

NCATS Day

Partnering with Patients for Smarter Science

Case Study in Translational Science Collaboration

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NCATS and The Alpha-1 Foundation/The Alpha-1 Project Partnership

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Alpha-1 Foundation

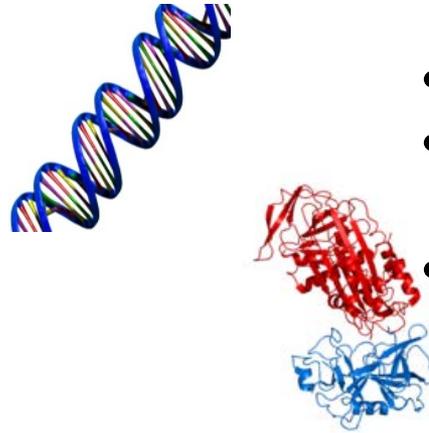


Accelerating Therapeutic DiscoverySM

Mission: Find cures and therapies for lung and liver diseases caused by alpha-1 antitrypsin deficiency and improve the quality of lives of alphas worldwide

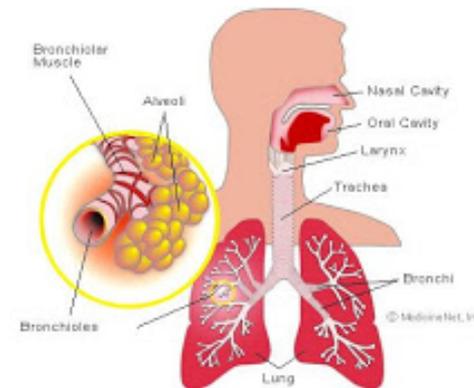
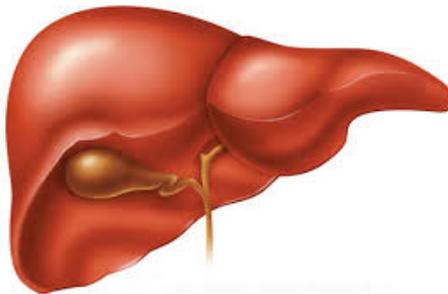


What is alpha-1 antitrypsin deficiency?



- Single defect in SERPINA-1 gene
- Misfolding of alpha-1 antitrypsin protein in liver
- Polymerized alpha-1 stays in liver

- Too much alpha-1 antitrypsin in liver
- Severe liver damage



- Not enough alpha-1 antitrypsin to protect elastin in lungs
- Severe lung damage

Timeline

2012	2013	2014	2015	2016	2017
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NCATS formed

Feb: Initial meeting w/ NCATS leadership

June: Workshop w/ Alpha-1 experts & NCATS

Aug: Steering committee formed

Sept: MOU signed

Nov: Job description done

Jan: Press release of collaboration

Feb: Job posted in NIH/NCATS/A1F websites

Dec: Mike Iannotti selected

Jan: Mike Iannotti starts

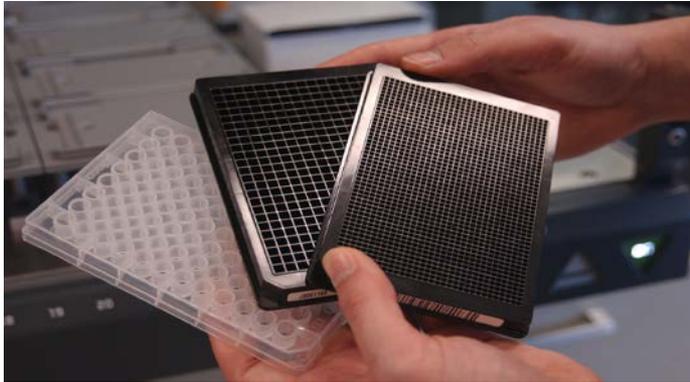


Scientific Advisory Committee (SAC)

- Selection of world-renowned Alpha-1 physicians and scientists
 - Adam Wanner, MD. Clinical pulmonologist
 - Jeffrey Teckman, MD. Clinical hepatologist and scientist
 - Darrell Kotton, MD. Clinical pulmonologist and scientist, stem cell specialist
 - Bibek Gooptu, BSc, MD, PhD, MRCP. Clinical pulmonologist and scientist, mechanisms of alpha-1 protein misfolding and polymerization/aggregation
 - Richard Sifers, PhD. Scientist, mechanisms of alpha-1 protein misfolding and quality control/degradation
- Why is the formation of a SAC important?



NCATS: Unique Resources and Capabilities to Enhance the Drug Discovery Process for Rare Diseases

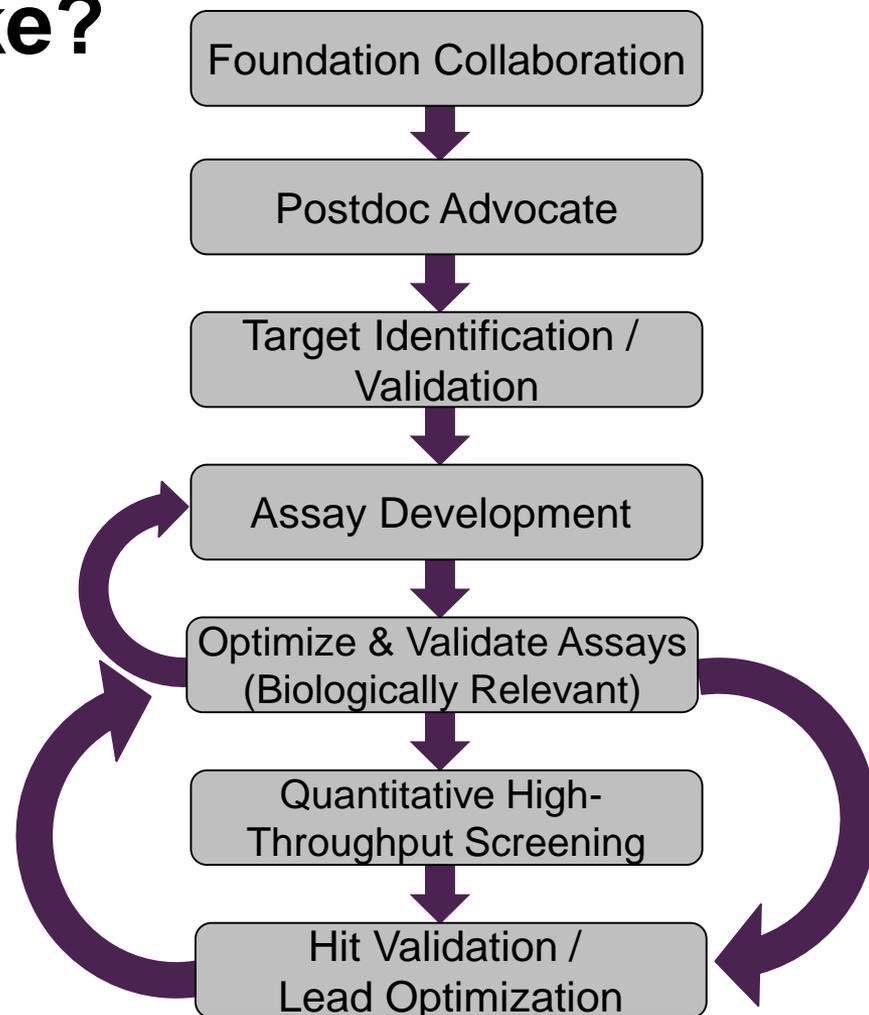


- NCATS mission: “...transform the translational process so that new treatments and cures for disease can be delivered to patients faster”
 - Explore commonalities between diseases
- NCATS utilizes highly innovative technologies and automation to rapidly test and develop new therapies



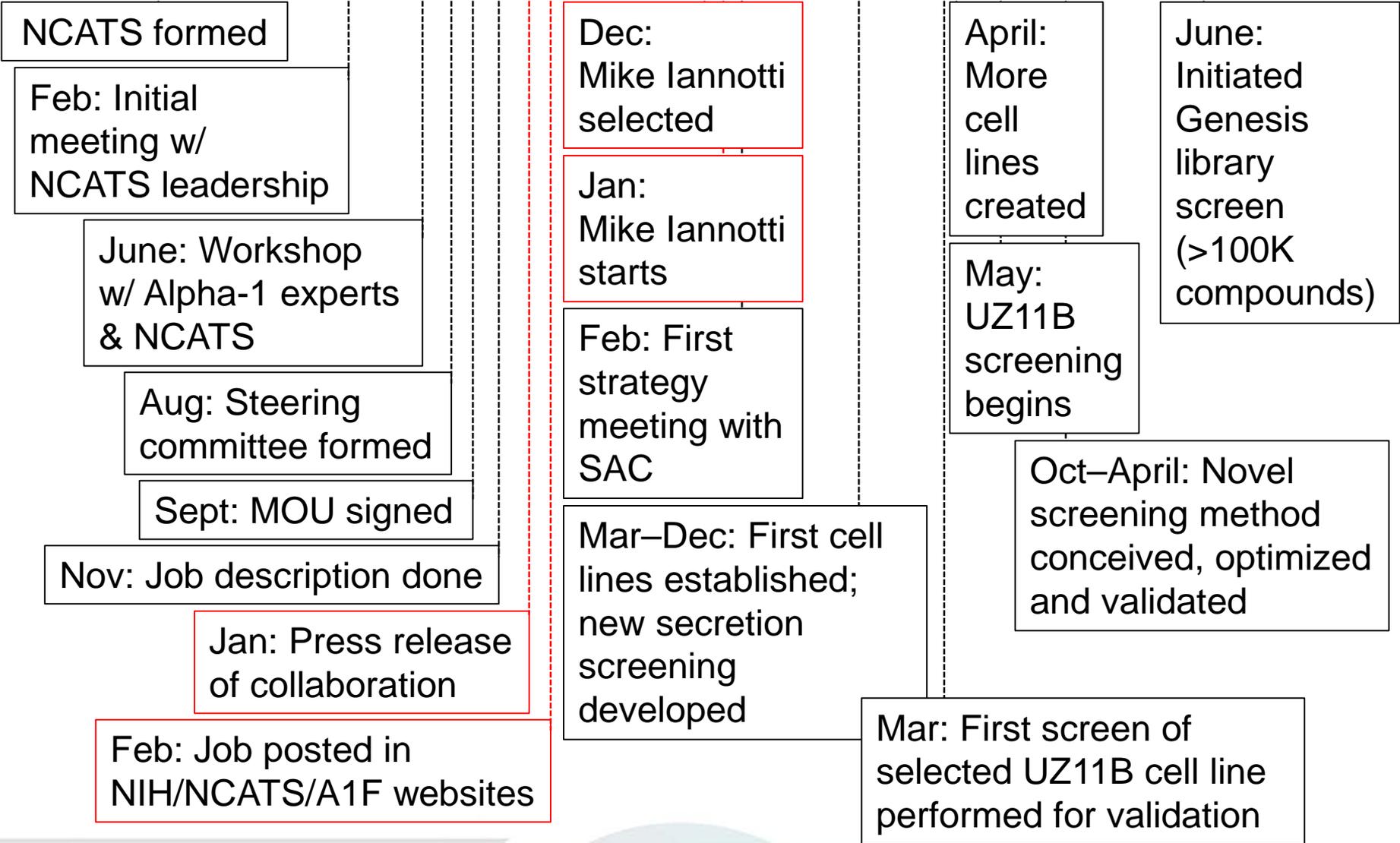
What does Alpha-1 research at NCATS look like?

- Collaboration between Alpha-1 SAC and NCATS ADST group; consult every 3-6 months
- Initial conferences to establish research goals and directions
 - Target identification/validation
 - Development of multiple assays directed around disease biology
- Optimization and validation of assays
 - Evidence that disease biology is being represented
 - Establish controls to illustrate assay is functioning correctly and effectively
- Quantitative high-throughput screening
- Further development of assays for confirmation of chemical hits



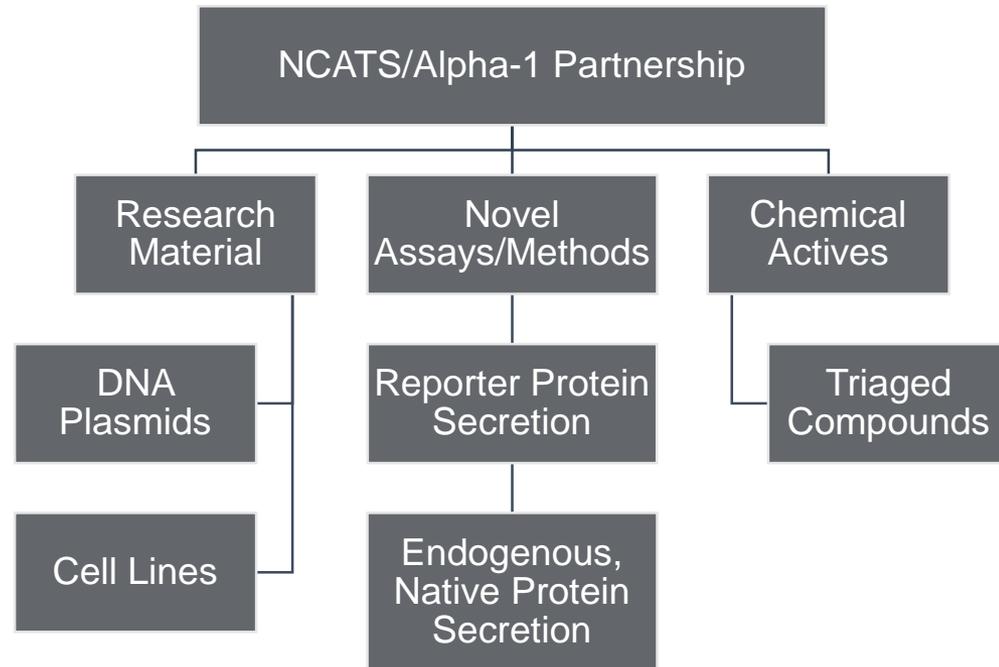
Timeline

2012 2013 2014 2015 2016 2017



Alpha-1 Scientific Accomplishments

- All research material created at NCATS is available to the Alpha-1 research community
- Variety of cell lines for research and screening purposes incorporating multiple technologies
- A novel method to screen for chemical modulators of Z variant protein secretion using bioluminescent reporter technology
- A novel method to screen for chemical modulators of unmodified, native Z variant protein
- Screening campaign utilizing generated cell lines
- After triage, collection of compounds to pursue by NCATS or Alpha-1 research community



Lessons from the NCATS – Alpha-1 Partnership

- What worked well
 - Clear objectives and deliverables
 - Hire the right person
 - Updates every few months
 - Steering Committee
 - Collaborative environment
 - Engaging with the patient community
- Advice for others:
 - Options to initiate: adapt existing cell models vs. develop new models



In conclusion: A successful partnership between a patient advocacy and the NIH/NCATS

- Leverages the core competencies from each
- Leaves a legacy for future research
- Adds to the tool box
- Brings us one step closer to finding a cure for Alpha-1.

