Effective Research Management Day

What to consider with Investigator Initiated Studies

John F. DiPersio MD, PhD
Division of Oncology
Department of Medicine
Siteman Cancer Center
Major steps for successful “IIT” (Investigator Initiated Trial)

Idea/science (preliminary laboratory data)

Hypothesis to be tested
Phase I (feasibility/toxicity); Phase I/II feasibility/efficacy
Phase II (efficacy); randomized phase II; phase II

Who will perform study (clinical collaborators, laboratory collaborators; Statistical collaborators)

Who will provide the drug or reagent (local, pharm co. CTEP)

Generate formal LOI

Identify current and future funding sources
Hints for successful applications:

1. Enlist mentor/mentoring group and stats support

2. Make sure the idea is interesting and important

3. Make sure you will have enough patients to complete study

4. Be realistic about goals “feasibility and toxicity” vs efficacy

5. Design key basic science correlative studies and make sure they can be done and will be informative. Completing these studies will mean the difference of getting the trial published or not and getting future funding and not

6. Ensure appropriate oversight with DSMP
Hints (continued)

1. Focus on non-competing idea/study

2. Try and get your own IND vs allowing a company to sponsor

3. Identify source of immediate funding (Division/pharma)

4. Identify source of long term funding (NIH/pharma/ASCO)

5. BEWARE of engaging other centers in therapeutic trials in which you hold the IND

Develop an “iron-clad” stats section!
Figure 1. HSC Mobilization. Indicates the release of stem cells from the bone marrow. G-CSF induces mobilization via downregulation of SDF-1 production by osteoblasts. In addition, G-CSF and IL-8 release proteases such as NE, CG, and MMP9 which directly cleave adhesion molecules. G-CSF and IL-8 also release KL, VCAM-1, CXCR4, and HSC, which are involved in the mobilization process. CD44 and HA are also involved in the extracellular matrix. SDF-1 mRNA is released by osteoblasts.
AMD15057 and AMD3100 induce rapid and transient mobilization of normal progenitors.
Hypothesis of chemo-sensitization

- The interaction of leukemia cells with the BM stroma may provide a survival benefit to leukemia cells.

- The interruption of this interaction may enhance the sensitivity to genotoxic stress such as chemotherapy or radiation therapy:
  - Others have shown modest benefit using G-CSF or GM-CSF to enhance the sensitivity of leukemia cells to chemotherapy.
(a) Spheroid Model: tumor-tumor interaction contributes to CAM-DR.

(b) FN Model: Tumor-FN interaction contributes to CAM-DR.

(c) Stromal Model: Tumor-Stroma interaction and adhesion induced soluble factors secreted by stromal cells and tumor cells contribute to CAM-DR.
Effect of direct contact between APL and stromal cells on APL viability

Graph showing the effect of direct contact between APL and stromal cells on APL viability. The x-axis represents the presence or absence of stroma, Ara-C 40 ng/mL, and DNR 40 ng/mL. The y-axis represents the percentage of Annexin V+ cells. The graph indicates that the presence of stroma and DNR 40 ng/mL significantly increases the Annexin V+ percentage compared to the absence of these factors.
SCHEMA

Mobilization Study Samples  Pharmacokinetic Study Samples  DNA Damage Study Samples

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

A  A  MEC  A  MEC  A  MEC  A  MEC  A  MEC

Mitoxantrone (8 mg/m², IV)  Etoposide (100 mg/m², IV)  Cytarabine (1000 mg/m², IV)

4h post-AMD  4.5h post-AMD  5.5h post-AMD  6.5h post-AMD
Good scientific idea
Solid hypothesis
Competent collaborators
Source of AMD3100: Genzyme
IND: WU
Solid stats Section: phase I/II study
Short term funding: Genzyme
Long Term Funding: NCI R21
Regulatory collaborators: SCC/Division of Oncology
Local commitment
58 patients (one year and no competing trials)
BMT approval. PRMC approval, IRB approval
Epitope tagging of suicide gene-expressing T cells
CD2 Locus Control Region Targeting Vector for Transgenic mice
ΔCD34-TK Transgenic (Tg) Mouse

extracellular ↔ cytoplasmic

huCD34

L HSV-TK

Pre-sort

huCD34

CD3

Post-sort

MACS

CD3

% survival

[ GCV ] (μM)

3.4
2.34
28.1
59.9
2.11
2.28
2.48
95.1
Mouse Transplant Model

Donor BM: H-2^b, Ly5.1^+

T cell Donor: H-2^b, Ly5.2^+, CD34-TK^+

Recipient: H-2^d, Ly5.2^+
In vivo suicide of CD34-tk expressing allogeneic T cells

Day + 21

No GCV  GCV (D1-D8)

Nontransgenic T cells

Transgenic T cells
Prevention of GVHD Using CD34-TK/GCV Suicide Gene Therapy

Days post-BMT

- BM only (n=17)
- + 2x10^6 TgT (n=17)
- + 2x10^6 TgT + GCV d1-7 (n=14)
- + 2x10^6 non-TgT + GCV d1-7 (n=7)
- Irradiation control (n=4)
ΔCD34-TK Transduction Protocol

Activate
Transduce
MACS

Day: -3
-2
-1
0

Pre-sort
Positive-sort

CD4-FITC
CD4-FITC

CD34-PE
CD34-PE
Transplant Model

GCV schedules

- No GCV
- Day 1-7
- Day 4-10
- Day 10-16

TCD BMT Cell Deplete

BALB/c:
- H-2K\textsuperscript{d}, CD45.2\textsuperscript{+}

Spleen
- 4 x 10\textsuperscript{6} ΔCD34-TK\textsuperscript{+}

B6:
- H-2K\textsuperscript{b}, CD45.1\textsuperscript{+}
- BM
  - 4 x 10\textsuperscript{6} TCD BM
  - T Cell Deplete

B6:
- H-2K\textsuperscript{b}, CD45.2\textsuperscript{+}
- Spleen
  - Transduce + select T cells
  - or
  - Naïve Tg T cells
  - 900 cGy
Prevention of GVHD Using ΔCD34-TK/GCV Suicide Gene Therapy

No GCV → Day 1-7
Good idea and important
Good preliminary data
Solid stats section: phase I feasibility/toxicity
BMT, PRMC, IRB, IBC, RAC and FDA/IND
Immediate funding: BJH and NCI R21
Long term funding: NCI RO1
Complicated approval process
GLC and GMP processes and procedures
Good institutional support
GMP facility (charge backs)
Multiple external contract commitments
Single institutional study
Duration of development: 5 years
Duration of trial: 1 year