Nonclinical Drug Development

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Disclosure Information
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• **Employment**: Forty Seven, Inc

• **Former Employment**: Janssen R&D/Johnson & Johnson

• **Stock**: Johnson & Johnson

• **Off Label Use**: I will not discuss off label use of any products
Nonclinical Drug Development

• **Broad Definition**: All the activities required before a new molecular entity can be administered to humans
  – Spans gap between *discovery/screening* to *FIH clinical trials*
  – Provides key pharmacological information about a drug candidate

• **Current Discussion**
  – Focus on *pharmacology, safety, toxicology, and translational scientific* strategies in nonclinical development
  – Will not discuss *API, CMC, and formulation* issues

*Bias Warning!: Industry, anticancer drug development perspective*
Nonclinical Drug Development
An Industrial Perspective

Guidance for Industry

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2010
ICH
S9 Oncology Specific Guidance

- Applies to targeted **small molecules** and **biopharmaceuticals** used for treating “**patients with advanced disease and limited therapeutic options**”
  - Advanced cancer is a progressive, fatal disease
  - Existing therapies have **limited effectiveness**
  - Treatment at or close to **adverse effect dose levels**

- Type, timing, and flexibility of **oncology studies** may **differ** from other therapeutic areas

- Does **NOT** apply to cancer **prevention**, **supportive care**, **healthy volunteers**, **radiopharmaceuticals**, **vaccines**, **cellular** or **gene therapies**

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*S9 Guidance for Industry, 2010*
Goals of Nonclinical Testing
S9 Oncology Specific Guidance

1. Identify the **pharmacologic properties** of a pharmaceutical

2. Establish a **safe initial dose level** of the first human exposure

3. Understand the **toxicological profile** of a pharmaceutical

-- S9 Guidance for Industry, 2010
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Nonclinical Drug Development

In Vitro Pharmacology Models

- **In vitro studies** performed in **cell lines** or **cell-free systems**
  - Often form the basis for screening and optimization during discovery
- **Oncology** uses **human tumor cell lines** for evaluation of:
  - Mechanism of **action**
  - Evaluation of **potency** and **selectivity**
  - Early **indication selection**
  - **Predictive biomarker** discovery
In Vitro Cell Line Analyses

Cisplatin

Carboplatin

Cell Lines

Relative Potency (GI_{50})
Limitations of 2D Tumor Models
Tumor Microenvironment

Humanized 3D Models
(for Advanced Biomarker and Drug Discovery Applications)

- Standard 2D Culture
- 3D-TGA
- ‘Humanized’ 3D-TGA
- ‘TME-Aligned’ 3D-TGA
- ‘Humanized’ xenografts

Tumor cells alone or co-culture
Tumor cells alone in 3D IrBME
Tumor cells + (10:1) hMSC/hCAF in 3D IrBME
Tumor cells + (10:1) hMSC/hCAF + hormones, pH, glucose in 3D IrBME
Tumor cells + (10:1) hMSC/hCAF + hormones in 3D IrBME implanted into xenografts

Abbreviations: TGA, tumor growth assay; IrBME, Irradiated basement membrane extract; hMSC, human mesenchymal stem cells; hCAF, human cancer associated fibroblasts; TME, tumor microenvironment

-- B. Hall
In Vivo Animal Models

• The ideal animal model should be:
  – Valid
  – Selective
  – Predictable
  – Reproducible

  “There is no perfect tumor model”
  “All models are wrong, some are useful”
Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth

In Vivo Efficacy Models in Cancer

- **Spontaneous** tumors
  - Idiopathic, endogenous: dog lymphoma studies
  - Carcinogen-induced
  - Transgenic/gene knockout animals: p53, RB, etc

- **Transplanted** tumors
  - Syngeneic animal tumors: Lewis lung, S180 sarcoma, B16 melanoma murine tumors
    - Valuable for immune-based therapies
  - Specialized: Human tumors growing in vivo in implantable hollow fibers
Human Tumor Xenografts Models

• Most **common** in vivo **preclinical efficacy model** in oncology
  – Current NCI standard in vivo efficacy testing system

• Consist of **human tumor cells** implanted in **immunocompromised** animals
  – Nude and SCID mice; nude rats

• Diverse **human tumor cell lines** propagated **in vitro** can grow as **xenograft** models
Nude Mouse Hosts for Xenograft Studies

- Athymic “nude” mice developed in 1960’s
- Mutation in *nu* gene on chromosome 11
- Phenotype: retarded growth, low fertility, no fur, immunocompromised
  - Lack thymus gland, T-cell immunity
- First human tumor xenograft of colon adenocarcinoma by Rygaard & Poulson, 1969
Differential Tumor Growth of Prostate Cancer Xenografts

\( n = 10 \)

(Mahajan, Cancer Res 2005;65:10514)
Xenograft Advantages

- **Diverse selection** of different human tumor types
  - Molecular characterization, GEP, available in public databases

- **Ease** and **speed of start up** and conduct of studies

- Simultaneous evaluation of **safety** and **efficacy** (therapeutic index)

- Some **correlation** with **clinical activity** in lung, colon, breast, and melanoma cancers

- Although **subcutaneous implantation** is most common, **orthotopic** injections are possible
  - Mammary fat pad, CNS, intraperitoneal, etc

- **Wide accessibility**

- Many **decades** of experience
Xenograft Disadvantages

- **Atypical** biological behavior
  - Metastases are rare
  - Survival not an ideal endpoint, with historical deaths from tumor bulk, not invasion
  - Short doubling times
  - Less necrosis, better blood supply

- **Positive predictive value** is poor

- Poorly mimics the **tumor microenvironment**
  - Human tumor cells with murine stroma
  - Host-directed therapies (immunomodulation, stromal tissue targets) may not be applicable
    - Species specific differences between humans and mice
  - Examples: Antibody biopharmaceuticals that only recognize human targets
    - Require use of mouse surrogates
Patient-Derived Xenograft Models

Consented patient → Surgically removed tumour (F₀) → Engraftment phase (F₁) → Expansion phase (F₂) → Treatment phase (F₃ ... Fₙ)

- Biologic studies
- Biomarker discovery
- Perpetual bank

Predictive biomarker development and validation

- Mutational status
- Copy number variation
- Gene expression

SEN + RES

Gain + Normal

Integrative genomic classifier

Clinical trials

Biomarker positive

Drug X

Biomarker negative

Vehicle

Drug X

Tryptic volume vs. Time (days)

Low Passage Patient Tumorgrafts

Primary human tumors


(Courtesy of W. Hait)
Patient Tumorgraft Clinical Correlations

Colorectal Tumorgraft
(Estrada et al, EORTC-NCI-AACR, 2010)

Myoepithelial Salivary Gland Tumorgraft

(Courtesy of M. Wick, START Laboratories)
Transgenic Animal Models of Cancer

- p53 or other tumor suppressor gene knockout animals have high incidence of endogenous tumor development

- Theoretically more analogous to human situation

**Advantages**
- Intact immune system
- Murine tumor and stroma
- Better for cancer prevention
- May be engineered for specific purposes

**Disadvantages**
- Long experimental start up times
- Variable penetrance
- Monitoring tumor growth in individual animals is challenging
Transgenic Animal Models

Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Safety Pharmacology Studies

- For non-oncology agents, a core battery of safety pharmacology tests is required (ICH S7A, Section 2.7)
  - Central Nervous System
  - Cardiovascular System
  - Respiratory System

- Additional supplemental studies must be individualized for each drug
  - May incorporate into general toxicology studies

- Oncology recommendations (S9 Guidance)
  - Vital organ assessment still required, but may not need stand alone safety studies in the absence of specific risk
  - Incorporate core vital organ evaluations into cGLP toxicology studies

- References
  - S9 Guidance 2010
  - S7A Safety Pharmacology Studies for Human Pharmaceuticals, 2000
Safety Pharmacology Studies
QTc Prolongation Risk Assessment

- **Prolonged QTc** caused by *delayed ventricular repolarization*
  - Increased risk of ventricular arrhythmias, especially Torsade de Pointes
  - Increased risk with hypokalemia, structural heart disease, or bradycardia

- **Late repolarization** of cardiac action potential
  - Mediated by efflux of K+ ($I_{Kr}$ and $I_{Ks}$) through delayed rectifier K+ channels

- Human ether-a-go-go-related gene (hERG)
  - Encodes the alpha subunit of the human K+ channel proteins responsible for IKr
  - Basis for preclinical in vitro testing for QTc prolongation risk

- Pharmaceuticals that prolong QTc can have **proarrhythmic** effects

- References
  - S7B, Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization, 2005
Nonclinical QTc Testing Strategy (ICH S7B, 2005)

- **Routine Nonclinical Tests**
  - In vitro $I_{Kr}$ (hERG) assay, and
  - In vivo QT assay in nonrodent species
    - May incorporate in CV core battery study
  - Assess chemical/pharmacological class for choice of reference compounds

- **Integrated Risk Assessment**
  - Consider all relevant nonclinical information
  - Consider follow up studies
    - Action potential, Rabbit wedge, etc

- Determine Evidence of Risk
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- **PK/ADME Studies**
- Toxicology
- Starting Dose Selection and study design issues for FIH
Nonclinical PK/ADME Studies for Oncology Studies

• Limited pharmacokinetic parameter estimation in nonclinical animal species
  – Cmax, AUC, and half-life

• Use to facilitate dose selection, schedule, and escalation in Phase 1

• Additional nonclinical ADME studies should be generated in parallel with clinical development(!)

• Reference
  – S9 FDA Guidance 2010
Nonclinical PK/ADME Studies

- **Cellular uptake and membrane transport**
  - MDR (*P*-glycoprotein), MRP, etc.
  - Predictions of bioavailability and distribution

- **In vitro drug metabolism**
  - P450 isoenzyme metabolism, inhibition or induction

- **Plasma protein binding** studies
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
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- PK/ADME Studies
- **Toxicology**
- Starting Dose Selection and study design issues for FIH
Nonclinical Toxicology Studies in Oncology

- **IND-enabling** general *toxicology* studies
  - Use the *same route* and *formulation* as clinical trial
  - *Approximate* the clinical schedule

- Small molecule toxicology testing usually includes *rodents* and *non-rodents* (i.e., dogs)
  - Non-human *primates* for biologicals

- Assess the *potential to recover* from toxicity
  - Terminal *non-dosing period* recommended
  - *Complete recovery* demonstration is *not* essential

- **Toxicokinetics** evaluations as appropriate

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*S9 Guidance for Industry, 2010*
Good Laboratory Practice (GLP)

- Most safety pharmacology and toxicology studies should be conducted with GLP
  - Full GLP may not be feasible in some safety pharmacology studies

- All core battery safety pharmacology studies should be GLP

- Primary pharmacodynamic (general pharmacology) studies do not need to be conducted in compliance with GLP

-- S7A Guidance Section 2.11
Reproduction Toxicology
(S9 Guidance)

- **Embryonic** and **fetal toxicology** studies required at the time of **marketing application**
  - In rare cases may not need at all for genotoxic agents that target rapidly dividing cells or known developmental toxins

- Typically conducted in **two different species**
  - **Biologicals** may use one relevant species

- **Fertility** and **early embryonic development** studies are not required for use in advanced cancer patients

- **Pre-** and **post-natal toxicology** studies not warranted for oncology

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*S9 Guidance for Industry, 2010*
Other Toxicology Studies
(S9 Guidance)

- **Genotoxicity**
  - Not essential for oncology clinical trials
  - Should be performed to support marketing application

- **Carcinogenicity**
  - Not warranted for marketing in oncology patients

- **Immunotoxicity**
  - May evaluate in general toxicology studies for oncology
  - May require more extensive study for known immunomodulators

- **Photosafety testing**
  - Initial phototoxic potential assessment prior to Phase 1 based upon known photochemical properties

-- *S9 Guidance for Industry, 2010*
Components of Nonclinical Drug Development

• Pharmacology Studies/Model Selection
• Safety Pharmacology
• PK/ADME Studies
• Toxicology
• **Starting Dose Selection and Study Design Issues for FIH**
Starting Dose for First in Human Studies in Oncology

• **Goal:**
  – Select a start dose that is expected to have **pharmacological effects** and is **reasonably safe** to use

• Based on **all available nonclinical** data

• Scale up from animal studies
  – For **small molecules**, normalize to body surface area
  – For **biologica**ls, scale to body weight, AUC or other exposure parameters

-- *S9 Guidance for Industry, 2010*
Duration of Nonclinical Toxicology Studies

- **Treatment duration** in Phase 1 oncology may continue according to patients response
  - New nonclinical toxicology studies not required

- **Phase 2 studies** may be supported by existing **nonclinical** and **clinical Phase 1 data**
  - Additional toxicology not required

- **Phase 3 studies** may require **repeat dose studies of 3 months duration**
  - Sufficient to support **marketing**

- **New drug combination** regimens do not require **specialized toxicology studies**
  - In vivo pharmacology studies of the combination may suffice

-- *S9 Guidance for Industry, 2010*
## Treatment Schedules to Support Initial Oncology Trials

*(S9 Guidance for Industry, March 2010)*

<table>
<thead>
<tr>
<th>Clinical Schedule</th>
<th>Nonclinical Treatment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once every 3-4 wks</td>
<td>Single dose</td>
</tr>
<tr>
<td>Daily for 5 days every 3 wks</td>
<td>Daily for 5 days</td>
</tr>
<tr>
<td>Daily for 5-7 days, alternating wks</td>
<td>Daily for 5-7 days, alternating wks (2-dose cycles)</td>
</tr>
<tr>
<td>Once a week for 3 wks, 1 wk off</td>
<td>Once a week for 3 weeks</td>
</tr>
<tr>
<td>Two or three times a week</td>
<td>Two or three times a week for 4 wks</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily for 4 wks</td>
</tr>
<tr>
<td>Weekly</td>
<td>Once a week for 4-5 doses</td>
</tr>
</tbody>
</table>
Oncology Small Molecule Dose Selection

- In oncology, the start dose at 1/10 the severely toxic dose in 10% of animals (STD$_{10}$) in rodents

- If non-rodent is most appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD)
  - HNSTD is the highest dose level that does not produce evidence of life-threatening toxicities or irreversible findings

-- S9 Guidance for Industry, 2010
Biologicals: MABEL Instead of NOAEL, MAYBE?

- New European recommendations based upon *Tegenero* (super agonist CD-28 mAb) FIH disaster
  - EMEA Guidelines, 2007

- **MABEL: minimal anticipated biological effect level**
  - Consider differences in sensitivity for the mode of action across species

- Consider selection of starting doses based upon MABEL determinations depending on **risk and mechanism of action**
  - Immuno-modulatory biologicals typical us MABEL derived starting doses
Calculation of MABEL
(EMEA Guidelines, 2007)

- MABEL calculations should utilize all nonclinical data available, including...
  - Target binding and receptor occupancy data in target cells in vitro
  - Concentration-response curves in vitro
  - Dose/exposure-response in vivo in relevant animals

- Wherever possible an integrated PK/PD modeling approach should be used

- May consider applying a safety factor to the MABEL for the recommended starting dose (i.e., 1/10 MABEL)
Nonclinical Translational Research Strategies in Drug Development
The Drug Discovery & Development Pipeline

Discovery

New Projects Per Year
- Target-to-hit: 24
- Hit-to-lead: 19
- Lead optimization: 15
- Preclinical: 12

Success
- 80%
- 75%
- 85%
- 69%

Time (yr)
- 1.0
- 1.5
- 2.0
- 1.0

Cost (USD)
- $94
- $166
- $414
- $150

Development

Phase I
- 9
- 54%
- 1.5
- $273

Phase II
- 5
- 34%
- 2.5
- $319

Phase III
- 2
- 70%
- 2.5
- $314

Submission to launch
- 1
- 91%
- 1.5
- $48

Launch

Total time = 13.5 years
Total cost = $1.778 billion*

* Capitalized costs

-- Modified from Paul et al, Nature Rev Drug Discov 2010
A Blueprint for a Successful Drug Development Organization

a Traditional
- Scarcity of drug discovery
- Preclinical development
  - CS
  - FHD
  - Phase I
  - Phase II
  - Phase III
  - FED
  - PD
  - Launch

b Quick-win, fast-fail
- Abundance of drug discovery
- Preclinical development
  - CS
  - FHD
  - POC
  - Confirmation, dose finding
  - Higher p(TS)
  - PD
  - Launch

- Increase critical information content early to shift attrition to an earlier, cheaper phase
- Leverage savings from shifted attrition to reinvest in the R&D 'sweet spot'

Paul et al, Nat Rev Drug Discov 2010
Our Translational Strategy

- Focus on **Molecularly Targeted Therapies**
- Integration of **Biomarker Strategies** into clinical development plans
- Utilize a **Model-based Drug Development** approach initiated during preclinical stages
- Implement novel biomarker-driven translational **Phase I FIH study designs**
- **Pharmacological Audit Trail (PhAT)** evaluation in preclinical and early clinical trials
Characteristics of Molecularly Targeted Therapies *(adapted from Paoletti 2005)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cytotoxic Agents</th>
<th>Targeted Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>Cell based, empirical</td>
<td>Receptor based screen, rationale</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Often unknown</td>
<td>Basis for screening</td>
</tr>
<tr>
<td>Pharmacological Effect</td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
</tr>
<tr>
<td>Specificity</td>
<td>Non-selective</td>
<td>Selective</td>
</tr>
<tr>
<td>Dose and schedule</td>
<td>Pulsed, cyclical at MTD</td>
<td>Continuous, at tolerable dose</td>
</tr>
<tr>
<td>Development Strategy</td>
<td>Biomarkers rarely used</td>
<td>Biomarkers for PD/MofA and CoDx for patient selection</td>
</tr>
</tbody>
</table>
The Biomarker Hypothesis
(adapted from Nic Dracopoli)

The use of biomarkers will....

• Improve decision making in early development
  – Early proof of mechanism of action
  – Selection of optimal dose and schedules
  – Better understanding of pharmacological behavior through PhAT evaluation
  – Better Go/No Go Proof of Concept decisions

• Increase probability of technical and registrational success (PTRS) in late stage development
  – Smaller, more focused, enriched study populations
  – Greater magnitude of clinical benefit

• Provide greater benefits for our patients through personalized medicine
  – Enable more cost-effective delivery of healthcare
  – Value-based pricing
  – Faster uptake and higher market penetration
Predictive Biomarker/CoDx Timelines

• Target ID/Valid.
• NME
• Ph I/II
• Ph III
• NDA

• Drug Development Timeline

• PD/MofA Biomarkers
  – Marker ID/Qualification
  – PK/PD Biomarker studies
  – Clinical robustness in tumor and surrogate tissues
  – Aid in PhAT evaluation

• Predictive Biomarkers
  – Marker ID/Qualification
  – In vitro/In vivo confirmation
  – Clinical applicability
  – Exploratory clinical testing
  – Clinical qualification as a co-diagnostic
  – Deliver a companion diagnostic at launch

• Companion Diagnostics
  – Assay and software validation
  – Reagent and instrument manufacture under Quality Systems Regulations
  – FDA submission
  – Co-promotion with Rx
Model Based Drug Development Example

**cMET Inhibition**

Sacrifice a subset at 1, 4, 8, and 24 h (n = 3 per time point)

- Dose at 3.1, 6.3, 12.5, 25, and 50 mg/kg

**Plasma PK Analysis**

**Tumor Growth Inhibition**

**Assay Tumor PD Biomarker**

--Adapted from Yamazaki et al Drug Met Dispos 2008
Model Based Drug Development

**Pharmacokinetics**

**PK in Plasma**

\[ C_p = \left( \frac{F \cdot \text{Dose} \cdot ka}{V \cdot (ka - k)} \right) \left( e^{-t} - e^{-t_{1/2}} \right) \]

**PK Simulation in Tumor**

\[ \frac{dC_e}{dt} = k_c 0 \cdot (C_p - C_e) \]

**Pharmacodynamics**

**cMet Phosphorylation**

\[ E = E_0 \left( 1 - \frac{E_{\text{max}} \cdot C_e}{E_{C50} + C_e} \right) \]

\[ \frac{dT}{dt} = k_{8a} \left( 1 - \frac{E_{\text{max}} \cdot C_p}{E_{C50} + C_p} \right) \cdot T \cdot k_{\text{out}} \cdot T \]

(Plasma PK) → (Tumor PK) → Biomarker Change → Antitumor Activity

(Yamazaki et al Drug Met Dispos 2008)
Translational Phase I Study with Biomarker-Defined Endpoints

- **Expansion Cohorts**
  - Collect mandatory sequential tumor biopsies
  - Examine molecularly defined subsets of various tumor types
  - Early readout on predictive biomarker hypothesis

- **“BED”**
  - Target PD biomarker effect in surrogate tissues or if any clinical activity

- **“MTD”**
  - Potential Phase 2 Dose Range
  - Maximum Tolerated Dose

- **“DLT”**
  - Expansion Cohort 1
  - Expansion Cohort 2
  - Expansion Cohort 3

- Tumor biopsies and/or Predictive biomarker selected pts
Improving Scientific Rigor for Dose Selection
The Pharmacological Audit Trail (PhAT V. 2.02)

Dose-PK/exposure predictable?

Active plasma concentrations achieved?

Target engaged?*

Modulation of downstream pathway?*

Biological effect achieved?*

Target modulating dose sustainable, and tolerable?

Clinical response or benefit?

Predictive biomarkers of activity?

POC population defined?

POC Decision!

Reduce Uncertainty

Reduce Uncertainty

* Requires PD Biomarkers for Dose Selection

-- Modified from Workman et al, Mol Cancer Therap 2003
How is Drug Development Changing?

Historical Approach: A linear, sequential process

Accelerated, Flexible ED Plans: Early efficacy signals trigger acceleration
Accelerated ED Study Designs: Dabrafenib/Trametinib Ph 1/2a/2b

A. Dose Escalation

- MTD or Full MonoRx Dose
- PK, tolerability
- Dose Escalation
- 3+3
- Establish MTD and RP2D

B. Expansion Cohorts

- BRAF mut
- Melanoma
- Dosed at D150/T2

C. Randomized POC Cohorts

- Dabrafenib
  - N = 54
- Dab/Trametinib 1 mg
  - N = 54
- Dab/Trametinib 2 mg
  - N = 54

Endpoints:
PFS, RR, incidence of SqCC

N = 247 patients(!) in parts 1b and 2b enrolled from March 26, 2010 to July 7, 2011 at 16 centers

Flaherty et al 2012
Phase 1 Registration Trials(??!!)

- **Ceritinib**: Small molecule ALK inhibitor with strong activity in crizotinib resistant NSCLC with EML4/ALK translocations
- **Ceritinib Timelines**: IND to approval **3.5 years**!!
- **Phase 1** dose escalation in **59 patients**, expansion **71 pts** for a total of **130 pts**
Summary

- **Nonclinical drug development** involves the collection of key pharmacology, safety, toxicology, and PK/ADME data prior to the initiation of FIH studies
  - Oncology programs have slightly different requirements

- Key period for formulating **Translational Research** plans for clinical development

- **Early phase clinical trials** are rapidly evolving to reflect early evaluation of pharmacologic and clinical endpoints
And Finally….

Translational Medicine

Nonclinical Pharmacology
- Efficacy/Safety
- Traditional animal studies
- PK/PD
- Toxicology
- Biomarkers & Molecular targets

Clinical Pharmacologist
“Model-based drug development”

Early Clinical Trials
- Traditional dose and toxicity endpoints
- Traditional PK/PD Biomarkers & Molecular endpoints
- Patient selection

It is a great time to be in drug development!