



Technology Focus

The protein engineers

BioCentury This Week

Cover Story

A growing number of protein engineering companies are aiming to create a new wave of protein therapeutics with improved effectiveness while avoiding IP entanglements.

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The protein revolution began with recombinant production methods, which were soon followed by the use of protein fragments and fusion proteins. Subsequent innovations such as molecular evolution have added high throughput technology for selecting mutant proteins with improved activity.

While all of these techniques are still in use, the newest wave of protein engineering companies is pressing forward with platforms designed to improve the safety, biodistribution, activity and frequency of dosing of protein therapeutics while, in some cases, offering the promise of lower manufacturing costs.

The specifics of each technology may vary but, in most cases, the platforms are variations on a single theme: engineering a molecular scaffold to have new or better medicinal properties (see "Engineering Space," A2).

Some companies have chosen to engineer novel activity into proteins that have not yet been used as biotherapeutics. In this vein, several have platforms to create antibody-like molecules using proteins that do not resemble antibodies. Other companies are improving or engineering in additional activity to existing proteins. This group includes those that have developed methods to increase the therapeutic properties of antibodies.

With a laundry list of proteins on the market, protein engineering platforms are tailor-made to mine value from clinically validated targets. But companies that have platforms to increase antibody specificity

'It is time to build an entire industry on synthetic proteins based on novel scaffolds.'

— Martin Poehlchen of Pieris

or modulate antibody effector function also are going after new targets. Likewise, companies that are using novel protein scaffolds to mimic the activity of antibodies also can use the same technology to create highly potent peptide agonists.

Engineering value

Given the success of drugs like Aranesp darbepoetin from Amgen Inc. (AMGN, Thousand Oaks, Calif.), no one is likely to dismiss the potential value of second-generation protein products. AMGN developed Aranesp by changing the amino acid backbone of the first-generation epoetin molecule and adding sialic acid to it (see *BioCentury*, Feb. 22, 2000).

Indeed, the prospective value of a protein engineering platform has been illustrated on more than one occasion. In 2000, Human Genome Sciences Inc. (HGSI, Rockville, Md.) acquired Principia Pharmaceutical Corp. (Norristown, Penn.) for \$120 million to develop protein therapeutics using Principia's recombinant albumin fusion technology. The technology fuses therapeutic proteins with albumin to prolong activity and reduce side effects by

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The Scottish Team

Regional Host Scottish Enterprise and its initial slate of Host Committee Members for BioEquity Europe 2004. Please see announcement following A20.

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allowing lower dosing.

Late last year, Eli Lilly and Co. (LLY, Indianapolis, Ind.) said it would pay even more — \$400 million — to acquire Applied Molecular Evolution Inc. (AMEV, San Diego, Calif.). LLY plans to use AMEV's directed evolution technology to develop improved versions of both marketed and novel biotherapeutics (see *BioCentury*, Nov. 25, 2003).

As protein engineering technologies have begun to proliferate, venture capitalists are looking at their potential to provide second-generation products with a better therapeutic profile and the potential to side-step intellectual property entanglements.

"A lot of the research has been done beginning 10 years ago. Now we're entering the phase where the research is mature enough to enter product development," said Hans Kuepper of Global Life Sciences Ventures (Munich, Germany).

Perhaps the biggest selling point is that protein engineering plays provide access to targets from which companies would otherwise be locked out. "IP is quite a minefield for antibodies — it's very diffi-

cult. But using a scaffold that can do basically the same work is an interesting prospect. So the potential upside for companies like Pieris is very big," said Kuepper. Pieris Proteolab AG uses the protein anticalin as a scaffold to generate its therapeutics.

But even if a technology provides access to a target by circumventing IP issues, that does not mean it is necessarily a platform worth investing in. "You have to come up a compound with improved performance," said Mark Carthy of Oxford Bioscience Partners (Boston, Mass.). In the protein engineering space, Oxford has invested in Trubion Pharmaceuticals Inc.

Part of the potential of protein engineering stems from the capability to go after a target in a unique way, which was a driver for Burrill & Co.'s investment in Catalyst Biosciences Inc., which engineers catalytic proteases to attack targets implicated in disease.

"There are not a lot of other mechanisms out there that basically chew up the protein or receptor that's expressed on the surface of the cell like proteases can," said Burrill's Bryant Fong.

By contrast, he said, "other companies are working on what are sort of better

antibodies — that's their shtick — better affinity, avidity, longer half-lives, etc. Basically, those companies offer ways to circumvent existing patents. They're building a better mousetrap."

'Effecting' function

Because antibodies comprise a sizable wedge of the biotherapeutics pie, it is no surprise that several private companies have emerged with engineering platforms that are focused at least in part on antibodies.

The overall structure of an antibody is a "Y" shape, with the antigen-binding regions at the end of each arm. The base of the antibody is termed the Fc region, which contains the parts of the antibody responsible for triggering effector function, the response to an antibody carried out by the immune system (see "Fc Function," A3).

While an antibody's affinity and specificity for its target play a large role in its activity, some antibodies — primarily those targeting cellular receptors — also rely on effector function. Thus, in addition to focusing on the antigen-binding region of antibodies, companies also are tailoring the Fc region to fit the desired profile.

Expressed primarily on cells in the immune system, all Fc gamma receptors bind to the same region of the antibody, which is located on the amino terminal portion of the antibody Fc region and the adjoining hinge region. An overlapping yet separate site on the antibody Fc region serves to dock complement C1q and initiate complement-dependent cytotoxicity (CDC). Indeed, although antibodies themselves are not usually cytotoxic, they can mediate cell death through either (CDC) and/or antibody-dependent cellular cytotoxicity (ADCC) through their Fc region.

"There is value in increasing effector function, but there is also value in decreasing effector function," said Bassil Dahiyat, CSO of Xencor Inc.

The company uses its Protein Design Automation (PDA) technology, a structure-based protein engineering platform, to alter the Fc region of antibodies. PDA couples computer algorithms with the three-dimensional structure of a protein and considers all possible changes at a desired position of a protein to generate new versions of the protein that have the desired characteristics.

"This is plug-and-play technology," said Dahiyat. "We are creating a suite of

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Engineering space

Selected private companies with protein engineering platforms.

Company	Platform
Affibody	Uses protein scaffold based on a domain in Protein A to develop antibody-like molecules
Ambrx	Adds non-encoded amino acids to proteins, enabling the synthesis of proteins with chemical diversity
BioRexis	Uses protein scaffold based on transferrin to develop antibody-like molecules, make fusion proteins and receptor agonists
Borean	Uses protein scaffold based on a C-type lectin to develop antibody-like molecules, protein trimerization technology
Catalyst	Engineers proteases to degrade targeted molecules
KaloBios	Develops improved methods for antibody humanization
Phylos	Uses protein scaffold based on a domain in fibronectin to develop antibody-like molecules
Pieris	Uses protein scaffold based on lipocalin to develop antibody-like molecules
Scil	Uses protein scaffold based on gamma-crystallin to develop antibody-like molecules
Selecore	Uses protein scaffold based on cysteine knots to develop antibody-like molecules
Trubion	Engineers desired effector function into its SMIP antibody-like proteins
Xencor	Uses its PDA technology to engineer desired effector function into antibodies and create dominant-negative proteins and proteins with enhanced properties

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Fc region variants that you can use to modulate the activity of any antibody for any antigen.”

Xencor (Monrovia, Calif.) has used its PDA technology to generate more stable versions of cytokines and growth factors as well to create dominant-negative proteins, which abrogate the function of their natural counterparts (see *BioCentury*, June 3, 2002 & Sept. 29, 2003). But the company now is focused on its antibody program, according to Dahiyat, “because it is an area that is ripe to be mined right now.”

Earlier this month, Protein Design Labs Inc. (PDLI, Fremont, Calif.) signed a deal to apply Xencor’s XmAb technology to certain of PDLI’s preclinical cancer antibodies (see *BioCentury*, Jan. 19).

Using XmAb, Xencor says it has tweaked antibody affinity for Fc gamma receptors to design versions of Herceptin trastuzumab and Rituxan rituximab that show 100-fold improvement in ADCC in culture.

Xencor hopes this in vitro activity will translate to clinical benefit, and there are clinical data to bear out this approach. Specifically, there is evidence from human trials that a particular allotype of the Fc gamma receptor IIIA (CD16A), allotype I58V, has a higher affinity for the Fc region of IgG and translates into increased activity.

In a study in 49 patients receiving Rituxan for previously untreated follicular non-Hodgkin’s lymphoma (NHL), the objective response rates at 2 and 12 months were 100% and 90%, respectively, in CD16A I58V homozygous patients compared with 67% and 51%, respectively, in patients with a CD16A I58F

allotype (p=0.03 for both time points).

Genentech Inc. (DNA, South San Francisco, Calif.) and Roche (SWX:ROCZ, Basel, Switzerland) market Herceptin for breast cancer. Biogen Idec Inc. (BIIB, Cambridge, Mass.), DNA and ROCZ market Rituxan for NHL.

Xencor also is using its technology to alter Fc binding to the neonatal Fc receptor (FcRn), which regulates antibody half-life, and to C1q, which triggers the complement cascade leading to the perforation of cell membranes, with the idea that different antibody applications mandate different Fc requirements.

“You might want to develop an antibody with an Fc region that has both ADCC and CDC capabilities, only ADCC, or neither, depending on the application and target,” said Dahiyat. “We can increase the ADCC by two logs and have little to no effect on CDC.”

Another company that is engineering custom effector function is Trubion (Seattle, Wash.). Trubion does this with its Small Modular Immuno-Pharmaceuticals (SMIPs), which are composed of the heavy and light chain variable regions — the region of antibodies involved in antigen binding — as well the Fc region.

“The structure of SMIPs differs from that of antibodies, but SMIPs still have a high affinity for their targets,” said President and CEO Peter Thompson. “We can modify SMIPs to have a different balance of effector functions.”

At the American Society of Hematology meeting last year, Trubion presented data for its TRU-015 anti-CD20 compound and its TRU-016 anti-CD37 compound (see *BioCentury*, Dec. 15, 2003).

“TRU-015 is more potent at B cell depletion than rituximab in a standard primate model, but is attenuated in functions that can cause side effects,” Thompson said. TRU-015 has been engineered to have increased ADCC activity and also seems to be insensitive to the CD16A allotype. Trubion plans to file an IND in the second half of this year.

Fc function

Selected Fc receptors, with their specific functions. Though antibodies themselves are not often cytotoxic, under certain circumstances they can lead to cellular death, which can increase efficacy but may compromise safety.

Antibody cytotoxicity is mediated through the Fc region, not by the region that binds antigen. Antibodies bound to the surface of a cell or pathogen can cause lysis by binding at the Fc region to complement C1q, leading to the formation of a protein complex that perforates the cell membrane.

The Fc region also provides communication with the cellular arm of the immune system through its interaction with Fc receptors. Antibodies bound on the surface of cells can promote antibody-dependent cellular cytotoxicity (ADCC), which is mediated by other cells of the immune system, such as natural killer (NK) cells. NK cells are activated by binding the cell-bound antibody via the Fc receptor on the surface of the NK cell.

Family member	Function
Fc gamma receptor I (CD64)	Cellular activation, phagocytosis
Fc gamma receptor IIA (CD32A)	Cellular activation, phagocytosis
Fc gamma receptor IIB (CD32B)	Inhibitory signal
Fc gamma receptor IIIA (CD16A)	Cellular activation, ADCC
Fc gamma receptor IIIB (CD16B)	Phagocytosis
Neonatal Fc receptor (FcRn)	IgG recirculation

Perfecting humanization

While some companies are addressing the relatively new tack of modifying effector function, KaloBios Inc. (Mountain View, Calif.) feels it has a new solution to one of the long-standing problems in antibody development: making high affinity antibodies that the immune system won’t recognize as foreign.

“We can take antibodies that are not fully human and are either marketed or in late-stage clinical development and quickly make a fully human antibody,” said President Mark Alfenito. “When we do that we can also improve some of the qualities that were lacking in the first generation product.”

According to Alfenito, the pitfall of both phage display and mouse technologies for making human antibodies is that these techniques actually replace the initially discovered antibody with a new antibody that binds the same target. As a result, functionality can be compromised by altered affinity, on-rate or off-rate.

“In some cases, the starting affinity of the murine antibody is on the cusp of efficacy. If you lose any efficacy making the human antibody created by phage display or mouse technologies, it’s commercially untenable,” he said.

PDLI, which has the dominant first-generation humanization technology, uses bioinformatics to identify and preserve the functional components of the original mouse antibody and genetically engineer the rest into the human form.

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KaloBios uses components of the original mouse antibodies to generate an equivalent human FAb antibody library that accurately reflects the components of the starting mouse library.

Alfenito declined to be more specific, making it difficult to compare KaloBios' technology to PDLI's. However, he said KaloBios creates its own libraries without using others' IP. "Existing intellectual property guards primer-driven amplification of antibodies — basically using PCR to make antibody libraries," he said. "Instead, we used techniques in the public domain in a novel combination."

To select antibodies, the company uses a modified bacterial expression system that links the molecular target or targets being studied with beta lactamase, a marker that confers antibiotic resistance.

KaloBios then links an inhibitor of beta lactamase to the original mouse antibody. The inhibitor has been engineered so that its affinity for the selector is so low that it isn't able to find the selector on its own. However, if the antibody binds the target, the inhibitor is able to bind and turn off the beta lactamase. When KaloBios screens its human antibody library in its bacterial selection system, human antibodies that bind displace the inhibitor-bound mouse antibody and the cell survives.

"Some antibodies that bind to the target bind better than the starting mouse antibody and we know they have the same selectivity because they are binding the same epitope — the same location on the target," Alfenito said. "The result is a human antibody with the same bioactivity and equal or higher affinity than the starting molecule."

By modifying the conditions of the selection assay, KaloBios can select for specificity, on-rate, off-rate and other characteristics.

According to KaloBios, the process takes about a third of the time needed to humanize antibodies using other technologies. "We can do it in four to eight weeks," said Alfenito.

Though it utilizes a bacterial component, KaloBios's system doesn't share the limitations of most bacterial systems, which generally are not able to recreate post-translational modifications. "Even though our system seems to be a completely bacterial-based system, it's not. We're not limited to bacterial post-translational modifications. We can select for any dec-

'We can do chemistry on proteins in a manner similar to that done with small molecules'

— Tom Daniel of Ambrx

oration you can think of," said Alfenito, who declined to discuss how this is done.

In addition to working with partners, KaloBios is looking to improve on existing antibody products for its own account. It aims to move two products — one anti-neoplastic and one anti-infective agent — into the clinic in 2005.

In addition to its discovery engine, KaloBios is gaining clinical development expertise through its planned merger with Celscia Therapeutics Inc. (South San Francisco, Calif.) (see *BioCentury*, Jan. 19). Celscia's management is experienced in developing antibodies and is working on in-licensing antibodies that are in or near clinical development.

The in-licensed compounds are intended to be developed as is, not modified using KaloBios' technology. The intention is that they will give the company a more advanced product or two while its own antibodies work their way through development.

Un-antibodies

In order to be effective, antibodies must be able to get to the appropriate site in the body, such as a tumor. But their relatively large size can be a barrier. To get around this problem, several companies are pursuing platforms that produce antibody-like function without using an antibody protein scaffold, creating proteins that have improved biodistribution and half-life as well as the potential for using cheaper production methods.

"The biodistribution of macromolecules is basically governed by two properties: diffusion and convection," said Trubion's Thompson. "In many cases, such as for tumors, convection is against you, so the real driver is diffusion." Convection is determined by pressure gradients, and tumors typically have higher hydrostatic pressure than the surrounding tissue.

Diffusion depends strongly on the size of the molecule. Trubion's SMIPs, which are roughly a third the size of antibodies,

have about a 10-fold increase in the coefficient of diffusion, Thompson said. "What we end up with is a compound that has different biodistribution. The kinetics are enhanced, and the half-life of SMIPs don't appear to be any shorter than that of antibodies."

At roughly half the size of an antibody, Trans-bodies from BioRexis Pharmaceutical Corp. also should have better tissue penetration than antibodies. Trans-bodies are antibody-like compounds based on an engineered version of transferrin, an extremely abundant protein found in the blood.

To create Trans-bodies, BioRexis (King of Prussia, Penn.) uses publicly available phage display technology to select peptides that bind the specified target with high affinity, and engineers the resulting peptides into surface-exposed loops in transferrin, yielding a macromolecular complex with high affinity to the specified target.

"There are multiple surface loops in the structure of transferrin that can be used to engineer in peptides without changing the overall structure of the protein," said CSO Christopher Prior. "We are not trying to mimic the structure of how antibodies bind. In fact, I don't know if it could even be done."

"We have looked at engineering in peptides at two of these loops, and this yields a protein with high biological potency, but we could put in more," added CEO David King.

As transferrin lacks an Fc region, BioRexis is not initially pursuing antibody applications that require cytotoxicity. "Our current application is towards Trans-bodies that block the function of the target and do not need to have an effector function," King said. "However, we do have the capability to use our technology to create bifunctional Trans-bodies — engineering in a peptide that seeks out the target and another that has a killing function."

Given transferrin's serum half-life of 14-17 days, Trans-bodies offer the potential to be dosed less frequently than antibodies. In addition, the variant of transferrin that BioRexis uses is not glycosylated, meaning production can be done in yeast, which is relatively inexpensive compared to mammalian cell cultures.

In addition to producing antibody-like products, protein scaffolds can be used to alter the activity and pharmacokinetics of other proteins and peptides.

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Thus, much as HGSI is doing with albumin, BioRexis also uses transferrin to create either N- or C-terminal fusions of peptides/proteins, giving the resulting compounds a much longer half-life.

BioRexis also has programs to integrate agonist peptides into the loops of transferrin. "The resulting proteins are slower to bind receptors, but elicit potent biological responses," said Prior.

While the properties of transferrin increase the stability and pharmacokinetics of the original peptide, transferrin also adds a favorable three-dimensional context to peptide agonists. "The spatial arrangement of the loops is such that the peptides are held in structural configurations that can drive receptor dimerization, leading to activation," Prior said. BioRexis hopes to have its lead product in the clinic this year.

Transferrin is not the only protein amenable to being used as an antibody-like compound. Pieris Proteolab AG uses anticalin as its scaffold (see *BioCentury*, Oct. 15, 2001).

Anticalins are derived from naturally occurring proteins called lipocalins. Lipocalins are small, robust proteins often involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Similar to transferrin, lipocalins have a stable backbone with four loops extending from the outer surface of the molecule that can be modified to be very similar to those of an antibody.

"Protein engineering and novel protein scaffolds will need some time and substantial investment before changing the markets," said Martin Poehlchen, CEO of Pieris (Freising, Germany). "But I believe that it is time to build an entire industry on synthetic proteins based on novel scaffolds similar to the success story of synthetic organic molecules for therapy."

Pieris is pursuing two strategies: using naked anticalins with an antagonistic mode of action, and using anticalins as targeting vehicles fused to cytotoxic agents or natural toxins. The company has compounds in preclinical research for both strategies, with a focus in oncology and cardiovascular diseases.

Affibody AB (Stockholm, Sweden) is using the Fc binding domain of Protein A from *Staphylococcus aureus* as its scaffold. "It's a protein that has been used to create phage display libraries and lends itself very readily to protein engineering," said Birger Jansson, director of research.

To create Affibodies, the company uses two-hybrid and phage display technologies as well as directed mutagenesis. "It's a very short cycle to make the mutants and reproduce them by comparison with antibodies," said CSO Lars Abrahmsen.

Because Affibodies are about 25 times smaller than antibodies, Affibody can construct single compounds containing multiple Affibody monomers coupled together to achieve greater target binding, without creating a molecule that is too large to be practical.

"We can make multimers up to pentamers containing five different Affibody molecules attached to each other," said Fredrik Nilsson, project manager of biotherapeutics.

Affibody's most advanced therapeutic targets an undisclosed cancer antigen.

Enzymatic engineering

Like other engineering companies, Catalyst (San Francisco, Calif.) is modifying natural protein scaffolds to create proteins with altered functionality. However, its starting point is proteases, which the company engineers to specifically cleave a target the protease normally wouldn't degrade.

Although the techniques used to modify proteases are not novel or proprietary, that does not mean the process has been reduced to a commodity. "Our protein engineers know how to alter the specificity of proteases so that they can recognize key target proteins for a disease," said Charlie Craik, Catalyst founder and a professor of pharmaceutical chemistry, pharmacology, biochemistry and biophysics at UCSF. "It's really know-how — similar to structure-based drug design."

But Catalyst does have proprietary technology that it says allows it to evaluate the specificity of an altered protease very rapidly. The screening technique is conceptually similar to microarrays. "You make combinatorial libraries of about half a million peptides and array them spatially with reporter groups on them. So when a protease cleaves a particular peptide you can immediately determine which peptide it is. As a result, you can get a read-out of what a protease recognizes."

The actual screening takes about 20 minutes, according to Craik. "It's making the proteases that's the limiting step." Catalyst creates these via mutagenesis and runs multiple cycles of mutagenesis and screening until it gets the desired selectivity.

Catalyst is predominantly focused on cancer, "especially where antibodies and small molecules have failed," Craik said. "If the cause is a protein/protein interaction, then it can be hard to make a small molecule that can interfere with that. At the same time, sometimes antibodies are limited because of their large size, since they can't penetrate the tumor."

In addition, Craik said the catalytic nature of proteases give them an advantage over antibodies. "An enzyme has multiple turnovers — it recognizes a molecule and converts it to something else in a cycle that regenerates the enzyme," he said. "The protease will recognize its substrate and cleave it, sometimes in multiple pieces. So an enzyme can turn over 1,000 molecules per minute. An antibody can bind to one molecule. It's a machine gun compared to a shotgun."

Building on nature

If protein engineering faces limitations, the constraint lies within the finite repertoire of the 20 naturally encoded amino acids that are the building blocks of proteins. Ambrx Inc. (San Diego, Calif.) has broken down this boundary with a platform that is able to specifically incorporate non-natural amino acids with the desired chemical properties. This can result, for example, in increased binding affinity.

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'IP is quite a minefield for antibodies — it's very difficult. But using a scaffold that can do basically the same work is an interesting prospect.'

— Hans Kuepper of
Global Life Science

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“The technology enables us to load a chemical species as a 21st, non-encoded, amino acid into defined positions in recombinant proteins,” said CSO Tom Daniel. In order to be able to insert non-encoded amino acids into proteins, Ambrx licensed methodology from co-founder Peter Schultz’s lab at Scripps Research Institute in La Jolla, Calif. It selects the desired transfer RNA (tRNA)/tRNA synthetase pairs.

During protein synthesis, amino acids are added to the nascent protein through the joint action of the ribosome and tRNA. Through its ability to pair with mRNA, tRNAs bring amino acids to the ribosome, which adds the amino acids to the growing polypeptide.

The addition of an amino acid to tRNA is catalyzed via 20 tRNA synthetases, each of which recognizes one amino acid and all of the tRNAs that are compatible, which is determined by the appropriate base pair sequence.

“The system depends upon specialized tRNAs and tRNA synthetases that won’t load normal amino acids,” Daniel said. Thus, the non-encoded amino acid is added to recombinant proteins at positions specified by placement of the appropriate codon. “It allows you to change the functionality of the protein anywhere you’d like,” he noted.

Ambrx says it can add amino acids with a desired chemical structure almost at will. In addition, several of the non-natural amino acids are chemically active, meaning that they can be used in a chemical reaction to add on additional chemical entities, increasing the chemical diversity allowed by Ambrx’s platform.

Importantly, Ambrx’s amino acids extend sites of chemical reactivity beyond the native amino acids, cysteine and lysine, to permit chemical modification of proteins without disruption of their structure.

Ambrx currently has tRNA/tRNA synthetase pairs for 16 non-encoded amino acids, though this is not the limit of the technology. “We can synthesize non-encoded amino acids to fit given requirements with the appropriate tRNA/tRNA synthetase pair,” said Daniel.

For example, using the crystal structure of a given protein/protein interaction, Ambrx can make chemical modifications to

‘An enzyme can turn over 1,000 molecules per minute. An antibody can bind to one molecule. It’s a machine gun compared to a shotgun.’

— Charlie Craik of Catalyst

maximize binding affinity. “We can do chemistry on proteins in a manner similar to that done with small molecules,” Daniel said.

In addition, Ambrx can use its technology to create glycosylated products derived from proteins made in bacteria (see *BioCentury*, Jan. 19, 2003).

The company expects to select a pre-clinical candidate early in 2005.

Emerging immunogenicity

While these protein engineering platforms have the potential to create better, cheaper biologics, one concern is that the more one mucks with proteins, the greater the odds that immunogenicity will arise.

“You have to confront this issue because if you don’t, you will be behind the 8 ball,” said Xencor’s Dahiyat.

“A protein engineer can make a protease that will recognize a particular substrate, but you want to change it as little as possible to keep it under the radar screen of human immune surveillance,” agreed Catalyst’s Craik.

In order to minimize changes to its proteases, Catalyst starts with a protease that is as close as possible to what it wants the finished product to be. In addition, all of the mutations in the enzyme are in its active site, which is often buried in a narrow pocket and thus not easily accessible to the immune system.

For its part, Xencor has acquired data on MHC class II allele expression distribution in the U.S., and with the help of a \$2 million Advanced Technology Program grant from the National Institute of Standards and Technology, is screening a library of peptides to determine which epitopes bind the most commonly expressed allele. Binding the MHC class II molecule suggests that the particular peptide sequence might be immunogenic.

“We couple this with assays on lymphocytes from genotyped donors to cross-correlate binding with T cell activation,” Dahiyat said.

While immunogenicity is always a potential issue, BioRexis has preclinical data to indicate that transferrin might actually reduce the immunogenicity of certain peptides. “We have put a peptide in that is very antigenic, and when it was put into transferrin it had reduced immunogenicity compared to the original peptide,” Prior said.

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Strategy

Cashing in its clinical chips

In its deal with Enzon Inc. last week, Inex Pharmaceuticals Corp. partnered out its entire clinical pipeline comprised of Onco TCS for six cancer indications. Nevertheless, President and CEO David Main said the partnership is exactly what the company needed to become more fully integrated.

Specifically, the deal gives Inex the option to build an oncology sales and marketing team at a discount. Indeed, according to Main, securing the option to co-promote Onco TCS in North America was the linchpin of the transaction. Assuming Inex exercises its option to build the sales force, the company will be able to position itself as a better partner for future product collaborations.

"We now expect to retain full commercialization rights in North America for all future products," Main told BioCentury.

Onco TCS is vincristine encapsulated in the company's Transmembrane Carrier System (TCS). The liposomal drug delivery technology is designed to extend circulation in the bloodstream, accumulate the drug at the tumor site and prolong the release of the drug.

Under the deal, Inex (TSE:IEX, Vancouver, B.C.) received \$12 million up front and is eligible for \$20 million upon FDA approval of Onco TCS. The drug has Fast Track designation, and the company expects to complete filing of its rolling NDA this quarter (see *BioCentury*, Dec. 8, 2003).

ENZN (Bridgewater, N.J.) gains exclusive North American marketing rights for all indications. Should IEX exercise its option to co-promote, ENZN will record all sales but will share the cost of building IEX's sales force. IEX also is eligible for a 20-30% royalty on North American sales (see B3).

The company had \$58 million in cash at Sept. 30, 2003, which it says will last more than two years. With the expected

cash infusions from ENZN, it now plans to start "aggressively pursuing" oncology in-licensing this year.

"An in-licensing deal would be to augment our R&D, not replace it. We expect to generate at least one internally developed preclinical compound every 12-18 months," Main said.

IEX's other products in development include a TCS formulation of topotecan, which is partnered with GlaxoSmithKline plc (LSE:GSK; GSK, London, U.K.). GSK is responsible for full development of the compound, which Main said is expected to start Phase I testing in the third quarter. IEX is eligible for about \$36 million in upfront payments and milestones, plus low double-digit royalties (see *BioCentury*, Dec. 3, 2001).

IEX's most advanced internal compound is a TCS formulation of vinorelbine, for which the company plans to submit an IND by year end (see "Almost Empty Nest").

Main added that IEX is likely to list on NASDAQ this year. With FDA action for

Onco TCS expected this year, Main expects the company to be generating revenue by 2005, a key criterion on which to base the decision to dual list. "2004 is going to be a transformational year for the company," he said. — *Aimee Dingwell*

Going, going ...

The exodus of a part of its management team doesn't signal a new strategy for VaxGen Inc., which hasn't been pursuing development of its AIDSvax vaccine since it failed in Phase III trials last year, and instead is focusing on its anthrax and smallpox programs. However, according to the departing executives, the exodus does highlight the need for an appropriate venue to pursue HIV vaccine research and the obstacles that this work faces.

Last week, VXGN president Donald Francis and Phillip Berman, senior vice president of R&D, announced they will leave the company at the end of the month to form a not-for-profit foundation to develop an HIV vaccine. Both Francis and Berman were previously at Genentech Inc., which spun out Genenvax Inc. — now VXGN — to conduct Phase III trials of a gp120 vaccine (see *BioCentury*, Feb. 26, 1996). Carter Lee, senior vice president of finance and administration at VXGN also will join the foundation.

"This idea initiated with the Gates Foundation's announcement that it intended to set up HIV vaccine development centers," said Berman. "The private sector is not going to support this type of research, so we are looking to other sorts

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Noteworthy this week



Inex: Cashing in its clinical chips

...

VaxGen: Going, going...

Almost empty nest

Inex has chosen to partner its entire clinical pipeline in exchange for the opportunity to build a commercialization capability.

Product	Indication	Status	Partner	Milestone
Onco TCS	Relapsed lymphoma	Ph III	Enzon	Complete NDA I Q04
Onco TCS	First line and relapsed lymphoma	Ph II	Enzon	
Onco TCS	Small cell lung cancer	Ph II	Enzon	
Onco TCS	Pediatric malignancies	Ph II	Enzon	
Onco TCS	Hodgkin's disease	Ph II	Enzon	
Onco TCS	Acute lymphoblastic leukemia	Ph II	Enzon	
Topotecan TCS	Cancer	Preclin	GlaxoSmithKline	Start Ph I 3Q04
Vinorelbine TCS	Cancer	Preclin		Submit IND by year end

Strategy,
from previous page

of funding.”

Though the foundation will be manned by VXGN management, it does not signal a second coming for AIDSvax, which failed to reduce the incidence of HIV infection in two Phase III trials (see *BioCentury*, March 3 & Nov. 17, 2003). “We made strides with the vaccine, but it is not a licensable product,” Berman said.

However, Berman said he has not given up on the idea of developing a vaccine that contains some manifestation of gp120. “We will certainly take another look at envelope proteins, and potentially join them with other products that are out there,” he said.

It is likely that the foundation will look to mix and match different adjuvant, pro-

tein and DNA vaccine technologies from industry and academia. But as yet nothing has been decided. “In terms of funding, right now the foundation has a goose egg,” Berman said.

For VXGN (Brisbane, Calif.), the management departure puts a more public face on the end of the AIDSvax era, but won't result in any significant changes. The company has not been funding the AIDSvax program internally for several months. “The restructuring really happened some time ago,” said CEO Lance Gordon.

Instead, VXGN is focused on its anthrax and smallpox biodefense programs. Last year, the company was awarded an \$80.3 million contract from the NIH for development of its rPA102 anthrax vaccine. The contract will fund two Phase II trials, scale-up and validation of the vaccine manufacturing process, and produc-

tion of three million doses of finished product (see *BioCentury*, Oct. 6, 2003). VXGN hopes to begin the first Phase II trial this quarter.

This year, VXGN also hopes to begin two trials of its attenuated smallpox vaccine, which it licensed from Chemo-Sero-Therapeutic Research Institute (Kumamoto, Japan). The first trial is expected to begin early next quarter.

Some remaining work is going on with AIDSvax, but not on VXGN's nickel. Funded by SBIRs, VXGN is working on sequence analysis of the HIV isolates from patients in its Phase III trials. In addition, the compound is in a Phase III trial in Thailand as part of a prime boost regimen with ALVAC from Aventis S.A. (AVE, Strasbourg, France). That trial is being sponsored by the U.S. government (see *BioCentury*, Jan. 19). — Keith Haan

Online links this week

Links to the following documents reside online at BioCentury's News Center at www.biocentury.com.

Biodefense

— Report from the Institute of Medicine evaluating the U.S. Department of Defense's efforts to develop biological warfare countermeasures (see *BioCentury Extra*, Friday, Jan. 23).

— Memorandum of understanding between FDA and EPA on collaborative R&D and emergency response efforts for homeland security.

Clinical trials

Homepage of Save European Cancer Research, and the EU's pending clinical trial directive (see A14).

Drug approvals

— Eight FDA new drug approval reports are listed in CDER's “What's New” page for Jan. 21 (see A13).

— List of drugs approved through December 2003 under the EMEA's Centralized Procedure.

EMEA actions

— Adopted 2004 budget for the European Agency for the Evaluation of Medicinal Products.

— Summary of actions taken at the January meeting of the EMEA's Committee for Orphan Medicinal Products (COMP).

GMOs

USDA notice of potential changes to regulation of genetically engineered organisms (see *BioCentury Extra*, Thursday, Jan. 22).

Immunosuppressive therapy

NICE Final Appraisal Determination on the use of immunosuppressive therapy for renal transplantation, including Simulect basiliximab from Novartis AG (NVS; SWX:NOVN), Zenapax daclizumab from Protein Design Labs Inc. (PDLI), CellCept mycophenolate mofetil from Roche (SWX:ROZ), Prograf tacrolimus from Fujisawa, and Rapamune sirolimus from Wyeth (WYE).

Insomnia

NICE Final Appraisal Determination on the use of Sonata zaleplon from King Pharmaceuticals Inc. (KG), Ambien zolpidem from Sanofi-Synthelabo S.A. (SNY), Estorra eszopiclone ((S)-zopiclone) from Sepracor Inc. (SEPR), and benzodiazepine hypnotics to treat insomnia.

Medicare drug benefit

Announcement of a CMS forum on Jan. 30 regarding a \$500 million demonstration project mandated by the new Medicare prescription drug law covering certain drugs and biologics not normally covered under Medicare Part B.

Parallel imports

EU Commission's response to recent Court of Justice rulings on parallel imports (see A14).

Pharmacogenomics

Draft FDA guidance on when and how to submit pharmacogenomics data, and how the data will be used in regulatory decision-making (see A13).

Product documentation

— Velcade: CPMP summary of positive opinion for Velcade bortezomib to treat relapsed, refractory multiple myeloma (MM), from Millennium Pharmaceuticals Inc. (MLNM).

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BioCentury organizes 3 major financial meetings and sponsors several other events during the year. See the Conference Center for current meeting activity.

Product Development**Cleaning out the ears**

Middle ear infections can turn into painful, long-term problems that must be treated with multiple courses of antibiot-



ics or even surgery. OctoPlus Technologies B.V. is hoping that its peptide-based compound targeting the toxic residues of the bacteria will reduce chronic infections and hence lower antibiotic use.

In mid-February, OctoPlus (Leiden, the Netherlands) plans to start a Phase I/II trial of OPT-145/01, which is designed to enable the body's own mechanisms to clear up chronic middle ear infections. While antibiotics kill the bacteria, OctoPlus is looking to remove the toxins

Bacteria in the ear typically produce two toxins — lipopolysaccharide (LPS) and lipoteichoic acid (LTA) — that can cause inflammation in the middle ear and eustachian tube. "When such inflammatory reactions occur, the mucociliary clearance system can no longer efficiently clear excess fluids and infection-causing bacteria or bacterial toxins, leading to chronic infections," said CEO Joost Holthuis.

According to OctoPlus, studies at Leiden University show that the company's 24 amino acid peptide binds to LPS and LTA in vitro, and in vivo restores the function of the mucociliary clearance system. "By binding to the LPS and LTA toxins, there will be an interference in the

infection process, allowing the body to use its own natural mechanisms to overcome the infection," said Holthuis.

The company believes that the compound could complement or even replace antibiotics in chronic middle ear infections. "People with chronic middle ear infection have to be continuously treated with antibiotics because the body can not overcome the infection," said Holthuis. "You have to remember that in many chronic infections, antibiotics do not work or they lead to resistance, so in these indications it may dramatically reduce the use of antibiotics."

He added that OctoPlus does not expect the body to develop resistance to its compound.

The Phase I/II trial, which will be run by Leiden University, will enroll 42 patients. The Phase I part will be a dose-ranging study in 16 patients, with a primary endpoint of safety and tolerability. The Phase II portion will be a double-blind, placebo-controlled trial in 26 additional patients. The endpoints are clinical improvement of middle ear mucosa, reduction of infection measured by a CT scan of the mastoid, and improved status of hearing.

If the compound, which is delivered via eardrops, is successful in middle ear infection, the next target indication could be acute middle ear infection. This is a shorter-term infection, usually associated with adults, that is typically treated with antibiotics, said Holthuis. Other potential indications include sinusitis and chronic bronchitis, which would be delivered via nasal spray and pulmonary delivery, respectively. — *Shaun Brown*

Marking Our 12th Year of Service to the Biotechnology Industry

"Both BioCentury and BioCentury Extra provide Rodman & Renshaw with the most complete and up-to-date news analysis of what's happening in clinical trials, approvals, M&A and financing in the biotech space. The breaking news items as well as the in depth feature stories make BioCentury our first read."

— **John J. Borer III**
Senior Managing Director
Rodman & Renshaw

Technology Briefing**Data mining not dead****By Susan Schaeffer
Staff Writer**

Most enabling technology deals are worth six figures, or at most low seven figures, which is why many of the post-genomics toolkit companies are no longer with us. But Iconix Pharmaceuticals Inc. last week announced not one, but two significantly sized chemogenomics deals, with Bristol-Myers Squibb Co. and Abbott Laboratories.

Iconix (Mountain View, Calif.) valued the BMY deal at \$24 million, excluding payments based on successful commercialization. While the value of the ABT deal was not disclosed, Iconix COO Leslie Browne described the two deals as “very similar in structure, very similar in the way they will be managed, and very similar in the size of the financial commitment.”

Both pharma companies received access to Iconix’s DrugMatrix chemogenomics reference database and its Drug Signature library of predictive biomarkers for use in the development and commercialization of therapeutics and diagnostics associated with those therapeutics.

While some pharma companies have in-house chemogenomics systems, and other service companies offer similar technology, Browne said that Iconix’s DrugMatrix reference database is the largest available. “Chemogenomics is the only thing we do, and we’re doing it on a bigger, grander scale than what others have done,” he said.

Chemogenomics — not to be confused with pharmacogenomics — combines pharmacology and toxicology, using genomics tools to predict biological response. Pharmacogenomics looks at a population’s genetics to identify patients more likely to respond to a drug.

Browne said that in guidance released last November, FDA divided the landscape into preclinical chemogenomics and clinical pharmacogenomics (see *Online Links, A8*). But he suggested that chemogenomics can be used in clinical development as well to get early feedback on efficacy and safety. For example, he said, “in a Phase I trial, you can use the Drug Signatures as a means to measure whether the compound is doing the right things, and

not the wrong things.”

The company’s DrugMatrix system provides a reference set of 600 compounds evaluated at the gene expression level. The set comprises compounds that are currently marketed or were once marketed but failed, standard toxicants and other reference standards.

The data on these compounds are derived from a combination of public and proprietary sources and are organized into four domains. In one domain are molecular pharmacology data collected from 130 biochemical assays run by Iconix’s partner MDS Pharma Services (MDZ; TSE:MDS, Montreal, Quebec). Another domain houses information collected from literature, such as clinical, pharmacological and toxicology data.

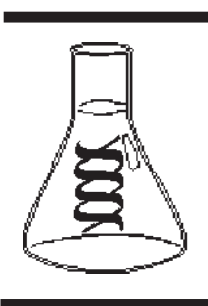
In the third domain are gene expression data, which Iconix collects by running in vivo experiments, harvesting 12 kinds of tissue samples, and determining the gene expression profiles of the samples. The final domain houses information on clinical changes, such as white blood cell counts, and histopathological changes, such as biliary hyperplasia and liver necrosis.

Iconix uses its own algorithms to mine its database for biomarker sets, which the company calls Drug Signatures. Browne said the Drug Signatures consist of “about 200 highly validated, nonredundant sets of biomarkers that can be used to predict the properties of compounds based upon their gene expression profiles. So we can mine out 10 to 20 genes that correlate with a biological endpoint.”

The deal with ABT (Abbott Park, Ill.) provides Iconix with the opportunity to develop an in vitro system to complement its in vivo data set. Iconix and ABT will collaborate to develop in vitro, high throughput, gene expression-based screens to determine the liver toxicity of early-stage compounds. Iconix retains commercialization rights to the in vitro platform.

Browne noted that in vitro screening requires less compound. That translates into cost and time savings, as well as the ability to use the technology earlier in the discovery process.

In the BMY deal, Iconix also will collaborate on “special projects” to evaluate preclinical and clinical compounds from BMY (Princeton, N.J.). In addition to an upfront payment and technology license fees, Iconix will receive “special project” fees and is eligible for payments based on successful commercialization.



Marking Our 12th Year of Service to the Biotechnology Industry

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— **Kenneth I. Moch**
Chairman, President & CEO
Alteon Inc.

Emerging Company Profile**Scion: Discovery by electrophysiology****By Christopher Maggos
Senior Writer**

Electrophysiology, the study of the relationship between electrical charge and cellular process, is generally too labor intensive and time consuming for use in medium to high throughput lead identification. The technique has been most often reserved for more focused lead optimization work. However, Scion Pharmaceuticals Inc. says it can do electrophysiology about 100 times faster than conventional methods, which brings the technology into the realm of the useful for lead identification.

The company plans to focus on neurology and cardiovascular indications, for which electrophysiology is particularly relevant.

Binding assays, which allow researchers to identify compounds that bind a given target, are a common tool used to identify leads. But binding assays don't give any information about the cellular response — electrophysiology does.

For Scion, function takes precedence over binding. "We're agnostic about binding," CEO Pravin Chaturvedi said. "When we test compounds, all we care about is whether or not they block ionic current. Is the ionic current going up or down? Binding assays wouldn't tell you this functional information. They just tell you whether or not you are binding the receptor."

Thus, Scion argues that data on binding isn't as predictive of functional outcome as is knowledge about what a compound does to a nerve cell's electrical current. "For example, is the functional result on a calcium channel of the brain different than it is for a calcium channel of the heart?" Chaturvedi said. Such information is important for predicting side

Scion Pharmaceuticals Inc.

Medford, Mass.

Technology: Ion channel-based drug discovery

Disease focus: Pain and atrial fibrillation

Clinical status: Preclinical

Founded: 2001 by Pravin Chaturvedi, David Farb and Mark Carthy

Corporate partners: None

University collaborators: Boston University School of Medicine

Employees: 38

Funds raised: \$21.5 million

Investors: Oxford Bioscience Partners; Lehman Brothers; Lancet Capital; Life Science Partners; Genechem Therapeutic Venture Fund; S.R. One; Gray Ghost; NeuroVentures; BU Community Technology Fund; Russek Foundation

CEO: Pravin Chaturvedi

Patents: 70 U.S. and 34 ex-U.S. covering composition of matter and method of use, high throughput electrophysiology and ion channel targets

effects and toxicity.

Indeed, Scion does not use binding assays, "Our company's tenet is based on using physiologically relevant assays — namely, electrophysiology assays combined with pharmacological assays in various animal models of disease," Chaturvedi said.

Because Scion can do electrophysiology in a high throughput fashion, skipping binding assays also saves time during lead identification. This allows identification and optimization to be done in parallel. "We can optimize for selectivity and po-

tency in a functional screening assay — it's one step away from animal studies," Chaturvedi said.

Scion believes that working on lead optimization in parallel with lead identification means moving faster and increasing the odds of finding better compounds. "The traditional hit rate in ion channel drug discovery has been between 0.1% and 0.5%. Our hit rate is between 1% and 5%. We get from target identification to preclinical pharmacology in about two years with about 15-17 FTEs compared to 35-40 FTEs and four to five years for the traditional drug discovery approach," Chaturvedi said.

The process begins with a small group of compounds pre-selected for activity against ion channels.

"We typically start with a library of 10 pre-selected compounds from commercial or internal sources and build them out using our chemistry capabilities to several thousand compounds," Chaturvedi said. "We also make sure we're working on targets that have some degree of validation. Preferably clinical, but at least preclinical."

In addition, he said, "we generally pick up a few chemical scaffolds that we like and explore drug design early on." During lead optimization, medicinal chemists typically generate multiple variations on a backbone or scaffold of interest in order to find the one that is most efficacious with the least side effects.

The company is focusing on subtype selective drugs for pain and atrial fibrillation, with chronic pain likely to be the lead indication. "We started screening for the pain program last September," Chaturvedi said. "We've gotten into lead optimization in 14 months and anticipate our first IND in the fourth quarter of 2004."

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Washington Notebook**Approval times improve, sort of**

**By Steve Usdin
Washington Editor**

FDA's approval times, which ran off the rails in 2002, look to be back on track, according to data released last week. The 2003 figures present a mixed message, however. Performance on NDAs with priority designation was substantially better than for standard applications, particularly in the case of new molecular entities.

Indeed, the total approval time for standard NME applications was the longest since 1994. Total approval time — the period from first submission of an NDA to approval — for standard NMEs was 23.1 months in 2003, up from 15.9 months in 2002 and 19 months in 2001. The standard review clock is supposed to be 10 months.

FDA attributed the increase to "statistical outliers" resulting from a small pool of applicants, and said it "anticipates a return to more standard levels if applications increase in the future."

Particularly long-lived standard applications included Crestor rosuvastatin, submitted by AstraZeneca plc (LSE:AZN; AZN, London, U.K.) in June 2001 and held up while the company provided additional safety data. It was approved in August 2003 as an adjunct to diet to treat various lipid disorders.

The agency was able to reverse the prior year's dramatic increase in median approval and review times for priority NDAs, which have a six-month review clock. The median total approval time for priority NMEs was 6.7 months in 2003, down from 16.3 months in 2002, while the median total approval time for all priority NDAs fell from 19.1 to 7.7 months.

According to FDA, the 2002 figures were an aberration caused by decreasing numbers of submissions with unusually long regulatory histories.

Long-lived priority NME applications approved in 2003 included Plenaxis abarelix, an LHRH/GnRH antagonist from Praeclis Pharmaceuticals Inc. (PRCS, Waltham, Mass.) to treat advanced symptomatic prostate cancer. The NDA was submitted in December 2000 and approved in November 2003, after the company agreed to substantially narrow the indication.

By contrast, Velcade bortezomib made an extraordinarily swift trip through the process. Close collaboration between Millennium Pharmaceuticals Inc. (MLNM, Cambridge, Mass.), FDA and academic scientists helped get Velcade approved to

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CBER approval times

The Center for Biologics Evaluation and Research regulates some products, such as blood products, that are not subject to user fees. Times are medians in months. 2003 numbers include biologics transferred to CDER. Number of actions includes complete responses, as well as approvals, withdrawals and refusals to file.

	2001	2002	2003
Number of actions	47	52	35
All BLAs approved	16	21	22
Total approval time	20.4	15.6	19.1
CBER review time	13.8	12.9	12.8
Approved: user fee	8	9	14
Total approval time	21.5	28.8	20.3
CBER review time	17.6	16.6	16.9
Approved: non-user fee	8	12	8
Total approval time	18.4	13.4	9.8
CBER review time	8.5	12.4	9.5
Approved: priority	2	6	5
Total approval time	13.2	14.7	22.2
CBER review time	11.5	12.0	12.1
Approved: standard	8	10	11
Total approval time	23.7	19.9	30
CBER review time	18.1	18.0	19.0
Refused for filing	2	0	0
Withdrawn	6	3	5

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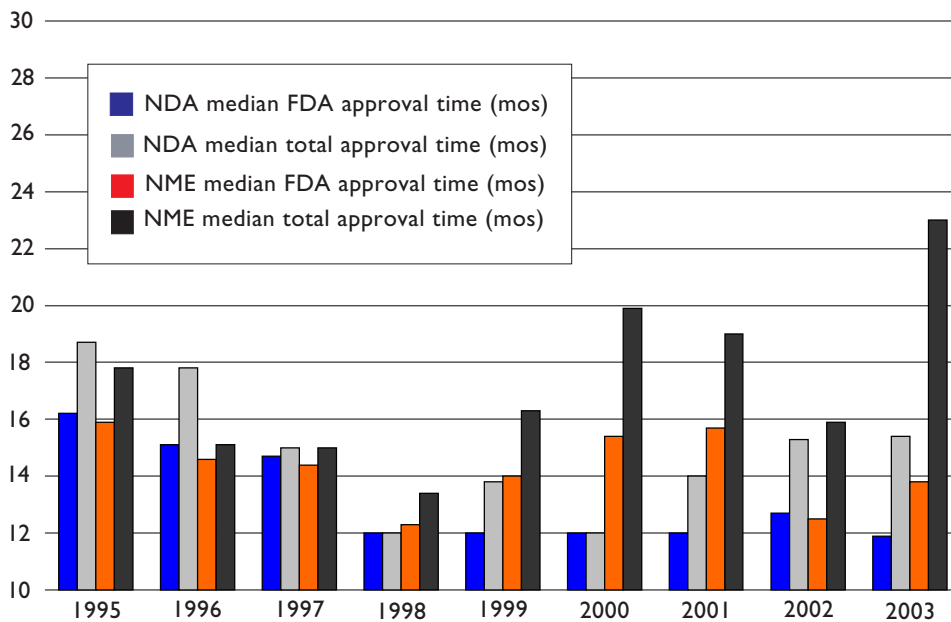
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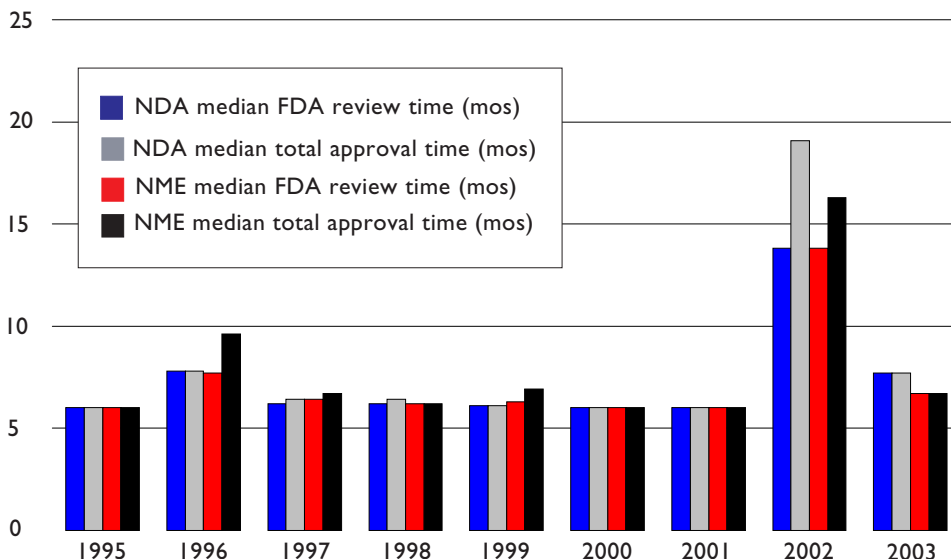
*Washington Notebook,
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FDA review time is the period an application is in the hands of FDA reviewers. Total approval time is the time from first NDA submission to NDA approval. It includes the sum of three periods: FDA review time for the first submission of an NDA to the agency, plus any subsequent time during which a pharmaceutical sponsor addresses deficiencies in the NDA and resubmits the application, plus subsequent FDA review time. NMEs are a subset of NDAs for products that contain an active substance that has never before been approved for marketing in any form in the U.S. The performance goal for FDA review for a standard NDA is 10-12 months. For priority reviews, the goal is 6 months. Source: FDA.

Standard NDAs and NMEs



Priority NDAs and NMEs



treat relapsed and refractory multiple myeloma (MM) less than four months after the NDA was submitted in May 2003 (see *BioCentury* May 19, 2003).

The median approval numbers present a more favorable picture than mean averages. The average total approval time in 2003 for standard NMEs was 20.5 months, virtually unchanged from 20.3 months in 2002. Average total approval times for priority NMEs improved to 12 months in 2003 from 14.2 months in 2002.

A total of 72 NDAs were approved in 2003, including 21 NMEs, compared to 78 NDAs in 2002, of which 17 were NMEs (see *Online Links*, A8).

As in previous years, it took CBER longer to review and approve BLAs than CDER required for NDAs.

FDA met all of its user fee performance goals in 2003. But the wide discrepancies between the review clock and total approval times highlight the impact of review cycles — which extend elapsed time but stop the review clock — on drug development timelines. While approval times reflect factors that can be outside FDA's control, such as the quality of data and completeness of submissions, sponsors and patients consider the total elapsed time to be a much more meaningful indicator of the efficiency of the approval process (see *BioCentury* June 30, 2003).

FDA has launched several initiatives to improve its internal procedures and to help sponsors submit better applications, both aimed at reducing the number of review cycles. But it will take some time for these process changes, new guidance documents and other initiatives to translate into faster reviews. The agency anticipates that improvements will be evident by fiscal year 2005, which starts in October 2004.

FDA has committed to reduce the average total review time by 30 days for priority applications and two months for standard applications for the first half of the approval cohort for applications submitted in fiscal years 2005-07 and beyond. This goal "correlates to at least a 10% reduction," according to the agency.

FDA reported that it received 119 NDAs last year, the highest figure since 1999, when 139 were submitted.

*European Notebook***Commission unbowed on parallel imports****By Ludger Wess
Senior Editor**

Although the EU Commission recently failed in an attempt to fine Bayer AG for illegal obstruction of parallel imports, it made clear last week that it stands firm on its policy of encouraging parallel imports of medicines as a means to cut drug prices.

Earlier this month, the European Court of Justice ruled that Bayer (FSE:BAY; BAYG, Leverkusen, Germany) was entitled to refuse to supply its drugs to wholesalers in certain countries from which the drugs were exported to countries with higher prices for medicines. According to the court, the Commission had failed to prove that BAYG had violated any contracts with its wholesalers (see *BioCentury*, Jan. 12).

In response, the Commission last week said that the ruling “does not alter the Court’s case law on free movement of goods or state measures regarding parallel imports.” In particular, the Commission said, the European Court of Justice had made clear in a series of rulings that the parallel importer even “may repackage a proprietary medicinal product and reattach the trade mark or indeed replace it with the trade mark used in the market of destination.”

According to Internal Market Commissioner Frits Bolkestein, the ultimate aim of the Commission “is to ensure patients and healthcare providers can benefit from parallel imports” (see *Online Links*, A8).

Unintended consequences

While the EU Commission and the European Parliament

frequently point out that it is important to encourage clinical trials sponsored by doctors, hospitals and other independent researchers, it now turns out that the EU’s draft directive on clinical trials would lead in the opposite direction.

Thousands of European scientists and medical doctors have signed a petition calling on the Parliament and the Commission to repeal directive EC/2001/20 on Good Clinical Practice, which is due to come into effect in May (see *Online Links*, A8).

“The heart of the problem lies in the increased obligations that the directive imposes on the sponsor of a trial,” Brian Moulton, a researcher at the Irish Clinical Oncology Research Group in Dublin, told *BioCentury*. “An individual or organization

now has to take total legal and financial responsibility for the clinical trial, including paying for all drug and device costs while patients are on study.”

As an example, under the pending law an academic sponsor, rather than the health service, will have to pay for all the drugs that a patient is receiving — including fully licensed drugs — if even only one component of the treatment is experimental.

“In a cancer trial, where patients receive a cocktail of three drugs plus the study drug, the price for the drugs may exceed several thousand Euros per patient,” Moulton said. “That is something no independent researcher is able to pay.”

He added that even a trial using aspirin would become a problem, as the directive is demanding repackaging of all drugs used and labeling of them as clinical trial material. “This, too, is extremely costly,” he added, “and in the case of aspirin, these costs by far exceed the price for the substance.”

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KuDos B7, B8
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Ebb & Flow**Pegging out**

**By Eric Pierce
& Shaun Brown
Senior Writers**

Comparing biotech stocks to other industries on a price-to-earnings basis can be a sticky proposition, because investors don't typically buy biotech for the current year's earnings stream. Instead, biotech investors are banking on the promise of future growth, making the P/E comparison between sectors in some cases nearly irrelevant.

To account for the importance of growth to investors, another metric was created: P/E to growth, or PEG ratios. Without the PEG metric, a biotech company with a P/E of 50 would look incredibly expensive relative to a pharma company with a P/E of 25.

But to an investor buying the future growth prospects of both companies, the biotech company might look like a bargain. If the biotech company has a long-term annual EPS growth rate of 40%, that would give it a PEG of 1.25. By comparison, the pharma company would have to have a growth rate of only 20% to have the same PEG.

Most investors use PEG for intra-industry comparisons (read: biotech-to-biotech), especially to calibrate whether an absolute P/E that may appear high could be justified by expected future growth. That said, some investors have applied the PEG metric to comparing the relative valuation of biotech to pharma. While it can be a stretch to compare a lower-growth industry (pharma) to a high-growth industry (biotech), looking at the differential between the two can lead to some striking comparisons.

Using 2004 EPS (forward P/E) and expected five-year growth rates, BioCentury calculates that the pharma PEG was 2.4 at the end of 2003 and the biotech PEG was 1.4, putting the biotech PEG at 58% of the pharma PEG. The differential between the two was 71% at the end of 2002.

Meanwhile, the gap between P/Es has narrowed: biotech P/Es were about 150% of pharma's at the end of 2002 and 130% at the end of 2003 (see "Growth at a Bargain?").

The bottom line is that investors still can buy biotech growth relatively more cheaply. In fact, falling pharma growth rates play a big part in pushing up the pharma PEG. Average projected EPS growth for big pharma was 11.5% at the end of 2002 and 10.5% at the end of 2003. Given that the long-term growth rate is the denominator in the PEG equation, slowing growth will significantly ratchet up the ratio.

At the same time, using forward EPS makes biotech look cheaper on a PEG basis, because it bakes in the upcoming year's growth — usually more robust than the pharma group, which compresses its PEG.

IPO watch

Investors and company managers will be closely watching the pricing of **Eyetech** — slated for this Thursday or Friday — as an indicator of the IPO window's strength. That's because the ophthalmic play is seeking the biggest valuation of the current crop of IPOs. Eyetech hopes to raise \$117-\$130 million through

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Growth at a bargain?

On a price/earnings basis, the premium that investors are willing to pay for biotech earnings compared to pharma has narrowed over the past year, although it still remains. When biotech's future growth is considered, it looks cheap relative to pharma: the average biotech PEG — P/E relative to long-term growth — continues to be well below the average pharma PEG. (A) Source: ThomsonFN.

Then (end of 2002)						& Now (end of 2003)				
Company	12/31 cls	2003 EPS (est) (A)	5-yr growth rate (A)	P/E	PEG	12/31 cls	2004 EPs (est) (A)	5-yr growth rate (A)	P/E	PEG
Amgen	\$48.34	\$1.74	20%	28	1.4	\$61.79	\$2.39	21%	26	1.2
Biogen	\$40.06	\$1.70	14%	24	1.7	NA	NA	NA	NA	NA
Biogen-Idec	NA	NA	NA	NA	NA	\$36.70	\$1.50	17%	24	1.4
Cephalon	\$48.66	NA	NA	NA	NA	\$48.41	\$2.02	24%	24	1.0
Chiron	\$37.60	\$1.45	20%	26	1.3	\$56.98	\$1.89	20%	30	1.5
Genentech	\$33.16	\$1.07	22%	31	1.4	\$93.57	\$1.49	25%	63	2.5
Genzyme	\$29.57	\$1.37	18%	22	1.2	\$49.29	\$1.73	20%	28	1.4
Gilead	\$34.00	\$0.67	38%	51	1.3	\$58.28	\$1.60	30%	36	1.2
Idec	\$33.17	\$1.10	30%	30	1.0	NA	NA	NA	NA	NA
MedImmune	\$27.17	\$0.93	25%	29	1.1	\$25.38	\$0.96	20%	26	1.3
Serono	\$13.56	\$0.66	20%	21	1.0	\$17.10	\$0.76	18%	23	1.3
Shire	\$18.89	\$1.56	20%	12	0.6	\$27.98	\$1.87	15%	15	1.0
Biotech avg				27	1.2				30	1.4
Pharma avg				18	1.7				23	2.4

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the sale of 6.5 million shares at \$18-\$20.

A \$19 price would raise \$123.5 million for the company and value it at \$731.1 million. That's nearly three times the \$270 million average valuation of the seven IPOs that have gotten out in this window. Banks on the deal are Merrill Lynch; Morgan Stanley; Bear Stearns; and CS First Boston.

Meanwhile, decisions surrounding the IPO market continue to take divergent paths: two companies pressed forward by updating their original filings, while another set aside its deal — at least for now.

The updaters included **Renovis** and **Corgentech**. The latter amended its IPO and now hopes to raise \$70-\$80 million through the sale of 5 million shares at \$14-\$16. A \$15 price would raise \$75 million and give Corgentech a post-money valuation of \$376.5 million. The company originally filed on Dec. 4, 2003, to raise up to \$86.3 million. Underwriters are CS First Boston; Lehman Brothers; CIBC; and Piper Jaffray.

Corgentech is developing transcription factor decoys for cardiovascular disease, inflammatory disease and cancer. The company's lead product, E2F Decoy, is in Phase III testing to prevent vein graft failure following coronary artery bypass graft (CABG) and peripheral artery bypass graft surgery. E2F Decoy is partnered with **Bristol-Myers Squibb** (BMY).

Renovis, which quietly amended its filing post-market the prior Friday, now hopes to raise \$71.5-\$82.5 million through the sale of 5.5 million shares at \$13-\$15. A \$14 price would raise \$77 million and value the company at \$330.8 million. Banks on the deal are Goldman; CIBC World Markets; SG Cowen; and Piper Jaffray.

Renovis' lead product is Cerovive, an intravenous compound in Phase III for acute ischemic stroke. It is partnered with **AstraZeneca** (LSE:AZN; AZN). Renovis also has REN-1654 in Phase II for neuropathic pain and REN-213 in Phase II for acute post-operative pain.

Acorda officially withdrew its IPO, after postponing the deal in December (see *BioCentury*, Dec. 22, 2003). The company was hoping to raise \$57-\$66.5 million through the sale of 4.75 million shares at \$12-\$14 through Banc of America; Lazard; Piper Jaffray; and RBC Capital Markets. A \$13 price would have valued the company at \$271.2 million.

Acorda still has plans to re-market the deal, according to spokesperson Tierney Saccavino, but is likely to wait until April, when it expects to have Phase III data in hand for its Fampridine-SR compound for improving spasticity in patients with chronic spinal cord injury. Fampridine-SR also is in Phase II trials to improve walking ability and muscle strength in patients with multiple sclerosis (MS).

A tidy profit

Proving that there is money to be made in European biotech, U.K. private equity investor HgCapital last week sold off its last block of shares in obesity company **Alizyme** (LSE:AZM) in order to take profits. HgCapital had held about 9 million AZM shares before it started selling the 9% stake to institutional investors. The firm had invested about £3.5 million (\$6.4 million) in several rounds since 1998, and said its profit of £7.5 million (\$13.7 million) amounted to a compound annual return of 37%.

The decision to sell was based on AZM's run of positive clinical and deal news over the last 12 months. In January 2003,

AZM raised £16.1 million (\$25.8 million) in a placing and open offer, and in October raised a further £11.4 million (\$19.3 million) through a private placement of 6.8 million shares. "We chose to start selling because we could sell into strength," said Lindsay Bibden, director of healthcare at HgCapital.

AZM is not slated to have any major news for some months, although Bibden expects the company to sign a global partner for its ATL-962 obesity treatment by year end. Last August, the company granted **Takeda** exclusive rights in Japan. The gastrointestinal lipase inhibitor completed a Phase IIb trial last year and may enter Phase III around the end of this year (see *BioCentury*, Sept. 22, 2003).

AZM has two other compounds that have completed Phase IIb: Renzapride for irritable bowel syndrome (IBS); and Colal-Pred prednisolone to treat ulcerative colitis (UC). Both are due to enter Phase III mid-year. Colal-Pred already is in a Phase III study for the maintenance of UC patients.

The stock as up 2p to 182.5p on the week to a market cap of £263 million (\$479 million).

Earnings watch

QLT (TSE:QLT; QLTI) closed Friday at \$18.56 after adding \$0.69 to \$18.70 on 1.6 million shares on Thursday in NASDAQ trading after marketing partner **Novartis** (SWX:NOVN; NVS) reported that 2003 sales of Visudyne verteporfin photodynamic therapy rose 24% (16% in local currencies) to \$357 million. QLT developed Visudyne, which is approved to treat certain forms of wet age-related macular degeneration (AMD) in the U.S. and Europe.

QLTI, which is slated to report earnings on Feb. 11, was up \$1.16 on the week. For the quarter, NVS beat the Street by a penny (see "One Miss," A18).

Well fertilized, again

Pharming (Euronext:PHARM) has turned around its cash position after raising €25 million (\$31.2 million) from undisclosed investors last week, and now expects to have about €30 million (\$37.7 million) in cash at the end of this month. In August 2001, the company filed for the equivalent of Chapter 11 in the Netherlands, as it had run out of cash and had about €24 million (\$22 million) in debt.

Also last week, PHARM presented interim results from an open-label Phase II trial of its human C1 inhibitor in hereditary angioedema (HAE) (see B10). PHARM expects to begin Phase III trials within the next four months.

The stock was off €0.02 to €1.59 on the week to a market cap of €62 million (\$79 million).

Venture tracks

Christian Leikert, formerly senior associate of Future Capital, has been appointed CEO and member of the executive board to succeed Michael Wrede at the German venture capital firm. Wrede passed away last month from a heart attack. He was 49. He is survived by his wife and two children.

Future Capital, which is financed 50-50 by the Hessen state government and **Aventis** (AVE), manages €63.9 million (\$80.4 million) in assets and invests €0.75-€5 million (\$0.9-\$6.3 million) per company in founding startups, supporting expansion.

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sion and preparing IPOs in the chemistry and life science sector.

Regulatory milestones

Millennium (MLNM) closed Friday at \$17.94 after slipping \$0.18 to \$17.85 on 3.7 million shares on Thursday's news that the CPMP recommended marketing approval of Velcade bortezomib for multiple myeloma. MLNM, which was up \$0.45 on the week, expects final approval of the MAA in the second quarter. The product is marketed in the U.S.

MM competitor **Pharmion (PHRM)** held up relatively well on the news. It was down \$0.81 to \$16.81 on the week after slipping \$0.60 to \$16.40 on 91,900 shares on Thursday. PHRM has a license from **Celgene (CELG)** to market thalidomide outside of North America, Japan, China, Taiwan and Korea. PHRM currently markets its Thalidomide Pharmion in Australia for relapsed and refractory MM, and is conducting a Phase III study in newly diagnosed MM patients.

Vicuron (MICU; NMer:MICU) added \$0.33 to \$23.33 on 608,262 shares in NASDAQ trading on Friday despite news that the FDA requested additional pharmacokinetic data for MICU's NDA for anidulafungin to treat esophageal candidiasis. The company does not believe the extension is related to safety or efficacy, and it still hopes to launch the product in the first half of the year. The new PDUFA date is May 25. MICU was down \$0.77 on the week.

OSI (OSIP) closed Friday at \$36.18 after popping \$3.38 (10%) to \$36.20 on 2 million shares on Wednesday's news that it began a rolling NDA for Tarceva erlotinib to treat certain forms of non-small cell lung cancer (NSCLC). OSIP, which was up \$3.75 (12%) on the week, expects data from a Phase III trial of Tarceva in NSCLC in the second quarter, after which it will submit additional components of the NDA.

Partner **Genentech (DNA)** also got a boost from the news, adding \$2.09 to \$94.40 on 2.2 million shares on Wednesday and closing up \$3.85 at \$96.60 on the week.

Biogen Idec (BIIB) closed Friday at \$44.32 after slipping \$0.30 to \$44.48 on 7.9 million shares on Thursday's news that marketing partner **Schering (FSE:SCH; SHR)** received European approval for Zevalin to treat certain forms of non-Hodgkin's lymphoma (NHL) that has relapsed or is refractory to therapy with Rituxan. BIIB was still up \$1.13 on the week.

Wednesday's news that VaxGen's anthrax vaccine received Fast Track designation from the FDA trumped Tuesday's post-market news of a management exodus. VXGN added \$0.61 to \$10.91 on 6.3 million shares on Wednesday. Post-market Tuesday, the company said that President Donald Francis and SVP of R&D Phillip Berman are leaving to form a not-for-profit foundation to develop an HIV vaccine. Carter Lee, SVP of finance and administration, also will join the foundation. VXGN was up \$1.43 (15%) on the week to \$10.92 (see *Strategy, A7*).

Clinical milestones

InterMune (ITMN) held up well on Wednesday's news that its Actimmune interferon gamma-1b did not reverse liver fibrosis

Money Raised in 2004

Total last week:	\$200.8M
IPOs YTD:	\$0M
Follow-on YTD:	\$68.4M
Venture YTD:	\$368.9M
Other YTD:	\$236.6M
Total YTD:	\$673.9M

In 2003 a total of \$19.3 billion was raised, including \$505.9 million in IPOs, \$3.8 billion in follow-ons, \$3.7 billion in venture capital, and \$11.2 billion in other fundraising. Totals include overallotments and warrants. (Source: BioCentury Financial Center)

caused by hepatitis C virus (HCV) in a Phase II study (see B9). ITMN added \$0.02 to \$21.18 on 859,485 shares on Wednesday and closed Friday at \$20.47, down \$0.28 on the week. The compound, which is approved to treat chronic granulomatous disease and severe, malignant osteoporosis, also is in Phase III testing to treat idiopathic pulmonary fibrosis (IPF) and ovarian cancer.

Ebb & Flow

Inex (TSE:LEX) closed Friday at C\$6.74 after popping C\$0.83 (15%) to C\$6.51 on 610,880 shares on Tuesday's news that it granted **Enzon (ENZN)** exclusive North American rights to Onco TCS formulation of vincristine to treat various cancers. The stock was up C\$1.23 (22%) on the week (see *Strategy, A7*).

The deal marks ENZN's second in-licensing of a later-stage compound since it and **NPS (NPSP)** scrapped their merger plans last June. A few weeks after the merger fell through, ENZN in-licensed North American rights to ATG-Fresenius S from Fresenius. The polyclonal antibody organ rejection product is on the market in Europe (see *BioCentury, June 23, 2003*). Next quarter, ENZN plans to start a late-stage clinical trial in the U.S. that it believes will serve as the basis for FDA approval.

ENZN was up \$0.24 to \$13.69 on the week after adding \$0.80 to \$14.25 on 1.3 million shares on Tuesday.

ViroPharma (VPHM) fell \$0.53 (14%) to \$3.17 on 2.1 million shares on Tuesday's belt tightening news. In an effort to stretch its cash through 2006, VPHM said it will cease development of pleconaril in serious or life-threatening diseases, reduce its headcount by 70% and discontinue its early-stage activities. The company will continue initial studies of an intranasal formulation of pleconaril to treat the common cold under its option agreement with **Schering-Plough (SGP)**, and it will continue its HCV collaboration with **Wyeth (WYE)**.

In 2002, the company received a non-approvable letter from the FDA for pleconaril to treat viral respiratory infection (VRI) in adults (see *BioCentury, June 10, 2002*). The stock was down \$0.70 (19%) on the week to \$3.

London & the Continent

Cyprotex (LSE:CRX) was up 3.5p (17p) to 24p on the week after closing two deals based on its Cloe Screen in vitro high throughput screening technology, which profiles ADME properties of compounds. CRX will provide liver metabolism profiles for compounds from **Altana (FSE:ALT)** in a deal that will run for one year. CRX also will use Cloe Screen on oral compounds from **AstraZeneca (LSE:AZN; AZN)** to provide data on their potential absorption through the gut (see B2). CRX has a market cap of £23 million (\$41 million).

Antisoma (LSE:ASM) jumped 6.5p (17%) to 45.3p on 13.2 million shares traded on no news. Over the last quarter, ASM's average weekly trading volume was about 5.5 million shares. Investors are anticipating news, as over the summer the company said it expected to complete its Phase III SMART trial of R15409 in ovarian cancer between December 2003 and February of this

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year (see *BioCentury*, July 21, 2003). **Roche** (ROCZ) took over development of the Yttrium-90 radiolabeled murine HMFG I antibody in late 2002. If approved, the drug should give ASM enough cash to take it through to profitability. The company's market cap is £120 million (\$219 million).

Phytopharm (LSE:PYM) was up 6p to 220p on the week after receiving a \$2 million milestone from **Yamanouchi** after PYM delivered Phase I trial results on its PYM50028 compound to treat Alzheimer's disease (AD). Under a 2003 deal, PYM could receive a further \$15 million over the next 18 months (see *BioCentury*, May 5, 2003). PYM has a market cap of £85 million (\$155 million).

Corrections

Barrier Therapeutics Inc., Princeton, N.J.
Business: Dermatology

The Jan. 19 *BioCentury* omitted that Geert Cauwenbergh is a founder. Partner Johnson & Johnson is not a founder. Barrier's second-generation retinoic acid metabolism blocking agent is Rambazole.

Corgentech Inc., South San Francisco, Calif.
Business: Cardiovascular

Corgentech disclosed in its December S-1 filing for an IPO that its cardiovascular deal with Bristol-Myers Squibb Co. includes \$320 million in sales milestones that were not disclosed in its original October announcement. Those milestones bring the total potential deal value to \$570 million. The Jan. 19 *BioCentury* used data based on the company's announcement.

Metabasis Therapeutics Inc., San Diego, Calif.
Business: Infectious, Endocrine

Metabasis' lead clinical compound, CS-917, is in Phase II trials for Type II diabetes. The oral gluconeogenesis inhibitor, which does not use the company's HepDirect prodrug technology, was omitted from the Jan. 19 *BioCentury*.

One miss

Wyeth (WYE), still struggling from weakness in the hormone replacement therapy market, proved the only black mark on last week's earnings group. WYE also disclosed on its conference call that it wrote down \$20 million of FluMist inventory in the fourth quarter, and declined to give 2004 sales guidance for the intranasal flu vaccine, which it licensed from **MedImmune** (MEDI).

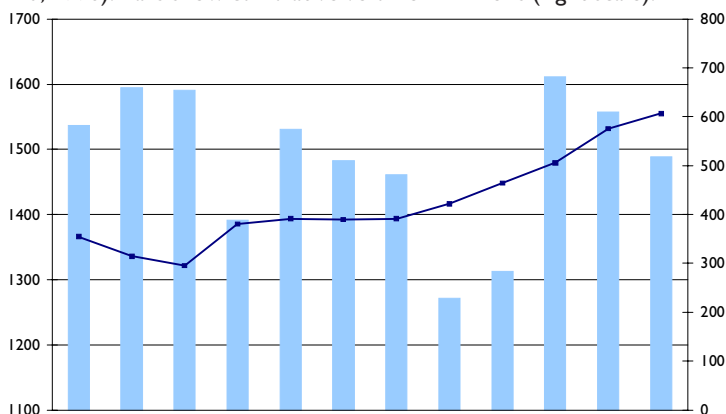
Amgen (AMGN) came in slightly ahead of the Street after backing out a one-time R&D payment. The company added \$2.46 to \$63.93 on 15.7 million shares on Friday on the earnings news, putting it up \$0.43 on the week. It appeared that investors were saving their fire-power for AMGN's actual earnings, because the stock didn't get much boost on Tuesday, when competitor **Johnson & Johnson** (JNJ) reported continued softening sales of EPO in its fourth quarter earnings (see below). JNJ's EPO sales have been under pressure since AMGN launched Aranesp darbepoetin in 2002. AMGN lost \$0.55 to \$62.95 on 9.4 million shares on Tuesday.

EPS growth measured by comparing non-GAAP (operating EPS) to same figure from 4Q02; (A) Fiscal third quarter ended 12/31; (B) US\$ used.

Company	4Q EPS est	4Q EPS actual	Outcome	Growth from 4Q02	1/23 cls	Wk chg	% chg	Mkt cap chg (\$M)	1/23 mkt cap (\$M)
Amgen (AMGN) 4Q03 EPS was \$0.46, which included an \$87M (\$0.04 post-tax) expense related to an upfront payment to Biovitrum . 4Q03 sales increased 38% to \$2.2B, with combined Epogen/Aranesp sales rising 40% to \$1.2B. 4Q03 sales of neutropenia products Neupogen and Neulasta increased 27% to \$688M. 4Q03 sales of rheumatoid arthritis product Enbrel increased 88% to \$384M. Currency rates increased 2003 revenues by about \$166M (2%).	\$0.48	\$0.50	Beat by \$0.02	43%	\$63.93	\$0.43	1%	\$552	\$82,022
Forest (FRX) (A) 3Q04 sales increased 19% to \$700M, boosted by Lexapro and Celexa antidepressants, which increased 30% to \$588M. FRX now expects fiscal 2004 EPS (ending March 31) to be "at the high end" of its previous guidance of \$1.82-\$1.92.	\$0.58	\$0.60	Beat by \$0.02	28%	\$74.75	\$4.23	6%	\$1,547	\$27,344
Johnson & Johnson (JNJ) 4Q03 sales increased 20% to \$11.3B, aided by a 6% favorable currency impact. 4Q03 sales of JNJ's EPO products Epex and Procrit fell 12% from 4Q02 to \$967M. U.S. sales (Procrit) fell 16% to \$671M; while international sales (Epex) added 1% to \$296M. For the year, sales of Epex/Procrit were \$4B, a decline of 7% from 2002, or a decline of 11% excluding currency rates. Actual 4Q03 EPS of \$0.62 included a \$142M (\$0.05) after-tax gain related to a legal settlement.	\$0.56	\$0.57	Beat by \$0.01	24%	\$53.00	\$2.55	5%	\$7,664	\$159,286
Novartis (SWX: NOVN; NVS) (B) 4Q03 pharma sales increased 21% (12% in local currencies) to \$4.4B. 2003 pharma sales increased 18% (11% in local currencies) to \$16B, leading to 2003 EPS per ADS of \$2.03, up 8% over 2002. NVS said 2004 EPS will exceed 2003 based on projected top line growth in the high single-digit range.	\$0.54	\$0.55	Beat by \$0.01	15%	\$46.92	\$1.31	3%	\$3,237	\$115,939
Pfizer (PFE) 4Q03 revenues increased 52% to \$14.2B. Human pharmaceutical sales increased 51% to \$12.4B. Sales growth was aided by the 2003 acquisition of Pharmacia and favorable currency exchange (about 4%). EPS growth was aided by higher than expected cost savings from the Pharmacia acquisition.	\$0.51	\$0.53	Beat by \$0.02	10%	\$36.14	\$1.14	3%	\$8,648	\$274,158
Wyeth (WYE) Expects FY04 EPS of \$2.60-\$2.70, below the Street's current consensus of \$2.75.	\$0.66	\$0.60	Missed by \$0.06	-8%	\$41.61	-\$2.54	-6%	-\$3,383	\$55,425

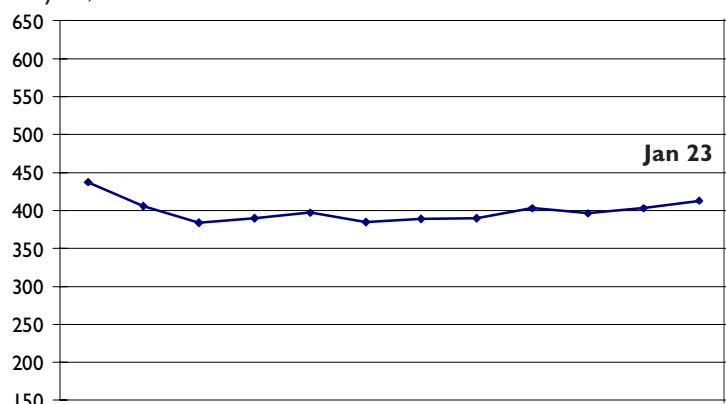
BioCentury 100 Price & Volume Trend

Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale, Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



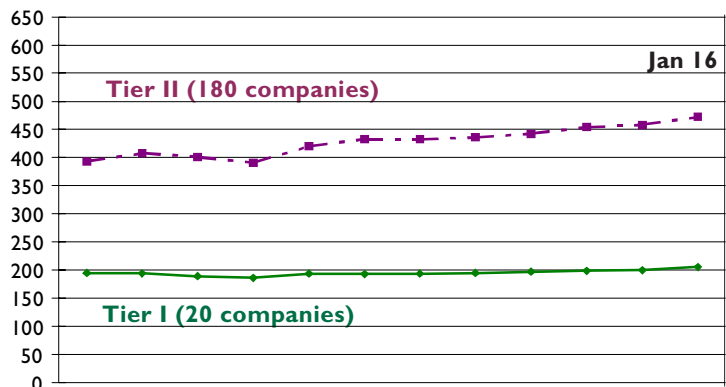
BioCentury London Index

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



TFCG Life Sciences Indexes

Weekly change in combined market capitalization. 12-week period. Tier I = market caps >\$1B; Tier II <\$1B. Base =100 on Dec. 31, 1998.



Source: Thomson Financial

BioCentury tracks 452 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends. TFCG Life Sciences Indexes are compiled by Thomson Financial, provider of market intelligence services to publicly held companies. Due to technical difficulties, the TF/Carson indexes do not include January 23.

Price Gains

Stocks with greatest % price increase in the week ended Jan. 23. (Priced above \$2.50; 25,000 minimum share volume)

Company	Ticker	\$Close	\$Chg	%Chg	Vol(00)
Miravant	MRVT	2.610	0.980	60%	39244
PharmaNetics	PHAR	2.900	1.060	58%	15048
Zonagen	ZONA	3.950	1.150	41%	2902
Aerogen	AEGN	3.710	0.990	36%	7644
CombiMatrix	CBMX	7.370	1.600	28%	88878
Palatin	PTN	3.940	0.810	26%	44184
Dyax	DYAX	10.700	2.161	25%	23974
Repligen	RGEN	3.130	0.600	24%	82882
Inex	IEX	C6.740	C1.230	22%	16549
Cellegy	CLGY	5.010	0.910	22%	6109
Genta	GNTA	13.030	2.200	20%	83862
OraSure	OSUR	9.460	1.560	20%	25912
Embrex	EMBX	13.989	2.289	20%	2359

Price Declines

Stocks with greatest % price decline (criteria as above).

Company	Ticker	\$Close	\$Chg	%Chg	Vol(00)
ViroPharma	VPHM	3.000	-0.700	-19%	35262
Lynx	LYNX	5.290	-0.980	-16%	6835
Aphton	APHT	7.250	-1.293	-15%	17913
Allos	ALTH	3.280	-0.490	-13%	37008
Nektar	NKTR	17.200	-2.110	-11%	88116
Genelabs	GNLB	2.590	-0.310	-11%	32920
Genome Therap	GENE	5.120	-0.600	-10%	66081
Inspire	ISPH	12.240	-1.360	-10%	31721
Polydex	POLXF	7.720	-0.811	-10%	250
Genencor	GCOR	13.599	-1.381	-9%	1578
Northfield	NFLD	6.880	-0.689	-9%	4193
Curis	CRIS	5.760	-0.510	-8%	37291
Caliper	CALP	8.960	-0.790	-8%	9826
Indevus	IDEV	6.560	-0.540	-8%	26550

Volume Gains

Greatest changes in volume above 25,000 shares.

Company	Ticker	Vol(00)	%Chg	\$Close	\$Chg
Cytos	CYTN	3042	1501%	CHF42	CHF1.5
GW Pharma	GWP	103367	1440%	205.5p	11p
Pharmexa	PHARMX	6970	928%	DKK37.5	DKK4.8
Sanochemia	SAC	701	409%	€6.170	€0.870
Biacore ¹	BCOR	1975	401%	24.000	0.020
Parexel	PRXL	14238	368%	16.660	-0.800
NeoPharm	NEOL	36184	355%	19.100	0.840
Pozen	POZN	14744	296%	10.458	-0.102
Miravant	MRVT	39244	289%	2.610	0.980
Phytopharm	PYM	7131	282%	220p	6p

¹ Includes volume from Stockholm Stock Exchange with converted ADSs (ADS = 1 share)

BioCentury 100 Advance-Decline Trend

Week ended	BCI00 Price level	BCI00 Stocks gaining	BCI00 Gaining vol. (00)	BCI00 Stocks declining	BCI00 Declining vol. (00)
Dec 26	1416.50	76	1568254	23	695875
Jan 02	1448.14	82	2149250	18	692521
Jan 09	1479.41	68	3881665	30	2921461
Jan 16	1531.82	74	3722863	26	2380085
Jan 23	1555.05	60	3299485	38	1819914

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BIA

BioCentury Part II

VOL. 11, No. 5

THE COMPLETE REPORT OF BIOBUSINESS NEWS

JANUARY 26, 2003

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Using BioCentury Part II

BioCentury Part II is a comprehensive compendium of business news for management and investors in bioscience companies. It is organized into three departments: Company News, Clinical News and Financial News.

The index on this page lists all the companies covered this week. The news items in each department are organized alphabetically by company. When more than one company is listed, the biotech company is shown first. Each brief is labeled with one or more applicable business categories from the following list:

ADMET; Agbio/Environmental; Antibodies; Autoimmune; Bioinformatics; Biomanufacturing; Biomaterial/Skin/Wound; Biopharmaceuticals; Cancer; Cardiovascular; Chemistry; Combinatorial biology; Computational chemistry/biology; Dental; Dermatology; Diagnostic; Drug delivery; Endocrine; Finance; Functional genomics; Gastrointestinal; Gene/Cell therapy; Generics; Genitourinary; Genomics; Hematology; Hepatic; High throughput screening; Infectious; Inflammation; Metabolic; Microarrays; Microfluidics; Musculoskeletal; Neurology; Nutraceuticals; Ophthalmic; Other; Pharmaceuticals; Pharmacogenetics; Proteomics; Pulmonary; Renal; Supply/Service; Transplant; Veterinary

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Biolipox/NicOx (NM:Nicox)
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COMPANY NEWS/Deals, Regulatory, Sales & Marketing, Management Tracks

DEALS

Aeterna Laboratories Inc. (TSE:AEL; AELA), Quebec City, Quebec
Solvay Pharmaceuticals B.V., Brussels, Belgium

Business: Genitourinary

AEL subsidiary Zentaris GmbH (Frankfurt, Germany) and Solvay Pharmaceuticals will jointly develop Zentaris' oral, low molecular weight peptidomimetic luteinizing hormone releasing hormone (LHRH) antagonists. Solvay gains exclusive global rights to all gynecological indications and benign prostatic hyperplasia (BPH), while Zentaris retains exclusive rights to all other indications. Solvay will fund further preclinical and clinical development costs up to an undisclosed fixed amount. The companies expect to have a preclinical candidate this year. Zentaris will receive an upfront payment of C\$5 million (US\$3.9 million), reimbursement for certain prior development costs, and milestones.

Alnylam Pharmaceuticals Inc., Cambridge, Mass.

Cold Spring Harbor Laboratory, Cambridge, Mass.

Business: Functional Genomics, Supply/Service

Alnylam non-exclusively licensed IP from Cold Spring covering induction of gene silencing in mammalian cells for therapeutic uses.

Ambion Inc., Austin, Texas

Applied Biosystems Group (ABI), Foster City, Calif.

Business: Proteomics

The companies will exclusively co-market Ambion's siRNA products and ABI's real-time PCR reagents. The combination will be used for performing and monitoring the gene knockdown effects of RNA interference (RNAi) in mammalian systems. Ambion will use ABI's TaqMan Assays-on-Demand Gene Expression Products to validate its siRNA products.

Altana AG (FSE:ALT), Bad Homburg, Germany

Cyprotex plc (LSE:CRX), Manchester, U.K.

AstraZeneca plc (LSE:AZN; AZN), London, U.K.

Business: ADMET, Functional genomics

CRX will use its Cloe Screen in vitro high throughput screening technology to provide liver metabolism profiles for compounds from ALT. The deal, which initially covers three assays, will run for one year and may be expanded to include additional assays. Cloe Screen profiles compounds for absorption, distribution, metabolism and excretion (ADME) properties.

Separately, CRX will use its Cloe Screen in vitro high throughput screening technology to provide data to AZN on the potential absorption of oral compounds through the gut. The ongoing work will run for six months.

Avantium International BV, Amsterdam, the Netherlands

Chiral Quest Inc., State College, Penn.

Business: Supply/Service, Chemistry, High throughput screening

Avantium will add Chiral's chiral ligand catalysts to its existing catalyst library for use with its high throughput screening and simulation technology.

Axonyx Inc. (AXYX), New York, N.Y.

Oxis International Inc. (OXIS), Portland, Ore.

Business: Neurology

AXYX will acquire approximately 14 million shares of OXIS in exchange for approximately 1.6 million unregistered shares of AXYX. Together with OXIS shares currently held by Marvin Hausman, AXYX's chairman and CEO, AXYX will control approximately 57% of OXIS voting stock. AXYX said it "has no current intention to acquire OXIS' remaining outstanding shares."

Cambridge Antibody Technology Group plc (LSE:CAT; CATG), Melbourn, U.K.

Lonza Group Ltd. (SWX:LONN), Zurich, Switzerland

Business: Antibodies, Biomanufacturing

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Pharming (Euronext:PHAR)
Phytomedics
Pluristem Life Sciences (PLRS)
RegeneRx (RGRX)
SelectX

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FINANCIAL NEWS

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Amgen (AMGN)
Ariad (ARIA)

'It's the BioCentury'TM

Deals,
from previous page

The companies extended to 2006 their 2001 deal, under which LONN subsidiary Lonza Biologics (Slough, U.K.) manufactures and supplies CAT with clinical grade antibody compounds (see *BioCentury*, Dec. 3, 2001).

Chromatin Inc., Chicago, Ill.

Cibus Genetics LLC, San Diego, Calif.

National Research Council of Canada, Ottawa, Ontario

Business: Agbio/Environmental

Under separate deals using Chromatin's mini-chromosome technology, Cibus and the council's Plant Biotechnology Institute will regenerate cells containing mini-chromosomes and develop them into mature canola plants. Initial work will focus on demonstrating the viability of mini-chromosomes. Later experiments will test the introduction of genes with commercial value, such as resistance to herbicides. Chromatin said that its mini-chromosome technology allows the simultaneous introduction of multiple genes into plants without disrupting the plant's own chromosomes. Initial results are expected this quarter.

CIPHERGEN Biosystems Inc. (CIPH), Fremont, Calif.

Genencor International Inc. (GCOR), Palo Alto, Calif.

Business: Biomanufacturing

Expanding on a 1997 deal between GCOR and BioSeptra, which CIPH acquired from Invitrogen Corp. (IVGN, San Diego, Calif.) in 2001. CIPH received exclusive worldwide rights to use GCOR's Hydrophobic Charge Induction chromatography technology to produce MEP membranes, as well as the MEP HyperCel sorbents covered under the original agreement. CIPH also gained the right to distribute products through its own or third-party channels, and the right to subcontract MEP HyperCel manufacturing to third parties.

CombiMatrix Group (CBMX), Newport Beach, Calif.

Washington University, St Louis, Mo.

Business: Microarrays

CBMX and the university partnered to develop a system to synthesize libraries of non-nucleic acid molecules. CBMX will synthesize the libraries using its NanoArrays technology. The university will explore the capabilities of NanoArrays to build diverse molecule libraries on a chip.

Cortex Pharmaceuticals Inc. (COR), Irvine, Calif.

Les Laboratoires Servier, Neuilly sur Seine, France

Business: Neurology

The partners expanded, for a second time, their 2000 deal to develop COR's Ampakine technology to treat anxiety (see *BioCentury*, Oct. 14, 2002 & Oct. 23, 2000). Under the terms, Cortex will receive about \$4.3 million in support over two years. The support may continue on an annual basis and is in addition to Servier's eight \$500,000 quarterly payments that started in October 2002. In addition, the partners selected a compound, S-40929, for advanced preclinical development (see B10).

CytoGenix Inc. (CYGX), Houston, Texas

Baylor College of Medicine, Houston, Texas

Business: Cancer, Genomics

The parties will test CYGX's ssDNA expression vector technology with Baylor's aerosol gene delivery technology in a mouse model of lung cancer.

Discovery Laboratories Inc. (DSCO), Doylestown, Penn.

Laureate Pharma L.P., Princeton, N.J.

Business: Biomanufacturing

Laureate will manufacture clinical material for DSCO's ongoing development programs, including DSCO's Surfaxin treatment for respiratory distress syndrome (RDS).

Elan Corp. plc (ELN), Dublin, Ireland

Enzon Inc. (ENZN), Bridgewater, N.J.

Inex Pharmaceuticals Corp. (TSE:IEX), Vancouver, B.C.

Business: Cancer

IEX granted ENZN exclusive North American rights to Onco TCS, a Transmembrane Carrier System (TCS) liposomal formulation of vincristine to treat various cancers. IEX will receive \$12 million up front, plus an additional \$20 million upon FDA approval of Onco TCS. IEX also is eligible for milestones of \$43.75 million, plus royalties.

In June, IEX completed a Phase II/III study of Onco TCS in relapsed non-Hodgkin's lymphoma (NHL), and IEX expects to submit a rolling NDA to the FDA this quarter. The companies anticipate market launch in early 2005. Onco TCS also is in Phase II studies for first-line NHL, relapsed small cell lung cancer, relapsed Hodgkin's disease and other cancers.

ENZN and IEX will share equally future development costs for North American approval, and ENZN will pay sales and marketing costs plus post-approval clinical development costs. IEX retains manufacturing rights and will initially manufacture and supply the drug and be reimbursed by ENZN. IEX has the option to co-promote Onco TCS, the costs of which will be shared equally, and ENZN will record all sales.

As a result of the deal with ENZN, ELN received a \$3 million milestone from IEX under the companies' 2001 joint venture to develop Onco TCS for NHL, which was ended last year (see *BioCentury*, April 7, 2003).

Elan Corp. plc (ELN), Dublin, Ireland

King Pharmaceuticals Inc. (KG), Bristol, Tenn.

Business: Neurology, Musculoskeletal, Inflammation

ELN received a \$25 million milestone from KG under the companies' 2003 deal relating to the sale of ELN's primary care business. The milestone was triggered by the ongoing patent exclusivity of Skelaxin metaxalone musculoskeletal therapeutic.

Elan Corp. plc (ELN), Dublin, Ireland

Sanders Morris Harris, Houston, Texas

Business: Neurology, Autoimmune, Inflammation

ELN is selling its manufacturing and R&D business, Elan Pharma S.A. (Mezzovico, Switzerland), to affiliates of investment bank Sanders Morris Harris. The sale includes the associated fast-melt and effervescent intellectual property. ELN also is selling its Segix Italia (Pomezia, Italy) manufacturing business to an MBO team. Also, ELN sold its San Diego office property to an undisclosed purchaser. ELN now rents the property.

Eli Lilly and Co. (LLY), Indianapolis, Ind.

Merck KGaA (FSE:MRK), Darmstadt, Germany

Business: Drug delivery

MRK subsidiary Biovation Ltd. (Aberdeen, U.K.) will apply its Delmmunisation technology to undisclosed biopharmaceuticals designed by LLY. Biovation will receive research revenues and is eligible for milestones and royalties if LLY elects to move forward with any compounds. Delmmunisation technology is designed to eliminate or reduce T cell responses.

See next page

Deals,
from previous page

Genentech Inc. (DNA), South San Francisco, Calif.

Inproteo LLC, Indianapolis, Ind.

Business: Supply/Service

Inproteo sublicensed to DNA rights to U.S. Patent No. 4,569,794 covering a His-tag fusion protein purification technique. Inproteo, which is a partnership between Indiana University, Purdue University and Eli Lilly and Co. (LLY, Indianapolis, Ind.), licensed the patent from LLY.

GeneSeek Inc., Lincoln, Neb.

A2 Corp., Auckland, New Zealand

Business: Agbio/Environmental

GeneSeek will provide high throughput DNA analysis to genotype dairy cattle for the beta-casein gene to enable the selection of cows for the production of A2 milk and other dairy products. A2 milk contains lower levels of the A1 form of beta-casein, which A2 Corp. claims has been linked to health risks such as heart disease.

Iconix Pharmaceuticals Inc., Mountain View, Calif.

Abbott Laboratories (ABT), Abbott Park, Ill.

Bristol-Myers Squibb Co. (BMY), Princeton, N.J.

Business: Chemistry, Genomics

Under separate deals, BMY and ABT received access to Iconix's DrugMatrix chemogenomics reference database and its Drug Signature library of predictive biomarkers. The pharma companies may use Iconix's technology to identify biomarkers for use in clinical development and commercialization of therapeutics, as well as to develop and market diagnostics associated with those therapeutics.

In addition, Iconix and BMY will collaborate on "special projects" to evaluate compounds from BMY. Iconix will receive an upfront payment, technology license fees and "special project" fees and is eligible for payments based on successful commercialization. Iconix valued the BMY deal at \$24 million, excluding payments for commercialization.

Separately, Iconix and ABT will collaborate to develop in vitro, high throughput, gene expression-based screening of compounds for liver toxicities. Iconix retains commercialization rights to the in vitro platform. Iconix will receive an upfront payment, technology access fees and research funding and is eligible for clinical milestones. Further terms of the ABT deal were not disclosed, but Iconix COO Leslie Browne described the deal as "very similar in the size of the financial commitment" to the BMY deal.

Ingenium Pharmaceuticals AG, Munich, Germany

Wyeth (WYE), Madison, N.J.

Business: Functional genomics

Ingenium will use its INGENOtyping technology to develop rat models with gene alterations specified by WYE.

Medarex Inc. (MEDX), Princeton, N.J.

Xerion Pharmaceuticals GmbH, Martinsried, Germany

Business: Antibodies

MEDX and Xerion partnered to develop human antibodies. Under the deal, Xerion will use its Xstream technology to identify targets, against which MEDX will use its UltiMab Human Antibody Development System to generate antibody product candidates. The companies will share equally the costs and responsibilities of product development and commercialization.

Metabolex Inc., Hayward, Calif.

Pfizer Inc. (PFE), New York, N.Y.

Business: Metabolic

The companies extended for one year their research collaboration to discover therapeutics to treat Type II diabetes. In July 2001, the companies chose to focus their collaboration on the discovery of drug targets related to insulin secretion (see *BioCentury*, July 9, 2001). Metabolex receives research funding from PFE and is eligible for royalties. The deal was originally signed in 1998 with Parke-Davis, which was acquired by PFE.

Micrologix Biotech Inc. (TSE:MBI; MGIXF), Vancouver, B.C.

Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan

Business: Infectious

Fujisawa subsidiary Fujisawa Healthcare Inc. (Deerfield, Ill.) returned all rights related to MBI's MBI-226 cationic peptide. The compound failed to show superiority over povidine iodine in a Phase III trial to prevent central venous catheter-related bloodstream infections (see *BioCentury*, July 28, 2003). MBI said it will seek a new partner. In addition, MBI said it met with the FDA to discuss NDA requirements for the compound using secondary endpoints — catheter colonization and catheter-related local infection — from the Phase III trial. The company said the FDA may require a second Phase III trial.

NeoStrata Co. Inc., Princeton, N.J.

Schering AG (FSE:SCH; SHR), Berlin, Germany

Business: Dermatology

NeoStrata partnered with SCH subsidiary Berlex Inc. to develop topical therapeutics using NeoStrata's formulation technologies, including Alpha-Hydroxyacid (AHA) and Polyhydroxy acid (PHA) formulations, for dermatology indications.

Orchid BioSciences Inc. (ORCH), Princeton, N.J.

Tepnel Life Sciences plc (LSE:TED), Manchester, U.K.

Business: Diagnostic

TED completed its previously announced acquisition of the product and services business of ORCH's Orchid Diagnostics unit in the U.S., U.K. and Belgium for \$3.5 million (see *BioCentury*, Nov. 3, 2003). The price was revised down from \$4.3 million due to market conditions.

Pfizer Inc. (PFE), New York, N.Y.

PPM Ventures Ltd., London, U.K.

Triton Private Equity, London, U.K.

Business: Diagnostic

PFE sold its in vitro allergy and autoimmune diagnostic testing business to Triton Private Equity and PPM for \$575 million. PFE was advised by Lazard and Cadwalader, Wickersham & Taft.

Phytopharm plc (LSE:PYM), Godmanchester, U.K.

Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan

Business: Neurology

PYM received a \$2 million milestone from Yamanouchi under the companies' 2003 PYM50028 Alzheimer's disease (AD) deal (see *BioCentury*, May 5, 2003). The payment was triggered by Yamanouchi's receipt of Phase I study results for PYM50028. PYM now has received \$5 million in milestones and could receive up to \$15 million more in the next 18 months.

RegeneRx Biopharmaceuticals Inc. (RGRX), Bethesda, Md.

Sigma-Tau S.p.A., Rome, Italy

Business: Biomaterial/Skin/Wound

Sigma-Tau subsidiary Defiante Farmaceutica L.d.a. (Funchal, Ma-
See next page

Deals,
from previous page

deira, Portugal) received exclusive European rights to RGRX's Thy-mosin beta 4 (TB4) for internal and external wound healing. Defiante will purchase all required TB4 from RGRX, which is eligible for royalties. RGRX has completed Phase I studies and plans to begin Phase II trials next quarter. Once RGRX has completed Phase II trials with positive results, Defiante must either pay RGRX \$5 million or begin Phase III trials in Europe. Defiante will be required to achieve clinical and regulatory milestones and to meet commercialization performance criteria, including minimum annual royalties. RGRX may sublicense the technology in non-European countries and retains U.S. rights. TB4 is a naturally occurring 43 amino acid peptide.

Royalty Pharma AG, Vordergasse, Switzerland
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Business: Hematology

Royalty acquired an undisclosed portion of the center's royalty interest in Neupogen/Neulasta for \$263 million in cash. The center is eligible for additional payments if the products' sales exceed certain hurdles. In addition, the center made a \$7 million investment in Royalty. Neupogen and Neulasta are marketed by Amgen Inc. (AMGN, Thousand Oaks, Calif.).

Scolr Inc. (SCLL), Bellevue, Wash.
Business: Nutraceuticals, Drug delivery

SCLL completed the previously announced sale of its nutraceutical/probiotics development and manufacturing business for \$2.7 million through a management buyout led by Steven Moger, formerly SCLL's VP of operations, CFO and general manager of probiotics (see *BioCentury*, Jan. 12).

Sequenom Inc. (SQNM), San Diego, Calif.
Health Protection Agency, London, U.K.
Business: Microarrays

The parties partnered to discover and develop genetic markers that differentiate pathogenic from non-pathogenic strains of major human pathogens, such as *Neisseria meningitidis*. SQNM will use its MassARRAY genetic analysis platform in the research.

Sicor Inc. (SCRI), Irvine, Calif.
Teva Pharmaceutical Industries Ltd. (TEVA), Jerusalem, Israel
Business: Generics

TEVA completed its previously announced acquisition of SCRI in a cash and stock deal worth \$3.4 billion. Under the deal, each SCRI share was exchanged for \$16.50 in cash and 0.1906 TEVA ADRs. Based on TEVA's Jan. 21 close of \$58.76, the per share consideration for each outstanding share of SCRI was \$27.70. SCRI shareholders will own about 7% of TEVA on a fully diluted basis. TEVA said the deal strengthens its injectable and oral generics business and adds biogenerics capabilities.

In conjunction with the acquisition, TEVA subsidiary Teva Pharmaceutical Finance II LLC raised \$1 billion through the sale of \$400 million in series A convertible senior debentures and \$600 million in series B convertible senior debentures, both due 2024. The series A debentures convert at \$75.80, a 29% premium over TEVA's Jan. 21 close. The series B debentures convert at \$70.51, a 20% premium.

REGULATORY

Amgen Inc. (AMGN), Thousand Oaks, Calif.
Wyeth (WYE), Madison, N.J.

Product: Enbrel etanercept
Business: Autoimmune

The EMEA granted marketing approval to WYE's Wyeth Pharmaceuticals unit for Enbrel to treat severe ankylosing spondylitis in adults who have had an inadequate response to conventional therapy. Enbrel already is approved in Europe for rheumatoid arthritis (RA) and psoriatic arthritis in adults, as well as juvenile chronic arthritis. Enbrel is approved in the U.S. to treat moderate to severe active RA, psoriatic arthritis and ankylosing spondylitis. WYE co-developed Enbrel with Immunex Corp., which AMGN acquired. WYE has marketing rights outside of North America, and the companies co-promote in North America.

Aventis S.A. (AVE), Strasbourg, France
Product: Mononine plasma-derived factor IX concentrate
Business: Hematology

The EMEA granted marketing approval for AVE's Mononine for continuous intravenous infusion to treat hemophilia B patients undergoing surgery, exposed to trauma or experiencing severe spontaneous hemorrhage.

Biogen Idec Inc. (BIIB), Cambridge, Mass.
Schering AG (FSE:SCH; SHR), Berlin, Germany
Product: Zevalin ibritumomab tiuxetan (IDEC-Y2B8)
Business: Cancer

BIIB's marketing partner SCH received European approval for Zevalin to treat adult patients with CD20-positive follicular B cell non-Hodgkin's lymphoma (NHL) that has relapsed or is refractory to therapy with Rituxan rituximab. BIIB markets Zevalin in the U.S. to treat NHL that is refractory to either chemotherapy or Rituxan. Rituxan is marketed by BIIB and partners Genentech Inc. (DNA, South San Francisco, Calif.) and Roche (SWX:ROZ, Basel, Switzerland). SCH, which holds marketing and distribution rights for Zevalin outside the U.S., hopes to launch the radioimmunotherapy in the next few months.

Digene Corp. (DIGE), Gaithersburg, Md.
Product: hc2 High-Risk human papillomavirus (HPV) DNA Test
Business: Diagnostic

France approved reimbursement of DIGE's HPV diagnostic for follow-up evaluation of women with borderline Pap test results. The agency also said it would study use of the test for routine, primary screening for cervical cancer in conjunction with the Pap test.

Galen Holdings plc (LSE:GAL; GALN), Craigavon, U.K.
Product: Ovcon-35 chewable contraceptive tablets
Business: Genitourinary

GAL subsidiary Warner Chilcott Inc. received 3-year Hatch/Waxman exclusivity for its Ovcon-35. The exclusivity will expire November 14, 2006.

Genentech Inc. (DNA), South San Francisco, Calif.
OSI Pharmaceuticals Inc. (OSIP), Melville, N.Y.
Roche (SWX:ROZ), Basel, Switzerland
Product: Tarceva erlotinib (OSI-774)
Business: Cancer

OSIP submitted to the FDA the preclinical and chemistry, manufacturing and controls (CMC) sections of a rolling NDA for Tarceva erlotinib to treat incurable, refractory stage IIIB/IV non-small cell lung cancer (NSCLC). OSIP expects data from a Phase III trial of Tarceva in NSCLC in the second quarter, after which it will submit additional components of the NDA. The oral small molecule inhibitor of the epidermal growth factor (EGF) receptor kinase has Fast Track designation in NSCLC, and is partnered with DNA and ROCZ.

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Regulatory,
from previous page

Millennium Pharmaceuticals Inc. (MLNM), Cambridge, Mass.

Johnson & Johnson (JNJ), New Brunswick, N.J.

Product: Velcade bortezomib (MLN341, LDP-341, PS-341)

Business: Cancer

The CPMP recommended marketing approval of MLNM's Velcade to treat patients with progressive multiple myeloma (MM) that is refractory to at least two prior therapies. MLNM expects the European Commission to approve the MAA in the second quarter. JNJ's Ortho Biotech Products L.P. unit has ex-U.S. commercialization rights, and MLNM is eligible for royalties. MLNM markets the small molecule dipeptide boronic acid proteasome inhibitor in the U.S. to treat progressive MM refractory to at least two therapies.

Pfizer Inc. (PFE), New York, N.Y.

Product: Zithromax azithromycin

Business: Infectious

The FDA granted marketing approval to PFE for Zithromax as a once-daily, three-day treatment for acute bacterial sinusitis (ABS). Zithromax already is marketed as a once-daily, five-day treatment for common bacterial infections.

Protein Design Labs Inc. (PDLI), Fremont, Calif.

Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan

Novartis AG (SWX:NOVN; NVS), Basel, Switzerland

Roche (SWX:ROCZ), Basel, Switzerland

Wyeth (WYE), Madison, N.J.

Product: Simulect basiliximab and Zenapax daclizumab

Business: Transplant

The U.K.'s NICE issued a final appraisal document on immunosuppressive therapy for renal transplantation that recommended use of NVS's Simulect and Zenapax from PDLI and ROCZ as part of a calcineurin inhibitor-based immunosuppressive regimen. NICE recommended the drugs for induction therapy in the prophylaxis of acute organ rejection in patients undergoing renal transplantation, and said the therapy with the lowest acquisition cost should be used.

NICE also said that in initial or maintenance immunosuppressive therapy, a doctors' choice between Prograf tacrolimus from Fujisawa and NVS's Neoral cyclosporine should be based on the relative importance of their side effect profiles for individual patients.

Finally, NICE said CellCept mycophenolate from ROCZ and Rapamune sirolimus from WYE should be used only in cases of proven intolerance to calcineurin inhibitors.

Sanofi-Synthelabo SA (SNY; Euronext:SAN), Paris, France

Product: Eloxatin oxaliplatin

Business: Cancer

SAN submitted an sNDA in the U.S. and an application for an extension of the European indication with Reference Member State France for Eloxatin as an adjuvant to treat patients with colon cancer.

The compound is marketed in the U.S. and Europe to treat advanced colorectal cancer in combination with 5-FU and leucovorin. It recently was approved in the U.S. for first-line treatment of metastatic colorectal cancer. Eloxatin was developed with Debiopharm SA (Lausanne, Switzerland).

Vicuron Pharmaceuticals Inc. (MICU; NMErc:MICU), King of Prussia, Penn.

Product: Anidulafungin (formerly V-Echinocandin)

Business: Infectious

The FDA requested additional pharmacokinetic data from MICU for

its NDA for anidulafungin to treat esophageal candidiasis. As a result, the FDA extended for 90 days to May 25 the review period for the NDA. MICU said "it is our understanding that this extension is not related to any specific concerns regarding safety and efficacy." MICU plans "to answer all the outstanding questions in the next seven to ten days" and does not expect the questions to directly affect labeling. MICU added that the FDA's requests do not relate to patient populations, drug/drug interactions or the elimination of the compound from the body. MICU still expects to launch the echinocandin antifungal in the first half of the year.

SALES & MARKETING

Dow Chemical Co. (DOW), Midland, Mich.

Business: Supply/Service

DOW's Dowpharma manufacturing services unit launched a next-generation microbial expression technology for the production of recombinant proteins. The technology uses specially designed strains of *Pseudomonas fluorescens* that increase cellular expression while maintaining solubility and activity of recombinant proteins.

Eksigent Technologies, Livermore, Calif.

Business: Microfluidics, Proteomics

Eksigent launched its NanoLC-2D Proteomics System, a high performance liquid chromatography (HPLC) system that incorporates fully automated two-dimensional HPLC separations with a direct pumping nanoscale HPLC. The product uses Eksigent's Microfluidic Flow Control (MFC) technology.

Gene Tools LLC, Corvallis, Ore.

Business: Bioinformatics

Gene Tools launched its Expression Arrest Zebrafish Morpholino Library, an antisense product for deciphering the gene function in multicellular vertebrates. Open Biosystems, Inc. (Huntsville, Ala.) will exclusively market the product.

Guilford Pharmaceuticals Inc. (GLFD), Baltimore, Md.

Business: Cardiovascular

GLFD doubled its sales force to 53 reps and relaunched Aggrastat tirofiban injection in the U.S. GLFD said that in the second half of this year, it plans to begin a Phase III trial of the glycoprotein GPIIb/IIIa (CD41/CD61) receptor antagonist in patients undergoing percutaneous coronary intervention (PCI). In October 2003, GLFD acquired from Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) the rights to Aggrastat for all platelet-mediated cardiovascular diseases in the U.S., Puerto Rico, the Virgin Islands and Guam. MRK continues to market Aggrastat in all other countries.

Lifecore Biomedical Inc. (LCBM), Chaska, Minn.

Hexal AG, Holzkirchen, Germany

Business: Autoimmune

Hexal will become the exclusive supplier of LCBM's generic hyaluronan knee injection in Germany, the Czech Republic, Denmark, Norway, Poland and Sweden, as well as selected Middle Eastern countries. LCBM may expand Hexal's exclusivity to other territories based on Hexal's performance.

Lion bioscience AG (FSE:LIO; LEON), Heidelberg, Germany

Business: Bioinformatics, Genomics

LIO launched its SRS Gateway for Oracle. The new software product combines the SRS and Oracle databases for drug discovery data searches.

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Sales & Marketing,
from previous page

QTL Biosystems LLC, Santa Fe, N.M.

Business: Supply/Service

QTL launched its QTL Lightspeed Protein Kinase A (PKA) Assay Kit, which uses a fluorescent polyelectrolyte-based super-quenching polymer.

Schering-Plough Corp. (SGP), Kenilworth, N.J.

Business: Infectious

SGP launched its Rebetol ribavirin oral solution for combination with Intron A interferon alfa 2-b to treat pediatric patients with chronic hepatitis C virus (HCV). Rebetol oral solution and capsules are both approved in combination with Intron A interferon alfa 2-b to treat chronic HCV infection in patients ages three and older with compensated liver disease who have not been previously treated with interferon alpha. Rebetol has Orphan Drug status for the pediatric indication.

OTHER NEWS

Biogen Idec Inc. (BIIB), Cambridge, Mass.

Corixa Corp. (CRXA), Seattle, Wash.

GlaxoSmithKline plc (LSE:GSK; GSK), London, U.K.

Business: Cancer

The U.S. District Court for the Southern District of California vacated a previous summary judgment in favor of BIIB, which ruled that four patents covering non-Hodgkin's lymphoma (NHL) drug Bexxar tositumomab from CRXA and GSK were unenforceable because of the inventors' "inequitable conduct in the prosecution of the underlying patent applications" (see *BioCentury*, Oct. 20, 2003). CRXA said the decision to vacate was based on new and previously unconsidered evidence. CRXA also said the Court denied BIIB's motion for summary judgment of inequitable conduct. CRXA said that although "pending litigation regarding these patents will continue in the U.S. District Court for the Southern District of California," there is no reason for CRXA to file an appeal to the Federal Circuit.

Idec Pharmaceuticals Corp., which merged with Biogen Inc. to form BIIB in November 2003, filed suit against CRXA, Coulter Pharmaceutical (which CRXA acquired in December 2000) and the Regents of the University of Michigan in 2001, seeking a declaratory judgment that Idec's Zevalin radioimmunotherapy for NHL does not infringe patents covering Bexxar, or that such patents were invalid. CRXA, the University of Michigan and GSK countersued, alleging that Zevalin infringed the four patents.

BioTie Therapies Corp. (HSE:BTT), Turku, Finland

Business: Cardiovascular, Cancer, Infectious

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BTT restructured and will close its Viikki-based unit, which employed 16 staff in discovery phase research and support functions. BTT has offered some of the staff positions in the Turku unit. For the nine months ended Sept. 30, 2003, BTT had a net loss of €20.4 million (\$23.4 million) and cash of €13.5 million (\$15.5 million).

BresaGen Ltd. (ASX:BGN; BSGNY), Adelaide, Australia
Business: Agbio/Environmental, Autoimmune, Cancer

BGN appointed Ferrier Hodgson as administrators. The appointment follows the termination of negotiations with CM Capital Investments, which was considering investing in BGN. BGN also temporarily suspended its trading on the Australian Stock Exchange.

Eli Lilly and Co. (LLY), Indianapolis, Ind.

Business: Pharmaceuticals

LLY will seek to partner with government-approved programs in conjunction with provisions of Medicare prescription drug legislation to make its drug discount card available to seniors with incomes below 200% of the federal poverty level, who do not currently have prescription drug coverage. LLY's discount card allows low-income seniors without prescription drug coverage to pay a flat fee of \$12 for a 30-day supply of any LLY retail products.

Labopharm Inc. (TSE:DDS), Laval, Quebec

Business: Neurology

Labopharm Europe Ltd., a subsidiary of DDS, opened a new office in Dublin, Ireland.

MANAGEMENT TRACKS

Boards of Directors

BresaGen Ltd. (ASX:BGN; BSGNY), Adelaide, Australia

Business: Agbio/Environmental, Autoimmune, Cancer

Appointed: Rudy Mazzocchi as chairman

Resigned: Peter Hart; Chris Juttner; and John Harkness

Cellegy Pharmaceuticals Inc. (CLGY), South San Francisco, Calif.

Business: Drug delivery, Metabolic, Dermatology

Appointed: Robert Rothermel, a partner at CroBern Management Partnership

Cellular Genomics Inc., Branford, Conn.

Business: Autoimmune, Inflammation, Cancer

Appointed: Nick Colangelo, managing director of Lilly Bioventures; and Douglas Reed, managing director of Vector Fund Management

InterMune Inc. (ITMN), Brisbane, Calif.

Business: Pulmonary, Cancer, Infectious

Appointed: Michael Smith, EVP, CFO and chief accounting officer of Anthem Blue Cross and Blue Shield

KuDos Pharmaceuticals Ltd., Cambridge, U.K.

Business: Cancer

Appointed: Zeev Zehavi, VP of Johnson & Johnson Development Corp.

Medicure Inc. (TSE:MPH), Winnipeg, Manitoba

Business: Cardiovascular

Appointed: Gerald McDole, former president and CEO of AstraZeneca plc's AstraZeneca Canada Inc. subsidiary

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Management Tracks,
from previous page

Molecular Staging Inc., New Haven, Conn.
Business: Proteomics, Genomics, Diagnostic
Appointed: Richard Barker, former CEO of Chiron Corp.'s Chiron Diagnostics unit, as executive chairman

Neurobiological Technologies Inc. (NTII), Richmond, Calif.
Business: Neurology
Appointed: F. Van Kasper, former chairman and CEO of Van Kasper and Co.

NitroMed Inc. (NTMD), Bedford, Mass.
Business: Cardiovascular, Inflammation
Appointed: Joseph Loscalzo, chairman of Boston University's department of medicine

Rigel Pharmaceuticals Inc. (RIGL), South San Francisco, Calif.
Business: Functional genomics
Appointed: Hollings Renton, president, CEO and chairman of Onyx Pharmaceuticals Inc.

SelectX Pharmaceuticals Inc., Worcester, Mass.
Business: Chemistry
Appointed: Robert Schier, partner at inventages venture capital GmbH

Spectrum Pharmaceuticals Inc. (SPPI), Irvine, Calif.
Business: Cancer
Appointed: Anthony Maida, chairman of BioConsul Drug Development Corp.

Teva Pharmaceutical Industries Ltd. (TEVA), Jerusalem, Israel
Business: Generics
Appointed: Carlo Salvi, formerly vice chairman of Sicor Inc.

VaxGen Inc. (VXGN), Brisbane, Calif.
Business: Infectious
Resigned: David Beier

Management

AmpliMed Corp., Tuscon, Ariz.
Business: Cancer
Hired: Robert Ashley as chairman, president and CEO, previously SVP of commercial development at CollaGenex Pharmaceuticals Inc.
Transition: Evan Hersh to VP medical affairs and CMO from CEO

Amsterdam Molecular Therapeutics B.V., Amsterdam, the Netherlands
Business: Gene/Cell therapy
Hired: Sander van Deventer as CSO, while remaining professor and head of Gastroenterology at the Academic Medical Center in Amsterdam.

ARYx Therapeutics Inc., Santa Clara, Calif.
Business: Chemistry
Hired: John Varian as COO, formerly CFO of Genset SA; Donn Dennis as VP pharmacology, formerly professor of anesthesiology and pharmacology at the College of Medicine at the University of Florida; and David Nagler as VP corporate affairs, formerly VP of human resources at Genentech Inc.

Atrix Laboratories Inc. (ATRX), Fort Collins, Colo.
Business: Drug delivery
Promoted: Stephen Warren to CSO, while remaining VP of R&D

Calypte Biomedical Corp. (CYPT), Alameda, Calif.
Business: Antibodies, Diagnostic
Promoted: Richard George to president and CEO from VP of governmental affairs; and Richard Van Maanen to VP of operations from director of marketing and director of international business development
Resigned: Jay Oyakawa as president, COO and a director

Hypnion Inc., Worcester, Mass.
Business: Neurology
Hired: Robert Poole as CMO, formerly VP and worldwide therapy leader for neuroscience clinical development at Pfizer Inc.'s Pfizer Global Research and Development unit

Idun Pharmaceuticals Inc., San Diego, Calif.
Business: Inflammation, Cardiovascular, Infectious
Hired: Jennifer Giottonini as VP of corporate development, formerly VP of business development at Isis Pharmaceuticals Inc.

Immusol Inc., San Diego, Calif.
Business: Cardiovascular, Infectious, Cancer
Hired: Nicholas Paoni as VP of therapeutics, formerly research professor in the department of chemistry and biochemistry at the University of Notre Dame; and Clark Springgate as VP of clinical and regulatory, formerly CMO of Glycogenesis Inc.

InterMune Inc. (ITMN), Brisbane, Calif.
Business: Infectious
Departing: James Pennington, as EVP of medical and scientific affairs; Dan Welch, president and CEO, will assume interim R&D responsibilities

KuDos Pharmaceuticals Ltd., Cambridge, U.K.
Business: Cancer
Promoted: Graeme Smith to research director from head of drug evaluation

NeoGenomics Inc., Fort Myers, Fla.
Business: Genomics, Diagnostic
Hired: Thomas White as CEO, formerly president and CEO of SmartPill Corp.

Pozen Inc. (POZN), Chapel Hill, N.C.
Business: Neurology
Resigned: Matthew Czajkowski as CFO; John Barnhardt, VP of finance and administration, will act as interim CFO

Sopherion Therapeutics Inc., New Haven, Conn.
Business: Cancer, Autoimmune, Inflammation
Hired: Gunnar Casserstedt as CFO and VP of finance, formerly VP of R&D finance at Pharmacia Corp.

VaxGen Inc. (VXGN), Brisbane, Calif.
Business: Infectious
Resigned: Donald Francis as president; Carter Lee as SVP of finance and administration; and Phillip Berman as SVP of R&D

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CLINICAL NEWS

Clinical activities and selected announcements for the week ended Jan. 23.

CLINICAL RESULTS

Avant Immunotherapeutics Inc. (AVAN), Needham, Mass.

Product: CholeraGarde

Business: Infectious

Molecular target: NA

Description: PERU-15 cholera vaccine

Standard indication: Cholera

Indication: Prevent cholera

Endpoint: Safety and immunogenicity

Status: Phase II

Milestone: Complete Phase II 2H04

Results from 70 adults in a Phase II trial in Bangladesh showed a single dose of CholeraGarde was well tolerated. AVAN said over 70% of patients had a favorable immune response. The company plans to present detailed data at the Vaccines for Enteric Diseases meeting in April, and will not disclose additional data until then. The trial also is enrolling 240 pediatric patients.

Curacyte AG, Munich, Germany

Product: Pyridoxalated hemoglobin polyoxyethylene (PHP)

Business: Cancer

Molecular target: Nitric oxide (NO)

Description: NO scavenger

Standard indication: Sepsis

Indication: Treat septic shock

Endpoint: 28-day all cause mortality, days alive and free of both cardiovascular dysfunction and ventilation

Status: Phase IIc

Milestone: Start Phase I/II 1Q04

In a placebo-controlled, U.S. Phase IIc study in 62 septic shock patients, PHP caused a trend towards meeting the dual primary endpoints. Curacyte said the trial size was too low to reach significance for the primary endpoints. PHP was safe and well tolerated. Curacyte will seek a development and marketing partner for PHP in septic shock prior to starting the Phase III studies. Also, Curacyte will start in the first quarter a Phase I/II study of PHP plus IL-2 to treat renal cell carcinoma and metastatic melanoma.

CV Therapeutics Inc. (CVTX), Palo Alto, Calif.

Product: Ranexa ranolazine

Business: Cardiovascular

Molecular target: Enoyl-CoA-hydratase

Description: Anti-ischemic agent; partial inhibitor of enoyl-CoA-hydratase

Standard indication: Angina

Indication: Treat chronic stable angina

Endpoint: Exercise duration, time to onset of angina, HbA1c levels

Status: Phase III data; approvable letter

Milestone: NA

Previously reported results of the double-blind, placebo-controlled, international Phase III CARISA trial showed Ranexa prolonged exercise duration and time to onset of angina. Survival for the 750 patients taking Ranexa during CARISA or its associated open-label study was 98.4% in the first year and 95.9% in the second year. Data were published in the *Journal of the American Medical Association*. In 2001, CVTX reported that Ranexa met the primary endpoint in the CARISA study (see *BioCentury*, Nov. 19, 2001). CVTX received an FDA approvable letter for Ranexa, in which the agency requested additional clinical data (see *BioCentury*, Dec. 12, 2003).

Forest Laboratories Inc. (FRX), New York, N.Y.

H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark

Merz + Co. GmbH, Frankfurt, Germany

Neurobiological Technologies Inc. (NTII), Richmond, Calif.

Product: Namenda (Ebixa in EU) memantine

Business: Neurology

Molecular target: NMDA receptor

Description: Oral NMDA receptor antagonist

Standard indication: Alzheimer's disease (AD)

Indication: Treat moderate to severe AD

Endpoint: Severe Impairment Battery (SIB), ADCS-ADL, and CIBIC-Plus measurement scale

Status: Phase III data; marketed

Milestone: FRX to seek label expansion for mild to moderate AD in mid-2004

Previously reported results of a double-blind Phase III trial in 403 patients showed memantine plus Aricept donepezil from Pfizer Inc. (PFE, New York, N.Y.) significantly improved scores on the SIB scale and ADCS-ADL scale compared to donepezil plus placebo, the trial's primary endpoint. Results from the trial were initially reported in 2002 (see *BioCentury*, Sept. 16, 2002). Memantine was discovered by NTII, and FRX has an exclusive license to market memantine in the U.S. from NTII partner Merz. LUN markets the compound in Europe. FRX expects to launch the compound this month in the U.S.

InterMune Inc. (ITMN), Brisbane, Calif.

Product: Actimmune

Business: Infectious

Molecular target: Interferon (IFN) gamma receptor

Description: IFN gamma-1b

Standard indication: Hepatitis C virus (HCV)

Indication: Treat liver cirrhosis caused by HCV infection

Endpoint: Reduction in fibrosis score on Ishak fibrosis scale

Status: Phase II; marketed to treat chronic granulomatous disease and severe, malignant osteopetrosis

Milestone: Phase III ovarian cancer results 1H04; Phase III IPF trial
See next page

Management Tracks,
from previous page**Xcyte Therapies Inc.**, Seattle, Wash.

Business: Cancer, Infectious

Hired: Robert Kirkman as CBO and VP, formerly VP of business development and corporate communications at Protein Design Labs Inc.

Scientific Advisory Boards**LifeCycle Pharma A/S**, Horsholm, Denmark

Business: Drug delivery

Appointed: Leslie Benet, professor of biopharmaceutical sciences at the University of California, San Francisco; Joseph Robinson, professor of pharmacy and ophthalmology at the University of Wisconsin

Clinical Results, from previous page

enrollment complete 4Q05

In a double-blind, placebo-controlled Phase II trial in 500 patients, Actimmune did not reverse liver fibrosis, the primary endpoint. ITMN said the result has no impact on ongoing Phase III studies of Actimmune to treat idiopathic pulmonary fibrosis (IPF) and ovarian cancer. ITMN said it is not pursuing Actimmune for fibrosis due to HCV infection.

Neurochem Inc. (TSE:NRM), St. Laurent, Quebec
Product: Alzhemed (NC-531)
Business: Neurology
Molecular target: Beta amyloid
Description: Inhibitor of beta amyloid interactions with glycosaminoglycans
Standard indication: Alzheimer's disease (AD)
Indication: Treat mild to moderate Alzheimer's disease (AD)
Endpoint: Safety, cognitive function as measured by ADAS-cog
Status: Phase II
Milestone: Start Phase III in 1H04

Nine month results from a 42-patient, open-label extension of a Phase II trial showed the average ADAS-cog score was +4.4 points in 30 patients who completed nine months of additional treatment with 300 mg of Alzhemed daily. NRM said this compares to +7.2 for historical controls. In the original study, 58 patients received placebo, 100 mg, 200 mg or 300 mg of Alzhemed daily (see *BioCentury*, June 30, 2003). The 9 patients who received 300 mg of Alzhemed in both the trial and the extension performed better, with an average ADAS-cog score of +2.0. The 18 patients with mild disease showed an average ADAS-cog score of +1.4, which NRM said compares to +5.6 for historical controls. Of the 12 who discontinued treatment, 1 did so due to a drug-related adverse event, which was nausea and vomiting.

Pharming Group N.V. (Euronext:PHARM), Leiden, the Netherlands
Product: rhC1INH
Business: Cardiovascular
Molecular target: Complement I (C1) esterase
Description: Recombinant human complement C1 inhibitor
Standard indication: Angioedema
Indication: Treat hereditary angioedema (HAE)
Endpoint: Time to beginning of relief compared to historical controls
Status: Phase II
Milestone: Updated data in 1H04; start U.S. and European Phase III trials 1H04

Interim results from an open-label, Dutch Phase II trial in an undisclosed number of patients showed rhC1INH gave a time to beginning of relief in the range of 15 minutes to 4 hours. PHARM said it will disclose whether or not it statistically improved the endpoint when it updates the data from the trial. Time to complete resolution was 1 hour to 48 hours. PHARM said HAE attacks typically last 2-5 days. No allergic or clinically relevant immune responses were observed. No patients had an HAE attack relapse.

PRECLINICAL RESULTS

Chrysalis BioTechnology Inc., Galveston, Texas
Product: Chrysalin 23-amino acid synthetic peptide
Indication: Musculoskeletal

In a preclinical model of maxillary sinus bone grafting, Chrysalin plus carrier bone grafting material generated significantly more new bone than carrier alone ($p < 0.005$).

Cortex Pharmaceuticals Inc. (COR), Irvine, Calif.
Les Laboratoires Servier, Neuilly sur Seine, France
Product: S-40929

Indication: Neurodegenerative diseases

In memory tests carried out in primates, S-40929 was about 2000 times more active than Ampakine CX516. Based on its effects on AMPA receptors, COR said S-40929 is more likely to increase the levels of neurotrophins, such as BDNF. The partners are co-developing S-40929 and other compounds (see B2).

Large Scale Biotechnology Corp. (LBSC), Vacaville, Calif., et al
Product: Plant-product alpha-galactosidase A
Indication: Treat Fabry's disease

Researchers published in *Preclinica* that plant-derived alpha-galactosidase A significantly reduced excessive lipid levels (GB3) in target organs in a mouse model of Fabry's disease. Tissue distribution studies showed proper targeting of the enzyme to affected organs and no apparent toxicity or tissue damage. No neutralizing antibodies were observed in extended infusion studies.

Maxim Pharmaceuticals Inc. (SSE:MAXM; MAXM), San Diego, Calif.
Myriad Genetics Inc. (MYGN), Salt Lake City, Utah
Product: MPC-6827 apoptosis inducing compound
Indication: Treat cancer

In a mouse model of pancreatic cancer, MPC-6827 significantly inhibited tumor growth to a greater extent than gemcitabine (38% vs. 17% inhibition compared to controls, respectively). In a mouse model of melanoma, 60% of mice treated with MPC-6827 were alive at the end of the study compared to 30% of mice treated with paclitaxel and 10% of control mice. In a mouse model of breast cancer, all three dose groups of MPC-6827 halted tumor progression. Under a 2003 deal, MYGN licensed rights to the compound from MAXM (see *BioCentury*, Dec. 8, 2003).

CLINICAL STATUS

Akzo Nobel NV (AKZOY; Euronext:AKZ), Arnhem, the Netherlands
Schering AG (FSE:SCH; SHR), Berlin, Germany
Product: Birth control for men
Business: Endocrine
Molecular target: NA
Description: Progestogen etonogestrel implant plus long-acting injected testosterone undecanoate
Standard indication: Contraception
Indication: Male birth control
Endpoint: Sperm count
Status: Phase II
Milestone: Results 4Q05

SCH and AKZOY's Organon NV (Oss, the Netherlands) started a double-blind, European Phase II study in 350 men, who will receive Organon's progestogen etonogestrel implant plus SCH's long-acting injected testosterone undecanoate birth control for men. The study will evaluate six dose levels of the combination.

Astralis Ltd. (ASTR), Fairfield, N.J.
Product: Psoraxine
Business: Autoimmune
Molecular target: NA
Description: Protein extract of Leishmania
Standard indication: Psoriasis
Indication: Treat stable, moderate psoriasis
Endpoint: Safety, PASI score and quality of life

See next page

Clinical Status,
from previous page

Status: Phase I

Milestone: Start Phase II in 2004

ASTR completed enrollment of 20 patients in a blinded Phase I trial.

Biolipox SA, Stockholm, Sweden

NicOx SA (NM:Nicox), Sophia-Antipolis, France

Product: NCX 1510

Business: Inflammation

Molecular target: Histamine receptor

Description: Nasal spray of nitric oxide-donating derivative of an undisclosed antihistamine

Standard indication: Rhinitis

Indication: Treat allergic rhinitis

Endpoint: Reported symptoms

Status: Phase IIa

Milestone: Results mid-2004

Biolipox started a double-blind, placebo-controlled, cross-over Swedish Phase IIa study in 36 patients. The trial will measure symptoms following out-of-season allergen provocation.

Epimmune Inc. (EPMN), San Diego, Calif.

Product: EP HIV-1090

Business: Infectious

Molecular target: NA

Description: DNA vaccine formulated with PVP polymer encoding 21 unique HIV CTL epitopes and EPMN's Padre helper T-cell epitope

Standard indication: HIV/AIDS

Indication: Treat HIV infection

Endpoint: Safety, immune response

Status: Phase I/II

Milestone: Results July 2004; start Phase II 2H04

EPMN completed enrollment in a double-blind, placebo-controlled, U.S. Phase I/II trial in 40 patients. The trial is divided into 4 dosing cohorts of 10 patients each, who are receiving the vaccine while remaining on HAART therapy. The company plans to begin in the second half of the year a Phase II trial in which patients will be immunized and then taken off HAART therapy as part of a structured treatment interruption.

ExonHit Therapeutics SA, Paris, France

Product: Ikomio (EHT 0201) pentoxifylline

Business: Neurological

Molecular target: Phosphodiesterase-4 (PDE-4)

Description: PDE-4 inhibitor

Standard indication: Amyotrophic lateral sclerosis (ALS)

Indication: Treat ALS

Endpoint: Survival

Status: Phase II

Milestone: Results 4Q04

An independent DSMB recommended that Exonhit continue its 400-patient, double-blind, placebo-controlled, European Phase II trial of Ikomio or placebo plus Rilutek riluzole from Aventis S.A. (AVE, Strasbourg, France).

Munich Biotech AG, Neuried, Germany

Product: MBT-0206

Business: Cancer

Molecular target: Tubulin

Description: Intravenous paclitaxel formulated with EndoTag tumor

endothelial cell targeting technology

Standard indication: Breast cancer

Indication: Treat advanced metastatic breast cancer

Endpoint: Tumor response

Status: Phase II

Milestone: NA

Munich started an open-label, European Phase II trial in about 50 patients. A control arm will be added to the trial if undisclosed milestones are met.

Standard indication: Pancreatic cancer

Indication: Treat metastatic pancreatic cancer

Endpoint: Survival

Status: Phase II

Milestone: NA

Munich started an open-label, European Phase II trial in about 70 patients. A control arm will be added to the trial if undisclosed milestones are met.

Nastech Pharmaceutical Co. Inc. (NSTK), Bothell, Wash.

Product: PYY3-36 (PYY)

Business: Endocrine

Molecular target: Neuropeptide Y (NPY) receptor

Description: Nasal spray formulation of PYY3-36

Standard indication: Obesity

Indication: Treat obesity

Endpoint: Safety, pharmacokinetics, appetite and food intake for 24 hours following administration

Status: Undisclosed

Milestone: NA

NSTK began a dose-ranging, cross-over, double-blind, placebo-controlled, U.K. trial in 12 patients with a body mass index of 27-40 kg/m².

Progen Industries Ltd. (PGLAF), Brisbane, Australia

Product: PI-88

Business: Cancer

Molecular target: NA

Description: Sulfated mannopentaose phosphate anti-angiogenic agent

Standard indication: Melanoma

Indication: Treat melanoma

Endpoint: NA

Status: Phase II

Milestone: NA

PGLAF started a U.S. and Australian Phase II study in multiple myeloma (MM) patients.

Seattle Genetics Inc. (SGEN), Bothell, Wash.

Product: SGN-30

Business: Cancer

Molecular target: CD30

Description: Monoclonal antibody against CD30

Standard indication: Lymphoma

Indication: Treat Hodgkin's disease or anaplastic lymphoma

Endpoint: Safety, tumor response

Status: Phase II

Milestone: NA

SGN began an open-label, U.S. Phase II trial in up to 80 patients, 40 each with Hodgkin's disease and anaplastic large cell lymphoma.

Xoma Ltd. (XOMA), Berkeley, Calif.

Product: XMP.639

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ANALYST PICKS & CHANGES

Amgen Inc. (AMGN), Thousand Oaks, Calif.

Business: Biopharmaceuticals

SG Cowen analyst Eric Schmidt reduced his 2006-2008 Aranesp sales estimate to \$3.5 billion, \$3.6 billion and \$4 billion from \$3.6 billion, \$4.2 billion and \$4.8 billion to reflect European competition for EPO products. He believes the barriers to adoption of biogeneric EPOs are low because of physicians' comfort with their safety profile and cost-containment pressure. He said several European biogeneric competitors to reach market in 2006.

The lower sales estimates result in estimated EPS reductions of \$0.05 in 2006, \$0.25 in 2007 and \$0.35 in 2008, bringing the estimates to \$3.35, \$3.65 and \$3.90, respectively.

Schmidt still expects AMGN to earn \$2.45 on \$10.2 billion in revenue in 2004, growing to EPS of \$2.95 on revenue of \$12 billion in 2005. AMGN closed Friday at \$63.93.

Ariad Pharmaceuticals Inc. (ARIA), Cambridge, Mass.

Business: Cancer

Adams, Harkness & Hill analysts Felicia Reed and Patrick Flanigan began coverage with a "buy" rating. The analysts expect the company's shares to advance toward their \$12 year-end 2004 price target as investors get more visibility on ARIA's anticancer compounds, AP23573 and AP23464. AP23573, an inhibitor of mTOR cell signaling protein, is in Phase I trials in cancer, while AP23464, which acts as a specific inhibitor of Src, is in preclinical development for cancer metastases and leukemia. ARIA closed Friday at \$8.59.

Cephalon Inc. (CEPH), West Chester, Penn.

Business: Neurology, Cancer

SG Cowen analyst Eric Schmidt lowered his rating to "market perform" from "strong buy" based upon valuation and what he sees as an uncertain long-term outlook. Schmidt feels CEPH's franchise extension strategies for Provigil modafinil for narcolepsy and Actiq oral fentanyl for breakthrough cancer pain still carry substantial risks related to regulatory timing, physician adoption rates and reimbursement pressures. CEPH closed Friday at \$56.00.

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Clinical Status, from previous page

Business: Dermatology

Molecular target: Lipopolysaccharide (LPS)

Description: Topical synthetic peptide derived from bactericidal/permeability-increasing protein (BPI)

Standard indication: Acne

Indication: Treat mild to moderate acne

Endpoint: Decrease in the number of inflammatory lesions, non-inflammatory and total lesions, Physicians Global Severity Assessment, safety

Status: Phase II

Milestone: Results and decision on starting Phase III by year end

XOMA started a double-blind, placebo-controlled, dose-ranging, U.S. Phase II study in 240 patients.

OTHER RESEARCH NEWS

Genencor International Inc. (GCOR), Palo Alto, Calif., et al.

Product: Interferon (IFN) beta

Use: Treat multiple sclerosis (MS)

Researchers published in *Genes and Immunity* the identification of an epitope in human IFN beta that activates CD4 T cells that could be involved in the development of neutralizing antibodies. The researchers suggest the information could be used to engineer a second-generation IFN beta that is less immunogenic.

Maxim Pharmaceuticals Inc. (SSE:MAXM; MAXM), San Diego, Calif.

Product: MXI28533 series of small molecules

Use: Treat SARS coronavirus (SARS-CoV) infection

In culture, the MXI28533 series inhibited SARS-CoV at concentrations as low as 0.02 µg/ml and had no toxic effect on uninfected cells at all concentrations tested. MAXM said the compounds will be further evaluated before selecting a potential development candidate.

Riken Brain Science Institute, Wako City, Japan

Product: Trehalose disaccharide

Use: Treat Huntington's disease (HD)

Researchers published in *Nature Medicine* that in a mouse model of HD, oral administration of trehalose decreased polyglutamine aggregates in cerebrum and liver ($p < 0.01$ for both values), improved motor dysfunction ($p < 0.05$) and extended life-span ($p = 0.0015$) compared to controls.

The Scripps Research Institute, La Jolla, Calif., et al.

Product: Cytochrome P450 inhibitors

Use: Treat ischemia/reperfusion injury

Researchers published in the *Proceedings of the National Academy of Sciences* that cytochrome P450 inhibitors reduced infarct size in multiple animal models of ischemia, and suggested that P450 inhibitors could be used to treat ischemia/reperfusion injury.

Syrrx Inc., San Diego, Calif.

Product: Dipeptidyl peptidase IV (DP4) inhibitors

Use: Treat diabetes

Researchers published in *Protein Science* the crystal structure of DP4. In addition, Syrrx announced it selected three preclinical candidates from its DP4 inhibitor program. The three candidates are part of the joint collaboration between Syrrx and PPD Inc. (PPDI, Wilmington, N.C.) to develop DP4 inhibitors to treat Type II diabetes and other metabolic diseases (see *BioCentury*, Nov. 25, 2003).

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OFFERINGS & SECURITIES TRANSACTIONS

Week ended 1/23/04. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don't include overallocments. Currency rates used in the week; C\$=US\$0.7748; €=\$1.258; £=\$1.82

Completed Offerings

Athenix Corp., Research Triangle Park, N.C.
Business: Agbio/Environmental
Date completed: 1/20/04
Type: Venture financing
Raised: \$12.5 million
Investors: Intersouth Partners; Polaris Venture Partners; Boston Millennia Partners; Hunt Ventures; Eastman Ventures

BioTime Inc. (BTX), Berkeley, Calif.
Business: Hematology
Date completed: 1/22/04
Type: Rights offering of units
Raised: \$3.6 million
Shares: 2.6 million
Price: \$1.40
Shares after offering: 16.5 million
Note: BTX sold units in the rights offering, consisting of one common share and one-half of a warrant. Each full warrant entitles the holder to purchase over the next five years an additional share at

\$2. BTX said it could raise up to an additional \$750,000 through the sale of 428,571 additional units to certain people who acted as guarantors of the offering. Also, certain BTX debenture holders agreed to exchange \$1.5 million of the notes for units if the guarantor units are sold.

Callisto Pharmaceuticals Inc. (CLSP), New York, N.Y.
Business: Cancer, Musculoskeletal
Date completed: 1/21/04
Type: Private placement
Raised: \$5.9 million
Shares: 3.9 million
Price: \$1.50
Shares after offering: 25.1 million

Cellular Genomics Inc., Branford, Conn.
Business: Genomics, Functional genomics, Proteomics
Date completed: 1/21/04
Type: Venture financing
Raised: \$22.3 million
Investors: Lilly BioVentures; Coastview Capital; Emerging Technology Partners; Connecticut Innovations; Flagship Ventures; MPM Capital; Vector Fund Management

Corautus Genetics Inc. (CAQ), San Diego, Calif.
Business: Gene/Cell therapy, Cardiovascular

Date completed: 1/21/04
Type: Private placement of common stock and warrants
Raised: \$5.3 million
Shares: 1.2 million
Price: \$4.38
Shares after offering: 11.8 million
Investors: Vertical Ventures and Ardsley Partners
Note: Investors also received warrants to purchase 240,000 shares at \$6.72 each

Geniera Corp. (GENR), Plymouth Meeting, Penn.
Business: Cancer, Ophthalmic, Pulmonary
Date completed: 1/22/04
Type: Private placement of common stock and warrants
Raised: \$20 million
Shares: 5 million
Price: \$4.04
Shares after offering: 43.3 million
Note: Investors also received warrants to purchase 990,100 shares at \$5.38 each

Medical Discoveries Inc. (MLSC), Twin Falls, Idaho
Business: Infectious
Date completed: 1/21/04
Type: Private placement
Raised: \$1.1 million
Shares: Not disclosed
Price: Not disclosed
Shares outstanding prior: 65 mil-

lion
Investors: Angel investors

NeoPharm Inc. (NEOL), Bannockburn, Ill.
Business: Cancer
Date completed: 1/22/04
Type: Follow-on
Raised: \$68.4 million
Shares: 3.8 million
Price: \$18.25
Shares after offering: 22.3 million
Underwriters: UBS; Robert W. Baird; First Albany; JMP Securities
Overallocation: 525,000
Note: The company filed to sell 3.5 million shares on Jan. 7, when its price was \$17.93

Orexigen Therapeutics Inc., Princeton, N.J.
Business: Metabolic
Date completed: 1/21/04
Type: Venture financing
Raised: \$11 million
Investors: Domain Associates; Kleiner Perkins Caufield & Byers; Sofinnova Ventures
Note: The company is developing drugs for obesity

Pharming Group N.V. (Euro-next:PHAR), Leiden, the Netherlands
Business: Biomanufacturing, Metabolic, Cardiovascular
Date announced: 1/19/04

See next page

Analysts,
from previous page

Ciphergen Biosystems Inc. (CIPH), Palo Alto, Calif.
Business: Proteomics, Microarrays

Pacific Growth analyst Adam Chazan initiated coverage with an "equal weight" rating. He projects revenues of \$58 million and \$80 million in 2003 and 2004, with CIPH turning a profit in 2005. CIPH closed Friday at \$10.70.

Neurocrine Biosciences Inc. (NBIX), San Diego, Calif.
Business: Neurology, Cancer, Endocrine

SG Cowen analyst Phil Nadeau upgraded his rating to "outperform" from "market perform" based on 2004 milestones, including the submission of an NDA for Indiplon for insomnia. He believes that NBIX's technology value should expand from the current \$1.3 billion to the \$2-\$3 billion range for his peer group, which includes

Icos Corp. (ICOS, Bothell, Wash.), ImClone Systems Inc. (IMCL, New York, N.Y.), Sepracor Inc. (SEPR, Marlborough, Mass.) and Amylin Pharmaceuticals Inc. (AMLN, San Diego, Calif.). He expects NBIX to approach breakeven in 2004, and turn a profit in 2005. NBIX closed Friday at \$58.30.

Nuvelo Inc. (NUVO), Sunnyvale, Calif.
Business: Cardiovascular, Cancer

Rodman & Renshaw analyst David Wood raised his price target to \$7 from \$5 after reviewing the market potential of ARC183 and alfineprase. Earlier this month, NUVO partnered with Archemix Corp. (Cambridge, Mass.) to develop ARC183, an antithrombin aptamer in preclinical development for use during coronary artery bypass graft (CABG) surgery and other acute anticoagulant indications (see *BioCentury*, Jan. 19). Alfineprase, a modified fibrinolytic thrombolytic, is in Phase II testing to treat peripheral arterial occlusion and is partnered with Amgen Inc. (AMGN). NUVO closed Friday at \$4.40.

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Completed Offerings,
from previous page

Type: Private placement
 Raised: €25 million (\$31.5 million)
 Shares: 18 million
 Price: €1.40 (\$1.76)
 Shares after offering: 66.1 million
 Placement agent: van der Hoop Effektenbank
 Advisor: First Dutch Capital
 Note: Investors also received one-year warrants to purchase 2.7 million shares at €2. PHARM plans to issue an additional 9.3 million shares to convert €5.8 million in short-term debt into equity. The company will have €0.3 million in debt outstanding after the conversion. Shares outstanding include those to be issued in the debt conversion.

Phytomedics Inc., Dayton, N.J.
 Business: Nutraceuticals, Autoimmune, Cancer
 Date completed: 1/20/04
 Type: Venture financing
 Raised: \$7.5 million
 Investors: inventages venture capital; Burrill & Co.
 Note: The company is developing botanical-based drugs and nutraceuticals

Pluristem Life Sciences Inc. (PLRS), Haifa, Israel
 Business: Gene/Cell therapy
 Date completed: 1/21/04
 Type: Private placement
 Raised: \$1.5 million
 Shares: Not disclosed
 Price: Not disclosed
 Shares outstanding prior: 22 million

RegeneRx Biopharmaceuticals Inc. (RGRX), Bethesda, Md.
 Business: Dermatology
 Date completed: 1/23/04
 Type: Private placement of common stock and warrants
 Raised: \$2.3 million
 Shares: 2.4 million
 Price: \$0.95
 Shares after offering: 32.6 million
 Investors: Sigma-Tau and other investors
 Note: Investors also received 30-month warrants to purchase 600,000 shares at \$1.50 each

SelectX Pharmaceuticals Inc., Worcester, Mass.
 Business: Chemistry
 Date completed: 1/22/04
 Type: Venture financing
 Raised: \$8 million
 Investors: inventages venture capital; TVM Techno Venture Management; Boston University Community Technology Fund
 Note: The company, which discovers and optimizes small molecules using biomedical chemistry techniques, said \$3 million of the financing is contingent upon achieving certain milestones

Proposed Offerings

Cepheid (CPHD), Sunnyvale, Calif.
 Business: Microfluidics, Diagnostic, Pharmacogenetics
 Date announced: 1/21/04
 Type: Direct public offering
 Shares: 5 million
 Shares after offering: 40.9 million
 Underwriter: UBS; William Blair; C.E. Unterberg, Towbin; Rodman
 Overallotment: 750,000
 Price prior: \$12.69

Dendreon Corp. (DNDN), Seattle, Wash.
 Business: Cancer
 Date announced: 1/20/04
 Type: Follow-on
 Shares: 8 million
 Shares after offering: 52.8 million
 Underwriter: UBS; Needham; Piper Jaffray; Lazard
 Overallotment: 1.2 million
 Price prior: \$11.29
 Note: The shares will be sold from a previously filed shelf registration

Amended Offerings

Corgentech Inc. (Proposed: CGTK), South San Francisco, Calif.
 Business: Cardiovascular
 Date announced: 1/20/04
 Type: IPO
 Shares: 5 million
 Price: \$14-\$16
 Shares after offering: 25.1 million
 Underwriter: CS First Boston; Lehman; CIBC World Markets;

Piper Jaffray
 Overallotment: 750,000
 Note: The company originally filed on Dec. 4, 2003, to raise up to \$86.3 million

Renovis Inc. (Proposed: RNVS), South San Francisco, Calif.
 Business: Neurology
 Date announced: 1/16/04
 Type: IPO
 Shares: 5.5 million
 Price: \$13-\$15
 Shares after offering: 23.6 million
 Underwriter: Goldman Sachs; CIBC World Markets; SG Cowen; Piper Jaffray
 Overallotment: 825,000
 Note: The company originally filed on Oct. 17, 2003, to raise up to \$75 million

Withdrawn Offerings

Acorda Therapeutics Inc., Hawthorne, N.Y.
 Business: Neurology
 Type: IPO
 Underwriters: Banc of America Securities; Lazard; Piper Jaffray; RBC Capital Markets
 Note: The company officially withdrew its offering, after postponing the deal in December 2003. Acorda originally filed to raise up to \$75 million on Sept. 29, 2003, then amended the filing on Dec. 2, 2003, to sell 4.75 million shares at \$12-\$14

Other Financial News

Amgen Inc. (AMGN), Thousand Oaks, Calif.
 Business: Biopharmaceuticals
 Date announced: 1/22/04
 AMGN disclosed in its earnings announcement that it spent \$578 million in the fourth quarter to repurchase about 10 million shares of common stock. For the year, AMGN spent \$1.8 billion to repurchase about 30 million shares.

Angiotech Pharmaceuticals Inc. (TSE: ANP), Vancouver, B.C.
 Business: Autoimmune, Cardiovascular
 Date announced: 1/21/04
 ANP's shareholders approved

a 2-for-1 split of the company's 41.6 million common shares. ANP expects to begin trading on a post-split basis on or around Feb. 3.

Atrix Laboratories Inc. (ATRX), Fort Collins, Colo.
 Business: Drug delivery
 Date announced: 1/16/04

ATRX filed a shelf registration covering the sale of up to \$150 million worth of debt, or common or preferred stock. ATRX, which closed Friday at \$25.00, now has 21.5 million shares outstanding.

Cellegy Pharmaceuticals Inc. (CLGY), South San Francisco, Calif.
 Business: Gastrointestinal, Genitourinary, Endocrine
 Date announced: 1/16/04

CLGY entered into a \$15 million equity financing facility through which Kingsbridge Capital is required to purchase 3.7 million shares of CLGY stock over the next two years. CLGY, which closed Friday at \$5.01, now has 20 million shares outstanding.

Galileo Genomics Inc., Montreal, Quebec
 Business: Genomics
 Date announced: 1/19/04

Galileo secured a C\$7 million (US\$5.4 million) loan from Investissement Quebec to discover genes related to 20 diseases. The company will rely primarily on its genetic data from the Quebec founder population.

Nanogen Inc. (NGEN), San Diego, Calif.
 Business: Microarrays, Genomics, Diagnostic
 Date announced: 1/15/04

NGEN filed a shelf registration covering the sale of up to 5 million shares. NGEN, which closed Friday at 11.46, now has 28.9 million shares outstanding.

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