

MVP's Project Evaluation: Striving to Ask All the Right Questions

The "Monday Call" is becoming a hallmark of MVP's business operation: Volunteer advisory board members and MVP staff meet via conference call to review the companies and projects seeking funding.

Each week MVP sends to its advisory board members an agenda for the meeting and posts background data about the projects of interest on a secure document site for review by the committee. During the call, the group discusses both the scientific rationale for the projects and the path forward for the companies.

The committee then offers advice as to whether the projects should move on to the review process, or whether changes are needed.

The weekly call format — patterned after a standard operating tool of the venture capital industry — is a key component of MVP's decision-making, and is designed to keep the deal flow process running smoothly and constantly.

The calls are just part of MVP's overall project evaluation process, and MVP officials aren't aware of any other venture philanthropy group using this format.

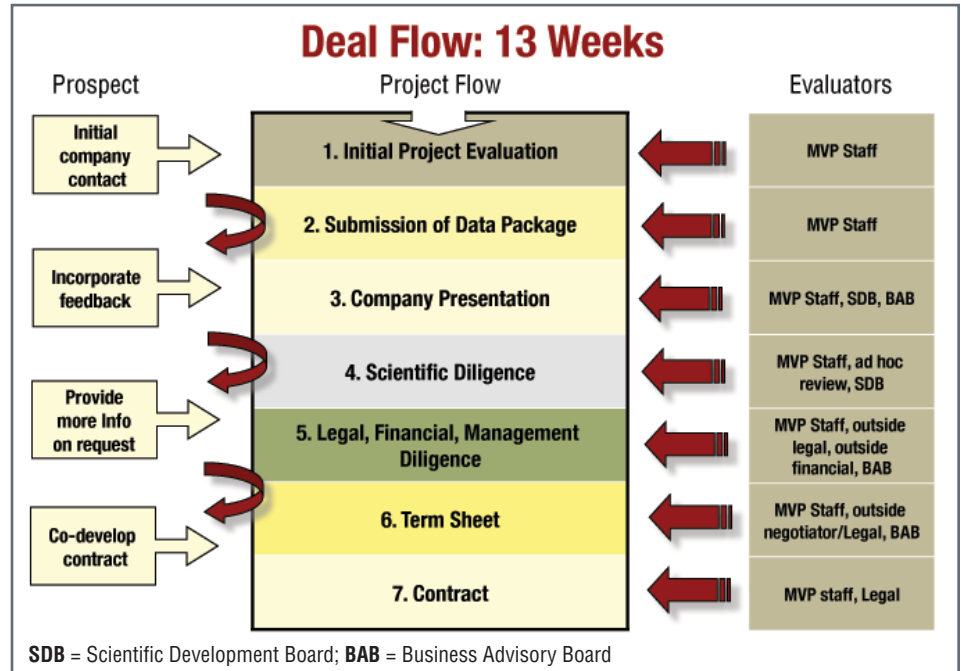
Improving projects for funding



Jane Larkindale

MVP staff devotes significant time to improving projects by resolving issues before they are ever put in front of advisers for review, said Jane Larkindale, Ph.D., MVP's portfolio director.

"We don't want to hold back a project because of a minor issue," Larkindale said, explaining that some critical questions must be answered before MVP will consider advancing a project to its advisers for review.



"First, does the approach have a reasonable chance of working? And if it does, is there a way to go forward? In other words, can it be tested? Can it gain FDA approval and get to market?" Larkindale said.

When those questions can be answered to MVP's satisfaction, the project is ready for the Monday Call and to be put through "very, very rigorous review by the scientific experts in the field," Larkindale said.

Companies with promising projects are asked to supply a detailed package of support data that is reviewed by ad hoc reviewers. These reviewers are experts selected to offer expertise directly related to each project, but who are not connected to the company involved or competing companies.

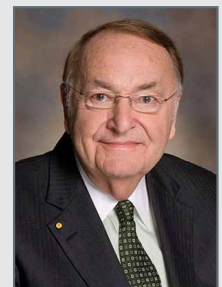
If advisers identify resolvable issues that could block a project's advancement toward funding, MVP — in consultation with

Welcome from MVP's Leadership

We're pleased to welcome you to this first edition of MVP's Quarterly Update. This publication is designed to bring you news and information related to MVP's mission, and to provide you with feature stories about the projects and people that are key to its process. Thank you for your interest, and please feel welcome to provide feedback or questions.



Jerry Weinberg
President & CEO
MDA and MVP



R. Rodney Howell, M.D.
Chairman of the Board
MDA and MVP

appropriate expert volunteers — will communicate with the company about these, Larkindale said.

MVP also looks to its expansive network of experts in other special circumstances.

An example: MVP is working to convene a panel of stem cell experts to determine criteria for considering stem cell clinical studies in ALS, she said.

Tough economy, tough review

The current turbulent economy adds another layer of importance to MVP's financial diligence of its funding applicants — typically small biotech or startup companies.

"We have to determine if companies are stable and solvent enough to see the project through," Larkindale said, "and whether there is an exit strategy in place."

When it approves a project, MVP will stipulate that if a drug or compound is abandoned by the company for non-scientific reasons, "MVP has the right to continue to develop it for the indication originally intended," Larkindale said.

Since holding the first call on March 3, the system seems to be working toward its goal of accelerating the drug development process in part by providing faster turnaround for funding decisions.

By the end of the second quarter of 2009, MVP had evaluated letters of intent from 21 companies, from which 10 full data packages were requested. Six projects have been rejected.

Lee Wrubel, M.D. is a member of the MVP Scientific Development Board, and previously served on the MDA "TRAC" — the Translational Research Advisory Committee — which reviewed MDA's Translational Research grants.

He and other advisers have reacted positively to MVP's process so far, and Wrubel likes how it takes the most successful elements of the TRAC and "is now applying them with greater sensitivity to broader market issues."

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"I think MVP is seeing a good number of interesting opportunities and has developed an appropriate evaluation system," said Wrubel, who is general partner of Foundation Medical Partners, a health care venture capital investment firm in Rowayton, Conn. "As MVP continues to formulate a strategy for accessing new research technologies, I think additional novel opportunities will present themselves, which will be exciting."

MVP Executive Director Sharon Hesterlee, who is the key architect of the process, said she is pleased with the tough standards that MVP advisers have held for its projects.

"We have really added an incredible amount of professional rigor to the review process — I think we've always been able to do superlative scientific diligence because of

our deep ties to the research community, but now we can add to that the type of financial and legal diligence required to turn a good idea into a drug." ■

Honoring an ALS Champion

The first issue of this newsletter is dedicated to our friend and colleague Sean Scott (1969-2009), who truly knew how to make things happen. ■



Sean Scott



Sharon Hesterlee,
MVP Senior Vice President & Executive Director

MVP STRATEGY When There's No "Drug Fairy"

I remember many years ago when I first started working in the Research Department at the Muscular Dystrophy Association — I was a newly minted Ph.D. who had done her thesis on neural development in the tobacco hornworm (the big green caterpillars you find on tobacco and tomato plants) and who was looking forward to seeing science applied more directly to helping the human condition.

Consequently, I started reviewing grant files on projects that were designed to develop treatments for neuromuscular disease and was dismayed to discover that, in some cases, investigators had been slightly tweaking the same idea year after year and applying for new funding. In other cases, the idea had been dropped entirely and the investigator was on to something else ... So I pulled together the most promising projects and started systematically calling the investigators to find out what their plans were for moving the ideas into the clinic. In other words, how do we turn the good idea into a therapy that can be prescribed by the local MDA clinic doc?

Again, I was dismayed to discover that many of the investigators just didn't know how to move these projects forward. Several suggested that they might be willing to form companies, particularly if MDA subsidized these high risk startups, although almost none of them had any business or regulatory experience. It was eye-opening to say the least. I think they thought that making an elegant and compelling case for their research meant that the Drug Fairy would swoop in to pick things up from there. I think we all thought that at one time.

And we were all counting on the Drug Fairy because that's really how things worked in some disease areas like heart disease, cancer or asthma. Angel investors, venture capital firms and Big Pharma were always on the prowl for the next new idea to treat big markets. The problem we have in neuromuscular disease is that all the disorders in MDA's program are technically "rare" — that

is, they affect less than 200,000 people in the United States. The markets aren't large and, without intervention, the business models weren't sustainable. So promising therapeutic ideas languished.

Now, if the mission of MDA were only to fund absolutely the best research in neuromuscular disease, we wouldn't have had a problem, because I think the organization accomplishes that goal routinely. But our mission is to develop therapies and cures for the diseases in our program — something new had to be tried.

In 2003, I was involved in launching MDA's Translational Research Program (nicknamed the "TRAC"), which provided incentives for companies to develop drugs for the diseases in MDA's program. Through that program we funded a total of \$31 million in projects, either directly to drug companies, or to academic groups developing the clinical infrastructure that would help subsidize the cost of doing clinical trials in neuromuscular disease. The industry projects included the gamut of small molecules, gene therapy, stem cell therapy and protein therapeutics (see For-Profit chart).

The MDA TRAC has now matured into MDA Venture Philanthropy (MVP) — a lean, mean drug development machine. MVP is a wholly controlled subsidiary of MDA that is solely focused on selecting and funding the best therapy prospects for neuromuscular disease. Its main portfolio areas are Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and spinal muscular atrophy (SMA). Projects in other disease areas also will be considered.

If the MDA TRAC was primarily a grant program that was able to fund biotechnology companies, MVP is primarily a venture fund with elements of a grant-making organization. MVP is a nonprofit organization, but we consider our grants to be investments, and we add to our ability to do thorough scientific diligence an ability to conduct financial and legal diligence at professional standards. The key to our success is the goal of making decisions "at the speed of business" rather than the speed of a typical grant-making organization. You'll see in the accompanying article about our review process and how we differ from the standard model.

MDA For-Profit Investments Since 2004

Company	Project	Investment
Asklepios BioPharmaceutical Inc.	Phase I/II Study of Mini-Dystrophin Gene in AAV Vector	\$1.57M
PTC Therapeutics Inc.	PTC 124 Treatment for Duchenne Muscular Dystrophy	\$1.47M
Asklepios BioPharmaceutical Inc.	Phase Ib/II Study of Mini-Dystrophin Gene in AAV Vector	\$2.5M
Insmed	Phase IIa Study of Iplex in Myotonic Muscular Dystrophy	\$2.1M
California Stem Cell Inc.	Stem Cell Transplantation Strategy for ALS	\$0.2M
Repligen Corporation	Lead Candidate Optimization of HDAC Inhibitor for Friedreich's Ataxia	\$1.0M

Another key advantage of MVP is our strong link with the mother ship — MDA. Because we are backed by such a large and venerable organization, which is currently funding almost 40 percent as much research in the muscular dystrophies as the federal government, we have access to hundreds of potential reviewers and experts as well as a massive database of promising academic projects from which to cull ideas. We are well-known in the research community — we know where the bodies lie, who has biases and who makes a good critical reviewer.

Another goal of MVP is to review not only what shows up on our doorstep (although as an aside, some of those “doorstep projects” look really, really good), but to always ask is this really the best strategy, and if not, what would be?

For example, we received applications from companies developing drugs that target an inflammatory pathway called the NfκappaB pathway. Rather than review only those two projects, we did a complete review of the pathway, cross-referencing all of the evidence in the scientific literature in which the pathway is relevant to muscular dystrophy. We then ran a query through Pharmaprojects, a subscription-only database, to see what other drugs were in development that hit the same path (the answer is many, but lots had dropped out of the development process due to toxicity).

By combining this sort of proactive review of potential drug targets with the ability to opportunistically review the “doorstep” projects, we should maximize our chance of success. At the end of the day, our objec-

tive is to take as many “shots on goal” as possible by ushering the best of those promising ideas into the drug development process, and we are looking for major gifts from like-minded individuals to support us in this endeavor. We understand the urgency of the need for effective drugs and have put together MVP’s infrastructure to make them happen as fast as possible. If you are interested, we have your magic wand waiting.

In subsequent issues of this quarterly newsletter, we’ll update you on our first investments, provide more detail on our drug development and investment strategies, better acquaint you with some of the spectacular talent serving on our business and scientific advisory boards, and introduce you to MVP’s small, but driven staff. Stay tuned for great things ... ■

Therapeutic Outlook for Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is caused by mutations in the gene for the dystrophin protein, which lead to progressive muscle wasting, and eventually breathing and cardiac problems. Our understanding of the series of cellular events that lead to muscle wasting has matured dramatically since mutations in the dystrophin gene were identified as the cause of DMD in 1986 by an MDA-funded team led by Dr. Louis Kunkel.

Today, the therapeutic approaches to treating Duchenne MD fall into one of two categories: 1) things that stop or decrease muscle wasting and 2) things that increase muscle mass. Both types of strategies may ultimately be needed in parallel if we want to stop the degeneration and then replace muscle previously lost.

All strategies listed below have received funding from MDA.

Strategies designed to stop or decrease the loss of muscle include:

- Replacement or repair of the dystrophin gene
 - [gene therapy](#)
 - chimeroplasty or other gene repair approaches
- Repair of the dystrophin messenger RNA
 - stop codon read-through
 - [exon skipping](#)
- Replacement or repair of the dystrophin protein
 - TAT-dystrophin delivery
- Replacement of the function of the dystrophin protein
 - substitution with other proteins (utrophin, agrin, laminin)
 - [membrane-altering compounds](#)
- Reduction of inflammation
 - [NfκappaB pathway](#)
 - [reduction of ROS](#)
- Reduction of fibrosis
 - TGF-beta pathway
- Blockage of the pathway that leads to muscle cell death
 - [blockage of mitochondrial transition pore](#)
 - blockage of other apoptotic proteins
 - blockage of protein breakdown pathways
- Improvement of membrane repair mechanism
 - [Hyper-stimulation of normal repair mechanisms](#)

Strategies designed to increase muscle mass include:

- Hyper-stimulating normal muscle growth
 - [remove normal inhibition to muscle growth by blocking myostatin pathway](#)
 - stimulation of growth with IGF-1
- Providing new muscle via stem cells (adult-derived or embryonic)
 - heterologous stem cells (from a donor)
 - “corrected” autologous stem cells (a person’s own cells)

■ *Projects under review by MVP*

■ *Projects being solicited by MVP*