Integration of chemotherapy and radiation therapy

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No Disclosures
U.S. Cancer Statistics - 1998

1.2 Million New Cases Each Year

600,000 Localized Tumors
570,000 Cured Via Surgery or Radiotherapy

600,000 Disseminated Tumors
70,000 Cured Via Chemotherapy
Outline

• Current Status
• Rationale for combination of chemotherapy with Radiation
• Mechanism of action and resistance
• Disease sites and toxicity of combination therapies
• New targets
The past decade

• Radiotherapy has Improved & will Improve Further
• Most Recent Advances Relate to Imaging & Planning
• Future Advances will be in New Delivery Approaches
• RT Dose and Fractionation Paradigms will Shift
• RT Target Volume “Rules” will Also Shift
• RT/Drug Interactions Could Dictate Dose & Fractionation
Reasons to use Chemoradiation

- Sterilize micrometastases outside of the XRT portal
- Tumor cell sensitization
- Improved nutrition and reoxygenation to hypoxic tumor cell (decrease tumor burden)
  - Better blood supply to remaining tumor cells
- Cells cycle into a more radiation sensitive phase
- Inhibit cell division between radiation doses
- Inhibit cellular repair of damage between therapies
Rationale for combined chemotherapy and radiotherapy

- Spatial cooperation
- Toxicity independence
- Action as a radiosensitizer (possible synergism)
- Eliminate need for surgical procedure.
  - Not all patients able to undergo anesthesia.
- Addresses systemic and locoregional disease.
  - Neoadjuvant chemotherapy delays local control component of surgery.
Spatial Cooperation

• Cytotoxic agents active against tumor cells located in areas not radiated.

• Radiation delivered to areas of sanctuary from chemotherapy
  – Idea used in treatments for Ewing’s sarcoma, Wilm’s tumor, rhabdomyosarcoma, ALL, breast cancer and small cell lung cancer
  – First use in practice is childhood ALL with cranial radiation
  – May cause need to decrease doses for tolerance of therapy
Rationale for combined chemotherapy and radiotherapy

• Improved functional/cosmetic outcome.
• Surgical salvage remains an option.
• Landmark studies (chemo-radiotherapy → surgery) suggest long term survivors have no tumor in resection specimen.
Timing of Chemotherapy Administration

• **Neoadjuvant**
  - May be given 2 months prior to XRT for micrometastasis sterilization
  - Used to reduce the number of clonogens in XRT portal
    • ability to decrease portal size
  - Could leave resistant cells or allow for proliferation during a break in XRT needed for toxicity

• **Concurrent**
  - Alternating
    • Chemotherapy alternates weekly with XRT
      – Lymphomas and small cell CA has some data
  - Simultaneously
    • Chemotherapy and XRT given at the same time
      – Most commonly used mode

• **Adjuvant**
  – Given after XRT finished
Clinical Results of Radiation Therapy and Chemotherapy

• Combined radiation therapy and chemotherapy may improve local control or survival
  – Rectal cancer (local control, survival)
  – Limited-stage small cell lung cancer (survival)
  – Hodgkin’s disease (local control)
  – Limited-stage non-Hodgkin’s lymphoma (local control, survival)
  – Rhabdomyosarcoma (local control, survival)
  – Anaplastic astrocytoma (local control, survival)
  – Esophageal cancer, Melanoma
  – Cervix cancer, Gastric cancer

• Combined radiation therapy and chemotherapy avoids debilitating surgery without compromising survival
  – Anal cancer
  – Bladder cancer
  – Head and neck cancer
  – Extremity sarcoma
  – Breast cancer
Combination of radiation and systemic agent (level I evidence)

<table>
<thead>
<tr>
<th>Primary</th>
<th>Systemic agent</th>
<th>Abs. improvement in Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma (Brain)</td>
<td>Temozolomide</td>
<td>14% at 2 yr</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Cisplatin, cetuximab</td>
<td>20% at 2 yr</td>
</tr>
<tr>
<td>Lung</td>
<td>Cisplatin</td>
<td>7% at 2 yr</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5FU + cisplatin</td>
<td>26% at 5 yr</td>
</tr>
<tr>
<td>Stomach</td>
<td>5FU + leucovorin</td>
<td>?</td>
</tr>
<tr>
<td>Rectum</td>
<td>5FU</td>
<td>15% at 5 yr</td>
</tr>
<tr>
<td>Anus</td>
<td>5FU + mitomycin</td>
<td>Improve local control</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cisplatin</td>
<td>14% at 5 yr</td>
</tr>
</tbody>
</table>
When Gemcitabine is combined with RT, toxicity is *site dependant*.

### Dose limiting toxicity of Gemcitabine + RT

<table>
<thead>
<tr>
<th>Site</th>
<th>Non-hematological toxicity</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Vomit and nausea, anorexia, fatigue, abdominal pain</td>
<td>Wolf CCR 2001</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Mucositis, pharyngitis, skin</td>
<td>Eisenbruch JCO 2001</td>
</tr>
<tr>
<td>Cervix</td>
<td>Diahorrhea, cystitis, nausea and vomit</td>
<td>Umazon GynOnc 2006</td>
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<tr>
<td>Lung</td>
<td>Esophagitis, pneumonitis, skin</td>
<td>Trodella JCO 2002</td>
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<tr>
<td>Brain</td>
<td>neurotoxicity</td>
<td>Huan ChMJ 2007</td>
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</tbody>
</table>
Maximal tolerated dose of Gemcitabine when combined with full dose RT

- **Brain**: 100-600 mg/m²/week
- **NSCLC**: 200 mg/m²/week
- **Bladder**: 100 mg/m²/week
- **Head and neck**: 10 mg/m²/week
- **Pancreas**: 50 mg/m²/week
- **Cervix**: 100 mg/m²/week
ONCOLOGY
Principles of chemotherapy
Electron micrograph of mitotic cell
Biological Basis of Chemotherapy

• Most anticancer drugs work by affecting DNA synthesis or function

• Effectiveness depends on the growth fraction of the tumor
  – i.e. fraction of cells actively cycling

• Cell cycle specific agents are active during a particular phase of the cell cycle
  – i.e. S-phase specific drugs

• Cell cycle non-specific agents
ONCOLOGY
Principles of chemotherapy

The mitosis stages

Daughter cells → Interphase → Prophase → Metaphase → Anaphase → Telophase → Daughter cells
# ONCOLOGY

## Principles of chemotherapy

### Classification of cytotoxic agents

<table>
<thead>
<tr>
<th>Alkylating Agents</th>
<th>Anti-Metabolites</th>
<th>Mitotic Inhibitors</th>
<th>Antibiotics</th>
<th>Others</th>
</tr>
</thead>
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<td>Mercaptopurine</td>
<td>Vindesine</td>
<td>Mitomycin-c</td>
<td></td>
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<tr>
<td>Ifosfamide</td>
<td>Methotrexate</td>
<td>Taxoids</td>
<td>Mitoxantrone</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>Gemcitabine</td>
<td></td>
<td>Plicamycin</td>
<td></td>
</tr>
</tbody>
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ONCOLOGY
Principles of chemotherapy

Action sites of cytotoxic agents

Cell cycle level

Antibiotics
Antimetabolites
Alkylating agents

G0
G1 (2-∞h)
M (0.5-2h)
G2 (2-32h)
S (2-6h)

Vinca alkaloids
Mitotic inhibitors
Taxoids
ONCOLOGY
Principles of chemotherapy
Action sites of cytotoxic agents

DNA synthesis

DNA transcription

DNA duplication

Antimetabolites

Alkylating agents

Intercalating agents

Mitosis

Spindle poisons

Cellular level
ONCOLOGY
Principles of chemotherapy

Side effects of chemotherapy

- Mucositis
- Alopecia
- Nausea/vomiting
- Pulmonary fibrosis
- Diarrhea
- Cardiotoxicity
- Cystitis
- Local reaction
- Sterility
- Renal failure
- Myalgia
- Myelosuppression
- Neuropathy
- Phlebitis
Anti-Metabolites

- Most inhibit nucleic acid synthesis either directly or indirectly - tend to be active mainly against proliferating cells
- Most are cell-cycle specific
- Toxicity reflects effect on proliferating cells; primarily seen in bone marrow cells GI mucosa
Anti-Metabolites (cont.)

• **Methotrexate**
  – Analog of vitamin, *folic acid*
  – Prevents the formation of reduced folate which is required for DNA synthesis; is a competitive inhibitor of **DHFR** (dihydrofolate reductase)

• **5-fluorouracil**
  – Closely resembles uracil and thymine bases
  – Interferes with both RNA and DNA metabolism, in particular *inhibits the enzyme thymidylate synthetase*

• **Cytidine Analogs**
  – **Cytosine arabinoside** (ara-C)
    • Competitive inhibitor of DNA polymerase, enzyme necessary for DNA synthesis; *causes death of S phase cells*
Anti-metabolites

- Enhances through altering cell kinetics of surviving cells
  - Mitotic cells have 3X response to XRT compared with late S-phase cells
  - **Methotrexate** kills s-phase cells leaving XRT resistant cells behind. Prior XRT leaves S-phase cells behind and allows for enhanced killing with MTX
    - Whole Brain XRT and High dose oral/IT MTX enhances late CNS damage. Especially if XRT precedes the MTX.
Leukoencephalopathy

Widespread destruction of white matter and diffuse atrophy

The patient was a 63-year-old man with meningeal lymphoma who underwent whole-brain radiation therapy. Several months later, his meningeal lymphoma recurred and was treated with intrathecal methotrexate. Progressive dementia developed.

Abeloff: Abeloff's Clinical Oncology, 4th ed.
Figure 16.9. Structures of uracil, thymine, and the analogue 5-fluorouracil.
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Principles of chemotherapy

Action sites of cytotoxic agents

- 6-MERCAPTOPURINE
- 6-THIOGUANINE
- METHOTREXATE
- 5-FLUOROURACIL
- HYDROXYUREA
- CYTARABINE
- ETOPOSIDE

**PURINE SYNTHESIS**

**PYRIMIDINE SYNTHESIS**

**RIBONUCLEOTIDES**

**DEOXYRIBONUCLEOTIDES**

**DNA**

**RNA**

**PROTEINS**

**ENZYMES**

**MICROTUBULES**

**ALKYLATING AGENTS**

**ANTIBIOTICS**

**L-ASPARAGINASE**

**VINCA ALKALOIDS**

**TAXOIDS**
XELODA (capecitabine) is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumor tissues. The clinical significance is unknown.
Capecitabine Chemical Structure

NH-CO-O-C$_5$H$_{11}$

O

F

N

\[ \text{XELODA} \]

5-FU

\[ \text{5-FU} \]
Some human carcinomas express thymidine phosphorylase in higher concentrations than surrounding normal tissues.
Thymididine Phosphorylase (TP)

- TP is known as tumor-associated angiogenic factor or platelet-derived endothelial growth factor (PD-EGF)
- Promotes neovascularisation and inhibits apoptosis
- Correlates with aggressive malignant growth and poor patient prognosis

Increased TP Activity in Tumor vs. Normal Human Tissues

TP activity (µg 5-FU/mg protein/hour)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Healthy tissue (n=)</th>
<th>Tumor tissue (n=)</th>
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<tbody>
<tr>
<td>Colorectal</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>Gastric</td>
<td>291</td>
<td>351</td>
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<tr>
<td>Breast</td>
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<td>309</td>
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<tr>
<td>Cervical</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Uterine</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Ovarian</td>
<td>14</td>
<td>23</td>
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<tr>
<td>Renal</td>
<td>24</td>
<td>37</td>
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<tr>
<td>Bladder</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Thyroid</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Liver</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Liver (metastasis)</td>
<td>16</td>
<td>20</td>
</tr>
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*p<0.05

Five Classes of Alkylation Agents

1. Nitrogen Mustard and derivatives
   • Cyclophosphamide, chorambucil, melphalan, cyclophosphamide are in widest clinical use for many cancers – dose limiting toxicity is myelosuppression

2. Ethylenimine derivatives
   • i.e. thiotepa

3. Alkyl sulfonylates
   • i.e. bisulfan

4. Triazene derivatives
   • i.e. dicarbazine

5. Nitrosureas
   • i.e. BCNU, CCNU, methyl CCNU
     ▪ Lipid soluble, penetrate into CNS-used for treatment of brain tumors
# ONCOLOGY

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ONCOLOGY
Principles of chemotherapy
Action sites of cytotoxic agents

DNA synthesis
- Antimetabolites
- Alkylating agents

DNA transcription

DNA duplication

Intercalating agents

Mitosis
- Spindle poisons

Cellular level
Classes of Agents and Mode of Action

- **Alkylating Agents**
  - Act through covalent bonding of alkyl –CH₂Cl to intracellular groups
    - E.g. macromolecules
  - May be *monofunctional or bifunctional*
    - i.e. can form cross-links; alkylation of DNA bases are major cause of lethal toxicity
  - **Cell-cycle nonspecific**
    - There are five classes of alkylating agents
Nitrogen Mustard (Mechlorethamine)

Chlorambucil

Melphalan (L-Phenylalanine Mustard)

Ifosfamide

Cyclophosphamide

BCNU

CCNU

Methyl-CCNU
Platinum Coordination Complexes

- These compounds alkylate N7 of guanine.
- They cause nephro- and ototoxicity. To counteract the effects of nephrotoxicity, give mannitol as an osmotic diuretic or induce chloride diuresis with 0.1% NaCl.
Alkylating Agents

• Cyclophosphamide (also ifosfamide)
  – Injury to cells is the same as radiation effect
  – Alternating cytoxan and XRT produces a maximum killing response
  – Limiting toxicities:
    • Bladder injury
      – concurrent administration with XRT not recommended
      – seen 1 week post administration and can persist for 1 year
      – seen with XRT 5 months after treatment
    • Increased injury seen in CNS, lung, esophagus, small bowel and skin
    • XRT and cytoxan interaction can be seen up to 9 months after either is given.
ONCOLOGY
Principles of chemotherapy

Metabolism of cytotoxic agents

CYCLOPHOSPHAMIDE

4-OH CYCLOPHOSPHAMIDE

ALDOPHOSPHAMIDE

PHOSPHORAMIDE

MUSTARD

ACTIVATION

HEPATIC CYTOCHROMES P 450

INACTIVATION

ALDEHYDE

DEHYDROGENASE

4-KETOCYCLOPHOSPHAMIDE

CARBOXYPHOSPHAMIDE

ACROLEIN

TOXICITY

CYTOTOXICITY
Reaction with DNA Bases

![Chemical structure of guanine and its reaction with nitrogen mustard](image)

**Figure 16.3.** Reactions leading to alkylation at the N-7 position of guanine by nitrogen mustard.
Alkylation Agents

- Cisplatin and carboplatin
  - Supra-additive effect with XRT
  - Impairs sub-lethal damage repair
    - works by free-radical related mechanism and biochemical mechanism
  - Hypoxic cell sensitizer at very high doses
    - not clinically achievable in humans
  - Hyperthermia increases the effects of the drug
  - Limiting toxicities:
    - kidney toxicity seen if given within 6 months prior to XRT but not seen if given after XRT
Natural Products

• ANTIBIOTICS
  – Anthracyclines – are planar multi-ring structures
    • Example doxorubicin (Adriamycin), daunorubicin – major limiting toxicity is cardiac damage
  – Doxorubicin – one of the most active anticancer drugs in clinical practice
    • Mechanisms of action
      – Can intercalate between turns of the double helix in DNA
      – Inhibit topoisomerase 11 (catalyzes the orderly breaking of DNA strands, unwinding of DNA, and relegation of DNA fragments during synthesis)
      – Formation of free radicals
**ONCOLOGY**

Principles of chemotherapy

Action sites of cytotoxic agents

- **Antibiotics**
- **Antimetabolites**
- **Alkylating agents**
- **Vinca alkaloids**
- **Mitotic inhibitors**
- **Taxoids**

**Cell cycle level**

- **G0**
- **G1** (2-∞h)
- **S** (2-6h)
- **G2** (2-32h)
- **M** (0.5-2h)
Antibiotics

• Dactinomycin (actinomycin D)
  – Intercalates with DNA binding noncovalently between purine and pyrimidine base pairs
  – Inhibits sublethal damage repair in some studies
    • With daily XRT drug can cause the enhancement of lung damage
  – Can cause radiation pneumonitis, acute skin and mucosal reactions, hepatic damage and late fibrosis
    • Recall reaction seen if drug is given after XRT. The portal outline is seen.
  – Enhances distant metastasis control in many tumors
    • Still used in pediatric tumors
      – Ewing’s Sarcoma
      – Wilm’s Tumor
      – Rhabdomyosarcoma
Antibiotics

• Doxorubicin
  – Intercalates between base pairs in DNA
  – Double strand break repair is inhibited
    • drug exposure before XRT gives maximal enhancement
  – Marked mucosal (esp. esophagus) and skin reaction is seen
    • increased delayed fibrosis and necrosis
  – Cardiac tolerance is reduced in people receiving XRT prior to chemotherapy
  – CONCURRENT USE IS AVOIDED
Figure 16.16. Structure of doxorubicin (Adriamycin), daunorubicin, and epirubicin.
Antibiotics

• Bleomycin
  – Radiomimetic
  – Causes single and double stranded DNA breaks
  • intercalation is partially the MOA
  • oxygen free-radicals are generated by bleomycin-oxygen-iron complexes
  • enhanced effects with dactinomycin
  • major effects are in the G2 and M phases
    – creates a G2-M blockade helping synchronize cells
Antibiotics

- **Bleomycin**
  - Lung damage is most enhanced
  - Skin and mucosal damage is also enhanced
  - Drug given before XRT is most enhancing esp 6 hours prior to therapy
  - Prolonged exposure increases damage
Antibiotics

- Mitomycin C
  - Alkylating agent which cross-links DNA strands and halts DNA synthesis
  - Interacts with XRT by killing hypoxic cells
  - Enhances XRT reaction in the skin and soft tissues
  - Used in cancers of
    - anus
    - head and neck
    - esophagus
The patient was treated with steroids, antibiotics, and a Pleurx catheter. CT scan approximately 1 year later, the patient's condition was stable with no evidence of recurrent cancer. The patient had discontinued steroid therapy but needed intermittent oxygen therapy for radiation fibrosis of the right lung.

Abeloff: Abeloff's Clinical Oncology, 4th ed.
Natural Products (cont.)

• VINCA ALKALOIDS
  – Vincristine, Vinblastine
    • Bind to tubulin and inhibit its polymerization into microtubules that form the mitotic spindle

• TAXANES
  – Paclitaxel, docetaxel
    • Semisynthetic derivative
    • Act by stabilizing microtubules
      – i.e. inhibit microtubular disassembly thereby preventing cell division

  – Radiosensitizes cells in the G1-S phase, G2-M blockade, commonly used in Lung, H&N, Bladder
  – Enhances XRT with nontoxic doses
Drug Resistance

• Factors influencing resistance to chemotherapy
  – Proliferative state of cells
    • i.e. cell cycle effects
  – Limited diffusion due to solid tumor environment
    • i.e. limited vascular access
  – Intrinsic resistance of tumor cells themselves, most important factor
    • i.e. drug therapy results in the selection or induction of this drug-resistant subpopulation with a tumor
Mechanisms of Intrinsic Resistance

- Decreased cellular uptake
- Reduced drug activation
- Binding of alkylating species to sulfhydryl cpds such as glutathion, followed by transport out of cell
- Increased removal of drug adducts from DNA
- Increased repair of DNA damage
- Increased efflux by MDR protein pumps
ONCOLOGY
Principles of chemotherapy

Drug resistance

EXTRACELLULAR

INTRACELLULAR

PGP_{170}

ATP

Drug

Plasma Membrane
Does resistance to chemotherapy translate into resistance to radiotherapy?
• Chemoresistance is usually due to a target
  – MDR, thymidylate synthase, topoisomerase I or II
• Radioresistance is multifactorial
  – Free radical formation, DNA repair, oxygen status
Radiation Recall Reaction

• The chemotherapy drugs that have been reported to cause radiation recall in more than 10 percent of patients include:
  • Cosmegen® (actinomycin)
  • Adriamycin® (doxorubicin)
  • Rheumatrex® (methotrexate)
  • 5-FU (fluorouracil)
  • Hydrea® (hydroxyurea)
  • Taxol® (paclitaxel)
  • Doxil® (liposomal doxorubicin)
Recall Phenomena
### Phase I Medical Oncology
### Phase I Radiation Oncology

<table>
<thead>
<tr>
<th>First in humans</th>
<th>Significant human exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicty - unpredictable</td>
<td>Toxicity - predictable</td>
</tr>
<tr>
<td>- systemic</td>
<td>- local</td>
</tr>
<tr>
<td>- acute</td>
<td>- medium / long term</td>
</tr>
<tr>
<td>Range of cancer types</td>
<td>Organ specific</td>
</tr>
<tr>
<td>Patients have failed multiple treatments</td>
<td>May be treatment naive</td>
</tr>
<tr>
<td>Pharmacokinetic studies</td>
<td>Not needed</td>
</tr>
</tbody>
</table>
Mechanisms of Radiosensitization

1. Cell cycle effects
2. Expose DNA to free radical damage
3. Inhibit DNA repair
4. Influence cell’s response to DNA damage, promote apoptosis
5. Spindle checkpoint removal, leading to mitotic death
Signaling Pathways

Therapeutic Targets in Cancer
Targeting the Tumor and Its Microenvironment

1. Growth factor signaling
2. Other growth stimulating/suppressing receptors
3. Microtubule dynamics
4. Histone acetylation/deacetylation
5. DNA replication, transcription, repair
6. Protein synthesis
7. Protein folding
8. Cell cycle
9. Activators and inhibitors of apoptosis
10. Metastasis
1. Growth factors
2. Growth factor receptors
3. Adaptor proteins
4. Docking proteins/binding proteins
5. Guanine nucleotide exchange factors
6. Phosphatases and phospholipases
7. Signaling kinases
8. Ribosomes
9. Transcription factors
10. Histones
11. Molecular chaperones
12. DNA
13. Microtubules
14. Cyclins
15. Cyclin-dependent kinases
16. Cell death receptors
17. Apoptosis-effector caspases
18. Caspase inhibitors
19. CD40-CD40L
Thank you