Chemotherapy defined...

- Chemotherapy is a treatment that selectively damages cancer cells
  - ‘Traditional’ drugs like methotrexate, carboplatin, CCNU, irinotecan, temozolomide (Temodar), etc.
  - Targeted therapy / Biologic therapy
    - Bevacizumab (Avastin), erlotinib (Tarceva)
  - Gene therapy / viral therapy
  - Immunotherapy
    - Dendritic cell vaccine therapy
How do normal cells become cancer cells?

They acquire **mutations and adaptations** that allow them to:

- **Replicate** in the absence of growth signals.
- **Ignore** the presence of cell death signals.
- **Find nutrients** more efficiently.
- **Evade** the immune system.
- **Invade** surrounding tissue.
How do normal cells become cancer cells?

They acquire **mutations and adaptations** that allow them to:

- **Replicate** in the absence of growth signals. *Block DNA synthesis, disrupt the cell cycle, block growth signaling.*
- **Ignore** the presence of cell death signals. *Block DNA repair.*
- **Find nutrients** more efficiently. *Block angiogenesis, disrupt metabolism.*
- **Evade** the immune system. *Activate the immune system.*
- **Invade** surrounding tissue. *Block invasion.*
Traditional ‘cytotoxic’ chemotherapy

DNA
- De Novo Synthesis
- Salvage Pathway
- Topoisomerase-mediated breaks
- Intercalation
- Free Radical Damage
- Alkylation

RNA
- Mercaptopurine
- Thioguanine

Protein
- Tubulin
- Vincristine
- Vinblastine
- Paclitaxel

Purines
- CMP
- dCMP
- dTMP
- FH₂
- FH₄

Fluorouracil
- dUMP

Methotrexate
- dCMP

Cytarabine
- CMP

Dactinomycin
- Doxorubicin
- Daunomycin
- Idarubicin

Mechlorethamine
- Cyclophosphamide
- Ifosfamide
- Melphalan
- Carboplatin
- Cisplatin
- Nitrosourea
- Busulfan
- Dacarbazine (Temodar)
- Procarbazine

Fluorouracil

Asparaginase
Traditional ‘cytotoxic’ chemotherapy

Common adverse effects:
- Decreased blood counts
- Nausea
- Fatigue

DNA

- Cytarabine
- Dactinomycin
- Doxorubicin
- Daunomycin
- Idarubicin
- Fluorouracil
- Methotrexate
- Mercaptopurine
- Thioguanine

RNA

- Etoposide
- Teniposide
- Intercalation
- Free Radical Damage
- Alkylation
- Doxorubicin
- Daunomycin
- Idarubicin
- Bleomycin
- Mechlorethamine
- Cyclophosphamide
- Ifosfamide
- Melphalan
- Carboplatin
- Cisplatin
- Nitrosourea
- Busulfan
- Dacarbazine (Temodar)
- Procarbazine
- Fluorouracil
- Asparaginase
- Carboplatin
- Cisplatin
- Nitrosourea
- Busulfan
- Dacarbazine (Temodar)
- Procarbazine

Protein

- Tubulin
- Vincristine
- Vinblastine
- Paclitaxel

De Novo Synthesis
Salvage Pathway

Leaving the Quest

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Targeted therapy / Biologic therapy
Targeted therapy / Biologic therapy
The future of “chemotherapy”

- Immunotherapy
- Targeting cancer stem-like cells
- Overcoming the blood-brain barrier
- Personalized medicine – finding the right targets for your tumor
Personalized medicine

Histology → DNA → RNA → Proteins

Epigenomics

Network Analysis

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What are clinical trials?

• **Investigative** treatments
  - new treatments OR old treatments for new indications
  - OR new treatment regimens
  - (sometimes they aren’t even treatments)
    - *eg*, non-therapeutic imaging trials

• **Not proven** to better than other available treatments

  *(BUT the *hope* of course, is that they are better…)*

• **A meticulously monitored** and **highly regulated** process with **defined outcome measures**
  - **Prospective** (not retrospective)
What clinical trials are not...

Clinical trials should **NOT**:  

- Be a sales job  
  - Be wary of overreliance on anecdotes and testimonials  
- Require you to believe in a conspiracy theory
The drug development process...

Drug Discovery / Preclinical Development

*File Investigative New Drug (IND) Application with FDA*

**Phase I Clinical Trial:** *Evaluate safety*

**Phase II Clinical Trial:** *Evaluate activity*

**Phase III Clinical Trial:** *Confirm effectiveness*

*Apply for New Drug Application (NDA) with FDA*
Clinical Trials:  Getting started...

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td><strong>A Study of Bevacizumab Therapy in Patients With Newly Diagnosed High-Grade Gliomas and Diffuse Intrinsic Pontine Gliomas</strong></td>
<td>Conditions: Newly Diagnosed High-Grade Gliomas, Diffuse Intrinsic Pontine Glioma</td>
<td>Interventions: Drug: Temozolomide, Drug: Bevacizumab, Drug: Inotecan</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td><strong>Molecular Analysis of Samples From Patients With Diffuse Intrinsic Pontine Glioma and Brainstem Glioma</strong></td>
<td>Conditions: Diffuse Intrinsic Pontine Glioma, Glioma of Brainstem</td>
<td>Interventions:</td>
</tr>
<tr>
<td>4</td>
<td>Completed</td>
<td><strong>Phase IIa Safety and Light Dose Escalation Study In Patients With Primary or Recurrent High-Grade Glioma Using the Lix® System to Confirm the Zone of Tumor Destruction During the Intraoperative Treatment of Glioma</strong></td>
<td>Conditions: Glioma; Glioblastoma Multiforme; Anaplastic Astrocytoma</td>
<td>Interventions: Drug: L511 (talapofin sodium); Device: Light source (interstitial light emitting diodes); Procedure: Intraoperative placement of device in glioma</td>
</tr>
<tr>
<td>5</td>
<td>Recruiting</td>
<td><strong>A Pilot Study of Glioma Associated Antigen Vaccines in Conjunction With Poly-ICLC in Pediatric Gliomas</strong></td>
<td>Conditions: Newly Diagnosed Pediatric Pontine Glioma; Newly Diagnosed Pediatric High Grade Glioma; Recurrent Pediatric High Grade Glioma; Recurrent Pediatric Low Grade Glioma.</td>
<td>Interventions: Biological HLA-A2 restricted synthetic glioma antigen peptides vaccine; Drug: Poly IC LC; Genetic: Reverse transcriptase-polymerase chain reaction; Other: enzyme-linked immunosorbent assay; Other: flow cytometry; Other: immunohistochemistry staining method; Other: laboratory biomarker analysis</td>
</tr>
<tr>
<td>6</td>
<td>Active, not recruiting</td>
<td><strong>Erlotinib and Radiation Therapy in Treating Young Patients With Newly Diagnosed Glioma</strong></td>
<td>Condition: Brain and Central Nervous System Tumors</td>
<td>Interventions: Drug: Erlotinib hydrochloride</td>
</tr>
<tr>
<td>7</td>
<td>Recruiting</td>
<td><strong>Lenalidomide and Radiation Therapy in High Grade Gliomas or Diffuse Intrinsic Pontine Gliomas</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Trials:  *Things to Consider*...

- **Eligibility considerations:**
  
  - Do you have the **right disease**?
    - Any ‘special’ tests required? (*eg*, MGMT promoter methylation; EGFR vIII)
  
  - Is your disease the **right stage**? (*eg*, newly diagnosed, first recurrence, etc.)
  
  - What **prior treatments** are allowed and disallowed? (*eg*, radiosurgery, Gliadel, bevacizumab)
  
  - How is your **general health and function**?
    - ‘Performance status’
    - ‘Normal’ labs
    - Previous malignancies
Clinical Trials: Things to Consider...

• Logistical considerations:
  o Where is the trial being offered?
  o Is the trial open? Actively recruiting?
  o What is the cost?
  o What is the trial design?
    ▪ What phase is the trial?
    ▪ What procedures have to be done at the study site?
    ▪ What is the schedule of visits?
    ▪ Is the trial randomized? Using what scheme?

• Biomedical considerations:
  o Prior experience with drug
  o Adverse effect profile
  o Can participation affect eligibility for future trials?
  o “Would you recommend this trial to your family?”
Clinical Trials: To participate or not participate?

It depends…

BUT

Hawthorne effect
Patients who participate in clinical trials have a tendency to do better.
So what happens when you enroll in a clinical trial?

- **Informed consent**
  - A lot of signatures
  - Some trials have optional substudies
  - Know your rights!
    - You can leave a trial for any reason at any time.

- **Baseline studies**
  - Sometimes including eligibility studies

- **Regular assessments** (MRI scans, blood draws)

- **Keep in mind, it often takes a long time for final trial results to become available.**
  - Most therapeutic trials are open-ended – as long as you are doing well, you can stay on the trial.
So what happens when you enroll in a clinical trial?

You get to work with a great team!
Thank you!