“Updates on Patients, Tests, and Treatments” (Brian McCloskey, Rick Stanton, and Brad Power) [#2]

March 30, 2022
Brad Power

“We were surprised at how many patients showed up, which is encouraging. We want to understand their needs, particularly with respect to our mission in increasing the speed at which diagnostic tools are integrated into our clinical care. We want to understand the challenges they face.” – Brian McCloskey

Meeting Summary

Advanced prostate cancer patients Brian McCloskey and Rick Stanton shared progress in the last week in their testing and treatment research and answered questions about the four main activities of the Prostate Cancer Lab:

- **Attract patients**: 9 patients have registered with the Prostate Cancer Lab. Brian has invited them to a meeting to learn about their needs and interests. We hope to use relationships with prostate cancer groups, such as AnCan, the Prostate Cancer Foundation, and the National Alliance of Prostate Cancer Coalitions to raise awareness of our work and attract patients who would go through our process. Brian described the relationship he has built with Gina Carithers, founder of Urotoday, and Chuck Ryan, new CEO at the Prostate Cancer Foundation. Zsuzsanna Devecseri, head of global oncology at Sanofi, offered to help with conversations with PCF.
- **Gather data**: Rick is trying to get access to spatial analysis and apply it to guide his treatment strategy. Rick is working with City of Hope to see whether he can get tissue for sequencing, spatial analysis, and/or an organoid, where Saul Priceman may help. He is also pursuing an IRB-approved workaround with TGen. Lucence is going to run a blood biopsy on Brian. Brian is talking to SEngine about getting an organoid made of his tumor tissue which could be used for testing. Through his relationship with Saul Priceman, Brian has organized a meeting this week with Peter Kuhn, a leader in blood biopsies and testing for prostate cancer.
- **Analyze data, find treatment options**: Laura Kleiman, founder and CEO at RebootRx, described the research they have been doing to prioritize opportunities to repurpose generic drugs for prostate cancer.
- **Define treatment strategy**: Rick Davis triggered a conversation focusing on Rick and Brian’s best next treatment, arguing they should try to get access to Pluvicto, a newly-approved prostate cancer drug that binds a radioactive nanoparticle (Lutetium) to antigens which are uniquely on the surface of prostate cancer cells (Prostate-Specific Membrane Antigen).

Requests

- Please invite to join us, or let us know, if there is anyone who could help us on our mission to accelerate access to emerging (research use only) tests to guide prostate cancer treatment decisions (“right to see”).

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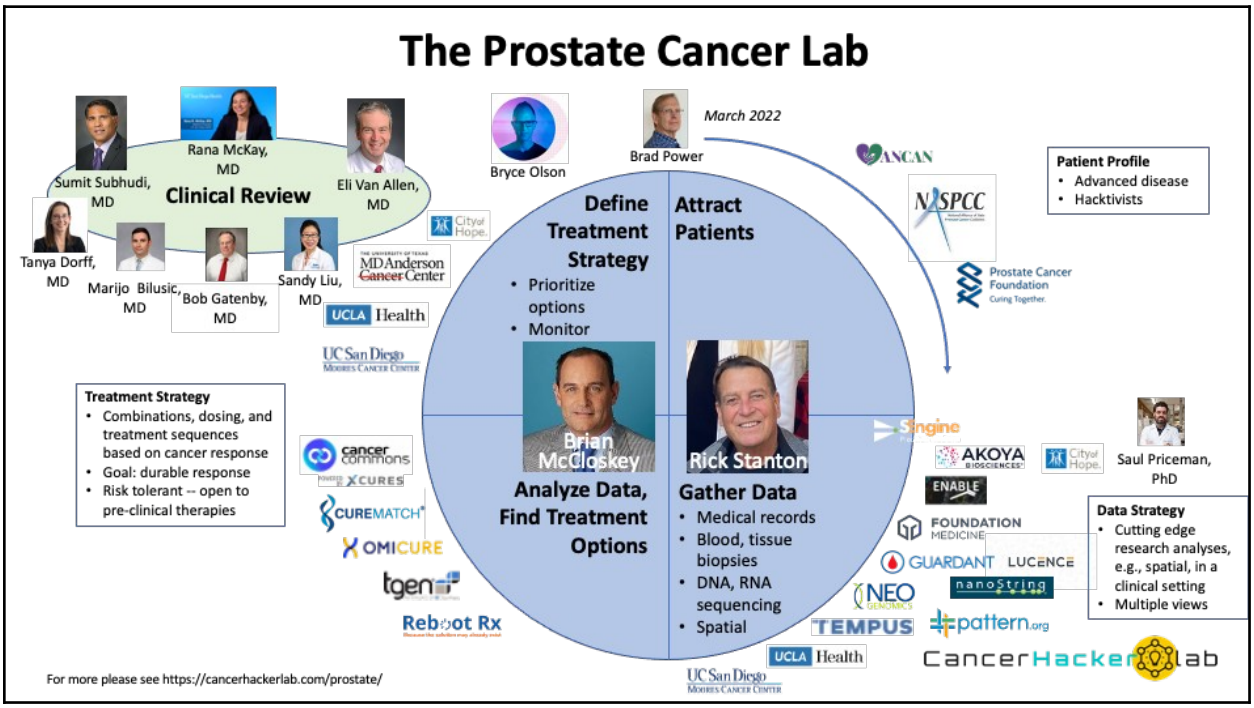
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Meeting Notes

Brad Power: We will use our process poster to update you on the activities of the Prostate Cancer Lab in the last week:



Attract Patients

Brad Power: 9 advanced prostate cancer patients have registered with Prostate Cancer Lab, and Brian has invited them to a meeting to understand their needs and interests.

Brian McCloskey: We were surprised at how many patients showed up, which is encouraging. We want to understand their needs, particularly with respect to our mission in increasing the speed at which diagnostic tools are integrated into our clinical care. We want to understand the challenges they face. We are looking for themes that will round out what we’re doing at Prostate Cancer Lab.

Brad Power: How about the conversations you’ve been having with prostate cancer advocacy groups? For example, people at AnCan? For example, Ben Nathanson is joining us today, and he heard about us through AnCan.

Brian McCloskey: There is more work to do with patients at AnCan.

Zsuzsanna Devecseri (Vice President, Head of Global Oncology Medical at Sanofi): I have a connection to the Prostate Cancer Foundation. If it would help, I can invite the Chief Scientific Officer of PCF to the next meeting or whatever would help here.

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Brad Power: Brian has had conversations with Chuck Ryan, PCF CEO, Howard Soule [the Chief Science Officer], and Gina Carithers, founder of Urology Today and does communications for PCF.

Brian McCloskey: I have had conversations with Howard Soule over the last year-and-a-half. My medical oncologist Rana McKay made the introduction to him, and he and I have talked about a number of different things. More recently I got connected with Gina Carithers, who is the founder of Urotoday, which is now owned by PCF. I recently spent about an hour-and-a-half speaking with her. She made an introduction to Chuck Ryan, CEO of the Prostate Cancer Foundation. And we spoke for about 90 minutes on the Prostate Cancer Lab and PCF 3.0, which is a new mission. I plan to reconnect with them in mid-April. They are open to helping us.

Brad Power: Our value proposition is to give them a patient leg to their heavily research-oriented leg. They fund a lot of research. They have their conventions where they share that experience. Brian is trying to bring a patient perspective to what they are already doing.

Zsuzsanna Devercseri: They organize a scientific meeting every year over three days where all the prostate cancer researchers are together. I attended in the last 15 years or so. They spend 82% of the money they raise on research. I would be happy to join your meetings with them.

Brian McCloskey: I’m going to take you up on that. Maybe there’s something we can do in tandem.

Brad Power: Brian, you went to the 3-day virtual PCF research symposium this year.

Brian McCloskey: It was in October, over three weeks. That was part of my conversation with Chuck Ryan. There is a lot of great research that PCF funds, but there are opportunities to bring it together and put the patient in the middle of that. And I walked him through some of my experience in the technology world, building consumer experiences. There are a lot of opportunities. Gina Carithers is very interested in bringing the patient voice to light in Urotoday. Chuck recognizes that medical oncologists need to get smarter about DNA reports, much less RNA, and here we are about to get into proteomics. He is using Urotoday to educate his medical oncologist constituents. He said, “Brian, you would be surprised at how many med oncs wouldn’t be able to interpret this information.” He has work to do to raise the water level of interpretation and understanding. Maybe the patient’s voice can be part of that education.

Zsuzsanna Devercseri: The scientific reports of those meetings, usually held over three days, spread over three weeks during the pandemic, were just released three weeks ago. If you don’t have it, I can share them with you. It’s a great summary of the state of the art in what’s going on in prostate cancer research.

Brian McCloskey: I got it.

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Gather Data

Brad Power: Gathering data is where Rick Stanton has been leading. In the last week Brian agreed to get a blood biopsy analysis from Lucence for himself and Rick. We are continuing to have conversations with TGen to expand the access they got for Rick to see his research data to other patients.

Rick Stanton: I had a chemo infusion yesterday and had a rough night last night. I tend to feel not so great immediately after getting the docetaxel, and better as the week goes on. The day before my infusion (on Sunday) I went out on my mountain bike, overdid it, and pulled my hamstring.
I’m looking forward to getting my PSA today. I started getting neuropathy in my hands, and I’m a guitarist, so I had my chemo dosage reduced slightly. My chemo either ended yesterday or I’ll get one more round, which would make six. They recommend six to ten rounds.
So I’m facing the question, “What drug should I go on next?” That’s where the tests come in. I’ve spoken to my care team, which is amazing, led by Tanya Dorff at City of Hope, Rana McKay at UCSD, and Sandy Liu at UCLA, running my Arcus clinical trial, about my next treatment options.

What tests have I had that would provide guidance?
I’ve had RNA seq on my primary tumor. I’ve been pushing for spatial analysis because I’m an electrical engineer and I know how to segment images and look for tumors. I’m very aware of how much value that would bring to the table beyond bulk RNA seq. It’s hard to get into the tests I’m hoping to have to guide my treatment.

When I failed darlutimide, a next-generation androgen receptor blocker, I wondered if I should go on a clinical trial. There are hundreds of clinical trials based on my profile.

None of my doctors put much credence into my molecular profile, e.g., my CDK12 mutations, in guiding that decision. They didn’t interpret the RNA seq. Spatial analysis is still coming on.
I am lucky to be a bioinformatics scientist and have interpreted mutations in a research pipeline. There are typically a thousand mutations, a handful of which are meaningful.
I have one meaningful mutation, and Brian has TP53 and a couple others.

When you get to immunotherapy you need to understand the tumor molecular environment and the signaling in that, so you can identify neighborhoods of immune cells and how they are situated next to cancer cells.

If you can answer a basic question, “Do you have T-cells, namely CD8, infiltrating your tumor?”, you have a better chance of responding to immunotherapy.

We want to identify TILs (tumor infiltrating lymphocytes) in your tumor, so that they can be activated by immunotherapy.

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If you have a “cold” tumor, which means you don’t have any TILs adjacent to your tumor that can perform the kill, it’s a lot harder for immunotherapies to work. Immunotherapies unleash that T-cell.

Brad Power: What’s the timing on that? You’ve made the case. When do you think you’ll be able to get that?

Rick Stanton: There are two vendors that I’m currently pursuing: NanoString with the GeoMx platform, and Akoya. Both are cutting edge and research use only. They are hesitant to pursue a test and reveal the results to a patient. Their goal is to become mainstream, but they are not currently approved.

My friend Nik Schork and his colleagues at TGen have been kind enough to put together a protocol which allows me to access research use only data as a patient.

At City of Hope they have the tissue and the technology.

But that analysis run is elusive.

I’m trying to get my tissue sliced and in the machine.

Brad Power: There are two ways to break the logjam: (1) Nik Schork and TGen providing an IRB-approved access for the patient to see research use only data, and (2) work in the system with your clinician requesting these tests. Could Saul Priceman, a bioinformatician at City of Hope, help?

Brian McCloskey: Saul Priceman runs the Priceman Lab at the City of Hope. He is the brains behind the amazing work that City of Hope is doing around CAR-T therapy and CAR-NK. We have developed a wonderful friendship.

He is introducing me to Peter Kuhn, who is the CEO of Epic Sciences and has his own lab. He is doing cutting edge blood biopsy work that can get down to looking at transcriptomics and proteomics. We will have a conversation on this on Friday. If he can get down to a protein level using liquid biopsy (not tissue), that would be a game changer.

Zsuzsanna Devercseri: Peter had also done amazing research on single cell analysis. It is important to connect with him since several years ago he was way ahead on this -omic analysis and single cell analysis.

Brian McCloskey: Saul has been an incredible champion in supporting me and this initiative. Because I am also being treated at City of Hope, we could leverage Saul to get some of Peter’s testing done through the City of Hope channel.

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Lucence reached out to me to do a liquid biopsy, a cell-free DNA test. I am happy to give blood all day for tests.

On the tissue front I have a primary tumor from 2016, my met tumor from 2020. My met tumor is fresh frozen. I am working with my primary medical oncologist Rana McKay to get access to that tissue so that I can run the spatial phenotyping that Rick was talking about.

Akoya Biosciences was here in San Diego last week for a conference, so I went to get educated. I was out of my element but learned a lot. Their platform is evolving very quickly. They can already test 80 antibodies simultaneously, almost at 100. They can cover immune profiling, advanced lymphocyte, myeloid immune activation, structural metabolism stress and death – a number of categories. They are installing these machines at UCSD. I don’t have a timeframe on when they will be available.

There was a doctor from Cedars-Sinai, Jaozheng Chu, developing organoids, but not from tissue, using Akoya’s spatial phenotyping technology to figure out how organoids work. Since tissue is scarce, finding ways to use blood or organoids are potential game changers to have more accessible and powerful diagnostics to add to the clinical conversations about various treatments.

I asked Oliver Braubach, who is the head of applications at Akoya, if they had used blood for their analyses, and he said that they had used PBMC (peripheral blood mononuclear cells). It is tricky because it smears, but this is something they are looking at.

As a layman, I figured they could just freeze it.

The pace of development is fast, and they are a great case for that.

Glenn Sabin: What is the availability of fresh tissue?

Brian McCloskey: I was just texting with Rana McKay about this. She is hesitant.
I have three met tumors in my peritoneum. The largest was about 2 centimeters. I also have caking as well, so they can’t do surgery. It’s microscopic.

My primary is gone – my prostate is gone. Though we have that tissue.

Glenn Sabin: You mentioned you might get more tissue and grow organoids. You could use SEngine and their PARIS test.

Brian McCloskey: I spoke to Carla Grandori, CEO of SEngine, about 2 or 3 weeks ago. That is a possibility. The challenge is that I am responding to abiraterone. My tumors are likely shrinking. Would it make sense to go in and do a biopsy? I’d like an opinion on that. Rana McKay was open to it, but she would typically do a biopsy on a tumor that is growing.

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Glenn Sabin: And you would need a washout period from whatever you are on.

Brian McCloskey: SEngine needs live, fresh-frozen tissue. The issue is whether I can get the biopsy.

Brad Power: Heather Messerly of Certis was on this call, and we learned in one of our previous hackathons in talking to folks at Certis that the quality of the tissue is really important. When they try to make mouse models, they are only successful 40% of the time. It’s dicey.

Glenn Sabin: I just went through this with a family member a few weeks ago. There was enough tissue, but it wouldn’t take.

Rick Stanton: TGen is trying to organize an organoid for me. I have multiple metastases at the nodal level. Rana McKay’s pathology team at UCSD felt they could harvest tissue. UCLA said my metastases were too hard to get to and too small.

Dr. Tanya Dorff recommended a bispecific treatment for me: PD1, CTLA-4, and olaparib. Olaparib is less compelling as a single agent drug, but she feels that in tandem with the other drugs, it will be good to try, in a clinical trial with Xencor.

A prerequisite of getting on that clinical trial is sequencing the metastases.

Dr. Dorff’s team of pathologists is going to look at whether they can get a biopsy to qualify me for that clinical trial.

As part of that biopsy, would I have enough tissue for sequencing, spatial analysis, and an organoid?

Analyze data, find treatment options

Brad Power: Laura could you tell us about RebootRx and how you might help Rick and Brian?

Laura Kleiman (founder and CEO of RebootRx): I’m not sure how we can help. That’s why I’ve joined and am engaged to figure that out.

We are a non-profit startup and our goal is to get affordable treatments to cancer patients faster using repurposed generic drugs. We are developing AI to sift through data on generic drugs to systematically prioritize these opportunities to repurpose drugs.

In collaboration with Brian we selected prostate cancer as our first cancer type to do a deep dive.

We’ve been working on this since the middle part of last year.

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We sifted through all of the PubMed studies that mentioned prostate cancer and any of the 1,000 non-cancer generic cancer drugs in 17,000 publications. We used our technology to find the relevant studies, where non-cancer generic drugs have been tested on prostate cancer to identify clinically-relevant outcomes. We identified 80 generic drugs that have been tested in a clinical setting for prostate cancer and developed a scoring algorithm that ranked the generic drugs with the most promise. We have identified some promising candidates and are moving them forward.

Our goal is not necessarily to promote any off label use of the drugs right now, but to gather definitive evidence that they are safe and effective for treating prostate cancer.
Many have been tested, but there often isn’t that definitive phase 3 evidence yet.

Rick Stanton: Are you looking mostly at small molecules?

Laura Kleiman: We’re looking at all FDA-approved drugs that have gone off patent, and are not approved for or commonly used to treat any cancer type, and are available as generics.

Rick Stanton: Are any of these drugs being selected specific to a patient, e.g, a mutation, RNA seq - not population-driven, e.g., prostate cancer?

Laura Kleiman: We have started with just analyzing the published literature, and in most cases there is nothing identifying a specific molecularly-driven population. We will be adding other data types, and our goal would be to get to that point of personalized recommendations.

Rick Stanton: I understand you have many drugs in a large, virtual pool that you are trying to find a best fit using an AI platform.

If we have an organoid, and your platform predicted seven small molecules that might be effective, could we pipette those prioritized drugs into clones of the organoids to test efficacy?

Laura Kleiman: We could do that in the future, but we’re not there now.

Zsuzsanna Devercseri: Will you have any access to data sources on how these drugs were used in the clinical setting and what worked to add to the evidence and help in decision-making? The FDA is open to adding new uses of existing generic drugs based on real-world evidence.

Laura Kleiman: Yes. That’s what we’re doing now.

Brad Power: I saw Saed Sayad of Rutgers do a similar analysis of repurposing existing drugs in the Shirley Pepke hackathon. Laura, are you acquainted with his work?

Laura Kleiman: His name sounds familiar. Please send his contact information.

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Define treatment strategy

Brad Power: Regarding clinician engagement, Brian, you mentioned the upcoming conversations with Saul Priceman and Peter Kuhn, and you also spoke to Michael Morris of Memorial Sloan Kettering. And you and I spoke to Marijo Bilusic.

Brian McCloskey: Michael Morris wants to be engaged. He’s busy. He encouraged us to think about pursuing a grant for this. We could use the grant to engage more clinicians in a way that is familiar to them. For example, Rana McKay and Tanya Dorff are pursuing a grant through PROMISE. He would be happy to help us if that’s the direction we want to go.

Brad Power: If you know of any clinicians who might help, please let us know. We’re trying to make it as easy as possible to engage as many as possible.

Rick Davis: This conversation has been very rewarding for the scientists, but what can we do for these patients right away? There was a huge sea change in the approval this past week of Pluvicto. If I was Brian or Rick, I would be getting my name onto a wait list as soon as possible for the Lutetium 177 PSMA 617, which has been retitled commercially at Pluvicto.

We know that both of you guys are PSMA avid. We know that from your scans. This treatment is very effective, even though it wasn’t effective for Bryce. We had a guy that didn’t do well on three high level doses. Then he went to a different trail with six lower doses. I would love to see both of you guys on that.

Where can you get this drug? We’re not sure because all of the managed access trials have been closed. That was a condition of the FDA approval. We aren’t really sure who has the hospital approvals in place to deliver these on a market basis. We think that UCLA does, which would be appropriate nearby for you guys. If you get hold of Calais [Dr. Jeremie Calais], he’s going to tell you if he can deliver it to you commercially. From a price standpoint, Advanced Accelerator Applications has made arrangements until Medicare covers it to subsidize payments. You can contact them at their Patient Connect program.

I cannot urge you enough to refocus your efforts over the next week to get access to Pluvicto.

Jan Soberialski: I heard from my oncologist that it’s available in Seattle at SCCA.

Rick Davis: That’s not the same. They’ve had it available for managed access trials. Those hospitals may not have been approved to deliver it outside of the trials.

Johns Hopkins gave one of our members, Herb Keller, access just before it was approved. AAA thinks that UCLA, University of Chicago, Mount Sinai, and Tulane (Dr. Sartor) will be offering market access. You have a relationship with Dr. Sartor. You should call him and see if you can get it there.