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# 20th Annual California Cancer Consortium Conference

## Everything You Wanted To Know About the PITT-CAL U24 PK Resource Laboratory (But Were Afraid To Ask)

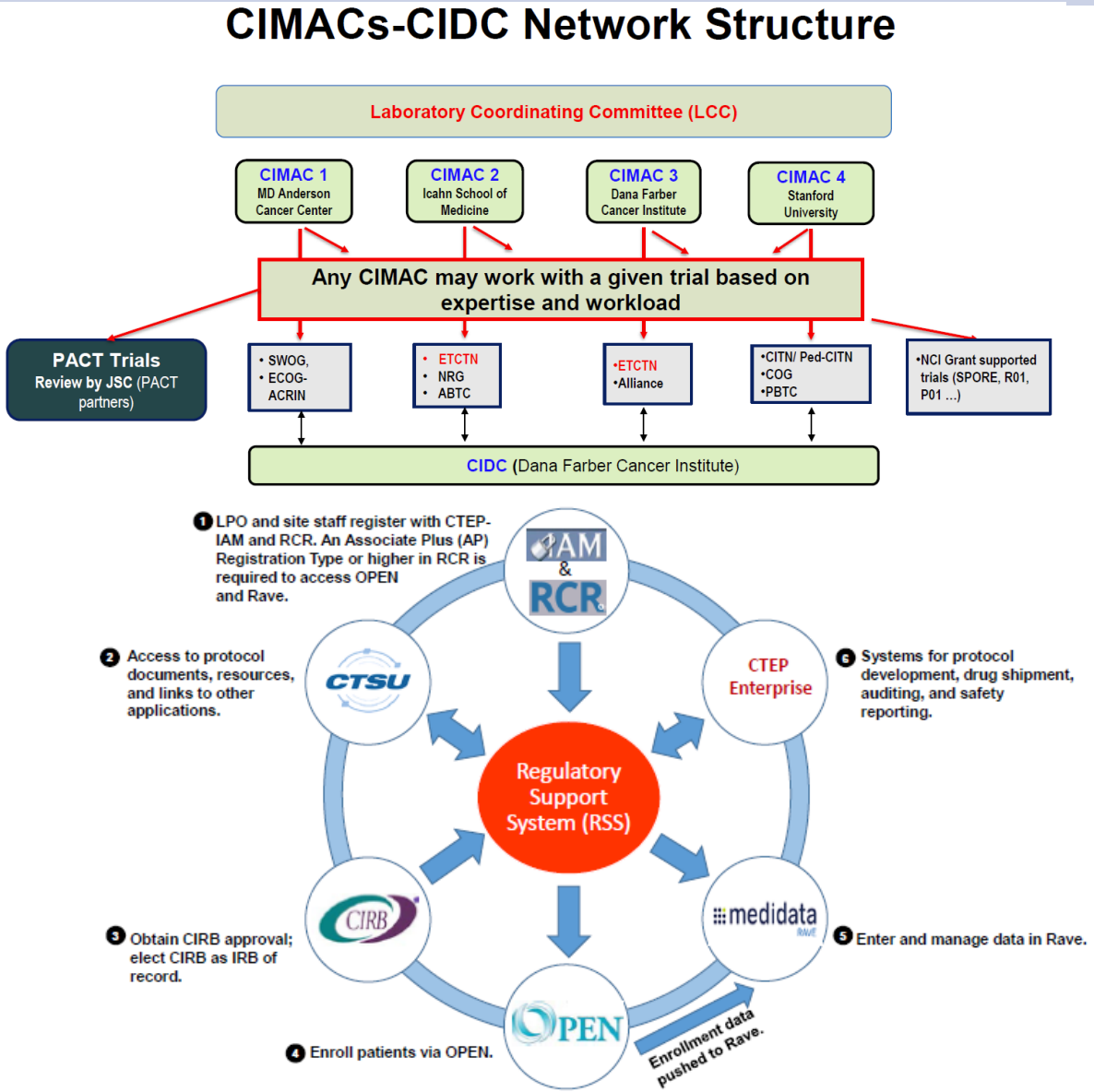
Tim Synold

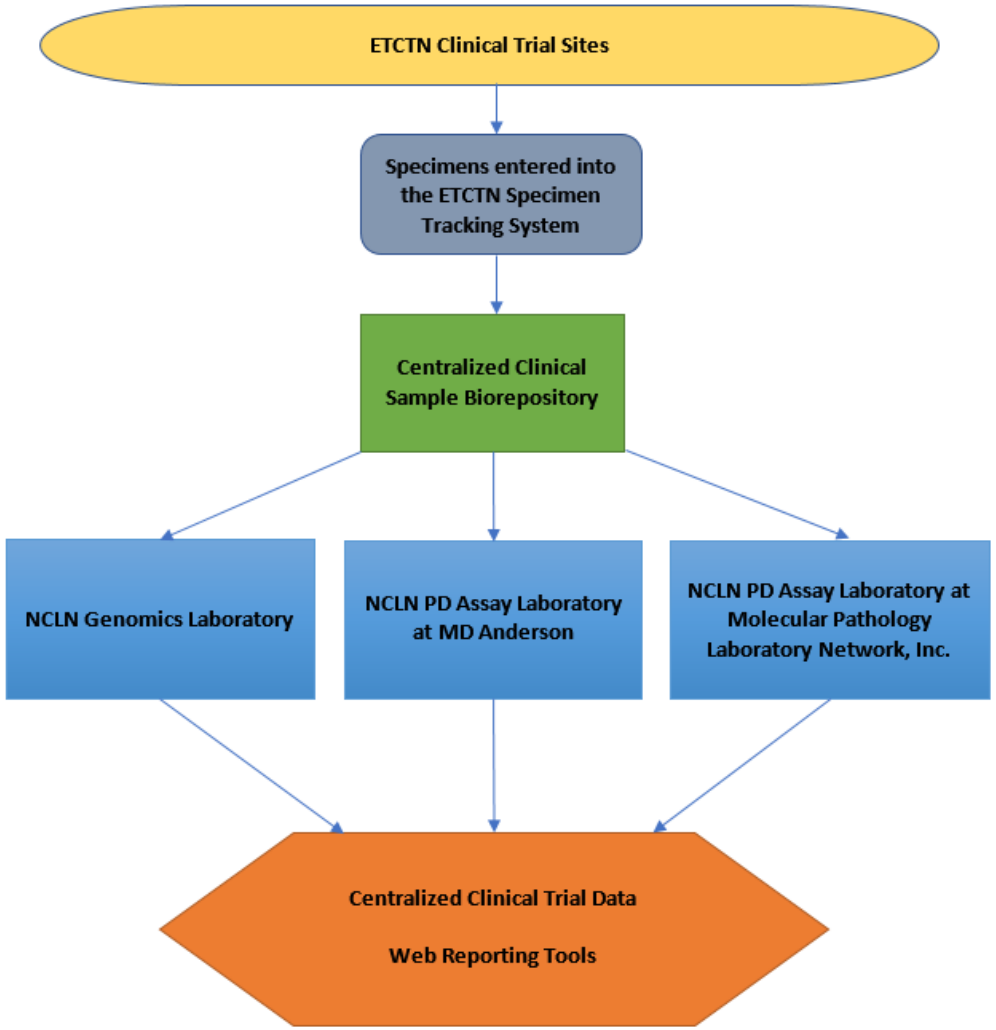
August 23rd, 2024

# ETCTN Objectives

- Conduct high quality early clinical trials in an efficient and timely manner
- Promote collaboration and foster career development
- Integrate pharmacology, cancer biology, and imaging

# Supporting the Science

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# Objectives of Early Trials

- **What is tolerable**
- **Does the drug get to the target** } PK
- **Does the drug engage the target** } PD

- **Early response assessment**
- **Exposure-toxicity & exposure-response**

- **Identify modifying factors**
  - Intrinsic (organ function, molecular status,..)
  - Extrinsic (DDI, smoking, food,..)

# Goals of PK

- **Phase I**
  - Disposition (Cmax, Tmax, AUC, CL, Vd, T1/2)
  - Dose dependence
  - Drug-drug interactions
  - Drug-disease interactions (co-morbidities, organ function, age, genotype, etc)
- **Phase II**
  - Relationship between exposure and outcome
  - Sources of PK variability

# U24 Cooperative Agreement

Department of Health and Human Services
Part 1. Overview Information

**Participating Organization(s)**
National Institutes of Health (NIH (http://www.nih.gov))

**Components of Participating Organizations**
National Cancer Institute (NCI (http://www.nci.nih.gov/))

**Funding Opportunity Title**
The Experimental Therapeutics Clinical Trials Network (ETCTN) Pharmacokinetic Resource Laboratories (U24 Clinical Trial Not Allowed)

**Activity Code**
U24 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=u24&Search.x=0&Search.y=0&sort=ac&Search_Type=Activity&text_prev=) Resource-Related Research Projects – Cooperative Agreements

**Announcement Type**
New

- FOA posted January 2019
- Goal was to create centralized PK Resource Laboratories to support ETCTN trials
- Two proposals representing four institutions chosen
- Funding began May 2020

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# U24 Consortia – ETCTN PK Resources

- **PITT-CAL**
  - Univ. of Pittsburgh - Beumer
  - City of Hope - Synold

- **ChOP-KC**
  - Johns Hopkins - Carducci
  - Ohio State - Baker (Phelps, Sparreboom)

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# U24 Specific Aims

- **AIM 1: Provide pharmacology expertise**
- **AIM 2: Analyze biological samples**
- **AIM 3: Perform PK data analyses**

# U24 Consortia – Division of Labor

**Project Team (PTMA) LOIs**

- Distributed based on bandwidth, interest, and equity

**Unsolicited LOIs (i.e. non-Project Teams)**

- Each U24 responsible for their UM1 LAOs
  - PITT-CAL = CCC (LAO) and PITT (LAO)
  - ChOP-KC = JHU (LAO) and OSU (LAO)
- Other UM1 LAOs (Princess Margaret, Dana Farber, Yale, and MD Anderson) to contact U24 PI's for assignment

# PITT-CAL Resources

- **Leverages two existing CCSG Shared Resources**
- **Capabilities include LC-MS/MS, HPLC/UV/FL/EC, ICP-MS, Luminex, ELISA, qPCR, flow cytometry**
- **GLP-compliant operations**
  - Assays validated to FDA standards
- **Current assay portfolio covers >200 analytes**
  - small molecules and metabolites
  - oligonucleotides
  - proteins (ADCs, monoclonals, and bispecifics)
  - cell therapies

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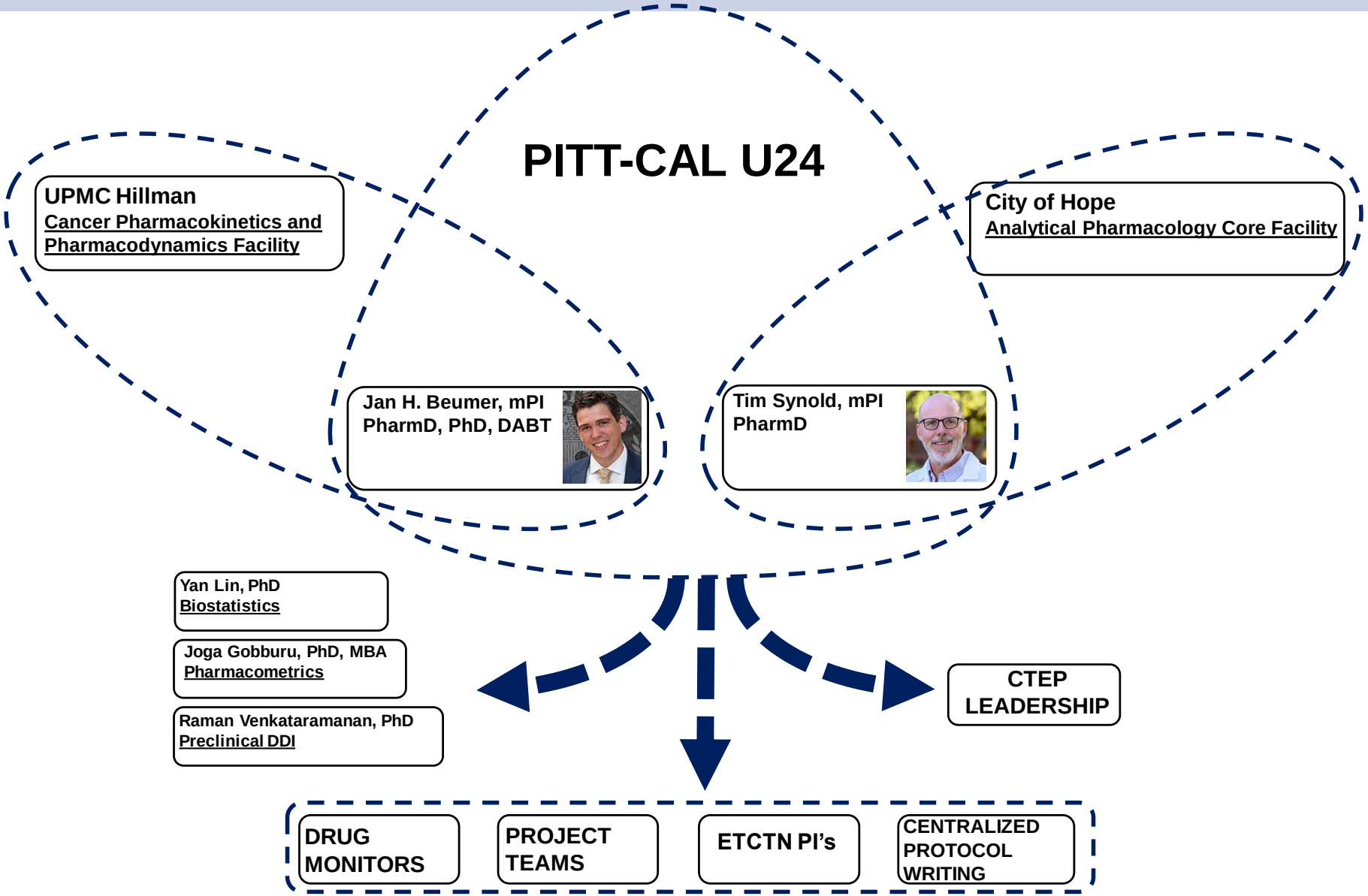
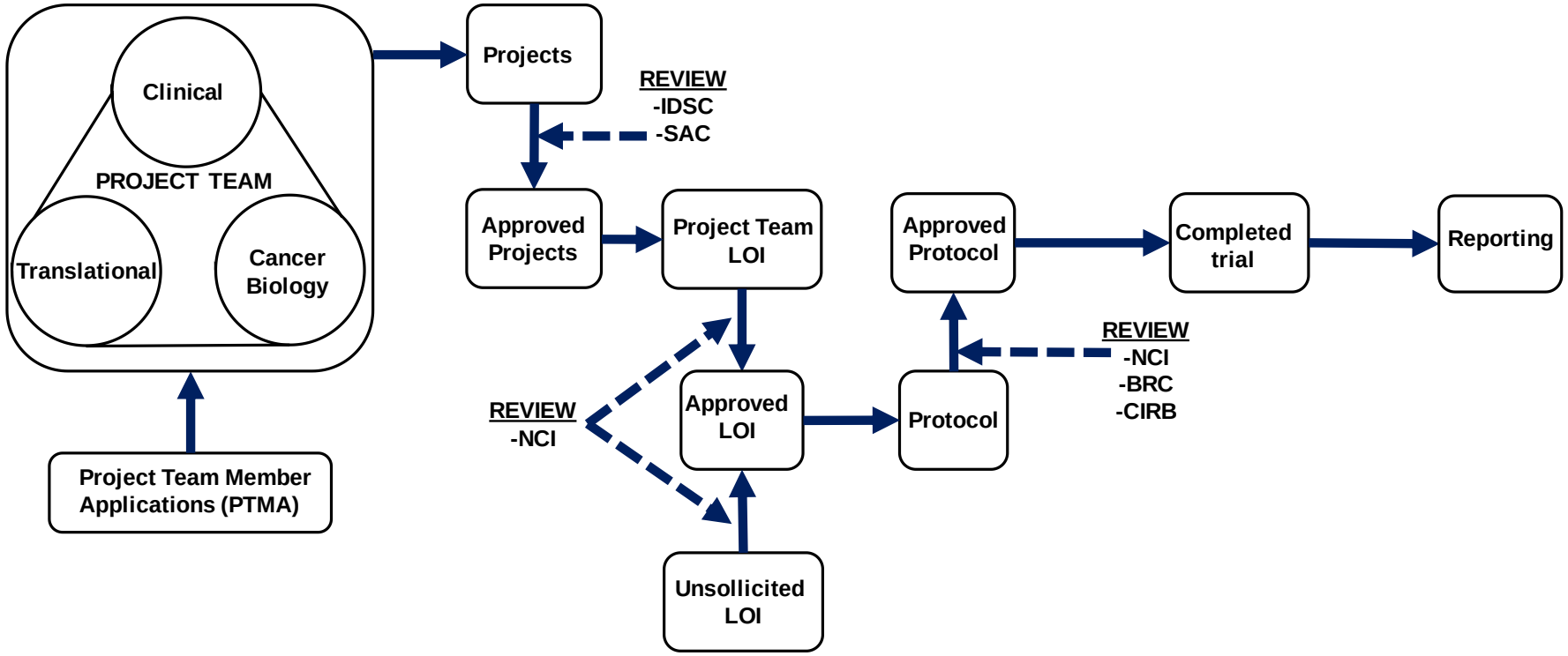
# PITT-CAL U24 Interactions



# PITT-CAL Activities




## PITT-CAL ACTIVITIES

- -Evaluate existing PK data
- -Identify PK needs and opportunities
- -PK integration into trial design
- -Inform and educate clinical team
- -Negotiate and design PK sampling
- -Develop PK statistic design
- -Draft PK sections
- -Operationalize sample collection, storage, shipment
- -Finalize statistic design
- -Sample receipt
- -Sample analysis
- -PK analysis
- -Interim PK reports
- -Draft PK reporting
- -Statistical analyses
- -Explore PK-PD relationships
- -Draft manuscript sections
- -Explore POP-PK analyses

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ETCTN

Experimental Therapeutics Clinical Trials Network

*Team Driven. Cancer Therapy Focused.*

## Pidnarulex Project Team


**Tim Synold, PharmD**
**City of Hope**
**mPI, U24 PITT-CAL PK Resource Lab**
**Director, Division of Molecular Pharmacology**
**Director, Analytical Pharmacology Core**
**PK Director, California Cancer Consortium**


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH

NATIONAL CANCER INSTITUTE

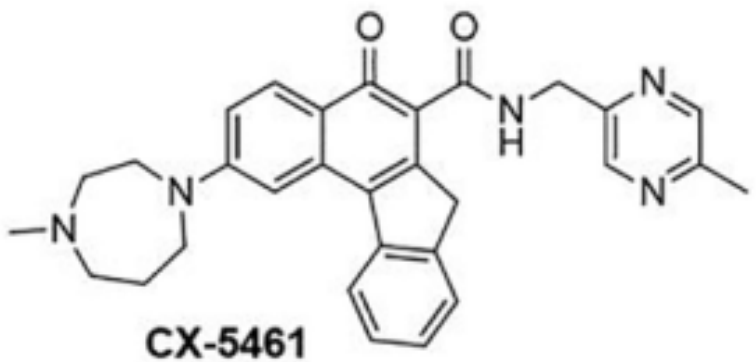
# Pidnarulex Non-Clinical PK

- IV administration over 1 hour
- Highly protein bound (>99%)
- Metabolized via CYP3A
- Major metabolite de-methylated
- Low-moderate CYP3A4 and CYP1A2 inhibitor (IC50 = 7-10 µM)
- Enzyme inducer status unknown
- Drug transporter substrate and inhibit status unknown

**Cmax (@ 170 mg/m2)**

**Total ≈ 3.3 µM**

**Free ≈ 0.03 µM**

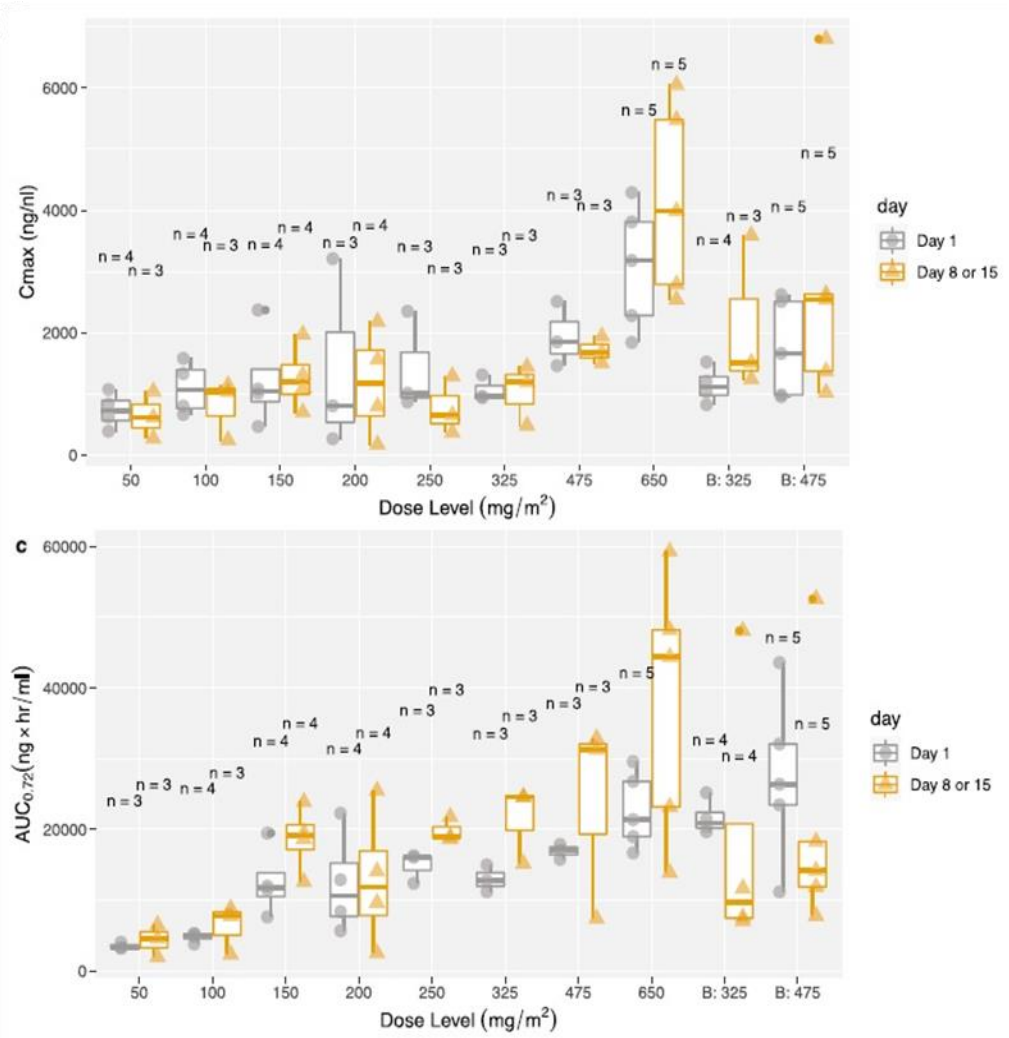



CX-5461

Tested: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

# Pidnarulex Clinical PK

- Data available from prior Phase 1 studies
- Long t1/2 (~60 hours)
- Evidence of enterohepatic recirculation
- Roughly dose proportional
- Minimal accumulation
- Large inter- and intra-subject variability



# Summary of Key PK Findings

- Metabolized via CYP3A4/5
- Highly protein bound
- Long elimination t1/2
- Evidence of enterohepatic recirculation
- Dose proportional over clinically relevant range
- Large inter- and intra-subject variability

# Key Gaps in PK

- **Status as DDI victim and perpetrator unknown**
  - ➢ Strong CYP3A4/5 inhibitors & inducers should be avoided
- **Routes of elimination unknown**
  - ➢ Renal and hepatic impairment should be excluded
- **Significance of metabolite unknown**

# Project Team PK Considerations

- **Further define PK variability and assess exposure-response relationships (parent and possible metabolites)**
  - All 5 PT proposals
- **Potential DDI's**
  - *A Phase I Study of Pidnarulex in Combination with 5-FU and Liposomal Irinotecan in Second-Line Treatment of Metastatic Pancreatic Adenocarcinoma*
  - *Phase 1b/2 study of Pidnarulex and Trastuzumab Deruxtecan in patients with HER2 expressing Breast Cancer*
  - *Pidnarulex plus PARPi in Platinum Sensitive Recurrent Ovarian Cancer*
- **In conjunction with PD to explore PK/PD relationships**

# U24 Portfolio – Study Design

| LOI/PT | Type | Lead Agent | Other Drugs | LAO | PI | Role/Activity |
|---|---|---|---|---|---|---|
| # | U, S, or PT | | | | | |
| ACTIVATED | | | | | | |
| 10324 | S | M3814 (PEPOSERTIB) | Doxil | LAO-MD017 | Grisham | Support trial and PK design |
| 10402 | S | BAY1895344 | IRINO/TOPO | LAO-CT018 | Das | Design PK protocol |
| 10403 | S | BAY1895344 | GEM | LAO-MA036 | Cleary | Design PK protocol |
| 10433 | U | ZEN-3698 | NIVO+/-IPI | LAO-PA015 | Mahdi | Support trial and PK design |
| 10406 | S | BAY1895344 | FOLFIRI | LAO-PA015 | Krishnamurthy | Support trial and PK design |
| 10483 | U | ERDAFITINIB | enfortumab-vedotin | LAO-11030 | Jain | Support trial and PK design |
| 10500 | U | TAZEMETOSTAT BELINOSTAT | | LAO-CT018 | Amengua | Design PK protocol |
| 10522 | U | CA-494 | paclitaxel | LAO-CT018 | Park | Design PK protocol |
| 10525 | U | ZEN-3694 | paclitaxel | LAO-MA036 | Garrido-Castro | Design PK protocol |
| 10558 | U | triapine | Lutathera | LAO-OH007 | Chauhan | Design PK protocol |
| 10563 | U | M3814 (PEPOSERTIB) | Doxil | LAO-MA036 | Haddox | Design PK protocol |
| 10579 | U | ZEN-3694 | capecitabine | LAO-PA015 | Hsu | Design PK protocol |
| NRG-GY028 | PT | IPATASERTIB | MPA | NRG | Grinsfelder/Onstad | Design PK protocol |
| NRG-GY031 | U | ZEN-3694, M1774 | | NRG | Simpkins | Design PK protocol |
| PENDING | | | | | | |
| 10527 | U | M3814 (PEPOSERTIB) | M1774 | LAO-MA036 | Cote | Design PK protocol |
| 10559 | U | ERDAFITINIB | | LAO-11030 | De La Fuente | Design PK protocol |
| 10630 | S | iadademstat | VEN AZA | LAO-PA015 | Galanina | Design PK protocol |
| 10640 | U | TIRAGOLUMAB, ATEZOLIZUMAB | | LAO-PA015 | Mantica | Consulted during LOI development |
| 10647 | U | TOLINAPANT | ERIBULIN | LAO-OH007 | Kelley | Consulted during LOI development |
| 10667 | U | PIDNARULEX | | LAO-NCI | Chen | Consulted during LOI development |
| 10670 | | ABEMACICLIB | FU | LAO-PA015 | Zhang | Consulted during LOI development |
| 10673 | U | M3814 (PEPOSERTIB) | mirdametinib | LAO-OH007 | Moschos | Consulted during LOI development |
| 10674 | U | CIRTUVIVINT | VEN AZA | LAO-MA036 | Stahl | Consulted during LOI development |
| 10707 | PT | CBX-12 | | LAO-PA015 | Kuang | Design PK LOI |
| 10703 | U | SAPANISERTIB | CABOZANTINIB | LAO-PA015 | Saeed | Consulted during LOI development |
| IN DEVELOPMENT | | | | | | |
| TBD | U | M1774 | COBIMETINIB | LAO-MD017 | Grant | Consulted during LOI development |
| TBD | U | M1774 | FOLFIRI | LAO-MD017 | Pishvaian | Consulted during LOI development |
| 10699 | U | TRIAPINE | RT | LAO-CA043 | Yoon | Consulted during LOI development |
| PROJECT TEAM INVOLVEMENT | | | | | | |
| - | S | PIDNARULEX | PARPi | LAO-CT018 | Dockery | Project Team member |
| - | S | PIDNARULEX | T-DXd | LAO-MA036 | Lynce | Project Team member |
| - | S | PIDNARULEX | ANTI-PD-(L)1 | LAO-MD017 | Lentz | Project Team member |
| - | S | PIDNARULEX | FOLFIRINOX | LAO-PA015 | Zhang | Project Team member |
| - | S | PIDNARULEX | | LAO-CT018 | Ibrahimi | Project Team member |

# U24 Portfolio – Assay Development and Analysis

| Trial # | Clinical Trial Name | LAO | PI | Pharmacology endpoints relevant to the U24 (i.e. PK endpoints) | Analytes | # New Methods Developed and Validated (or Cross-validated) for Trial (RP) | # New Methods Developed and Validated (or Cross-validated) for Trial (Cumulative) |
|---|---|---|---|---|---|---|---|
| 8846 | Phase I Pharmacokinetic Study of Be | NCI | Takebe | E-R, IND | BELINOSTAT | | |
| 9892 | Phase I Dose-Escalation Bioavailabil | LAO-PA015 | Taylor | DLin, E-R | TRIAPINE | | |
| 9938 | Phase I Clinical Trial of VX-970 in Co | LAO-PA015 | Villaruz | DDI, E-R | M6620, IRINO+ | | |
| 9938 | Phase I Clinical Trial of VX-970 in Co | LAO-PA015 | Villaruz | DDI, E-R | M6620, IRINO+ | | |
| 9947 | A Randomized Phase 2 Trial of Cisp | LAO-CA043 | Pal | E-R | M6620, GEM | | |
| 9947 | A Randomized Phase 2 Trial of Cisp | LAO-CA043 | Pal | E-R | M6620, GEM | | |
| 9950 | A Phase I Study of M6620 (VX-970) | LAO-MD017 | Owonikoko | E-R | M6620 | | |
| 10217 | A Phase 1b Biomarker-Driven Combi | LAO-TX035 | Yap | DDI, E-R | COPAN, OLA, DURVA | | OLA |
| 10273 | A Phase 1 Study of M3814 in combir | LAO-CA043 | Jonas | DDI, E-R | M3814, MITOX, ETOP+, araC | | M3814+ |
| 10273 | A Phase 1 Study of M3814 in combir | LAO-CA043 | Jonas | DDI, E-R | M3814, MITOX, ETOP+, araC | ETOP+ | ETOP+ |
| 10273 | A Phase 1 Study of M3814 in combir | LAO-CA043 | Jonas | DDI, E-R | M3814, MITOX, ETOP+, araC | | araC+ |
| 10276 | A Phase I/II Study of M3814 and Ave | LAO-11030 | Spencer | IND | M3814+, Avelumab | | M3814+ |
| 10324 | A Phase I/Ib Dose Escalation Study | LAO-MD017 | Grisham | DDI, E-R | M3814+, DOXIL+ | | M3814+ |
| 10324 | A Phase I/Ib Dose Escalation Study | LAO-MD017 | Grisham | DDI, E-R | M3814+, DOXIL+ | DOXIL+ | DOXIL+ |
| 10313 | A phase IB and randomized open-lab | LAO-PA015 | Villaruz | E-R | M6620, GEM+ | | |
| 10313 | A phase IB and randomized open-lab | LAO-PA015 | Villaruz | E-R | M6620, GEM+ | | |
| 10355 | A Phase I Study of DS-8201a in Com | LAO-MA036 | Lee | IND | OLA | | OLA |
| 10366 | A Phase 1/2 Study of M3814 in Com | LAO-MD017 | Davis | IND | M3814+ | | M3814+ |
| 10388 | A Phase I Trial of Triapine and Luteti | LAO-OH007 | Chauhan | E-R | TRIAPINE | | |
| 10401 | A Phase 0 window-of-opportunity pha | LAO-MD017 | Stone | E-R | TRIAPINE (plasma) | | |
| 10401 | A Phase 0 window-of-opportunity pha | LAO-MD017 | Stone | E-R | TRIAPINE (tumor) | | |
| 10402 | BAY 1895344 Plus Topoisomerase-1 | LAO-CT018 | Das | IND, E-R | BAY1895344, TOPO+, IRINO+ | | BAY1895344 |
| 10402 | BAY 1895344 Plus Topoisomerase-1 | LAO-CT018 | Das | IND, E-R | BAY1895344, TOPO+, IRINO+ | | TOPO+ |
| 10402 | BAY 1895344 Plus Topoisomerase-1 | LAO-CT018 | Das | IND, E-R | BAY1895344, TOPO+, IRINO+ | | |
| 10403 | Phase 1 Trial of Gemcitabine Combi | LAO-MA036 | Cleary | IND, E-R | BAY1895344, GEM+ | | BAY1895344 |
| 10403 | Phase 1 Trial of Gemcitabine Combi | LAO-MA036 | Cleary | IND, E-R | BAY1895344, GEM+ | | |
| 10404 | A Phase 1 Trial of the ATR Inhibitor E | LAO-CA043 | Parikh | IND, E-R | BAY1895344, GEM+ | | BAY1895344 |
| 10406 | Phase I/Ib Trial of ATR Inhibitor BAY | LAO-PA015 | Krishnamurthy | IND, E-R | BAY1895344, FU, IRINO+ | | BAY1895344 |
| 10406 | Phase I/Ib Trial of ATR Inhibitor BAY | LAO-PA015 | Krishnamurthy | IND, E-R | BAY1895344, FU, IRINO+ | | FU |
| 10406 | Phase I/Ib Trial of ATR Inhibitor BAY | LAO-PA015 | Krishnamurthy | IND, E-R | BAY1895344, FU, IRINO+ | | |
| 10433 | Phase I/Ib trial evaluating the safety a | LAO-PA015 | Mahdi | DLin, E-R | ZEN-3698 | | ZEN-3694+ |
| 10449 | A Phase I Study to Investigate the Sa | LAO-TX035 | Piha-Paul | D-Lin, DDI, E-R | ZEN-3694+, Binimetinib | | ZEN-3694+ |
| 10450 | A Phase 1b Study of M3814 (Pepose | LAO-OH007 | Chauhan | IND | M3814 | | M3814+ |
| 10483 | Phase Ib trial of Erdafitinib combined | LAO-11030 | Jain | DDI, E-R | ERDAFITINIB, MMAE | | ERDAFITINIB, MMAE |
| 10492 | Phase 1/1b Study of AKT Inhibitor Ip | LAO-11030 | Mattes | E-R | IPATASERTIB, M1 | | IPATASERTIB+ |
| 10500 | Phase 1/Expansion Study of Tazeme | LAO-CT018 | Amengual | E-R, DDI | TAZEMETOSTAT | TAZEMETOSTAT | TAZEMETOSTAT |
| 10527 | A Molecularly Driven Phase 1b Dose | LAO-MA036 | Cote | E-R, DDI | M1774 | | |
| 10563 | A Phase 1 Study of Peposertib (M38 | LAO-MA036 | Haddox | DDI, E-R | M3814+, DOXIL+ | | |
| 10563 | A Phase 1 Study of Peposertib (M38 | LAO-MA036 | Haddox | DDI, E-R | M3814+, DOXIL+ | | |
| 10579 | Phase I trial of ZEN003694 (ZEN-369 | LAO-PA015 | Hsu | E-R, DDI | ZEN-3698, CAPECITABINE | | ZEN-3694+ |
| 10579 | Phase I trial of ZEN003694 (ZEN-369 | LAO-PA015 | Hsu | E-R, DDI | ZEN-3698, CAPECITABINE | CAPECITABINE | CAPECITABINE |

# Summary

- PK and PD essential for successful drug development and dose optimization (preclinical → post-marketing)
- Can guide dosing decisions, explain variability in response and toxicity, inform rational combinations and precision medicine approaches
- PK and PD resources are available within the CCC and ETCTN

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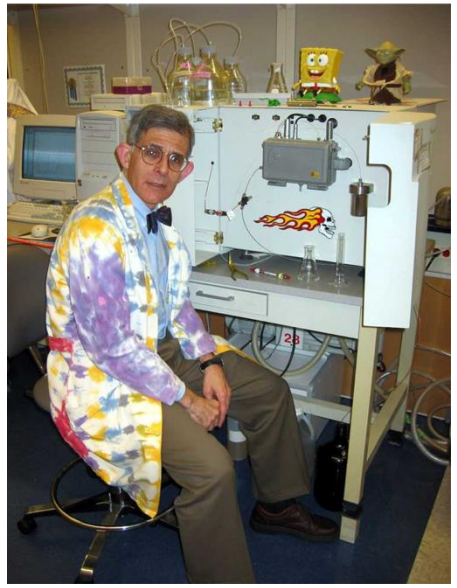
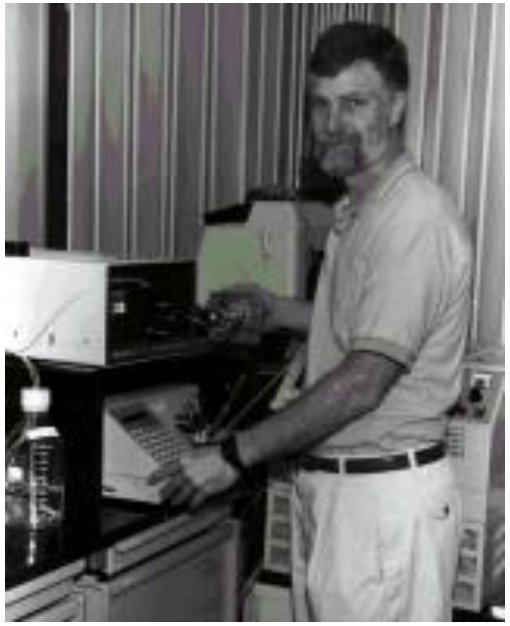
# Standing on the Shoulders of Giants



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# Thanks For Your Attention

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