Oncology Drug Development

A Reviewers Personal Observations

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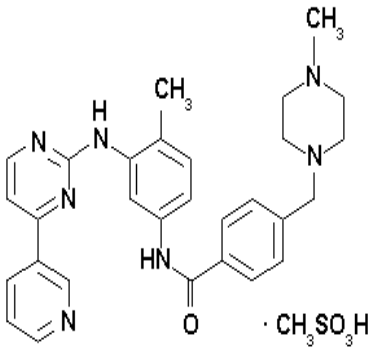
They Make Me Say This

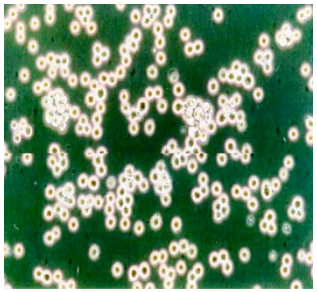
- *Disclaimer*
  - This presentation is not an official FDA guidance or policy statement. I do not intend to convey official support or endorsement by the FDA and you should not infer any such support or endorsement.
- *Financial Interest Statement*
  - I have no financial interest in any of the topics 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

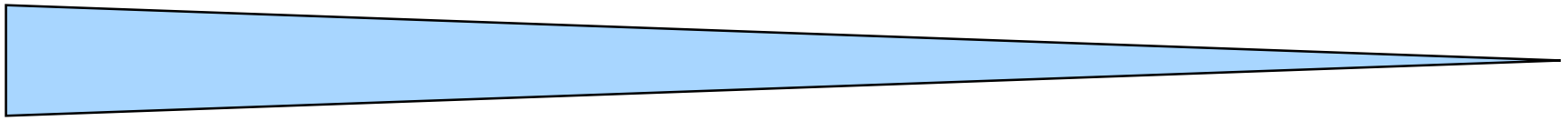
Market

IND

NDA

>500,000 compounds

1 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

[redacted]

- 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

FDA Purview

- 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

But

- 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_{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)

pharmacological targets?

- Example: a new drug interacted with the following pharmacological targets in a standard set of assays
  - A_{2A} receptor, IC_{50} = 3 μM
  - adenosine A_3 receptor, IC_{50} = 7 μM
  - central benzodiazepine receptor, IC_{50} = 2 μM
  - P2Y purinergic receptor, IC_{50} = 10 μM
- BUT

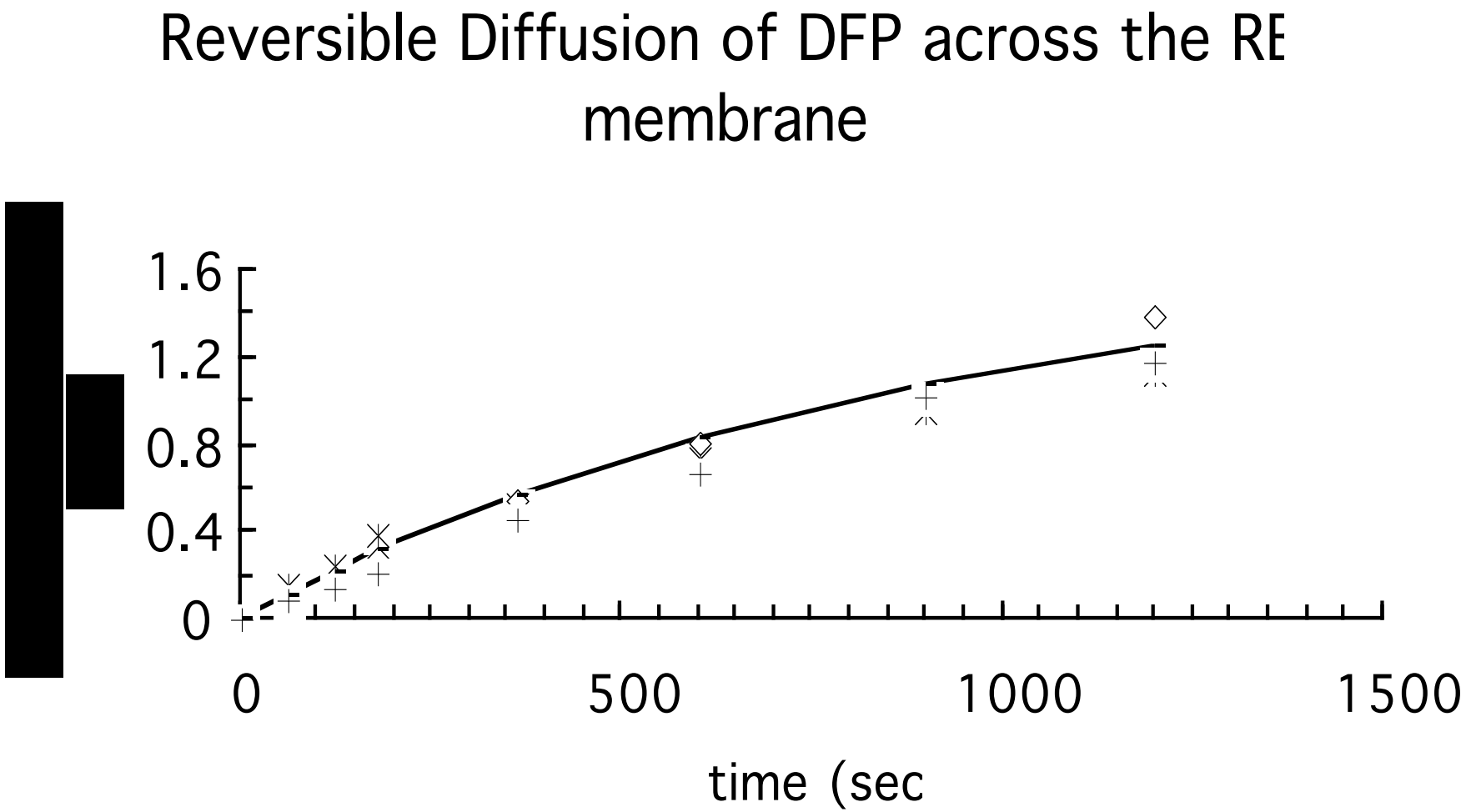
[redacted]

- 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

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 RE
membrane
1.6
1.2
0.8
0.4
0
0
500
1000
1500
time (sec

What do you do Next?

"Edwards, you fool, I'm Dr. Blake—the experiment worked! It means riches and fame for me—us! I meant us!"

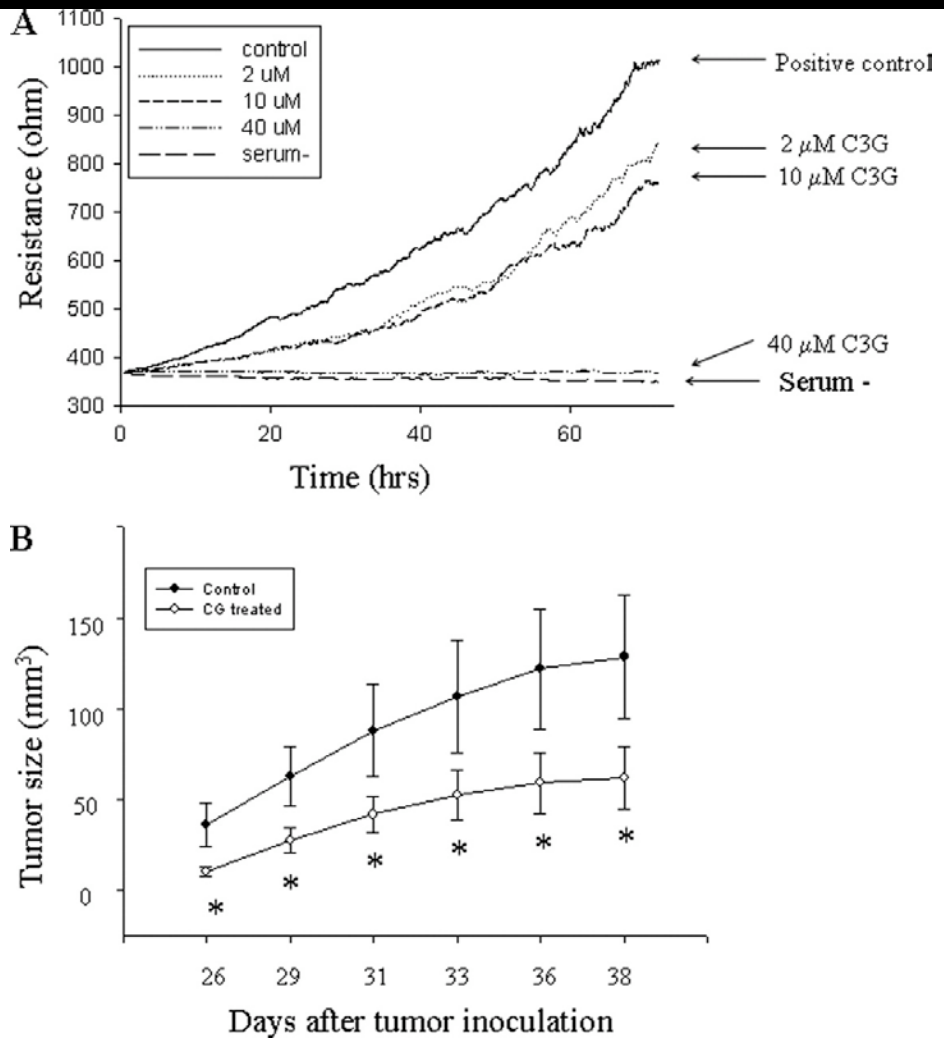
Try the New Drug in an Animal Model?

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

[redacted]

- By this I mean tumor implant studies
- Don’t get carried away
- We do not review most of them, these test 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”

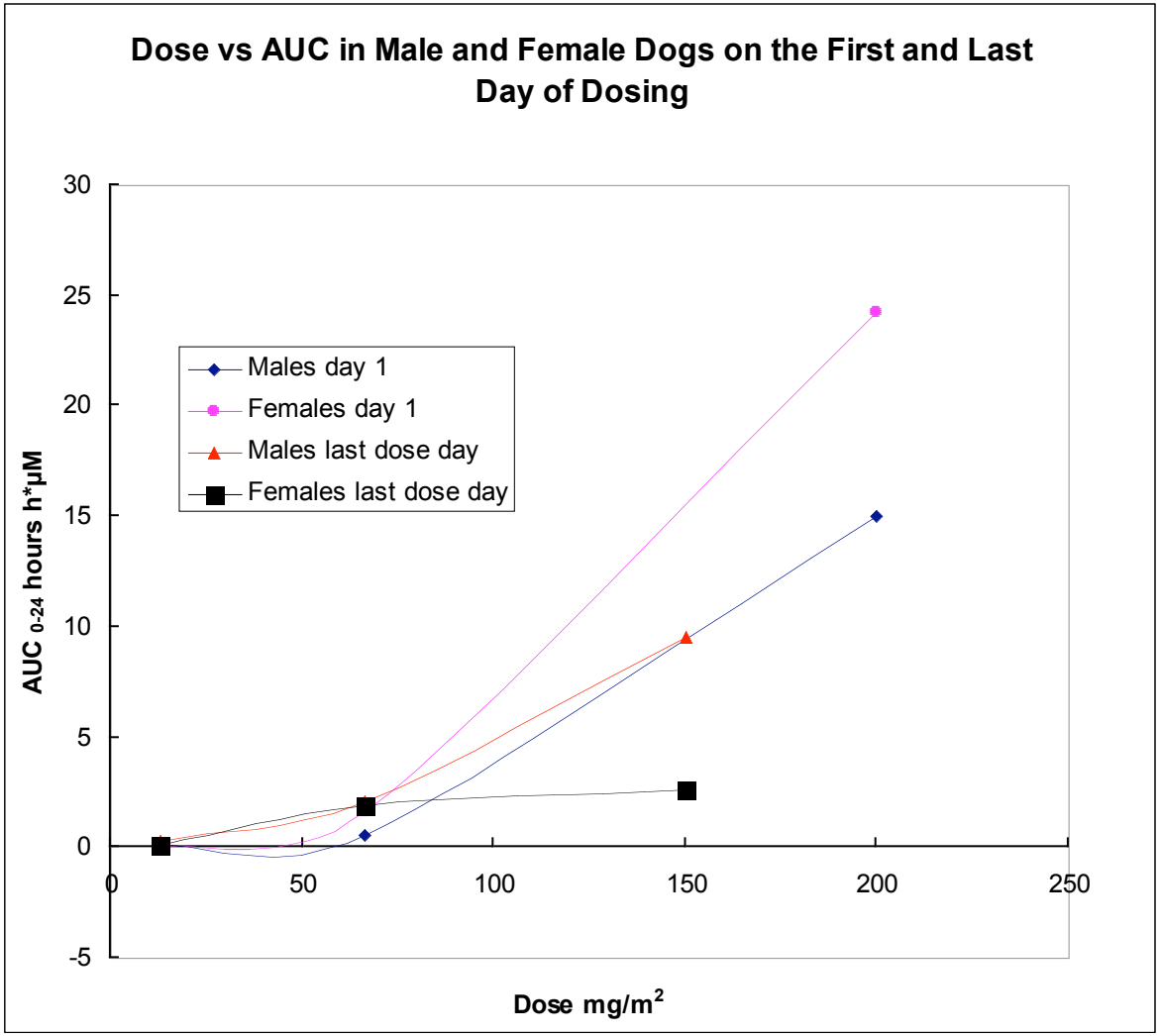


Ding M et al. J. Biol. Chem. 2006;281:17359-17368

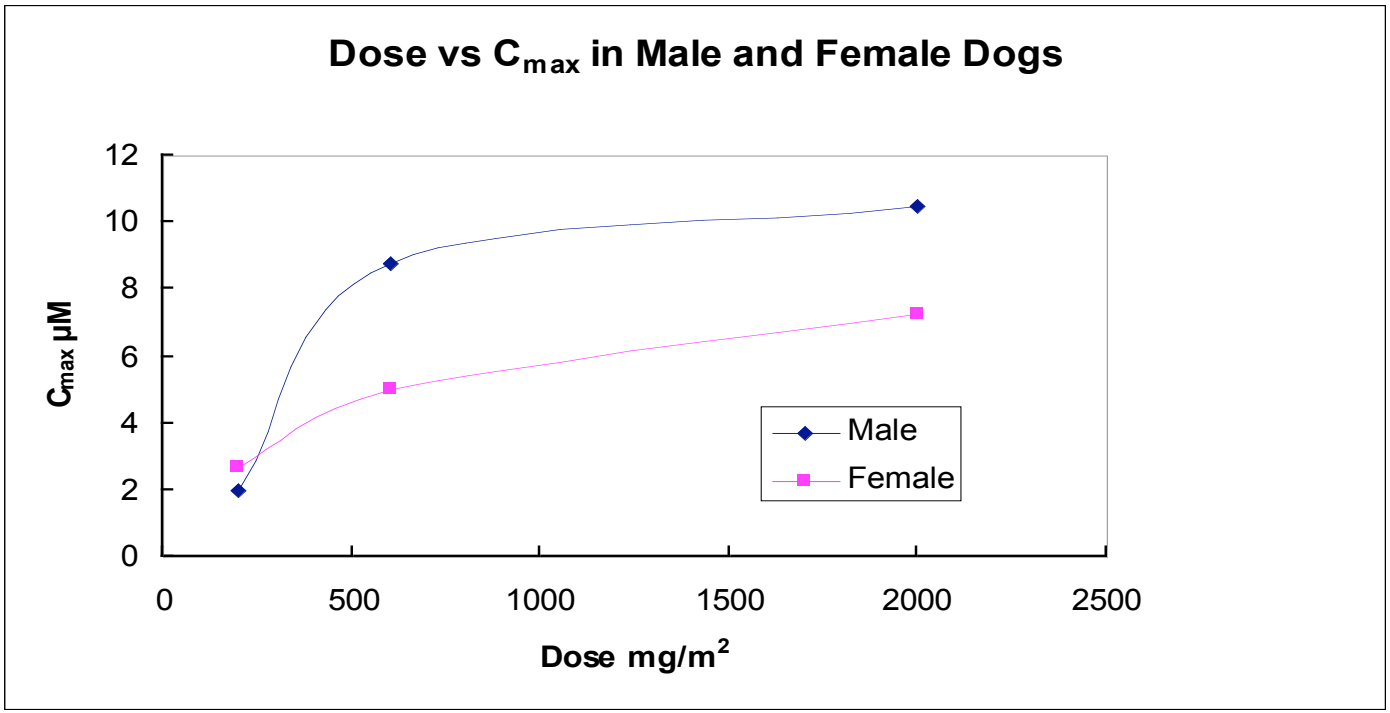
Much

- *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)

and Species Selection



Problems in Reaching an Dose



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

[redacted]

- 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_{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
FIND-A-CURE, INC.
WOO-HOO! I MADE A BREAKTHROUGH THAT'LL REQUIRE A LOT MORE RESEARCH!!
MUCH BETTER

Don't do too much work!

- 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

[redacted]

- 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

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

How We Look At Toxicities

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

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)

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

Toxicology Studies on Clinical Phase 1

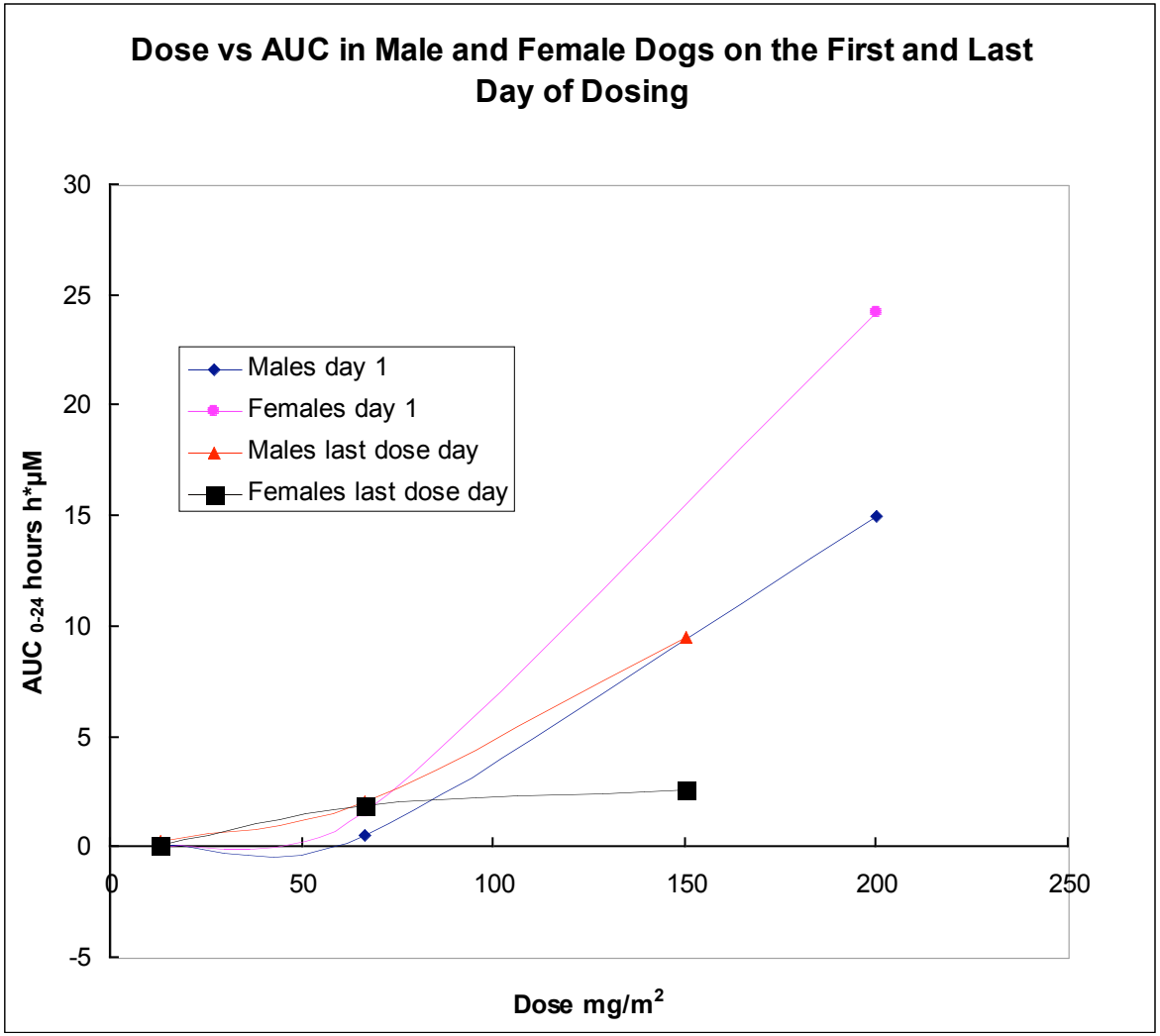
Assumptions

- Small Molecule
- Effective pharmacological dose eventually determined to be 6 mg/m^2
- 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/m^2 basis

Doses

- Non-clinical Rodent Study Results
  - 0.1 mg/m^2 No Clinical Signs
  - 1 mg/m^2 NOAEL
  - 10 mg/m^2 Observed adverse effects
- Clinical Consequences:
  - Starting dose $1/10^{th}$ the NOAEL = 0.1 mg/m^2
  - Escalation requires 7 levels or 56 Subjects to reach pharmacological dose (6 mg/m^2)

Only 4 fold between little toxicity and death



True NOAEL

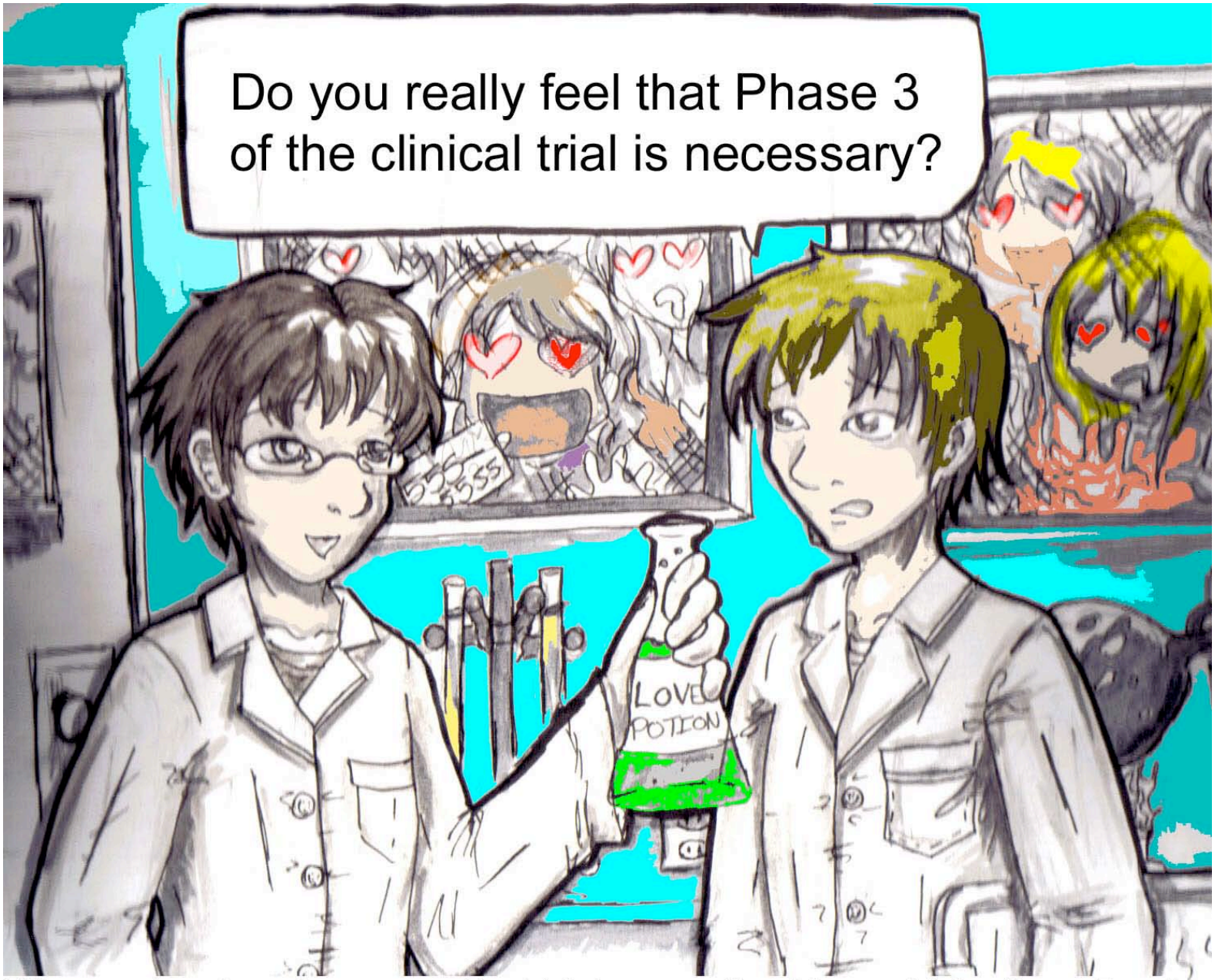
- Non-Clinical Rodent Study Results
  - 1 mg/m^2 no clinical signs
  - 5 mg/m^2 NOAEL
  - 10 mg/m^2 Observed Minor Adverse Effects
  - 15 mg/m^2 Obvious toxicity
- Clinical Consequences:
  - Starting dose is $1/10^{th}$ the NOAEL = 0.5 mg/m^2
  - Escalation takes only 5 levels or 40 Subjects
  - Toxic dose response curve is well defined

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 $ 320000 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



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

References

- All ICH guidelines – http://www.ich.org/cache/compo/502-272-1.html
- National Center for Replacement, Refinement and Reduction of Animals in Research – http://www.nc3rs.org.uk/
- Johns Hopkins Center for Alternatives to Animal Testing – http://caat.jhsph.edu/
- Camilla Buoen, Ole J. Bjerrum and Mikael S. Thomsen. How First-Time-in-Human Studies Are Being Performed: A Survey of Phase I Dose-Escalation Trials in Healthy Volunteers Published Between 1995 and 2004. *J. Clin. Pharmacol*. 2005; 45; 1123
- WT Robinson. Innovative Early Development Regulatory Approaches: expIND, expCTA, Microdosing. *Nature*, February 2008, 83(2):358-360.
- Graham Lappin & R Colin Garner, The utility of microdosing over the past 5 years, *Expert Opin. Drug Metab. Toxicol. (2008) 4(12):1499-1506*
- *Graham Lappin and R. Colin Garner,* Big physics, small doses: the use of AMS and PET in human microdosing of development drugs. *Nature Reviews, Drug Discovery*, March 2003, 2:233-240.

FDA Guidance

- www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005.
  - 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

FDA Guidance Cont.

- Photosafety Testing. May 2003
- Recommended Approaches to Integration of Genetic Toxicology Study Results. March 2006
- Reference Guide for the Nonclinical Toxicity Studies of Antivial Drugs Indicated for the Treatment of N/A Non-Life Threatening Disease Evaluation of Drug Toxicity Prior to Phase I Clinical Studies. March 1998
- Safety Testing of Drug Metabolites February 2008
- Single Dose Acute Toxicity Testing for Pharmaceuticals August 2006
- Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals. May 2001
- Nonclinical Safety Evaluation of Pediatric Drug Products. February 2006
- Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients. May 2005