What is a cancer?

• The hallmark of neoplasms (cancers) is altered tissue organization.
• Tumors are more complex and less organized than normal tissues.
• Neoplasms are diagnosed by pathologists, and *only by pathologists*, by using light microscopes.
Since when has cancer been studied?

- **1850s to 1900s.** Cancer as a *tissue-based* disease (Ribbert and others, precursor of the Tissue Organization Field Theory).

- **1914-present.** Cancer as a *cell-based* disease (Boveri's theory, considered a precursor of the Somatic Mutation Theory).

- **1908-1925.** Development of cell culture techniques.

- **1935-1950s.** Cancer as a developmental disease (Waddington, Needham, Orr, precursors of the TOFT).

- **1953-present.** Molecular biology revolution (“greedy” reductionism).

- **1960s-present.** SMT became the dominant paradigm in cancer (*cell-based* disease; oncogenes, suppressor genes).

- **1999.** The Society of Cells. TOFT (*tissue-based* disease).
Why is it necessary to adopt a theory to explain cancer?

- Scientific theories provide organizing principles and construct objectivity by framing observations and experiments.

- "It is the theory which decides what can be observed."

  (Einstein, oral remark)
<table>
<thead>
<tr>
<th>CAUSES</th>
<th>EXPLANATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Viruses (hepatitis, HPV, herpes, etc)</td>
<td>• Somatic Mutation Theory (SMT)</td>
</tr>
<tr>
<td>• Radiation (X, α, γ-rays)</td>
<td>• Tissue Organization Field Theory (TOFT)</td>
</tr>
<tr>
<td>• Environment (tobacco, DDT, BPA, BP, asbestos, hormones, etc)</td>
<td></td>
</tr>
<tr>
<td>• Inflammations (Leishmania, Schistosomas, <em>H. pilori</em>, EBV, etc)</td>
<td></td>
</tr>
<tr>
<td>• Germ line mutations (retinoblastoma, BRCA)</td>
<td></td>
</tr>
</tbody>
</table>
What are the differences between CANCER CAUSES AND EXPLANATIONS?

<table>
<thead>
<tr>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoughtful preventive (avoid exposure, vaccines) and “therapeutic” (antibiotics) measures have effectively dealt with a few proximate causes of some cancers. However, these measures are neither cancer “cures” nor help in explaining cancer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXPLANATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Somatic Mutation Theory (SMT)</td>
</tr>
<tr>
<td>• Tissue Organization Field Theory (TOFT)</td>
</tr>
</tbody>
</table>
Which are the current theories on carcinogenesis?

- **Somatic mutation theory (SMT),** centered at the *cellular* level of biological organization.

- **Tissue organization field theory (TOFT),** centered at the *tissue* level of biological organization.
WHICH ARE THE PREMISES AND RATIONALE OF THE CURRENT CANCER THEORIES?
What is a Default State?

A DEFAULT STATE HAPPENS WHEN NOTHING HAPPENS TO PREVENT IT.

• In physics, the default state is INERTIA.

• In biology, the default state is PROLIFERATION AND MOTILITY.
Which are the premises of the Somatic Mutation Theory of Carcinogenesis?

Premises:

• The default state of animal cells is *quiescence*.

• The neoplastic phenotype is due to somatic mutations in the DNA of *a single epithelial cell*. Thus, the putative clonality of tumors.
Corollary 1: Carcinogenesis is a problem of control of cell proliferation/differentiation.

Corollary 2: Carcinogenesis may be studied *in vitro* (in 2D cultures); that is, by exposing normal cells of a single cell type to a carcinogen (epithelial cells when studying carcinomas).

Corollary 3: Cancers are clonal; cancer cells proliferate autonomously and cancer is irreversible.
How are organs formed?  
The kidney as an example

Organs are formed by means of reciprocal interactions among tissues (nephrogenic mesenchyme and Wolffian duct) present in the organization field (kidney field).
Which are the premises of the Tissue Organization Field Theory?

Explicit premises:

• The default state of cells is *proliferation with variation and motility* (consistent with evolutionary theory). And

• The targets of carcinogens are *tissues*.

Normal morphogenetic unit (organization field)
How can the Tissue Organization Field Theory of Carcinogenesis be explained?

Carcinogens disrupt the reciprocal interactions among cells and tissues
The Tissue Organization Field Theory: corollaries

- **Corollary 1**: Cancer is a problem of tissue organization comparable to organogenesis during development, but gone awry.

- **Corollary 2**: Cancer is reversible
Why should SMT and TOFT not be merged into a single theory?

**ANSWER:** Because they are founded in opposite and thus, incompatible premises.
CONCLUSION: Theories do matter!

• “It is the theory which decides what can be observed” (Einstein)

• The theory determines the type experiments to be done.
  – The SMT focuses on the inside of cells (DNA mutations): cancer is irreversible.
  – The TOFT focuses on the reciprocal relations among cells and tissues: cancer is reversible.
THANKS TO ALL!

QUESTIONS?