Director's Report

NCATS Advisory Council and CAN Review Board

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS

JANUARY 15, 2015

NCATS

NIH National Center for Advancing Translational Sciences

New Format for Director's Report

- Council requested more discussion time
- NCATS successes have multiplied → comprehensive accounting of progress in presentation form impractical
- Current presentation features selected highlights only
- Details and more complete accounting of progress since last Council/CAN Board meeting hyperlinked from Agenda, with embedded links to further details
- Feedback welcome

NCATS FY 2015 Budget
Update

- In December, the President signed the CRomnibus
  - It is a combination of a CR for the Department of Homeland Security (through February 27, 2015),
  - And an omnibus covering funding for the rest of the government (through September 30, 2015)
- It includes funding for NCATS at approximately the same overall level as last year ($635 million, 0.3% increase)
- We are currently working on the FY 2016 Budget request, which is expected to be released on Monday, February 2, 2015

Congressional Briefings

- **21st Century Cures Initiative**
  - http://energycommerce.house.gov/cures
  - Dr. McInnes participated in a BIO-organized event with Rep. Joe Pitts (R-PA) and a roundtable with Rep. Tim Murphy (R-PA)

  - Dr. Austin participated in a roundtable with Reps. Fred Upton (R-MI) and Diana DeGette (D-CO) as a kickoff to FasterCures meeting
  - Dr. Austin met with Committee staff several times

NIH
National Center for Advancing Translational Sciences

Congressional Briefings

- **Technology Transfer Caucus – "Next Generation R&D Partnerships: The NCATS Success Story"**
  - Hosted by Rep. Ben Lujan (D-NM)
  - Participants:
    - Joe Allen, Allen & Associates
    - Chris Austin, NCATS
    - Ron Bartek, Friedreich's Ataxia Research Alliance
    - Steve Seiler, AesRX
    - Bruce Trapnell, Cincinnati Children's Hospital
    - Paul Kaplan, Genzyme

NIH
National Center for Advancing Translational Sciences

Congressional Visits to NCATS

- Senate Appropriations Subcommittee Staff
- Senate Health, Education, Labor, and Pensions (HELP) Committee Staff
- Technology Transfer Caucus and DOE Staff
- Tox21 Program (co-hosted by NCATS and NIEHS)
  - House Energy and Commerce Subcommittee on Environment and Economy staff
  - Senate Environment & Public Works Committee staff

NIH
National Center for Advancing Translational Sciences

Ebola Medicines Day

- **NCATS and NIAID hosted an Ebola Medicines Day on November 24, 2014.**

- **Participants:**
  - Representatives from the biopharmaceutical industry, Bill & Melinda Gates Foundation, USAMRIID, DTRA, FDA, and NIH

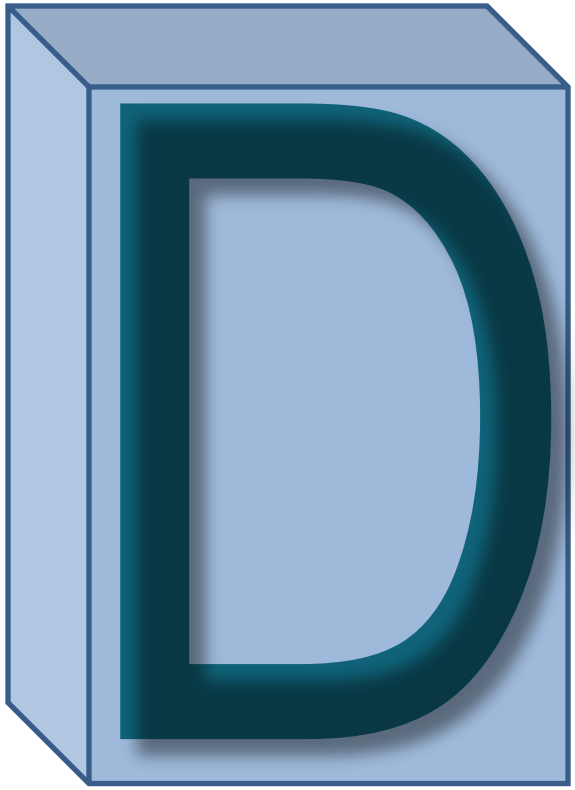
- **Purpose:**
  - To provide industry representatives with state-of-the-science information on virus biology and host response.

NIH
National Center for Advancing Translational Sciences

NCATS Mission

To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS "3D's"



evelop

emonstrate

isseminate

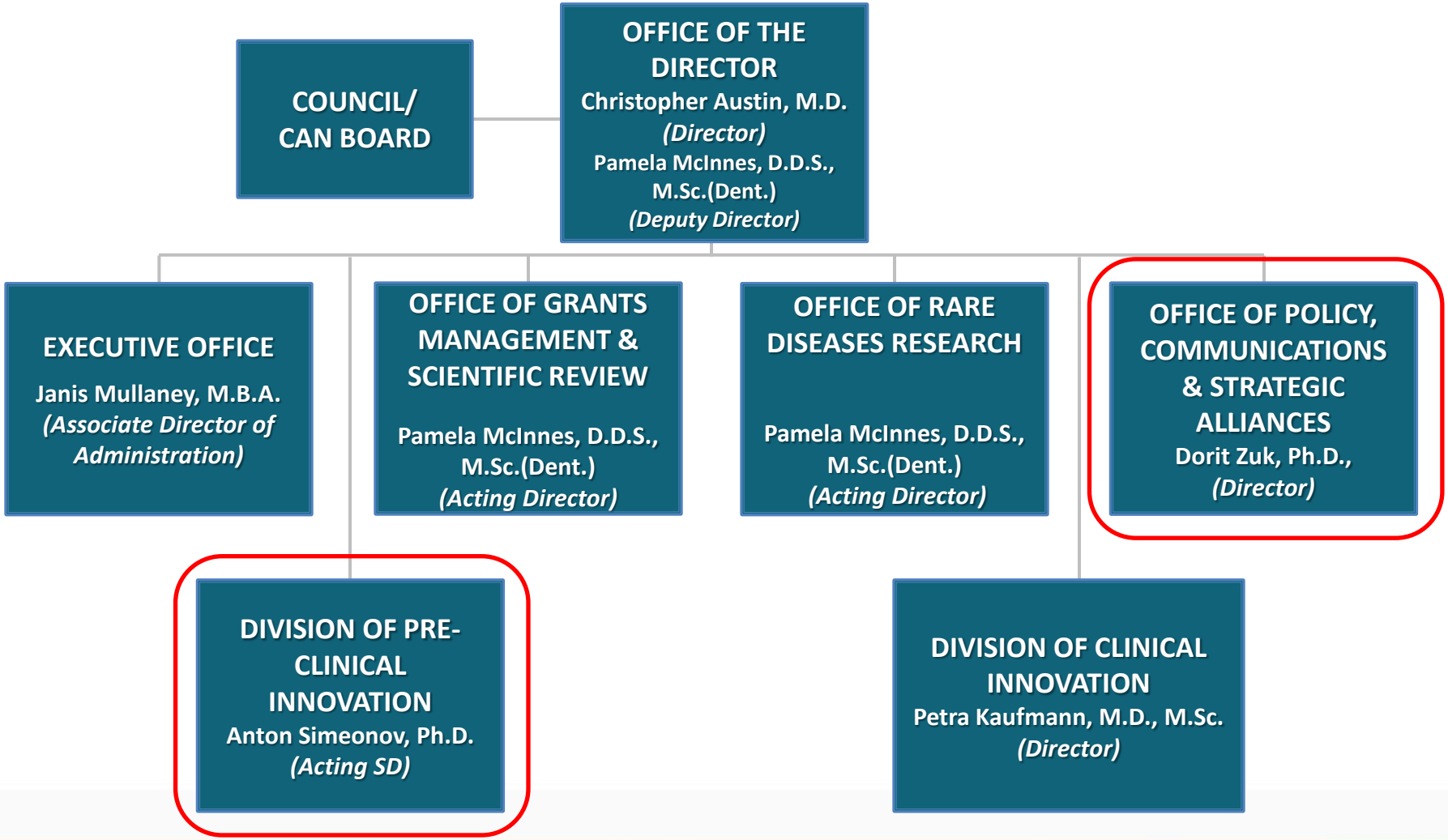
Translational Innovation at NCATS
Three Selected Highlights

- *Early-stage translation:* chemical probe/lead development for target validation and therapeutic hypothesis testing
  - » High cost and inefficiency of high-throughput screening
- *Mid-stage translation:* preclinical development to first-in-human studies
  - » Inefficiency/ineffectiveness of rare disease therapeutic development
- *Late-stage translation:* large-scale studies in humans
  - » Protracted time, high cost, inefficiency of clinical translational studies, including clinical trials

NIH
National Center for Advancing Translational Sciences

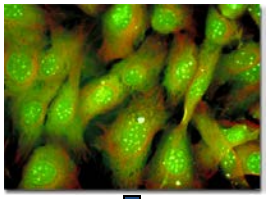
Innovation in early-stage translation:

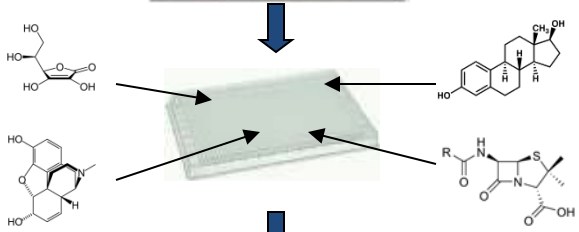
High cost and inefficiency of high-throughput screening

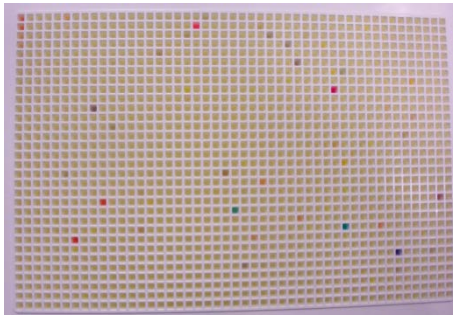


What is High-Throughput Screening?

HTS defined as testing of >100,000 chemicals per day for a biological activity







Same cells or gene in each well of 1536-well plate

+

Different chemical in each well of 1536-well plate

+

Robots, laser detectors, and computers

Identification of which chemicals affect the cell's function

High cost and inefficiency of high-throughput screening

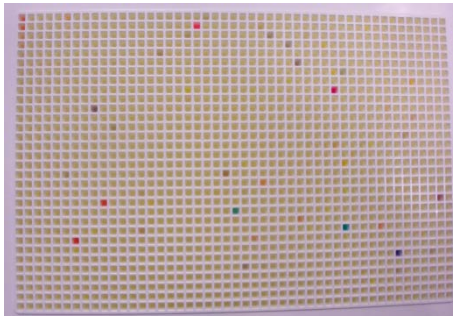
- NCATS DPI HTS (3M samples tested) utilizes
  - » 1500-2000 microplates/screen
  - » 50 screens/yr
  - » 100,000 microplates/yr
- Cost: many laboratories are spending $MM annually on microplate consumables before overhead or disposal
- Waste: waste stream for microplates is substantial

Q: WHY NOT CLEAN AND RE-USE PLATES?

NIH
National Center for Advancing Translational Sciences

WHY NOT CLEAN AND RE-USE PLATES?

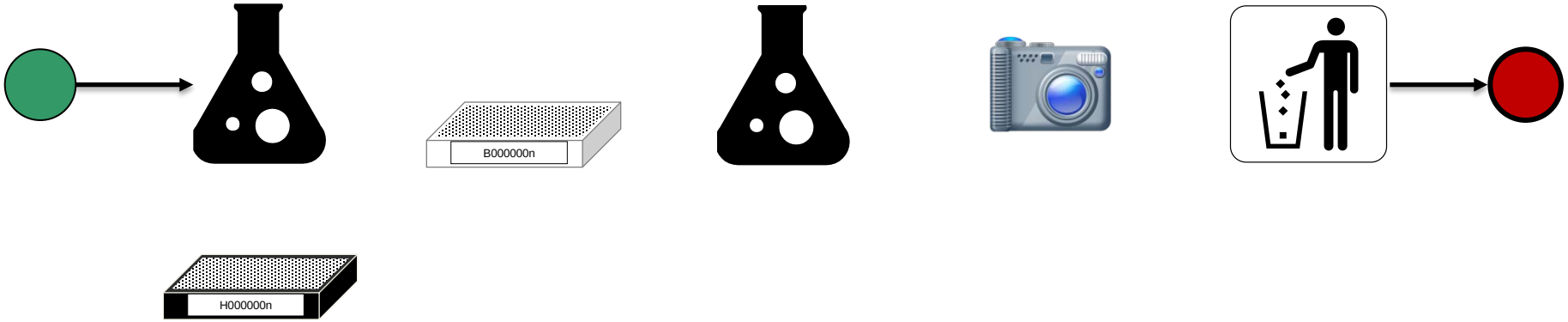
1 well
267 mm (10.5 inch) diameter surface
Flat
Round



1536 wells
1 mm (0.004 inch) diameter surface
8 mm deep
Square

NIH
National Center
for Advancing
Translational Sciences

Generic Assay Protocol



1. Add Reagent to Assay Plate
2. Transfer Compound to Assay Plate
3. Add Detection Reagent to Assay Plate
4. Read Assay Plate
5. Dispose of Assay Plate

Reusing Plates
Demonstration of Proof of Principle at NCATS

- Typical large screen uses 1600 1536-well plates full of experiments
- Instead of 1600 plates, DPI now uses 40 plates for entire screens – each plate used 40 times
- Since 2011, NCATS has screened ~50,000 plates of experiments using only ~1400 assay plates
  - » 48,600 plates kept out of landfill
  - » $472,000 saved
- Q: Could this principle be industrialized and disseminated?

NIH
National Center for Advancing Translational Sciences

‘Plate Cleaner’
Identifying Potential

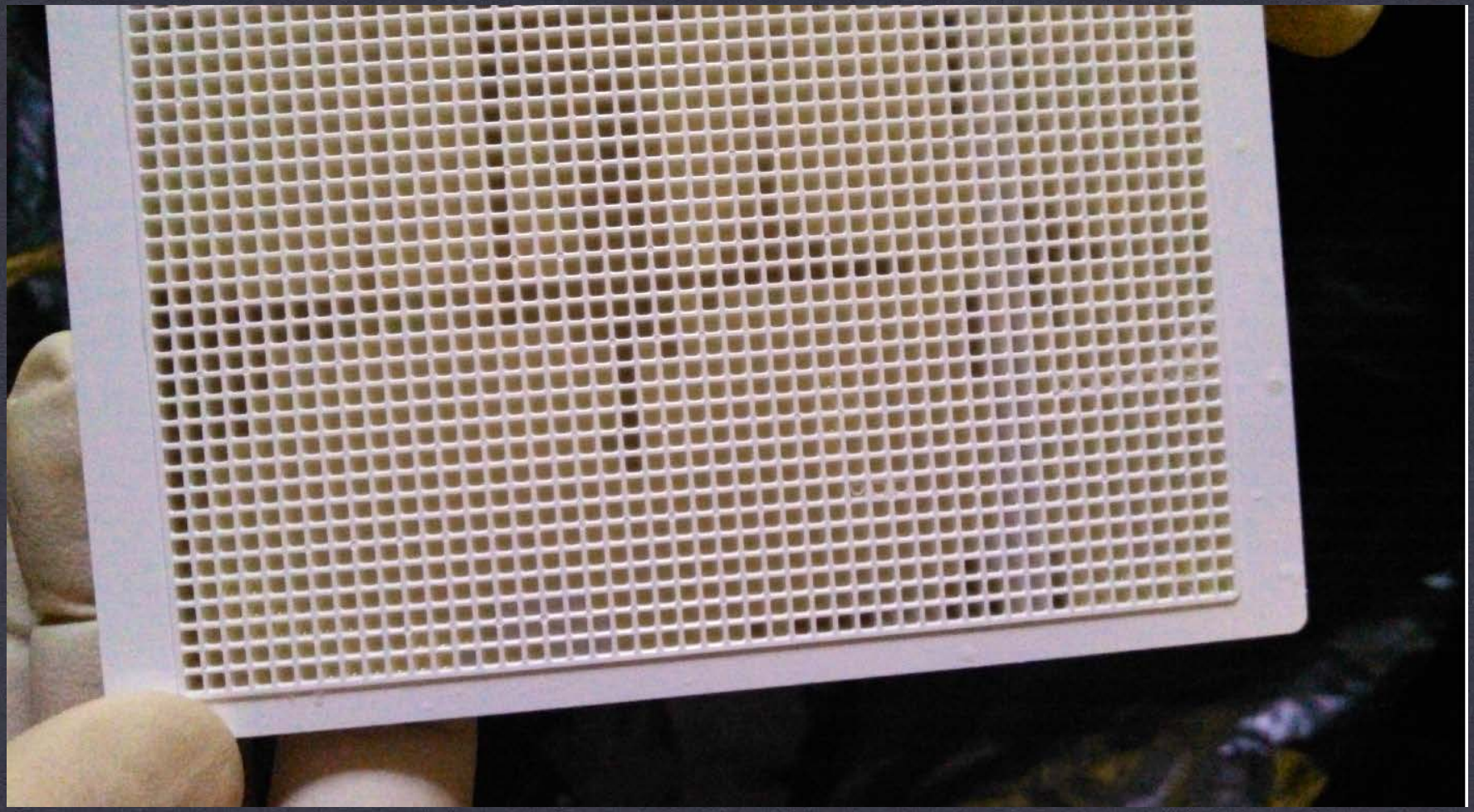
- NCATS identified a gap – the need to develop automated instrumentation to clean previously used plates, making them suitable for reuse
  - » Given the large quantities of plates required for HTS, a device could have viable commercial product potential

- NCATS saw an opportunity – to include “**Automated Instrument to Clean Microtiter Plates**” as part of the 2012 NIH SBIR Contract Solicitation

- SBIR Contract awarded to small business **IonField** (Moorestown, NJ)

IonField's "Plasma Knife" Approach

- Working with NCATS, IonField analyzed what's needed to clean plates to background – regardless of format or assay
- Benchmark for 'clean': no measureable carryover using qPCR or ion chromatography
- Two step process
  1. Optimized wash removes 99.9% of assay reagents from wells
  2. "Plasma knife" removes remainder of residual material



PROJECT

SBIR PHASE I

TYPICAL 1536 PLATE PROCESSED

DATE SPRING 2013

CLIENT NIH/NCATS

PROJECT

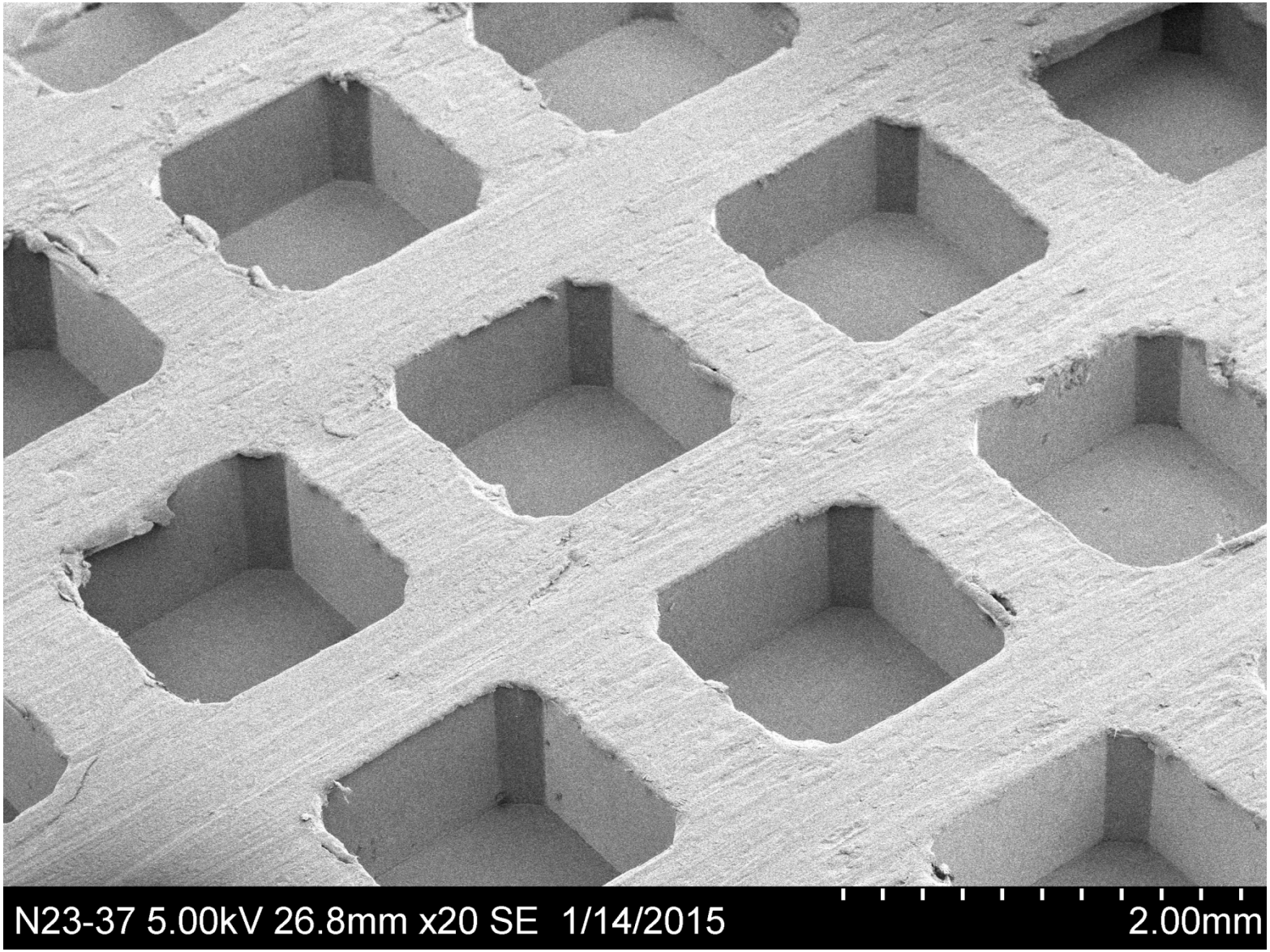
SBIR PHASE I

POST SOLVENT WASH

DATE SPRING 2013

CLIENT NIH/NCATS

Post-cleaning 1536 well plate by SEM



Plasma Knife Technology
Dissemination

- NCATS SBIR Phase I confirmed proof of principle; Phase II award ($1M) is funding commercial development
- Development of prototype instruments to be installed at beta program sites
  - » To provide data for high volume applications in exchange for exclusive, early access to technology
  - » Interest in beta program spans from big pharma to nonprofits (e.g., Novartis, AstraZeneca, Merck, Abbvie, BGI, Sanford Burnham)
- Working with reagent companies such as Promega to help develop cleaning protocols

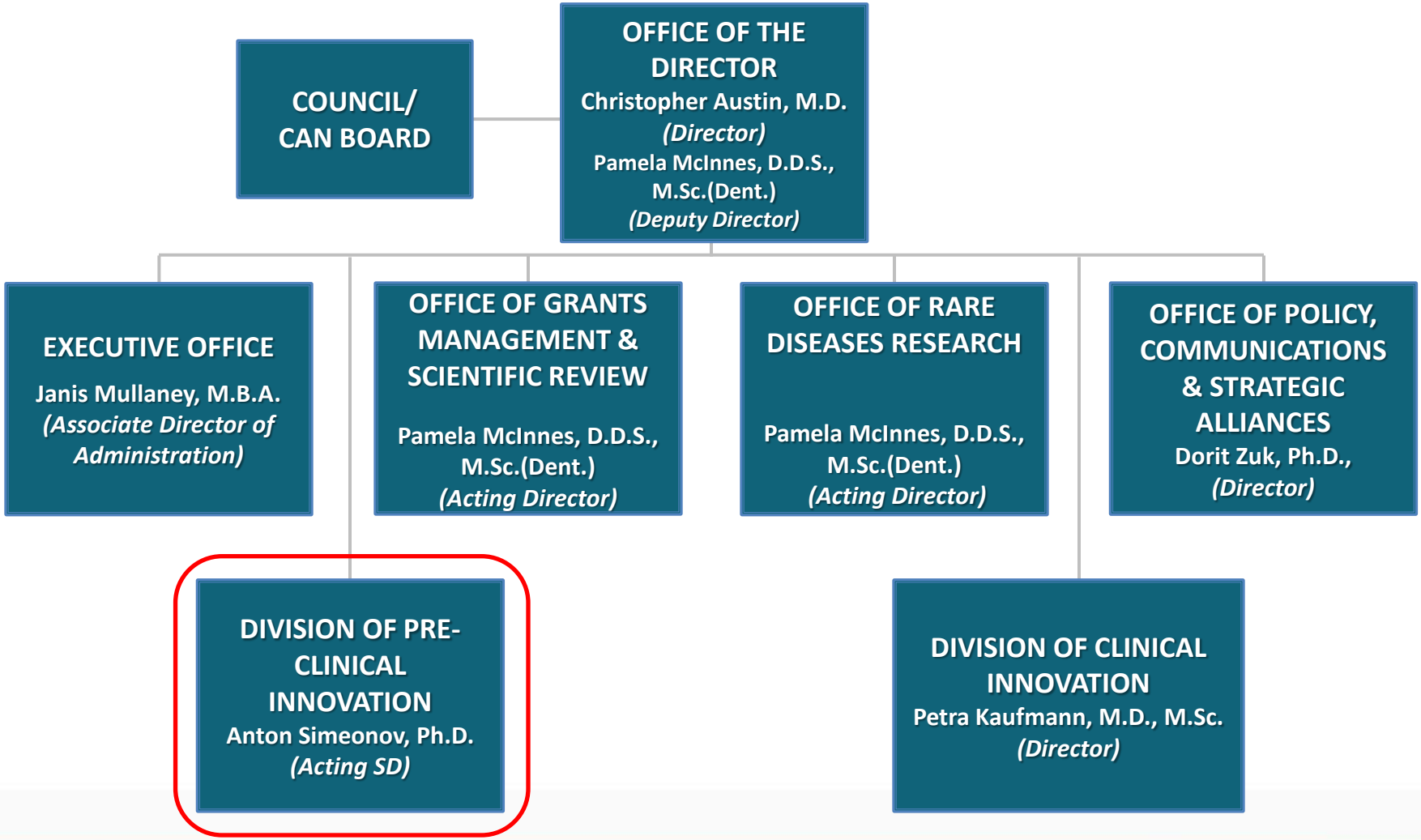
3Ds in Early-Stage Translation

- DEVELOPED new technology to reuse microplates, reducing cost and waste in SBIR-driven public-private partnership
- DEMONSTRATED effectiveness at NCATS
- DISSEMINATING technology, creating new business opportunity for via SBIR partner

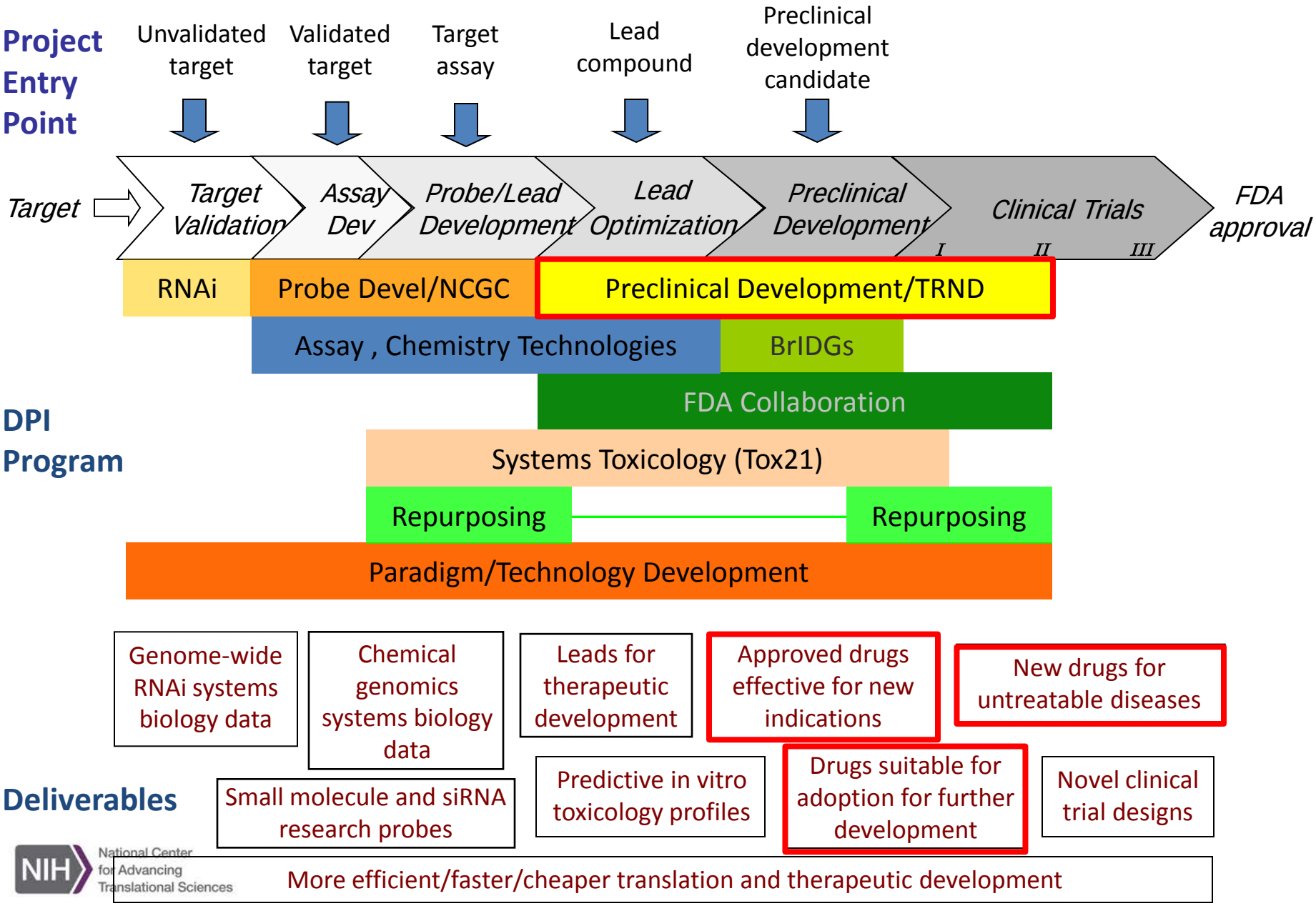
NIH
National Center for Advancing Translational Sciences

Innovation in mid-stage translation:

Inefficiency/ineffectiveness of rare disease therapeutic development



NCATS DPI: A Collaborative Pipeline



Lysosomal Storage Diseases (LSDs)

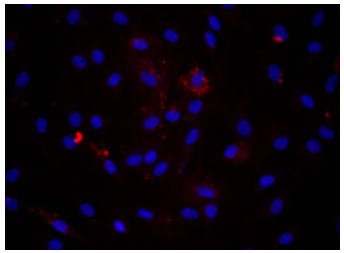
- Also known as lipid storage diseases
- Comprise 50 rare inherited disorders that usually affect children
- Fatty materials accumulate in the cells and tissues of the body
- These diseases can result in damage to the brain, peripheral nervous system, liver, and other organs and tissues; they are often fatal

NIH
National Center for Advancing Translational Sciences

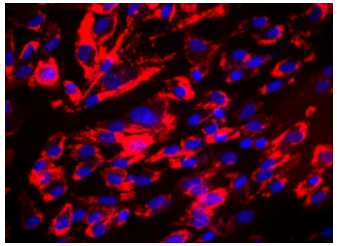
Niemann-Pick Disease, type C (NPC)

- Autosomal recessive disease
  - Mutated genes are NPC1 (95%) and NPC2 (5%)
- Defects in NPC1 or NPC2 proteins cause cholesterol accumulation in lysosomes; a lysosomal storage disease
- Clinical manifestations:
  - Enlargement of the spleen (splenomegaly) and liver (hepatomegaly)
  - Progressive neurological disorders including cerebellar ataxia, swallowing problems, and progressive impairment of motor and intellectual function in early childhood

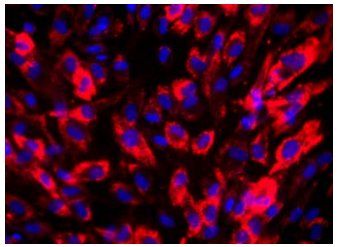
Normal



NPC1



NPC2



Lysosome size enlarged in NPC1 and NPC2 cells. Red: lysosome, Blue: nuclei

NPC Collaboration

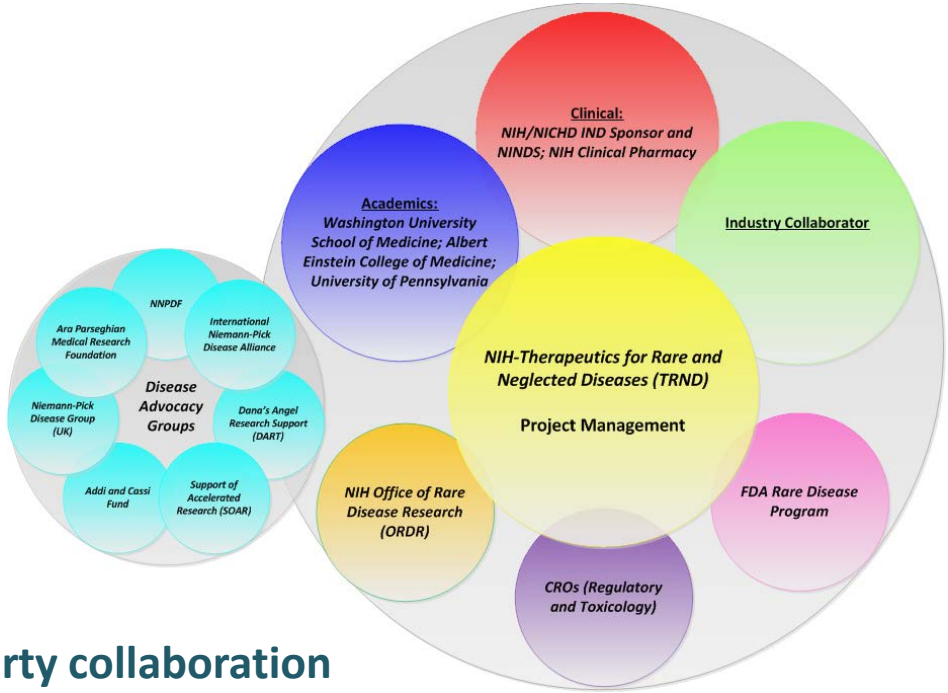
- Project started in 2006 with multiple NPC patient foundations
- Basis of project was finding by multiple academic investigators that cyclodextrin had beneficial effects in NPC1 animal models

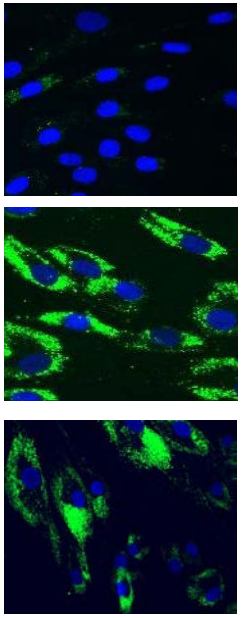
- NCATS TRND:
  - » Validated cyclodextrin as a potential drug candidate
  - » Pre-clinically developed cyclodextrin as part of project initially focused on finding treatments for NPC1
  - » NCATS found that cyclodextrin and δ-tocopherol also lowered the buildup of lipid byproducts for several other LSDs

TRND Development of Cyclodextrin

for the Treatment of Niemann-Pick Type C1 Disease

- **Collaborators:** Multi-party collaboration involving NIH, academia, patient advocacy groups, and industry
- **Objective:** Develop HP-β-CD as a therapy for Niemann-Pick Disease, type C (NPC), an LSD where defects in NPC1 or NPC2 proteins cause cholesterol accumulation in lysosomes
- **Scope:** A comprehensive pre-clinical program to support a Phase I trial for HP-β-CD in NPC, 1st by intraventricular injection, later changed to lumbar intrathecal (IT injections)
- **Status:** Phase I clinical trial started at NIH Clinical Center in February 2013 and is on-going





WT

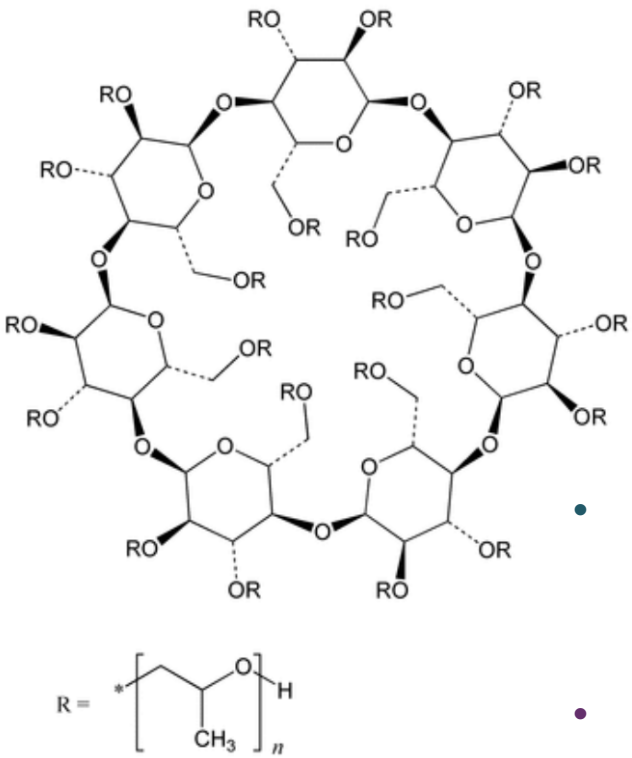
NPC

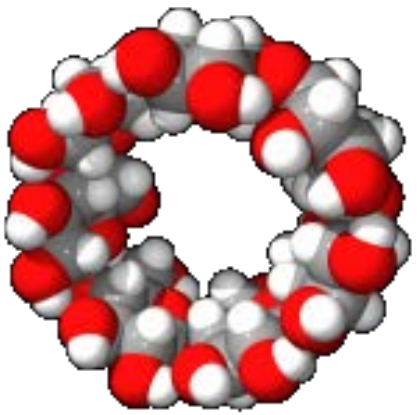
NPC + HPBCD

Multi-party collaboration

NIH National Center for Advancing Translational Sciences

Molecule: HP-β-CD

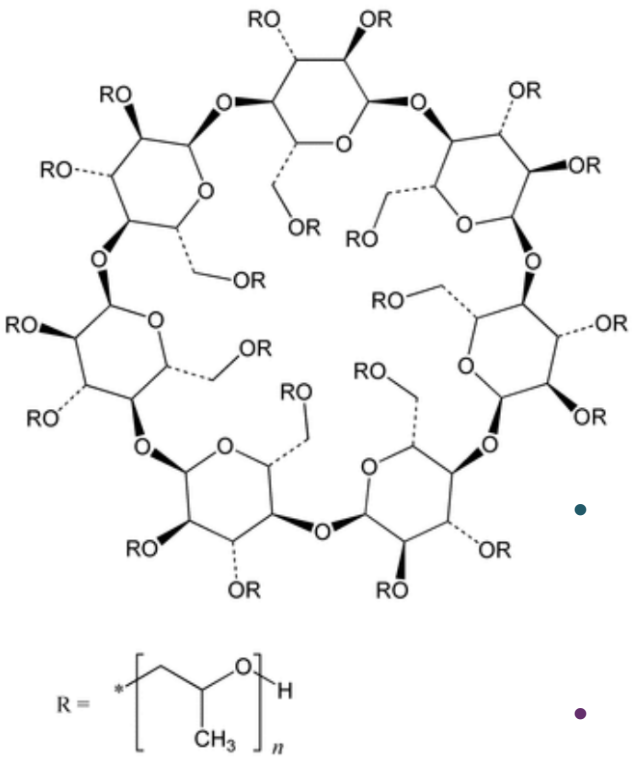


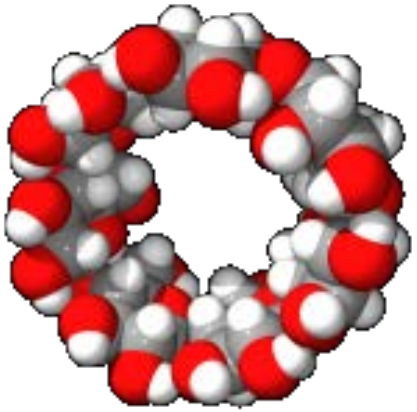


- Used as a pharmaceutical excipient due to ability to increase solubility of and dissolution rate of poorly water-soluble drugs
- β-cyclodextrin is found in the FDA "generally recognized as safe" (GRAS) list, and its derivative, HP-β-CD, is referenced in the USP/NF and EP and is cited in the FDA's list of inactive pharmaceutical ingredients

Loftsson *et al.*, 2005, Loftsson *et al.*, 2007.

Molecule: HP-β-CD





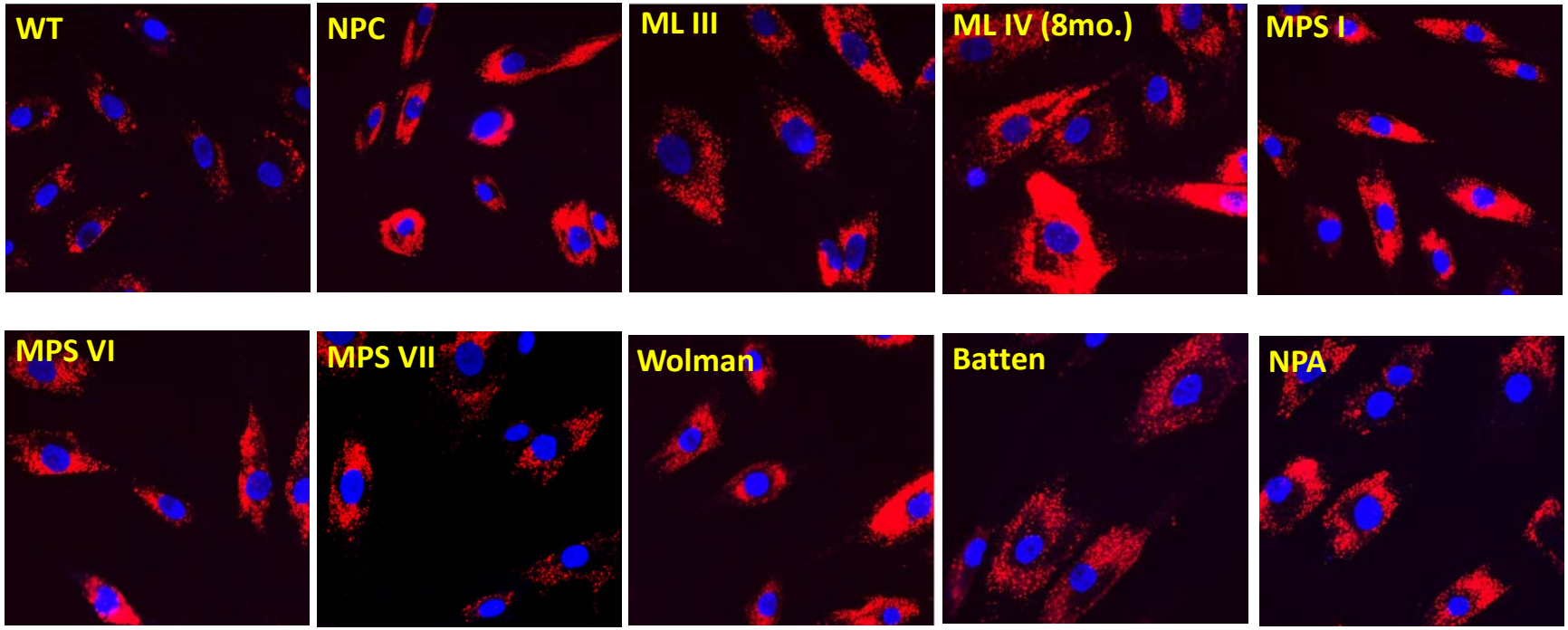
- Used as a pharmaceutical excipient due to ab
  increase solubility of and dissolution
  water-soluble drugs
- β-cyclodext the FDA "generally
  rec (GRAS) list and its derivative,
  referenced in the USP/NF and EP and is
  ted in the FDA's list of inactive pharmaceutical
  ingredients

Repurposing effort of a food additive!

Loftsson *et al.*, 2005, Loftsson *et al.*, 2007.

Phenotypic Disease Relevant Assay-Based Profiling Across LSDs

LysoTracker-red dye stains enlarged lysosomes in LSD patient cells:



Agreement with Vtesse January 7, 2015

Advancing treatments for Lysosomal Storage Disorders

- CRADA: NCATS - NICHD – Vtesse (Gaithersburg, MD)

For Immediate Release: Wednesday, January 7, 2015

NIH teams with industry to c
treatments for Niemann-Pick
disease

8+1 7

Researchers from the National Institutes of Health h
agreement with biotechnology company Vtesse, Inc.,
Maryland, to develop treatments for Niemann-Pick d
and other lysosomal storage disorders.

Lysosomal storage diseases, also known as lipid stor
comprise about 50 rare inherited disorders that usu
Fatty materials accumulate in the cells and tissues c
diseases can result in damage to the brain, periphe
liver, and other organs and tissues; they are often f

Researchers at the National Center for Advancing Tr
National Institute of Child Health and Human Develo
other lysosomal

3. Pfizer, NEA orphan drug project launches its first biotech on PhII/III threshold

By John Carroll Comment | Forward | Twitter | Facebook | LinkedIn

Less than two years after New Enterprise Associates and Pfizer Ventures got together to launch Cydan, an incubator for new orphan disease drug developers, the group is spawning its first new biotech with a $25 million round and a program for Niemann-Pick disease type C ready to go straight into a Phase II/III study.

The venture backing provides enough money to get the pivotal data needed to know whether or not they have a product, says Chris Adams, who runs Cydan out of Cambridge, MA, and is on the board of the newly created Vtesse. The same syndicate that set up Cydan--NEA, Pfizer ($PFE), Lundbeckfond Ventures, Bay City Capital and Alexandria Venture Investments--is also backing the startup, he adds, which is being run by the experienced drug developer Ben Machielse and his small but knowledgeable team.

It's a virtual operation, notes Machielse, but there's also a wide group of investigators at the NIH and elsewhere who have pitched in to get VTS-270--a formulation of 2-hydroxypropyl-beta-cyclodextrin--to the threshold of a pivotal study.

"I actually got approached by Dave (Mott, NEA partner and former MedImmune CEO) in May to actually see if I could help out with this particular opportunity," says Machielse, a MedImmune veteran and former CEO of Omthera, which was acquired by AstraZeneca ($AZN). Vtesse licensed in the program but will continue to work with public investigators to take it the final step in the clinic.

Ben Machielse

"This public/private model is pretty cool," says Machielse, adding that this particular biotech business model should be something that can be replicated in other developers. Machielse is keeping the biotech close to home--and the NIH--in Gaithersburg, MD.

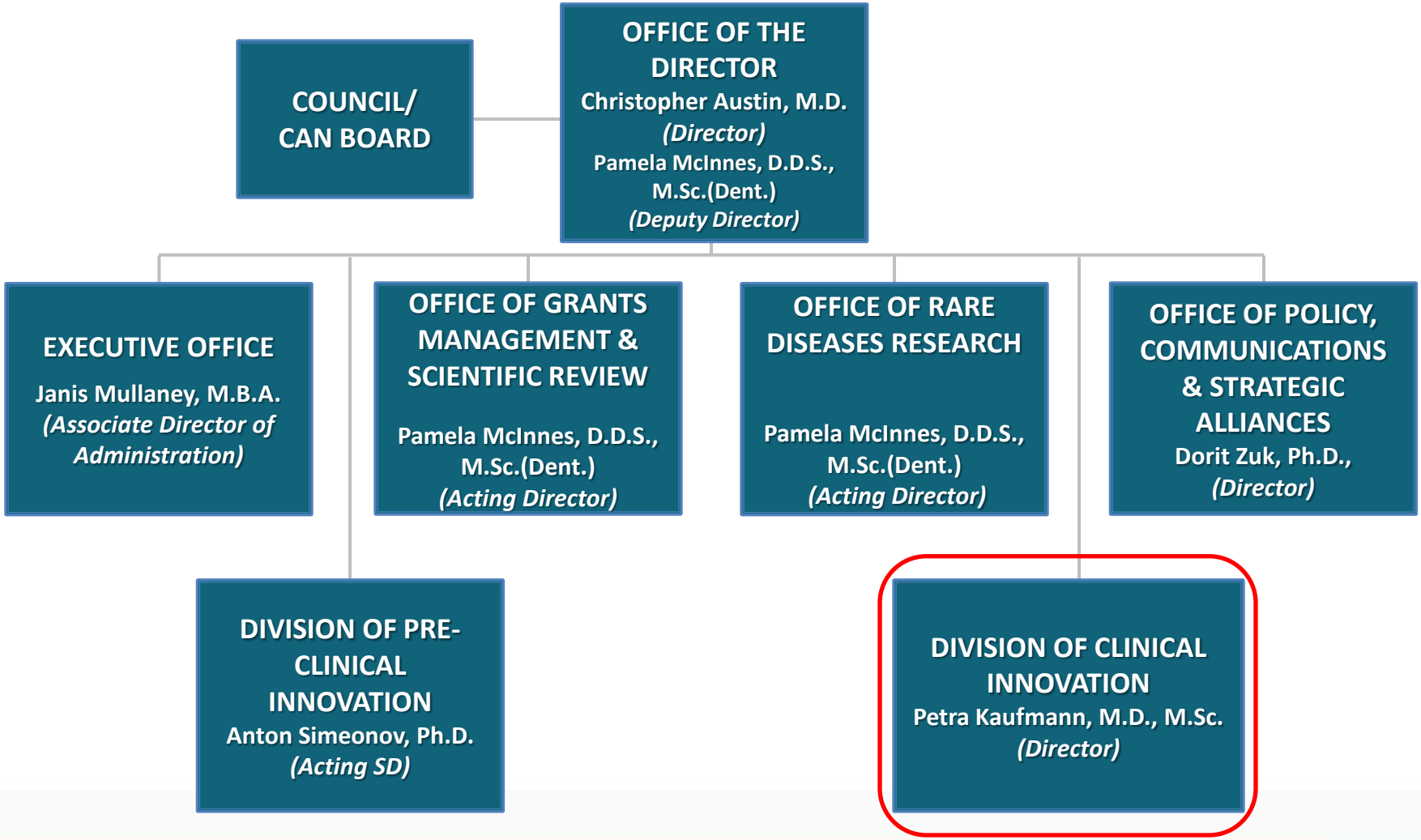
Their lead drug, VTS-270, is designed to clear away the cholesterol that builds up inside the cells of Niemann-Pick patients. But there are also plans to add to the pipeline. Vtesse is starting up with a Cooperative Research and Development Agreement, or CRADA, with the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Center for Advancing Translational Sciences at NIH. Vtesse and NCATS forged a licensing agreement for the current rights held by NIH for the worldwide use of cyclodextrin, delta-tocopherol, and derivatives of tocopherol for lysosomal storage diseases, including NPC.

FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

NIH
National Center for Advancing Translational Sciences

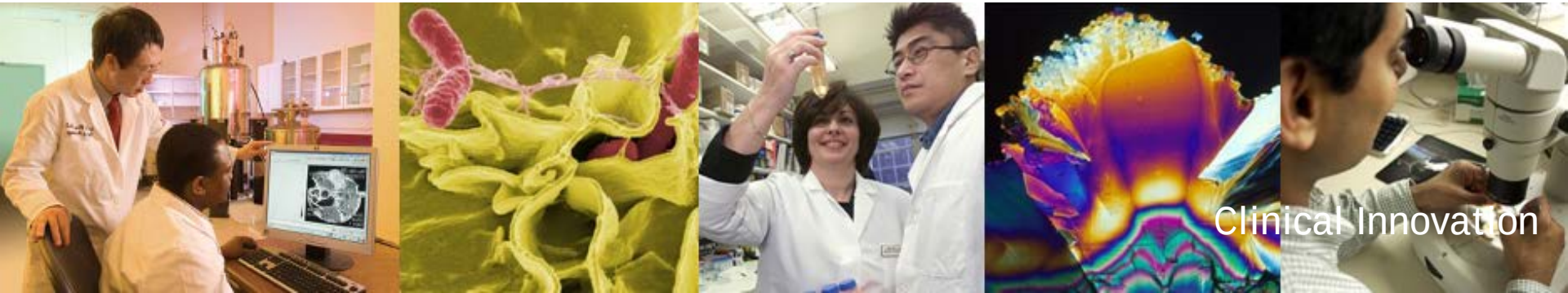
Innovation in late-stage translation:

Inefficiency of clinical translational studies, including clinical trials



NCATS Division of Clinical Innovation Strategic Goals

1. **Train, develop and cultivate future leaders in translational science**
2. **Innovate in translational science**
   1. Engage patients and **communities** in every phase of the translational process
   2. Promote the **integration** of special and underserved populations in translational research across the lifespan
   3. Innovate **processes** to increase the quality and efficiency of translational research, particularly of multi-site trials
   4. Advance the use of modern **informatics** in translation
3. **Communicate effectively with internal and external audiences using clear, timely, and consistent messages**
4. **Measure success of the CTSA program through a set of common metrics**
5. **Partner effectively with NIH and other stakeholders**



From IOM to Implementation

- Based on the IOM report and Advisory Council WG recommendations, created new CTSA Steering Committee
- Steering Committee and CTSA PIs identified critical needs and opportunities
- Four demonstration projects initiated in mid-2014 to pilot solutions prior to implementation via new FOAs

Ongoing Consortium-wide Demonstration Projects

1. Transforming Multi-Site Trials: Central IRBs for the CTSA Program

2. Innovating Research Participant Recruitment

3. Enhancing Clinical Research Professionals' Training and Qualification

4. Innovating Scientific Review for the CTSA Program

NIH
National Center for Advancing Translational Sciences

Evolving the Program to Transform Clinical Translational Science

CTSA Hubs

TIC:
Trial Innovation Centers
Central IRB
Contracting
Budgeting
Other support PRN

RIC:
Recruitment Innovation Centers
Feasibility Assessment
Recruitment Plan and Implementation

Multi-site Study funded by NIH IC or others

Clinical Lead

Stats/Data Management

No need to re-build trial components each time

Discussion