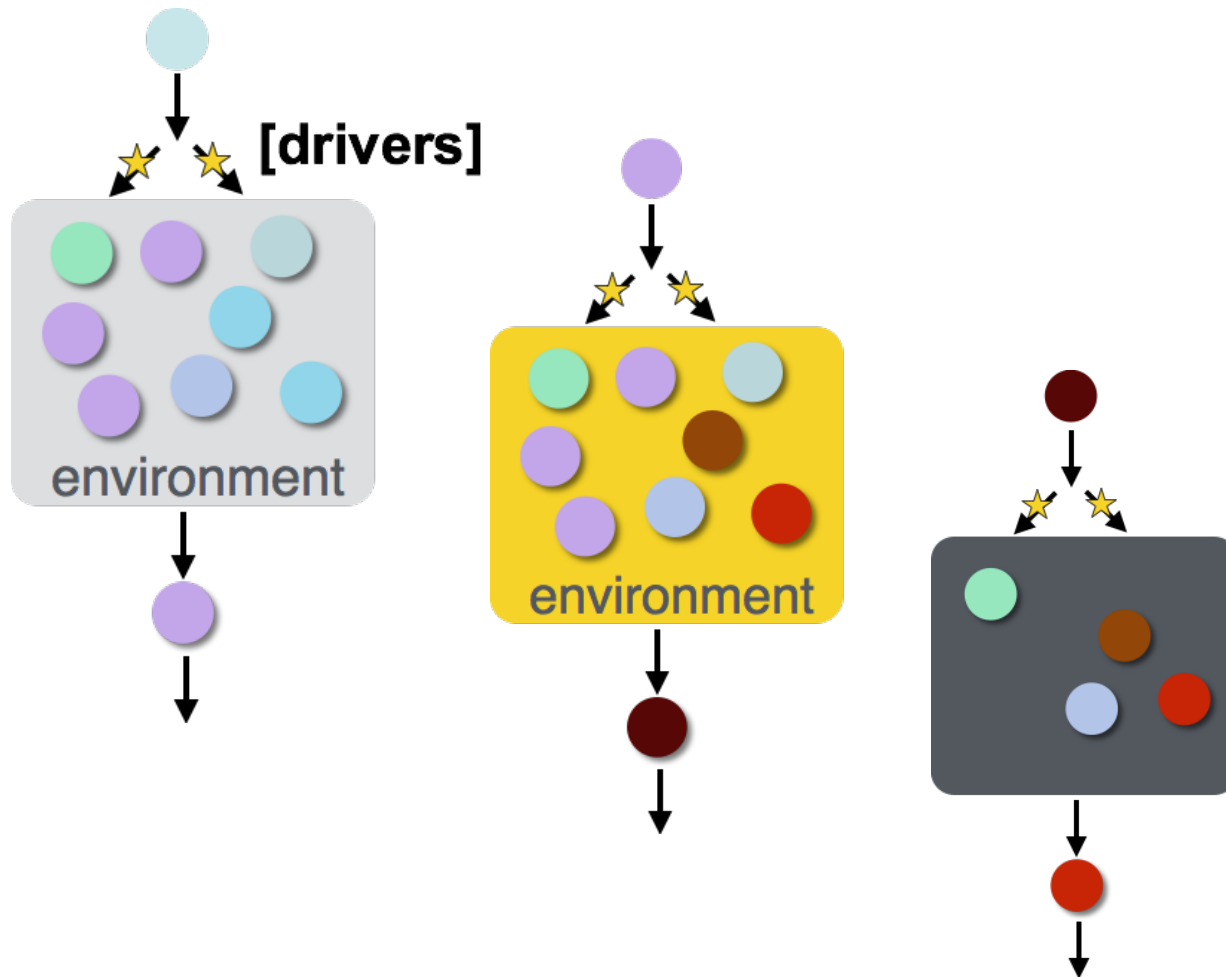
- Oncogenes -- need to be activated
 - by mutations (within a gene or regulatory regions)
 - by chromosomal alterations
 - overexpression/modifications
- Tumor suppressors -- need to be inactivated
 - mutations, chromosomal loss, modifications

[drivers]

Cancer: series of driver mutations



Cancer: is hard to stop because it's an evolutionary process

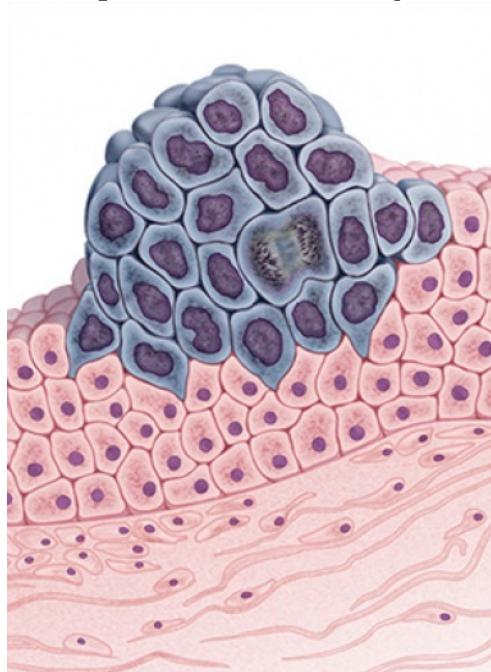


Main points

1. Cancer is an evolutionary process
2. Cancer genomics allows to look under the hood of this process
3. Treating cancer using its own evolutionary mechanisms

Cancer genomics

- Get a sample of **cancer** sequence =>
- Get a sample of **normal tissue** (from the same patient) =>



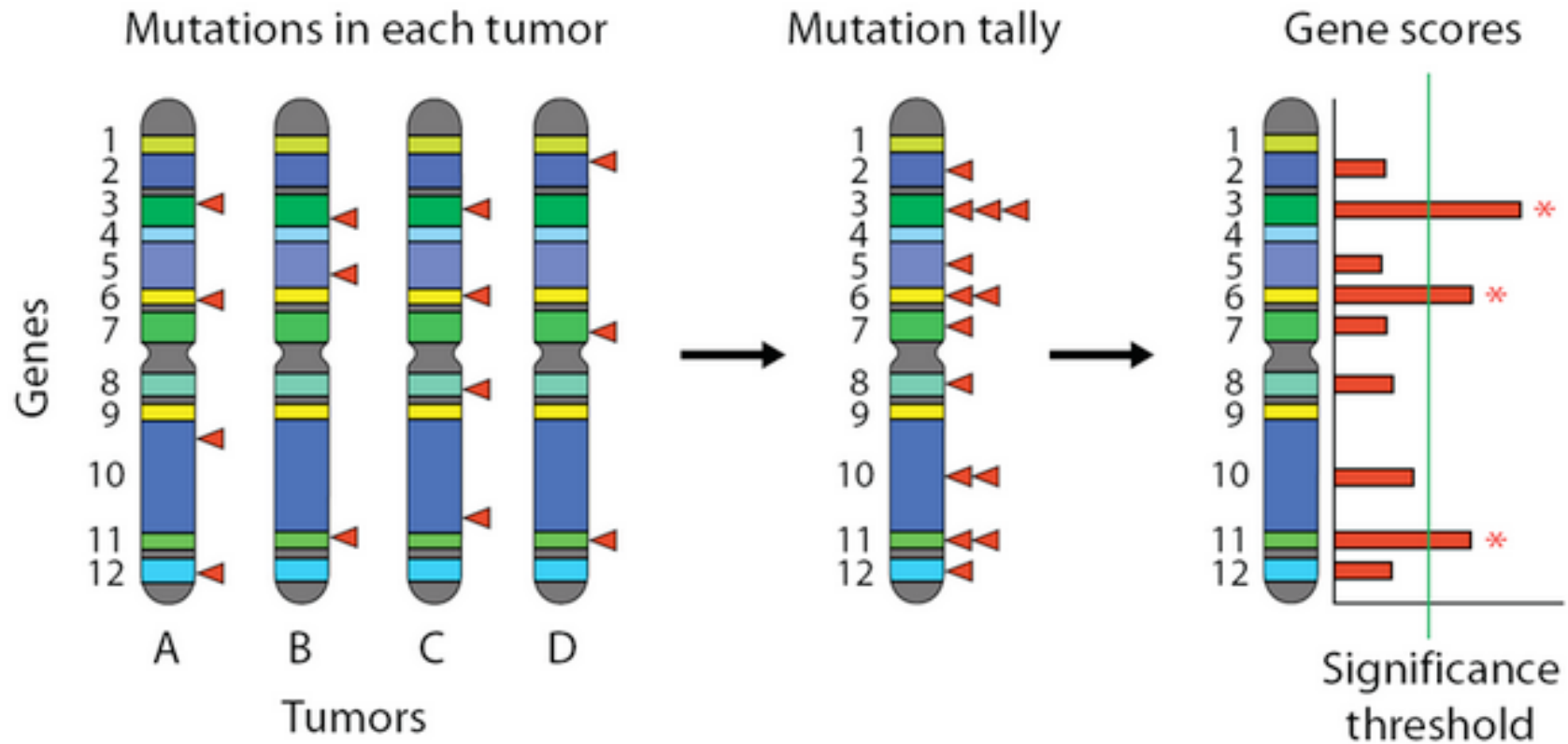
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Cancer

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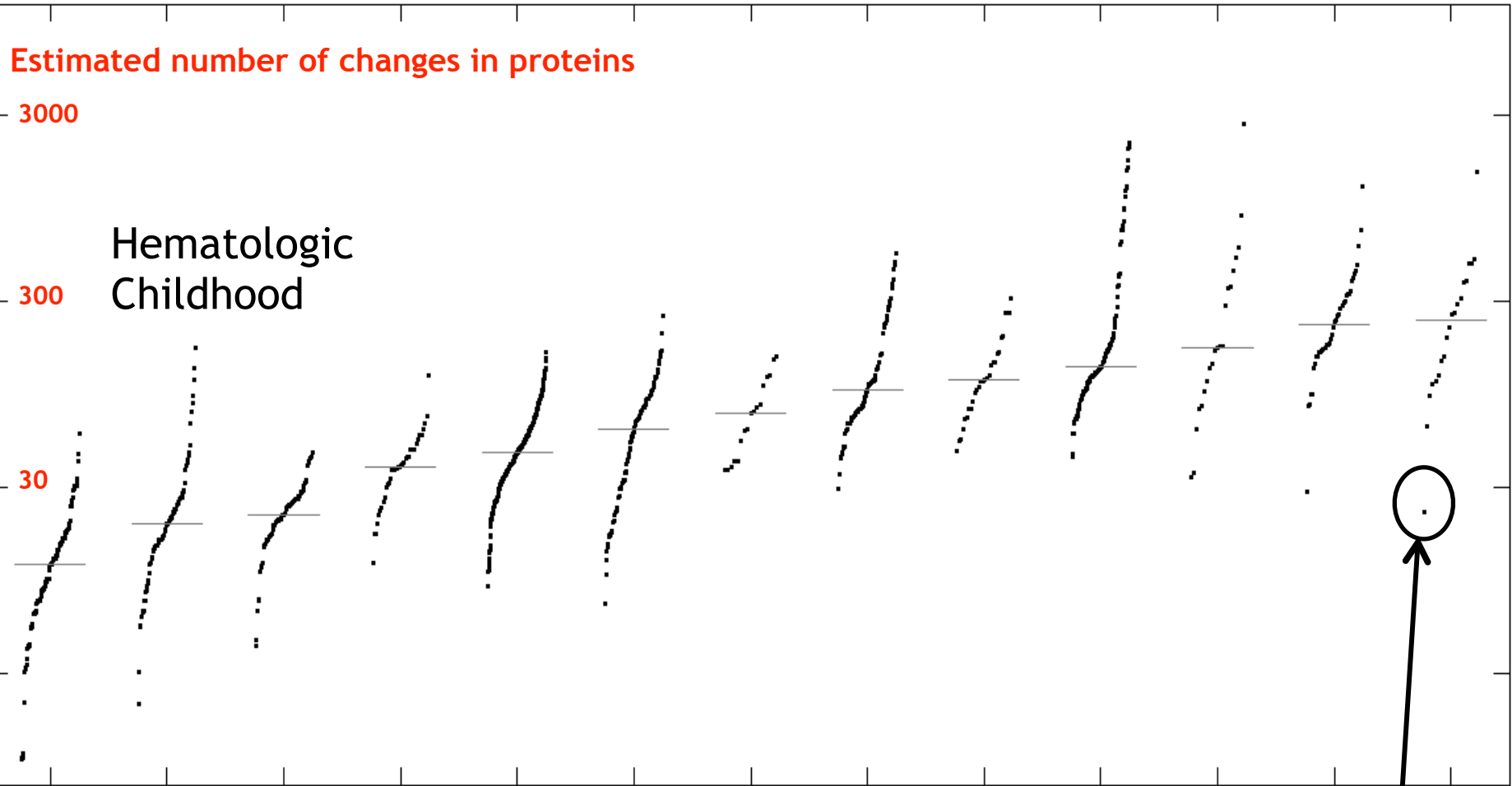
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Finding driver events

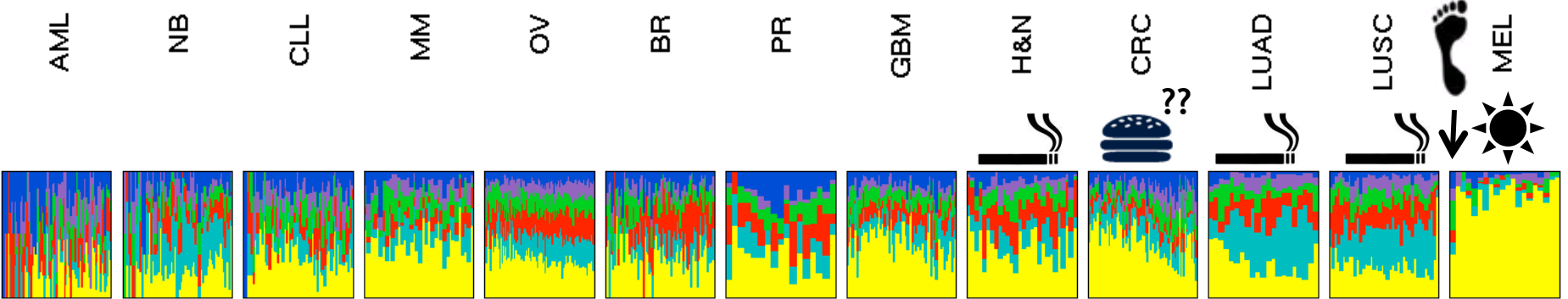


Rates of somatic mutation vary across cancers: [G.Getz]

n=109 81 64 38 316 100 17 82 28 119 21 40 20



- C->T
- C->A
- C->G
- T->C
- T->A
- T->G



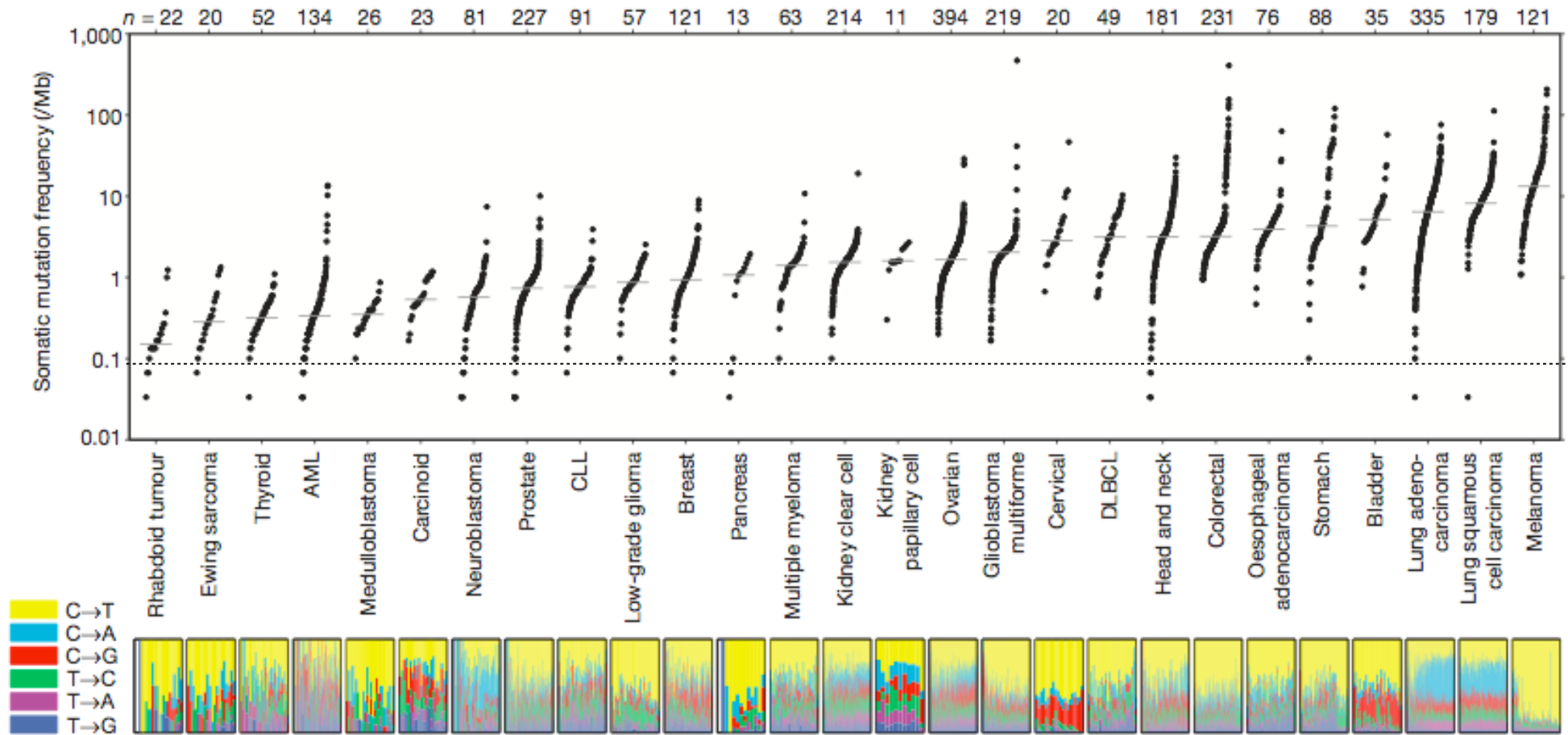


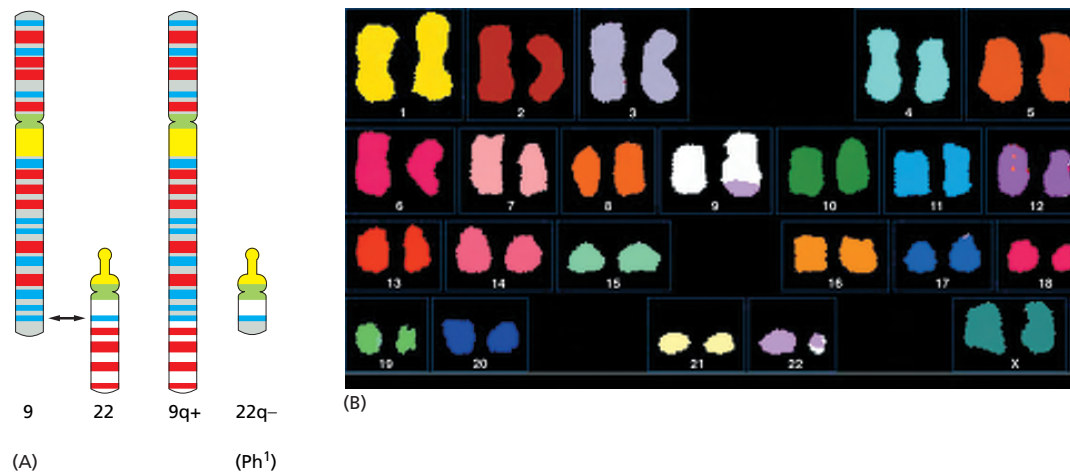
Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour-normal pairs. Each dot corresponds to a tumour-normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens

such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.

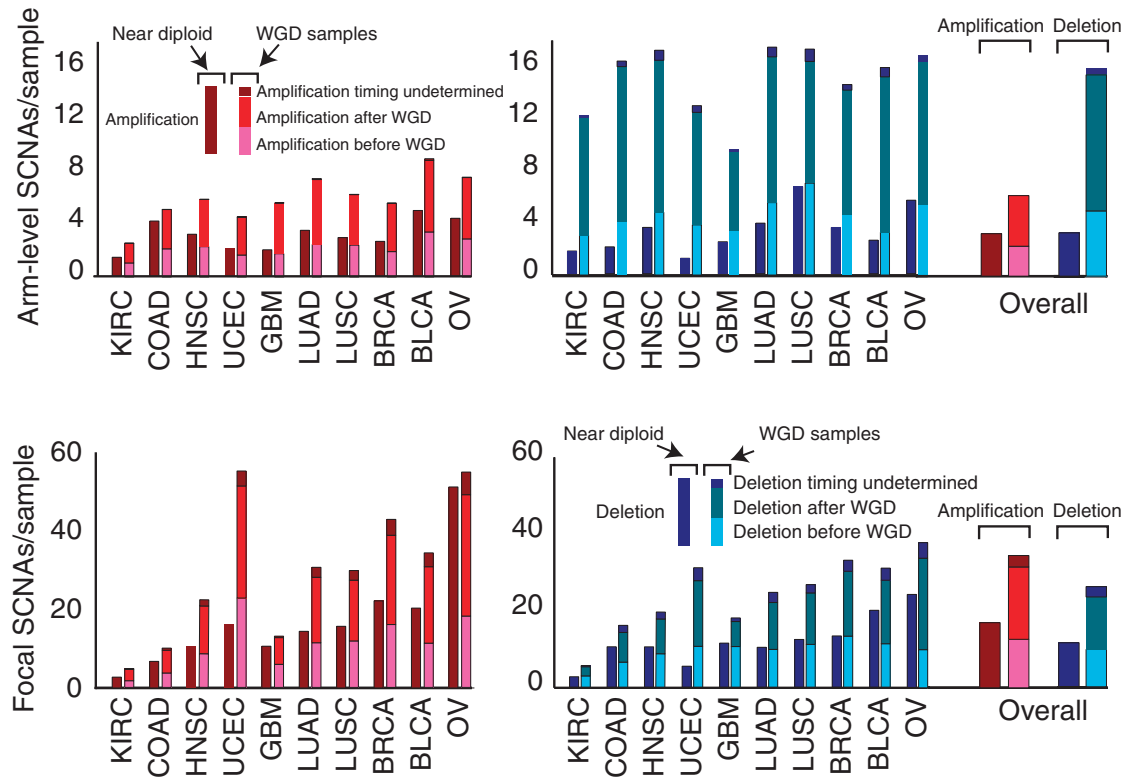
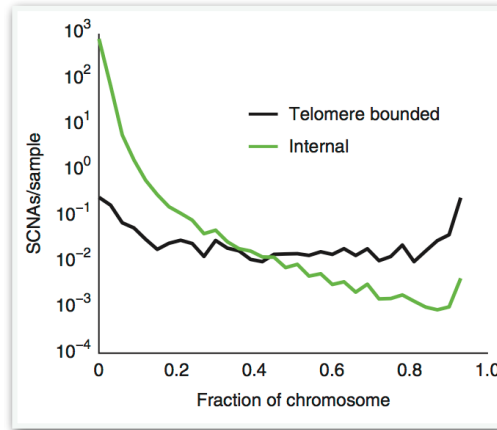
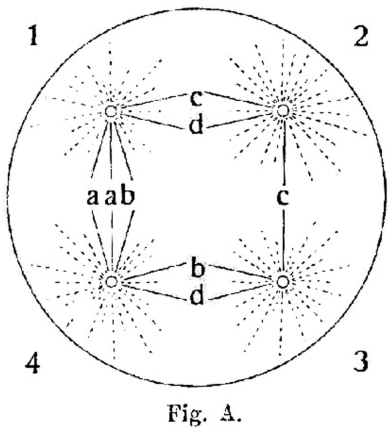
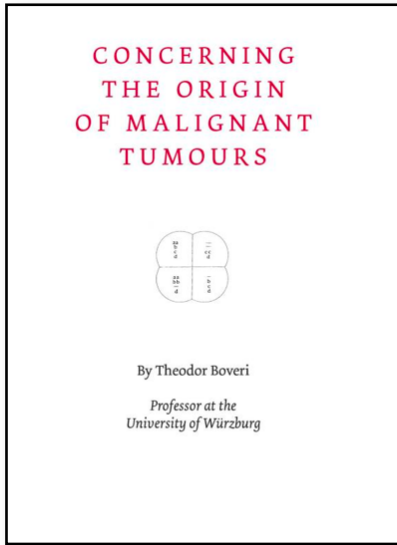
Cancer genomics

- Whole-genome sequences (cancer vs normal)
- Whole-exome sequences (cancer vs normal)

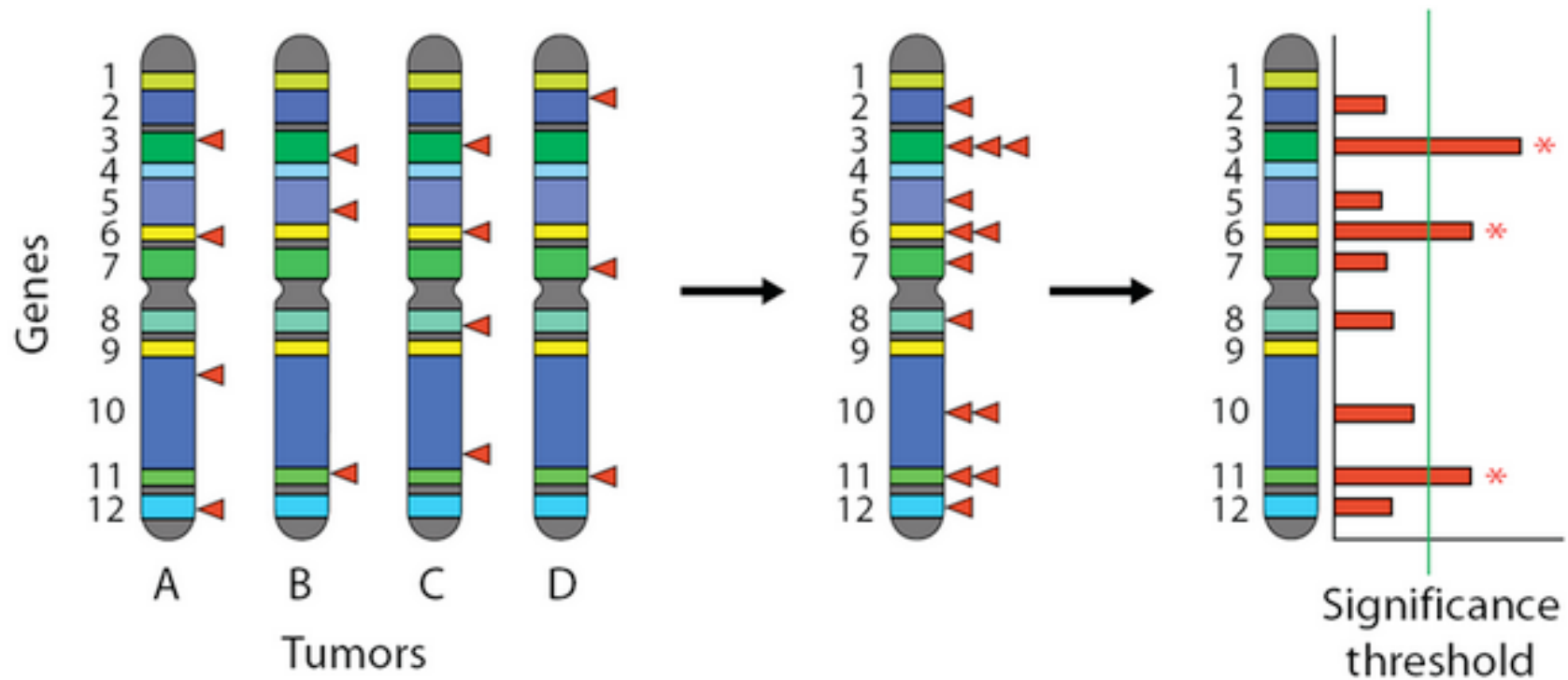
Chromosomal alterations



Somatic Copy Number Alterations (SCNAs)



Finding oncogenes and tumor suppressors



Deletions Amplifications

tumor suppressors and oncogenes



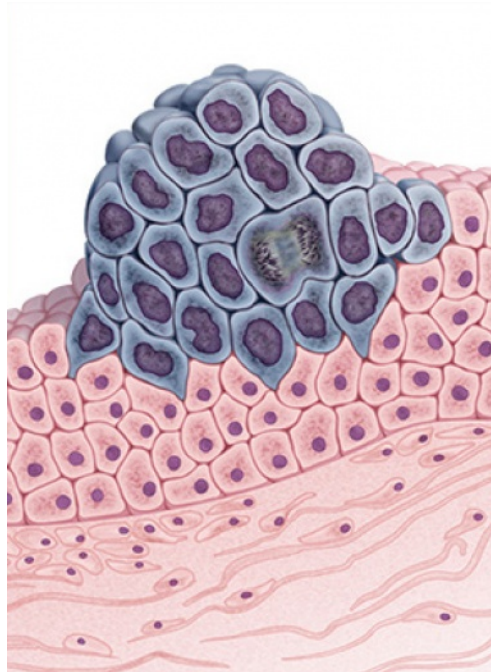
Cancer genomics

Finding new oncogene and tumor suppressors

Whole mutational landscape of cancer

Precision medicine:

mutations in each patient



Main points

1. Cancer is an evolutionary process
2. Cancer genomics allows to look under the hood of this process
3. Treating cancer using its own evolutionary mechanisms

Cancer genomics

100-400 amino acid substitutions

10-40 chromosomal alterations

2-5 **drivers**

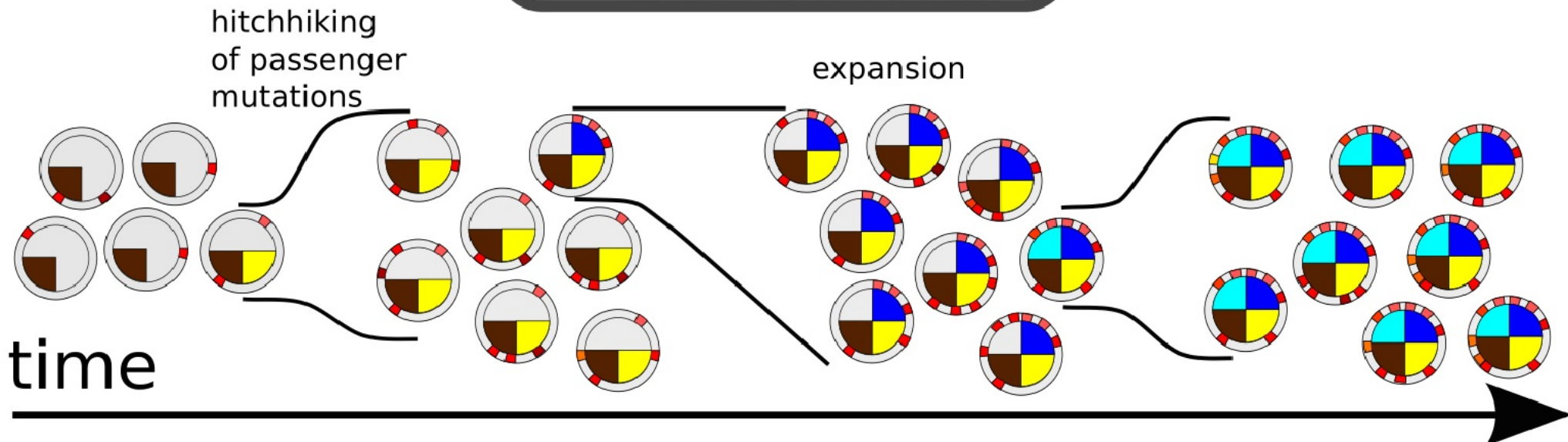
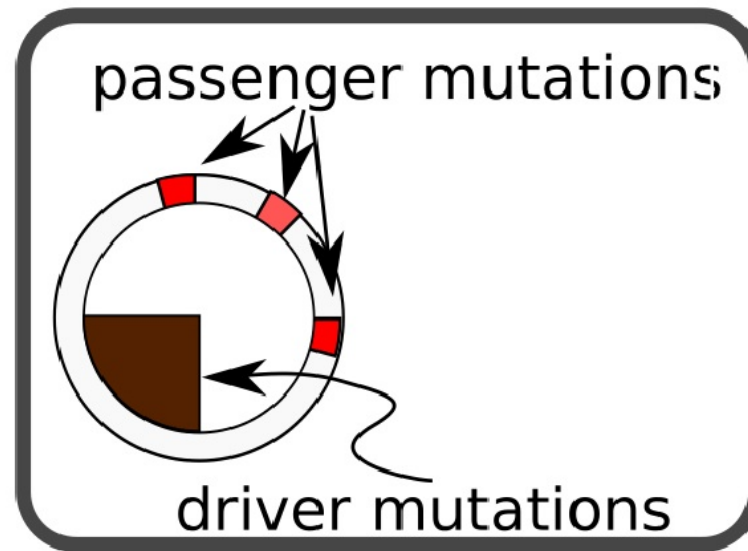
the rest are **passengers**

Can some **passengers**

... be deleterious to cancer cells?

... affect progression?

Passengers hitchhike of drivers



Passengers hitchhike to fixation

Theory

PNAS

Impact of deleterious passenger mutations on cancer progression

Christopher D. McFarland^a, Kirill S. Korolev^b, Gregory V. Kryukov^{c,d}, Shamil R. Sunyaev^{a,c,d}, and Leonid A. Mirny^{a,b,c,e,1}

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<https://www.pnas.org/content/110/8/2910>

PNAS

Tug-of-war between driver and passenger mutations in cancer and other adaptive processes

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Experiments

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Molecular and Cellular Pathobiology

Cancer
Research

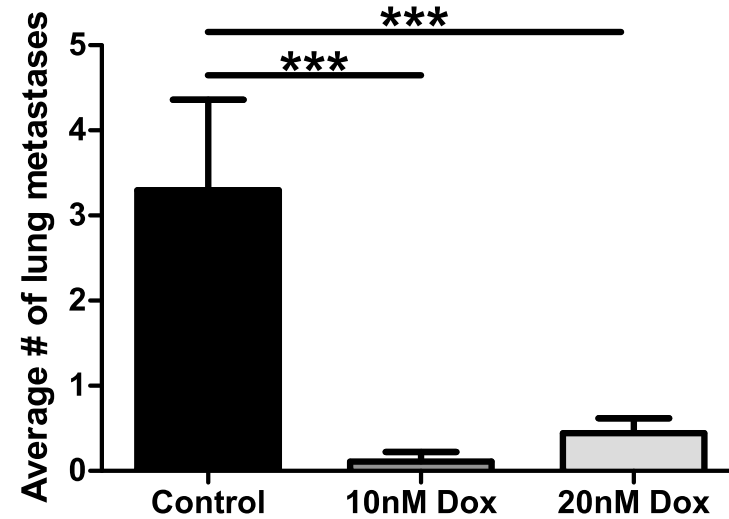
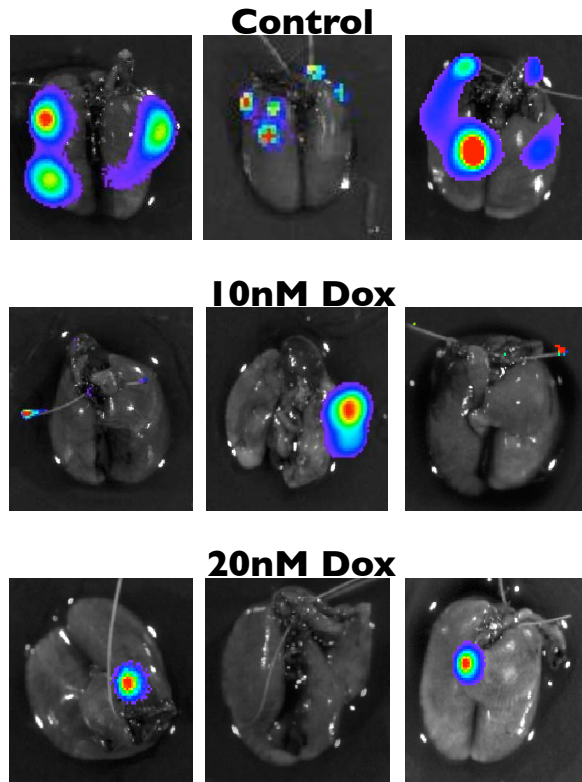
The Damaging Effect of Passenger Mutations on Cancer Progression

Christopher D. McFarland¹, Julia A. Yaglom², Jonathan W. Wojtkowiak³, Jacob G. Scott⁴, David L. Morse³, Michael Y. Sherman², and Leonid A. Mirny^{5,6}

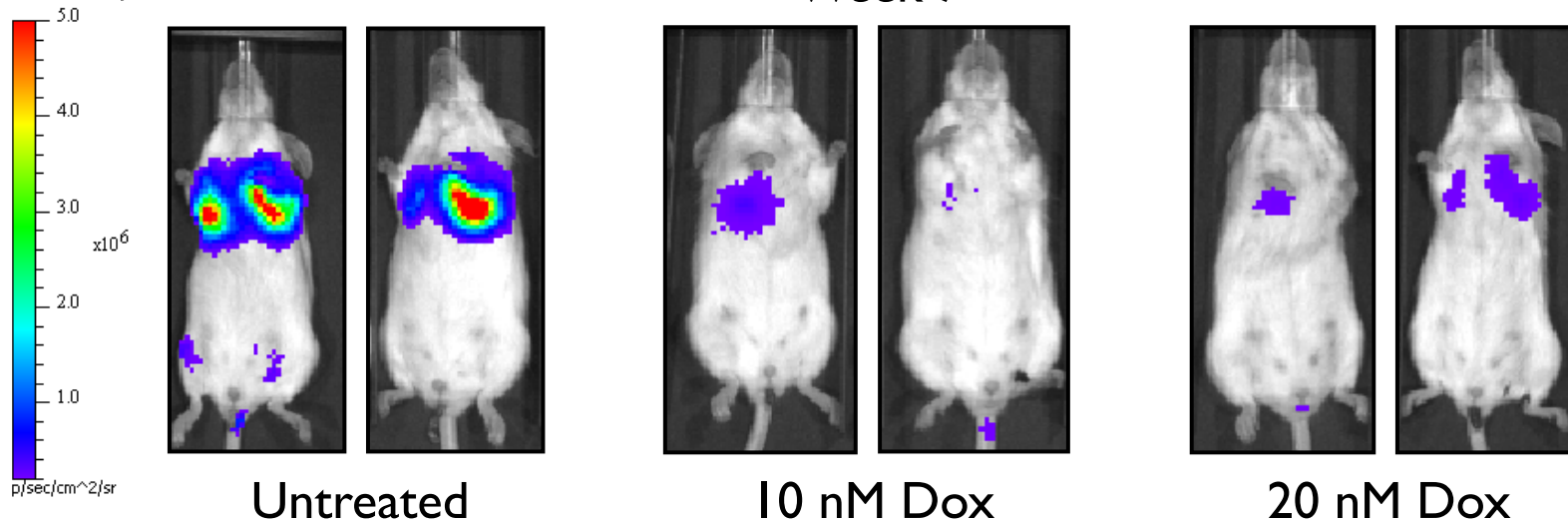


<https://cancerres.aacrjournals.org/content/77/18/4763.long>

Passanger load negatively correlates with metastasis



Week 7

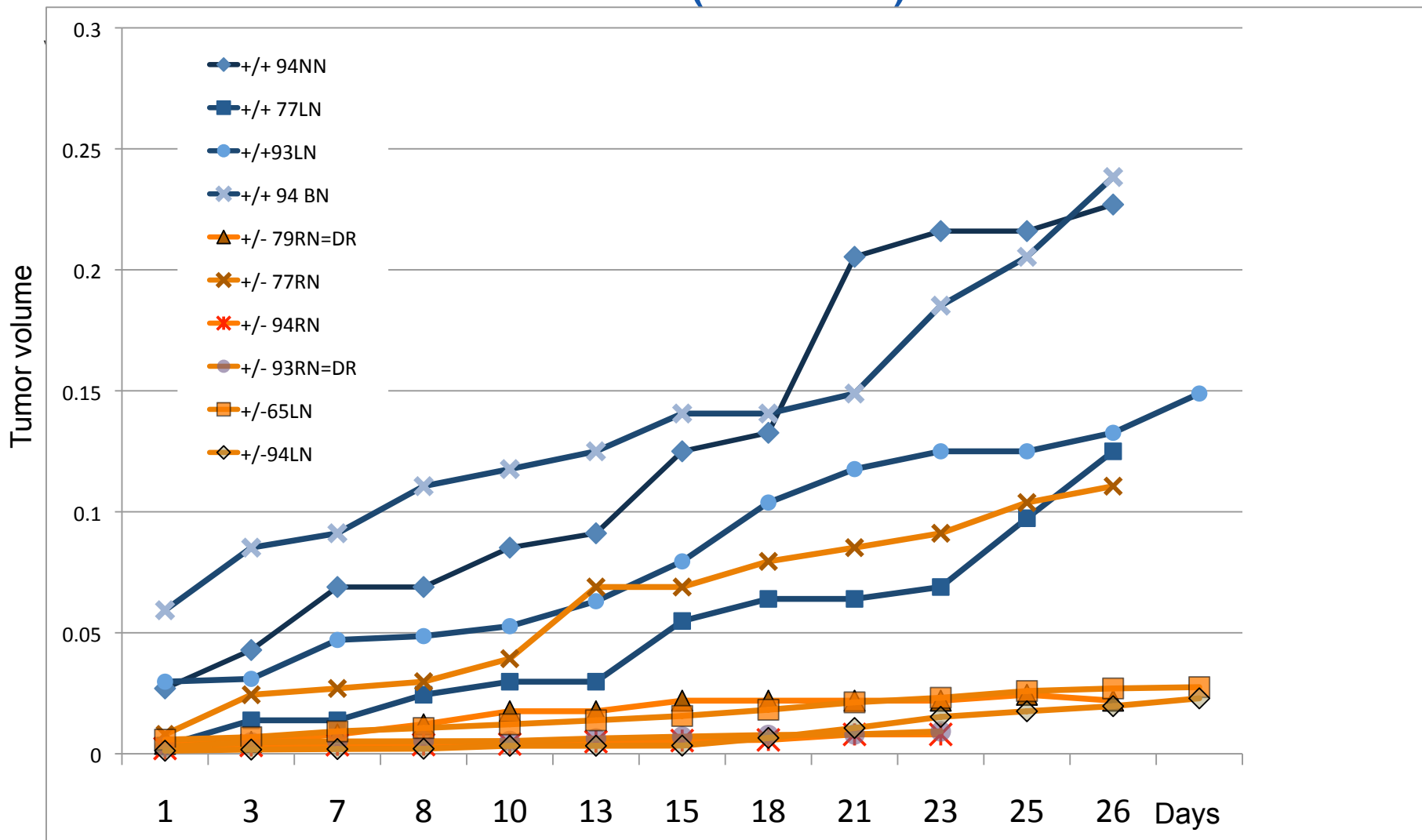


Passengers slowdown cancer

New Experiment: Her2+ breast cancer mouse model:

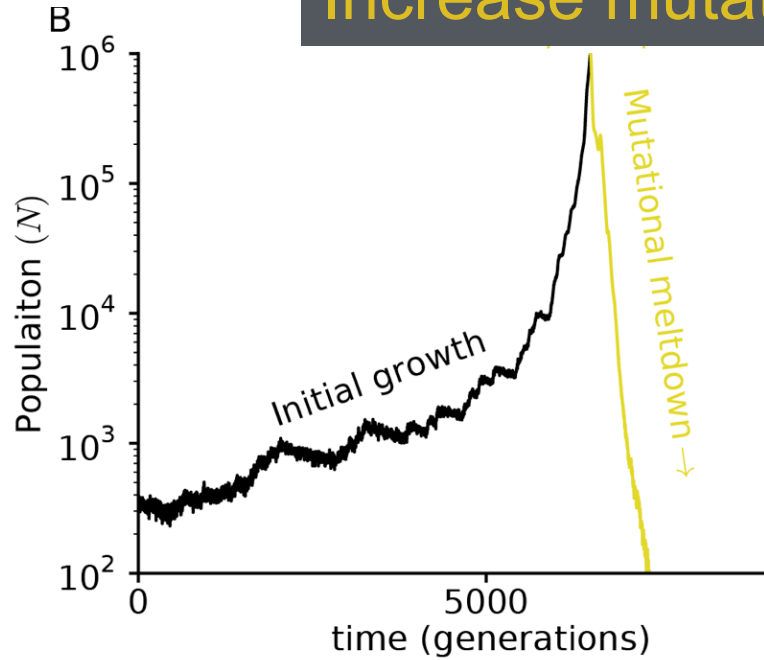
mildly elevated mutation rate (H2AX+/-)

normal mutation rate (control)

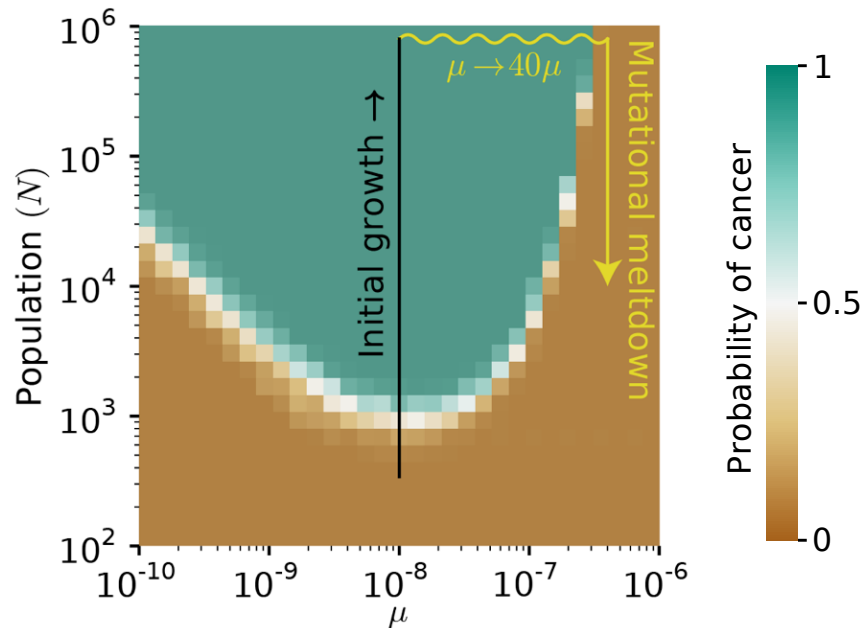


Passenger-based treatment

Increase mutation rate

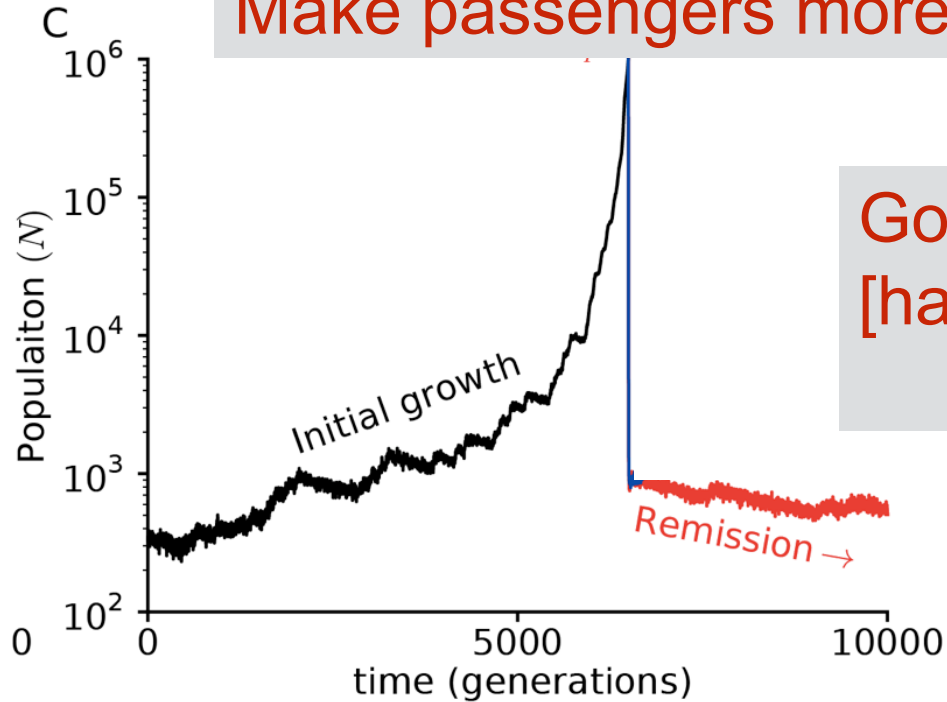


- Mutagenic chemo
- requires very high mutation rate
- likely relapse

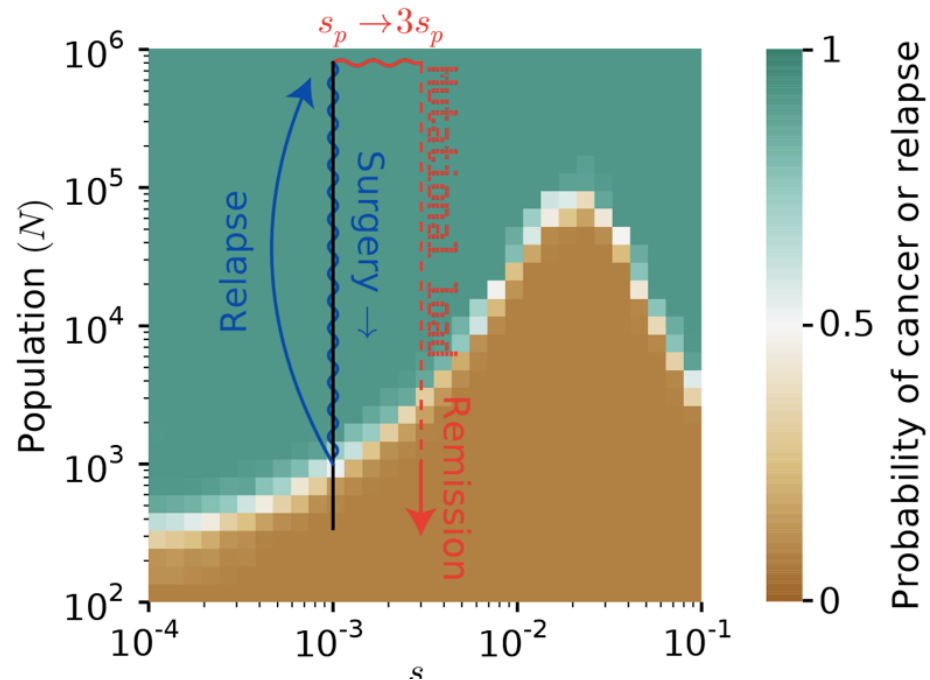


Passenger-based treatment

Make passengers more damaging



Going with evolution, not against it
[hackers lingo:
passenger load is an **exploit**]



Main points

1. Cancer is an evolutionary process
2. Cancer genomics allows to look under the hood of this process
3. Treating cancer using its own evolutionary mechanisms

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Metastatic potential



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Genomics

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