CIRM Critical Path Workshop

Designing Preclinical Studies to Optimize FIH Studies

Joy Cavagnaro, PhD, DABT, ATS Fellow, RAC, Fellow RAPS

jcavagnaro@accessbio.com

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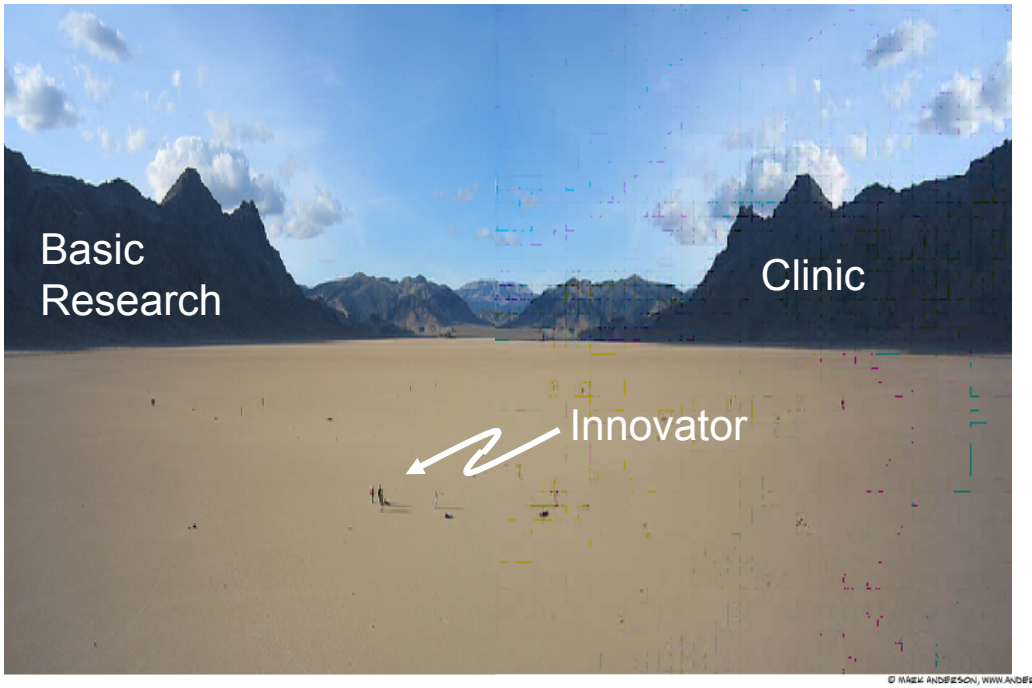
Access BIO

First clue that the latest medical breakthrough isn't quite there yet.

We have had much success in navigating a path for developing safe and effective medicines for mice!

The Critical Path



Directions for novel therapies

Why drugs fail in late stage trials

Late-stage failure

Root causes of Phase III trial failures

Driver		Definition	Failures, % (n = 73)	
Efficacy vs placebo		Failure to demonstrate significant difference from placebo in treatment effects	50	50
Safety vs placebo	Confirmation of early safety concerns	Safety issues that were either raised in earlier trials or seen in similar class of on-market compounds	8	31
	Unclassifiable	Inability to determine from outside-in the cause of safety failure (includes compounds that failed with prior signals and idiosyncratic safety issues)	23	
Lack of differentiation	Efficacy	Given similar safety profile, failure to demonstrate superior efficacy vs an active comparator	16	19
	Safety	Given similar efficacy, failure to demonstrate superior safety vs an active comparator	3	

Source: EvaluatePharma; Pharmaprojects; McKinsey analysis

Animals may not have been predictive **Humans were definitely not predictive!**

Challenges for Novel Therapies

The Preclinical Dilemma

- Schizophrenic use of data
  - Believe efficacy
  - Question toxicity (e.g. increased sensitivity of species)
- Inefficient use of "proof of concept" models
  - Active dose (+/- dose response)
  - Rarely include safety endpoints
- Concern about seeing toxicity in a toxicity study
  - Dose extrapolation (conservative)
  - Use of normal animals to assess toxicity and extrapolate to patients (may not reflect physiology)
- Designed to satisfy a discipline
  - ...rather than providing answers to questions for clinical decision-making

The Clinical Dilemma

- By definition are potentially high risk due to uniqueness / novelty
  - Proposed patient population also most likely to show toxicity (related or unrelated AEs)
  - Defining risk vs. benefit?
    - Continuing development?
  - "Irresistible urge" to continuously improve the product
  - Initial FIH in patients (vs. HNV) to assess safety but also "some activity" **cure ????**

But The Major Challenges

- "The **scientist** whose hard-fought, extramurally funded survival comes mainly from mechanistic, discovery-based science may have few resources to indulge in the opined "importance" of independently replicating experiments using different …models
  - The **vast majority of scientists** would find large-animal unattainable, even if the validated injury modes were widely available to confirm efficacy in such species."

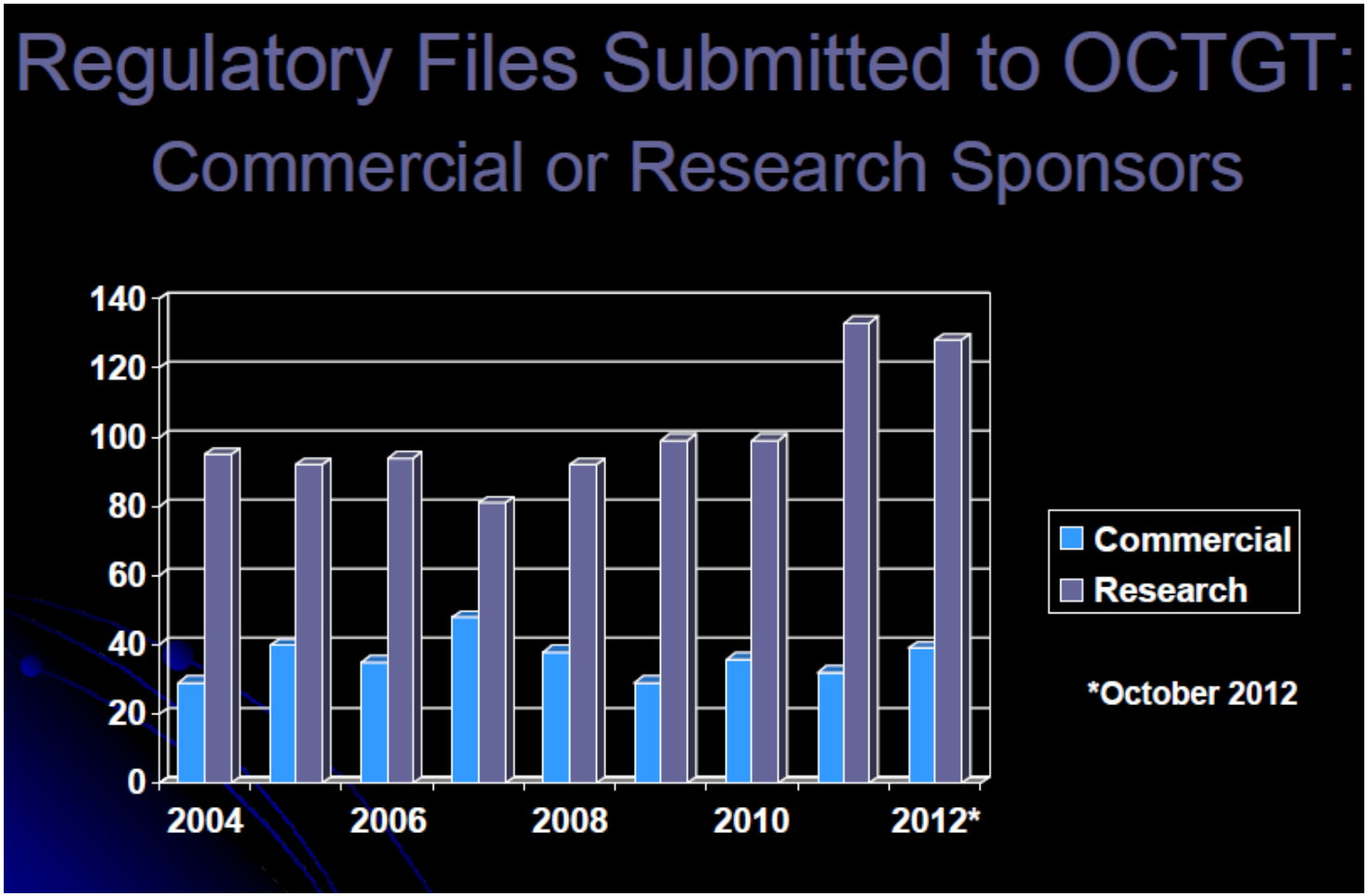
- "**Industry sponsors** …have entirely valid intellectual property issues that may clash with the scientific mantra of peer-reviewed dissemination."

- "**Full-time clinicians**, eager to try anything that appears to be safe and efficacious on their patients….have little interest in waiting for an endless stream of animal experiments."

Kwon et al. J (2010) Neurotrama 27:21-33

Regulatory Hurdles?

Clinical Investigation vs. Development?



Favorite Sponsor Quotes as a Regulator

"We' re talking regulatory now…not science."??

"My study is 70% GLP is that OK?"

Most Frequent Question as a Consultant

"What is the least amount I have "To DO" to get into the clinic?"

DIDYADOO?

	Biopharmaceuticals	Pharmaceuticals
Off-target screening	■TCR **required** for mAbs and mAb derivative	■**Required**
Safety pharmacology	■ Some endpoints **may be** incorporated into general toxicology studies	■Stand alone studies (rodent and non-rodent) **required**; some cases combined
Genotoxicity testing	■**Generally not required**	■**Required**
General toxicology **(2wk, 4wk, 13wk, 6mos, 9mos/12 mos)**	■**Generally** up to 6 months – rodent and non-rodent ■May only have one relevant species	■Up to 6 months rodent **required** ■Up to 9 to12 months non-rodent **required** ■**Requires** 2 species
Reproductive toxicology **(Seg I, II, III; I/II, II/III etc)**	■**May be** conducted in one species only	■**Required** ■Generally **requires** 2 species (rat and rabbit)
Carcinogenicity testing	■**Case-by-case** assessment	■**Required** (2 species)
Local Tolerance	■ **Generally** incorporated into general tox studies	■**Required**
Phototoxicity testing	■**Generally not required**	■**Required** for drugs that absorb in the 290-700 nM range
Metabolic profiling	■**Not done**	■**Required**

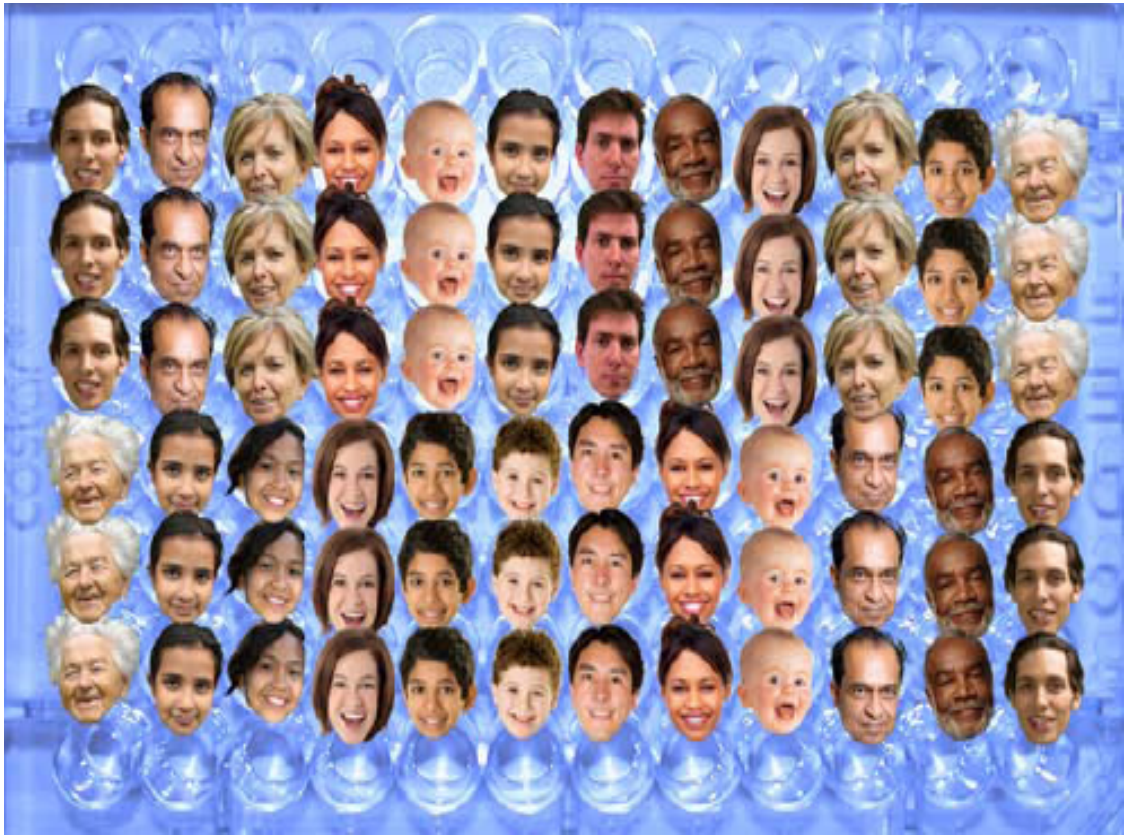
Flashback ….circa 199X

'FDA should not require animal studies to support FIH of human cancer vaccines'

"FDA No Longer Requires Preclinical Studies to Support First in Human Trials"

Cavagnaro- Gene Therapy Meeting
Williamsburg, 199X

But if it were true…
how best to go from
“plate-to-people”…“dish- to-dose”?



Lack of Preclinical Safety Data

- Design of clinical trial?
  - Don't know how high you can go, so start very low
  - Don't know how fast you can go, so go very slow
  - Don't know what to monitor, so have to monitor "everything"
  - Don't know how long to monitor, so have to monitor for a "long time"
  - Don't know who "best" to include
  - Don't know who "best" to exclude
- Faster to… endpoints, approval, patients?
- Cost savings?

Predictive Value of Animal Efficacy Studies?

Genomic responses in mouse models poorly mimic human inflammatory diseases

Seok et al. (2013) PNAS-Feb 11

Concordance of preclinical and clinical pharmacology and toxicology of therapeutic monoclonal antibodies and fusion proteins: cell surface targets

Bugelski and Martin (2012), BJP 166:823-846

Translational Research in Spinal Cord Injury: A Survey of Opinion from the SCI Community

Kwon et al. J Neurotrama 27:21-33 (2010)

Preclinical Toxicity

- Findings that modify clinical development
  - Cross-reactivity (e.g. endogenous molecules, tissues)
  - Narrow therapeutic index
  - Similar toxicity (across species, within a product class)
  - “Difficult to monitor” target organ effects

Preclinical Toxicity

- Findings that modify clinical development
  - Delayed toxicity
    - Infection
    - Neoplasia
  - Transmission of infection/ disease
  - Enhanced toxicity
    - Duration
    - Disease model

Species/Animal Model Selection

- Key considerations when no relevant species
  - Use transgenic animals
    - Humanized (e.g. expressing human receptor-use of clinical material)
    - KIs (e.g. assess worst case-over expression)
    - KOs (e.g. assess worse case- maximum inhibition)
    - Capability to generate stable phenotype
      - Acceptable fecundity
    - Demonstration: similar pharmacological activity
    - Determine comparability for extrapolation
      - e.g. epitope density, localization/compartmentalization, turnover expression, signal transduction pathways, regulation, etc.

Use of animal models of disease to assess preclinical toxicity

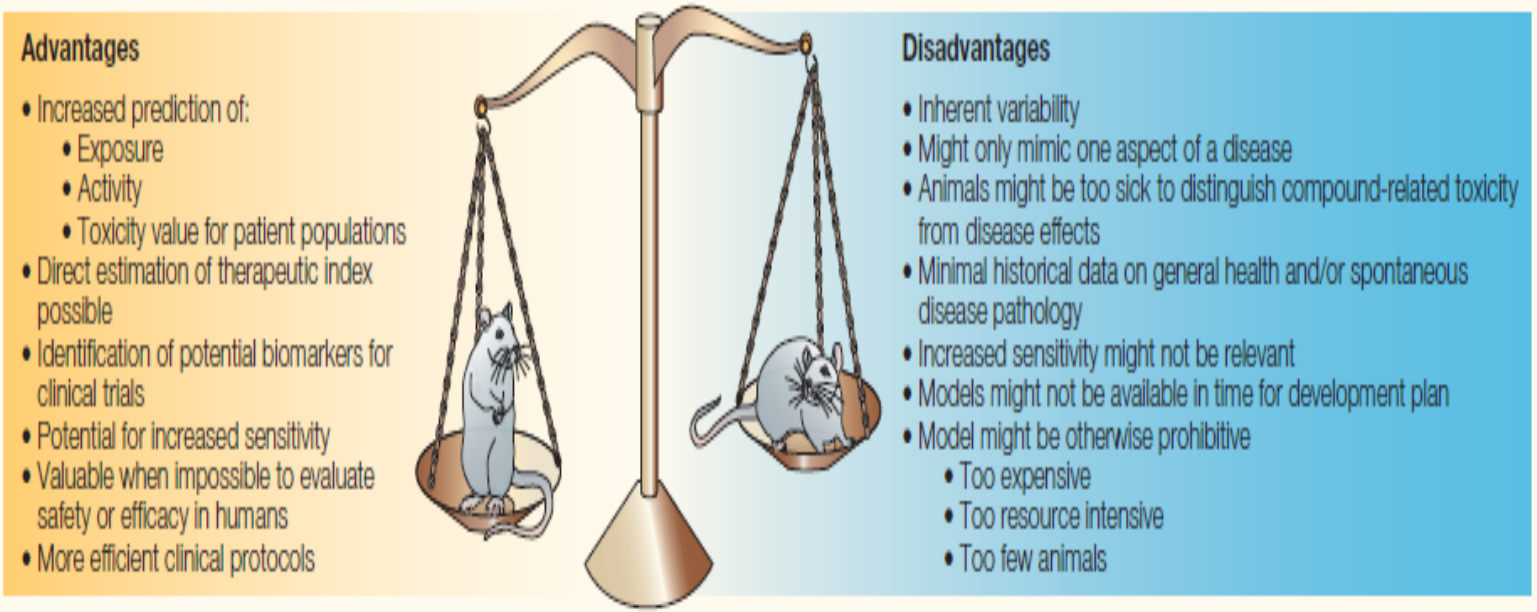


Figure 2 | **Weighing the advantages and disadvantages of testing biotech products in animal models.**

Cavagnaro (2002) Nat Rev Drug Discov 1: 469-475

A New Approach to Preclinical Evaluation
"Case-by-case" approach (late 80s/early 90s)

- Is **not** …
  - a **minimalist** approach
  - consistent with **"traditional practices"** for pharmaceuticals –i.e. checklist
  - **Easy to predict** if "acceptable" to regulatory authorities

- **Must…**
  - **establish effective dialogue** between developer and regulator
    - to ensure success

- Is…
  - **science-based, questions-based**, data driven, practical
  - consistent with **"traditional principles"**
  - **targeted based upon product attributes**
  - designed to obtain maximum information with judicious animal use
  - rational, **limitations/** knowledge gaps are **identified**
  - **flexible**, based on knowledge base
  - **innovative**, as new models to replace "outdated" models to answer new questions are ongoing activities

Preclinical Development of Biological Drugs

WHY "Case-by-Case" Approach

"All mAbs are not created equal"

- Structure
  - Whole molecule or fragment
  - Murine, chimeric, humanized, fully humanized
  - Different isotypes
  - Produced in various cell substrates including transgenic animals
  - Monospecific, bispecific, trispecific…
  - Naked or conjugated
  - Uniquely species specific (human or chimp), NHP only, broad specificity, no target or off-target binding in any "normal" animal species – [consideration of homologous/analogous/ surrogate molecules]
- Function
  - Antagonist (bind to target and block interaction) or agonist (bind to receptor and turn on downstream process)
  - Endogenous epitope or foreign epitope
  - Catalytic antibodies
- "Antibody-like" molecules
  - Fc fusion molecules
  - Peptibodies

WHY "Case-by-Case" Approach

"All cell-based therapies not created equal"

- Source of cells/donor tissue
- Heterogeneity of cell cultures; cell products
- X potency; X differentiated or "stemness"
  - Toti, Pluri, Multi
  - Un, Partially, Fully
- Degree of foreignness
  - Autologous; Allogeneic; Xenogeneic
- Reactivity to environment
- Disease specificity
- Dependency on survival for function?
- Uncontrolled proliferation?

- For Example
  - Peripheral- & cord blood-derived stem cells
  - Progenitor or differentiated cells derived from various types of human tissues, ESCs, iPSCs
  - Cells derived by transdifferentation
  - Modified cells (e.g. engineered T cells)
  - Differentiated cells, e.g. islet cells, cartilage cells etc.

Product Attribute	Cell-based therapy	Biopharmaceutical (mAb)	Pharmaceutical
Manufacture	Biological cell/tissue	Biological synthesis	Chemical synthesis
Purity	"Heterogeneous"	Heterogeneous mixture	Homogeneous – typically a single species
Impurities	Difficult to qualify	Easy to qualify	Easy to qualify
Potency	Needed (Difficult)	Needed	Not needed
Delivery System	Sometimes device	Generally simple formulation	Complex
Dose Interval	Once, intermittent	Intermittent	Often daily
Half-life	Months/years/ lifetime	Days to months	Minutes to hours
Species Specificity	Generally	Sometimes	Relatively species independent
Toxicity	Usually related to MOA and/or host response	Related to exaggerated pharmacology or non-toxic	Often unpredictable; metabolites
Immunogenicity	Often-requiring immuno-suppressive Rx	Often	Hypersensitivity/ Allergic rxns-rare

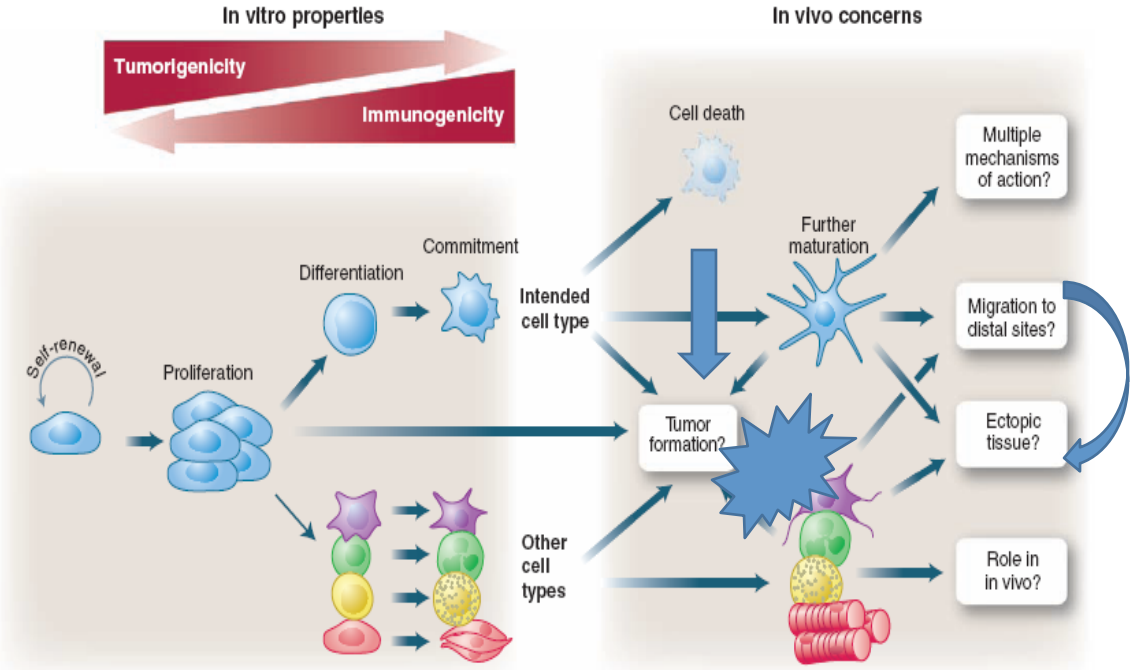
Principle	Practice Cell-based	Practice Biopharmaceutical (mAb)	Practice Pharmaceutical
Test article	Clinical candidate; sometimes animal analogue	Clinical candidate; animal analogues	Clinical candidate
PK/ADME	Cell migration; cell trafficking; site for intended activity, distribution outside target site, migration at local site, time course	Generally PK and absorption; distribution limited by size; catabolized, CYP450 independent	PK/ADME; wide distribution; metabolized by CYP450 and other enzymes to active and non-active metabolites
Route of administration	Access of anatomic site with intended delivery device	Generally via IV or SC	Generally oral or topical
Dose Levels	Safety margin or maximum feasible dose (MFD); optimum biological dose (OBD) based on BW, BSA or target area.	Safety margin or MFD, No observable adverse effect level (NOAEL), pharmacologically active dose (PAD), Minimal active biological dose (MABEL) based on body weight (BW)	Generally MTD; highest non severely toxic dose (HNSTD); NOAEL based on body surface area (BSA) to calculate human equivalent dose (HED)

In vivo safety concerns for stem-cell based products

- **Ectopic tissue formation-** process by which normal tissue forms in an abnormal anatomic location

- **Tumorigenicity**- process by which transplanted cells [grown in tissue culture] grow into tumors following administration to host

- **Oncogenicity**-process by which administration of cell based therapies or contaminants promote neoplastic processes leading to tumors in host tissue



Fink 2009

Case-by-Case Approach: What is the Question?

- What is the optimal procedure/route/anatomical site for product delivery?
- What is the optimal timing for product delivery?
- Where does the product go?
- Will repeat administration be needed?
- Will chronic immune suppression be needed?
- What is the risk/benefit for the planned patient population?
  - Is there potential to see any activity in early trials?
- Is the proposed FIH in a disease and/or vulnerable population?

Preclinical Toxicity Study Design

- Ideally
  - Conducted in one or more relevant species
  - Use of test article representative of the clinical material
  - In some cases analogous/homolgous/surrogate material
  - ROA similar to intended clinical ROA
    - Use of similar delivery devices
  - Frequency and duration equivalent or longer than the clinical trial
  - Assessment of dose multiple to provide a margin of safety
    - Definition of safe starting dose and dose escalation scheme

Need to Know

- Test article [clinical candidate or analogous product]
- What are the best assays to characterize the cellular product?
- How best to deliver the cells?
- What is the fate of the cells?
- What is the toxicity of the cells “off –target; on-target”
- Impact of other drugs on safety and efficacy
- What are the specific risks/benefits in the intended population?

Specific Challenges for Cell-based Therapies

- Dose administration
  - concentration, volume, optimal site of delivery (location of injection), number of injections, cell stability etc.
- Dose extrapolation
  - # cells delivered- expanded; encapsulated, scaffold, sheet
  - Scaling factors (e.g. BW, BSA, target organ)
  - Cross species validation?

Toxicology Study Design Considerations- ”**The Practice**” Cell-basedTherapies

- Normal animals or animal models of disease
- Appropriate controls
  - Placebo, sham, positive
- Mimicking clinical treatment as closely as possible
  - Product, ROA [device?], formulation including cell concentration (cells therapy), device, dose regimen etc.
  - Timing of administration relative to disease/injury
    - “window of opportunity”
- Consider interim, term, recovery assessments
- Reasonable group size
  - Generally 5-10 sex/time point [rodents]; 4-6/sex/time point non-rodents
  - Plan for attrition based upon surgical procedure/ disease model-
    if applicable [could be as high as 50%]

Specific Toxicological Endpoints Included in Study Designs

- Endpoints –"over time"
  - Mortality, clinical observations, BW, food consumption, specific assessment of site of delivery, clinical labs, specific biomarkers, specific functional assessments, non-invasive imaging modalities, gross pathology, histopathology (special stains e.g. HuNA, Ki67)
    - Morphological alterations in either target/non-target tissues
      - Macroscopic and microscopic
- Tumorigenicity potential [stem cell-based therapies] –dose, controls, study duration, sensitivity, validity?

Overall considerations for tumorigenicity assessment

General

- Data interpretation
- Risk/Benefit
- Target patient population
- Need for immunosuppression; duration
- Long term follow up -patients

Cell Specific "case-by-case"

- Proliferative capacity of the cell product
- Cytogenetic stability
- End of production limit
- Availability of relevant animal model
- Route of administration/site of delivery
- Mode of action
- Maximum feasible dose
- Positive Control
- Study Duration

Regulatory Expectations

- IND submissions
  - Provide complete study reports for all preclinical studies used to support the safety and rationale of proposed clinical trial(s)
    - Prospectively defined protocol and protocol amendments
      - Describe “GLPness”
    - Detailed description of the study design (e.g. description of animals species/models, control and test articles used, dose levels, detailed procedures for test article administration and collection of all study protocol parameters.)
    - Results of all parameters evaluated for each animal on study
    - Analysis and interpretation of study data

Making the Case for Case-by-Case Approach for Preclinical Development

- "Case-by-case"/Science-based/Questions-based
  - Product-specific design of programs
  - Defined by studies to ask specific questions
    - To support clinical decision-making
  - To obtain maximum information
    - Judicious use of animals
  - Modified, based upon knowledge base
  - NOT a minimalist approach
  - Limitations/knowledge gaps are identified
  - New models are encouraged to replace 'outdated' models to answer new questions

Adapted from Cavagnaro (2002) Nature Rev Drug Discov 1: 469-75

Thank you for your attention!

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QUESTIONS?