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U.S. DEPARTMENT OF ENERGY

# Traitement de la contamination aux radionucléides : Nouveaux développements aux USA

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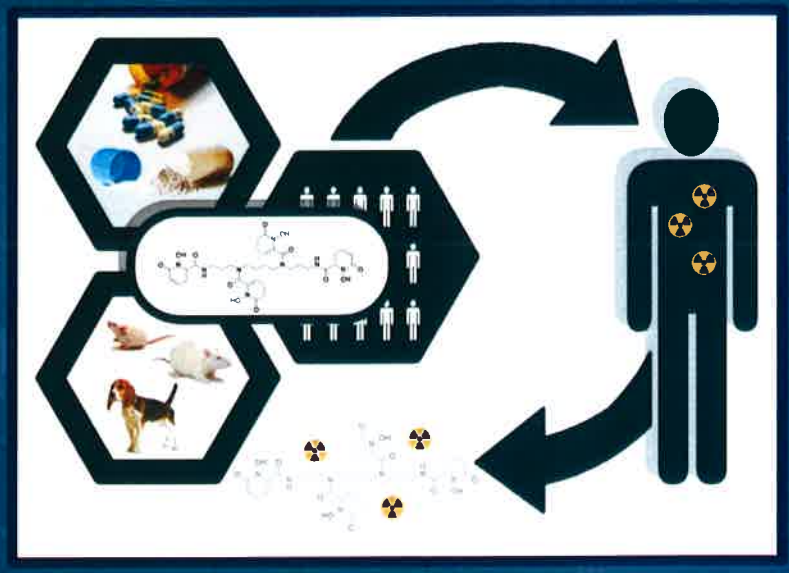
Lawrence Berkeley National Lab

Journée SFRP
06 octobre 2015
Paris (UIC)



FDA: Food and Drugs Administration "Guidance for Industry:
Internal Radioactive Contamination - Development of Decorporation Agents" (2006)

| | | | | |
|---|---|---|---|---|
| Am-241 | α, γ | Bone | I/W | Ca-DTPA, Zn-DTPA |
| Cf-252 | γ, α, η | Bone | I/W | Ca-DTPA, Zn-DTPA |
| Ce-141,144 | β, γ | GI, lung | I/GI | Ca-DTPA, Zn-DTPA |
| Cs-137 | β, γ | Body | I/S/GI | Prussian blue |
| Cm-244 | α, γ, η | Bone | I/GI | Ca-DTPA, Zn-DTPA |
| I-131,132,134,135 | β, γ | Thyroid | I/GI/S | KI |
| Pu-239,238 | α, γ | Bone | I/W | Ca-DTPA, Zn-DTPA |
| Po-210 | α | Lung | I | Dimercaprol |
| Sr-89,90 | γ | Bone | I/GI | AlPO4 |
| 3H | β | Body | I/S/GI | Forced $H_2O$ |
| U-238,235,239 | α, β, γ | Bone | I/S/W | $NaHCO_3$ |

Co-60, Ir-192, Ra-226, …

# Méthodes actuelles de traitement de la contamination

- Saturation of target organ: KI for I in thyroid


- Complex formation: DTPA for Pu, Am, Cm
  lack of oral formulation (UNC, SRI)

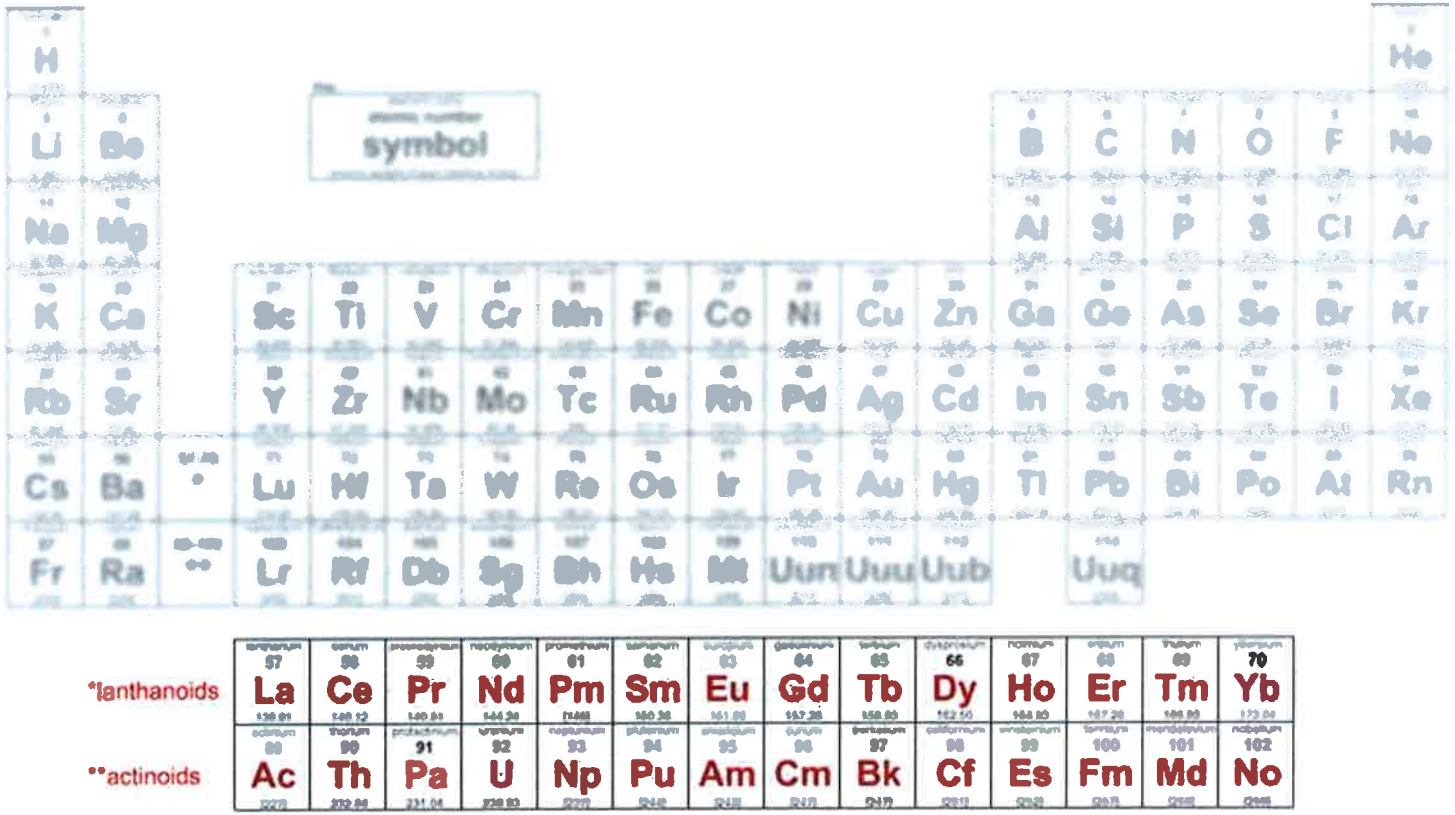
- Ion exchange in gastrointestinal tract:
  prussian blue for $^{137}Cs$
  lack of pediatric formulation (Heyltex)

- Acceleration of metabolic cycle by isotope dilution:
  water for $^{3}H$

- Precipitation of radionuclide:
  barium sulphate/aluminium phosphate for $^{90}Sr$

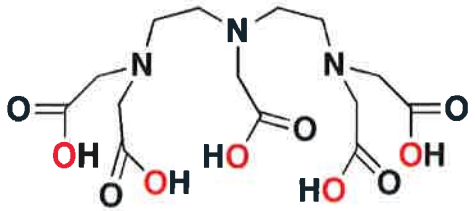
# Programme de décorporation au LBNL

## Développement d'un traitement de chélation par voie orale pour la décontamination des lanthanides et actinides



# Chélation des actinides: Un nouveau candidat-médicament

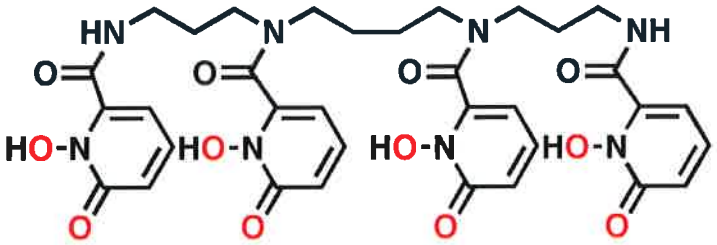
DTPA: le seul traitement approuvé par la FDA pour la chélation des actinides



Acide diéthylène triamine penta acétique

- Améliore ou prévient les lésions dues aux effets radiatifs et a la toxicité chimique
- Utilisé sous forme CaNa3- ou ZnNa3-
- Ligand octadentate
- Faible absorption orale
- Indication: Pu, Am, Cm (iv ou nb)

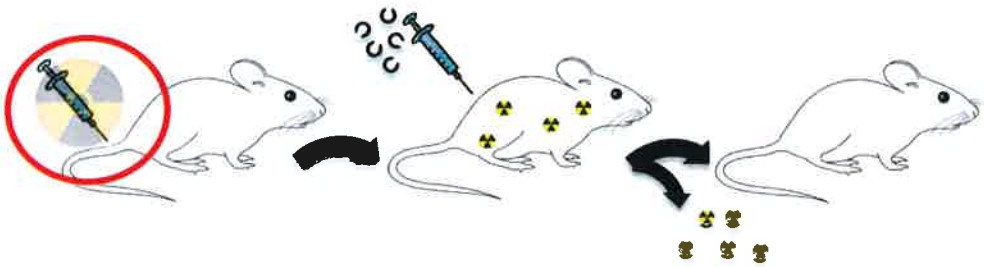
Ligand sélectionné
Inspiré des sidérophores
Modifié en fonction de la chimie des actinides en solutions



3,4,3-LI(1,2-HOPO)

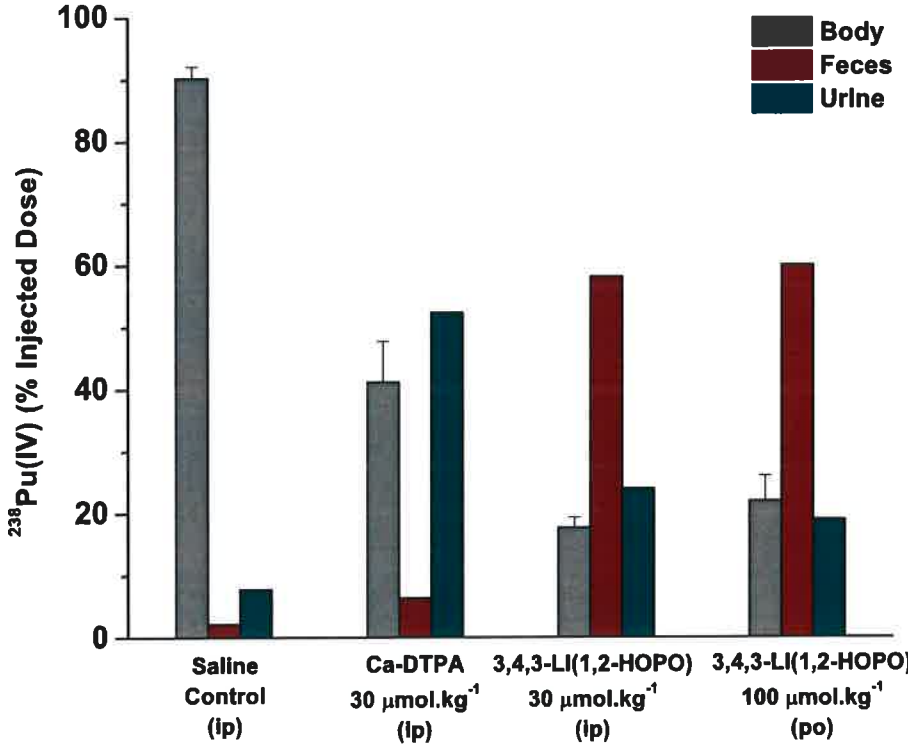

Gorden A.E.V. *et al.*, *Chem. Rev.* **2003**, *103*, 4207
Durbin P. W. *Health Phys.* **2008**, *95*, 465
Abergel R.J. *et al.*, *Health Phys.* **2010**, *99*, 401

# Premières études



$^{238}$Pu-citrate injected iv
Ligand injected ip or po at 1 h
Mice euthanized at 24 h

Radio-analysis




Abergel R.J. *et al.*, *Health Phys.* **2010**, *99*, 401

# Partenaires Clés

**LBNL – Chemical Sciences**
Management, synthèse, caractérisation, efficacité, formulation, règlementation

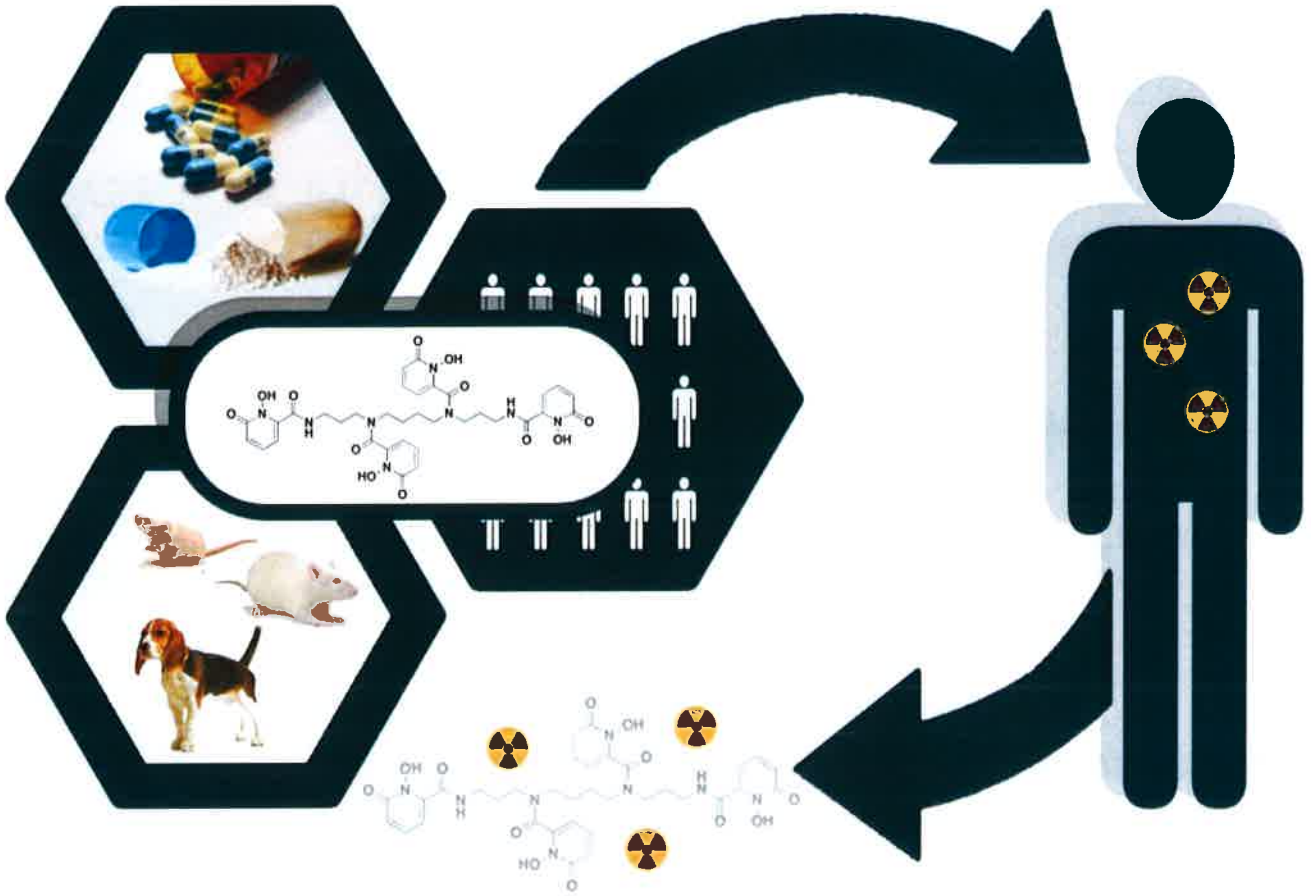
**SRI International**
Pharmacologie, toxicologie, règlementation

**Lovelace Respiratory Research Institute**
Efficacité

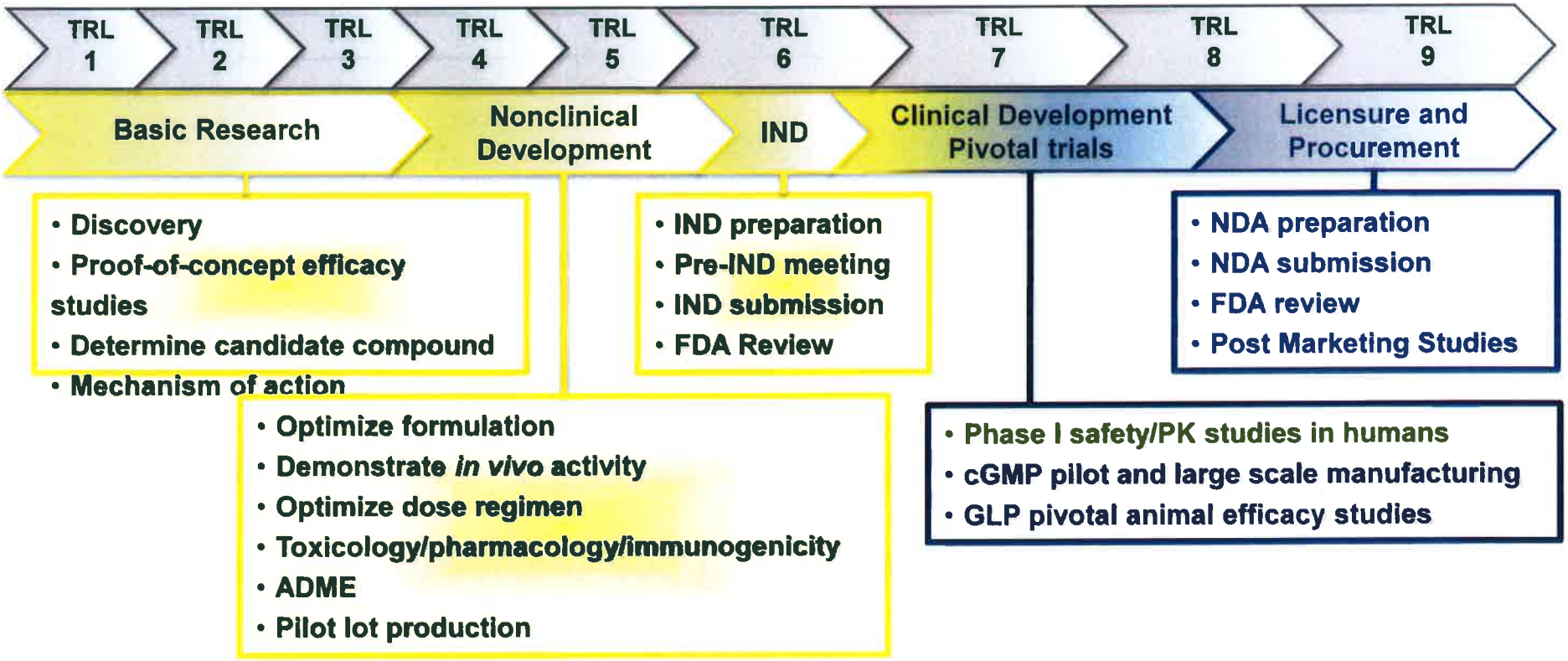
**Ash Stevens, Inc.**
Production (API)

**Formurex, Inc.**
Production (formulation)

# Règlementation et autorisation: “FDA’s Animal Rule”



# Plan de Développement




**Aout 2014:** **IND (Investigational New Drug)**
**Autorisation de la FDA pour poursuivre les essais cliniques**

# Outline

**Chemistry and Manufacturing Controls – Chimie et Production**

**Nonclinical Pharmacology and Toxicology – Pharmacologie & toxicologie**

**Nonclinical Efficacy – Efficacité chez l'animal**

**Regulatory affairs - Règlementation**

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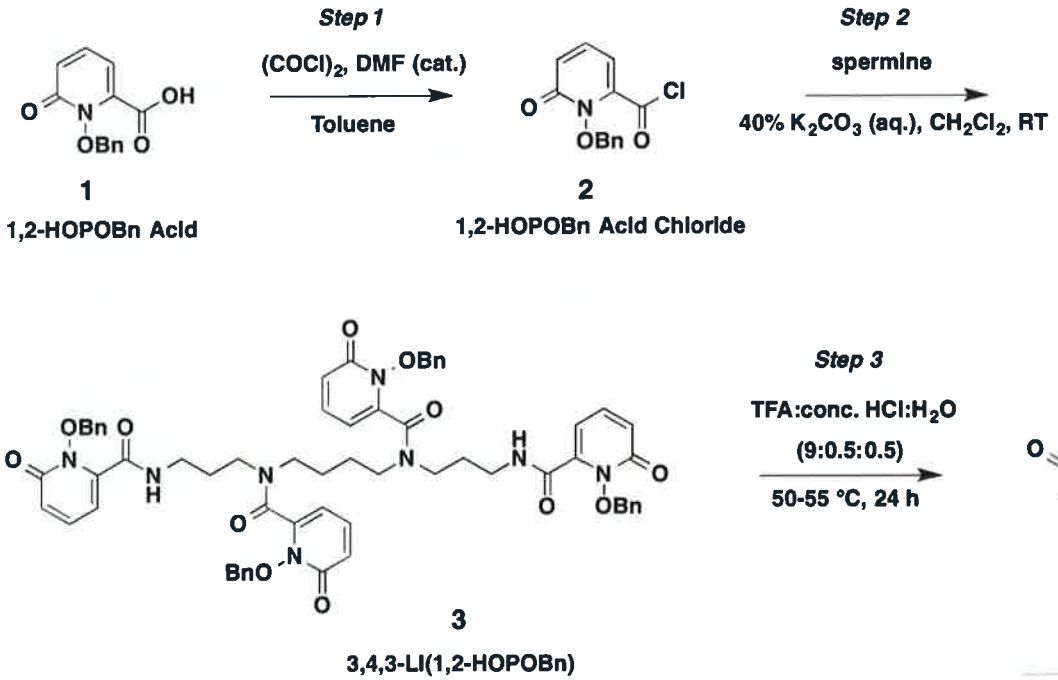
# Chimie et Production

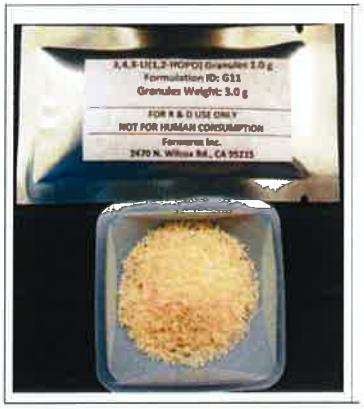
## LBNL - Programme de Décorporation des Actinides

# Synthèse du 3,4,3-LI(1,2-HOPO)




- **5 kg API Lot (Ash Stevens, Inc.)** - ML-11-276, 98.5% purity by HPLC
- Impurities identified and characterized with both 2 HPLC Methods (1 validated)
- Bulk stability determined at 40° C/75% RH for 6 mo, 25° C/60% RH for 12 mo
- Continuous ongoing bulk stability verification at 5° C
- Isotopically labeled API synthesized and characterized (C-13 and C-14)
- Bioanalytical methods validated (dog plasma, human plasma, urine, feces)

# Développement d'une formule orale





- Solution state stability
- pH-stability
- Distribution coefficients
- Permeability enhancement (46 PE PAMPA-tested, GIT lipid membranes)
- Excipient compatibility
- Dosage form selection
- Ongoing stability determined at 40° C/75% RH, and 25° C/60% RH for 6 mo
- Drug product HOPO 14-1 – hard gelatin capsules filled with blend (API/PE)
- Pilot lot manufactured

Panyala NR *et al. J. Pharm. Biomed. Anal.*, **2014**
Liu M *et al. J. Pharm. Biomed. Anal.*, **2014**

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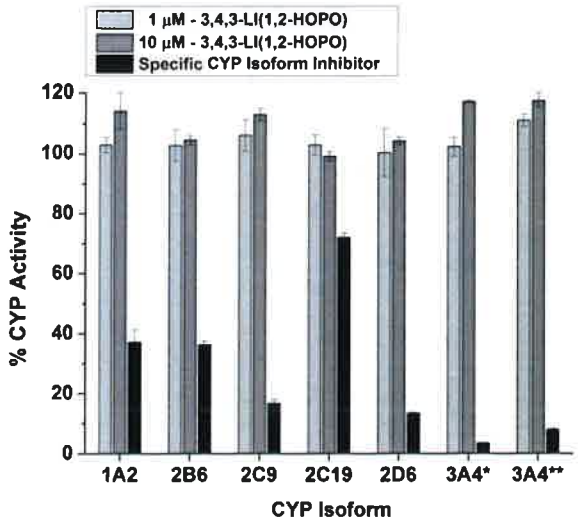
# Pharmacologie et Toxicologie Pré-cliniques

## LBNL - Programme de Décorporation des Actinides

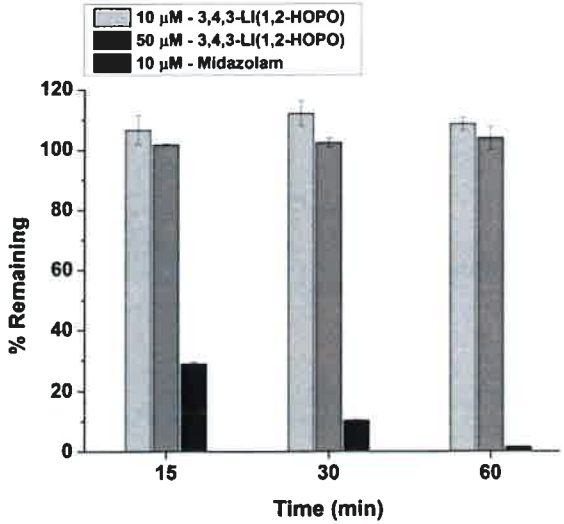
# Etudes précliniques de pharmacologie – in vitro ADME

- Permeability – Caco-2 assay
- Stability in simulated gastric fluid
- Plasma protein-binding

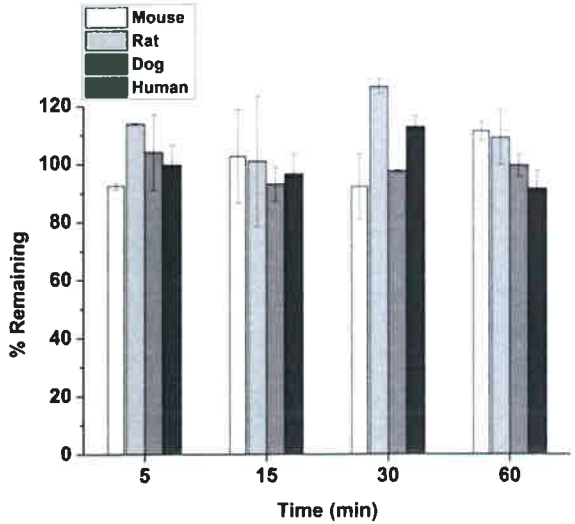
- CYP inhibition




- Microsomal stability



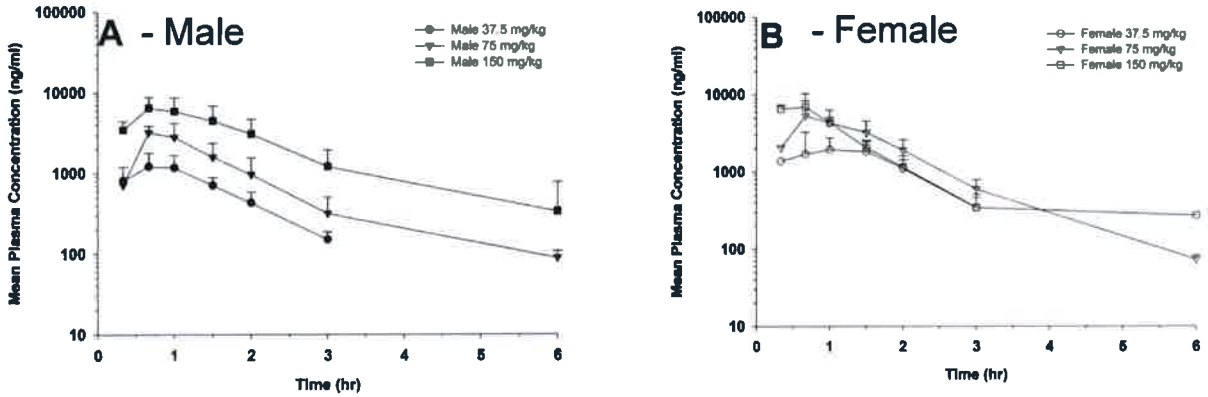

- Plasma stability




Choi TA *et al. J. Pharm. Sci*, **2015**

# Etudes précliniques de pharmacologie – in vivo

- **pK in Sprague-Dawley Rats (Single dose API, LC-MS/MS Detection)**
- **ADME in Sprague-Dawley Rats and Swiss-Webster Mice ($^{14}$C-API, LSC)**
- **pK in Beagle Dogs (Single and 7-daily dose API, LC-MS/MS Detection)**




- **Cardiovascular Safety Pharmacology**
  hERG channel inhibition assay (GLP)
  Rabbit cardiac Purkinje fiber assay (GLP)
  Electrocardiogram and blood pressure assessment in beagle dogs (GLP)

Choi TA *et al. Drug. Dev. Res*, **2015**

# Etudes précliniques de toxicologie

- **GLP Single Oral Dose Safety Study in Beagle Dogs**
  Capsules, 3 dose levels, single dose, 3M/3F per group, D2 and D15 time points

  *NOAEL in dogs: 37.5 mg/kg (50 µmol/kg) or 1215 mg for a 60 kg human (132 lbs).*

- **GLP Sub-Chronic Oral Safety Study in Sprague Dawley Rats**
  API, 3 dose levels, 28 daily doses, 5M/5F per group, D30 and D43 time points

- **7-Day Maximum Tolerated Dose Study in Sprague Dawley Rats**
  API, 4 dose levels, 7 daily doses, 3M per group, D8 time point

  *MTD in rats: 400 mg/kg/day (532 µmol/kg/day) or 3840 mg/day for a 60 kg human (132 lbs).*

- **Genetic Toxicology**
  Bacterial reverse mutation Ames assay (GLP)
  Mammalian Chinese hamster ovary chromosome aberration assay (GLP)

Bunin DI *et al. Radiat. Res.*, **2013**, *179*, 171-182

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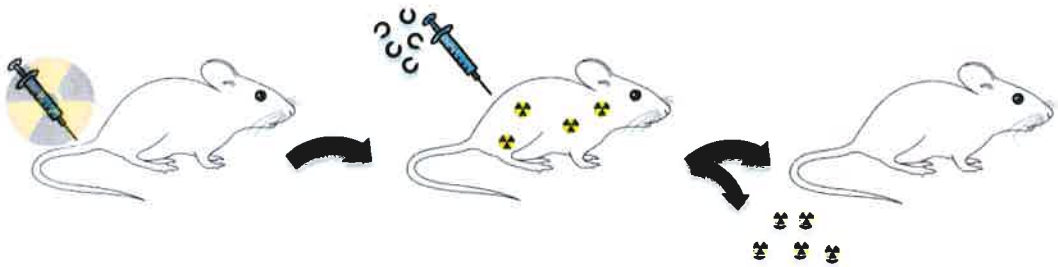
# Efficacité

## LBNL - Programme de Décorporation des Actinides

# Expériences de décorporation chez l'animal



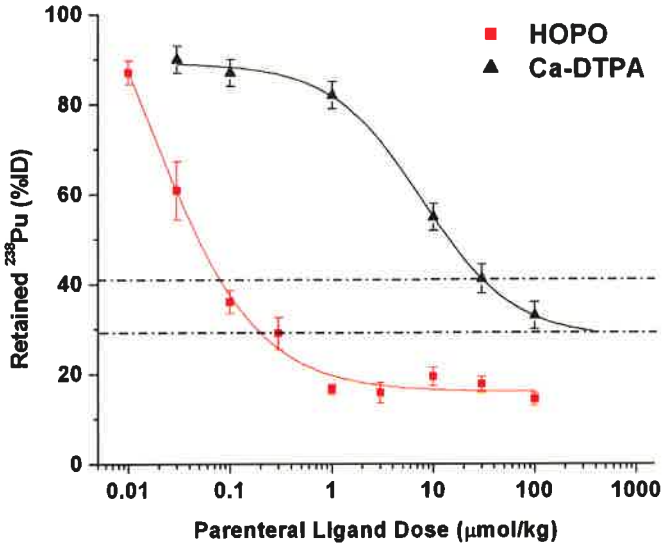
Radionuclide exposure
Treatment
Excreta Collection
Euthanasia
Radio-analysis

- Animal Species (mouse / rat / dog / NHP / mini-pig)
- Exposure route (injection / inhalation / ingestion / wound)
- Radionuclide (metal / isotope)
- Exposure level (activity / concentration)
- Treatment regimen (dose / onset / frequency / duration)
- Analytical methods (radiological / chemical)

# Determination de la posologie

$^{238}$Pu-citrate injected iv,
Ligand injected ip or po at 1 h
Mice euthanized at 24 h

Radio-analysis



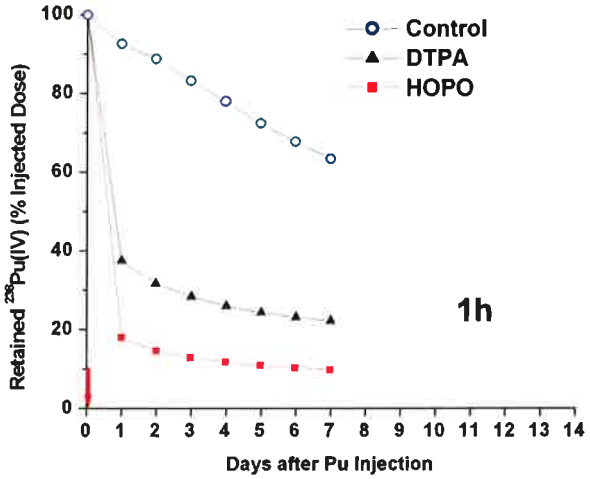

**[Ca-DTPA] (ip)**
**30 µmol/kg**
**370 µmol/kg**

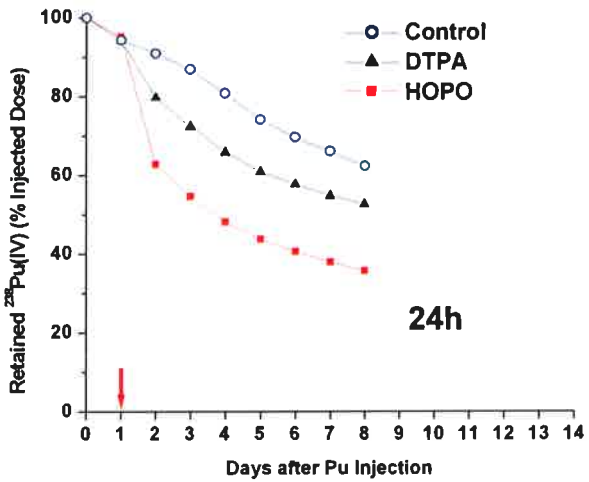
Bunin DI *et al. Radiat. Res.*, **2013**, *179*, 171-182

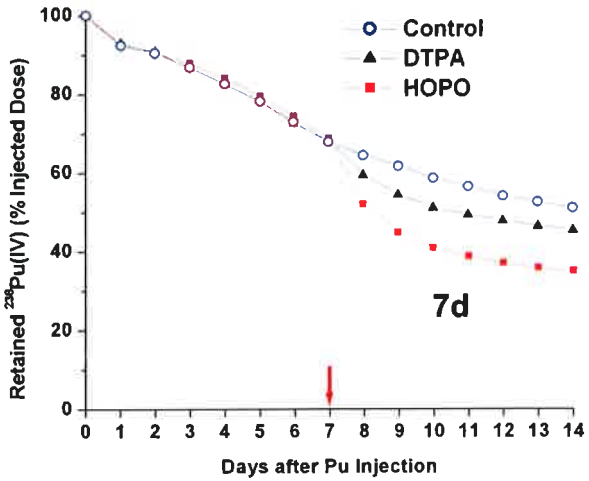
# Posologie: Initiation, fréquence, durée?

$^{238}$Pu-citrate injected iv,
Ligand injected ip once at
1h to 7d post exposure
Euthanasia 7d post-treatment

Radio-analysis

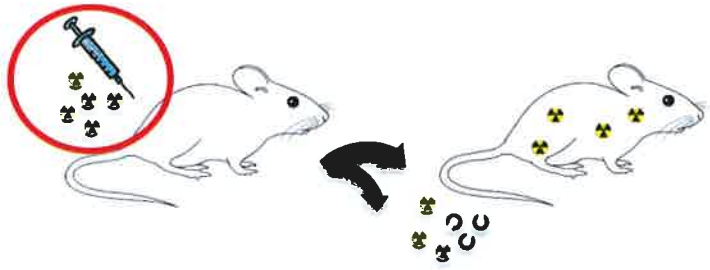


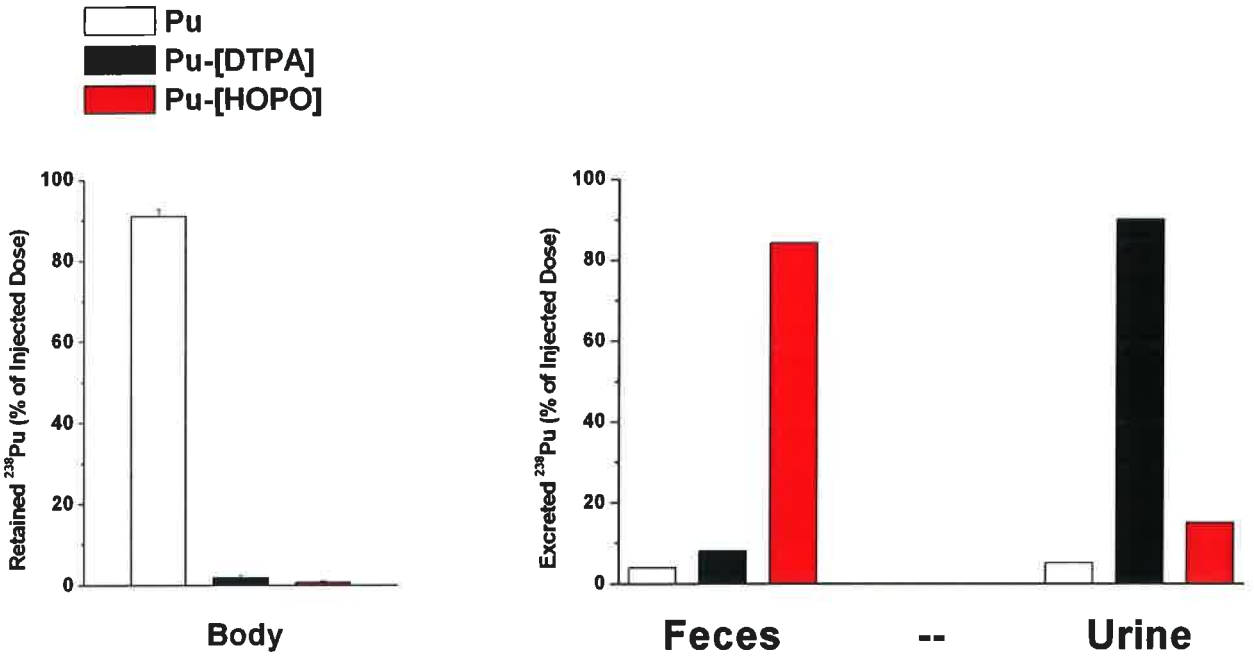

→ Impacts toxicology studies

# Mécanisme d'action: Stabilité du complexe in vivo



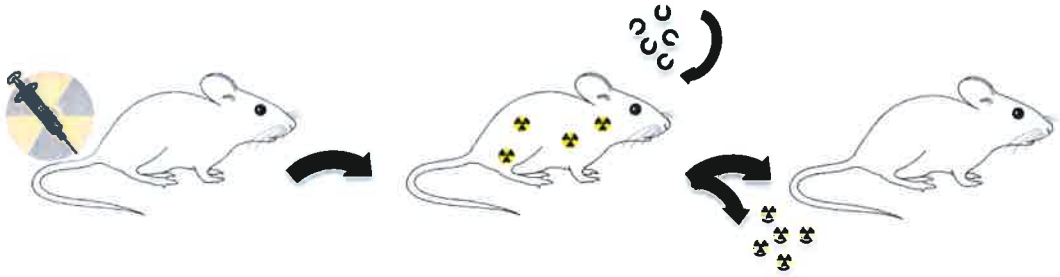
$^{238}$Pu-complexes injected iv or ip
Mice euthanized at 24 h

Radio-analysis

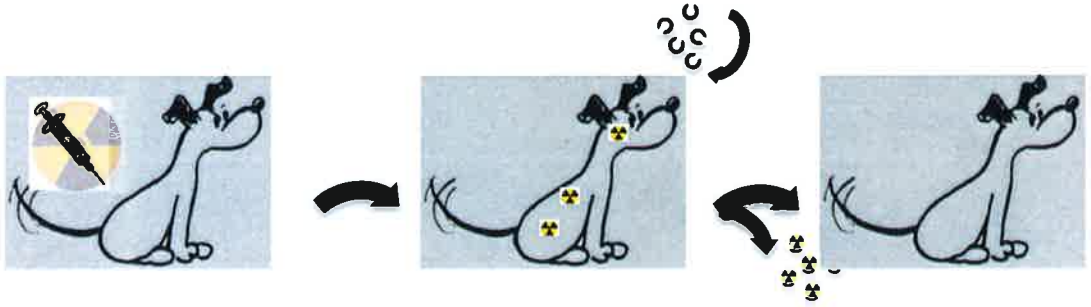



Kullgren B *et al. Toxicol. Mech. Methods*, **2013**, *23*, 18-26

Male and female data are important.
Multiple treatment and fractionation studies were needed.
Understanding differences in animal species is crucial.



Male & Female Cohorts
Metabolism Cages



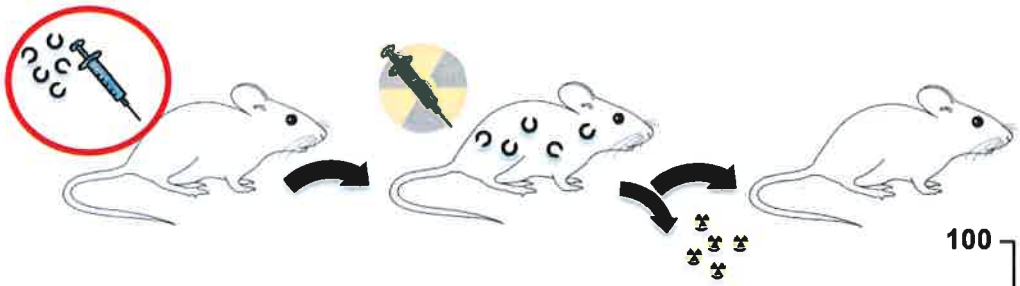
$^{238}$Pu- or $^{241}$Am-citrate injected iv,
Ligand given ip or po at 24 h
1x or 2x per day for 6 days
Mice euthanized at 2d, 4d, 8d, or 15d post-contamination

Radio-analysis

$^{239}$Pu- or $^{241}$Am-citrate injected iv,
Ligand po at 3 dose levels once at 1h, 12h, 3d, or 7d
Euthanasia at 7d post-treatment

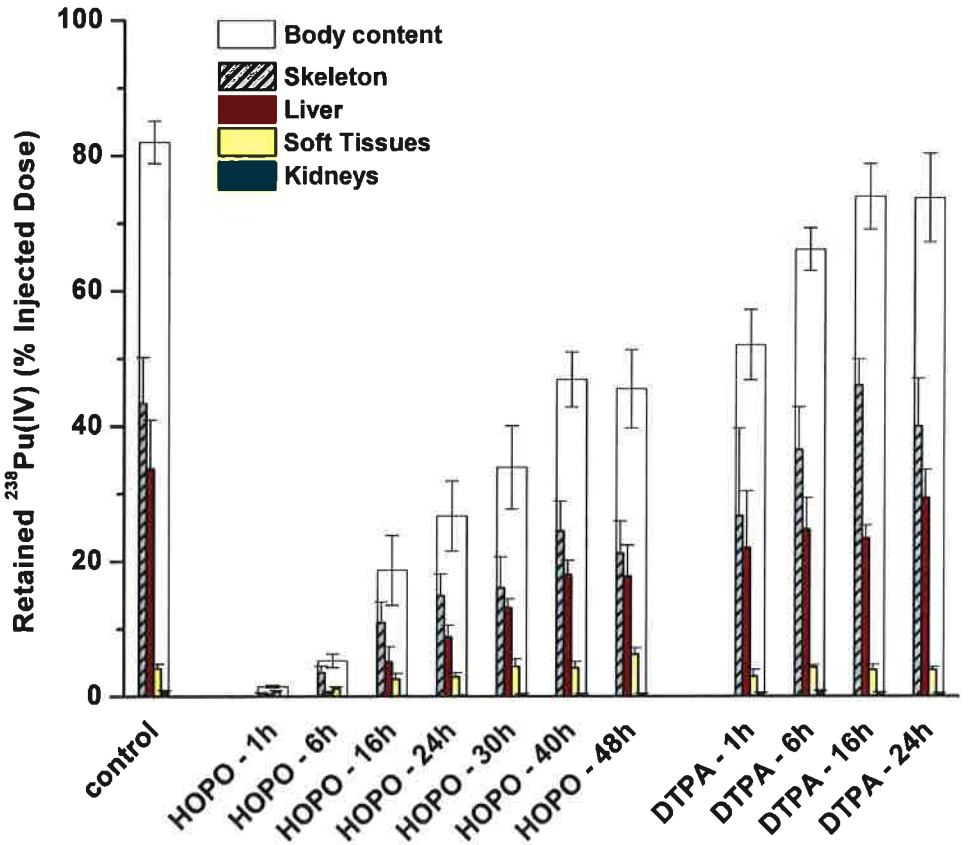
Radio-analysis

# Action prophylactique: 3,4,3-LI(1,2-HOPO)



Ligand injected ip before contamination
$^{238}$Pu-citrate injected iv at ≠ times
Mice euthanized 72 h after contamination

Radio-analysis



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# Règlementation

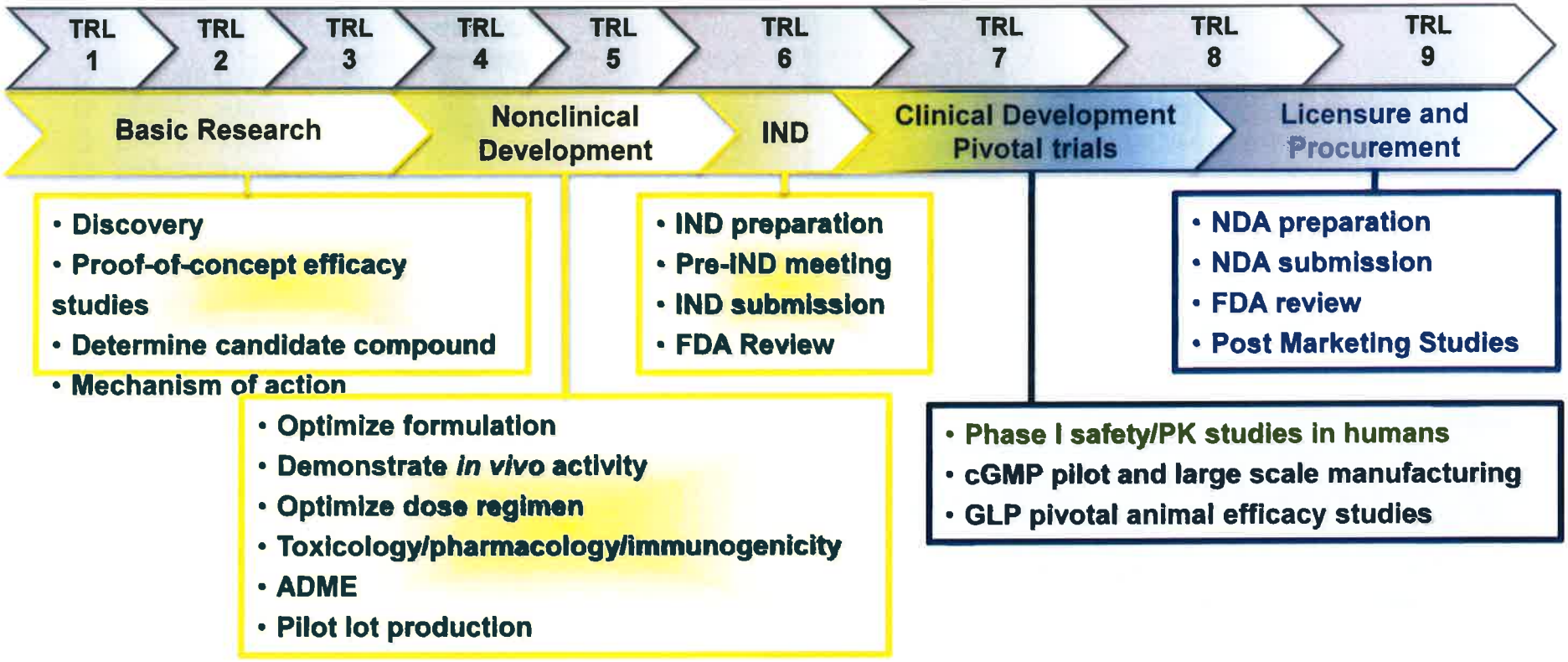
## LBNL - Programme de Décorporation des Actinides

**Indication:**
**Decorporation agent used to treat individuals exposed to actinides**
**Agent décorporant pour traiter les individus contaminés aux actinides**

# Echanges avec la FDA

| | |
|---|---|
| 2 aout 2011: | Premier meeting pré-IND avec la FDA pour 2 composes<br>5-LIO(Me-3,2-HOPO) pIND 112,262<br>3,4,3-LI(1,2-HOPO) pIND 112,264 |
| 20 mai 2013: | Second meeting pré-IND (TC) avec la FDA pour pIND 112,264<br>Mise au point du plan de développement et rapports de toxicité (GLP) soumis a la FDA |
| 4 avril 2014: | Protocole clinique (SAD) soumis a la FDA pour une première évaluation – Commentaires reçus le 8 mai 2014 |
| 3 juillet 2014: | IND – Reçue par la FDA le 8 juillet 2014 |
| 23 juillet 2014: | Questions sur la partie CMC - Réponses envoyées a la FDA le 28 juillet 2014 |
| 11 aout 2014: | Téléconférence avec la FDA et autorisation des premiers essais cliniques (étude SAD) |

# Plan de Développement




Après l'IND:

Traitement oral pour le stockpile
Etudes de post-marketing
Formules pédiatriques
Usage prophylactique (urgence, militaire, démantèlement)

**Lawrence Berkeley National Laboratory**
Dr. Manuel Sturzbecher-Hoehne
Dr. Taylor Choi
Dr. Nagender Panyala
Dr. Ben Allred
Dahlia An
Jonathan Villalobos
Chris Rosen
Stacey Gauny
Birgitta Kullgren
Erin Jarvis
Joel Morales-Rivera
Kathy Bjornstad

Actinide Chemistry Group
Prof. Kenneth Raymond
Dr. David Shuh

**SRI International**
Dr. Polly Chang
Dr. Debbie Bunin
Dr. David Sahner

**Lovelace Respiratory Research Institute**
Dr. Raymond Guilmette
Dr. Dunstana Melo
Dr. Waylon Weber
Dr. Melanie Doyle-Eisele


BARDA

NIH National Institute of Allergy and Infectious Diseases

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BIOACTINIDE GROUP

http://actinide.lbl.gov/gtsc/BioAn/index.html



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