Recasting natural product research

Can the commercial sector capitalize on the merger of high-throughput technology and natural products? Cormac Sheridan investigates.

The recent fanfare surrounding Warp Drive Bio, a startup with an ambitious agenda to marry natural products–based drug discovery with modern genomics, signals that there may still be life in what has become a moribund niche of the pharmaceutical industry. Although natural products research has historically been a mainstay of drug developers—in previous eras, around half of all drugs had their origins in natural sources—interest in the area has dwindled in recent decades.

Warp Drive Bio, based in Cambridge, Massachusetts, is not the first company to undertake a genomics-based approach to natural products discovery. Pioneers such as TerraGen, Ecopia Biosciences and Kosan Biosciences tried and failed to develop new drugs based on various genome-mining approaches. However, at the time, they didn't have the high-throughput sequencing technology and other advanced DNA-handling methods that Warp Drive Bio has at its fingertips. "If we had those in '95, obviously the business plan of Kosan would have read differently," says Chaitan Khosla, a cofounder of Kosan (now part of New York–based Bristol-Myers Squibb), a professor of chemical engineering at Stanford University in Stanford, California. "It's the right time to revisit this—I'm interested in how they do."

Been there, done that

On paper, at least, Warp Drive Bio seems to have enough financial and scientific muscle to establish whether nature still harbors untapped reserves of bioactive molecules from which new drugs can be fashioned. The company's promoters come with big reputations. It was cofounded by the Boston-based venture capital firm Third Rock Ventures and Greg Verdine, a partner at Third Rock and a professor of chemistry at Harvard University in Cambridge, Massachusetts. Other scientific founders include George Church, a professor of genetics at Harvard Medical School in Boston, and James Wells, an authority on protein engineering and fragment-based drug discovery at the University of California, San Francisco. The company has secured up to $125 million in equity and research funding, with $75 million in equity investment coming from a consortium comprising Third Rock, Greylock Partners of Menlo Park, California, and Sanofi, based in Paris. Sanofi is collaborating on several Warp Drive programs and has an option to acquire the new company should it achieve certain undisclosed milestones. Warp Drive Bio remains independent for now, however, and it is free to enter partnerships with other pharmaceutical firms as well. As yet, it is not committed to any particular therapeutic area.

The single biggest problem facing natural products research is the field's lack of recent progress. The discipline has been stuck in a negative feedback loop for more than a decade, and any prospect of success has, at least so far, been undermined by the resulting lack of serious investment. "The whole area has become mired with negative outcomes," says Tony Buss, chief executive officer (CEO) of Singapore-based MerLion Pharmaceuticals, which continues to operate a service business based on its extensive natural product libraries (although its core business is now based on synthetic drug development). "It's gone nowhere—it's really fallen out of favor," says Chris Newton, managing director of BioFocus DPI, the Saffron Walden, UK–based drug discovery–services arm of Mechelen, Belgium–based Galapagos. BioFocus offers clients access to natural product libraries through its partnership with InterMed Discovery of Dortmund, Germany. It's a minority pursuit, however. "It is not a popular weapon. It's regarded as an option of last resort," Newton says.

An abundance of riches. MerLion Pharmaceuticals has collected several hundred thousand strains of microbes and plants for drug screening. Source: MerLion Pharmaceuticals.

This is the case for several reasons, including the difficulty of screening natural products—complex mixtures rather than purified solutions are the norm—and the scarcity of many of the resulting compounds. The high redundancy associated with current approaches to screening natural products seems to threaten the very feasibility of such screening. "All too often you find something that's been found before, that's been worked on before and that's been discarded before," says Newton. That view points to a deeper, underlying argument, which posits that the best natural products have already been found. The argument is that "it's like a seam of coal that's been extracted to oblivion. There's nothing left," according to Newton.

A fresh approach

The very existence of Warp Drive Bio is a rejection of that particular view. "To me, that makes no sense. It's a little like saying in physics in 1904, 'We know everything,'" says Alexis Borisy, interim CEO of the company and a partner at Third Rock. Warp Drive Bio's high-level vision is based on two highly entangled ideas: that classic microbiology offers a very narrow view of microbial diversity and that our understanding of the metabolic potential of microbes—nature's most abundant source of chemical diversity—is similarly restricted. "At most, 10% of microbes culture readily in the lab—and that's a high estimate," says Borisy. Moreover, under laboratory conditions, bacteria produce only about 10% of the range of metabolites they are capable of making. That implies that no more than 1% of the compounds that bacteria can make have ever been looked at.

What distinguishes natural products from synthetic compounds is that they are privileged structures. They have evolved to bind biological targets and elicit biological effects. Julian Davies, an emeritus professor at the University of British Columbia in Vancouver and the founder of TerraGen, coined the term 'parvome' to describe the full gamut of secondary metabolites—including polyketides, nonribosomal peptides, alkaloids, terpenoids, aminoglycosides and shikimate-derived molecules—that are produced in the natural world, often for signaling purposes[1]. From a drug developer's perspective, secondary metabolites can modulate difficult targets and readily enter cells, attributes that medicinal chemists cannot easily capture. "People forget [one thing] about Lipinski's rules,"

says Borisy, referring to Lipinski's Rule of Five, which defines the general physical properties shared by most small-molecule drugs. "The last of Lipinski's rules is that 'natural products violate all my rules'," Borisy says. "We don't understand what it takes to make a drug of 600 or 800 molecular weight, but nature does," he adds.

Moreover, once a promising natural product has been isolated and purified, it tends to require less chemical modification than synthetic compounds to acquire drug-like properties, but it often does require some modification to optimize its pharmacokinetic and safety profiles. That modification process can be challenging. "All the molecules have complicated structures, and the synthetic processes are complex," says Carmen Cuevas, director of research and development at Madrid-based PharmaMar, which has isolated novel structures from marine organisms and their microbial symbionts and successfully commercialized the marketed cancer drug Yondelis (trabectedin).

Obtaining sufficient quantities of material is also a major issue. "From my point of view, this is the biggest difficulty in this area," Cuevas says. Large-scale production of clinical-grade material can also be a significant challenge. "It's something which is largely overlooked," says Guy Carter, CEO of Carter-Bernan Consulting, a natural products consultancy based in New City, New York. "No one is paying attention to how you're going to produce the material." Funding for academic research in this area is not available, he says. "Nobody in pharma is doing this because pharma is doing other things—so who's doing it?" Yet Khosla says that this concern can be exaggerated. "People spend a lot of time sweating about that particular issue. I personally think that's the wrong way to look at it," he says. "If you can find a molecule that's worth making, you can make it."

A natural products hit parade

Although the portfolio of successful natural product exemplars has run thin of late, new drugs based on structures originally isolated from nature continue to gain approval, even if most have only modest commercial success. "The last real big one was probably FK506," says Newton, referring to tacrolimus, an immunosuppressive calcineurin inhibitor for preventing organ-transplant rejection, which is marketed as Prograf by Astellas Pharma of Tokyo. It was originally isolated from the soil bacterial species *Streptomyces tsukubaensis*. Carter identifies the novel lipopeptide antibiotic Cubicin (daptomycin), marketed by Cubist Pharmaceuticals of Lexington, Massachusetts, as another example. "The history there is a bit convoluted, but it is an example of revisiting a natural product that had been abandoned and making a decent product out of it," he says.

Other recently approved drugs based on natural product isolates include Gilenya (fingolimod), a sphingosine-1-phosphate (S1P) receptor agonist marketed by Basel-based Novartis for multiple sclerosis; Halaven (eribulin mesylate), a microtubule inhibitor marketed by Tokyo-based Eisai for metastatic breast cancer; and Istodax (romidepsin), a histone deacetylase inhibitor marketed by Celgene of Summit, New Jersey, as a treatment for cutaneous T-cell lymphoma. Natural products are also playing a part as cytotoxic moieties in the emerging field of antibody-drug conjugates. "That's certainly a popular area, and it looks to natural products for a payload," says Carter.

But even if the basic vision underpinning natural products research—that nature still offers a vast trove of valuable bioactive molecules—remains intact, finding a way to consistently realize that vision has proved elusive. Certain aspects of natural products screening have changed very little in recent decades. "Nobody has really changed the way microorganisms can be isolated from soil or seawater," MerLion's Buss says. Fermentation conditions have remained largely unchanged for the past 50 years, he adds, even though compound purification and analytical processes have improved.

Enter Warp Drive Bio

Warp Drive Bio, much like a previous generation of genomics companies, is turning the whole process on its head by hunting for genes and gene clusters associated with the production of secondary metabolites, rather than for bioactive molecules directly. "Now you can go and pick up a handful of dirt; you can sequence everything that's in that dirt; you can bioinformatically read that sequence to identify what the clusters are and you can chemoinformatically predict what those clusters will make," says Borisy. Davies's TerraGen was the first to undertake a metagenomics approach to mining the soil for new genes and new organisms. Although the company did find novel organisms, biosynthetic pathways and compounds, its efforts were hobbled by technological limitations, even after its acquisition by Cubist in 2000. "[The work] was not backed up by any sequencing. We had hoped we would be able to do more sequencing," Davies recalls.

TerraGen's general approach was, however, vindicated by genome sequence analyses of abundant producers of natural products, such as *Streptomyces* species, which indicated that the cryptic biosynthetic pathways that give rise to putative secondary metabolites tend to be grouped in clusters. Moreover, the genome sequences are predictive of the novel chemical structures they give rise to, even if they have never been expressed under laboratory conditions. "If you have a nonribosomal peptide sequence, you can pretty much predict what the structure is going to be," Davies says. "For a polyketide you can get a pretty good idea." Warp Drive Bio is also tapping into this concept. "You're looking for a 'chemomeme', a structural motif of a part of a molecule," Borisy says. Extrapolating the activity of a novel molecule from its structure remains a work in progress, however. "That, I would say, can be somewhat unpredictable," Davies says. "Activity testing is still relatively random."

Warp Drive Bio's general approach, as several observers have noted, is reminiscent of that pursued by Ecopia BioSciences, a Montreal-based company that was regarded as a pioneer in this area until Caprion Pharmaceuticals acquired it in 2007 to create Dorval, Canada–based Thallion Pharmaceuticals. Ecopia described its approach to using genomic analyses to infer novel secondary metabolites in a series of papers published in 2003–2006 (refs. 2–5). Company scientists were able to use genomic data to predict molecular structures that could be simply confirmed—rather than identified *de novo*—in HPLC profiles of fermentation extracts. They then sought to switch on the associated biosynthetic pathways by varying the fermentation conditions of the producing strains rather than engineering them into another host. "Their approach—it worked," says Mervyn Bibb, a professor of molecular microbiology at the John Innes Centre in Norwich, UK. "Now, with high-throughput sequencing, it would be so much more efficient."

Academic labs are able to follow the same basic approach, but not on an industrial scale. "It's a numbers game," says Bibb. "You need a platform that is going to generate not half a dozen but hundreds, if not thousands, of compounds, because the attrition rate is very high." High-throughput sequencing opens up that possibility, although it does not preclude the need to switch on silent biosynthetic gene clusters in either the original producing species or a suitable host. That task is not trivial. "These are very large gene clusters. Their regulation is very complex," says Bibb, who researches 'superhosts', bacterial species engineered to express large gene clusters. "It's a flux through a pathway."

Cambridge, UK–based Biotica has stayed faithful to the idea of metagenomics as applied to the polyketide synthase genes, which are associated with the biosynthesis of polyketides, a diverse family of secondary metabolites that has already yielded around 50 approved drugs (**Table 1**). The company bolstered its position in this field by acquiring intellectual property from Bristol-Myers Squibb after the latter's takeover of Biotica's erstwhile rival, Kosan of Hayward, California. Biotica recently disclosed its identification of sangamides, a class of cyclophilin inhibitors that have potential in interferon-free

Table 1 Natural product companies

Company	Product sources	Lead compound	Indication	Clinical status
AnalytiCon Discovery (Potsdam, Germany)	Plants and microbes	Libraries	Not applicable	Not applicable
Biotica	Polyketides	nPT-mTOR; nPT-CyP	Multiple sclerosis; lupus; hepatitis C	Preclinical
BioAlvo (Lisbon)	Marine bacteria isolated from hydrothermal vents	BLV0704	Central nervous system	Preclinical
InterMed Discovery	Microbial, marine and plant collections	IMD-026259	Central nervous system	Preclinical
Magellan BioScience (Tampa, Florida)	Marine microorganisms; fungi	Libraries	Not applicable	Discovery
MerLion Pharmaceuticals	Microbial, fungal and plant collections	Finafloxacin (oral)[a]	Infection	Phase 2
Nereus Pharmaceuticals	Marine microorganisms	Plinabulin	Oncology	Phase 2
NovoBiotic Pharmaceuticals (Cambridge, Massachusetts)	Unculturable microorganisms	Novel quinone; glycosylated macrolactam antibiotics	Infection	Preclinical
Noscira[b] (formerly Neuropharma; Madrid)	Marine organisms	Tideglusib (NP-12)	Central nervous system	Phase 2
Optimer Pharmaceuticals (San Diego)	Microorganisms	Fidaxomicin	Infection	Approved
PharmaMar[b]	Marine organisms	Yondelis (trabectedin)	Oncology	Approved in 70 countries, excluding US
Pharnext	Traditional medicinal plants	PXT03003[a]	Charcot-Marie-Tooth disease	Phase 2
Terpenoid Therapeutics (Coralville, Iowa)	Macaranga schweinfurthii	Not available	Oncology	Discovery
Thallion Pharmaceuticals[c]	Nonpathogenic microorganisms	TLN-4601	Oncology	Phase 2
Trius Therapeutics[d]	Marine microorganisms	Not available	Infection	Preclinical
Warp Drive Bio	Microbial collections	Not available	Not available	Discovery

[a]Synthetic compounds. [b]Majority shareholder is Zeltia Group. [c]Thallion also has a clinical-stage antibody development program. [d]Trius's lead drug, a synthetic antibiotic, is in phase 3 trials.

drug regimens for treating hepatitis C infection[6]. However, New York–based Pfizer last year exited a potential $195-million alliance, which Biotica originally entered with Wyeth (now owned by Pfizer), to develop rapamycin analogs for inflammatory conditions.

Another company, Paris-based Pharnext, is including natural products in its network-pharmacology research, which aims to decipher disease-associated biological networks and then use a cocktail of low-dose generic drugs and other bioactive compounds to restore the network to a healthy state. It has established a subsidiary in Phnom Penh, Cambodia, called Medikhmer, to explore that country's heritage of plant-based medicines. "We are making an inventory of all medicinal plants in Cambodia and their indications," says company CEO and cofounder Daniel Cohen. "Cinnamon has been used for many, many years in China and Cambodia to treat diabetes," he says.

Genomics is not the only prism through which natural products are being looked at anew. Although its main focus is on synthetic drug development, Trius Therapeutics also has an ongoing natural products discovery program, which exploits the company's capabilities in structure-based drug design. Trius has received funding from the US Department of Defense to screen for novel antibiotics in marine natural product libraries built up by William Fenical, a pioneer of marine natural products research at the Scripps Institution of Oceanography at the University of California, San Diego. The program aims to build on classical screening approaches. "Screening technology can get you so far—screening technology can get you a hit," says Karen Shaw, senior vice president of biology at Trius Therapeutics in San Diego. To get beyond that, the company is employing its ability to quickly obtain crystal structures of hit molecules bound to their corresponding targets. The resulting data provide structural and functional insights that can guide subsequent chemical design modifications. "If you use a different tool you can sometimes come up with a different answer," says Shaw.

Another San Diego firm, Nereus Pharmaceuticals, has already identified several anticancer compounds from Fenical's libraries, and it has moved two molecules into clinical development: marizomib, a proteasome inhibitor; and plinabulin, a vascular-disrupting agent. Nereus has several other novel structures in its preclinical pipeline, although its focus is now on clinical development rather than further discovery. "If we had the resources, we would have discovered numerous additional compounds—no question about it," says Nereus CEO Kobi Sethna. He does not link the present state of natural products research to any intrinsic shortcomings the field may have. "I don't think it's got anything to do with technology—it's to do with interest," he says. Big pharma simply no longer has any. "They don't have an interest because they don't have microbiologists on staff anymore to focus on this," claims Sethna.

The question is whether Sanofi's partnership with Warp Drive Bio heralds renewed interest in the area on the part of big pharma. The outcome of their alliance could have a major bearing on the evolution of natural products research. "In the end, it will all come down to results," says Newton. "A blockbuster coming out of Warp Drive Bio would probably revive natural products research considerably."

"We recognize there's a lot of challenge, and maybe it won't work," says Borisy. "For it to be productive, the pieces all have to work in a very efficient manner." So, although Warp Drive Bio is not exactly boldly going where no other biotech company has gone before, the startup is hoping it will get to hits faster and develop them further than its predecessors.

Cormac Sheridan, Dublin

1. Davies, J. & Ryan, K.S. *ACS Chem. Biol.* **7**, 252–259 (2012).
2. Zazopoulos, E. *et al. Nat. Biotechnol.* **21**, 187–190 (2003).
3. McAlpine, J.B. *et al. J. Nat. Prod.* **68**, 493–496 (2005).
4. Banskota, A.H. *et al. J. Antibiot. (Tokyo)* **59**, 168–176 (2006).
5. Banskota, A.H. *et al. J. Antibiot. (Tokyo)* **59**, 533–542 (2006).
6. Moss, S.J. *et al. Med. Chem. Commun.* doi:10.1039/C1MD00227A (2012).