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Backstory

Interdisciplinary case study: from fly-to-bedside, translating basic research to the clinic

Marshall Posner[1] and Ross Cagan[2]

There are unique obstacles in finding the right therapeutics to treat rare diseases and specifically rare cancers. Lower patient numbers mean there is less background knowledge of the best treatment, and resistance can arise to commonly used therapeutics. Precision medicine—the idea of providing a personalized treatment plan for a specific patient—can help patients who are participating in clinical trials and inform future routes for therapy. However, since patients and cancers are diverse, by definition, the solution provided by precision medicine approaches is unique to the patient. This challenge has led to the development of "avatars", which are organisms engineered to have the same genetic background as a living patient's tumor and have become a powerful tool in providing precision medicine.

Ross Cagan (an expert in *Drosophila* genetics) and Marshall Posner (an oncologist and clinical trial specialist) have led an interdisciplinary team, with expertise spanning from fly research to clinical oncology, to develop a unique N-of-1 clinical trial. Typically, these two types of specialties are not found working on the same projects. In this backstory, R.C. and M.P. discuss some of the challenges and rewards of working together as basic scientists and practicing clinicians. Together, the team developed a fly-to-bedside workflow to harness the power of *Drosophila* as a screening platform for identifying bespoke treatments that are then available to treat the patient.

"Flyboy" Professor Ross Cagan (left) and Clinician Professor Marshall Posner (right) have learned how to talk each other's professional language to collaborate.

In this article published recently at *iScience* (https://www.cell.com/iscience/fulltext/S2589-0042(21)00,180-2), this approach was carried out for a patient with adenoid cystic carcinoma, a rare salivary gland tumor with approximately 1,200 new cases annually in the USA.

PROXIMITY

Who were the researchers in this project, and how did you bring everyone together?

Ross: Basically, I had no idea how to run a clinical trial; this current paper highlights a patient we treated. I cold walked into a few offices, and they all said the same thing: "Go see Marshall". Once we struck up a partnership, his extensive knowledge of how to run clinical trials took over.

Marshall: And when Ross came to see me, I saw he was addressing a long-standing problem in oncology—personalized treatment models in a way that was out of the box and brilliant. I thought *"Wow, this could be very interesting and a lot of fun to do!"*

How did moving institutions from the USA to the UK affect the collaborations in this project?

Ross: By itself, this probably would not have impacted our clinical trial, as we had completed the screening process for most of our enrolled patients. However, the COVID lockdown proved a much bigger challenge, as it changed the priority of the hospital. A year in the life of a cancer patient is long.

LANGUAGE

How did you bridge the language gap among different disciplines?

Ross: This really required two key steps. First, Marshall and I established a strong working relationship through a long series of conversations. I explained how we were seeing the impact of genetic complexity on drug response and my desire to take these findings into the clinic. Marshall walked me through what was required, and off I went to find others to join us. The second key was establishing a consistent weekly meeting. This has been important for any multi-disciplinary challenge my lab has taken on. By building a team and creating a weekly rhythm, attendance stayed strong and allowed us to learn how to speak each other's language.

Marshall: I had to learn from Ross the history and connection of fly genetics to human developmental biology and physiology to understand that this was feasible and that the biology was functional. This is one of the big barriers that we ran into among our reviewers at various steps in the process.

We needed pharmacists and clinical coordinators to prepare a protocol, IRB approval, etc. then have them work with us to interpret that data and understand the combinations of drugs that came from the fly.

One very important factor early on was that Ross and I shared a commitment to consistent, quality data, that is, the process was repeatable. We had to know that our data was reliable and as complete as we could get it. Particularly for me not being a laboratory geneticist and him not being a clinician.

The fly team (plus some). From left: Jen Diaz, Chana Hecht, Juani Feliz, Christian Bahamon, Ross Cagan, Denis Malyshev, Denise Laspina, Wesley Yon, Erdem Bangi, Alex Teague, Jared Gatto, and Sindhura Gopinath.

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RESEARCH METHODS

Did this project require tailoring your research methods to translate your findings to the clinic?

Ross: First, I cannot emphasize how strange the world of clinical trials proved to be to me and presumably to my laboratory. An emphasis on patient safety was paramount—patients often have multiple health issues—which impacted many of our decisions. Cost and accessibility of drugs turned out to be a constant source of conversation that also permeated every decision we made. Eventually, these became "habits" in our way of thinking.

Regarding research methods, the challenge was getting a research team—separate from the clinical team—that could generate avatars and data with high fidelity. The complexity of dealing with so many patients in a short window of time was a challenge, especially because patients' health situations and time frames were often fluid. This is where the brilliance of Erdem Bangi came into play. His smart and methodical approach is hard to fully appreciate when a publication is put together, but the patients benefited.

Marshall: This individualization of the treatments and the amount of effort that went into validating and approving each treatment was considerable. We met with pharmacists and clinical experts on our specialized boards to validate pharmacokinetics, drug interactions, and side effects; we needed this information to come up with dosing, scheduling and adjustments based on outcomes. Deciding when to start treatment and how to get the drugs supplied for the individual patients when they were not approved for that indication or paid by insurance took considerable effort and collaboration aside from the science and clinical judgment. As with anything that is a first - it took a lot of work.

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PUBLICATION

What are the challenges during publication of this kind of research?

Ross: Most work from my laboratory synthesizes data from fly and mammalian models/patients. Moving across models is a strong way to do science, but it comes with challenges. I had no idea how to write the patient section of the paper; that fell to the clinicians. Same with the bioinformatics. A greater challenge can be reviewers, who often wonder why there isn't more in the manuscript on flies or on humans or on drugs, whatever their specific expertise is. It can be difficult to step back, add up all the disparate threads, and appreciate the breadth of work. My colleagues assure me this challenge is common in multi-disciplinary papers.

FUTURE

What do you think the future prospects and challenges are for precision medicine treatments developed from the fly-to-bedside project?

Ross: We are still assessing the approach, which to date has a small sample size. I do think the overall approach of capturing genetic complexity, then using empirical screening has promise. My priority now is to build on our initial work to keep innovating with an eye towards patient impact.

Are there any other challenges you encountered that aren't discussed here?

Marshall: There were three major challenges for me. I was not an expert in genetic sequencing technology and tools, and I did not have time to access and learn it in depth or to interpret pipelines to make calls for the fly model. Second, it was immensely difficult to educate the disparate members (and disciplines) on the safety review boards as to what exactly we were doing. For example the FDA got it, they approved us because we were doing N-of-1 trials and we did not need FDA approval for each patient as long as we reviewed the plans with an expert panel, which we did. Whereas, especially early on, our IRB (internal review board) members had a difficult time understanding our approach. Third, our genetic data methods were undergoing tremendous technical changes and quality development as we were starting out, which strained our trust of the data until we were able to work closely with them to set quality standards.

A major challenge for us, and I am repeating it again here, was the initial biases about models that we encountered. It was difficult for some colleagues who work in cell culture or murine models or in clinical

trials to understand the fundamental differences of working in flies and see the strengths as well as the weaknesses of each model.

FINAL THOUGHTS

What did you learn about interdisciplinary research from the project and what tips would you give to anyone considering undertaking such work?

Ross: Be bold in approaching clinicians; they appreciate good science and are frustrated by the lack of better options for their patients. Their motivation can be high, even if they are busy with their day job. Bench/clinical collaborations can move the treatment needle, and, sometimes, just putting your head down and pushing the project forward is the right way to get things done. Sometimes this also means ignoring well-meaning advice regarding pushing work towards the clinics. Fortunately, my colleagues have been overall strongly supportive, which helped us get this unusual project off the ground.

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Marshall: The best collaborations are ones where you enjoy each other's company and sharing ideas. We had a freewheeling process founded on learning from each other.