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THE ONES TO WATCH

A PHARMA MATTERS REPORT.

JULY-SEPTEMBER 2008

Expert review from Thomson Reuters of the most promising drugs changing clinical phase, receiving approval and launched this quarter, based on the strategic data and insight of *Thomson Pharma*[®], the world's leading pharmaceutical competitive intelligence solution.



Despite reports you may have read to the contrary, the pharmaceutical industry as a whole remains buoyant. Certainly we're seeing sluggish performance in established markets, especially the US, where a combination of factors is conspiring to both stifle research and depress profits. But even here there is still growth—and in the emerging markets, pharmaceutical sales are increasing rapidly.

It's clear that the current global economic uncertainty is having an effect. In the US, fewer patients are presenting themselves in the clinics, meaning fewer prescriptions and falling sales for the innovators, and there is a continuing shift toward generics. Government-paid schemes, too, such as in the UK, are squeezing down prices and favoring generics. But it remains to be seen if this hopefully short-term turmoil will exert any long-term harm on research and development, the most vulnerable part of a company's budget.

This quarter's *The Ones To Watch* suggests that for now, at least, the answer is no. We've highlighted a number of the novel therapies and first-candidate drugs moving through clinical trials, each of them an encouraging success story that may help to shape the pharmaceutical industry in the future.

As the days of the blockbuster fade into memory, potential profits are revealing themselves in the specialist markets, particularly oncology. New technologies, especially the use of biomarkers, are driving up innovation, as this publication demonstrates with *every* issue. We're confident that we'll continue to report on an industry that is not only surviving, it's showing incredible creativity and dedication, from bench to launch and beyond, in the face of trying circumstances.

So let's take a closer look at the five most promising drugs launched or receiving approval, and moving through each of the clinical phases, between July and September 2008.

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THE FIVE MOST PROMISING DRUGS LAUNCHED OR RECEIVING APPROVAL

DRUG	DISEASE	COMPANY
Zeftera™	Complicated skin and soft tissue infections	Basilea Pharmaceutica
Firazyr®	Hereditary angioedema	Jerini
Bridion®	Reversal of muscle relaxants	Schering-Plough
Cleviprex™	Perioperative hypertension	The Medicines Company
Xarelto®	Venous thromboembolic events	Bayer/ Ortho-McNeil Pharmaceutical

In recent years, the cleanliness of hospitals has become a growing concern, prompting ever more stringent measures to improve routine hygiene and minimize infection. Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and drug-resistant *Streptococcus pneumoniae* are increasingly common. The situation is exacerbated because hospitalized patients may not respond to traditional antibiotic treatment for the infections they acquire due to the medication they take for their illness.

This is particularly the case with patients suffering from diabetic foot infections, pneumonia, and severe skin infections. Some of the most common of all hospital-acquired diseases are complicated skin and soft tissue infections (cSSSI), predominantly due to the Gram-positive microbe *Staphylococcus aureus*. Each year, approximately 5 million patients worldwide are treated for cSSSI. Patients with chronic wounds or those who have recently received antibiotics may also be infected by Gram-negative microbes.

Zeftera™, active ingredient ceftobiprole medocartil, is the first approved broad-spectrum anti-MRSA antibiotic belonging to the cephalosporin class. It is designed to bind the penicillin-resistant targets in many Gram-positive bacteria of the cocci-type, resulting in bactericidal activity towards MRSA and penicillin-resistant *Streptococcus pneumoniae*. According to Basilea Pharmaceutica, it also demonstrates broad-spectrum activity against many of the other Gram-positive and Gram-negative bacteria associated with community and hospital-acquired infections.

The drug, developed in collaboration with two Johnson & Johnson subsidiaries, Cilag and J&J Pharmaceutical Research and Development, was first launched in Canada in September 2008 for the treatment of cSSSI, including diabetic foot infection. *Thomson Pharma* predicts sales of \$22 million in 2008 and \$430 million in 2011.

Hereditary angioedema (HAE) is a form of edema where the skin of the face, hands, limbs and elsewhere become swollen, often with severe pain. Where the throat is affected, the patient can die of respiratory arrest. Patients can also suffer vomiting, diarrhea

and weakness, as well as intense abdominal pain. There is often no known cause and it is impossible to predict when and where on the body the next attack will occur. At its worst, sufferers have to deal with episodes every week, with each one lasting as long as 5 days.

Jerini, under license from sanofi-aventis, has developed the selective bradykinin B2 antagonist icatibant (brand name [Firazyr®](#)) for the condition. It was approved in Europe in July 2008, apparently the first drug to secure EU-wide approval for HAE, with launch in UK and Germany as this edition of *The Ones To Watch* goes to press. Its European Orphan Drug status grants Jerini 10 years' marketing exclusivity. The company is also investigating Firazyr for drug-induced angioedema and capillary leak syndrome.

This is an important win not just for sufferers of HAE, who are dearly in need of the treatment, but also for Jerini, as Firazyr is its first marketed product and the remainder of its pipeline is still at the early stage of development. Indeed, its next most advanced product is JSM-6427, which is currently in phase I trials for age-related macular degeneration.

Approval in the US hasn't been so smooth. Jerini filed an NDA for Firazyr with the FDA in October 2007, and was granted priority review that December. However, in April this year the FDA issued a non-approvable letter. Jerini plans to submit a complete response by November 2008, when the future of the drug in the US will become clearer. We suggest sales of \$4 million in 2008, rising to as much as \$92.9 million in 2011.

Anesthesiologists use muscle relaxation to improve surgical conditions and to facilitate intubation and mechanical ventilation. After surgery, reversal agents enable patients to regain normal muscle function sooner and breathe on their own. However, current reversal agents are slow and are associated with undesirable side effects including cardiac rhythm disturbances and gastrointestinal and pulmonary side effects. Schering-Plough has demonstrated that its sugammadex (brand name [Bridion®](#)) is effective within three minutes. It was launched in September 2008 in Sweden.

There, Bridion is indicated for routine and immediate reversal of commonly used steroidal muscle relaxants such as rocuronium and vecuronium. An injectable, synthetic cyclodextrin-based host molecule, its novel mechanism of action involves encapsulating the muscle relaxant molecule and rendering it inactive. The drug should provide greater control of muscle relaxation through to the end of a surgical procedure. Launch in the UK, Germany and several other European countries is expected by early 2009.

Bridion also has potential use in the recovery of surgery patients who have undergone steroidal NMB-induced anesthesia. NDAs have also been filed in Japan and the US, but like Firazyr the road to approval has been rockier in America. In July 2008,

the FDA issued a non-approvable letter for the drug, stating issues with hypersensitivity or allergic reactions. Nevertheless, *Thomson Pharma* predicts sales of \$16 million this year, rising to \$304 million by 2011.

Schering-Plough claims that Bridion is the first major pharmaceutical advance in its field in two decades. A similar claim is made by The Medicines Company for clevidipine (brand name *Cleviprex™*)—according to the company, the drug is the first new intravenous antihypertensive agent introduced to the market in the last decade. It believes *Cleviprex* will give physicians an option to treat a broad array of patients who need rapid and precise blood pressure control.

The therapy, developed under license from AstraZeneca, is a short-acting dihydropyridine calcium antagonist. It was approved by the FDA in August for perioperative hypertension when oral therapy is not possible, and launched in the US in October 2008.

It comes with impressive phase III trial results. The drug reduced systolic blood pressure by 6% within three minutes, by 15% after 9.5 minutes and by 27% (55 mmHg) after 18 hours. Target blood pressure was reached in a median time of 10.9 minutes, and 89% of patients achieved their target within 30 minutes. After 18 hours of continuous *Cleviprex* treatment, the majority of patients (92%) did not require other intravenous antihypertensive agents, and there were no reported serious adverse events.

In September 2008, Bayer and Ortho-McNeil Pharmaceutical, a subsidiary of Johnson & Johnson, launched rivaroxaban (brand name *Xarelto®*) in Canada. This is a direct Factor Xa inhibitor tablet for the prevention and treatment of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism. The following month, the drug was also approved in the EU for the prevention of venous blood clots in adults undergoing elective hip or knee replacement surgery and is now available in Germany and the Netherlands. An NDA for the prevention of DVT and pulmonary embolism in patients undergoing hip or knee replacement surgery was filed in the US in July.

Thomson Pharma predicts success for the brand, based on sales for the current standard of care, sanofi-aventis's enoxaparin (*Lovenox®*), which reached \$3.6 billion in 2007. Phase III trials demonstrated that *Xarelto* is more effective than enoxaparin at reducing DVT, pulmonary embolism, major venous thromboembolism and all-cause mortality. We pencil in sales of \$1.2 billion in 2011.

Bayer and Ortho-McNeil Pharmaceutical are also developing the drug for other cardiovascular diseases such as acute coronary syndrome and stroke prevention in atrial fibrillation, and Bayer is investigating the drug for the potential treatment of disseminated intravascular coagulation.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE III TRIALS

DRUG	DISEASE	COMPANY
MAP-0004	Migraine	MAP Pharmaceuticals
linaclotide	Irritable bowel syndrome, constipation	Ironwood Pharmaceuticals
Lucanix®	Lung cancer	NovaRx
retaspimycin	Gastrointestinal stromal tumor	Infinity Pharmaceuticals/ MedImmune
ramucirumab	Breast cancer	ImClone Systems

The standard of care for chronic migraine and debilitating migraines that last more than 72 hours is usually considered to be dihydroergotamine (DHE). However, this is generally administered intravenously, meaning that patients need to travel to a medical facility to receive it. Intranasal formulations are available, but this method of administration may lead to inconsistent and poorly-controlled dosing levels.

[MAP-0004](#) is an inhaled formulation of DHE, incorporating Tempo drug delivery technology. Developer MAP Pharmaceuticals claims it provides consistent and convenient dosing, a rapid onset of action and the proven efficacy of DHE. In phase II trials, MAP-0004 reduced pain at 10 minutes and 2 hours, which was sustained at 24 hours, compared with placebo. A positive trend was also seen in the reduction of phonophobia, photophobia, and nausea.

This is encouraging news for MAP-0004, which entered phase III trials in July 2008. The market is huge—the US National Headache Foundation estimates there to be 30 million sufferers in that country alone—given that as many as 40% of patients do not respond fully to the current leading migraine therapies, the triptans. In addition, MAP-0004's onset of action is significantly quicker than the 45–90 minutes you can expect from an oral triptan. The prospect is good that it can take a significant bite out of the triptans' sales—\$2.2 billion in 2007.

We've always been encouraged by novel therapies, and highlight them whenever possible. This edition of *The Ones To Watch* has a greater number than ever before. For example, Ironwood Pharmaceuticals' candidate is the first guanylate cyclase-C agonist to reach phase III trials, a fact that, coupled with Thomson Pharma's predicted first year sales (in 2011) of \$57.5 million, makes [linaclotide](#) particularly promising.

The drug is a 14-mer peptide and is under development by Ironwood and its US licensee Forest Laboratories as a potential oral treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation. Our predicted sales reflect the huge potential market—as many as

one in six of all adults in developed countries suffer from IBS, and the disorder accounts for 12% of all adult visits to primary care physicians in the US. Ironwood's treatment addresses the approximate 30–40% of this total (9 million in the US alone) that have the constipation-predominant form, for which there are few available therapies.

We're not the only ones optimistic about the drug. As we go to press, Ironwood has raised \$50 million in a private equity financing to fund its phase III program, which began in September 2008.

Late-stage non-small-cell lung cancer (NSCLC) typically responds poorly to standard therapy. NovaRx hopes to change this with its therapeutic cancer vaccine belagenpumatucel-L, developed under the trade name [Lucanix](#)[®]. Phase III trials began in August 2008 to build on the impressive efficacy the candidate showed in a phase II trial. There, half the patients entering the trial with stable disease who received Lucanix survived more than 44 months, compared with less than 12 months for patients given standard of care. In patients given Lucanix after up to five prior chemotherapy treatments, one-year survival was 61% and two-year survival was 41%.

The drug consists of four non-small-cell lung cancer cell lines that have been genetically engineered to shut off their immune suppressive properties. These cell lines are then modified to block a molecule called transforming growth factor-beta (TGF-beta), which is commonly produced by cancer cells as a block against the body's natural immune system. When TGF-beta is blocked, the immune system can mount an anti-tumor response. Lucanix, which is applied intradermally, could treat not only NSCLC but other cancers as well.

An alternative therapy is proposed by Infinity Pharmaceuticals and MedImmune, a subsidiary of AstraZeneca. This is an intravenous formulation of [retaspimycin](#), an Hsp90 inhibiting 17-AAG analog. The companies believe it could be effective against NSCLC, multiple myeloma (MM) and gastrointestinal stromal tumor (GIST) and metastatic melanoma.

The mechanism of action is familiar: Hsp90 is a popular target in cancer therapy, with a large number of drugs in development. However, Infinity Pharmaceuticals and MedImmune claim that their targeted Hsp90 chaperone inhibitor therapy may represent a significant, currently unaddressed strategy, since retaspimycin hydrochloride is a novel, targeted anti-chaperone agent that shows potent and selective inhibition of Hsp90.

Phase I trials of an oral formulation of retaspimycin for solid tumors commenced in July 2008. Phase I/II trials of the intravenous formulation in NSCLC were initiated in January 2008, and phase II trials in melanoma in April 2008. But our focus here is on the drug's potential to treat GIST.

In the UK, the standard of care for patients whose GIST cannot be fully removed by surgery is Novartis's Gleevec®. Trials of retaspimycin in patients resistant to Gleevec showed that 76% achieved stable disease, rising to 83% if you include those who achieved partial response. It entered phase III trials in August 2008.

Cancer is also the focus of [ramucirumab](#), a fully human anti-VEGFR-2 monoclonal antibody for the potential intravenous treatment of cancer, including renal cell carcinoma, prostate and ovarian cancer, melanoma and hepatocellular carcinoma. The treatment is derived from Dyax Corp's native phage display library.

Developer ImClone Systems believes the drug prevents a unique opportunity to optimize the therapeutic approach of blocking VEGFR-2, on which the growth of breast cancer is dependent. It binds to the VEGFR-2 receptor itself, blocking many VEGF ligands from activating it. This is in contrast to Genentech's bevacizumab (Avastin®), which targets only a single ligand, and small molecule drugs that target many unrelated receptors.

A global phase III trial for metastatic breast cancer began in August 2008. Like retaspimycin, ramucirumab is in various stages of development for different forms of cancer: phase II prostate cancer studies also began in August 2008, while phase II trials for advanced HCC began in February 2008, phase II trials for patients with metastatic malignant melanoma began in August 2007, and phase II trials for ovarian cancer in September 2008. Phase III gastric cancer studies are expected to begin by July 2009.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE II TRIALS

DRUG	DISEASE	COMPANY
CAD-106	Alzheimer's disease	Cytos
TC-5214	Depression	Targacept
Prolarix™	Hepatocellular carcinoma	Protherics
NLX-P101	Parkinson's disease	Neurologix
AG-011	Crohn's disease, ulcerative colitis	ActoGeniX

Turning to the most promising drugs entering phase II trials, we see [CAD-106](#), a beta amyloid-modulating lead in a series of therapeutic vaccines based on the Immunodrug™ technology developed by Cytos. The candidate, which entered phase IIa trials initiated by Novartis in Switzerland, is a potential injectable treatment for Alzheimer's disease. This disease still lacks in an effective treatment to reverse its effects (current therapies slow disease progression only), despite which market leader Aricept® from Pfizer notched up sales of \$2.5 billion in 2007.

In its phase I trial, a specific antibody response was induced by CAD-106 against Aβeta and against Qβeta in 16 of the 24 treated patients, with results indicating that the dose was well tolerated in the majority of recipients. Follow-on studies with a further cohort of patients are planned. Meanwhile, we wait to see how CAD-106 will compare against Elan and Wyeth's ACC-001, the only one of a number of other Alzheimer's disease vaccines *Thomson Pharma* is tracking through the development pipeline, to precede it into phase II trials.

Millions of patients suffering from depression do not respond well to the currently available first-line therapies. This was highlighted in a study of major depressive disorder (MDD) by the National Institute of Mental Health between 2001 and 2006: of approximately 2,800 sufferers given citalopram for 12 to 14 weeks, only about a third reached remission. However, many of those who did not respond or only partially responded to citalopram fared better when their regime was augmented with a new medication or when they were switched to a different treatment. A quarter of these participants reached remission.

Clearly, then, the potential market for effective second and third line treatments is enormous.

Hopes are high for [TC-5214](#), a stereoisomer of the nicotinic acetylcholine receptor antagonist mecamylamine under development by Targacept. It's progressing rapidly, having entered phase I in March 2008 and just five months later shifting to a phase IIb trial as an augmentation therapy for MDD. *Thomson Pharma* confirms the company's assertion that the drug's mechanism is novel for the therapy area.

Another novel technology is [Prolarix™](#), an NQO2-based prodrug therapy for the potential intravenous treatment of cancer, in particular liver and colorectal cancers, under development by Protherics.

This is a therapy area in dire need of good news: hepatocellular carcinoma (HCC) is the sixth most common cause of cancer in the world, but prognosis is poor. Despite the recent approval of Onyx/Bayer's sorafenib (under the brand name Nexavar®), a new chemotherapy which is being adopted as the standard of care, life expectancy remains less than 12 months from diagnosis. Protherics estimates the global market for an effective treatment at more than \$500 million.

Protherics's scientists found that the NQO2 enzyme, generally absent in healthy body tissue but present in certain tumor types, particularly HCC, is active in the presence of the co-substrate caricotamide, converting the prodrug tretazicar into its cytotoxic form. Prolarix treatment comprises of co-administration of caricotamide and tretazicar, killing target tumor cells while minimizing harm to healthy body tissue.

A phase IIa trial for HCC began in August 2008 in Belgium, with additional sites in Asia to follow. Protherics hopes to release data in the second half of 2009.

[NLX-P101](#) is the latest promising candidate in the battle against Parkinson's disease. Again, we're overdue some good news, since this is an incurable disease with little effective treatment. Neurologix believes its drug could have disease-modifying activity by targeting glutamic acid decarboxylase (GAD). The therapy is an adeno-associated virus gene therapy delivered by infusion to the subthalamic nucleus, where it causes nerve cells to release gamma aminobutyric acid, inhibiting or dampening the uncontrolled movement associated with the disease.

Thomson Pharma's research shows that NLX-P101 is the only non-dopamine-based Parkinson's gene therapy in development. Phase I trials showed an improvement in motor function on the side of the body corresponding to the treated part of the brain—the untreated side showed no benefit. Activities of daily living score also improved. PET scans showed that the treated side of the brain had a decrease in abnormal metabolism, while the untreated side showed an increase in abnormal metabolism. The therapy was safe and well tolerated, with no evidence of adverse effects or immunologic reaction. Phase II trials began in the USA in August 2008.

In an edition of The Ones to Watch notable for its firsts, we are also encouraged by [AG-011](#), a genetically-engineered Lactococcus strain expressing IL-10, generated with ActoGeniX's proprietary TopAct platform for the potential oral treatment of Crohn's disease and ulcerative colitis. It is the only IL-10-targeting therapy in development for this area.

IL-10 is a signaling molecule that plays a critical role in the immune system, acting as a central factor in the induction and maintenance of immune tolerance. Though it was discovered many years ago, the immunological effects of IL-10 were never fully recognized, perhaps because clinicians administered treatment by injection, where it was only modestly effective and had significant side effects at high dosage. Being an oral treatment, AG-011 aims to reverse this perception.

A phase I/IIa trial in ulcerative colitis began in July 2008. Phase II studies in Crohn's disease are expected to run through 2009.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE I TRIALS

DRUG	DISEASE	COMPANY
PMX-30063	Bacterial infections	PolyMedix
PMX-60056	Heparin reversal	PolyMedix
CTP-347	Vasomotor symptoms	CoNCERT
CVT-3619	Diabetes, heart disease	CV Therapeutics
OMP-21M18	Cancer	OncoMed Pharmaceuticals

At the top of our list of notable candidates entering phase I trials this quarter, [PMX-30063](#) is the lead in a series of peptidomimetics of plant defense proteins being developed by PolyMedix for the potential treatment of bacterial infections. It's another important first: not only the first defensin mimetic ever to enter clinical trials, but the first clinical candidate for PolyMedix.

Initial data are promising. At the GTCbio 5th Annual Anti-Infectives Partnering and Deal-Making Summit in Philadelphia in March 2008, PolyMedix demonstrated that compounds in the series are potent antimicrobials, with a broad-spectrum activity against drug-resistant bacteria including MRSA and vancomycin-resistant enterococcus infections. They are also rapidly bactericidal, and are selective for bacterial cells versus mammalian cells. The compounds were active in animal models of bacterial infection, with similar efficacy to vancomycin. Moreover, studies suggested that it was not likely that bacterial resistance to the compounds could develop easily.

PolyMedix describes PMX-60063 as "a synthetic chemical mimic of host defense proteins, one of the oldest and most effective antimicrobial defense systems found in virtually all living creatures". It commenced phase I trials in Canada in August 2008, with a second clinical study under consideration.

Uniquely for *The Ones To Watch*, the second most promising drug on our list is also the second candidate from PolyMedix. [PMX-60056](#) followed PMX-60063 into clinical trials a month later. Since each of the two candidates targets a completely different disease area, the twin successes, coming from a

company with no previous clinical track record, are especially notable. They suggest that PolyMedix has an ambitious R&D program—we look forward to following their development in future issues.

PMX-60056 is the lead in a series of injectable small-molecules and oligomers that bind tightly to low molecular weight heparin (LMWH), and so has potential use as a heparin and LMWH reversing agent. Heparin is used widely during cardiothoracic surgery to prevent blood clots, but when surgery is complete its effects must be reversed. LMWH is used for long term management of chronic thrombosis.

It is hoped that PMX-60056 will form an effective alternative to protamine, the only agent currently available, but one which has a number of significant drawbacks, including potential allergic reactions, immunogenicity risk and poor fibrokinetics. In addition, protamine is not active against LMWH, and is not generally clinically effective at reversing the risk of bleeding associated with use of the treatment.

Yet another notable first comes from CoNCERT Pharmaceuticals. In September 2008 it too entered its first ever phase I trials, this time for [CTP-347](#), a deuterated form of the selective serotonin reuptake inhibitor paroxetine, for the potential oral treatment of vasomotor symptoms (VMS) such as hot flashes. The company's technology, selectively replacing hydrogen atoms with the deuterium isotope, appears to be completely novel.

Currently, there are no FDA-approved non-hormonal treatments for VMS, which can lead to depression and insomnia. While hormone replacement therapy can be effective, it is not suitable for patients with breast or ovary cancer, or a history of these cancers in their family, and many women are concerned about its long-term health risks.

Paroxetine, most familiar as an antidepressant, is also effective against VMS, but it is a potent and irreversible inactivator of CYP2D6, a key liver enzyme responsible for the metabolism of many commonly-described drugs. CoNCERT has shown that CTP-347 significantly reduces CYP2D6 inhibition while preserving paroxetine's pharmacological activity.

We continue to see encouraging activity to find effective treatments for diabetes and heart disease. *Thomson Pharma* highlights [CVT-3619](#), developed by CV Therapeutics, as another first-in-class therapy entering clinical trials this quarter.

The drug is the oral lead from a series of A1 adenosine receptor partial agonists for the potential treatment of type 2 diabetes, dyslipidemia and other cardiometabolic diseases. CV Therapeutics believes it targets so-far untreatable aspects of dysfunctional metabolism in these patients, and commenced phase I trials in September 2008.

Finally in this quarter, [OMP-21M18](#) is yet another unique therapeutic approach, the lead in a series of humanized monoclonal antibodies under development by OncoMed Pharmaceuticals for the potential treatment of cancer. OncoMed believes that cancer stem cells, the small population of cells that may drive cancer growth and metastasis, differ from normal stem cells in that they have accumulated oncogenic mutations. These mutations can therefore be exploited in therapies selectively targeting tumor initiating cells and not normal stem cells.

The candidate highlights the importance of in-licensing innovative drugs and technologies to the big pharmaceutical companies which have the economy of scale and resources to run with them. GlaxoSmithKline has the option to acquire up to four of OncoMed's antibodies, a deal that *Thomson Pharma* suggests could potentially be worth up to \$1.4 billion, plus sales royalties.

Clearly, both companies are excited by the possibilities of this new area of drug discovery. Phase I trials began in August 2008.

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