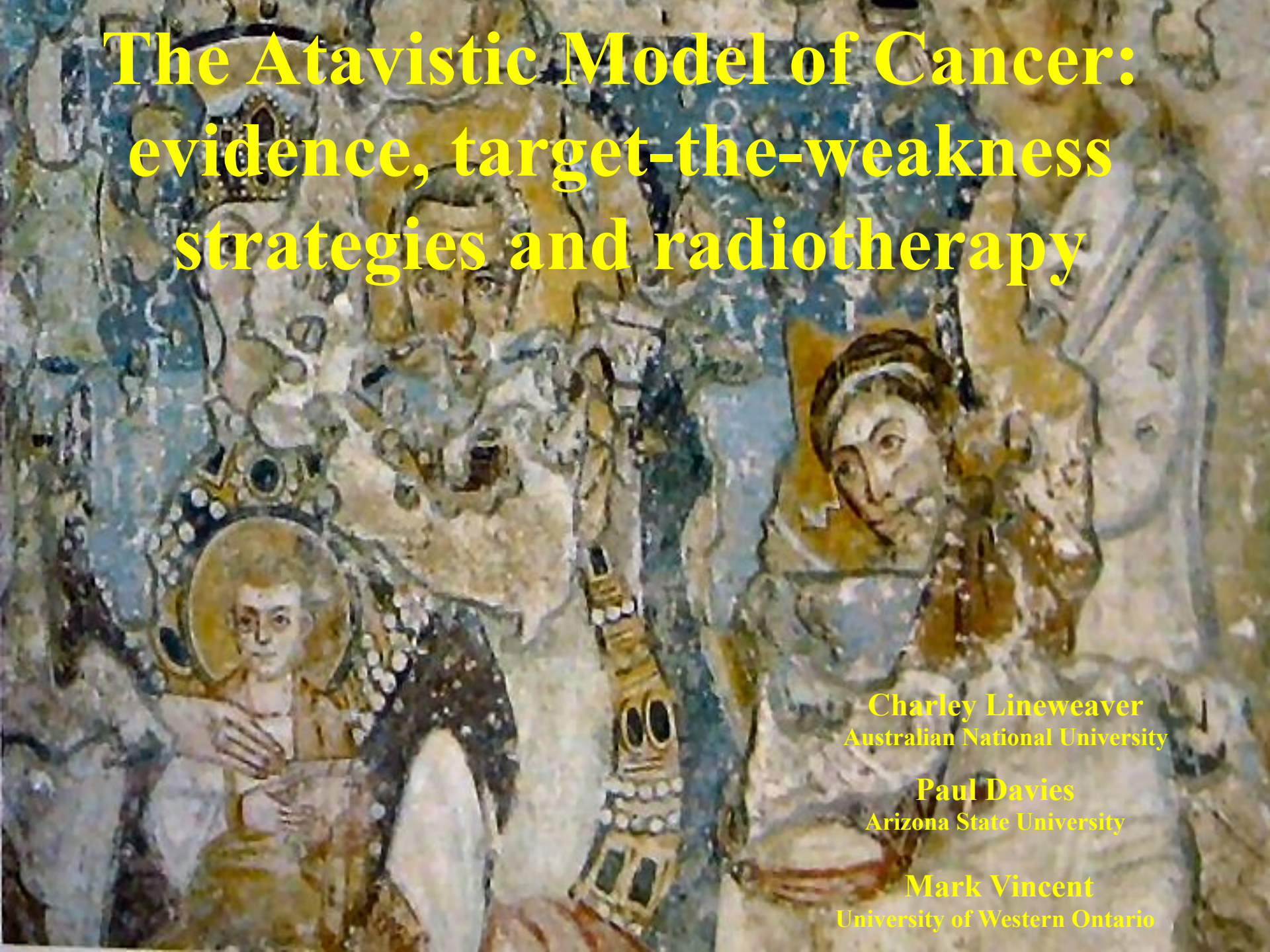
The Atavistic Model of Cancer: evidence, target-the-weakness strategies and radiotherapy



Charley Lineweaver
Australian National University

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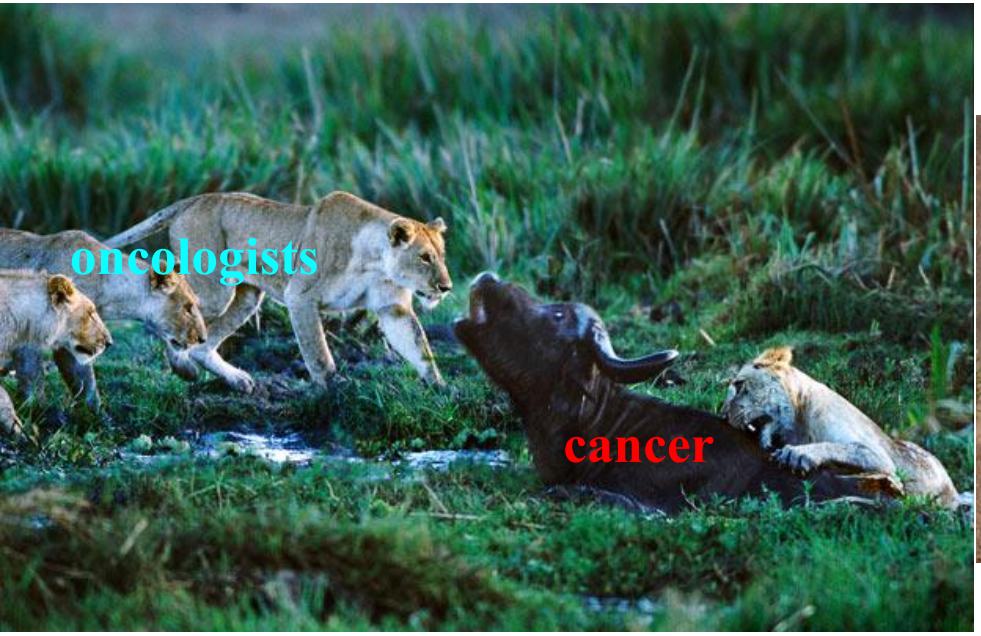
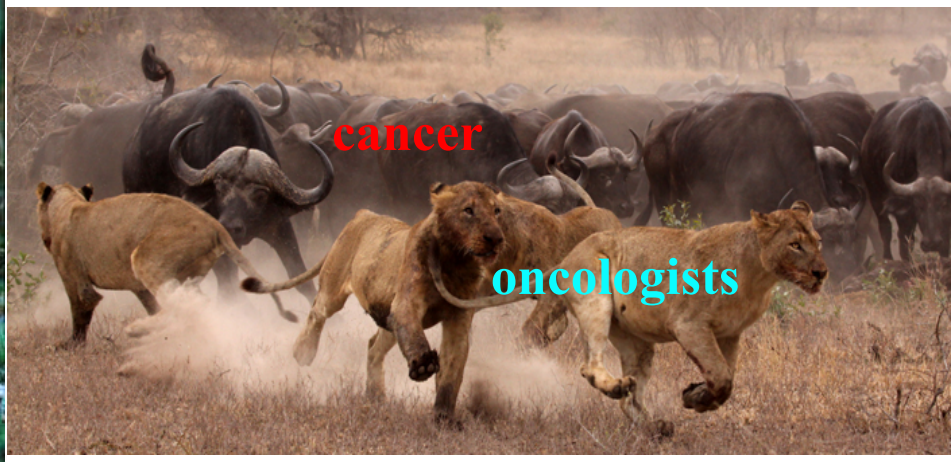
Targeting Cancer's Weaknesses



Not It's Strengths



Therapeutic implications of the atavism model

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Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors

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Abstract

The genes of cellular cooperation that evolved with multicellularity about a billion years ago are the same genes that malfunction to cause cancer. We hypothesize that cancer is an atavistic condition that occurs when genetic or epigenetic malfunction unlocks an ancient 'toolkit' of pre-existing adaptations, re-establishing the dominance of an earlier layer of genes that controlled loose-knit colonies of only partially differentiated cells, similar to tumors. The existence of such a toolkit implies that the progress of the neoplasm in the host organism differs distinctively from normal Darwinian evolution. Comparative genomics and the phylogeny of basal metazoans, opisthokonta and basal multicellular eukaryotes should help identify the relevant genes and yield the order in which they evolved. This order will be a rough guide to the reverse order in which cancer develops, as mutations disrupt the genes of cellular cooperation. Our proposal is consistent with current understanding of cancer and explains the paradoxical rapidity with which cancer acquires a suite of mutually-supportive complex abilities. Finally we make several predictions and suggest ways to test this model.

derepresses

Somatic mutation model

"Natural selection occurs in neoplasms because (epi)genetic mutations generate heritable variation, and some mutations confer a selective advantage or disadvantage on the cell. All the hallmarks of cancer lead to the differential reproductive success of a clone." (Merlo et al 2006)

Cancer evolves during the lifetime of the patient.

Selection acting on (what is usually assumed to be) random variation produces the acquired capabilities of cancer.

acquired

Atavistic model

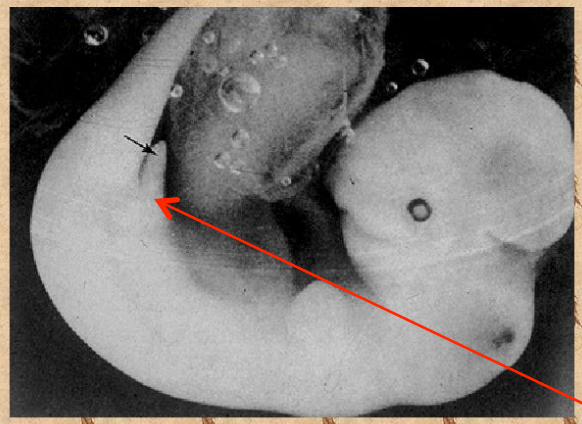
Natural selection occurs in neoplasms because (epi)genetic mutations damage regulation of otherwise repressed adaptive capabilities. These adaptive capabilities, when derepressed, show up as the hallmarks of cancer.

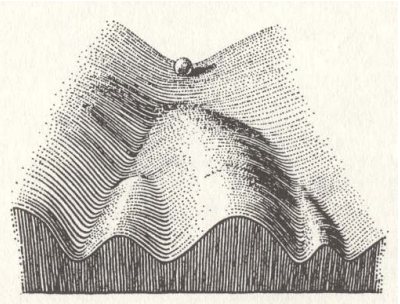
Cancer evolved ~ billion years ago and it is derepressed during the lifetime of the patient.

The capabilities of cancer are reacquired atavisms.

reacquired

Hind Limbs in a Whale Embryo





development of a whale

continuous cascade of maturing cells

(embryogenesis, tissue maintenance, wound healing,)

fertilized egg

germ cells

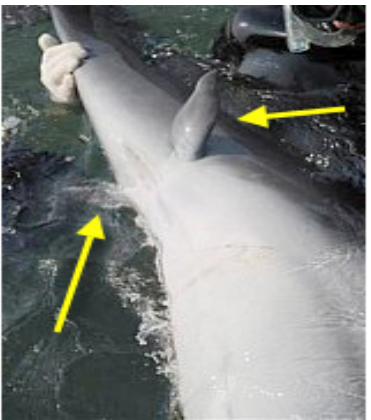
start making leg

leg suppressor (absent in other tetrapods)

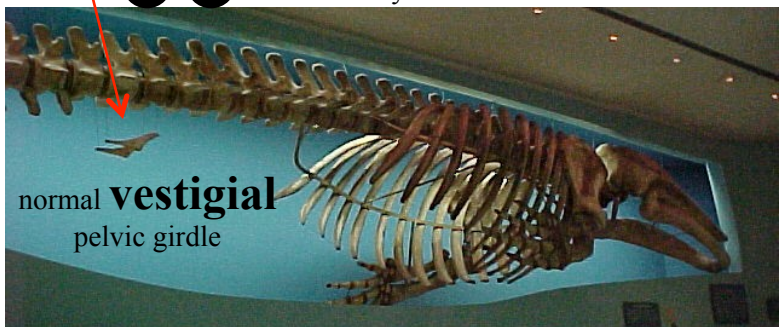
~30 Mya

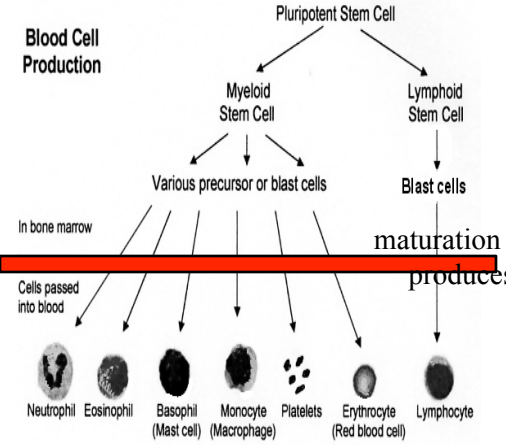
atavism produced by leg suppressor alteration, or "derepression of leg program"

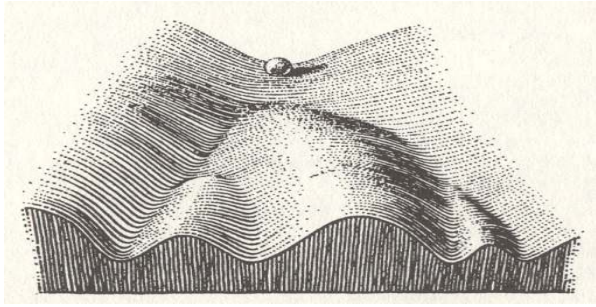
abnormal **atavistic** leg



terminally differentiated cells of different cell types and different organs,







Waddington's epigenetic landscape
S. Huang 2011

development of cancer

fertilized egg

maturation block but not proliferation block produces a cascade of immature cells: e.g. leukemia

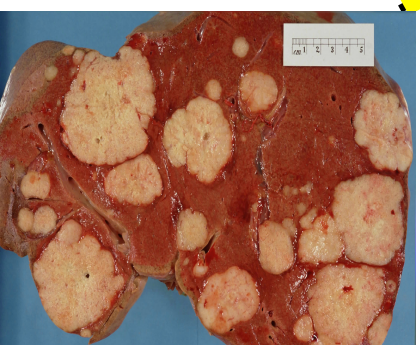
~1 Gya

tumor suppressor (absent in colonial basal metazoans and damaged in cancer)

continuous cascade of maturing cells
(embryogenesis, tissue maintenance, wound healing)

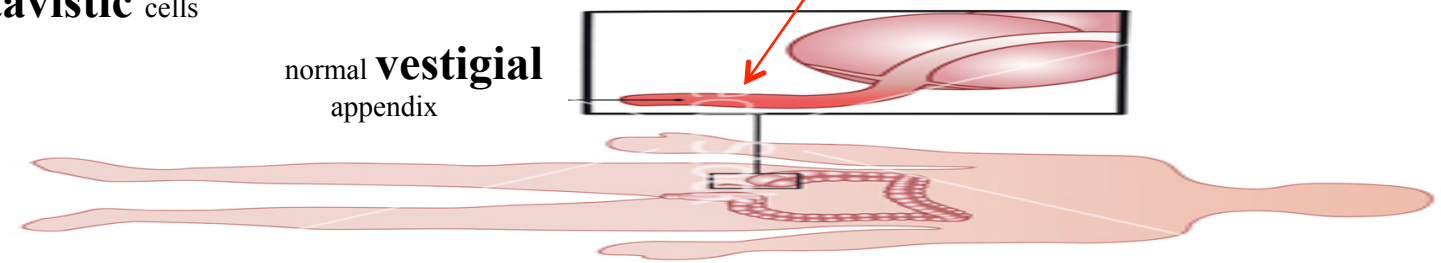
cancer produced by tumor suppressor alteration

abnormal **atavistic** cells

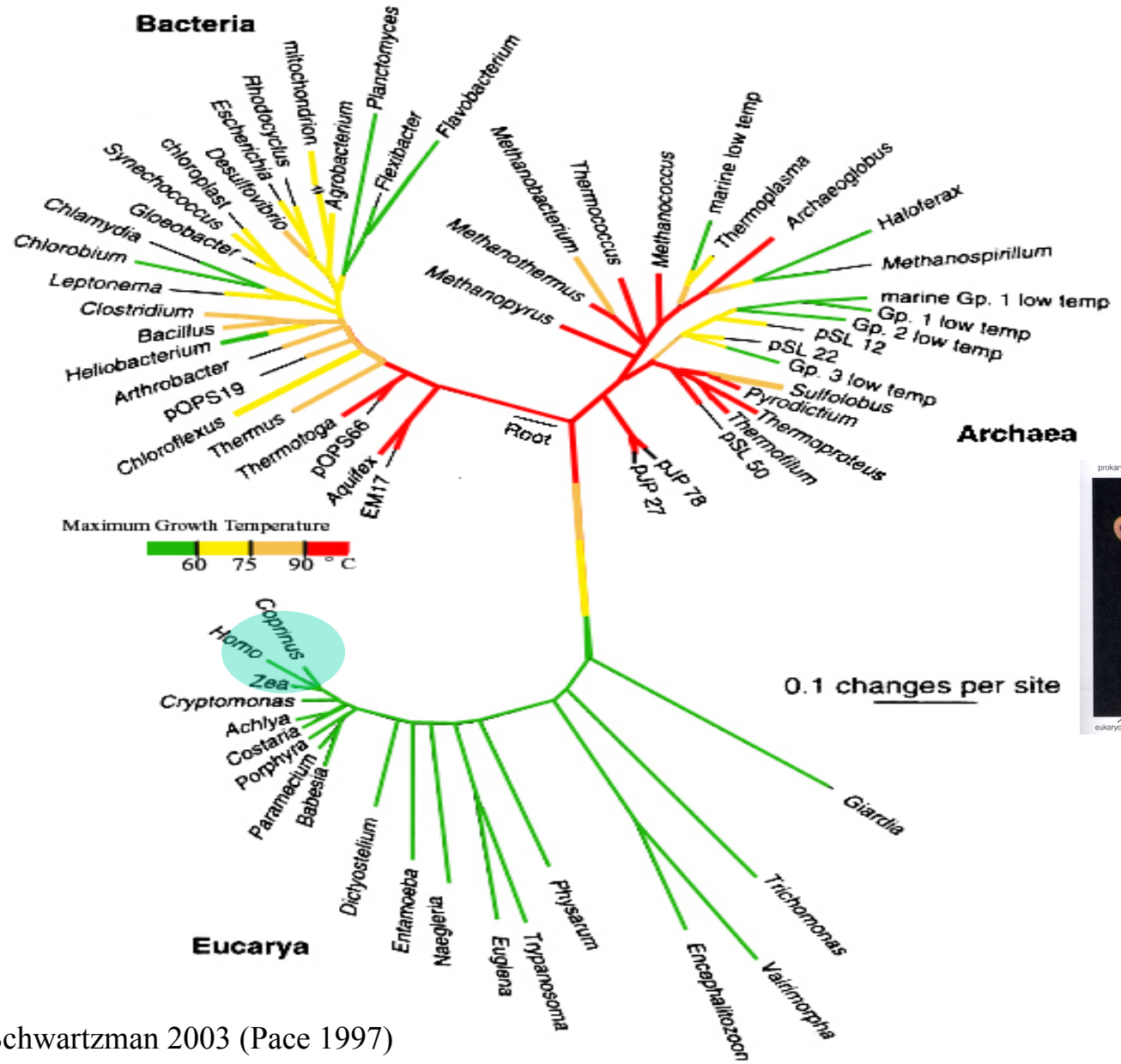


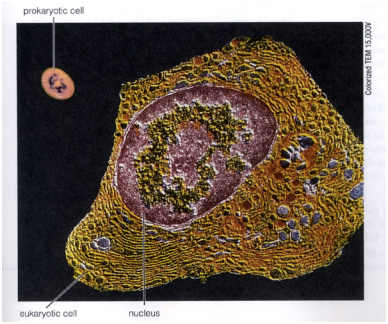
terminally differentiated cells of different cell types and different organs,

normal **vestigial** appendix

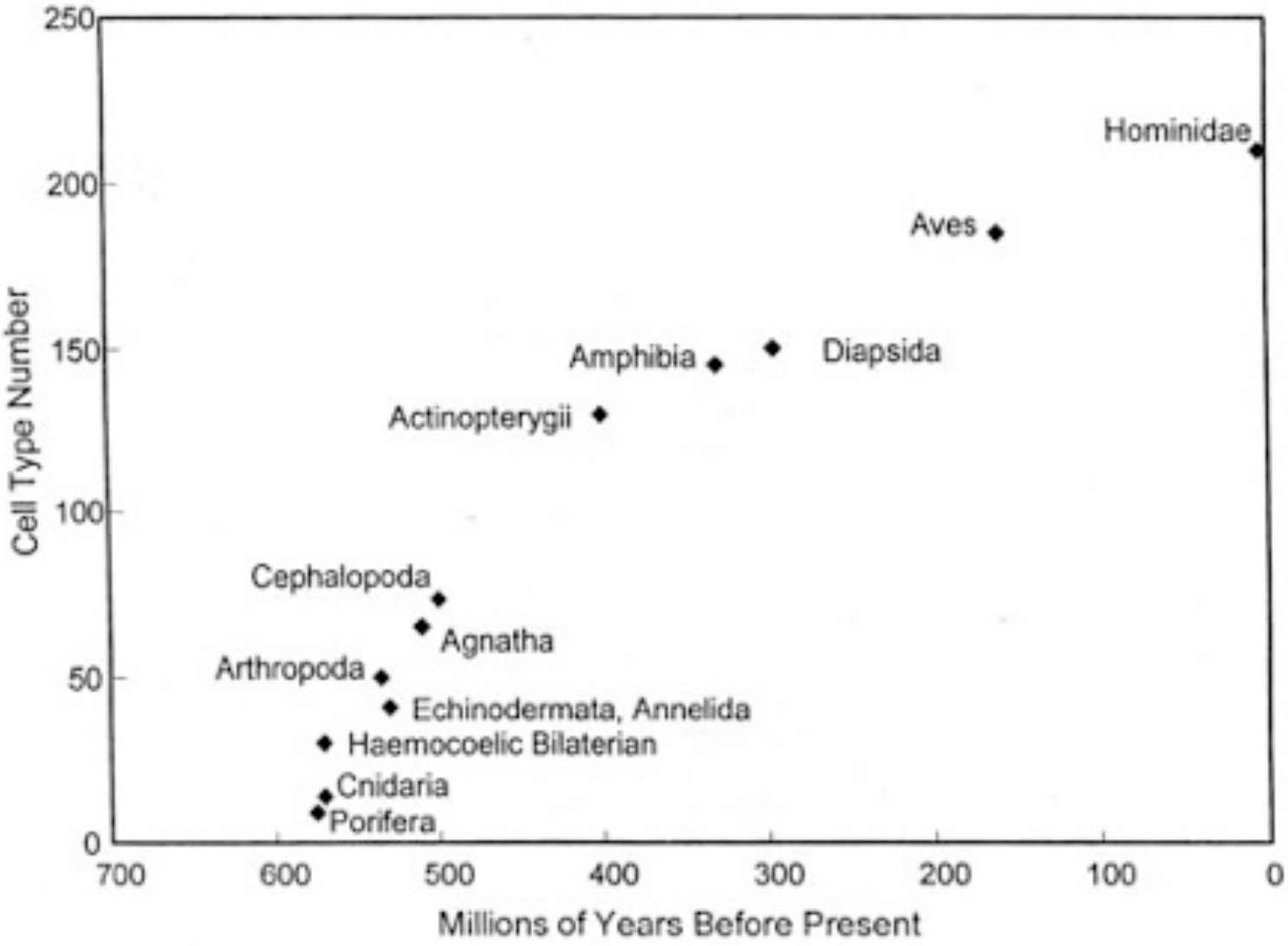


non-differentiated cells ➔ differentiated cells

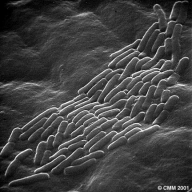




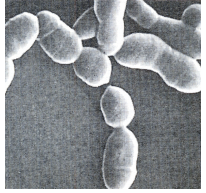
Lineweaver & Schwartzman 2003 (Pace 1997)



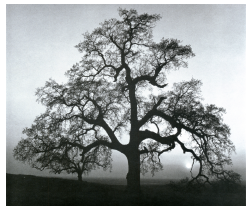
Valentine 2004?



E. coli



Methanogens



plants

fungi

jellyfish

insects

human

Eubacteria

Archaeaa

Bikonts plastids

Holomycota

Radiata

protostomes

0.8

deuterostomes

1.0

Bilateria

1.4

Holozoa

1.6

Unikonts

cyanobacteria

organelles

LECA

alpha proteobacteria

2.0

mitochondria

organelles

karyogenesis

nucleated cells

spirochete

flagella, basal bodies,
mitotic spindles

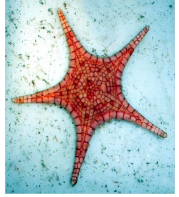
3.0

stem eukaryotes

4.0

Archaea

evolution of everything

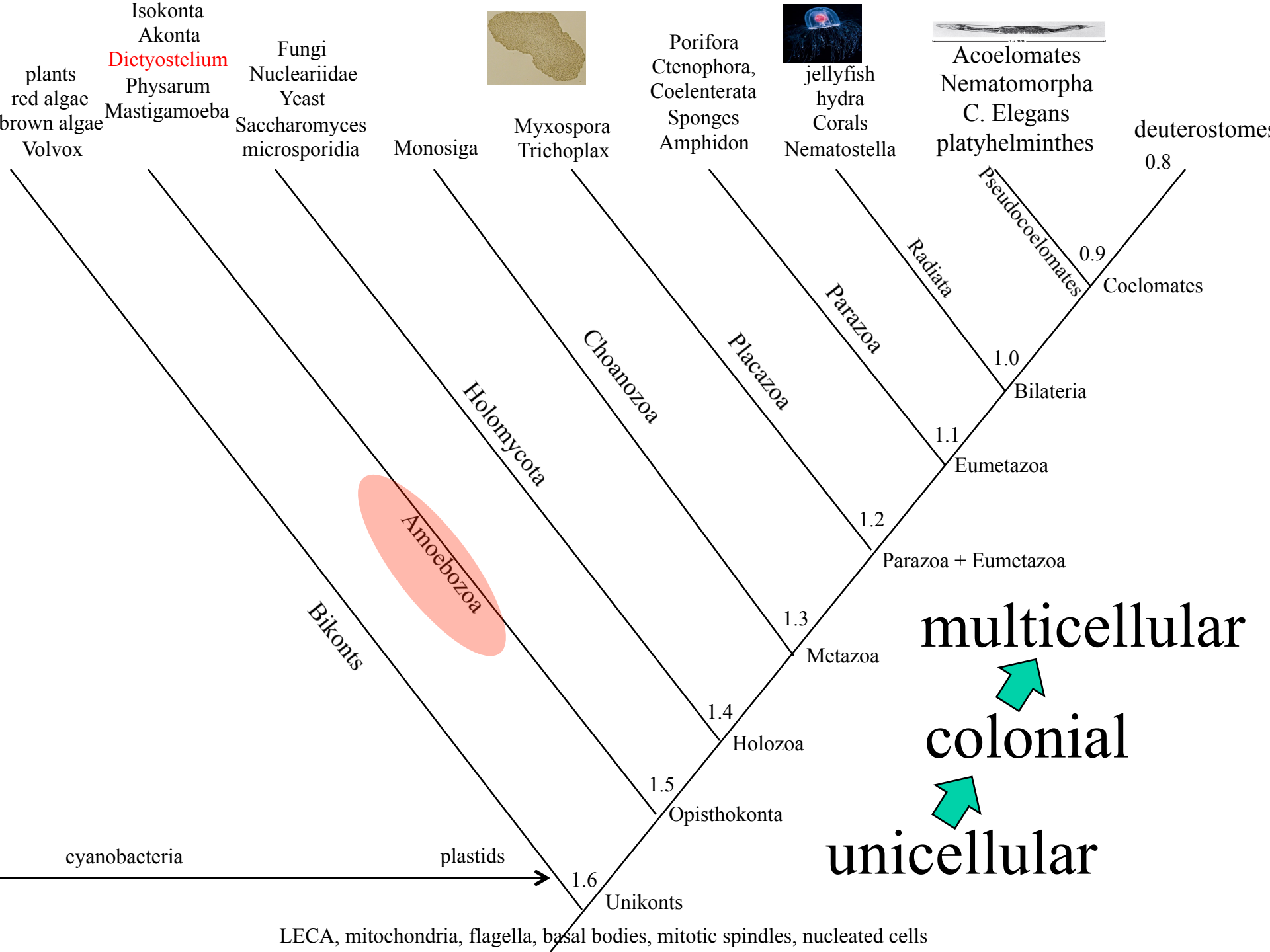




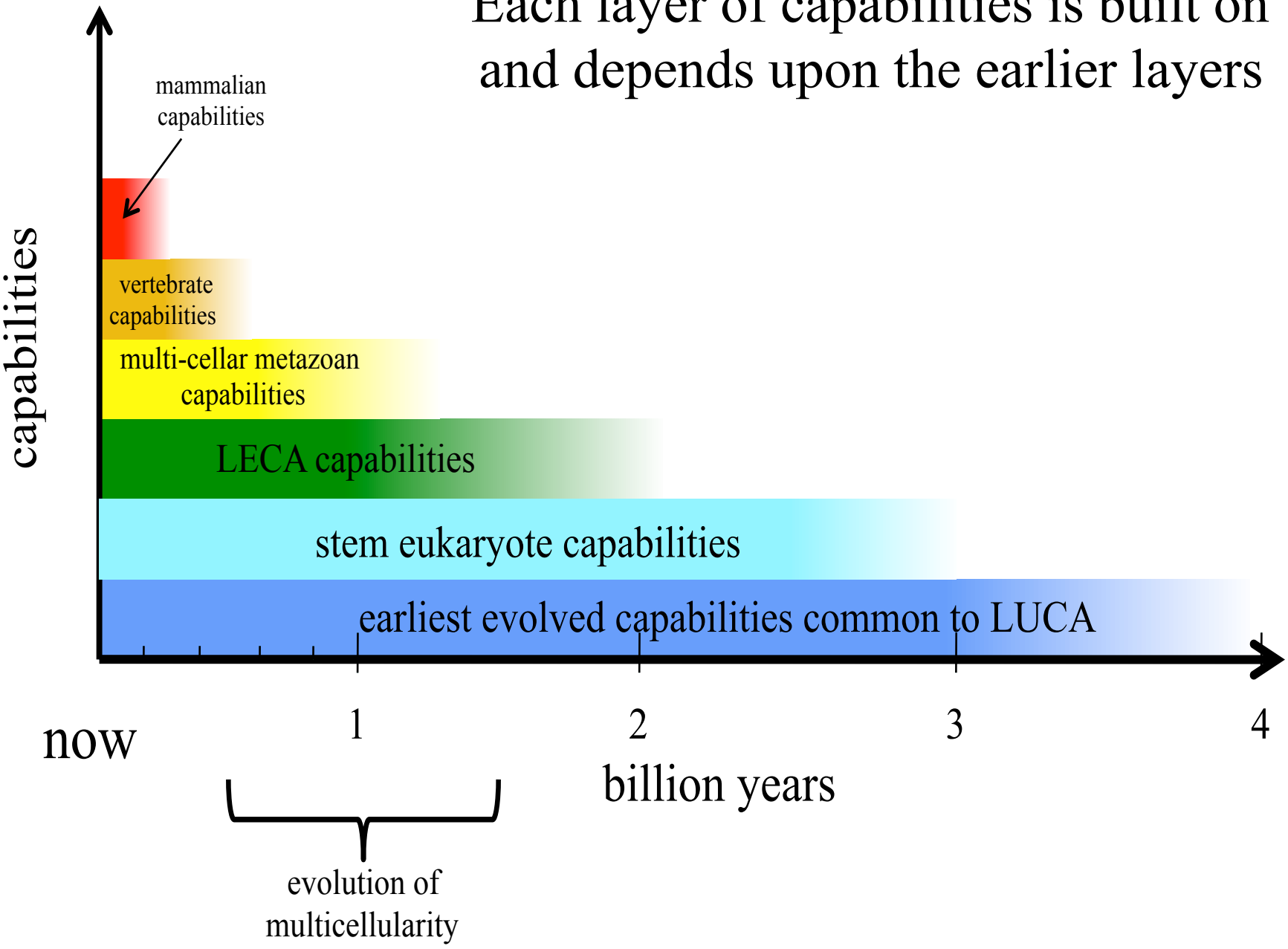




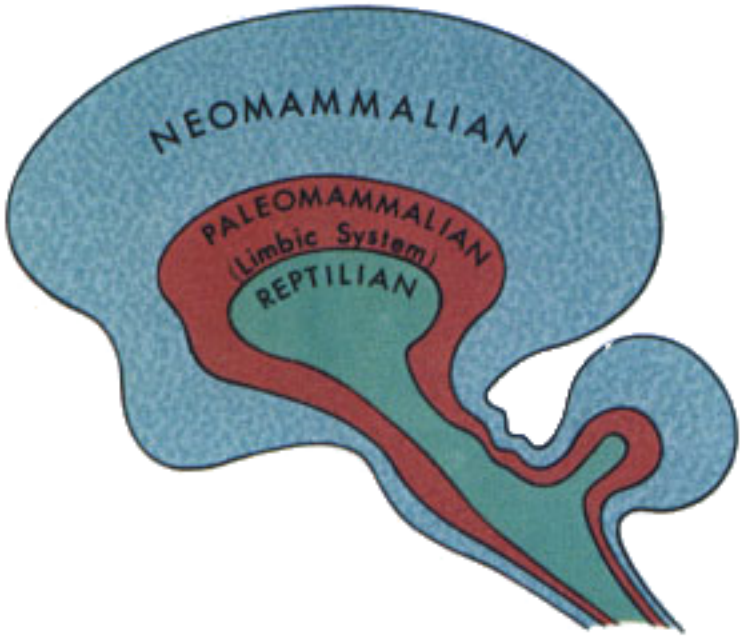
insect
starfish
hagfish
sharks
ray-finned fish
frog
bird
echidna
kangaroo
mouse
chimp
human
rodents
marsupials
monotremes
reptiles
amphibians
ray-finned fish
cartilaginous fish
jawless fish
Echinoderms
protostomes
80
primates
160
placentals
210
eutheria
320
mammals
350
amniotes
450
lobe-finned fish
500
bony fish
600
jawed fish
700
chordata
800
deuterostomes


plants
red algae
brown algae
Volvox
Isokonta
Akonta
Dictyostelium
Physarum
Mastigamoeba
Fungi
Nucleariidae
Yeast
Saccharomyces
microsporidia
Monosiga
Myxospora
Trichoplax
Porifora
Ctenophora,
Coelenterata
Sponges
Amphidon
jellyfish
hydra
Corals
Nematostella
Acoelomates
Nematomorpha
C. Elegans
platyhelminthes
deuterostomes
0.8
Pseudocoelomates
0.9
Coelomates
Radiata
1.0
Bilateria
Parazoa
1.1
Eumetazoa
Placazoa
1.2
Parazoa + Eumetazoa
Choanozoa
1.3
Metazoa
Holomycota
1.4
Holozoa
Amoebozoa
1.5
Opisthokonta
Bikonts
cyanobacteria
plastids
1.6
Unikonts
multicellular
colonial
unicellular
LECA, mitochondria, flagella, basal bodies, mitotic spindles, nucleated cells

Each layer of capabilities is built on and depends upon the earlier layers



The Onion Model of differentially protected, conserved genes.

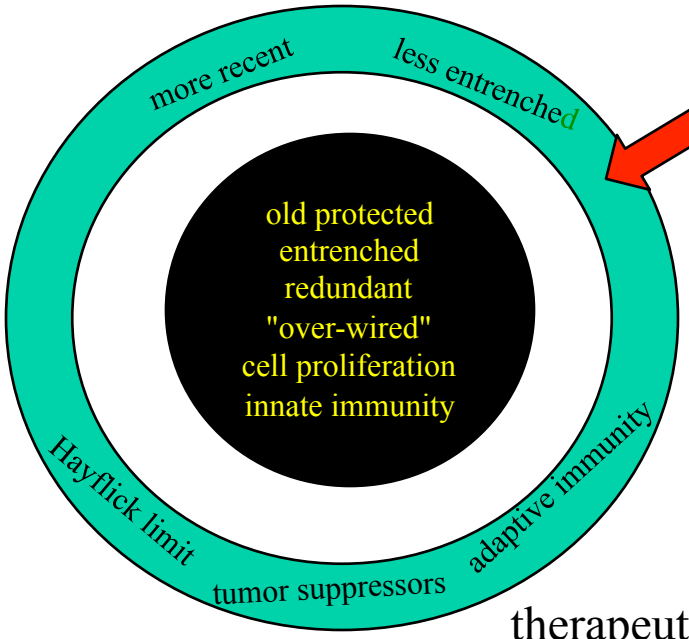


Atavistic model has therapeutic implications

Current therapeutic treatments predominantly target what cancer cells, and all cells, have deeply embedded in their genomes -- cellular proliferation. It may seem rational to treat a proliferative disease with antiproliferative drugs however, after ~ 4 billion years of evolution (the first ~ 3 billion of which were the largely unregulated proliferation of unicellular organisms) cellular proliferation may be the most protected, least vulnerable, most redundant and most entrenched capability that any cell has. The redundant and robust supports for cellular proliferation are ~ 2 billion years older than the many layers of recent differentiation and regulation that evolved with multi-cellular eukaryotes.

cancer as a castle-without-a-moat

normal cell



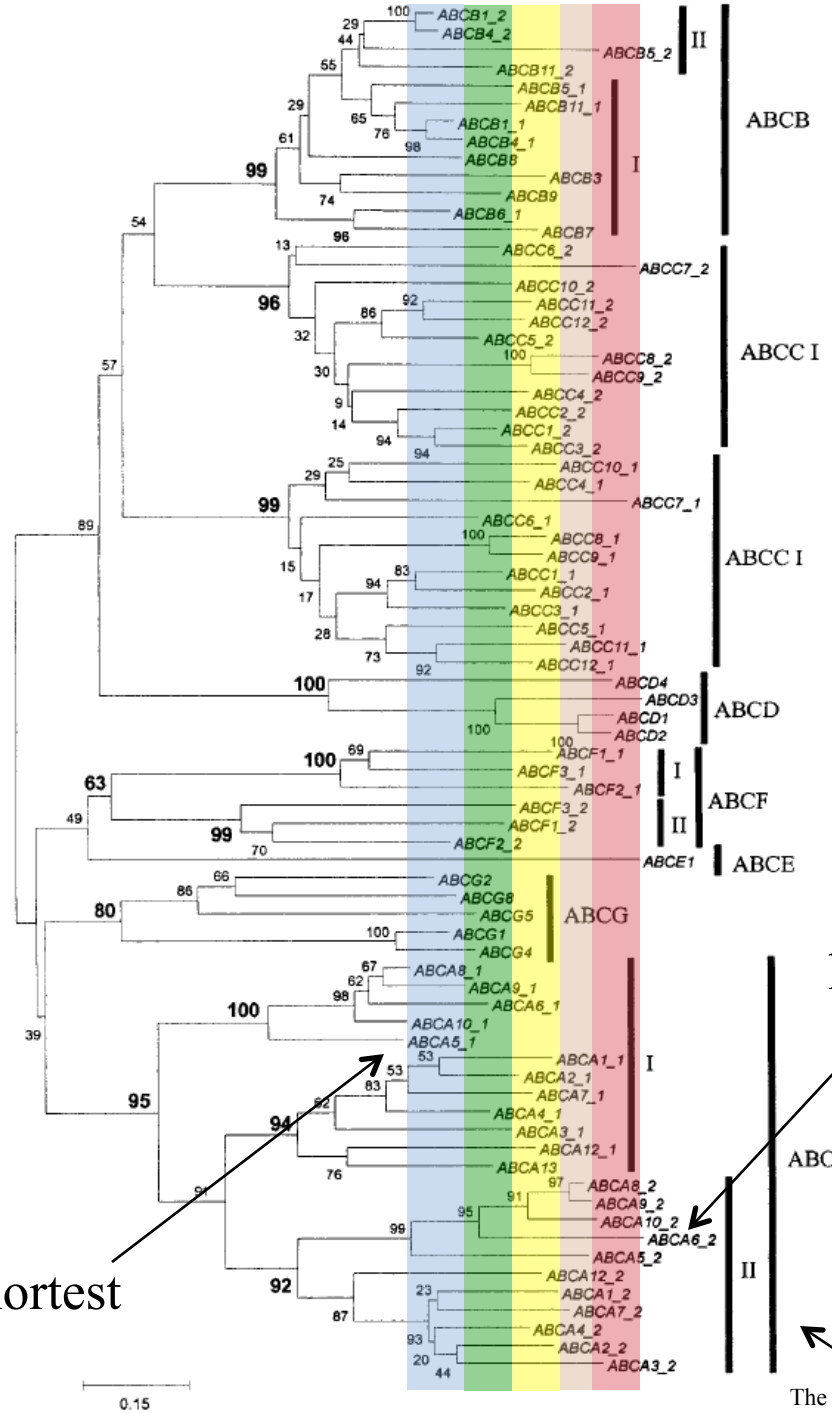
moat

cancer cell

therapeutic strategy: exploit the absence of the moat:
attack with fierce non-swimming warriors
they will drown when they try to attack normal cells

Target the Weakness Applied to ABC Pumps

Some ABC pumps are heavily implicated in multiple drug resistance.
All ABC pumps did not evolve at the same time.
Some are older, some are newer. Identify which is which.
Prediction of the Atavistic Model: in cancer cells the newer ones will be damaged and down-regulated compared to normal cells.
The older pumps will be up-regulated and responsible for cancer's abilities.
This seems to be true at the ~ 2 sigma level.
Therapy: identify the specific strengths of the new ones..ie they are more efficient at pumping out X. Attack cancer cells with X.
If these new pumps are missing in cancer, then cancer cells won't be able to pump out X. And they won't be able to mutate their missing pumps back into existence. And normal cells will be able to deal with X.



shortest

longest

~ 2 σ

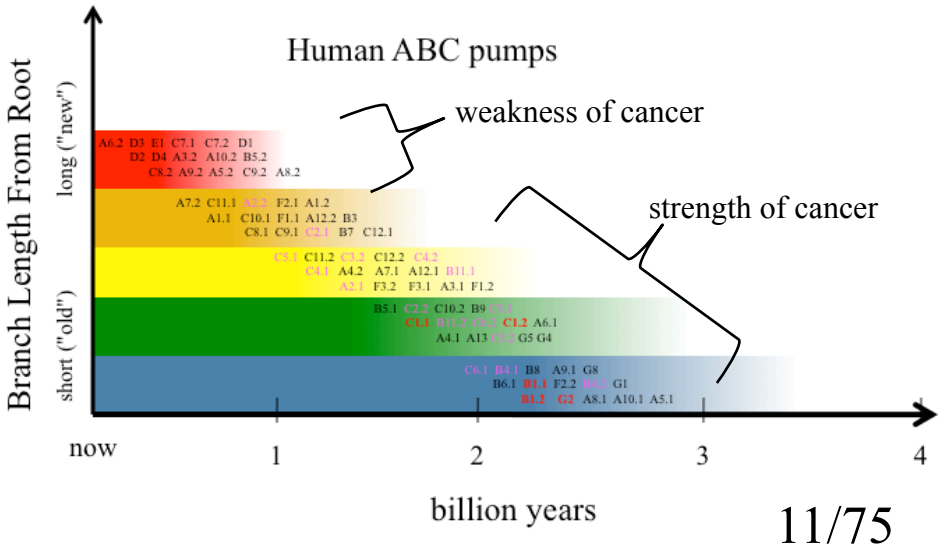


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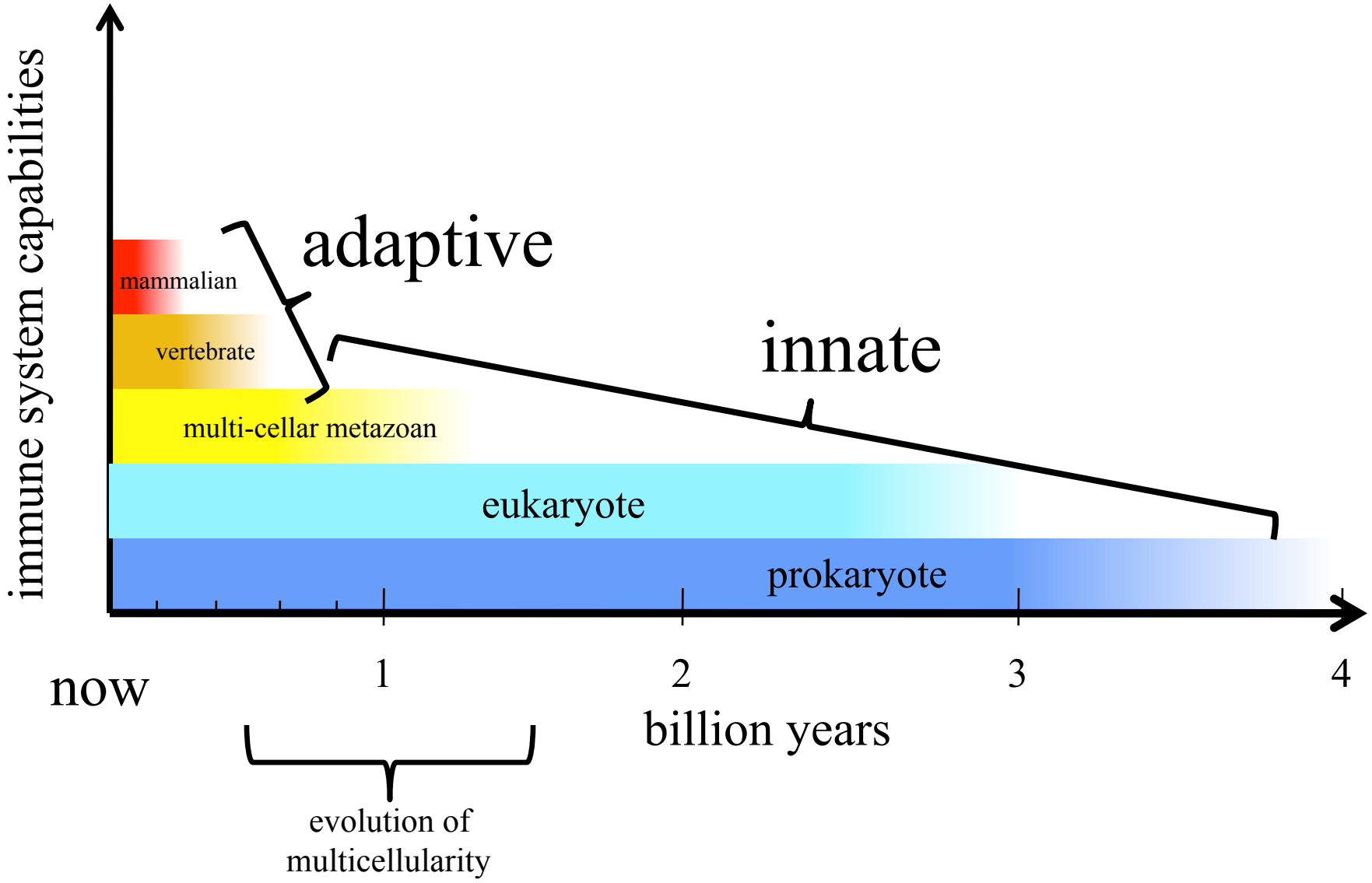
Table 1 | **Tissue localization and possible functions of ABC transporters**

Common Name	Systematic name	Tissue	Non-chemotherapy substrates	Chemotherapy substrates (known and suspected)	Defects in human disease	References
PGP/MDR1	ABCB1	Intestine, liver, kidney, placenta, blood–brain barrier	Neutral and cationic organic compounds, many commonly used drugs	Doxorubicin, daunorubicin, vincristine, vinblastine, actinomycin-D, paclitaxel, docetaxel, etoposide, teniposide, bisantrene, homoharringtonine (STI-571)	None known; altered sensitivity to drugs	8
MDR2	ABCB4	Liver	Phosphatidylcholine, some hydrophobic drugs	Paclitaxel, vinblastine	Progressive familial intrahepatic cholestasis	31,33,66,67
MRP1	ABCC1	All tissues	Glutathione and other conjugates, organic anions, leukotriene C4	Doxorubicin, epirubicin, etoposide, vincristine, methotrexate	None known	20–24
MRP2, cMOAT	ABCC2	Liver, kidney, intestine	Similar to MRP1, non-bile salt organic anions	Methotrexate, etoposide, doxorubicin, cisplatin, vincristine, mitoxantrone	Dubin–Johnson syndrome	24,60–63
MRP3	ABCC3	Pancreas, kidney, intestine, liver, adrenal glands	Glucuronate and glutathione conjugates, bile acids	Etoposide, teniposide, methotrexate, cisplatin, vincristine, doxorubicin	None known	37,38
MRP4	ABCC4	Prostate, testis, ovary, intestine, pancreas, lung	Nucleotide analogues, organic anions	Methotrexate, thiopurines	None known	39,40
MRP5	ABCC5	Most tissues	Nucleotide analogues, cyclic nucleotides, organic anions	6-Mercaptopurine 6-Thioguanine	None known	41,42
MRP6	ABCC6	Liver, kidney	Anionic cyclic pentapeptide	Unknown	Pseudoxanthoma elasticum (substrate unknown)	43–46,58
MXR, BCRP, ABC-P	ABCG2	Placenta, intestine, breast, liver	Prazosin	Doxorubicin, daunorubicin, mitoxantrone, topotecan, SN-38	None known	25–29,54
BSEP, SPGP	ABCB11	Liver	Bile salts	Paclitaxel	Progressive familial intrahepatic cholestasis	30,47,48, 64,65
ABCA2	ABCA2	Brain, monocytes	Steroid derivatives, lipids	Estramustine	Intracellular steroid transport	7,34,35

Gottesman et al 2002
Multidrug Resistance in Cancer:
Role of ATP-dependent Transporters,
Nature Reviews Cancer, 2, 48-58

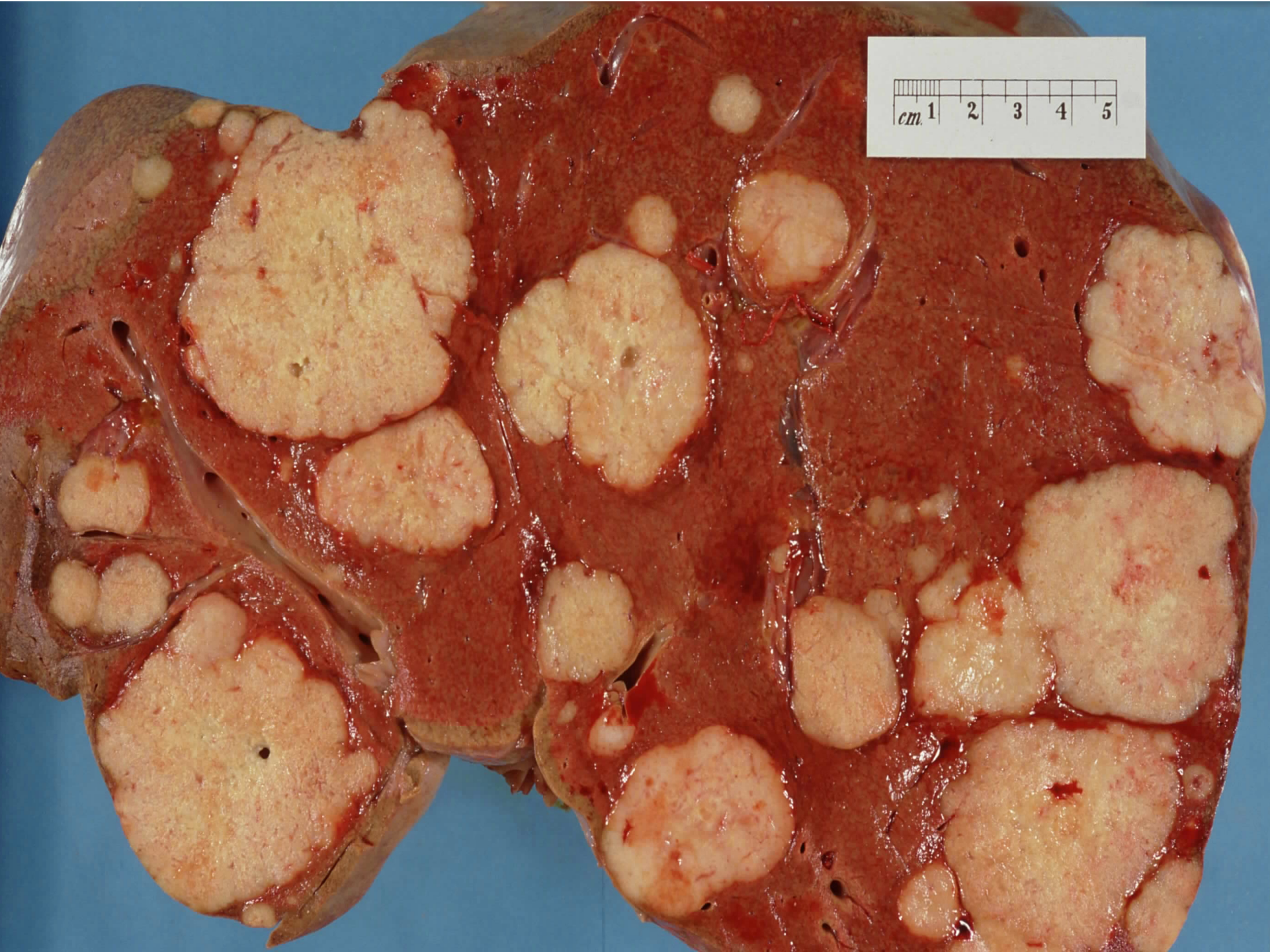
Dean, Rzhetsky & Allikmets, 2001, Genome Research,
The Human ATP-Binding Cassette (ABC) Transporter Superfamily


immune system capabilities
adaptive
innate
mammalian
vertebrate
multi-cellar metazoan
eukaryote
prokaryote
now
1
2
3
4
billion years
evolution of
multicellularity

Targeting Cancer's Weaknesses (not its Strengths):
Therapeutic Strategies of the Atavistic Model.

by Charles H. Lineweaver, Paul C.W. Davies & Mark Vincent

…a therapeutic strategy for targeting cancer: design challenges that can *only* be met by the recently evolved capabilities no longer functional in cancer cells. One example of an exploitable weakness of cancer is the absence of an effective adaptive immune response in immunosuppressed tumor environments. This leaves tumor cells more vulnerable than healthy tissue, to pathogenic attack. Such a target-the-weakness therapeutic strategy has a broad application and contrasts with current therapies that target the main strength of cancer: cell proliferation.


cm. 1 2 3 4 5

Recipe for targeting the weakness.

The weakness is the absence of adaptive immunity in the tumor environment.

a) Identify a highly effective vaccine that protects the host organ (and the body in general) from a specific virus, bacterium or parasite that targets the host organ.

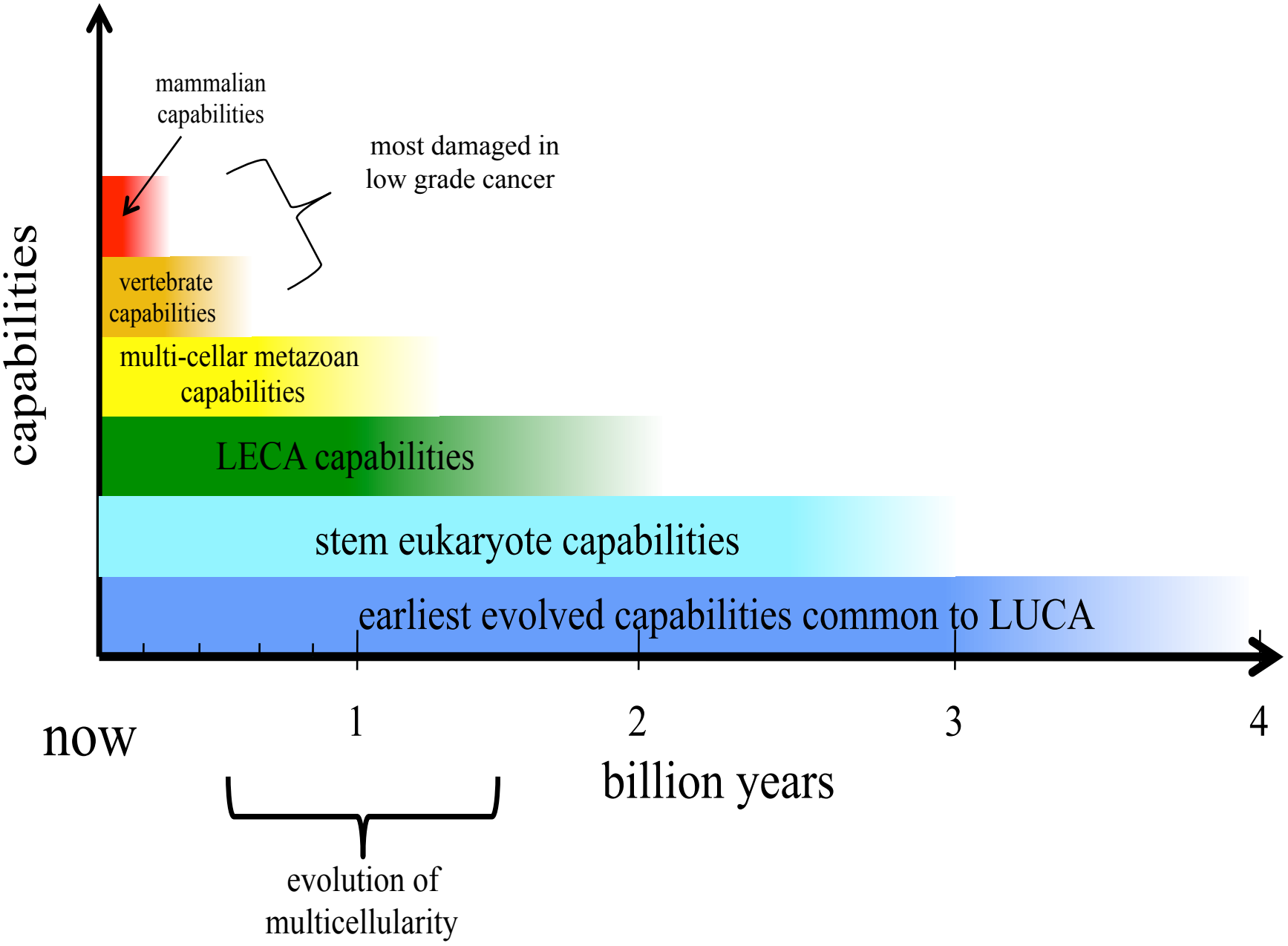
b) Vaccinate the patient (or verify that the patient has been previously vaccinated)

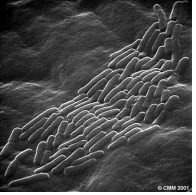
c) Inoculate the affected organ (specifically the tumors in the organ) with the disease-causing infectious agent at a dosage that will allow the vaccine-primed adaptive immune system to protect normal cells but, because of tumor immunosuppression, will be less able to protect tumor cells from the disease.

This therapy should be most effective in cases of strong immunosuppression. The more advanced the cancer, the more immunosuppressed the patient and the more difference there is between normal and tumor cells in terms of communication with the adaptive immune system. Thus, this therapy may complement standard cancer immunotherapies which are *least* effective in highly immunosuppressed patients.

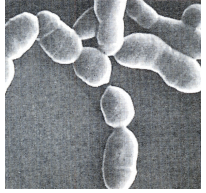
In the case of metastasis: modify the approach of Quispe-Tintaya et al (2013). After vaccination against *Listeria*, an inoculation with *non-attenuated Listeria* is carried out. TAMs should be preferentially susceptible to attack from the *Listeria*, but normal macrophages at wound-healing sites will be relatively well-protected by the adaptive immune system. Since non-attenuated *Listeria* is not just the carrier but also the killer, *Listeria* reproduction increases its effectiveness with time.
No dilution of the killing agent (= radiation).

This is not Coley, BCG or immunotherapy.
The goal is not to induce an adaptive immunity response against the tumor.
The infectious agent is not attenuated.

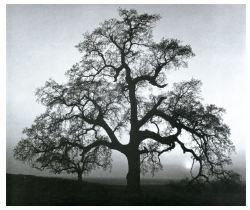

capabilities
mammalian capabilities
most damaged in low grade cancer
vertebrate capabilities
multi-cellar metazoan capabilities
LECA capabilities
stem eukaryote capabilities
earliest evolved capabilities common to LUCA
now
1
2
3
4
billion years
evolution of multicellularity



E. coli



Methanogens



plants

fungi

jellyfish

insects

human

Eubacteria

Archaeaa

Bikonts

plastids

Holomycota

Radiata

protostomes

0.8

deuterostomes

1.0

Bilateria

1.4

Holozoa

1.6

Unikonts

cyanobacteria

organelles

LECA

alpha proteobacteria

2.0

mitochondria

organelles

karyogenesis

nucleated cells

spirochete

flagella, basal bodies,
mitotic spindles

3.0

stem eukaryotes

4.0

Archaea

evolution of everything