Cancer Biology I
BIO-471
Fall Semester

Teachers:

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Cancer Biology I :

Topics covered

Week 1:

- Lecture 1 **Hallmarks of cancer – an overview; DNA damage**
- (Chapters 2, 4, 7 (Weinberg book))
- Exercises: Wednesday 13:15-16:00: room **CE1103** **Oncogenes and tumor suppressor genes**

Week 2:

- Lecture 2 (Monday 14:15-16:00: room **AAC132**):
- **p53, genome instability and DNA repair of DNA double strand breaks; Synthetic lethality**
- Exercises: Wednesday 13:15-16:00: room **CE1103**

Week 3:

- Lecture 3/Exercises: **DNA repair and the DNA damage response**

Week 4:

- Lecture 4/Exercises: **p53 and apoptosis**
- (Chapters 9 (Weinberg))

Viral Oncogenes

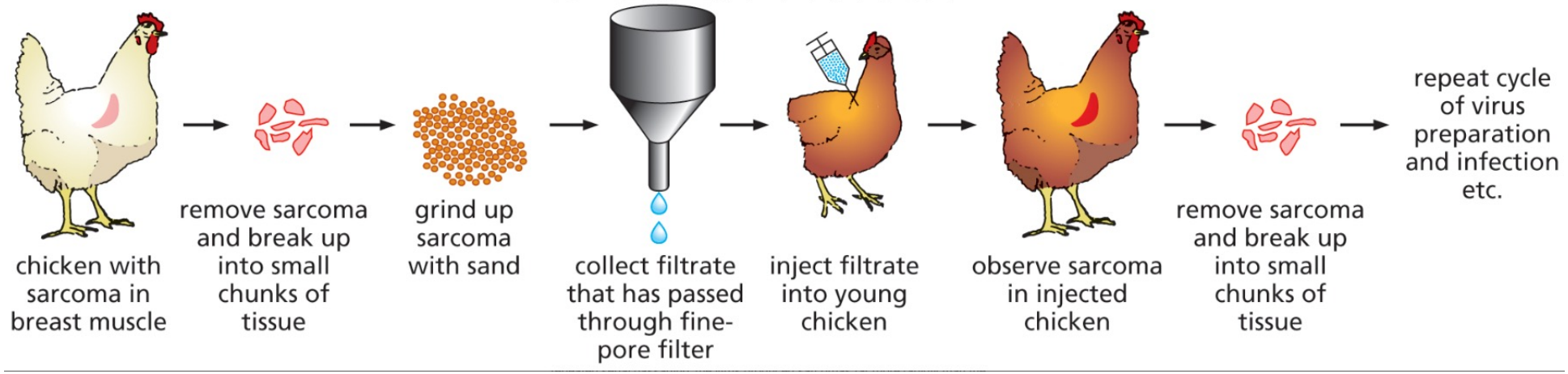


Figure 3.1 The Biology of Cancer 2023

Viral Oncogenes are Derived from Cellular Proto-oncogenes

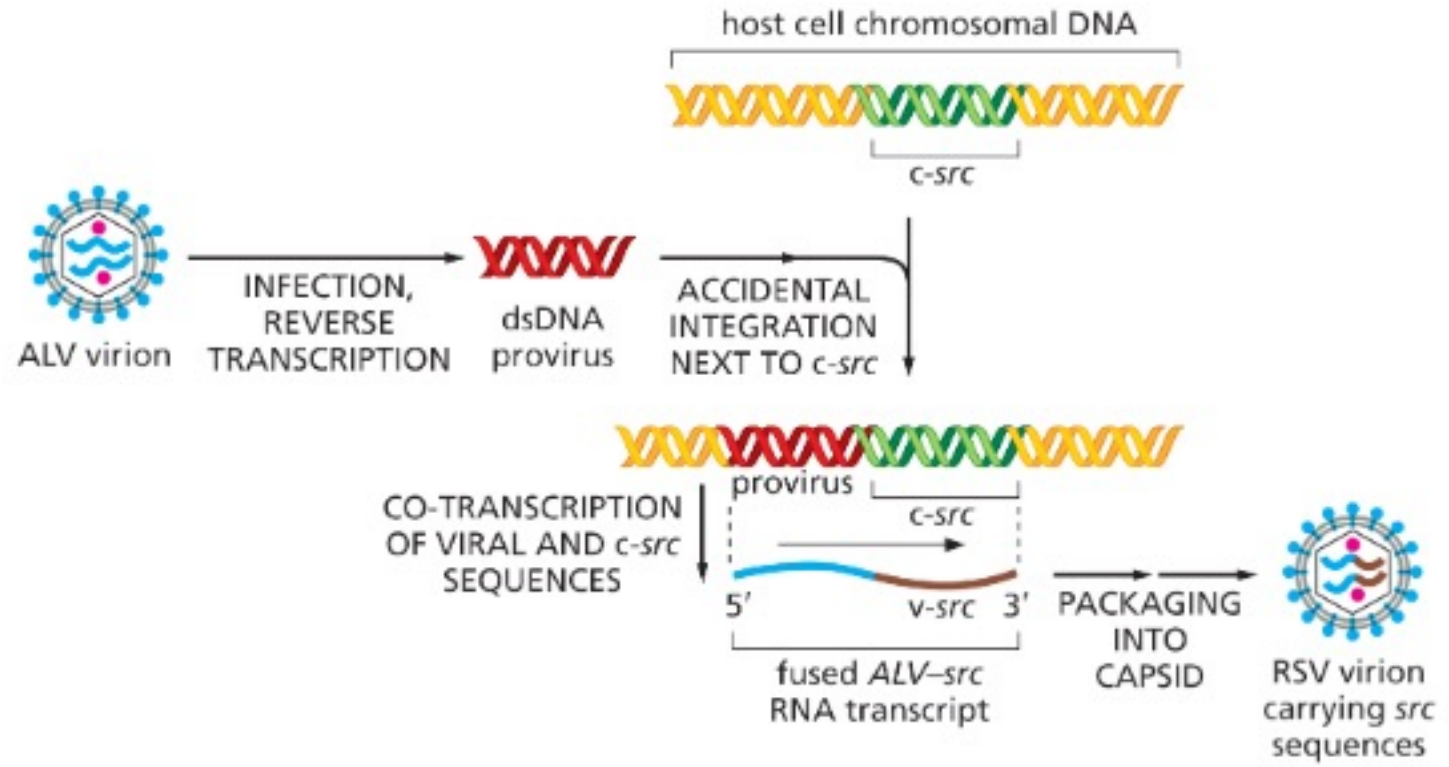


Figure 3.14 The Biology of Cancer 2023

Cellular Proto-oncogenes

- 1970's: tumor viruses were suspected to be the cause of many human cancers. The study of tumor viruses led to the understanding of molecular principles in many human cancers.

- But: Of the > 100 tumor types, only cervical carcinoma (papilloma virus) and hepatomas (hepatitis virus) could be linked to viruses. Though, there are probably others…

Cellular Proto-oncogenes

Hypothesis:

- Carcinogens function as mutagens
- They mutate critical growth-controlling genes (proto-oncogenes)
- The mutated alleles function as active oncogenes

Cellular Proto-oncogenes

To test the hypothesis:

- Development of gene transfer protocols
- Extract DNA from cancer cells
- Choose appropriate recipient cells

Nonviral oncogenes

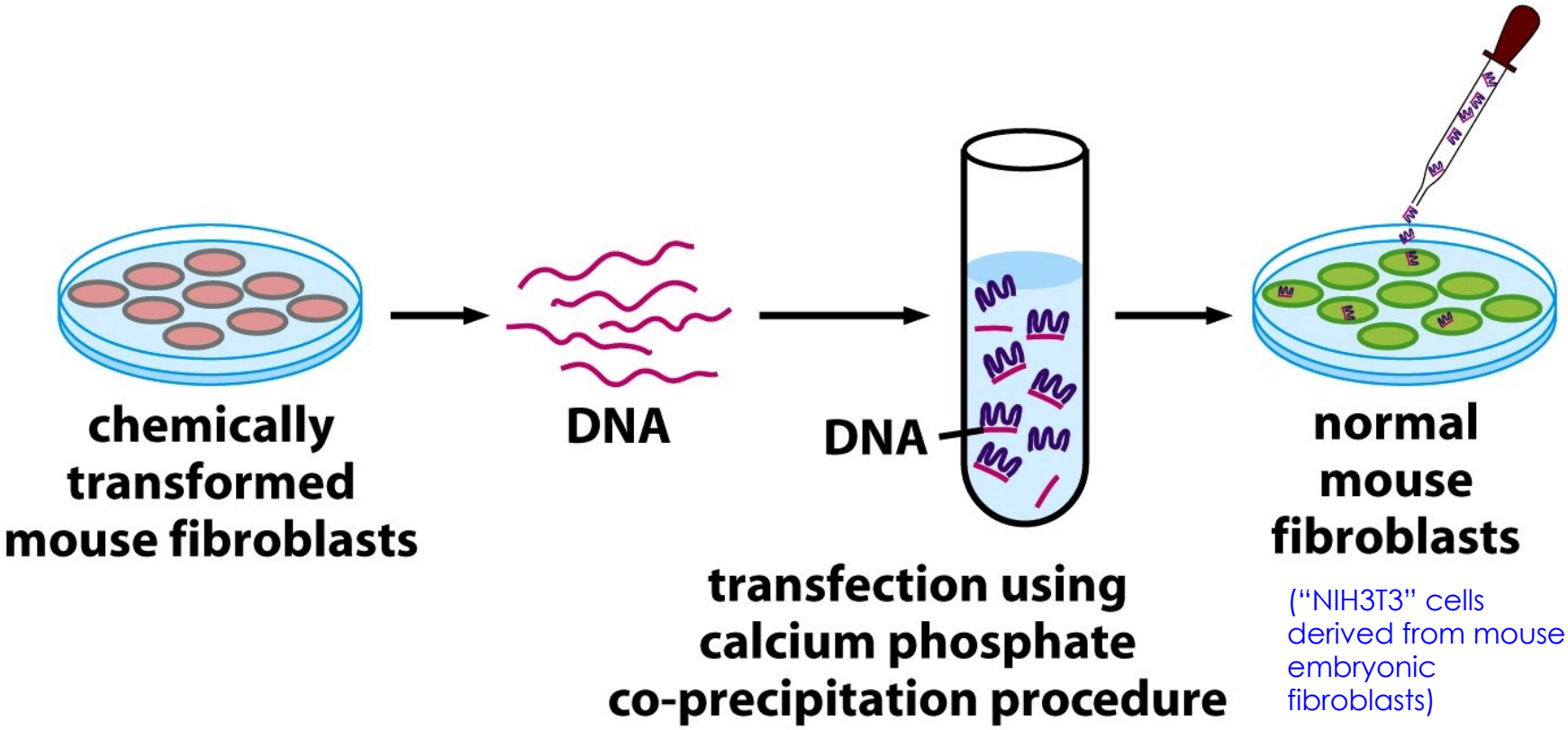


Figure 4.1 (part 1 of 2) *The Biology of Cancer* (© Garland Science 2014)

Nonviral oncogenes

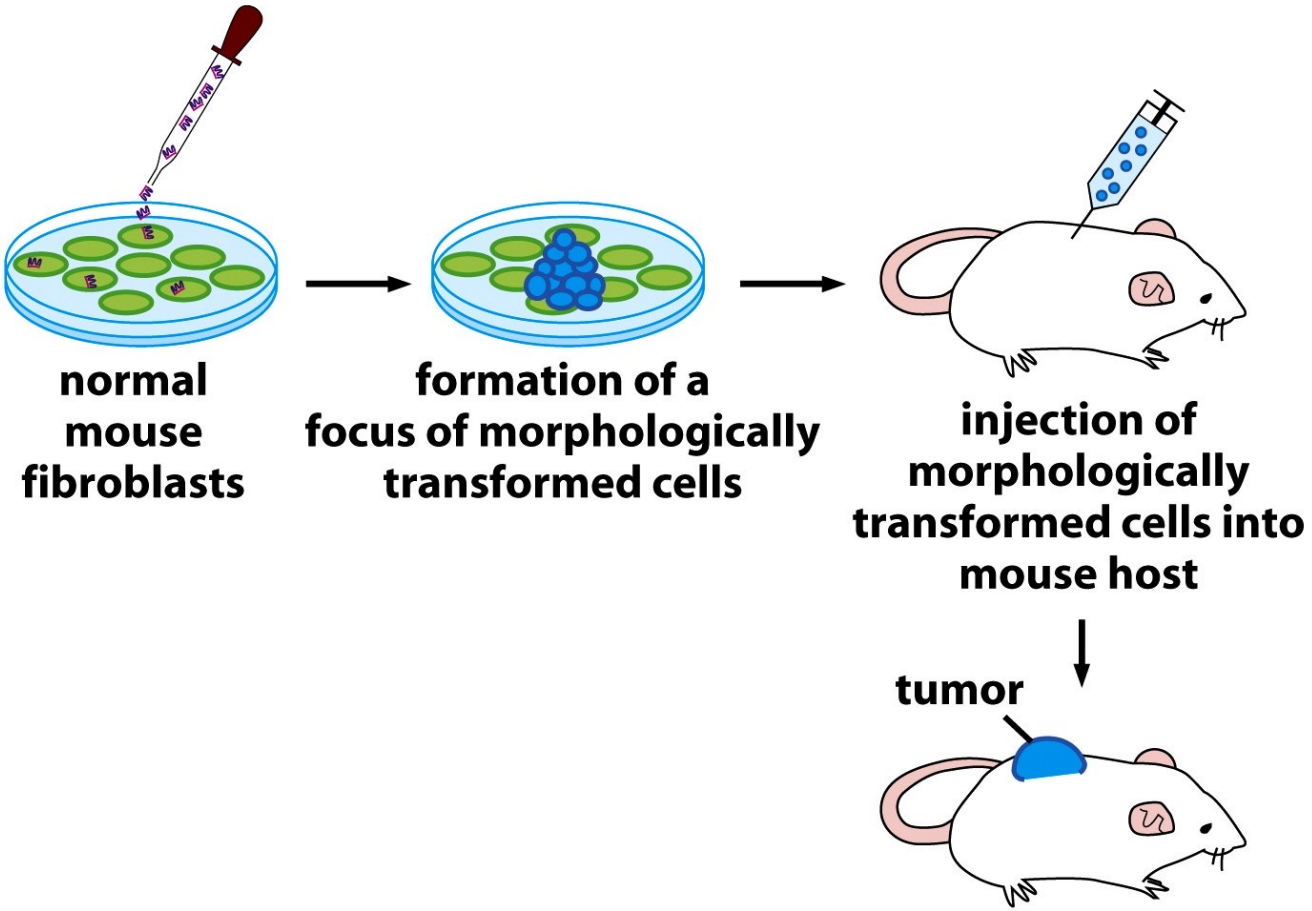


Figure 4.1 (part 2 of 2) *The Biology of Cancer* (© Garland Science 2014)

Human tumor DNA can also transform NIH3T3

Transformed NIH3T3

Untransformed NIH3T3

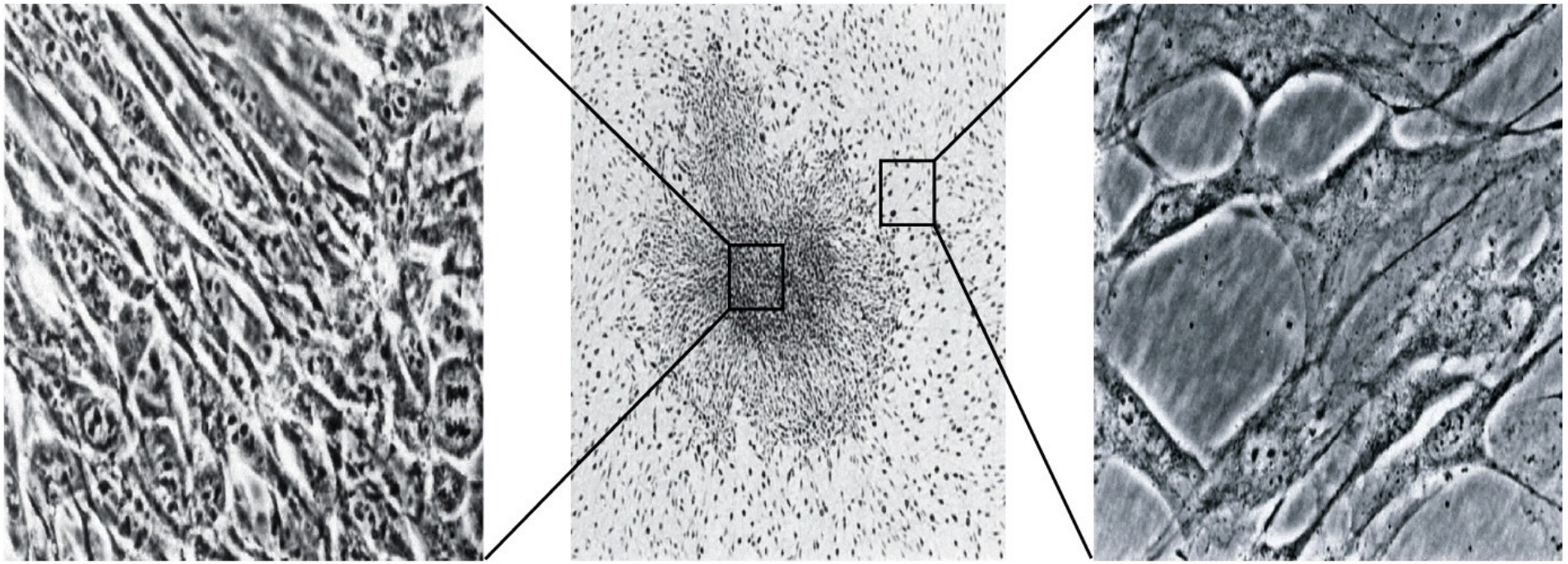


Figure 4.2 The Biology of Cancer (© Garland Science 2014)

Cloning of Transfected Human Oncogenes (DNA from bladder carcinoma cells)

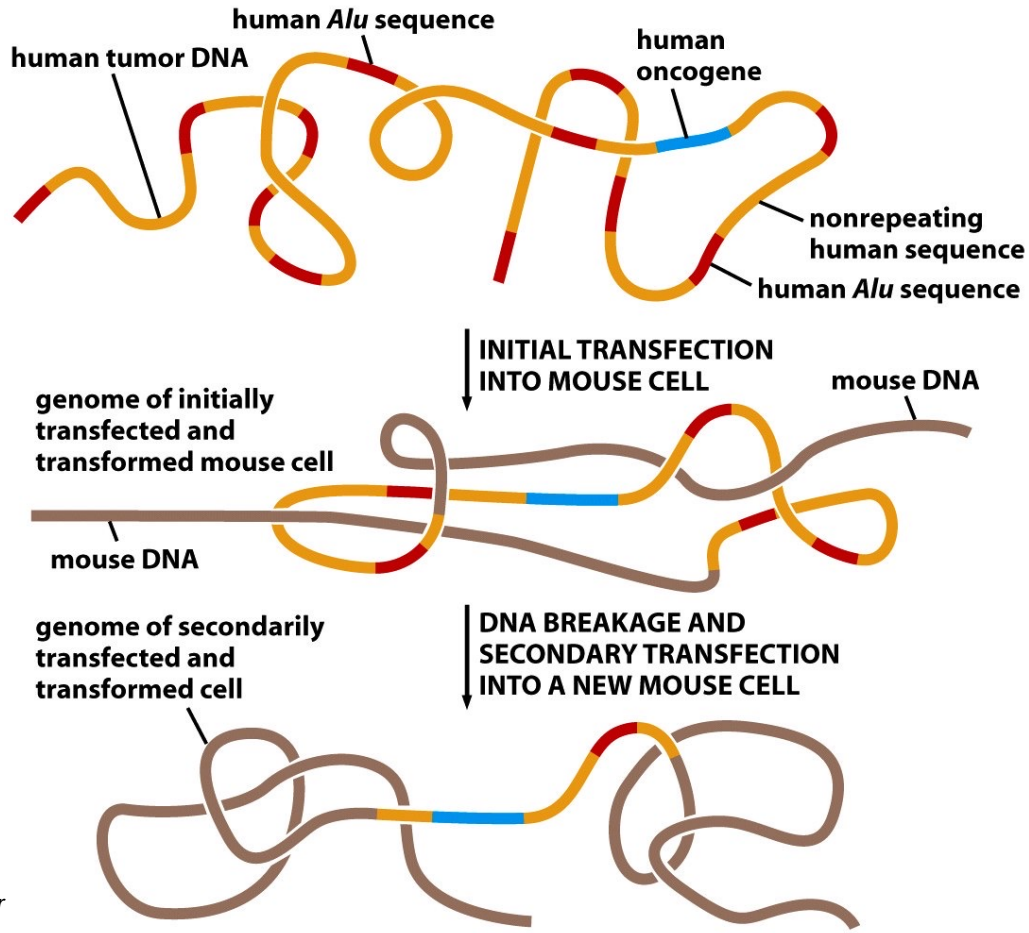


Figure 4.7 *The Biology of Cancer*

Mutation Responsible for H-ras Oncogene Activation

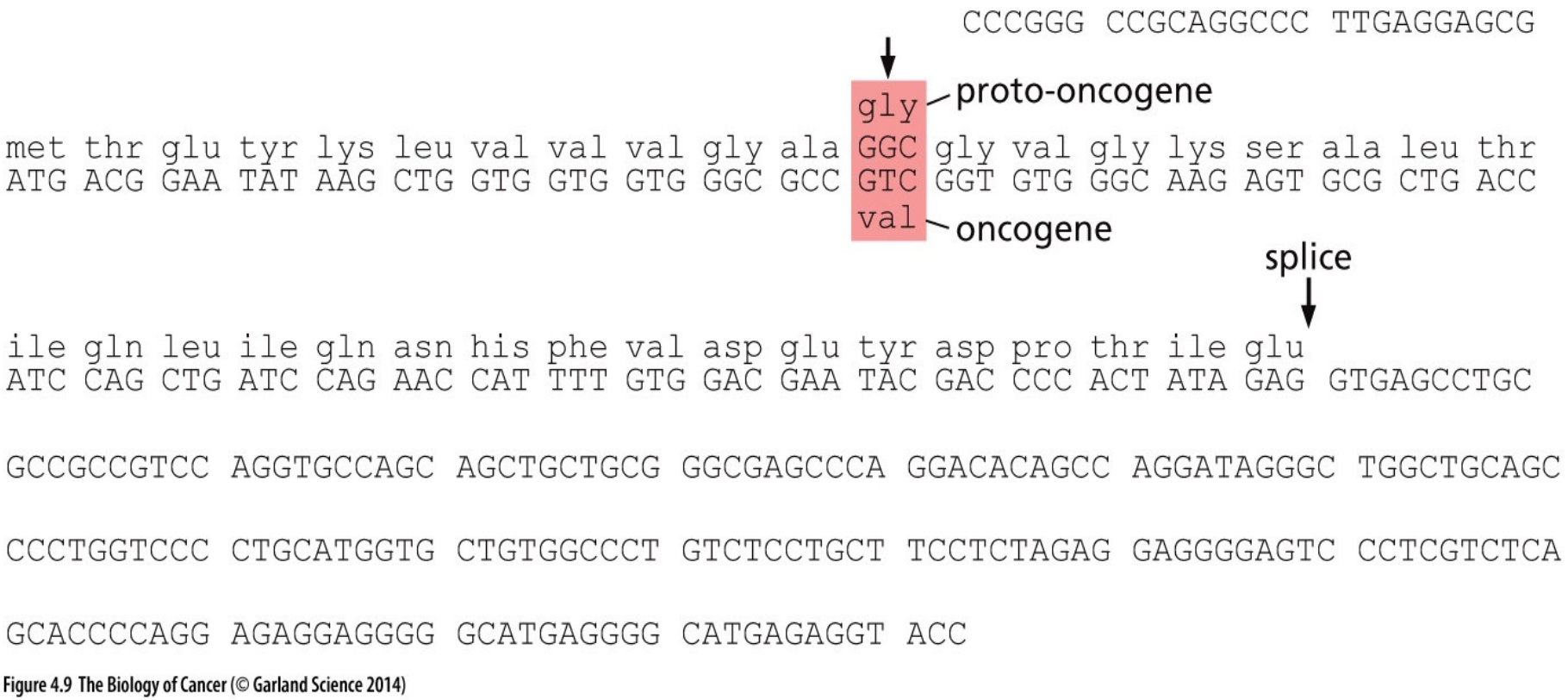


Figure 4.9 The Biology of Cancer (© Garland Science 2014)

Concentration of point mutations in K-ras

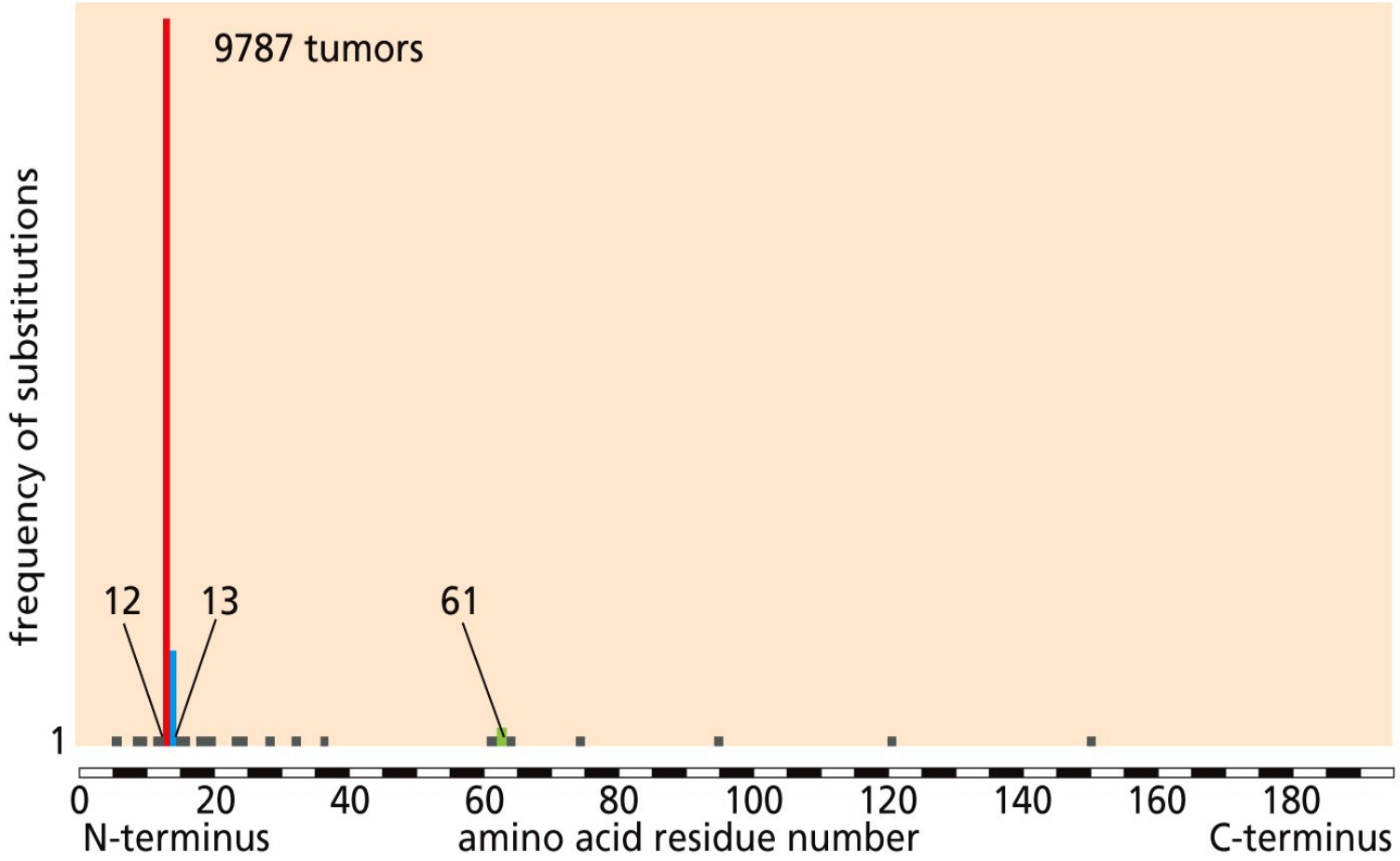


Figure 4.10 The Biology of Cancer (© Garland Science 2014)

Amplification of the *erb2/neu/HER2* Oncogene in 30% of Breast Cancer

Erb2/Neu: membrane surface-bound receptor tyrosine kinase

- drives the cell cycle
- protects from apoptosis

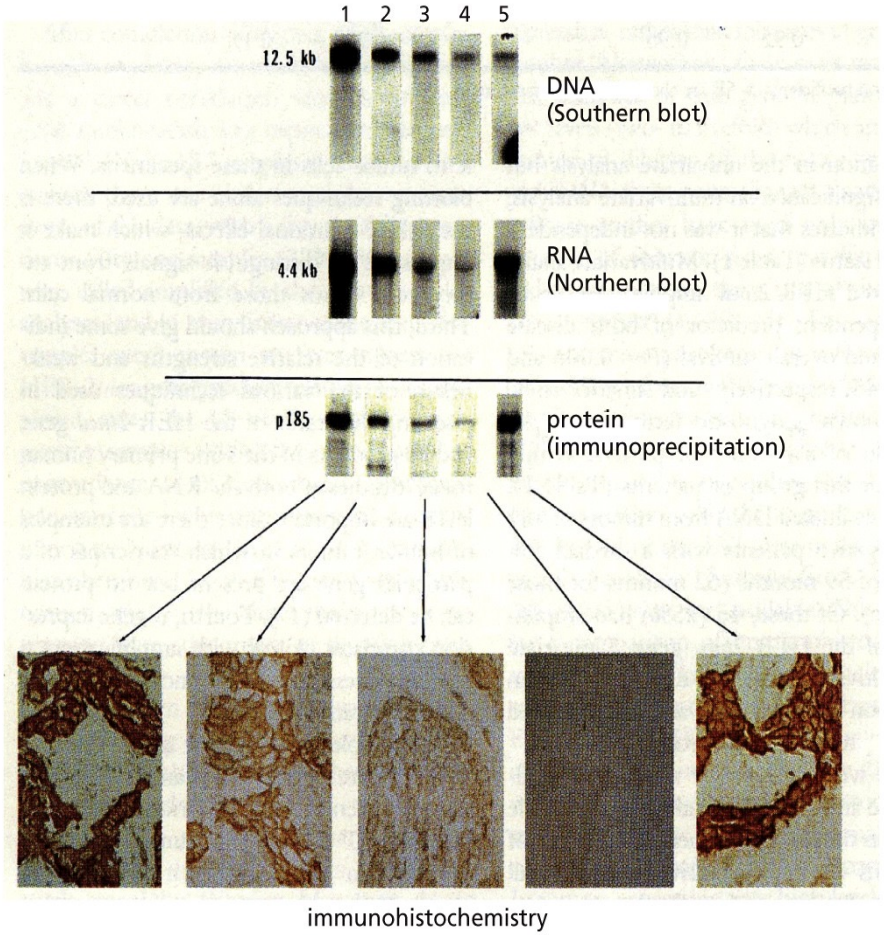


Figure 4.4a The Biology of Cancer (© Garland Science 2014)

Kaplan-Meier Plot: Relapse after Diagnosis and Treatment

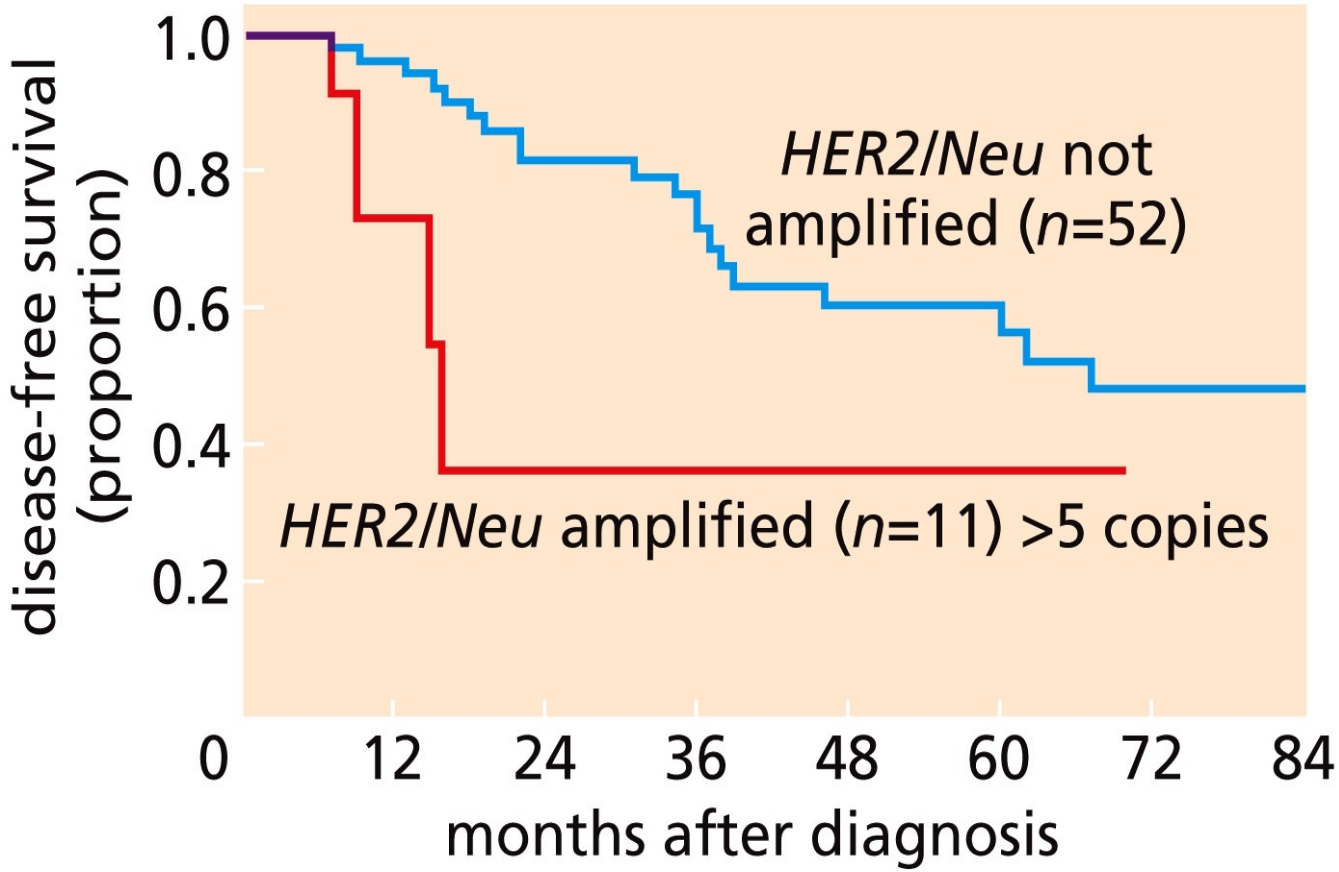
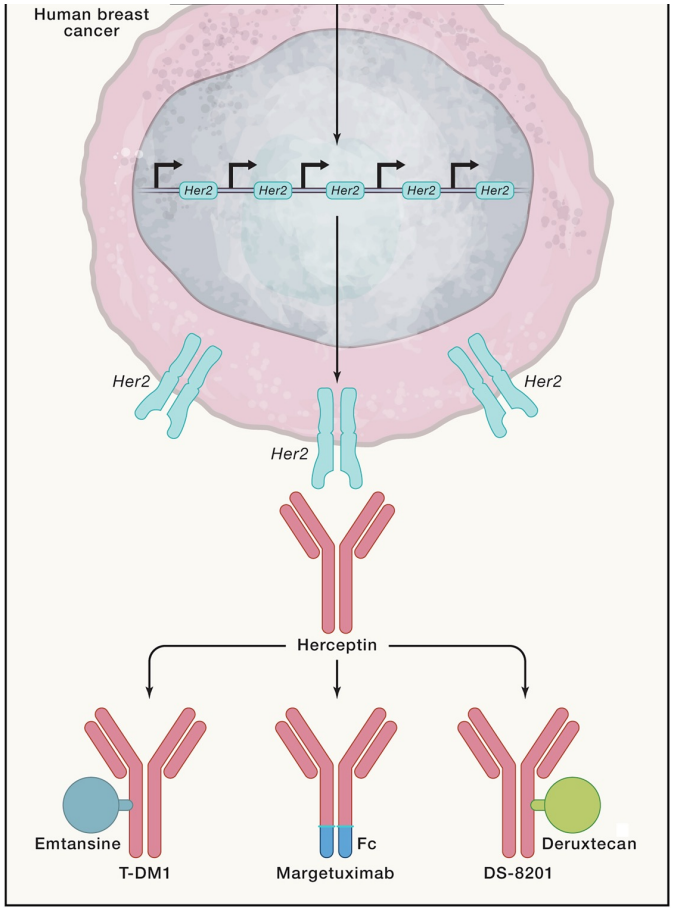


Figure 4.4b The Biology of Cancer (© Garland Science 2014)

Monoclonal Antibodies ("Herceptin") Against HER2 for Treatment of Breast Cancer



From Sawyers Cell 179, 8 (2019)

N-myc amplification in Pediatric Neuroblastoma

The gene is detected by fluorescence in situ hybridization (FISH) with fluorescent dye-labeled N-myc specific oligonucleotide probes.

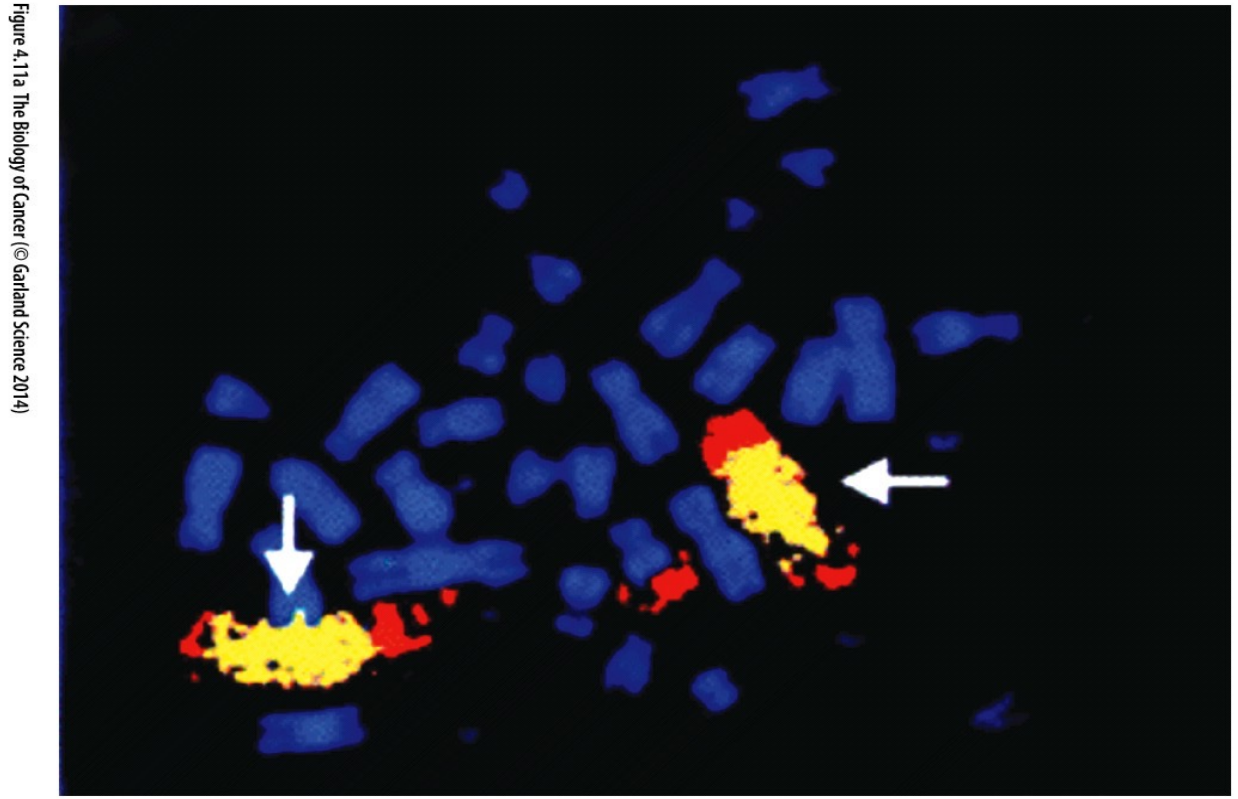


Figure 4.11a The Biology of Cancer (© Garland Science 2014)

Kaplan-Meier Plot: Event-Free Survival of Children Suffering from Neuroblastoma

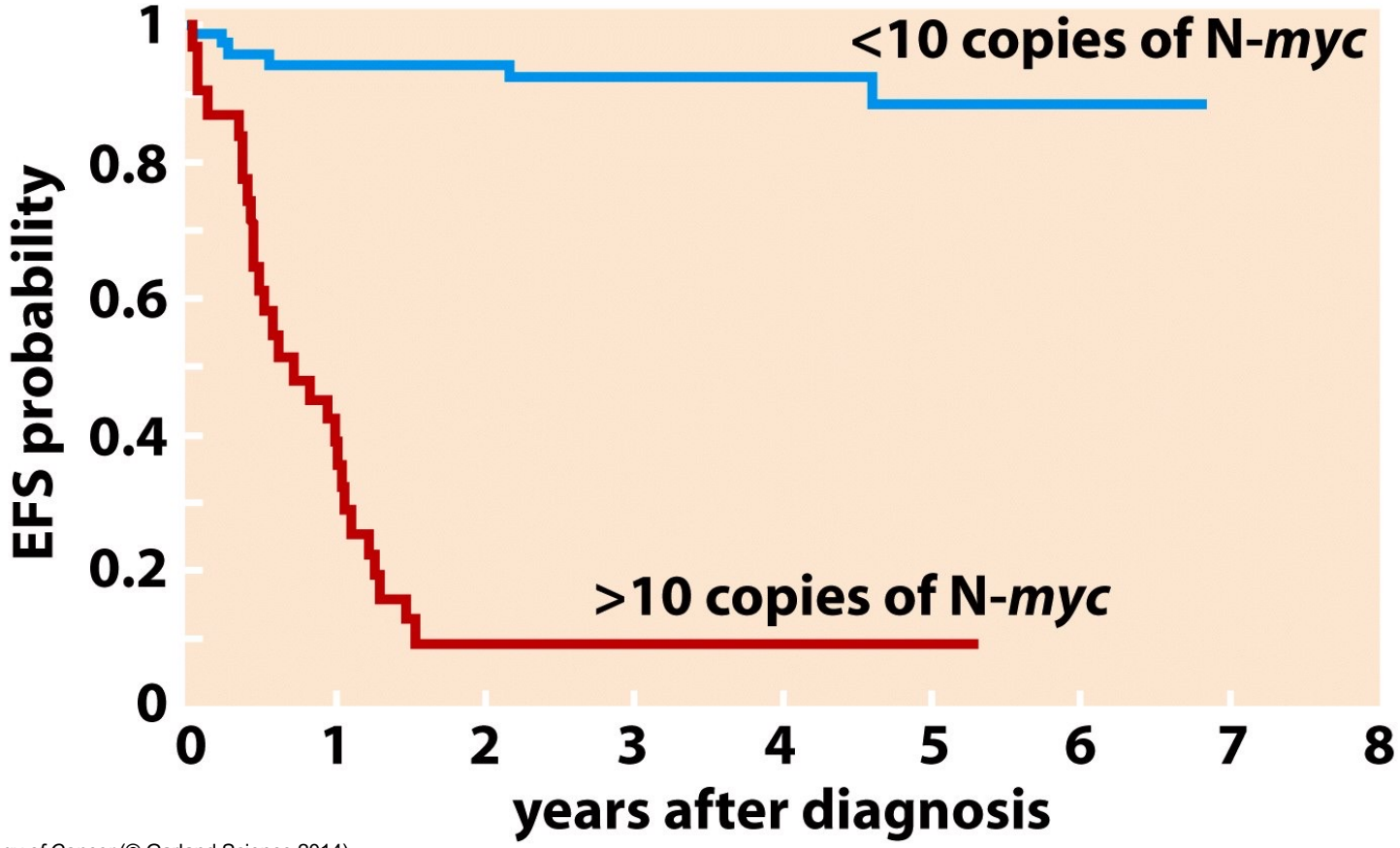


Figure 4.11b *The Biology of Cancer* (© Garland Science 2014)

Burkitt's Lymphoma: Translocation Brings *c-myc* Gene under Control of an Ig Gene

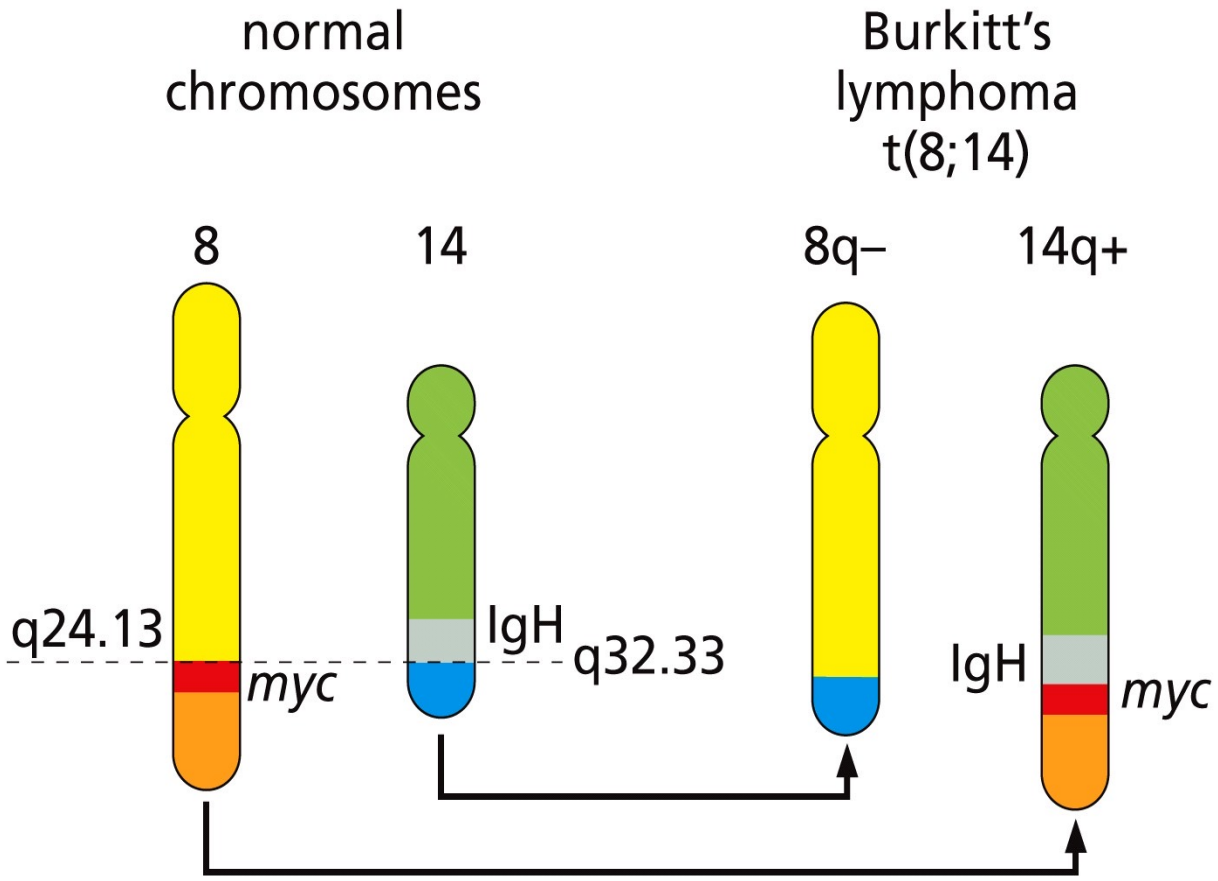


Figure 4.13a The Biology of Cancer (© Garland Science 2014)

Reciprocal Translocation

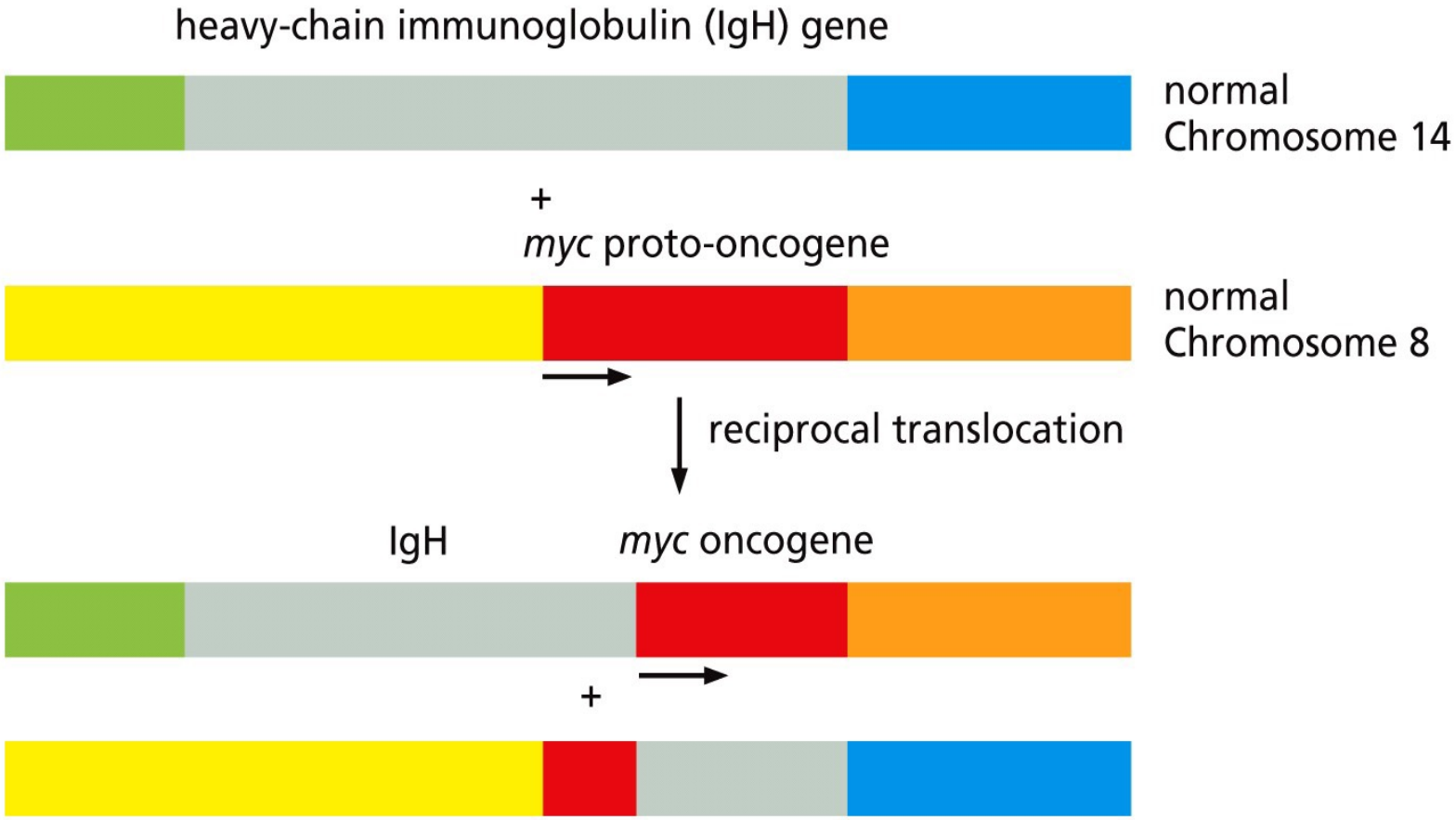


Figure 4.13b The Biology of Cancer (© Garland Science 2014)

Tumor Suppressor Genes

Genes whose partial or complete inactivation, occurring in either the germ line or the genome of a somatic cell, leads to an increased likelihood of cancer development

- Gatekeeper genes - operate to regulate cell proliferation or to regulate cell number by controlling cell differentiation or cell death. Loss of a gatekeeper gene removes an impediment to cell proliferation and thus to the appearance of populations of neoplastic cells

- Caretaker genes - encode a proteins that maintain the integrity of the genome and thereby prevent the accumulation of mutations and, in turn, the formation of neoplastic cells

Dominance and Recessiveness of the Tumorigenic Phenotype

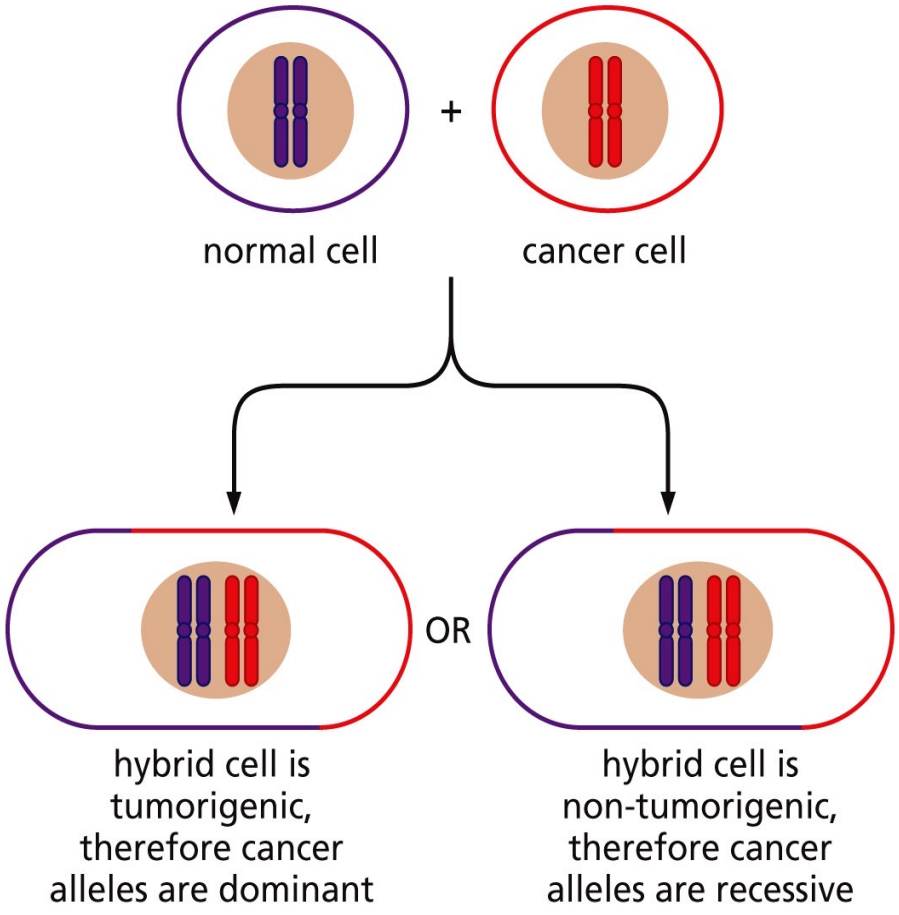
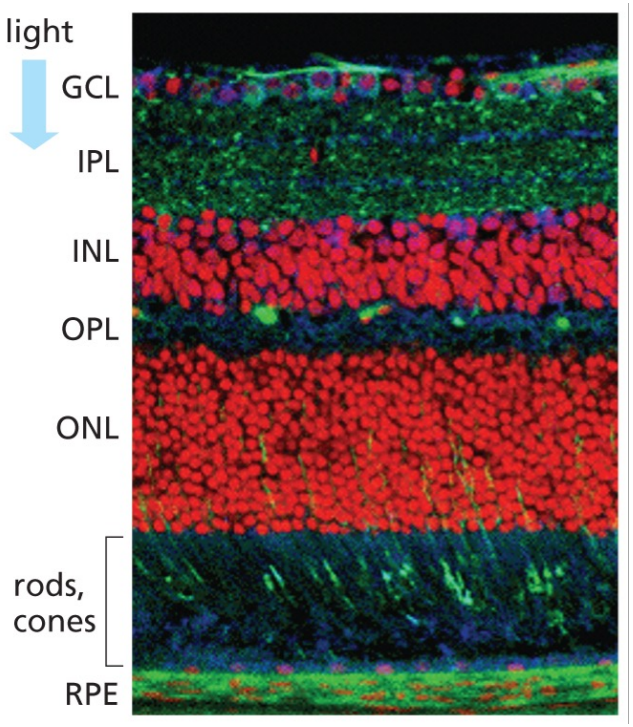


Figure 7.2 The Biology of Cancer (© Garland Science 2014)

Retinoblastoma: Develops from Retina Cell Precursor



Affects 1/20’000 children

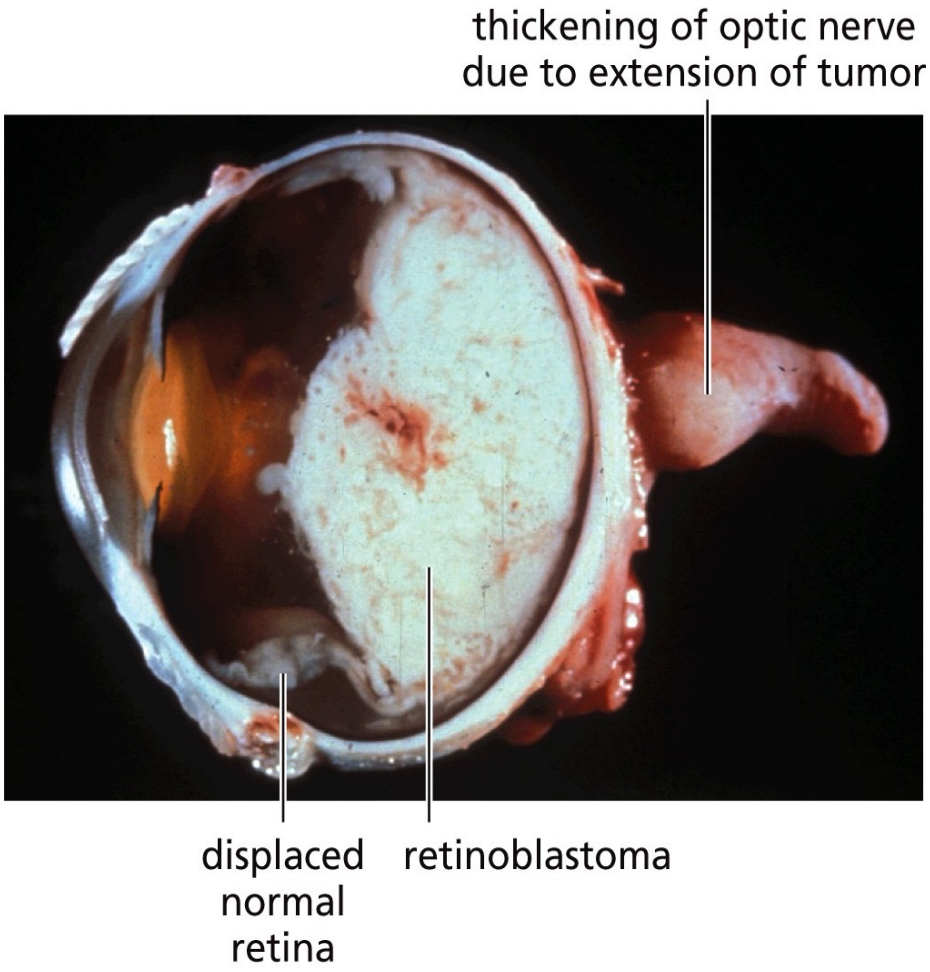


Figure 7.3c The Biology of Cancer (© Garland Science 2014)

Dynamics of Retinoblastoma Formation

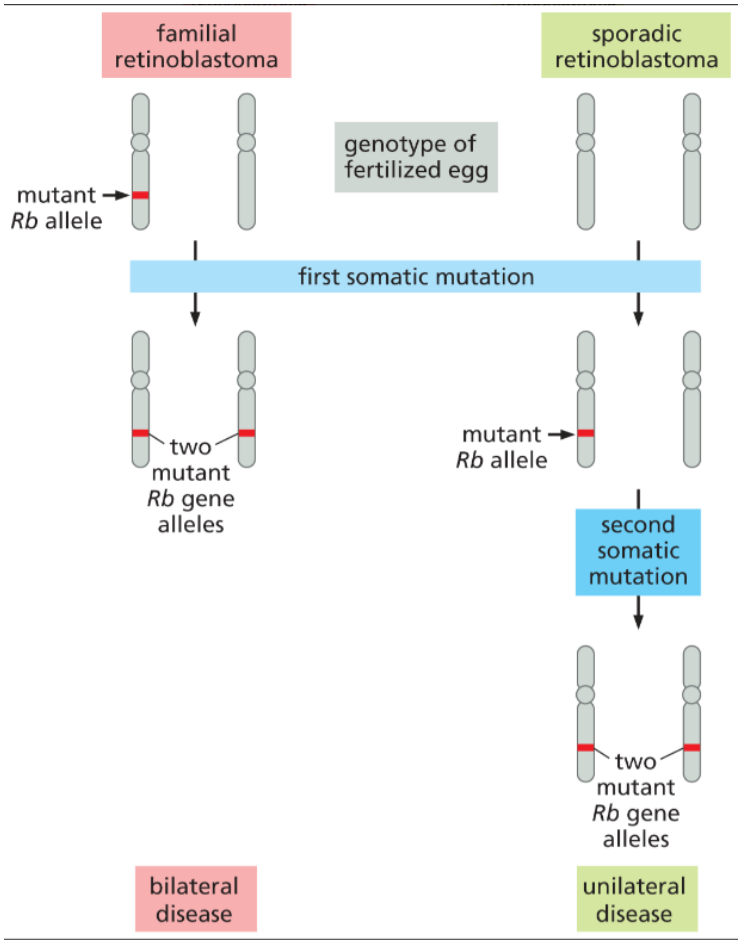


Figure 7.5 The Biology of Cancer 2023

Loss of Heterosygosity

- Mitotic Recombination

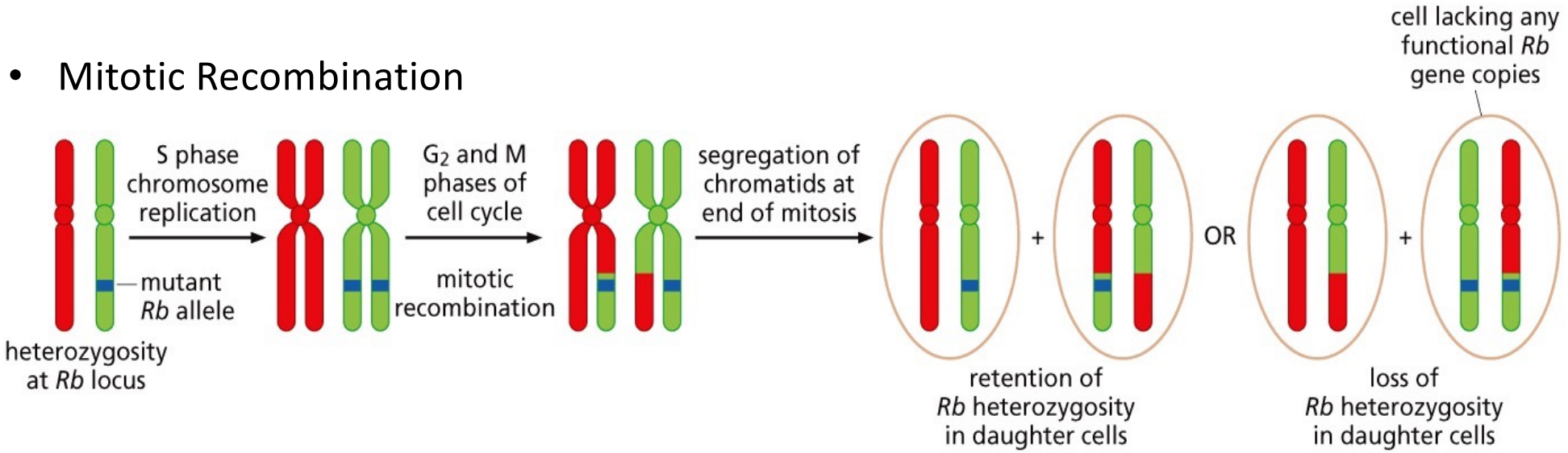


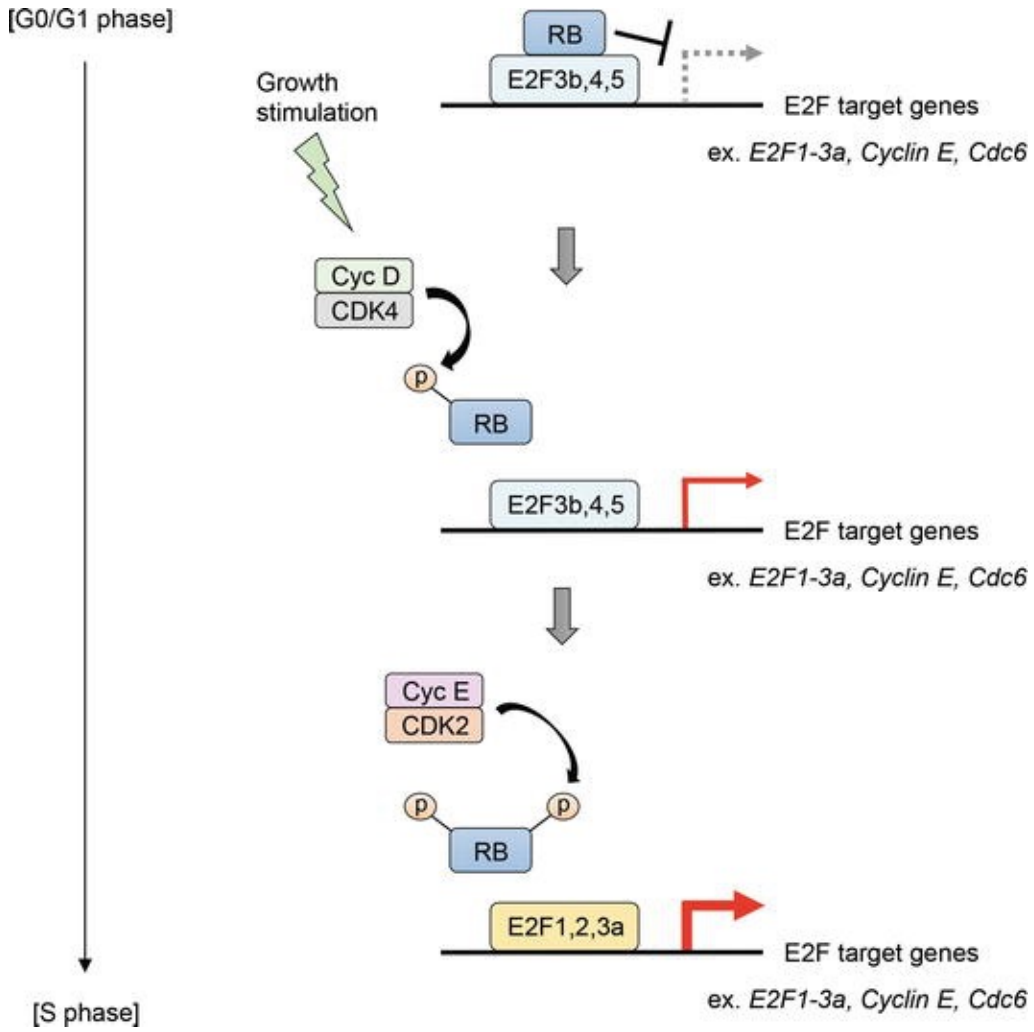
Figure 7.7 The Biology of Cancer (© Garland Science 2014)

- Nondisjunction: LOH through loss of an entire chromosome
- Promoter methylation can also lead to inactivation of tumor suppressor genes (MeCpG)

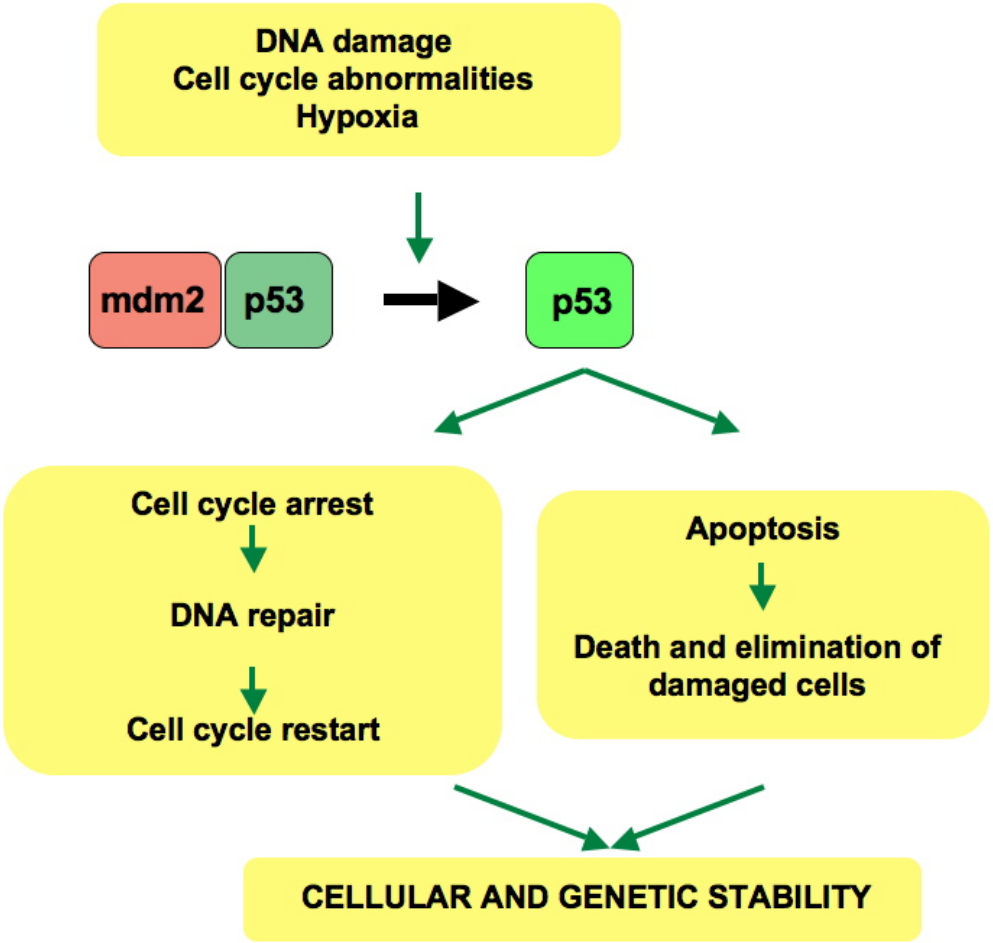
Rb action

E2F target genes:

- cell cycle regulators
  - cyclin E
  - cyclin A
  - cyclin D1
  - Cdc2
  - Cdc25A
- DNA synthesis enzymes
  - dihydrofolate reductase (DHFR)
  - DNA polymerase α
- DNA replication proteins
  - Cdc6
  - ORC1
  - MCM proteins
- Apoptotic genes
  - Apoptosis protease-activating factor 1 (Apaf1)
  - P73
  - ARF



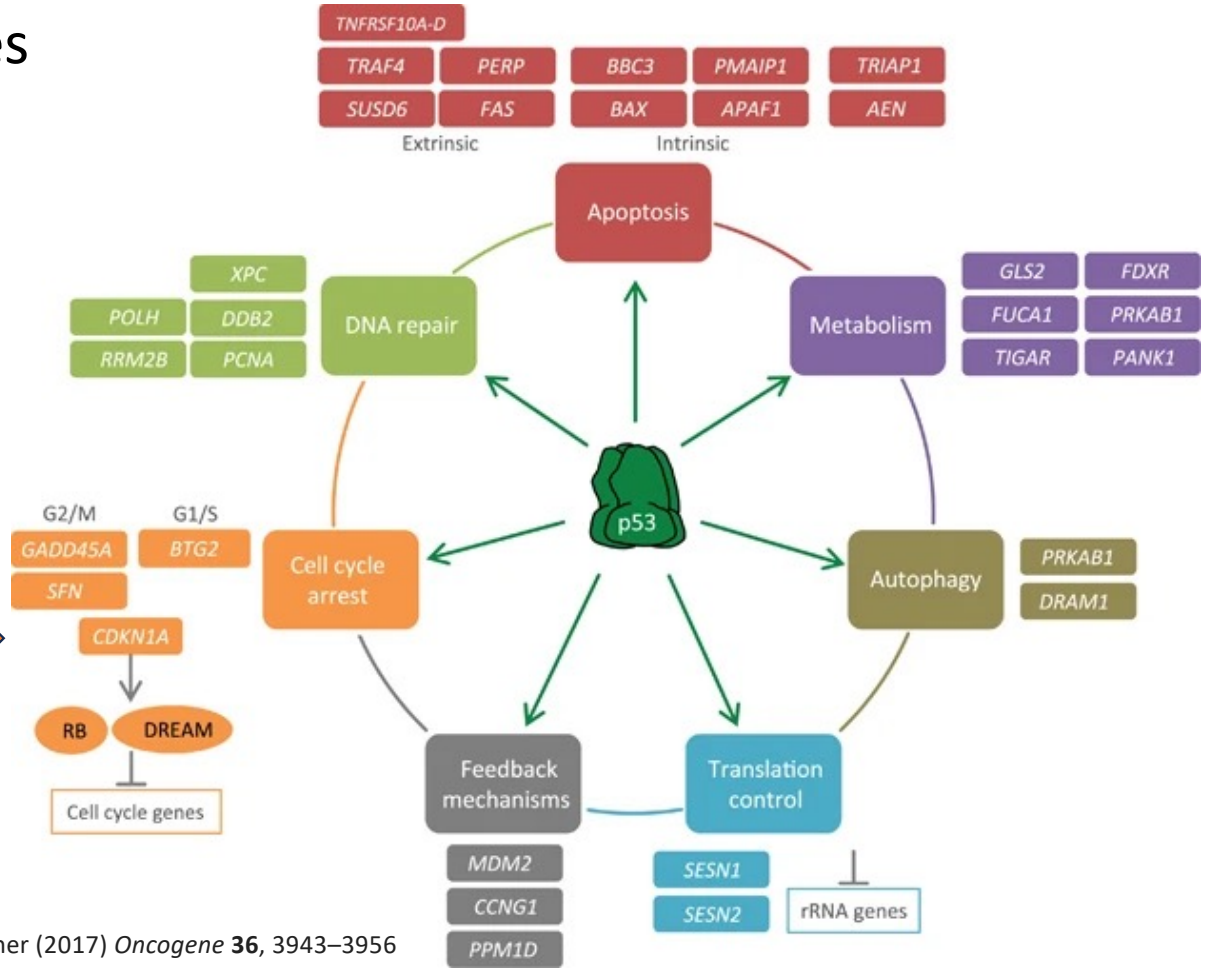
p53: Master Guardian



p53 is a transcription factor

More than 300 target genes

Gene downregulation by p53 is indirect and requires p21



Fischer (2017) *Oncogene* **36**, 3943–3956

Consensus DNA sequence bound by p53

- Analyzed 1546 sites; consensus sequence: relative size of letter indicates frequency of DNA base at the position

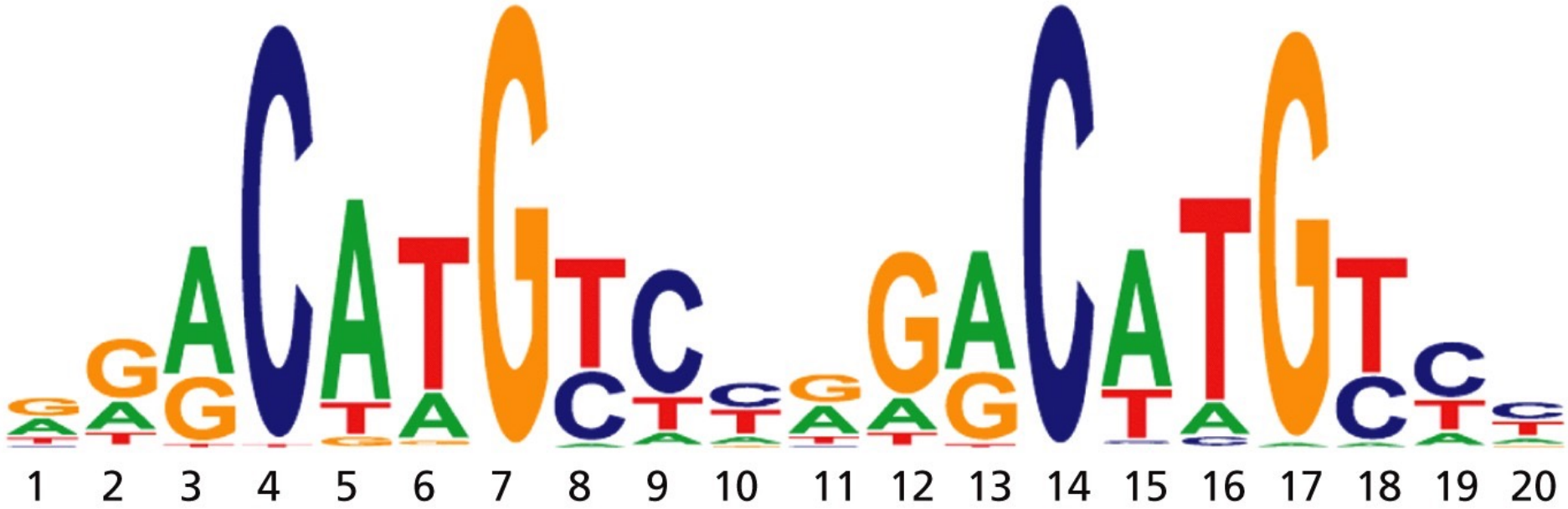
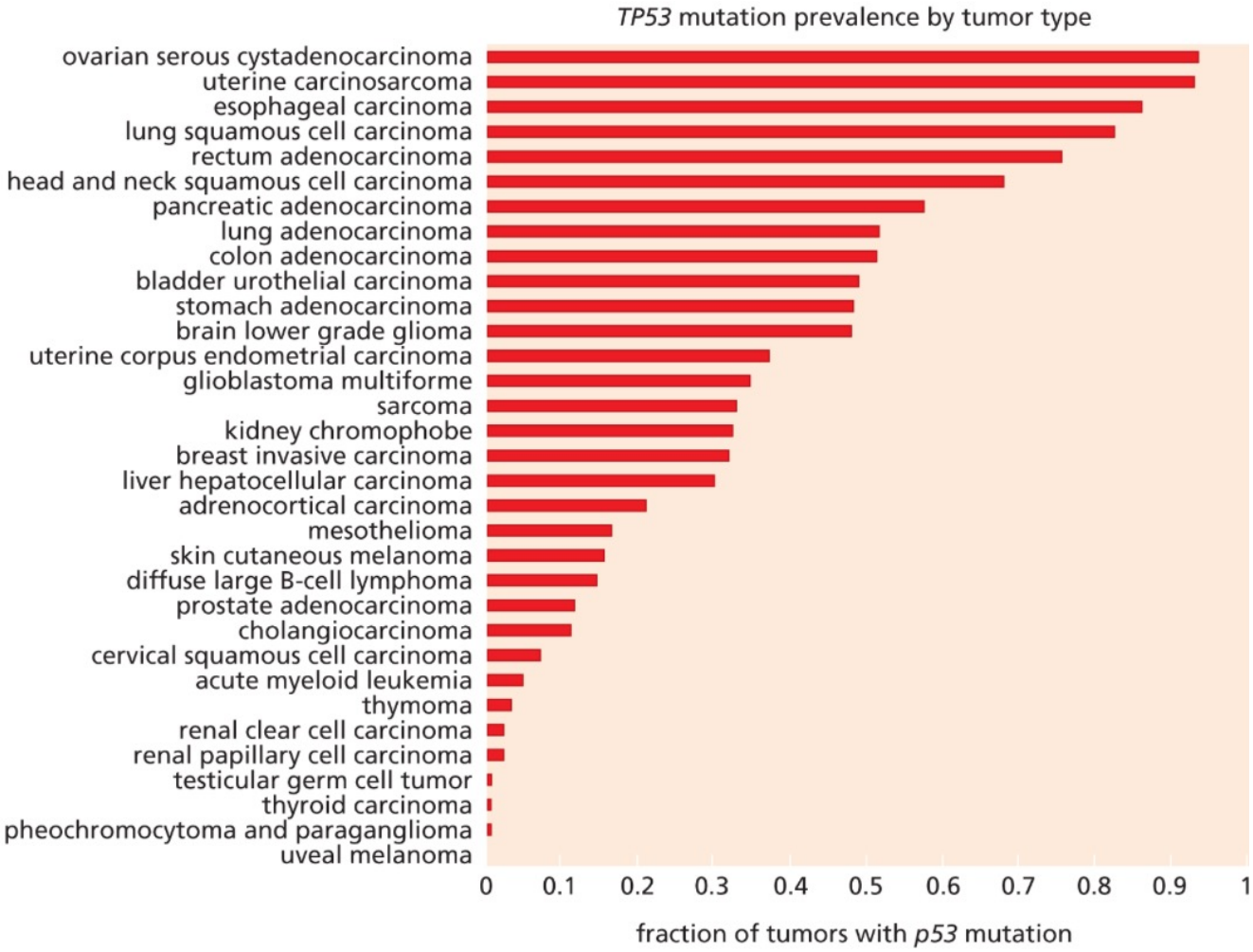


Figure 9.12c The Biology of Cancer (© Garland Science 2014)

TP53 is the most frequently mutated gene in cancer



Effects of mutant p53 alleles in the mouse germ line

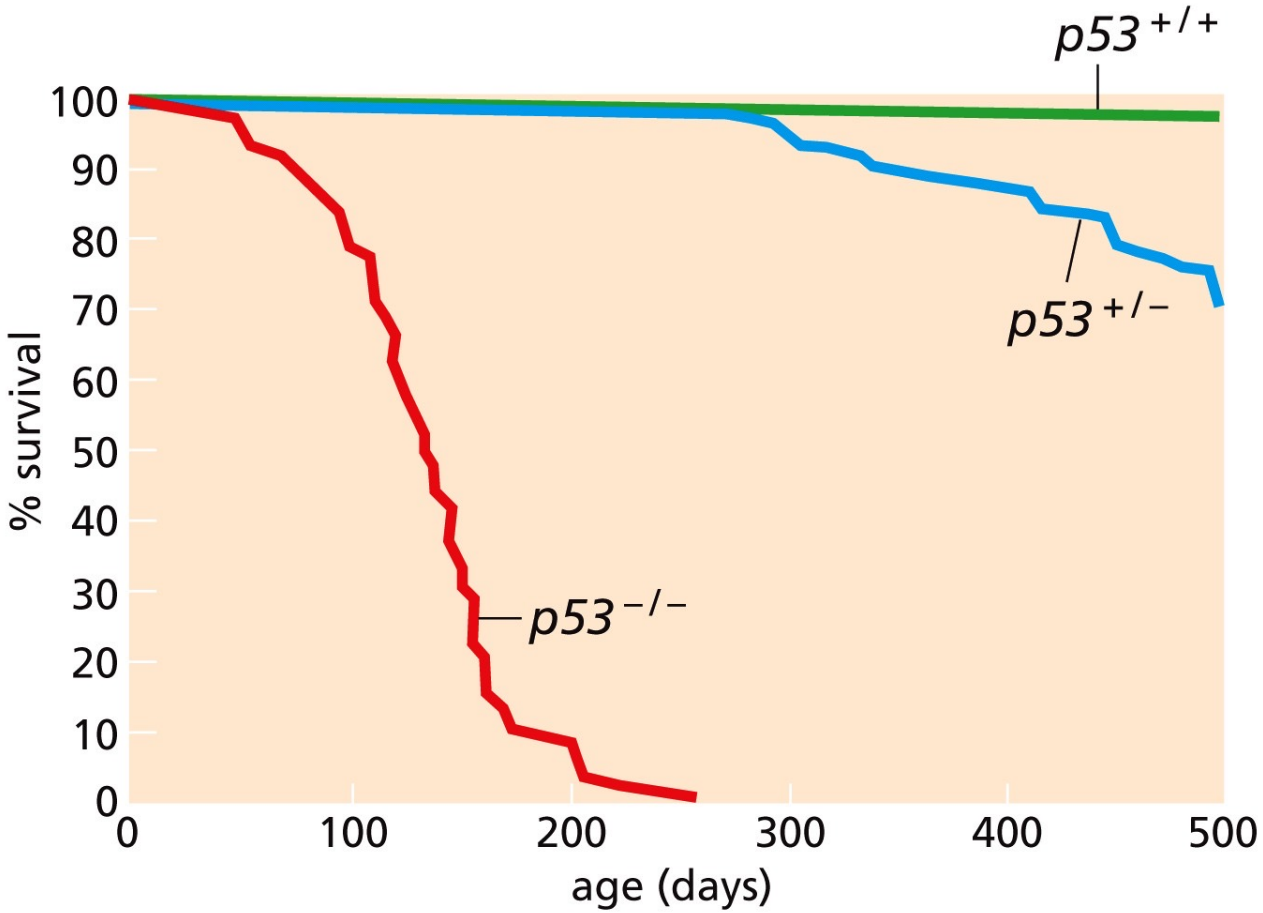


Figure 9.5 The Biology of Cancer (© Garland Science 2014)

Most of the mutations in p53 are missense

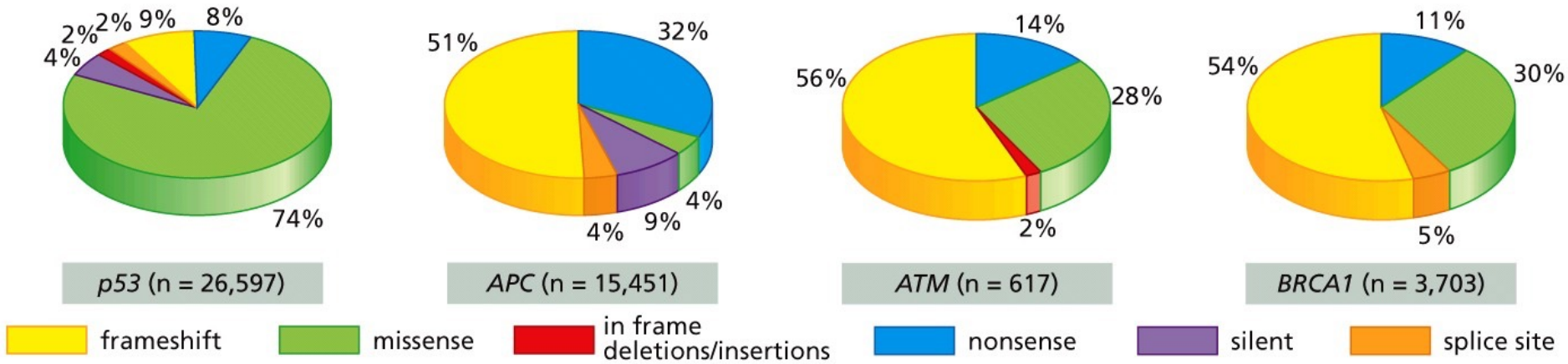


Figure 9.6a The Biology of Cancer (© Garland Science 2014)

p53: Binds DNA as a Tetramer

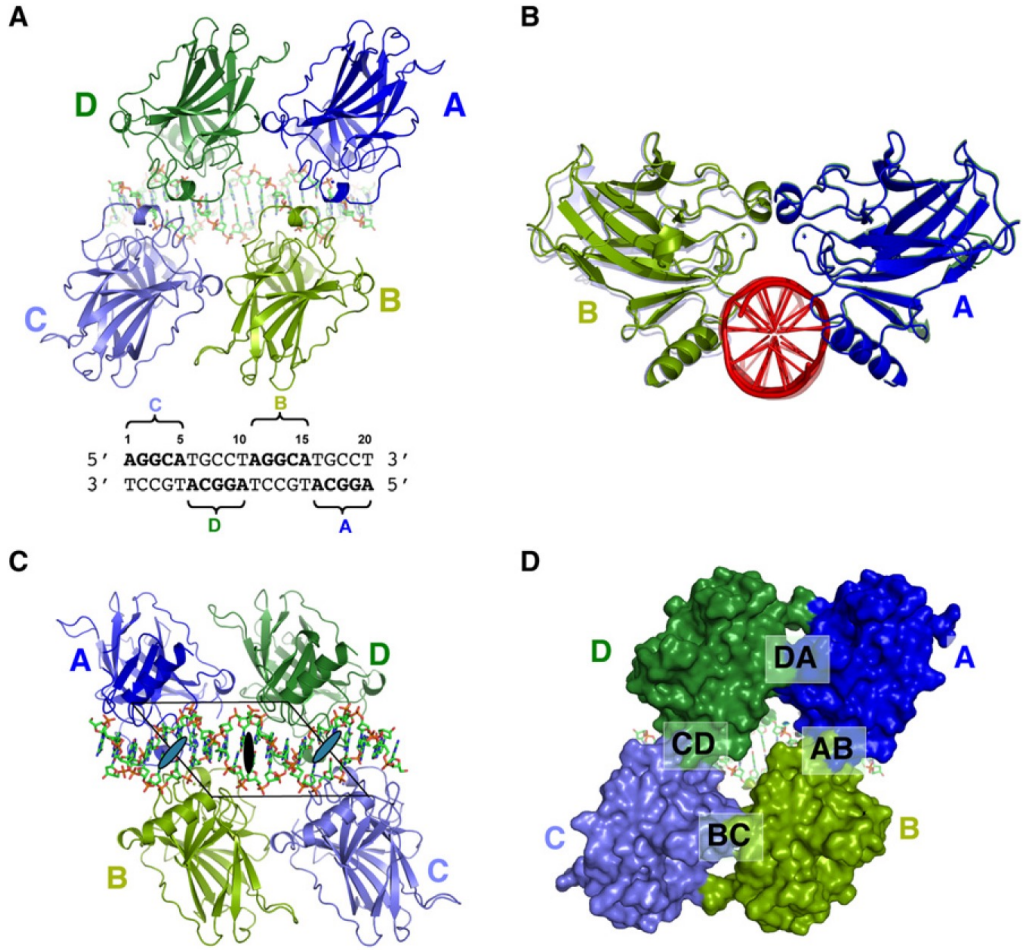


Figure 1. Overall Structure of the p53 Core Domain Bound to DNA as a Tetramer

(A) The tetramer viewed from the protein side. The four monomers are colored in blue (A), light green (B), light blue (C), and green (D). The same color scheme is used throughout the illustration unless indicated otherwise. The DNA is in stick model with its sequence shown below. The four pentameric motifs (quarter site) and their corresponding monomers are indicated in the sequence.

(B) A view of the tetramer along the DNA axis. This view shows that the tetramer has a planer structure wherein the A-B dimer (front) and C-D dimer align almost perfectly along the DNA axis.

(C) The tetramer viewed from the DNA side. The parallelogram is shown together with the global two-fold axis (dark oval) and the two local dyad aces (gray ovals).

(D) A surface model of the tetramer view in the same orientation as (A). The four protein-protein interfaces are indicated.

From Chen et al. Structure 18, 246–256, 2010

Most of the missense mutations in p53 affect DNA-binding Domain

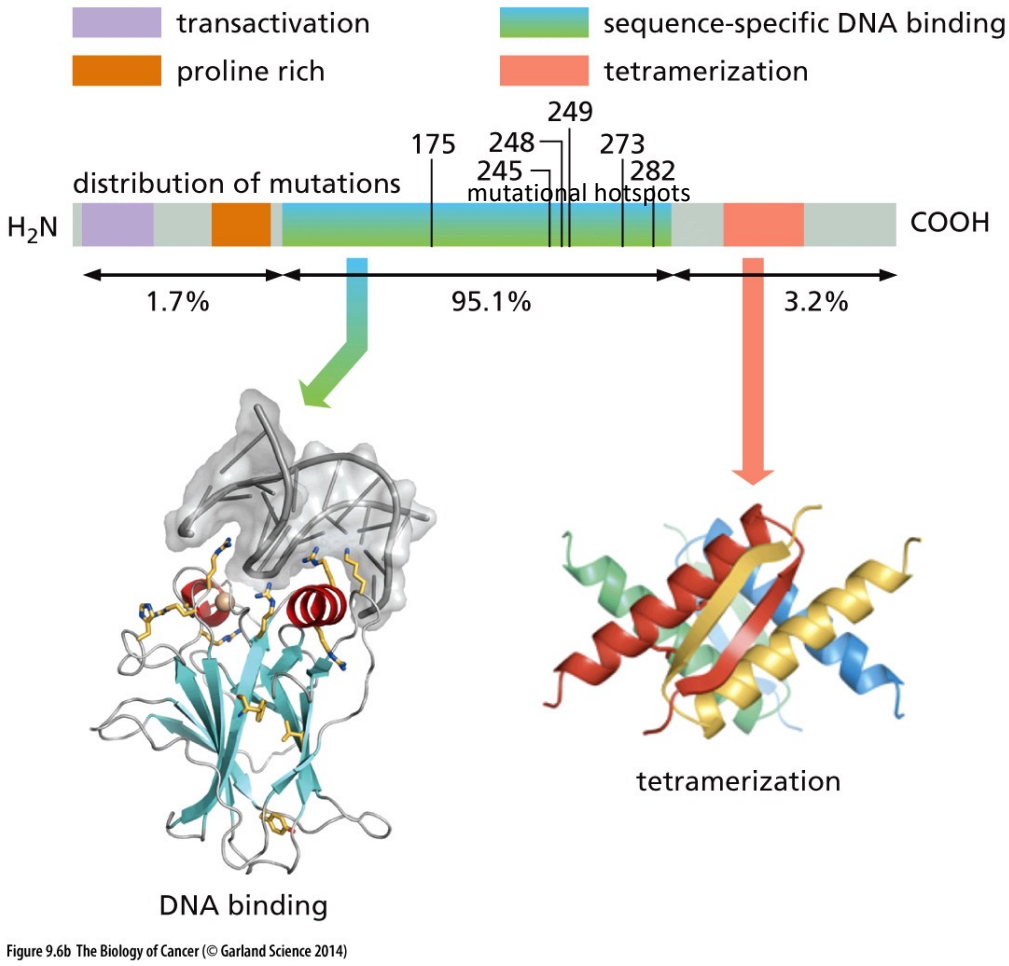


Figure 9.6b The Biology of Cancer (© Garland Science 2014)

Dominant-Negative Mutations in p53

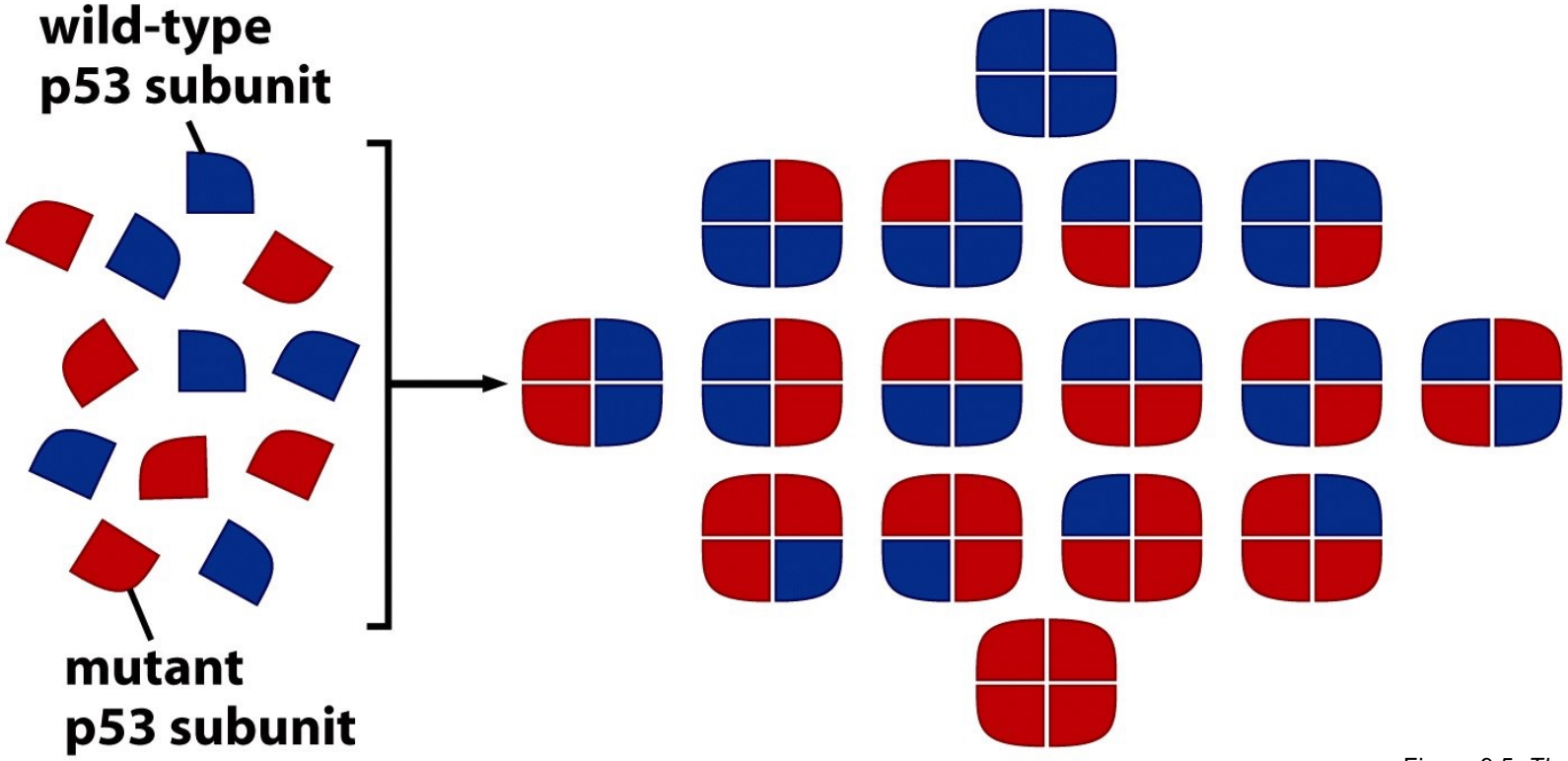
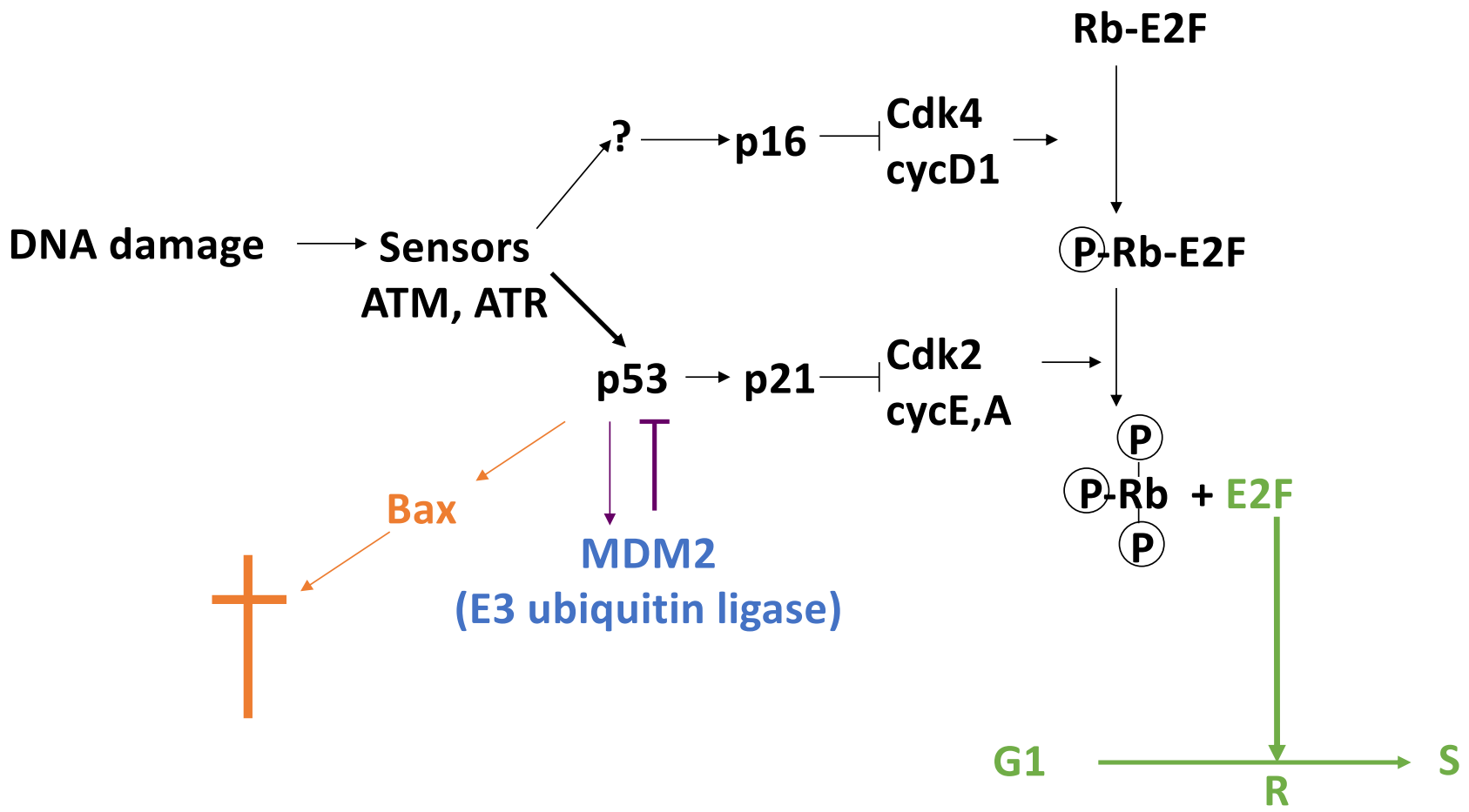


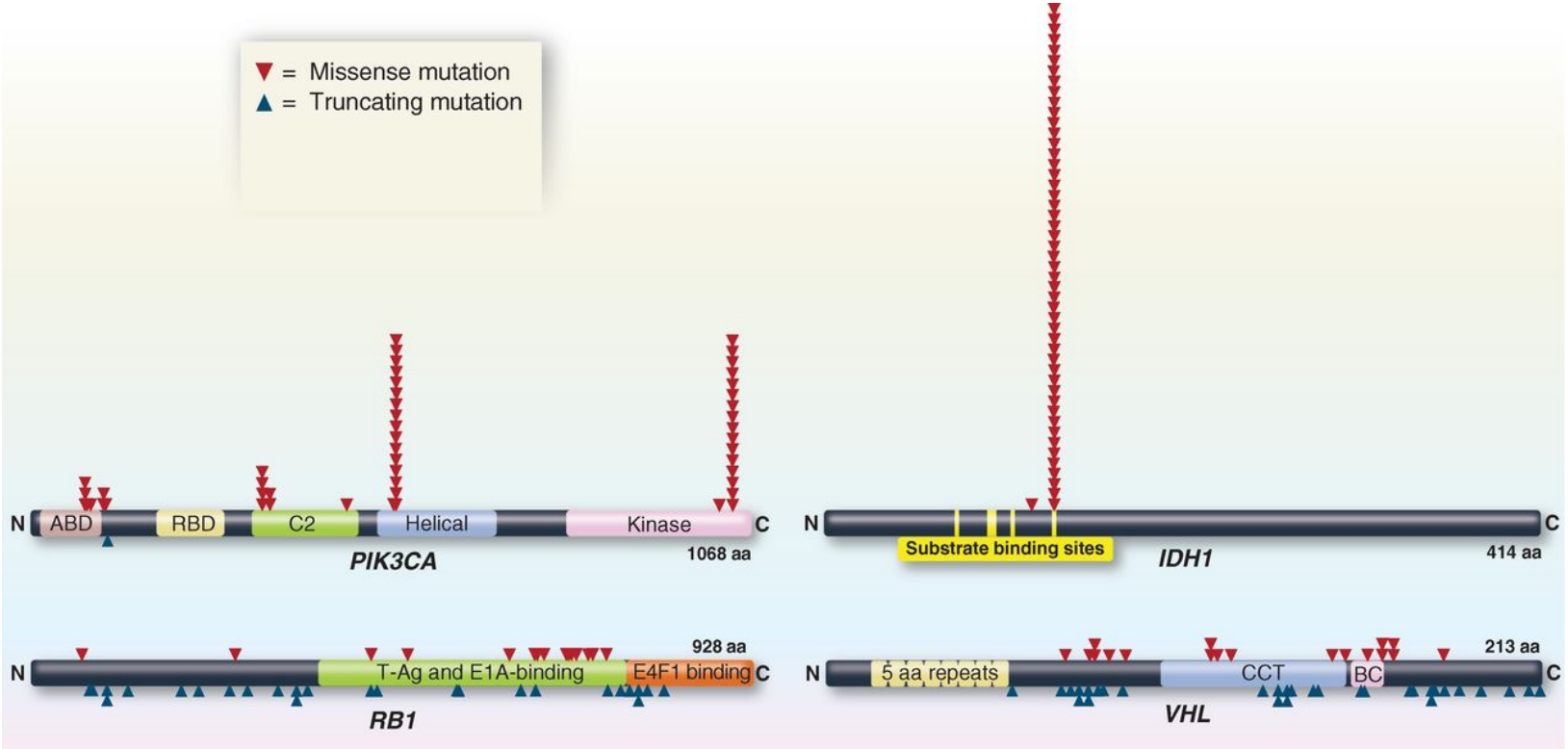
Figure 9.5 *The Biology of Cancer*

Illustration of dominant negative effect of p53 missense mutations in myeloid malignancies: Boettcher et al., Science **2019** 365: 599-604

Activation of p53 Upon DNA Damage



Distribution of mutations in two oncogenes and two tumor suppressor genes



B Vogelstein et al. Science 2013;339:1546-1558

Sequence data from http://cancer.sanger.ac.uk/cosmic

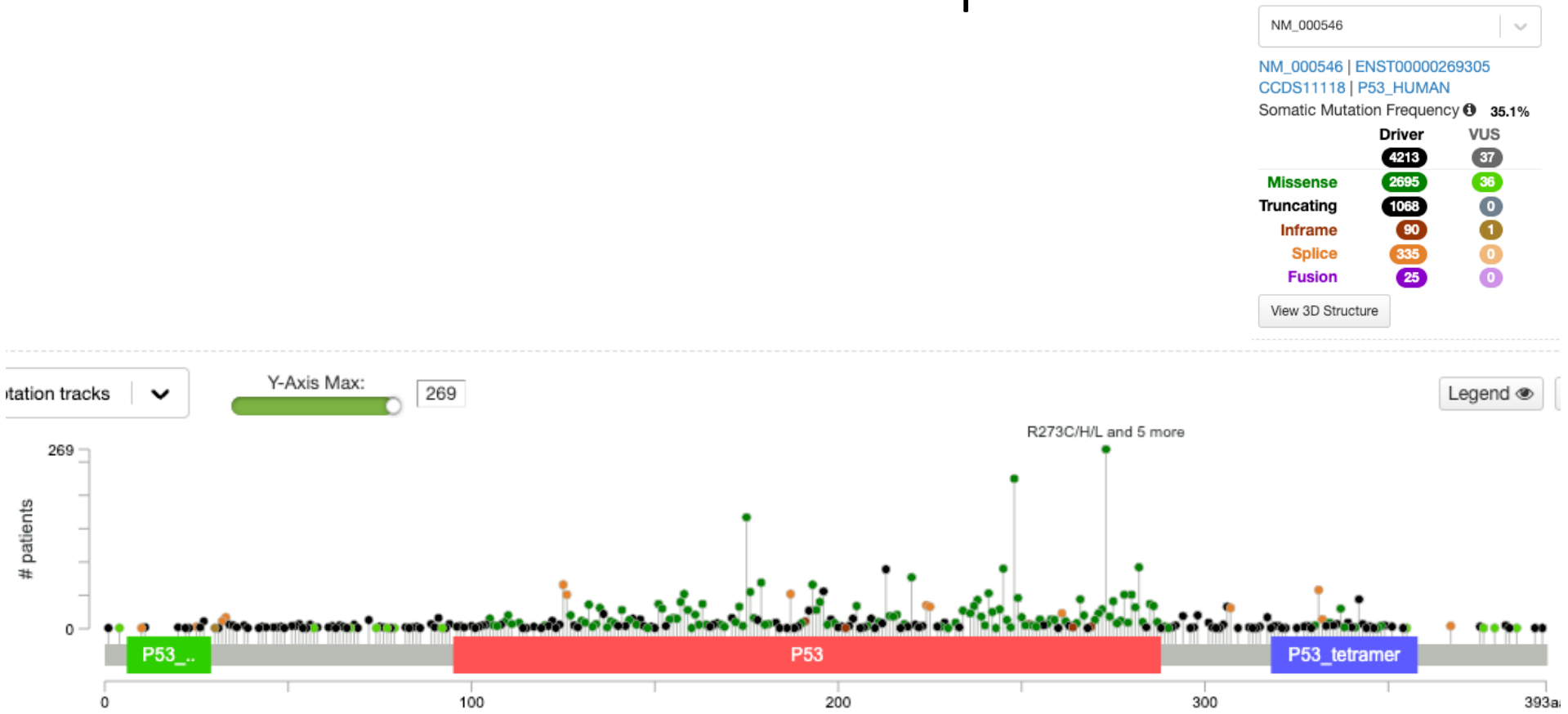
20/20 rule

- Oncogene classification: >20% of recorded mutations are at recurrent positions and are missense
- Tumor suppressor gene classification: >20% of the recorded mutations in the gene are inactivating
- *TP53*: Oncogene score: 73%; TSG score: 20%

but classified as TSG because well-studied oncogenes rarely harbor premature stop codons

B Vogelstein et al. Science (2013);339:1546-1558

Distribution of mutations in p53



Key Concepts

- An oncogene is a mutated gene that contributes to the development of a cancer. In their normal, un-mutated state, oncogenes are called proto-oncogenes.

- Tumor suppressor genes, originally called antioncogenes, function to suppress the development of cancerous growth.

- Retinoblastoma protein (pRb) is a tumor suppressor protein that becomes dysfunctional in many types of cancer. In its active state, pRb is phosphorylated and able to act as a tumor suppressor by inhibiting cell cycle progression.

Key Concepts

- p53 is a transcription factor. As such, p53 can induce cell cycle arrest or apoptosis
- p53 turnover is blocked during cell-physiologic stress or DNA damage
- p53 mutations that occur in cancer are often dominant-negative
- p53 protein levels are controlled: to be discussed in detail later in the context of apoptosis! (week 4)

Exercise

CDKN2A, MET, FGFR3, RET, WT1, NF1, GNAQ, SMAD4, STK11,KIT

Is it possible to distinguish oncogenes from tumor suppressor genes by analyzing the mutations that occur in these genes in tumors?

Explore www.cbioportal.org

- Check out the mutation spectrum occurring in tumors in a given gene.
- Is there any pattern? Is it a tumor suppressor or an oncogene?

How do mutations in oncogenes and tumor suppressors affect cancer therapies?

Check out your gene in https://www.oncokb.org/

- Which mutations in oncogenes are associated with resistance to targeted therapies?
- Are there mutations in tumor suppressor genes that contribute to poor response to therapy? If yes, how?
- How does the mutation type (e.g., loss of function vs. gain of function) affect drug resistance in cancer?