Q&A with David Topham

(Editor's note: The Respiratory Pathogens Research Center is funded through a seven-year contract with the National Institutes of Health's NIAID Division of Microbiology and Infectious Diseases. The goal of the center is to help protect citizens against bacteria and viruses that infect the respiratory system. These cause pneumonia and flu, as well as a host of other infections caused by lesser-known but still-deadly microbes such as coronaviruses, metapneumoviruses, parainfluenza viruses, and respiratory syncytial virus (RSV), as well as a host of bacteria.

Created in 2011, the center currently is working on 24 projects. In addition to Director and PI David Topham and Co-Director and co-PI Ann Falsey, the center has 10 other core leaders from the University. It currently is working with researchers at six other universities and institutes as well.)

Q. How did you come to be the PI for the Respiratory Pathogens Research Center? Did you have previous experience leading a center like this or applying for this kind of project?

Yes. You would never be competitive if you hadn't done something similar to this before.

This started for me in 2005 when a group of us -- including Hulin Wu, Martin Zand, Tim Mosmann, and a number of other faculty members -- won a research contract for the Center for Biodefense Immune Modeling. That gave me one of my first forays into team science as an investigator.

In 2007 John Treanor and I got the New York Influenza Center of Excellence. I was co-director and co-PI. John and I learned a great deal from that. This was much bigger in scope. It was not just the University of Rochester, but other institutions, part of a network. We learned a lot about how to manage large, ambitious, multi-investigator, multi-institution projects.

Q: What were some of the key lessons from that?

1. One of the key lessons was staying organized. We hired a professional project manager from Hewlett Packard to come in and work with us to keep all the projects on track. John and I don't have the skill set to do that. We're good at other things, but not at that.

2. When things are not working in one or more projects, we learned we have to be willing to cut it. We have to be willing to move the money around; we have to be able to change as we go. You can not fix a set of projects in place and run them to the end . . . When we went back for renewal in 2013, we were more selective about who we asked to participate. It had to be labs that had a very good track record of productivity. Projects had to be integrated, so the center as a whole is now focused on one central question. And the way we run it now, we are much more willing to be Draconian, if we have to be, to move resources around to where we think they will be best used. That's what NIH wants us to do. I run the Respiratory Pathogens Research Center exactly the same way. I look at what is good for center as a whole, not just an assemblage of projects.

This is not like getting a grant with a fixed dollar amount and you get to carry it forward from year to year and use it up eventually. Each year, whatever funding you don't use goes back. So in managing something like that, it's up to me to make sure we use all the resources we're given to be as productive as possible.

So I've gained a lot of experience in managing these multi-investigator projects and realized that's its actually one of my skills. Not everybody can do it. It's not always obvious how to get people to work together.

Q: So how do you do it?

The first thing, something I learned from Tim Mosmann (Professor of Microbiology and Immunology and Director of the Center for Vaccine Biology and Immunology), is to get everybody in the room and get them talking together.

You need to foster their contributions, and encourage them to express themselves and give their ideas. Sometimes people will sit and wait until you tell them what to do, or wait until you ask them a specific question. What you really want is to hear everything they're thinking about. It is critical to make sure they feel like they are active participants and any input they provide is valid. Then people are more likely to participate.

The other important thing is staying organized and setting clear expectations and timelines. People need to know what they're supposed to do, and when they're supposed to do it. Especially with multi-investigator projects that have many parts to them. We've had a couple of examples where someone is trying to put together a multi-investigator proposal, and they waited until the last minute to figure our what everybody needed to do. They hem and haw and can't really decide. You've got to be able to make those decisions early on and commit. When people don't do that, the proposals come across as not very cohesive. You have to allow enough time to get it organized, to show how the different parts fit together, how it's going to work. That's how you make these applications competitive.

When I'm submitting a proposal like this, I have to get my own science done early so I can spend almost as much time on the organization and structure as everything else.

Q: From a personal standpoint, how has your career as a researcher changed for better or worse by taking on these projects? Does this cut into your own time to do research?

It depends on how you measure success. One of my attributes is that I'm just as satisfied, if not more so, watching others around me -- people who I've helped and supported -- succeed and get credit, as I am in getting credit myself. That's a critical trait to have. If you're selfish about these things, people won't work with you, or they won't contribute everything that they could, because they're not getting the credit for it; you're taking the credit instead.

So yes, if you look at my publication output, it stems and flows based on whether I'm submitting one of these applications, or whether I have just been funded for one and have to set a center up, which takes about a year. During those times my publication rate goes way down, and in between it goes way up. But there's only so much time in a day.

We're in a lull right now, so I'm trying to make time to write papers and get them out the door. If you don't write the papers you don't get any more money. You've got to be productive, and obviously it helps that everyone else in the center is doing that.

Q: When the contract with NIH was approved in 2011, creating the Respiratory Pathogens Research Center here, many of the projects were not identified yet. That's interesting, because usually researchers have to pin that down in grant applications. Why was this different?

It's not a grant; it's a contract. The way it was competed was, we were asked to respond to a set of research questions. For example: Address respiratory syncytial virus severe disease (RSV is a common and highly contagious virus that infects the respiratory tract of most children before their second birthday). And we want you to use systems biology approaches, a lot of gene expression studies and microbiomics. So all the projects were designed to be hypothetical. We had no idea which ones they would choose, if any of them. They made it very clear there was no promise, implied or stated, that anything we proposed would be funded.

We were allowed to announce only the first year of funding ($4.7 million), even though it is a seven-year program, because technically they had awarded only the first year. In reality we've been getting that plus some more every year -- anywhere from $3 to $6 million for three to six innovation projects, which varies from year to year, and another $1.3 to $2.6 million on top of $5 million or so. So it's pretty big.

Q: So over a seven-year period you're talking $40-50 million?

Easily $50 million. We estimate it could be anywhere between $50 and $80 million.

We anticipate that a year and half before the contract ends, there will be a request for proposals and they'll re-compete. They will go with the offer that doesn't

necessarily have to be cheapest but gives them the most of what they're looking for. We will put a proposal together and go back in and try to get it renewed.

Q: You would think you would have a leg up.

Not necessarily. When we submitted our proposal, NIH was soliciting for two centers, a bacterial respiratory pathogens center, and a viral center. We submitted for the viral center. In the process of negotiations, NIH told all the bacterial applicants they were out. They started asking us if we could do bacterial as well as viral. In the end they gave us both centers.

Those were both pre-existing centers. So you can't take anything for granted.

My approach in these applications is, you don't hold back. I told our investigators I want you to think of this as the Manhattan Project. I want your best; I want the most ambitious, most impactful studies we can think of. Don't be put off by the cost or the difficulty. I want to go in there with everything we've got, never expecting that all of it would get funded, but just to demonstrate what our capacity is.

In the end they funded the two biggest projects we proposed.

Q. The Respiratory Pathogens Research Center website shows that at least 19 papers have been published by the center as of July. Are there other things the center has accomplished?

I think regardless of how many papers we publish, we're going to change how premature infants are cared for; we' going to change how we identify which ones are at risk and which ones aren't, and we're going to change how we treat them. I think we're going to make their lives substantially better.

I mentioned earlier that two of the largest projects we submitted ended up being funded.

One is led by Ed Walsh (Professor of Medicine/Infectious Diseases) looking at mild versus severe disease in infants with RSV infections – the issue being you can have two perfectly healthy kids six months old, who each get infected with RSV in the same season. One kid gets a runny nose and mild fever for a few days, the other ends up in the ICU on a respirator, and we don't know why. We're trying figure out what it is about the disease process that results in severe diseases or, better yet, finding something we can use to predict who is going to have a more severe disease before it occurs. And I thing we're going to nail it.

The other project is led by Gloria Pryhuber (Professor of Pediatrics) who is looking at extremely premature infants versus full term, studying their immune system development and function, the patterns of respiratory infections they get over the first year of life (as initially proposed, now extend to the first three years of life), their gut and respiratory microbiomes (the totality of microorganisms and collective

genetic material present), host gene expression -- you name it, we're measuring it. There are 300 babies in that study and it's a massive data set. Nobody has done anything even close to this, particularly in this population, which is very difficult to access.

We've only just begun. We have barely even tapped all of the data. I think of this of a miniature Framingham-type project (a long-term, ongoing cardiovascular study involving residents of Framingham, Massachusetts. The study began in 1948 with 5,209 adult subjects from Framingham, and is now on its third generation of participants). There is so much data to mine, and that data will live on well past the period of this particular contract. We will make it publically available so others can come in to extract more knowledge from it. And it's such a difficult data set to produce that I don't think you're going to see anything like it for a long time.

So I think we're going to have real impact. And that's very satisfying.

I think this is also changing our reputation at the Medical Center to some extent, solidifying it in some ways but also giving us credibility in doing these ambitious, systems biology-oriented clinical studies with high levels of complexity.

I should also mention that one thing that made us very competitive for this contract was that I also direct the Health Science Center for Computational Innovation (HSCCI). I was told by NIH that this was critical, a distinguishing characteristic of our application because we have access to sophisticated computational tools that allow us to handle these large data sets.

That set us apart from everybody else. It's helped us with our studies; it's helped us get the awards; it's changed the landscape for us.

Q: Any advice to other faculty members who might be interested in these kinds of projects?

For young faculty, I very much agree with building your experience when you're just starting out, by serving as an investigator or participating with other more senior people.

That's even good advice for students and postdocs. There's a lot of discussion now about changing our training programs and curriculum to foster skills that are needed for team science, such as training people to deal with communications issues, and how to get people into a room. What's getting funded now is team science. The days of the single investigator, single RO1 (Research Project Grant, the original and historically oldest grant mechanism used by NIH) -- that's not the majority of what's getting funded these days, and it doesn't look like that's where the resources are going to go. We've got to train at every level in these skills so that people can become team leaders. I certainly didn't get formal training in this, and I wish I had. It's been trial by fire.

Q: Any advice for more senior faculty members interested in being a PI for a large, multi-investigator project?

You have to stay organized and delegate as much as possible and empower the people around you to do more. People ask me how I run three centers and all the other things I do. I can do it because I have really good people around me and, to the extent possible, I empower them to lead themselves to do more. I can't do it all.

If you're somebody who holds everything close to the vest, this isn't going to work.

Don't micromanage. Yes, you have to keep an eye on things and steer, if you will. But if you're trying to micromanage everything that everybody is doing, first of all, you'll probably die of exhaustion or go crazy. It's not possible. You have to trust that these are good people and they know what they're doing -- and they are. Remember, the first step is getting good people around you and into the room -- and letting them do their thing.

One of my pet peeves is when to I go to meetings that don't have an agenda or clear set of objectives, and I don't know why I'm in the meeting or what it is we're supposed to do. And on top of that, meetings where nobody writes down what was decided and who will do it, and a month later, it hasn't been done and nobody can remember who was going to do what.

I will walk out. I will not go to meetings like that.

All our meetings have minutes taken, and action items identified, and we follow up to see whether things were done. And every meeting has an agenda so we know exactly what we're there for.

Q. I notice Ann Halsey (Professor of Medicine/Infectious Diseases) is your co-PI for the RPRC. How do you split things up?

Ann is a fantastic co-investigator and co-PI and is really just as instrumental in this as I am. Ann is a clinical infectious disease researcher, so she handles all the human subject issues – protocols, and reporting, and those sorts of issues.

Having that clinical and basic experience and expertise (between us) is very valuable because I don't think either one of us could do this on our own. I have the same kind of relationship with John Treanor at the Influenza Center. He's a clinical adult infectious disease researcher and I'm the PhD. I bring in the basic science and he thinks about and deals with all the clinical issues. They are very different perspectives and our approaches to problems are every different, but they complement each other.

It's the Rochester thing. The culture of collaboration here makes it relatively easy to do these things compared to a lot of places. I know for a fact that one of the last three competitors for the RPRC contract was a place that has outstanding respiratory pathogen and immunology research, but a very poor culture of

collaboration. The basic researchers and clinicians don't interact, and that killed them. The reviewers could see it in the application. You can try to cover it up, but you can tell. The proposal comes across as modular and not well integrated -- a lot of individual things that are good, but it's not clear how things fit together.