

# R&D Directions

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An executive briefing on pharmaceutical research and development

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## 100 GREATEST INVESTIGATIONAL DRUGS

Novel compounds for unmet needs head R&D Directions' list of potentially important products

742457 • 773812 • Abagovomab • ABT-263 • ABT-874 • AD01 • Aflibercept • AGG-523 • Alveparmycin • Amigal  
APD125 • APD791 • Apixaban • Apremilast • Arzoxifene • AT 1001 • Atiprimod • AVE5026 • Axitinib • AZD3480  
Azedra • Azixa • Bapineuzumab • Bevasiranib • Bevirimat • Biovaxid • BL-1020 • Boceprevir • Bosutinib  
Bronchitol • Caprosin • DG051 • Desclomol • Elexacaftor • Evgacorus • FTY720 • GSK-2702068 • Hepa-1  
Denosumab • DG051 • Desclomol • Elexacaftor • Evgacorus • FTY720 • GSK-2702068 • Hepa-1  
Iclaprim • IPH 2101 • Karenitecin • Laquinimod • LCP-Morfen • LGD-466 • Linacloctide • Liraglutide  
Loxoprofen • MEM 3454 • Menveo • NKT-102 • NKTR-102 • NKTR-102 • NKTR-102 • NKTR-102 • NKTR-102  
NU1172 • Nuncacalib • Olanumab • Pazopanone • Pertuzumab • P3187207 • PL-4032 • prGCD • Rimegepant  
PYY3-36 Nasal Spray • R7128 • RDEA806 • Rivaroxaban • Romidepsin • Saxagliptin • SGN-33 • SGN-40 • SNX-5422  
SOM 230 • ST-246 • TB-401 • Telaprevir • Telavancin • TG 4010 • TG100801 • TMC-207 • TRC105 • Trodusquemine  
Vandetanib • Varespladib • Vicriviroc • VRX496 • VX-770 • XP13512 • ZO-201

# Fighting the odds

**Even as concern grows over the regulatory slowdown of drug approvals and the industry's need to become more innovative, companies are developing many novel drugs for unmet needs in treating cancer, HIV, hepatitis C, and Alzheimer's disease.**

By Michael D. Christel

**W**ith more pharmaceutical and biotech companies targeting unmet medical needs, specialty products continue to propel novel drug-development activity. Even as a heightened level of regulatory caution slows down the number of new molecular entities approved by FDA and European regulators, the intense focus on specialty drugs could help plug some of the leaks in R&D productivity.

Nine out of the 17 new molecular entities and two biologic license applications approved by FDA in 2007 had received priority review status, a designation given to compounds that are considered to offer major advances in treatment, or provide a treatment for which no effective therapy exists. FDA, while under heat from drugmakers for allegedly being too hypervigilant in the wake of some recent high-profile safety issues, does seem to be more cautious when weighing the risks and benefits of these products. Language in the recently passed FDA Amendments Act of 2007 emphasizes encouraging more innovation aimed at serious diseases with significant unmet medical needs.

Many compounds aimed at these diseases, designed by large and small companies throughout the world, were

selected for inclusion in *R&D Directions*' seventh-annual list of 100 great investigational drugs in development. Although cancer makes up the largest target group on the list, followed by HIV, which has seven molecules included, other treatment-challenged conditions are also well represented.

Six drugs for Alzheimer's disease, some also targeting other cognitive disorders, were chosen, including candidates from Wyeth (wyeth.com), GlaxoSmithKline (gsk.com), and AstraZeneca (astrazeneca.com).

Reflecting the high R&D activity around hepatitis C, still considered a major area of unmet medical need, *R&D Directions* selected six compounds there as well, including Vertex Pharmaceutical's (VRTX.com) investigational hepatitis C protease inhibitor, **telaprevir**, which is just beginning Phase III studies, and a Phase II vaccine candidate, **IC41**, under development by **Intercell** (intercell.com). Presently, there is no vaccine against hepatitis C.

Seven other vaccine candidates made the list, including **Sanofi-Pasteur's** (sanofi-pasteur.com) **dengue vaccine** for dengue fever and **Novartis'** (novartis.com) vaccine, **Menveo**, for meningococcal disease.

All the substances included on *R&D Directions*' list of 100 great investigational drugs were selected because they

show potential in a major or growing therapeutic area and are actively in development.

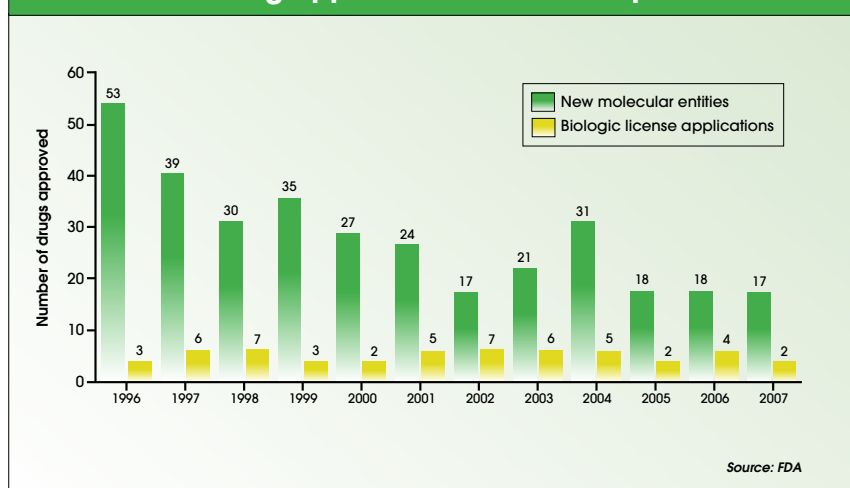
These developmental compounds are promising but they face tough times as companies that find winning approvals for investigational drugs continues to be a tough task. On top of the five-year low in federal approval of new drugs in 2007, the number of approvable letters — issued when additional data is required before FDA will approve a new drug — increased from 20% in 2006 to 28% in 2007, according to a report by Sagient Research Systems.

"I never imagined in my wildest dreams the level of regulatory conservatism that we're seeing right now," says Robert Ruffolo, Ph.D., president, Research and Development, Wyeth Pharmaceuticals, senior VP, Wyeth. "I view this as the greatest threat to the industry, but also the greatest threat to patients and future innovation. I am literally in a state of shock when I see what positions the regulators have taken, primarily on primary-care drugs, but even drugs for critical diseases like cancer. I'm worried that the pendulum has swung in the other direction and I'm waiting for it to swing back. I'm not so sure it's going to swing back."

Less innovation by pharmaceutical companies has also been blamed for the industry's struggles to maintain strong pipelines. Company pipelines are full of already marketed drugs being developed for second or third indications. Experts say the R&D business model is changing and larger drug companies will need to form more collaborations and alliances with other biopharmaceutical and specialty companies, as well as with academia, particularly in the early stages of drug development.

According to Datamonitor, companies are also doing more licensing to bolster sagging profits and fill in the gaps within their pipelines. At the same time, the search for late-stage developmental products is becoming tougher and more expensive, which means companies are now more willing to in-license earlier-stage compounds. By 2012, Datamonitor forecasts the top 20 pharmaceutical companies will amass one-third of their prescription drug revenue from licensed products. This will offset part of the sales erosion in store as many key products face patents expiration in the coming years. According to Datamonitor, small molecules remain the target of choice for licensing, but biologics will be driving market growth, with the biologics sector forecast to grow by 10% year-on-year through 2012.

**Drug approvals continue to dip**



## 100 GREAT INVESTIGATIONAL DRUGS

### 742457 — Alzheimer's disease

742457 is a novel treatment being developed by **GlaxoSmithKline** (gsk.com) that selectively targets the 5HT<sub>6</sub> receptors concentrated within the brain that are associated with learning and memory. Available treatments for Alzheimer's disease, such as cholinesterase inhibitors, are not brain specific and alter the cholinergic system throughout the body leading to possible side effects. Two large Phase II trials investigating the potential of 742457 as monotherapy and as adjunctive

therapy in patients with mild-to-moderate Alzheimer's disease are expected to start this year.

### 773812 — Schizophrenia

Being from the atypical antipsychotic class of medicines, 773812 has the potential to deliver efficacy similar to present antipsychotics without the troublesome tolerability problems. **GlaxoSmithKline** (gsk.com) is developing the compound with selectivity towards those receptors that are associated with efficacy, such

as the dopamine D<sub>2</sub> and serotonin 5HT<sub>2</sub> receptors, while having minimal activity on receptors — including dopamine D<sub>1</sub>, histamine H<sub>1</sub>, muscarinic M<sub>1</sub>, alpha, and beta adrenergic receptors — believed to be responsible for side-effects. Phase IIb trials for 773812 are expected to start this year, measuring benefits of the drug versus two commonly used treatments for schizophrenia.

### Abagovomab — Ovarian cancer

Abagovomab is a biotech vaccine being

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**742457** — Alzheimer's disease  
**773812** — Schizophrenia  
**Abagovomab** — Ovarian cancer  
**ABT-263** — Cancer  
**ABT-874** — Psoriasis  
**AD01** — Alzheimer's disease  
**Afibbercept** — Cancer  
**AGG-523** — Osteoarthritis  
**Alvespimycin** — Metastatic breast cancer  
**Amigal** — Fabry disease  
**APD125** — Insomnia  
**APD791** — Thrombosis  
**Apixaban** — Blood clots  
**Apremilast** — Psoriasis  
**Arzoxifene** — Osteoporosis, breast cancer  
**AT 1001** — Celiac disease  
**Atiprimod** — Advanced carcinoma cancer, multiple myeloma  
**AVE5026** — Venous thromboembolism  
**Axitinib** — Pancreatic cancer, thyroid cancer, lung cancer  
**AZD3480** — Alzheimer's disease, cognitive disorders in schizophrenia  
**Azedra** — Neuroendocrine tumors  
**Azixa** — Non-small cell lung cancer, advanced primary and metastatic tumors,  
**Bapineuzumab** — Alzheimer's disease  
**Bevasiranib** — Wet age-related macular degeneration  
**Bevirimat** — HIV infection  
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**BL-1020** — Schizophrenia  
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**Bosutinib** — Chronic myelogenous leukemia  
**Bronchitol** — Bronchiectasis, cystic fibrosis  
**Caprospinol** — Alzheimer's disease  
**CH-1504** — Rheumatoid arthritis  
**Cleviprex** — High blood pressure  
**CPP-109** — Cocaine addiction  
**CYT006-AngQb** — Hypertension  
**Darusentan** — Resistant hypertension

**Dengue vaccine** — Dengue fever  
**Denosumab** — Osteoporosis  
**DG051** — Heart attack  
**Elesclomol** — Metastatic melanoma  
**Everolimus** — Advanced kidney cancer  
**FTY720** — Multiple sclerosis  
**Golimumab** — Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis  
**GS 9137** — HIV infection  
**Hepaconda** — Hepatitis C  
**IC41** — Hepatitis C  
**Iclaprim** — Complicated skin and skin structure infections, hospital-acquired pneumonia  
**IDX899** — HIV infection  
**IPH 2101** — Acute myeloid leukemia  
**Karenitecin** — Advanced ovarian cancer, metastatic malignant melanoma, advanced non-small cell lung cancer, primary brain tumors  
**Laquinimod** — Multiple sclerosis  
**LCP-AtorFen** — Mixed dyslipidemia  
**LGD-4665** — Muscle and bone loss  
**Linacotide** — Irritable bowel syndrome, chronic idiopathic constipation  
**Liraglutide** — Diabetes, obesity  
**Locteron** — Hepatitis C  
**MB07811** — hyperlipidemia  
**MEM 3454** — Schizophrenia  
**Menveo** — Meningococcal disease  
**MORAb-009** — Pancreatic cancer  
**MT103** — Metastatic cancer cells  
**NicVAX** — Nicotine addiction  
**NKTR-102** — Colorectal cancer  
**NKTR-118** — Opioid-induced bowel dysfunction  
**NsG0202** — Alzheimer's disease, Parkinson's disease, epilepsy  
**NU172** — Blood clotting during surgery  
**Odanacatib** — Osteoporosis  
**Ofatumumab** — Hematologic malignancies

**Pazopanib** — Renal cell carcinoma, ovarian cancer, soft tissue sarcoma  
**Pertuzumab** — Advanced breast cancer  
**PF-03187207** — Glaucoma  
**PLX4032** — Cancer  
**prGCD** — Gaucher disease  
**Proxinium** — Head and neck cancer  
**PYY3-36 Nasal Spray** — Obesity  
**R7128** — Hepatitis C  
**RDEA806** — HIV infection  
**Rivaroxaban** — Venous thromboembolism  
**Romidepsin** — Cutaneous and peripheral T-cell lymphoma, non-Hodgkin lymphoma  
**Saxagliptin** — Type 2 diabetes  
**SGN-33** — Acute myeloid leukemia  
**SGN-40** — Non-Hodgkin lymphoma  
**SNX-5422** — Solid tumors, hematological tumors  
**SOM 230** — Cushing's disease  
**ST-246** — Smallpox  
**TB-402** — Thromboembolic disorders  
**Telaprevir** — Hepatitis C  
**Telavancin** — Skin and skin structure infections, hospital-acquired pneumonia  
**TG 4010** — Advanced non-small cell lung cancer  
**TG100801** — Macular degeneration  
**TMC278** — HIV infection  
**TRC105** — Cancer  
**Trodusquemine** — Type 2 diabetes, obesity  
**Vandetanib** — Non-small cell lung cancer  
**Varespladib** — Cardiovascular disease  
**Vicriviroc** — HIV infection  
**VRX496** — HIV infection  
**VX-770** — Cystic fibrosis  
**XP13512** — Restless legs syndrome, neuropathic pain  
**ZIO-201** — Soft tissue and bone sarcomas, ovarian and pediatric cancers

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developed by **The Menarini Group** (menarini.com) in Phase II studies. The vaccine induces the immune system to selectively kill tumor cells to prevent tumor relapse. About 50% to 80% of patients with ovarian cancer suffer a relapse even after a successful treatment with surgery and chemotherapy.

### ABT-263 — Cancer

ABT-263 is **Abbott** (abbott.com) and **Genentech's** (genentech.com) Bcl-2 family protein inhibitor in Phase I development. The drug corrects defects in cancer cells that allow them to escape programmed cell death. In preclinical studies, ABT-263 showed single agent activity against small cell lung cancer and hematologic tumors, and demonstrated synergy in combination with multiple chemotherapeutic agents and radiation therapy.

### ABT-874 — Psoriasis

Results from an extension to a Phase II study evaluating the effectiveness of **Abbott's** (abbott.com) investigational anti-IL-12/23 antibody, ABT-874, showed that a majority of patients who initially responded to treatment maintained a high level of response following discontinuation of therapy. In the study, patients who achieved 75% improvement in psoriasis signs and symptoms at 12 weeks stopped receiving ABT-874. At 24 weeks, more than two-thirds of these patients maintained at least 50% improvement.

### ADO1 — Alzheimer's disease

ADO1 is an Alzheimer's disease vaccine in Phase I developed from **Affiris GmbH's** (affiris.com) patented Affitope technology, which is based on mimotopes and allows customized vaccines to be manufactured cost-effectively. The technology enables Affiris to manufacture a vaccine to target the relevant structures of human rogue proteins. ADO1, for example, can be used to target a specific structure of beta amyloid protein, which occurs on the surface of brain cells and causes Alzheimer's disease.

### Aflibercept — Cancer

Aflibercept is a fully human soluble vascular endothelial growth factor (VEGF) receptor fusion protein with a unique mechanism of action. The angiogenesis inhibitor binds VEGF-A more tightly than monoclonal antibodies and blocks all VEGF-A isoforms plus placental growth factor, another angiogenic growth factor that appears to play a role in tumor

angiogenesis. Aflibercept is being developed by **Sanofi-Aventis** (sanofi-aventis.com) and **Regeneron Pharmaceuticals** (regeneron.com). A large-scale Phase III program is under way studying the drug as combination therapy in major cancer indications.

### AGG-523 — Osteoarthritis

**Wyeth Pharmaceuticals** (wyeth.com) is conducting a Phase I trial for investigational aggrecanase inhibitor AGG-523 in subjects with severe osteoarthritis requiring total knee replacement. The main purpose of the study is to find out if, after four weeks of dosing, signs of AGG-523, or its effects, can be measured in urine, blood, or the knee joint.

### Alvespimycin — Metastatic breast cancer

Alvespimycin is **Kosan Biosciences Inc.'s** (kosan.com) second-generation Hsp90 inhibitor for patients with HER2-positive metastatic breast cancer. Alvespimycin is in Phase II clinical trials. The drug has demonstrated the potential to disrupt the activity of multiple oncogenes and cell signaling pathways implicated in tumor growth, including HER2, a key signaling pathway in breast cancer.

### Amigal — Fabry disease

Amigal is a pharmacological chaperone designed to selectively bind to and stabilize alpha-galactosidase, or  $\alpha$ -GAL. This enzyme facilitates proper trafficking of Amigal to the lysosomes, where it is needed to break down the accumulation of globotriaosylceramide (GL-3) believed to cause the various symptoms of Fabry disease, including pain, kidney failure, and increased risk of heart attack and stroke. Amigal, in Phase II clinical trials, is being developed by **Amicus Therapeutics** (amicus-therapeutics.com) in partnership with **Shire Human Genetic Therapies**, a business unit of Shire Plc. (shire.com).

### APD125 — Insomnia

APD125 is an orally available drug candidate discovered by **Arena Pharmaceuticals** (arenapharm.com) that is being evaluated in insomnia patients who have difficulty maintaining sleep after initial sleep onset. According to Arena, by selectively targeting the 5-HT<sub>2A</sub> receptor, APD125, now in Phase II trials, acts through a different mechanism than that of marketed insomnia drugs and inhibits one of several activating pathways of the central nervous system.

### APD791 — Thrombosis

APD791 is an oral, selective inverse agonist, or inhibitor, of the 5-HT<sub>2A</sub> serotonin receptor intended for the treatment of arterial thrombosis. Serotonin activation of the 5-HT<sub>2A</sub> receptor on platelets and vascular smooth muscle is thought to play an important role in events leading to thrombosis, and elevated serotonin levels have been associated with increased cardiovascular risk. APD791 is being developed by **Arena Pharmaceuticals** (arenapharm.com) and is undergoing a Phase Ib trial to further evaluate the compound's safety, pharmacokinetics, and pharmacodynamics.

### Apixaban — Blood clots

Apixaban is a promising orally active inhibitor of coagulation Factor Xa with anticoagulant activity. The experimental candidate directly inhibits Factor Xa, thereby interfering with the conversion of prothrombin to thrombin and preventing formation of cross-linked blood clots. In spring 2007, **Pfizer** (pfizer.com) agreed to help **Bristol-Myers Squibb** (bms.com) develop and market Apixaban, which in clinical trials has shown to reduce rates of death and clots in the legs and lungs of patients who have undergone orthopedic surgery, compared with standard treatments. Apixaban is presently undergoing Phase III trials in the prevention of strokes among people with atrial fibrillation, or irregular heartbeat. I

### Apremilast — Psoriasis

Apremilast (CC-10004) is **Celgene Corp.'s** (celgene.com) lead investigational drug in a class of anti-inflammatory compounds intended to impede the production of multiple pro-inflammatory mediators. The drug, in Phase II clinical trials, inhibits PDE4, which reduced TNF-alpha as well as interleukin-2, IL-17 and IL23, interferon-gamma, leukotrienes, and nitric oxide synthase. Celgene is accelerating its clinical and regulatory strategies for apremilast in psoriasis and psoriatic arthritis, as well as embarking on exploratory clinical trials in additional rheumatic, dermatologic, and inflammatory diseases.

### Arzoxifene — Osteoporosis, breast cancer

Arzoxifene is a benzothioephene second-generation selective estrogen receptor modulator, or SERM, under development by Eli **Lilly** and Co. (lilly.com) for the treatment of osteoporosis and breast cancer. A Phase III prevention trial was completed

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late last year. The trial studied arzoxifene in comparison with Lilly's commercially available drug Evista in about 300 postmenopausal women with osteoporosis to determine percentage change in the lumbar spine bone mineral density. An additional five-year Phase III study, fully enrolled with more than 9,300 patients, is examining arzoxifene's potential in vertebral fractures and breast cancer risk reduction. Lilly expects regulatory submission to FDA in 2009.

### AT 1001 — Celiac disease

AT-1001 is an inhibitor of barrier dysfunction that has been shown to block intestinal permeability and the genesis of some autoimmune diseases, either as a result of reduction of antigen presentation to the body's immune system, or through some unknown inhibitory, direct effect on gastrointestinal associated lymphoid tissue. AT-1001, developed by **Alba Therapeutics** (albatherapeutics.com), has been granted fast-track designation by FDA for Celiac disease. The drug is in Phase II trials for this indication. AT-1001 is also being evaluated for type 1 diabetes and Crohn's disease.

### Atiprimod — Advanced carcinoid cancer, multiple myeloma

Atiprimod is an orally bioavailable small molecule drug being studied in two clinical trials by **Callisto Pharmaceuticals Inc.** (callistopharma.com) — a Phase II trial in advanced carcinoid cancer patients, and a Phase I/IIa trial in relapsed or refractory multiple myeloma patients. Atiprimod has been shown to be antiangiogenic, inhibit secretion of VEGF and IL-6, elicit programmed cellular death, and inhibit phosphorylation of key kinases involved in tumor progression and survival.

### AVE5026 — Venous thromboembolism

AVE5026 is an ultra-low-molecular-weight heparin being developed by **Sanofi-Aventis** (sanofi-aventis.com) with best-in-class potential for preventing venous thromboembolism. Phase IIb results demonstrated potentially greater efficacy than Lovenox with a comparable safety profile. A large-scale Phase III program is scheduled.

### Axitinib — Pancreatic cancer, thyroid cancer, lung cancer, breast cancer

According to preliminary data from a randomized Phase II trial, axitinib, **Pfizer's** (pfizer.com) investigational oral, selective inhibitor of vascular endothelial growth

factor receptors 1, 2, 3 combined with gemcitabine, showed a trend towards prolonged overall survival in patients with advanced pancreatic cancer compared with gemcitabine alone. Axitinib is being examined in several other Phase II studies as a potential treatment for metastatic refractory thyroid, renal cell, non-small cell lung, and breast cancer.

### AZD3480 — Alzheimer's disease, cognitive disorders in schizophrenia

AZD3480, a novel small molecule also referred to as TC-1734, is being developed by **AstraZeneca** (astrazeneca.com) and **Targacept Inc.** (targacept.com) for the treatment of Alzheimer's disease and cognitive deficits in schizophrenia in Phase II trials, and is being studied for other conditions marked by cognitive impairment. AZD3480 enhances the release of acetylcholine from the cortex. In early trials, the drug exhibited memory-enhancing properties in rats and mice.

### Azedra — Neuroendocrine tumors

Azedra is **Molecular Insight Pharmaceutical's** (molecularinsight.com) lead oncology molecular radiotherapeutic candidate for the treatment of neuroendocrine tumors such as carcinoid, pheochromocytoma, and neuroblastoma. Developed using Molecular Insight's proprietary Ultratrace technology, Azedra, which is free of unnecessary cold contaminants, is designed to maximize the radiotherapy delivered to neuroendocrine tumors while minimizing side effects. Azedra, which has fast track and orphan drug designations from FDA, is in Phase I trials.

### Azixa — Non-small cell lung cancer, advanced primary and metastatic tumors

**Myriad Genetics** (myriad.com) is conducting a third Phase II trial of its therapeutic candidate Azixa (MPC-6827) in patients with non-small cell lung cancer that has spread to the brain. Two previous clinical trials are studying the drug for primary brain cancer and melanoma that has spread to the brain. According to Myriad, Azixa has a dual mode of action. In preclinical studies, the drug was shown to act as a vascular disrupting agent and a cytotoxin. Company executives believe that Azixa selectively disrupts tumor vasculature, and not healthy tissue, by inhibiting the formation of microtubules.

### Bapineuzumab — Alzheimer's disease

Bapineuzumab is a humanized monoclonal antibody which acts on the nervous system and has shown promise for clearing the beta amyloid plaques believed to be a major cause of Alzheimer's disease. The fast-track designated compound, being co-developed by **Wyeth Pharmaceuticals** (wyeth.com) and **Élan Pharmaceuticals** (elan.com), entered into Phase III trials in December 2007.

### Bevasiranib — Wet age-related macular degeneration

Bevasiranib is a first-in-class small interfering RNA drug designed to silence the genes that produce vascular endothelial growth factor, or VEGF, believed to be largely responsible for the vision loss of wet age-related macular degeneration. The drug, being developed by **Opko Health** (opko.com), is the first therapy based on RNA interference technology to advance to Phase III clinical trials.

### Bevirimat — HIV infection

Bevirimat is the first in a new class of oral HIV therapeutics under development called maturation inhibitors. This class of drugs was discovered by **Panacos Pharmaceuticals** (panacos.com) and its academic collaborators. Based on its novel mechanism of action, bevirimat, now in Phase II trials, is designed to have potent activity against a broad range of HIV strains, including those that are resistant to existing classes of drugs.

### BiovaxID — Non-Hodgkin's lymphoma

**Biovest International Inc.** (biovest.com) is conducting a pivotal Phase III clinical trial for BiovaxID, a patient-specific anti-cancer vaccine focusing on the treatment of follicular non-Hodgkin's lymphoma. BiovaxID, which has been granted fast-track status by FDA, is a hybridoma-produced full copy of the tumor specific antigen. In a Phase II study at the National Cancer Institute and in an independent study at the University of Navarra, the vaccines was demonstrated to elicit an immune response in 80% of patients.

### BL-1020 — Schizophrenia

BL-1020 is an orally available GABA-enhanced antipsychotic candidate for the treatment of schizophrenia. According to developer **Biolinerx Ltd.** (biolinerx.com), studies have shown that BL-1020, which is in Phase II trials, has high dopamine blocking potency and activates GABA receptors in the brain. These properties may contribute

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to the safety profile of the drug by limiting extrapyramidal side effects.

### **Boceprevir — Hepatitis C**

Boceprevir, **Schering-Plough's** (sgp.com) investigational oral hepatitis C protease inhibitor, is being evaluated in combination with Peginteron and Rebetol for the treatment of patients chronically infected with hepatitis C virus genotype 1. In two large Phase II studies, more than 800 patients have received boceprevir.

### **Bosutinib — Chronic myelogenous leukemia**

Bosutinib, a new drug for chronic myelogenous leukemia, works for patients who have developed resistance to frontline therapy and causes fewer side effects than other medications in its class. In early Phase II results, researchers say bosutinib, which is being developed by **Wyeth Pharmaceuticals** (wyeth.com), has shown good efficacy and very little toxicity compared with other tyrosine kinase inhibitors at this stage.

### **Bronchitol — Bronchiectasis, cystic fibrosis**

**Pharmaxis** (pharmaxis.com) is developing Bronchitol as a treatment to improve mucus clearance in the lungs of patients with bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary diseases. According to Pharmaxis, Bronchitol, in data from a 362-subject Phase III study for bronchiectasis, met its two primary efficacy endpoints — quality of life and mucus clearance.

### **Caprospinol — Alzheimer's disease**

Caprospinol (SP-233) is reportedly the first drug to demonstrate in animals that there is a correlation between clearing beta-amyloid from the brain and the recovery of memory function. Developer **Samaritan Pharmaceuticals Inc.** (samaritanpharma.com) will test caprospinol on a small group of patients in a Phase I human safety trial set to begin in the second quarter of 2008. Molecular modeling experiments have suggested that caprospinol inserts itself inside the folded structure of the beta-amyloid peptide, preventing amyloid molecules from joining together into the highly neurotoxic amyloid-derived diffusible ligands.

### **CH-1504 — Rheumatoid arthritis**

CH-1504 is an orally available and metabolically inert antifolate with potent anti-inflammatory and anti-tumor properties.

**Chelsea Therapeutics International Ltd.** (chelseatherapeutics.com) has initiated a Phase II trial designed to compare the efficacy and tolerability of CH-1504 against methotrexate, which is considered to be the standard treatment for rheumatoid arthritis.

### **Cleviprex — High blood pressure**

Cleviprex is a novel investigational intravenous infusion antihypertensive for the treatment of acutely elevated blood pressure, when the use of oral therapy is not feasible or desirable. Cleviprex, developed by **The Medicines Company** (themedicinescompany.com), is metabolized in the blood and does not accumulate in the body, making it a suitable treatment for patients with end-organ damage. Six Phase III trials of the drug met all of their primary endpoints, according to The Medicines Company.

### **CPP-109 — Cocaine addiction**

CPP-109, composed of the chemical vigabatrin, is an orally administered, small molecule drug that inhibits psychostimulant-induced dopamine release. The Phase II compound being developed by **Catalyst Pharmaceutical Partners** (catalystpharma.com) works by inhibiting an enzyme that normally breaks down gamma aminobutyric acid, or GABA, a dopamine-modulating neurotransmitter. The resulting excess GABA suppresses the increase in dopamine release caused by cocaine.

### **CYT006-AngQb — Hypertension**

CYT006-AngQb is a therapeutic vaccine in Phase II development for the treatment of hypertension. The drug is designed to instruct the patient's immune system to produce an antibody response against angiotensin II, which is a small peptide in the body and part of the renin-angiotensin system, an important regulator of blood pressure. Angiotensin II causes blood vessels to narrow, resulting in increased blood pressure. CYT006-AngQb is being developed by **Cytos Biotechnology AG** (cytos.com).

### **Darusentan — Resistant hypertension**

Darusentan is a propanoic-acid class endothelin receptor antagonist being investigated in clinical trials as an add-on oral therapy for patients with resistant hypertension. **Gilead Sciences Inc.** (gilead.com) is conducting Phase III clinical trials of darusentan. The trials will determine if the drug is a safe and effective treatment for reducing systolic blood pressure

and diastolic blood pressure in resistant hypertension patients who are already being treated with full doses of three or more antihypertensive medications, one of which is a diuretic.

### **Dengue vaccine — Dengue fever**

**Sanofi-Pasteur's** (sanofi-pasteur.com) vaccine candidate for Dengue fever, a deadly mosquito-borne disease affecting up to 100 million people each year, cleared a significant hurdle late last year with the release of promising Phase II trial findings. Immunization with the compound generated a sero-neutralizing antibody response against all four serotypes of the virus responsible for dengue fever in 100% of adults who participated in the U.S. trial. The results have prompted Sanofi-Pasteur, the vaccines division of Sanofi-Aventis, to immediately expand ongoing clinical trials in Asia and Latin America. Submission for registration is anticipated in 2012.

### **Denosumab — Osteoporosis**

Denosumab is the first fully human monoclonal antibody in late-stage clinical development. The drug specifically targets RANK ligand, the essential mediator of osteoclasts, which are the cells that break down bone. Denosumab, according to developer **Amgen** (amgen.com), inhibits all stages of osteoclast activity through a targeted mechanism that does not incorporate into bone matrix. Denosumab, in Phase III clinical trials for osteoporosis, is being studied in a range of bone loss conditions including postmenopausal osteoporosis, rheumatoid arthritis, and cancer treatment-induced bone loss, as well as for its potential to delay bone metastases and inhibit and treat bone destruction across many stages of cancer.

### **DG051 — Heart attack**

DG051 is a first-in-class, small-molecule inhibitor of leukotriene A4 hydrolase, or LTA4H, discovered by **DeCode Genetics'** (decode.com) chemistry unit. The drug is in Phase II development for the prevention of heart attack. LTA4H is encoded by one of the genes DeCode has linked to increased risk of heart attack. The at-risk versions of these genes confer increased risk of heart attack by increasing the production of the pro-inflammatory molecule LTB4. DG051 is designed to decrease the risk of heart attack by decreasing the production of LTB4.

### **Elesclomol — Metastatic melanoma**

Elesclomol (formerly STA-4783) is an

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injectable, investigational drug candidate being developed by **Synta Pharmaceuticals** ([syntapharma.com](http://syntapharma.com)) and **GlaxoSmithKline** ([gsk.com](http://gsk.com)). The drug is believed to kill cancer cells by elevating oxidative stress levels beyond a breaking point, triggering apoptosis, or programmed cell death. FDA has granted orphan drug designation to elesclomol, which is in Phase III for patients with metastatic melanoma.

### Everolimus — Advanced kidney cancer

An independent data monitoring committee stopped a major Phase III trial of **Novartis'** ([novartis.com](http://novartis.com)) investigational drug everolimus (RAD001) last month after interim results showed significantly better progression-free survival in patients with advanced kidney cancer who received everolimus compared to placebo. The committee stopped the trial of more than 400 patients conducted in 12 countries because the study met its primary endpoint. Everolimus is an oral inhibitor of mTOR and is being studied in multiple tumor types. In cancer cells, everolimus inhibits mTOR, a protein that acts as a central regulator of tumor cell division, cell metabolism, and blood vessel growth.

### FTY720 — Multiple sclerosis

FTY720 is a novel, once-daily, oral treatment in Phase III development. The trials will test the drug's safety and efficacy as a disease-modifying therapy for relapsing-remitting multiple sclerosis, which affects about 85% of people with multiple sclerosis. According to developer **Novartis** ([novartis.com](http://novartis.com)), preclinical data suggests that FTY720, which is composed of fingolimod, directly reduces neurodegeneration and enhances repair of the central nervous system damage caused by multiple sclerosis by interacting with sphingosine-1-phosphate receptors expressed on brain cells.

### Golimumab — Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis

Golimumab is being developed by **Centocor** ([centocor.com](http://centocor.com)) and **Schering-Plough** ([sgp.com](http://sgp.com)). The next-generation human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody is in the most comprehensive Phase III development program to date for an anti-TNF-alpha biologic therapy. With ongoing studies for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, golimumab is being studied as a monthly subcutaneous injection

and an every 12-week intravenous infusion therapy which is administered in about 30 minutes. Golimumab targets and neutralizes both the soluble and membrane-bound forms of TNF-alpha.

### GS 9137 — HIV infection

GS 9137, comprising the chemical elvitegravir, is an investigational new drug for the treatment of HIV infection. The compound, which acts as an integrase inhibitor, is undergoing Phase II trials conducted by **Gilead Sciences** ([gilead.com](http://gilead.com)), which licensed the drug from Japan Tobacco in 2005.

### Hepaconda — Hepatitis C

Hepaconda is a combination of bezafibrate and chenodeoxycholic acid. As single compounds, both chemicals have demonstrated activity against hepatitis C infection in clinical trials, according to developer **Giaconda Ltd.** ([giacondalimited.com](http://giacondalimited.com)). Company executives believe that the combination of bezafibrate with chenodeoxycholic acid may offer a synergistic advantage over available treatment. Giaconda is expected to report on the Phase IIa trial results of Hepaconda early this year.

### IC41 — Hepatitis C

**Intercell AG** ([intercell.com](http://intercell.com)) has released the analysis of Phase II data for its peptide-based therapeutic hepatitis C vaccine, IC41, in an exploratory clinical study targeting treatment-naive hepatitis C patients. The vaccine comprises five synthetic T-cell peptides and Intercell's first-generation poly-arginine adjuvant, IC30. IC41 is designed to stimulate T-cell responses against viral protein structures conserved throughout the major hepatitis C virus genotypes to reduce viral load in the blood of chronically infected patients.

### Iclaprim — Complicated skin and skin-structure infections, hospital-acquired pneumonia

**Arpida Ltd.** ([arpida.com](http://arpida.com)) recently received authorization from FDA to conduct a Phase II "intravenous-to-oral" switch trial with iclaprim in patients with complicated skin and skin-structure infections. Iclaprim is a potent late-stage antibiotic that targets severe infections requiring hospital treatment, including those caused by methicillin-resistant *Staphylococcus aureus*. The drug is also being developed as an intravenous formulation for hospital-acquired pneumonia, an indication in Phase II trials.

### IDX899 — HIV infection

IDX899 is a non-nucleoside reverse transcriptase inhibitor being developed for the treatment of HIV. Earlier in 2008, developer **Idenix Pharmaceuticals** ([idenix.com](http://idenix.com)) reported that in the first dosing cohort of an ongoing Phase I/II study, eight HIV-1 infected treatment-naive patients receiving 800 milligrams of IDX899 once daily achieved a mean reduction in virus level of 2.01 log(10), or 99%, after seven days of treatment. Idenix plans on examining lower doses in future studies.

### IPH 2101 — Acute myeloid leukemia

The therapeutic principle of IPH 2101 (NN 1975) is based on the activation of natural killer, or NK, cells by a monoclonal antibody that blocks the NK's KIR inhibitory receptors, thereby potentiating NK cells' anti-cancer action. IPH 2101, developed by **Novo Nordisk** ([novonordisk.com](http://novonordisk.com)) in collaboration with **Innate Pharma SA** ([innate-pharma.com](http://innate-pharma.com)), was administered for the first time in humans early last year as part of a Phase I clinical trial for patients with acute myeloid leukemia.

### Karenitecin — Advanced ovarian cancer, metastatic malignant melanoma, advanced non-small cell lung cancer, primary brain tumors

**BioNumerik Pharmaceuticals Inc.** ([bionumerik.com](http://bionumerik.com)) is developing karenitecin, also known as BNP1350, as an investigational new anti-tumor drug in the camptothecin class of chemotherapy drugs. Four Phase II clinical trials of intravenously administered karenitecin have been completed in the United States in patients with advanced ovarian cancer, metastatic malignant melanoma, advanced non-small cell lung cancer, and primary brain tumors.

### Laquinimod — Multiple sclerosis

Laquinimod is a novel once-daily, orally administered immunomodulatory compound in Phase III studies that is being developed as a disease-modifying treatment for relapsing-remitting multiple sclerosis. **Active Biotech** ([activebiotech.com](http://activebiotech.com)) developed laquinimod and licensed it to **Teva Pharmaceutical Industries** ([tevapharm.com](http://tevapharm.com)) in June 2004.

### LCP-AtorFen — Mixed dyslipidemia

LCP-AtorFen is a fixed-dose combination therapy in Phase II trials for the treatment of high cholesterol levels using atorvastatin, which is the active ingredient of Lipitor,

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and the lowest dose of fenofibrate without food effect. LCP-AtoFen, which is being developed by **LifeCycle Pharma** (lcpharma.com), is designed to address three primary cardiovascular risk factors: low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, and triglycerides.

### **LGD-4665** — Muscle and bone loss

LGD-4665 is an oral, small-molecule drug that mimics the activity of thrombopoietin, a growth factor that promotes growth and production of blood platelets. Developer **Ligand Pharmaceuticals** (ligand.com) recently disclosed results from a Phase I trial examining three dosing regimens for LGD-4665 and stated that the drug was well-tolerated and demonstrated an encouraging safety profile at all dose levels and all dosing regimens.

### **Linaclotide** — Irritable bowel syndrome, chronic idiopathic constipation

Linaclotide is a first-in-class compound that acts by a mechanism distinct from previously developed products for irritable bowel syndrome and chronic constipations. Linaclotide, developed by **Microbia Inc.** (microbia.com) and **Forest Laboratories** (frx.com), is an agonist of the guanylate cyclase type-C receptor found in the intestine. The drug, expected to begin Phase III studies later in 2008, is administered orally but acts locally in the intestine with no measurable systemic exposure.

### **Liraglutide** — Diabetes, obesity

Liraglutide is **Novo Nordisk's** (novonordisk.com) once-daily GLP-1 analogue presently in Phase III development for the treatment of type 2 diabetes and Phase II for obesity. Results from four of five Phase III studies in people with type 2 diabetes have been reported. Findings from the final study should be reported soon, and Novo Nordisk expects to file in the middle of the year for regulatory approval of the drug for the treatment of type 2 diabetes. A Phase III study in Novo Nordisk's LEAD program confirmed last year that liraglutide treatment leads to both glucose and weight reduction with a low risk of hypoglycaemic events.

### **Locteron** — Hepatitis C

Locteron is designed to be a best-in-class therapeutic for patients with chronic hepatitis C, with the potential to reduce side effects, improve patient compliance, and provide a more convenient once-ev-

ery-two-week dosing schedule compared with available therapies, according to developer **OctoPlus NV** (octoplus.nl). The company has commenced patient dosing in its Phase IIa PLUS study, which will take place in the United States and evaluate the safety, tolerability, pharmacokinetics, and viral kinetics of Locteron.

### **MB07811** — hyperlipidemia

MB07811 is a novel, orally administered, beta-subtype-selective thyroid hormone receptor agonist designed to specifically target the liver and thereby avoid well known side-effects of thyroid hormone receptor agonists at doses that reduce LDL-cholesterol and triglyceride levels. A Phase 1b trial conducted by **Metabasis Therapeutics** (mbasis.com) is evaluating MB07811 dosed once-a-day for 14 days in healthy volunteers.

### **MEM 3454** — Schizophrenia

**Memory Pharmaceuticals** (memorypharma.com) has begun dosing the first subject in a randomized, double-blind, placebo-controlled Phase IIa trial of MEM 3454, the company's lead nicotinic alpha-7 receptor partial agonist, in cognitive impairment associated with schizophrenia. Memory also plans to conduct a clinical study of MEM 3454 on two biomarkers of schizophrenia — P50 sensory gating and mismatch negativity — in patients with schizophrenia. The biomarker study, and additional formulation and manufacturing activities for MEM 3454, will be funded by **Roche** (roche.com).

### **Menveo** — Meningococcal disease

New Phase II data proved promising for **Novartis** (novartis.com) when the results showed that the company's vaccine candidate, Menveo, may protect infants using a schedule beginning at two months of age against four of the most common causes of meningococcal disease. According to Novartis, Menveo is the only meningococcal vaccine shown to generate protection against a broad range of serogroups in infants, potentially filling a large unmet medical need. Menveo is in multiple Phase III trials involving infants, young children, adolescents, and adults. Novartis plans submissions for the vaccine in the European Union and the United States sometime in 2008.

### **MORAb-009** — Pancreatic cancer

MORAb-009 is a monoclonal antibody that blocks the function of mesothelin, a cell surface protein on pancreatic tumor

cells that can allow the tumor cells to attach, metastasize, and grow. The drug is in Phase II clinical trials. According to developer **Morphotek Inc.** (morphotek.com), a subsidiary of **Eisai Co. Ltd.** (eisai.com), preclinical data support the theory that MORAb-009 achieves its pharmacological effect by two mechanisms — first by blocking mesothelin's ability to interact with its target, and second by recruiting the patient's immune system to the tumor to specifically destroy those cells bound by the antibody.

### **MT103** — Metastasized cancer cells

**MT103**, which is being developed by **Micromet Inc.** (micromet.com) and **MedImmune**, (medimmune.com), is a BiTE antibody in Phase I and Phase II trials for patients with non-Hodgkin's lymphoma and other blood-related cancers. MT103 specifically targets the CD19 antigen, which is present on B-cells and B-cell-derived tumors, but not on other types of blood cells or healthy tissues. Micromet created BiTE — a platform of antibodies the company says that for the first time, enables the body's serial killing T cells to "see" cancer cells and attack them anywhere in the body.

### **NicVAX** — Nicotine addiction

NicVAX is an investigational vaccine being developed by **Nabi Biopharmaceuticals** (nabi.com) to treat nicotine addiction and prevent smoking relapse. The vaccine, in Phase II trials, is designed to stimulate the immune system to produce antibodies that bind to nicotine. According to Nabi, NicVAX blocks nicotine from reaching its receptors in the brain and prevents the highly addictive pleasure sensation experienced by smokers.

### **NKTR-102** — Colorectal cancer

**Nektar Therapeutics** (nektar.com) is developing NKTR-102, a PEGylated form of irinotecan. The drug was invented by the company using its small molecule PEGylation technology platform. Irinotecan, also known as Camptosar, is an important chemotherapeutic agent used for the treatment of solid tumors, including colorectal and lung cancers. According to Nektar, by applying the company's PEGylation technology to irinotecan, NKTR-102, which is in Phase II trials, may prove to be a more powerful and tolerable anti-tumor agent.

### **NKTR-118** — Opioid-induced bowel dysfunction

NKTR-118 is an oral drug in Phase II that combines **Nektar Therapeutics'** (nektar.com) advanced small molecule PEGyla-

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tion technology platform with naloxol, a derivative of the opioid-antagonist drug, naloxone. NKTR-118 targets opioid receptors within the enteric nervous system, which mediate opioid-induced bowel dysfunction, a symptom complex resulting from opioid use that encompasses constipation, bloating, abdominal cramping, and gastroesophageal reflux.

### NsG0202 — Alzheimer's disease

NsG0202 for the treatment of Alzheimer's disease is the first candidate in a pipeline of disease-modifying products based on **NsGene A/S'** ([nsgene.dk](http://nsgene.dk)) encapsulated cell biodelivery platform. The advanced implant product represents a novel treatment method aimed at restoring brain function, not just alleviating symptoms. In December 2007, NsGene announced that its clinical trial application to start a Phase Ib study of NsG0202 for Alzheimer's disease was approved by the Swedish Medical Products Agency.

### NU172 — Blood clots

NU172 is an aptamer designed to directly inhibit thrombin's ability to stimulate blood clot formation in the setting of medical procedures where human blood is exposed to foreign materials. The drug is in Phase I development by **Archemix Corp.** ([archemix.com](http://archemix.com)). Specifically, NU172 is being studied for use as a potential short-acting anti-coagulant during procedures such as coronary artery bypass graft surgery and percutaneous interventions.

### Odanacatib — Osteoporosis

Odanacatib, formerly known as MK-0822, is a new class of osteoporosis drug that works by inhibition of the cathepsin K enzyme, which is believed to play a role in bone loss and in degrading the protein component of bone. The inhibition of the cathepsin K enzyme by odanacatib is a mechanism of action different from that of approved treatments such as the bisphosphonates. The drug is being developed by **Merck & Co.** ([merck.com](http://merck.com)). According to researchers, odanacatib significantly increased bone mineral density after 12 months in a Phase III trial involving 399 post-menopausal women with low bone mineral density.

### Ofatumumab — Hematologic malignancies

Ofatumumab is an investigational monoclonal antibody undergoing clinical trials for a number of serious conditions,

including chronic lymphocytic leukaemia; diffuse large B-cell lymphoma, the most common sub-type of non-Hodgkin's lymphoma in the Western world; follicular lymphoma; rheumatoid arthritis; and multiple sclerosis. **GlaxoSmithKline** ([gsk.com](http://gsk.com)) and **Genmab A/S** ([genmab.com](http://genmab.com)) have a worldwide agreement to jointly develop ofatumumab, which targets a distinct antibody binding site, or epitope, of the CD20 molecule on the cell membrane of B-cells.

### Pazopanib — Renal cell carcinoma, ovarian cancer, soft tissue sarcoma

Pazopanib is an investigational, oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-kit, which are important proteins in the angiogenic process. Pazopanib is in Phase III clinical trials for the treatment of advanced or metastatic renal cell carcinoma, after completing patient enrollment several months ahead of schedule, according to developer **GlaxoSmithKline** ([gsk.com](http://gsk.com)). The drug is also being studied in a number of other trials across various tumor types, including ovarian cancer and soft tissue sarcoma, both in Phase II.

### Pertuzumab — Advanced breast cancer

Pertuzumab is the first in a new innovative class of targeted agents known as HER dimerization inhibitors. The antibody is designed to bind to the HER2 receptor and inhibit the ability of HER2 to interact with other HER family members (HER1, HER2, HER3, and HER4). **Roche** ([roche.com](http://roche.com)) is conducting Phase III trials of pertuzumab in advanced breast cancer

### PF-03187207 — Glaucoma

PF-03187207 is being developed by **Pfizer** ([pfizer.com](http://pfizer.com)) for the treatment of glaucoma. The drug is in an ongoing Phase II proof-of-concept study in the United States that will compare the safety and efficacy of PF-03187207 versus Xalatan in lowering intraocular pressure, or pressure within the eye.

In January, Pfizer initiated a similar Phase II study for PF-03187207 in Japan. PF-03187207 is the lead candidate generated under the August 2004 collaboration agreement between Pfizer and **NicOx SA** ([nicox.com](http://nicox.com)).

### PLX4032 — Cancer

**Plexxikon Inc.** ([plexxikon.com](http://plexxikon.com)) is conduct-

ing a Phase I clinical trial in collaboration with **Roche** ([roche.com](http://roche.com)) to evaluate PLX4032, an orally available anti-cancer agent designed to specifically inhibit the B-Raf(V600E) protein. Enrollment has completed for the dose escalation phase of the trial, which is being conducted in cancer patients.

The next phase of the trial will test the efficacy of the drug only in melanoma patients who have the B-Raf(V600E) mutation, and will include radiologic imaging studies such as positron emission tomography scans and CT scans to assess anti-tumor activity. Patients will be selected for the study using an investigational diagnostic test developed by Roche Molecular Diagnostics in collaboration with Plexxikon. Enrollment is expected to be completed by the end of 2008. To date PLX4032 has been safe and well-tolerated even at the highest doses administered.

### prGCD — Gaucher disease

**Protalix BioTherapeutics Inc.** ([protalix.com](http://protalix.com)) is conducting a Phase III trial for the company's lead product candidate, prGCD, a proprietary plant cell-expressed recombinant form of human glucocerebrosidase for the treatment of Gaucher disease, a lysosomal storage disorder in humans.

The trial, launched through FDA's special protocol assessment process, is taking place in centers in the United States, Israel, and other locations worldwide. The trial design consists of 30 male and female patients with Gaucher disease in a randomized, double-blind, dose-ranging study, with two parallel groups.

### Proxinium — Head and neck cancer

Proxinium, **Viventia Biotech Inc.**'s ([viventia.com](http://viventia.com)) lead drug candidate, is a humanized antibody fragment conjugated to the cytotoxic protein *Pseudomonas* exotoxin A. The drug is in a global pivotal Phase III trial in patients with advanced head and neck cancer. Proxinium has orphan-drug status in the United States and Europe and has been designated as a fast-track product by FDA.

### PYY3-36 Nasal Spray — Obesity

**Nastech Pharmaceutical Company Inc.** ([nastech.com](http://nastech.com)) in January completed enrollment for its Phase II clinical trial of PYY3-36 Nasal Spray to treat obesity. The company enrolled 551 obese patients at multiple clinical sites in the United States for a six-month, randomized, placebo-controlled dose ranging study. The study is

designed to evaluate three different doses of PYY3-36 Nasal Spray compared with placebo and Meridia, with the primary endpoint being weight loss.

Peptide YY is a naturally occurring hormone that is believed to function as a physiologic inhibitor of food intake. PYY is released into the blood stream from specialized endocrine cells in the gut after a meal and is believed to trigger the feeling of satiety, or fullness. Because PYY is a peptide, initial studies focused on PYY delivery by injection. Nastech developed the nasal spray formulation of PYY as a unique, non-invasive treatment option for obesity.

### R7128 — Hepatitis C

R7128 is an orally administered prodrug modified from PSI-6130, a cytidine nucleoside analogue polymerase inhibitor of the hepatitis C virus. The compound is being developed by **Pharmasset** Inc. (pharmasset.com) through the company's collaboration with **Roche** (Roche.com).

Pharmasset executives have stated that preliminary results from an early stage trial of R7128 showed promise. The drug, which has received fast-track status from FDA, demonstrated potent antiviral activity and was generally safe and well-tolerated in a 14-day Phase I multiple ascending dose monotherapy study.

### RDEA806 — HIV infection

RDEA806 is a novel non-nucleoside reverse transcriptase inhibitor for the potential treatment of HIV infection. Based on preclinical and clinical studies to date, developer **Ardea Biosciences** Inc. (ardeabio.com) believes that RDEA806 possesses several attractive properties, including potential for potent antiviral activity against a wide range of HIV viral isolates, including those that are resistant to the already approved drug Sustiva.

Other favorable properties Ardea attributes to RDEA806 is a high genetic barrier to resistance; the potential to be administered in a patient-friendly, oral dosing regimen; limited pharmacokinetic interactions with other drugs; and the ability to be co-formulated with other HIV antiviral drugs. In February 2008, Ardea Biosciences announced that Phase II data for RDEA806 demonstrated potent activity against the HIV virus. A Phase IIa clinical trial with the compound is in enrollment with data expected in the first quarter of this year.

### Rivaroxaban — Venous thromboembolism

Phase III clinical trial results released in December 2007 show that rivaroxaban, the oral, once-daily, investigational anticoagulant, was significantly more effective than enoxaparin, the standard of care, in preventing venous thromboembolism in patients undergoing total hip or knee-replacement surgery.

According to joint developers **Bayer HealthCare** (bayer.com) and **Johnson & Johnson** Pharmaceutical Research & Development (jnjpharmarnd.com), rivaroxaban-treated patients consistently experienced lower rates of venous thromboembolism events compared with enoxaparin-treated patients across three large studies as well as demonstrating a similar rate of major bleeding events. Data from the RECORD 1 study indicates that rivaroxaban reduced the incidence of all types of venous thromboembolism or blood clot risk 70% more than **Sanofi-Aventis'** (sanofi-aventis.com) enoxaparin group. For major venous thromboembolism risk, the figure was 88%. Bayer submitted a regulatory filing to EMEA at the end of October 2007 for approval to market rivaroxaban in the EU for the prevention of venous thromboembolism. A filing for a similar indication in the United States is planned this year.

### Romidepsin — Cutaneous and peripheral T-cell lymphoma, non-Hodgkin lymphoma

Romidepsin is a novel histone deacetylase inhibitor undergoing pivotal Phase II studies for patients with cutaneous T-cell lymphoma and patients with peripheral T-cell lymphoma. The drug is being developed by **Gloucester Pharmaceuticals** Inc. (gloucesterpharma.com). Romidepsin has received orphan-drug designation from FDA for the treatment of non-Hodgkin T-cell lymphomas, which includes cutaneous T-cell lymphoma and peripheral T-cell lymphoma.

In addition, EMEA has issued orphan-drug status for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma. Fast-track status for the two indications has also been designated by FDA. Romidepsin is in clinical trials for a variety of other hematological malignancies and solid tumors, including hormone-refractory prostate cancer, pancreatic cancer, and multiple myeloma. These trials are being conducted by Gloucester or the National Cancer Institute under a cooperative R&D agreement with Gloucester.

### Saxagliptin — Type 2 diabetes

Saxagliptin is an investigational drug being developed by **Bristol-Myers**

**Squibb** (bms.com) and **AstraZeneca** (astrazeneca.com) as a once daily antidiabetic in the class of dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes. Data from Phase III clinical trials have shown that saxagliptin, in combination with metformin, exhibited a statistically significant improvement in glycemic control in subjects with type 2 diabetes through 24 weeks of treatment compared with metformin alone.

### SGN-33 — Acute myeloid leukemia

SGN-33, or lintuzumab, is a humanized monoclonal antibody that targets the CD33 antigen, which is expressed on a number of hematologic malignancies, including acute myeloid leukemia, myelodysplastic syndromes, and several myeloproliferative diseases.

Developer **Seattle Genetics** Inc. (seattlegenetics.com) unveiled favorable data late last year from a Phase Ia trial of SGN-33, demonstrating multiple complete remissions at well-tolerated doses in patients with acute myeloid leukemia. Preclinical data were also presented indicating the anti-leukemic activity of SGN-33 both as a single agent and when used in combination with lenalidomide in acute myeloid leukemia.

### SGN-40 — Non-Hodgkin's lymphoma

SGN-40 is a humanized monoclonal antibody that targets the CD40 antigen, which is expressed on most B lineage hematologic malignancies, including non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia. CD40 is also found on many types of solid tumors, including bladder, renal and ovarian cancer. **Seattle Genetics** Inc. (seattlegenetics.com), which is developing SGN-40 with **Genentech** (genentech.com), recently initiated a Phase IIb trial of the drug in combination with Genentech's Rituxan plus chemotherapy for patients with relapsed or refractory diffuse large B-cell lymphoma.

### SNX-5422 — Solid tumors, hematological tumors

SNX-5422 is a synthetic, orally bioavailable, small molecule that was discovered using the proprietary chemoproteomics technology platform of developer **Serenex** (serenex.com). The platform allows for the screening of a compound/compound library against a wide array of proteins from virtually any tissue or cell source in a single assay. In preclinical studies, SNX-5422, now in Phase I trial, demonstrated strong efficacy in multiple tumor models, including refractory breast cancer, prostate, colon,

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and melanoma, both as a single agent and when used in combination with other targeted or cytotoxic agents.

### SOM 230 — Cushing's disease

SOM 230, comprising the chemical pasireotide, is a novel, multi-ligand somatostatin analogue that exhibits high binding affinity to four of the five

somatostatin receptor subtypes, sst 1,2,3 and sst 5, potentially offering therapeutic benefits in conditions where these sst receptors are important, such as gastroentero-pancreatic neuroendocrine tumors, acromegaly, and Cushing's disease. SOM 230 is being developed by **Novartis** (novartis.com) and is in Phase III trials for Cushing's disease, an endocrine disorder caused by high

levels of cortisol in the blood.

### ST-246 — Smallpox

**Siga Technologies** Inc. (siga.com) recently completed a Phase I human trial for ST-246, an advanced smallpox treatment which has previously demonstrated significant antiviral activity in various animal models of poxvirus

## developers of 100 great investigational drugs

### Abbott

**ABT-263** — Cancer  
**ABT-874** — Psoriasis

### Active Biotech

**Laquinimod** — Multiple sclerosis

### Affiris

**AD01** — Alzheimer's disease

### Alba Therapeutics

**AT 1001** — Celiac disease

### Amgen

**Denosumab** — Osteoporosis

### Amicus Therapeutics

**Amigal** — Fabry disease

### Anthera Pharmaceuticals

**Varespladib** — Cardiovascular disease

### Archemix

**NU172** — Blood clotting during surgery

### Ardea Biosciences

**RDEA806** — HIV infection

### Arena Pharmaceuticals

**APD125** — Insomnia  
**APD791** — Thrombosis

### Arpida

**Iclaprim** — Complicated skin and skin structure infections, hospital-acquired pneumonia

### Astellas Pharma

**Telavancin** — Skin and skin structure infections, hospital-acquired pneumonia

### AstraZeneca

**AZD3480** — Alzheimer's disease, cognitive disorders in schizophrenia  
**Saxagliptin** — Type 2 diabetes  
**Vandetanib** — Non-small cell lung cancer

### Bayer HealthCare

**Rivaroxaban** — Venous thromboembolism

### BiolineRx

**BL-1020** — Schizophrenia

### BioNumerik Pharmaceuticals

**Karenitecin** — Advanced ovarian cancer, metastatic malignant melanoma, advanced non-small cell lung cancer, primary brain tumors

### Biovest International

**BiovaxID** — Non-Hodgkin's lymphoma

### Bristol-Myers Squibb

**Apixaban** — Blood clots

### Callisto Pharmaceuticals

**Atiprimod** — Advanced carcinoid cancer, multiple myeloma

### Catalyst Pharmaceuticals

**CPP-109** — Cocaine addiction

### Celgene

**Apremilast** — Psoriasis

### Centocor

**Golimumab** — Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis

### Chelsea Therapeutics

**CH-1504** — Rheumatoid arthritis

### Cytos Biotechnology

**CYT006-AngQb** — Hypertension

### DeCode Genetics

**DG051** — Heart attack

### Elan Pharmaceuticals

**Bapineuzumab** — Alzheimer's disease

### Eli Lilly & Co.

**Arzoxifene** — Osteoporosis, breast cancer

### Forest Laboratories

**Linacotide** — Irritable bowel syndrome, chronic idiopathic constipation

### Genaea

**Trodusquemine** — Type 2 diabetes, obesity

### Genentech

**ABT-263** — Cancer  
**SGN-40** — Non-Hodgkin lymphoma

### Genmab

**Ofatumumab** — Hematologic malignancies

### Giaconda Limited

**Hepaconda** — Hepatitis C

### Gilead Sciences

**Darusentan** — Resistant hypertension  
**GS 9137** — HIV infection

### GlaxoSmithKline

**742457** — Alzheimer's disease  
**773812** — Schizophrenia

### Elesclomol

melanoma

**Ofatumumab** —

Hematologic malignancies

**Pazopanib** — Renal cell carcinoma, ovarian cancer, soft tissue sarcoma

**XP13512** — Restless legs syndrome, neuropathic pain

### Gloucester Pharmaceuticals

**Romidepsin** — Cutaneous and peripheral T-cell lymphoma, non-Hodgkin lymphoma

### Idenix Pharmaceuticals

**IDX899** — HIV infection

### Innate Pharma

**IPH 2101** — Acute myeloid leukemia

### Intercell

**IC41** — Hepatitis C

### Johnson & Johnson

**Rivaroxaban** — Venous thromboembolism

### Kosan Biosciences

**Alvespimycin** — Metastatic breast cancer

### LifeCycle Pharma

**LCP-AtorFen** — Mixed dyslipidemia

### Ligand Pharmaceuticals

**LGD-4665** — Muscle and bone loss

### The Medicines Company

**Cleviprex** — High blood pressure

### MedImmune

**MT103** — Metastasized

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disease, including the complete protection of primates from lethal doses of monkeypox and smallpox virus. Siga will use animal efficacy data as part of its full FDA approval submission under the FDA's "animal efficacy rule."

### TB-402 — Thromboembolic disorders

TB-402 is a recombinant human mono-

clonal antibody in Phase I trials that has shown a beneficial partial inhibition of the blood coagulation Factor VIII. Developer **ThromboGenics** NV (thrombogenics.com) says the long half life — approximately three weeks — enables the drug to produce a stable and long-acting inhibition.

### Telaprevir — Hepatitis C

Telaprevir (VX-950) is an investigational oral inhibitor of HCV protease, an enzyme essential for viral replication, and is one of the most advanced investigational antiviral agents in development that specifically targets the hepatitis C virus. Developer **Vertex** Pharmaceuticals Inc. (vrtx.com) is launching a Phase III development program for telaprevir.

cancer cells

**Memory Pharmaceuticals**  
**MEM 3454** — Schizophrenia

#### The Menarini Group

**Abagovomab** — Ovarian cancer

#### Merck & Co.

**Odanacatib** — Osteoporosis

#### Metabasis Therapeutics

**MB07811** — hyperlipidemia

#### Microbia

**Linaclotide** — Irritable bowel syndrome, chronic idiopathic constipation

#### Micromet

**MT103** — Metastasized cancer cells

#### Molecular Insight Pharmaceuticals

**Azedra** — Neuroendocrine tumors

#### Morphotek

**MORAb-009** — Pancreatic cancer

#### Myrriad Genetics

**Azixa** — Non-small cell lung cancer, advanced primary and metastatic tumors

#### Nabi Biopharmaceuticals

**NicVAX** — Nicotine addiction

#### Nastech Pharmaceutical

**PYY3-36 Nasal Spray** — Obesity

#### Nektar Therapeutics

**NKTR-102** — Colorectal cancer

**NKTR-118** — Opioid-induced bowel dysfunction

#### Novartis

**Everolimus** — Advanced

kidney cancer

**FTY720** — Multiple sclerosis  
**Menveo** — Meningococcal disease

**SOM 230** — Cushing's disease

#### Novo Nordisk

**IPH 2101** — Acute myeloid leukemia

**Liraglutide** — Diabetes, obesity

#### NsGene

**NsG0202** — Alzheimer's disease, Parkinson's disease, epilepsy

#### OctoPlus

**Locteron** — Hepatitis C

#### Opko Health

**Bevasiranib** — Wet age-related macular degeneration

#### Panacos Pharmaceuticals

**Bevirimat** — HIV infection

#### Pharmasset

**R7128** — Hepatitis C

#### Pharmaxis

**Bronchitol** — Bronchiectasis, cystic fibrosis

#### Plexxikon

**PLX4032** — Cancer

#### ProtalixBioTherapeutics

**prGCD** — Gaucher disease

#### Pharmasset

**R7128** — Hepatitis C

#### Pfizer

**Apixaban** — Blood clots

**Axitinib** — Pancreatic cancer, thyroid cancer, lung cancer

**PF-03187207** — Glaucoma

#### Regeneron

**Pharmaceuticals**

**Afibcept** — Cancer

#### Roche

**Pertuzumab** — Advanced breast cancer

**PLX4032** — Cancer  
**R7128** — Hepatitis C

#### Samaritan

**Pharmaceuticals**  
**Caprospinol** — Alzheimer's disease

#### Sanofi-Aventis

**Afibcept** — Cancer  
**AVE5026** — Thrombosis  
**Dengue vaccine** — Dengue fever

#### Schering-Plough

**Boceprevir** — Hepatitis C  
**Golimimumab** — Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis  
**Vicriviroc** — HIV infection

#### Seattle Genetics

**SGN-33** — Acute myeloid leukemia  
**SGN-40** — Non-Hodgkin lymphoma

#### Serenex

**SNX-5422** — Solid tumors, hematological tumors

#### Shire Human

**Genetic Therapies**  
**Amigal** — Fabry disease

#### Siga Technologies

**ST-246** — Smallpox

#### Synta Pharmaceuticals

**Elesclomol** — Metastatic melanoma

#### Targacept

**AZD3480** — Alzheimer's disease, cognitive disorders in schizophrenia

#### TargeGene

**TG100801** — Macular

degeneration

#### Teva Pharmaceuticals

**Laquinimod** — Multiple sclerosis

#### Theravance

**Telavancin** — Skin and skin structure infections, hospital-acquired pneumonia

#### ThromboGenics

**TB-402** — Thromboembolic disorders

#### Tibotec Therapeutics

**TMC278** — HIV infection

#### Tracon Pharmaceuticals

**TRC105** — Cancer

#### Transgene

**TG 4010** — Advanced non-small cell lung cancer

#### Vertex Pharmaceuticals

**Telaprevir** — Hepatitis C  
**VX-770** — Cystic fibrosis

#### VIRxSYS

**VRX496** — HIV infection

#### Viventia Biotech

**Proxinium** — Head and neck cancer

#### Wyeth

**AGG-523** — Osteoarthritis  
**Bapineuzumab** — Alzheimer's disease  
**Bosutinib** — Chronic myelogenous leukemia

#### XenoPort

**XP13512** — Restless legs syndrome, neuropathic pain

#### Ziopharm Oncology

**ZIO-201** — Soft tissue and bone sarcomas, ovarian and pediatric cancers

## 100 GREAT INVESTIGATIONAL DRUGS

### **Telavancin — Skin and skin-structure infections, hospital-acquired pneumonia**

Telavancin is a novel lipoglycopeptide injectable antibiotic discovered by **Theravance** Inc. (theravance.com). The drug is engineered to have a unique, multifunctional mechanism of action by inhibiting the formation of the bacterial cell wall and disrupting bacterial cell membrane function. The drug is being jointly developed by **Astellas Pharma** US Inc. (astellas.com) and is being considered in the United States and Europe for the treatment of complicated skin and skin-structure infections. Telavancin is also in Phase III studies for the treatment of hospital-acquired pneumonia.

### **TG 4010 — Advanced non-small cell lung cancer**

TG 4010 is a therapeutic cancer vaccine candidate developed by **Transgene** (transgene.com) in Phase IIb trials. The drug is an active specific immunotherapy that targets specifically the MUC1 tumor-associated antigen.

### **TG100801 — Macular degeneration**

TG100801 is a small molecule, topically applied, multi-target kinase inhibitor designed to suppress VEGF mediated leakage and additional kinase targets associated with inflammation, edema, and angiogenesis. Developer **TargeGen** Inc. (targegen.com) initiated a Phase II trial for the drug last year.

### **TMC278 — HIV infection**

TMC278 is a novel new non-nucleoside reverse transcriptase inhibitor developed by **Tibotec** therapeutics (tibotec.com), a subsidiary of **Johnson and Johnson** (jnj.com). The drug, which is in Phase II clinical trials, is potent and highly active against wild-type HIV and retains activity against NNRTI-resistant HIV strains in vitro.

### **TRC105 — Cancer**

TRC105 is a first-in-class human chimeric monoclonal antibody that inhibits tumor growth by binding to CD105, or endoglin, a receptor overexpressed on proliferating endothelium that is required for angiogenesis. TRC105, in Phase I trials by **Tracon** Pharmaceuticals Inc. (traconpharma.com), has shown activity — as monotherapy or when combined with chemotherapy — in preclinical studies

of breast and colorectal cancer.

### **Trodusquemine — Type 2 diabetes, obesity**

Trodusquemine (MSI-1436) is a centrally and peripherally-acting appetite suppressant in Phase I development by **Geniera** Corporation (geniera.com). The drug is the first highly selective inhibitor of protein tyrosine phosphatase 1B, which is central to controlling the function of the leptin and insulin pathways.

### **Vandetanib — Non-small cell lung cancer**

Vandetanib, also known as Zactima and ZD6474, is an antagonist of the vascular endothelial growth factor receptor and the epidermal growth factor receptor. **AstraZeneca** (astrazeneca.com) is conducting the first of four Phase III trials for the once-daily oral drug. Data from the trials are expected this year.

### **Varespladib — Cardiovascular disease**

Varespladib (A-002) is an anti-inflammatory drug for the treatment of chronic and acute diseases. The drug acts by inhibiting secretory phospholipase A2 (sPLA2), one of a family of enzymes that causes inflammation. Developer **Anthera** Pharmaceuticals (anthera.com) reached manufacturing agreements with **Albemarle** Corp. (albermarle.com) and **Patheon** Inc. (patheon.com) for the two companies to begin large-scale clinical production of varespladib, allowing Phase III trials to begin.

### **Vicriviroc — HIV infection**

Vicriviroc is a next-generation extracellular inhibitor of HIV infection designed to block entry of infectious virions into uninfected CD4 cells via antagonism of the CCR5 co-receptor. The drug is being developed by **Schering-Plough** Corp. (sgp.com). Phase II results demonstrated potent and sustained viral suppression through 48 weeks of therapy in treatment-experienced HIV-infected patients, when vicriviroc was administered once-daily as a single tablet in combination with an optimized ritonavir-boosted protease inhibitor containing an antiretroviral regimen.

### **VRX496 — HIV infection**

VRX496 is a gene therapy for the treatment of AIDS. The drug is being developed by **VIRxSYS** Corporation (virxsys.com). VrX496, which is in Phase II

development, uses a different viral vector than those used in previous gene therapy trials. VRX496 is derived from HIV-1 itself and has its disease-causing elements removed. Unlike other viral vectors, lentiviral vectors appear to sustain expression of the delivered genes of interest for a longer period of time.

### **VX-770 — Cystic fibrosis**

VX-770 is a new compound called a “potentiator” that may act to restore the function of the cystic fibrosis transmembrane conductance regulator protein, the defective cell membrane protein responsible for the progression of cystic fibrosis. **Vertex** Pharmaceuticals (VRTX.com) is conducting a Phase II trial to evaluate the safety and pharmacokinetics of VX-770, and how the drug affects biomarkers of the cystic fibrosis transmembrane conductance regulator protein in patients with genotype G551D.

### **XP13512 — Restless legs syndrome, neuropathic pain**

XP13512 (is a patented, new chemical entity designed to improve upon the clinical utility of gabapentin by taking advantage of high-capacity transport mechanisms in the gastrointestinal tract to improve absorption. In February, developers **XenoPort** Inc (xenoport.com) and **GlaxoSmithKline** (gsk.com) release positive top-line results from the final pivotal Phase III trial of XP13512 for the treatment of moderate-to-severe symptoms of primary restless legs syndrome.

Patients were treated with 1,200 milligrams or 600 milligrams of XP13512 or placebo, given once per day. Results from the pre-specified analysis indicate that treatment with 1,200 milligrams of XP13512 was associated with statistically significant improvements in the co-primary endpoints compared with a placebo.

### **ZIO-201 — Soft tissue and bone sarcomas, ovarian and pediatric cancers**

ZIO-201, the active moiety of ifosfamide, is a bi-functional alkylator that causes irreparable inter-strand DNA cross-linking resulting in cell death. Unlike ifosfamide, which is a pro-drug, ZIO-201 is directly active against cancer cells. ZIO-201, which is being developed by **Ziopharm Oncology** Inc. (ziopharm.com), is in an ongoing Phase II trial in advanced sarcoma. Trials in ovarian and pediatric cancers are in the planning stage and an oral form of ZIO-201 is in advanced preclinical development.



# Clinical crossroads

**T**he pressure pharmaceutical companies are under today to sustain their pipelines is immense. Add to the equation an aging population desperate for new therapies, particularly those for unmet medical needs, and the demand for promising investigational compounds has never been greater.

Experts say to revive their pipelines, companies must significantly build their innovative efficiencies. One way is by establishing more long-lasting partnerships and collaborations with external organizations, especially early in the drug-discovery process. The business of R&D is never an exact science and the reality is most investigational compounds in development will likely fail. Some of the ones that do not often treat such a small target population that the return on investment is limited.

Terri Cooper, Ph.D., national leader, life sciences R&D practice, Deloitte Consulting LLC (deloitte.com), has advised pharmaceuticals companies on a broad range of strategic services for 13 years, including creation of global business models. Her new report, "The R&D Process in the Future Pharmaceutical Landscape," is being published this month.

Dr. Cooper sat down with *R&D Directions* Senior Editor Michael Christel during the magazine's Drug Discovery Summit last month in Amelia Island, Fla., where she gave a presentation titled "Strategies for success in 2015: The New Paradigm for Research & Development."

Dr. Cooper discussed the challenges facing the pharmaceutical industry in the years ahead and emphasized the necessity for larger drug companies to adapt their R&D models to an increasingly fragmented market, not just for their financial well-being but for the future advancement of medical science.

**Q:** Reflecting on some of the strategies you highlight in your report on the future of R&D in the pharmaceutical industry, what should companies be doing now to improve their pipelines?

**A:** A lot of companies have relatively good pipelines, but the other element of that is really looking to be a lot

more effective around their ability to establish collaborations and partnerships with academic institutes. But having said that, we really need to have quite a bit of focused ideas on what they're actually trying to do, what they're trying to acquire. The reason that I say that is that it's become incredibly competitive. When you are looking at many of the big pharmas, many of them are trying to play on the same field. So as a result of that, if there is some interest in a technology platform, or an interest in a new kind of product that's in the very early stages of discovery, then it's become a lot more competitive.

It is around those acquisitions, but we also need to have scientists that are pretty good at the "drug hunt," as opposed to being Ph.D.s in biology or Ph.D.s in chemistry. Going out and finding these potential targets and knowing what they're looking for and being savvy in the way in which they can strike some of these negotiations and business deals. There's the external around the acquisition and trying to find the compounds; and then internally — around increasing that productivity — is really understanding what you're doing at each of those phases of discovery, around the target validation — how stringent are you going to be in actually spending time to do that and making sure that you're doing everything you can before moving on to the next sort of milestone.

**Q:** A product focus is typically not looked at as critical in the very early stages of drug development. How can research scientists become more mindful of the commercial potential of a drug candidate even during its infancy?

**A:** The struggle that big pharma has had to some extent is, historically, that scientists within the research environment of big pharma have really behaved to a large extent as though they are more of an academic institute, so they dabble in things that are of real interest. There's now the move to say, no, we need to be more focused and we really need to understand the commercial potential and we really do need to be clear around our priorities and where we're investing our efforts.

If you have a history of purely focusing on small molecules in the past, but now you have the ability to collaborate with people who think about things from a



**TERRI COOPER** "We need to have scientists that are pretty good at the 'drug hunt,' as opposed to being Ph.D.s in biology or Ph.D.s in chemistry."

vaccine approach or who think about things from a biologic approach — that's the right way to go forward as a scientist. To think about what are all the different modalities that I have to actually address a disease as opposed to, "I'm a small-molecule scientist." That to me I find really interesting — around that integration of ideas.

**Q:** The blockbuster model is obviously changing. Can you describe how companies are evolving their strategies when it comes to the development of big blockbusters?

**A:** Historically, the blockbuster model has been very much around treating symptoms as opposed to really understanding the disease, and not actu-

ally preventing the disease or changing the molecular pathway. If you think about Lipitor and others, it's around lowering cholesterol. There's no indication about, well, why was the cholesterol high in the first place? What is the molecular pathway that would lead to that? Whereas if you look at compounds like Enbrel and others — Enbrel now actually modifies the molecular pathway. Primarily, that's the major difference between the old blockbuster strategy, which was around treating symptoms. A lot of that was because when many of those blockbuster products were launched, we didn't have all of the science that we have now. (For example,) historically, what probably would have happened with Alzheimer's (disease) is you would have thought, is there anything that you can do that can treat the symptom that would actually improve somebody's cognitive functions and memory? Now what we're trying to do is to say, we truly believe that the reason that people develop Alzheimer's is that you have a buildup of the amyloid plaque. If we can prevent the buildup of the plaque, it's a real disease effect — you can target the cause as opposed to treating symptoms.

**Q:** *Do you see more pharmaceutical companies realizing the days of relying on purely a blockbuster-driven market are over?*

**A:** Absolutely. I don't think any company is necessarily going to give up entirely on blockbusters, but they realize the risk associated with pursuing the blockbuster because they're huge investments put into one product. You see in our survey, (where we asked executives) what is the most critical strategy that you have to be successful in 2015? Seventy-four percent of responders said that we have to have a robust R&D pipeline. So there is huge, huge pressure in doing that. Then the question is, how are you going to build that pipeline? Then they have the dilemmas of doing that entirely internally. So, ultimately now you're looking (for help) through acquisitions, collaborations, etc. You look at what AstraZeneca announced, that it's spinning off parts of their GI research — selling it out to a new biotech company (Albireo Pharma) and then taking some level of royalty back, saying, "OK, you guys may have more success with this than we do, and we just benefit."

**Q:** *You mention how the fragmentation of the market will alter the landscape for the pharmaceutical industry. How do you see the role of big*

***"I truly believe in 2015 — I'm not so sure whether you'll see big pharma as it is now. You'll see a lot more agile, flexible, far more external collaborations."***

**pharma changing seven or eight years from now?**

**A:** I truly believe in 2015 — I'm not sure whether you'll see big pharma anymore as it is now. You'll see a lot more agile, flexible, far more external collaborations. You'll see a decrease in the number of internal employees and they'll be leveraging a lot more as a virtual organization externally.

**Q:** *With that in mind — this emphasis on collaborating more with other companies — do you see better opportunities in store for the small and mid-tier biotech and specialty companies?*

**A:** They have an advantage from the point of view of where they are right now — that they have a truly biological focus. Where they need the help as well is that they don't necessarily have the skills and expertise around how do you then do the manufacturing, how do you do all of the other components? Brian Daniels (senior VP, global clinical development, Bristol-Myers Squibb) summed it up very well — at the moment big pharma tries to do absolutely everything, end to end. The question then will be if you really want to improve your probability of success, I can see companies saying we are no longer going to have an internal research; we're going to actually fuel the rest of our organization purely through collaborations and acquisitions of products. But we truly believe we're excellent at rapid development of products. And we're going to have really strong clinical development, we'll drive it through, we'll get them licensed.

But we haven't necessarily demonstrated that with all the billions of dollars that we invest in research — having our own internal big research sites — that that's been profitable. We might as well take, let's say — more on the research end — \$2 billion versus \$6 billion. We might take that \$2 billion and say, rather than supporting a huge infrastructure, we're going to invest that \$2 billion in actually collaborating and finding the products externally. Then there may be other companies that say we're really, really good at research — we're just going to

become that research but we're no longer going to take on the costs of the development. There's going to probably be fewer big pharma companies that you're going to have a lot of what we call new entrants, that are more targeted around what they want to do, supported by some of these specialist companies. It will be much, much more fragmented in the way in which they deliver the services and get a product to market.

**Q:** *Changing subjects a bit — how concerned should the industry be over the slowdown in the number of drugs gaining FDA approval?*

**A:** The FDA at the moment is in a very difficult situation, because the public has become very risk-averse. They're under a phenomenal amount of pressure to actually ensure that they area really looking at the overall safety of compounds. The difficulty there is that any product that we take is predominately a poison. It's never going to be 100% safe. So they've got a dilemma. Then, in addition to that, because the science and the technology has made them so fast, they have the other dilemma around having individuals that are actually qualified or have had enough experience to actually do the validation and review of some of these newer compounds. There's a disconnect between this sort of level of trials and the level of investigation.

In a way, you're trying to take a biologic and treat it the same way as a conventional blockbuster. If you have a really clearly defined endpoint, a biomarker endpoint, then the question is why do you have to do all these other phenomenally huge trials? Because you should be able to identify very explicitly who are the patients that are going to benefit from that treatment.

The whole thing is in a bit of flux right now around how the FDA actually addresses a number of those issues. I think they recognize the challenges in the industry. I think they're trying to do everything that they can to work with the industry to think about moving forward. But they're in this catch 22 because of the recent publicity around safety profiles of projects.