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TRANSLATIONAL NOTES

# A conversation with Gregory Verdine

*By Joanne Kotz, Senior Editor*

What will drugs look like in the coming decade? This is the question being posed by Gregory Verdine and the next-generation therapeutic modalities team he leads at **Third Rock Ventures**. One answer, Verdine believes, is hybrid platforms of synthetically modified biomolecules that combine the advantages of small molecules and biologics.

*SciBX* met with Verdine at his **Harvard University** office to talk about the science that is driving the discovery of new drug modalities and the challenges of bridging the gap between good science and commercialization. Verdine is director of the program in cancer chemical biology at the **Dana-Farber Cancer Institute**, a professor in the Department of Chemistry and Chemical Biology at Harvard and, since 2009, a venture partner at Third Rock.

*SciBX*: Where do you see opportunities emerging for new types of drugs?

*Gregory Verdine*: I believe that 10 years from now, when we look at the types of molecular structures that we consider to be 'drug-like', these structures will be considerably more diverse than now. In other words, we are entering a period in which we will see a significant expansion in the types of molecules that succeed as drugs. This process is already underway, as many pharmaceutical companies have begun explicit efforts at broadening the structural base of targeting molecules. These new modalities are likely to include nucleic acids beyond antisense and siRNA, carbohydrates and peptides, among others, but also interesting fusions, such as small molecule–protein conjugates. Some of these classes of molecules have a back-to-the-future aspect to them, for example peptides and natural products, but recent scientific advances have suggested that they should be looked at in a new light.

*SciBX*: How does Third Rock go about launching new companies in such emerging areas?

*GV*: We recently launched a new company with **Flagship Ventures**, **Eleven Biotherapeutics Inc.**, with the concept of bringing truly rational drug design to bear on the discovery and development of next-generation protein therapeutics. This illustrates our process. We brought together five founders that included myself; a biological engineer, Dane Wittrup [**Massachusetts Institute of Technology**]; a cytokine structural biologist, Chris Garcia [**Stanford University**]; an expert in Th17 [T helper type 17 cell] cytokine biology, Casey Weaver [**The University of Alabama at Birmingham**]; and a practicing clinical ophthalmologist, Reza Dana [**Massachusetts Eye and Ear Infirmary**].

Once assembled, this team of founders got together around six times a year, plus an internal company concept team at Third Rock met daily, with the key goal of creating a research and business plan—figuring out how to reduce the universe of all possible avenues to something that is achievable in a reasonable period of time. Through this process, we built a fabulously creative, talented, goal-oriented team of founders and key early employees who really took ownership over the process and the company, who were really excited and who wanted to do something

**Table 1. Companies developing new classes of peptide-based therapeutics.**

| Company | Platform technology | Clinical stage programs |
|---|---|---|
| Aileron Therapeutics Inc. | Chemically cross-linked helices | |
| Anchor Therapeutics Inc. | Lipopeptides for modulating G protein–coupled receptors | |
| Angiochem Inc. | Blood brain barrier–penetrating peptides conjugated to drugs | Partner Geron Corp. (NASDAQ:GERN) to start Phase II trial of GRN1005 (ANG1005), an angiopep-2 vector conjugated to three paclitaxel molecules, in 2H11 to treat brain metastases |
| Bicycle Therapeutics Ltd. | Chemically constrained bicyclic peptides | |
| Cosmix Verwaltungs GmbH | D-Peptides | |
| Esperance Pharmaceuticals Inc. | Membrane-disrupting peptides conjugated to ligands | EP-100, a fusion protein consisting of a luteinizing hormone–releasing hormone (LHRH) ligand conjugated to a membrane-disrupting peptide, is in Phase I testing for various cancers |
| Mercator Therapeutics Inc. | Targeting peptides conjugated to drugs | |
| Pepscan Therapeutics B.V. | Chemically constrained peptides | |
| PeptiDream Inc. | Cyclic peptides incorporating non-natural amino acids | |
| Polyphor Ltd. | Cyclic peptide-like molecules that mimic protein epitopes | POL7080, a modified peptide targeting the *Pseudomonas* LPS-assembly protein (OstA; LptD; lmp), is in Phase I trials for pseudomonas infections |
| Ra Pharmaceuticals Inc. | Undisclosed | |

transformative. This think tank approach is an organic way to identify who is committed enough to the commercialization of the science to actually spend time on it, who is willing to link their professional reputation to that of the company and who is willing to throw their best ideas into the mix.

*SciBX*: Which potential new drug scaffolds are attracting the most current commercial interest?

*GV*: The peptide area is particularly active, and we are tracking this space very closely. There are a number of interesting companies already developing modified peptides as new therapeutic platforms (*see* **Table 1, "Companies developing new classes of peptide-based therapeutics"**). Although peptides can readily be identified that selectively interact with a target, the poor pharmacological properties of unmodified peptides limits their usefulness as drugs.

A common feature of many of the new peptide platforms being developed is the incorporation of synthetic modifications to improve the peptide's pharmacology.

For instance, outside the Third Rock realm, Greg Winter [**MRC Laboratory of Molecular Biology**] has cofounded a company called **Bicycle Therapeutics Ltd.**, which is developing a way of locking synthetically modified peptides into polycyclic structures.

Jack Szostak [**Massachusetts General Hospital**] is involved in a company called **Ra Pharmaceuticals Inc.** that is doing work along similar lines.

There is a cool company in Japan called **PeptiDream Inc.**, founded by Hiroaki Suga [**The University of Tokyo**], that has done really exciting work combining directed evolution with the ability to incorporate unnatural amino acids into cyclic peptides.

**Aileron Therapeutics Inc.**, a company I cofounded in 2005 based on technology invented in my labs at Harvard and Dana-Farber, is developing what we call stapled peptides. These are helical peptides that are stabilized by a chemical cross-link that increases the peptide's affinity for its molecular target, its circulation time in the bloodstream and, most importantly, enables robust cellular uptake through vesicular trafficking.

Each of these new platforms may provide a way to drug targets like intracellular protein-protein interactions that are difficult to modulate with small molecules or mAbs.

*SciBX:* What are [some] recent academic advances that could have an impact in peptide-based therapeutics?

*GV:* A very interesting area, although not quite ready yet for commercialization, is the use of peptides as targeting agents.

For instance, Erkki Ruoslahti [**University of California, Santa Barbara**] is using phage display to identify peptides that bind to the vasculature, and Kathlynn Brown [**The University of Texas Southwestern Medical Center at Dallas**] is using a similar approach to identify cell-specific or tumor-specific peptides. Fusing these targeting peptides to small molecules or antibodies could create novel therapeutics that are exquisitely targeted to particular physiologic sites, for example, to tumors, skeletal muscle or the brain. Such targeting is expected in many cases to increase the efficacy and to decrease the toxicity of drugs.

Also, David Craik [**The University of Queensland**] and Jennifer Cochran [Stanford University], among others, have begun developing knottins, highly disulfide cross-linked peptides that are readily diversifiable through directed evolution approaches, seem to be incredibly stable, may be relatively nonimmunogenic and show some evidence of blood brain barrier penetration. These molecules could prove useful for a variety of disease indications in humans, especially those for which mAbs are unsuitable for various reasons.

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***—Gregory Verdine, Third Rock Ventures***

*SciBX:* What are [some] scientific advances that would propel increased investment in peptide therapeutics?

*GV:* It's still early days in the resurgence of peptide therapeutics, but the scientific breakthroughs that really command attention are those that overcome some of the key obstacles of unmodified peptide drugs—advances that could enable oral bioavailability, substantially extend peptide half-life, protect peptides from proteolysis, enable active cellular uptake or allow peptides to cross the blood brain barrier. To my knowledge, no peptide platform developed to date combines all these features.

*SciBX:* What broad trends have you seen in early venture funding?

*GV:* There is no question that most venture funds have moved later to try to reduce the time that it takes to reach a value inflection, the achievement of a milestone that increases the valuation of a company. For these later stage investments, the value inflection is typically tied to drug approval. Though this strategy was considered by some to be conservative, in practice it has often proven quite risky because the costs of late stage clinical testing, and the opportunities for failure, are high.

Third Rock's idea is that if you find an area of science and medicine in which there's a real value inflection earlier than drug approval, then it makes sense to work in that area. But you have to make sure it's in a space where there is high pent-up demand for transformative products.

An added challenge for early stage discovery is that the venture investors are often extracting technologies from academic centers, and therefore the body of available data often has significant gaps, particularly in pharmacology studies.

Our first action item is often to work with the academic centers and the entrepreneurs to get these studies done so that a more informed decision can be made about a full-throttle investment.

University conflict-of-interest regulations that prevent an academic founder from participating in a research collaboration with a company

in which he or she has an equity interest can also pose challenges. These regulations have been instituted at many universities because of a few individuals who abused the system, but the resulting rules end up affecting everyone, and in some cases they end up stifling development of the technology.

*SciBX:* Are there other sources of early funding that are filling this gap in venture money?

*GV:* Pharma is beginning to externalize more and more research, and this is a trend that is very likely to continue. But it's not like the old days, where the money flowed into the academic lab and the company sponsor hoped for results somewhere down the road.

Now, if research support is going to an academic lab, it is being managed professionally by a company liaison and the professor has to make regular reports. I think this will turn out to be an improvement on the old system, because it prevents the research from wandering too far afield from the original objective, and it keeps the interests of the sponsor and grantee aligned.

On the other hand, the potential for investigators to use their existing **NIH** grants for seed money has been all but eliminated. Academics used to be able to do what is called bootstrapping—using a fraction of one grant to fund the inception-phase experiments of a new project—but this federal source of early stage funding has essentially evaporated.

As a result of concerns that a federal audit will reveal deviations from the approved research objectives, universities have instituted something close to a prohibition against bootstrapping. To protect their access to federal research dollars, universities have decided to become vigilant about grant compliance.

This turn of events is not necessarily good for American science—bootstrapping has provided one of the very few sources of seed capital for scientific research, and the projects supported in this way have tended to be particularly high on innovation.

Perhaps a solution would be to codify the practice that any NIH grantee has the freedom to divert up to 15% or 20% of their budget to research not listed in the original Specific Aims of that grant, provided that the research results are reported in the program reports.

*SciBX*: In this challenging funding environment, what do academics need to do to attract venture money?

*GV*: The biggest challenge is assembling a package of data that gets a venture group excited about the opportunity and where enough of the obvious risks have been removed that the VC feels that the science is ready to go right now.

For instance, imagine you are working on a new biological pathway and you come up with a molecule that works in that pathway. Typically a VC would want some *in vivo* evidence of efficacy and some type of pharmacology with the molecule, preferably repeated in independent laboratories. Essentially, you need to show that you have a decent model and a decent molecule if you hope to gain the serious attention of an experienced investor.

But where in academics does anyone have pharmacology? Most likely an academic will have to outsource the pharmacology, and many academics and universities do not have the experience or the money to do this. So you have this terrible problem that research gets to a certain stage where there is not really enough data to file a strong patent and so the university either has no IP or weak IP that needs to be bolstered.

Third Rock has started companies, for instance the epigenetics company **Constellation Pharmaceuticals Inc.**, with no lead molecule in hand because the area was clearly going to be exceptionally important.

But instances of an emerging area of biology that are as medically compelling as epigenetics are few and far between.

One solution for academics is to form collaborative teams of chemists, pharmacologists and disease biologists, so the entire effort remains nested in the academic center until a stronger data package has been acquired.

I had always hoped that if the federal government decided to become seriously engaged in drug discovery, it would decide to provide a resource that would offer the academic community access to pharmacology services and expertise. The current effort to found the 'people's pharmaceutical company' within the NIH intramural program focuses exclusively on intramural drug discovery and development programs and, because of this, misses the opportunity to harness the full potential of the discovery science going on in the academic community.

*SciBX:* Thank you very much for your time.

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## COMPANIES AND INSTITUTIONS MENTIONED

**Aileron Therapeutics Inc.**, Cambridge, Mass.
**Bicycle Therapeutics Ltd.**, Cambridge, U.K.
**Constellation Pharmaceuticals Inc.**, Cambridge, Mass.
**Dana-Farber Cancer Institute**, Boston, Mass.
**Eleven Biotherapeutics Inc.**, Cambridge, Mass.
**Flagship Ventures**, Cambridge, Mass.
**Harvard University**, Cambridge, Mass.
**Massachusetts Eye and Ear Infirmary**, Boston, Mass.
**Massachusetts General Hospital**, Boston, Mass.
**Massachusetts Institute of Technology**, Cambridge, Mass.
**MRC Laboratory of Molecular Biology**, Cambridge U.K.
**National Institutes of Health**, Bethesda, Md.
**PeptiDream Inc.**, Tokyo, Japan
**Ra Pharmaceuticals Inc.**, Boston, Mass.
**Stanford University**, Stanford, Calif.
**Third Rock Ventures**, Boston, Mass.
**The University of Alabama at Birmingham**, Birmingham, Ala.
**University of California, Santa Barbara**, Calif.
**The University of Queensland**, Brisbane, Queensland, Australia
**The University of Tokyo**, Tokyo, Japan
**The University of Texas Southwestern Medical Center at Dallas**, Dallas, Texas