REPRINT FROM SEPTEMBER 17, 2012

BioCentury

THE BERNSTEIN REPORT ON BIOBUSINESS™

Product Discovery & Development

Excited about cycling

By Chris Cain
Senior Writer

New synthesis and screening technologies and the allure of access to previously undruggable targets are driving an explosion of new company formation and deal-making around macrocycles and constrained peptides.

While it remains to be seen whether the *in vitro* promise of these platforms will translate into viable drug candidates, the clinical successes of macrocyclic natural products provide tantalizing hints of what could be achieved by the systematic exploration of this compound class.

Macrocycles may be capable of hitting new classes of targets because their ring structure causes them to behave differently than most small molecules.

Macrocycles are chemically defined by a ring structure of at least 12 atoms. They are typically 500-2,000 daltons in size. In contrast, most small molecules weigh less than 500 daltons, which has been considered the upper limit for a compound to be cell permeable and orally bioavailable.

"The easy targets have now been done; enzymes and GPCRs largely have been addressed through small molecules," said **Ensemble Therapeutics Corp.** CSO Nick Terrett. "Protein-protein interactions with large surface areas are very difficult to address with small molecules, and macrocycles are a very effective way of getting to a size that allows enough interaction with the protein."

A similar approach is to create constrained peptides by artificially linking linear peptides into specific structures possessing improved drug-like properties including cell permeability.

Ensemble is one of at least 12 biotechs developing platforms for synthesizing or screening macrocycles and constrained peptides *(see "Building Cycles," page 3)*.

As a group, these companies are enjoying a rush of attention from big pharma — there have been at least 27 discovery partnerships with biopharma partners in the last five years *(see "Cycle Shops," page 6)*.

"There is no doubt that within the last 3-4 years it has been a lot easier to get pharma's attention from a collaboration standpoint," said **Tranzyme Inc.** VP of IP and operations Mark Peterson. Tranzyme partnered its macrocycle discovery platform with **Bristol-Myers Squibb Co.** in 2009.

Indeed, collaboration looks to be essential to solving the puzzle of cell access. At this point, all the lead programs disclosed thus far are aiming at extracellular targets.

Editor's Note: This report is prepared in conjunction with the first SciBX Summit on Innovation in Drug Discovery & Development, being held in Boston this week by partners BioCentury and Nature Publishing Group. A concluding report from the summit will be published in SciBX on Oct. 4.

Natural history lessons

The model macrocyclic drug that inspired these development efforts is cyclosporine, a fungal-derived natural product developed as an immunosuppressant more than 30 years ago by Sandoz AG (now a unit of **Novartis AG**). Approved by FDA in 1983 as Sandimmune, the drug is an orally bioavailable and cell permeable 1,200-dalton cyclic peptide made up of 11 amino acids.

Cyclosporine suppresses the immune system by binding to cyclophilin A, which then drives the formation of a protein-protein interaction that inhibits calcineurin. NMR studies have shown that cyclosporine can adopt different conformations depending on its chemical environment, which may explain how it can possess drug-like properties despite its size.

"Cyclosporine is the poster child for this field because it violates Lipinski's Rules, and there are lots of other cyclic peptide natural products with molecular weight over 1,000 that are cell permeable. Since these compounds are well outside what is normally considered drug-like, their structures might suggest a path toward the design of synthetic, non-Lipinski compounds as we go after more challenging targets like protein-protein interactions," said Scott Lokey, associate professor of chemistry and biochemistry at the **University of California, Santa Cruz**.

In 1995, Christopher Lipinski consolidated observations from the literature into a set of five rules related to drug absorption. Lipinski's Rules state that molecules with molecular weights above 500 daltons, more than five hydrogen-bond donors or more than 10 hydrogen-bond acceptors are likely to be poorly absorbed. (*see BioCentury, Jan. 28, 2002*).

Terrett noted that cyclosporine's conformational flexibility allows it to adopt a form with increased hydrophobicity when the

See next page

Product Discovery & Development,
from previous page

molecule needs to get through a cell membrane.

This flexibility is "an inherent positive aspect of macrocycles, but it can be hard to computationally predict," he said.

Other naturally derived macrocycles include the antibiotics erythromycin and vancomycin, and the immunosuppressant tacrolimus.

However, natural macrocycles are chemically complex and difficult to synthesize, which has prevented the large-scale synthesis of compound libraries. In addition, computational challenges make SAR difficult.

Early attempts to design macrocycle drugs were based on screening peptide libraries against targets of interest, then attempting rational design of analogs with improved pharmacokinetic properties.

Doug Treco, CEO of **Ra Pharmaceuticals Inc.**, told BioCentury these efforts were largely unsuccessful. "There are almost no examples of anybody taking such a peptide and then using medicinal chemistry to successfully make it into an orally available drug," he said.

While peptide libraries could be generated using phage display and mRNA display, a major obstacle was that peptides could not be systematically cyclized or otherwise structurally constrained in a way that would confer drug-like properties.

"The limitation was that you could only use natural amino acids and generate disulfide-linked peptides," said Patrick Reid, CSO of **PeptiDream Inc.**

"Cyclosporine is the poster child for this field because it violates Lipinski's Rules, and there are lots of other cyclic peptide natural products with molecular weight over 1,000 that are cell permeable."

Scott Lokey, UC Santa Cruz

Peptide potpourri

To solve this problem, companies including Ra and PeptiDream set out to develop chemical methods to improve the drug-like properties of peptides by constraining their structure and increasing their diversity, often in conjunction with platforms that enabled the screening of large libraries of cyclic molecules.

PeptiDream was founded in 2007 based on technology developed by Hiroaki Suga at the **University of Tokyo** that enables incorporation of modified unnatural amino acids into mRNA display peptide libraries. This includes the incorporation of N-methylation, a modification that increases a peptide's ability to permeate cells (*see SciBX: Science-Business eXchange, Jan. 26*).

Reid told BioCentury PeptiDream has active target discovery deals with eight companies, including **AstraZeneca plc**'s **MedImmune LLC** unit, **Amgen Inc.**, **Mitsubishi Tanabe Pharma Corp.**, **Daiichi Sankyo Co. Ltd.**, **Pfizer Inc.**, BMS and Novartis. The remaining partnership is undisclosed.

He also said the company is planning an IPO on the Tokyo Stock Exchange next year.

Ra was founded based on technology from Jack Szostak's lab at **Harvard Medical School** and **Massachusetts General Hospital**. Ra also is using an mRNA display peptide library to display peptides that contain unnatural amino acids (*see BioCentury, July 16*).

Treco said differences in peptide library design are the key differentiating factor between the companies.

"We've made progress in generating unique molecules with a mixture of natural and unnatural amino acids," he said. "Our feeling is, if we can build in enough features that will confer lipophilicity and hydrophobicity in the right configurations to a molecule, we can probably work with molecules in the 700- to 1,100-dalton range."

Indeed, the challenge for macrocycle and constrained peptide technologies is not just to identify potent candidates, but to improve medicinal chemistry properties to make the peptides cell-penetrant and more drug-like.

For that reason, **Aileron Therapeutics Inc.** CSO Tomi Sawyer said his company decided to focus on structure-based design of stapled alpha helical peptides, rather than on extensive screening efforts.

"The beauty of it is that after five years and literally many thousands of stapled peptides, we have a pretty good knowledge base to define proprietary rules for how to lead optimize, in terms of length, charge and hydrophobicity," he said.

In 2010, the company signed the largest disclosed deal in the space when it partnered with **Roche** to develop stapled peptides to target intracellular protein-protein interactions. Aileron received $25 million in technology access fees and R&D support and is eligible for up to $1.1 billion in milestones, plus royalties (*see BioCentury, Aug. 30, 2010*).

Another player developing constrained peptides to inhibit protein-protein interactions is **Protagonist Therapeutics Inc.**, which is engineering disulfide rich peptides using a combination of approaches including computational design, phage libraries and directed evolution. CEO Dinesh Patel said disulfide rich peptides can improve stability *in vivo* and can offer "the potency of biologics and the pharmacokinetics of small molecules."

Protagonist has discovery deals with therapeutic peptide companies **Zealand Pharma A/S** and **Ironwood Pharmaceuticals Inc.**

In the past three years, two additional companies have been built around constrained peptide technologies. In 2009, **Bicycle Therapeutics Ltd.** was founded to generate bicyclic peptides containing natural amino acids using phage display. Bicyclic peptides contain two cyclic loops that can interact with their target, allowing them to exhibit bivalent binding similar to mAbs (*see BioCentury, Nov. 2, 2009*).

Bicycle obtained a non-exclusive license to use CLIPS (chemical linkage of peptides onto scaffolds) technology from **Pepscan Therapeutics B.V.** in phage display. The companies are collaborating on therapeutic peptide projects.

Pepscan CTO Peter Timmerman told BioCentury his company is seeking co-discovery partnerships to apply its technology to specific targets nominated by the partner. Partners include **Johnson & Johnson**, **Phylogica Ltd.**, Zealand and Alvos Therapeutics Inc. (now part of **Arrowhead Research Corp.**).

In 2010, **Lanthio Pharma B.V.** was founded to use a *Lactococcus lactis* expression platform to generate peptides structurally constrained by lanthionine bridges. CSO Gert Moll said the company expects to announce the close of a series A round

See next page

Product Discovery & Development,
from previous page

within the next few months (*see BioCentury, Feb. 20*).

Parallel synthesis

In parallel with efforts to develop cyclic peptides, at least half a dozen companies have developed new chemical approaches to synthesize smaller, non-peptidic macrocyclic compounds that could offer improved cell permeability and retain enough potency to block protein-protein interactions.

Polyphor Ltd. began its efforts using PEMfinder, a platform designed to synthesize cyclic peptides, but has since added to its capabilities by developing MacroFinder, a platform that can synthesize non-peptidic molecules 400-800 daltons in size. CSO Daniel Obrecht said molecules in this size range "intrinsically are a better starting point for achieving cell permeation and oral bioavailability and act more like small molecules."

Polyphor announced macrocycle discovery partnerships with Novartis in 2010 and with **Boehringer Ingelheim GmbH** this year (*see BioCentury, July 16*).

Peterson said Tranzyme took a similar tack with its MATCH

See next page

Building cycles

At least 12 companies are developing macrocycle and constrained-peptide synthesis technologies. (A) Disclosed financings; (B) Formed following the merger of Tranzyme Inc. with Neokima Inc. in 2003; *Source: BCIQ: BioCentury Online Intelligence; company press releases and websites*

Company	Platform technology	Lead program	Founded	Raised (A)
Aileron Therapeutics Inc.	Alpha-helical stapled peptides	ALRN-5281, a preclin long-acting growth hormone-releasing hormone (GHRH) agonist for adult growth hormone (GH) deficiency, HIV lipodystrophy and GH-deficient abdominal obesity	2005	$60M
Bicycle Therapeutics Ltd.	Phage display of bicyclic peptides	Undisclosed preclin programs	2009	$6.1M
Encycle Therapeutics Inc.	Amphoteric cyclization	Undisclosed preclin programs	2012	$1M
Ensemble Therapeutics Corp.	DNA-programmed chemistry for macrocycle synthesis	Preclin antagonist of interleukin-17 (IL-17) for autoimmune/inflammatory diseases	2004	$38.5M
Lanthio Pharma B.V.	Lanthionine constrained peptides produced in *Lactococcus lactis*	Preclin lanthionine-Ang(1-7) peptide targeting the MAS receptor to treat acute lung injury (partnered with **Tarix Pharmaceuticals Inc.**)	2010	$784K
Oncodesign S.A.	Nanocyclix medicinal chemistry	Disclosed preclin programs include inhibitors of kinases including leucine-rich repeat kinase 2 (LRRK2) to treat Parkinson's disease (PD) (partnered with **Ipsen Group** (Euronext:IPN; Pink:IPSEY); FMS-like tyrosine kinase 3 (FLT3; CD135) and germ cell associated 2 (haspin) for cancer; neurotrophic tyrosine kinase receptor (TRK) for pain; and CDC-like kinase (CLK) for CNS indications	1995	$4.6M
Pepscan Therapeutics B.V.	CLIPS (chemical linkage of peptides onto scaffolds)	Disclosed preclin programs include an HIV-fusion inhibitor (partnered with **Johnson & Johnson** (NYSE:JNJ))	2000	$14.8M
PeptiDream Inc.	mRNA display of modified cyclic peptides containing natural and unnatural amino acids	Undisclosed preclin programs	2006	ND
Polyphor Ltd.	MacroFinder macrocycle platform and PEMfinder (protein epitope mimetics) cyclic peptide platform	POL6326, a CXC chemokine receptor 4 (CXCR4) inhibitor in Ph II to treat cancer using hematopoietic stem cell (HSC) transplantation	1996	ND
Protagonist Therapeutics Inc.	Disulfide rich peptides (DRPs)	Disclosed preclin programs include orally stable interleukin-6 (IL-6) peptide antagonists and oral DRPs for inflammatory bowel disease (IBD)	2006	$9M
Ra Pharmaceuticals Inc.	mRNA display of modified cyclic peptides containing natural and unnatural amino acids	Preclin plasma kallikrein inhibitor for hereditary angioedema (HAE)	2008	$27M
Tranzyme Inc. (NASDAQ:TZYM)	MATCH (macrocyclic template chemistry)	TZP-102, an oral ghrelin agonist in Ph II for diabetic gastroparesis	2003 (B)	$140M

Product Discovery & Development,
from previous page

(macrocyclic template chemistry) platform.

"We wanted to stay within the small molecule realm," he said. "Unlike people now trying to explore the intermediate space, our focus was on trying to capture the advantages of macrocycles in terms of potency and selectivity but to do it within a small molecule package, between 400 and 600 daltons."

Ensemble's DPC (DNA-programmed chemistry) platform synthesizes non-peptidic macrocycles called Ensemblins, which are typically 600-1,000 daltons. The technology uses DNA as a template to generate macrocycles using synthetic building blocks.

Terrett said this approach can be used to generate highly diverse libraries of macrocycles containing different ring sizes and different domains, some of which are often found in naturally occurring macrocycles, such as polyketides and terpenoids.

Since April 2009, Ensemble has entered into three partnerships to use its macrocycle discovery platform with BMS, Pfizer and Roche's **Genentech Inc.** unit.

When Genentech chose Ensemble as a partner in June, James Sabry, VP of partnering at Genentech, specifically pointed to protein-protein interactions as an area where the company was interested in exploring the potential of Ensemblins *(see BioCentury, June 11)*.

GlaxoSmithKline plc obtained a similar DNA-encoded library technology when it acquired Praecis Pharmaceuticals Inc. in 2007. Barry Morgan, VP of molecular discovery research at GSK and former VP of chemistry at Praecis, said the platform has been used to generate over a billion macrocyclic molecules up to 1,000 daltons in size.

In 2010, **Oncodesign S.A.** entered the macrocycle development space when it in-licensed macrocyclic chemistry technology that had been developed at J&J by Jan Hoflack, who led J&J's European medicinal chemistry team.

Hoflack, now CSO and head of drug discovery at Oncodesign, told BioCentury the company is focusing on Nanocycles, which are macrocycles that weigh 300-400 daltons and are generally composed of ring structures of 12-18 atoms. Oncodesign is using its platform to develop selective kinase inhibitors and plans to eventually use the technology on other classes of targets.

Last week, Oncodesign signed a deal with **Sanofi** to discover and develop inhibitors against undisclosed kinase targets. In January, the biotech announced a deal with **Ipsen Group** to discover and develop leucine-rich repeat kinase 2 (LRRK2) inhibitors.

> ***"There is no doubt that within the last 3-4 years it has been a lot easier to get pharma's attention."***
>
> **Mark Peterson, Tranzyme**

The newest disclosed company in the space is **Encycle Therapeutics Inc.**, which was spun out of the **University of Toronto** by **MaRS Innovation** to commercialize the work of Andrei Yudin, a professor of chemistry at the university. The company is developing compounds dubbed *nacellins* using proprietary amphoteric cyclization reagents.

While the technology can be used to cyclize peptides or non-peptidic molecules, Yudin said he plans to focus on smaller ring structures of 9-18 atoms. The company was incorporated in January and has raised $1 million in seed funding largely from the **Quebec Consortium for Drug Discovery** (CQDM).

In addition to these non-peptidic macrocycle approaches, **Forma Therapeutics Holdings LLC** is attempting to design molecules that disrupt protein-protein interactions in cancer through a four-year partnership with Boehringer Ingelheim announced in January.

CEO Steve Tregay said the company is not specifically developing macrocyclic compounds but is aiming to address some of the same problems as macrocycles using its diversity-oriented synthesis (DOS) platform, which engineers extensive stereochemistry into small molecules to maximize the potential to disrupt protein-protein surface contacts.

Clinical aspirations

While much of the excitement over macrocycles is due to their potential to disrupt intracellular protein-protein interactions, every currently disclosed lead program in the space targets an extracellular protein. This reality reflects the challenge of developing a potent and cell-penetrant macrocyclic compound.

Tranzyme and Polyphor are the only companies with macrocyclic compounds

See next page

BioCentury
THE BERNSTEIN REPORT ON BIOBUSINESS™

Editorial & Research
Newsroom: pressreleases@biocentury.com
San Carlos, CA: +1 650-595-5333; Fax: +1 650-595-5589
Chicago: +1 312-755-0798; Fax: +1 312-755-0658
Washington, DC: +1 202-462-9582; Fax: +1 202-667-2922
Oxford, UK: +44 (0)1865-512184; Fax: +1 650-595-5589

www.biocentury.com

BioCentury

BioCentury®; the Bernstein Report on BioBusiness™; Because Real Intelligence is Hard to Find; BCIQ; The BioCentury 100; and The Clear Route to ROI are trademarks of BIOCENTURY PUBLICATIONS, INC.

Product Discovery & Development,
from previous page

in the clinic. Polyphor's lead compound is POL6326, a conformationally constrained peptide that antagonizes CXC chemokine receptor 4 (CXCR4; NPY3R). It is in Phase II testing to treat multiple myeloma (MM) using autologous transplantation of hematopoietic stem cells.

Tranzyme's lead compound is TZP-102, an orally administered ghrelin receptor agonist in Phase IIb testing to treat diabetic gastroparesis.

Two weeks ago, Aileron announced it hopes to start clinical development of its lead internally developed program in 2013. The compound, ALRN-5281, targets the growth hormone-releasing hormone (GHRH) receptor.

Aileron's most advanced protein-protein interaction disrupting stapled peptide is a dual Mdm2 p53 binding protein homolog (MDM2; HDM2) and Mdm4 p53 binding protein homolog (MDM4; MDMX) antagonist. The stapled peptide is in preclinical development and is partnered with Roche. Sawyer said Aileron plans to publish detailed results describing a stapled peptide developed as part of this program.

"It is the translation to the clinic that will be the critical next step for the field."

Barry Morgan, GlaxoSmithKline

The targets of preclinical lead programs that have been disclosed are also extracellular, including Ra's program targeting the plasma enzyme kallikrein, and Ensemble's program targeting interleukin-17 (IL-17), which is expected to enter the clinic in 2014.

"There is no question there is a simple approach when the target is extracellular and when you have IV administration, and there is no question the first stories will happen in that area," said Juerg Zimmerman, head of global discovery chemistry, oncology & exploratory chemistry & infectious diseases at Novartis.

"The most difficult area is intracellular targets, and there is a challenge to get these macrocycles into the cell, but there is no question it can be overcome," he said. "The real value of these molecules is that they will be able to interfere with protein-protein interactions."

GSK's Morgan voiced similar conclusions. "Most people engaged in drug discovery are accepting of the fact you can get macrocycles and peptides that are effective biochemically, in cells and *in vivo*. However, it is the translation to the clinic that will be the critical next step for the field," he told BioCentury.

Spiros Liras, head of medicinal chemistry in cardiovascular, metabolic and endocrine diseases at Pfizer, said the pharma's interest is in galvanizing the scientific community to solve the issue of cell permeability. "From the get go, we have decided that it wasn't going to be a topic that any single group could possibly solve alone," he said.

Pfizer is working with Lokey and collaborator Matt Jacobson, professor of pharmaceutical chemistry at the **University of California, San Francisco**, to computationally predict drug-like properties for macrocycles.

Separately, Lokey and Jacobson this year founded a macrocycle company that is operating in stealth mode.

See next page

BioCentury®

BioCentury's mission is to provide value-added business information & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

BioCentury Publications, Inc.
BioCentury International Inc.

Main Offices
PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

Chicago: +1 312-755-0798; Fax: +1 312-755-0658

Washington, DC: +1 202-462-9582; Fax: +1 202-667-2922

Oxford, UK: +44 (0)1865-512184; Fax: +1 650-595-5589

www.biocentury.com

Corporate
Karen Bernstein, Ph.D., Chairman & Editor-in-Chief
David Flores, President & CEO
Thomas Carey, Vice President/Commercial Operations
Bennet Weintraub, Vice President/Administration & CFO
Kris Hall, Executive Administrator

Eric Pierce, Publisher
Tim Tulloch, Associate Publisher
Julia Kulikova, Senior Director/Operations
Jeffrey Fitzgerald, Director/Multimedia Operations
Jamie Gould, Director/Multimeida Business Development
Greg Monteforte, Director/Marketing & Promotional Services
Susan Morgan, Director/Administration & Human Resources
Jenny Nichols, Production

Subscriber Services
Subscriber Services: subscribe@biocentury.com
Account Managers: Orlando Abello, Matt Krebs, Michelle Ortega, Ron Rabinowitz

Business Services
Accounting & Billing: finance@biocentury.com
Conferences: conferences@biocentury.com
Data Solutions Support: support@biocentury.com
Privacy Policy: privacy@biocentury.com
Reprints/Permissions: businessservices@biocentury.com

Privacy & Advertising
In accordance with its Privacy Policy, BioCentury does NOT sell its customer information or usage data to third parties.

BioCentury does NOT sell advertising in the *BioCentury, the Bernstein Report on BioBusiness* or *BioCentury Week in Review*. BioCentury is pleased to acknowledge its conference partners and sponsors through unpaid promotional announcements in its publications. BioCentury MAY accept paid promotional messages from sponsors, which are displayed only on BioCentury's websites.

Product Discovery & Development,
from previous page

COMPANIES AND INSTITUTIONS MENTIONED

Aileron Therapeutics Inc., Cambridge, Mass.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Arrowhead Research Corp. (NASDAQ:ARWR), Pasadena, Calif.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bicycle Therapeutics Ltd., Cambridge, U.K.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568), Tokyo, Japan
Encycle Therapeutics Inc., Toronto, Ontario
Ensemble Therapeutics Corp., Cambridge, Mass.
Forma Therapeutics Holdings LLC, Watertown, Mass.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Ipsen Group (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France
Ironwood Pharmaceuticals Inc. (NASDAQ:IRWD), Cambridge, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Lanthio Pharma B.V., Groningen, the Netherlands
MaRS Innovation, Toronto, Ontario
Massachusetts General Hospital, Boston, Mass.
MedImmune LLC, Gaithersburg, Md.
Medivir AB (SSE:MVIR B), Huddinge, Sweden
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508), Osaka, Japan
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Oncodesign S.A. (Dijon, France)
PeptiDream Inc., Tokyo, Japan
Pepscan Therapeutics B.V., Lelystad, the Netherlands
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Phylogica Ltd. (ASX:PYC; Xetra:PH7), Subiaco, Australia
Polyphor Ltd., Allschwil, Switzerland
Protagonist Therapeutics Inc., Redwood City, Calif.
Quebec Consortium for Drug Discovery (CQDM), Nuns' Island, Quebec
Ra Pharmaceuticals Inc., Boston, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY)
Tranzyme Inc. (NASDAQ:TZYM), Durham, N.C.
University of California, Santa Cruz, Calif.
University of California, San Francisco (UCSF), Calif.
University of Tokyo, Tokyo, Japan
University of Toronto, Toronto, Ontario
Zealand Pharma A/S (CSE:ZEAL), Glostrup, Denmark

Cycle shops

At least 27 corporate drug development partnerships using macrocycle technologies and constrained peptide technologies have been announced since 2007, with several pharmas sampling more than one technology. **Bristol-Myers Squibb Co.** (NYSE:BMY) has disclosed deals for three different technologies, while **Roche** (SIX:ROG; OTCQX:RHHBY), **Pfizer Inc.** (NYSE:PFE), **Novartis AG** (NYSE:NVS; SIX:NOVN) and **Zealand Pharma A/S** (CSE:ZEAL) each have two. *Source: BCIQ: BioCentury Online Intelligence; company press releases and websites*

Company	Deal description	Partner	Financial terms	Date
Aileron Therapeutics Inc.	Discover, develop, and commercialize stapled peptide therapeutics	**Roche** (SIX:ROG; OTCQX:RHHBY)	$25M technology access fees and R&D support; $1.1B in milestones, plus royalties	Aug-2010
Ensemble Therapeutics Corp.	Use DNA-Programmed Chemistry technology to screen and identify macrocyclic Ensemblins against partners' undisclosed targets	**Bristol-Myers Squibb Co.** (NYSE:BMY)	$5M up front; $7.5M in research support; $30M in milestones per compound, plus royalties	Apr-2009
		Genentech Inc./Roche (SIX:ROG; OTCQX:RHHBY)	Undisclosed upfront payments, milestones and royalties	May-2012
		Pfizer Inc. (NYSE:PFE)	Undisclosed upfront payments, research funding, milestones and royalties	Jan-2010
Lanthio Pharma B.V.	Exclusive, worldwide rights to lanthionine-Ang(1-7) peptide targeting MAS receptor in preclinical development for acute lung injury	**Tarix Pharmaceuticals Ltd.**	Undisclosed milestones and royalties	Feb-2012
Oncodesign S.A.	Discover and develop compounds using Nanocyclix medicinal chemistry technology; Nanocyclix is based on macrocyclic chemistry technology from **Johnson & Johnson** (NYSE:JNJ)	**Ipsen Group** (Euronext:IPN)	Undisclosed technology access fee and funding; €115M ($148.8M) in opt-in fees and milestones	Jan-2012
		Sanofi (Euronext:SAN; NYSE:SNY)	€130M ($166.2M) technology access fee and milestones, plus low single-digit royalties	Sep-2012

See next page

Cycle Shops,
from previous page

Company	Deal description	Partner	Financial terms	Date
Polyphor Ltd.	Use Macrofinder and/or Protein Epitope Mimetics (PEM) finder technologies to identify macrocyclic molecules	**Allergan Inc.** (NYSE:AGN)	$7M up front; $61M in milestones, plus royalties.	Oct-2008
		Axxam S.p.A. (ion channel targets)	ND	Apr-2010
		Axxam S.p.A. (glucagon-like peptide-1 receptor (GLP-1R) modulators)	Funding from Eurostars grant	Jul-2011
		Boehringer Ingelheim GmbH	Undisclosed upfront payments, research funding, milestones and royalties	Jun-2012
		Novartis AG (NYSE:NVS; SIX:NOVN)	Undisclosed upfront payments, research funding, milestones and royalties	May-2010
PeptiDream Inc.	Use cyclic peptide mRNA display technology to identify and develop hits against partners' undisclosed targets	**Amgen Inc.** (NASDAQ:AMGN)	ND	Oct-2010
		Bristol-Myers Squibb Co. (NYSE:BMY)	ND	Nov-2010
		Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568)	ND	Jul-2012
		MedImmune LLC/AstraZeneca plc (LSE:AZN; NYSE:AZN)	ND	Jul-2007
		Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508)	ND	Dec-2010
		Novartis AG (NYSE:NVS; SIX:NOVN)	ND	Aug-2010
		Pfizer Inc. (NYSE:PFE)	ND	Dec-2010
Pepscan Therapeutics B.V.	Develop peptides using constrained peptide chemistry technology	Alvos Therapeutics Inc. (now part of **Arrowhead Research Corp.** (NASDAQ:ARWR))	Undisclosed research funding, milestones and royalties	Jan-2011
		Bicycle Therapeutics Ltd.	ND	Nov-2009
		Johnson & Johnson (NYSE:JNJ)	Undisclosed research funding, milestones and royalties	Sep-2010
		Phylogica Ltd. (ASX:PYC; Xetra:PH7)	ND	May-2011
		Zealand Pharma A/S (CSE:ZEAL)	Fund a portion of the work through a €860K ($1.2M) EUREKA Eurostars grant; no other details disclosed	Mar-2011
Protagonist Therapeutics Inc.	Discover and develop disulfide rich peptides (DRPs) against partners' undisclosed targets	**Ironwood Pharmaceuticals Inc.** (NASDAQ:IRWD)	Undisclosed upfront payments, milestones and royalties	Jan-2011
		Zealand Pharma A/S (CSE:ZEAL)	Undisclosed upfront payments, milestones and royalties	Jun-2012
Tranzyme Inc. (NASDAQ:TZYM)	Macrocyclic Template Chemistry (MATCH) technology to discover, develop and commercialize macrocyclic compounds	**Bristol-Myers Squibb Co.** (NYSE:BMY)	$10M up front; additional research funding; $80M in milestones per target program, plus tiered royalties	Dec-2009