From Pilots and Panels to Funded Projects: The CCTS Runway to Success

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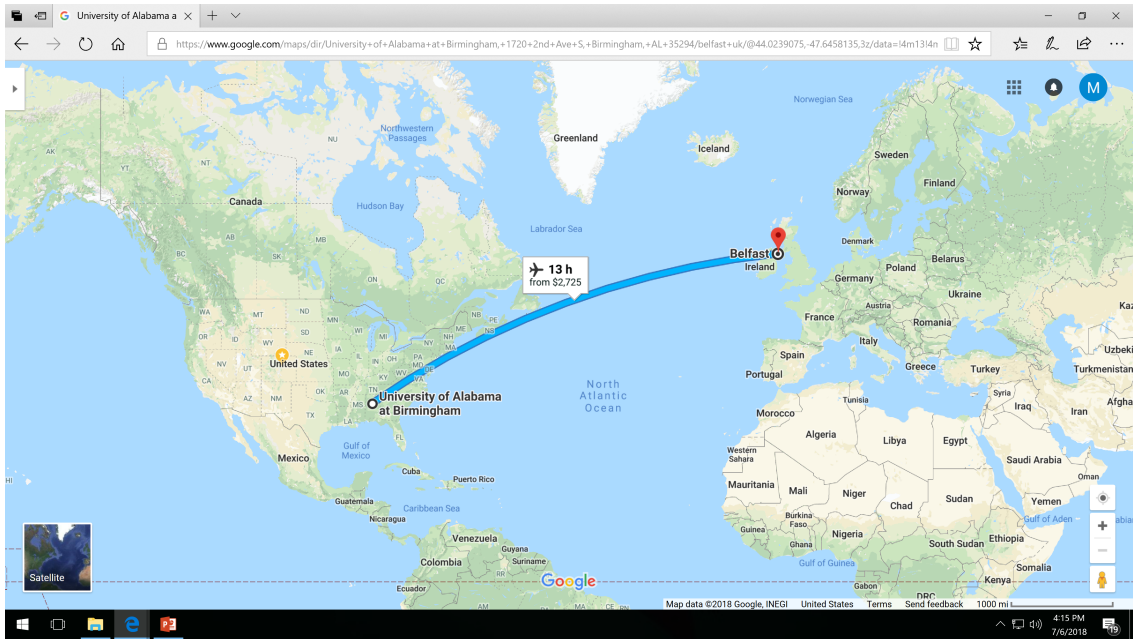
Passenger ID: My story

- Assistant Professor in Pediatric Pulmonology
- Associate Scientist in the Gregory Fleming James Cystic Fibrosis Research Center
- Research Focus: Targetable Modifiers of CF Lung Disease
  - Basic Science: TGF-β pathobiology, Wound Repair, Remodeling
  - Translational Science: miRNA target site blockade with antisense oligonucleotides

What’s the destination?



- Destination
  - CF translational Scientist
- Route
  - Established
    - CFF support
    - NIH Roadmap
- Needs
  - CCTS Pragmatics
    - What to expect?
    - How to prepare?
    - What do I need to do?
    - What is expected?

CCTS Runway

- CCTS Nascent Projects Panel
  - Discussion re: K08 Preparation
- CCTS Partner Network Pilot Panel
  - Partnering with CCTS Investigators
  - Reaching beyond UAB alone
  - Building the Pilot proposal
- Project Development Teams
  - Respond to Preliminary Data
  - Refine the scope of the investigatin

Preparing for take-off:
1. The CCTS Nascent Project Panel (K08)

My Proposal

- Career Development Aims
  - Training in CF Preclinical Drug Development
  - Translation of *in vitro* data into preclinical CF models
  - *In vivo* measurement of CFTR

Panel Response

- Narrow the focus
  - Avoid general fields such as drug discovery and development
  - Emphasize training in miRNA science
  - Career development will follow the science
  - Emphasize local resources

Preparing for take-off:
The CCTS Nascent Project Panel (K08)

My Proposal

- Research Aims
  - Identify TGF-β dependent targetable mechanisms of CFTR inhibition in airway epithelia
  - Quantify benefit of TGF-β manipulation to improve CFTR function in murine models
  - Utilize TGF-β antagonist to augment CFTR correction in CF animal models

Panel Response

- Narrow the focus
- Be hypothesis driven
- Focus on mechanism:
  - miRNA mediated TGF-β inhibition of CFTR

Listen to your captain
2. CCTS Partner Network Pilot Proposal Panel

My Proposal

- Evaluate mechanism of miR-145 downregulation of CFTR in airway epithelia
- Quantify benefit of miR-145 manipulation to improve CFTR in murine models
- Augment CFTR correction with miR-145 antagonism in preclinical models

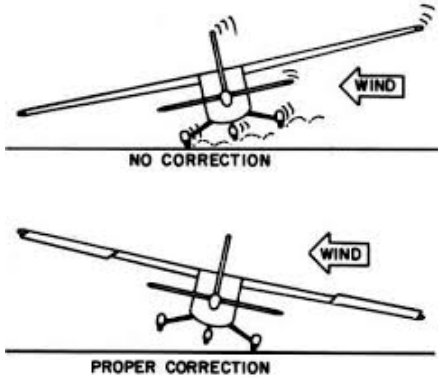
Panel Response

- What is the novelty?
- What is the proposed mechanism of interaction?
- How will this award advance your career?

Fly the Friendly Skies
K08 application

- Career Development Plan
  - Develop expertise in mechanisms of miRNA pathobiology
  - Learn *in vivo* methods of miRNA delivery and manipulation
  - Become facile with *in vivo* measurement of CFTR function in CF animal models.
- Research Plan
  - Determine the *in vitro* mechanism of miR-145 inhibition of CFTR in CF airway epithelia
  - Establish *in vivo* relevance of miR-145 manipulation to improve CFTR function
  - Augment CFTR correction with miR-145 antagonists in preclinical CF animal models

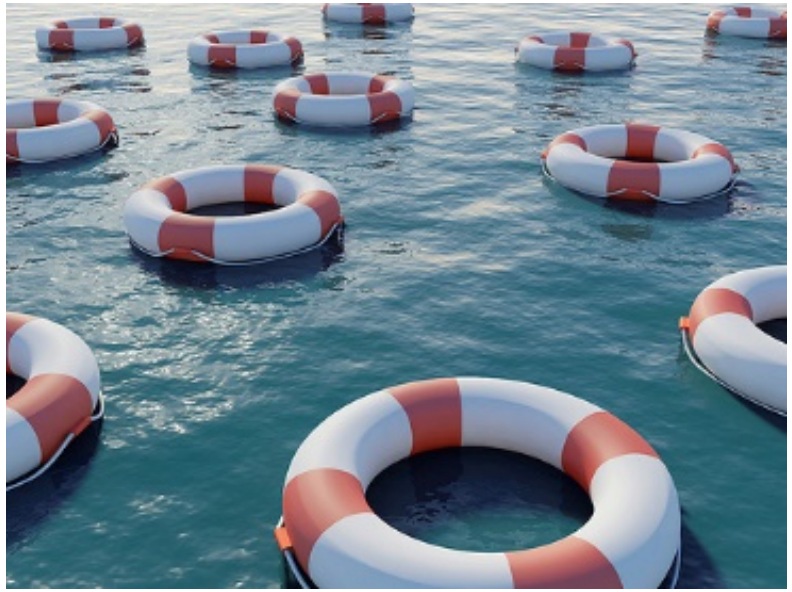
In flight correction:
3. CCTS Project Development Teams



- Test the main ideas of miRNA interaction *in vitro* before *in vivo* study
- Confirm the interaction of miR-145 with rodent CFTR
- Identify the optimal *in vivo* readout of CFTR function
- Identify additional animal models that respond to miRNA intervention
- Test utility of miRNA manipulation on next-generation CFTR modulators and in additional CFTR mutations

Benefit of CCTS Support Structure

- Experienced Panel
  - NIH-level considerations
  - Familiarity with funder expectations
  - Impartial, supportive, skeptical audience
  - Established success
- Organized Process
  - Streamlined approach
  - Proposal discussion
  - Relevant faculty participation
  - Supportive staff
  - Helpful summary statement



The flight may be bumpy: The reality of funding

BHM

ATL

DUB

BFS

Harry Shwachman Clinic Research Award, **CF Foundation**	Myofibroblast differentiation in CF
CF Research Scholar, **Gilead Sciences**	Mechanisms of pulmonary fibrosis in CF lung disease
Vertex Pharmaceuticals	VX14-809-109, VX15-809-124, VX16-661-113, VX16-809-122
Pilot Project, **UAB CCTS Partner Network**	miR-145 manipulation to improve CFTR correction in pediatric CF
Pilot Project, **CF Foundation**	miR-145 mediated TGF-beta pathobiology in CF
K08 Career Development Award, **NIH/NHLBI**	Overcoming barriers to F508del CFTR correction

Mechanisms of travel: Planes, Trains, and Automobiles

- Commitment to the destination
- Complimentary funding sources
  - Intramural: CFRC, KPRI, PIRC, CCTS
  - Extramural: CFF, Gilead/Vertex, NIH
- Consistent research themes
  - Narrow enough to be focused
  - Broad enough to adapt to funding sources
  - miRNA bridges both remodeling and CFTR regulation
- Collaborate
  - CF animal models (Humanized mouse, rat, ferret, pig)
  - ASO (Ionis pharmaceuticals)

CCTS Panel Results: My review

- Refined focus
  - TGF-β in general to miRNA specifically
- Organization of Aims
  - Career development from CF preclinical drug development to acquisition of training in miRNA science
- Longitudinal perspective
  - Nascent Panel to Pilot Project to K08 Project Development Team
- Collaboration
  - Identification of Bill Gerthoffer of USA as expert in miR-145 delivery

Enjoy your flight

- CCTS support beneficial at any stage
- Outstanding infrastructure to assist junior investigators
- Panel discussions refine (and mature) the approach
- Wealth of expertise will benefit any proposal

RESEARCH COMMONS

Center for Clinical and Translational Science

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