Oncogenes, Quarks and Cancer Care: Hadron therapy in the 21st Century

Bright Horizons 8

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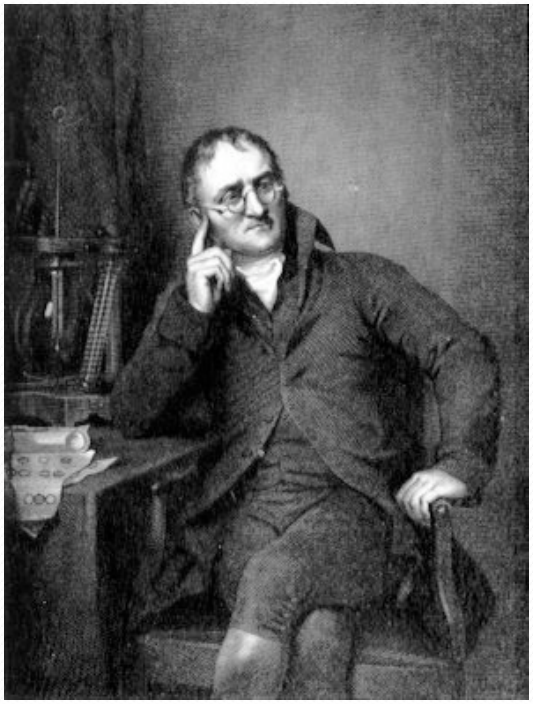
Origins of Atomism

- Leucippus 450 BCE
  - The first "atomist" (? Possible origins in India one century earlier???)
- Democritus – "The Laughing Philosopher"
  - Student of Leucippus
  - "Atomos" – unbreakable
  - 60 "books" on subject
- Plato and Aristotle – opponents of atomism
- Epicurus 341-270 BCE
  - 300 "books" – not one survived the Dark Ages
- Lucretius 96-55 BCE
  - De Rerum Natura (On the Nature of Things)
  - ONE copy (!) survived and discovered in 1417

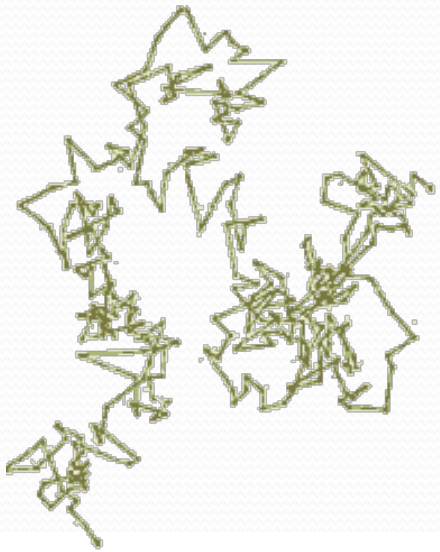
Chemistry and Atomism

- Robert Boyle
  - Father of the science of chemistry
  - *The Skeptical Chemist*
  - PV = k or $P_1V_1 = P_2V_2$ (Boyle's Law)
  - Best explained in terms of atoms
- John Dalton
  - First to introduce term "Atom"
  - 1808 *New System of Chemical Philosophy*
  - Laws of chemistry best explained if each element corresponds to a specific type of atom



Proof of Atoms and Molecules

- 1827 Robert Brown - Scottish botanist
- Studied pollen grains suspended in water
- Initially believed seemingly random motion was due to a “force of life”



A

BRIEF ACCOUNT

OF

MICROSCOPICAL OBSERVATIONS

Made in the Months of June, July, and August, 1827,

ON THE PARTICLES CONTAINED IN THE POLLEN OF PLANTS;

AND

ON THE GENERAL EXISTENCE OF ACTIVE MOLECULES

IN ORGANIC AND INORGANIC BODIES.

BY

ROBERT BROWN,

F.R.S., Hon. M.R.S.E. and R.I. Acad., V.P.L.S.,

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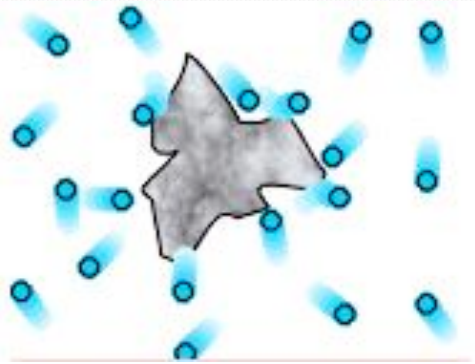
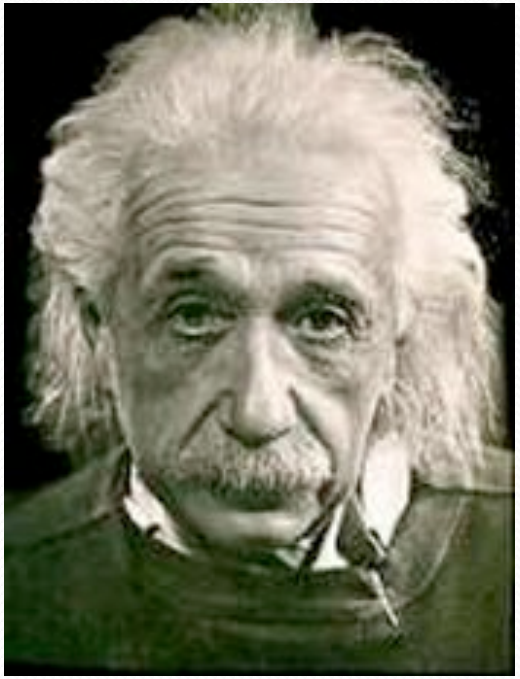
Proof of Existence

- 1902 Theodore Svedberg
  - A name well known to those who are interested in ribosomes!
- Wondered… Could Brownian motion be due to water molecules bombarding the pollen grains?
- A detailed analysis required someone else's contributions…



Einstein's Famous Equation of 1905

Well, one of them… Well maybe not so famous…



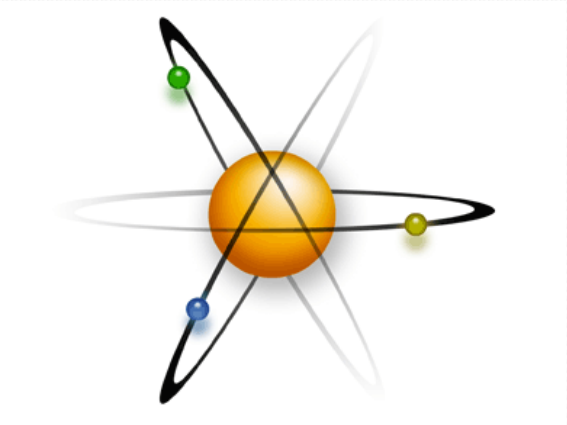
$$d = \sqrt{2Dt} \propto \sqrt{t}$$

Proof of Existence

- Einstein's analysis converted most doubters into believers of the atomic/molecular theory
- Exquisite experimental confirmation obtained by Perrin in 1908
  - Proved Einstein was correct
- Left no doubt about existence of molecules
- Perrin was actually able to work out sizes of constituent atoms

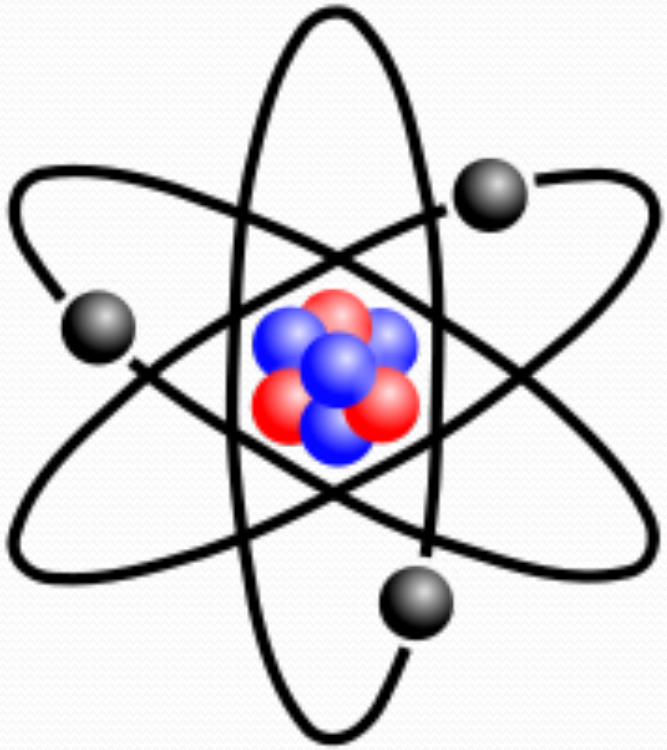
Atomic Models

- JJ Thomson – discoverer of the electron
  - "Plum pudding" model
- Hantaro Nagaoka –Planetary model of orbiting electrons
  - Beautiful (and enduring) visual picture even if not very realistic (great for Sci Fi fans though!)



Atomic Models

- Rutherford showed nucleus to be far smaller and denser than previously believed
- William Draper Hawkins suggested the existence of another nuclear particle – the neutron
- Initially thought of as a fusion of an electron and proton
  - Further consideration of Spin showed this was not possible
  - e.g. Net spin of Nitrogen-14 (with 14 total nucleons vs 21 total nucleons if neutron was a proton/electron combo) led to conclusion that the neutron must be an independent entity
- Confirmed by Chadwick in 1932



Problems with Beta Decay

- Unlike monoenergetic alpha emissions, beta emissions demonstrated a spectrum
- Seemed to violate conservation laws
  - Energy
  - Momentum

Problems with Beta Decay

- 1930 Pauli suggested another particle that would conserve energy and momentum – and would also conserve "electron number"
- Fermi offered the name "neutrino" (little neutral one)
- Cowens and Reines (1956) - *Anti*neutrino detection
- Reines (1965) Underground perchloroethylene – detected solar neutrinos
  - But discovered a "Solar Neutrino Deficit"
  - Recently solved by neutrino flavor oscillations

More

- Carl David Anderson - 1932
  - Cosmic rays
  - An "electron going the wrong way"
  - But predicted: The **positron** of Dirac
- Segre, Chamberlain, Wiegand and Ypsilantis
  - Antiproton – also predicted
- Cecil Powell – Cosmic ray experiments
  - A charged particle of 273 electron masses (in between mass of electron and proton – a "meson" for "intermediate"
  - The exchange particle predicted by Yukawa
    - Pi meson (pion)
- Anderson, Neddermeyer, Street and Stevenson
  - A "fat and slow electron" ~207 electron masses
  - NOT predicted! Isidor Rabi: "Who ordered **THAT**?!?!"

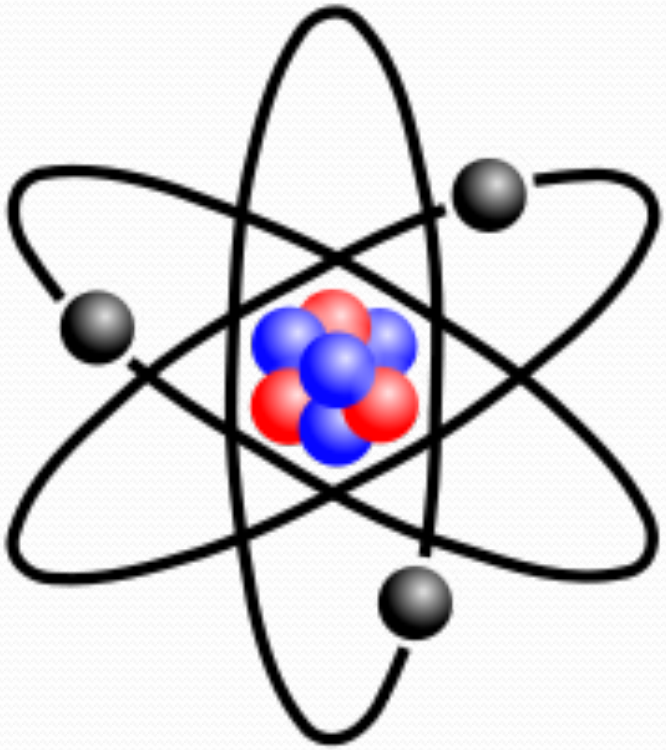
Proliferation

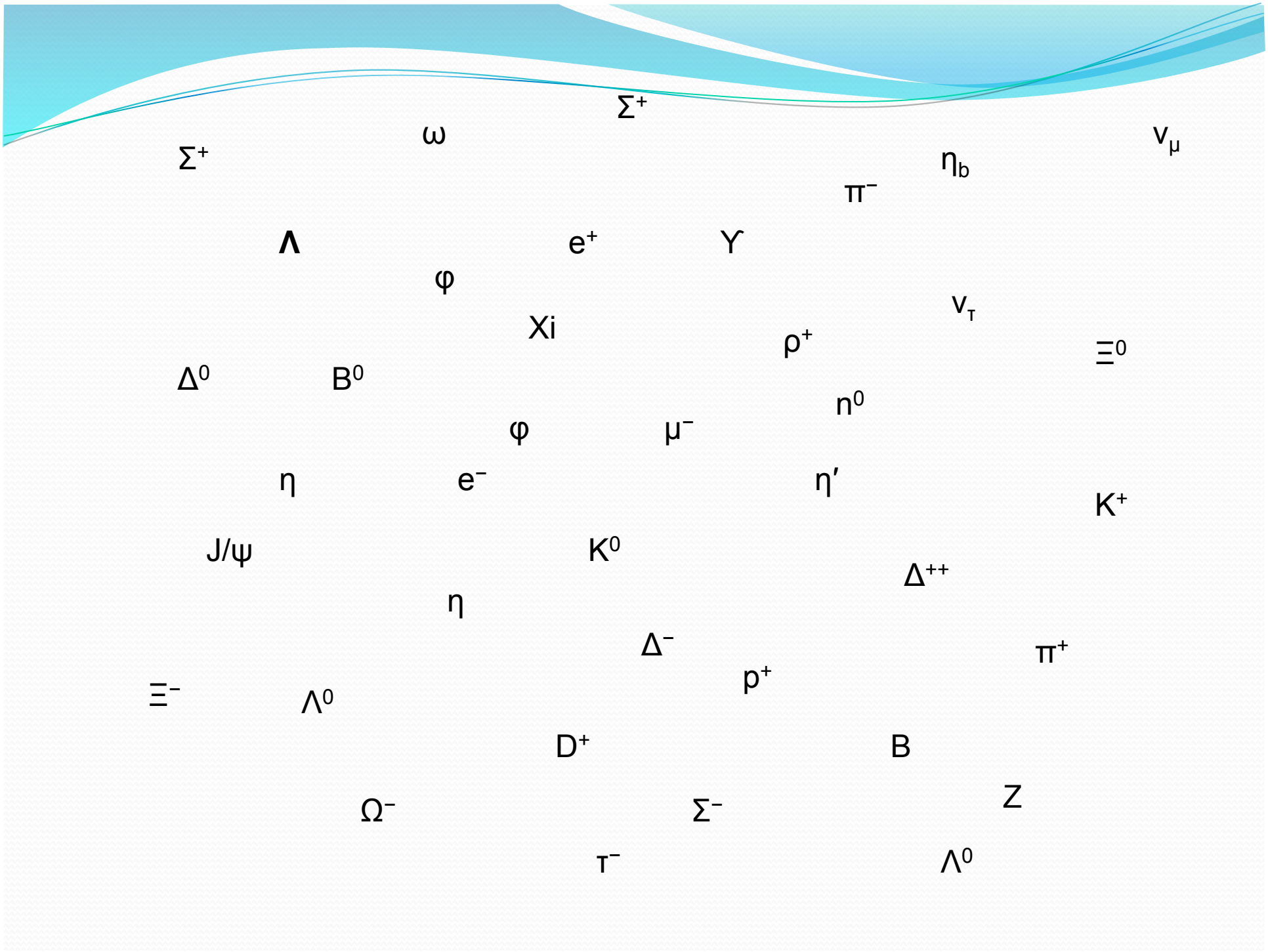
- The pion was a "true meson" similar in many ways to protons and neutrons
- Pions and relatives – **Mesons**
- Protons and neutrons – **Baryons**
- Both are **Hadrons** (subjected to strong force)
- The muon appeared to be a fundamental particle just as the electron is (despite its mass which classed it as a "meson" in the old system since it was in between the electron and the proton/neutron)
  - Not subjected to strong force = **Leptons**

Proliferation

- Unfortunately…
- The pion wasn't the last meson
  - And the muon wasn't the last lepton
  - And the nucleons weren't the last baryons…
- Once the particle accelerators came about dozens of new particles were discovered including numerous "hyperons" (i.e. heavier than protons and neutrons)

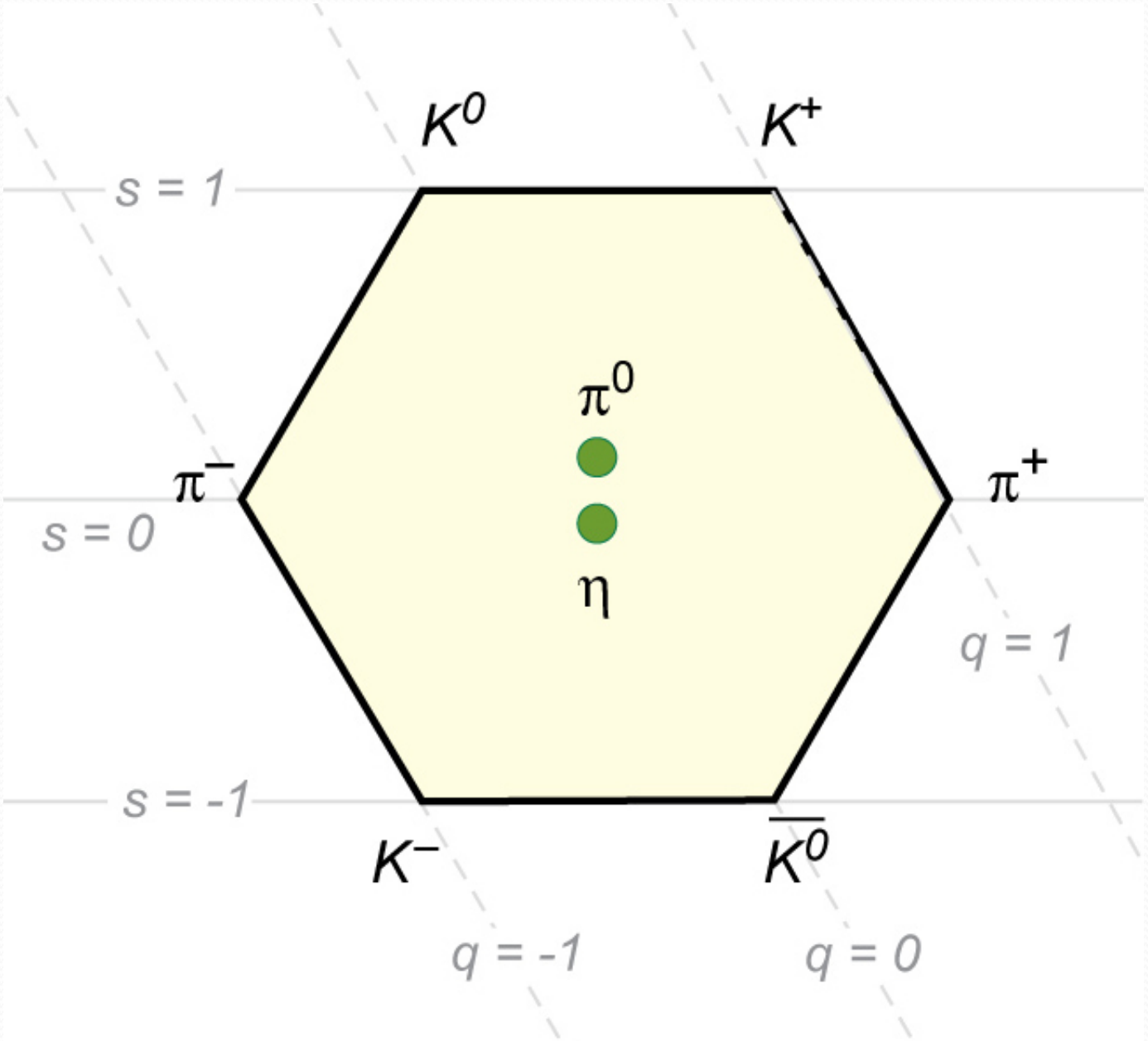
This beautiful and simple concept had to be replaced…




Σ^+
ω
ν_μ
Σ^+
η_b
π^-
Λ
e^+
Υ
φ
ν_τ
Xi
ρ^+
Ξ^0
Δ^0
B^0
n^0
φ
μ^-
η
e^-
η′
K^+
J/ψ
K^0
Δ^{++}
η
Δ^-
π^+
p^+
Ξ^-
Λ^0
D^+
B
Z
Ω^-
Σ^-
τ^-
Λ^0

Seeking some order

- 1932 – Heisenberg suggested that the proton and neutron were really the same particle except for charge
- Eugene Wigner introduced idea of "Isotopic Spin" or Isospin
- Gell-Mann and Ne'eman – Grouping of hadrons in certain ways revealed patterns (e.g. diagonal lines had same charge)
- Plot of {Baryon Number + Strangeness} ("Hypercharge") vs Z-projection of Isospin
- The "Eight-fold Way" or SU(3)


K^0
K^+
s = 1
π^0
π^-
π^+
s = 0
η
q = 1
s = -1
K^-
$\overline{K^0}$
q = -1
q = 0

The Eightfold Way

- Hinted at some kind of underlying organization
  - Analogous to Mendeleev's Periodic Table
    - Periodic Table proved its merit by prediction and subsequent discovery of previously unknown elements
    - Eightfold Way proved its merit by prediction and subsequent discovery of previously unknown hadrons
    - Omega minus (BNL 1964)
- Understanding of Periodic Table had to await quantum mechanics and electron orbital theory
- What was the underlying organization for the hadrons???

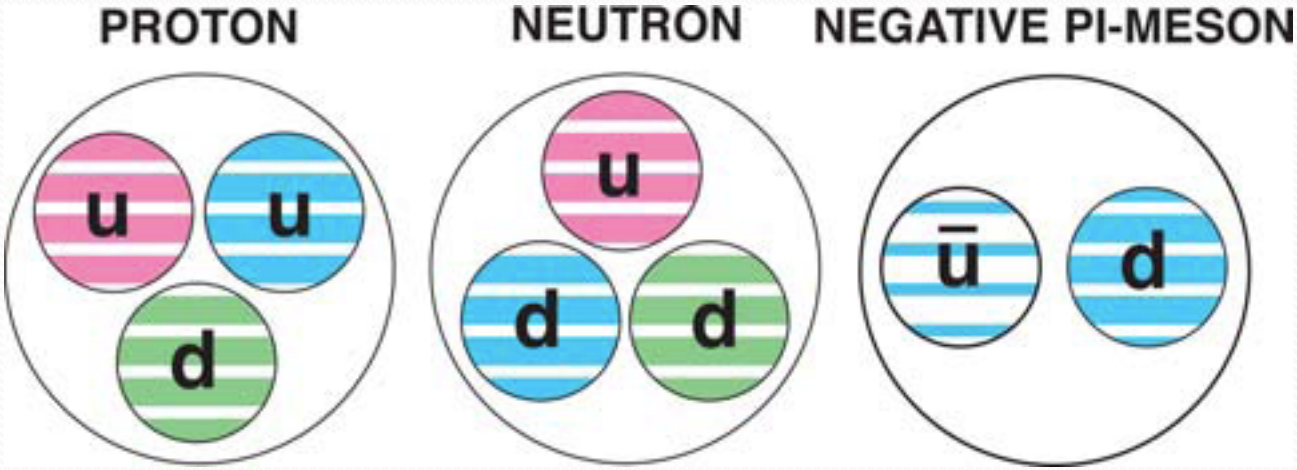
- Robert Hofstadter – electron bombardment of protons and neutrons
  - Consistent with shells of electric charge within
  - First suggestion of fractional charges?
- Gell Mann and Zwieg – suggested truly fundamental particles with fractional charges
  - “Partons” vs “Quarks”
  - SLAC team provided some evidence
  - So… Hadrons are made of quarks
    - Baryons = 3 quarks
    - Mesons = quark/antiquark pairs
- 6 flavors of quarks in 3 generations
- 6 flavors of leptons in 3 generations
  - Comprise all matter

Baryons behaving badly?

- Leptons and quarks have half-integral spin – FERMIONS
  - But fermions should obey Pauli Exclusion Principle
  - So… Quarks should behave like electrons in an atom (e.g. no two electrons in an atom can have all four quantum numbers identical)
- But 3 quarks together in a baryon..?
  - Appears to violate exclusion Principle!
  - Unless there is some subtle difference – such as an unknown quantum number???

Color

- Solution: Differences in “Color Charge”
  - Quarks come in 3 possible colors
  - Red, Green or Blue
- All hadrons must be “color neutral” or “White”
- Solutions:
  - 3 different colors in a baryon
  - Color/“Anti-color” in a meson


PROTON
u
u
d
NEUTRON
u
d
d
NEGATIVE PI-MESON
ū
d

Confinement

- Strong force is mediated by gluon exchange between quarks within hadrons
- Upon exchange of gluons, quarks change color
  - Force of attraction = kr^x
  - F approaches infinity at r = 1 Fermi (10^{-15} m)
  - i.e. exchange of gluons becomes more and more rapid with distance
- Thus *quark color must change more and more rapidly with distance*…

A corollary?

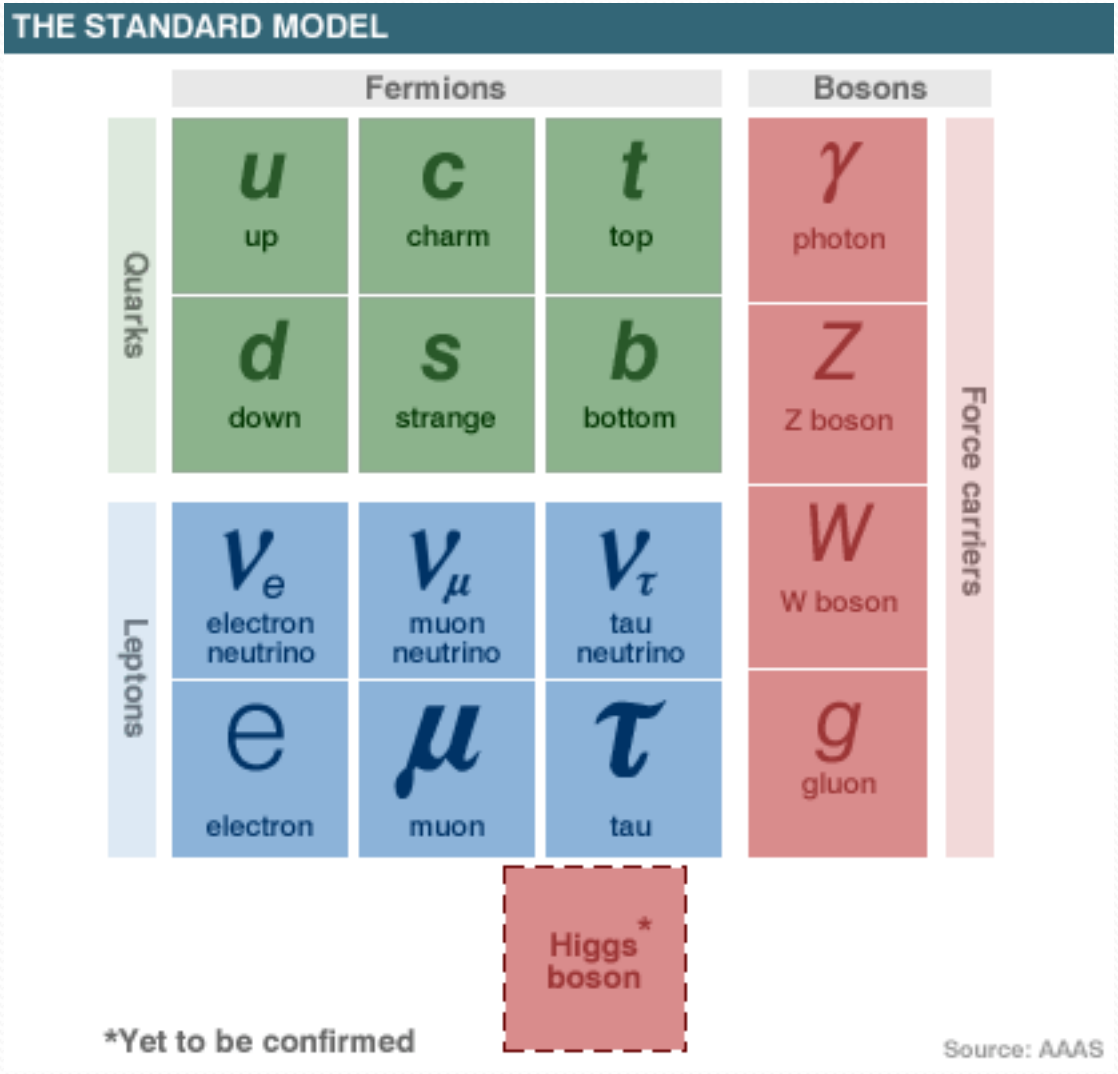
- $\Delta x \cdot \Delta p > h/2\pi$
- $\Delta E \cdot \Delta t > h/2\pi$
- Expressions of the uncertainty principle

- ??? ΔC and Δr ???

Confinement

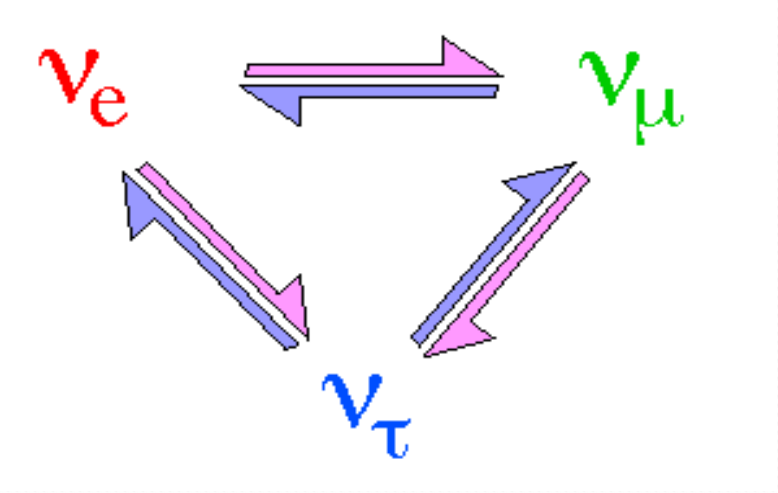
- $\Delta x \cdot \Delta p > h/2\pi$
- $\Delta E \cdot \Delta t > h/2\pi$

- ??? $\Delta C/\Delta r$??? ---- The BH(8) Uncertainty Principle?


THE STANDARD MODEL
Fermions
Bosons
Quarks
u
up
c
charm
t
top
γ
photon
d
down
s
strange
b
bottom
Z
Z boson
Leptons
ν_e
electron neutrino
ν_μ
muon neutrino
ν_τ
tau neutrino
W
W boson
e
electron
μ
muon
τ
tau
g
gluon
Force carriers
Higgs* boson
*Yet to be confirmed
Source: AAAS

Neutrino flavor oscillations

- Solves solar neutrino deficit problem but suggests neutrinos have a finite mass



Gauge bosons

- Photons and gravitons
  - Massless and infinite in range
- Gluons
  - Massless but exchange color and thus not infinite in range
- Weak interaction particles
  - Short range but no color exchange – thus massive
  - Race to find the W^- W^+ and Z^0 won by CERN team
  - Carlo Rubbia and Simon van der Meer
    - Analyzed 140,000 events
    - Found 5 potential candidates for W^- & W^+
    - Announced discovery in January 1983
    - Z^0 discovery announcement May 1983
    - Nobel Prize 1984

The Other End of the Spectrum

- Rubbia and van der Meer: incredible pace, incredible work - and incredibly rapid reward with Nobel Prize in one year
- Peyton Rous – 1911
- Conducted work with chickens with tumors
- Applied Koch's Principles
  - Concluded the sarcomas were caused by an infectious agent – a virus
  - Nobel Prize 1966(!) – 55 years to formally recognize the significance!

Rous Sarcoma Virus

- A "retrovirus" – like HIV (Human Immunodeficiency Virus)
  - RNA is reverse transcribed into DNA
- Genome contains only 4 genes!
  - Yet can cause cancer!
- Mutants containing only 3 genes and unable to cause cancer
  - Led to the discovery of the src gene
- V-src – the first "oncogene"
- A gene that causes cancer

What is Cancer?

- A disease that afflicts 10 million people annually
  - Perhaps 20 million per year by 2020
- Hippocrates in 5th Century BC called the disease cancer for the Latin word for "crab"
- Trivia (or perhaps confirmation that the two disciplines really ARE related) – Hippocrates and Democritus were both born the same year – 460 BC
  - According to legend Hippocrates was commissioned to cure Democritus of his madness (uncontrollable laughing)
  - Hippocrates' diagnosis was that Democritus simply had a happy disposition…
  - Thus, Democritus is known as "the laughing philosopher"

What is Cancer?

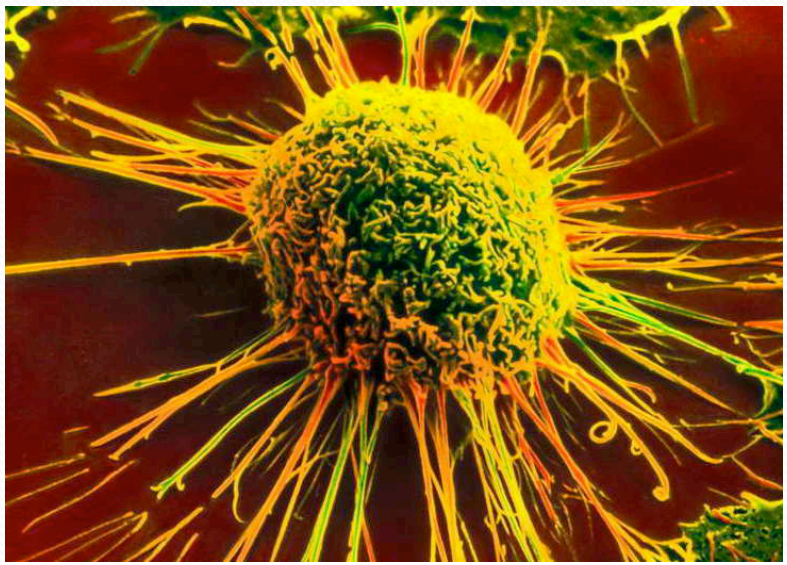
- "A family of diseases in which abnormal cells proliferate and spread in an uncontrolled fashion, eventually choking off the life of the organism"

A "Cellular Disease"

- Unlike heart, lung, liver or brain disorders
- The malignant cells can start anywhere and spread anywhere
- A drastic change in "cellular philosophy"… Disregard for the "laws"
  - Normal cells cooperate
  - Cancer cells compete - With their benign neighbors and with each other
  - They disrespect other's boundaries and invade territories they shouldn't
- Normal cells can't compete (since they don't even try) and lose out

Evolution through Natural Selection

- Any time there is competition in biology there is natural selection
- Natural selection among the competing cells leads to ever-increasingly bizarre phenotypes



Evolution through Natural Selection

- Eventually the cells become very different from their parent organ
  - Become self-sufficient
  - Capable of growing without growth signals
  - Capable of inducing new blood vessels to supply their constant energy demands
  - Become immortal
  - Become capable of invading and spreading (metastasizing) to other places
- All thanks to competition and selection (i.e. evolution) at the cellular level

The Causes

- Chemical carcinogens
- Physical carcinogens (e.g. UV radiation, ionizing radiation)
- Chronic inflammation

- Infections (!) – cause approximately 1.5 million cases (~15% of worldwide total) per year!
  - Schistosoma hematobium (Egypt)
  - Opisthorchis sinensis
  - Helicobacter pylori
  - Chlamydia psattaci
  - Campylobacter jejuni
  - Borrelia burgdorferi
  - Most (~11% of worldwide total) are due to viruses (e.g. Hepatitis B & C, HPVs, HTLV1, KSHV)

Can one directly "catch cancer"?

- Depends…
- If you are a *Sarcophilus harrisii* the answer is definitely YES!
  - The wild Tasmanian devil population could very well face extinction due to the contagious cancer, Devil Facial Tumor Disease, first observed in the 1990's and directly transmitted as a *non-rejected* xenograft (i.e. transplant)
- If you are a *Canis familiaris*, the answer is also yes… but you would not likely die of the cancer
  - Canine transmissible venereal tumor or Sticker sarcoma of dogs is also passed along as a xenograft – but as with most transplanted organs or tissues, is rejected

Prevention of cancer

- Reduction of carcinogen exposure
- 1761 – Dr John Hill noticed increased incidence of nasal cancer among chronic snuff users

Sir Percivall Pott (1714-1788)

- Noted that scrotal cancer was more prevalent among chimney sweepers
- Soot = carcinogen
- Virtual eradication of scrotal cancer through application of this knowledge (hygiene)
- First successful public health campaign!

Search for the root causes

- *HOW* do cells turn malignant?
- Maybe those simple retroviruses hold the answer???
- Rous sarcoma virus has v-src
- Makes a protein that is a "protein kinase"
  - Specifically a tyrosine kinase
- Could this molecule be ***the*** cause of cancer??

Some problems with this simple hypothesis

- Several other retroviruses besides RSV cause cancers
- And contain ***different*** oncogenes
  - v-sis
  - v-Hras
  - v-jun
  - v-erbB
  - v-fos
  - v-ets
  - v-Kras
  - v-fms
- And some weren't tyrosine kinases…

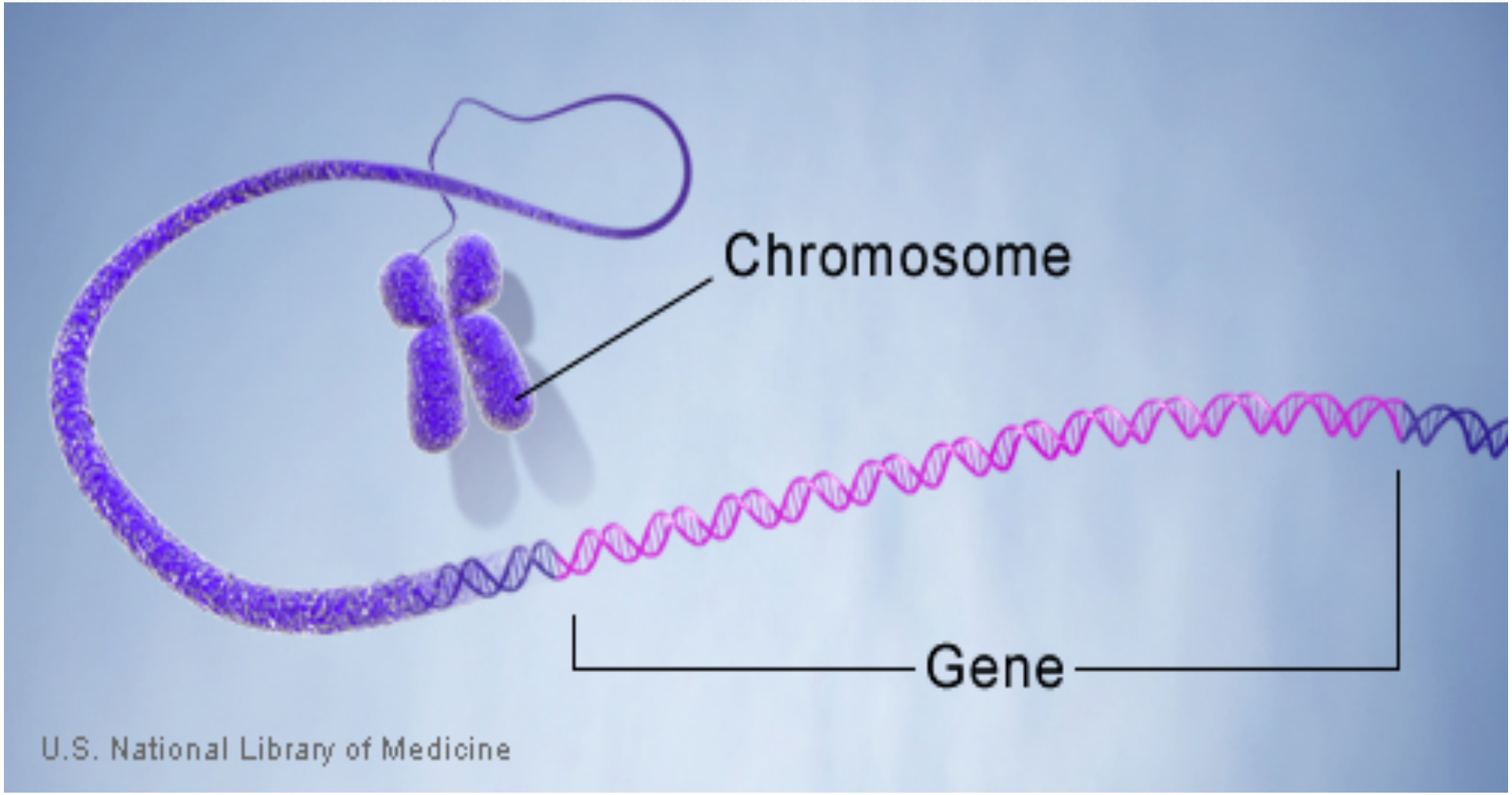
Some problems with this simple hypothesis

- Some other viruses didn't even have oncogenes – but still caused cancer!?!
  - Avian leucosis virus (ALV)
- "Insertional carcinogenesis" – the virus inserts itself into the bird genome and seems to cause a ***normal*** gene to go haywire
  - Inserts itself next to a gene called myc
  - Over-stimulates myc gene
  - Causes overproduction of myc protein

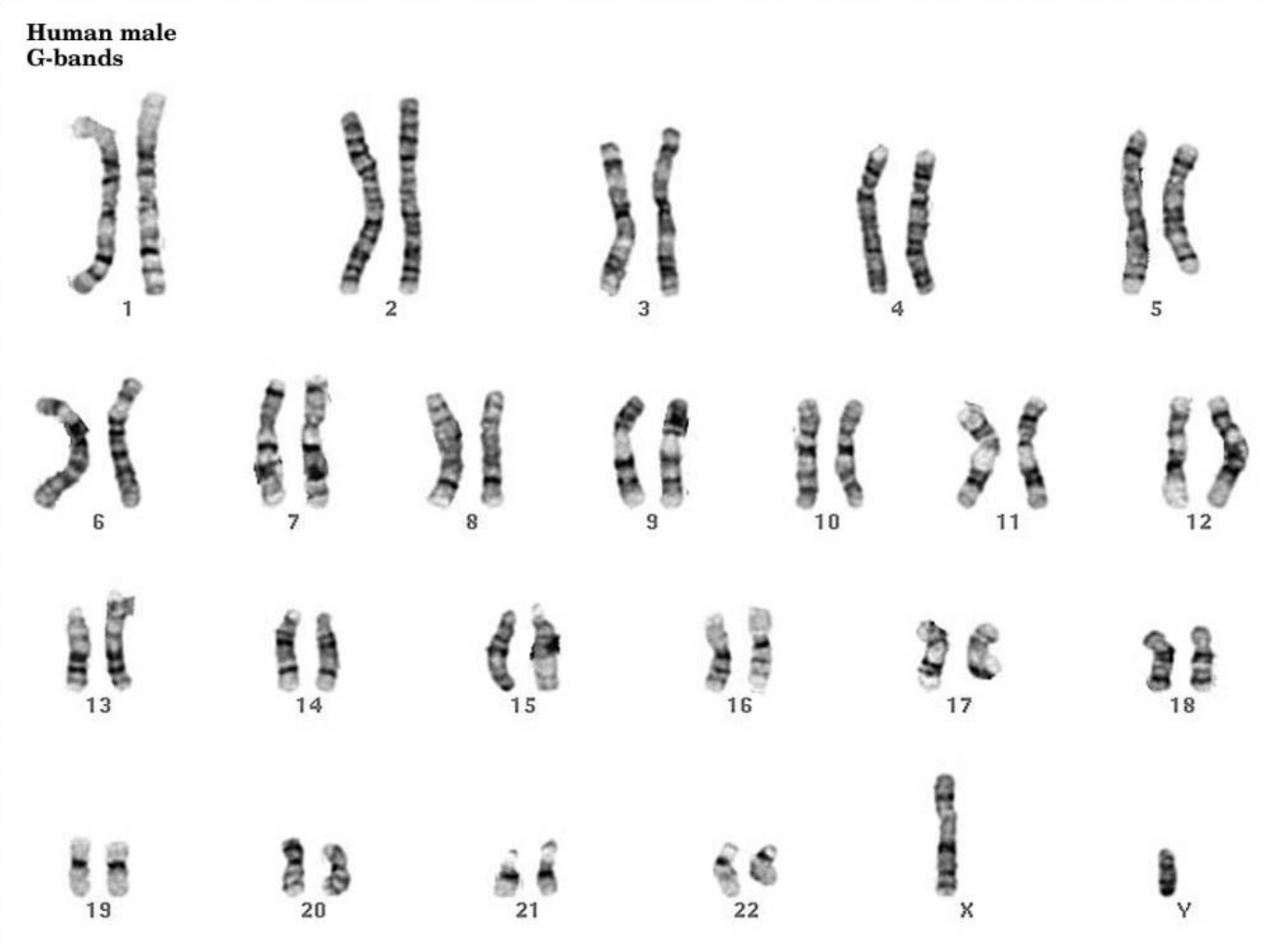
Some problems with this simple hypothesis

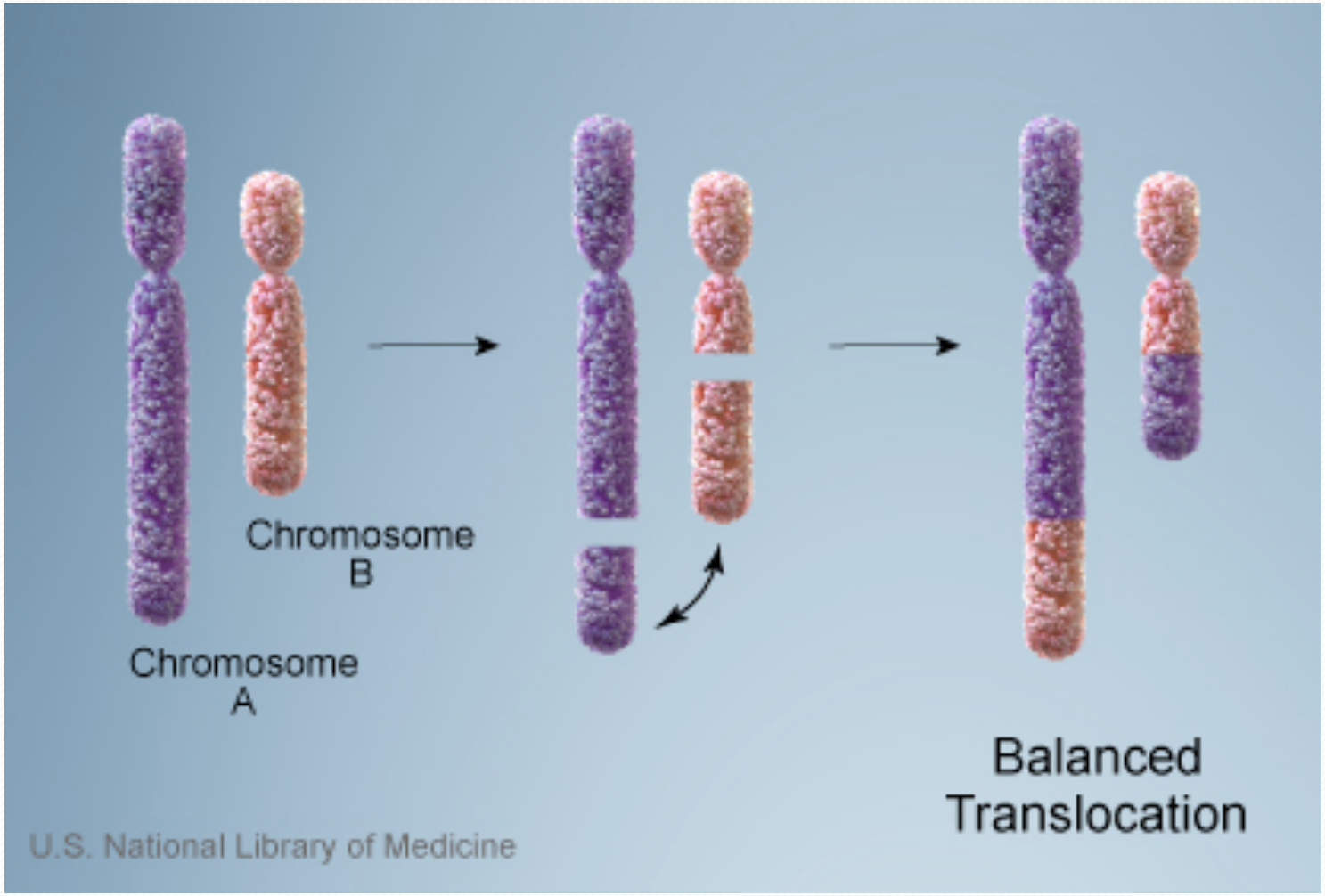
- But most HUMAN cancers are NOT caused by retroviruses…
  - So is any of this relevant to people?
- The human *MYC* gene is similarly over-expressed in certain human cancers
  - e.g. Burkitt lymphoma (named for British surgeon Dennis Burkitt who ran a clinic in central Africa)
- A pediatric cancer in Central Africa
  - ***chromosomal rearrangements*** → Burkitt lymphoma

Genes are specific DNA sequences on the chromosomes



Humans have 46 total chromosomes: 23 pairs
"46, XY" - The normal human male karyotype



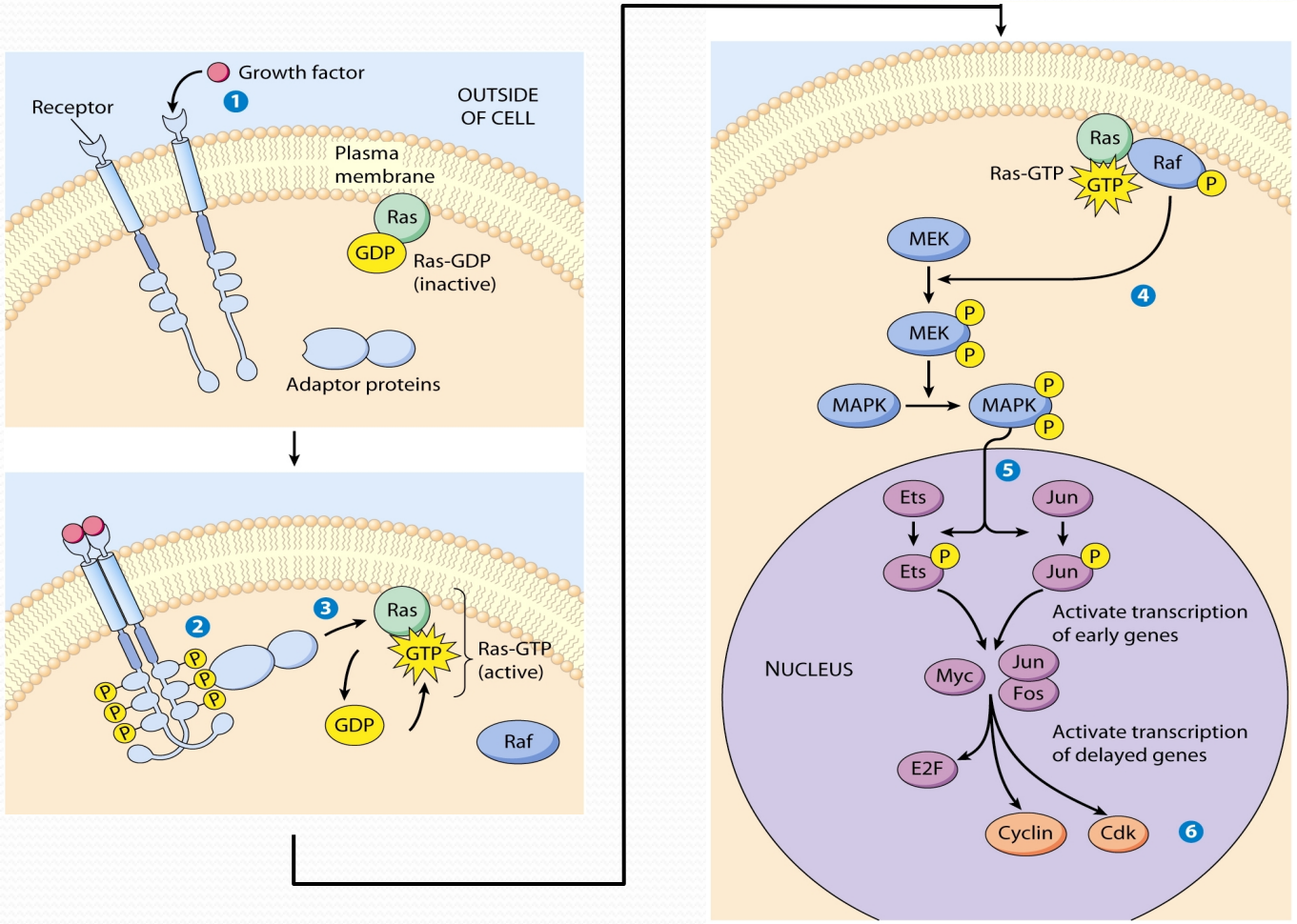

Chromosome
B
Chromosome
A
Balanced
Translocation
U.S. National Library of Medicine

So *MYC* is overactive in certain human cancers

- Somehow the chromosomal translocations (e.g. t (8;14)) activates the *MYC* gene and leads to cancer
- But *MYC* is a normal human gene that is present in all cells
  - Such genes are called "proto-oncogenes"
- Myc protein is a "transcription factor"

RAS in another proto-oncogene that has a central role in cell proliferation pathways – and when overactive can lead to trouble

Ras is a so-called “G-protein” because of the central importance of GDP and GTP in its function



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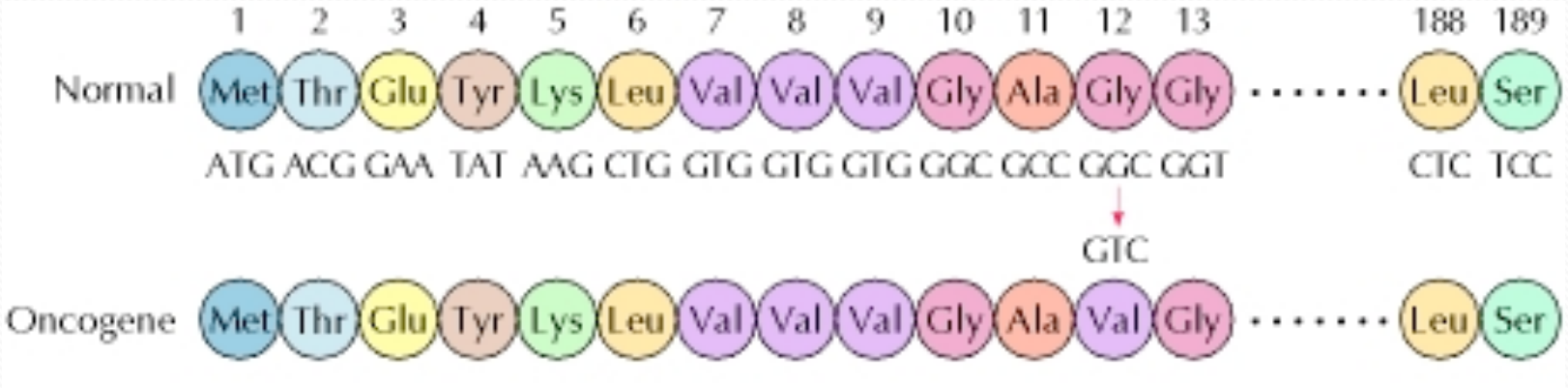
Point mutations can activate *RAS* even when no growth signal is present - "Constitutively active"

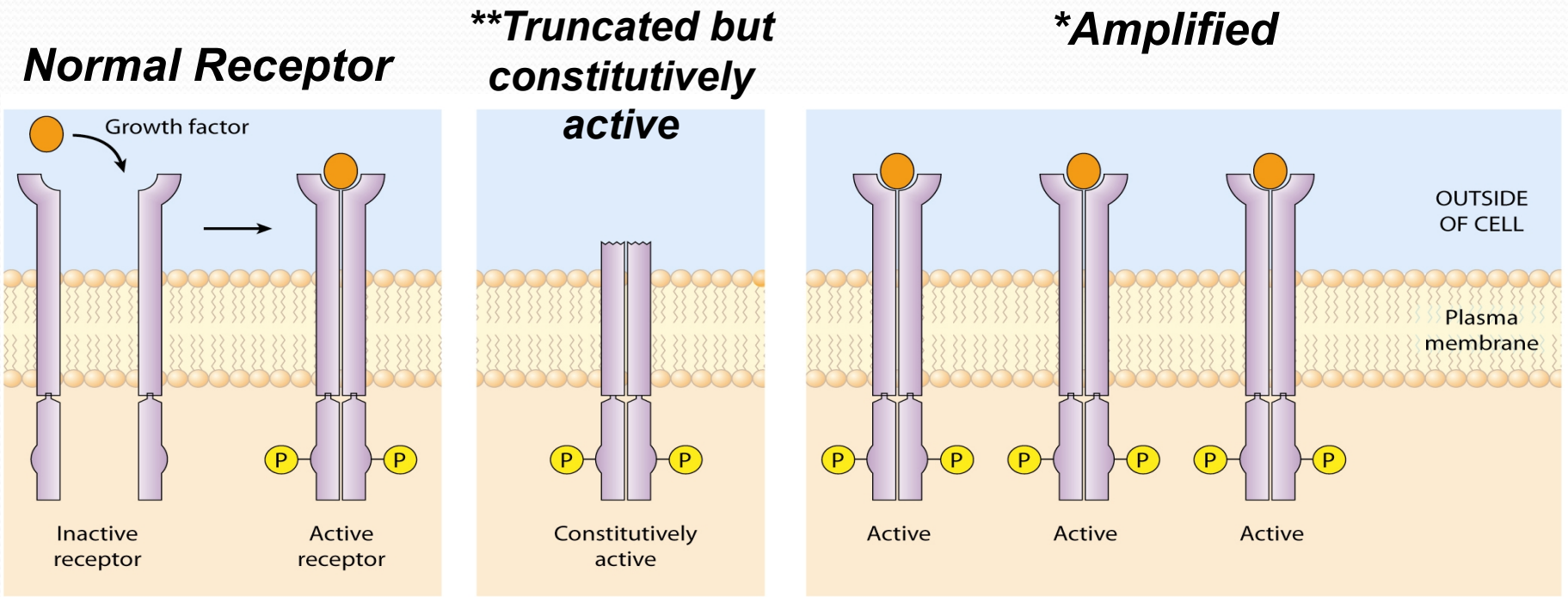


Silent Point Mutations

- "Silent" mutations are DNA base changes that yield *the same amino acid* (because of redundancy in the genetic code)
- …and thus yield the *same protein sequence*
  - Long assumed to be of little significance
  - Theoretically no difference should be seen
  - Recently found that silent mutations in the *MDR1* gene can speak loudly!
  - Fascinating molecular mechanism…
    - "Codon bias" is the cause (results in a change in 3D conformation of the final protein)

Receptors are often abnormal in cancer cells

- *30% of breast cancers have overexpression (amplification) of EGFR (a receptor tyrosine kinase)
- **50% of glioblastomas overexpress EGFR or make a constitutively activated form



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Mechanisms of oncogene activation

- So normal human cells harbor proto-oncogenes with important functions in normal cells
- But ***if inappropriately activated***, they wreak havoc
- Can be activated by many mechanisms:
  - Chromosomal translocations
  - Point mutations, other mutations (deletions, insertions)
  - Gene amplification
  - Viral infection
  - ***All result in hyperactive proto-oncogenes (which are then called "oncogenes"***

Oncogenes have various functions

- Oncogenes produce proteins that serve as:
  - Growth factors
  - Growth factor receptors (receptor tyrosine kinases)
  - G-proteins
  - Intracellular protein kinases
  - Transcription factors
  - Cell cycle/cell death regulators
    - These last oncogenes are involved in **either ignoring death signals (apoptosis)** or **differentiation** signals

Six classes of Oncogenes

- With these 6 functions are we done?
- Do we now fully understand the molecular biology of cancer?

- Not even close…

Hereditary Cancer Syndromes

- Another line of investigation identified another set of genes involved in cancer…
  - Hereditary retinoblastoma
  - Li-Fraumeni syndrome
  - Cowden syndrome
  - Lynch syndrome (HNPCC)
  - Familial adenomatous polyposis (FAP)
  - Peutz-Jeghers syndrome
  - Xeroderma pigmentosum, ataxia telangiectasia, Fanconi anemia, Bloom syndrome, etc, etc, etc.
- Revealed "Anti-oncogenes" – ***Tumor Suppressor Genes***

Retinoblastoma

- Most common primary eye tumor in children
- Hereditary and non-hereditary forms
  - Hereditary characterized by early onset and bilaterality
  - and sometimes "***trilateral retinoblastoma***"
  - i.e. with pineoblastoma
- Molecular mechanisms serve as a model for other cancer susceptibility syndromes

Hereditary Retinoblastoma (OMIM #180200)

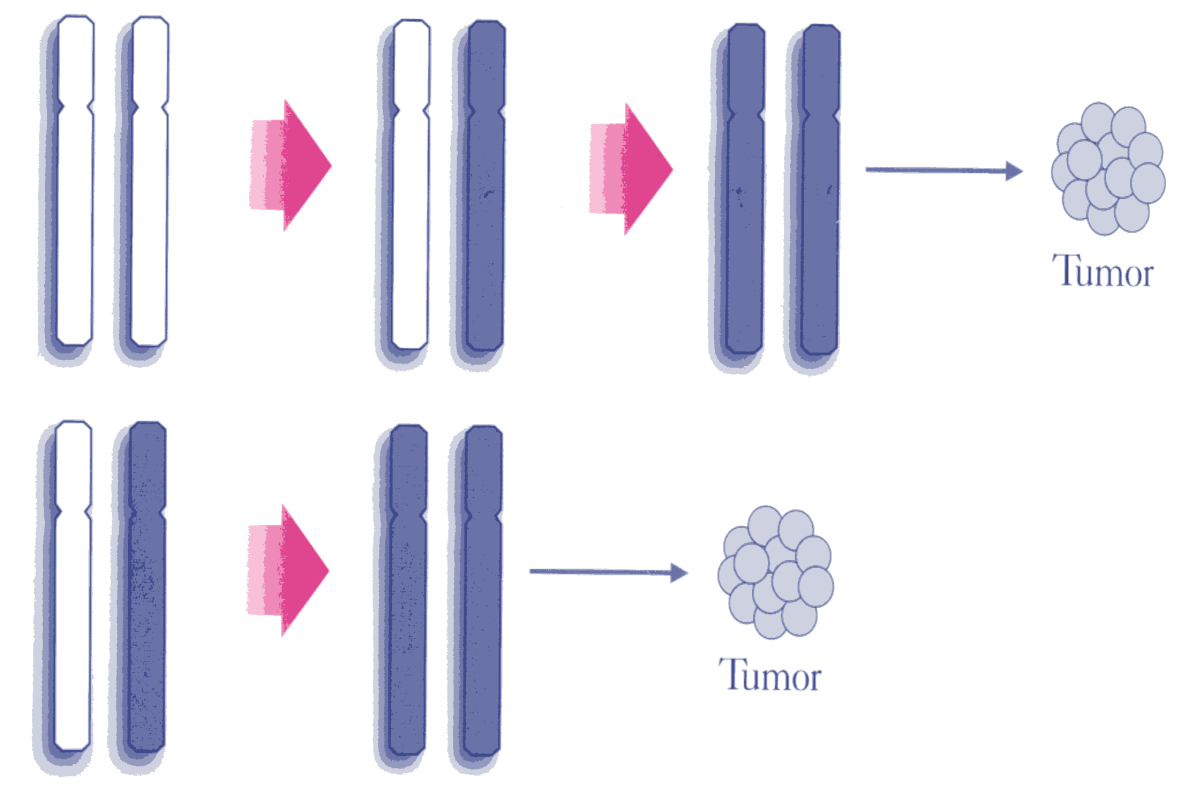
- *RB1* gene on chromosome 13
  - First tumor suppressor gene identified
  - Function is to restrain cell proliferation
- Serves as basis for the "Knudson 2-hit hypothesis"
  - Both alleles of the *RB1* gene must be inactivated for the cell to become cancerous

Knudson 2-Hit Hypothesis

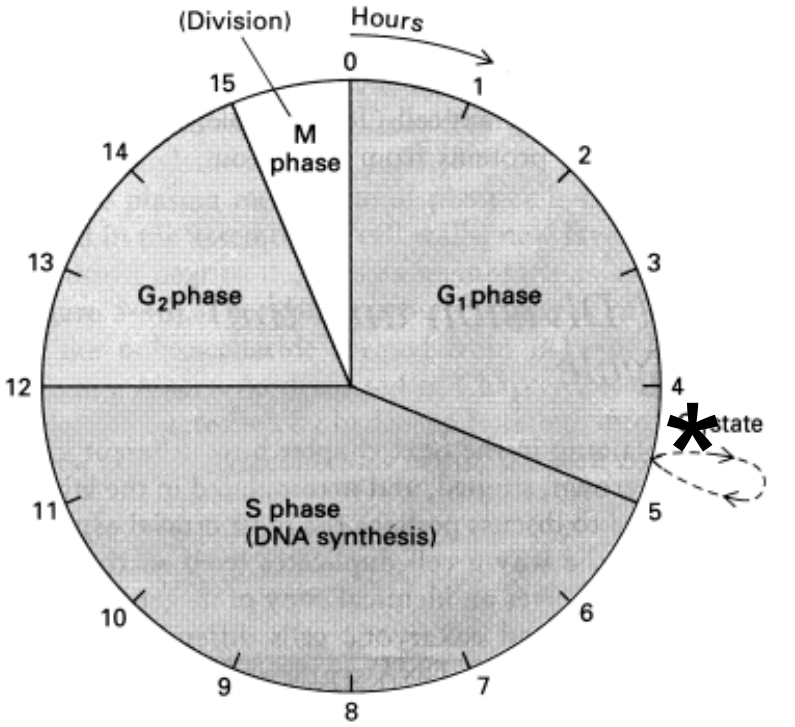
Patients with hereditary form already have one of the 2 "hits" required to get retinoblastoma

Sporadic

Hereditary



The Cell Cycle and Rb Function



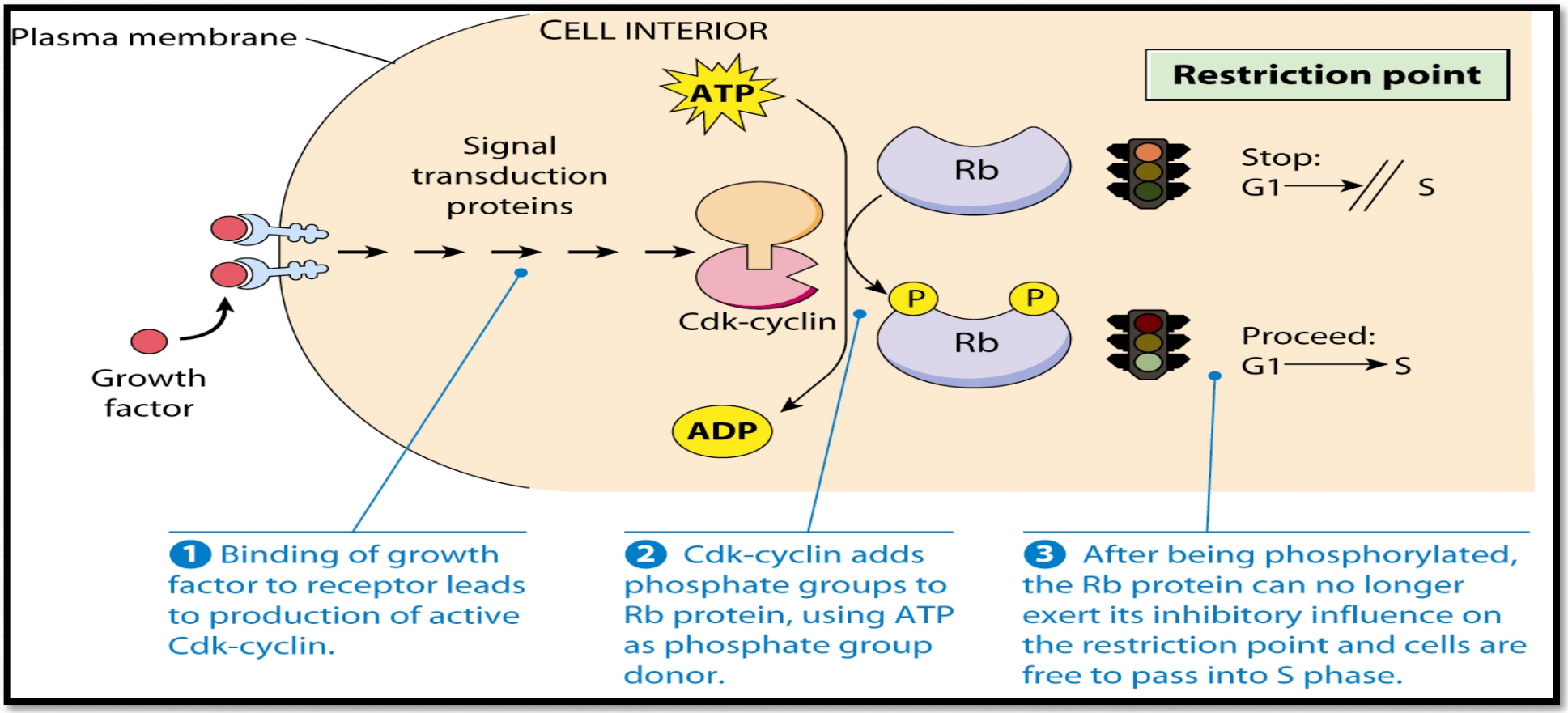
Rb protein holds cells at the G1 restriction point*– i.e. RB is a cell division repressor

RB can be induced to releases its brakes when the right signal is given

RB is a cell division repressor

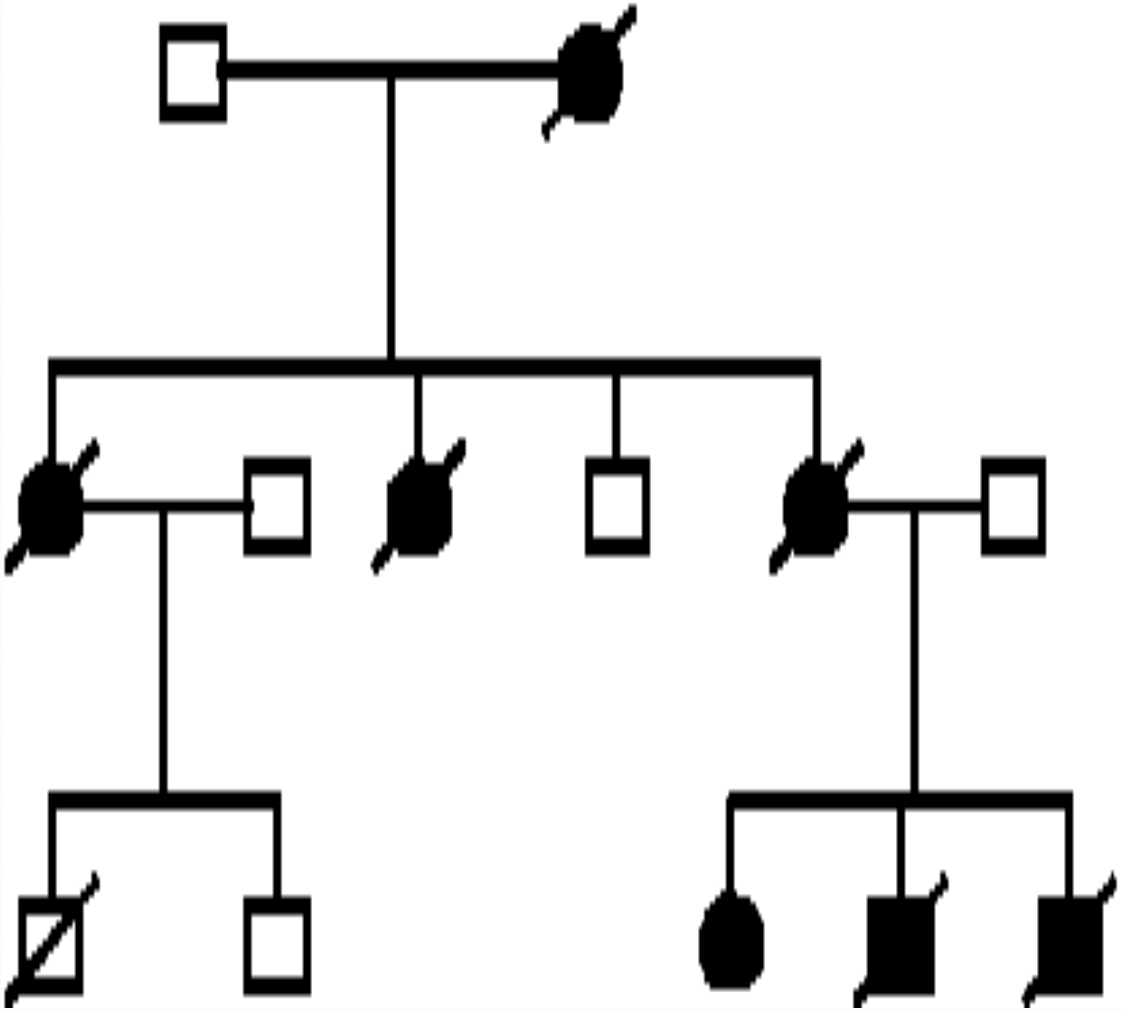
Can be thought of as a "***brake" or "stop signal***" on the cell cycle

Loss of both sets of brakes means cell division can't stop



From L. J. Kleinsmith, *Principles of Cancer Biology*. Copyright (c) 2006 Pearson Benjamin Cummings.

A Concerning Pedigree

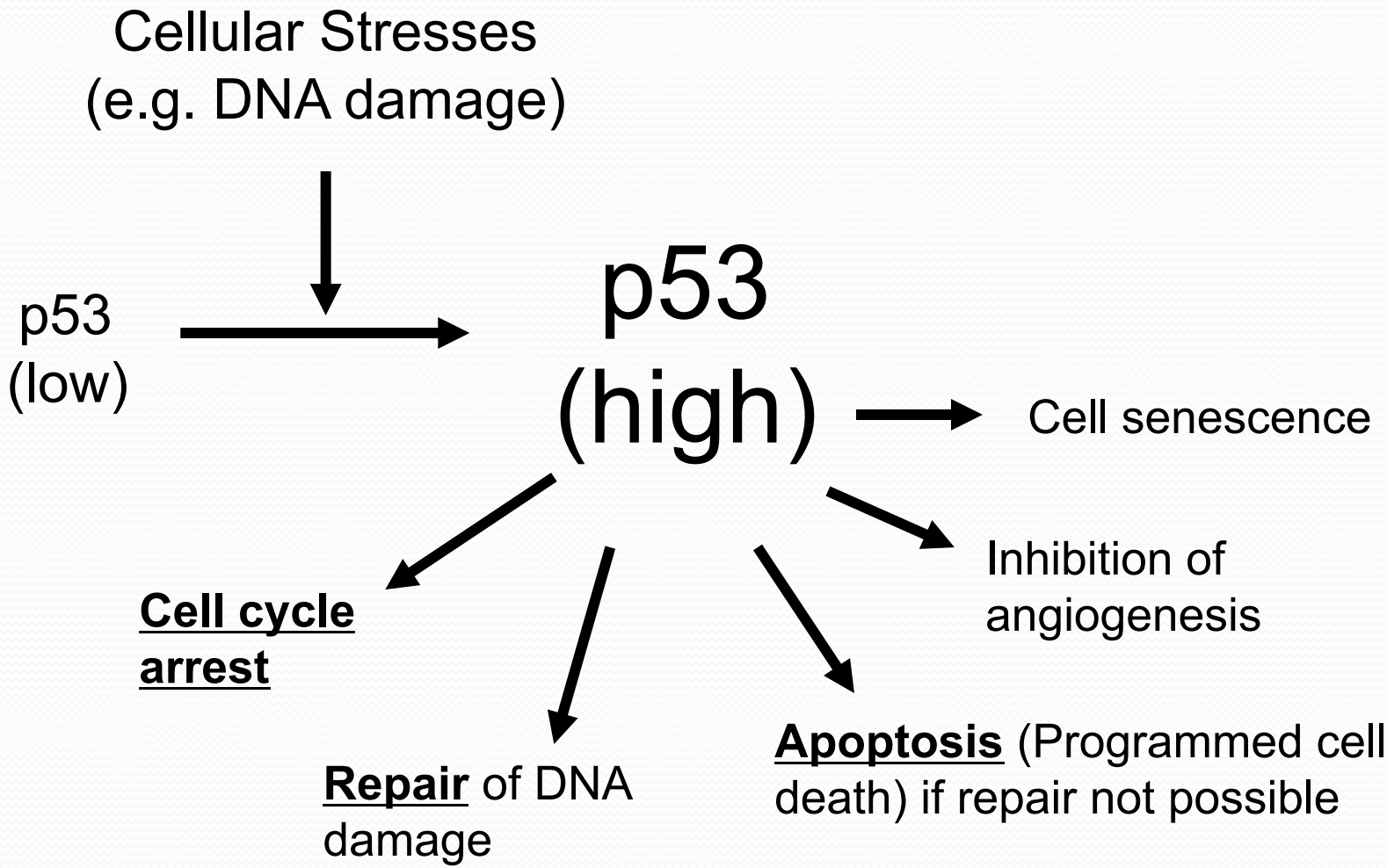


Typical LFS pedigree
I-2 bilateral BrCa age 40
II-1 brain tumour at 35
II-3 BrCa at 33,soft tissue sarcoma at 19
II-5 BrCa age 32
III-3 Osteosarcoma age 8
III-4 Leukaemia age 2
III-5 Soft tissue sarcoma age 3

Li-Fraumeni syndrome

- soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma and cancer of the colon, pancreas, stomach, lung, adrenal cortex and brain
- Often at an early age
- Sometimes multiple cancers
- The overall risk of some type of cancer is ~90%
- Due to a mutation in the *P53* gene on chromosome 17

The Basic Paradigm of p53 Function



Central role of p53

- The “guardian of the genome” - but does a lot more than that
- “Loss of function of p53 causes a number of molecular malfunctions that can transform cells into a malignant phenotype”

- When bad things happen to p53…
- Bad things happen to the cell – including cancer

Viruses that cause human cancer sometimes work by disrupting the p53 and Rb pathways

- Some HPV strains can cause cervical cancer
  - The "E6 protein" binds/inactivates p53
  - The "E7 protein" binds/inactivates RB
- Not all people are equally susceptible
  - Genetic polymorphisms in the p53 protein lead to differences in susceptibility to cancer
- People who have arginine at one site (instead of proline) have a **7x increased risk**
  - The Arg may make the p53 more easily degraded by HPV E6

Cowden syndrome

- A high risk of certain cancers:
  - Breast cancer
  - Thyroid cancer
  - Endometrial cancer
- Due to defects in *PTEN* gene
  - *PTEN* abnormalities also seen in Proteus syndrome
  - "Elephant Man" Joseph Merrick might have had Proteus Syndrome (rather than NF1?)

Cowden syndrome and *PTEN*

- The tumor suppressor protein PTEN is a lipid phosphatase that dephosphorylates PIP3 yielding PIP2
- PTEN thus counters the action of oncogenes that that lead to excessive activity of the PI3Kinase-Akt pathway (a pathway which promotes cell survival)
- ***Loss of function (LOF) mutations*** in *PTEN* lead to a rise in PIP3 concentration, leading to enhanced cell survival and proliferation
- Patients with Cowden syndrome are born with germline loss of function in one of the two *PTEN* genes in all cells

Lynch Syndrome

- AKA HNPCC (Hereditary nonpolyposis colorectal cancer)
- Up to 80% lifetime risk for colon cancer
  - As well as endometrial, stomach, brain, genitourinary and other cancers
- Due to inherited mutations in *MLH1, MSH2*, MSH6* (and possibly *PMS1, PMS2*, and a few others)
- These genes are responsible for **repair of DNA damage**
- Specifically "DNA mismatch" repair
  - i.e. Mistakes in Watson-Crick base pairing

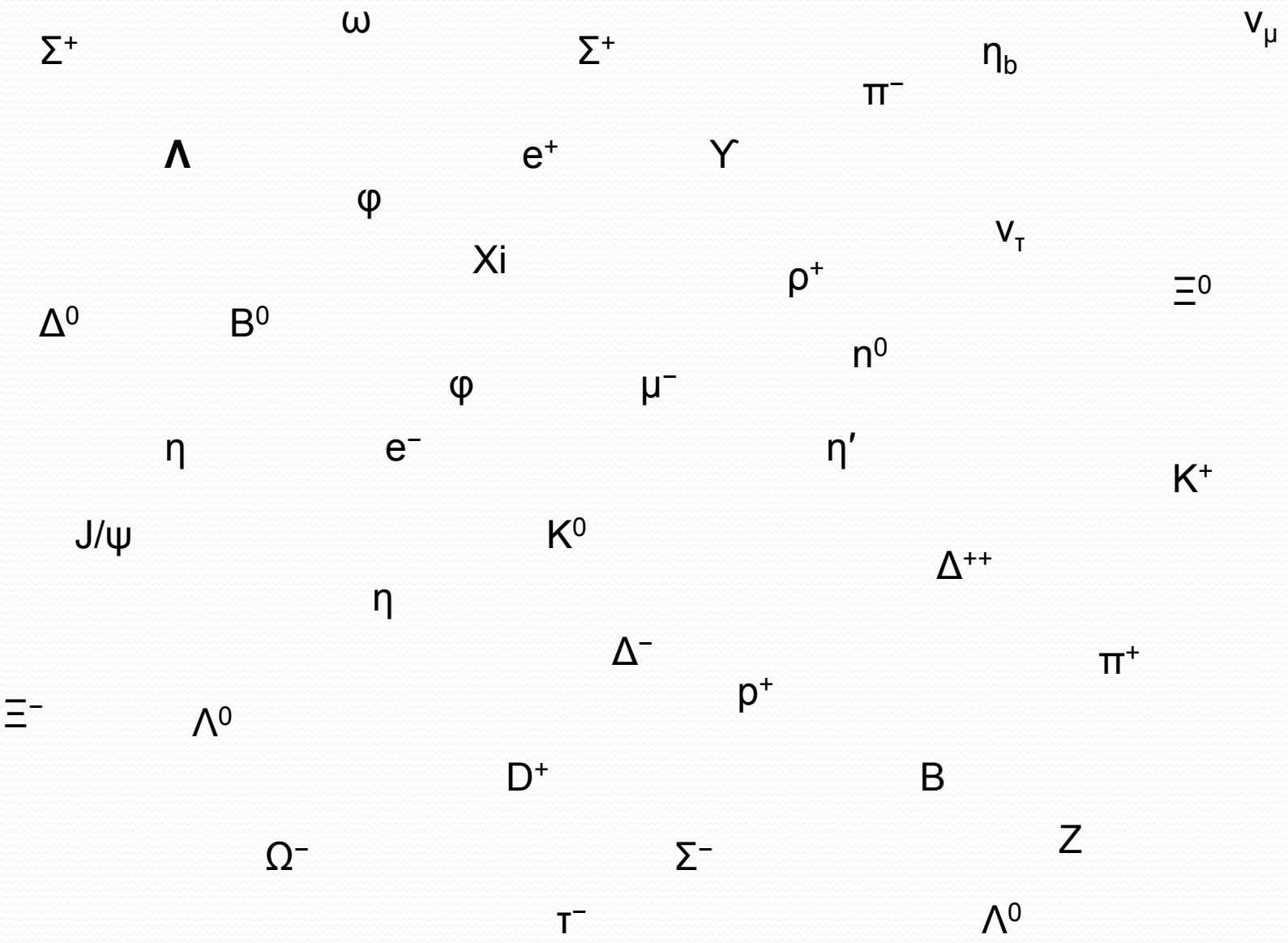
Hereditary Breast and Ovarian Cancer Syndrome

- Due to mutations in *BRCA1* and *BRCA2*
- High (up to ~80%) risk of breast cancer as well as ovarian cancer, pancreatic and a few others
- *BRCA1/2* genes are involved in **repair of double strand DNA breaks**
- Like genes involved in Lynch Syndrome, these are genes associated with **repair of DNA damage**

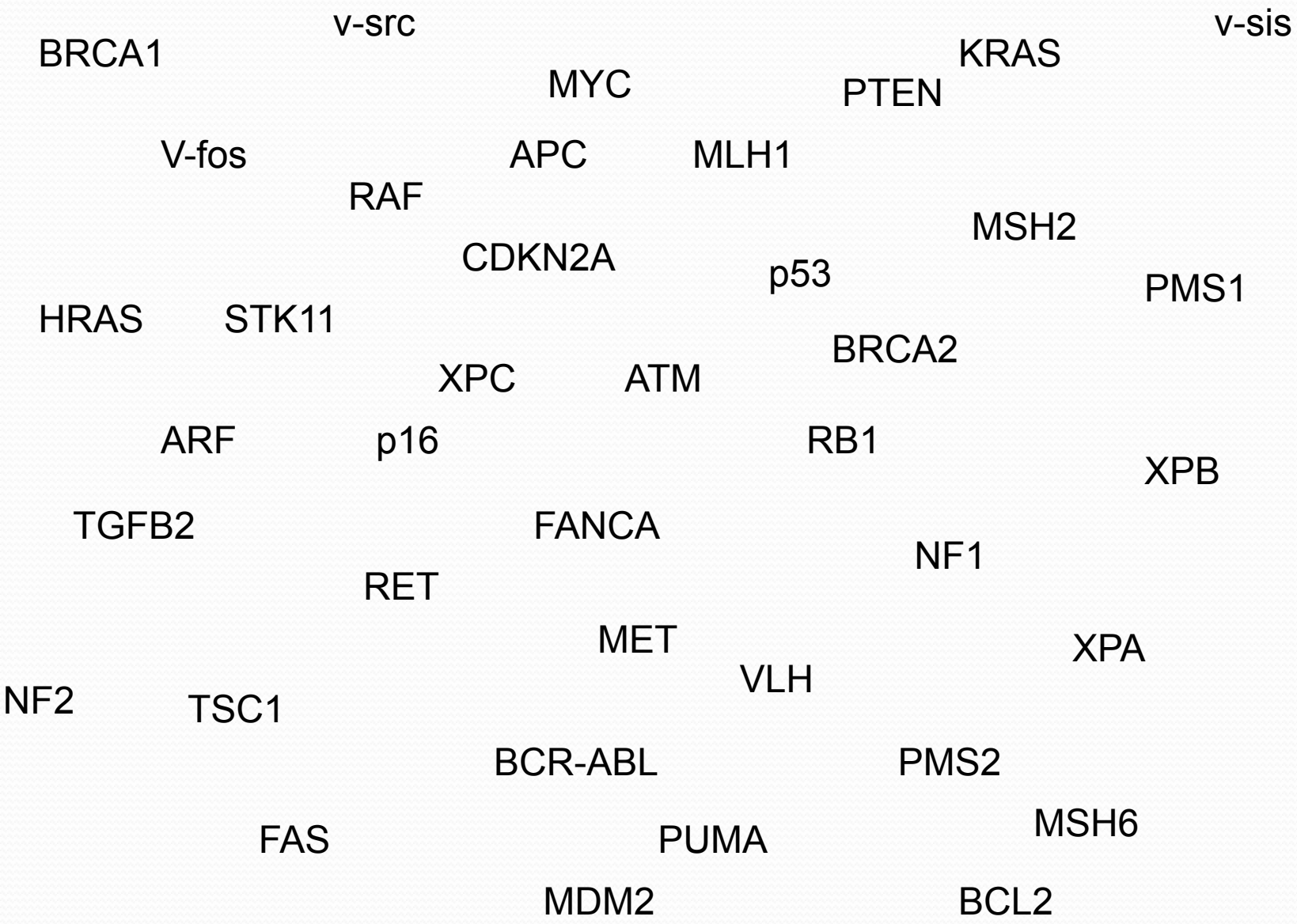
There are many more hereditary cancer syndromes…

- And there are over a hundred oncogenes and several dozen tumor suppressor genes…

The Particle Zoo



The Oncogene and Tumor Suppressor Gene Zoo

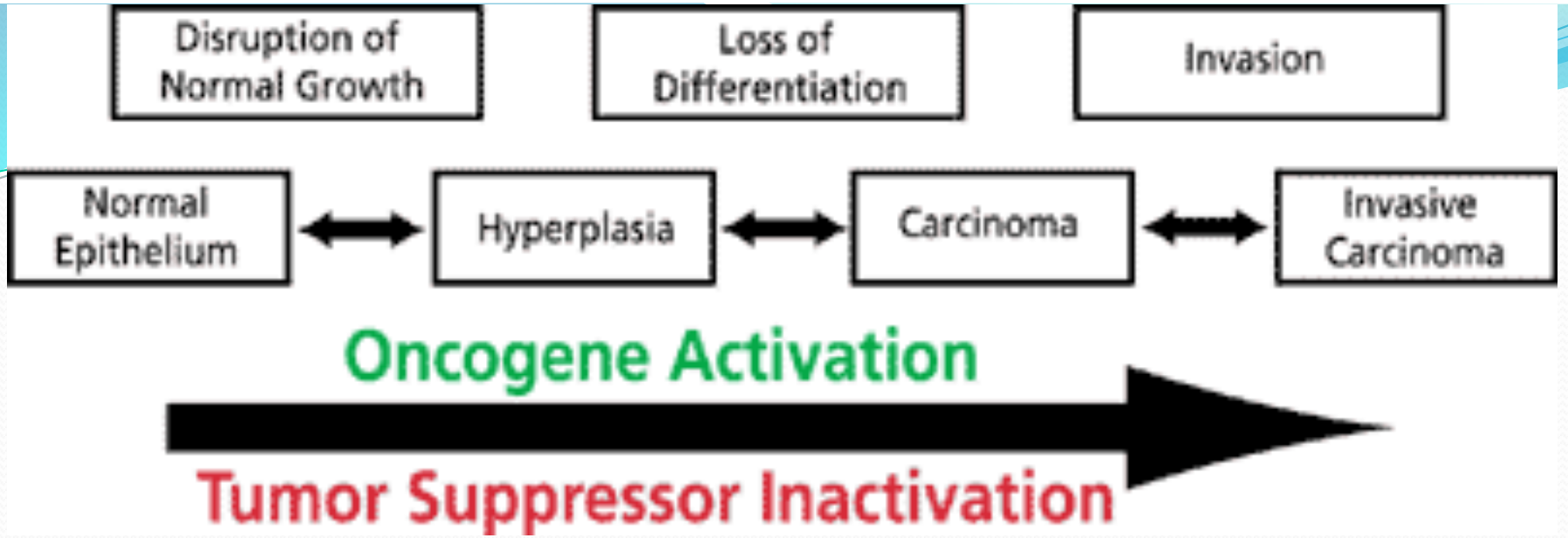


Summary of Tumor Suppresser Genes

- Two general functions –
  - Control of cell cycle (i.e. proliferation, growth and survival) and
  - Maintaining integrity of DNA
- Now categorized as:
- "Gatekeepers" – Brakes or Stop Signals for cell cycle
- "Caretakers" – DNA/Chromosome repair and maintenance

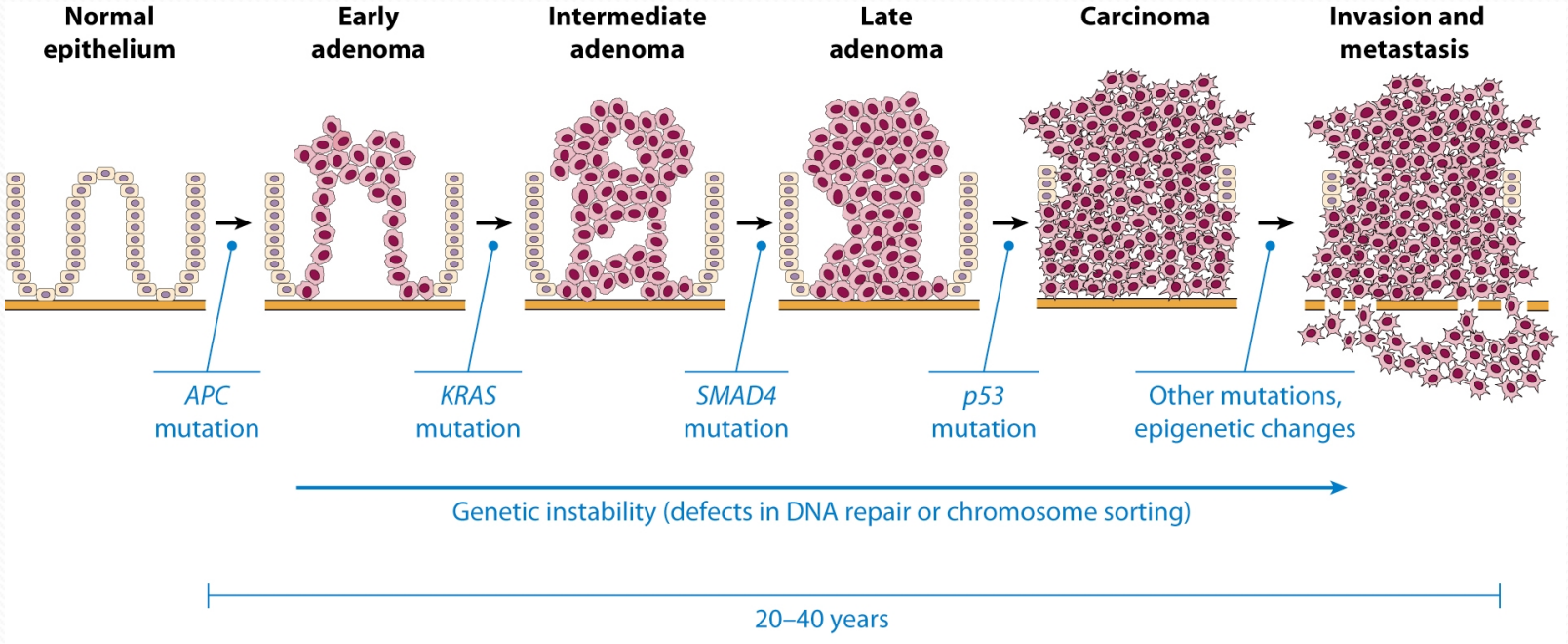
Summary of Oncogene Function

- Oncogene produce proteins that serve as:
  - Growth factors
  - Growth factor receptors (receptor tyrosine kinases)
  - G-proteins
  - Intracellular protein kinases
  - Transcription factors
  - Differentiation/cell death regulators



- Cancer is a multi-step process that is driven by mutations in Oncogenes and Tumor Suppressor Genes
  - Gain of Function in Oncogenes - ***Stuck gas pedal***
    - **One** activated gene is all that is required cause problems
  - Loss of Function of Tumor suppressor genes - ***No brakes***
    - Requires inactivation of **both** alleles (paternal and maternal)

An example of the gradual stepwise progression of cancer evolution – Colon Cancer



Note: Mutations do not have to occur in this particular sequence

From L. J. Kleinsmith, *Principles of Cancer Biology*. Copyright (c) 2006 Pearson Benjamin Cummings.

The Hallmarks of Cancer

In addition to the 1.) overactive "GO" signals and 2.) loss of "STOP" signals which together lead to uncontrolled proliferation, cancer cells ALSO…

3.) Evade apoptosis and terminal differentiation (Disregard rules and regulations of normal cell behavior)

4.) Are immortal (no Hayflick limit)

5.) Recruit new blood vessels (Angiogenesis)

6.) Capable of Invasion and Metastases (Decreased cell-cell adhesion, Increased motility, and Increased degrading proteases)

- How do cancer cells acquire all these features???

Genetic instability is another hallmark of cancer!

- Evolution occurs via natural selection among cells that compete with each other
- But for evolution to occur, there must be a source of new variants to select among…
- **Cancer cells are primed to create new variants (i.e. mutants)**
  - Cancer cells are hypermutable
  - The "mutator phenotype"

Epigenetics

- An important point: DNA mutation is not everything
- DNA function can be affected by alterations in base sequence (mutations) ***OR*** by epigenetic changes
  - e.g. DNA methylation and histone acetylation affect gene expression
- DNA Methylation - tends to shut genes off
- Histone acetylation - tends to turn genes on
- Genes involved in cancer can be turned on or off just as readily by epigenetic changes as by mutations…

The Hallmarks at a Molecular Level

- Gain of Function in Oncogenes
  - Growth factors – e.g. v-sis
  - Receptor tyrosine kinases - SRC
  - G-protiens - RAS
  - Intracellular protein kinases - RAF
  - Transcription factors - MYC
  - Cell cycle/cell death regulators BCL2
- Loss of Function in Tumor Suppressor Genes
  - Gatekeepers – RB, PTEN, etc
  - Caretakers – BRCA1/2, MLH1, etc
- Evasion of apoptosis and differentiation – e.g. BCL2
- Immortality – activation of *telomerase*
- Recruitment of new blood vessels – activation of VEGF or other mechanisms

Putting it all together: A "Standard Model" of Oncology

- **GOF** in Oncogenes:
  1.) That stimulate proliferation
    - **STUCK GAS PEDALS**

  2.) That stimulate angiogenesis
    - **UNLIMITED FUEL SUPPLY**

  3.) Telomerase
    - **IMMORTALITY**
- **LOF** in Tumor Suppressor Genes:
  A) "Gatekeepers"
    - **LOSS OF BRAKES**

  B) That prevent invasion
    - **CONFERS ALL-WHEEL DRIVE CAPACITY**

  C) That cause apoptosis or differentiation
    - **REFUSAL TO PULL OVER OR OBEY TRAFFIC SIGNS**

  D) "Caretakers" → Leads to **Genetic instability**
    - **CONVERTS RUNAWAY SEDAN INTO A JEEP THEN INTO A TANK!**

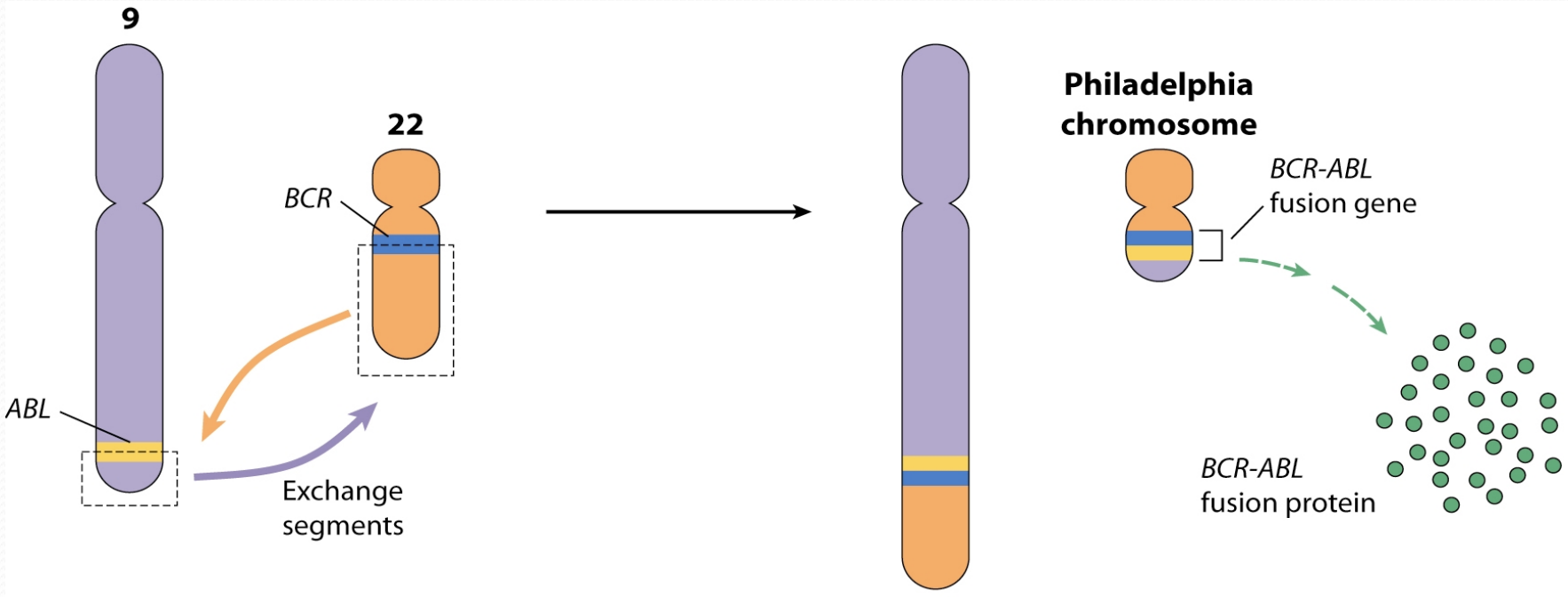
A coherent model

- An understanding of Cancer Biology has come a very long way in the past few decades and at a very fast pace recently
- As new oncogenes, tumor suppressor genes, pathways and other carcinogenic mechanisms are discovered…
- They should fit into this current general scheme
- There is no Higgs particle to find but there is something we are seeking…
  - Effective treatments for the disease!

Applications in Cancer Therapy

- Gleevac (Imatinib) and Chronic Myleogenous Leukemia (CML)
- CML has the "Philadelphia Chromosome"
  - A translocation involving chromosomes 9 and 22
  - t(9;22)
- This creates a new oncogene (called *BCR-ABL*) with abnormal functions – a hyperactive tyrosine kinase
- Gleevac targets that abnormal tyrosine kinase

Translocation between chromosomes 9 and 22 Formation of the "BCR-ABL" fusion oncogene



Does it work?

- No treatment (3 yrs)
- Standard chemotherapy (4 yrs)

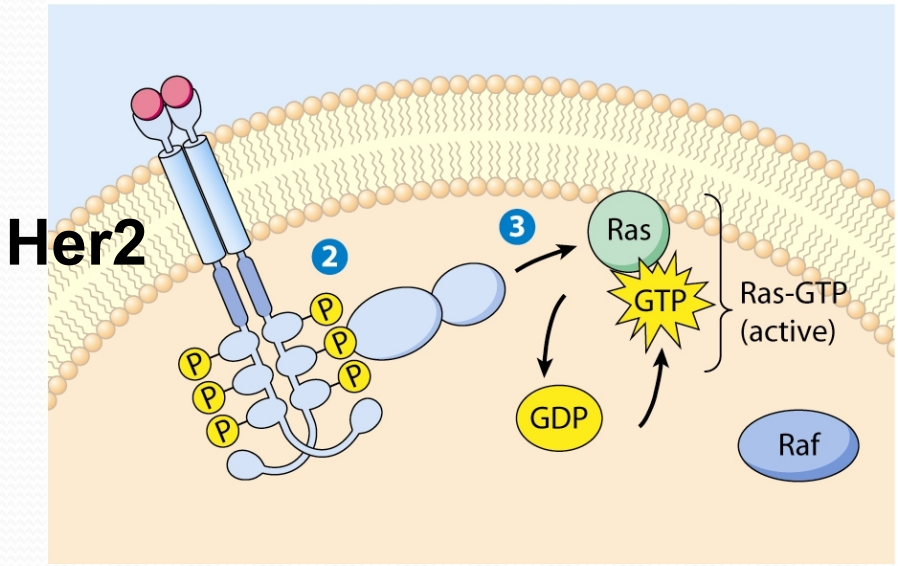
Does it work?

- No treatment (3 yrs median survival)
- Standard chemotherapy (4 yrs)
- Imatinib mesylate (95% alive at 6 years)

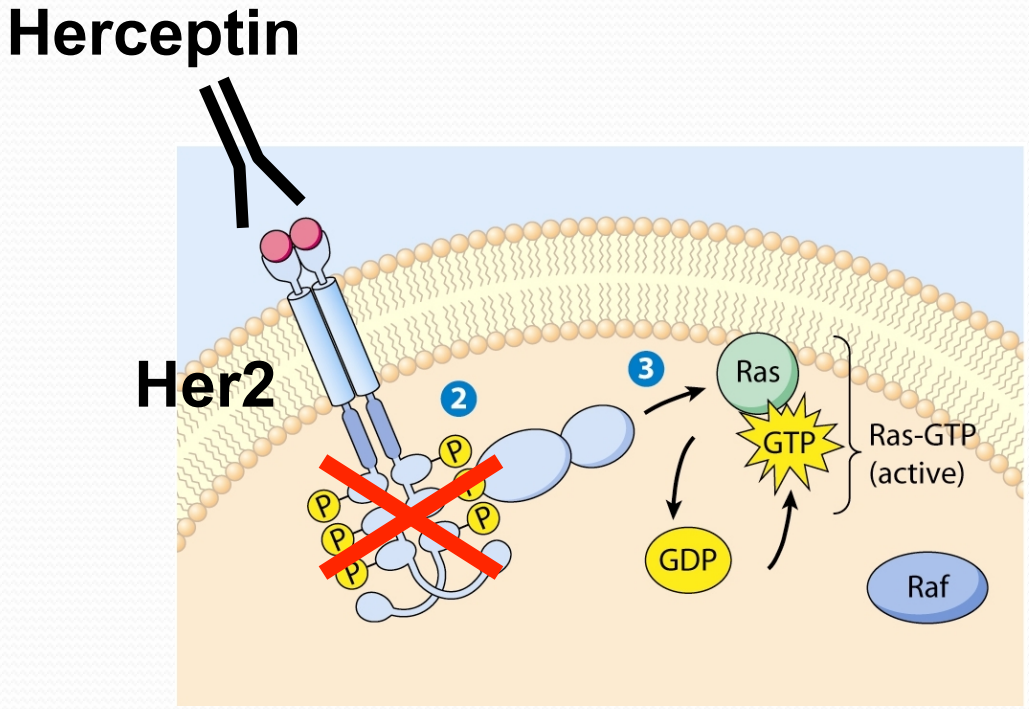
HER2 and breast cancer

- Approximately 10-20% of breast cancers will have amplification of the HER2 oncogene
- Gene amplification leads to overexpression of HER2 - which codes for a growth factor receptor

Her2 – a receptor tyrosine kinase in the EGFR family



Herceptin (Trastuzumab) – a monoclonal antibody against Her2



Other "Molecular Targeted Agents"

- Cetuximab (Erbitux) – a monoclonal antibody directed against EGFR
- Bevicizumab (Avastin) – monoclonal antibody directed against VEGF
- Thalidomide(!) – has anti-angiogenic properties
  - Being investigated for **macular degeneration** and renal cell carcinoma and multiple myeloma
- Temsirolimus and everolimus – inhibitors of mTOR which is a final common denominator in the PI3K-Akt pathway
  - Approved **yesterday** for subepenymal giant cell astrocytoma!

Conventional Radiotherapy

- External beam radiation therapy (Teletherapy)
  - Hi-energy photons (bosons)
  - Electrons (fermions/leptons)
- Brachytherapy
  - Permanent vs Temporary
  - Low dose-rate vs High dose-rate
  - Photon emitters (^{125}I, ^{103}Pd, ^{103}Cs, ^{192}Ir, ^{125}Cs, ^{103}Au) vs beta emitters (^{32}P, ^{90}Y, ^{90}Sr)
- What about hadrons?

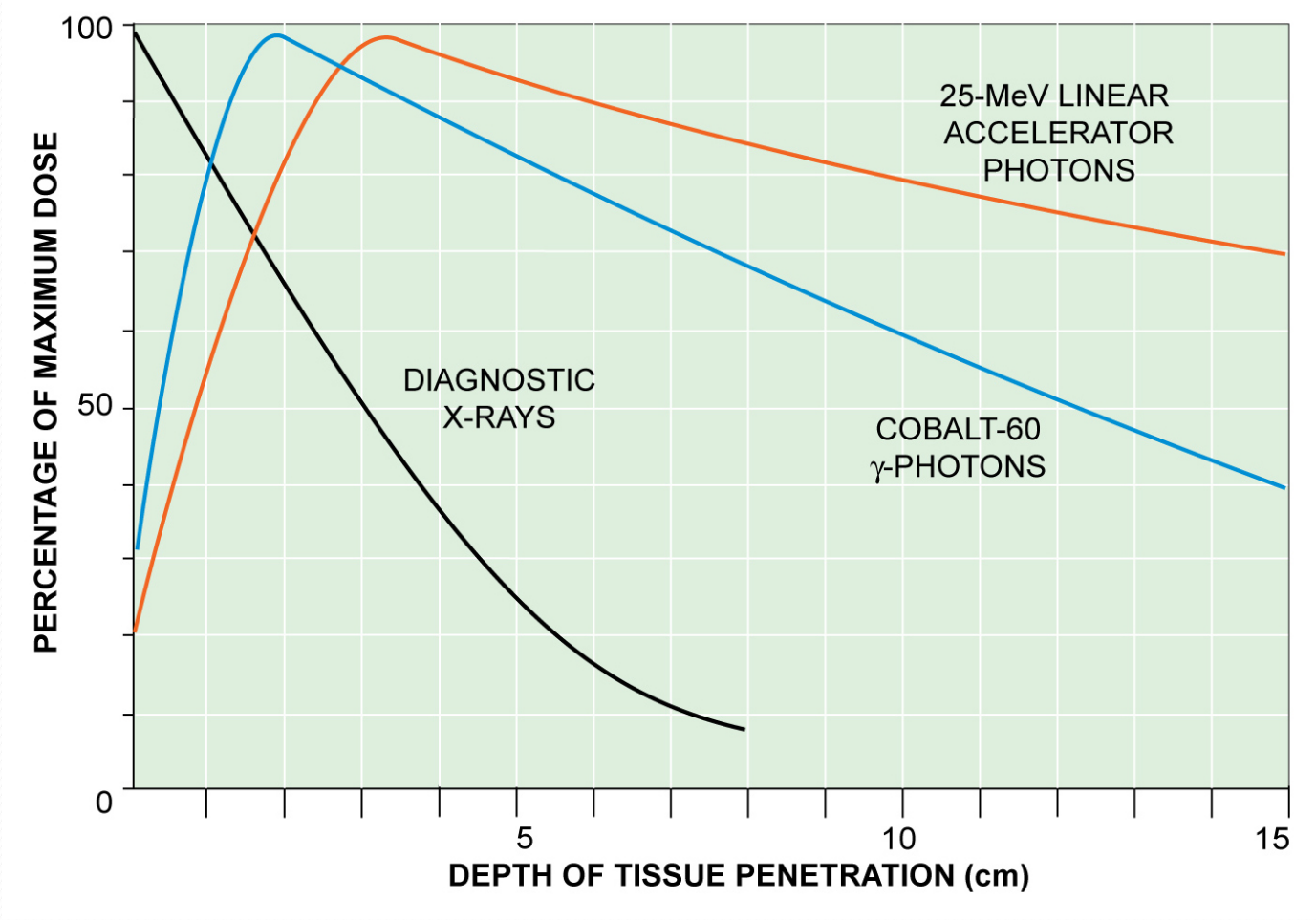
Boron neutron capture therapy

- Specific boron-containing compounds *might* accumulate in certain malignant tumors
  - Glioblastoma multiforme and melanoma have been evaluated
- If these boron-laden tumors are then exposed to thermal neutrons…
- Boron-10 has a large "cross section" for thermal neutron capture an undergoes fission
  - $^{10}B + n \rightarrow {}^{4}He + {}^{7}Li$
  - $^{10}B(n, \alpha)^{7}Li$
  - ~200 MeV per fission

Conventional external beam radiation therapy is done mostly with high-energy photons

- Higher energy yields better depth-dose profiles (i.e. better penetration into tissues rather than giving majority of dose to skin)
- Thus, Cobalt-60 teletherapy (1.17 and 1.33 MeV; _average photon energy = 1.25 MeV) units appeared in the 1950's
- These were largely replaced by even higher energy linear accelerators
- High energy photons interact with matter primarily via
  - Photoelectric effect
  - Compton scattering
  - Pair production
  - Photonuclear disintegrations

High-energy Photons

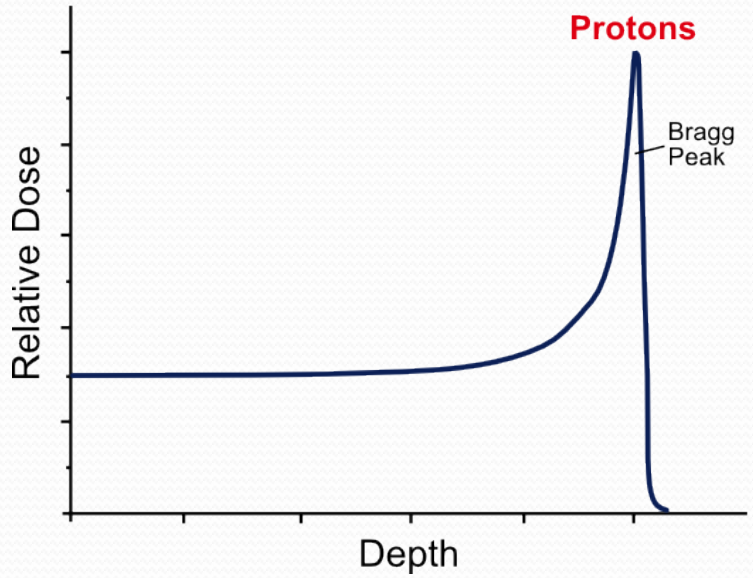


James S. Welsh. Quarks, leptons, fermions, bosons: the subatomic pharmacology of radiation therapy. Science & Medicine: Volume 10 Number 2

Protons have a very different pattern of radiation dose deposition in tissue

- Entrance dose is low but as protons slow down and come to end of their range they deposit energy more densely causing a sharp peak in dose deposition called the Bragg Peak
- Following the Bragg peak, protons largely cease dose deposition sharply which is one of the key reasons for their clinical applications
- The idea of proton therapy dates back to Robert Wilson: *Radiological Use of Fast Protons Radiology 47 487 (**1946**)*

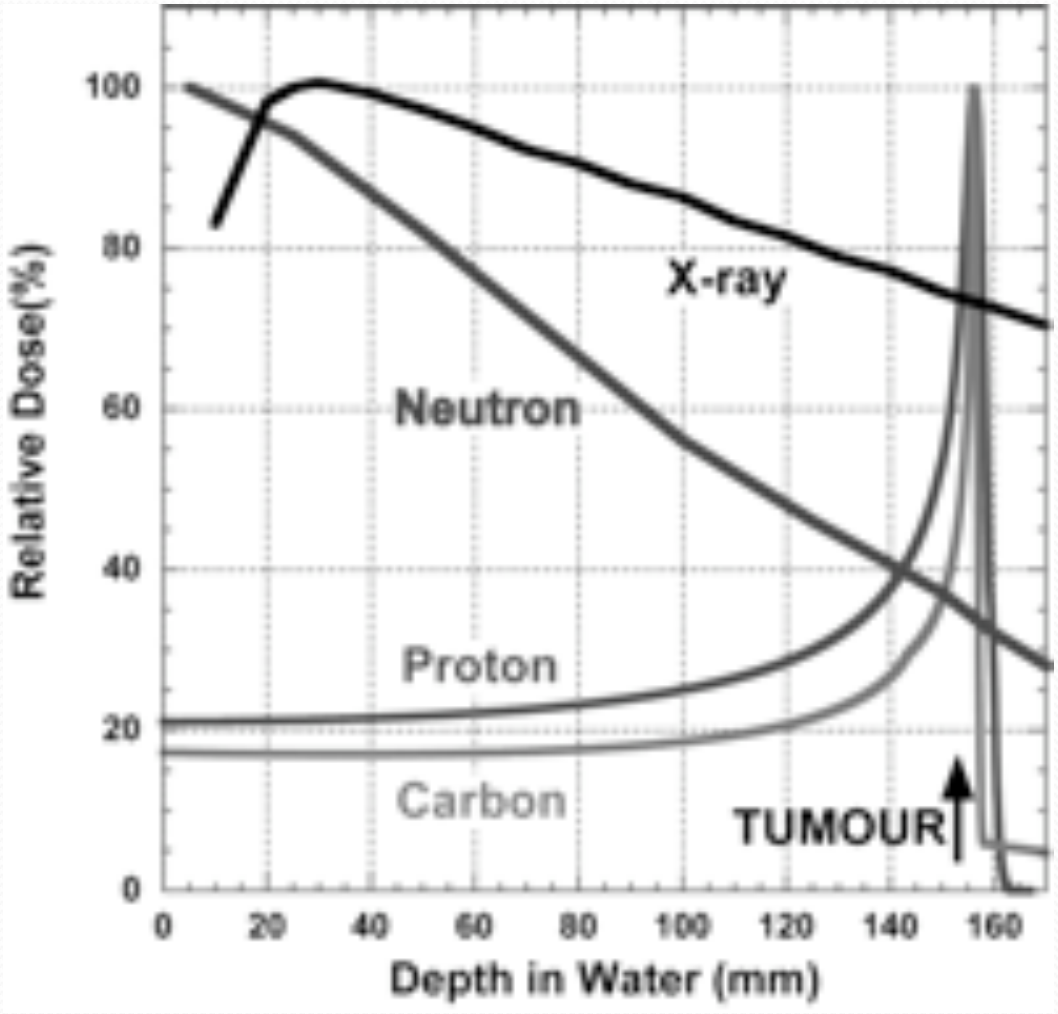
As protons come to the end of their range they deposit dose at a faster rate (the Bragg peak) then come to an abrupt end



http://www.ptcri.ox.ac.uk/research/introduction.shtml

What about neutrons?

- More radiobiological "punch" (high RBE or radiobiological effectiveness) but…
- Inadequate depth-dose profiles (i.e. poor dose distributions in vivo) make neutron therapy generally difficult
  - Effective and safe neutron therapy is available at only a very few specialized centers (e.g. Fermilab)
- Carbon ions have high RBE (like neutrons) and have a Bragg peak (like protons) although there is a slight "tail" of unwanted dose beyond the expected end of their range



Fukumura et al. CARBON-ION RADIOTHERAPY: CLINICAL ASPECTS AND RELATED DOSIMETRY Radiat Prot Dosimetry. first published online October 7, 2009

Cyclotron principles

$C = 2\pi r$

$C = vt$

$Vt = 2\pi r \rightarrow v = 2\pi r/t$

$F = mv^2/r$

$F = Bqv$

$Bqv = mv^2/r$

$Bq = mv/r \rightarrow v = Bqr/m$

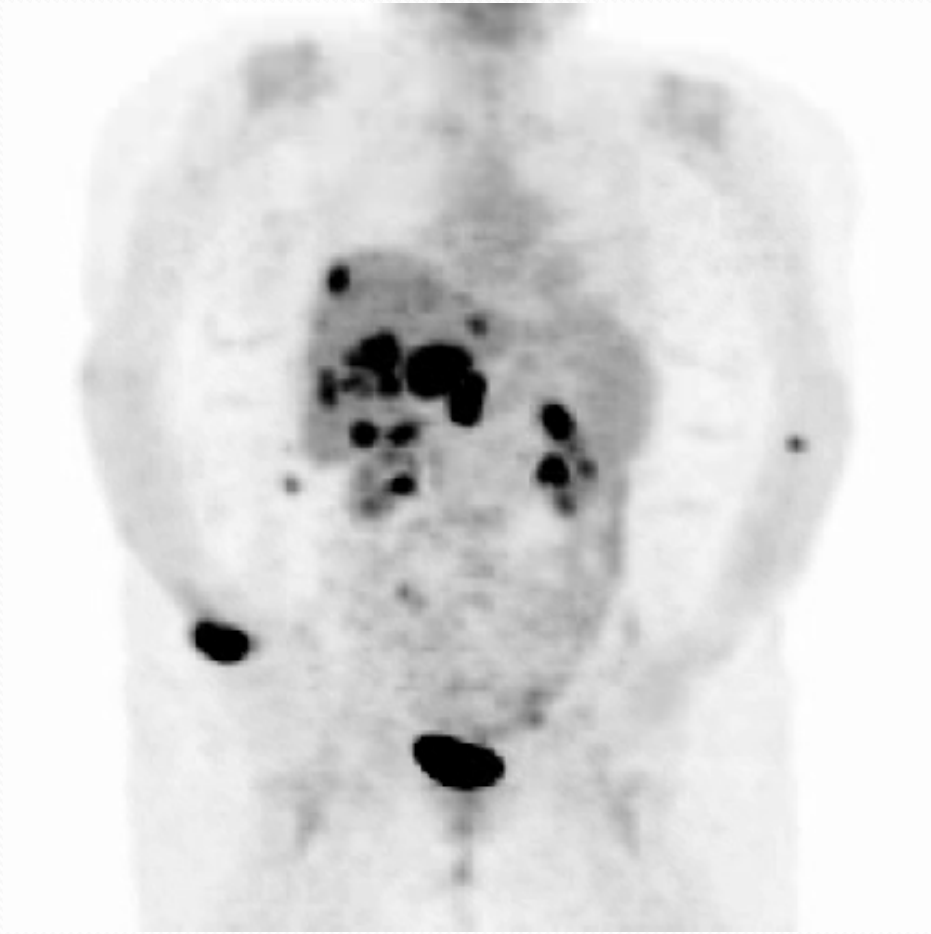
$$\mathbf{Bqr/m = 2\pi r/t}$$

$$\mathbf{Bq\cancel{r}/m = 2\pi\cancel{r}/t \rightarrow t = 2\pi m/Bq}$$

- EO Lawrence's "Eureka!": "r cancels r!!!"

Cyclotrons in Medicine

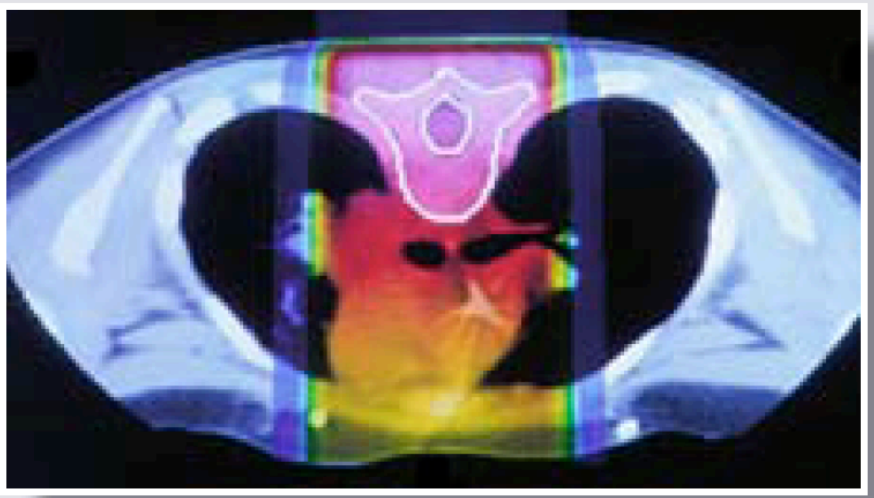
- Synthesis of radioisotopes for Positron Emission Tomography (PET scan)
  - $^{18}O(p,n)^{18}F$ - reaction for synthesis via cyclotron
- Fluorine-18 is a **Positron emitter**
  - $^{18}F \rightarrow {}^{18}O + \beta^{+} + \nu_e$
- When the positron slows down and meets an electron…
  - Mutual annihilation → 2 gamma rays of 511 keV diametrically opposed
- FDG (^{18}F fluorodeoxyglucose) – a glucose analogue
- Glucose is taken up by tumors; FDG is taken up by tumors – but FDG **can't get out**



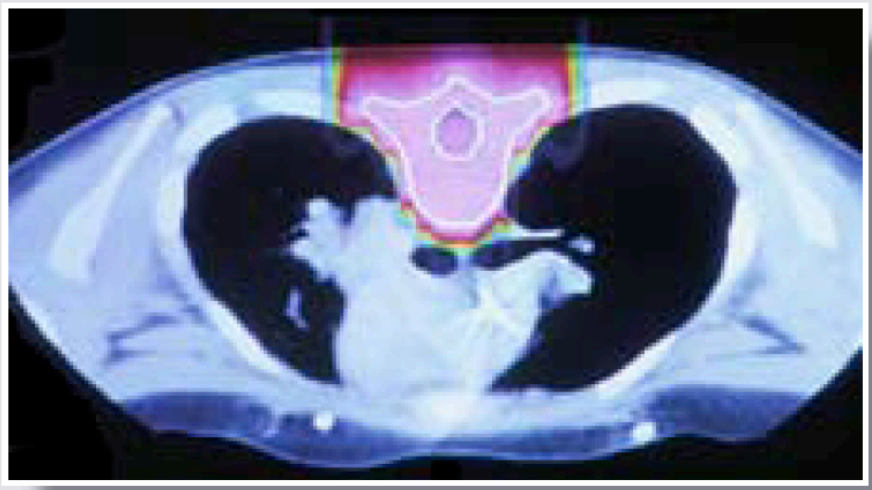
Challenges for cyclotrons

- As particles speed up to relativistic velocities they gain mass
- They become out of synch…
  - A practical limit for accelerating protons with a cyclotron is around 25 MeV – too low for modern hadron therapy
- One solution: increase the magnetic field with radius
  - "Isochronous Cyclotron"
- Another solution: synchronize the accelerating RF field with the increase in mass of the particles
  - "**Synchrocyclotron**"

X-rays vs Protons in dose-distributions



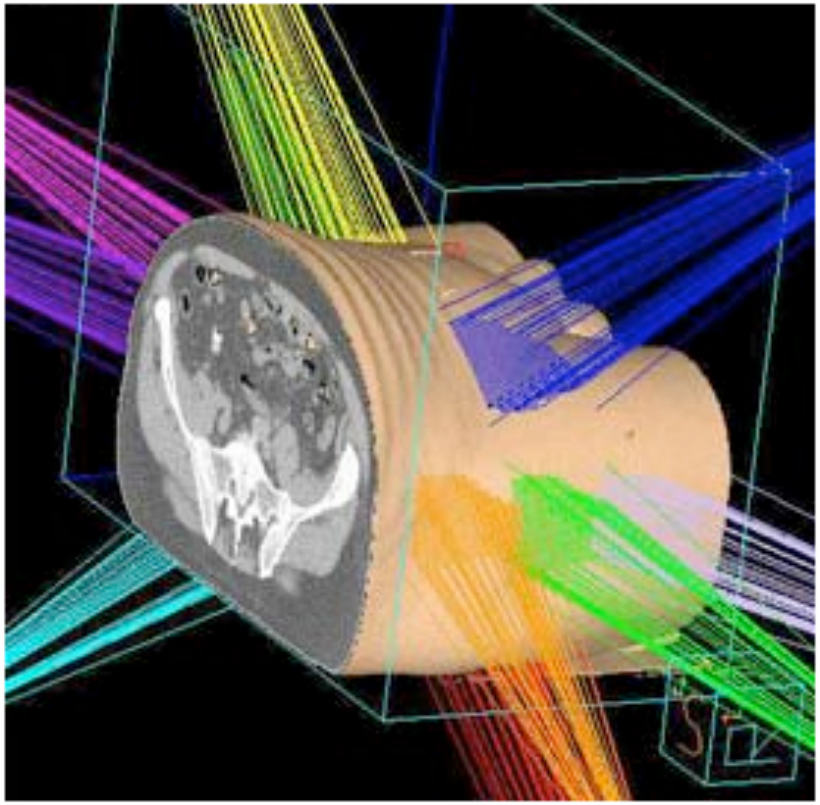
X-Rays

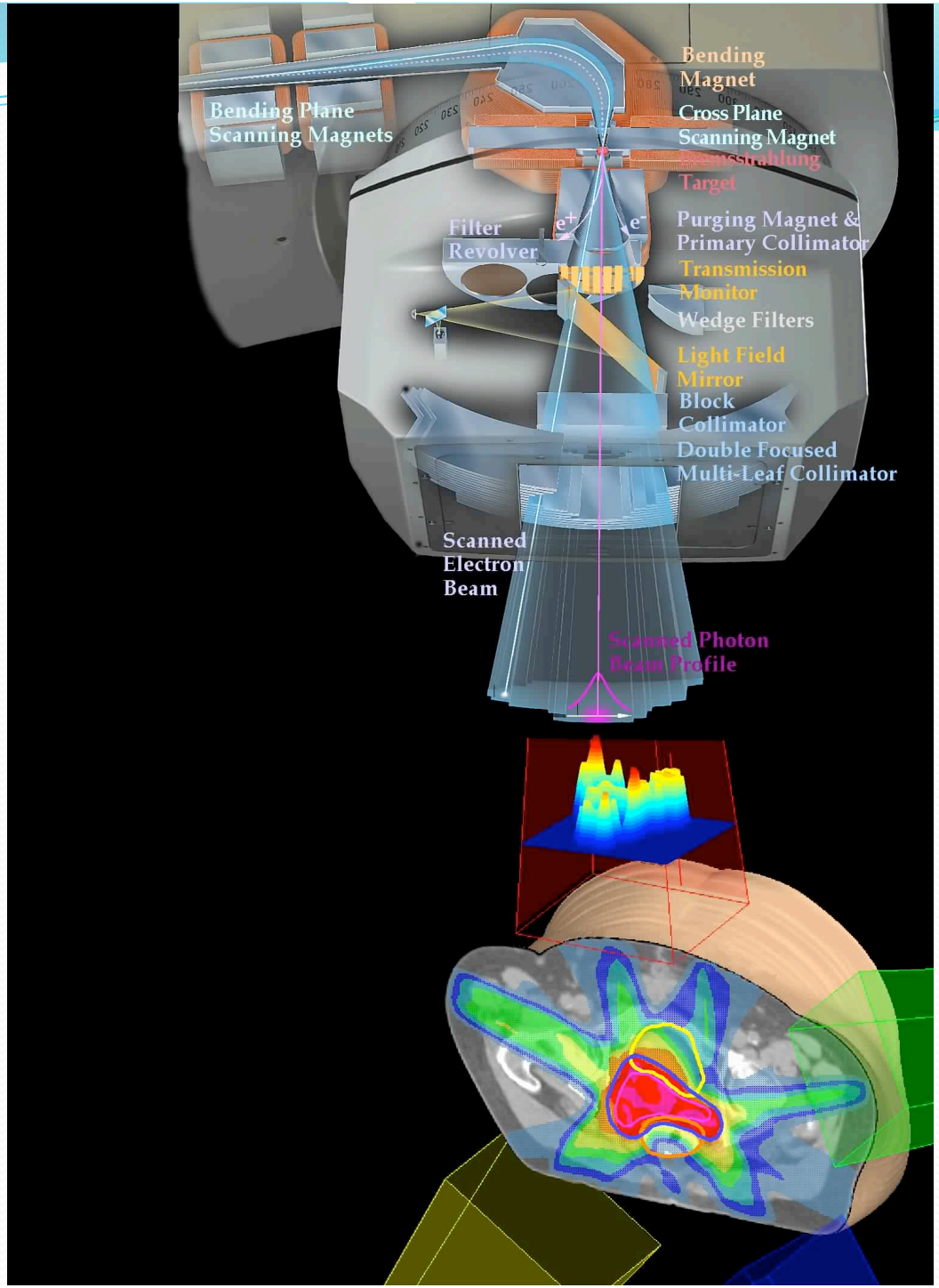


Protons/Ions

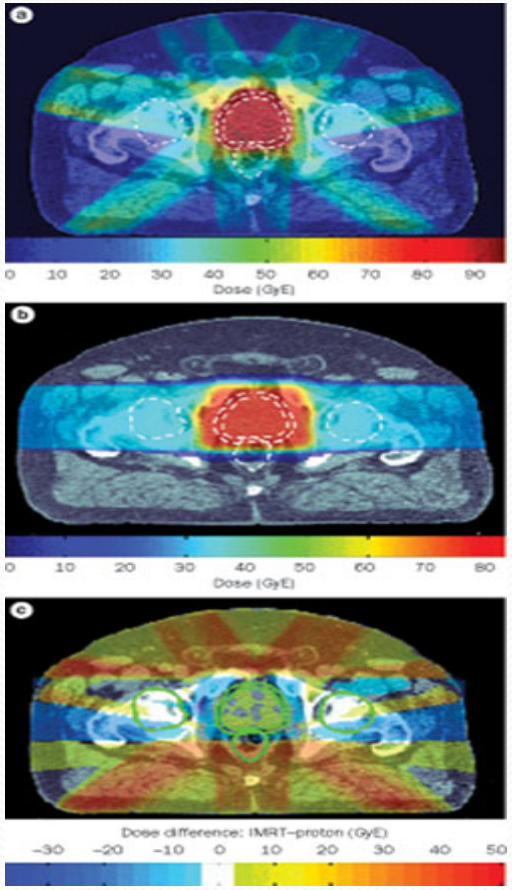
Miralbell R, et al. *IJROBP 2002;54:824-9*

Photon-based radiotherapy has evolved considerably over the past couple of decades with 3D conformal radiation therapy and Intensity-modulated Radiation Therapy (IMRT)




Bending Magnet
Bending Plane Scanning Magnets
Cross Plane Scanning Magnet
Bremsstrahlung Target
Filter Revolver
e+
e-
Purging Magnet & Primary Collimator
Transmission Monitor
Wedge Filters
Light Field Mirror
Block Collimator
Double Focused Multi-Leaf Collimator
Scanned Electron Beam
Scanned Photon Beam Profile

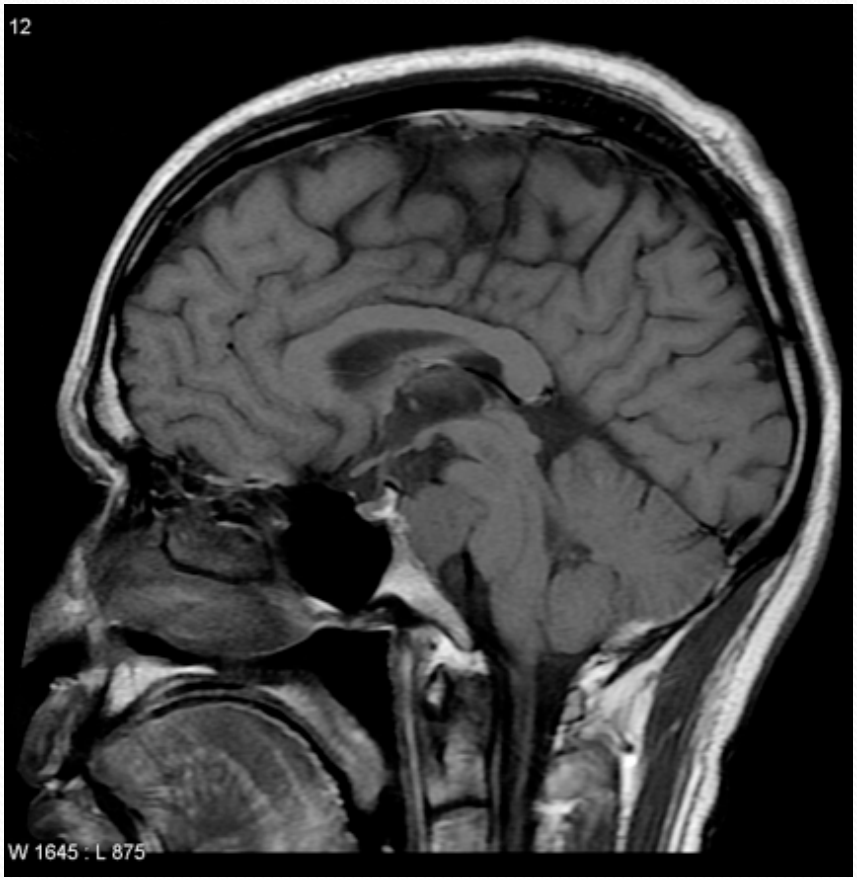
However even though vast improvements have been made, protons still have some theoretical dosimetric advantages over photons



John J. Coen & Anthony L. Zietman. Proton radiation for localized prostate cancer. Nature Reviews Urology 6, 324-330 (June 2009)

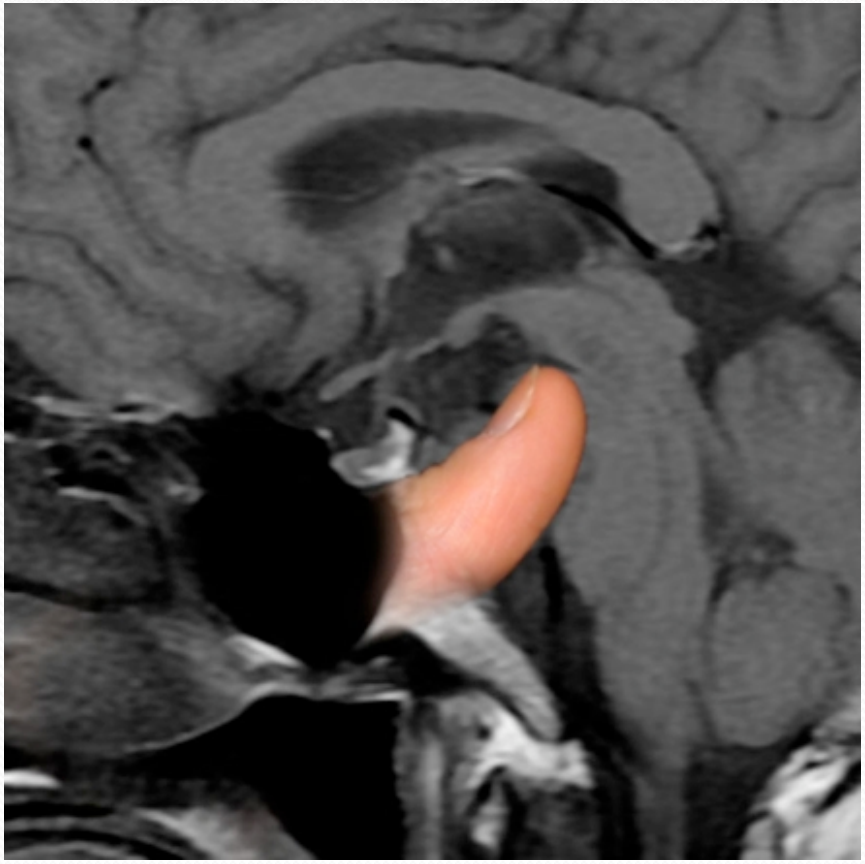
- The dosimetric advantages might be most important for cases that require high dose for cure and are located in areas surrounded by sensitive normal structures (for example intracranial/brain tumors) and in pediatric cancer management

Can you see the tumor?



Dr Frank Gaillard http://Radiopaedia.org

Sticking out like a sore thumb!



Dr Frank Gaillard http://Radiopaedia.org

Chordoma

- From “Chordate”

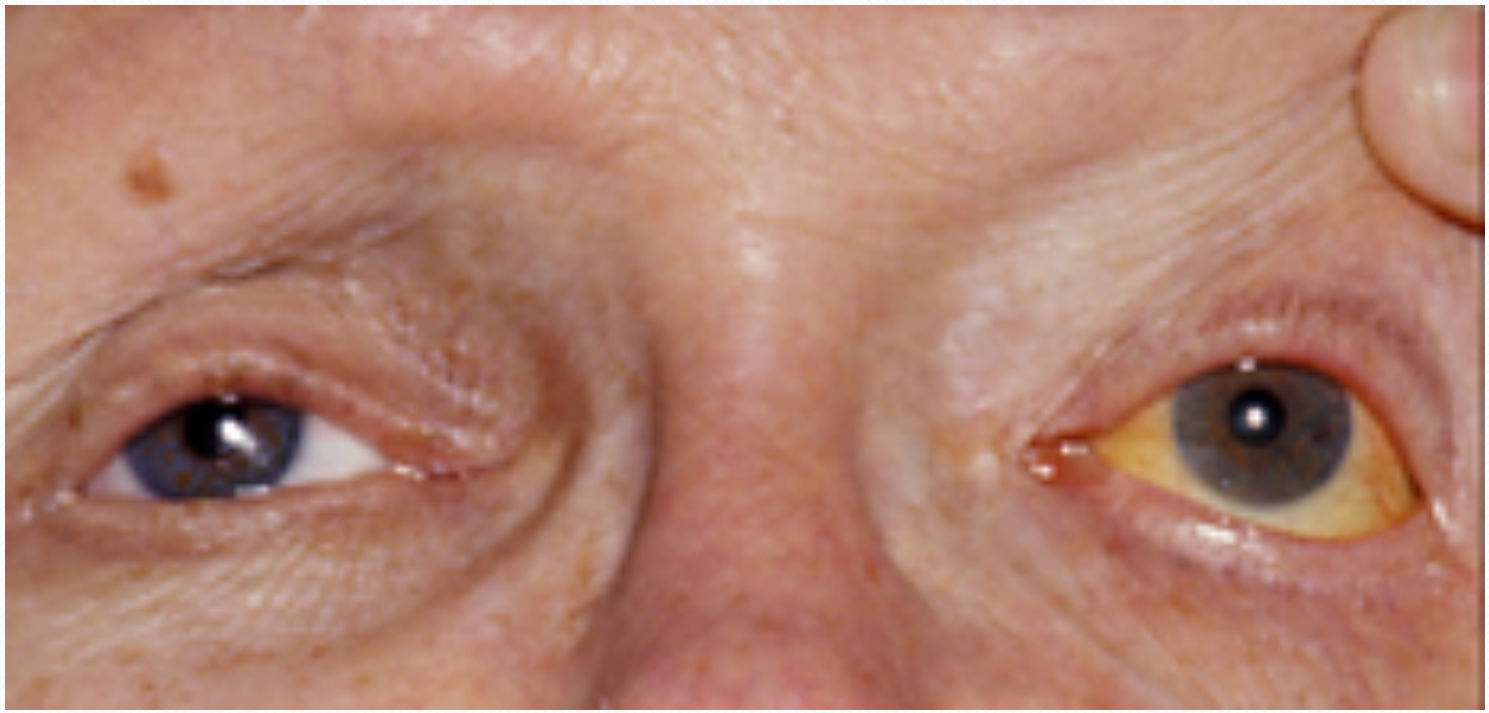
Chordoma

- From “Chordate”
  - Hollow dorsal nerve tube
  - Pharyngeal gill slits
  - Notochord

Craniopharyngioma

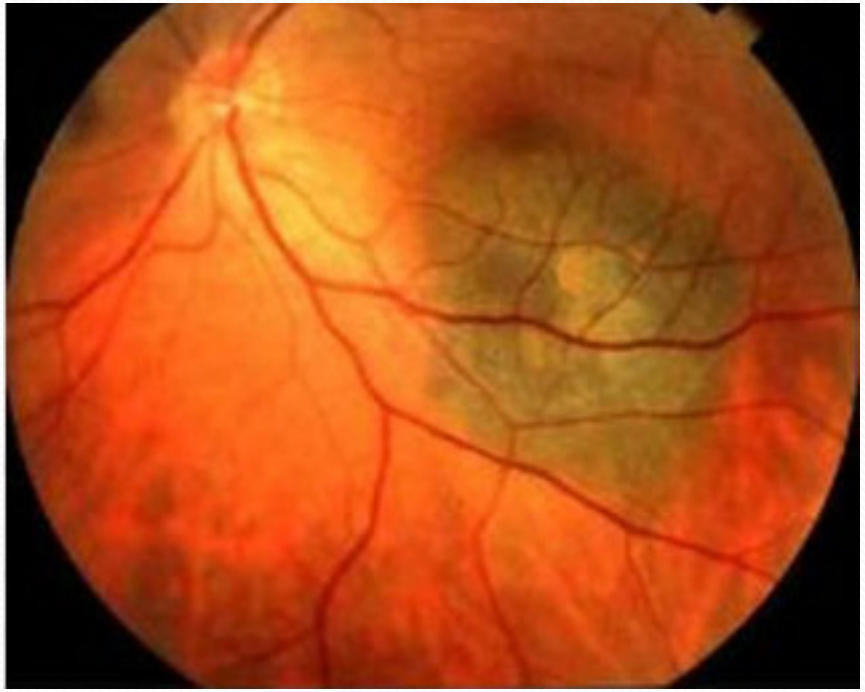
- Remnants of Rathke's pouch can become neoplastic
- "Suprasellar" mass near optic chiasm and hypothalamus
- Sometimes surgery is not advisable - but it might be possible to sneak in a meaningful dose of radiation…

A case of unilateral scleral icterus
What happened here?



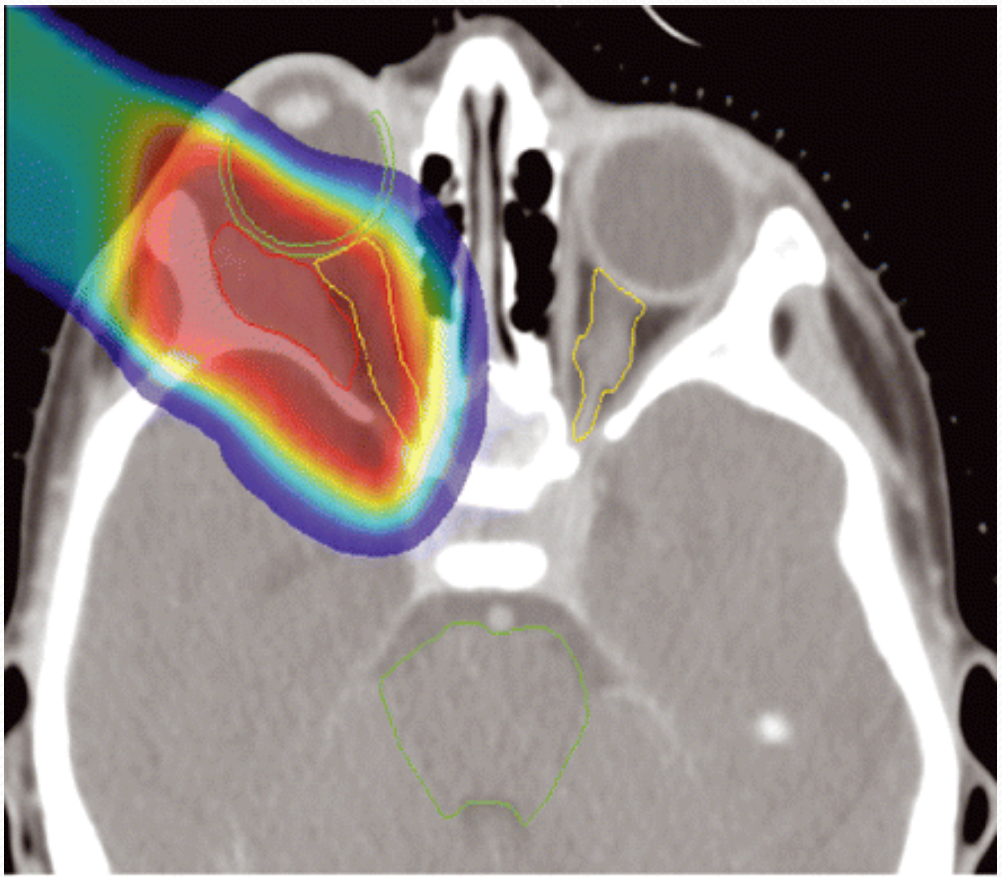
http://cnx.org/content/m15019/latest/
Images of Memorable Cases: Cases 28 & 29
Module by: Herbert L. Fred, MD, Hendrik A. van Dijk

Ocular melanoma

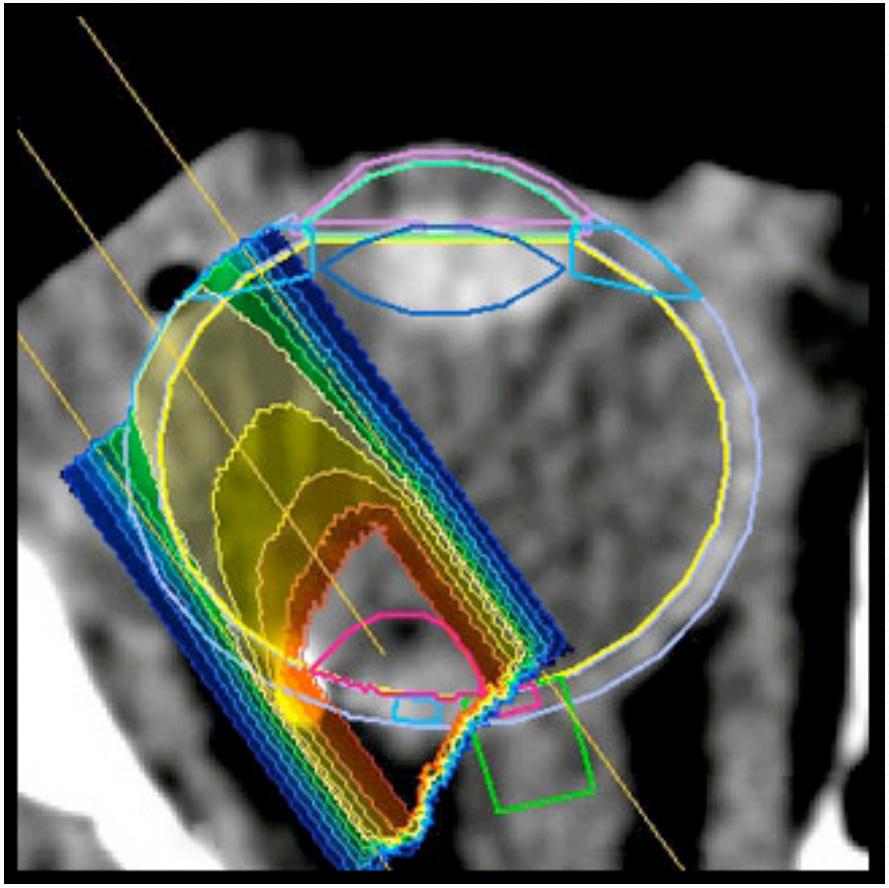


http://www.helmholtz-berlin.de/angebote/pt/en/treatment_de.html

Proton therapy is a reasonable choice for certain ocular tumors because of the excellent radiation dose distributions as in this retro-orbital mass causing proptosis



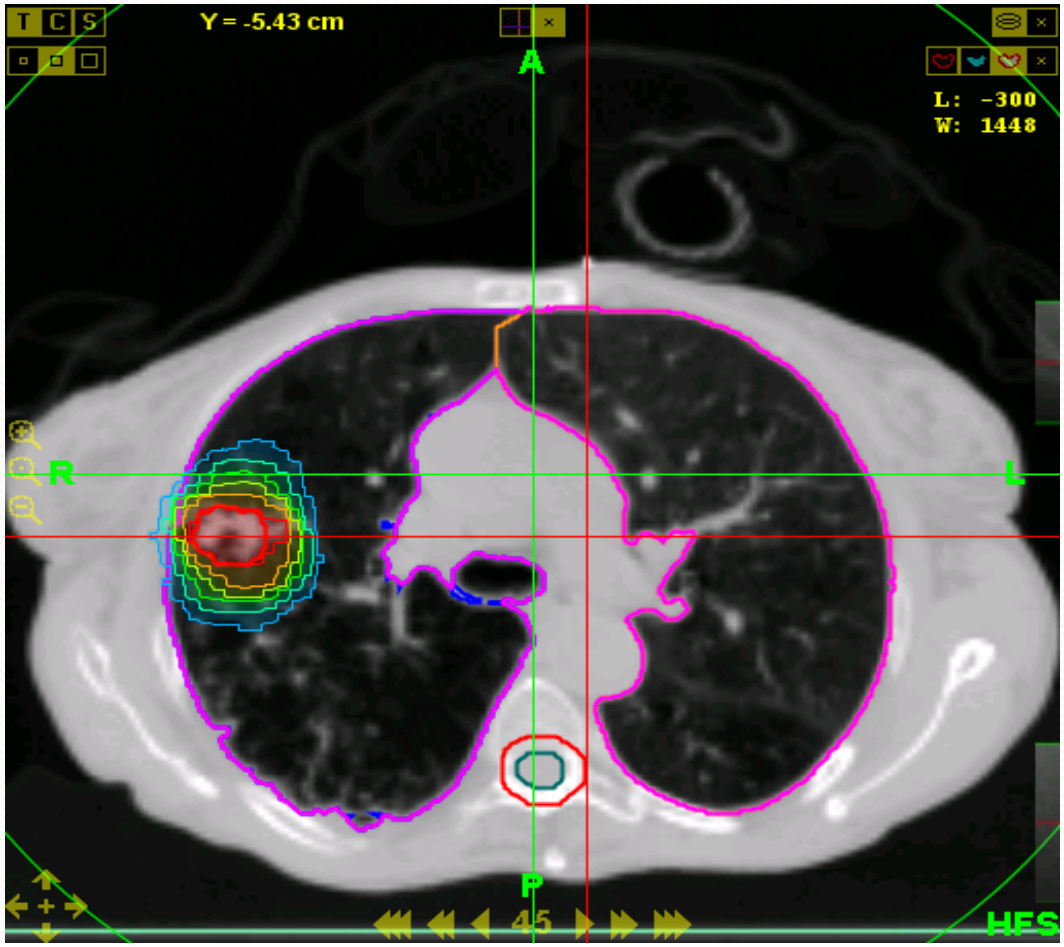
Proton therapy radiation dose distributions in case of choroidal melanoma



http://www.helmholtz-berlin.de/angebote/pt/en/working/index_de.html

Stereotactic Body Radiation Therapy (SBRT) for lung cancer – a relatively new and highly effective treatment for early stage non-small cell lung cancer

Another opportunity for further improvements via proton therapy???

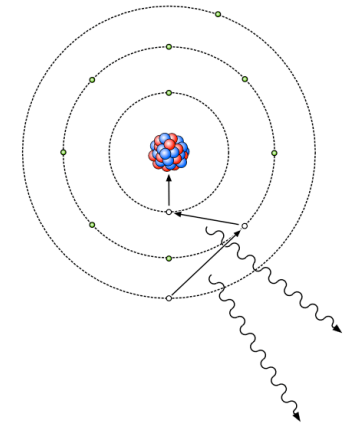


How about (Charged) Pions?

- High radiobiological punch – like neutrons
- Can be focused well and has a Bragg peak – like protons
- Half-life measured in nanoseconds – should not even reach tumor but relativistic effects allow survival through time dilatation
- π^- decay into muons and muon anti-neutrinos
  - which decay into electrons and electron anti-neutrinos
- But can be captured by a nucleus for some really interesting effects…

Pi-meson atoms:

- Emission of
  - Characteristic x-rays and Auger electrons are emitted as pion “cascades” down energy levels towards nucleus and eventually enters nucleus itself leading to “Star” formation
  - The “Star” is nuclear fragmentation that leads to a localized dose of very biologically-effective radiation
  - Unfortunately, the high costs and impracticality have limited research and clinical applications in this area



Summary

- At one time particle physics was deceptively simple but as knowledge increased it entered a state of chaos
  - The Standard Model has again restored order and simplicity
- Molecular oncology once appeared seemingly simple but as knowledge increased it too entered a very confusing state of chaos
  - But there is now a much clearer, simpler and better understanding
- Importantly, the two seemingly disparate disciplines with curious historical analogies are presently intersecting in our quest for better treatments for people with cancer