Day 2 Agenda

Session 5: Ongoing initiatives and partnership opportunities
MODERATOR: Carolyn Shore, The Pew Charitable Trusts

- Francesca Chiara, Wellcome Trust, CARB-X
- Jane Knisely, National Institute of Allergy and Infectious Diseases
- David Pardoe, Medical Research Council Technology (presentation not included)
- Rob Stavenger, GlaxoSmithKline, Innovative Medicines Initiative Translocation project (presentation not included)
- Jonathan Thomas, OMEGA project (presentation not included)

Session 6: Information-sharing platform on compound penetration and efflux
MODERATOR: Pooja Kothari, The Pew Charitable Trusts

- Brad Sherborne, Merck
- Barry Bunin, Collaborative Drug Discovery
- Philip Gribbon, Fraunhofer IME, Innovative Medicines Initiative Translocation project

Session 5: Ongoing initiatives and partnership opportunities

The Wellcome Trust:
An Overview of our Funding

Francesca Chiara PhD
Drug-Resistant Infections Team

7th Feb 2017

Who we are

We are an independent global charitable foundation, dedicated to improving health.

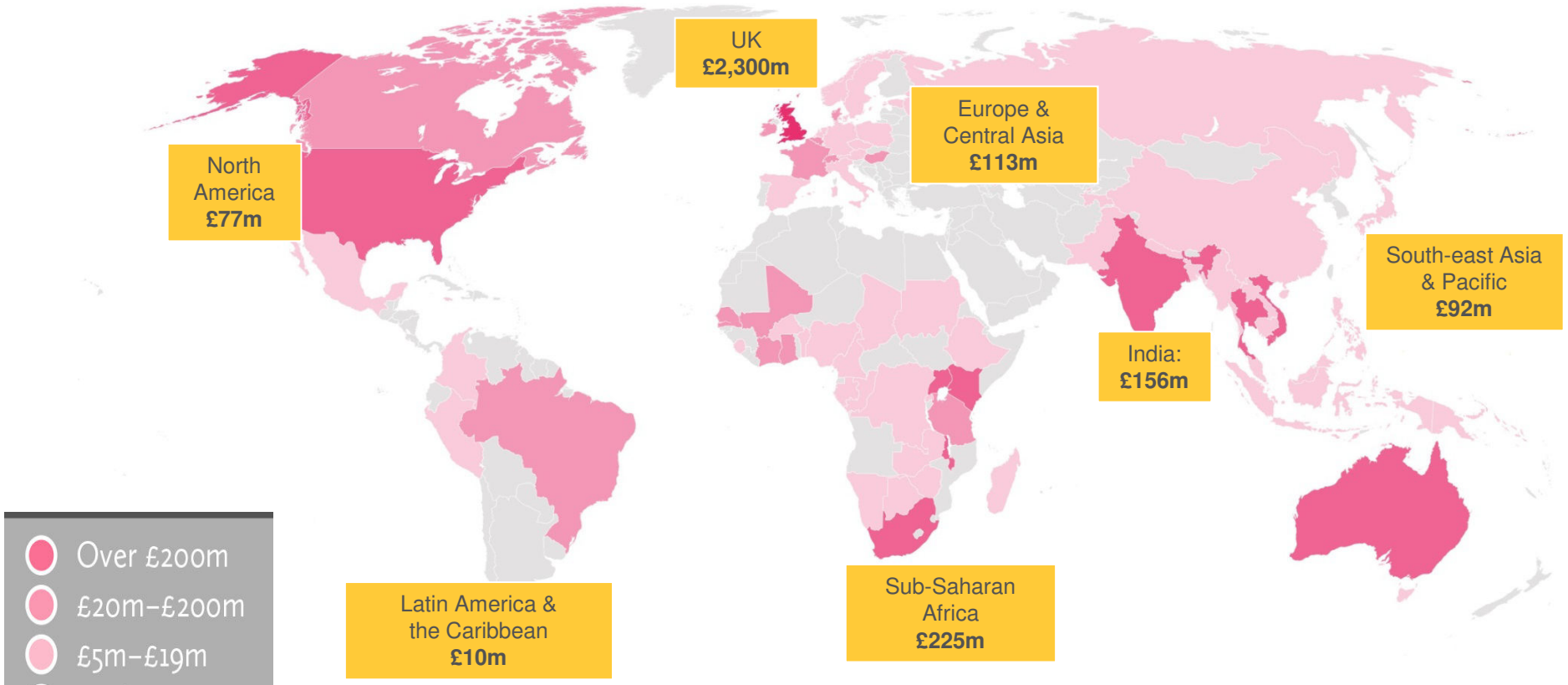
We remain true to the vision and values of our founder, Sir Henry Wellcome, a medical entrepreneur, collector and philanthropist.

Our Philosophy: Good health makes life better. We want to improve health for everyone by helping great ideas to thrive.

Since 1936, our support has helped to save and improve millions of lives around the world through science, research, evidence and engagement with society.

Science, Innovations, Culture & Society

Where we work



Wellcome Investments

Response-mode funding

- Discovery Science
- Product Development
- Social Sciences

Institutional Support

- Sanger Institute
- Major Overseas Programs
- Research Centres

What’s new?

Seizing Opportunities

To be more focused and proactive in specific areas.

We want to connect experts from different disciplines, build partnerships, and lead advocacy, policy development, communications and public engagement. We will do this by providing focused support that creates a step change over five to ten years.

Research Ecosystems in Africa and Asia: Build partnerships in low- and middle- income countries more scientists in these places can pursue world-class research.

Our Planet, Our Health: Build understanding of how global food systems and urbanisation connect to health, improving the evidence base for public policy.

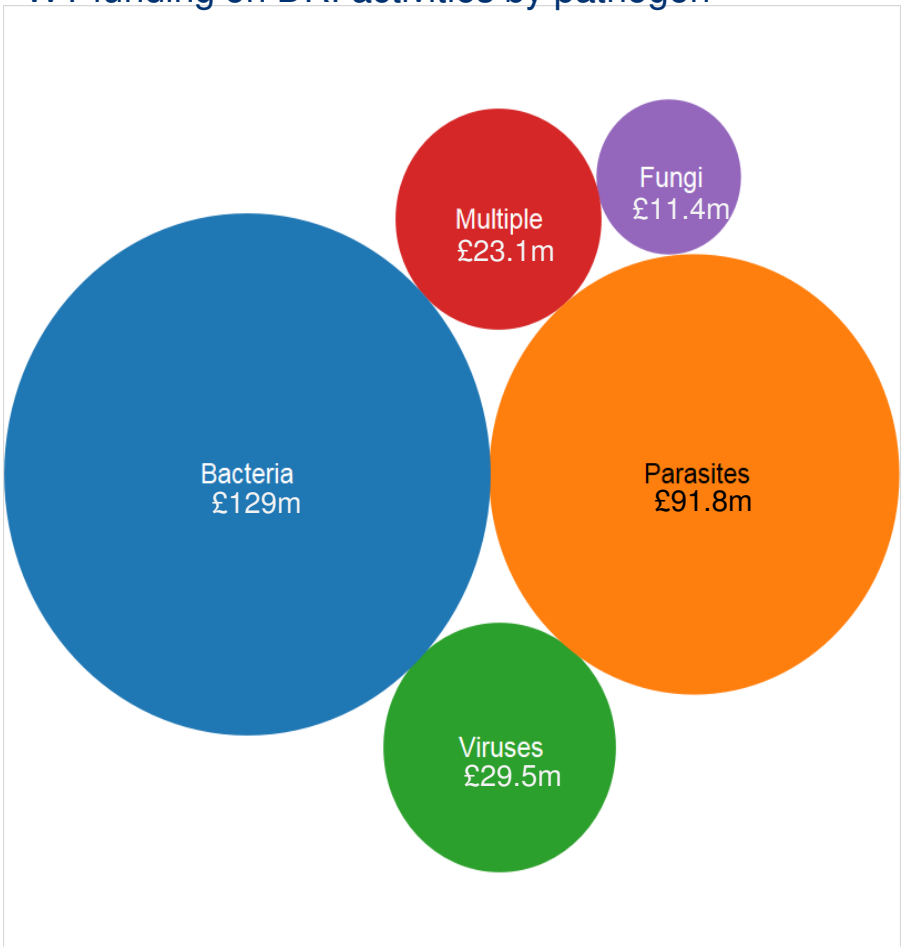
Drug-resistant infections: Explore how best to use and protect the treatments we have and to encourage the development of new ones.

Vaccines: Explore how best to stimulate research, technology development and policy to address critical unmet needs.

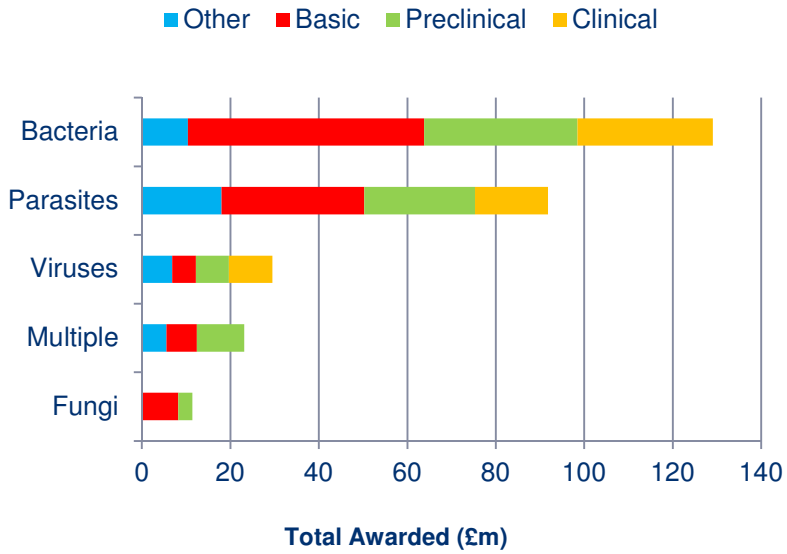
Drug-Resistant Infections at Wellcome

Drug-resistant infections: what we've funded 2005-2016

WT funding on DRI activities by pathogen



Distribution by pathogen type and stage of development



Drug-resistant infections:
our new funding activities

Drug-Resistant Infection is a global health threat that undermines the progress made in the fight against infectious disease in the last century.

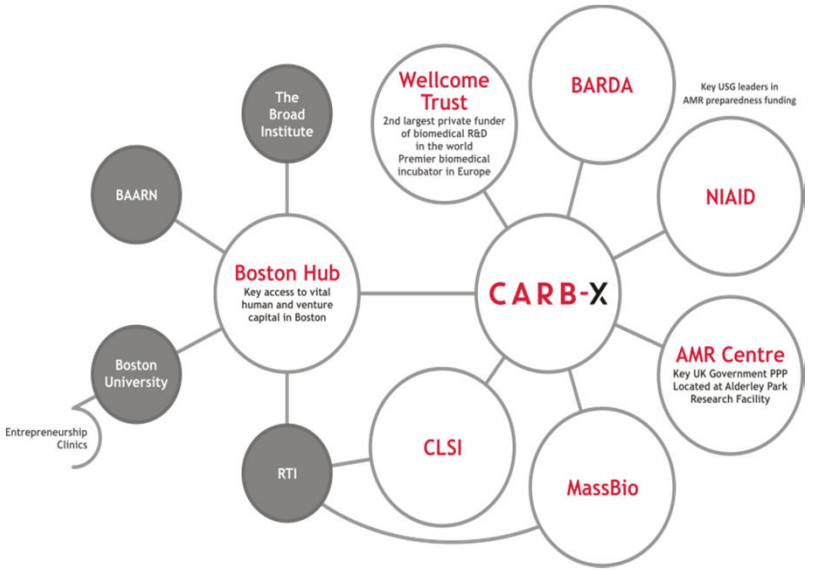
Our strategy will deliver a reduction in the impact of DRI

- **Epidemiology of Drug-Resistant Infection**
- **New treatments**
- **Accelerating clinical assessment**
- **Global governance**

Drug-resistant infections:

CARB-X *Xccelerating global antibacterial innovation*

- Leverage **$250 million** in BARDA funds with matching funds from Wellcome and the AMR Centre
- Support the development of products that protect human health from the most serious bacterial threats, including therapeutics of all types, preventives such as vaccines, diagnostics and devices
- In the first year, the CARB-X portfolio will primarily focus on therapeutics to treat Gram-negative bacteria on the Serious or Urgent Threat List prepared by the CDC as well as any non-traditional approaches.
- We have received overwhelming interest and the first funding round will conclude in April



Thank you

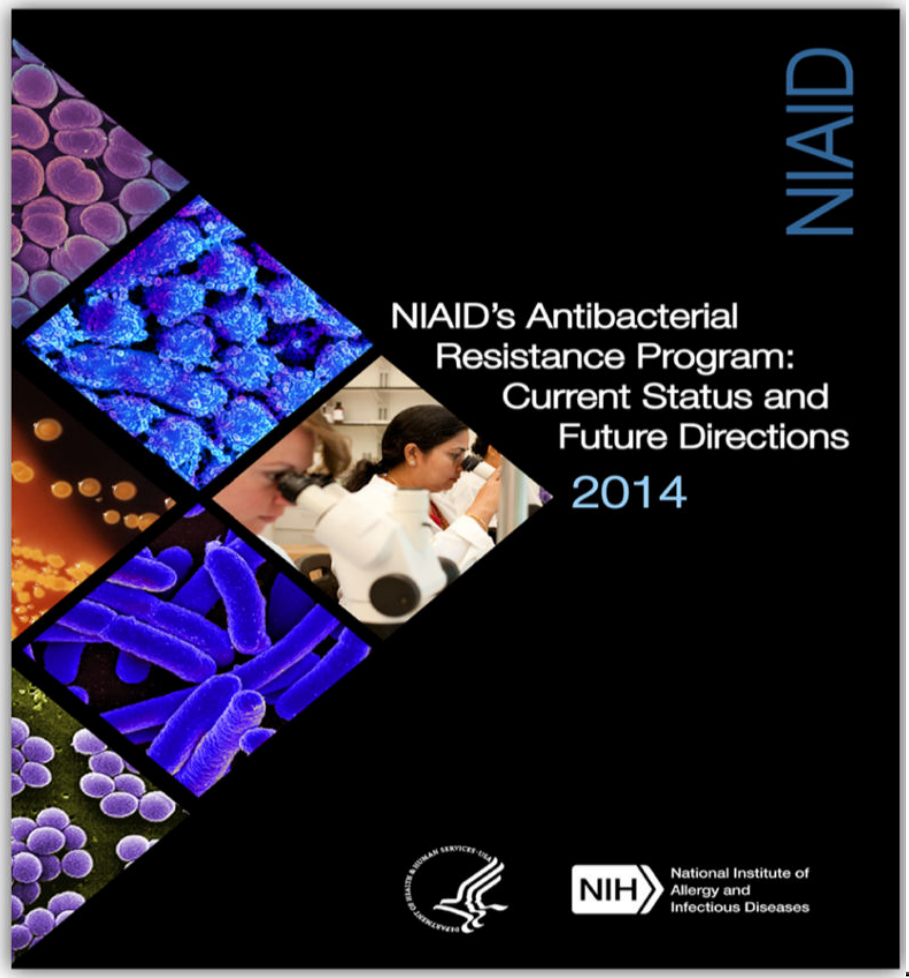
f.chiara@wellcome.ac.uk

NIAID support for G- drug discovery and development

Jane Knisely, PhD
Program Officer
Division of Microbiology and Infectious Diseases
NIAID/NIH/HHS

G- entry/efflux workshop
February 7, 2017

National Institute of Allergy and Infectious Diseases

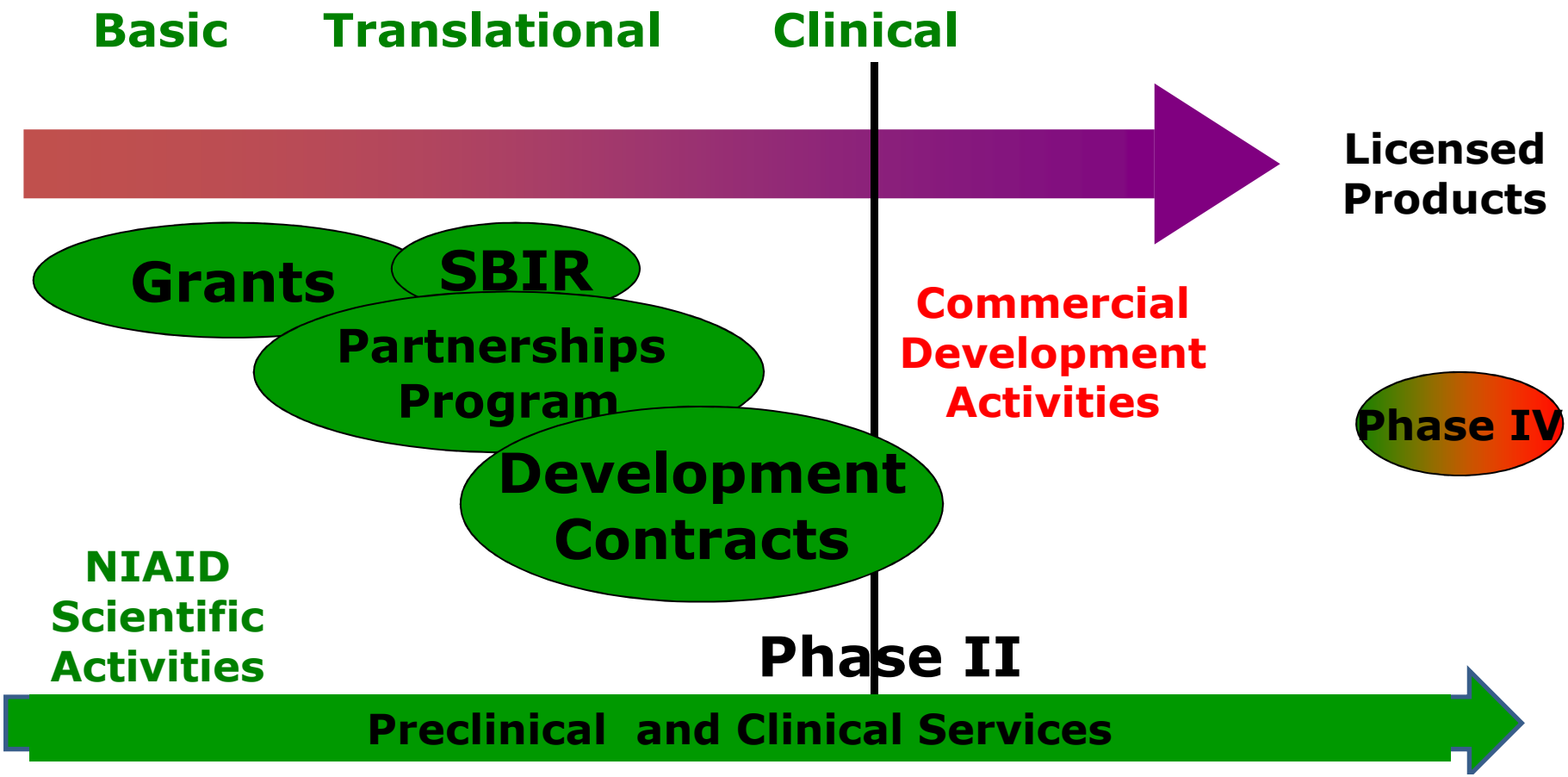


NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

THE WHITE HOUSE

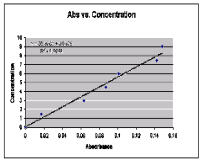
Multiple Programs to Lower Drug Development Risk



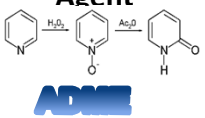
Product Development Services

Therapeutics

In Vitro Assessment of Antimicrobial Activity



Interventional Agent

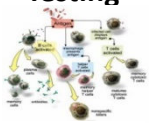


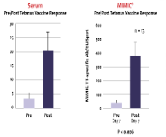
Biopharmaceutical Products

Chemistry, Manufacturing, and Controls (CMC) Documentation for IND

Vaccines

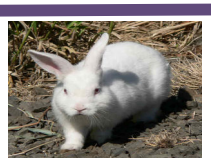
Testing



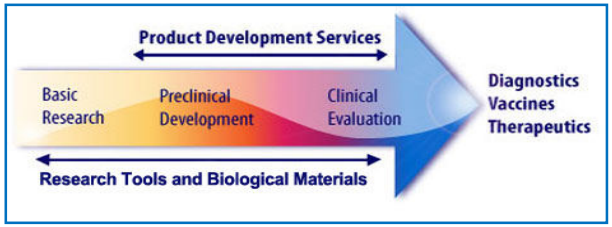


Manufacturing

Animal Models



Reagents
Genomics
Bioinformatics



Clinical

- **Phase I Units**
- **Vaccine Testing and Evaluation Units (VTEUs)**

ARLG
Antibacterial Resistance Leadership Group

NIAID AR Funding Opportunities

- RFA-AI-16-081:Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria (R01)
  - milestone-driven projects
  - novel predictive assays, models and/or research tools based on penetration and efflux of small molecules to facilitate therapeutic discovery for select Gram-
  - Multi-disciplinary teams, academic/industry collaborations encouraged
- Complete list of recent funding opportunities and council-cleared concepts at NIAID's Drug Resistance website
- For updates on Funding Opportunities, subscribe to NIAID Funding News

Upcoming Workshops

- March 1: **FDA** -- Current State and Further Development of Animal Models of Serious Infections Caused by Acinetobacter and Pseudomonas
- April 18-19: Single Cell Technologies for Infectious Disease
- June 14-15: Standardization and Use of PKPD Models for Development of Therapeutics against Bacterial Pathogens

Thank you

Contact:

Jane Knisely, Program Officer, Bacteriology and Mycology

Jane.Knisely@nih.gov

Session 6: Information-sharing platform on compound penetration and efflux

Future, Past and Present

Imperative, Focus and Actions for data sharing

Brad Sherborne, Merck

Imperative

- NIAID RFA A1-16-081
  - 15x centers breaking the mold for G- drug design starting 2018
  - New assays + Old or New compounds
- Efforts we've talked about today

- **So what do we want meeting three years from now?**
  - NOT
    - 15+ slide presentations
    - Dozens of Publications (with SI)
    - Emailed data tables

Imperative

- NIAID RFA A1-16-081
  - 15x centers breaking the mold for G- drug design starting 2018
  - New assays + Old or New compounds
- Efforts we've talked about today

- **So what do we want meeting three years from now?**
  -
    - .
    - .
    - .
  - **Coordinated, multi-project, multi-site efforts**
  - **Meta analyses**
  - **Sense of persistence …**

Desiderata

>1000 training compounds for machine learning models

2245 compounds for the Lipinski / Rule of Five analysis

- Emerging Design Principles
  - Could be just "Avoid …"
- Robust data
  - Comparable analyses of compounds in
  - Comparable assays
- Integrated data & methods (& materials)
  - Strains, conditions
  - Chemical transport modifiers

~20 representatives from each class of antibiotic

3+ Assays per strain / species representing WT, efflux compromised

>20,000 new results Multi-site, multi-center activity

Lessons from Industry

- Experience right now
  - Orphaned data, presentations, project databases
- Data entry
  - Method registration completeness
    - Development vs. Production
  - Ease, integration, value add
- Publication
  - Rich reporting
    - Detail mining
  - No db entry, not usable, not actionable
  - Automated prediction model updates
- Integrate browsing, analyses

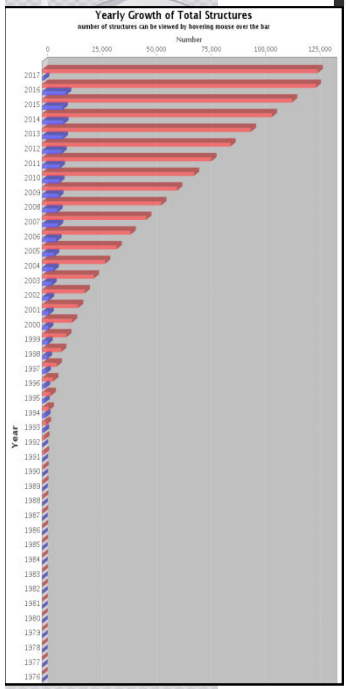
Effort
It won't just happen

Alignment
Reduce barriers, excuses

Encouragement
Data entry = More success

Platform
Next step = Insights

Protein Data Bank (PDB) platform



- 1971 Searchable repository for protein structures
- 1989 Guidelines for data deposition at publication
  - NIGMS funding dependent on open sharing of structural data
- Instrumental in Science Develo
  - Insight into Biology
  - Enabled whole fields such as Simulation

12,754
Citations by the year 2000

Actions for the Present

Ensure	Action
• Take up	• Ready at project start • SI becomes link to database ◦ Journal Requirement
• Use	• Metric for Project progress ◦ Link to future funding
• Sustain	• Funding ◦ Coordination and maintenance

CDD Vault Embraced from Small Groups to Complex, Large-Scale Collaborations

CDD COLLABORATIVE DRUG DISCOVERY

AMRI GLOBAL SMARTSOURCING

BRIGHAM AND WOMEN'S HOSPITAL

SOUTHERN RESEARCH
Legendary Discoveries. Leading Innovation.

EMORY UNIVERSITY

Neuroscience
NIH Blueprint
CDD VAULT

New

UC San Diego

SRI International
R&D for Government and Business

Old

Trevena

UNIVERSITY of WASHINGTON

tetra
TETRA DISCOVERY PARTNERS

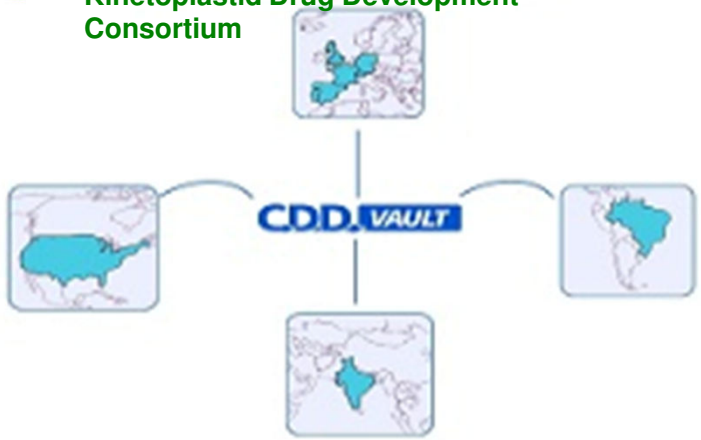
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

BILL & MELINDA GATES foundation

Pharmaceutical Companies:
abbvie MERCK SANOFI Lilly
AstraZeneca gsk Bayer
CDD VAULT

Research Institutions:

KINDReD
Kinetoplastid Drug Development Consortium



MM4TB: 25 organizations

EPFL	AstraZeneca India Private Limited	Uppsala University	University of Pavia	University of Cambridge
Queen Mary University of London	Institut Pasteur	Bach Institute of Biochemistry (RAS)	University of Padova	Comenius University
Vichem Chemie	John Innes Centre	Indian Institute of Science	Cellworks Research India Private Limited	University of Piemonte Orientale
Collaborative Drug Discovery (CCD)	University of the Basque Country	Tydock Pharma Srl	Universidad de Zaragoza	ETHZ
Alere Tech. GmbH	Sanofi Aventis R&D	University of Cape Town	SCIPROM	Institut Pasteur de Lille (INSERM)

Bill & Melinda Gates Foundation Sponsored CDD TB DB for Tuberculosis Research

- 6 Academic/Non-Profit/Government Labs and 7 Big Pharmas
- CDD Vault accepted with Pharma's rigorous legal and IT requirements
- Private, Collaborative and Public data sharing routinely supported
- IP protection rules for secure sharing of lead series
  - Structures set up as private until rele
  - Software enables s
- 10 year collaboration

Public SAR Database Mirrors: CDD Vault w/ Pubchem, Chembl, ZINC, ChemSpider, etc.

Where Informatics Can Help?

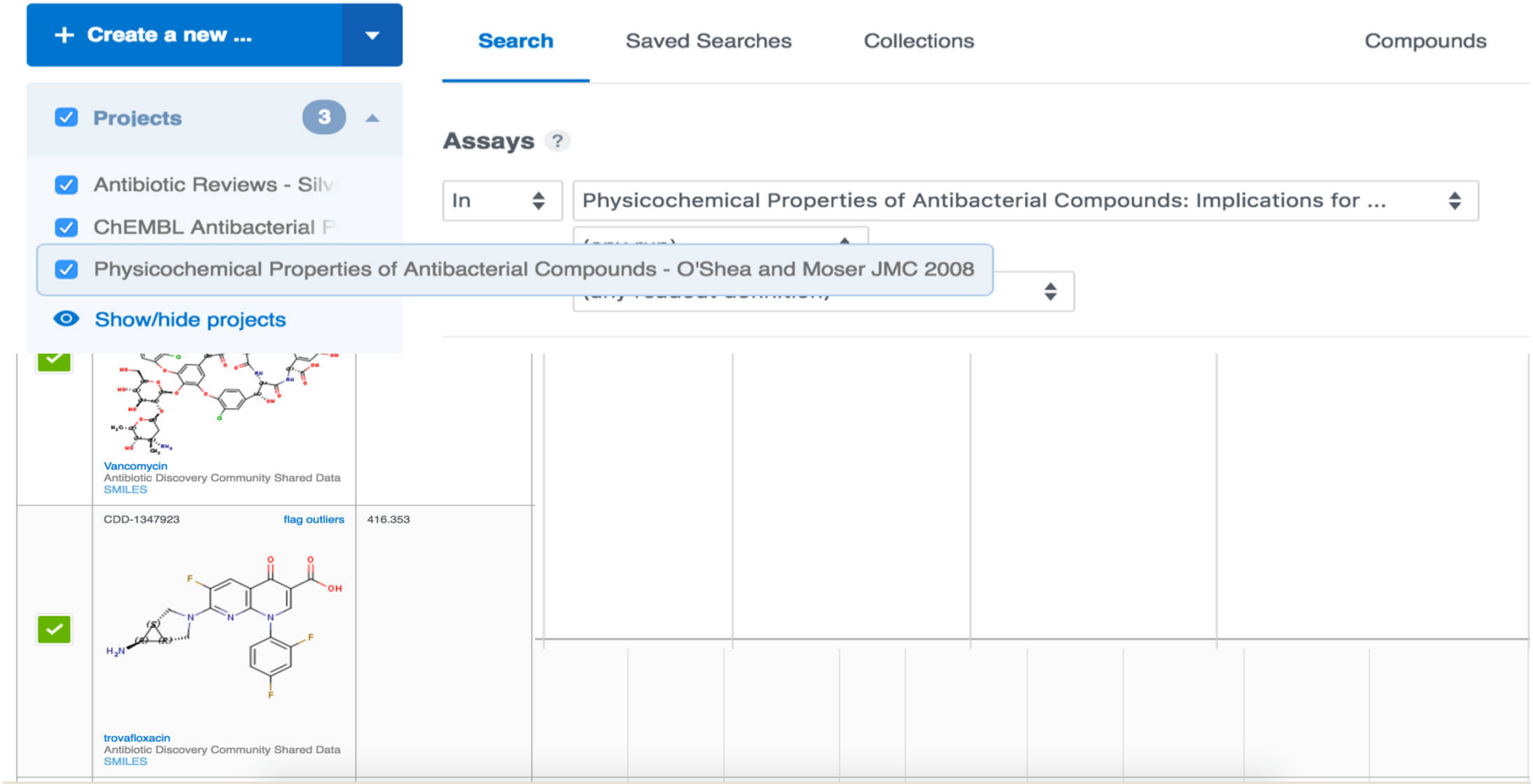
Roadmap for Antibiotic Discovery Three Key Priority Areas

1. Understand and overcome barriers for drugs targeting Gram-negative bacteria in order to generate and tailor new chemical matter for antibiotic discovery.
   - **Transport, Target, Resistance**
2. Evaluate and validate alternative, non-traditional therapies for the treatment of systemic bacterial infections.
   - **Non-Traditional Informatics, Correlate Bioinformatics to Chemoinformatics**
3. Create a framework for efficient sharing of information, expertise, and materials across the research community.
   - **CDD Vault, Bioassay Express (BAE), Pubchem, ChEMBL, etc.**

➢From: Shore, C. K., Coukell, A. *Nature Microbiology* 26 May 2016 (Personal opinions on areas where informatics can help in **bold**).

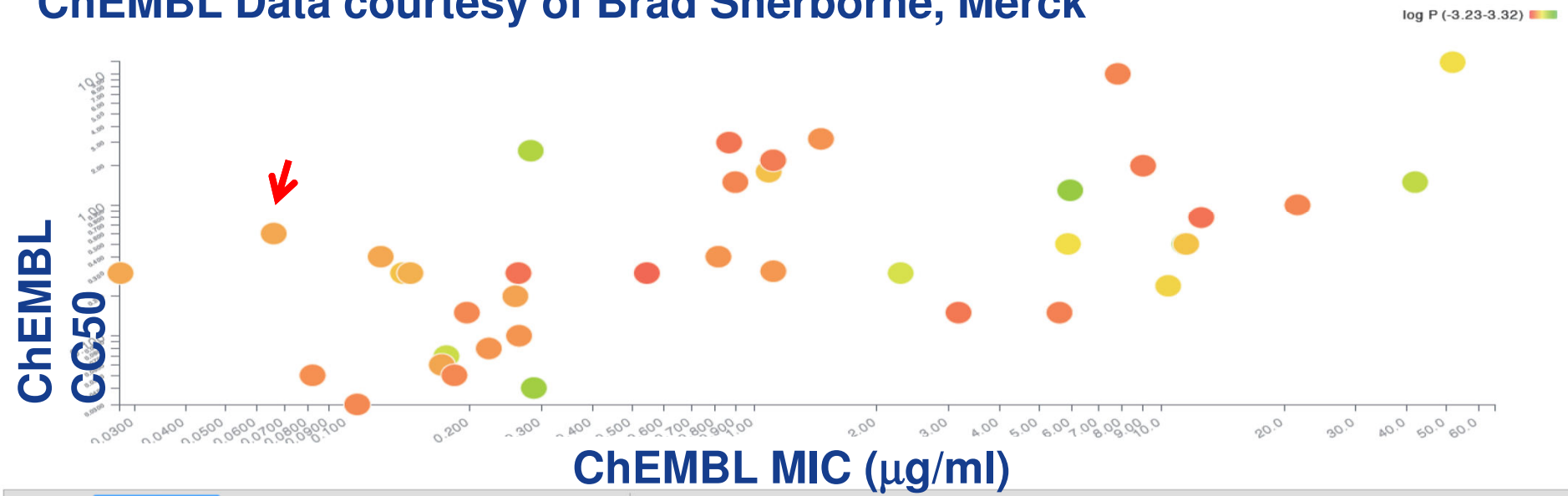
Keys for Successful PPP Information Sharing

How an Information Sharing Platform Benefits Researchers Working on Compound Penetration and Efflux



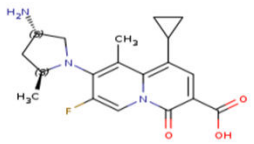
Information & Analyses the Scientific Community Needs in an Information Sharing Platform

Antibacterial Permeability Example: Gyrase CC50 vs. MIC vs. Log P
ChEMBL Data courtesy of Brad Sherborne, Merck



1 Selected: Launch Vision | Plot | Export | Add to collection | Build model | Customize your report | Save this search

ChEMBL Antibacterial Permeability with both Ki/IC50 and MIC data

Molecule	Collections	Standard Type	Relation	Standard Vaule	Standard Units	BAO Endpoint	UO_UNITS	QUDT_UNITS	DESCRIPTION	ASSAY_ORGANISM	BAO_FORMAT	TID	TARGET_CHEMBLID
flag outliers  CHEMBL420286 Challenges of Antibiotic Discovery Review		MIC	=	1.56	ug.mL-1	BAO_0002146	UO_0000274	http://www.openphacts.org/units/MicrogramPerMilliliter	In vitro antibacterial activity against gram-positive organism Staphylococcus aureus 1775	Staphylococcus aureus	BAO_0000019	104885	CHEMBL2097174

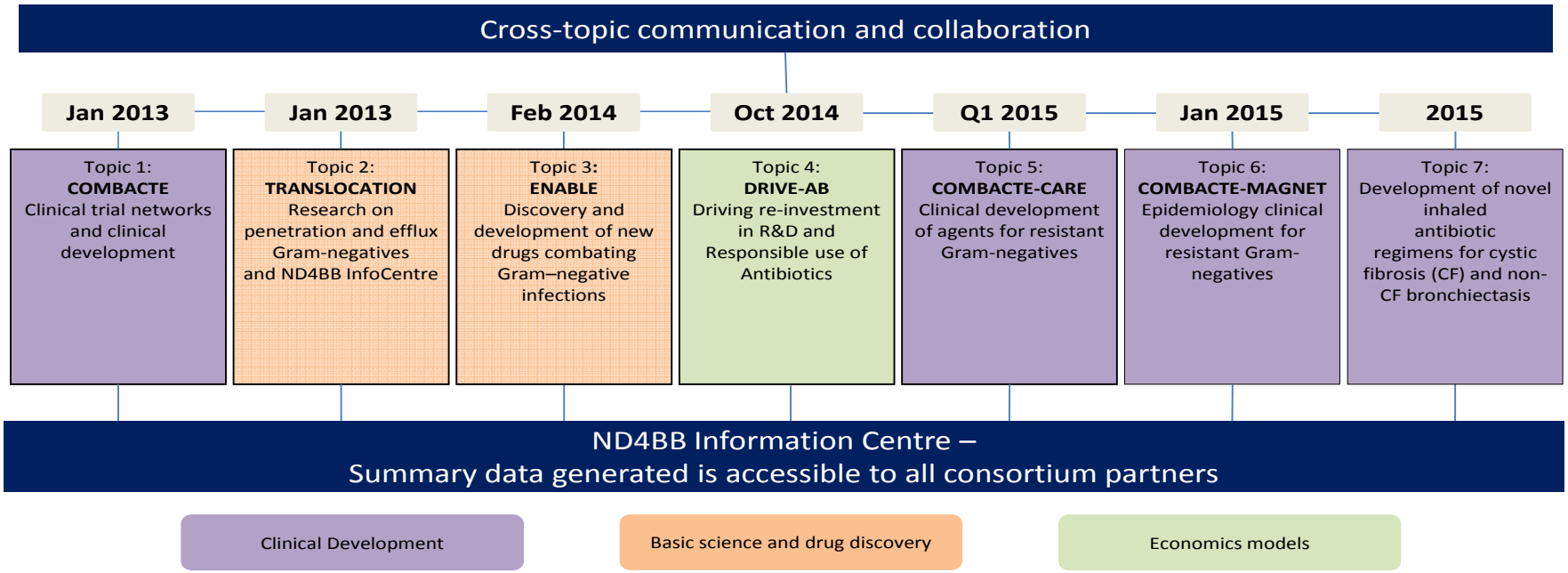
Fluoroquinolone Example: J. Medicinal Chemistry 1996.

Information sharing in Antibiotic Research

The research leading to these results discussed here was conducted as part of the TRANSLOCATION consortium (http://www.translocation.eu/) and has received support from the Innovative Medicines Initiative (IMI) Joint Undertaking under Grant Agreement no. 115525, resources which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. This presentation reflects the author's views and neither IMI JU nor EFPIA nor the European Commission is liable for any use that is made of the information contained therein.

36

ND4BB-Structure



Specific barriers

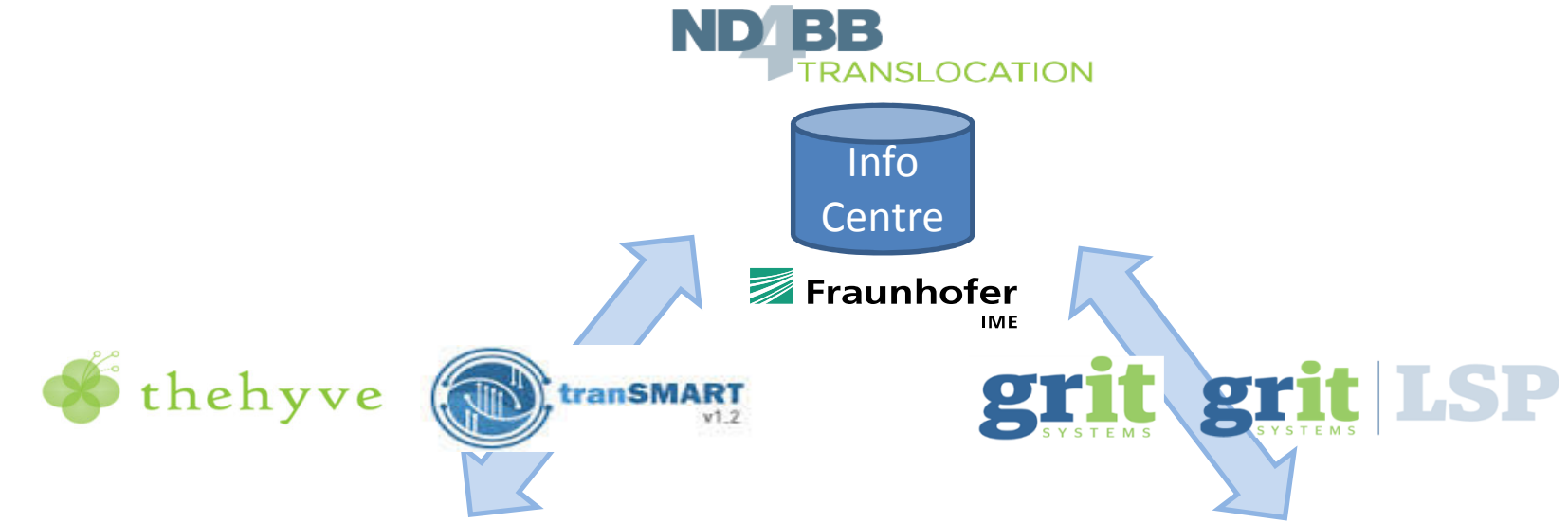
Scientific priorities for antibiotic discovery

- Generate and tailor chemical matter for antibacterial discovery
  - Goal: Understand and overcome barriers to drug penetration and efflux avoidance for Gram-negative bacteria
  - Goal: Generate and tailor chemical matter for antibacterial discovery
- Conduct key proof-of-concept studies for nontraditional therapies
  - Goal: Assess whether single-target antibacterials can be used in combination to overcome resistance
  - Goal: Validate nontraditional therapies
- Share data, materials, and knowledge across disciplines and between sectors
  - Goal: Share data and information
  - Goal: Share materials
  - Goal: Share knowledge and expertise
- Models for antibiotic discovery
  - Governance and organizational structure
  - Intellectual property
  - Funding

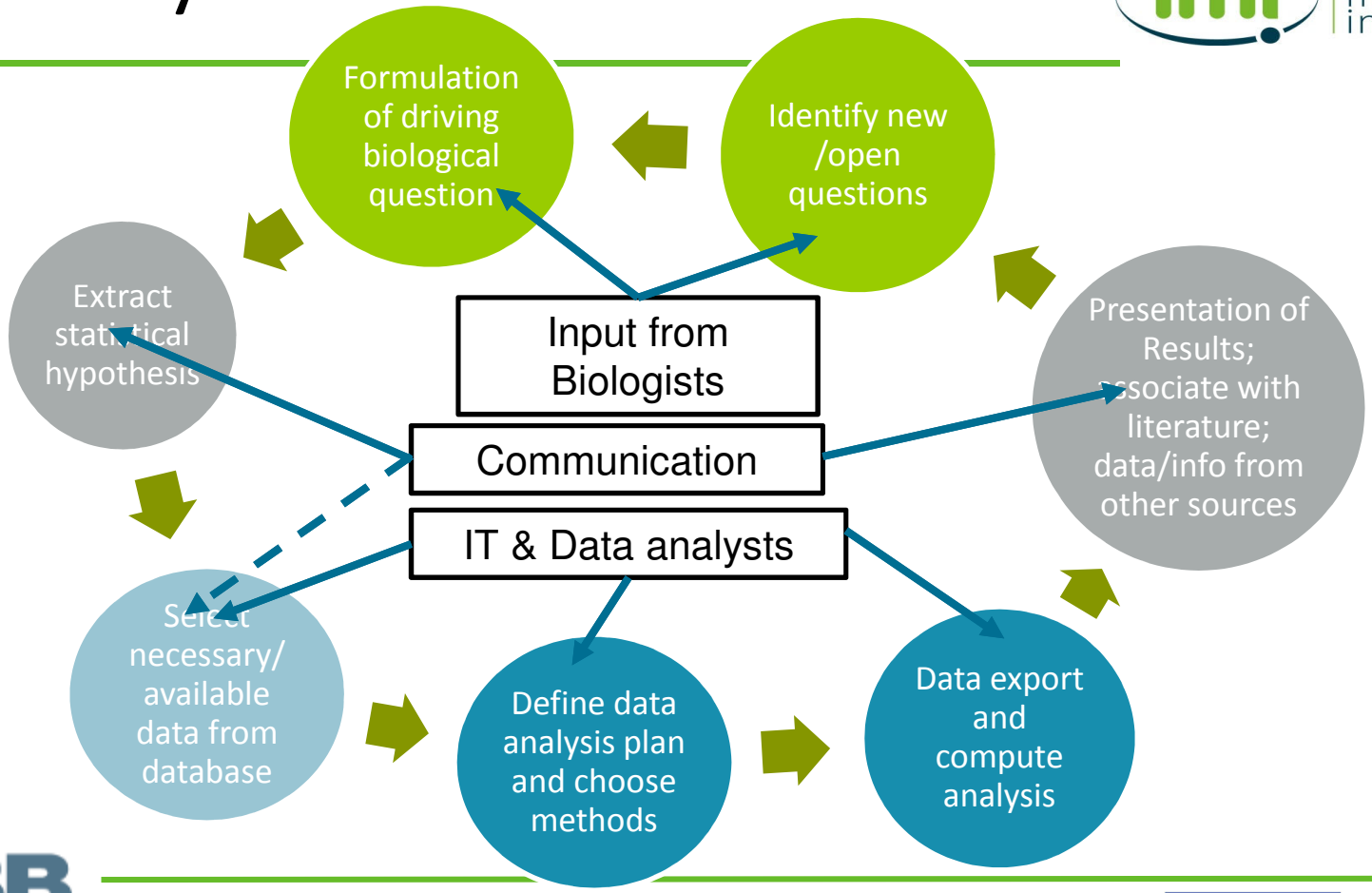
Major bottlenecks

- Lack of
  - information record, management and storage
  - data sharing along the discovery pipeline
  - data integration from different sources
- Waste of resources by
  - repeating failed experiments
  - repeating successful experiments
  - Preparing experiments without sufficient documentation

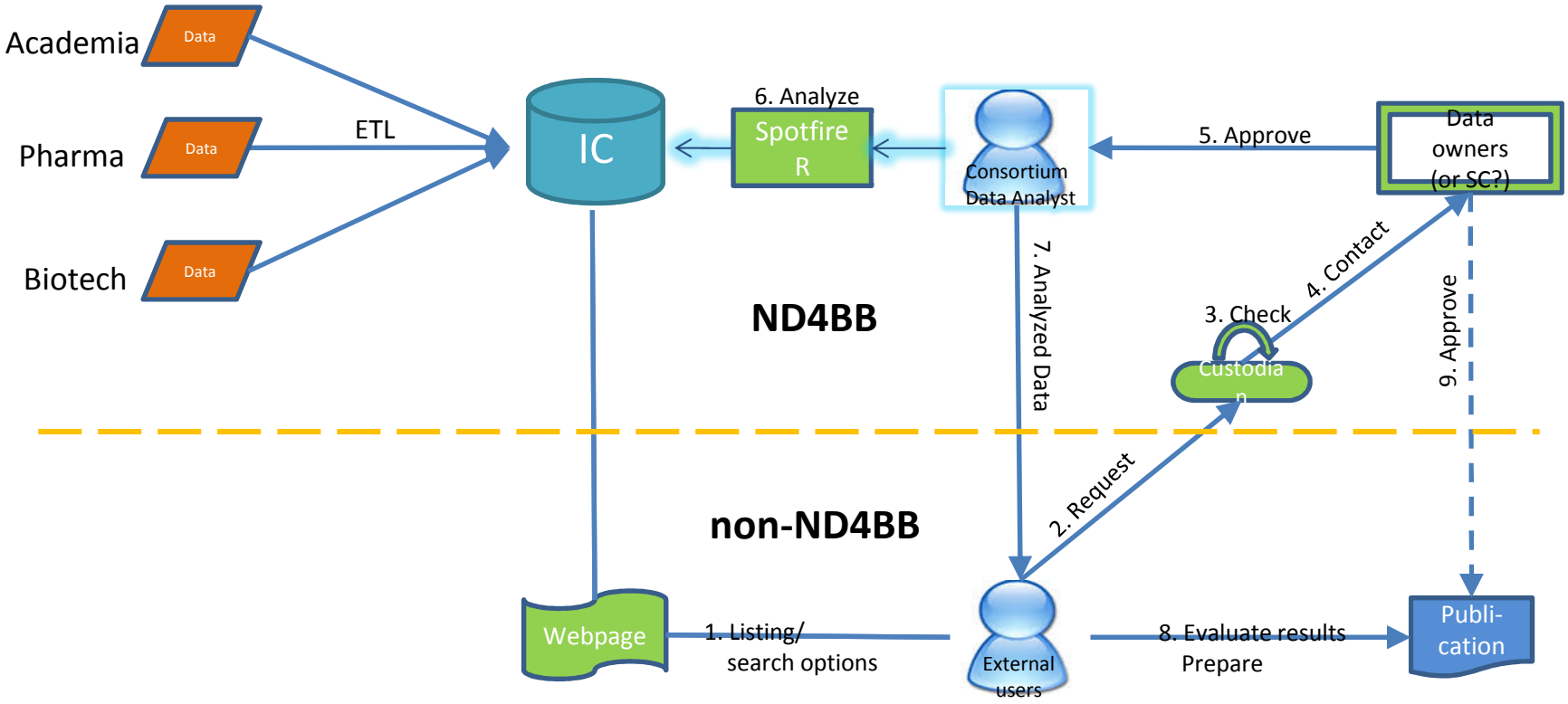
Integration with other knowledge based systems



Data analysis



Proposed Collaborative Access (ColA) for external, non-ND4BB users



Summary

- ND4BB InfoCentre operational
  - Data managers assigned
    (align annotation of delivered data e.g. protocol definition)
  - Data analysis team established
    (open for members of ND4BB)
  - **Data provision ongoing**
  - Planning for sustainability until 2020 and beyond
    (Translocation runs thru Dec 2017)