Nonclinical Drug Development:

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Translational Medicine Early Development
Oncology Therapeutic Area
Janssen R&D/Johnson & Johnson

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Disclosure Information
Chris H. Takimoto, MD, PhD

Employment: Ortho Biotech Oncology R&D/Centocor R&D, Inc., a member of the Johnson & Johnson family of companies

Stock: Johnson & Johnson

Off Label Use: I will not discuss off label use of any product but I will refer to previously presented Phase I investigational study data
The Drug Discovery & Development Funnel

A chart is shown indicating the % of success, amount of time in years, and cost for drug discovery and development. Total time = 13.5 years and Total cost = $1.778 billion*

* Capitalized costs

Drug Development

Drug discovery & screening

Nonclinical development

Animal scale up

Phase I studies

Phase II studies

Phase III studies

Specific examples from anticancer drug development
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
Goals of Nonclinical Testing of Small Molecule Drugs and Biologicals

- Identify the pharmacologic properties of a pharmaceutical
- Establish a safe initial dose level of the first human exposure
- Understand the toxicological profile of a pharmaceutical
  - e.g., identification of target organs, exposure-response relationships, and reversibility

*S9 Guidance for Industry, 2010*
Anticancer Therapeutics

• Desirable to provide new, effective anticancer drugs more expeditiously

• Used to treat cancer in patients with serious and life threatening malignancies

• Treatment at or close to adverse effect dose levels is common
  – Design and scope of nonclinical studies to support anticancer pharmaceuticals may differ from other therapeutic areas

• Flexible nonclinical data to support Phase 1 studies (in patients)
  – Clinical Phase 1 data sufficient for moving to Phase 2 in 1st or 2nd line therapy in advanced cancer patients

-- S9 Guidance for Industry, 2010
Nonclinical Pharmacology Evaluation

• Select appropriate models based on target and MofA

• These studies can:
  – Provide nonclinical proof of principle regarding mechanism of action and efficacy
  – Guide schedule and dose escalation schemes
  – Provide information for selection of test species
  – Aid in start dose selection
  – Selection of investigations biomarkers
  – Justify pharmaceutical combinations
  – Understand pharmacodynamic properties

-- S9 Guidance for Industry, 2010
Nonclinical Pharmacology Evaluation:
In Vitro Studies

• In vitro studies performed in cell lines, cell-free systems
  – Often form the basis for screening and optimization during discovery
• Cellular uptake and membrane transport
  – MDR, MRP, etc
  – Predictions of bioavailability and distribution
• In vitro drug metabolism:
  – P450 isoenzyme inhibition or induction
• Effects on hERG channels (prolonged QT interval risk)
• Preliminary protein binding studies

-- S9 Guidance for Industry, 2010
Nonclinical Pharmacology Evaluation: In Vivo Studies in Oncology

• Animal screening is too expensive for routine use

• Efficacy demonstrated in disease specific animal models: Proof of therapeutic principle
  – Groundwork for clinical development planning

• Evaluation of therapeutic index
  – Toxicity versus efficacy

• Animal pharmacokinetics can guide dose and schedule selection
  – ADME data can be generated in parallel with clinical development

• Preliminary evaluation of candidate biomarkers

-- *S9 Guidance for Industry, 2010*
Ideal Animal Model

- Validity
- Selectivity
- Predictability
- Reproducibility

“There is no perfect tumor model”
Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth

Photo of an Endostatin-treated rat and a saline-treated rat. The saline treated rat has a very large tumor whereas the Endostatin-treated rat does not.
In Vivo Efficacy Models in Cancer

• Spontaneous tumors
  – Idiopathic
  – Carcinogen-induced
  – Transgenic/gene knockout animals: p53, RB, etc

• Transplanted tumors
  – Animal tumors: Lewis lung, S180 sarcoma, etc
  – Human tumor xenografts: human tumor lines implanted in immunodeficient mice (current NCI standard in vivo efficacy testing system)
  – Human tumors growing in vivo in implantable hollow fibers
Human Tumor Xenografts

• 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
Athymic Nude Mice

Six photos of Athymic nude mice
Murine Xenograft Sites

• Subcutaneous tumor (NCI method of choice) with IP drug administration
  • Intraperitoneal
  • Intracranial
  • Intrasplicenic
  • Renal subcapsule
  • Site-specific (orthotopic) organ inoculation
Inhibition of Tumor Growth in Human Prostate Cancer Xenografts

Plot showing tumor volume (mm$^3$) over days post injection. The tumor volume increases with days post injection.

Photo of a rat with no tumor growth on one side and rapid tumor growth on the other side

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

Many different human tumor cell lines transplantable

Wide representation of most human solid tumors

Allows for evaluation of therapeutic index

Good correlation with drug regimens active in human lung, colon, breast, and melanoma cancers

Several decades of experience
Xenograft Disadvantages

Brain tumors difficult to model

Different biological behavior, metastases rare
   Survival not an ideal endpoint: death from bulk of tumor, not invasion

Shorter doubling times than original growth in human

Less necrosis, better blood supply

Difficult to maintain animals due to infection risks

Host directed therapies (angiogenesis, immune modulation) may not be applicable
   Human vs. murine effects
   Ability to mimic the human tumor microenvironment is limited
Other Efficacy Models

Orthotopic animal models: Tumor cell implantation in target organ
  Metastatic disease models
Transgenic Animal Models
  P53 or other tumor suppressor gene knockout animals
  Endogenous tumor cell development
  May be of high value for mAb therapies
Three-dimensional co-culture models
  Reconstitution of the tumor microenvironment
Low passage xenograft tumors
  Direct implantation from patients to animals
Nonclinical Safety Studies

Safety pharmacology
Pharmacokinetic and toxicokinetics studies
Genotoxicity studies
Reproductive toxicity studies
Carcinogenicity studies
Formal toxicology studies
  Single dose toxicity studies
  Repeated dose toxicity studies
Excellent references
  For oncology agents, FDA Guidance for Industry, S9 Nonclinical evaluation for anticancer pharmaceuticals, March 2010
Nonclinical Toxicology Studies in Oncology

GLP Toxicology is expected
   Use the same route and formulation
   Use the approximate clinical schedule

For small molecules, general toxicology testing usually includes rodents and non-rodents (i.e., dogs)
   Non-human primates for biologicals

Assessment of the potential to recover from toxicity should be provided

Embryofetal toxicity studies of oncology agents should be available when marketing application is submitted

Genotoxicity studies not essential for clinical trials in advanced cancer
   Perform to support marketing

Carcinogenicity studies not warranted for advanced cancer

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

(S9 Guidance for Industry, March 2010)

The Clinical schedule and the nonclinical treatment schedule are listed.
Maximum Recommended Starting Dose (MRSD) for FIH Trials

Step 1: Determination of the No Observed Adverse Effect Level (NOAEL)

Step 2: Conversion of NOAEL to Human Equivalent Dose (HED)

Step 3: Selection of the most appropriate animal species

Step 4: Application of a safety factor to determine MRSD

Step 5: Compare MRSD with pharmacologically active dose (PAD)

Selection of MRSD

(FDA Guidance 2005)
Selection of MRSD
(FDA Guidance 2005)

Flow chart of this selection process is shown.
Step 1: Determination of No Observed Adverse Effect Level (NOAEL)

NOAEL Definition
The highest dose level that does not produce a significant increase in adverse effects in comparison to the control group
Not the same as the no observed effect level
Review all available data in all species tested
Adverse events can be overt toxicities, surrogate laboratory markers, or exaggerated PD effects
   Adverse effects defined as events that are considered unacceptable if produced by the initial dose in a Phase I clinical trial

-- FDA Guidance for Industry July 2005
Step 2: Convert Animal Dose to Human Equivalent Dose (HED)

Normalization of toxic dose levels across species often based upon body surface area. Deviations from BSA normalization must be justified.

Animal dose in mg/kg is converted to mg/m$^2$ and reconverted to mg/kg. Many cancer treatments are dosed based on BSA (mg/m$^2$).

-- FDA Guidance for Industry July 2005
HED Calculation

\[
\text{HED (mg/kg)} = \frac{\text{Animal Km} \times \text{Animal Dose (mg/kg)}}{\text{Human Km}}
\]

**Km: mg/kg to mg/m}^2 \text{ conversion factor**}

- Adult human = 37
- Child (20 kg) = 25
- Dog = 20
- Mouse = 3
- Rat = 6
- Cynomolgus, rhesus or stumptail monkey = 12

-- FDA Guidance for Industry July 2005
Exceptions to BSA Scaling

Weight based (mg/kg) scaling
- Oral therapies limited by local toxicities
- Exposure parameters that scale by weight predict toxicity
  - Example Cmax for antisense molecules
- Proteins administered IV with Mr > 100,000

Other scaling factors
- Alternate routes of administration (e.g. topical, intranasal, subcutaneous, intramuscular
  - Normalize to area of application or to mg
- Administration into anatomical compartments with limited outside distribution (e.g. intrathecal, intravesical, intraocular, or intrapleural)
  - Normalize to compartmental volumes
Step 3: Most Appropriate Species Selection

After the NOAEL from all toxicology studies are converted to HED, then the MRSD must be derived from the most appropriate species.

By default, use the most sensitive species, but must also consider…

- Pharmacokinetic ADME differences
- Class pharmacodynamic effects
- Agent pharmacology, receptor cross reactivity, etc

Example

- Phosphorothioate antisense DLT in humans and monkeys is complement activation
- Does not occur in rodents

-- FDA Guidance for Industry July 2005
Step 4: Application of a Safety Factor

Applied to the HED derived from the NOAEL from the most appropriate species
Divide the HED by the safety factor to determine the MRSD
By default, a safety factor $= 10$ is recommended
   May raise or lower with justification
Altering the Safety Factor

Increasing the safety factor
- Steep dose response curve
- Severe toxicities anticipated
- Non-monitorable toxicity
- Toxicities without premonitory signs
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large PK variability
- Non-linear PK
- Inadequate dose-response data
- Novel therapeutic target
- Animal models with limited utility

Decreasing the safety factor
- Requires highest quality toxicology data
- Well characterized class of drugs
- If NOAEL is based on toxicity studies of longer duration than the proposed clinical trial
Step 5: Adjustments Based on the Pharmacologically Active Dose

If a robust estimate of the pharmacologically active dose (PAD) is available from preclinical studies
Convert to HED and compare to the MRSD
If PAD < MRSD consider decreasing the starting dose
In oncology, the start dose at 1/10 the severely toxic dose in 10% of animals (STD10) 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?

In the wake of the Tegenero FIH disaster, new recommendations exist for starting dose selection in Europe
EMEA Guidelines, 2007

MABEL: minimal anticipated biological effect level
   The anticipated dose level leading to a minimal biological effect level in humans
Consider differences in sensitivity for the mode of action across species

Consider selection of starting doses based upon reduction from the MABEL, not NOAEL dose
Calculation of MABEL

(*EMEA Guidelines, 2007*)

MABEL calculations should utilize all in vitro and in vivo information from PK/PD experiments, including…

- Target binding and receptor occupancy data in target cells in vitro in human and animals
- Concentration-response curves in vitro in target human cells and dose/exposure-response in vivo in relevant animals
- Exposures at pharmacological doses in relevant animals

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

Apply a safety factor to the MABEL for the recommended starting dose

If NOAEL method gives a different estimation, use the lowest value unless otherwise justified
The Biomarker Hypothesis

(adapted from N Dracopoli)

Increase probability of technical and registrational success
  Predictive toxicology
  Early proof of mechanism of action
  Deeper PK/PD exploration
  Precise determination of biologically effective dose

Permit focused clinical studies with higher probability of demonstrating clinical benefit
  Adaptive trial designs
  Prospective screening of patients for enrollment in clinical trials

Enable more cost-effective delivery of healthcare
  Personalized medicine
  Value-based pricing
Biomarkers in Drug Development

Pharmacodynamic/Mechanism of Action Biomarkers

Inform about a drug’s pharmacodynamic actions

Most relevant to early development

Dose and schedule selection

Define pharmacological behavior in patients

Goal: Improve efficiency of early development

Predictive Biomarkers

Identify patients who will/will not respond to treatment

Most relevant to mid/late development

Basis for stratified/personalized medicine

Develop co-diagnostic biomarker assays

Goal: Enrich treatment population to maximize benefit
An Oncology Example:
How Preclinical Studies Can Drive Clinical Drug Development
Why New Strategies for Oncology Drug Development are Needed

Poor efficiency of historical oncology drug development efforts
  Yet costs continue to rise
  Oncologic diseases face specific challenges

Modern treatments are molecularly targeted in contrast to conventional cytotoxic chemotherapy
  Previously, mechanism of action was irrelevant to clinical trial design

Emphasis on biomarkers and individualized drug therapies
FDA's Critical Path Report 2004: Innovation or Stagnation?

- Biomedical Research Spending 1993 - 2000

This plot shows how spending has risen from 1993 through 2003.

- New NDA and BLA FDA Submissions 1993 - 2000

This plot shows the overall downward trend in NDA and BLA FDA submission from 1993 through 2000.

- -- Challenge and Opportunity on the Critical Path to New Medical Products, FDA, March 2004
Clinical Success by Therapeutic Area

A bar chart illustrating this success is shown and the success of oncology at approximately 5% is highlighted.

Nature Reviews/Drug Discovery

• -- Kola and Landis, Nature Rev Drug Discov 2004
## Characteristics of Molecularily 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>Cytoxic</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 for decision making is rare</td>
<td>Biomarkers for PD/MofA and patient selection</td>
</tr>
</tbody>
</table>
Our Strategy

Pharmacological Audit Trail (PhAT) evaluation in preclinical and early clinical trials

Model-based Drug Development approach initiated during preclinical stages

Novel Translational Phase I FIH study designs with formal biomarker-defined endpoints
The Pharmacological Audit Trail

The title portion of a commentary in Vol. 2 131-138, February 2003 Molecular Cancer Therapeutics page 131 is shown that reads as follows:

COMMENTARY

“Auditing the Pharmacological Accounts for Hsp90 Molecular Chaperone Inhibitors: Unfolding the Relationship between Pharmacokinetics and Pharmacodynamics¹

Paul Workman², Cancer Research UK Center for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey SN2 RNG United Kingdom”

The beginning of the article, and most of the article are not shown.

A photograph of the author, Dr. Paul Workman, is shown.
The Pharmacological Audit Trail

- A series of sequential questions or benchmarks to evaluate in early drug development
  - Likelihood of failure decreases as each successive benchmark is addressed
- Stepwise approach to proof of principle
  - Modulation of the intended target results in clinical benefit
- Organize strategic thinking about early development assets
  - Allows for critical decision making based upon biomarker and clinical endpoints
- Applies equally to preclinical and early clinical development
The Pharmacological Audit Trail (PhAT)

(modified from Workman et al, Mol Cancer Therap 2003)

A flow chart is shown illustrating this audit trail.
Requirements for Preclinical PK-PD Modeling: Example cMET Inhibition
# Unified Preclinical PK-PD Biomarker Model Prior to Clinical Testing

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma PK → Tumor PK</td>
<td>Biomarker → Antitumor Change Activity</td>
</tr>
</tbody>
</table>

(Yamazaki et al Drug Met Dispos 2008)
PK-PD Model-Based Drug Development

Model-Based Drug Development
Preclinical PK/PD/biomarker models with direct relevance to clinical setting

Requires extensive resource investment
preclinical pharmacology studies
Discovery Research -- Clinical Pharmacology
Biomarkers -- Clinical/Transl Medicine

Essential for evaluation of the PhAT benchmarks in first-in-human Phase 0 or 1 clinical trials
But how do we incorporate this approach into our early development clinical trial designs?
A New Approach

Translational Phase I study with Biomarker Defined Endpoints
   A new study design for targeted oncology agents

PD/MOA biomarkers are formal study endpoints
   Biologically effective dose (BED): biomarker defined
   Maximum tolerated dose (MTD): toxicity defined
   Recommended Phase 2 dose range: toxicity and biomarker defined

Allows for the objective evaluation of the PhAT benchmarks
Translational Phase I Study with Biomarker-Defined Endpoints

Flow chart identifying the endpoints

Biologically effective dose (BED) defined in by
Prespecified change in biomarker seen in a defined fraction of patients, or
Any clinical antitumor activity
Maximum tolerated dose (MTD) defined in standard manner
Expansion cohorts have mandatory tumor biopsies
Phase 2 dose range defined by BED in tumor biopsies and by MTD
New Phase I Study Design Requirements

Validated/qualified PD/MOA biomarker assay
  Robust and reproducible

Measurable signal in normal and malignant tissues
  Surrogate tissues: skin, buccal mucosa, PBMC, etc.
  Tumor biopsies

Prestudy definition of a positive biomarker signal
  What change is associated with antitumor activity?

Phase I centers and study support staff comfortable with tissue biopsies
Example
Phase 1 Pharmacokinetic (PK) and Pharmacodynamic (PD) Study of JNJ-26854165 (Serdemetan*) in Patients with Advanced Refractory Solid Tumors

Josep Tabernero¹, Luc Dirix², Patrick Schöffski³, Andrés Cervantes⁴, Jose Antonio Lopez-Martín⁵, Jaume Capdevila¹, José Baselga¹, Ludy van Beijsterveldt⁶, Brett Hall⁶, Hans Winkler⁶, Silvija Kraljevic⁶, Janine Arts⁶, Sen Hong Zhuang⁶

¹Vall d’ Hebron University Hospital, Barcelona, Spain; ²AZ Sint Augustinus, Wilrijk, Belgium; ³University Hospitals Leuven, UZ Gasthuisberg, Belgium; ⁴Hospital Clínico Universitario de Valencia, Spain; ⁵Hospital Universitario 12 de Octubre, Madrid, Spain; ⁶Ortho Biotech Oncology Research and Development, a Division of Johnson & Johnson Pharmaceuticals, Beerse, Belgium
JNJ-26854165: Serdemetan, A Novel Oral Anticancer Agent

Designed to modulate p53 expression

Increased p53 levels lead to:
  Apoptosis
  Senescence
  Cell cycle arrest
  Block of angiogenesis & metastasis

Chemical structure of JNJ-26854165
Study Design

Standard 3 + 3 patient Phase I dose escalation design
  Toxicity defined endpoints: Dose limiting toxicity (DLT) and Maximum tolerated dose (MTD)

Continuous PK-PD monitoring
  Pharmacokinetics: standard PK profiling, drug-drug interaction (DDI) profile and food intake effect

Pharmacodynamic (PD) activity
  Sequential and skin biopsies in all patients for IHC for p53, Ki67, TUNEL
  Selected tumor biopsies for IHC (similar to skin)
  Plasma: MIC-1 (p53 response gene product), CK18 (apoptosis); LC/MS: proteomics and metabolomics

Anti-tumor activity
### Actual Dose Escalation Cohorts

<table>
<thead>
<tr>
<th>Cohort No.</th>
<th>Dose (mg QD)</th>
<th>Number of patients treated (evaluated*)</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>4</td>
<td>4 (3)</td>
<td>None</td>
</tr>
<tr>
<td>C2</td>
<td>8</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>C3</td>
<td>20</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>C4**</td>
<td>40</td>
<td>4 (3)</td>
<td>None</td>
</tr>
<tr>
<td>C5</td>
<td>60</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>C6</td>
<td>90</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>C7</td>
<td>150</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>C8</td>
<td>225</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>C9</td>
<td>300</td>
<td>7</td>
<td>1 (Gr 3 QTc)</td>
</tr>
<tr>
<td>C10</td>
<td>350</td>
<td>4 (3)</td>
<td>None</td>
</tr>
<tr>
<td>C11</td>
<td>400</td>
<td>3</td>
<td>2 (Gr 3 QTc, Gr 3 rash)</td>
</tr>
</tbody>
</table>

* Subjects evaluated for DLT determination

** Drug Drug interaction (DDI) cohort
Clinical Pharmacokinetics

Two plots are shown
Pharmacodynamics – p53 induction in skin
Pharmacodynamics  p53 induction in skin

Four skin biopsies are shown.

Patient #5013
300 mg

\[ C1D1 = 9.4\% \]

\[ C1D21 = 61.5\% \]

Patient #5014
300 mg

\[ C1D1 = 4.6\% \]

\[ C1D21 = 58.6\% \]

(p3 IHC; percentage of p53+ nuclei)
JNJ-26854165 Phase I Study

Flow chart

- Active PK plasma concentrations achieved based upon animal studies
- Biologically effective dose (BED) defined in by p53 change in skin biopsies
- DLT and MTD defined by toxicity endpoints
- Range of potential Phase 2 doses to be explored in expansion cohorts with tumor biopsies
PhAT Phase I Evaluation of JNJ-26854165 (Serdemetan)

Flow chart
Phase I Study of JNJ-26854165 (Serdemetan)

Study accrual is completed

This trial was not originally designed with formal biomarker-defined endpoints, but clinical trial data matches well with this study design

Further work on this class of agents is ongoing
Conclusions

PK-PD model-based drug development is the cornerstone for our early development strategy
    Requires substantial investments in preclinical testing

The Pharmacological Audit Trail can help organize strategic thinking for the early development of molecularly targeted therapies

Novel study designs are required for the optimal implementation of this strategy
    Example: Translational Phase I study with biomarker-defined endpoints

It is a great time to be working in oncology drug development!!
And Finally….

TRANSLATIONAL MEDICINE

Preclinical Pharmacology  Clinical Pharmacologist  Early Clinical Trials

“Model-based drug development”  Traditional dose and toxicity endpoints

Traditional Animal studies  Development
PK/PD Toxicology

Biomarkers & Molecular targets  Traditional PK/PD Biomarkers & Molecular endpoints Patient selection

What is the biggest secret about drug development?

“It is all Clinical Pharmacology!!”