Case Study: Safety and ADMET Aspects of Nanotechnology in Parenteral Drug Products

Bidirectional Interaction between Nanoparticles and the Mononuclear Phagocyte System (MPS)

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Source of Drugs or Studies: UNC Investigators, NCI, NIH, & Pharmaceutical Co.

**UNC LCCC & UNC ESOP Analytical Chemistry & Pharmacology Labs**
Director = W. Zamboni

**UNC LCCC & UNC ESOP C-CCNE Analytical and PK Core**
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**Translational Oncology and Nanoparticle Drug Development Initiative (TOND₂I) Lab**
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Head Analytical Chemist = A. Schorzman
Analytical Chemist = S. Metzger
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**Steering Committee**
Dr. Dees, LCCC
Dr. Sharpless, LCCC MP1U
Dr. Frye, CICBDD
Dr. DeSimone, CCCNE
Dr. Jay, ESOP
Dr. Brouwer, ESOP
Industry Rep = TBD

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**Consultants**
Dr. Madden, MD Anderson CC
Dr. Baxter, PhD, OpAns
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Types of Nanoparticles and Carrier-Mediated Agents

Nanoparticles

- Gold nanoparticles
- Dendrimers
- Quantum dots
- Liposomes
- Nanocrystals
- Polymers

Conjugates

Monoclonal Antibodies
Antibody Drug Conjugates (ADC)

DM1 = Linker -thioether- Trastuzumab (3 to 4 per IgG) -LysNH₂ (random)
Clearance of Nanoparticles and CMAs Via the Mononuclear Phagocyte System (MPS)
Pharmacologic Issues of Nanoparticle/Liposomal Agents: Characterize Encapsulated/Released Drug & PK Variability

**S-CKD602**

**Carrier**

**Warhead**

**Encapsulated / Conjugated**

**Goal in Plasma:**
- Remain within or Attached to carrier
- Decrease toxicity

**Sum Total = Encapsulated + Released**

**Goal in Tumor:**
- Release drug from carrier
- Decrease toxicity

DM1 = \(\text{Linker} \cdot \text{Thioether} \cdot \text{Trastuzumab (Her2G1)} \cdot \text{LysNH2 (random)}\)
Pharmacologic Methods to Characterize CMAs In Vitro and In Vivo

**Analytical and PK Studies of Nanoparticle Agents**

**Phenotypic Interaction between Nanoparticles and RES/MPS**

**New PK/PD Metrics for NPs**
Pharmacologic Methods to Characterize CMAs In Vitro and In Vivo

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Pharmacologic Methods to Characterize Nanoparticles In Vitro and In Vivo

Analytical and PK Studies of Nanoparticle Agents

Phenotypic Interaction between Nanoparticles and RES/MPS

These projects can be performed at:

Pharmaceutical Development Center (PDC) CRO
Active Research Programs Evaluating Nanoparticle Pharmacology and the MPS

- Brain
- Heart
- Lung
- Liver
- Kidney
- Pancreas
- Plasma and Blood Cells
- Spleen
- Muscle and Fat
- Tumor

IV/PO
Active Research Programs Evaluating Nanoparticle Pharmacology and the MPS

Muscle and Fat
Brain
Heart
Lung
Pancreas
Kidney
Liver
Spleen

IV/PO

Tumor
Plasma and Blood Cells

Muscle and Fat
Brain
Heart
Lung
Pancreas
Kidney
Liver
Spleen
Pharmacologic Methods to Characterize Nanoparticles In Vitro and In Vivo

Analytical and PK Studies of Nanoparticle Agents

Phenotypic Interaction between Nanoparticles and RES/MPS

New PK/PD Metrics for NPs

Name of Presentation
Phase I and PK Study of S-CKD602 in Patients with Refractory Solid Tumors:
Factors Affecting the PK Disposition

WC Zamboni, S Ramalingam, DM Friedland, CP Belani, RG Stoller, S Strychor, NB Modi, RP Nath, ME Tonda, RK Ramanathan.
S-CKD602 Phase I PK: S-CKD602 Encap AUC vs Dose
High Inter-patient PK Variability
S-CKD602 Phase I PK: S-CKD602 Encap AUC vs Dose
High Inter-patient PK Variability

AUC (ng/mL-h) vs Dose (mg/m²) chart showing a 100x magnification.
S-CKD602 Phase I PK: S-CKD602 Encap AUC vs Dose
High Inter-patient PK Variability
Increased PK Variability in Liposomal Formulations Compared to Non-Liposomal Formulations of Anticancer Agents

PK Variability for Individual Agents

Relationship of Clearance Rate and PK Variability

y = -335.39x + 55.808
R² = 0.3859
Bi-directional Interaction between Monocytes and Liposomal Agents:

Phase I and PK Study of S-CKD602 in Patients with Refractory Solid Tumors

Relationship between Clearance of Encapsulated Drug and Release of Drug from Carrier and % Decrease in Monocytes

- Encapsulated CKD-602 CL (L/h/m²) vs. % Decrease in Monocytes: $R^2 = 0.57$

- Released CKD602 AUC in Plasma vs. % Decrease in Monocytes: $R^2 = 0.62$
Reduction in Doxil Clearance Associated with Reduction in Precycle Monocyte Count

Decrease Doxil CL C1 to C3

Decrease Pre-Monocytes

Changes in Precycle Monocyte Count and Changes in Pegylated Liposomal Doxorubicin Clearance From Cycle 1 to Cycle 3

Gabizon, CCP 2008

Irene La-Beck, CCP 2011
Active Lactone Form

Acidic pH

Active Lactone Form

Monocyte

Migration out of Vessels

Macrophage

Age Related Effect on Released CKD-602:
< 60 yo = Greater Release?

Reduction in Monocytes in Blood

Age Related Effect on Monocytes:
< 60 yo = Greater Decrease
PhenoGLO™: UNC Study Evaluating Phenotypic Probes to Predict Doxil Efficacy & Toxicity in Patients with Ovarian Cancer

PhenoGLO Phenotypic Probes

- Imaging
- Blood Cell
- Tumor Expression
- Genotype

Function of MPS Cells

PK: Clearance → Dose

PD: Efficacy

PD: Toxicity
PhenoGLO™: UNC Study Evaluating Phenotypic Probes to Predict Doxil Efficacy & Toxicity in Patients with Ovarian Cancer

**PhenoGLO Phenotypic Probes**

- Imaging
- Blood Cell
- Tumor Expression
- Genotype

**Function of MPS Cells**

**PK: Clearance → Dose**

**PD: Efficacy**

**PD: Toxicity**

**Drug**

**Graph:**

- X-axis: Phenotypic Measures of RES Function
- Y-axis: S-CKD602 Clearance (L/h/m²)
PhenoGLO™: UNC Study Evaluating Phenotypic Probes to Predict Doxil Efficacy & Toxicity in Patients with Ovarian Cancer

PhenoGLO Phenotypic Probes

- Imaging
- Blood Cell
- Tumor Expression
- Genotype

“High Throughput” Screening System For Nanoparticles

Function of MPS Cells

PK: Clearance → Dose

PD: Efficacy

PD: Toxicity

Drug

Genotype
PhenoGLO-IT™/PhenoGLO-PP™: UNC Study Evaluating Phenotypic Probes to Predict Doxil Efficacy & Toxicity in Patients with Platinum Refractory Ovarian Cancer

Interaction between Nanoparticles and MPS

Doxil PK (Encap and Released Doxorubicin)

Phenotypic Probes of MPS Predict Doxil Encap AUC

Doxil Encap AUC And Response (PFS)

Days -7 to -1

Days 1 to 7

Results

Phenotypic Probe: Phagocytic Activity

Encap Doxorubicin Cycle 1 AUC (h*ng/mL)

Days 1 to 7

Results
Evaluation of MPS Imaging Probe (Tc99m-Sulfur Colloid; TSC) to Predict Doxil PK and PD (Efficacy & Toxicity)

Doxil (110 nm)

TSC (<200 nm)

<200 nm after filtration
Relationship between TSC CL in Blood and Encapsulated Doxorubicin CL in Plasma

Encapsulated Doxorubicin Plasma Clearance (mL/h) vs. TSC Blood Clearance (mL/h)
All Patients (n=8)

$R^2 = 0.61$

Encapsulated Doxorubicin Plasma Clearance (mL/h) vs. TSC Blood Clearance (mL/h)
Doxil Monotherapy Patients (n=5)

$R^2 = 0.81$
Inter- and Intra-Patient Relationship between MPS Function and the Clearance of Various Nanoparticle Agents

![Graph showing the relationship between MPS Function and Nanoparticle Clearance for Patient 1, Patient 2, and Patient 3. The graph includes lines for TSC, Non-PEG-Lipo, and PEG-Lipo for each patient.]
Can TSC PK in hands can be used to predict the development of hand-foot syndrome (HFS) toxicity?
PD Results – TSC Predicts HFS: NP issue PK follows MPS Cells

Methods and Calculations

**Figure 4.** Equation determining the AUC encapsulated doxorubicin in the hands based on the relationship established in Figure 3 and the study variables.

\[
\text{Maximum HFS Toxicity Grade vs. Equation Estimated Encapsulated Doxorubicin AUC in Hands for All Patients}
\]

\[
TSC \text{ AUC}_{\text{Hand}} = \frac{\text{TSC Hand}}{\text{Encapsulated Doxorubicin Concentration in Hands}} \times \frac{\text{Encapsulated Doxorubicin AUC}_{\text{Plasma}}}{\text{TSC AUC}_{\text{Estimated}}}
\]

**Maximum HFS Toxicity Grade**

\[
y = 23,852.031785x + 1,750.660.707124
R^2 = 0.428420
\]

\[
=0.77
p\text{-value}=0.02
\]
**Active Lactone Form**

**Acidic pH**

**Bi-Directional Interaction Between Nanoparticles and MPS**

**Patient Characteristics:**
- Age
- Gender
- Body Composition
- Race
- Type of Cancer
- Comorbidities
- Others

**Cofactors:**
- Hormones
- Chemokines
- Complement
- Others

**Treatment:**
- Chemotherapy
- Radiation
- Other drugs
- Steroids
- Others

**Feedback Loop?**

**Reduction in Monocytes in Blood**
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New PK/PD Metrics for NPs
Are all solid tumors conducive to nanoparticle delivery?
Relationship between Tumor Disposition of S-CKD602 and Tumor MPS (Macrophages/DC)

Immunostaining for MPS Cells

Distribution of S-CKD602 To Tumors

Relative Exposure

Monocytes & Dendritic Cells in Tumors

Release of CKD-602 in Tumors

Tumor Sensitivity

Zamboni et al, J Lipo Res 2010
Variable MPS in Orthotopic Tumors and Effects on MPS in Liver

MPS in Tumor = Affects Tumor Delivery?

MPS in Tumor = Affects MPS in Liver & NP Clearance?
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Nanoglo

MPS Phenotypic Probe
PhenoGLO-HTSTM: Profiling the Interaction between Nanoparticle Agents and MPS System

> 300 NP anticancer agents in development

Profile interaction between NP and MPS in animal and human samples

Flow cytometry screening platform of MPS response and activity

Database of results & mathematical models of NP characteristics and MPS

8 measures of NP interactions with MPS
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  - Sample Processing
  - Analytical
    - HPLC
    - LC-MS/MS
    - Exactive
    - Orbitrap

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