CTSA Program Webinar

Wednesday, February 27, 2019
2:00 PM – 3:00 PM ET

Agenda

Time	Topic	Presenter
2:00 - 2:05	Welcome NCATS and CTSA Program Updates	Clare Schmitt
2:05 - 2:25	DTF/WG Function & Structure 2.0: Building on the DTF Successes	Kathleen Brady & Clare Schmitt
2:25 - 2:30	Common Metrics and Spring CTSA Program Group Meetings - Updates	Martin Zand & Deborah Ossip
2:30 - 2:55	A New CTSA Initiative: Drug Repurposing Screening Collaborations	Nikki Rogers Alvarez
2:55 - 3:00	Adjourn	

NIH National Center for Advancing Translational Sciences

NCATS and CTSA Program Updates

Clare Schmitt

Welcome
NCATS Deputy Director
Dr. Joni Rutter

National Center for Advancing Translational Sciences

CTSA
Clinical & Translational Science Awards Program

CLIC
Center for Leading Innovation & Collaboration

Research Efforts to Address Rural Health Disparities

Congress embedded language within our FY19 appropriations to encourage the CTSA Program to expand translational research efforts that address rural health disparities as well as the significant burden of conditions that disproportionately affect minority and special populations.

Recent CTSA Program Enhancements:

- NCATS Notice of Information (NOT-TR-19-015) emphasizes the CTSA Program's interest in improving rural health outcome and reducing health disparities. CTSA Program investigators and investigators supported by Institutional Development Award (IDeA) Program Infrastructure for Clinical and Translational Research (IDeA-CTR) awards are encouraged to work together to address translational science barriers.
  - January's CTSA Program Webinar highlighted the IDeA-CTRs and described some of the partnerships in place with CTSAs
  - NOT-TR-19-016 – Notice for the Collaborative Innovation Award U01 (PAR-19-099):
    - An application must involve investigators who are supported by CTSA Program hub institutions from at least three different and currently funded CTSA Program hubs as of the due date of the application *or alternatively, an application may involve investigators from at least two different and currently funded CTSA Program hubs (of which one must be the contact PI on the application) and one or more currently funded NIH Institutional Development Award (IDeA) Program Infrastructure for Clinical and Translational Research (IDeA-CTR) participating institution*, as of the due date of the application.

Un-Meeting on Rural Health and Health Equity

- This event will focus on catalyzing new collaborations to bridge the translational science, cooperative extension and other sectors to improve rural health and achieve health equity. Discussion topics will be identified and prioritized by attendees in real time, but examples of potential topics of interest include **food insecurity, the opioid epidemic, geographic disparities in life expectancy, experiential learning opportunities, social determinants of health, healthy environments, rural diversity and cultural identity, access to health care, occupational health, bridging silos across sectors and disciplines, and opportunities for regional collaboration.**
- **Hosted by:** University of Florida Clinical and Translational Science Institute and the University of Florida Institute of Food and Agricultural Sciences
- **Support from:** Center for Leading Innovation and Collaboration (CLIC)
- **Date:** April 7-8, 2019
- **More Info:** https://www.ctsi.ufl.edu/an-un-meeting-on-rural-health-and-health-equity/

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Collaboration & Engagement DTF Health Disparities WG

- **Leads:**
  - Co-Lead: Lloyd Michener (Duke University)
  - Co-Lead: Sergio Aguilar-Gaxiola (University of California, Davis)
  - Co-Lead: Katrina Kubicek (University of Southern California)
  - C/E DTF Lead Team Liaison: Laurene Tumiel-Berhalter (University of Buffalo)
- **Goals:**
  - Make recommendations to CTSA Consortium about opportunities for partnership and collaboration on assessing and reducing health disparities
    - Strengthen and leverage capabilities and assets of CTSAs nationwide
    - Contribute understanding of and solutions of health disparities translational research
- **Objectives:**
  - Compile comprehensive list of current community and state partnerships on reducing health disparities
  - Map this list to CTSA hubs to find opportunities to collaborate
  - Facilitate these partnerships with tools and guidance

The University of Rochester Center for Leading Innovation and Collaboration (CLIC) is the coordinating center for the Clinical and Translational Science Awards (CTSA) Program, funded by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH), Grant U24TR002260.

Notice to CTSA Program FOA PA-18-940 (NOT-TR-19-014)

Updates in Overall Core:

- Updated info in the Letters of Support:
  - "The application must include a letter of support from an authorized institutional official stating that the institution is willing to *comply with the NIH single IRB policy* for multi-site research *and in particular is willing to sign or is a current signatory to the CTSA Program SMART IRB Reliance Agreement*, is willing to use master subcontract agreements/trial agreements (see for example https://www.ott.nih.gov/resources#MCRDA) and is willing to work under a transparent cost structure for per patient cost.

Updates in NRSA Training Core:

- Clarified that the core does not provide support for personnel
- Clarified that in **Other Direct Costs: Trainee Travel:** Enter the total costs for Trainee Travel *(up to $1,500 per year per trainee)*

NCATS website updated with this information: https://ncats.nih.gov/ctsa/funding/par-information

Questions? CTSAFOAQuestions@mail.nih.gov

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NCATS / Eli Lilly Externship Update

- **Objective**
  - Promote experiential rotation opportunities for CTSA investigators and trainees in “real world”, private sector setting
- **Program Characteristics**
  - Embedded in functional teams, mentoring by Eli Lilly scientists
  - 6 months, based in Indianapolis at Eli Lilly
  - Shared funding between NCATS and Eli Lilly
- **Examples of Projects worked on at Eli Lilly (2016-2018 cohorts)**
  - Mechanistic Modeling of the Tau Pathway in Alzheimer’s disease
  - Translational pharmacology of diabetes
  - FDA approval process for a new oncology drug

Program enhancements coming, 2020…

2019 Cycle, expect to announce by mid-March 2019
Anticipated start date: July 2019
https://ncats.nih.gov/ctsa/training/resources/lilly-externship
(live video vignette of Dr. Taverna now on NCATS website)
Contact: Joan Nagel, M.D., M.P.H. joandav@mail.nih.gov

Featured above: Christopher P. Austin, M.D., Director, NCATS; Joan Nagel, M.D., M.P.H., Medical Officer, Division of Clinical Innovation, NCATS; Danise Subramaniam, Ph.D., Senior Director, Global Regulatory Affairs-NA Eli Lilly and Company; Josephine Taverna, M.D., NCATS Eli Lilly Scholar;
Michael Kurilla, M.D., Ph.D., Director, Division of Clinical Innovation, NCATS

Notice of Intent to Publish a Funding Opportunity Announcement for Administrative Supplements for Research on Bioethical Issues (NOT-OD-19-045)

- **Purpose:**
  - The National Institutes of Health (NIH) Office of Science Policy within the NIH Office of the Director (OD) intends to publish a Funding Opportunity Announcement for administrative supplements to support research on bioethical issues to inform future policy directions or embed bioethics within NIH-supported research. Applicants may propose to supplement parent awards focused on bioethics or to add a component related to bioethics to a parent award in which bioethics was not the focus.
- **Funding Information:**
  - Estimated Total Funding: TBD
  - Expected Number of Awards: 5-15
  - Estimated Award Ceiling: Up to $100,000 direct costs for 1 year
- **Inquiries:**
  - Jennifer Plank-Bazinet, PhD, NIH Office of Science Policy; Email: jennifer.bazinet@nih.gov

DTF/WG Function & Structure 2.0: Building on the DTF Successes

Kathleen Brady & Clare Schmitt

History

- **Original purpose of the Domain Task Forces: Execute the NCATS Advisory Council Working Group (ACWG) recommendations.**
  - **Provide NCATS/CTSA with input from all stakeholders to set direction and priorities for CTSA projects**
  - **Focus on short and long term needs with the goal to enable translational science and provide patients with access to treatment more quickly**
  - **Provide a structure where high priority issues (that relate to ACWG and CTSA goals) can be studied**
  - **Inclusive process where all Hubs can participate and have access**
  - **Foster communication and collaboration at all levels**
  - **Discrete objectives, timelines and deliverables for every activity**

- **These activities continue to be central to a robust CTSA Program**

Background

- **November 2014 DTFs Created**
- **April 2018 Steering Committee F2F Meeting**
  - **Reviewed Domain Task Force Packet/Updates**
    - **Included Suggested Enhancements for the DTFs**
  - **Convened a Steering Committee Work Group on Enhancing the DTFs**

MEMBERS	
Kathleen Brady	Samantha Jonson (NCATS)
Ebony Boulware	Erica Rosemond (NCATS)
Bradley Evanoff (Methods/Processes DTF)	Clare Schmitt (NCATS)
Dan Cooper (Lifespan DTF)	Martin Zand
Melissa Haendel	Joel Tsevat (Collaboration/Engagement DTF)
Donald Lloyd-Jones (Informatics DTF)	Susan Smyth (Workforce DTF)

CLIC Coordination:
- Kate Fetherston
- Scott McIntosh
- Debbie Ossip

  - **July 2018 Launched DTF Survey**

DTF Survey – Key Responses (n=275; July 2018)

- **Generally Supportive**
- **Overall DTF Structure**
  - **Well-Informed about DTF Activities: 11% YES***
  - **Addressing Important Issues: 43% YES**
  - **Valuable: Scale of 1-10 6-10 = 50% (5-10 = 73%)**
  - **"Right" Structure: 50% YES**

Yes includes only agree/strongly agree responses

- **Issues Identified**
  - **Communications**
  - **Provide Resources for DTFs; Unfunded Mandate**
  - **DTFs Too Broad; Need Focus, Timelines, Deliverables**
  - **Strengthen Collaborative Efforts**
  - **Change DTF Name to Avoid a Problematic Acronym and Better Reflect Function**

DTF & WG List

Collaboration & Engagement DTF

- Full Team
- Lead Team
- Workgroups:
  - D & I Science
  - Methods to Assess Community Engagement
  - JWG Research Training
  - Developing Measures – writing paper

Informatics DTF

- Full Team
- Lead Team
- Workgroups in Development:
  - Sustainability Phase Two
  - Secondary Models
  - WG - Text Analytics & De-Identification

Methods & Processes DTF

- Full Team
- Lead Team
- Workgroups:
  - Institutional Readiness for Team Science Secondary Models
  - Regulatory Science to Advance Precision Medicine

Lifespan DTF

- Full DTF
- Lead Team
- Workgroups:
  - ELE – newly supporting Life Course Writing Group
  - Single Disease
  - JWG Research Training

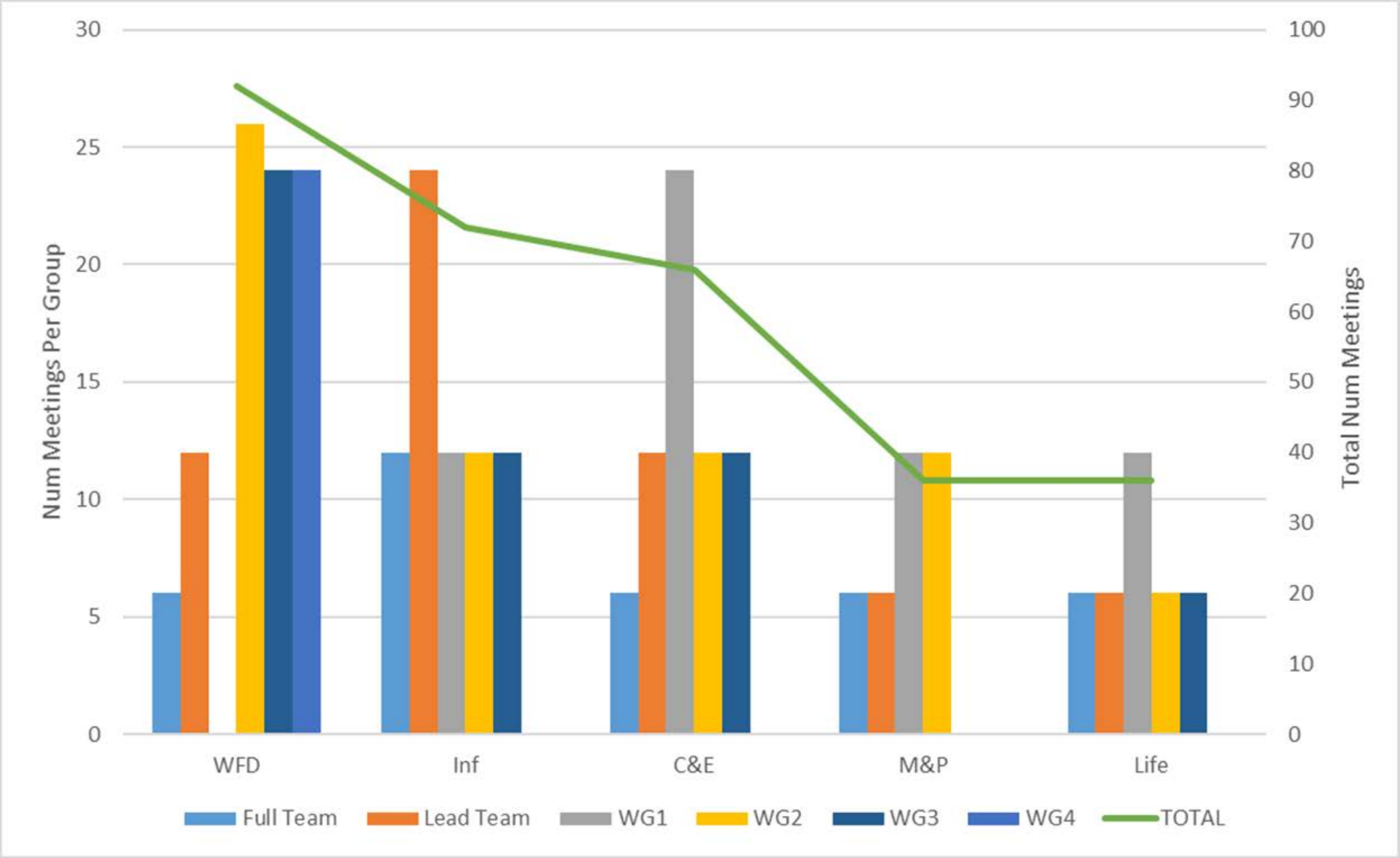
Workforce Development DTF

- Full DTF
- Lead Team
- Workgroups:
  - Mentoring TL1 & KL2
  - Methods to Assess Community Engagement
  - Harmonizing Competencies
  - Clinical Research

Key

- Fully active
- In Development
- Inactive
- Sunsetting
- Ad hoc

Number of DTF Meetings Per Year



Objectives & High-Level Summary of Proposed Changes

- **Optimize efforts**
- **Formalize and focus actions, efforts, and resources on a limited number of highest-priority CTSA Program and Consortium actions**
- **Increase NCATS & SC leadership and involvement**
- **Retain original purposes of DTFs & Work Groups (WG); limit number**
- **Rename DTF to reflect function → *Enterprise Committees (EC)***
- **Increase flexibility: Minimum requirement of hub membership in one EC**
- **Encourage cross-consortium collaborations through ECs, WGs, and Discussion Forums**
- **Enhance SC involvement in ECs & WGs**
- **Manage & forecast CLIC support**
- **Transition gradually and thoughtfully over 2019**

SC DTF WG Model Begins to Address Key Requests

April 2018 DTF Packet Comments Suggested Enhancements for the DTFs

- Engagement of DTF members
- Dedicated funding for various DTF activities
- Planning platforms for subsequent applications
- Trans-DTF WGs
- Smaller in-person meetings
- Promote sharing and dissemination of resources
- Direction from CTSA Program Leadership
- Develop best practices, conduct evaluation, develop WG outcomes that can be implemented

July 2018 DTF Survey Key Issues

- Communications
- Provide resources for DTFs; unfunded mandate
- DTFs too broad; need focus, timelines, deliverables
- Strengthen Collaborative Efforts
- Change DTF name to avoid a problematic acronym and better reflect function

Proposed Model

CTSA Program Steering Committee

No Change

CTSA Program Consortium Committees

- Administrators
- Communications
- KL2
- TL1

DTFs: Renamed to Reflect Function

Enterprise Committees*

New

Discussion Forums

Similar

Work Groups*

***Requires SC approval & on-going review**

CTSA Program Steering Committee

CTSA Program Steering Committee

Mission	Provide input and leadership for the CTSA Program and their Pods
Functions	Discuss common interests, gaps, and opportunities **Review & provide input on priority areas, ECs, & WGs** Suggest PI Webinar topics **Serve as planning committee for annual meetings**
Required Output	Annual Report to Consortium
Potential Outputs	Proposal for Work Group
Steering Committee	**Approve ECs & WGs** **Review Reports and Topics** **Provide Input to ECs & WGs**
Resources	Digital Workspace CLIC Call Support & F2F Mtg

Minor Tweaks

Consortium Committees

CTSA Program Consortium Committees

- **Administrators**
- **Communications**
- **KL2**
- **TL1**

Mission	Facilitate innovative practices
Functions	Identify gaps & opportunities Generate & disseminate best practices
Required Output	Annual Report & Presentation to SC
Potential Outputs	Best practices Proposal for Work Group
Steering Committee	Approve Formation Review annual report & provide input
Resources	Digital Workspace CLIC Call Support & F2F Meeting
Limit	Size / CLIC Resources

No Change

Discussion Forums

Discussion Forums

Functions	Informal, Self-Selected Discussion Space
Potential Outputs	Proposal for Work Group
Resources	Digital Workspace

New

Enterprise Committees

Enterprise Committees

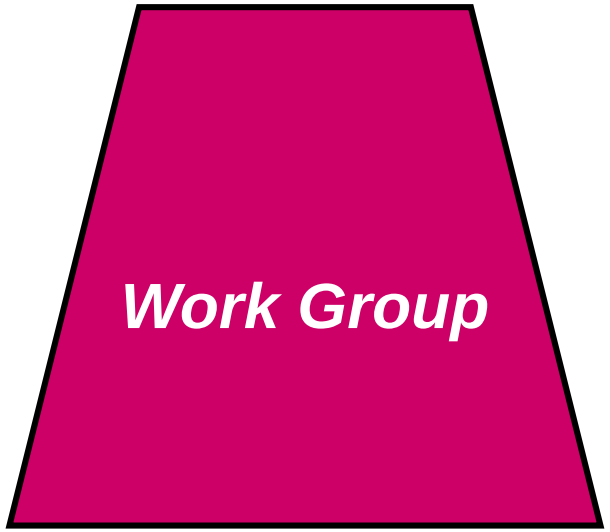
DTFs!

Mission	Promote collaboration & innovation across key areas
Functions	Discuss Consortium Goals Landscape Analyses to identify gaps & opportunities Generate & disseminate best practices
Required Output	Annual Report & Presentation to SC
Potential Outputs	Proposal for Work Group Discussion Forums
Steering Committee	Approve Work Groups/Topics Review Annual Report and Provide Input
Resources	Digital Workspace CLIC Call Support & FTF Meeting **CLIC Support for Annual Joint EC Chairs Webinar**
Limit	Number / Size / Duration / CLIC Resources

Enterprise Committee Leadership

- **Current DTF Governance**
  - **DTF Chair: an individual from the DTF Lead Team**
  - **DTF Co-Chair: an individual from the SC**
- **EC Leadership**
  - **EC Chair: an individual from the EC Lead Team**
  - **EC Co-Chair: none**
  - **Separation of SC & EC allows SC to focus efforts on SC activities, such as review of Work Group proposals and ongoing updates from Work Groups, and avoids any appearance of conflict**

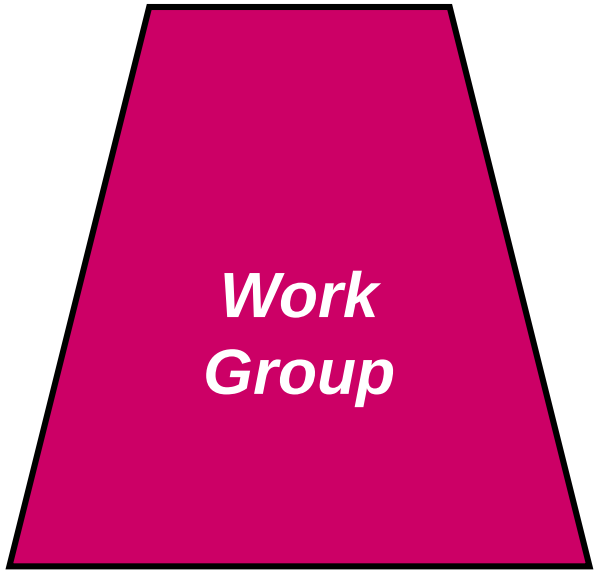
Work Groups to Address TS Issues



Mission	Consider & develop solutions around a specific translational science issue and create synergy across the consortium
Required Output	Bi-annual Report & Presentation to SC
Potential Outputs	Consensus Papers/White Papers/Publications Workshops/Symposiums/Meetings/Conferences Funding thru CCIAs or supplements*
Steering Committee	Approve Work Group Formation Review Bi-annual Report and Provide Input
Resources	NCATS Team Co-Chair Digital Workspace CLIC Support: >Calls >Science Writers >Meetings >Data Analysis >Other?
Limit	Number / Size / Duration / CLIC Resources

NCATS considers information from multiple sources for funding initiative topics

Work Groups



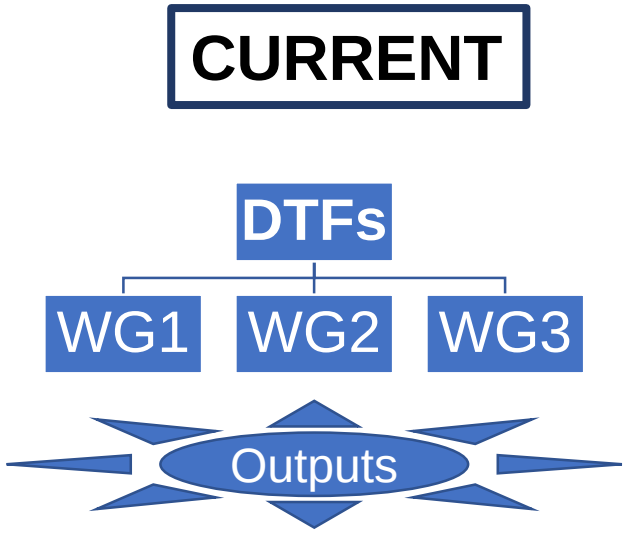
Fewer
More Focused

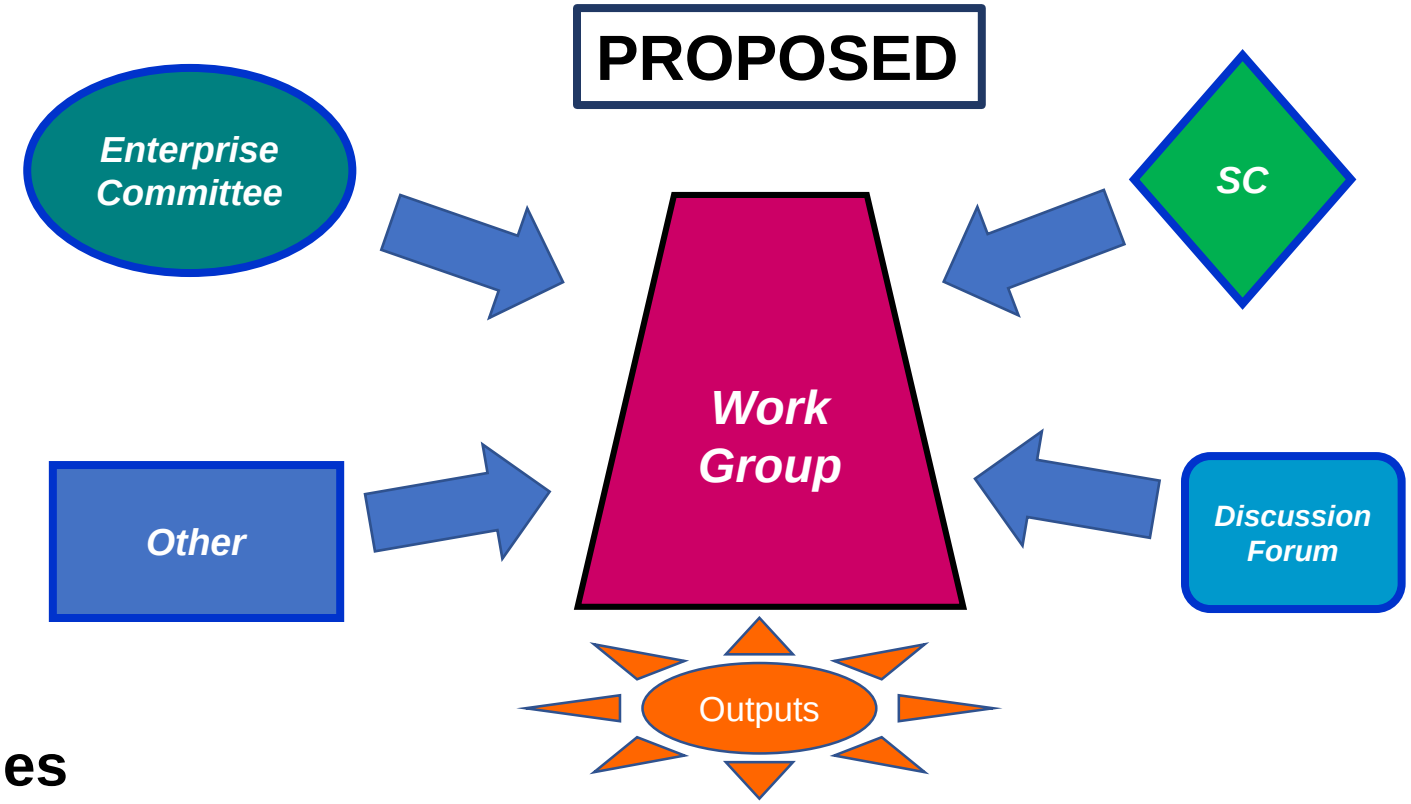
- **SC-approved and will consider & develop solutions for a specific translational science issue and create synergy across the consortium**
- **Proposals may originate from across the consortium**
- **SC will facilitate team develop with appropriate expertise**
- **Outputs may be addressed via CLIC, CD2H, TIN, ACT, or other consortium resources**
- **Limited number of active WGs**

<u>Work Group Proposals</u>

1. Specific Objective
2. Timeline w/ Milestones
   - Duration ≤24 mo.
3. Output/Deliverable
4. Broader context/goal

Note: Although WGs may not be used to specifically develop a grant application for a CCIA or other FOA, the result of a WG may be appropriate as a foundation for a collaborative group to work together to develop a grant application.





<u>SAME</u>: Overall functions & activities

Maintain some "evergreen" Work Groups/Standing Committees*

<u>DIFFERENT</u>: Names, CLIC support, and increased input from SC & NCATS

SC review/renew/revise Enterprise Committee and WG topics

DTFs transition to Enterprise Committees

Limit number of active Enterprise Committees to 5

Limit number of active Work Groups to 12

Ex. Regulatory Science to Advance Precision Medicine

Work Group Selection Process

Work Group Proposals Submitted by:

- Enterprise Committees
- Consortium Committees
- Discussion Forums
- PODs
- Steering Committee
- NCATS
- Other

Work Group Proposal

1. Specific Objective(s)
2. Timeline (≤24 mo.) w/ Milestones
3. Output/Deliverable(s)
4. Broader context/goal

Submission/review cycle TBD

CTSA Program Steering Committee (includes NCATS Leadership)

- Review & approve WGs
- Facilitate WG Team Dev
- Ensure appropriate expertise
- Receive Updates
- Provide Input

Work Group

Examples of Prior WG Products

>SMARTIRB >ACT
>GCP >TIN
>DIAMOND >N-Lighten
>STARWORK >Opioid Landscape
>Education Course Sharing

OUTPUTS

Required
>Bi-annual Updates to SC

Possible, with CLIC Support
> Consensus Papers/Publications
> Workshops/Symposiums/Meetings/Conferences

Possible, with other support:
> e.g., CD2H, TIN, ACT, other consortium resources
> Funding thru CCIAs or supplements*

RESOURCES

NCATS Team Co-Chair
Call Support
Digital Workspace

***For all FOAs, NCATS monitors and identifies emerging issues and trends in the translational science community. This is one way that initiatives are informed, and it is the first step in the development of FOAs**

2019 Transition Plan

2019 Transition Plan: Existing DTFs

- **Assess existing work groups and develop a Transition Plan – transfer same topic and objectives to an Enterprise Committee or propose a new Enterprise Committee?**
  - **<u>Existing WGs</u>: Review of recent DTF WG reports suggests that most, if not all, existing WGs can complete their activities and sunset by Dec. 2019. If unable to do so, the following options are available:**
    1. **Provide a detailed sunset plan with timelines and milestones to the SC for review**
    2. **Transition to a Discussion Forum with digital workspace.**
  - **<u>New WGs Proposed to end by Dec. 2019</u>: Proposals to SC must describe Specific Objective, Timeline w/ Milestones, Output/Deliverable, and the Broader context/goal, and should be submitted to the SC along with the charter. The SC will review proposals and approve/reject.**

2019 Transition Plan: CLIC & SC

- **<u>CLIC</u>**
  - **Propose a phasing plan for the staggered submission, review, and start of new WGs**
  - **Develop templates for WG proposals, EC annual reports, WG bi-annual reports**
  - **Propose improved communication strategy**

- **<u>Steering Committee</u>**
  - **Review and provide input on DTF-Enterprise Committee Transition Plans**
  - **Review and provide input on the phasing plans developed by CLIC**
  - **Consider revised/new Enterprise Committees & proposed WGs**
  - **Review & approve improved communication strategy proposed by CLIC**

2019 Transition Plan

- **Consortium groups/committees/other stakeholders**
  - **Suggest topics for Discussion Forums**
  - **Suggest topics for WGs**

Enhanced Communications Strategy

- **Under Development by CLIC**

SOURCE

SKILLS
GOAL
VISION
COMMUNICATION
TEAMWORK
?+ =!
CREATIVITY
RESEARCH
COLLABORATION
LEADERSHIP

SOURCE

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CLIC Updates:

Common Metrics
Spring Program Group Meetings
CLIC Un-Meeting

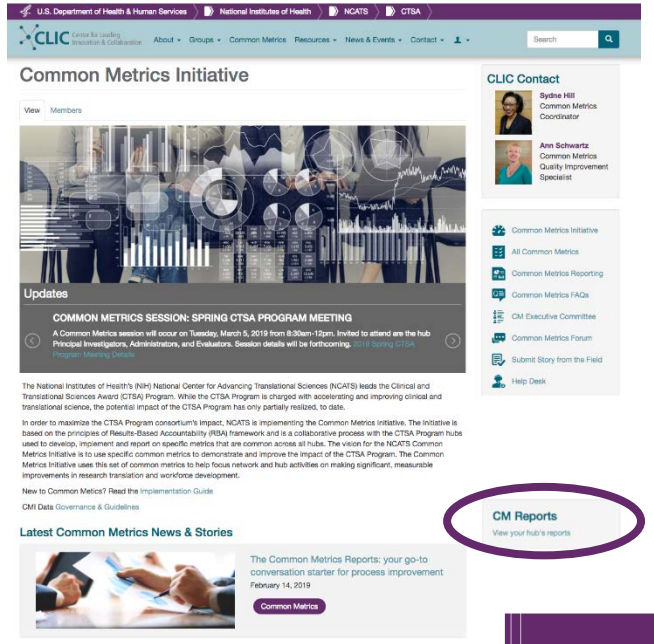
Deborah Ossip & Martin Zand

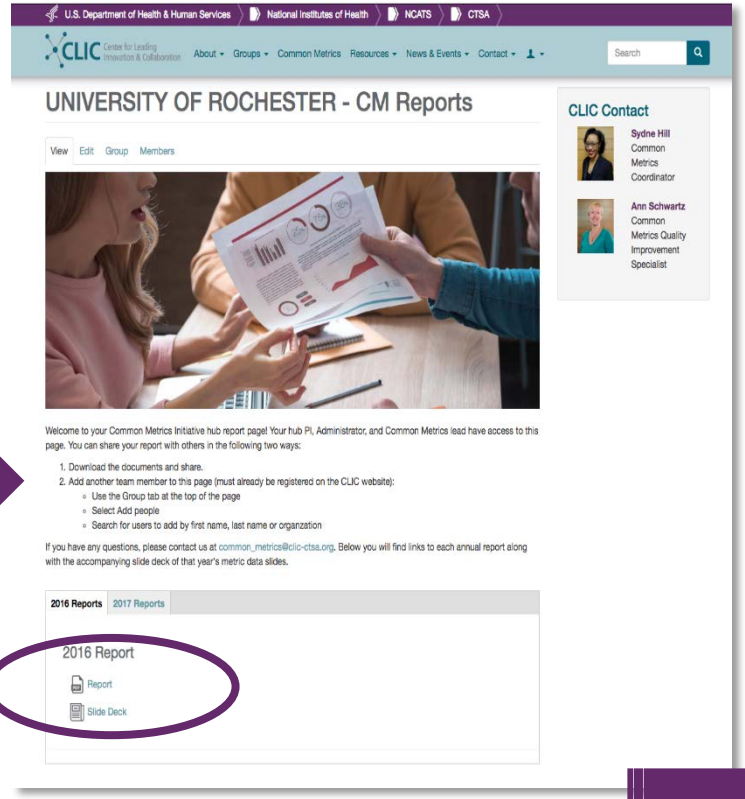
CTSA Program Webinar

February 27, 2019

Multi-Year CM Report

"New" Common Metrics Initiative page





Release date: Thursday, February 28
Accessible to: PIs, Administrator, Evaluator

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Post-Report Release Webinars

The objectives of the webinars are to:

- Provide hubs with a description of the analysis processes used to generate the report visuals
- Explain the strategies used to identify featured hubs
- Answer your questions regarding the report
- Discuss steps going forward for using the hub report data

Register for the date most convenient to you:

- March 18th @ 4pm (ET) - Register here
- March 26th @ 12noon (ET) - Register here

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Spring CTSA Program Group Meetings

MONDAY, MARCH 4	
10:00 AM - 5:00 PM	CTSA Program Steering Committee Meeting
10:30 AM - 2:30 PM	CTSA Program Hub Communicators Meeting
4:30 PM - 7:00 PM	Methods & Processes DTF Meeting
TUESDAY, MARCH 5	
8:00 AM - 12:30 PM	Career Professional Development for the Clinical and Translational Science Workforce, a joint meeting of the Workforce Development DTF/ KL2 Directors / TL1 Directors*
8:30 AM – 12:00 PM	Common Metrics Initiative Meeting
1:00 PM - 4:00 PM	Collaboration/ Engagement DTF Meeting

Total registrations: 444

Zoom participants: 174

Registration (both in person and online) has now CLOSED

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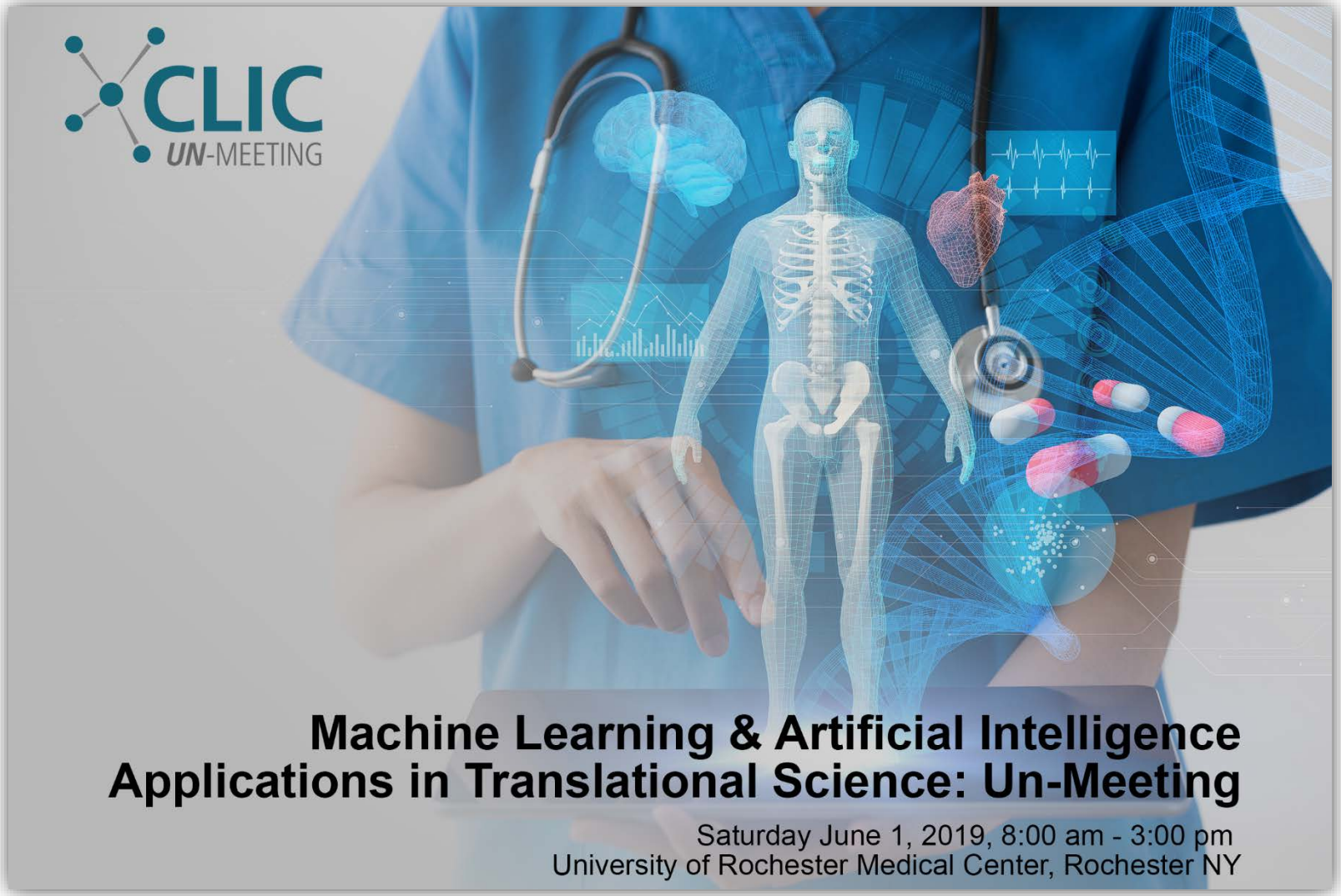
Save the Date: CLIC Un-Meeting 2019



A New CTSA Initiative: Drug Repurposing Screening Collaborations

Nikki (Rogers) Alvarez, Ph.D.

Associate Director, Alliances (Calibr, Scripps Research)

Drug Repurposing Screening Collaborations in the CTSA

Non-profit drug discovery leveraging ReFRAME to accelerate translation

Nikki (Rogers) Alvarez, PhD

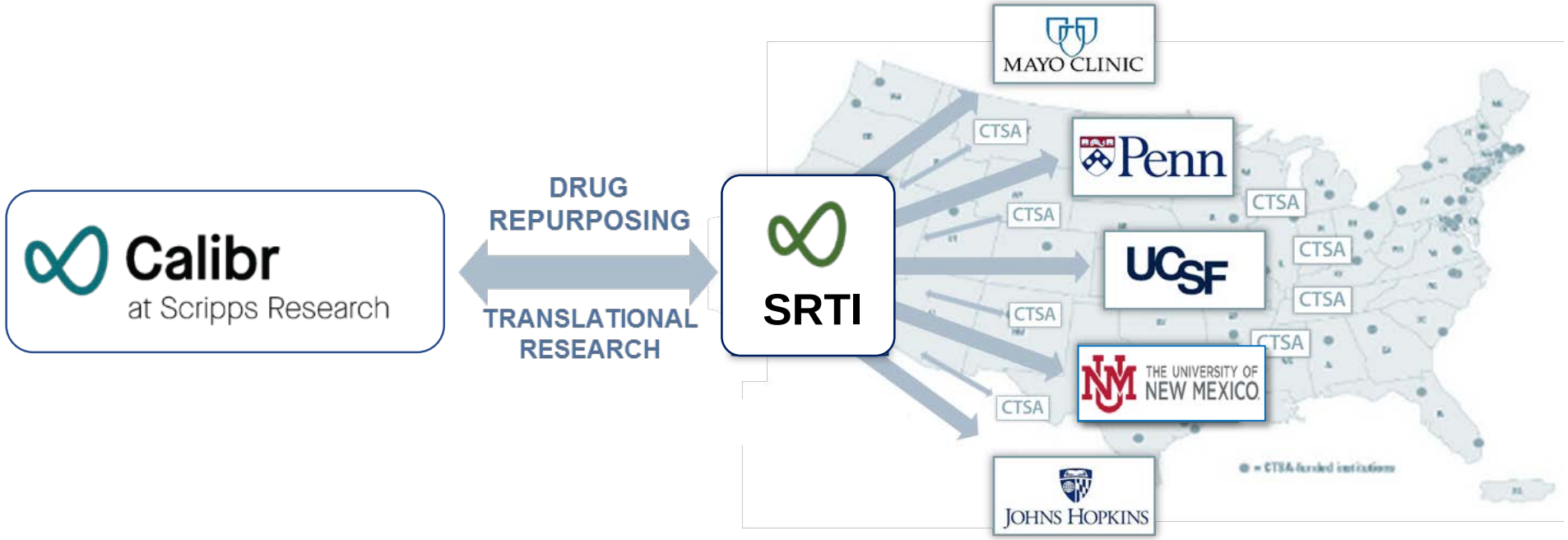
Associate Director, Alliances (Calibr, Scripps Research)

Calibr
at Scripps Research

CTSA Drug Repurposing with ReFRAME

CTSA Drug Repurposing Screening Collaborations

- **Ready for incoming screening proposals!**
- Rolling-out consortium wide application process
- Hope to connect with various Hub PIs to explore site-specific mechanisms for optimizing outreach and launching the application process regionally



OVERVIEW OF CALIBR: NON-PROFIT DRUG DISCOVERY

Calibr

A New Paradigm for Translational Research

Founded as an independent non-profit institute accelerating the translation of biomedical research to innovative therapies that address unmet medical needs.

- Founded in 2012 as an independent 501c3 non-profit by Pete Schultz, PhD
- Professor at Scripps (1999-present) and founding Director of GNF (1999-2010)
- Organized and operated like a biotech company, but with a tax-exempt mission and financial structure
- Preclinical and early clinical drug discovery and development expertise

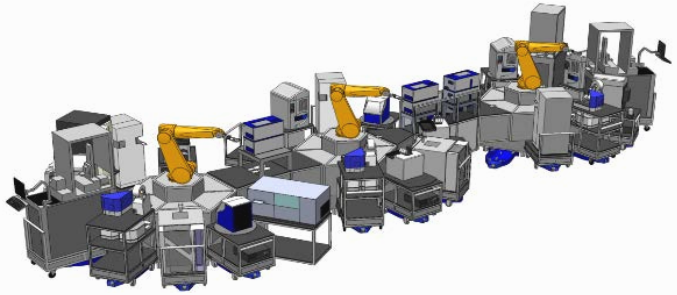
- Grew to ~100 employees in 2016
- Funding from both foundations and pharma partners
- Collaborations with academic peers and biotech partners

- In 2016, began creating scientific, operational, and leadership synergies with Scripps
- In 2018, completed a formal merger to become an operating division of Scripps

Calibr Translational Capabilities & Infrastructure

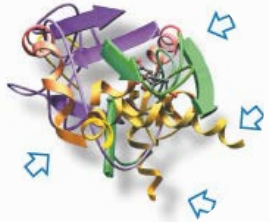
SMALL MOLECULE DISCOVERY

- Library of > 850,000 drug-like compounds
- Best-in-class drug repurposing collection
- State-of-the-art robotics
- Expertise in cell-based screening and mechanistic deconvolution



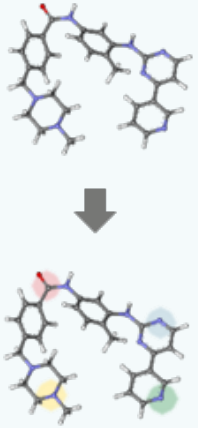
PROTEIN ENGINEERING

- Fusions of antibodies with bioactive peptides and proteins
- Semi-synthetic peptide technology



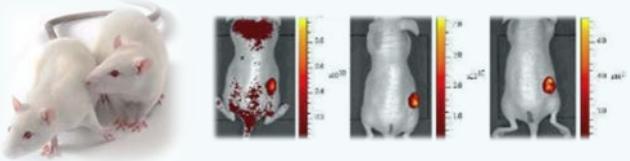
MEDICINAL CHEMISTRY

- Nimble hit-to-lead campaigns for early discovery efforts
- Lead/late-lead optimization capabilities to nominate development candidates
- Novel bio-conjugate/rational design platforms for tissue-targeting



PHARMACOLOGY & SAFETY

- Dedicated core group supports rapid model development and proof-of-concept rodent studies
- In-house/CRO support for PK/PD, in vitro safety assessment and toxicology

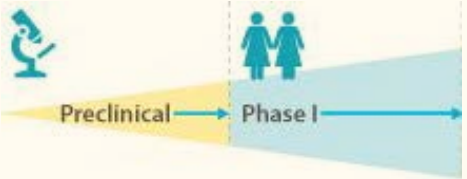


IND-ENABLING STUDIES

- Dedicated internal team and network of trusted contractors and consultants
- Process development and GMP manufacturing: small and large molecules
- GLP toxicology and safety studies
- Multi-species PK and allometric scaling
- Regulatory expertise

CLINICAL SAFETY & PROOF-of-CONCEPT

- Phase 1 safety and Phase 1b/2a proof-of-concept (PoC) studies
- Capacity to take a number of programs through early clinical studies
- Leverage non-profit clinical partners to gain unique access and speed (e.g., Cedars-Sinai)



DISCOVERY → ***OPTIMIZATION*** → ***TRANSLATION***

Calibr
at Scripps Research

From "Bench-to-Bedside"

Research Collaborations Around the World

- Calibr offers unique capabilities, know-how and willingness to contribute resources to advance common interests
- Non-profit status allows Calibr to rapidly form new collaborations both locally and globally

General Programs

INSTITUTE	PI	FOCUS
UC San Diego	C. Glass	LXR
Salk Institute	K. Jones	Myc-MAX
UC San Francisco	K. Shokat	Kinase Biology
Harvard Univ.	D. Kahne	LPS Trafficking
MD Anderson	S. Mani	EMT
Weill Cornell	L. Cantley	Cancer metabolism
Columbia Univ.	B. Stockwell	Ferroptosis

JDRF Programs

INSTITUTE	PI	FOCUS
Univ. of Bremen	K. Maedler	MST1
Harvard Univ.	G. Hotamisligil	UPR
Univ. of Brussels	D. Eizirik	Mito Stress
Washington Univ.	F. Urano	ER Stress
Indiana Univ.	R. Mirmira	eIF2a

Gates Foundation Programs

INSTITUTE	PI	FOCUS
Sanford-Burnham Prebys	S. Chanda	Anti-virals
UC San Diego	E. Winzeler	Malaria
Cornell Univ.	D. Russell	Tuberculosis
UMass Amherst	R. Aroian	Helminths
IOCB – Prague	Z. Hostomsky	Nucleosides
USAMRIID	S. Bavari	Ebola, bioterrorism
Texas Biomed. Res. Inst.	R. Davey	
Univ. of Rhode Isl.	A. De Groot	Novel vaccines
AECOM	B. Jacobs	Tuberculosis
TropIQ	K. Dechering	Vectors
GSK Open Labs	L. Ballell	Leishmaniasis
UC Santa Cruz	B. Sullivan	Cryptosporidium
Univ. of Vermont	C. Huston	

PRIMER Portfolio: Late Stage Preclinical & Clinical Programs

The PRIMER portfolio targets diverse unmet medical needs in cancer, regenerative medicine, and chronic diseases of aging. The assets are staged to create a robust pipeline of clinical opportunities:

PCC Selection

LA GMCSF | Parkinson's disease
PCC declaration in Q1-2019

LA GLP-2 | Crohn's disease
PCC declaration in Q2-2019

Fibrosis/S1PR3 | Lung Fibrosis
PCC declaration in Q4-2019

Novel STING | Immuno-onc
PCC declaration in Q2-2020

Chemical Vaccine | Lyme
PCC declaration in Q4-2019

γδ T cell | Immuno-onc
PCC declaration in Q1-2020

IND-Enabling

sCART-19 | Lymphoma
IND in Q2/Q3-2019

DUPA-CD3 | Prostate Cancer
IND in Q2/Q3-2019

Anti-Muscarinic/combo
Multiple sclerosis
IND in H1-2020 (w/ partner)

Clinical

KA34 | Osteoarthritis
4 center, 60 patient study
Study report Q3-2020 ★

Auranofin | Tuberculosis
Patient studies ongoing w/ SoC
(w/ Bill & Melinda Gates Foundation)

Clofazimine | Cryptosporidiosis
66 patient study
(w/ Bill & Melinda Gates Foundation)

REPURPOSED DRUGS

Calibr
at Scripps Research

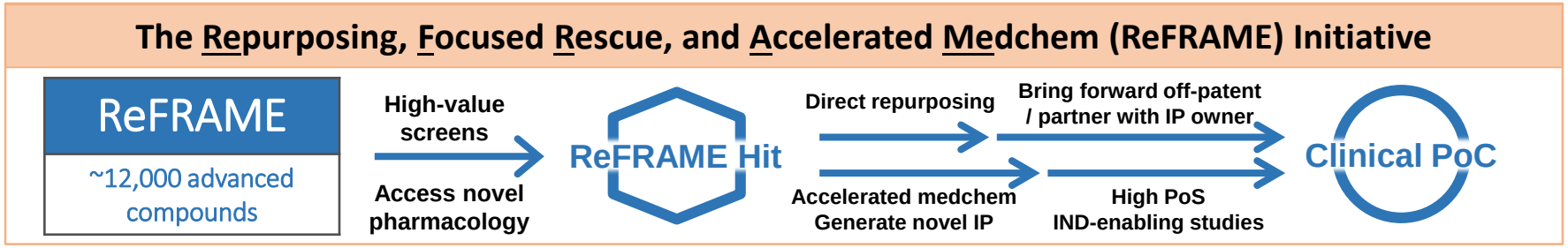
The ReFRAME Initiative

Rationale for High-Value Screening Collections

- Screening smaller collections of advanced compounds can greatly enable and accelerate new drug discovery efforts (either through direct repurposing or as mature leads) and allow high-value complex assays to be deployed
- This approach can significantly decrease the cost and time associated with finding new therapies and be especially useful in challenging therapeutic areas that have a paucity of leads

Deployment of a Unique Resource

- Calibr built a best-in-class repurposing library of ~12,000 high-value compounds called ReFRAME
- Includes both registered drugs and investigational new drugs (INDs) currently or previously at any stage of clinical development; far greater reach than typical FDA-approved drug libraries
- Intellectual property policy allows investigators to freely pursue and commercialize findings
- Calibr now has a number of examples of direct repurposing (e.g., auranofin, clofazimine) programs derived from ReFRAME screens entering the clinic



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The ReFRAME Initiative

Broad competitive intelligence resources

~55% commercial

~45% synthesized

'Best guess' yields > 1000 unique structures

~12K compounds available for screening

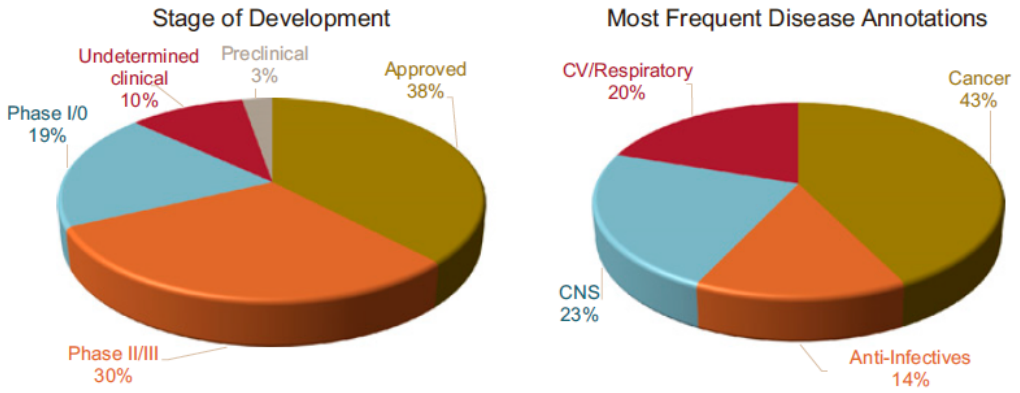

Fig. 2. Distribution of ReFRAME entries across stages of clinical development and disease indications. CV, cardiovascular.

Table 1. Compositional breakdown of the ReFRAME compound library

Description	No. of entries
Total entries with structure in three drug databases	13,904
Purchased compounds from commercial sources	6,805
Synthesized compounds from disclosed structures	4,194
Entries without structure annotation	2,204
Structure-elucidated	794
Elucidated structures synthesized	522
Close analogs in collection as part of synthesis efforts	427
Total ReFRAME compounds plated and ready to screen to date	11,948

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Chatterjee, et al. (2018) PNAS; 115 (42)

Previous success with known drug screening

Examples of direct repurposing and accelerated lead optimization programs derived from known drugs

Screen	Known Drug Hit	Repurposing Opportunity
Screen for inducers of remyelination	Benztropine (FDA-approved to treat Parkinson's)	Multiple sclerosis; exhibits mutual dose-sparing efficacy when combined with S1P modulators; move directly into Phase 2 proof-of-concept study
Screen against non-replicating or dormant Mtb	Auranofin (FDA-approved to treat RA)	Tuberculosis; entering a drug combination study in patients with BMGF
HCI phenotypic screen for inhibitors of intracellular *C. parvum* proliferation	Clofazamine (FDA-approved to treat leprosy)	Clinical testing underway in immune-compromised adults; formulation being optimized for pediatric treatment
Cell-based cytotoxicity screen	Fluralaner (Approved oral animal health drug)	Oral insecticide as part of integrated control of vector-borne diseases (e.g., malaria, Zika); approval-in-principle from IP holder; FIH 2019
Screen for MST1 inhibitors	Approved breast cancer drug	Removed off-target kinase activities; substantially changed on-target vs. MST1 potency of original drug; advancing towards IND-enabling developoment for T1D

Collaborative ReFRAME Screens in the CTSA

Drug repurposing screens in collaboration with investigators throughout broader CTSA network

- Ready-to-take applications and launch submission processes at interested CTSA hubs
- Calibr can either provide pre-spotted library to investigators for screening at their preferred site OR bring screen-ready assays to Calibr

– *CTSA Hub PIs are encouraged to seek innovative proposals and leverage relevant disease expertise and clinical infrastructure at their hub*

CTSA

Simple submission process

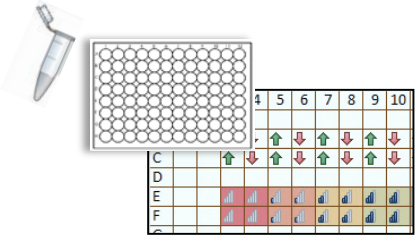
– *Investigators submit brief summary of proposed screen (template provided)*

– *Selection based on potential impact on patients and the ability to follow up clinically if a repurposing opportunity is identified*

– *Identify / develop optimal primary screening assay and establish collaborative workplan*

– *Execute screen and identify confirmed hits*

ReFRAME Screens



Calibr at Scripps Research

Clinical Trials with Repurposed Drugs

Clinical drug repurposing across CTSA consortium

- Hits with appropriately documented clinical safety can bypass GMP process development and Phase 1 studies and be evaluated directly in Phase 2 efficacy studies – ***ideally clinical aspect draws upon relevant resources & expertise of the collaborating CTSA hub***
- Engage relevant resources in the Consortia and appropriate regulatory expertise to optimize clinical protocol
- Work together to map out the most high-impact and cost-effective Phase 2 proof-of-concept study in patients and seek Institutional Review Board approval for study

– *Identify hits with safety profile and history of use that support direct repurposing in the desired clinical indication*

ReFRAME Screen Output

Accelerated translation to patients

– *Initiate phase 2 patient studies in collaboration with CTSA hub that originated the screen and/or possesses unique capabilities to recruit & evaluate patients*

– *Leverage CTSA network to engage world-class clinical expertise*

CTSA

Calibr
at Scripps Research

CTSA Drug Discovery – Simple Application Process

Scripps Research Translational Institute
Calibr at Scripps Research

DRUG REPURPOSING ⟷ TRANSLATIONAL RESEARCH

CTSA

SPECIAL REQUEST FOR PROPOSALS FOR:

DRUG REPURPOSING SCREENING COLLABORATIONS

- **Powerful new resource now available to CTSA-affiliated investigators**
- **Access to the most comprehensive drug repurposing library in the world**
- **Platform for building new collaborations and partnerships, including help with drug discovery and high-throughput screening**

PURPOSE

Scripps Research Translational Institute (SRTI) and drug discovery affiliate Calibr **invite proposals** for **collaborative drug repurposing screens**. This translational endeavor aims to partner clinical proficiencies throughout the CTSA network with drug discovery resources. CTSA-affiliated researchers and clinicians who have identified potential drug targets, pathways or screening approaches and are interested in **accelerated translation into patients through drug repurposing** are encouraged to respond. Working closely with Calibr scientists to develop an innovative assay or idea, investigators will have an **opportunity to screen a best-in-class drug repurposing collection** containing nearly all small molecules in any phase of clinical development. The program will give CTSA investigators **access to small molecule screening capabilities and associated support**, including assay optimization and miniaturization, hit identification and triaging, hit characterization, medicinal chemistry and *in vivo* pharmacology. Seeking synergy, a clear ability to execute on potential direct repurposing opportunities will be a key factor in selecting collaborative screens, in addition to innovation, enablement, and impact.

ABOUT REFRAME

Repurposing, Focused Rescue, and Accelerated Medchem (**ReFRAME**) is a screen-ready collection of approximately **12,000 clinical compounds** created with financial support from the Bill & Melinda Gates Foundation. This unique drug repurposing library contains not only FDA-approved drugs, but also **investigational new drugs (INDs) that are or were in any phase of clinical development**, including >1000 non-commercially available compounds with undisclosed structures manually determined using broad competitive intelligence resources. **The scale and comprehensiveness of ReFRAME** – *the first collection built by systematically querying all available clinical data and obtaining compounds through purchase (~57%) or resynthesis (~43%) without regard to mechanism of action, availability, patent status or cost* – **represent a far greater reach than typical FDA-approved drug libraries**.

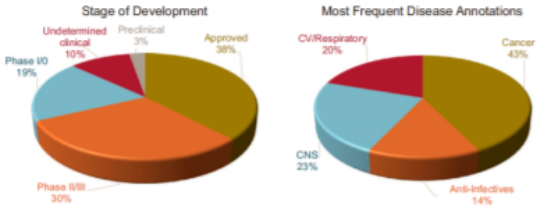


Figure 1. ReFRAME distribution across stages of clinical development and disease indications

Calibr's prior success employing collaborative ReFRAME screens highlights how **enabling a unique resource like ReFRAME can be for the non-profit scientific community**. For example, a partnership focused on infectious and neglected disease recently supported more than a dozen ReFRAME screens in leading academic labs around the world, fostering **strong new inter-institutional partnerships** and resulting in the **discovery of multiple promising repurposed drug candidates**, including candidates for tuberculosis and diarrheal diseases currently being evaluated in clinical trials. With support from the CTSA, Calibr and SRTI now aim to expand the model by making **ReFRAME** and Calibr's **translational expertise accessible to the broader CTSA network**.

OBJECTIVES / SCOPE

This call for proposals is designed to accelerate drug discovery and facilitate the translation of unique biology discovered in the laboratory or clinic into new medicines for patients. Teaming up with scientists and clinicians throughout the CTSA consortium, Calibr and SRTI envision **collaborative ReFRAME screens to identify repurposed drug candidates** that can be **quickly evaluated in patients in clinical trials**. Applicants do not need to have previous knowledge or experience in high-throughput screening, and responses do not need to include a specific plan for adapting biological insights into high-throughput screens. Calibr's staff has expertise ranging from assay development to medicinal chemistry, allowing support and execution of activities throughout the screening campaign, such as assay design and optimization leading up to the screen and hit triaging after the screen.

Hit compounds identified from these screens can be channeled through one of two possible accelerated paths based on their appropriateness for direct repurposing. If the safety profile and history of use of a given drug support clinical repurposing in the new indication, the parties will work together to map out a **Phase 2 proof-of-concept study in patients**. Ideally this study will **leverage the collaborating CTSA center** that originated the screen, with the hope that the center possesses unique capabilities to readily recruit and evaluate patients. Should optimization of a hit compound be required to ultimately treat the target patient population (e.g., improve tolerability to enable chronic use), then a focused medicinal chemistry campaign can ensue, engaging Calibr resources and expertise to optimize hit compound(s) for the desired alternative indication and expedite assessment of safety and efficacy in humans.

SELECTION OF SCREENS & COLLABORATIVE WORKFLOW

Applicants should use the attached template to submit a brief proposal to their CTSA Hub PI. Hub-approved submissions will be competitively reviewed by a committee of scientists at SRTI and Calibr and **prioritized based on unmet medical need, scientific merit/feasibility, and the ability to follow up clinically if a repurposing opportunity is identified**. Once a screen has been selected for the program, Calibr scientists will work directly with the CTSA investigator to develop a workplan to optimize the assay for screening (as needed) and execute the screen. Calibr has efficient mechanisms for bringing screen-ready assays in-house or providing the library to investigators in a ready-to-use format for screening at their preferred site. Sharing will be subject to a standard collaboration and MTA template that has been developed for ReFRAME. In addition to providing compounds for primary screening and hit confirmation assays, Calibr will be available to assist as needed with pre-screening assay optimization and miniaturization, developing hit triage workflow, resynthesis of confirmed hits, and engaging in discussions on the merits of direct repurposing versus accelerated medicinal chemistry.

ABOUT CALIBR

Calibr is a non-profit drug discovery institute established in 2012 with the mission of filling a translational gap between innovative biological research in academia and drug discovery activities in biotech and pharma. In 2018 Calibr became an operating division of Scripps Research, creating the unique opportunity for SRTI to serve as an accelerated drug discovery hub amongst the CTSA network. In addition to the one-of-a-kind ReFRAME drug repurposing library, Calibr has broad drug discovery capabilities, including state-of-the-art robotics and high-throughput screening facilities, on-site medicinal chemistry, *in vivo* pharmacology resources, and a core strength in cell-based screening. **By partnering with the broader CTSA network, the hope is to create a powerful platform for the identification of novel therapies coupled with direct translation to patients,** all within the non-profit sector.

Cali
at Scripps Research

CTSA Drug Discovery – Simple Application Process

CTSA REFRAME SCREEN PROPOSAL

SUBMITTED BY:

DATE OF SUBMISSION:

1. Summary Statement

State the overall scope and purpose of the project in 1 sentence.

Click here to enter text.

2. Scientific Background and Rationale

Less than 1 page. Briefly describe the background and scientific rationale for the proposed screen. Include the primary indication and information related to medical need and what is known about the proposed patient population(s).

Click here to enter text.

3. Therapeutic approach

Less than 1 page. What is the target, pathway, or cellular phenotype? What biological findings support modulation of this target, pathway or cellular phenotype as a therapy? What is the envisioned therapeutic paradigm? (e.g., would it be used as a stand-alone therapy? any known or predicted side effects with modulation of this target?)

Click here to enter text.

1

4. Discovery Approach

Less than 1 page. Describe the proposed biological assay or idea for an assay and degree to which it has been developed, validated, optimized, and/or miniaturized. What methods are available to assess modulation of this target, pathway, or cellular phenotype? Are reference or positive/negative controls available? Include relevant info for any compounds, proteins, peptides, antibodies, RNAi reagents, or mutant cell types that may serve as reference or control conditions. Have you or others previously engaged in high-throughput screening for this target, pathway, or phenotype?

Click here to enter text.

5. Enabled Clinical Development

Describe available resources and tools to enable testing efficacy of repurposing candidates in proof-of-concept clinical trials in patients. Highlight all relevant clinical capabilities and any information related to the ability to follow-up clinically if a repurposing opportunity is identified. List collaborators for the project with potential synergies, including skills, resources, etc.

Click here to enter text.

2

Cal
at Scr

Contact:

Nikki (Rogers) Alvarez, PhD

nalvarez@scripps.edu

858-242-1078

Link to Application Materials:

www.scripps.edu/_files/pdfs/science-medicine/translational-institute/CTSA_ReFRAME_call_for_proposals_Jan_2019.pdf

www.scripps.edu/_files/pdfs/science-medicine/translational-institute/CTSA_ReFRAME_screen_submission_template_Jan_2019.docx

www.scripps.edu/_files/pdfs/science-medicine/translational-institute/CTSA_ReFRAME_cover_page_Jan_2019.doc