Funding and Grantsmanship in IBD Research

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Disclosures

• Consulting / Advisory boards
  – Abbvie
  – Amgen
  – Janssen
  – Lycera
  – PRIME Medical Education
  – Takeda
  – UCB

• Member of consortium (with Genentech and Amgen) developing PROs for UC and CD

• Patents
  – Anti-fibrotic medications
    • US20140187521 A1
  – Machine learning algorithms
    • US20150095069 A1
    • US20160078184
    • US20080288227
Background

- PI of two IBD clinical R01 grants
- Two CCFA Senior Research Awards
- Seven IIS grants
- 64 IRB-approved currently active clinical studies
- 21 active IBD trials
- Six full time IBD study coordinators
- Co-chair of CCFA Clinical Research Alliance
- Director of Michigan Ambulatory Clinical Trials Support Unit
Our Journey

• Funding
  – Why do you need funding?
  – Where is the Money?

• Grantsmanship
  – The Long Game
  – How do you get $$

• Running a Small Business
Why Do You Need Funding?

• You want to do high quality research
• You need reproducible processes
• You need consistency in samples and data
• You need **people** with time
• Good people are expensive
  – Dedicated to task
  – Reliable
  – Dedicated to quality work
But Volunteers!

- Free labor, right?
  - Not as reliable
    - Other priorities (med school letters, job)
    - Need to make $$ to live (somehow)
  - Lower quality
    - Not as focused on project
    - Less likely to follow SOP, processes
    - Less likely to have OCD over data quality
  - Ethical issues
    - An unpaid intern economy is *not* a good thing
Why Do You Need Funding?

• **Quality** Stuff is expensive
  – Databases – double data entry, logic checks
    • More people, more programming $$
  – Freezers $$$$  
    • Temperature alarms $$
    • Backup generators $$
    • Notification systems (text, page, phone) $$
  – Cryotubes and storage media $$
  – Microbiome analysis $$
  – Cytokine ELISAs $$
Funding Sources

WHERE IS THE MONEY?

Why do you rob banks, Willie?
- Because that’s where the money is

Willie Sutton Apocrypha
Foundations

- **CCFA**
  - Senior Research Award, 3 years X 105K

- **ACG**
  - Clinical Research Award, 50K or 15K for pilots

- **AGA**
  - AGA-Pfizer pilot in IBD 35K
NIH

- **R01**: Individual investigator, single center
  - Bulletproof preliminary data
    - Usually follows some form of pilot
  - 250-500K per year, up to 5 years

- **R21**: Individual investigator, single center, exploratory
  - Highly innovative, higher risk
  - 275K over 2 years

- **U34/U01**
  - Planning, then execution of multicenter study
  - Can be up to 5-6M
Industry

• Investigator-Initiated Studies
  – You send an idea to Pharma partner, ask for funding

• Partnerships
  – IIS idea may be too big for one site
  – You discuss idea, end up collaborating

• Participating in Pharma-initiated studies
  – Pharma writes protocol
  – You budget carefully, recruit at your site
Investigator-Initiated Study Success Story

• Dr. Regueiro has a good idea for post-op prevention w/IFX
  – Applies for pilot IIS: $200K for 1 year
  – Ends up extending to $400K for 2 years
  – Impressive result

• Idea matures into PIS: PREVENT
  – ~ $90M spent on large prospective trial
  – Confirms endoscopic endpoint
Donors

• Donors can support infrastructure
  – Biobanks, databases
  – Most granting agencies will not support infrastructure

• Donors can provide a one-time boost
  – May not be sustainable without a lot of work
  – Cultivate existing donors
  – Search, cultivate more donors

• Donors’ goals may not align with yours or even with science
Obtaining Funds

GRANTSMANSHIP
Where to Start

- Define a Problem

- Find the Gap
  - What we Don’t Know

- Identify a new tool/approach to studying this

The incidence of Crohn’s disease in children of couples in which one parent has CD is high

How to prevent this, reduce the incidence of CD in children of high-risk parents

Treatment of high-risk mothers with oral Ω3 fatty acids during weeks 12-40 of pregnancy
You Need

- **A clear question**
- **2-3 testable, specific hypotheses**
- **Realistic methods**
  - Consider confounders!!!
    - Antibiotic use
    - Age at Dx of parent
    - Ω3 fatty acid level in pregnant subject

- Can treatment of high-risk mothers with oral Ω3 fatty acids during weeks 12-40 of pregnancy reduce the incidence of CD?

- Treatment will reduce prevalence of low diversity gut microbiome dysbiosis at age 3 from 30% to 10%

- Treatment will reduce prevalence of elevated fecal calprotectin at age 3 from 25% to 5%

- Treatment will reduce diagnosis of CD by age 3 from 5% to 0%
Timing

- Publications in the field
  - IBD, childhood IBD
- Publications in this specific area
  - Ω3 fatty acids in IBD, prevention of IBD
- Publications with needed collaborators
  - Microbiome expert
  - Ω3 fatty acid measurement lab
- You are a leader in this new area
Planning Ahead

- Where is the field going to be in 5 years?
- What are the big questions that are NOT going to be solved soon?
- What are the novel important tools?

I skate to where the puck is going to be, not where it has been.
- Wayne Gretzky
Build Credibility

• You have the study materials
  – Patients, biosamples/biobank in sufficient numbers
• You have the expertise/technology
  – You want novelty (exciting! Innovation!)
  – You have to prove you can make it work
    • Do you have all the techniques in hand?
    • No publications = no evidence
    • Or find Collaborator who **DOES** have expertise
      – Preferably at your site / in your city
Credibility

- Translational work adds innovation!
  - Cutting edge science, new techniques
- May not be your expertise
  - Need an expert on your side
  - Proven collaboration (papers x years)
  - Regular meetings
  - Enthusiastic letter of support
  - Probably effort on grant (for PI or grad student)
Clarity

• Downfall of most grants
• What *exactly* are you going to do?
• What are your specific aims?
• What are your testable specific hypotheses?
• How will you test them?
• Define *a priori* success/failure for each Aim
  – If you can’t do a sample size calculation, you either:
    • Aren’t being specific enough, or
    • Need more pilot data
THE ONES WHO ARE CRAZY ENOUGH TO THINK THAT THEY CAN CHANGE THE WORLD, ARE THE ONES WHO DO.

STEVE JOBS
Impact

• How you close the deal
• If this study is successful, how will the world change?
  – In a way that matters to the funder
    • Understanding of IBD?
    • Diagnosing/Monitoring of IBD?
    • Therapy of IBD?
• NOT how this will lead to papers and grants
  – Unless it is a career award (CDA, K23)
Important Writing Stuff

• Most people in the room will *not* read your entire grant
• 3 people will read the whole thing
  – Your primary reviewers
• The rest will read the Aims page, look at the pictures, and listen to discussion
  – These folks can have a big effect on your score
Important Writing Stuff

- Writing for 2 distinct audiences
  - Those that read the whole grant
  - Those that only read aims/look at pictures
- Aims page has to be amazingly compelling
- Figures have to be clear with great captions

Aim 1 → Aim 2 → Aim 3 → Reduced

IBD

40%
Writing Timeline

• Specific Aims ~ 6-12 months in advance
  – Have multiple people read & critique
  – It must be compelling – this **must** be done, you should do it.
  – Identify any gaps in preliminary data

• Complete draft 3-4 months in advance
  – Have insiders & outsiders to critique
  – Try to give them 4 weeks (don’t look at it)
  – Come back to it with fresh eyes and the critiques with 2-3m left.
Grantsmanship

• Build the evidence that you can do this project years ahead
• Search NIH Reporter – who funds this?
  – If anything similar, identify the NIH Program Officer, call
  – Send a draft Specific Aims page to the PO, discuss portfolio
• Build in stages
  – Pilot grants – preliminary data
  – Career Award – CCFA CDA or NIH K23
  – Clinical R01 or CCFA SRA
CCFA Clinical Research Alliance Pilot Grants

- $100-200K
- Nail down protocol, CRFs, IRB, contracting
- Test at 4-6 CRA sites & debug the inevitable problems
- Help from experienced clinical investigators on steering committee
- If successful, you can apply for CCFA Senior Research Award to scale up to the whole CRA
Managing Your Research Portfolio

- NIH grants add stability
  - Consistent dollars, more indirects
  - Caveat: this could change in 7 days.
- Pharma-initiated studies can smooth cash flow
- Foundation $ and IIS can help supplement
- Donor dollars are a bonus
  - Can dry up in a recession
- Having multiple revenue streams is helpful.
Building a Sustainable Clinical Trials Infrastructure

RUNNING A SMALL BUSINESS
You Are Running a Small Business

The bad news: Most small businesses fail.
50% by 5 years
66% by 10 years
Why Do Most Businesses Fail?

• Cash Flow

Cash Flow (revenue from clinical trials) and Cash Outflow (costs of running your clinical trials).
Costs of Clinical Trial Operation

- **Fixed costs**
  - Unaffected by changes in level of trial activity
  - SC salaries
  - Rent for space
- **Variable costs**
  - Vary with level of activity
  - Colonoscopies, labs, MREs
- **Capital costs**
  - Freezer, computer, desk, filing cabinets

Constant drain. Kills businesses in January.

Only kills you if you budget badly, or costs increase rapidly.

Classic startup mistake is overspending on capital costs. Reduces your margin of error to get through lean months.
Revenue Cycle for Clinical Trials

![Revenue Cycle Graph]

- Study Startup
- IRB Approval
- Recruit to Induction
- Maintenance
- OLE
Net Income in a Clinical Trial Lifecycle

- Study Startup
- IRB Approval
- Recruit to Induction
- Maintenance
- OLE

Breakeven point, Ideally ~ 2 patients enrolled
You Have to Know

• Your Costs
  – And likely inflation (salary raises, lab costs) over lifecycle
  – Costs do *not* only occur at visits.

• Know your *invisible* (non-visit) budget
  – SC time
    • Recruiting
    • Doing amendments
    • SC Data entry / PI reviewing lab results
    • Answering queries before data lock

• Make sure the budget actually reflects SC and PI effort / time
You Have to Know

• What is your breakeven point?
• Will you recruit successfully?
  – Know the inclusion & exclusion – look for problems!
  – TNF naïve – what percent?
  – Will your colleagues refer?
• Are there competing options?
  – Vedolizumab, Ustekinumab just approved
  – Competing CD trial at your center or nearby center?
Smoothing Out the Cash Flow

You need multiple sources of clinical study revenue at different stages of the study Lifecycle.

Near-death experience for business
Economy of Scale in Clinical Trials

• It is better to have multiple studies to smooth cash flow
  – At different stages of the life cycle
• It is better to have multiple study coordinators
  – Able to handle multiple studies
  – Able to cover for each other if needed
  – Infrastructure becomes robust, can tolerate departures
  – Experienced SCs can help train new SCs
• But how can I manage 6 SCs?
The Struggle Cycle in Clinical Trial Infrastructure

Transition States

There is more work with more SCs. But it is a dramatically more stable state.
# You Need to Know FTE Flow to Grow

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Project full time equivalents based on studies and projected enrollment. Adjust quarterly. Can hire incremental SC when you have N+1 stable FTEs for > 1 year.
Know the Local Money Rules

• Can you find ways to save $$?
  – Efficiency produces net margins.
• Do you have to spend 80% of funds before end of grant?
  – Institutions are a vacuum for extra $$
• Can you build up a rainy-day fund?
  – Cash on hand is your insurance
  – But expect that success may be punished.
• Share success with the team
Rules to Live By

• Invest little in capital expenses, until you are sure you can afford it (cash on hand)
• Invest a lot in people
  – Teaching / Training – weekly QI meeting (not progress mtg)
  – Salary – resist turnover
  – Support
• Be prepared for turnover
  – Have a plan for coverage
  – Always think about recruiting new SCs – smarts >> experience
    • Your track record matters
Conclusions

• There are multiple sources of clinical research funding
• Play the long game, and build your credibility
• Build your team & invest in people
• Find collaborators with skills and techniques that complement what you can do.
• Understand your cash flow and FTE flow.
• Once you have funding, Use it to do amazing IBD clinical research.
Thank You