Clinical Trial Design and Regulatory Issues

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Taking a Technology from Bench to Bedside
An Immunotherapeutic Product can be classified as:

(1) Active immunotherapy (*Therapeutic vaccines*)

(2) Adoptive cellular immunotherapy:
   a) Transfer of immune cells [T and B cell therapies]
   b) Transfer of precursor cells [autologous or allogenic]
   c) Transfer of gene modified autologous or allogenic cells [Chimeric CAR/TCR engineered T cells]

(3) Passive immunotherapy
   (administration of antibody or receptor/ligand).
Biological product development overview

Interferon alfa-2b [INTRON A]
- Was originally approved for a 6-months treatment plan for Hep C
- After a postmarketing study
- Results indicated that treatment for 12 months doubled the number of patients obtaining benefit
Biological product development overview

3-6 yrs

IND Submitted

Pre-IND

Development

Preclinical

Phase 1

Phase 2

Phase 3

BLA Submitted

BLA

Marketing

Quality

Safety

Evaluation of safety & efficacy

“*The development of immunotherapeutic products for cancer poses unique challenges to the drug development process*”

Product characterization:

| Early-phase product development | Late-phase product development |

A product should be sufficiently characterized at an early to discern changes of product overtime.

Define the product with regards to its critical quality attributes (CQA)
Criteria for Product Characterization During an early Phase:

1) **Identity:** Identity assays include cell surface markers, major histocompatibility complex (MHC) antigen markers, gene expression, genetic polymorphisms, secreted molecules, and peptide sequences.

2) **Purity:** Product purity includes assays for pyrogenicity/endotoxin and for contaminants such as *unintended cell populations* (e.g., distinguished by phenotypes), *residual proteins or peptides* used to stimulate or pulse cells, and *materials used during the manufacturing process*, such as cytokines, growth factors etc..

3) **Viability:** A minimum viability release criterion should be established for cellular immunotherapeutics. FDA’s guidances recommend that this specification be at least 70% for products administered by the intravenous route of administration.

4) **Potency:** Potency is defined as “the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product”
Biological product development overview

The development of immunotherapeutic products for cancer poses unique challenges to the drug development process. Product characterization:

**DEVELOPMENT**

- **Early-phase product development**
- **Late-phase product development**

A product should be sufficiently characterized at an early stage to discern changes over time. Define the product with regards to its critical quality attributes (CQA).

**Production scale-up:**
- Changes of manufacturing facilities
- Changes of equipment related to growth, processing, and storage
- Process changes.

1.2 million sq. ft
General considerations required during all stages of product development

Safety testing and acceptance criteria

(1) Sterility:
(2) Mycoplasma
(3) Adventitious viral agents

Example……………..

• Sterility (bacterial and fungal) testing on the final product should be performed according to the requirements in 21 CFR 610.12.

• A 14-day direct inoculation test method as described in the United States Pharmacopoeia (USP) <71> is typically used to evaluate sterility of cellular immunotherapeutics.

• Samples for sterility testing should be obtained after final product manipulation.
A sample (cells and supernatant) should be taken 48–72 hours prior to the final harvest.

An interim reading test is conducted.

An interim result will contribute to a sterility determination.
A positive final sterility test ????

Physician and patient notification

Careful monitoring of the patients ..

*Action plan* should be submitted to the authorities

*Identification* and sensitivity testing of the contaminant, *investigation* and *corrective actions*, and *reporting* of the incident to the IRB and FDA as an adverse event within 15 calendar days.
Biological product development overview

Preclinical evaluation

General considerations for the preclinical assessment of immunotherapy products

The **overall goal is to provide data to support safety of the product**

Safety concerns for these products can exist at multiple levels:

A) **Product related:**
   a. Replication of a viral vector *in vivo*
   b. Autoimmunity due to a high homology between an immunogenic epitope and an endogenous target)

B) **Process itself**
   a. the introduction of adventitious agents
   b. cell transformation due to ex vivo manipulation),

C) **Biological function**
   a. polarization of the immune system
   b. overstimulation of the immune system due to immunomodulation
Cell-based immunotherapeutic products

A safety concern for some of the cell-based immunotherapeutic products is uncontrolled proliferation in vivo.

Office of Biotechnology Activities

Recombinant DNA Advisory Committee

A recent example is the persistence in situ of K562-GM-CSF cells (GM-CSF-expressing human leukemia cell line) Vaccine after subcutaneous administration in humans even though the tumor cells were irradiated prior to inoculation.

The prolonged expression of GM-CSF from these cells may have contributed to the leukocytosis observed in the patient which subsequently lead to his death.
After Extensive Investigation

Prolonged survival of irradiated K562 cells in vivo (3 months)

Some surviving K562 cells manifested replicative capacity but retained radiation sensitivity in vitro

Multiple immune defects related to allo HSCT and AML may have contributed to K562 cell persistence

Careful design in preclinical studies

Consider that the administration of a cytokine with a cell-based immunotherapeutic product may affect the in vivo function and safety of the cell-based product. The potential for such interactions should be considered when designing preclinical studies.
Following infusion of CART-19 T cells in patients, the T cells expanded approximately 1000-fold or more, with concomitant significant increase in proinflammatory cytokine levels, and associated adverse effects.

Kalos M, Science Transl Med. 2011, 3:95
Thus, preclinical studies for these products should assess the proliferation status and the potential for clonality of the cells through in vitro and/or in vivo testing.
Preclinical studies conducted to support immunotherapeutic product development

1) identify potential target organs/tissues of toxicity and determine if these toxicities are reversible

1) identify an appropriate starting dose level and inform the dose-escalation scheme and the dosing regimen of a first-in-human trial

1) identify parameters for safety and activity monitoring in humans.

4) Adequate numbers of animals for statistical analysis

4) Appropriate control groups

5) A dosing regimen and route of administration similar to those planned for the clinical trials

4) Adequate study duration to allow for comprehensive assessment of potential adverse findings
Preclinical studies **CHALLENGES??**

Species-specific Differences in target and effector function

Often Impossible to obtain a relevant animal model

CAR T cells: Testing for their potency:

1) Challenging----- Do we correlate the potency with transduction efficiency ( % of transduced cells)?

 ..........NOT NECESSARILY as cells expand anyway post infusion
Biological product development overview

3-6 yrs 6-7 yrs 1-7 yrs

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BLA

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CONSIDERATION FOR EARLY CLINICAL TRIALS

1) PATIENT POPULATION

Conventional model for clinical development of a chemotherapeutic agent is in patients with advanced/metastatic diseases.

However, the time interval from administration of study agent to subsequent disease progression in patients with metastatic cancer may be short.

This time may be insufficient for development of an anti-tumor immune response needed for activity/effectiveness of a cancer vaccine.

In contrast, testing cancer vaccines in patients with minimal burden of disease may provide adequate time for the cancer vaccine to elicit a detectable immune response.
19809-105 A Patient who has been cured after receiving vaccine.

Kandalaft et al, In Prep
INNOVATIVE CLINICAL TRIAL DESIGNS

INNOVATIVE CLINICAL TRIAL DESIGNS

Modeling of CAR-T cell expansion in vivo in the lymphodepleted host

Without infusion of bulk untransduced PBL on Day 2.

With infusion of bulk untransduced PBL on Day 2.

WELL COORDINATED TEAM EFFORT AND CAREFUL REAL TIME MONITORING

Dying man has new lease on life after his immune system is trained to kill cancer with reconstructed form of HIV

By DAILY MAIL REPORTER
UPDATED: 10:35 GMT, 14 September 2011

A New Jersey man diagnosed with leukaemia has a new lease on life after taking a gamble on an experimental cancer treatment that saw him injected with a harmless form of HIV.

Bill Ludwig, 65, is one of only three patients who have received the groundbreaking treatment at the University of Pennsylvania for the most common form of leukaemia, called CLL.

And the results are so incredible researchers believe it could mark the beginning of a major advance in cancer treatment.

...... At first, nothing happened. But after 10 days, hell broke loose in his hospital room. He began shaking with chills. His temperature shot up.

......doctors moved him into intensive care and warned that he might die.

Well coordinated careful efforts of the team With Real Time Monitoring
...identified the elevated cytokines (IL-6 spike)

Patient got IL-6 Antibody (tocilizumab)
...... and is now alive
Disease progression/recurrence immediately or shortly after the initial administration of immunotherapeutic products

In oncology practice, patients are normally taken off current treatment when they have disease progression/recurrence.

Because immunotherapeutic products may need time to elicit or amplify an immune response that could manifest as biological activity (i.e., a tumor-specific immune response), a delayed effect can be expected in the subjects who received the vaccine.
Patient on A Personalized Vaccine Study .......... Delayed Response

- DC + autologous oxidized tumor lysate
- Unpulsed DCs
- PBMCs only

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Clinical endpoints for cancer immunotherapy studies

MUST CONSIDER CHANGE IN ENDPOINTS

Clinical Response may need time to develop

Overall Survival is recommended

Disease Progression does not always mean progression

........................................MUST define withdrawal criteria

Improvement in how a patient feels, as measured by patient-reported outcome instruments (PRO’s), if properly validated, could constitute a clinical benefit supporting licensure;
Monitoring the immune response and immunogenicity

We can learn so much from Proper Immune Monitoring

Follow the persistence of T cells,

Monitor Cytokines
FOR IMMUNOTHERAPEUTICS THE CHALLENGES SEEM TO INCREASE...
Ingredients for a successful Immunotherapy Program

- Research environment full of fundamental science and technology cores
- Critical mass of highly translational laboratories
- Preclinical R&D
  - Clinical tool development
- Clinical transition infrastructure
- Clinical group able and willing to conduct phase I/II studies
- Solid clinical operation (safety, efficiency, knowledge based care)
- Technologically advanced, multidisciplinary hospital environment
Department of Oncology in CHUV/LAUSANNE

- Medical Oncology
  - Centers Of Excellenc e
    - H&N
    - Breast
    - Lung
    - Sarcoma
    - Melanoma
    - GI
    - Brain
    - GU/GYN

- Radiation Oncology
  - Ly/My
  - Leu/MDS
  - Benign Heme

- Hematology
- Immuno-oncology

- Fundamental oncology
- CHUV groups

- Experimental Therapeutics Center
  - Biobank
  - Oncology Translational Core Facility
  - GMP Facility
    - Clinical Trials Unit
    - Phase I out/inpatient Unit

- CHUV Partners
  - Surgery
  - Pathology
  - Radiology
  - Genetics

- Pathology
- Pharmacology
- Genetics

- CHUV Partners
- BIL
CTE/CTU - Cellular Manufacturing Facility

- A 750 m² facility *(GMO/Non GMO spaces)*
- Capacity to treat 200-400 patients

**Status:**
- Concept Design was approved by *Swissmedic* in April 2014
- Construction to begin in Nov 2014
- Projected to have first patient in first ¼ of 2016

**Manufacturing:**
- Genetically engineered T cell products,
- Tumor infiltrating lymphocytes
- Dendritic cell vaccine

*Juli De Graw, PhD*
CTE - Phase 1 Unit (1,400 m²)

- Investigational Pharmacy
- On-site Clinical Trial Unit
- Exam Rooms
- New Drug Development Unit
- Outpatient Immunotherapy Unit
CTE/CTU - Inpatient Unit (550 m²)

- 10 beds with intermediate-intensive care
- Cardiorespiratory monitoring capabilities
- A small laboratory for biospecimens.
CTE - Translational Core Facility (760 m²)
CTE - TRANSLATIONAL PLATFORMS

ONCOLOGY LIVE CELL PLATFORM

- TUMOR PROCESSING FACILITY & CTE BIOBANK
- IMMUNE MONITORING CORE
- DRUG SCREENING UNIT

ONCOLOGY PATHOLOGY PLATFORM

- BIOMARKER LAB
- ONCOSEQUENCING LAB
Immune Monitoring Core

Alexandre Harari, PhD

- Harmonization with LICR in MSKCC, in collaboration with Drs Phillip Wong and Jianda Yuan.

- Integration of IMC into international efforts of harmonization and standardization

  - CIC ICS Gating Panel, ELISpot proficiency panel
  - FlowPET leadership committee (CIMT)
  - Biomarkers Task Force Working Group 2 (SITC)

CAPABILITIES

- Flow cytometry  FORTESSA FACS (5 lasers)
- Flow Imaging
- Fluidigm single cell analysis
- Cytof2
- High Content Analysis - Operetta
- MSD (Mesoscale discovery) multiplexed immunoassay platform
ESTABLISHING A UNIQUE IMMUNE LANDSCAPE

CTE - Biomarker Discovery Lab

Periklis Foukas, MD

Robotic slide loader.
Capacity: 200 slides

CCD camera with Liquid Crystal Tunable Filter

- Detection range: 420-720nm
  (Separate up to 4 markers in brightfield mode and up to 10 markers including autofluorescence in fluorescence mode)

Analysis software

- Spectral unmixing
- Learn by examples algorithm
- Quantitative data output
Thank you !!!