Clinical Research

1. Asks *fundamental* questions using different experimental tools
   - Tends to focus on disease processes
   - The particles tend to be larger
   - Some of them can talk back

2. All good research is characterized by the use of an inductive reasoning process
   - Testing the validity of alternate hypotheses
   - A willingness to throw away hypotheses and keep facts
Testing Hypotheses in Clinical Trials

1. It is difficult to test a fundamental hypothesis in a clinical trial.

2. Clinical trials are rarely designed to exclude a hypothesis.

3. Ethical considerations usually dictate testing hypotheses in a model system prior to clinical trials.

4. There is a need to distinguish between the testing of a fundamental issue and applied science.
“Developmental Therapeutics”
Clinical Trials

1. Practicing physicians need and use information derived from clinical trials in their practices.

2. Coincident with the revolution in biology there is a backlog of new approaches to preventions, diagnosis, and treatments awaiting testing in clinical trials.

3. Failure to initiate and complete clinical trials in a timely fashion is the major reason for delay in technology transfer.

4. Participation in clinical trials is inadequate.

5. Adaptation of new treatments from clinical trials to private practice is often faulty, which leads to dilution of the reported affect, discouragement, and failure to participate in clinical trials.
The Ingredients of the Clinical Experiment

1. Patients
2. Patient support programs
3. Hospital beds
4. Doctors, nurses, social workers, technicians
5. Equipment
6. Laboratory support
7. Staff and equipment for data collection and analysis
8. Ideas
9. Patience
10. Longevity
Logistical Problems in Clinical Research

1. Economic consideration in day-to-day practice
2. Tradition
3. Public understanding of the benefits of clinical research
   a. Informed consent
   b. Fear of being a research object; randomization in clinical trials
4. Lawsuits
5. Specialty competition: Who will be the oncologist of the future?
The "Assay Systems:"
Signal Endpoints for Clinical Investigators Using Chemotherapy as:

<table>
<thead>
<tr>
<th>Induction Therapy of Advanced Disease</th>
<th>Adjuvant Therapy</th>
<th>Primary Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Response rate</td>
<td>1. Effect against advanced disease</td>
<td>1. Complete response rate</td>
</tr>
<tr>
<td>2. Complete response rate</td>
<td>2. Relapse-free survival</td>
<td>2. RFS of complete responders</td>
</tr>
<tr>
<td>3. RFS of complete responders</td>
<td>3. Survival</td>
<td>3. PR rate with pathologic confirmation</td>
</tr>
<tr>
<td>4. Survival</td>
<td></td>
<td>4. RFS of PR's after resection or RRx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Survival</td>
</tr>
</tbody>
</table>
DRUG DEVELOPMENT

RANDOM SCREENING

LOGICAL DESIGN

ANIMAL DATA

FORMULATION

PHASE I TRIALS

PHASE II TRIALS

PHASE III TRIALS

CLINICALLY USEFUL NEW AGENT

USE AS ADJUVANT IF CIRCUMSTANCES EXIST

COMBINE WITH OTHER ACTIVE AGENTS IN ADVANCED DISEASE
Major Limitations of Current Cancer Treatment

1. The inability to monitor the impact of treatment on cancer cells, *in vivo*, on a moment by moment basis.

2. Specific and "permanent" resistance to anti-cancer drugs.

3. The inability to determine whether an apparently localized tumor has metastasized.

4. The inability to easily and reliably detect minimal residual disease.
Major Questions in Clinical Research

1. Can you prevent and/or control cancer by interrupting the oncogene-suppressor gene cascade?

2. Can you identify subsets of the population at risk for developing cancer using molecular technology?

3. Can patterns of gene expression predict treatment outcome?

4. Can you detect tumors that are not yet capable of metastasizing and can the metastatic process be interrupted?

5. Can we monitor the effects of treatment on a moment by moment basis?

6. Can the components of the signal transduction system be used as therapeutic targets?

7. Can we readily detect residual cancer after treatment?
Hodgkin’s Disease: NCI Study Chronology

1963  MOMP pilot trial started: It was possible!
1964  MOPP study started: can you cure Hodgkin’s?
1970  MOPP paper published: mortality begins to decline.
1972  MOPP complications identified: cure has a price.
1973  Maintenance study published: it didn’t work and why should it?
1978  Early stage study started: the test of the “inverse rule”.
1978  MOPP vs. MOPP/CABS study started: a test of the Goldie-Coldman hypothesis.
1979  MOPP salvage paper published: are some second remissions cures?
1988  MOPP 20-year followup published: more confidence in cure.
1991  Early stage study published: the “inverse rule” applies.
1991  MOPP vs. MOPP/CABS published: the Goldie-Coldman hypothesis is *not* validated in this case.
1992  MOPP long-term salvage results published: yes, there are some cures, but at a steep price.
The Current Climate

1. Critical mass of "usable knowledge"
2. Rate limiting steps
3. Statistics
## Evolution of Cancer Treatment

<table>
<thead>
<tr>
<th>RSR</th>
<th>Date</th>
<th>Surgery</th>
<th>Radiation Therapy</th>
<th>Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>±0</td>
<td>1894</td>
<td>Radical Mastectomy</td>
<td>Xrays discovered</td>
<td>Transplantable rodent tumors</td>
</tr>
<tr>
<td>20%</td>
<td>1920</td>
<td></td>
<td>250 KV units</td>
<td>Antibiotics</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1946 Supportive care</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1955 Radical surgery</td>
</tr>
<tr>
<td>33%</td>
<td>1957</td>
<td>Micrometastases</td>
<td>Cobalt units</td>
<td>1961 Linear accelerator</td>
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<tr>
<td>36%</td>
<td>1970</td>
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<tr>
<td></td>
<td>1971</td>
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**NATIONAL CANCER ACT**
## Evolution of Cancer Treatment

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<th>Date</th>
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<th>Radiation Therapy</th>
<th>Systemic Therapy</th>
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</thead>
<tbody>
<tr>
<td>(41%)</td>
<td>1980</td>
<td>Conservative surgery</td>
<td>Particle therapy</td>
<td>Hybridomas/MoABS</td>
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<td></td>
<td></td>
<td>Reconstructive surgery</td>
<td>Neutron generators</td>
<td>Biologics</td>
</tr>
<tr>
<td>(49%)</td>
<td>1985</td>
<td>Tailoring procedures to other treatments</td>
<td>Treatment planning with CT scans</td>
<td>Dose intensity/auto-transplants</td>
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<tr>
<td></td>
<td>1990</td>
<td></td>
<td>Conformal RRx</td>
<td>Primary chemotherapy</td>
</tr>
<tr>
<td>(52%)</td>
<td></td>
<td>Laparoscopic surgery</td>
<td>Radiolabeled antibodies</td>
<td>Modulating the cell cycle</td>
</tr>
<tr>
<td>(62%)</td>
<td>2003</td>
<td>Telemedicine</td>
<td>IMRT</td>
<td>Gene therapy</td>
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<td></td>
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<td>Vaccines</td>
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<td>Mini-allografting</td>
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<td></td>
<td></td>
<td>Anti-angiogenesis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Molecular targeting</td>
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</tbody>
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