Oncology Drug Development

A Reviewers Personal Observations

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• **Disclaimer**
  – This presentation is not an official FDA guidance or policy statement. I do not intend to convey official support or endorsement by the FDA and you should not infer any such support or endorsement.

• **Financial Interest Statement**
  – I have no financial interest in any of the topics I am presenting. If I did they would fire me.

• My comments may not necessarily pertain to biological compounds
Drug Development Process

Chemistry

Nonclinical (Preclinical)

Clinical

Market

>500,000 compounds

IND

NDA

1 drug
Investigational New Drug

- A FDA process that regulates clinical drug development
- A permissive process, not an approval process
- The IND is initiated with the submission of all initial *in vitro* and *in vivo* information necessary to support the trials of the drug in humans for the first time
  - Whether the compound is reasonably safe for initial use in humans
  - Whether biological plausibility of the compound is demonstrated
• Phase 1 trial – first study in humans
  – Determines pharmacological dose and safety parameters, and sometimes PK parameters
  – PK may drive escalation
• Phase 2 trial – initial exploration of efficacy
• EOP2 – end of Phase 2
  – Consultation with FDA on future development
• Phase 3 trial – randomized, controlled (usually) study to provide statistical confirmation of safety and efficacy
• NDA – New Drug Application
  – Complete package of clinical and nonclinical information submitted to the FDA to support approval of a new drug for marketing and sale
  – There are specific requirements for non-clinical studies that must be included in this package depending on the drug indication
• What we do not regulate
  – Drugs that have NO component that crosses state lines
  – Herbs, natural products (Hatch Act)
• What we do regulate
  – Any therapy the components of which are marketed across state lines
  – Herbs and natural products when the dose greatly exceeds traditional well established ones
Drug Discovery

• Not monitored by the FDA
• Mechanism of Action NOT always necessary
  – Products that show pharmacological activity prior to the characterization of their mechanism
  – Drugs with unpredicted secondary pharmacology
    • e.g. sildenafil
  – You do need to demonstrate biological plausibility
  – Plausible – Kinase inhibition, traditional medicines
  – Implausible – Homeopathy, Aluminum foil hats
• In many cases it is impossible to establish a true causal link between *in-vitro* results (e.g. inhibition) and clinical efficacy
  – e.g. Many natural products
• Characterization of the pharmacology helps in the design of the toxicology studies

  – Without a binding constant you cannot make estimates about required plasma concentrations
    • If your feasible $C_{\text{max}}$ is 10 fold lower than your binding constant. (e.g. biological plausibility)
  – Without characterization of the distribution of the target receptor you cannot predict secondary pharmacologies or toxicities
    • Cardiac toxicities of tyrosine kinase inhibitors
    • PET Scan for binding (see M3)
Does the drug have other pharmacological targets?

• Example: a new drug interacted with the following pharmacological targets in a standard set of assays
  – $A_{2A}$ receptor, $IC_{50} = 3 \, \mu\text{M}$
  – adenosine $A_3$ receptor, $IC_{50} = 7 \, \mu\text{M}$
  – central benzodiazepine receptor, $IC_{50} = 2 \, \mu\text{M}$
  – P2Y purinergic receptor, $IC_{50} = 10 \, \mu\text{M}$

• BUT
Correlated Toxicities

- Adenosine A$_{2A}$ receptor when activated increases blood flow in the coronary arteries via vasodilatation and is involved in respiratory rhythm
- Adenosine A$_3$ receptor is also involved in cardiac regulation
- Central benzodiazepine receptor - muscle relaxation, sedation, anti-seizure
- P$_{2Y}$ purinergic receptor G-protein coupled receptors with all kinds of activity depending on tissue
- Rats had convulsions at high doses
- Rats became hypoactive after a single dose and had decreased respiratory rate
- Dogs had an increase in arterial pressure and heart rate
- All at C$_{max}$ values above the IC$_{50}$ values for these receptors
Or how about some Enzymology

- I almost never see this – Why?
  - Is anyone around trained to do this work?
  - Does anyone understands kinetics of molecular interaction?
  - Can anyone interpret the kinetics relative to the *in vivo* situation?
  - Is there good assay for the activity of the compound?
  - Is the mechanism too complicated?
  - If we did it would we like what we found?
- BF Krippendorff et al. Nonlinear pharmacokinetics of therapeutic proteins resulting from receptor mediated endocytosis
  *Pharmacokinet Pharmacodyn* (2009) **36**:239–260
Reversible Diffusion of DFP across the RBC membrane
What do you do next?

Try the New Drug in an Animal Model?

“Edwards, you fool, I’m Dr. Blake—the experiment worked! It means riches and fame for me—us! I meant us!”
Consultation among Toxicologists, Chemists & Physicians is Essential

- The schedule that is planned clinically should be the schedule you propose for toxicology studies
  - This will depend on the pharmacology
- The route should be the same (to get similar PK)
- The formulation should be as close to the final formulation as possible (again because of PK)
- Get all disciplines around a table and talk about development at every stage
  - Toxicologists, physicians, chemists, clinical pharmacologists
In Vivo Testing for Activity

- By this I mean tumor implant studies
- Don’t get carried away
- We do not review most of them, these tests are for your benefit
- They have almost no predictive value for tumor type and are questionable for predicting clinical schedule
- Everything cures cancer in the mouse
- To make my point I searched PubMed for
  - “Xenograft and mouse and blueberries”
Suppression of proliferation and tumor growth of human lung carcinoma cells by C3G in vitro and in vivo.

Ding M et al. J. Biol. Chem. 2006;281:17359-17368
Much

• *In vitro* metabolism
• Plasma protein binding data for animals and humans
  – Essential to understand exposure and potential binding at the active site
• Systemic exposure data in the species used for repeated-dose toxicity studies
  – Can be done in conjunction with the multi-dose animal studies
  – Studies can demonstrate exposure in cases where there is little or no toxicity associated with the drug
• (ICH S3A, Ref. 7)
Kinetics Can Greatly Aid Dose and Species Selection

Dose vs AUC in Male and Female Dogs on the First and Last Day of Dosing

- Males day 1
- Females day 1
- Males last dose day
- Females last dose day
Problems in Reaching an Optimal Dose

Dose vs $C_{\text{max}}$ in Male and Female Dogs

- Male
- Female

Dose mg/m$^2$

$C_{\text{max}}$ μM
Drug-Drug Interactions

- Treatment in Oncology is almost always poly-therapy
  - Patients are sick and require lots of support
- A Drug-Drug interaction will almost never kill your drug if it can anticipated and controlled
- Not always well predicted by animal studies
  - Rats do not have a Cytochrome P450 3A4 equivalent
- *In vitro* testing for inhibition and metabolism much simpler than it use to be
- Testing for induction can be part of the multi-dose studies
Safety Pharmacology Studies

• Cardiovascular – hERG, Purkinje Fibers, ECG (telemetry)
  – ECG monitoring time is critical
  – Ion Channel related or chronic cardiac damage?
• Respiratory systems – can be done with *in vivo* cardiovascular studies
• CNS – Irwin battery and others
• Can be combined with toxicology studies!!
  – Do this – it minimizes animal use
  – Not essential for entry into phase I with oncology drugs
• For normal volunteers the rules are the same as M3
Most drugs that exhibit cardiac toxicity do so by causing ion channel blockade.

Not the case with most oncology drugs:
- They are frequently negative in the hERG assay
- And frequently show no changes in the ECG after a single dose even at $C_{\text{max}}$

But they can cause long term damage:
- Mitochondria inhibitors
- Cardiac remodeling (RNA, chaperonins, protein transport)
- HDAC inhibitors
Toxicities

• Cancer drugs are almost always escalated to a Maximum Tolerated Dose
• What toxicity do you anticipate will be Dose Limiting?
• Can the toxicity be monitored Clinically?
• Is the toxicity reversible in the animals?
• Possible examples of unacceptable Phase 1 toxicities
  – Seizures, irreversible ataxia, irreversible cardiac damage?
Killing

• Oncologists are accustomed to dealing with toxicities
• A toxicity seen in a non-clinical study should rarely kill an oncology drug
  – If you have a troublesome toxicity don’t diminish it
  – Characterize it as well as you can
  – If possible determine the mechanism
• A thorough characterization will make it easier to manage the toxicity clinically
• It will also help to make the Package Insert informative and comprehensive
WOO-HOO! I DID IT! I FOUND A CURE!!
THAT’S GREAT, RALPH...NOW WHAT’LL WE DO?

UH... WHAT DO YOU MEAN, FRANK?

WELL, NOW THAT YOU’VE FOUND A CURE, ALL OUR FUNDING WILL BE SENT TO ANOTHER DIVISION.

WOO-HOO! I MADE A BREAKTHROUGH THAT’LL REQUIRE A LOT MORE RESEARCH!!

MUCH BETTER
• Decide early if you are going to move to non-life threatening conditions – the rules start to change
• For patients with curable disease the rules move toward M3
• For patients with extended prognosis (indolent disease) you may need longer studies
• Do only studies needed to support the indication and avoid redundant durations
  – For example doing a 6 month study plus a 9 month study is almost always unnecessary
Reproductive Toxicology

• Embryofetal Toxicity studies should be available when the NDA is submitted

• Are not considered essential to support clinical trials intended for the treatment of patients with advanced cancer

• Are not considered essential for the purpose of marketing applications for pharmaceuticals that are genotoxic and target rapidly dividing cells … or belong to a class that has been well characterized as causing developmental toxicity
Combination Drugs

• The Combination Rule
  – Both drugs need to contribute to the clinical efficacy
  – If you plan to give a new drug with a well established cancer drug, combination studies are almost never needed

• This class includes situations where a primary drug is given in combination with a drug that modifies its metabolism or elimination
Photodynamic Therapy (PDT)

- You give the patient a compound that absorbs light
  - Most are Porphyrin derivatives (think Heme)
  - The drug partitions to tissue by phagocytosis
  - Many studies have tried to show greater uptake in tumors
  - You irradiate the tissue (tumor) with an activating wavelength
  - The PDT drug forms a radical that propagates through the tissue causing necrosis and apoptosis
Conjugates

• Usually refers to an antibody conjugated to a cytotoxin
• Is the conjugate stable or is it hydrolyzed to release the cytotoxin in vivo?
• Is the cytotoxin (sans antibody) well characterized?
• Is the cytotoxin a genotoxin?
• Is there a linker molecule?
• Is the distribution of the conjugated molecule significantly different from that of the cytotoxin?
  – Almost certainly
• What toxicity studies are needed to characterize these molecules?
## Toxicities with the Non-Clinical

<table>
<thead>
<tr>
<th>Clinical Incidence N=207 (%)</th>
<th>Rat</th>
<th>Monkey</th>
<th>Mouse</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site adverse event</td>
<td>35</td>
<td>Injection site damage</td>
<td>Injection site damage</td>
<td>Injection site damage</td>
</tr>
<tr>
<td>Weight increase</td>
<td>9</td>
<td>Weight loss males - chronic, Weight increase females - chronic</td>
<td>Weight increase - male acute low dose</td>
<td>Weight loss males - chronic, Weight increase females - chronic</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>inflammatory response</td>
<td>Hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>decreased testosterone</td>
<td>Hypothermia, inflammatory response</td>
<td>cold extremities - acute Inflammatory response</td>
</tr>
<tr>
<td>Hot Flash</td>
<td>26</td>
<td>decreased testosterone</td>
<td>decreased testosterone</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>Changes in Alkaline phosphatase and deoxypyridinoline</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>Changes in Alkaline phosphatase and deoxypyridinoline</td>
<td>Changes in Alkaline phosphatase and deoxypyridinoline</td>
<td>Inflammation of the spinal cord</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>Changes in Alkaline phosphatase and deoxypyridinoline</td>
<td>Changes in Alkaline phosphatase and deoxypyridinoline</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5</td>
<td>Increased urine output</td>
<td>Increased urinary pH - acute</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>Slowed GI transit time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>
How We Look At Toxicities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day</th>
<th>Control</th>
<th>Low</th>
<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males **</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Retulocytes</td>
<td>3</td>
<td>4.1</td>
<td>-9.8%</td>
<td>-17.1%</td>
<td>-43.9%</td>
</tr>
<tr>
<td>Retulocytes</td>
<td>3</td>
<td>313</td>
<td>-8.3%</td>
<td>-16.6%</td>
<td>-44.1%</td>
</tr>
<tr>
<td>MCV</td>
<td>30</td>
<td>54.9</td>
<td>-1.3%</td>
<td>0.4%</td>
<td>-6.9%</td>
</tr>
<tr>
<td>MCH</td>
<td>30</td>
<td>19.2</td>
<td>0.5%</td>
<td>2.1%</td>
<td>-5.7%</td>
</tr>
<tr>
<td>Plattlets</td>
<td>3</td>
<td>1217</td>
<td>-20.8%</td>
<td>-10.8%</td>
<td>-23.3%</td>
</tr>
<tr>
<td>WBC</td>
<td>3</td>
<td>10.2</td>
<td>-0.5%</td>
<td>-29.1%</td>
<td>-44.4%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>3</td>
<td>1.71</td>
<td>-16.4%</td>
<td>-30.4%</td>
<td>73.7%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>30</td>
<td>1.6</td>
<td>-4.4%</td>
<td>-16.9%</td>
<td>364.4%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3</td>
<td>7.92</td>
<td>4.4%</td>
<td>-29.4%</td>
<td>-71.7%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>30</td>
<td>9.19</td>
<td>-16.8%</td>
<td>-52.4%</td>
<td>-71.4%</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>3</td>
<td>0.07</td>
<td>-14.3%</td>
<td>-57.1%</td>
<td>-42.9%</td>
</tr>
<tr>
<td>Basophils</td>
<td>3</td>
<td>0.06</td>
<td>0.0%</td>
<td>-33.3%</td>
<td>-66.7%</td>
</tr>
<tr>
<td>Basophils</td>
<td>30</td>
<td>0.03</td>
<td>-33.3%</td>
<td>-66.7%</td>
<td>-66.7%</td>
</tr>
<tr>
<td>APIT</td>
<td>30</td>
<td>21.7</td>
<td>4.1%</td>
<td>-6.5%</td>
<td>-7.8%</td>
</tr>
</tbody>
</table>
The Guiding Principles

• Concern for the patient is paramount

• **Just do good Science**

• We are concerned with *efficient* development because
  – It can speed approval
  – It limits the use of animals
  – We do not want unnecessary studies
Pre-IND meeting with the FDA

• **Brief** outline of
  – Completed and proposed pharmacology
  – Completed and proposed toxicology
  – Completed and proposed chemistry
  – Proposed Clinical Phase I development
    • You need not have all the information to support the clinical study at the time of the Pre-IND
    • You may be proposing to do more than necessary to support the clinical study (Yes we will tell you)
Ideal Dose Levels in Toxicology Studies

- Low dose should determine NOAEL
  - non-life threatening indications
- High dose should determine an MTD or limit dose
  - To determine the spectrum of toxicities
- Mid dose should show some toxicity
- Thus, 3 doses would ideally determine the top, middle and bottom of the dose response curve
  - The use of 3 dose groups is arbitrary.
  - Using more dose levels helps define the dose response curve
- Decade doses will almost never do this (1, 10, 100)
  - The high dose will cause too much toxicity
  - Or the low dose will be useless as it is below the NOAEL
  - Toxic dose response curves rarely span more than 10 times the highest non-toxic dose
Examples of the Effect of Toxicology Studies on Clinical Phase 1 Assumptions

- Small Molecule
- Effective pharmacological dose eventually determined to be 6 mg/m²
- Eight Subjects per Dose Level During Escalation
  - six receive active drug, two controls per cohort
  - Dose doubling between cohorts
- Dose scales 1:1 on a mg/m² basis
Doses

• Non-clinical Rodent Study Results
  • 0.1 mg/m² No Clinical Signs
  • 1 mg/m² NOAEL
  • 10 mg/m² Observed adverse effects

• Clinical Consequences:
  – Starting dose 1/10th the NOAEL = 0.1 mg/m²
  – Escalation requires 7 levels or 56 Subjects to reach pharmacological dose (6 mg/m²)
Only 4 fold between little toxicity and death
True NOAEL

- Non-Clinical Rodent Study Results
  - 1 mg/m² no clinical signs
  - 5 mg/m² NOAEL
  - 10 mg/m² Observed Minor Adverse Effects
  - 15 mg/m² Obvious toxicity

- Clinical Consequences:
  - Starting dose is 1/10th the NOAEL = 0.5 mg/m²
  - Escalation takes only 5 levels or 40 Subjects
  - Toxic dose response curve is well defined
Consequences of Dose Selection for Toxicology Studies

- For each factor of 10 you miss the true NOAEL on the low side you add an extra 4 escalation steps to Phase 1
  - This assumes dose doubling, it will result in more steps with more cautious escalation
  - In oncology each patient costs $15,000 to $20,000 or a total of $240,000 to $320,000 extra in our example above
  - This does not consider the added time of development
  - Talk with the physicians and figure out if you are really saving money by skimping on dose range finding or excluding that extra dose group from the toxicology study
Conclusion

• Non-clinical drug development is a scientific process
  – It is not about checking off boxes for a regulatory agency
• The process is sequential
  – Not all development needs to be done up front
  – This saves time, money & animals if early clinical trials fail to show efficacy
• The process is flexible
  – It allows for the development of new drugs with a variety of different mechanisms
• The process is multi-disciplinary
  – Talk to your physicians, chemists and clinical pharmacologists
• When in doubt talk to the regulatory agency
  – They really do want good new drugs approved
Do you really feel that Phase 3 of the clinical trial is necessary?

When extensive pharmaceutical trials pay off..., Happy Valentines Day."

• National Center for Replacement, Refinement and Reduction of Animals in Research – [http://www.nc3rs.org.uk/](http://www.nc3rs.org.uk/)

• Johns Hopkins Center for Alternatives to Animal Testing – [http://caat.jhsph.edu/](http://caat.jhsph.edu/)


• www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  – Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products October 2000
  – Exploratory IND Studies, January 2006
  – Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application, February 1987
  – Immunotoxicology Evaluation of Investigational New Drugs Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities. November 2001
  – Nonclinical Safety Evaluation of Drug or Biologic Combinations March 2006
  – Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route. March 2008
– Photosafety Testing. May 2003
– Recommended Approaches to Integration of Genetic Toxicology Study Results. March 2006
– Safety Testing of Drug Metabolites February 2008
– Single Dose Acute Toxicity Testing for Pharmaceuticals August 2006
– Nonclinical Safety Evaluation of Pediatric Drug Products. February 2006
– Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients. May 2005