

SCRIP

DRUG MARKET DEVELOPMENTS

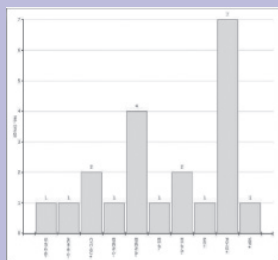
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Pipeline Watch

Worldwide Late-Stage Clinical Developments Combinations
Page 8



Each month, *Scrip Drug Market Developments* tabulates the most recently reported late-stage clinical developments from the more than 7,000 drug candidates currently under active research worldwide, to help ensure you keep fully up-to-date with competitor R&D activity. In this issue, we highlight 101 events in therapeutic categories including:

- Cancer
- Dermatology
- Infectious Diseases
- Nervous System
- Reproductive Health

Are combinations and reformulations of old drugs the answer to the obesity epidemic?

Obesity has been labeled a global 'epidemic' responsible for rising healthcare costs, but current treatments have been beset with side effects or have shown insufficient efficacy. With several new treatments now in late-stage development, the obesity sector is likely to see new therapies become available. Some of the most interesting agents – reformulations and combinations of established drugs – show impressive activity towards the upper end of the scale of placebo-adjusted weight loss. **Page 3**

Can Phase I data help appease cardiac stem cell trials controversy?

Cardiac stem cell trials are moving forward, despite fierce debate over the underlying mechanism of healing. As data from Phase I trials roll in, it is hoped that the trials are putting fears over safety to rest. So far the various cardiac treatments appear to be safe, but the debate continues. As questions over the mechanism of action have yet to be fully answered, critics argue the therapies may prove to offer little benefit to patients. Others say the first round of studies have shown great promise. **Page 17**

From blockbuster drugs to blockbuster alliances

Licensing agreements, collaborations, and acquisition activities in the biopharmaceutical industry have steadily increased in recent years, as pharmaceutical companies attempt to fill their early and late stage pipelines. Deals now occur in earlier development stages, at higher levels of risk and at higher prices. Increased pharmaceutical company demand for biotech products, coupled with a weak market for initial public offerings (IPO), has led founders and venture capitalists of biotech companies to view acquisition as the most viable exit strategy. **Page 24**

Emerging legal issues of advanced therapies: a European perspective

The new regulation on advanced therapy products has closed a gap in the EU regulatory framework, providing for a consistent legal structure governing the collection, testing, processing, storage and distribution of human tissues, cells and blood and the manufacturing of ATPs as well as the post-authorization and post-marketing safety aspects relating to this specific type of products. The regulation is similar to the regulatory framework set up in the US under the authority of the FDA, though it is much more systematic and comprehensive. **Page 13**

Telomerase: an ideal diagnostic marker and cancer target?

The significance of cancer in the modern world needs no introduction: 7.6 million people died from cancer in 2007, accounting for roughly 13% of all deaths. Clearly, there is a vast market available for any effective cancer treatment. Studies have found high levels of telomerase activation in many types of cancer, including approximately 90% of breast cancers. Thus, telomerase could be an ideal diagnostic or prognostic marker for cancer progression, or even an alternative therapeutic target. **Page 21**

Antibiotic-resistance: fighting the superbugs

In recent years, antibiotic-resistant bacteria have become a significant obstacle to the future treatment of bacterial infections, and an ongoing challenge for healthcare services worldwide. This is set against a paucity of new drug approvals for antibiotics as companies focus their R&D on higher profit-margin products and antibiotic agents that are in development face a tougher regulatory environment from the US FDA. However, with the continued development of new therapies, there is hope that antibiotics can overcome the threat posed by such bacteria, and continue to be effective in the future. **Page 28**

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Dear subscriber

As many of you know, Scrip Drug Market Developments (SDMD) has been published, in one guise or another, for 18 years. It began publication in 1990 as Drug and Market Developments and its original mission was to provide readers with information not easily obtained including unknown start-up companies, private conference coverage and putting clinical research into a business market context. This service has been added to over the years to ensure that our readers receive informative, relevant and interesting articles that are pertinent to their role in the pharmaceutical and biotechnology industries.

The key to the success of SDMD has been to retain an open mind to what our readers would like and to evolve and adapt to changes in the market place. With the publishing environment undergoing rapid changes, driven by faster and more efficient web-based daily services, the time has come to review print-based publications in our portfolio and assess whether they are serving the subscriber in the best capacity they can.

Against that backdrop, it has been decided that Scrip Drug Market Developments will cease publication in its current format with this August issue being the last.

However, the high quality content that you have come to rely on will still be available to you. SDMD will be amalgamated with its sister publication, Scrip World Pharmaceutical News, which is able to offer a high-tech web-based platform to ensure that the information is delivered to you in a more timely manner.

Your subscription to SDMD will automatically transfer to Scrip World Pharmaceutical News for the remainder of your current subscription. We believe that you will find this enhanced subscription to be of good value. However, if you do not believe Scrip World Pharmaceutical News will be useful to you please contact Philip Jarvis (philip.jarvis@informa.com).

Scrip World Pharmaceutical News has been published for more than 30 years and is the leading global information service for those working in the pharmaceutical and biotechnology industries. Drawing upon a pool of over 20 journalists worldwide, Scrip World Pharmaceutical News is able to offer readers a daily on-line based news service where you can read the headlines and full articles of all of the day's global news. This is in addition to a weekly roundup print issue as well as detailed Market Insights that are similar to the longer in-depth feature articles that you are familiar with in SDMD. The worldwide late-stage clinical developments pipeline watch that has been the signature feature in SDMD will continue to be published in Scrip.

We hope that you will enjoy the fresh new coverage and dynamic delivery of information that this merger with Scrip World Pharmaceutical News offers.

Meanwhile, in this last issue of SDMD, we feature articles on antibiotic resistance, obesity, telomerase inhibitors, cardiac stem cells, the changing nature of alliances in business development and the legal aspects of advanced therapy use in Europe.

As always, we invite you, as valued subscribers, to contact us at any time with feedback on any issue you may have. Thank you for your support and ongoing interest and we hope that you enjoy the August issue.



Managing Editor



Publisher

Could new formulations and combinations of old drugs be the answer to the obesity epidemic?

Over the past few years obesity has been labeled a global 'epidemic' responsible for rising healthcare costs, but current treatments have been beset with side effects or have shown insufficient efficacy. With several new treatments now in late-stage development, the obesity sector is likely to see new therapies become available. Some of the most interesting agents – combinations and reformulations of established drugs – show impressive activity towards the upper end of the scale of placebo-adjusted weight loss. However, Merck & Co's taranabant, which is the next obesity agent anticipated to be filed with the FDA, appears unlikely to receive approval.

By Jacob Plieth

Obesity affects a large and increasing proportion of the population, including over 30% of Americans. Numerous medical conditions have been associated with being overweight, and it is largely because of this that the sharp rise in obesity has started to be seen as such a significant global health problem. Most important among the co-morbidities is type 2 diabetes, but they also include hypertension, stroke and heart disease, and even the risk of malignancies and psychological disorders. This is a particularly interesting issue because obesity treatments can be seen as more than just 'lifestyle drugs', given that a reduction in weight of as little as 5% has been associated with a 50% decrease in co-morbidities (according to the American Heart Association). This is therefore an area that has potential for reimbursement.

The high-profile failures of Wyeth/Servier's fenfluramine and dexfenfluramine, the so-called "Fen-Phen" diet drug combination (the name refers to the drugs' widely used off-label combination with phentermine, an earlier anti-obesity agent which is still sold) and Sanofi-Aventis' rimonabant; a greater understanding of complex underlying pharmacological pathways; and concerns about side effects have pointed the way towards new drug development. Current projects target multiple path-

ways, with an increasing focus on combination therapy.

The coming two years should determine the extent to which obesity is still a viable area for therapeutic intervention and big pharma involvement and, if so, which companies stand the most chance of achieving near-term success. 2008 is likely to see the first US filing of an anti-obesity project since rimonabant in 2006 which failed to receive approval. The product is Merck & Co's taranabant. However, it is widely expected not to be approved because it has the same mechanism of action as rimonabant, raising similar safety issues.

There are numerous anti-obesity agents in studies at present. Several approaches are being investigated to treat the condition centrally, including cannabinoid receptor antagonism, neuropeptide Y and leptin to name a few, as well as using a peripheral approach by preventing the absorption of fat in the intestine.

FDA approvals

Although prescription pharmaceuticals for treating obesity have been available for most of the 20th century, their

Table 1 – US FDA approvals of anti-obesity drugs

Year Approved	Drug name	Notes
1947	desoxyephedrine/ methamphetamine	
1956	phenmetrazine (Preludin)	
1959	phendimetrazine (Bontril)	Withdrawn by CPMP in 2000 – decision overturned 2003
1959	phentermine (Fastin, Ionamin)	
1959	diethylpropion (Tenuate)	
1960	benzphetamine (Didrex)	
1972	fenfluramine (Pondimin)	Withdrawn 1997
1973	mazindol (Sanorex)	
1996	dexfenfluramine (Redux)	First approval for long-term use; withdrawn 1997
1997	sibutramine (Meridia)	Approved for long-term use
1999	orlistat (Xenical)	Approved for long-term use

Source: Presentation by Dr David Orloff, former director of US FDA's division of metabolic and endocrine products.

development has been beset with problems. Most have been associated with limited efficacy and significant side effects. Before 1996 all obesity drugs were approved for short-term treatment (ie, a few weeks) – a standpoint that contrasts with the current view of obesity as a chronic disease.

Table 1 outlines post-war FDA approvals of drugs for treating obesity. There have only been three drugs approved for long-term treatment – dexfenfluramine (withdrawn in 1997), Abbott's sibutramine (Meridia) and Roche's orlistat (Xenical).

The market launch of rimonabant, a first-in-class selective CB1 (cannabinoid 1) antagonist, was eagerly awaited, the drug having been billed by some as the most promising weight loss treatment since Fen-Phen. However, in June 2006 an expert advisory panel to the FDA voted against its approval, citing unresolved safety concerns.

This view was echoed by the FDA, which subsequently refused to approve the product. Rimonabant has been available in Europe (as Acomplia) since its approval by the EMEA in June 2006. While Sanofi-Aventis has not given up on developing rimonabant in the US, it appears unlikely that the drug will be approved there in the near future, especially given the continued caution with which the FDA is progressing.

Market potential

It is generally recognized that the global market for obesity medications could be worth billions of dollars, given the large and growing population of the overweight and obese. However, because of the side effects and limited efficacy of currently approved drugs, as little as 2% of the obese population in the US was treated with a pharmaceutical intervention in 2005 (Frost & Sullivan), and no currently marketed anti-obesity treatment generates blockbuster sales.

Treatment approaches

Treatments for obesity consist of behavioral modification, pharmaceutical therapies and surgery, largely dependent on how obese the patient involved is. Modifications to diet and exercise are the preferred initial treatment, although on their own these measures tend only to be effective in the longer term among those with a relatively low body mass index (BMI).

Surgery, including gastric bypass and gastric banding, is the approach taken in extreme cases of obesity, typically for obese individuals with a BMI of over 40kg/m². Surgery can be highly effective – sometimes helping patients lose 50% or more of their total body weight – but can be associated with potential complications including a long recovery time, substantial costs and death.

Pharmaceutical therapies, therefore, can be seen as targeting a large subsection of the obese patient population with a BMI of under 40kg/m² and generally those in whom behavioral modification alone has failed. Approval for treating obesity has not yet been sought for any other drug since rimonabant, although a number are in mid- to late-stage clinical studies.

Mechanisms of action

Targets for anti-obesity agents include the cannabinoid receptor, 5HT, leptin, neuropeptide Y, peptide YY, ghrelin, α -melanocyte-stimulating hormone, corticotropin-releasing hormone, urocortin, galantamine, amylin, orexin, GLP-1 and bombesin.

Because of the condition's complex nature and presence of feedback loops, many drugs that operate via single mechanisms have shown limited benefits in terms of efficacy, and a combination approach is increasingly being seen as a promising one to follow. A number of companies are attempting this, some with patent-protected agents, such as Amylin's pramlintide plus metreleptin, and others with combinations of off-patent drugs – Orexigen Therapeutics and Vivus specialize in this.

Furthermore, it could be the case that many of the drugs currently being developed as single agents end up being prescribed in combination (possibly off-label), as happened in the 1990s with fenfluramine and dexfenfluramine, and as it has been suggested might happen with Arena Pharmaceuticals' lorcaserin, although the company has repeatedly refused to be drawn on this issue.

The only late-stage product that acts peripherally (ie, non-centrally) is Alizyme's cetilistat, which has completed Phase II trials. This uses the same mechanism of action as orlistat and appears to result in a similar (ie, relatively low) level of placebo-adjusted weight loss, but does hold the promise of no CNS-related side effects. In terms of tolerability, however, cetilistat is likely to be associated with similar side effects as orlistat owing to its action of fat binding in the intestine, although early studies have suggested that this effect is less pronounced.

Comparison of clinical data

In general, the lipase inhibitors (orlistat and cetilistat) tend to exhibit activity at the lower end of the spectrum, but have the benefit of no issues on the CNS. Activity of the CB1 antagonists (rimonabant, taranabant, otenabant etc) appears to be in the mid-range, while possibly the most interesting agents – reformulations of established drugs – show impressive activity towards the upper end of the scale of placebo-adjusted weight loss. These include Orexigen's Empatic and Vivus's Qnexa.

While some agents with novel mechanisms of action have shown extremely impressive activity this has to be treated with caution as side effects are likely to prove a limiting factor in the future. It is particularly worthy to note that the side effects of rimonabant did not become fully apparent until the product was studied in long-term trials in thousands of patients; accordingly, companies with novel products are likely to tread cautiously, probably opting to test lower doses of their agents in longer studies, preferring to see somewhat reduced efficacy than risking potential side-effect issues at more active doses.

Late-stage anti-obesity projects

Table 2 profiles the most important anti-obesity projects currently in development in Phase II or beyond. Many of the additional candidates presented here could prove equally or even more promising, capturing a significant share of the market, but are not profiled in detail mainly because they are relatively further away from launch.

Six companies (Alizyme, Amylin, Arena, NeuroSearch, Orexigen and Vivus) each have Phase II data, some of significant duration, and each offer a relatively high-risk, but also potentially high-reward investment opportunity if Phase III data are positive and respective products can be licensed to significant big pharma players.

Table 2 - Anti-obesity drugs in development at Phase II and above

Drug name	Company	Status	Mechanism of action	Notes
Acomplia (rimonabant)	Sanofi-Aventis	marketed in Europe	CB1 antagonist	US filing withdrawn after being rejected by FDA. EMEA reviewing data.
taranabant	Merck & Co	Phase III	CB1 inverse agonist	Due to be filed in US in H208. Latest Phase III study in 2,500 patients gave statistical significance, and 2mg chosen as best dose. Higher doses associated with increased psychiatric adverse events.
Contrave (naltrexone + bupropion)	Orexigen	Phase III	bupropion = dopamine & noradrenaline reuptake inhibitor; naltrexone = opioid antagonist.	Last of four Phase III studies initiated in November 2007; two are now fully recruited. Total pivotal program comprises 4,500 patients.
lorcaserin	Arena	Phase III	selective 5HT2C receptor agonist	'Safer fenfluramine' thanks to 2C receptor selectivity. Complete Phase III program to enrol 7,000 patients.
otenabant	Pfizer	Phase III	CB1 antagonist	Four active long-term Phase III trials in a total of over 5,500 patients. Completion due between early 2009 and early 2010.
Qnexa (phentermine + topiramate)	Vivus	Phase III	topiramate = GABA and other agonist properties	Full Phase III program (three studies, 4,500 patients) underway. Additional formulation in development.
Empatic (zonisamide + bupropion)	Orexigen	Phase IIb	bupropion = dopamine & noradrenaline reuptake inhibitor; zonisamide = GABA agonist	Recently initiated Phase IIb matrix design study in over 600 patients to determine optimal dose ratio(s) for further development. Phase III to begin in H109.
pramlintide	Amylin	Phase IIb	amylin analogue	Injectable. Marketed for types 1 and 2 diabetes. Also in combination with metreleptin, peptide YY3-36 and other agents.
AVE1625	Sanofi-Aventis	Phase IIb	CB1 antagonist	Surinabant also tested in obesity, but that is now a smoking-cessation project.
tesofensine	Neuro-Search	Phase IIb	dopamine/noradrenalin/5HT reuptake inhibitor	Phase IIb proof-of-concept study in 203 obese patients showed statistical significance after 24 weeks. Open-label extension under way. Previously studied for Alzheimer's and Parkinson's diseases.
velneperit	Shionogi	Phase IIb	neuropeptide Y5 receptor antagonist	12-week Phase IIa study gave statistical significance after four-week diet run-in. No statistical significance in second arm.
obinipitide	7TM Pharma	Phase II	neuropeptide Y agonist	In Phase IIa study to evaluate weight loss after subcutaneous treatment for 28 days. Will enrol 180 patients with BMI of 30-40.
liraglutide	Novo Nordisk	Phase II	GLP-1 analogue	Injectable project, in Phase III for diabetes, with filing possible in 2008. Phase II obesity data showed 7kg loss in liraglutide group vs 3kg (placebo) and 4kg (orlistat).
betahistine	Obecure*	Phase II	histamine receptor activation	Phase II study in 281 patients failed to show statistical significance. Betahistine marketed outside the US for vertigo.
cetilistat	Alizyme	Phase II	lipase inhibitor	Phase III dependent on signing a partner.
CP-866087	Pfizer	Phase II	not disclosed	In 12-week Phase II trial in 96 obese subjects. Also in development for alcohol dependence and female sexual arousal disorder.
ibipinabant	BMS/ Solvay	Phase II	CB1 antagonist	600-patient Phase II/III study was to start in March 2008. Trial withdrawn from Clinicaltrials.gov.
N-5984	Nisshin Kyorin	Phase II	selective β3 antagonist	May improve obesity and have less cardiac effect than previous compounds.
peptide YY3-36 nasal spray	Nastech	Phase II	peptide YY3-36	Six-month, dose-ranging trial has recruited 551 obese subjects and will compare the nasal spray with placebo and sibutramine.
CE-326597	Pfizer	Phase II	CCK receptor antagonist	200-patient study due to be completed in September 2008.
JNJ28431754	Johnson & Johnson	Phase II	SGL T2 inhibitor	12-week study in 400 patients testing 50mg, 100mg and 300mg doses started February 2008.
R256918	Johnson & Johnson	Phase II	gut-selective MTP inhibitor	12-week study in 320 patients testing 5mg, 10mg and 15mg doses completed June 2008.
SCH-497079	Schering-Plough	Phase II	histamine H3 receptor antagonist	12-week study in 300 patients started in April 2008.
THR-4109	Theracos*	Phase II	venlafaxine = norepinephrine and 5HT uptake inhibitor; rivastigmine = cholinesterase inhibitor	Combination of venlafaxine and rivastigmine. 24-week study in 220 patients was due to have been completed July 2008.
Adyvia	Innodia*	Phase IIa	adipose triglyceride lipase & PI3 kinase activator	Results of 12-week trial in 100 patients were due by end of 2007.

Note: *Privately owned company. Source: Edison Investment Research

Alizyme

Alizyme's cetilistat is the only peripherally acting anti-obesity project in late-stage development. Cetilistat inhibits gastrointestinal lipase, thus preventing fat absorption in the gut, and exerts no action on the CNS, a factor the company believes could offer considerable safety benefits in light of the FDA's rejection of Sanofi-Aventis' centrally acting rimonabant.

In terms of tolerability, however, cetilistat is likely to be associated with similar side effects as orlistat owing to its action of fat binding in the intestine, although early studies have suggested that this effect is less pronounced. More evidence as to the extent of this unpleasant side effect will be sought from a six-month Phase II trial that was carried out by Alizyme's Japanese partner, Takeda. This trial is due to be reported in 2008, and will indicate for the first time how cetilistat performs over more than 12 weeks.

Although cetilistat is ready to enter Phase III trials in the US and the program has been agreed with the FDA, Alizyme must first find a partner to fund it. The trial is expected to involve 4,000 patients for one year in three or four placebo-controlled studies with the primary endpoint being the proportion of patients who lose at least 5% of their body weight.

Amylin Pharmaceuticals

Amylin Pharmaceuticals already markets pramlintide, an analogue of the naturally occurring pancreatic hormone amylin, to treat diabetes and it has obtained promising efficacy with the compound in the treatment of obesity. In a 52-week, Phase II study, pramlintide alone led to an average weight reduction of 7-8% compared with 1% for placebo. The company is now looking to combine it with other molecules, in particular metreleptin, an analogue of human leptin, as well as possibly PYY3-36 and PYY3-36 plus leptin. A six-month, Phase IIb trial of pramlintide plus metreleptin started in May and Phase I data of the pramlintide/PYY3-36 combination are expected later this year.

Arena Pharmaceuticals

Arena's lead compound, lorcaserin, is the subject of one of the largest Phase III obesity trials underway, enrolling almost 7,000 patients. The molecule works by a similar mechanism to fenfluramine, but aims to circumvent the heart valve damage that led to its withdrawal by having much greater 5HT2 selectivity. The first Phase III trial of the product revealed no increase in heart valve abnormalities and the all clear was given for the 7,000 patient Phase III trial to commence. However, given the relationship between its mechanism of action and that of

Table 3 - Obesity projects in early-stage development

Drug name	Company	Mechanism of action	Notes
TM30339	7TM Pharma	neuropeptide Y4 receptor agonist	Entered Phase I/II in early 2007. Mimics action of pancreatic polypeptide, a natural satiety hormone.
oral protein YY ₃₋₃₆	Emisphere	protein YY3-36	Phase I results were due Q208.
AZD-1175	AstraZeneca	CB1 antagonist	Phase I.
V-24343	Vernalis	CB1 antagonist	16-day Phase I study of 5-100mg/day doses in 32 volunteers showed placebo-adjusted weight loss of up to 4.5kg.
THCV	GW Pharmaceuticals	Tetrahydrocannabivarin	Multidose proof-of-principle Phase IIa trial in type 2 diabetics due to begin in 2008.
PF-04415060	Pfizer	DGAT-1 inhibitor	Licensed from Bayer. Phase I.
JTT-553	Japan Tobacco	DGAT-1 inhibitor	Phase I.
ATHX-105	Athersys	5HT2C agonist	Phase II trial is planned for 2008.
BVT-74316	Biovitrum	5HT6 receptor antagonist	Safety and tolerability seen in Phase I trial in 98 healthy volunteers.
TTP435	TransTech Pharma*	AgRP inhibitor	Phase I.
trodusquemine	Genaera	inhibition of protein tyrosine phosphatase and dopamine and norepinephrine reuptake transporters; downregulation of AgRP and NPY hormone expression	Six-month Phase I trial in 28 obese patients with type 2 diabetes testing single ascending doses 3-15mg/m ² . Completion was expected in June 2008.
TKS-1225	Thiakis*	oxyntomodulin analogue	Injectable. Previous Phase I 28-day trial at Imperial College, London, showed 1.8kg placebo-adjusted weight loss in volunteers.
NGD-4715	Neurogen	melanin concentrating hormone-1 receptor antagonist	Phase II proof-of-concept trial requires a licensing partner.
AP1030	Action Pharma*	targets MCR4	Phase I.
remogliflozin	GlaxoSmith-Kline/Kissei	sodium-dependent glucose transport inhibitor	Phase I.
PF-2575799	Pfizer	not disclosed	Phase I.
PF-4325667	Pfizer	not disclosed	Biological product in Phase I.
PSN602	OSI Pharmaceuticals	5HT and norepinephrine reuptake inhibitor	First Phase I study began in June 2008.

Source: Edison Investment Research

fenfluramine, lorcaserin is likely to result in increased scrutiny from the FDA and other regulators.

NeuroSearch

NeuroSearch's tesofensine has shown some of the most impressive weight loss data in an anti-obesity agent in a clinical study to date. Data reported last year from a dose-finding Phase IIb study for tesofensine revealed that 203 patients receiving 0.25mg, 0.5mg or 1mg of the compound over 24 weeks resulted in average weight loss of 6.7kg, 11.3kg and 12.8kg respectively, against a weight loss of 2.2kg in the placebo group.

Data from an open-label Phase IIb extension study evaluating tesofensine's safety profile, tolerability and weight reduction effect for up to 12 months is expected shortly. The compound has already been tested in Phase II for the treatment of Alzheimer's and Parkinson's diseases (but was discontinued owing to poor efficacy) and this safety data can be added to the compound's profile in obesity.

Orexigen Therapeutics

Orexigen's two lead anti-obesity projects – Contrave and Empatic – comprise new formulations of established drugs that have been approved for other indications and have established post-marketing safety records. Contrave is a fixed-dose formulation of bupropion (indicated for smoking cessation and depression) and naltrexone (alcohol/opiate addiction) and is in four Phase III trials involving around 4,500 patients over a 12-month period. Empatic contains bupropion formulated with zonisamide (anti-epileptic), and recently saw data from a 48-week Phase IIb study showing strong efficacy; a second Phase IIb study, in around 720 non-diabetic obese patients, has just begun. Contrave could be filed with the FDA in late 2009 while Empatic is unlikely to be filed before 2011. Both products are unpartnered.

Vivus

Vivus's Qnexa is also a combination of two established drugs, phentermine (obesity) and topiramate (anti-epileptic), designed to complement the former's appetite-reducing properties with the latter's satiety-increasing properties. Although development of topiramate for obesity was stopped owing to CNS side effects, Qnexa contains it at a low dose. Three Phase III studies are enrolling up to 4,500 patients and data are expected to be published in the second half of 2009 alongside a potential filing with the FDA. Qnexa appears to be only one of two anti-obesity projects (the other being Novo Nordisk's liraglutide) to show a significant decrease in blood pressure in obese hypertensive patients. Vivus recently reported data from a 28-week study in type 2 diabetics, showing a statistically significant reduction in systolic and diastolic blood pressure in Qnexa-treated patients vs placebo.

Early-stage anti-obesity agents

Table 3 outlines anti-obesity projects that are at an earlier stage of clinical development.

Near-term triggers

A number of important near-term triggers will determine the future course of the sector and indicate whether treatment of obesity with therapeutic intervention remains a possible blockbuster area worthy of multi-million dollar investment.

The success or failure of one or more projects currently in late-stage development will shape the level of interest shown by big pharma in the obesity sector. At present, most of the late-stage projects remain unpartnered.

A growing focus is expected on the development of therapies comprising a combination of two or more products. Projects currently in standalone development could ultimately be developed for combination use or prescribed in combination off label.

Safety will remain the number one concern for the FDA. As such, we believe that treating obesity with a CB1 antagonist is no longer a viable strategy and it is unlikely that Merck & Co's taranabant, which is expected to be the next obesity compound filed with the FDA, will receive approval following the agency's refusal to approve rimonabant and the continued association of this drug class with psychiatric adverse events.

We expect 5-10% placebo-adjusted weight loss from baseline over 52 weeks to represent sufficient efficacy to warrant US approval, with activity below 5% acceptable only in the presence of significant safety/side-effect advantages.

This article draws on a report, "Fat Chance", recently published by Jacob Plieth, analyst at Edison Investment Research. For a copy of the full report, email enquiries@edisoninvestmentresearch.co.uk.

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WORLDWIDE LATE-STAGE CLINICAL DEVELOPMENTS

Each month *SDMD* tabulates the most recently reported late-stage clinical developments from the more than 7,000 drug candidates currently under active research worldwide, to help ensure you keep fully up-to-date with competitor R&D activity. In this issue, we highlight 101 events in therapeutic categories including: cancer, dermatology, infectious diseases, nervous system, pulmonary diseases, and reproductive health.

Compound	Company	Indication	Mechanism of Action	Development Status	Comments
Anticancer					
bavituximab	Peregrine Pharmaceuticals	Cancer, lung, non-small cell	Tubulin antagonist Angiogenesis inhibitor Phosphatidylserine inhibitor	Initiation of Phase II trials	
blinatumomab	Micromet	Cancer, leukemia, acute lymphocytic	CD19 antagonist	Orphan drug status granted	The US
bortezomib	Takeda	Cancer, myeloma	Proteasome inhibitor Transcription factor NF-kappaB inhibitor	Additional approval	The US
cetuximab	ImClone Systems	Cancer, colorectal	Epidermal growth factor receptor (EGFR) antagonist	Additional approval	Japan
contusogene ladenovec	Introgen Therapeutics	Cancer, head and neck	p53 stimulant	Registration submissions	The EU and the US
CR-011-vcMMAE	CuraGen	Cancer, breast	Microtubule inhibitor	Initiation of Phase II trials	
EC-145	Endocyte	Cancer, lung, non-small cell	DNA synthesis inhibitor Microtubule inhibitor Cell cycle inhibitor Mitotic inhibitor Vinca alkaloid agonist Folate receptor antagonist	EC-147	Initiation of Phase II trials
FolatImmune	Endocyte	Cancer, renal	Unidentified pharmacological activity	Initiation of Phase II trials	
GTI-2040	Lorus Therapeutics	Cancer, leukemia, acute myelogenous	Ribonucleoside triphosphate reductase inhibitor	Orphan drug status granted	The EU
IMA-901	immatics biotechnologies	Cancer, renal	Immunostimulant	Initiation of Phase II trials	
lapatinib ditosylate	GlaxoSmithKline	Cancer, breast	ErbB-2 tyrosine kinase inhibitor ErbB-1 tyrosine kinase inhibitor	Additional approval	The EU
omacetaxine mepesuccinate	ChemGenex Pharmaceuticals	Cancer, leukemia, chronic myelogenous	Apoptosis agonist Angiogenesis inhibitor	Registration submission	The US
paclitaxel	Abraxis BioScience	Cancer, breast	Taxane Beta tubulin antagonist Microtubule stimulant Mitotic inhibitor Cell cycle inhibitor	Additional approval	China
panitumumab	Amgen	Cancer, colorectal	Epidermal growth factor receptor (EGFR) antagonist	Registration submission	Japan
ProLindac	Access	Cancer, ovarian	DNA antagonist	New licensee	Jiang Aosaikang Pharmaceutical; China including Hong Kong and Taiwan
PRX-321	Protox Therapeutics	Cancer, glioma	Protein synthesis antagonist	Orphan drug status granted	The EU
Rexin-G	Epeius Biotechnologies	Cancer, sarcoma, soft tissue	Cyclin G1 inhibitor	Rexin-G	The US
sunitinib malate	Pfizer	Cancer, gastrointestinal, stromal	Endothelial growth factor receptor kinase inhibitor Platelet-derived growth factor receptor kinase inhibitor Flt-3 kinase inhibitor C-kit inhibitor Colony stimulating factor receptor 1 inhibitor	Additional launch	Japan

Compound	Company	Indication	Mechanism of Action	Development Status	Comments
Anticancer					
tamibarotene	Nippon Shinyaku	Cancer, leukemia, acute myelogenous	Retinoic acid alpha receptor agonist	tamibarotene	The US
tesetaxel	Daiichi Sankyo	Cancer, colorectal	Taxane Microtubule stimulant Mitotic inhibitor Cell cycle inhibitor	Resumption of development	Following FDA-imposed clinical hold
veltuzumab	Immunomedics	Cancer, lymphoma, non-Hodgkin's	CD20 antagonist	New licensee	Nycomed; Worldwide (exclusive)
vincristine	Tekmira Pharmaceuticals	Cancer, melanoma, uveal	Colony stimulating factor receptor 1 inhibitor Tubulin antagonist Microtubule inhibitor Vinca alkaloid agonist Mitotic inhibitor Cell cycle inhibitor	Orphan drug status granted	The US
XL-184	Exelixis	Cancer, thyroid	MET tyrosine kinase inhibitor Endothelial growth factor receptor-2 kinase inhibitor C-kit inhibitor Flt-3 kinase inhibitor TIE-2 tyrosine kinase inhibitor RET tyrosine kinase inhibitor	Initiation of Phase III trials	
Cardiovascular & Blood					
antithrombin alfa	GTC Biotherapeutics	Antithrombin III deficiency	Thrombin inhibitor	New licensee	Ovation Pharmaceuticals; The US
ARC-1779	Archemix	Thrombosis, arterial	Factor VIII inhibitor	Orphan drug status granted	The EU
argatroban	Mitsubishi Tanabe Pharma	Thrombosis, arterial	Direct thrombin inhibitor Thrombin inhibitor	Additional approval First launch	Japan
ART-123	Asahi Kasei Pharma	Disseminated intravascular coagulation	Protein C subunit activator		Japan
ATI-5923	ARYx Therapeutics	Thrombosis, general	Platelet aggregation antagonist	Initiation of Phase II/III trials	
carperitide	Daiichi Sankyo	Heart failure	Atrial natriuretic peptide agonist	Discontinued	In the EU and the US
CD-NP, Nile	Nile Therapeutics	Heart failure	Diuretic	Initiation of Phase II trials	
eltrombopag olamine	GlaxoSmithKline	Thrombocytopenic purpura	Thrombopoietin agonist	Orphan drug status granted	The US
everolimus eluting stent	Abbott	Restenosis	mTOR kinase inhibitor Angiogenesis inhibitor Cell cycle inhibitor	Additional launch	The US
icatibant	Sanofi-Aventis	Odema, general	Bradykinin B2 receptor antagonist	First approval	The EU
irbesartan	Sanofi-Aventis	Hypertension, general	Angiotensin II 1 antagonist	Additional launch	Japan
MK-6213	Merck & Co	Atherosclerosis	Unidentified pharmacological activity	Initiation of Phase II trials	
nitroglycerin	MediQuest Therapeutics	Raynaud's disease	Guanylate cyclase stimulant Nitric oxide agonist	Registration filing	The US; Priority review
paclitaxel stent	Angiotech	Restenosis	Tubulin antagonist Microtubule stimulant	First launch	New Zealand
plerixafor	Genzyme	Stem cell mobilization	CXC chemokine receptor 4 antagonist	Registration filings	The EU and the US
PMD-2850	Protherics	Hypertension, general	Immunostimulant Angiotensin antagonist	Initiation of Phase II trials	Novel formulation
ranolazine ER	CV Therapeutics	Angina, general	Partial fatty acid oxidation inhibitor Sodium channel antagonist	Additional approval	The EU
treprostinil sodium, inhaled	United Therapeutics	Hypertension, pulmonary	Prostacyclin agonist	Registration filing	The US

Compound	Company	Indication	Mechanism of Action	Development Status	Comments
Dermatological					
ALS-00T2-0501	Apollo Life Sciences	Psoriasis	Tumor necrosis factor antagonist	Initiation of Phase Ib/II trials	
dapsone, SMP, QLT	Allergan	Acne	Dihydrofolate reductase inhibitor	Product divestment	Allergan
miltefosine	JADO Technologies	Urticaria	Membrane integrity antagonist Interleukin 12 antagonist	Initiation of Phase II trials	
ustekinumab	Johnson & Johnson	Psoriasis	Interleukin 12 antagonist	Approval recommendation	The US
Endocrinology and Metabolic					
AKP-020	Akesis	Diabetes, Type II	Unidentified pharmacological activity	Discontinuation of a Phase II Trial	Larger replacement trial planned
EUR-1008	Eurand	Pancreatic insufficiency	Unidentified pharmacological activity	Approvable letter	The US
INT-747	Genextra	Steatohepatitis, non-alcoholic	Farnesoid X receptor agonist	Initiation of Phase II trials	Phase II trial initiation in NASH and Phase I trial results reported
lipase	Altus Pharmaceuticals	Pancreatic insufficiency	Lipase stimulant Proteolytic enzyme stimulant Amylase stimulant	Initiation of Phase III trials	
liraglutide	Novo Nordisk	Diabetes, Type II	Glucagon-like peptide 1 agonist Insulin secretagogue Incretin mimetic	Registration filing	Japan
metformin + repaglinide	Novo Nordisk	Diabetes, Type II	Biguanide Meglitinide Gluconeogenesis inhibitor AMPK stimulant Insulinotropin agonist Insulin secretagogue ATP-sensitive potassium channel antagonist	First approval	The US
metformin + vildagliptin	Novartis	Diabetes, Type II	Biguanide AMPK stimulant Dipeptidyl peptidase 4 inhibitor Glucagon-like peptide 1 agonist Gluconeogenesis inhibitor Insulin secretagogue	First launch	The UK
Infection					
ALN-RSV01	Anylam	Infection, respiratory syncytial virus	Gene expression inhibitor	New licensee	Kyowa Hakko; Asia
cefixime	Astellas	Infection, general	Cell wall synthesis inhibitor	New licensee	Ascend Therapeutics; The US
ceftobiprole medocartil	Basilea Pharmaceutica	Infection, skin and skin structure, complicated	Cell wall synthesis inhibitor	First approval	Canada
ciprofloxacin, AERx	Aradigm	Infection, pseudomonal	DNA topoisomerase ATP hydrolysing inhibitor	Initiation of Phase II trials	
clevudine	Bukwang	Infection, hepatitis-B virus	DNA directed DNA polymerase inhibitor	Registration submissions	India, Indonesia and the Philippines
DTP + polio vaccine	GlaxoSmithKline	Infection, diphtheria prophylaxis	Immunostimulant	First approval	The US
etravirine	Johnson & Johnson	Infection, HIV/AIDS	RNA directed DNA polymerase inhibitor Non-nucleoside reverse transcriptase inhibitor	Registration submissions	Australia, Canada, Russia and Switzerland
fluconazole	Boryung	Infection, fungal, general	Cell wall synthesis inhibitor Sterol demethylase inhibitor	First approval	S Korea

Compound	Company	Indication	Mechanism of Action	Development Status	Comments
Infection					
IC-51	Intercell	Infection, Japanese encephalitis virus prophylaxis	Immunostimulant	Registration submission	Canada
influenza vaccine	CSL	Infection, influenza virus prophylaxis	Immunostimulant	First approval	Australia
influenza vaccine	Novartis	Infection, influenza virus prophylaxis	Immunostimulant	Withdrawal of registration submission	The EU; Additional data requested
levofloxacin	Mpex	Infection, pseudomonal	DNA topoisomerase ATP hydrolysing inhibitor	Initiation of Phase II trials	
meropenem	Dainippon Sumitomo Pharma	Infection, respiratory tract, lower	Cell wall synthesis inhibitor	New licensee	Cubist Pharma; The US
miconazole	BioAlliance Pharma	Infection, Candida, general	Sterol demethylase inhibitor Cell wall synthesis inhibitor	Additional launches	Denmark and Germany
oritavancin	Eli Lilly	Infection, skin and skin structure, complicated	Cell wall synthesis inhibitor	Registration submissions	The EU
peramivir	BioCryst Pharmaceuticals	Infection, influenza virus	Neuraminidase inhibitor	Initiation of Phase II trials	
pertussis vaccine	Sanofi-Aventis	Infection, pertussis prophylaxis	Immunostimulant	Additional approval	The US
raltegravir	Merck & Co	Infection, HIV/AIDS	HIV integrase inhibitor	Additional launch	Japan
silver sulfadiazine	Research Corporation Tech	Infection, general	PABA antagonist	New licensee	York Pharma
tipranavir	Boehringer Ingelheim	Infection, HIV/AIDS	HIV protease inhibitor	Additional approval	The US; In patients 2-18yr
Musculoskeletal					
adalimumab	AstraZeneca	Arthritis, rheumatoid	Tumor necrosis factor antagonist	Additional launch	Japan
certolizumab pegol	UCB	Arthritis, rheumatoid	Tumor necrosis factor alpha antagonist	Registration submission	The EU
chondroitinase ABC	Seikagaku	Spinal disc herniation	N Acetylgalactosamine 4 sulfatase stimulant Cyclooxygenase 1 inhibitor	Initiation of Phase II/III trials New licensee	
diclofenac	Nuvo Research	Arthritis, osteo	Cyclooxygenase 2 inhibitor		Paladin Labs
etanercept	Amgen	Arthritis, rheumatoid	Tumor necrosis factor antagonist	Additional launch	Japan
etoricoxib	Merck & Co	Ankylosing spondylitis	Cyclooxygenase 2 inhibitor	Approval recommendation	The EU
golimumab	Johnson & Johnson	Ankylosing spondylitis	Tumor necrosis factor alpha antagonist	Registration submission reported	The US
hPTH (1-34), transdermal	TransPharma Medical	Osteoporosis	Parathyroid hormone agonist	New licensee	Eli Lilly; Worldwide
hyaluronic acid, pain	Anika Therapeutics	Arthritis, osteo	Hyaluronic acid agonist	First launch	The EU
parathyroid hormone	Bone Medical	Osteoporosis	Parathyroid hormone agonist Osteoclast inhibitor	New licensee	Hyundai Pharm; S Korea
risedronate sodium	Procter & Gamble	Paget's disease	Bisphosphonate		Japan
ropinirole, transdermal	Jazz Pharmaceuticals	Restless legs syndrome	Dopamine D2 agonist	Initiation of Phase II trials	

Compound	Company	Indication	Mechanism of Action	Development Status	Comments
Gastronintestinal					
ATI-7505	ARYx Therapeutics	Gastro-esophageal reflux	5 Hydroxytryptamine 4 agonist		Procter & Gamble
fosaprepitant dimeglumine	Merck & Co	Chemotherapy-induced nausea and vomiting	Neurokinin 1 antagonist	First launch	The UK
methylnaltrexone	Progenics Pharmaceuticals	Constipation	Opioid mu receptor antagonist	Additional approvals	The EU, Iceland, Liechtenstein and Norway
MGX-006	Victory Pharma	Nausea and vomiting, general	Unidentified pharmacological activity	Initiation of Phase III trials	
N-acetylcysteine, RxKinetix	Endo Pharmaceuticals	Chemotherapy-induced mucositis	Unidentified pharmacological activity	Termination of Phase III trial	
ondansetron, RapidFilm	Applied Pharma Research	Nausea and vomiting, post-operative	5 Hydroxytryptamine 3 antagonist	Initiation of Phase III trials	
palonosetron hydrochloride	Helsinn	Nausea and vomiting, post-operative	5 Hydroxytryptamine 3 antagonist H+ K+ transporting ATPase inhibitor	Additional launch	The US
rabeprazole sodium	Eisai	Gastro-esophageal reflux	Gastrin inhibitor	Additional approval	The US; in adolescents
Nervous System					
beclometasone dipropionate	DOR BioPharma	Transplant rejection, general	Glucocorticoid agonist Arachidonic acid antagonist Immunosuppressant Arachidonic acid antagonist Immunosuppressant	New licensee	Numoda Corporation
gusperimus	Nippon Kayaku	Transplant rejection, general	Immunosuppressant	Approval submission withdrawal	The EU
interferon	Novartis	Multiple sclerosis, relapsing-remitting	Interferon beta 1 agonist	Additional approval	The EU
Ophthalmological					
difluprednate, ophthalmic	Senju	Uveitis	Glucocorticoid agonist Arachidonic acid antagonist Immunosuppressant	First approval	The US
loteprednol etabonate	Bausch & Lomb	Uveitis	Phospholipase A1 inhibitor	Additional launch	The UK
sodium hyaluronate	Lantibio	Xerophthalmia	Hyaluronic acid agonist	Additional launch	The UK
triamcinolone acetonide	Merck & Co	Odema, macular, diabetic	Arachidonic acid antagonist Immunosuppressant	Initiation of Phase II trials	
triamcinolone	Allergan	Odema, macular	Arachidonic acid antagonist Immunosuppressant	First approval	The US
Reproductive					
ethinylestradiol+levonor	Barr Pharmaceuticals	Contraceptive, female	Estrogen agonist Progesterone agonist	New licensee	Procter & Gamble; Canada
Urological					
fesoterodine fumarate	UCB	Overactive bladder	Muscarinic antagonist	First launch	The UK
VA-483	Vantia	Nocturnal polyuria	Vasopressin 2 antagonist	Initiation of Phase II trials	

Source: Pharmaprojects, 2008.

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Emerging legal issues relating to advanced therapies: a European perspective

The new regulation on advanced therapy products has closed a gap in the EU regulatory framework, providing for a consistent legal structure governing the collection, testing, processing, storage and distribution of human tissues, cells and blood and the manufacturing of ATPs as well as the post-authorization and post-marketing safety aspects relating to this specific type of products. The regulation is similar to the regulatory framework set up in the US under the authority of the FDA, though it is much more systematic and comprehensive.

By Dr Wolfgang Rehmann and Dr Gareth Morgan

The human body has become an important source for components of pharmaceuticals and medical devices used to treat diseases and malfunctions. Increasingly, these so-called “advanced therapy products (ATPs)” are being developed from blood, cells, skin, bone and human tissues. Their use has revolutionized the treatment of several diseases and injuries such as cancer, Parkinson’s disease, burns or cartilage injuries.

Given their growing use, regulating advanced therapies has become an issue for governments around the world. For example, whereas products derived from genes and cells were until recently mostly classified as pharmaceuticals in the EU, tissue engineered products were not explicitly covered by the existing legal framework and thus only partly classified as pharmaceuticals or as medical devices. Also, regulations were not harmonized across the EU’s many member states.

In the US, the regulatory scheme for advanced therapies at first was limited to human blood and basic tissues, such as bone, skin, ligaments, tendons and others intended for homologous use. In 2005, the FDA amended its regulatory framework by adding a number of components dealing with the eligibility of donors of human cells, good tissue practices, testing, labelling and other important requirements for guaranteeing product safety. The FDA does not only require compliance with the relevant standards, which are constantly evolving and set out in guidelines, but also requires that the product receives authorization before its marketing as a drug, biological or medical device. The extensive federal control is based on the FDA’s use of sec. 361 of the PHS Act¹ and thus, contrary to recent developments in the EU, not based on a new regulatory framework implemented specifically for advanced therapies. Such a new legal framework has been implemented most recently in the European Union and will apply as of December 30th, 2008.²

Below is a comparative discussion of the approaches taken by the EU and the US in developing their respective regulatory frameworks for advanced therapies.

EU regulation on advanced therapies

In Europe, agreement was reached on the regulation on advanced therapies including tissue engineering at the health council on May 31st, 2007. The new regulation (No. 1394/2007) was published in the official journal of the European Communities on December 10th, 2007 and entered into force on December 30th, 2007. The regulation will apply 12 months after this date, ie, on December 30th this year.

Objectives

The new EU regulation completes the framework on advanced therapies, which already contained rules and regulations setting standards for the donation, procurement, testing, processing, storage and distribution of human tissues and cells.³ The new regulation applies to advanced therapy products over and above the requirements of the European medicinal regulatory regime set out in Directive 2001/83/EC (as amended). Therefore, it should be remembered that the regime outlined below is additional and complementary to those regulatory requirements already set out for “mainstream” medicinal products.

The main elements of the legal framework established by the new regulation are: a centralized market authorization procedure to harmonize and facilitate access to the EU market; the creation of a new expert committee, the Committee for Advanced Therapies within the European Medicines Agency (EMA) to assess ATPs; new, tailor made technical requirements for the products at stake; risk management and traceability requirements; and special incentives for small and medium-sized enterprises to stimulate technological entrepreneurship.

By 1997, the US FDA had already outlined five areas of regulatory concern regarding therapies derived from human tissues and cells, namely preventing transmission of communicable disease, safe processing and handling, clinical safety and effectiveness, promotional claims and monitoring of industry. Subsequently, the FDA developed a regulatory system

for the oversight of these products and brought together the relevant concepts and regulatory principles under the overarching principle of good tissue practice (GTP). While it has undergone significant evolution, the FDA's model does not encompass the increasingly broad nature of advanced therapies under one comprehensive regulatory scheme. It is this regulatory framework that the new EU Regulation intends to achieve.

Scope

Both the European and US regulatory schemes at first focused on human blood and basic tissues intended for homologous use. However, the new EU regulation, together with the proceeding directives, now provides for an overall legal framework for commercial ATPs. It covers the three groups of products described below.

- Gene therapy products (GTPs) that are obtained through a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene, to human/animal cells and its subsequent expression *in vivo*.
- Somatic cell therapy products (SCTPs) are defined as products used in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered to obtain a therapeutic, diagnostic or preventative effect through metabolic, pharmaceutical and immunological means.
- Tissue engineered products (TEPs) contain or consist of engineered cells or tissues used to regenerate, repair or replace human tissue.

By setting these clear definitions, the European regulation aims to correct past uncertainty regarding what constitutes an advanced therapy for the purpose of establishing the scope and applicability of regulations. It also provides clarity for the oversight agencies, regulators, academics and companies that work in this area. Previously each stakeholder group had their own way of classifying what was and what was not considered to be an advanced therapy. The regulation also provides one framework for the manufacture and marketing of advanced therapies, as well as issues related to approvals, labelling, monitoring, and risk management. The clear definitions also establish what is not covered by the regulation. This includes ATPs produced in a clinic for one-time use by a doctor for a single patient. Products harvested from a patient for use only in that patient are also exempt. In the case of hospitals producing ATPs for wider use, they would be treated under the regulation as any company producing or marketing advanced therapies.

Centralized marketing authorization and transitional periods

The central objective of the new EU regulation is to create a single, harmonized framework for approving ATPs. This ensures universal standards of safety, quality and efficacy on the one hand and access to the whole European market on the other. The regulation also creates specific rules for ATPs regarding the evaluation of their efficacy and therapeutic claims. When an ATP enters clinical development, the same requirements used for other pharmaceuticals apply, but additional requirements also have to be met regarding the specifics of ATPs.

Thus ATP clinical development plans should include pharmacodynamic studies, pharmacokinetic studies, mechanism of action studies, dose finding studies and randomized clinical trials as required for other medicinal products. But due to specific biologic characteristics of the ATP, alternative approaches to Phase I-Phase II clinical trials might be required and acceptable for clinical development, which must be justified on a case-by-case basis. The EMEA has produced a guideline on human cell-based medicinal products that will come into effect on September 1st, 2008. This document contains general guidance relating to quality and manufacturing, non-clinical and clinical data that will be required in order to assemble a dossier for the approval of an ATP. This guidance replaces the document entitled "Points to Consider on the Manufacturing and Quality Control of Human Somatic Cell Therapy Medicinal Products"⁵⁷.

This regulatory approach is (or has the potential to be) in marked contrast to the situation in the US. There, the FDA has very much adopted a case-by-case analysis of ATPs with little product "class" guidance to instruct compliance. The relevant department of the FDA that deals with ATPs is the Centre for Biologics Evaluation and Research (CBER) and, within this section, the Office of Cellular, Tissue and Gene Therapies (OCTGT). This office will typically arrange a pre-IND meeting⁶ with prospective applicants and agree a specific protocol which will eventually lead to a biologics licence application (BLA) for approval of the product.

Although this sounds straightforward, recent history has demonstrated that the data required in order to complete a BLA to the requisite standard could cause problems for ATPs. Contained within the BLA is a section which requires the applicant to demonstrate that the production process for the ATP is sufficiently controlled as regards to characterization and quality. Clearly ATPs that involve modifying a patient's own cells have a variable content that makes compliance with the above FDA requirement difficult. Most notably, Dendreon, with its prostate cancer vaccine product Provenge, has been engaged with the FDA for the past few years and has not yet satisfied this criterion.

The new EU regulation is attempting to create a more standardized procedure within Europe than exists in the US. The detailed consultation that is ongoing seeks to add technical bones to the regulatory skeleton established in the new regulation.

As noted above, the biological effects of ATPs can be highly dependent on the *in vivo* environment, and may be influenced by the replacement process or the immune reaction either from the patient or the product. The respective requirements therefore must be investigated during clinical development as they will have to be taken into account for the final use of the specific ATP being considered. Also standardization and optimization should be an integral part of the clinical development studies. All this influences the study design. For new ATPs, where limited guidance exists, consultation with regulatory authorities on the clinical development plan is therefore highly recommended and the formation and involvement of specialist committees within the EMEA will be of critical importance.

A transitional period provided in Art. 29 of the EU regulation stipulates that ATPs other than tissue engineered products legally on the community market on December 30th, 2008,

must comply with the regulation by no later than December 30th, 2011. For tissue engineered products the transitional period ends on December 30th, 2012. Applications submitted for the authorization of these products shall be free of charge.

Committee for advanced therapies

The EU regulation also called for the formation of the Committee for Advanced Therapies (CAT) to bring together the best available expertise on ATPs. It is composed of five members or co-opted members of the CHMP, one member and one alternate appointed by each member state where the national competent authority is not represented answering the members of the CHMP, two members and two alternates appointed by the Commission to represent clinicians and two members and two alternates appointed by the Commission to represent patients' associations.

This composition ensures appropriate representation of the relevant scientific areas. Its tasks are inter alia to give advice on the classification of a given product where the classification as medical device, pharmaceutical or ATP is in question, to evaluate ATPs with regard to their safety or efficacy and to contribute to the development of scientific advice in the area of ATPs and their respective safety standards. The CAT has an advisory function only. It is not a decision making body as also the EMEA is not. All decisions made under the regulation are those to be made by the Commission and subject to legal review/oversight by the Court of First Instance in Luxembourg as a consequence.

The input that the CAT will give for prospective applicants for authorizations for ATPs is likely to be key. In the US, one feature of the FDA's system that is highly valued by prospective applicants is the advice given in pre-IND meetings. Such advice can be invaluable in guiding applicants into the correct design for pivotal clinical studies and can give an early indication of the adequacy of the non-clinical and early clinical data already generated such that any perceived defects can be remedied at an early stage. It is hoped that the CAT will provide prospective applicants with a similar source of advice and will permit prospective applicants at an early stage to design their clinical studies to ensure a smooth regulatory path moving forward. In an area such as ATP, where the products might be inherently variable due to the use of a patient's own tissue in the product, such input for design of clinical studies is critical.

It is hoped that the CAT will offer prospective applicants for the approval of ATPs within Europe the same comfort that the FDA Special Protocol Assessment (SPA) procedure provides. The SPA procedure is seen in the US as an important part of a prospective applicant's due diligence in reducing the risk that any obstacles lie in wait late on in the regulatory process. The CAT will be called upon to provide such reassurance via both the scientific advice procedure to advise on the design and adequacy of clinical study design and also the certification of early stage data.

The new regulation provides the opportunity for prospective applicants to approach the EMEA and obtain certification for their quality and non-clinical data. It is anticipated that the CAT will also play a key role in this process. The reassurance that is provided through this certification is likely to become an obligatory part of a responsible company's regulatory risk management.

Combined products

Combined products, which have a medical device element as well as a cellular or tissue component are evaluated by the EMEA alone, which would then grant EU-wide marketing authorizations in a centralized procedure. Approval for combined products rests with the EMEA, but it may also request any results from a qualified body that has previously assessed the product. If no such results are available, the EMEA may commission a notified body to assess the product in conjunction with the centralized EMEA application process. The involvement of a notified body, however, is not required, where the CAT feels it has sufficient expertise to perform the assessment on its own. The submission of combined products to the centralized procedure also aims to avoid classification problems which could lead to uncertainties as to which legal framework is to be applied, namely the framework on medical devices only or the framework on advanced therapies.

Again this co-ordinated approach to the approval of such combination products is likely to mean that the approval of combined ATP/device products will be simplified within Europe.

Post-authorization requirements

The EU regulation creates a mechanism for reporting and documenting adverse reactions and issues involving efficacy for ATPs after they are approved and available for public use. This is a key component in monitoring the safety of ATPs. As a result, manufacturers will be required to file an EU Risk Management Plan (RMP) as described in the Guideline on Risk Management Systems for Medicinal Products for Human Use.⁷ Long-term safety issues, such as infections, immunogenicity/immunosuppressant and malignant transformation as well as the *in vivo* durability of the associated medicinal device/biomaterial component must be addressed in the RMP. The Commission may, as part of the market authorization, require that the risk management system be set up in a specific way to ensure its efficiency and safety. The EMEA with the assistance of CAT will give guidance to the Commission in this respect. The decision taken by the Commission in the product authorization is binding upon the manufacturer and product authorization holder. It can, however, be appealed to the Court of First Instance.

As ATPs are designed and designated to remain in the human body for a long, if not indefinite, period of time, a system allowing compete traceability of the patient as well as the product and its starting point are crucial to monitor the safety of advanced therapies. The establishment and maintenance of the system must follow the rules and regulations set out in Directive 2004/23/EC in respect of human tissues and cells and in Directive 2002/98/EC for the collection, testing, processing, storage and distribution of human blood and blood compounds. Traceability along the donor-product-recipient axis or between product-recipient for autologous products is required in all circumstances. Art. 14 (4) of the regulation requires the EMEA to draw up detailed guidelines to the post-authorization follow-up of efficacy and adverse reaction and risk management. A draft guideline has been published most recently by the EMEA on May 6th, 2008.⁸

Any manufacturer of ATPs that does not closely follow those safety rules and standards including those specified in the product authorization at stake, is exposing himself to responsibil-

ity under product liability, if an adverse event occurs. Product liability provides for strict liability, apart from official enforcement of the manufacturer's public obligations under the respective legal framework, and thus leads to substantial risks.

Ethical matters

ATPs are associated with high levels of public interest and issues which are under constant societal debate. In particular, the strong resistance to the use of embryos as sources of therapeutic products demands appropriate caution and sensitivity. In light of this, the regulation does not impose EU-wide ethical guidelines. Instead, it provides that decisions regarding whether certain ATPs will be available in a member state will be left to the member states themselves. This approach has been confirmed by the EU Parliament and therefore decisions of ethical nature in the EU are dealt with on a national level.

Incentives for small and medium-sized enterprises

Article 18 of the regulation provides that small and medium-sized enterprises (SMEs) developing ATPs may submit to the EMEA quality and, where available, non-clinical data, for specific evaluation and certification. For reasons of coherence and transparency it is proposed the definition of micro, small and medium-sized enterprises provided in Commission regulation 2003/361/EC⁹ should apply. The certification procedure is likely to be independent from any application for marketing authorization. The procedure will help to strengthen the development of new ATPs and to encourage small and medium-sized enterprises to contribute to this development. The certification procedure prepares the applicant's data package for product authorization and is performed for SMEs at a lower cost by the EMEA.

In this respect the new regulation provides similar assistance by way of reduced fees to SMEs as does the US regime. Thus both systems recognize the importance of SMEs as key drivers of innovation within the new ATP industry sector.

Summary

The new regulation on ATPs has closed a gap in the EU regulatory structure. It provides for a consistent legal framework governing the collection, testing, processing, storage and

distribution of human tissues, cells and blood and the manufacturing of ATPs made from human materials as well as the post-authorization and post-marketing safety aspects relating to this specific type of products. The regulation is similar to the regulatory framework set up in the US under the authority of the FDA, though it is much more standardized, systematic and comprehensive. One point of interest will be to review whether this standardized strategy is successful in Europe given that it is very much the type of approach the FDA has decided is not easily applied to products such as ATPs.

The EMEA will continue to advise manufacturers and other stakeholders regarding how to make use of this legal framework, and it remains to be seen how efficiently it will be implemented, used, and further refined over time. Further guidance from the European Commission is expected with regard to the implementation of the regulation and practice will show where further amendments and guidance will be needed. It is clear that the role of the CAT within the new ATP regulatory regime will be vital. The CAT is likely to be the cornerstone of the efficacy and flexibility of the European ATP regulatory regime. Its first actions will be viewed with intense interest.

References

- 1 Brady/Horton/Chung Tissue Issues, Legal Tissues, 20 June 2005; <http://pharmalicensing.com/public/articles>
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Can Phase I data help appease cardiac stem cell trials controversy?

Cardiac stem cell trials are moving forward, despite fierce debate over the underlying mechanism of healing. As data from Phase I trials roll in, the trials are hopefully putting fears over safety to rest. So far the various cardiac treatments appear to be safe, but the debate continues. As questions over the mechanism of action have yet to be fully answered, critics argue the therapies may prove to offer little benefit to patients. Others say the first round of studies have shown great promise.

By Amy Coombs

Embryonic stem cells continue to spark well-publicized controversy (and receive widespread coverage in both the popular and scientific press) because they can be derived from human embryos and aborted fetuses. At the same time, alternative methods for making embryonic stem cells are slowly developing. These include “therapeutic cloning”—in which a nucleus from an adult cell is transplanted into an egg. Despite their promise these options are still years away from practical use.

Adult stem cells, by contrast, are less controversial because they can be taken from the bone marrow, skeletal muscle or blood of an adult patient. Because there are fewer limiting regulations, adult stem cells have already been used in a variety of clinical trials—many in the cardiology field, where researchers hope treatments can be used to heal scarring following heart attacks and to repair damaged tissue regions.

While the source of these cells is relatively uncontroversial, the safety of cardiac stem cell trials was nevertheless initially the subject of fierce debate. Due to what some call a glaring lack of data about the molecular mechanisms involved in healing, Phase I trials initially almost did not make it off the ground.

“There was huge anxiety in the field two or three years ago,” says Joshua Hare, a cardiologist at the University of Miami Miller School of Medicine who helped launch many of the first US FDA-approved trials for stem cells in the heart. “There were editorials in *Nature* and *Nature Medicine*, and front page articles in the *New York Times* questioning whether or not we knew enough to do clinical trials.”

Now just a few years later, information is beginning to pour in, and the second round of clinical trials is about to start. So far the various cardiac treatments appear to be safe, but the debate continues. The question today is whether the cells will effectively help patients heal. As questions over the mechanism of action have yet to be fully answered, critics argue the therapies may prove to offer little benefit to patients. Others say the first round of studies have shown great promise.

Mesenchymal stem cells

At the center of the controversy lie the mesenchymal stem cells, one of the most commonly used stem cell therapies.

“Much of the debate over mechanism [of healing] in cardiac

trials comes back to the role of mesenchymal stem cells in transplant procedures,” says Pranela Rameshwar, a professor at the New Jersey Medical School.

Mesenchymal stem cells are well-characterized and can differentiate into a range of tissue types, including fat, cartilage, bone, tendon and ligaments. In cardiac studies, the usual objective is for the cells to grow into myoblasts, or muscle cells.

Mesenchymal stem cells are usually taken from a patient’s own bone marrow, expanded and purified in the lab, and then introduced to the heart via an intravenous drip, or by a surgical procedure. These so-called autologous (or self-derived) preparations can take months to grow and purify in the lab, limiting their usefulness in emergency surgeries.

Only a small fraction of the cells in the bone marrow, skeletal muscle or blood are stem cells, and these can only replicate a limited number of times. These properties mean it is very hard to make autologous cells in sufficient quantity for therapeutic use.

Mesenchymal stem cells can also be delivered as part of an allogeneic—or non-self—process in which cells are derived from young, healthy donors and then stored on the shelf for later use. The initial supply of stem cells is higher in allogeneic preparations (as they can be taken from many donors), and since the cells can only go through a set number of division cycles, beginning the process with more total cells is potentially a huge advantage. More commonly, allogeneic preparations are expanded from established cell lines, and then prepared in the lab before being given to a patient.

Importantly, mesenchymal stem cells do not appear to come with any of the immunity-related reactions seen with other allogeneic stem cell transplants, which have to be accompanied by heavy doses of immunosuppressive drugs.

This is because the cells do not produce much of the Major Histocompatibility Complex II (MHC-II) antigen—a cell surface marker that helps the immune system recognize foreign cells. In fact, after mesenchymal stem cells differentiate, they often produce even lower levels of MHC-II. The cells also release a panel of immune-signaling proteins called cytokines, which trick the immune system into tolerating them.

Hare describes mesenchymal stem cells as being “immuno-privileged” in this respect. “You can use them without any im-

muno suppression. It's the one cell type that has [this quality]."

The controversy

It has been only a few years since the first trials using mesenchymal stem cells to treat cardiac diseases were launched. As the new millennium dawned, a wide-sweeping debate began over whether the FDA should even allow the controversial treatments to be tested on humans. While the traditional drug discovery and development process is unpredictable, stem cells add an extra layer of uncertainty. For example, it is hard to know beforehand what cells will differentiate into after they are transplanted.

"The growth of new tissue doesn't necessarily mean that the right tissue is growing," says Kenneth Chien, a cardiologist at the Harvard Stem Cell Institute known for his critical approach to cardiac stem cell trials.

While animal studies have shown that transplanted mesenchymal stem cells correctly differentiate into muscle cells that aid the diseased heart, this is much harder to show, with certainty, in humans. Consider that in animal studies transplanted cells are often engineered to produce a fluorescent label visible under the microscope. Weeks after transplant, the animal is sacrificed and the cells are removed and studied. These methods clearly are not applicable in humans (except in the case of patients who die after surgery, allowing their hearts to be studied).

Another problem is that stem cells can fuse with heart cells, and take on their appearance, yet fail to beat completely in sync with the rest of the heart. "The cells might look like heart cells, and in some ways act like heart cells, but in fact not really be capable of helping the heart heal," says Dr Chien.

"No one has really proven the mechanism by which the cells bring about healing in human patients," says Drr Rameshwar, "or [even] if they [do] bring about healing."

Such question marks led many researchers to protest the first wave of Phase I studies. In the regulator camp, the FDA was initially very cautious as well. Like other experimental medicines, stem cells have to be filed as INDs and they need the agency's approval before they can be used as a human therapy. Long after cardiac stem cell treatments began to be offered on an experimental basis in Thailand and Europe—sparking a healthy medical tourism industry in some cities—the FDA remained adamant that there was not enough data on mesenchymal stem cells to warrant treatments. As a result, the green light for Phase I trials was initially slow in coming.

While bone marrow transplants—which by their very nature involve stem cells—had been used for decades, mesenchymal stem cells received more scrutiny. This is in part because the cells have to be taken from the patient, purified and then expanded in the lab. The cells are usually taken from the bone marrow, and then introduced into a different part of the body, in which they did not originate. The FDA was arguably more lax with new bone marrow strategies because the cells—usually hematopoietic stem cells—are not manipulated much in the lab, and are used for their natural purpose.

Phase I trials show success

Based on case studies from abroad, and efforts made by proponents, clinical trials of mesenchymal stem cells for cardiac

diseases eventually gained approval in the US. The first wave of trials began in 2005, and encouraging data have been released. So far mortality rates have been low.

"Even though the trials remain controversial, no safety flags were raised during the first batch of trials," admits Chien. He still believes the data were far too scant to justify the trials taking place, but fortunately the safety results proved promising.

A review published last February in the *Journal of the American Medical Association* highlighted the new set of results.¹ 33 trials that used stem cells for heart and vascular diseases were reviewed, representing nearly 2,000 total cardiac patients. Overall, the results were encouraging. In line with earlier findings, many trials saw no deaths, and the overall mortality rates were comparatively very low.

By contrast, stem cell trials in autoimmune diseases have reported death rates anywhere between 1% to 23%, depending on the accompanying chemotherapy regime. Leukemia and autoimmune patients can receive chemotherapy before undergoing hematopoietic transplants, and this has been shown to be detrimental in some cases. The near-perfect safety results seen in cardiac trials are generally attributed to the absence of chemotherapy in these regimens, as well as the safety of the individual procedures.

At the end of 2007, the US-based stem cell company Osiris Therapeutics completed the first human trial to use allogeneic stem cells for the treatment of heart disease. An intravenous drip was used to deliver non-self mesenchymal stem cells to patients that had recently suffered a heart attack. No deaths occurred, and the treatment is now widely touted as safe. 53 patients were treated as part of the Phase I trial, and 42% saw overall improvements in their condition—(a much higher figure than the 11% of placebo patients who also improved).

By delivering stem cells just a few days after a heart attack, Osiris aims to prevent fibrotic scars from forming. Fibrotic scars prevent the heart from beating in rhythm, as the scar tissue does not carry the same electric current as normal heart tissue. A Phase II study is set to begin this summer.

Another US life science company, Angioblast Systems, completed a much smaller Phase I trial of allogeneic mesenchymal precursor cells last year. Only six congestive heart failure patients participated in the study, but as safety results proved promising, a much larger trial is set to begin. In early June, Angioblast announced it had received FDA approval for a Phase II study of 60 patients. The stem cells will be injected into damaged heart muscle by a cardiac catheter in an attempt to heal failing tissue regions.

A new wave of trials

So far studies have proven only moderately successful at healing heart conditions. Osiris' trial had some of the best data, yet was still not helpful in 58% of the patients treated. Critics argue that those who did heal saw only slight improvements, and the study size was far too small to draw sweeping conclusions about efficacy. New Phase II trials will be critical in this respect. Researchers will be devoting great attention to the selection of study end-points and patient groups.

"We are going to expand the number of patients and have a more homogeneous population of patients," says Randal Mills, chief executive officer at Osiris. This summer the company

will begin Phase II trials on 200 heart attack patients. In order to produce the best efficacy data, patients with more serious conditions will be treated. “We expect that healing will be more dramatic in the next study,” says Mills, “because we are starting with patients that have more room for improvement.”

Because Phase I trials were so controversial, only patients with relatively mild cases were selected. Many researchers argue this resulted in marginal efficacy results, as healthier patients have less room for improvement. Osiris found that patients who suffered the most severe heart attacks saw a 6.5% increase in ejection fraction – the amount of blood the heart can pump – after treatment. In comparison, those with more mild cases saw only a 5.4% increase.

The Boston-based Massachusetts General Hospital treated its first cardiac stem cell trial participants in February and March. The nationwide Phase II clinical trial, called ACT-34 CMI, involved 150 patients and was sponsored by Baxter. The corresponding Phase I study had shown that the 24 patients enrolled experienced no unexpected problems.

“ACT-34 CMI marked the first time that human cardiac stem cell transplantation has been done at Mass General,” says Dr Drachman, a cardiologist at the hospital, who followed patients through the procedures. Along with other collaborators, Dr Drachman and his cardiovascular colleague Dr Kenneth Rosenfield harvested stem cells called endothelial progenitor cells from each patient’s blood, and used a catheter to inject the cells directly into the areas of the heart muscle where blood flow was most needed. The trial is designed to study whether such stem cell therapy may help patients who suffer from debilitating chest pain due to chronic impairment of blood flow to the heart muscle.

Phase II trials of stem cells are gaining momentum in England as well. In February doctors from Bristol University began injecting bone marrow stem cells called CD133+ into patients who had undergone bypass surgery. The stem cells are collected from each patient’s own bone marrow, and the hope is that they will help heal bypass scarring.

In total, 60 patients will be treated, and MRI scans will show whether the stem cells reduce scarring six months after surgery. Small studies have shown that the approach is safe, but this will be the first large-scale, placebo-controlled trial of its kind.

Given that many of the patients enrolled in the trials are “no option patients,” ie, for whom other methods of treatment have failed, Dr Drachman says this new wave of trials is an important landmark.

While there are no data indicating how many patients are turned away from US-based cardiac stem cell trials, doctors say they are bombarded with calls from patients in need. It has also been reported that as many as one out of five people are turned away by doctors with side practices overseas, where regulatory restrictions are less stringent.²

Researchers say this makes FDA approved trials all the more critical. Not only are patients being denied the treatments they need, but quality control issues are at stake. While patients have often received legitimate stem cell therapies in Thailand, Barbados and other countries, researchers say the line between profiteering and medicine is often crossed, making it all the more critical to establish well-run trials in the US.³

The debate shifts to efficacy

If treatments are to be made available to the general public, the complex question of the healing mechanism must be put to rest. As Dr Drachman points out, the next round of human trials may provide vital clues into how the stem cells work following transplantation.

For example, in the ACT-34 CMI trial, researchers hope that stem cells harvested from the blood will generate new blood vessels in the heart, bringing better blood flow to the damaged tissue where it is most needed. Even though microscopic cameras cannot be transplanted into the heart to prove that the blood vessels have formed, there are other surrogate measures that may suggest that this mechanism exists, says Dr Drachman. Nuclear imaging and MRI studies may demonstrate whether blood flow has increased in areas of the heart which were previously jeopardized. Echocardiography—a form of ultrasound for the heart—may identify if the heart is able to beat with greater contractile force after stem cell transplantation, and treadmill studies may reveal whether or not patients are able to walk further without chest pain—a major clinical goal and hard endpoint of the trial.

“If these parameters point toward improvement, in a very practical and pragmatic sense, it’s more than likely that the stem cells did something positive,” says Dr Drachman.

However, the problem is that results have not been this straightforward. According to the February JAMA report,¹ the biggest stem cell trial conducted to date, the REPAIR-AMI study involving 20 heart attack patients, saw only a 5.5% improvement in ejection fraction. (It should be remembered of course that Phase I trials are not designed to measure efficacy).

Even if patients are healed, researchers argue that unforeseen problems could arise further down the line. “If you don’t know how a treatment works, you can’t prove that it will be safe for the long term,” says Dr Chien.

Dr Rameshwar strikes a similarly cautious note. Very little immunological data have been collected on mesenchymal stem cells following transplant, and they could potentially trigger a reaction down the road, despite their presumed immunocompatibility. “It’s possible that the heart cells that differentiate after transplant will lose this compatibility over time,” she says.

She has already carried out some work to back up this claim. In a study published this May in *Clinical and Translational Science*, Dr Rameshwar and colleagues showed that ectodermal neurons, which differentiate from mesenchymal stem cells, might lose their immunocompatibility if a patient gets sick at a later date.⁴ While these cells do not produce MHC-II molecules under normal conditions, Dr Rameshwar was able to induce production by exposing them to lymphocytes and the cytokine interferon-gamma—both of which increase during an infection.

Even though her findings specifically looked at neurons, Dr Rameshwar argues they could apply to myoblasts, adipocytes and other kinds of differentiated mesenchymal stem cells. “Given that the areas of the heart that are damaged might suffer from inflammation to begin with, and given that the procedure used to introduce the transplanted cells might cause an infection, it may be that the mesenchymal stem cells will begin producing MHC-II molecules later,” says Dr

Rameshwar. This in turn could lead to the transplant being rejected.

In Dr Chien's opinion, it is more likely that stem cells will lead to no therapeutic benefit, and that the scant evidence of efficacy collected to date is in fact the result of other physiological processes.

For example, some trials have tried to stimulate new blood vessel formation in the heart through the introduction of stem cells. Even though slight benefits have followed such treatments, critics argue that this could be due to inflammation. It is possible that no blood vessels are forming, says Dr Chien, and that any number of processes are causing a low grade infection, recruiting immune cells to the site of damage and resulting in low levels of tissue healing.

Interestingly, although Dr Chien once had his doubts about studying stem cell therapies in man, he is now quite vocal about the need for more research, perhaps a sign that the debate over cardiac stem cell trials is now moving forward.

"I even advocate for increased government funding for the trials," he says, "I'm not convinced they are going to work, but they probably aren't going to be dangerous."

The ultimate efficacy test will be patients' lifespan, but of course good survival studies require up to 5,000 people, and can take around five years to complete. Hence it will likely be some years before we see much progress on this front.

"The debate about whether or not stem cell therapies will offer hope for the "no options patient" is one that is sure to hold all of us in wrapt suspense for many years to come," says Dr Drachman.

In the meantime, we can expect the next wave of Phase II trials to keep the debate moving forward. Whether the trials will help people remains to be seen, so larger and better-designed studies are the only way to put that question to rest.

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Telomerase: an ideal diagnostic marker and cancer target?

The significance of cancer in the modern world needs no introduction: 7.6 million people died from cancer in 2007, accounting for roughly 13% of all deaths. Clearly, there is a vast market available for any effective cancer treatment. Studies have found high levels of telomerase activation in many types of cancer, including approximately 90% of breast cancers. Thus, telomerase could be an ideal diagnostic or prognostic marker for cancer progression, or even an alternative therapeutic target.

By Peter Ruscoe

In some Western countries such as the US and the UK, cancer is now overtaking cardiovascular disease as the leading cause of death. One in three people can expect to suffer cancer at some stage in their lifetime, with one in four going on to die from the disease. In developing countries, the incidence is far lower, largely due to higher mortality from infectious diseases. However, as control over the spread of diseases such as malaria and tuberculosis improves, the incidence of cancer is expected to rise in these regions.

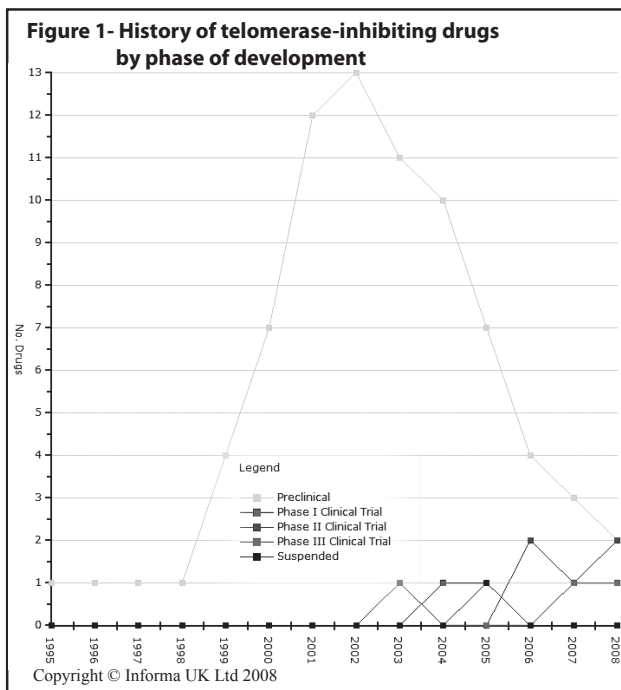
Existing treatment options for cancer include surgery, whereby non-hematological solid cancers are physically removed; chemotherapy, utilizing cytotoxic drugs to target rapidly dividing cells; radiation therapy, using ionizing radiation to kill cancer cells; immunotherapy, where the host's own immune system is induced to fight the cancer and experimental therapies such as angiostatic treatments and gene therapy.

Many cancers are multifactorial, with contributing factors being infectious agents, toxic chemicals, and the activation of previously-silenced or regulated cancer-causing genes within the body, so-called oncogenes. Oncogenes activated in cancer cells can give them their distinctive new properties such as overactive growth, division, and protection against apoptosis. Tumor suppressor genes on the other hand are frequently deactivated in cancer cells, resulting in the loss of normal functions and features such as accurate DNA replication, cell cycle checkpoints and adhesion molecules. Transformed cancer cells may also exhibit other features, such as the activation of the chromosome-capping enzyme, telomerase.

Telomeres

Telomerase was discovered by Carol Greider and Elizabeth Blackburn in 1984 in the ciliate *Tetrahymena*. Blackburn noticed that the DNA on the ends of chromosomes was actively growing and shrinking, and hypothesized that a form of reverse transcriptase must be at work. When DNA replicates during cell division, an RNA primer is required to allow the cellular machinery to copy the DNA strand. Since the primer will rarely attach to the very end of the replicating strand, the new copy will be missing a stretch of DNA - this is known as the 'end replication problem'. This process will be repeated each time the cell divides, with the copied DNA strand losing more of the end section every cycle.

This leads to the question: How do our cells have any DNA left? The answer is telomeres. Human telomeres are repeated TTAGGG nucleotide sequences on the ends of chromosomes ending in G-rich single-stranded 3' overhangs, forming a lariat structure called a 't-loop'. They are analogous to the plastic tips on shoelaces, preventing both the loss of essential sequences during replication cycles and chromosome ends from fraying and 'sticking' to one another. In germline cells, telomerase is the enzyme responsible for the addition of these repeat sequences to the ends of chromosomes, thus making these cells effectively immortal. Normal somatic cells also contain basal telomerase activity levels when they have first developed, but do not endogenously express telomerase. The level of telomerase in their progeny is therefore decreased markedly with every division, and is insufficient for telomere upkeep, so their telomeres grow shorter and the cells age. Cells can normally divide 50 to 70 times, with their telomeres getting progressively shorter, until the cells senesce or die.



Human telomerase is an RNA-protein complex, consisting of a telomerase reverse transcriptase catalytic subunit (hTERT), and an RNA component (hTR) acting as a template for adding telomeric TTAGGG repeats to the end of the chromosome.

As a mutated cell progresses to becoming cancerous, collecting more and more mutations on the road to malignancy, it divides more often. If its telomeres get too short the cell may halt division, enter senescence, and eventually die. The cell can escape such a fate if it coincidentally achieves telomerase activation in the course of random mutation, which will prevent further telomere shortening. A rare cell which gains telomerase activation and maintains telomeres therefore becomes effectively immortal, much like a stem cell, and this is hypothesized as a critical step in cancer progression. Studies have found high levels of telomerase activation in many types of cancer, including approximately 90% of breast cancers. Thus, telomerase could be an ideal diagnostic or prognostic marker for cancer progression, or even an alternative therapeutic target.

A diagnostic and prognostic target

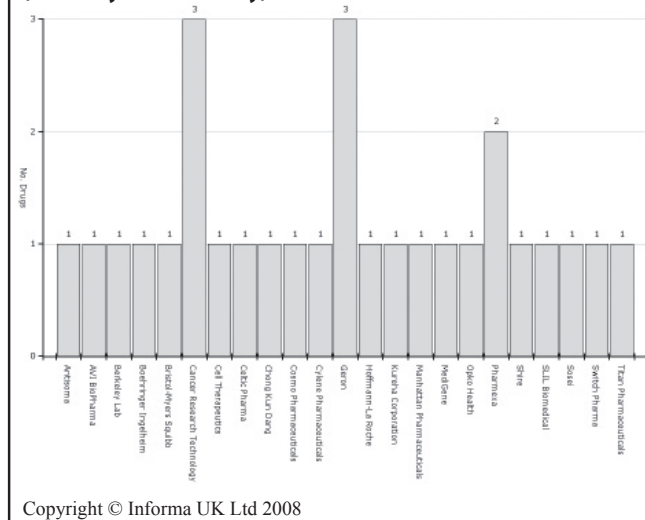
Cancer diagnostics currently apply only to a single or limited number of cancer types, as they rely on molecules expressed only by specific cancer types. However, telomerase-detection based diagnostics could potentially address a broad range of cancers. A highly sensitive PCR-based technique known as the telomeric repeat amplification protocol (TRAP) assay allows telomerase activity to be easily quantified in human cancer cells. Not only has positive telomerase expression been detected in many human cancers by this method, but increases in telomerase levels with concomitant progression in the severity of histopathological change have also been observed. Assays using real-time quantitative reverse transcriptase PCR have revealed a link between hTERT mRNA levels and the malignancy of breast tumors.

Several studies have demonstrated a correlation between clinical outcome and expression of telomerase in certain cancers. High levels of the enzyme in neuroblastoma and gastric cancers have been shown to indicate a poor clinical outcome, whereas some patients with tumors not expressing telomerase have experienced spontaneous regression. These data could be utilized in predicting the development of the disease, and in making decisions on treatment options dependent on the estimated threat to the patient.

However, other studies with variations to the TRAP protocol have not shown a correlation between telomerase activity and relapse-free survival in breast cancer patients. Telomerase activation may occur after the selection of mutations that stimulate abnormal cell proliferation, and thus telomerase activation may be a relatively late event in tumor development that allows for genome stability after cells gain cancer-associated mutations.

It has been argued that because hTERT expression is observable at early stages of dysplasia, telomere shortening and selection for telomerase activation may occur before critical mutations are also gained for truly malignant growth. Alternatively spliced, post-translationally modified, or catalytically inactive forms of hTERT have been reported, which may also be detected by PCR assays. Clearly, controversy still exists

Figure 2 - Breakdown of companies developing (currently or historically) telomerase inhibitors



over the role of telomerase in a tumor cell's path to malignancy, and this is reflected in cautious development regimes by a select few specialist developers.

A therapeutic target

Cancer cells generally have far shorter telomeres and show a higher rate of division than normal somatic cells. This coupled with the practical absence of telomerase in normal somatic cells means telomerase could be a very attractive therapeutic target. There is the danger of stem cells being affected by such a therapy, but their lengthy telomeres could theoretically rescue them from the critical-length cycle-arrest system responsible for combating systemically treated cancerous and normal cells simultaneously. This way, drug resistance and the severe side-effects suffered by patients on current cancer treatments, particularly chemotherapy, could theoretically be avoided.

Therapeutically, antisense oligonucleotides, dominant negative mutant hTERT and reverse transcriptase inhibitors have been developed to various early stages. GRN-138098 was the first telomerase inhibitor recorded in Pharmaprojects in 1995, with no more under investigation until three years later, in 1998, when there was a steep increase in the number of agents reported to be under development. The number of inhibitors peaked at 12 agents in 2001, and since then there has been a steady decline up until the present day. As relatively cheap compound libraries and preclinical *ex vivo* studies were gradually ruled out, the majority of telomerase-inhibitors have had their development ceased. However, in 2006 both Pharmacia's GV-1001 and Geron's GRN-136L became the first telomerase-inhibitors to reach Phase II trials, and in 2007, GV-1001 successfully entered Phase III clinical trials (Figure 1).

Cancer Research Technology has three telomerase-inhibitor compounds to its name (Figure 2), although only one of these is still reported to be in active development, currently under evaluation at the early preclinical stage. So far it has shown efficacy as a single agent and with chemotherapeutics in mouse xenografts.

Cosmo Pharmaceuticals is developing CB-10-01, a transgenic lymphocyte immunization vaccine against telomerase, which has reached Phase II trials. Leucocytes from the patient are treated *ex vivo* using gene therapy to recognize telomerase as an antigen, and are then returned to the patient. By doing this, it is hoped that cancer cells expressing telomerase will be targeted by the modified leucocytes, which will in turn illicit an immune response against them.

The Californian biotech firm Geron currently has the largest telomerase-targeting drug portfolio past and present, with two drugs currently in preclinical trials, and one in Phase I/II. It has taken a different approach to Cosmo Pharmaceuticals, by synthesizing oligonucleotides (GRN163 and GRN163L) that target the template region of telomerase; these have demonstrated highly potent inhibitory activity in biochemical assays, various cellular systems and animal studies. GRN163L is currently in dose-escalation Phase I/II trials treating patients with chronic lymphocytic leukemia as well as other types of cancer. Interim results have shown the agent to be well tolerated thus far.

Also under development by Geron is GRNVAC1, a telomerase-expressing dendritic cell vaccine. The therapy involves *ex vivo* uptake of RNA encoding hTERT into autologous dendritic cells and their re-administration to the patient. The patient's T-cells are thus activated to kill telomerase-expressing cells. In Phase I/II trials, patients all showed robust cellular immune responses to telomerase based on tests assessing the generation of telomerase-specific cytotoxic CD8 and CD4 lymphocytes. Through Roche Diagnostics, Geron is also developing fluid-based telomerase detection tests for clinical *in vitro* diagnostics. The tests are based on telomerase detection assays that have already been commercialized by Geron for the research use-only market. The company hopes that the detection of telomerase may have significant clinical utility for cancer diagnosis, prognosis, monitoring and screening.

The only agent utilizing telomerase as a therapeutic target to have reached Phase III trials to date is Pharmexa's GV-1001, a peptide vaccine which has also been granted orphan drug designation in Europe. It activates T-cells of the immune system to recognize and kill telomerase-expressing cancer cells. In the trial (the TeloVac study), GV-1001 is being tested together in combination with the chemotherapy compounds gemcitabine hydrochloride and capecitabine in 1,110 patients, including those with inoperable pancreatic cancer. Pancreatic cancer is currently mainly treated with chemotherapy, with little or no effect.

In May this year, however, the agent suffered a serious setback, with enrollment into another Phase III trial (the PrimoVax study) being terminated. It was concluded that administering GV-1001, pre-gemcitabine chemotherapy, was no more efficacious than gemcitabine chemotherapy alone.

The TeloVac study protocol of GV-1001 administered simultaneously with chemotherapy still continues, but doubt is now cast over the future of what until recently seemed such a promising therapy.

AIDS

Cancer is not the only therapeutic area in which telomerase-targeting therapies may have potential. Research has shown

that telomere loss in cytotoxic T-lymphocytes is accelerated in AIDS patients, and that this is a contributing factor to the loss of their anti-HIV activity over the course of infection. In addition, it has been shown that introduction of the telomerase gene into these T-cells increases their lifespan, enhancing the anti-HIV function of these cells. Looking to counter this feature of HIV-infection, Geron and TA Therapeutics are developing TAT-0002, a small-molecule telomerase activator and modulator of telomere length for the treatment of AIDS and skin conditions. In a culture of TAT-0002 and CD8 T-cells from HIV-positive donors, TAT-0002 reduced mean virus levels by 2.5 times for all donors compared to control, and in preclinical HIV studies, it stimulated T-cell proliferation and increased the cytolytic activity of CD8+ T-cells. Geron is currently planning on escalating development of TAT-0002 to Phase I/II trials.

The future

The early-stage status of the majority of these programs does not bode well for a telomerase therapy reaching the market any time soon; this coupled with the 'background' failure rate of 34% for all cancer therapies at Phase III means that the future of Pharmexa's GV-1001 is not yet completely assured, especially with the recent PrimoVax termination. Anticancer therapeutics tend to stall in Phase III clinical trials, compared to the rapid progress in enrolling new drugs into Phases I and II. It is also difficult to progress from Phase II to III as 67% of anticancers fail to demonstrate efficacy at this critical stage. In addition, regardless of the huge potential market available to an effective cancer therapy, companies are still discouraged from developing agents due to the controversy over the effectiveness of targeting telomerase as a therapeutic target.

Another hurdle comes from patent issues. Geron holds a broad intellectual property portfolio on telomerase over many countries, including the gene itself, immunogenic telomerase peptides and scientific methods involving telomerase, including its detection and elements of the TRAP assay. Many developers fear moving into the field due to the potentially very expensive litigation which may ensue. This can be seen in recent legal battles being fought between Pharmexa and Geron over GV-1001. Thus far, Pharmexa has managed to retain rights to the intellectual property utilized in GV-1001 against fierce opposition, but failed in an attempt to obtain claims that would read on Geron's telomerase cancer vaccine, GRNVAC1.

As exciting as the therapeutic strategy appears, it can be seen that telomerase-based therapeutics have a long way to go before they may come into widespread clinical use. Specialist companies such as Geron and Pharmexa are however clearly making good progress in potentially exploiting the properties of telomerase, and so long as legal bureaucracy and scientific uncertainty are resolved in a fair and timely manner, one of these companies discussed could be on the verge of a veritable breakthrough; of which both the profitability and lifesaving potential could be highly significant.

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From blockbuster drugs to blockbuster alliances

Licensing agreements, collaborations, and acquisition activities in the biopharmaceutical industry have steadily increased in recent years, as pharmaceutical companies attempt to fill their early and late stage pipelines. Deals now occur in earlier development stages, at higher levels of risk and at higher prices. Increased pharmaceutical company demand for biotechnology, coupled with a weak market for initial public offerings (IPO), has led founders and venture capitalists of biotech companies to view acquisition as the most viable exit strategy.

By Tim Tankosic, MD

Biotechnology alliances have produced top selling drugs and are now being used to fill ailing pharmaceutical pipelines. The biotech industry is mature, its share of the pharmaceutical market is very significant and it continues to grow. In 2006, the 200 top-selling drugs (pharmaceutical and biotechnology) achieved total sales of \$302 billion. Forty-one (21%) were biotech drugs, and their total sales were \$64 billion. Of this figure, \$36 billion was generated from sales of compounds that were partnered for development, highlighting the pivotal role played by the pharma/biotech alliance in driving biotech drug growth. And more biotech drugs are on the way. Of the 200 compounds currently in pre-registration in the US (ie, an NDA has been submitted), 118 (59%) are from the biotech industry. Of these 118, 65% are the products of alliances and 21% came from pharma/biotech acquisitions.

Increased competition for biotech products has changed the rules of deal making. Trends in recent years include an increasing number of early-stage deals and renewed interest in technology platforms, both of which represent higher risk. Pharma companies are also paying higher prices for biotech alliances, including higher pre-launch (up-front and milestone) payments (see Table 1).

Table 1— Number of new alliances with \$100M+ in pre-launch payments

Development stage	2005	2006	2007
Formulation	0	1	1
NDA submitted	3	3	2
Phase III	11	14	17
Phase II	7	21	28
Phase I	6	12	11
Preclinical	6	15	19
Lead	6	5	5
Discovery	9	12	31
Total	45	83	114

Source: *Recombinant Capital*

More big-ticket deals are being struck. Fewer than half a dozen alliances potentially worth more than \$1 billion were signed between 2001 and 2006, while more than 10 such “blockbuster partnerships” were struck in 2007. Up-front

payments, particularly for headline deals, are high. Total up-front payments made to biotech companies have increased markedly, from approximately \$500 million per year in the period 2001-2004, to about \$1.3 billion in 2005, almost \$2.5 billion in 2006 and more than \$2.5 billion in 2007.

A rebirth of interest in platform technologies is notable in the recent spate of deal making. After years of focusing principally on late clinical stage compounds for licensing, the pharmaceutical industry is now demonstrating renewed interest in discovery platforms. Table 2 lists advantages and disadvantages of platform companies.

In 2007, 25 deals valued at \$200 million or more were struck for technology platforms. Fifteen were for discovery only, while eight included both discovery and anchor compounds. Table 3 lists \$200 million+ platform deals struck in 2007. The developmental phases of the compounds included in the discovery compound(s) agreements ranged from lead/pre-clinical to Phase II. In its \$1.5B deal with Targacept, Glaxo-SmithKline picked up TC-2696, which was in Phase II for acute post-operative pain (and later failed to meet endpoints in a Phase II post-dental surgery trial), and also the preclinical drug candidate, TC-6499, for neuropathic pain. The other Phase II compound was part of a \$420M Merck Serono/Idera Pharmaceuticals agreement. Merck Serono acquired rights to IMO-2055, a DNA-based TLR9 agonist, which was in a Phase IIa trial in renal-cell carcinoma. It is notable that, of the \$1B+

Table 2— Advantages and disadvantages of platform companies

Advantages	Disadvantages
Often involve world-class, breakthrough science	Very few true platform companies with multiple successful products derived from the engine
Lead to molecules with intellectual property	Difficult for small companies to have the expertise to develop products in multiple therapeutic areas
Multiple shots on goal; no one-trick pony	Very few successful initial public offerings during the last 8 years - a high bar for success
Often able to partner off one or more assets to help finance the rest of the platform	

Source: *Chris Ehrlich, Partner, InterWest Partners*

Table 3– Platform technology deals worth \$200M+ in 2007

Discovery only		Discovery + compound		
Companies	Valuation	Companies	Valuation	Development phase
Boehringer Ingelheim/Ablynx	\$2.1B (2 deals)	GlaxoSmithKline/Targacept	\$1.5B	Phase II, Preclinical
GlaxoSmithKline/Anacor Pharmaceuticals	\$1.3B			
Bristol-Myers Squibb/Adnexus Therapeutics	\$1.3B	GlaxoSmithKline/OncoMed	\$1.4B	Preclinical
GlaxoSmithKline/Galapagos	\$1.0B	Janssen/Galapagos	\$1.1B	Preclinical
Celgene/Array BioPharma	\$1.0B	Sanofi-Aventis/Regeneron	\$1.1B	Phase I
Roche/Alnylam Pharmaceuticals	\$1.0B	GlaxoSmithKline/Santaris Pharma	\$700M	Preclinical
Merck Serono/Archemix	\$740M (2 deals)	Merck Serono/Idera Pharmaceuticals	\$420M	Phase II
AstraZeneca/Argenta	\$500M	Pfizer/Icagen	\$397M	Lead
AstraZeneca/Silence Therapeutics	\$430M	Ortho-McNeil/Isis Pharmaceuticals	\$290M	Preclinical
Biogen Idec/Neurimmune Therapeutics	\$380M			
Merck & Co/Nicholas Piramal	\$350M			
Lilly/Galapagos	\$328M			
AstraZeneca/Palatin Technologies	\$310M			
Takeda/Archemix	\$260M			
Merck & Co/Avalon Pharmaceuticals	\$200M			

Source: *Recombinant Capital*

deals listed in Table 3, six were for discovery only, and two of the four that included compounds were for preclinical stage compounds.

The figures above were presented by Mark Edwards, managing director of Recombinant Capital, at the company's Allicense 2008 symposium, held in May in San Francisco, CA. The major theme of the conference was the ways in which pharma, biotech and financial industry companies can capitalize on the alliances that are transforming pharmaceutical innovation.

Aggressive pharmaceutical company strategies

Pharmaceutical companies use licensing agreements, alliances and acquisitions to gain access to cutting-edge developmental products and technologies. They are using a variety of models to identify the best partners, contracting with them, and structuring and managing alliances for optimal productivity. Many pharmaceutical companies describe their alliance programs as "flexible". On a case-by-case basis, they and the alliance or acquisition partner determine which structure will prove most productive.

Pfizer

Obtaining the best external science is critical to Pfizer in order to meet its aggressive goals for rebuilding its Phase III pipeline and launching new products, according to William Ringo, senior vice-president, strategy & business development. The company is focused on six key disease areas: oncology, pain, immunology/inflammation, diabetes/obesity, Alzheimer's disease and schizophrenia. Pfizer projects 15–20 Phase III starts in 2008–2009, 24–28 programs in Phase III by the end of 2009 and 15–20 submissions in 2010–2012. The company's goal, beginning in 2010, is two new externally sourced product introductions per year, each with revenues of \$300-500 million.

The Biotherapeutics & Bioinnovation Center-Pfizer Global Research and Development (BBC-PGRD) model was designed to combine the best of academia, biotech, and the pharma

industry. BBC-PGRD, under the direction of its president, Dr Corey Goodman, has been up and running since late 2007 in South San Francisco. It allows Pfizer to bring the small companies it has acquired into the fold without immediately integrating them into the larger corporate organization. Instead, independent biotherapeutic R&D units are maintained, and BBC-PGRD links them to Pfizer's global R&D function on the east coast of the US. According to Mr Ringo, advantages of this model include:

- Leveraging the best of big pharma's scale and small biotech's entrepreneurship;
- BBC-PGRD can act as an internal venture capitalist, managing risk and return across the company's portfolio;
- Attracting the best talent to drive cutting-edge pipeline, technology and innovation.

As of March 5th, Pfizer had 86 biotherapeutics in its pipeline, 60 in discovery and 26 in preclinical or clinical development

Wyeth

In addition to increasing its number of early-stage licensing agreements and research collaborations, Wyeth has reduced its in-house focus from nearly 50 indications to fewer than 30. According to Thomas Hofstaetter, senior vice-president corporate business development, Wyeth is seeking "deeper, more meaningful collaborations with academia", providing funds for start-ups and incubators and conducting pre-competitive consortia. Pre-competitive consortia are temporary agreements between biopharmaceutical companies and/or academic researchers designed to speed development of early stage technologies by bringing scale, coordination and funding to R&D. Wyeth has established R&D partnerships in neuroscience with two universities in Ireland, funded by the Irish government and the company, and under which intellectual property rights are shared with the academic partners. A partnership has also been

established with four universities in Scotland: Aberdeen, Dundee, Edinburgh and Glasgow. In 2006 Wyeth entered into a strategic alliance with GVK Biosciences, an Indian contract research organization, under which Wyeth obtained the services of 300 chemists at one-third of the cost of the same staff in the US.

Like other pharma companies, Wyeth is also implementing new approaches to improve the efficiency of its clinical development programs. Mr Hofstaetter told the symposium that companies are attempting to identify the winners and weed out the losers at the earliest stages of clinical development. Issues include detection of efficacy signals during proof-of-concept trials, improving protocol design to increase the probability of producing positive results and cutting cycle times. Wyeth believes its Phase III success rate should be 90%. The company has developed early clinical development centers (ECDCS) and introduced a "learn and confirm" process to achieve greater efficiency and knowledge from its clinical trials (eg, early proof-of-concept). Wyeth is developing ECDCS Phase II supercenters in population dense areas around the world.

GlaxoSmithKline

The Center of Excellence for External Drug Discovery (CEEDD) is the product of GlaxoSmithKline's push for "virtualization", aimed at expanding its drug discovery portfolio through risk-sharing alliances with external partners. According to Richard Keenan, vice-president, chemistry, the CEEDD evolved from the company's desire to increase its R&D effort without significantly increasing its internal R&D headcount of approximately 20,000 scientists. Acting as a virtual company within GlaxoSmithKline, the CEEDD is accountable for taking leads through to proof-of-concept, partnering with early- and late-stage organizations to transform targets into drugs across all therapeutic areas. It comprises approximately 20 scientists of various backgrounds.

Deals can be made at any stage from target identification and screening, through preclinical or clinical development. Alliance companies take their programs through proof-of-concept, at which point GlaxoSmithKline has the exclusive option to in-license the asset. For the CEEDD, there is no such thing as a "typical deal structure" and no research funding is provided, explained Mr Keenan. Instead, funding is milestone driven (eg, for lead identification). Although full-time equivalents (FTEs) for R&D are not provided, collaborators receive significant up-front and milestone payments.

The CEEDD receives input from the commercialization company from the earliest stages of development, as a company would for in-licensed product development. However, in contrast to in-licensing, CEEDD agreements do not take the asset from the development company, which retains the incentives that drive entrepreneurial zeal. Incentives for GlaxoSmithKline and the partner company are fully aligned, said Mr Keenan, because the CEEDD has no internal portfolio and depends on the collaborative program as much as does the alliance company. The CEEDD and the collaborator agree on a single contract and governance committee to guide a long-term relationship, which facilitates the collaborator's work across multiple programs (ie, without separate negotiations for each program)..

New alliances established in 2006 included ChemoCentryx (chemokine receptors), Epix Pharmaceuticals (3D model-

ing of GCPR structures), Neurosearch (expansion of earlier agreement for neurological indications), Pharmacoepia (small molecule therapeutics), Praecis (chemical-synthesis and screening technology) and Galapagos (anti-infective drugs; expanded in 2007). In 2007, new alliances were established with Targacept (nicotinic receptors) and OncoMed (cancer stem cell antibodies). In December 2007, a CEEDD program reached fruition when GlaxoSmithKline exercised its option to further develop and commercialize XL-880, an anticancer C-met inhibitor developed by Exelixis.

Roche

Roche is focusing its R&D efforts on five disease biology areas (DBAs): oncology, CNS, metabolic disorders, inflammation and virology. Robert Silverman, global licensing director of Roche told the symposium about his company's long history of working with a global network of independent partners, shining examples being Genentech and Chugai, which Roche acquired but allowed to function as independent companies. Roche's strategic portfolio committee evaluates opportunities in the five DBAs through dedicated disease biology leadership teams (DBLTs). Under this R&D model, each DBLT consists of heads of discovery, clinical research and experimental development, clinical development and strategic marketing. The Swiss company's interface with the external R&D world is Roche Pharma Partnering, a compact unit with decision-making authority, comprising approximately 90 senior professionals based in Basel, the US, Japan and China. Their functions include transacting in-/out-licensing collaborations, divestments and M&As.

In Roche's collaborations, explained Mr Silverman, the company looks for a "strategic fit" within the five DBAs, scientific merit and value for both partners. Technologies that "fit" include potentially disruptive emerging technologies (eg, RNA-based therapeutics, stem cells), enabling platforms (eg, peptides, antibodies, topicals and discovery platforms such as in silico prediction and safety and clinical modeling), biomarkers (eg, genetics, genomics, proteomics) and delivery and formulation technologies.

Mr Silverman spoke about his company's ongoing partnership with the RNAi company Alnylam Pharmaceuticals. This partner's therapeutic expertise is aligned with Roche's DBAs (cancer, metabolic disorders and respiratory disorders, with options to extend into virology, CNS and other areas). In addition, the alliance gives the pharma company access to a potentially disruptive emerging technology to create clinically differentiated drugs. The deal, with a \$331 million up-front payment and potential payout of up to \$1 billion, for non-exclusive licenses was attractive to Roche because of Alnylam's very strong intellectual property position, which provides Roche with freedom to operate in the RNAi space. With the up-front payment, Roche also bought a 5% stake in Alnylam and acquired its 40-person German research center.

Eli Lilly

According to Ted Bumol, vice-president, biotechnology research, Eli Lilly is currently "the fifth largest biotechnology company by biotherapeutics sales", and the company is utilizing strategic alliances in protein engineering technologies and therapeutics (proteins, peptides, monoclonal antibodies) to maintain innovative R&D. Biotech products now represent 30-35% of Lilly's portfolio. The company's lead and preclinical candidate portfolio has quadrupled since 2001. Between

1997 and May 2008, 20 clinical trials evaluating biotechnology-based therapeutics were initiated, and four more are planned for the rest of this year.

In October 2007, Lilly established a partnership with MacroGenics for the development of teplizumab, a humanized MAb for the treatment of type 1 diabetes and autoimmune/inflammatory diseases (irritable bowel syndrome (IBD), psoriasis, psoriatic arthritis, lupus, rheumatoid arthritis (RA), multiple sclerosis (MS) and others). Teplizumab is a re-engineered anti-CD3 MAb (OKT3) that inactivates T cells and induces

Tregs and immunological tolerance. MacroGenics had taken its compound to an advanced stage, but as a result of the alliance Lilly has found many unexpected properties, which produced new intellectual property. Lilly is also working on protein engineering of next generation anti-CD MABs. AME-133v is tailored for particular patients (ie, Fc RIIIa genotype) and demonstrates more potent antibody-dependent cellular cytotoxicity activity than rituximab. Clinical studies are ongoing.

Dr Tankosic is a drug development consultant.

Alllicense conference sound bites

Barbara Kosacz, head of Cooley Godward Kronish's life sciences practice, and chair of a roundtable addressing alliance strategy and management asked panel members several questions including, What are the most important questions for biotech CEOs to ask about prospective pharma partners? Here are a few take-home messages that emerged from the discussions:

- Is the pharma company capable of maximizing the long-term value of my products and company? Can the company improve the chances of regulatory approval of my products? Regulatory approval is the most important factor for biotech company success. Shared risk and reward is a fundamental of alliances, the largest payout of any deal depends on obtaining regulatory approval and successful commercialization. *(Joseph McCracken, vice-president, business & commercial development, Genentech)*
 - Are there internal champions at the pharma company who will bring my asset all the way through the process, from discovery or early stage development through regulatory approval and commercialization? For early stage technologies and products, is there strong grass-roots scientific support? The pharma company may seem committed when making the deal, but development is a long process and priorities may change, especially without internal champions. *(Graham Brazier, vice-president and head of business development, Bristol-Myers Squibb)*
 - How does the pharma company make portfolio decisions? Who will defend my baby? Do not accept the formerly prevalent black box explanations for how these decisions are made. The biotechnology company should negotiate for the right to be involved in decision-making and be present when relevant issues (eg, early kills) are discussed. *(Jules A. Musing, vice-president, licensing and business development, Johnson & Johnson)*
 - Is the pharma company competent and committed in my therapeutic or technology areas? Look at the pharma company's direction and evaluate its resources and the competitive landscape. *(Dr Klaus K. Wilgenbus, corporate senior vice-president, head of global licensing, Boehringer Ingelheim)*
 - Biotech CEOs should elevate specialty pharmaceutical companies to their A-list when considering potential partners. Specialty pharma companies can be very effective in their specific areas of drug development and commercialization. Ask pharma companies what percentage of their compounds make it all the way through the development process and are approved, and compare it to specialty pharma success rates. *(Gwen Mellincoff, senior vice-president, business development, Shire)*
- How do you decide to kill projects? (Barbara Kosacz)**
- A well-run company will evaluate internally and externally developed projects equally and evaluate them for highest return on investment. *(Joseph McCracken)*
 - At Bristol-Myers Squibb, we cannot afford to flog a dead horse because we spend only \$3 billion per year on development. A pharma company can test whether killed projects should have been killed by putting them out for licensing. We have felt vindicated when we have done with projects we have killed because the low or no offers we received tell us that we did not kill potential blockbusters. *(Graham Brazier)*
 - Some pharmaceutical companies have had difficulty addressing products that are not the products of their internal research. The biotech company should be present when issues surrounding an early kill decision are discussed. Internal R&D units at pharmaceutical companies are now in the process of evolving to accommodate the increased externalization of R&D. Successful evolution is based in part on greater understanding of the business unit's needs. *(Jules Musing)*
- Biotech's obsession with M&A has intensified issues of control. To what extent do pharma companies need to control their acquisitions? (Barbara Kosacz)**
- We do not always need to have control anymore. To my surprise, one of our business units allowed a company they respect to maintain control over development. This approach represents a big change in mentality. *(Jules Musing)*
 - Control is an issue, it is difficult to share it. *(Gwen Mellincoff)*
 - We think it comes down to risk when considering an acquisition, not control. How big a risk do you want to take? We always consider acquisition, and we evaluate it under purely economic terms. For Bristol-Myers Squibb, however, the lifeblood of the company is collaborations. *(Graham Brazier)*
 - Boehringer Ingelheim has grown almost exclusively by in-house organic growth, with few acquisitions. *(Klaus Wilgenbus)*
- Are there new exit strategies for biotech companies on the horizon?**
- It is not clear what, if any, new exit strategies will emerge. Many observers at the conference expect that the IPO option will regain momentum, but few would predict when that might occur. Two potential new exits were discussed at the conference:
- Venture capitalists and private equity funds may eventually buy bundles of future royalty streams from biopharmaceutical products, which could provide the basis for a new type of exit. *(Mark Edwards)*
 - A secondary venture capital market might emerge for venture-funded companies that are not yet ready for an IPO at five years. New venture capitalists could recapitalize such companies by buying out the original venture capitalists at the current value. *(Stelios Papadopoulos, chairman, Exelixis).*

Antibiotic resistance: fighting the superbugs

From the early beginnings of 80 years ago, antibiotics have become the mainstay of treatment for bacterial infections. In recent years, however, antibiotic-resistant bacteria have become a significant obstacle to the future treatment of bacterial infections, and an ongoing challenge for healthcare services worldwide. With the continued development of new therapies, there is hope that antibiotics can overcome the threat posed by such bacteria, and continue to be effective in the future.

By Jonathan Stephens and Lisa Davies

Since the development of the first antibiotics, resistant strains of bacteria, in particular *Staphylococcus aureus*, have become an increasing obstacle to the successful use of this class of drugs. When penicillin was first introduced in 1943, resistant *S. aureus* infections were almost unheard of. However, just four years later, a resistant strain was identified. By 1950, around 40% of nosocomial *S. aureus* infections were penicillin-resistant, and this figure rose to around 80% by 1960. Penicillin resistance in *S. aureus* is mediated by β -lactamase. This enzyme, produced by the bacterium, hydrolyses the β -lactam ring of the penicillin structure, rendering it inactive.

In the face of increased penicillin resistance, methicillin, a narrow spectrum β -lactam antibiotic became the first-line choice in the treatment of *S. aureus* infections. Like penicillin, methicillin acts by disrupting bacterial cell wall synthesis.

However, in 1961 a strain of *S. aureus* resistant to methicillin was identified in the UK. This strain, which has since become known as the 'superbug' methicillin-resistant *Staphylococcus aureus* (MRSA) became resistant to treatment with all β -lactam antibiotics, including methicillin, oxacillin, nafcillin and dicloxacillin. MRSA is present on the skin and nasal passages of one in three people, without becoming pathogenic. However, if MRSA enters the body, it is able to cause infection. MRSA infections commonly occur in the hospital setting, often in immunocompromised patients, or those with open surgical wounds, ulcers or intravenous catheters. The symptoms depend on the type of infection, but can include boils, abscesses, styes and carbuncles, as well as skin infections such as cellulitis and impetigo. More serious MRSA infections include septicemia, septic shock, infective endocarditis and pneumonia.

The incidence of MRSA is increasing. A 2007 report by the US Centers for Disease Control and Prevention (CDC) estimated that the number of MRSA cases in the US more than doubled from 127,000 in 1999 to 278,000 in 2005, with over 17,000 attributable deaths. Similarly, the UK Office for National Statistics reported 6,201 MRSA-related deaths in England and Wales in the period 2002-2006, compared to 5,280 in the four-year period 2001-2005. In 1993, there were just 51 MRSA-related deaths. Bacterial infections in general are now considered the fourth leading cause of death in the US, with approximately 100,000 deaths per year.

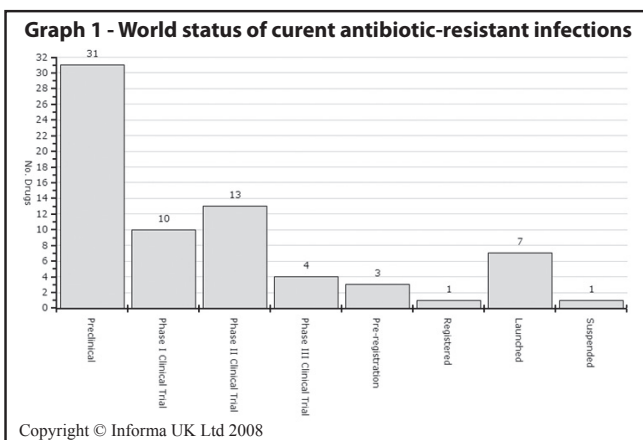
The emergence of MRSA has meant that the glycopeptide

antibiotic vancomycin became the drug of choice for treating MRSA. However, strains of MRSA which are resistant to vancomycin have recently emerged. While not as prevalent as MRSA, VRSA may pose a problem for the future of antibiotic therapy. In 1986, another common antibiotic-resistant bacterium was identified - vancomycin-resistant enterococcus (VRE). Enterococci are bacteria commonly found in the feces of humans, and are commonly responsible for urinary tract and wound infections. Until recently, enterococcus infections were readily treatable with antibiotics.

Clostridium difficile is a Gram positive bacillus. First described in 1935, it is so-named due to the difficulty in growing the bacteria on culture medium. A commensal bacterium of the gut, *C. diff.* does not usually present a disease risk. However, use of broad-spectrum antibiotics can lead to a disruption of the gut flora, giving rise to conditions such as antibiotic-associated diarrhea, caused by overgrowth of *C. diff.* The bacterium is also resistant to most antibiotics, and forms heat resistant spores which are able to tolerate extreme temperatures. Therefore, *C. diff.* has also become a problem in the hospital environment, and even commonly-used hospital disinfectants can fail to kill it.

Treatments for resistant infections

The Infectious Diseases Society of America believes that the commitment to develop new antibiotics has fallen out of favor with big pharma over the past two decades, largely be-



cause of the lower profit margins associated with this therapy class. The result has been a paucity of new approvals to deal with the increasingly serious problem of antibiotic resistance. Between 1983-1987, the US FDA approved 16 new antibiotics, but in the five-year period from 2002-2007, this figure dropped to just five.

Currently there are at least seven treatments available for antibiotic resistant infection (although not all are available in all global markets), including Sanofi-Aventis' Synercid (dalbapristin and quinupristin), Wyeth's Tygacil (tigecycline), Pfizer's Zyvox (linezolid), Salix Pharmaceuticals' Xifaxan (rifaximin), Cubist Pharmaceuticals' Cubicin (daptomycin), Merck & Co's Invanz (ertapenem sodium) and Unimed's Alima (nitazoxanide).

Sanofi-Aventis' Synercid was launched in 1999 as an injectable drug consisting of two synergistic streptogramin antibiotics, dalbapristin and quinupristin. Synercid is launched in several countries worldwide, and for both MRSA and vancomycin-resistant *E. faecium*.

In 2002, Wyeth launched Tygacil for the treatment of nosocomial antibiotic-resistant infections, such as MRSA. A derivative of tetracycline, tigecycline represents the first clinically-available drug in a new class of antibiotics known as glycylcyclines. While structurally similar to tetracycline, a substitution at the D-9 position gives tigecycline a broader spectrum of action. Tigecycline is launched in several markets, including Australia, Germany, the UK and the US, and is awaiting registration in Canada, India, South Africa, Switzerland and Venezuela.

Another novel development in antibiotic therapy is Pfizer's Zyvox, a first-in-class oxazolidinone antibiotic. Linezolid is the only currently available agent in this class. In a Phase III trial in patients with MRSA infection, treatment with linezolid decreased hospital admission time over a two-week period compared to vancomycin. Linezolid is currently launched in Japan for the treatment of MRSA and VRE infections, and is launched in several other markets for the treatment of VRE, as well as nosocomial and community-acquired pneumonia.

Regulatory hurdles

Part of the reason for the paucity of newly-approved antibiotic agents, say observers, is the stricter FDA stance regarding such products. Last October the agency issued draft guidance suggesting that drug sponsors should provide justification for effect sizes and margins for all developmental programs relying on non-inferiority studies. It also states that sponsors should re-evaluate all ongoing or completed non-inferiority studies for antibacterial indications, even those that have a special protocol assessment. There are several new antibiotics that are pending approval in the US but do not seem to appease the regulatory agency.

Basilea Pharmaceutica

The Swiss firm, Basilea Pharmaceutica, and its partner Johnson & Johnson, received an approvable letter in March for its antibiotic, ceftobiprole, for the treatment of complicated skin and skin structure infections. The agency has requested more information on the drug's impact on diabetic foot infections, wants more time to assess the data and wants a review of the study sites used to test the

compound. It did not find any safety issues however and is not requesting any further studies at this time.

Ceftobiprole is the first broad-spectrum cephalosporin with MRSA activity, and is effective against both Gram-positive and negative bacteria, and penicillin-resistant *Streptococcus pneumoniae*. Basilea says the product can be used before knowing the exact bacteria causing a patient's infection.

Despite the delays in the US, the compound was approved and launched in Canada, its first market, in July. Basilea co-promotes it with Janssen-Ortho (part of Johnson & Johnson) as Zeftera for the treatment of complicated skin and skin structure infections. Analysts believe that ceftobiprole's good safety profile, low bacterial resistance and broad-spectrum activity could lead it to reach sales of \$1.2 billion by 2019.

Last year, Basilea reported positive results from a Phase III trial in patients with community-acquired pneumonia requiring hospitalization, an additional indication. However, the company has not commented on whether it plans to make additional filings in this indication.

Pfizer's dalbavancin

Pfizer is awaiting EU and US approval of its once-weekly intravenous antibiotic Zeven (dalbavancin) for the treatment of adults with skin and skin structure infections, including those caused by MRSA. Last December, the company received a third approvable letter, which it is currently addressing.

The product is a lipoglycopeptide antibiotic, in the same class as vancomycin. The submission to the regulatory agencies included three Phase III trials in more than 1,500 patients with SSSIs caused by MRSA. The studies met the primary endpoint of non-inferiority compared with the three most widely used antibiotics in these infections – linezolid, cefazolin and vancomycin.

Theravance's telavancin

In addition, Theravance's telavancin is still awaiting approval in the EU and US for the treatment of complicated skin and soft tissue infections, including MRSA.

Theravance first filed an NDA in December 2006 based on the Phase III ATLAS I and II trials and the FDA issued an approvable letter requesting further clinical data, revised labeling and a resolution of good manufacturing practices. The FDA informed the company in February this year that it wanted to evaluate further site monitoring and conduct of the ATLAS program, calling into question the integrity of the clinical trial data that had been collected by a contract research organization. As a consequence, it cancelled its panel meeting and also an anti-infective drugs advisory committee review.

Theravance responded to the FDA's requests in March although the FDA is not expected to take final action on the NDA until it finishes evaluating study site monitoring.

In the Phase III ATLAS trials, telavancin treatment achieved clinical cure in 78% of patients, compared with 70% for vancomycin. In 1867 cSSSI patients, including 719 MRSA patients, 10mg/kg once-daily for 7-14 days produced clinical cure and microbiological eradication rates of 90.6 and 89.9%. Telavancin is a once-daily injectable lipidated glycopeptides antibiotic, for the treatment of Gram positive infections. It has a broad spectrum of action, inhibiting the transglycosyla-

tion step of peptidoglycan synthesis, thereby disrupting the formation of bacterial cell walls.

Filed

Several companies have recently filed new antibiotic submissions and hope to avoid the delays that their competitors are experiencing.

Arpida's iclaprim

Arpida filed its lead product, the intravenous antibiotic iclaprim (licensed from Roche), with the FDA in March for the treatment of complicated skin and skin structure infections. The firm has requested a priority review and the product has US fast-track status.

The filing is based on the Phase III ASSIST-1 and ASSIST-2 trials in a total of around 1,000 patients. Both met their primary endpoint of non-inferiority to Pfizer's market leader, Zyvox. Clinical cure rates in the intent to treat population in ASSIST-1 were 86% with iclaprim and 92% with linezolid, while the corresponding rates in ASSIST-2 were 83% and 86%. Both trials had a high incidence of MRSA.

Iclaprim has shown bactericidal action against a broad spectrum of pathogens including multidrug-resistant bacteria. It is a synthetic diaminopyrimidine while linezolid is an oxazolidinone antibiotic. Iclaprim could have benefits over Pfizer's product, which can cause myelosuppression. Patients on Zyvox also need regular blood count monitoring.

Targanta's oritavancin

Targanta Therapeutics has filed its lead candidate, oritavancin, in the EU and US for intravenous treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria, including MRSA. The company is also developing an oral formulation of oritavancin. Oritavancin is a novel semi-synthetic lipoglycopeptide antibiotic, developed originally by Lilly to kill a broad range of Gram-positive bacteria. The filing is based on results from 19 trials, including two pivotal Phase III studies, both of which met their primary endpoints in treating cSSTIs.

Late-stage trials

Advanced Life Sciences' cethromycin

Advanced Life Sciences' cethromycin is a once-daily oral antibiotic that has been tested in more than 5,000 patients and has been found to be potent against a broad range of respiratory tract pathogens, community-acquired pneumonia (CAP) and inhaled anthrax. It also overcomes penicillin and macrolide resistance, is active against fluoroquinolone resistant *S. pneumoniae* without causing collateral damage and has shown *in vitro* activity against the predominant strain of community-acquired MRSA.

Data from a Phase III trial in CAP comparing cethromycin with the current market treatment, Abbott's Biaxin (clarithromycin), found that cethromycin cured CAP in 94% of patients, while Biaxin cured 93.8% of patients.

Advanced Life Sciences' CEO Mike Flavin thinks that cethromycin is the right drug at the right time. "With collateral damage and bacterial resistance stemming from the overuse of current treatment options, we believe cethromycin can

become an important option for CAP patients by overcoming these key challenges."

In a separate *in vitro* study, cethromycin demonstrated significant activity against community-associated MRSA. The results suggest that cethromycin exhibits the ability to treat infections caused by CA-MRSA, further supporting the potential of the drug as a front-line treatment for respiratory tract infections.

ALS plans to file an NDA with the FDA for cethromycin to treat CAP this year and is also looking for a partner that can contribute a primary care sales force to market the product upon approval. The company acquired the product from Abbott Laboratories in 2004.

Rib-X's delafloxacin - RX-3341

Rib-X, a privately-owned US firm, has a broad pipeline of compounds to treat multidrug-resistant bacterial infections. Its lead compound, delafloxacin (RX-3341), is a fluoroquinolone in a Phase II trial for complicated skin and skin structure infections (cSSSI) with an intravenous formulation. Delafloxacin has demonstrated activity against a broad spectrum of bacteria including MRSA and as a result has the potential for use in the acute care market as an IV or an oral agent.

Rib-X's CEO, Dr Susan Froshauer, said that delafloxacin is differentiated from other quinolones in both spectrum (expanded to include MRSA and activity against some quinolone-resistant organisms) and potency. It has been tested in more than 1,200 patients so far and found to be safe and efficacious in multiple Phase I trials and two previous Phase II trials with the oral formulation.

The company is also developing radezolid (RX-1741), an oxazolidinone that was discovered by Rib-X using a proprietary discovery process. It is in two separate Phase II trials – one for community-acquired pneumonia and the other for uncomplicated skin and skin structure infections, with results expected in the third quarter of 2008. Dr Froshauer believes that radezolid may prove to be a more potent, safer alternative to Pfizer's Zyvox which is expected to have sales in excess of \$1 billion this year.

Rib-X has developed the majority of its pipeline of compounds using a structure-based drug design (SBDD) process which uses a combination of specialized computational tools and proprietary knowledge of the ribosome's structure to optimize leads and create compounds that work against antibiotic resistant bacteria and can be differentiated from their competitors. Specifically, the approach is based on two assets – high resolution crystal structures of the small, large and complete ribosome (30S, 50S and 70S respectively) and SBDD modeling algorithms, combined with traditional medicinal chemistry and antibiotic drug discovery expertise.

Dr Froshauer believes that the SBDD technology will provide the company with a sustainable pipeline. "By using our high-resolution crystal structure capabilities, we can visualize exactly where and how antibiotics bind to the ribosome. This allows us to efficiently design completely new classes that have activity against key emerging pathogens and that overcome drug resistance," she said.

Forest's ceftaroline

Forest Laboratories' investigational antibiotic ceftaroline, a cephalosporin with anti-MRSA activity, was recently shown

in two Phase III trials (CANVAS I and CANVAS II) to be non-inferior to vancomycin plus aztreonam and to be well tolerated in patients with complicated skin and skin structure infections. Top-line data across both studies revealed that 91.6% of patients treated with ceftaroline achieved a clinical cure, compared with 92.7% of patients treated with vancomycin plus aztreonam. Over 30% of patients with a confirmed pathogen had an MRSA infection. Ceftaroline is also in Phase III trials in community acquired pneumonia. Forest plans to file in the US for approval of ceftaroline in both indications in 2009.

Oscient's ramoplanin

Oscient Pharmaceuticals is conducting a Phase III trial of ramoplanin for the treatment of *C. difficile*-associated disease. The compound has fast-track status from the FDA and the trial also has special protocol assessment.

Optimer's OPT-80

Optimer Pharmaceuticals is also developing an antibiotic for the treatment of *C. difficile* infection. OPT-80 (formerly known as PAR-101 or difimicin) acts by inhibiting RNA polymerase which results in the death of specific bacteria such as *C. difficile*.

The company says that OPT-80 represents a new class of antibiotics and offers advantages over current treatments including low rates of recurrence of the infection, evidence of low resistance, minimal systemic exposure, limited disruption of normal gastrointestinal bacteria and a convenient dosing regime.

Phase III trials commenced in 2007 comparing OPT-80 against oral vancomycin in patients with *C. difficile* infection and data are expected in 2009. If successful, an NDA filing will follow. Optimer is also planning trials for additional indications of OPT-80 including the prevention of nosocomial infections by vancomycin-resistant Enterococci and the prevention of MRSA.

Cosmo's rifamycin SV

The Italian firm Cosmo Pharmaceuticals is developing rifamycin SV for the treatment of infectious diarrhea. The compound is a broad-spectrum, semi-synthetic antibiotic that is taken in an oral form and delivered directly to the colon owing to its delivery technology, targeting the exact site of the infection and leaving other gut bacteria unharmed. Positive preliminary results from a Phase II/III trial have been reported. A Phase III trial is underway.

Paratek Pharmaceuticals' PTK 0796

Paratek recently raised additional funds to support Phase III trials of its advanced broad-spectrum antibiotic, PTK 0796. The compound is being developed to treat complicated skin and skin structure infections and moderate to severe community-acquired pneumonia and is being evaluated against Zyvox.

Early-stage trials

In response to the challenge of antibiotic resistance, pharmaceutical companies continue to develop novel antimicrobials which may lead to a new generation of drugs for the treatment of such infections. While many 'traditional' antibiotics act by disrupting cell wall synthesis, today pharmaceutical companies are employing various novel mechanisms of action in order to combat these resistant bacteria by targeting the very protein the bacteria are mutating.

Several early stage compounds are currently in development for antibiotic-resistant infections. The South Korean pharmaceutical company Dong-A Pharma is developing DA-7218, the lead in a series of orally-available oxazolidinone drugs for the treatment of Gram positive infections. It is currently in a US multiple ascending-dose Phase I study in patients with Gram positive infections, including MRSA, to assess safety, tolerability and pharmacokinetics. Previous studies have shown potential for daily dosing with DA-7218. Dependent on further development, approval is expected in 2013.

Several preclinical compounds are also showing early promise. Merck & Co's platencin, a natural product and dual inhibitor of FabH and FabF, has shown potent activity in preclinical studies, with no toxicity observed. Platencin does not show cross-reactivity to antibiotic-resistant strains such as MRSA and VRE. Also in preclinical development is Replidyne's diaryldiamine anti-infective, REP-3123, indicated for the treatment of antibiotic-resistant *C. diff* infections. A hamster model has previously shown REP-3123 to be superior to vancomycin. It also inhibited moxifloxacin- and clindamycin-resistant strains of *C. diff*. Replidyne expects to file an IND in the second half of 2008.

Phynova, meanwhile, is developing PYN-6. Currently in preclinical studies, PYN-6 has shown activity against MRSA and vancomycin- and teicoplanin-resistant bacteria. Phase I trials are planned for 2008, with Phynova seeking to out-license PYN-6 after completion of Phase II.

Is prevention better than cure?

Another possible breakthrough in the fight against antibiotic resistance is the development of prophylactic vaccines. Originally developed as an immunogen to develop a hyper-immune globulin passive vaccine, Acambis' ACAM-CDIFF vaccine has shown early promise in the prevention of *C. diff* associated diseases (CDAD). In a US Phase I trial in 50 healthy young adults, a single injection of ACAM-CDIFF vaccine produced 10-fold higher levels of anti-toxin-A and -B IgG compared with patients who had previously recovered from a *C. diff* infection. In another Phase I trial in elderly patients, seroconversion rates were 100% and 75% for *C. diff* toxin-A and -B, respectively. Side-effects were mild, with no serious adverse events reported.

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