Experimental Cancer Therapeutics II

Frank Wuest, PhD

Oncologic Imaging, Edmonton PET Centre, CCI
wuest@ualberta.ca

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Outline – Specific Topics

• Introduction to cancer drug design and discovery
  ➔ First generation of cancer drugs
  ➔ Molecularly targeted small molecule cancer drugs

• New approaches to molecular cancer therapeutics
  ➔ Process of developing new molecular-targeted therapeutics
  ➔ Druggable genome
  ➔ Lead generation and lead optimization

• Application of Biomarkers
  ➔ Role of molecular imaging (PET) in cancer drug development
Cancer drug design and development:


Biomarkers and molecular imaging:


Modern cancer drug design and discovery:

Integrating ➔ Targets

➔ Technologies

➔ Treatments

FOCUS: Opportunities and challenges in the discovery and the design of molecularly targeted small-molecule cancer drugs
Modern cancer drug design and discovery

1. Molecular targets of contemporary drug discovery projects:

- Reflection of our increasing understanding of genes and signalling pathways responsible for the initiation and malignant progression of cancer
- How can potential new molecular targets be considered, validated and prioritized?

Human genome discovery
- '88-'00: Mapped
- '98-'10: Analyzing SNP’s

Human proteome discovery
- '00-'20: Discovering protein relationship to genes

Disease target identification

Cancer drug
2. Integrated application of a range of powerful drug discovery and drug evaluation technologies:

- Genomics
- High-throughput screening (HTS)
- Molecular imaging
- Structural biology

**GOAL:** Multi-parameter optimization of lead structures towards effective cancer drugs
Modern cancer drug design and discovery

3. Novel treatments:

- Reflection of the success of **new mechanism-based molecular therapeutics** which act on cancer-causing targets

- Novel treatments which benefit from technological innovations in drug design

Prostate cancer drug abiratone targeting active site of cytochrome P450

Effect of abiratone treatment on reducing bone metastases in prostate cancer patients using $^{99m}$Tc-MDP SPECT

Modern cancer drug design and discovery

CONCLUSION:
Design, discovery and evaluation of cancer drugs are leading the way in the development of personalized molecular medicine

Key: Identification of biomarkers for:

- Patient selection
- Monitoring treatment effects (Molecular imaging!!!)

The future... personalized medicine

Detect & Predict  Pinpoint  Prevent & Treat
Molecular diagnostics  Molecular imaging  Molecular therapeutics

ONCL 520 – Experimental Cancer Therapeutics II
Modern cancer drug design and discovery

Changing times:
First generation of cancer drugs
- Almost all acted as cytotoxic agents (often based on natural products)

Mode of action:
- DNA damage
- Inhibition of DNA synthesis
- Interference with mechanisms of cell division

Examples:
- Topoisomerase inhibitors
  - Camptothecin
- Microtubuli-binding drugs
  - Paclitaxel
- DNA alkylating agents
  - Cyclophosphamide
Drugs developed in the first, cytotoxic era of cancer drug development were not designed to take advantage of our current knowledge of the genetic and molecular basis of cancer.

**But:** Many acted according to the “molecular targeting” approach. Designed according to contemporary medicinal chemistry including SAR and X-ray crystallography.

**E.g.** Antifolate thymidylate synthase inhibitors (anti-metabolites)

Structures of antifolate drugs (anti-metabolites)

http://clincancerres.aacrjournals.org/content/10/3/1080.full
Modern cancer drug design and discovery

Success and limitations:

Notable successes with conventional cytotoxic drug treatment of cancer

But: Effectiveness of drug treatment varies across the different anatomical, histological, and molecular types of cancer

😊 Major improvements in the treatment of leukemias, lymphomas, testicular cancer, and children’s malignancies

😔 Cancer still second most frequent cause of death in the Western world
No major improvement through simple fine-tuning of classical cytotoxic agents

This view coincided with the arrival of novel molecular targets emerging from basic cancer research and genomics

Emerging of “molecular cancer therapeutics”
Novel mechanism-based drugs acting on drug targets involved in the molecular causation of cancer
Modern cancer drug design and discovery

What has changed? - A brief summary -

1. Today’s molecular targets reflect our increasing understanding of the genes and signaling pathways responsible for initiation and malignant progression of cancer

2. Integrated application of a range of powerful drug discovery technologies

3. New treatments which reflect the success of mechanism-based molecular therapeutics
**Novel molecular cancer therapeutics**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target for agent</th>
<th>Targeted cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>EGFR</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>ERBB2</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
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<td>Bevacizumab (Avastin)</td>
<td>VEGF</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>CD20</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin)</td>
<td>CD20</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
</tr>
<tr>
<td>Tositumomab-I²¹ (Bexxar)</td>
<td>CD20</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
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<tr>
<td>Gemtuzumab ozogamicin (Mylotarg)</td>
<td>CD33</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
</tr>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>CD52</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma</td>
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<tr>
<td><strong>Small-molecule inhibitors</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Imatinib mesylate (Gleevec)</strong></td>
<td><strong>TKs (BCR-ABL, KIT, PDGFR)</strong></td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>TK (EGFR)</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>TK (EGFR)</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>TKs (VEGFR, PDGFR, KIT, FLT3)</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Kinases (B-Raf, VEGFR2, EGFR, PDGFR)</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>28S protease</td>
<td>NSCLC, Breast cancer, CRC, GIST, Renal cancer, Pancreatic cancer, HNSCC, AML, B-cell lymphoma, Multiple myeloma</td>
</tr>
</tbody>
</table>

**Gleevec:**
First successful small molecule for molecularly targeted cancer therapy

Source: Nat Rev Cancer © 2006 Nature Publishing Group
Gleevec: How it works – An example for molecular targeting

Chronic myelogenous leukemia (CML): $30,000 - $100,000 per year
Gastrointestinal stromal tumors (GIST): $65,000 per year

Novel molecular cancer therapeutics

Current challenges of oncology drug discovery and development with respect to small-molecule drug development:

- Many of recently approved drugs are mAbs
- Others are not first-in-class agents

Assessment of overall success rate for oncology drug development:

- Failure rates for cancer drugs in clinical trials (1990-2000) were worse than for most other therapeutic areas (Kola and Ladis, 2004)
- Only 5% of oncology drugs entering the clinic went to gain regulatory approval for marketing (95% failed!!!, other disease fields have 11% success rate)
- Longer development timelines for oncology drugs than for other therapeutic areas
- Large number of cancer drug failures occurred in an advanced stage clinical evaluation (high costs!!!
Novel molecular cancer therapeutics

New Product Development – A Risky and Expensive Proposition

Compound Success Rates by Stage

- 5,000–10,000 Screened
- 250 Enter Preclinical Testing
- 5 Enter Clinical Testing
- 1 Approved by the FDA

Net Cost: $802 Million Invested Over 15 Years

Source: Tufts Center for the Study of Drug Development
Novel molecular cancer therapeutics

Reasons for failure:
- In early 1990s: Poor pharmacokinetics
  Limited bioavailability

Development of a predictive assay (ADME):

Absorption
Distribution
Metabolism
Excretion

Introduction of ADME assay led to a fall in clinical failure rate from 40 to 10% in 2000!!!
Novel molecular cancer therapeutics

Today’s reason of attrition of a cancer drug:

- Insufficient therapeutic efficacy !!!

How to address the problem:

1. Selection of the best possible molecular target
2. Use of animal models of human cancers with improved predictive power
3. Better prediction of on-target and off-target toxicity (side effects!!!)
4. Careful selection of biomarkers to identify the most responsive patients and to provide proof-of-concept for the proposed molecular mechanism (molecular imaging)
Integrated small-molecule drug discovery and development

The process of developing new molecular-targeted drugs:

Interplay between:

- Genetics
- Genomics
- Bioinformatics
- Cell and molecular biology
- Structural biology
- Pharmacology
- Tumor biology
- Medicinal chemistry
- Experimental medicine


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New molecular targets: The “druggable“ cancer genome

Selection of best possible molecular target

Crucial to the success of drug discovery

Factors influencing the choice of target:

1. Involvement of the target in the initiation and progression of cancer
2. Technical feasibility (or “druggability“) of the target

Concept of the “druggable“ genome (Hopkins and Groom, 2002)
Classes of genes and biological mechanisms involved in cancer

Activation of oncogenes (RAS, RAF)

Genes that support oncogenic pathways (genes encoding Hsp90)

Inactivation of DNA repair genes (BRCA1, BRCA2)

Hijack of multiple signal transduction pathways

Deactivation of tumor suppressor genes (p53)

Genes involved in tumor microenvironment (HIF-1α)

Phenotypic hallmarks of cancer
- Increased proliferation
- Inappropriate survival
- Decreased apoptosis
- Immortalization
- Invasion
- Angiogenesis & metastasis

Cancer
New molecular targets: The “druggable“ cancer genome

Quelle: Drug Discovery Today, August 2005
New molecular targets

Best molecular targets for drug development of highly effective cancer drugs with minimal side effects will be those that are responsible for major differences between cancerous and healthy cells.

Drugs acting on essential function would have a narrower therapeutic index than those that interfere with non-essential functions.
New molecular targets: Druggable targets

The druggable genome

High priority to:

- Receptors for small endogeneous molecules
- Enzymes with well-defined active site (kinases)
- Protein-protein interactions involving small domains

Currently not druggable or difficult:

- Phosphatases
- Large domain-size protein-protein interactions
- Mutant RAS G protein, mutant p53

New molecular targets: Druggable targets

Comparison of the druggable genomes of selected eukaryotes

<table>
<thead>
<tr>
<th></th>
<th>Homo sapiens</th>
<th>Drosophila melanogaster</th>
<th>Caenorhabditis elegans</th>
<th>Saccharomyces cerevisiae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of predicted genes</td>
<td>~30,000</td>
<td>13,601</td>
<td>18,424</td>
<td>6,241</td>
</tr>
<tr>
<td>Number of proteins in proteome*</td>
<td>21,688</td>
<td>13,849</td>
<td>17,946</td>
<td>6,127</td>
</tr>
<tr>
<td>Number of estimated druggable targets</td>
<td>3,051</td>
<td>1,714</td>
<td>2,267</td>
<td>508</td>
</tr>
<tr>
<td>Percentage that are predicted druggable targets</td>
<td>~10–14%</td>
<td>12%</td>
<td>12%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Not druggable targets:

Knowledge of biochemical pathway to allow selection of downstream targets e.g. no inhibition of RAS ➔ Targeting of downstream MEK kinases

New molecular targets: Druggable targets

Molecular targets of “rule-of-five“ compliant drugs

Lipinski’s “Rule-of-Five“

The rule describes molecular properties important for a drug’s pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active. Poor ADME, when:

- Molecular mass: >500
- Lipophilicity (logP): >5.0
- >5 H-bond donors (e.g. OH und NH)
- >10 H-bond acceptors (e.g. N und O)
From drug target to development candidate

After target selection ➔ Generation of lead compounds

The heart of small molecule drug discovery is the iterative cycle of chemical synthesis and biological evaluation

Natural products vs. synthetic compounds

[Diagram showing the iterative cycle of chemical synthesis and biological evaluation]
**From drug target to development candidate**

**Natural products**: Pre-optimized through selective forces of evolution

- Privileged structures

**Reported GPCR ligands containing spiropiperdines as recognition motives**
From drug target to development candidate

Challenge to use natural products

Bioactive concentrate → Purified bioactive compound → New compound → Potential lead → Drug development

- Bioassay-based Separation and purification
- Structure elucidation
- SAR Synthesis of derivatives Scale-up synthesis
- Medicinal chemistry

Known Compound?

Required Amount of compound

1-10 µg

1-10 mg

1-10 g

100 g

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From drug target to development candidate

Challenge to use synthetic compounds

Small molecule compounds: Very rarely clinical candidates

Need for substantial structural modifications

Chemical starting points: - Structure of endogenous biological ligands
  - Existing drugs
  - Natural product pool

Alternative: Compound libraries from HTS

⇒ Biological HTS of 100,000 to 2,000,000 chemically diverse small compounds
Selected histories of lead generation and lead optimization

PKC inhibitors with BCR-ABL cross-reactivity

Selective BCR-ABL Inhibitors

Gleevec

BCR-ABL

c-KIT

PDGFR

CRAF inhibitor from HTS

(IC_{50} = 17 \mu M)

Potent lead

(IC_{50} = 0.23 \mu M)

Combinatorial chemistry

Potency and in vivo efficacy optimization

Nexavar

CRAF, BRAF

VEGFR, PDGFR

c-KIT, FLT3

CCT018159

HSP90 inhibitor from HTS

(IC_{50} = 9 \mu M)

Structure-based design

VER49009

Potent, cell-active HSP90 inhibitor

(IC_{50} = 25 nM)

NVP-LAK974

HDAC inhibitor from HTS

In vivo efficacy and tolerability optimization

NVP-LAQ824

Clinical candidate

HDAC inhibitor

http://www.nature.com/nchembio/journal/v2/n12/images/nchembio840-sc1.jpg
Kinase binding selectivity for inhibitors using the human kinome
Fragment-based drug discovery

‘Rule of three’ for fragments:
MW < 300, logP < 3, number of H-bond donors and acceptors each should be < 3

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### Typical physicochemical and biological properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Fragment</th>
<th>Lead</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>&lt;300</td>
<td>&lt;400-450</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Lipophilicity (logP)</td>
<td>&lt;3</td>
<td>&lt;4</td>
<td>&lt;5</td>
</tr>
<tr>
<td>H-bond donors</td>
<td>≤3</td>
<td>≤4-5</td>
<td>≤5</td>
</tr>
<tr>
<td>H-bond acceptors</td>
<td>≤3</td>
<td>≤8-9</td>
<td>≤10</td>
</tr>
<tr>
<td>Polar surface area</td>
<td>N/A</td>
<td>N/A</td>
<td>≤140-150 A²</td>
</tr>
<tr>
<td>Chemically reactive groups</td>
<td>N/A</td>
<td>None present</td>
<td>None present</td>
</tr>
<tr>
<td>Target activity (IC₅₀; Kᵢ)</td>
<td>&gt;&gt;10⁻⁵-10⁻⁶ M</td>
<td>10⁻⁶-10⁻⁶ M</td>
<td>10⁻⁸-10⁻⁹ M</td>
</tr>
<tr>
<td>Structure-Activity-Relationship (SAR)</td>
<td>NMR or X-ray</td>
<td>Useful SAR established</td>
<td>Full SAR understood</td>
</tr>
</tbody>
</table>
Hit to lead generation

„we do better with structure...“

Binding sites (lead structure)

Optimization of lead structure
Hit to lead generation

„we do better with structure...“

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**Novel molecular cancer therapeutics**

**Summary – Conclusions:**

- Shift of paradigm

  Focus on mechanism-based drugs acting on drug targets involved in the molecular causation of cancer

  Careful selection of molecular target ("Druggable" cancer genome)

  Interplay between chemical biology and structural biology (we do better with structure)

  Complex hit to lead to drug developing process
Biomarkers and molecular imaging

Non-invasive assessment of dynamics of a given biological process at the cellular and molecular level in the physiological intact organism over time

Impact on:
- Diagnosing and staging of cancer
- Monitoring therapy
- Functional/anatomical imaging
- Drug development & evaluation

Molecular imaging ➔ Molecular medicine
Molecular imaging methodologies

Optical imaging
- Advantages: High-throughput screening for target confirmation and compound optimization, High sensitivity
- Disadvantages: Limited clinical translation, Low depth penetration

Magnetic resonance imaging
- Advantages: Clinical translation, High resolution and soft-tissue contrast
- Disadvantages: Costs, Imaging time

Ultrasound imaging
- Advantages: Clinical translation, High spatial and temporal resolution, Low costs
- Disadvantages: Operator dependency, Targeted imaging limited to vascular compartment

PET imaging
- Advantages: Clinical translation, High sensitivity with unlimited depth penetration
- Disadvantages: Cost

SPECT imaging
- Advantages: Clinical translation, Unlimited depth penetration
- Disadvantages: Limited spatial resolution

CT imaging
- Advantages: High spatial resolution (bone/lung), Clinical translation
- Disadvantages: No target-specific imaging, Radiation, Poor soft-tissue contrast

What to image: Selected PET radiotracers in oncology

Glycolysis
- [18F]FDG

Membrane metabolism
- [11C]Choline
- [18F]Fluoroacetate

Amino acid transport
- [18F]OMFD
- [11C]methionine

Nuclear receptors
- [18F]FES

Hexokinase
- GLUT

Membrane-bound receptors
- [18F]-Peptides, [18F]-Kinase-inhibitors, [18F]-σ2-ligands

Hypoxia
- [18F]MISO, [18F]FAZA

Proliferation
- [18F]FLT

Nucleoside-transporter
- TK

Apoptosis
- [18F]Annexin, [18F]Caspase inhibitors

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Positron emission tomography (PET)

PET: A multidisciplinary approach
**PET – A multidisciplinary approach**

<table>
<thead>
<tr>
<th>Radionuclide production</th>
<th>“Smart” radiotracers</th>
<th>Nuclear medicine Drug research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radionuclide</strong></td>
<td><strong>Half-life</strong></td>
<td></td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 min</td>
<td></td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>9.96 min</td>
<td></td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2.03 min</td>
<td></td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>109.8 min</td>
<td></td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>762 min</td>
<td></td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>68.3 min</td>
<td></td>
</tr>
<tr>
<td>$^{76}$Br</td>
<td>966 min</td>
<td></td>
</tr>
<tr>
<td>$^{120}$I</td>
<td>88 min</td>
<td></td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>4.15 d</td>
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</tbody>
</table>

- Design
- Synthesis (automation if possible)
- Quality control

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PET in drug development

1. Optimization chemical collection using μ-PET data
2. Radiolabeled lead compounds (radiotracers) for in vivo studies
3. In vitro selectivity
4. Non-invasive disease surrogates
5. Early PK analysis
6. Complete PK (humans, μ-dosing?)
7. Human PK (dosing, receptor occupancy, metabolites…)
8. Patient selection, diagnosis, response. Images as marketing tools
Application of PET Imaging in Drug Development

Determination of the relation between administered dose and clinical outcome

GOAL: Understanding the events related with:

- Drug administration
- Drug adsorption
- Drug distribution
- Drug metabolism
- Drug excretion
- Drug response to target organs and biochemical effector systems

PET as a general *in vivo* tracer method allows:

- Performance of non-perturbed observations *in vivo* (research animals & man)
- Studies at very low concentrations (< $10^{-9}$ M; tracer concept, *PET-microdosing*)
Drivers for change

Ability to make rational decisions in development
  Go/No go decisions with confidence

Use clinical technologies to better understand
  Proof of Target
  Proof of Mechanism
  Proof of Efficacy

Can we make these decisions sooner?
  Impact of translational imaging

Longer term impact to human healthcare
  Individualized medicine
Application of biomarkers in therapeutic drug development

Three definitions of biomarker (PET radiotracer) levels to describe the particular application of a biomarker

Rigor in Validation

Level 1
Hit Target?
Proof of Target
Confirm pharmacological MOA

Level 2
Affect Mechanism?
Proof of Mechanism
Predict biological MOA

Level 3
Monitor disease progression?
Proof of Efficacy
Predict clinical outcome

Confidence in Efficacy
Level One Biomarkers -- Proof of Target

PET receptor occupancy to assist in a No/Go decision

- Very popular for neuroreceptor mapping

Level 1
Hit Target?
Confirm pharmacological MOA

Control
25 mg
25-40% occupancy

25 mg
60-83% occupancy

50 mg
60-72% occupancy
Level Two Biomarkers -- Proof of Mechanism

- Early Response -- Faster than tumor shrinkage?
- Effective Response -- Affect mechanism?

**Predictive response of therapeutic or clinical benefit?**

PET imaging in oncology drug development
- FDG metabolism
- FLT proliferation
SU11248, sunitinib maleate (Sutent)

• Selective multi-target inhibition of:
  – PDGFR
  – VEGFR
  – cKIT
  – FLT3

• Antitumor and anti-angiogenic activity

What types of information can PET provide to the exploratory development phase of novel targeted cancer therapies?
Two Phase 1 trials of SU11248 used PET Imaging

- A Phase 1 study of SU011248 in the treatment of patients with malignant Gastrointestinal Stromal Tumor (GIST) who are intolerant of, or with disease progressing on imatinab mesylate (Gleevec)

- Pilot study of PET imaging to assess biological response to SU011248 L-malate salt
A quick word about Phase 1 trials in oncology

- Primary endpoint of any Phase 1 study is **safety & tolerability**
  - Dose escalate to target
  - Normal volunteers

- Oncology – patients with end stage disease

- In oncology Phase 1 studies
  - Clinical benefit is not expected
    - Not necessarily the target patient population
    - However tumor size assessment by CT is conducted
[\textsuperscript{18}F]FDG – marker of tumor metabolism

- FDG reveals metabolic shutdown
- Widely available
- PET/CT has opened a new window on cancer imaging
SU11248 (Sutent) in GIST

Metastatic GIST FDG-PET response to SU011248 in a patient resistant to Gleevec™

50 mg/day (2 wks on 2 wks off)

Link metabolic response to
- plasma levels (PK)
- serum and biopsy markers (PD)

ASCO 2003 Abstract #3273

Baseline

After treatment

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Is the PET response predictive of clinical outcome?

- For SU11248 (Sutent) it is too early to say, but...

- For Gleevec in GIST
  - FDG PET response is highly correlated with cKIT genetic variants
    - Exon-11 (70%) -- major effect
    - Exon-9 (15%) -- minor effect
    - Wild-type -- no effect (PDGFR-α drives disease)

Source: G. Demetri NCI FDG-PET Workshop Washington Jan 2005
FLT reveals proliferative response

- Cells are not dead, but cannot divide
- Cells will still be metabolically active
  - Will it be an earlier response indicator than FDG?
FDG/FLT PET after SU11248 (Sutent) treatment

Metastatic malignant melanoma

FDG

Baseline

Week 2

FLT

Baseline

Week 2
PET provides rapid whole body assessment of tumor burden
  – Quickly identify heterogeneous responses
  – With PET/CT – guide tumor biopsy?

FDG PET provides rapid feedback for early metabolic response

FLT provides similar information on proliferation response
  – Combination of the two provides significant amounts of information within a subject

For SU11248 (Sutent) -- Value of PET is significant
  – PET data increased the confidence around the biological activity
    • Allowed to make faster decisions around going into Phase II
### Monitoring of metabolic changes after treatment

#### Other examples

<table>
<thead>
<tr>
<th>Targeted probe/drug</th>
<th>MRS observed metabolic alterations</th>
<th>PET observed metabolic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP90 inhibitors (17-AAG, CCT018159)</td>
<td>(+)GPC, (+)PC, (+)PME, (+)PE (cells), (-)NTP (tumor xenografts)(^{45,49,66})</td>
<td>(-)FDG, (+)(^{11\text{C}})choline, (-)(^{14\text{C}})methionine uptake (cells)(^{59})</td>
</tr>
<tr>
<td>BRAF-MEK1/2 inhibitors (U0126, PD0325901, PLX4032)</td>
<td>(-)PC (cells)(^{52})</td>
<td>(-)(^{18\text{F}})choline uptake (tumor xenografts)(^{53}) (-)FDG uptake (tumor xenografts)(^{54,55})</td>
</tr>
<tr>
<td>PI3K-AKT-mTOR inhibitors (LY294002, wortmannin, PI-103, PX-866, everolimus)</td>
<td>(-)PC, (-)total choline (cells),(^{51,57,58}) (-)pyruvate-lactate exchange (cells and tumor xenografts, DNP analysis)(^{59})</td>
<td>(-)FDG uptake (tumor xenografts)(^{60,61})</td>
</tr>
<tr>
<td>HDAC inhibitors (LAQ824, SAHA)</td>
<td>(+)PC (cells and tumor xenografts), (+)PME, (+)PE, (+)choline, (-)GPC, (-)GPE, (-)PCr, (-)NTP, (+)Pi, (-)Glucose (tumor xenografts)(^{72})</td>
<td>(-)FDG uptake (patient tumors)(^{90})</td>
</tr>
<tr>
<td>BCR-ABL, PDGFR inhibitor (imatinib)</td>
<td>(-)PC, (-)lactate, (-)glucose, (+)NTP (cells),(^{73,74}) pyruvate-lactate exchange (tumor xenografts, DNP analysis)(^{75})</td>
<td>(-)FDG uptake (patient tumors)(^{91,92})</td>
</tr>
</tbody>
</table>

The signs (+) and (-) signify an increase and a decrease in metabolite levels, respectively.