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Alexis Howerton On Starting Up From New Science

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Alexis Howerton

It is not often I meet my interview subject in the elevator on the way to our meeting room. By the time we get to the right floor, Alexis Howerton, the founding CEO of Spruce Biosciences, has recognized me from a photo and introduced herself, and we have already started the conversation.

Our meeting was set only a day or so before we both attended this industry event, and I come knowing next to nothing about Spruce or its lead drug candidate, SPR001, now in midstage development for treating congenital adrenal hyperplasia (CAH).

The program is a revival for an older drug class, which had once raised hopes as a possible source of blockbusters, but failed in the targeted indications. (Regulatory records give the chemical name, which would be several lines long here.) Howerton saw other potential for the class and jumped feet first into obtaining the ideal candidate compound and starting a company to develop it.

Spruce is a private company drawing on experienced, talented people from whom Howerton had the good sense to learn and draw direction. This compact conversation reveals a scientist-turned-CEO who is fully ready to talk about any aspect of her company. Howerton appears to be plotting an informed and logical course in building the company and developing its one and only product into something greater.

ONE PRODUCT, ONE FOCUS

Spruce has the rare distinction as a startup of focusing on a single drug, initially for a single indication. Because the roots of the company were the scientific research Howerton and others conducted in a specific class of compounds, it helps to know a bit more about the history, potential, and mechanics of the particular drug it chose to develop for CAH.

WHAT IS YOUR SCIENTIFIC PREMISE, WHAT SPARKED THE IDEA OF TURNING THAT INTO A BUSINESS, AND HOW DID YOU BECOME INVOLVED IN THAT?

HOWERTON: I have a Ph.D. in neuroscience, and I did my work at Penn in the class of compound for which we are developing an inhibitor — CRF (corticotropin-releasing factor). I was really passionate about the potential for taking this older class that had been developed for blockbuster indications in psychiatry, but didn't pan out for them, and I wondered whether there were appropriate patients to whom we could better target this drug.

My first idea was to write to pharma companies and suggest how they might do it, but my approach morphed over time. I went on to do a post-doc at Stanford in biomarker identification and patient stratification strategies and then circled back to this class of compound and was very fortunate to connect with a handful of mentors who had done this type of project before; that is, take a compound that has gone through safety testing and get it to its greatest value inflection point, proof-of-concept, by matching the right science with the right drug.

We spent about a year and a half fundraising, finding the right asset, and choosing the right indications, culminating in 2016 with a $20-million Series A, which spearheaded the company. Our lead investors, Novo Ventures and RiverVest Venture Partners, have really good experience in this type of strategy, and we've been busy building up the team and getting into the clinic. We are now in a Phase 2 program in CAH, our lead indication.

EXPLAIN THE COMPOUND'S MECHANISM OF ACTION.

Our drug works by blocking the production of ACTH [adrenocorticotropic hormone] through inhibition of the CRF type-1 receptor, working at the most upstream level of the pathway to control the most problematic aspects of disease. Suffice it to say, there is a serious unmet need in this disease, and we're fortunate to be in a position to provide a real treatment option for these patients.

Classic CAH is a genetic disease diagnosed through newborn screening shortly after birth. Newborn screening has been a lifesaver for many babies; it used to be that babies with CAH would experience adrenal crisis in the early days of life, which has a very high mortality rate. Since newborn screening came along, that's no longer the case. This disease has shifted from one of early-life mortality, to one of high disease burden that lasts throughout life, where patients are susceptible to both adrenal crisis and hyperandrogenism.

Patients experience precocious puberty, testicular adrenal rest tumors, stunted growth, infertility, acne, mood disturbances, hirsuitism, and alopecia due to high androgen exposure. The current standard of care, which is not FDA-approved, is to treat with high doses of glucocorticoids, which are associated with numerous and serious adverse effects (e.g., osteoporosis, gastritis, and stunted growth).

THAT REMINDS ME OF THE SITUATION WITH LUPUS.

It's similar in terms of the many problems those patients face with high-dose steroids being the only viable treatment option. And there has been little innovation in treatment for lupus in the last 20 years. For CAH, there is still no FDA-approved product, but a handful of different companies are starting to open their eyes to it. CAH is a very well-understood disease. That helps when looking at target engagement and other avenues to understand whether a drug is working. When you can see a biomarker change within 24 hours, it gives you good confidence in your regulatory and development strategies. That is where we are right now.

WHAT ARE YOUR BIOMARKERS?

They are hormones in the androgen pathway, including the hormones that physicians use to titrate steroid use, and a handful of other markers that affect the disease severity and change rapidly.

PATHWAY TO PLATFORM

Although Howerton is quite open about the CAH program, she and the company remain circumspect about the future development plans for SPR001. Yet she defines the considerable possibilities for its further applications. The vision is expansive — not just about finding a nice use for an old compound, but building a mechanistic foundation for many different conditions stemming from the same pathway.

YOUR PIPELINE CHART SHOWS YOU ARE THINKING BEYOND CAH, BUT YOU'RE NOT DISCLOSING WHAT INDICATIONS YOU ARE EXPLORING AT THIS POINT.

Yes, there are a couple of other indications that are really ripe for our small molecule. Unlike in many rare diseases, where each drug has only a single indication, SPR001 is targeting a really important pathway — the stress pathway — that has implications across many different diseases. We know that dysfunction in the stress pathway exacerbates almost every neuro- and inflammatory disease you can think of, from Alzheimer's to lupus. We have this first indication, CAH, which has a huge unmet need, but also a very clear index of target engagement where the drug is working. Once we have clearly established the right doses, it opens up a lot of opportunities for using the drug to treat other diseases.

IF A DRUG FAILS A PIVOTAL TRIAL IT'S USUALLY CONSIDERED A FAILURE, BUT YOU MAY BE DEMONSTRATING THE OPPOSITE POSSIBILITY BY TAKING AN OLDER COMPOUND AND APPLYING IT IN A NEW WAY.

Actually, our drug was only put on pause by the previous sponsor. The drug made it nicely through safety, but then it was deprioritized, and that happens for a lot of reasons. There was so much science, time, and money that went into its development, and fortunately we've had the opportunity to match all that with the right indication based on new science. When this drug was first made, I don't think the science was necessarily there to support it in the way it is now. Now we have genotyping, and we have a lot more involvement from patient advocacy groups to turn this into reality. Sometimes, time is on our side.

ARE THE CAH PATIENTS GENERALLY WELL-INTERESTED IN YOUR CLINICAL TRIALS?

Yes, we are currently enrolling for our Phase 2 study. It is an open-label, adaptive trial design, and the first part of enrollment is intensive in capturing a lot of patient data. We had five overnight visits, and we were surprised that patients were not only willing, but came out of the woodwork to participate. That speaks a lot to the unmet need here. We also have received orphan-drug designations from both the FDA and EMA.

DO YOU HAVE ANY PARTICULAR MANUFACTURING CHALLENGES WITH SPR001?

It's a small molecule, so everything has been reasonably straightforward. It has been a streamlined development process overall, fortunately, and right now we're a single-asset company, so the team is 100 percent focused on this disease and this compound.

THERE IS A LOT TO BE SAID FOR THAT. HOW ARE YOU DOING WITH FUNDING?

We raised $20 million in 2016, and that will get us through our Phase 2 program. It will last through discussions with the FDA at the end of Phase 2 meeting and give us some additional runway. We are now looking at what the next stages of development will be like to launch into a pivotal trial.

WHAT NEW DEVELOPMENTS FOR THE COMPANY HAVE YOU HAD MOST RECENTLY OR DO YOU ANTICIPATE IN THE NEAR FUTURE?

We're pleased to have launched a new registry for patients with congenital adrenal hyperplasia, which went live on Rare Disease Day (February 28). This study is a "virtual" trial that allows patients from all over the country to participate by sharing information about their biology and personal experience with CAH. The NIH has actually been conducting a terrific natural history study on patients with androgen excess, including CAH, for the past decade, from which we've learned so much. Our program supplements this by finding a way to include all patients throughout the country, even those not currently under the care of a CAH specialist, or who are unable to travel to the NIH. This allows us to better understand the disease in the "real world" and also is giving us the opportunity to help support patients and find the best care for them. We've seen a tremendous amount of interest over the past few months, which really underscores the unmet need in this therapeutic area. It's a great source of motivation for the team to watch patients and parents write to us almost daily about their interest.

ARE YOU FACING ANY OTHER CHALLENGES AT THIS POINT?

Every day is a new challenge (laughs.) I'm a first-time CEO, so that comes with a lot of challenges, but a lot of learning, and I have a good team, so I'm fortunate that they've all done this before.