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Jim Wilson's rethink of funding model underscores ultrarare headwinds

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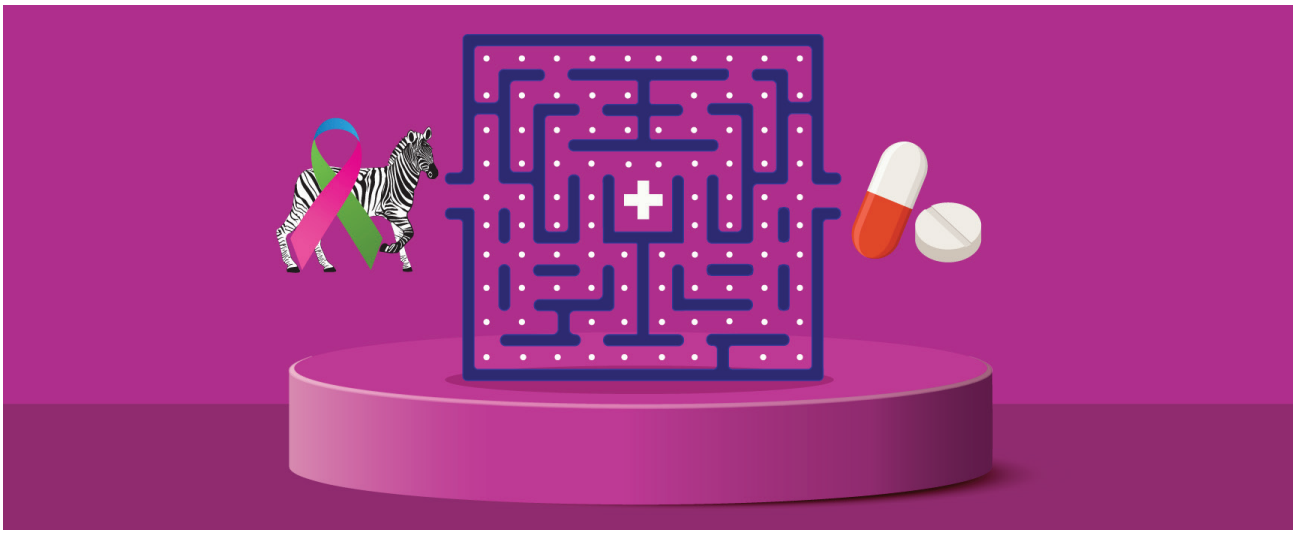

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Despite FDA's attempts to ease the regulatory path for ultrarare disease therapies, venture capital remains largely uninterested. That's the reality AAV gene therapy pioneer Jim Wilson confronted as he set out to develop and fund gene therapies for ultra-orphan indications, but the hurdles he encountered during the first year prompted him to overhaul the funding model to keep the mission alive.

Jim Wilson left his academic post at the University of Pennsylvania's Orphan Disease Center in 2024 to found Gemma Biotherapeutics Inc., an AAV gene therapy company that intended to take on what most others have avoided: developing one-time treatments for rare diseases, even those affecting only handful of patients.

One year later, Gemma has restricted its focus to the most prevalent rare diseases; those that promise billion-dollar markets and can attract VC funding. In October, the ultra-orphan programs initially at the heart of the biotech's mission were spun out into a new company, Rare Disease Therapeutics Inc. (RareTx), also led by Wilson. RareTx will rely on private funding and public-private partnerships.

Ultrarare drug development has never been very attractive to investors or pharmas due to the challenges of recruiting for trials, gaining reimbursement agreements and reaching sufficient revenues to justify the investment. Wilson believed he had found a solution by taking advantage of government incentives, executing strategic product licenses, and leveraging platform technology redundancies.

Gemma's original model was rational. The biotech had licensed clinical ultra-orphan AAV programs that would require limited investment in clinical development before reaching the market. It would then use priority review vouchers and product revenues to fund subsequent programs based on the same core platform technology.

"I thought we had a great plan when I last talked to you," Wilson told BioCentury. Its collection of clinical ultrarare disease programs included one already in discussions about a BLA submission. "These were the neuropathic lysosomal storage diseases that had the line of sight, I felt, into approvals, and with approvals would come priority review vouchers," as well as revenues.

In hope of satisfying investors, Gemma had also brought on preclinical programs in indications that were less rare, but at this year's J.P. Morgan Healthcare Conference in San Francisco, the VCs Wilson met with viewed the more advanced ultrarare programs as "distracting" from the real opportunities in the larger orphan indications. "They didn't buy the plan; it didn't resonate."

Three months after announcing Gemma's launch, Wilson had to rethink the strategy.

Now, Gemma will move its lead preclinical program into a clinical trial in Brazil expected to start this quarter, while RareTx advances its programs for GM1 gangliosidosis (GM1), Krabbe disease and metachromatic leukodystrophy using alternative funding sources. The newco will decide which ultrarare programs to add based on funder interests and feasibility.

Since financing ultra-orphan indications "simply to de-risk" Gemma's path to more common diseases did not appeal to VCs, Wilson said "we had to find stakeholders who would invest in ultra-orphans because of the impact it would have on patients."

Those funders, he said, include family offices and high-net-worth individuals who have children with rare diseases. "They're individuals who are interested in supporting a program with revenue sharing on the backend." Several are patient groups, he added, who see RareTx as a place for their programs.

Gemma and Rare have also formed public-private partnerships with the governments of Brazil and the United Arab Emirates. Through the partnerships, the biotechs gain financing to run trials in the regions, connections with the review authorities, and pre-negotiated pricing and reimbursement agreements. The companies are in discussions with three other countries.

Regulatory incentives in the U.S.

Though Gemma has funding to start clinical development in Brazil, Wilson also plans to develop the rare and ultra-rare gene therapies for the U.S. market. That will happen outside of the public-private partnership model that is more feasible in regions where a single health authority regulates review, pricing, reimbursement, and public health. In the U.S., he will look to his network of collaborators to stand up trial sites, and he's optimistic that regulatory incentives for ultra-rare drug development will help make that possible.

FDA has said it intends to prioritize rapid approval pathways for ultrarare disease therapies, and Wilson cited the agency's new Rare Disease Evidence Principles (RDEP) program as a step in the right direction. The program creates a framework for accelerating development and approval of therapies for serious diseases affecting fewer than 1,000 patients.

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"I'm incredibly excited about FDA's support for exactly what we're trying to do," said Wilson. If an indication meets FDA's criteria, "It's game on," he said. "Accelerated approval? They'll work with you. They'll facilitate getting things moving."

However, while RDEP is a positive development, other signals out of the agency suggest the bar could be rising for accelerated approval across rare diseases more broadly. Recent regulatory actions suggest the agency is increasingly relying on intermediate clinical endpoints and may be reluctant to accept surrogate biomarkers as approvable endpoints.

"For other diseases that are not ultra-orphan, I don't think you're going to have the same accommodations or an easier time justifying investment," he said. "It appears that the requirements for an accelerated approval are not going to be simply a biomarker."

Another obstacle to Wilson's original plan — and for any company developing therapies for rare diseases — was the sunsetting of the rare pediatric priority review voucher (PRV) program last December.

Wilson's funding model assumed that PRVs would be awarded for each therapy that met the indication requirements. Although a new type of voucher is available through the commissioner's national priority voucher (CNPV) program, those awards are made at the commissioner's discretion and do not stem from predictable eligibility criteria tied to rare diseases, making them unlikely to incentivize drug development in the space.

Because the foundation of both Gemma and RareTx is an AAV platform, FDA's platform technology designation could help both companies streamline development by leveraging existing data from regulatory submissions of products that used the same AAV vector. The initial programs at the two companies are based on the AAV vector technology that originated in Wilson's lab at Penn.

"The idea is bundling programs within platforms, where all you do is change the gene between the diseases, and then if

you're successful early, you can simplify development and manufacturing. Absolutely, that's key to our strategy," Wilson said.

The rollout of the platform technology designation has been slow and unpredictable, but viral vector technology does appear to be eligible. That wasn't clear early on when former CBER Director Peter Marks suggested AAV vectors weren't a good fit for platform designation, based on their complex manufacturing process. Since, then FDA has granted its first two designations and both went to viral vector technologies, although one has already been revoked.

The first company to announce receipt of platform designation was Sarepta Therapeutics Inc. (NASDAQ:SRPT), for the AAVrh74 vector used in its approved Duchenne muscular dystrophy product and its investigational therapy for limb girdle muscular dystrophy. The designation came just weeks before a third patient died after treatment with the DMD therapy, Elevidys delandistrogene moxeparvovec, which raised concerns about the safety of the vector in musculoskeletal diseases and led to revocation of the designation in July.

Last month, Krystal Biotech Inc. (NASDAQ:KRYS) became the second company to announce receipt of the designation, which it gained for the HSV-1 vector used in its re-dosable eye drop gene therapy KB801 for neurotrophic keratitis. The same vector is used in the company's Vyjuvek beremagene geperpavec gene therapy for epidermolysis bullosa.

Marks had also signaled that the requirement for an approved reference product built with the same tech would be removed, which would have made the designation useful to many more companies. As things stand, Wilson's AAV technology won't be eligible for the designation until after the first therapy receives approval.

While the boundaries of FDA's new designations are still taking shape, Wilson sees the agency's willingness to engage on ultra-rare disease programs as a sea change. "It really is moving very quickly, and I think we are going to benefit enormously from the commitment health authorities are making toward the very thing that we're trying to do."

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