Overview of the core ideas in cancer research

Paul Edwards

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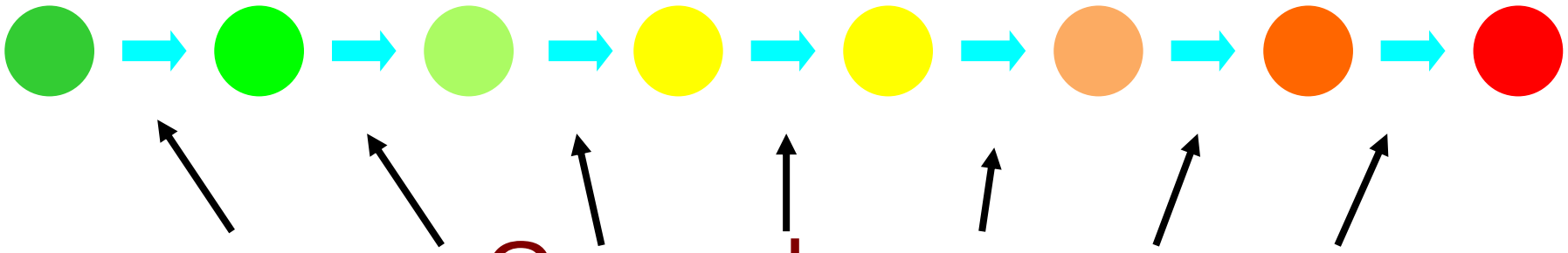
Cancer is caused by alteration of a cell's genes

Normal Cell → **Slightly Abnormal** → **More Abnormal** → **Malignant**

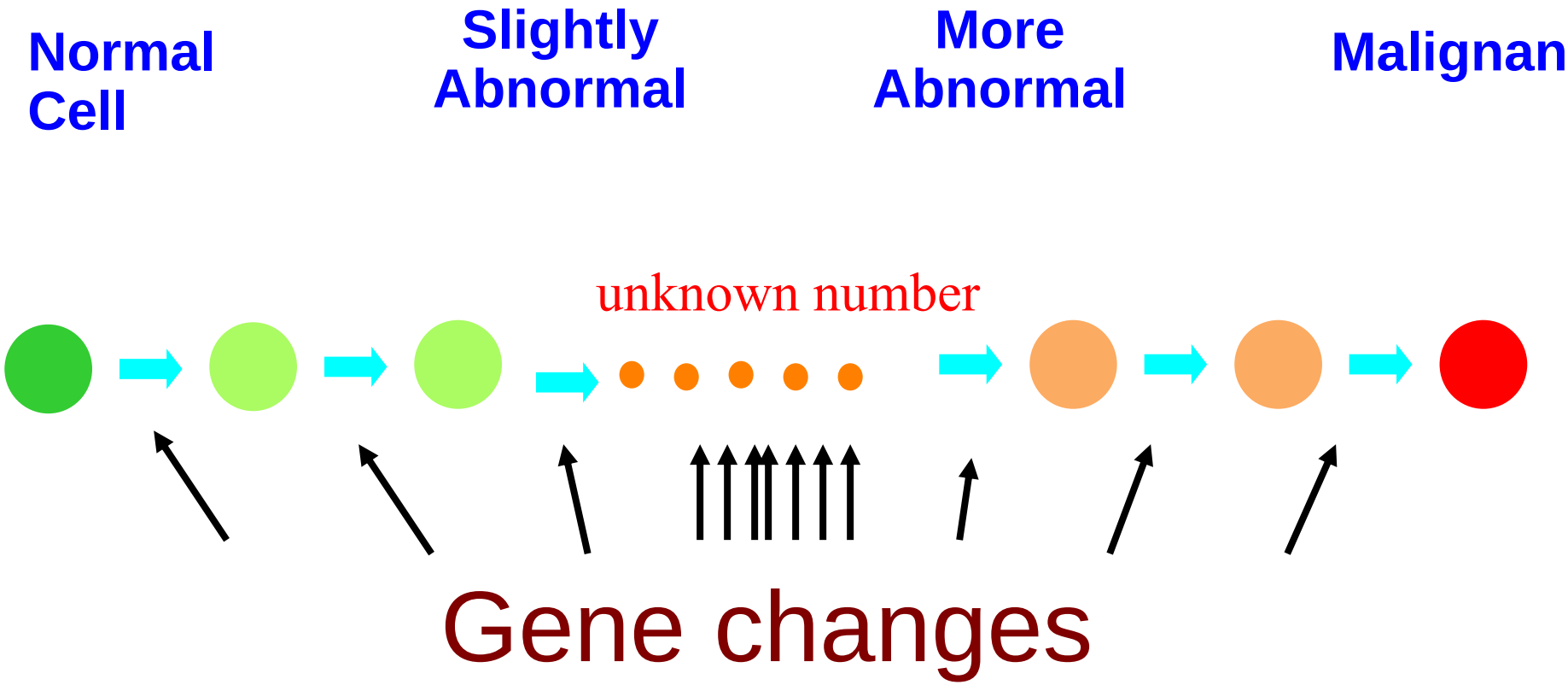


Gene changes

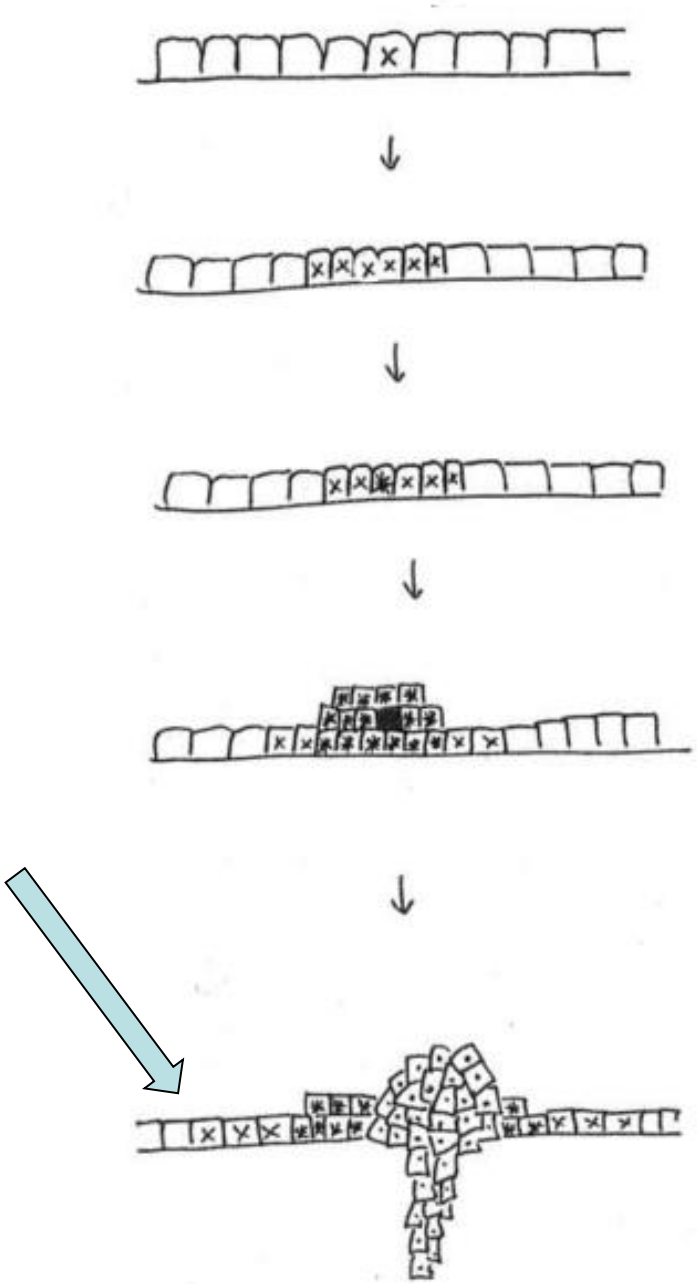
mutations (all kinds) + epigenetic change + viruses

+ mobile elements, etc

Cancer is caused by alteration of a cell's genes



Tumours develop by Clonal Evolution = Natural Selection



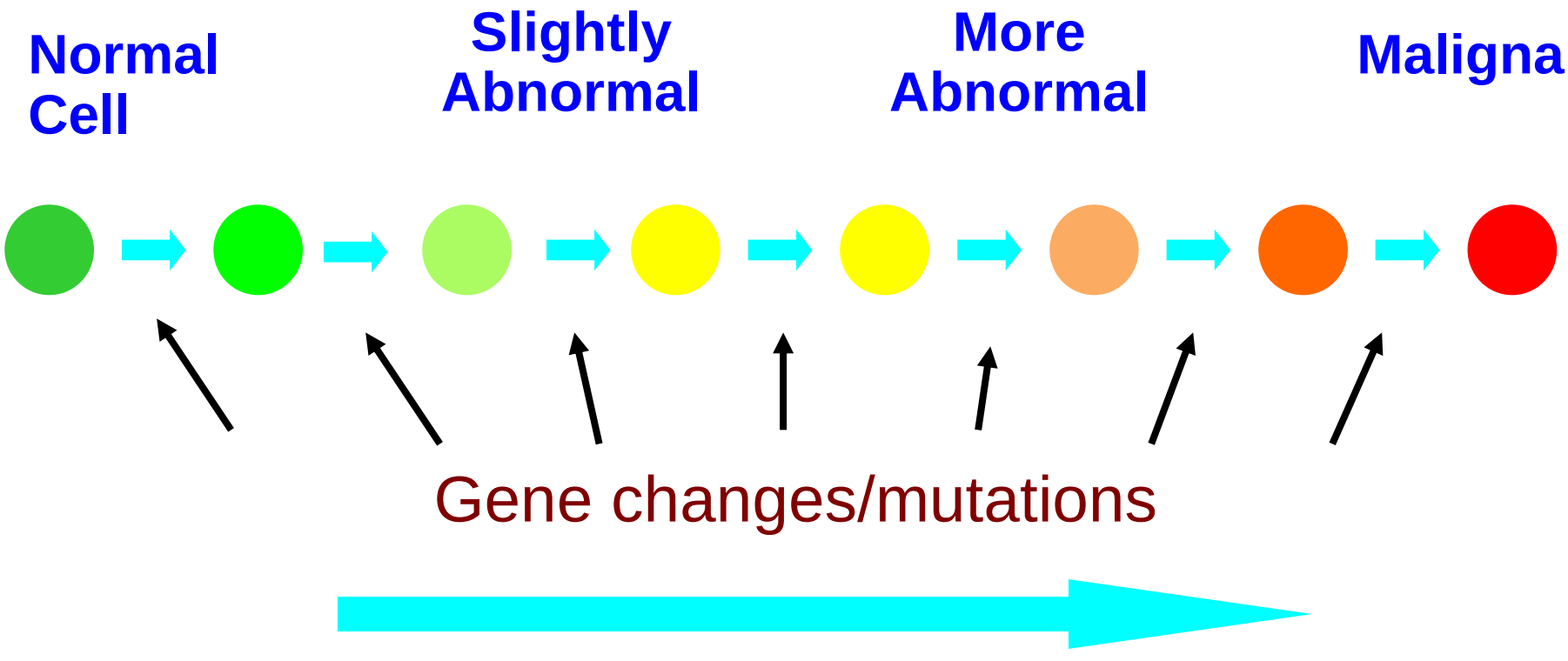
'progression'

Evidence that tumours are clonal is that cells have the same mutations

so tumours develop in stages by successive clonal expansions; mutation that leads to lack of expansion is unlikley to lead to further development; note that, in bulk, tumours will be a mix of clones, with the most recent/aggressive generally a minor clone

genetic instability

Development of a cancer



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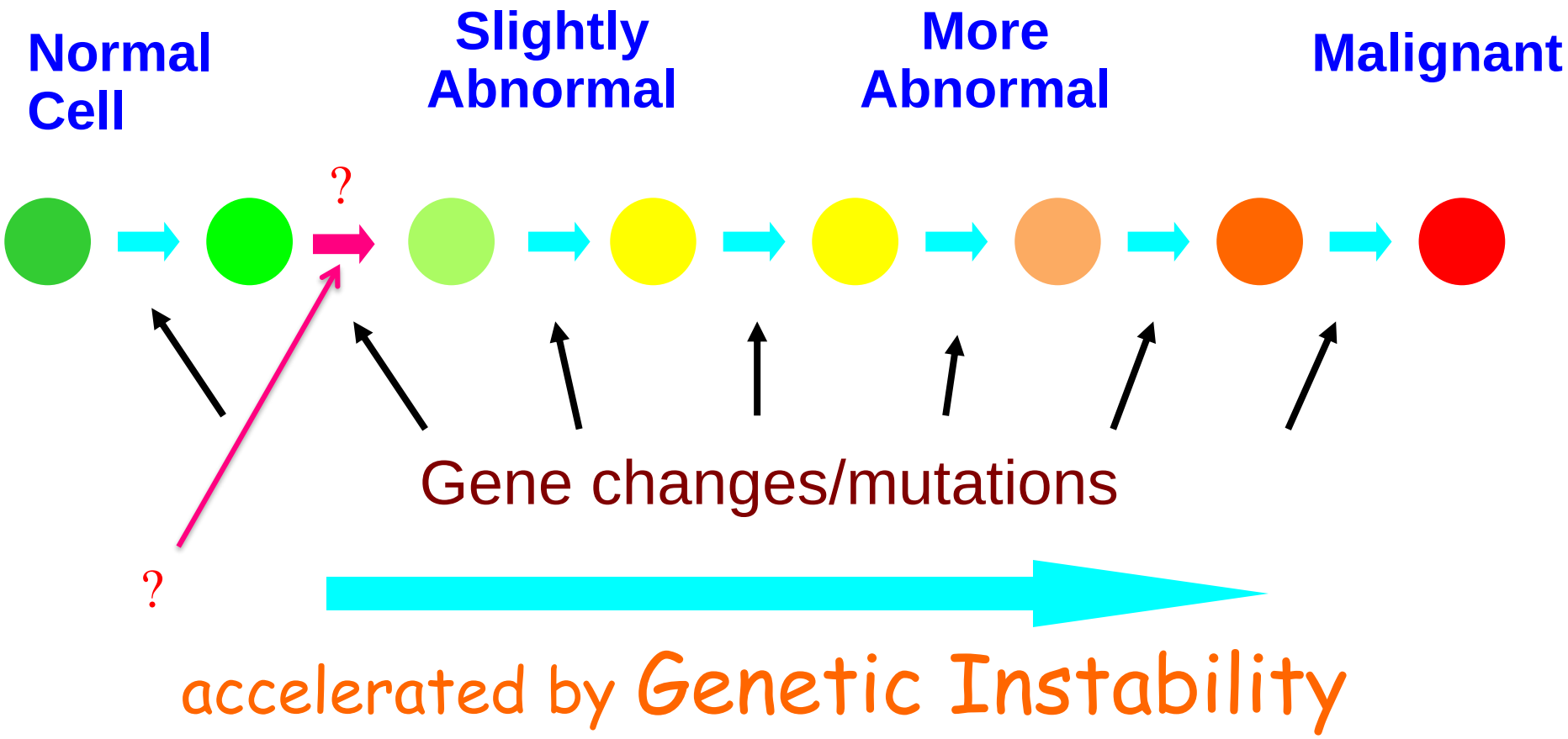


Human cancers are often Genetically Unstable

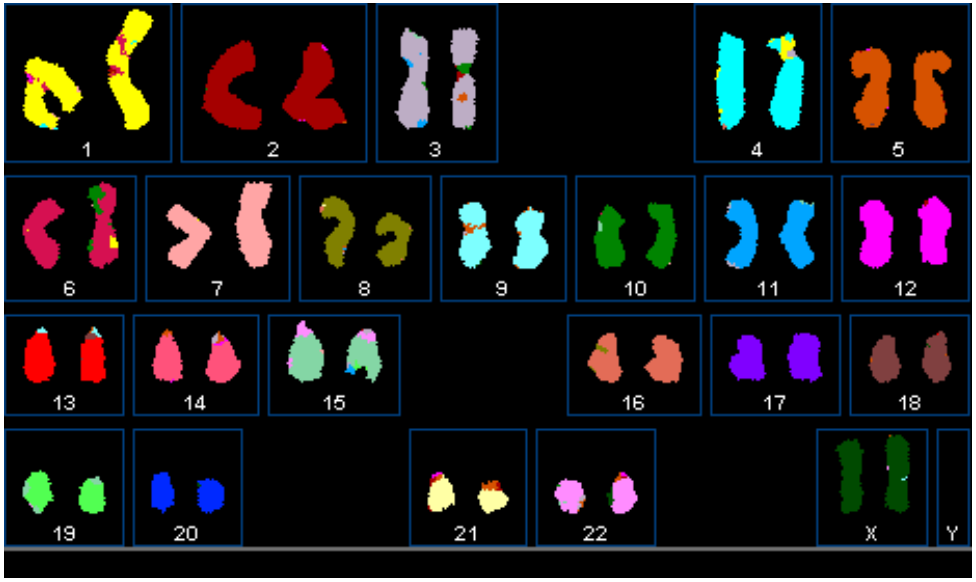
- Most human cancers seem to show genetic instability of some kind

- Not just a consequence of malignancy (e.g. rapid cell cycling) because:

different tumours have different instability

Genetic Instability is a Specific Abnormality

Tumour A

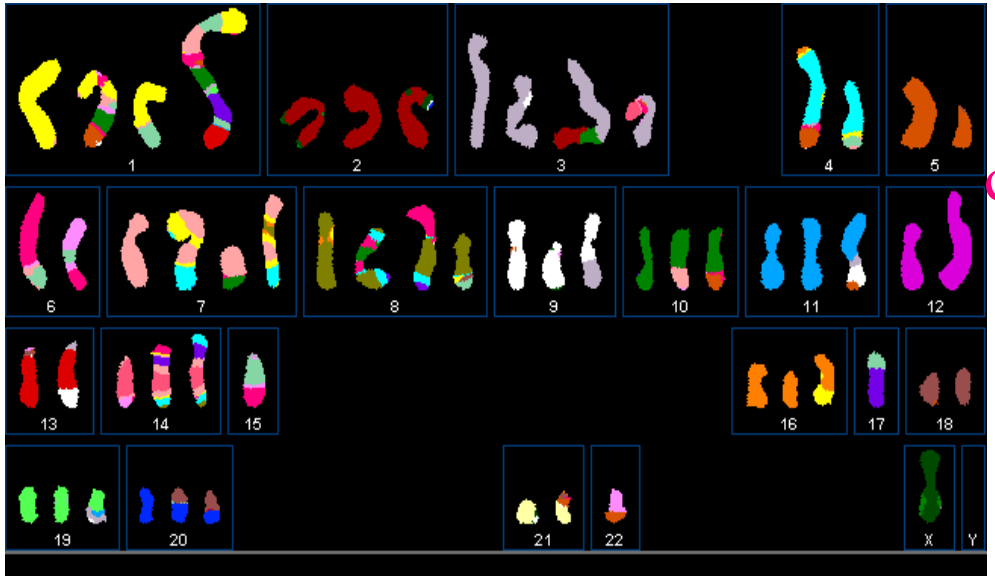


chromosomes stable

Sequence instability

100X rate single-base mutations

Tumour B



chromosome instability 'CIN'

Sequences stable

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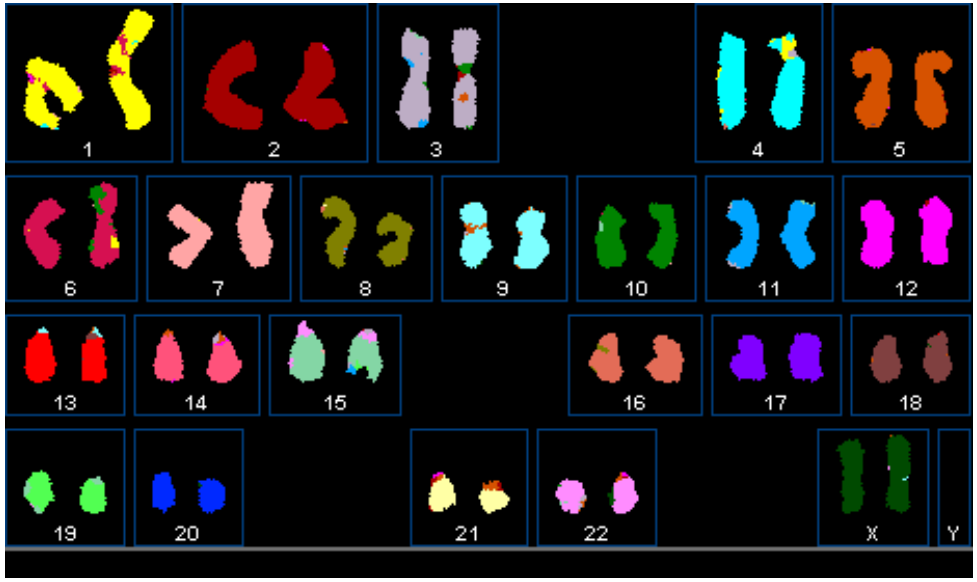
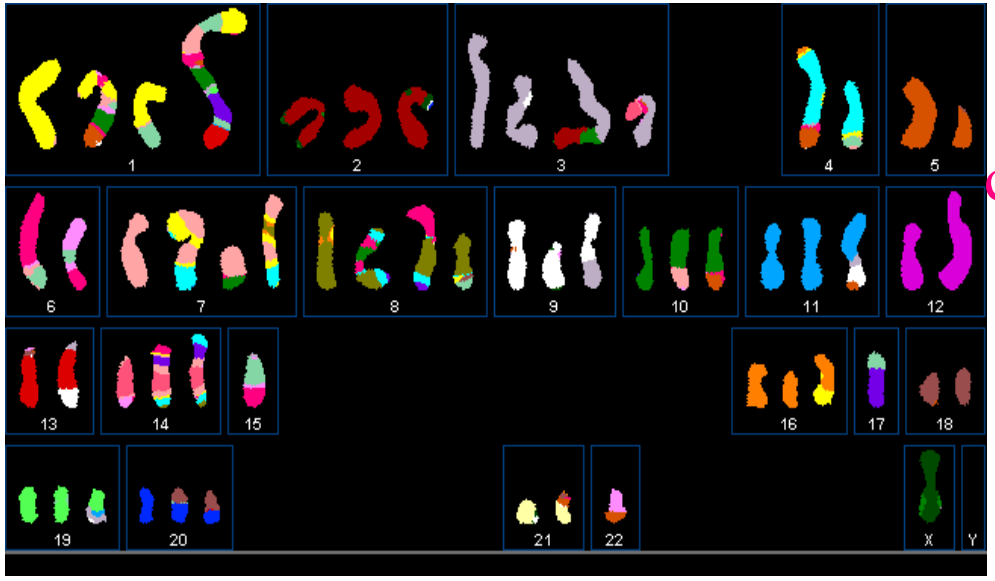


chromosomes stable

Sequence instability

e.g. Mutation in mismatch DNA repair

Tumour B



chromosome instability 'CIN'

Sequences stable

e.g. Mutation in strand break repair

Genetic Instability:

Basic proposition: Cancers arise in cells that are genetically unstable

Theoretical Argument (controversial): so many mutations are needed for cancer that they would rarely happen at normal mutation rate.

Safer version: in reality, most cancers arise from genetically unstable cells

Lots of different types/mechanisms

How could genetic instability come about?

	Sequence instability	chromosome instability
Failure to repair DNA damage	√	√
Errors in replication or mitosis	√	√

e.g. mismatch repair

~15% colon cancers have mutations in DNA mismatch repair

How could genetic instability come about?

	Sequence instability	**chromosome instability**
Failure to repair DNA damage	√	√
Errors in replication or mitosis	√	√

e.g. mismatch repair

e.g. BRCA1, BRCA2

How could genetic instability come about?

perhaps:

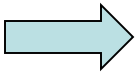
	Sequence instability	chromosome instability
Failure to repair DNA damage	√	√
Errors in replication or mitosis	√	√

e.g. mismatch repair

e.g. BRCA1, BRCA2

e.g. polymerase mutant

some colon cancers have mutations in DNA polymerase epsilon



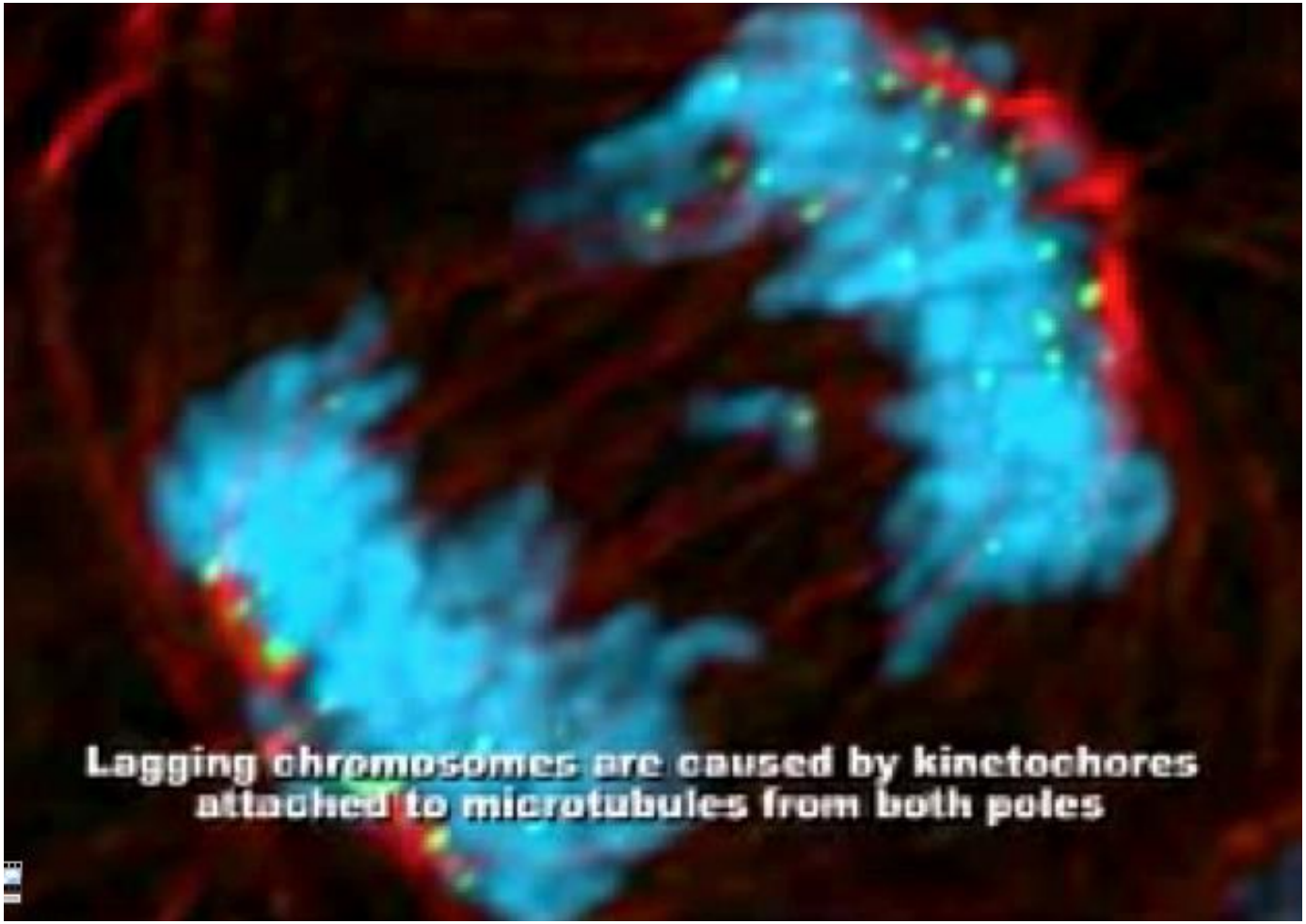
very high point mutation rate

How could genetic instability come about?

	Sequence instability		chromosome instability	
Failure to repair DNA damage	√	e.g. mismatch repair	√	e.g. BRCA1, BRCA2
Errors in replication or mitosis	√	e.g. polymerase mutant	√	e.g. lagging chromosomes

Errors in mitosis:Abnormal mitosis End

Movie by Duane Compton and Sarah Thompson, Dartmouth USA



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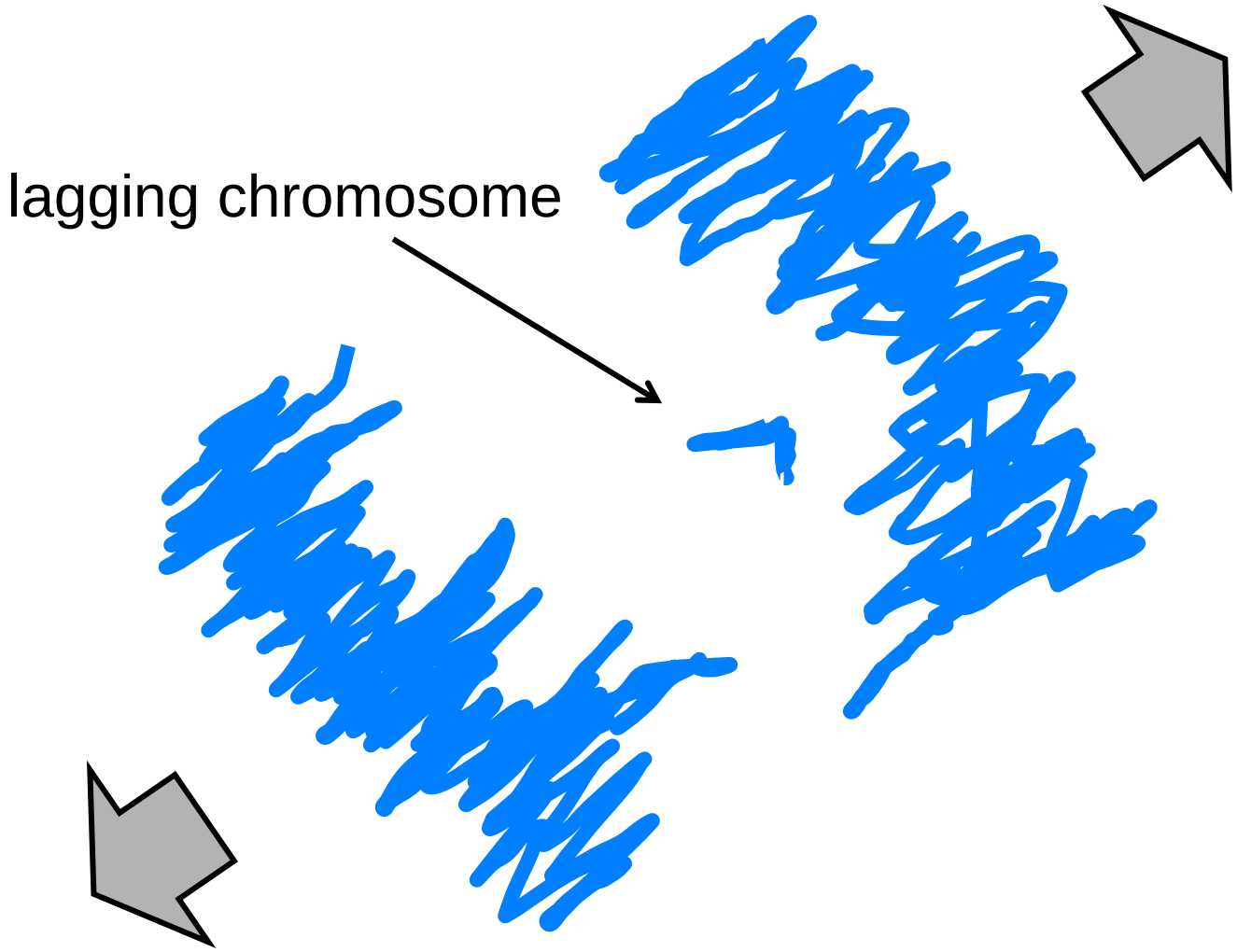
Error in mitosis: Lagging chromosome



There are many kinds of genetic instability

perhaps:

For most human cancers we don't yet know what their genetic instability is

Failure to repair DNA damage	√	e.g. mismatch repair	√	e.g. BRCA1, BRCA2
Errors in replicati mitosis		epsilon mutant		ging chromosomes

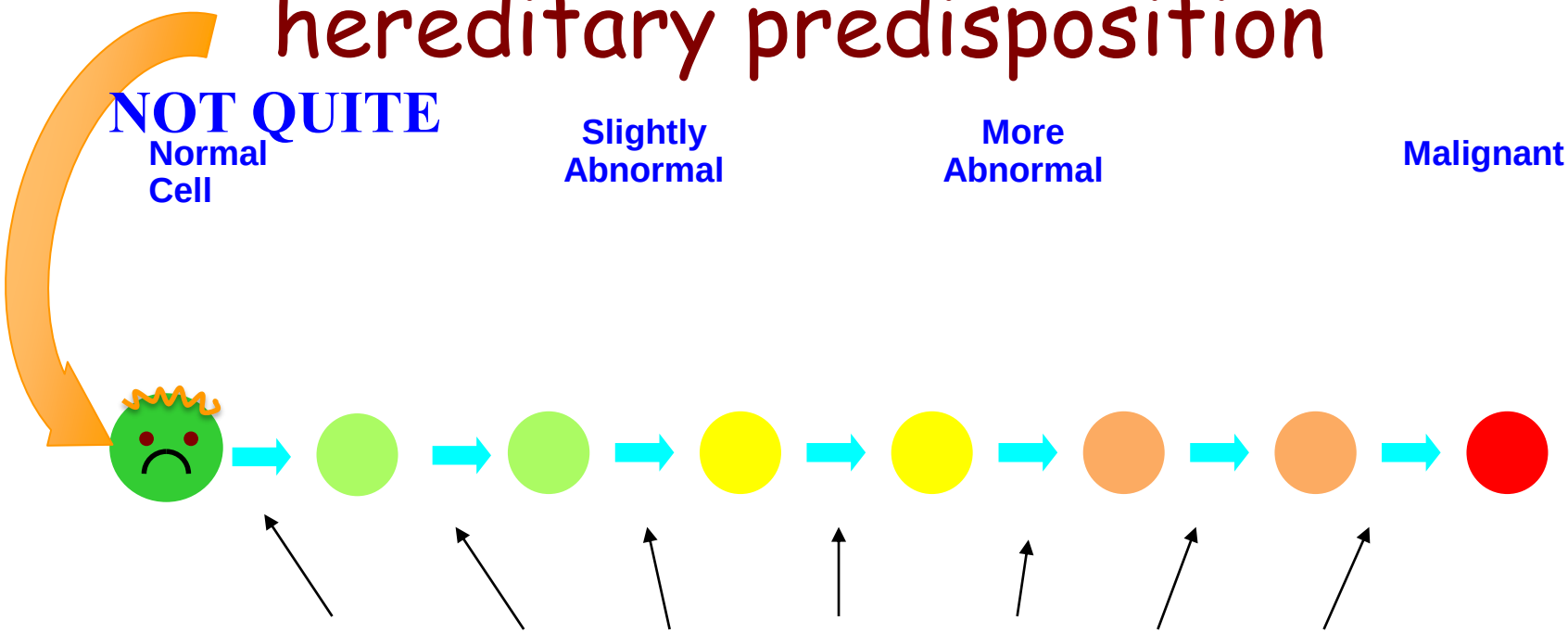
target for therapy!

.....and there is probably ***Epi***genetic instability as well !

.....and activation of mobile elements

hereditary predisposition

hereditary predisposition



- either growth control or genetic instability

- v. important genetic diseases

hereditary predisposition examples

	gene
Retinoblastoma	Rb1
Polyposis coli (colon)	APC
Lynch syndrome (mostly colon)	MLH1 (mismatch repair)
Breast	BRCA2

growth control

genetic instability (DNA repair)

What do gene changes do to cells ?

not just control of cell proliferation

Malignant cells have acquired a number of properties

- The 'Hallmarks of Cancer'

(Hanahan & Weinberg, 2000, revised 2011)

Abnormal proliferation and survival control:

- **Independence of positive growth signals**
- **Resistance to negative signals**
- **Resistance to Apoptosis, cycle arrest**
- **Abnormal (often blocked) Differentiation**
- **Immortality/resistance to stress arrest**

Genetic Instability
Metastasis ?
Angiogenesis ?
Metabolic changes?
Immune response?

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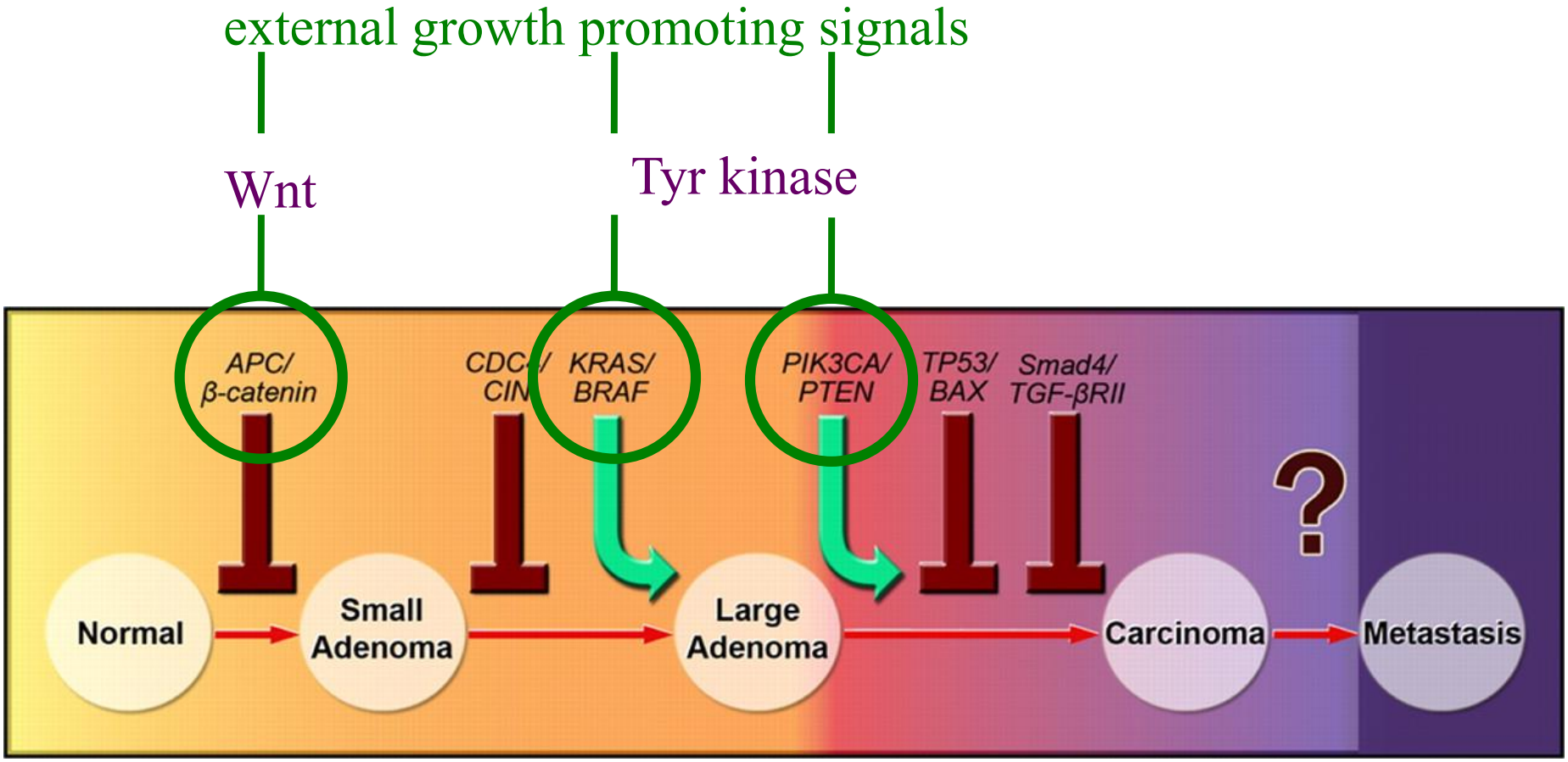
Vogelstein's model of colon cancer (2008 version)



Jones S et al. Proc Natl Acad Sci USA. 2008

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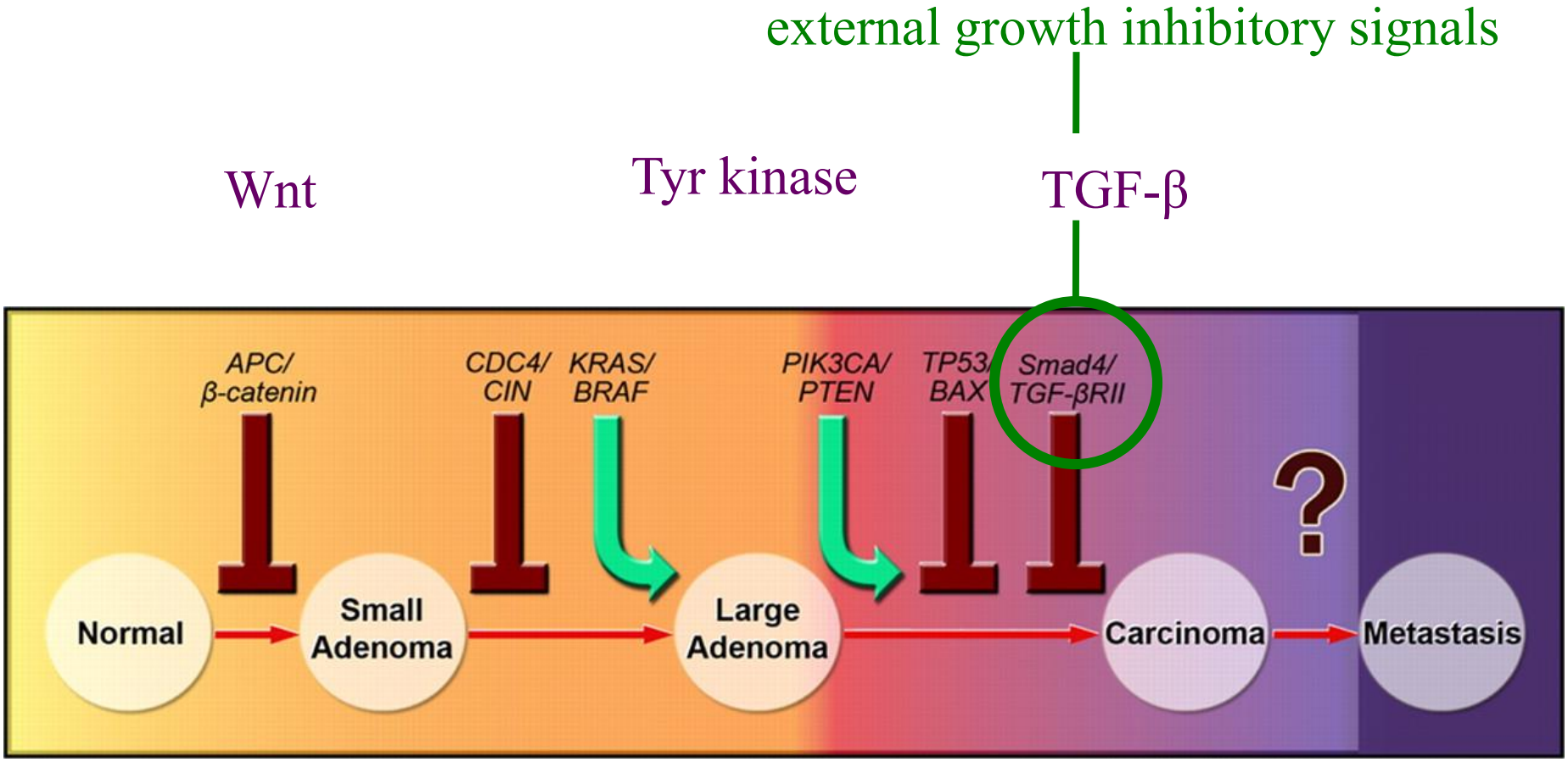

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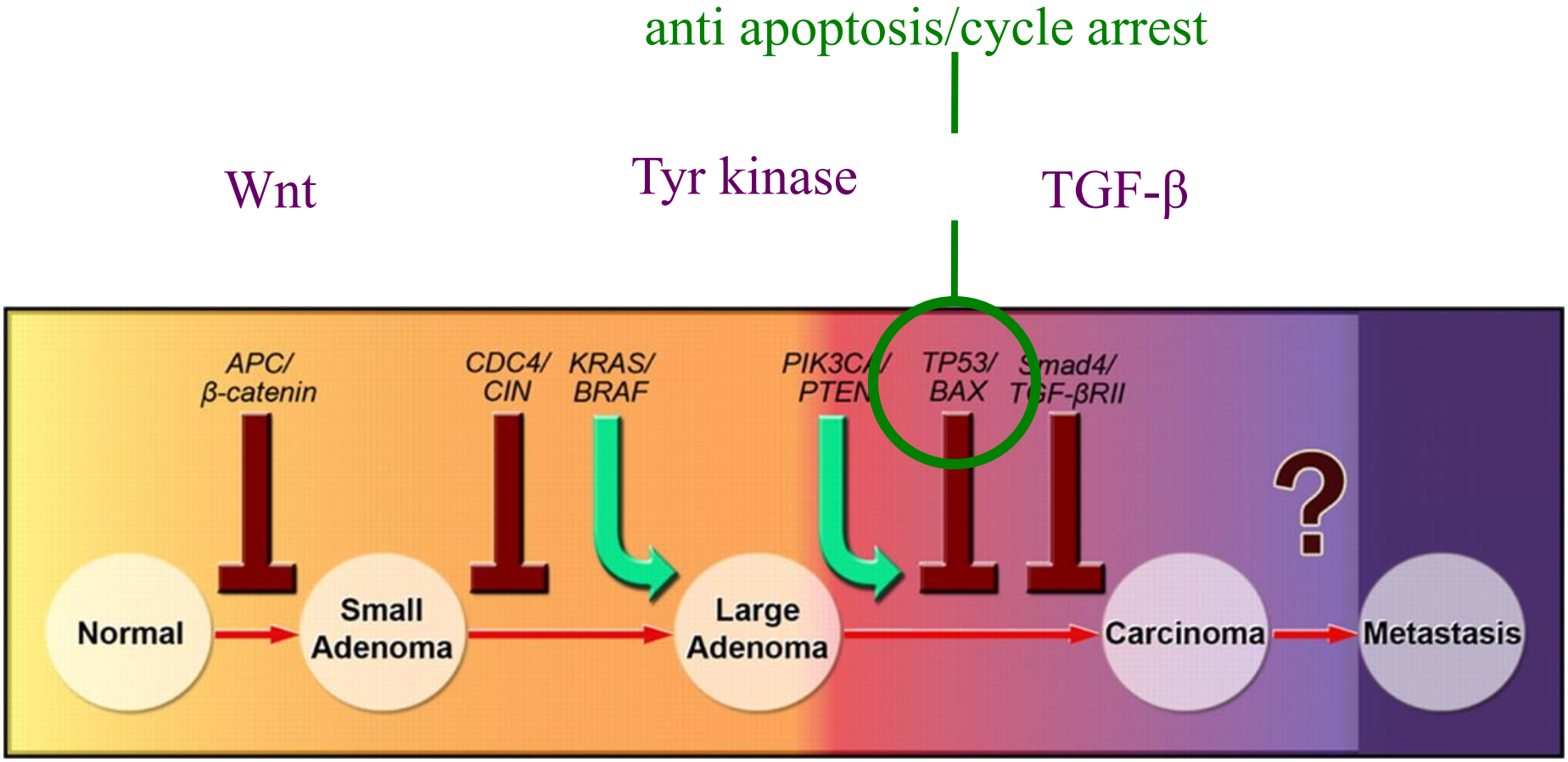

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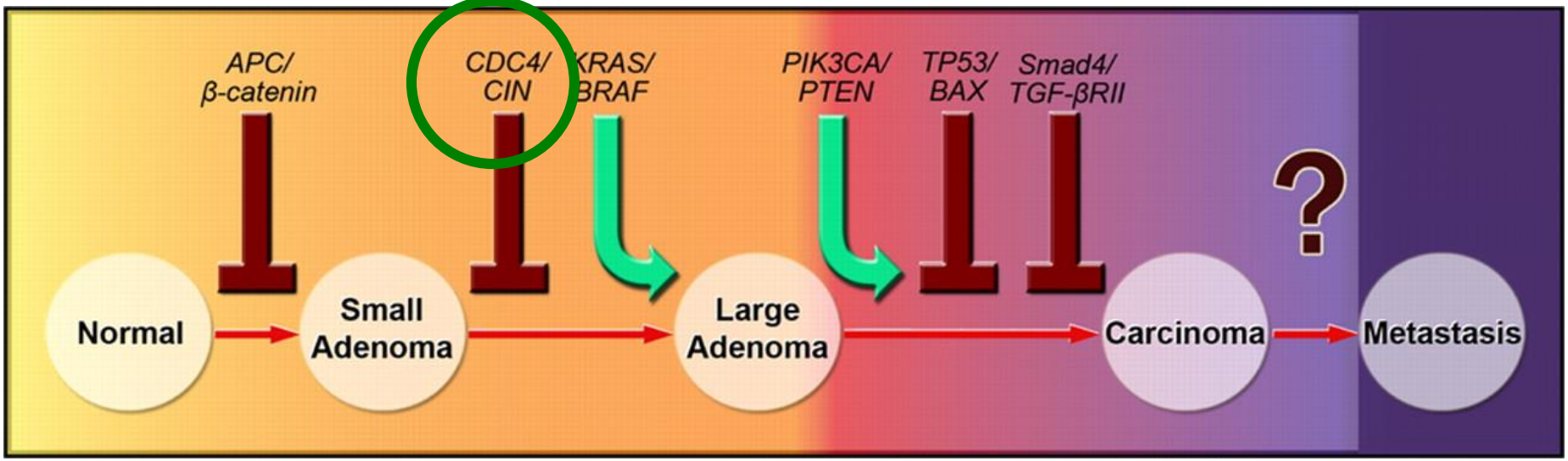
genetic instability

Wnt

Tyr kinase

TGF-β



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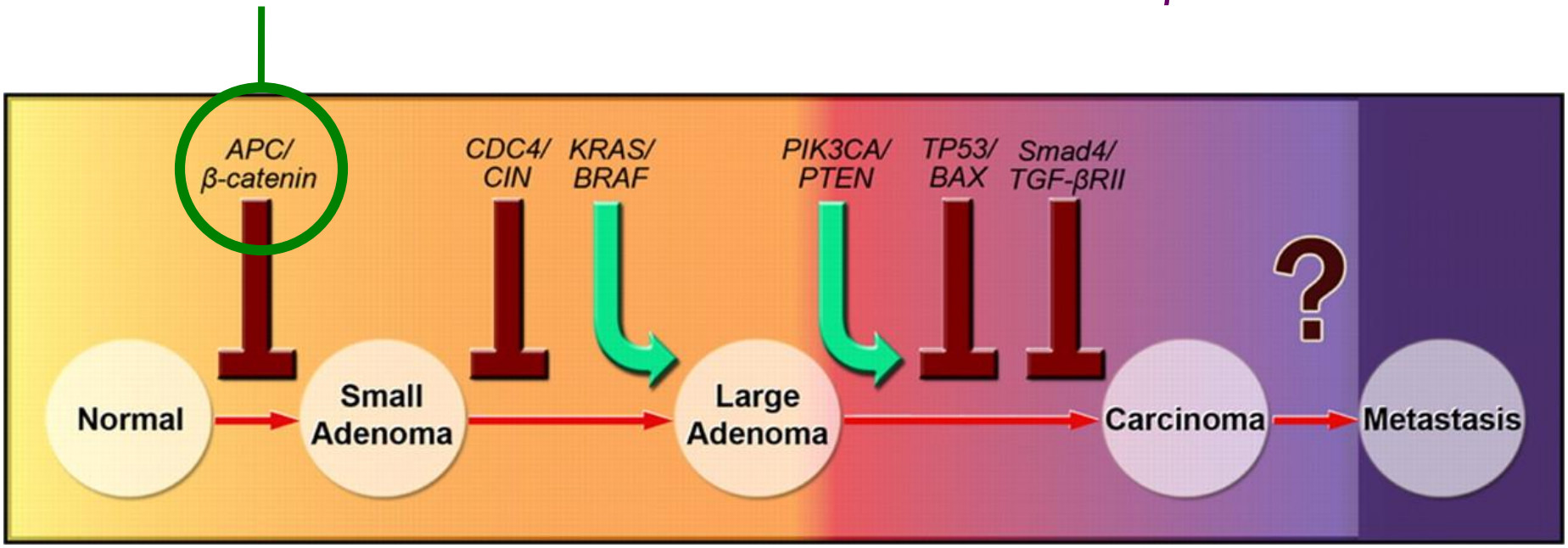
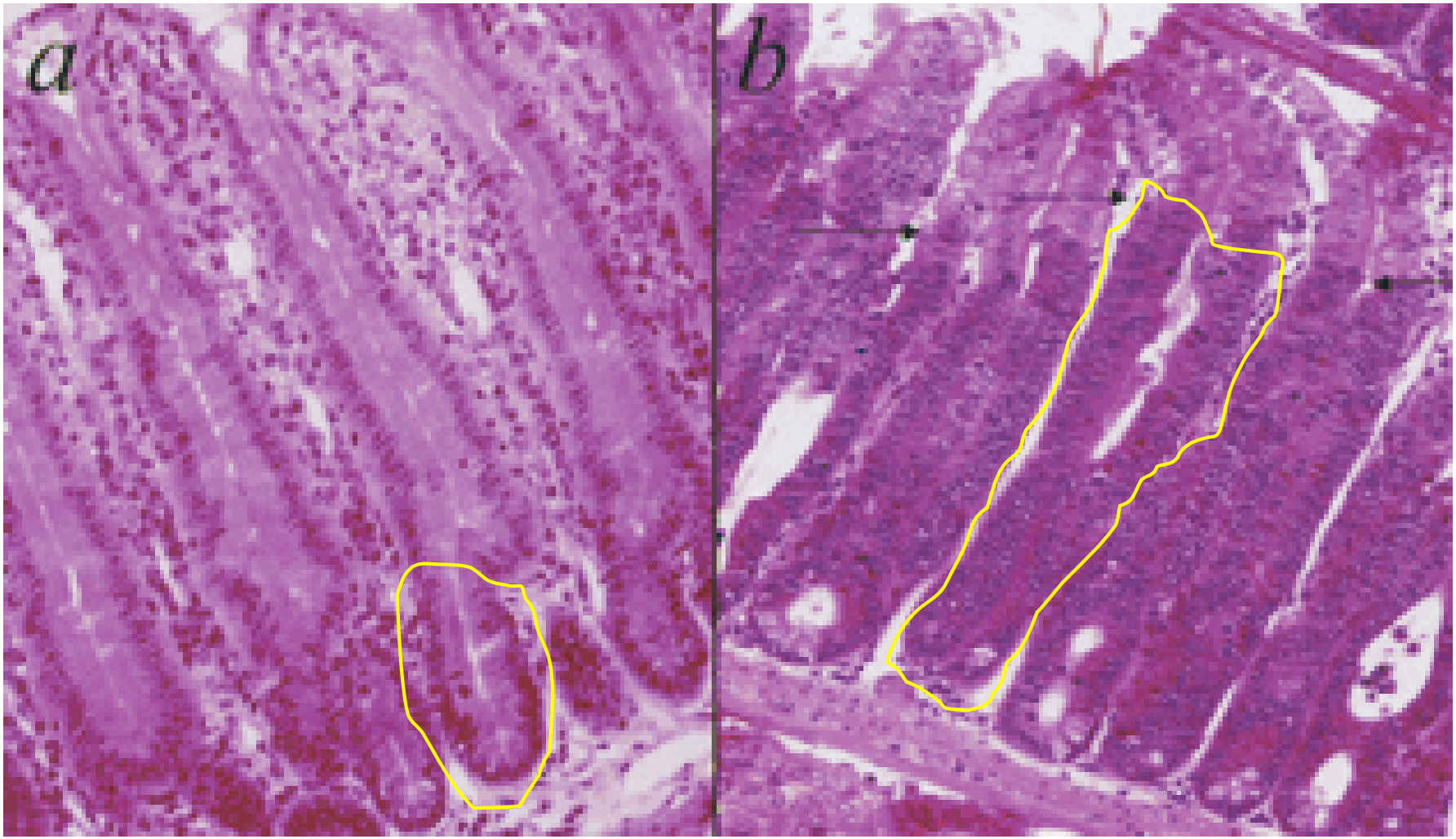


Deleting the APC gene in colon

Wild-type

APC deleted



Crypt region

Crypt region has expanded

Sansom, O.J. et al., 2004. Genes & development

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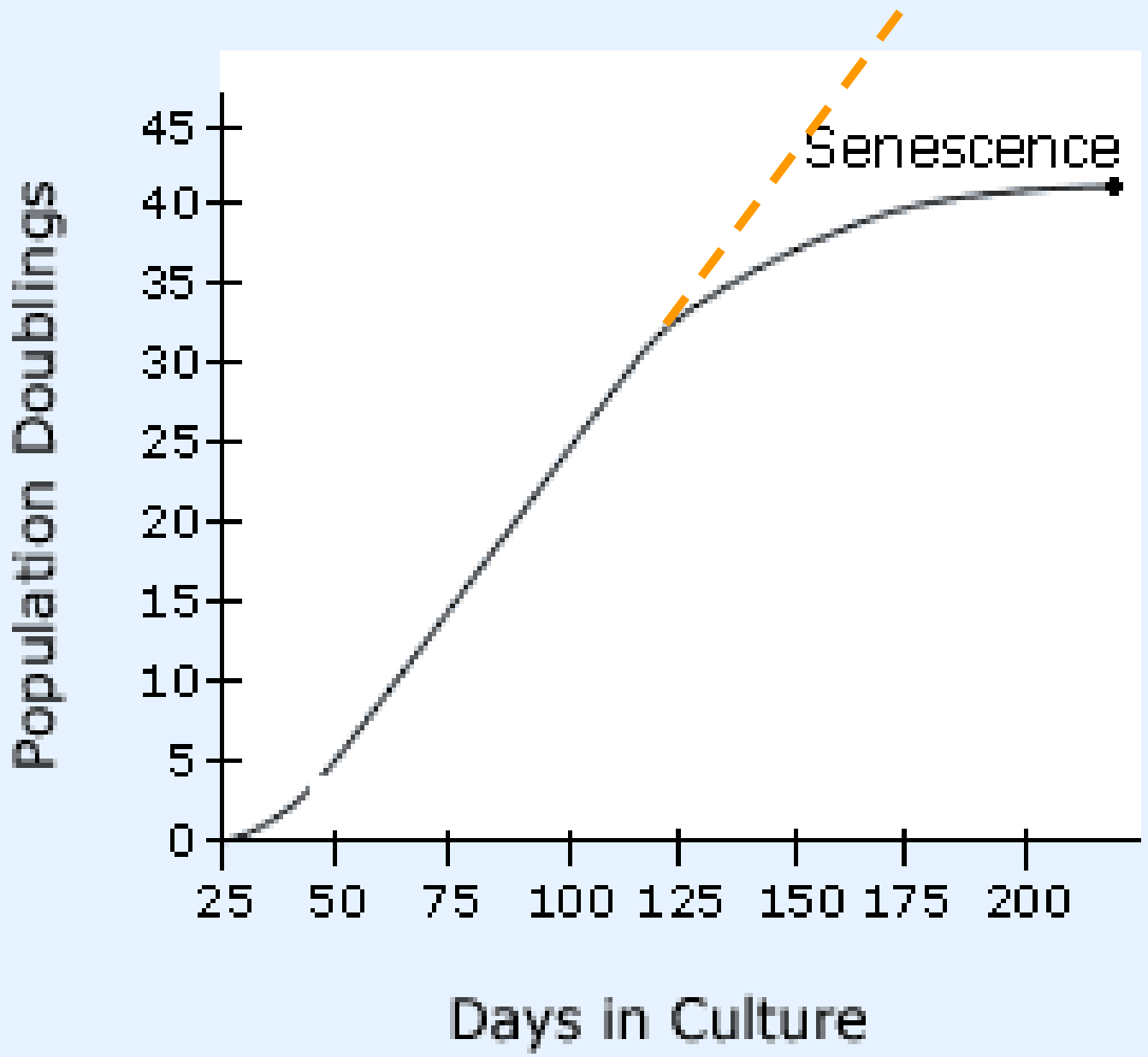
The Hayflick Limit: 'Senescence'



Immortality, Telomeres & Senescence

Senescence: Cells in culture cycle arrest after a set number of divisions.

Immortalisation: certain cancer mutations can take cells through this block –

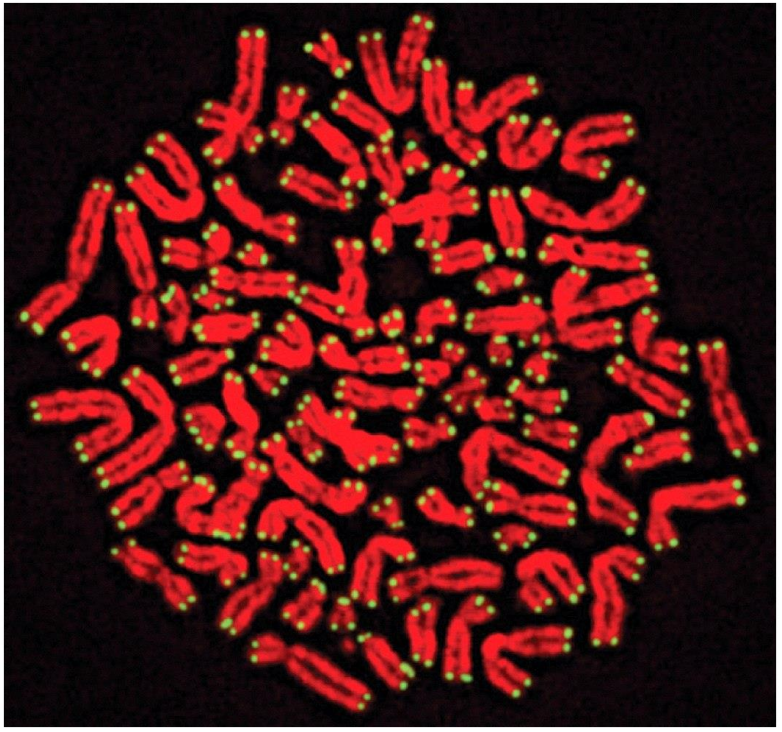
Cancer cells are 'immortalised'

Divisons are measured by telomeres:

Telomeres shorten at DNA replication

short telomeres -> senescence.

Expression of telomerase-> immortality



Immortality, Telomeres & Senescence

Senescence: Cells in culture cycle arrest after a number of divisions.

Senescence is now recognised as a stress response

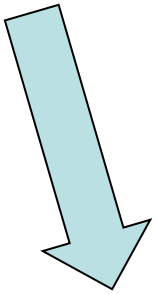
Immortalisation: certain cancer mutations can take cells through this block - 'immortalise' the cells

-> Cancer cells thought to be 'immortalised'

Proposed that telomere shortening at DNA replication measures cell cycles and controls senescence. Expression of telomerase-> immortality

Senescence

Telomere shortening



‘sensescence’ phenotype

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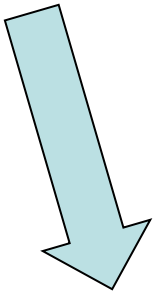
Telomere shortening



‘sensescence’ phenotype

Senescence is now recognised as a stress response

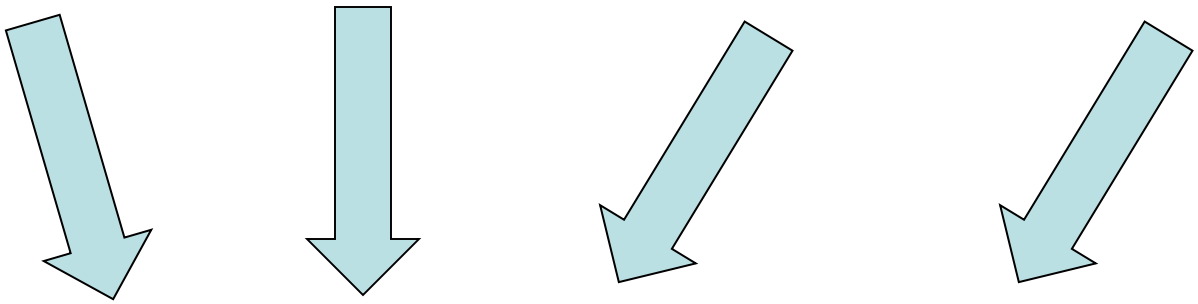
Stresses

Telomere shortening

DNA damage

Abnormal signalling

etc.



‘sensescence’ phenotype = ‘stressed’ phenotype

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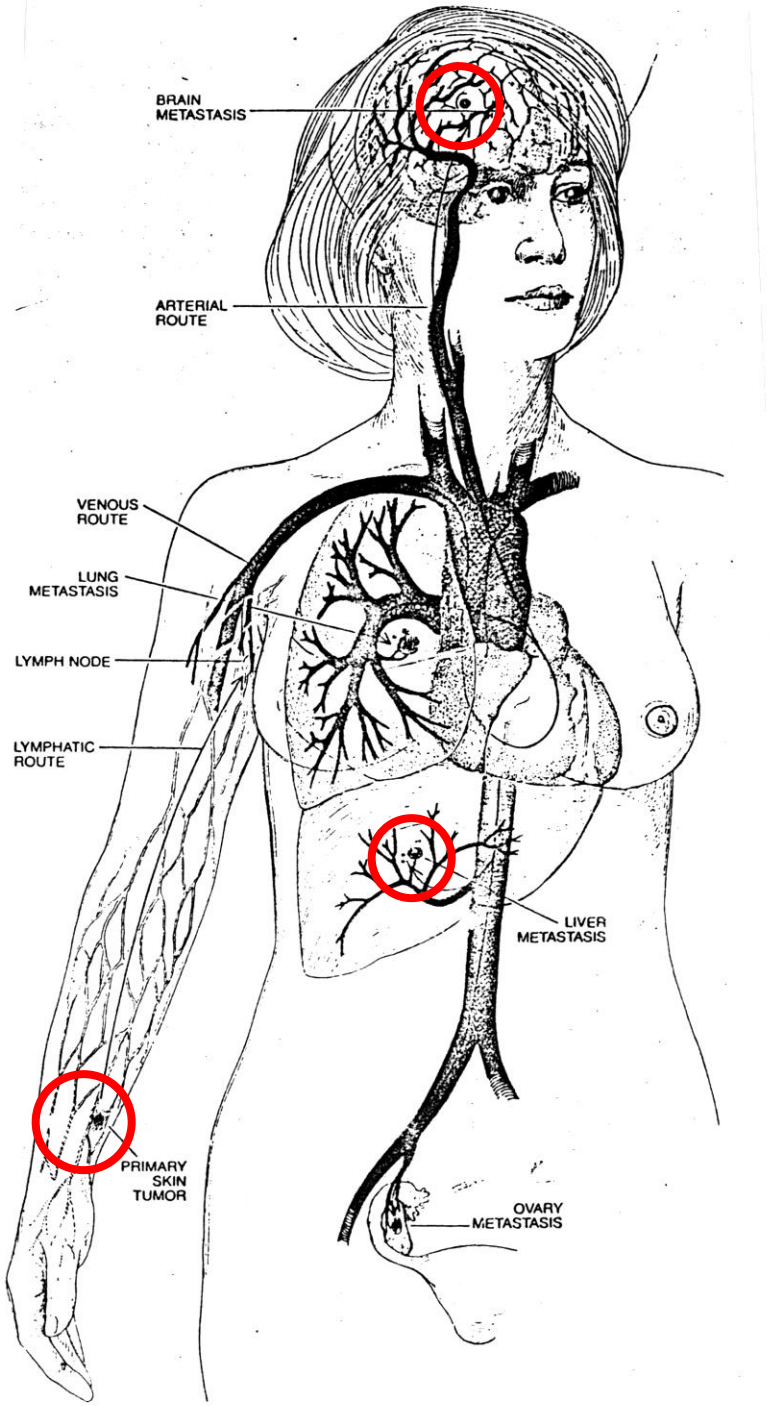
Malignancy/ Metastasis is the central problem, both clinically and intellectually



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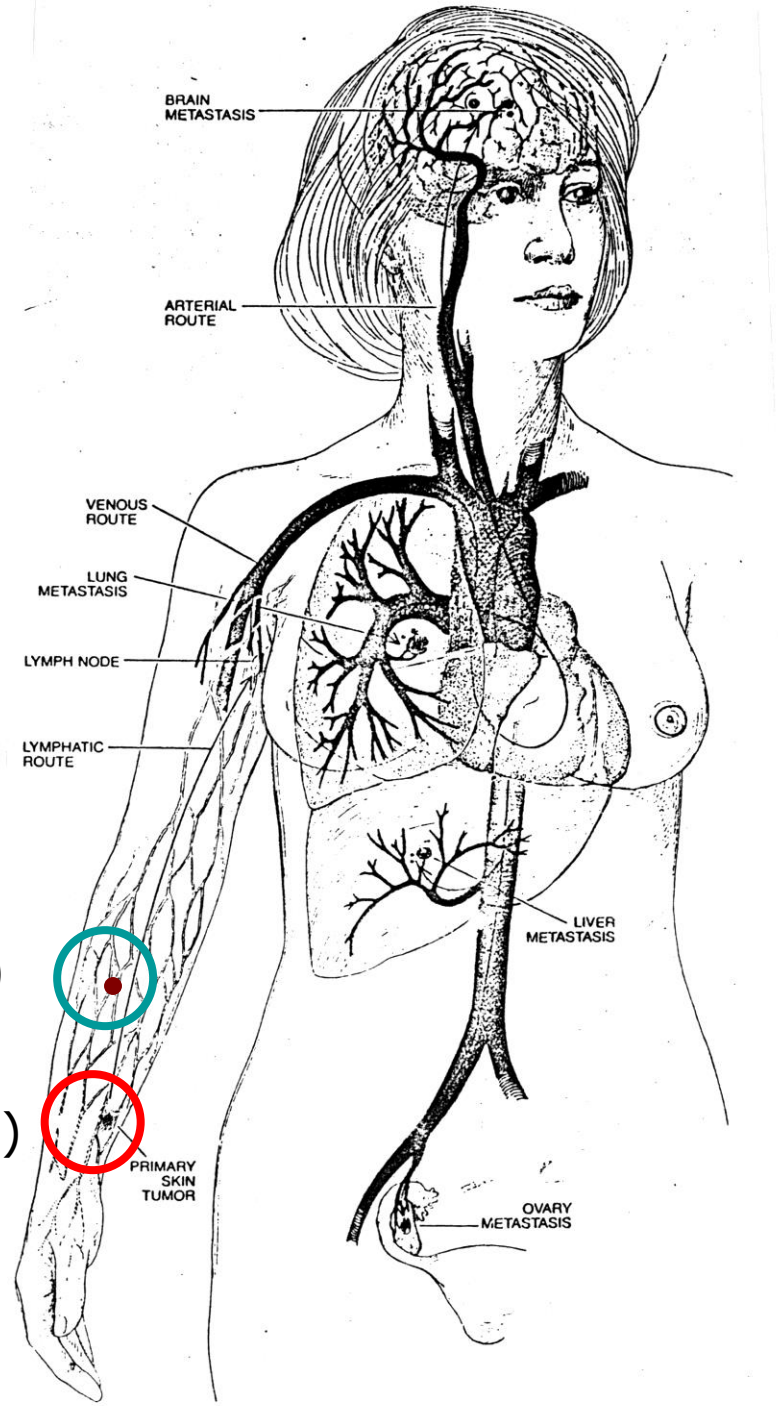
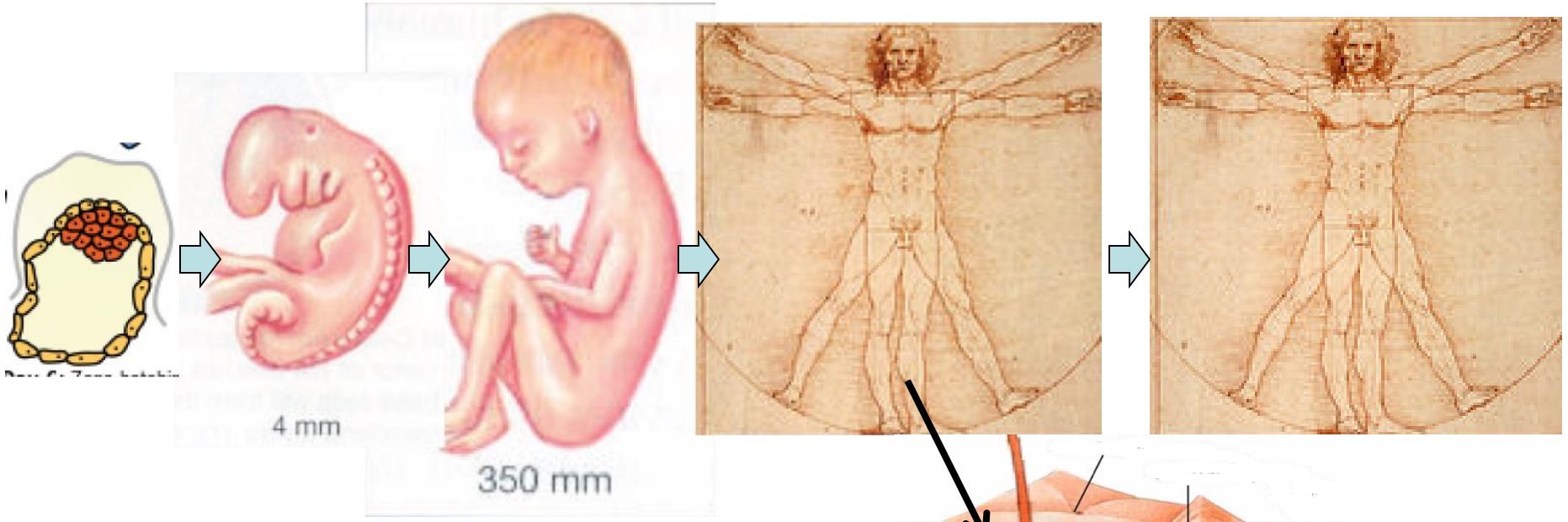
Benign tumour (mole)

malignant tumour (melanoma)



What is Malignancy ?



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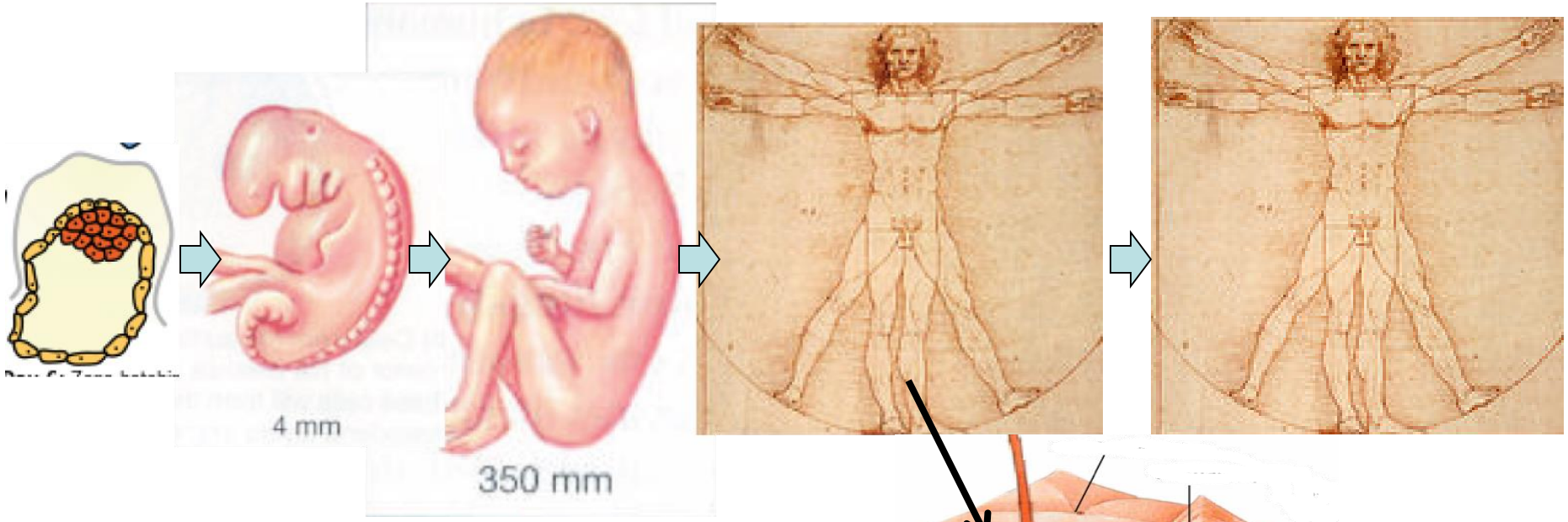

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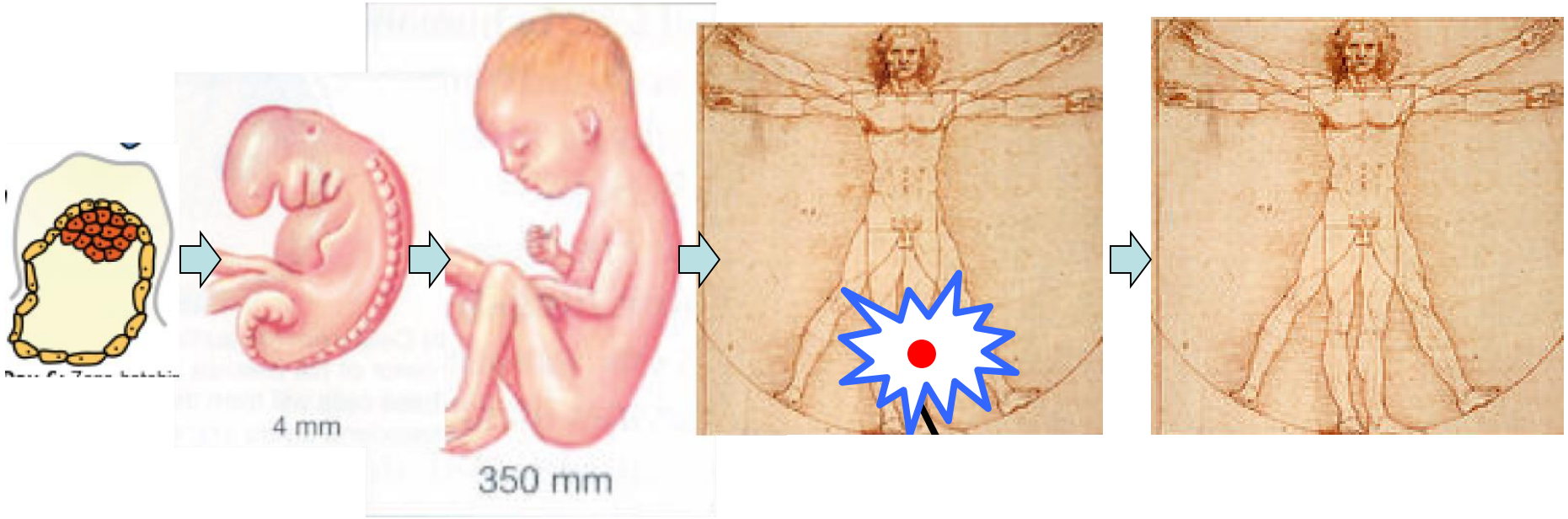

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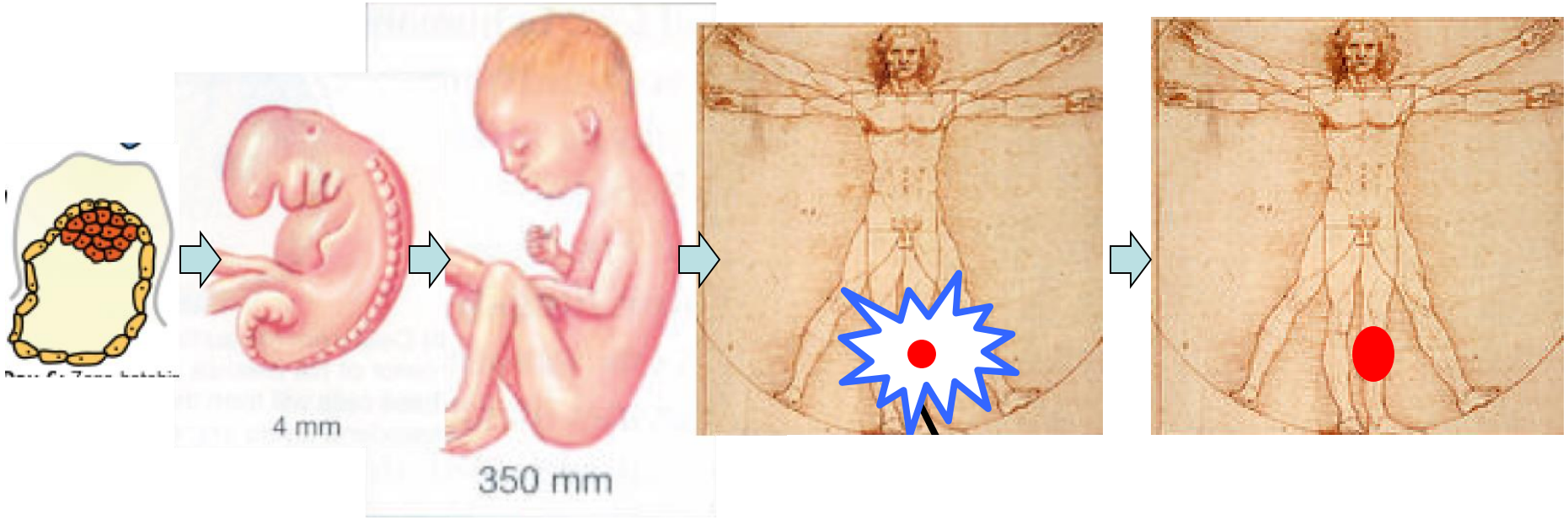

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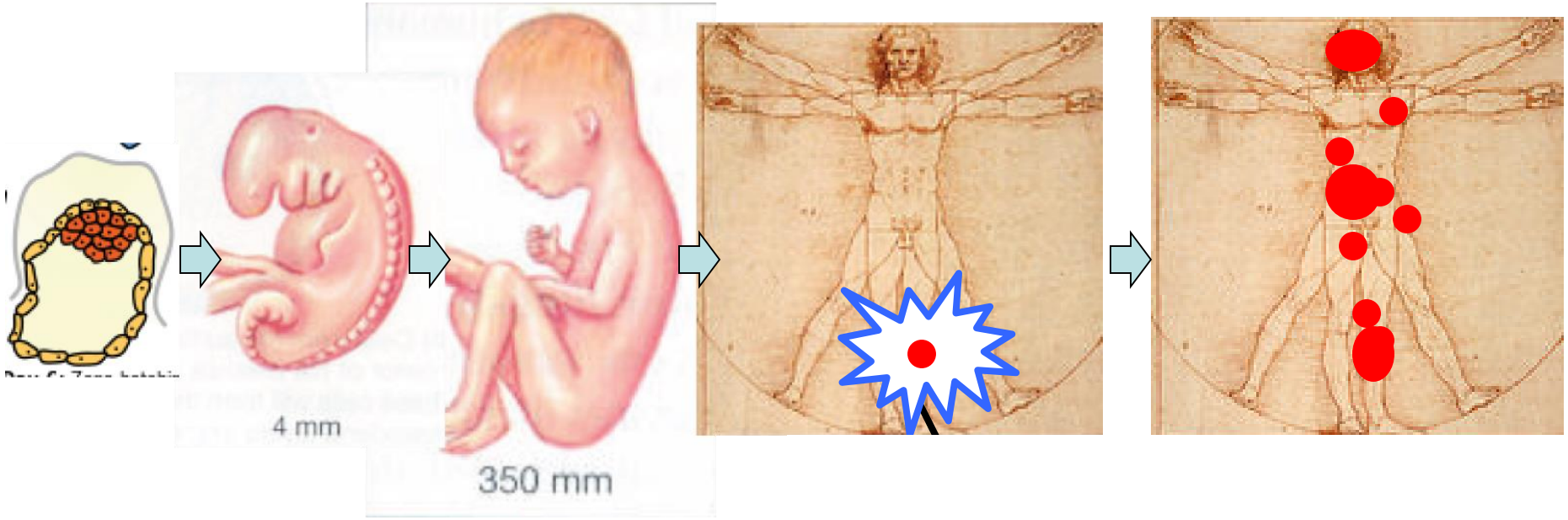

growth in alien environment

failure of 3-D growth control

failure of repair/wound healing = “EMT” ?

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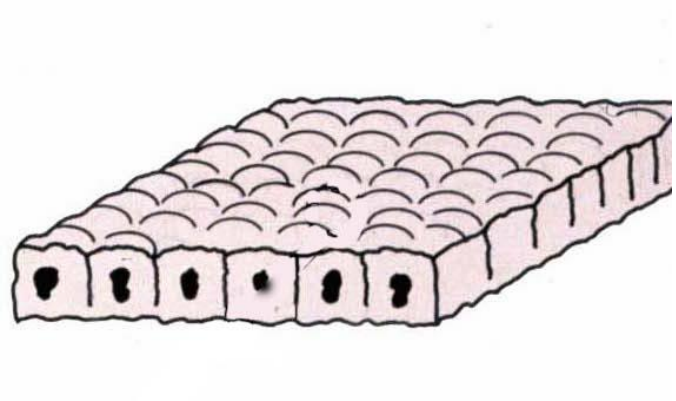

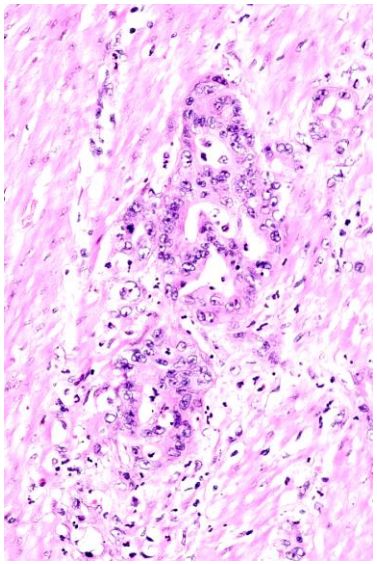

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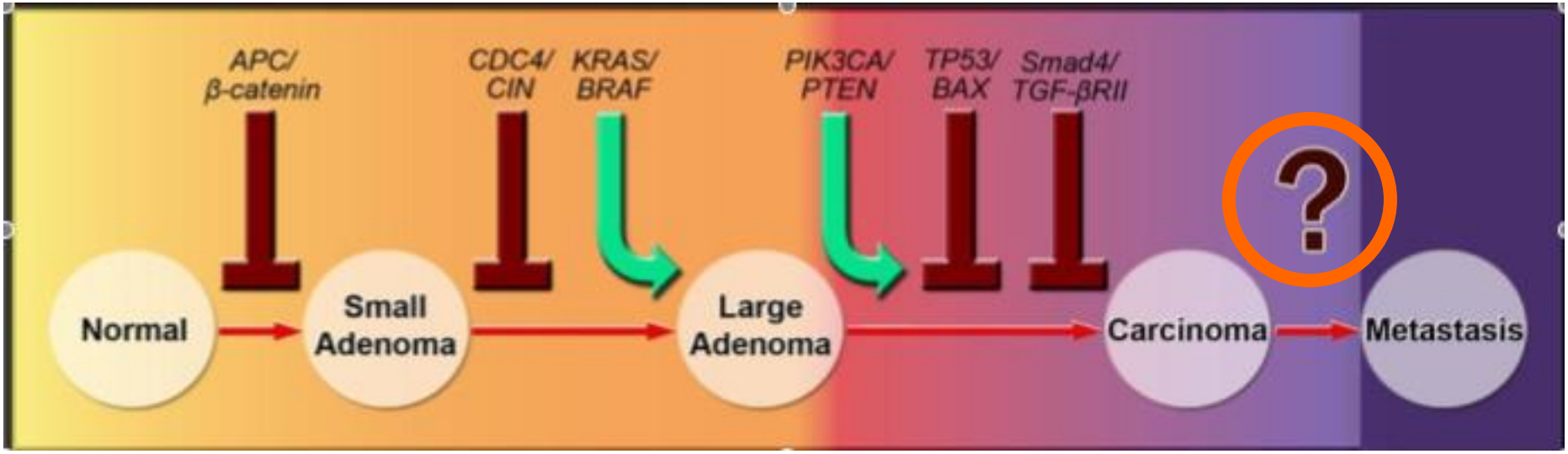
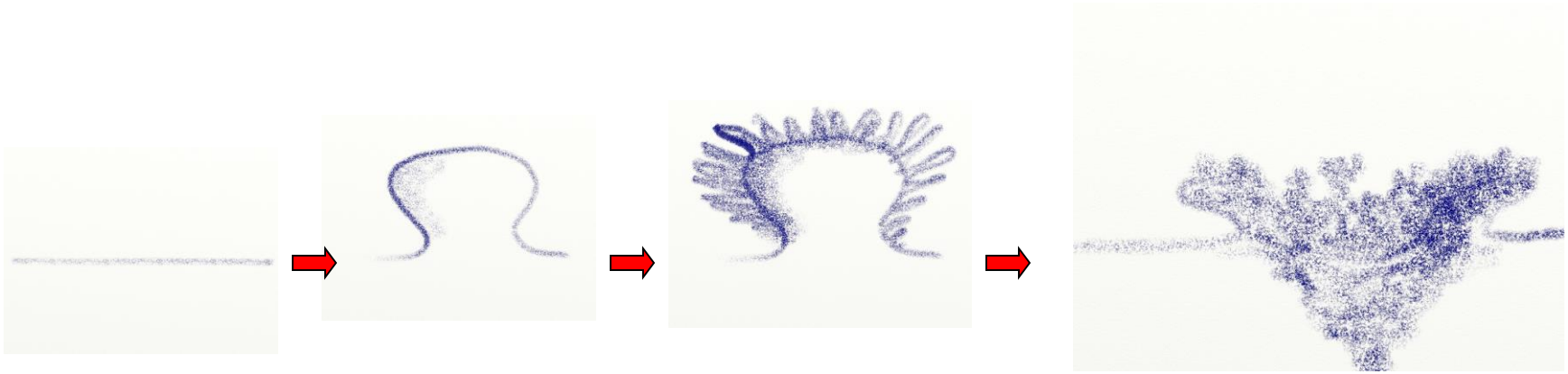




Jones S et al. Proc Natl Acad Sci USA. 2008

Malignancy, Invasion & Metastasis

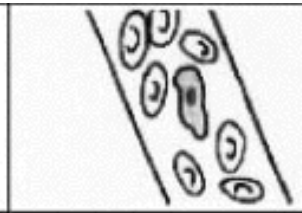
Most that is written is *a priori* and therefore at best suspect, e.g.

'invasion out of vessels is abnormal'

Malignancy, Invasion & Metastasis

(exit into circulation)

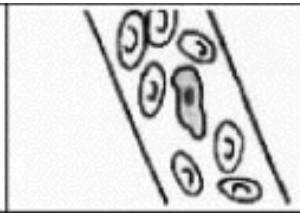
TEXTBOOKS

Survival in the circulation		Inefficient -cells die
Arrest in organ		Abnormal
Extravasation		Abnormal, difficult
Survival of cells after extravasation		abnormal

Malignancy, Invasion & Metastasis

(exit into circulation)

Experiment - Ann Chambers

Survival in the circulation	
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Abnormal

Abnormal, difficult

abnormal

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- wrong, normal cells exit vessels efficiently (Chambers)

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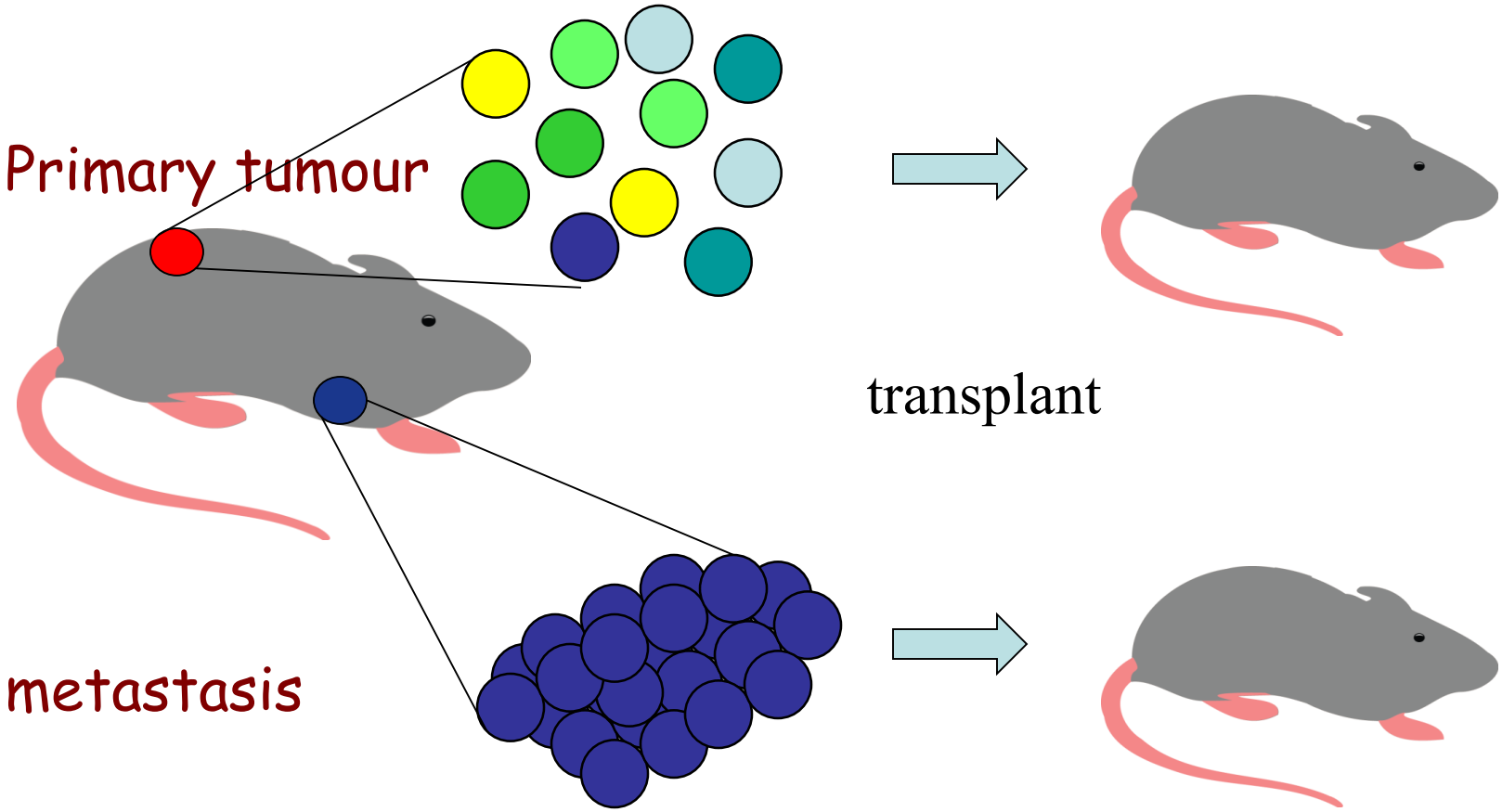
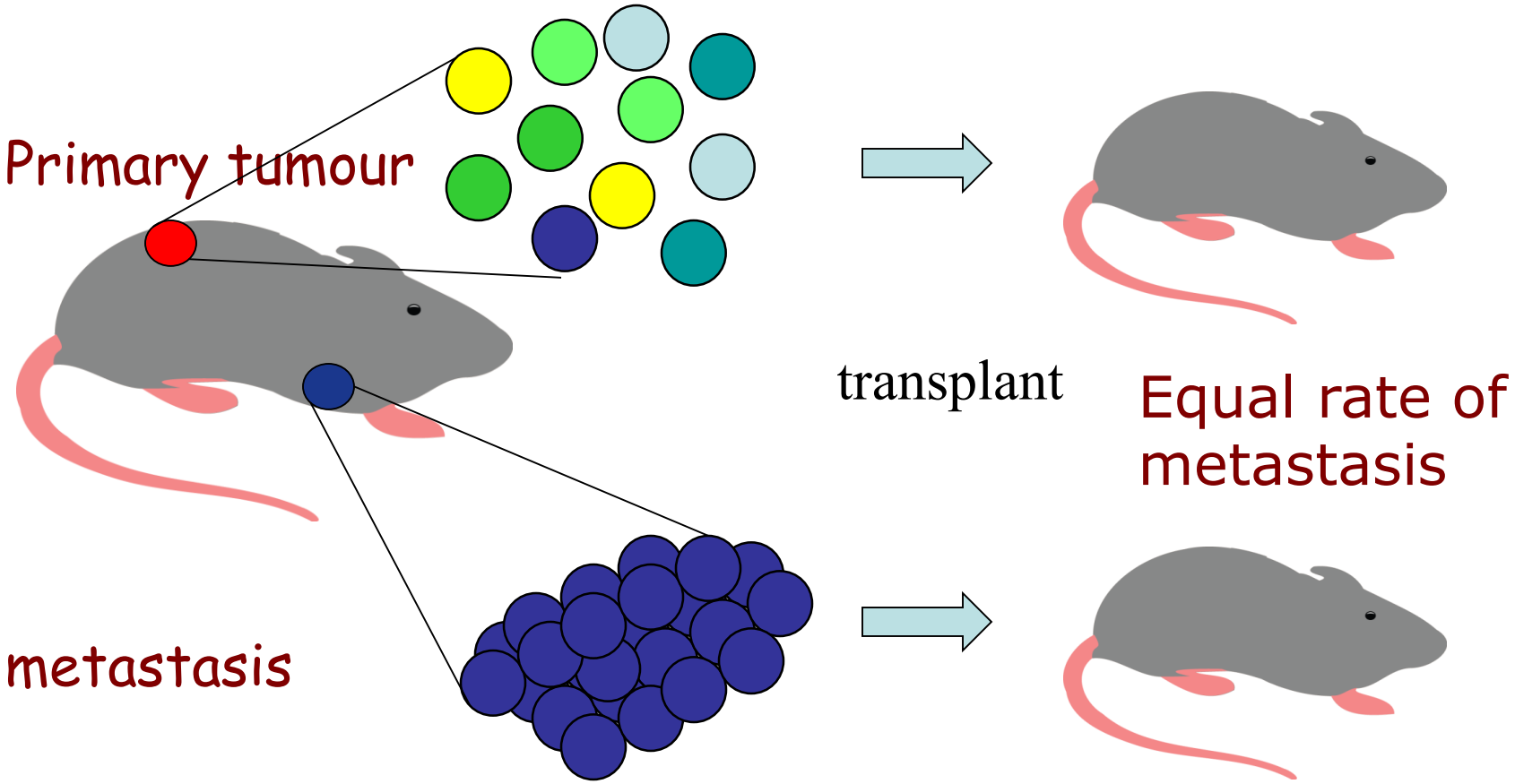
'a small subpopulation of primary tumour is uniquely capable of metastasis'

Leonard Weiss's retransplantation expt



Leonard Weiss's retransplantation expt

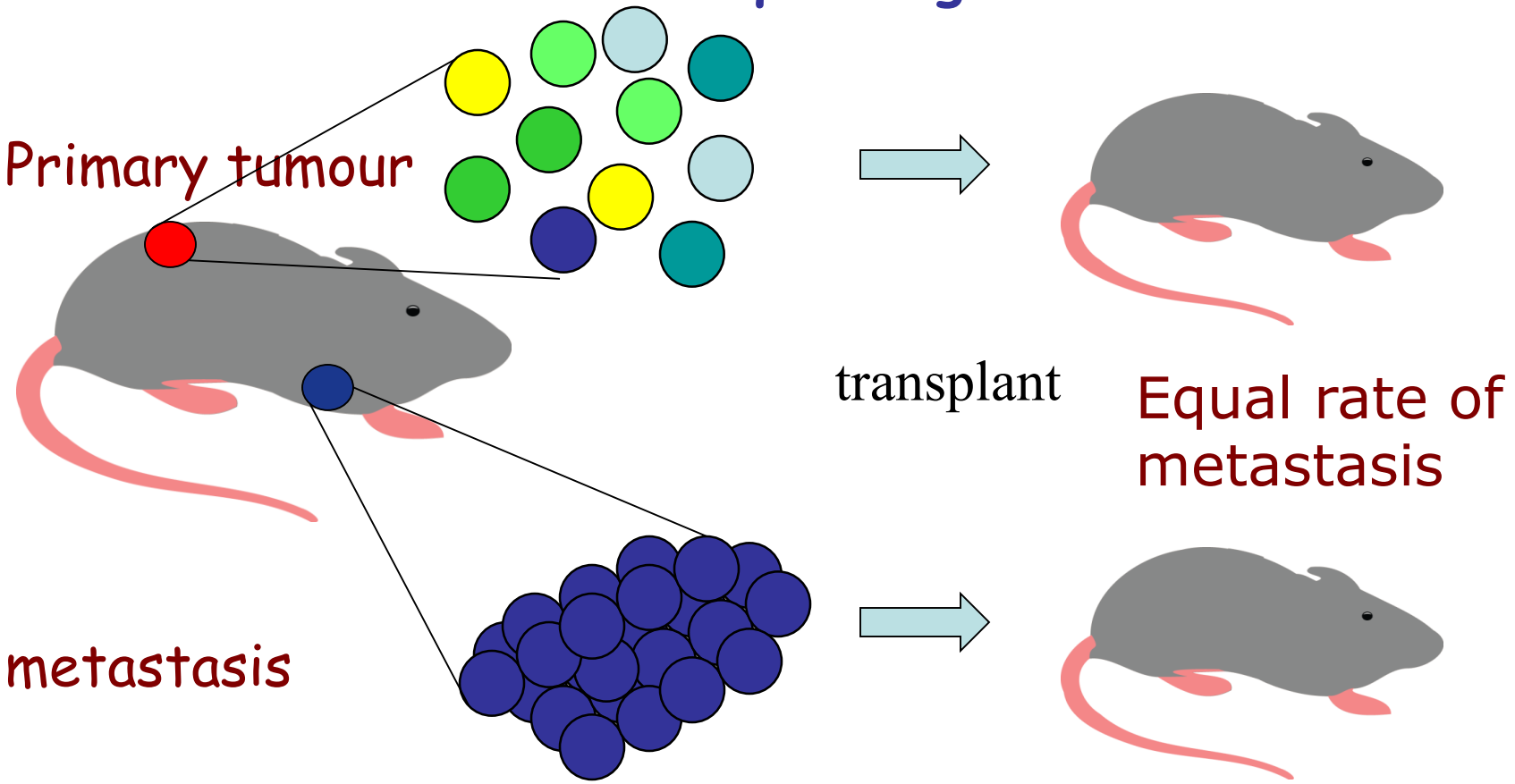


=> No evidence for special metastatic subpopulation

No evidence for major mutation/selection between primary and metastasis

Leonard Weiss's retransplantation expt

AND recent metastasis sequencing



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Malignancy, Invasion & Metastasis

Most that is written is *a priori* and therefore at best suspect, e.g.

'invasion out of vessels is abnormal'

- wrong, normal cells exit vessels efficiently (Chambers)

'a small subpopulation of primary tumour is uniquely capable of metastasis'

- probably wrong (Weiss + Kerbel + Weinberg & Bernards)

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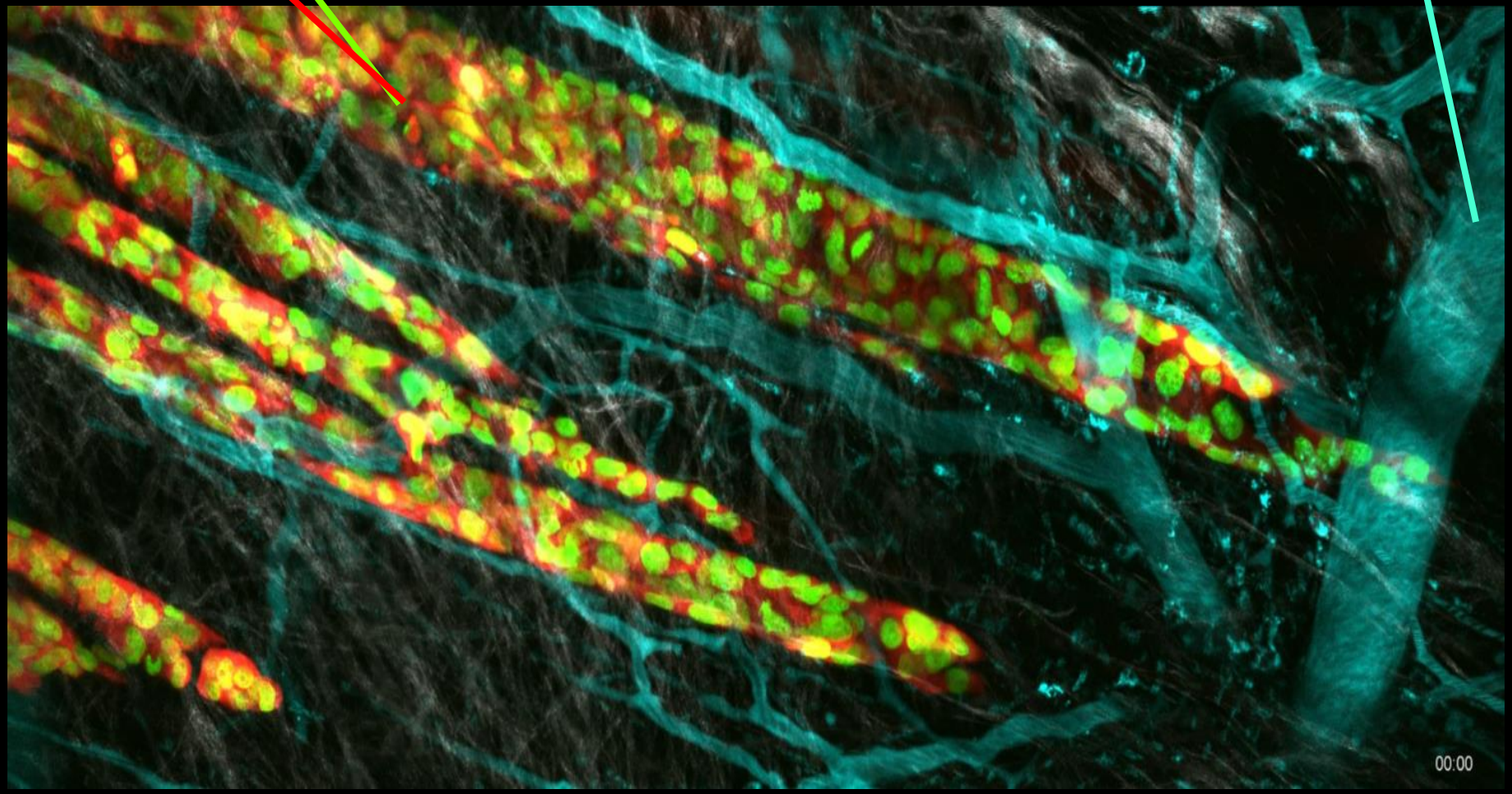
'tumour cells are invasive'

- depends what you mean by 'invasive'. Tumours **spread** but it's not clear how active this is.

-Tumours follow pre-existing channels between cells*

- In some in vitro systems, normal cells more invasive than cancers

**Friedl*



Movie by: S. Alexander & P. Friedl
MD Anderson Cancer Center

Nuclei (H2B-GFP) DsRed2
Blood vessels (70kDa dextran) SHG (collagen)

4 hours

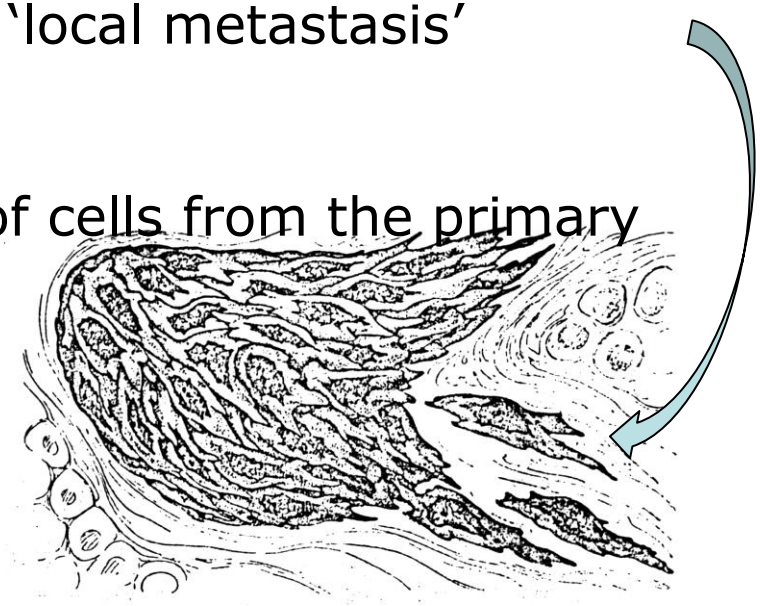
Metastasis: a *personal* conclusion

Malignant cells can grow in an alien environment

No evidence (yet) for a major change (e.g. crucial mutations) between malignant primary and metastasis

Pathologist's 'invasiveness' is a kind of 'local metastasis'

-> Maybe metastasis is just 'leakage' of cells from the primary



Malignancy is what matters