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 investigation
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

| 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
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