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Biology of Ovarian Cancer

John W. Moroney, M.D.
Associate Professor
Department of Obstetrics and Gynecology
Department of Medicine
University of Chicago Pritzker School of Medicine

Disclosure

- No conflicts of interest

Biology?

- BORING ! ! ! !

- Until…
  - We can see how it affects our lives

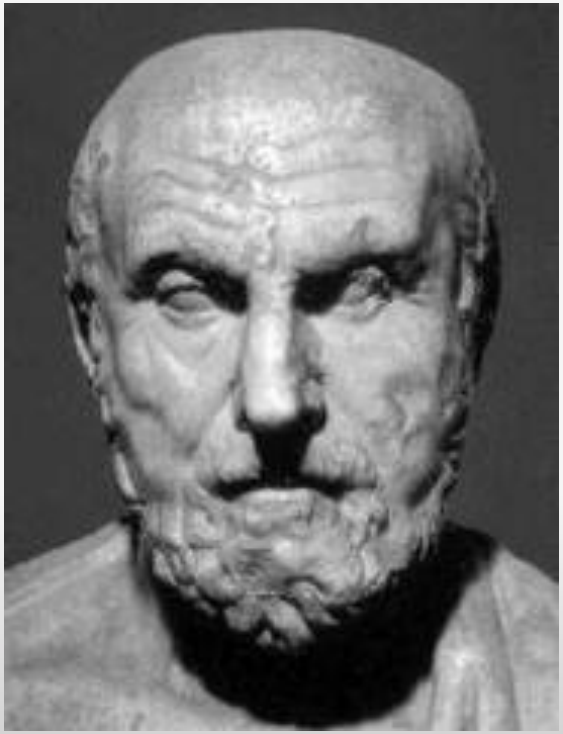
Goals

- Brief review of cancer biology history
- Explain how normal cells become cancerous
- Describe different ovarian cancer subtypes
- Explain how an increased understanding of DNA mutations and intracellular molecular signaling are key to more effective treatments

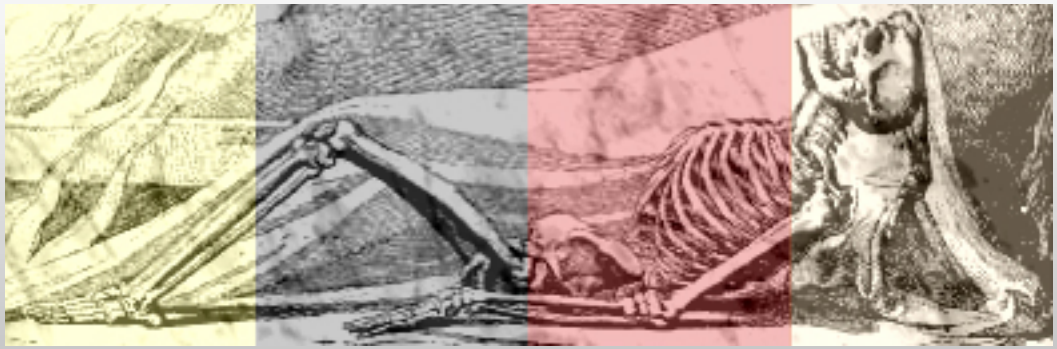
1st descriptions of cancer

- Imhotep (~2600 B.C.): Egyptian physician described a case of breast cancer. Under therapy: “There is none”
- 440 B.C.: Herodotus described Atossa, queen of Persia with breast cancer

“Humorism” as a way to understand disease



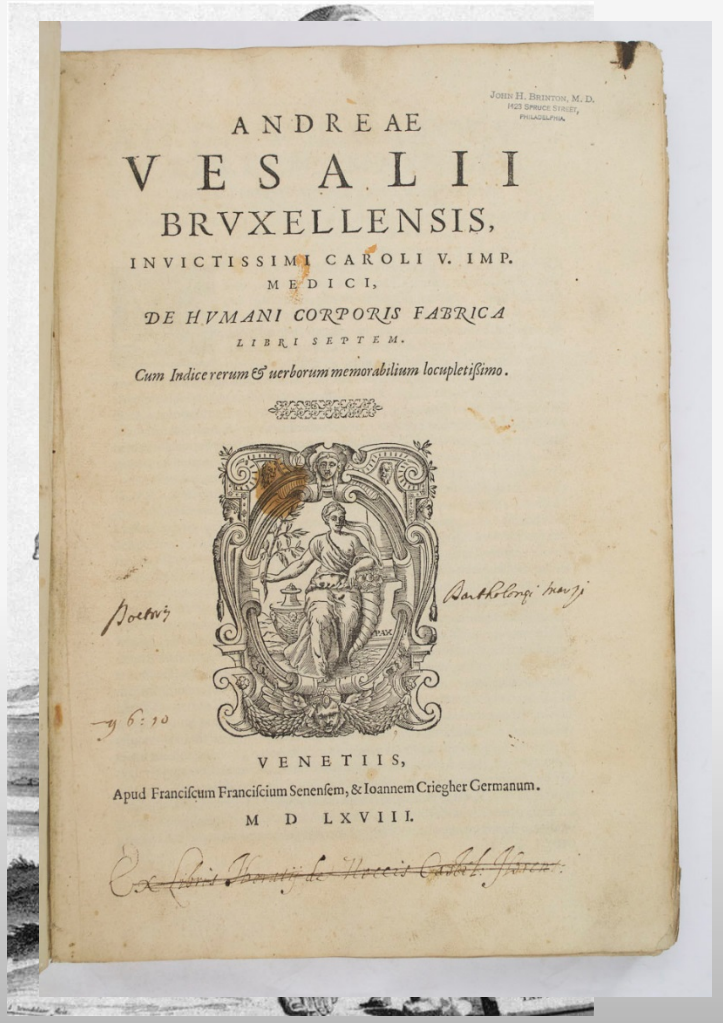
- Humorism: all ilnesss due to an imbalance of fluids = “***humors***”
- Hippocrates (460–370 BC):
  - ***4*** cardinal fluids / humors:
    - Blood, ***black bile***, yellow bile and phlegm



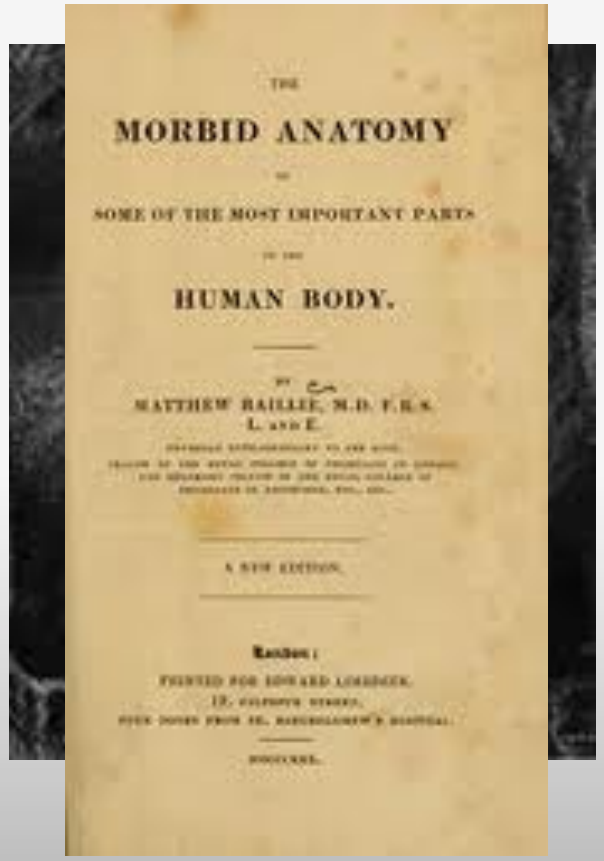
> 1200 years: Where's the black bile?

- Andreas Vesalius
  - Father of modern anatomy
- Prolific, detailed descriptions of normal anatomy
  - 1538: "*De humani corporis fabrica*"

- ***No black bile***



> 1500 years: Where's the black bile?


THE
MORBID ANATOMY
OF
SOME OF THE MOST IMPORTANT PARTS
OF THE
HUMAN BODY.
BY
MATTHEW BAILLIE, M.D. F.R.S.
L. AND E.
A NEW EDITION.
LONDON:
PRINTED FOR EDWARD LONGMAN,
13, PATERNOSTER ROW,
FIVE DOORS FROM ST. PAUL'S CHURCH-YARD.

- Matthew Baillie (1761-1823): English physician, anatomist
  - Emphasized ***pathologic*** vs normal anatomy
  - ***No black bile***

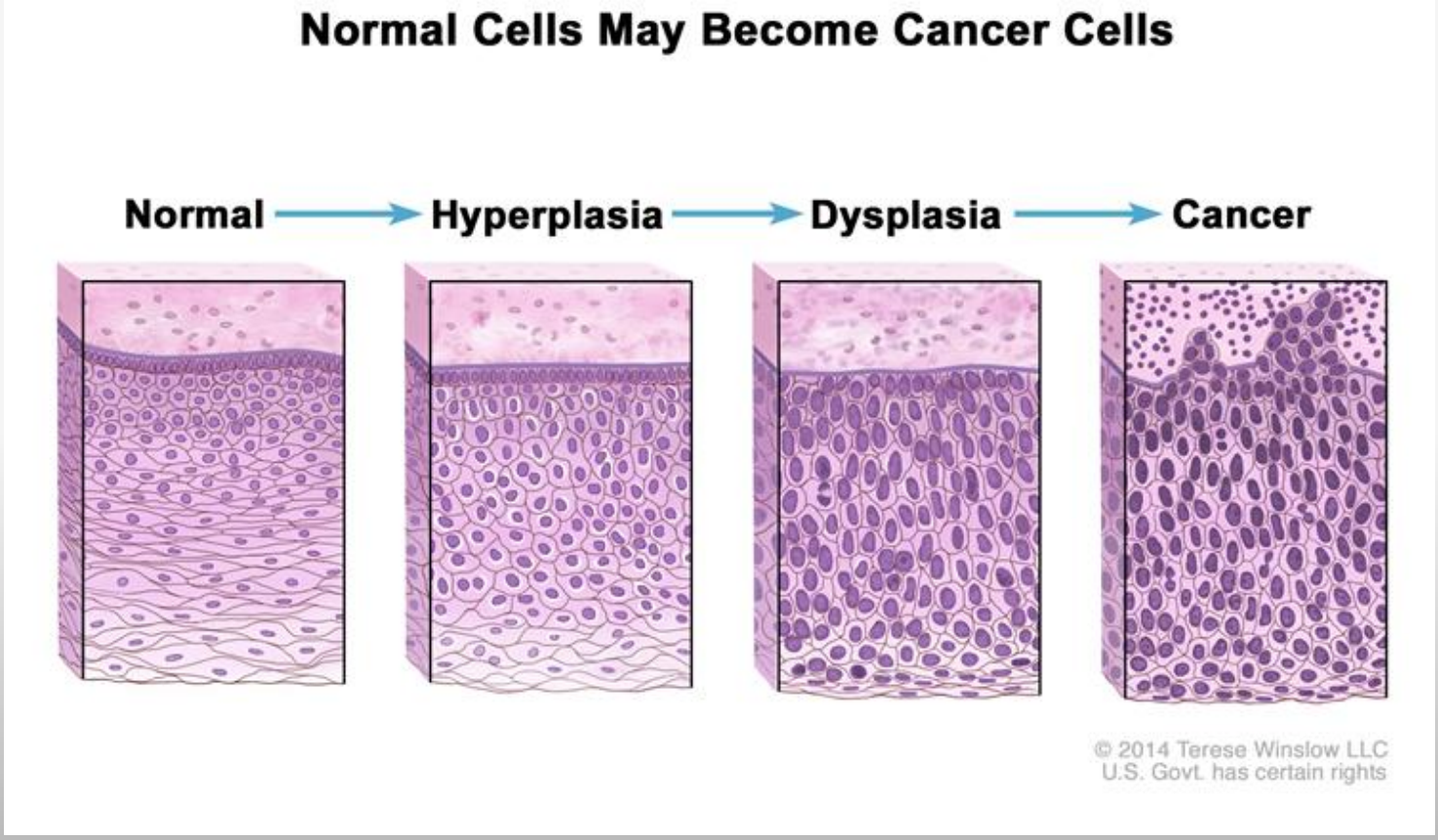
– ***The end of black bile as an explanation for cancer***

Cell theory

- 1838: "Cell theory"
  1. All living things compromised of cells
  2. Cells only arise from other cells:

- 1857: Rudolf Virchow:
  - Armed with a microscope:
    - Revolutionized the study of disease
    - Specific to cancer: ***hyperplasia***

Neoplasia – broad term includes:



Cancer vs dysplasia: *Invasion?*

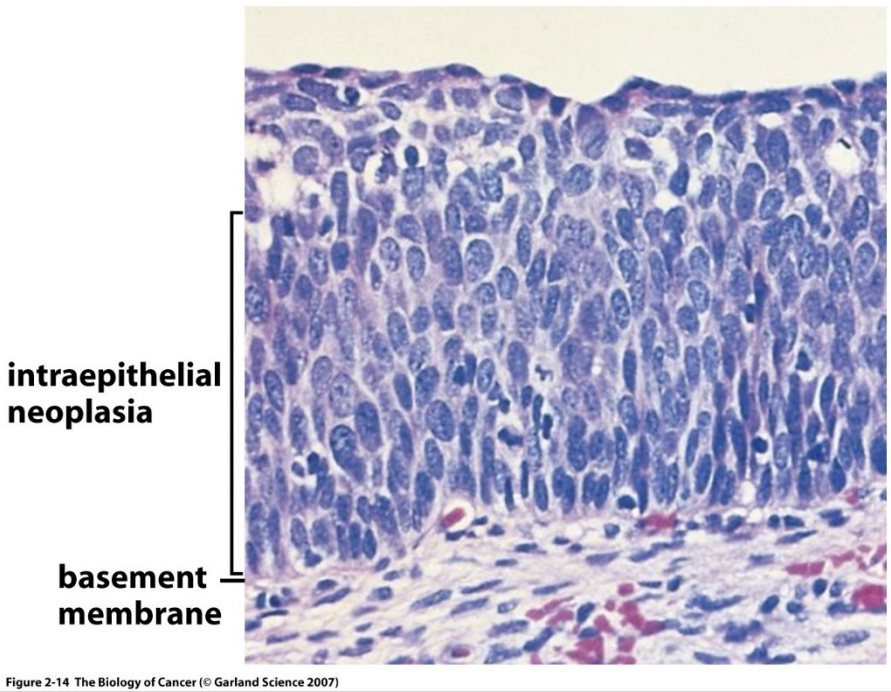


Figure 2-14 The Biology of Cancer (© Garland Science 2007)

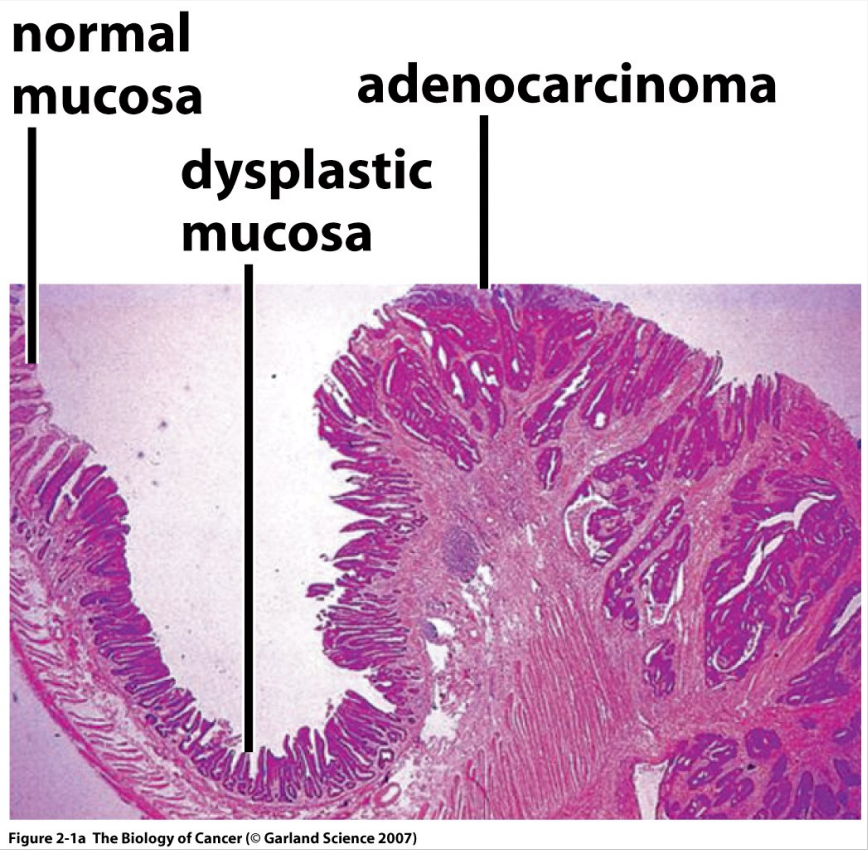
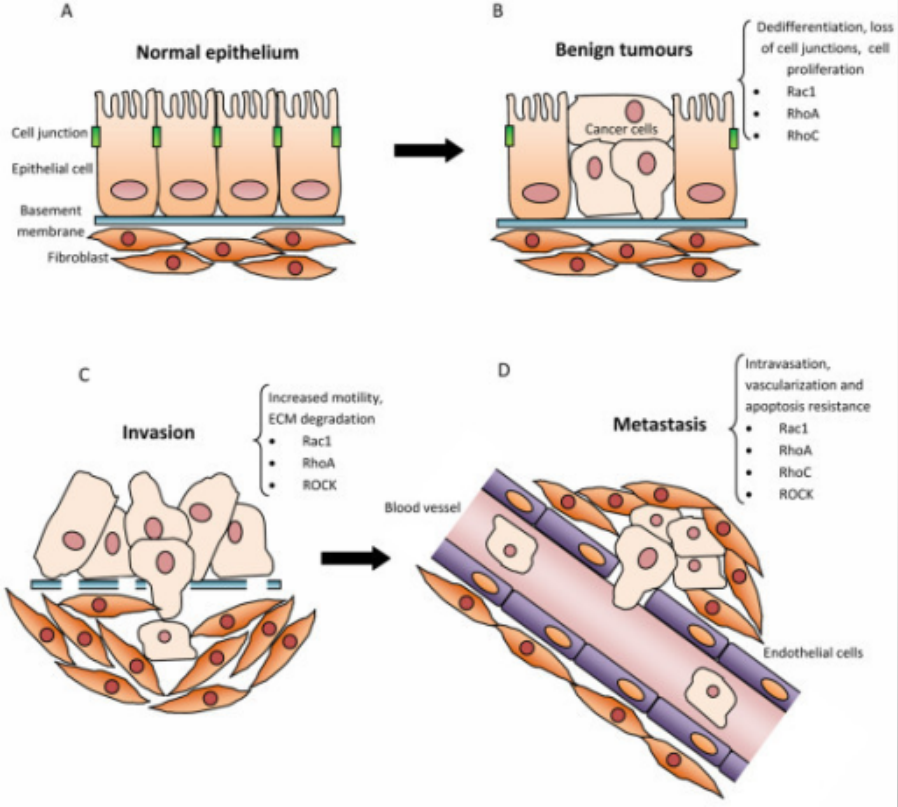
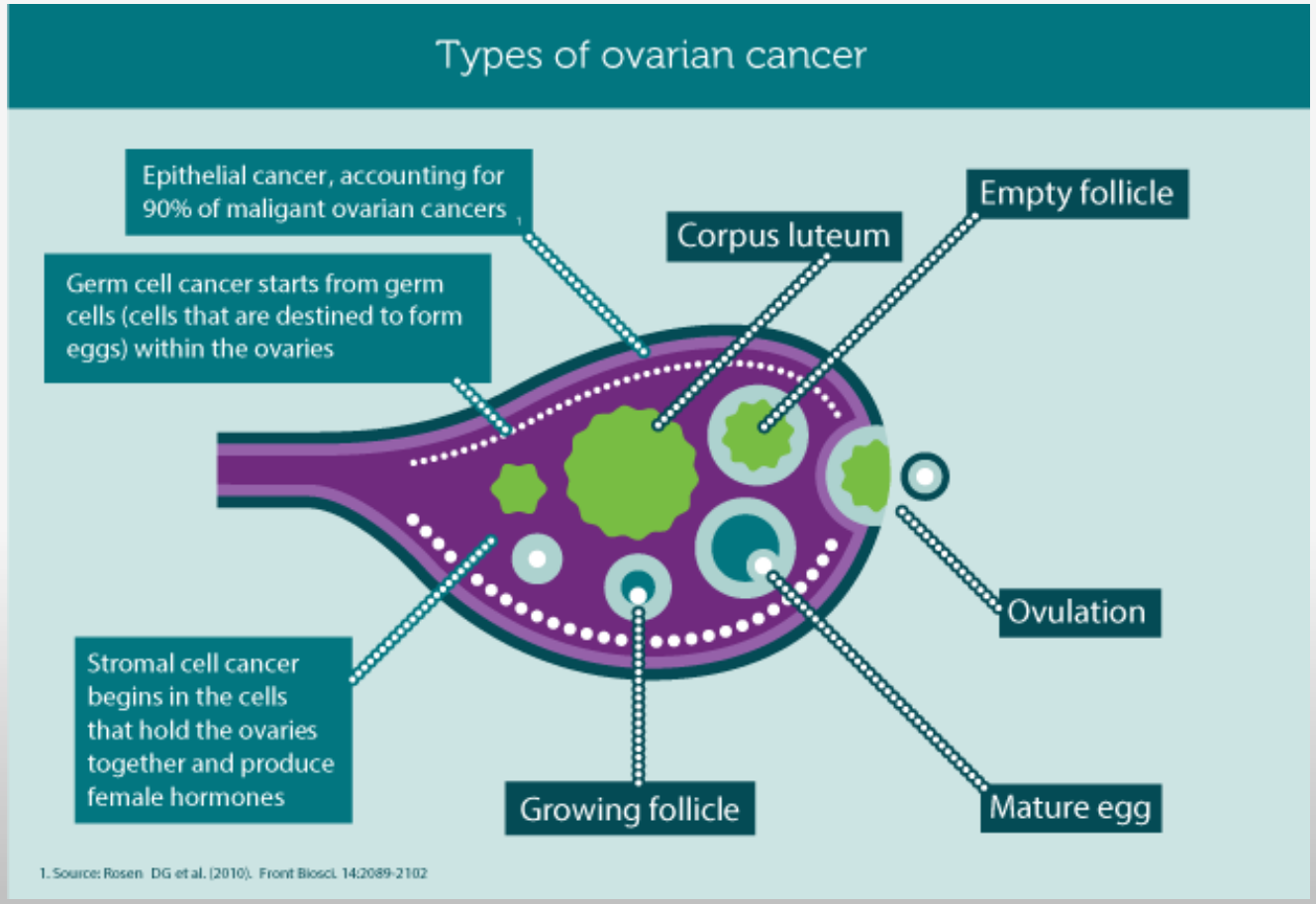


Figure 2-1a The Biology of Cancer (© Garland Science 2007)

Normal → Dysplasia → Cancer → Metastasis



Ovarian cells and cancer



Epithelial Ovarian Cancer subtypes (histologies)

- More differentiated
  - ***Serous***
  - Endometrioid
  - Mucinous
- Less differentiated
  - Clear cell
  - Carcinosarcoma
  - Transitional
  - Small cell
  - Others…

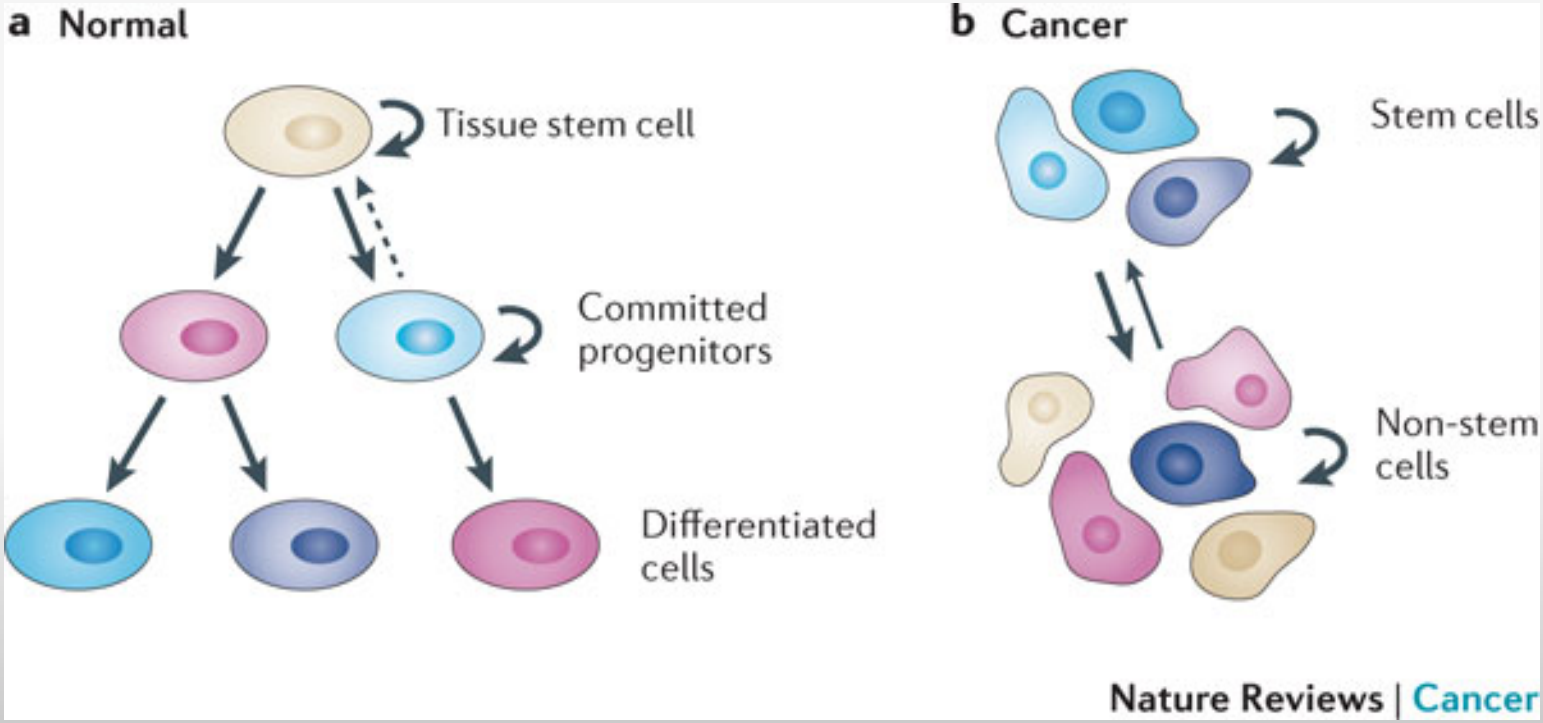
Differentiation?

Cellular differentiation in cancer

- Cancer Stems cells: issue is “potency”
  - Totipotent (early embryonic cells) differentiate into “Pluripotent” lineages

- Accumulated DNA mutations → “***de***-differentiation”
  - Reversion to stem (pluripotent) cell like growth
  - How an ovarian cancer cell can look and behave differently

Cellular differentiation in cancer



DNA coding

- 4 basic proteins (nucleosides)
  - Adenosine (A)
  - Thymine (T)
  - Cytosine (T)
  - Guanine (G)

- **Mistakes happen!?!?**
  - **Aging (more cell divisions)**
  - **Carcinogenic exposures**
  - **Heredity**
    - **Faulty DNA repair (germline)**

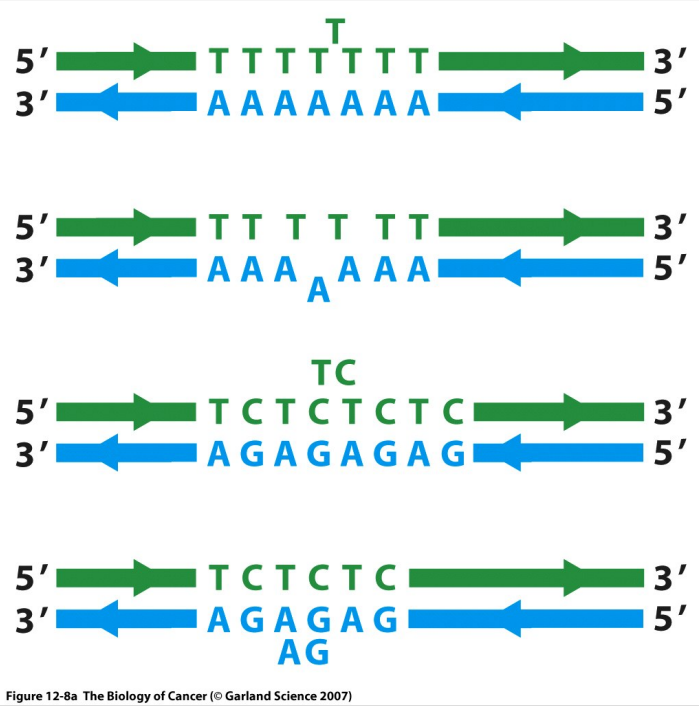


Figure 12-8a The Biology of Cancer (© Garland Science 2007)

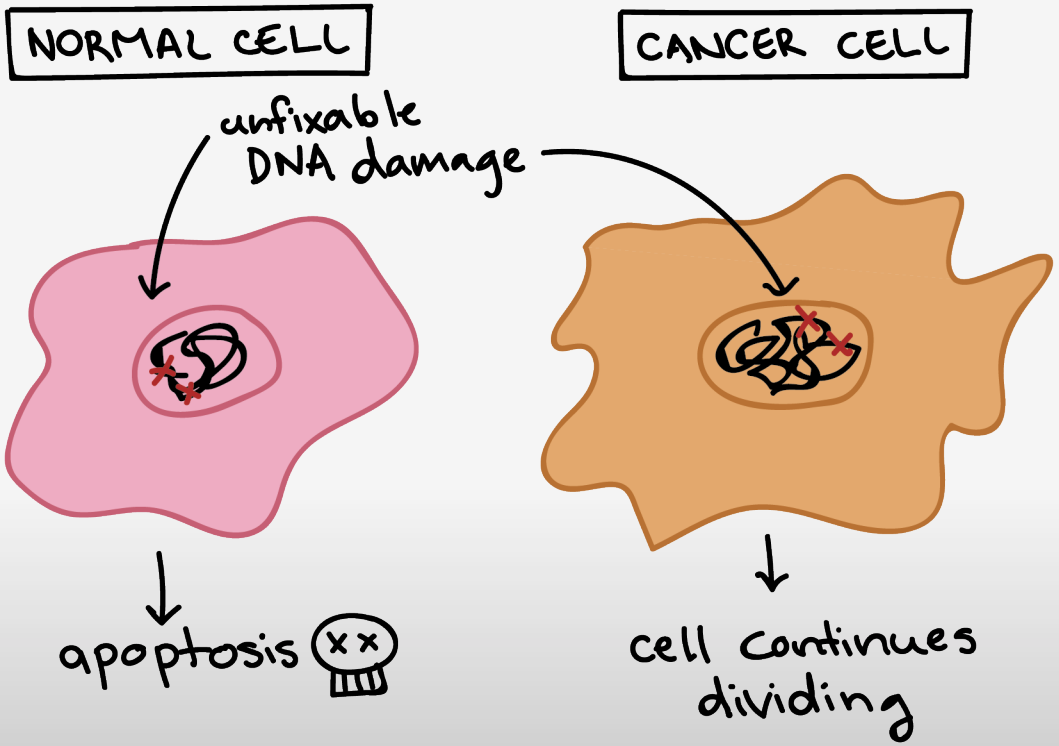
Intact DNA repair is vital

- Why?
  - Normal cell: To prevent carcinogenic mutations
  - Cancer cell: To avoid apoptosis and enable continued proliferation / cell division

- No DNA repair? → normal cell *dies* via apoptosis
  - Alternative? → dysplasia → cancer

- Faulty DNA repair machinery (germline) accounts for most hereditary forms of cancer
  - ***Important implication for the treatment of BRCA and BRCA-"like" mutated ovarian cancers***

When DNA damage occurs



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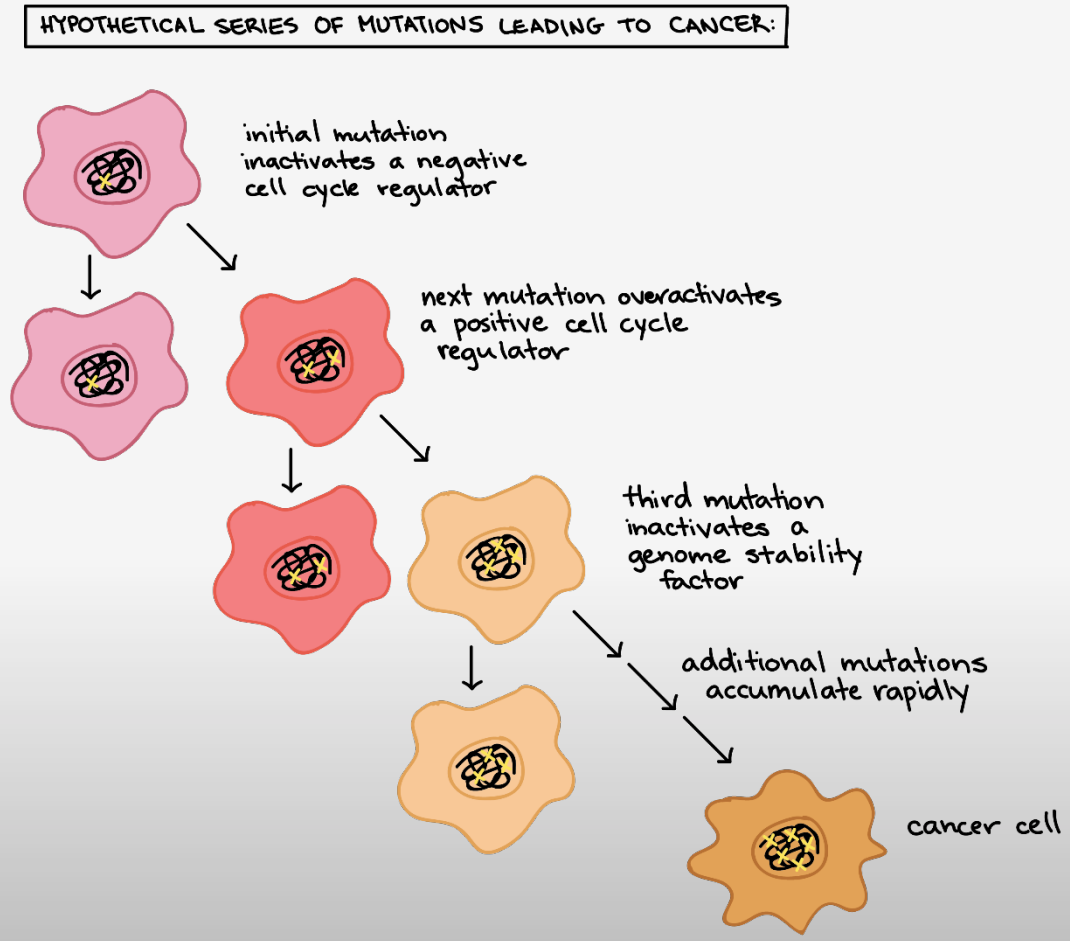
Accumulated DNA mutations



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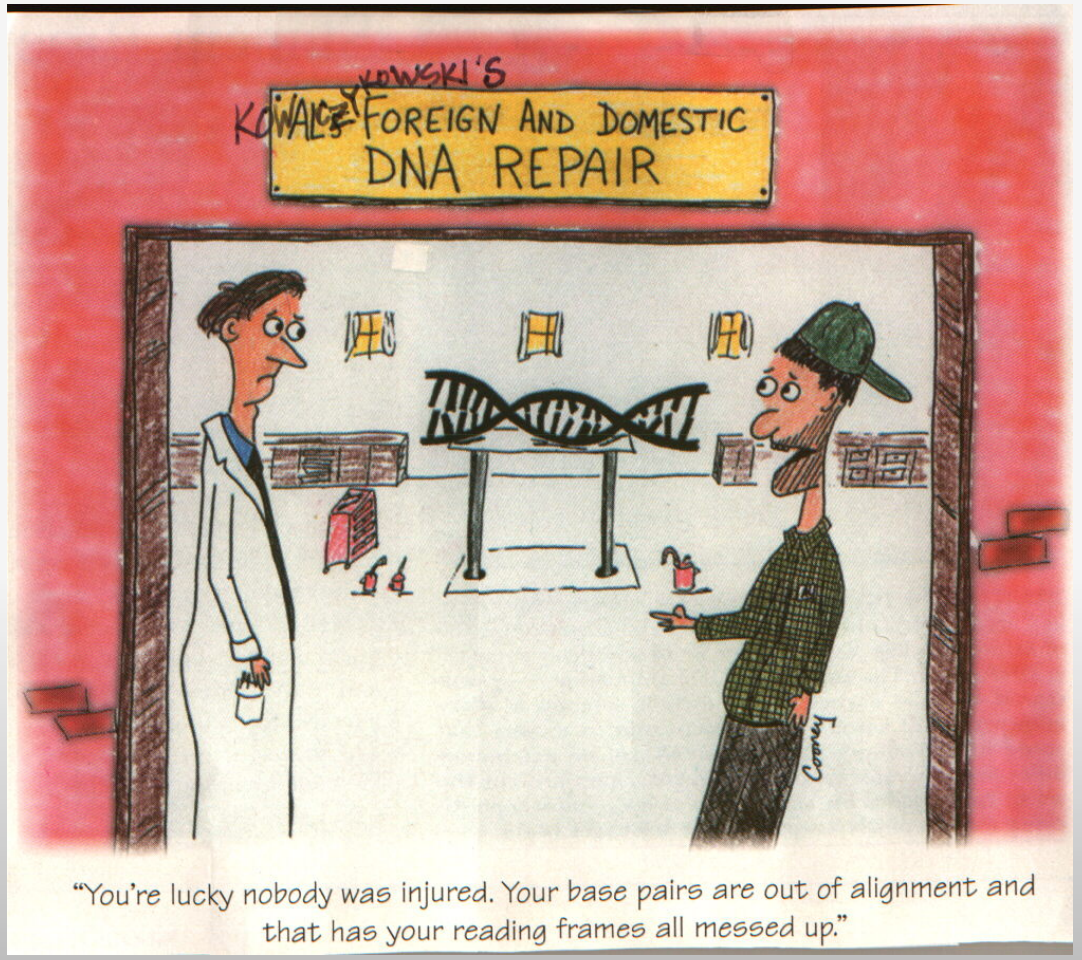
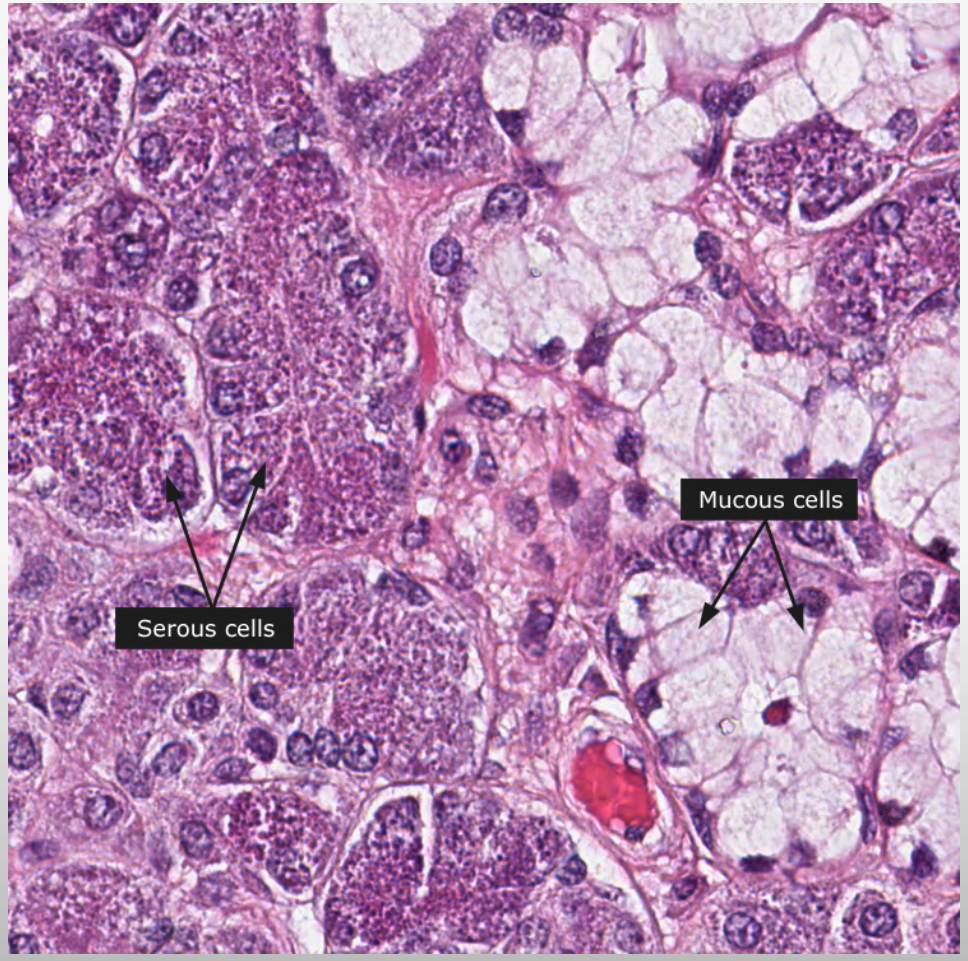
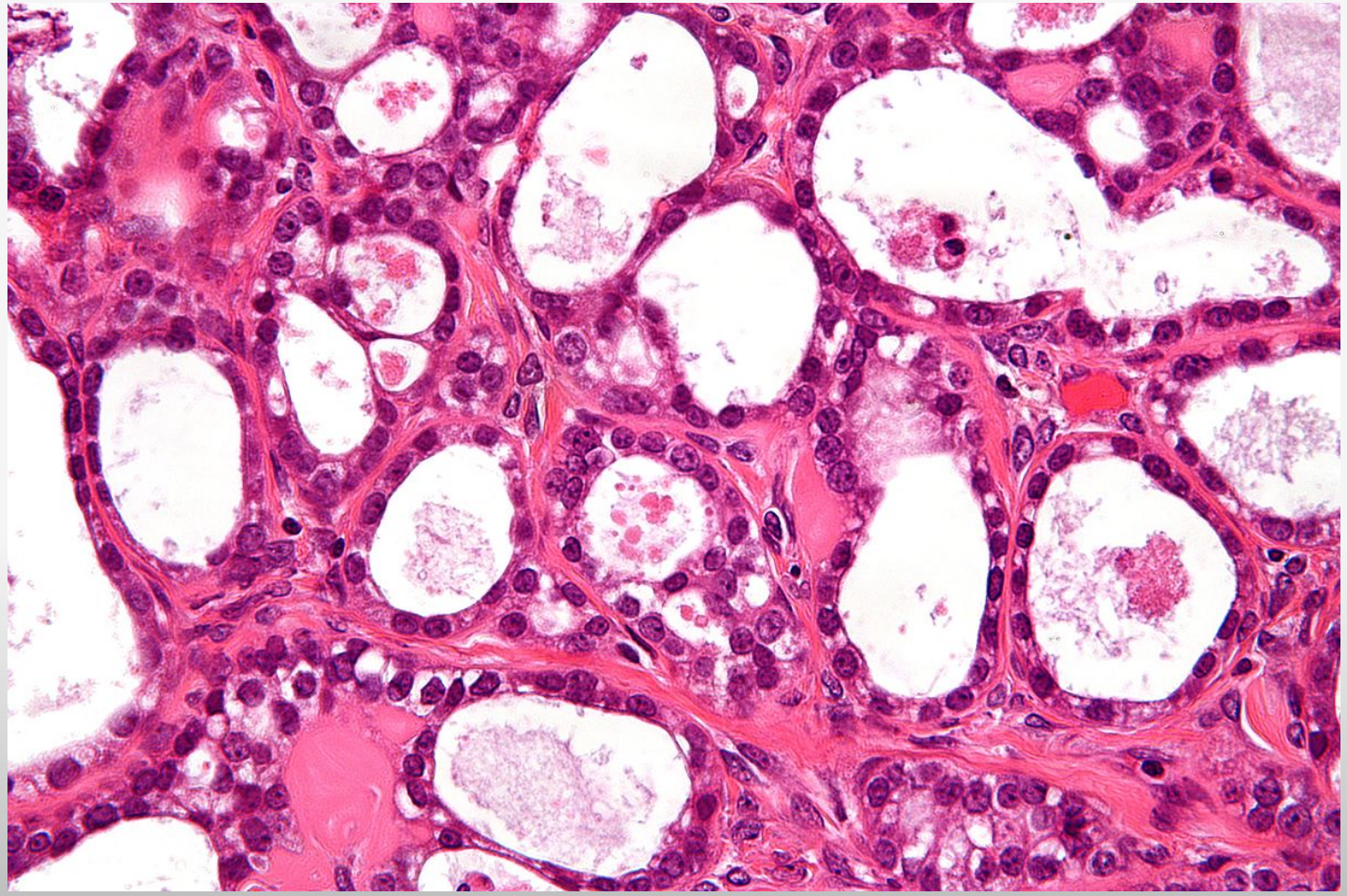
DNA repair mechanics



Serous and Mucinous



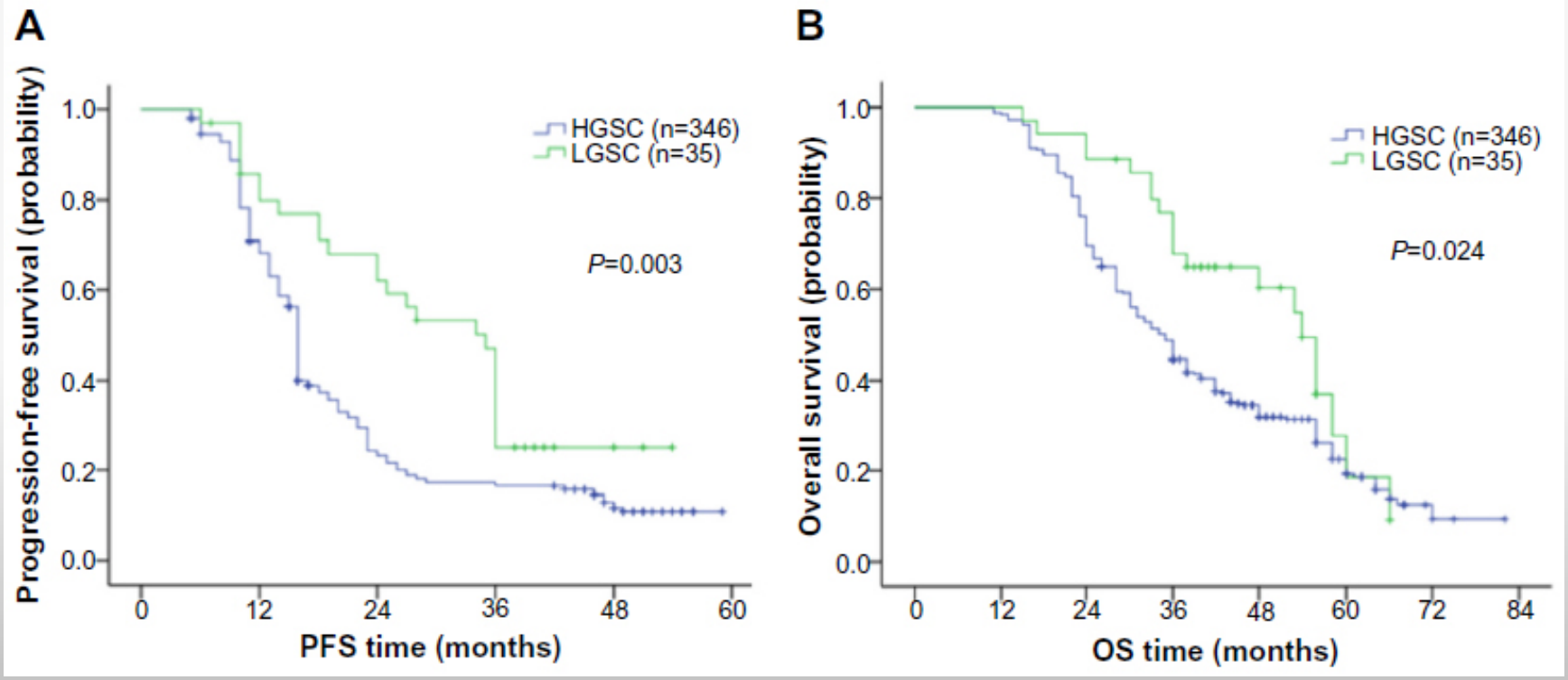
Clear cell



Ovarian cancer histology affects prognosis

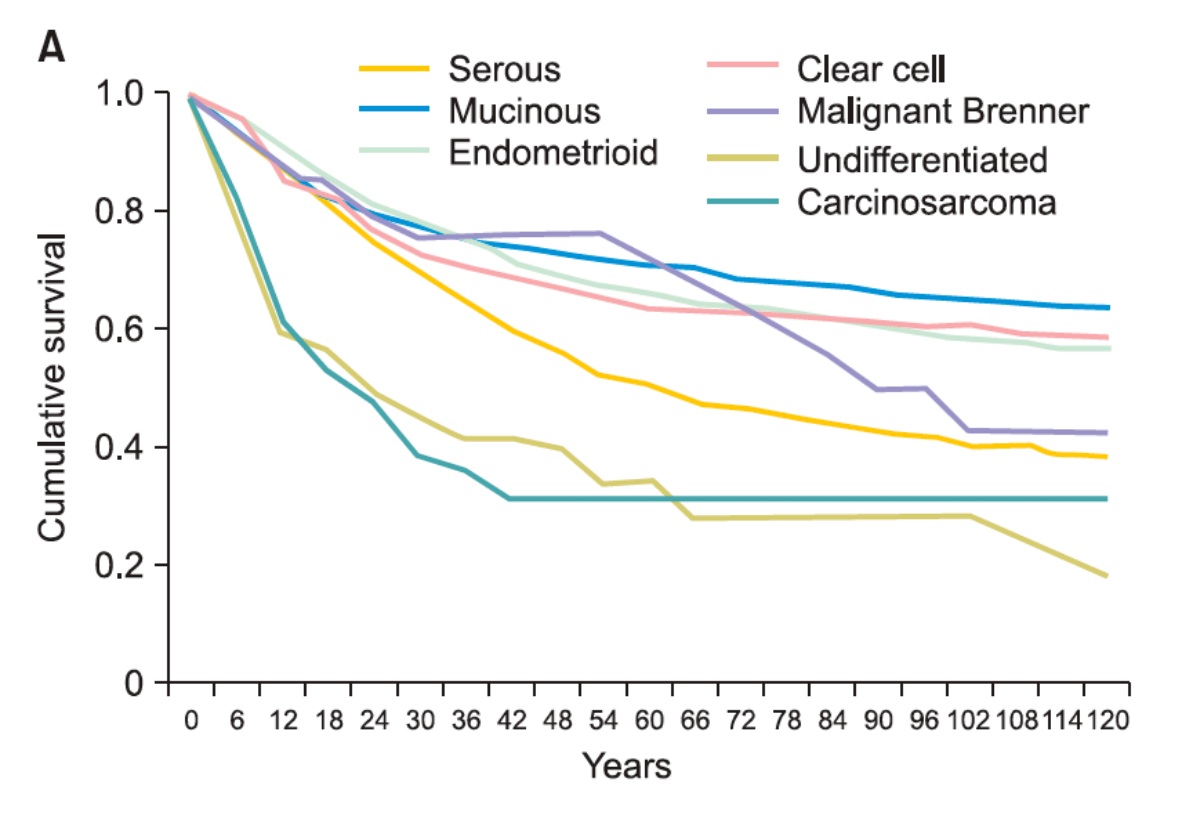
- Serous / endometrioid: relatively responsive to treatment
  - "High" grade YES, "Low" grade NO
- Clear cell / carcinosarcoma: less responsive
- Treat differently?
  - Hopefully soon

Different behavior: LG vs HG serous ovarian cancer



Onco Targets Ther. 2014 Oct 16;7:1891-9.

Ovarian cancer histologies: survival



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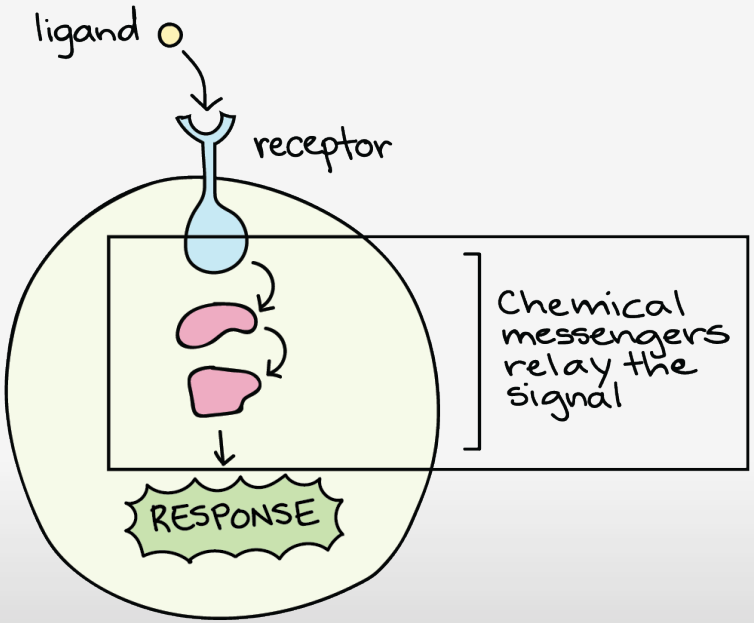
Why so few cures?

- Fundamental issue:
  - ***Chemotherapy resistance***

- To improve?:
  - Better understand DNA mutations and downstream molecular cell signaling
    - The Cancer Genome Atlas (TCGA)
    - DNA, RNA, proteomics


DNA ANALYSIS

Molecular cell signaling



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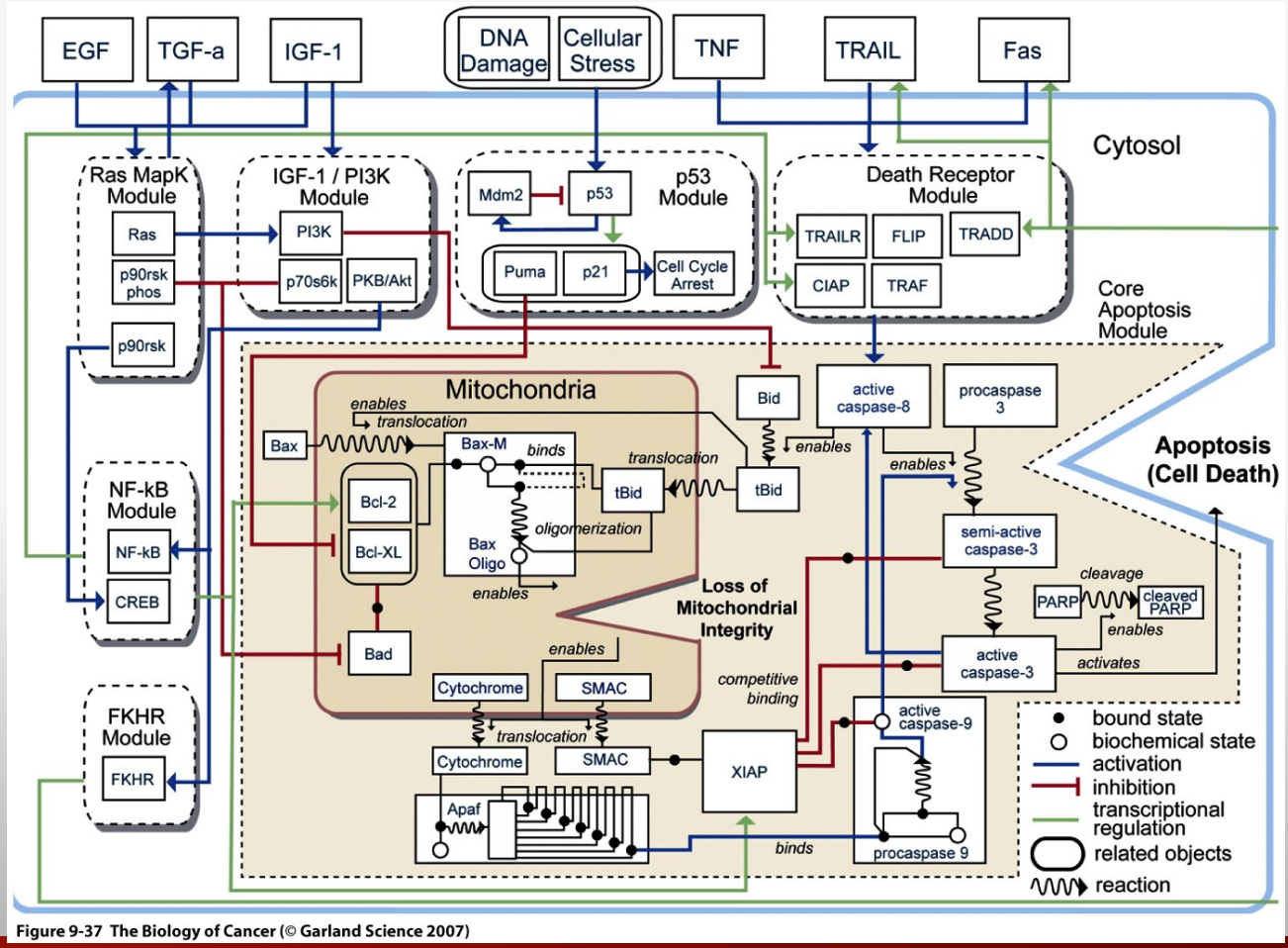
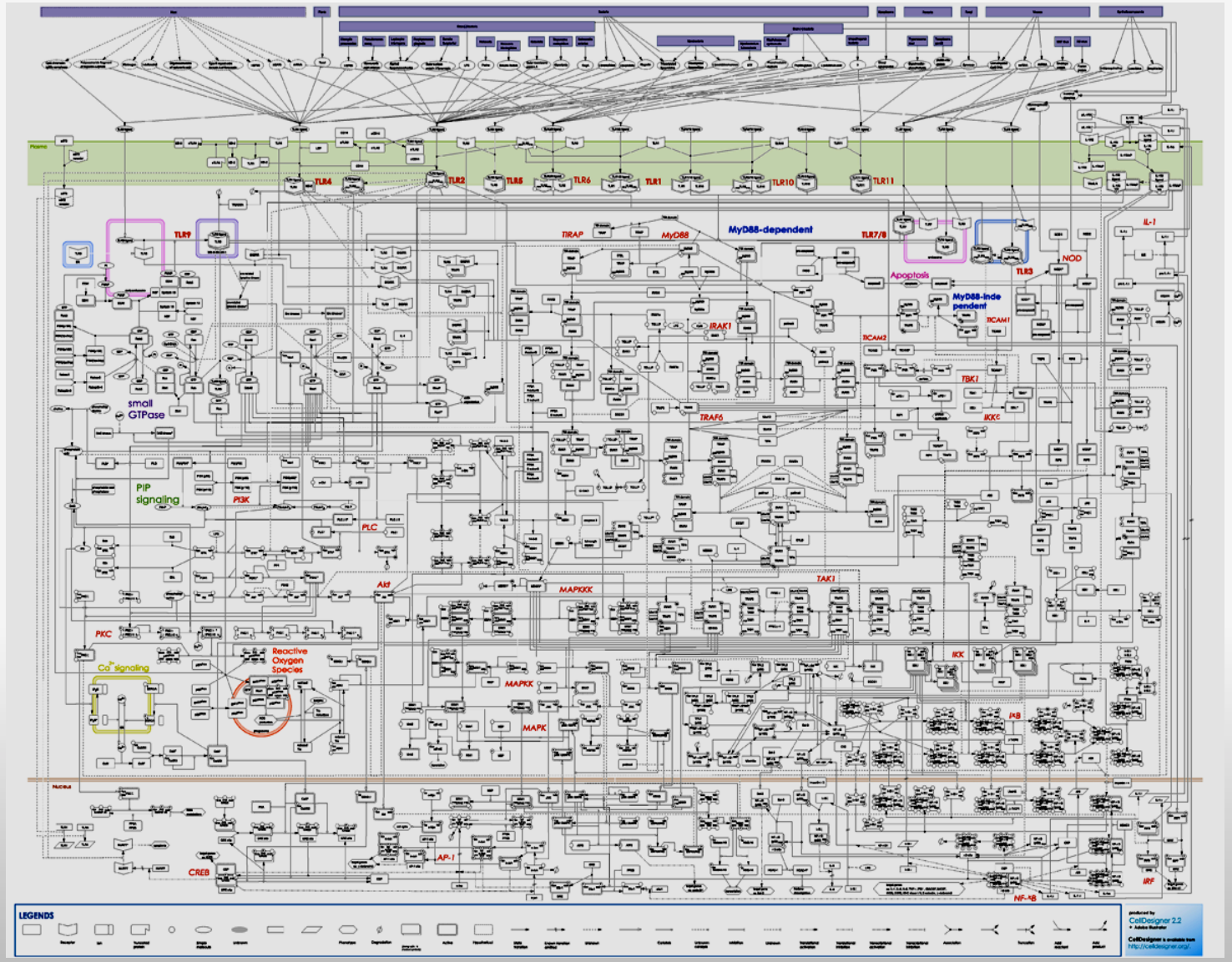


Figure 9-37 The Biology of Cancer (© Garland Science 2007)


TLR4
TLR2
TLR5
TLR6
TLR1
TLR10
TLR11
TLR9
TIRAP
MyD88
MyD88-dependent
TLR7/8
TLR3
NOD
IL-1
Apoptosis
MyD88-independent
IRAK1
TICAM1
TICAM2
TBK1
IKKε
TRAF6
small GTPase
PIP signaling
PI3K
PLC
Akt
MAPKKK
TAK1
PKC
Ca2+ signaling
Reactive Oxygen Species
IKK
MAPKK
MAPK
IκB
AP-1
CREB
NF-κB
IRF
LEGENDS
CellDesigner 2.2

Ovarian cancer: future direction

- Past and current:
  - Organ site / histology based classification
    - E.g. “ovary” vs “uterine” vs “breast”
    - E.g. “serous vs clear cell vs endometrioid
- Current and future:
  - Molecular / genetic classification
  - Tailored “molecular” therapies

- Ida Muligninsy
  - 61 year old with abdominal bloating and pain
  - Advanced abdominal disease (CT scan)
  - Omental tumor biopsy:
    - PIK3CA, pTEN mutated, KRAS wild type molecular signature, germline BRCA-1 mutated
    - Treatment:
      - PARP-I, PIK3CA, PTEN inhibitors
      - And maybe some surgery…. →


HANAUPORT

CURE!!