Veracity Health

Synopsis

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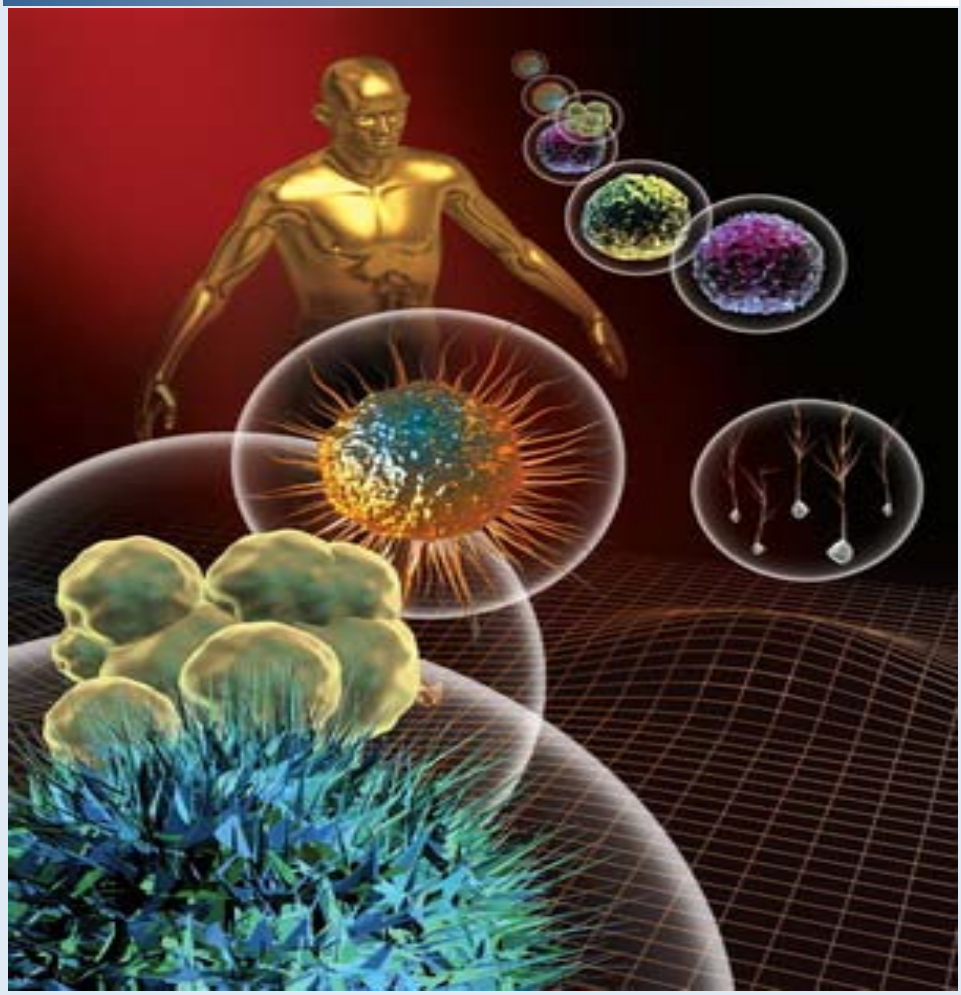


Contents

Welcome to the second edition of Veracity Health's in-house publication, *Synopsis*. In this issue we look at market opportunities which are presenting themselves in stem cell therapies and in combating MRSA infections. We provide an interview with Dr Joseph Kim of Inovio Biomedical and review briefly some interesting news stories which we noted since the beginning of the 2010.

An Executive Summary is provided for each of the articles covered in this issue:

MRSA– An expanding opportunity for Devices, Diagnostics and Pharmaceuticals
It is now recognized that MRSA, which accounts for 25-40% of nosocomial *S. aureus* infections, is a tremendous health and financial burden for healthcare systems. The cost of treating antibiotic-resistant bacteria in the US alone is over $5 billion per year, and prevalence in some countries may be as high as 75%. Current research indicates that community MRSA (CA-MRSA), also a significant source of infection, appears to be a different, more virulent strain of MRSA. Market opportunities include prevention, utilizing hand washing/monitoring devices and technologies; detection via the development and marketing of diagnostic assays; and therapies such as genetically-altered antibiotics, and vaccines against MRSA. Likely there will not be a one-size-fits-all solution to the problem of MRSA infections.

Regenerative Medicine – the market impact of advances in stem cell technologies
The large pharma companies have begun to take note of the potential in regenerative medicine. For example, in November 2008, Pfizer invested $100m in stem cell research. The goal is to bring the enormous potential in stem cells into the market. One way would be to make reprogrammed induced pluripotent stem (iPS) cells a source of patient-specific cells for use in medicine, enabling the body to regenerate, repair, replace, and restore diseased or damaged cells, tissues, and organs. One opportunity in the stem cell arena lies in therapies for ophthalmic disorders; treatment of ophthalmic disorders represents a market in excess of $20bn per year. Another attractive target is the treatment of neurological disorders, including MS, amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), stroke and Parkinson's disease (PD). Other potential treatment areas include cardiology, orthopaedics, peripheral arterial disease (PAD), development of vaccines against cancer, and advanced wound care. At this point the total market size cannot be calculated with accuracy, but there is little doubt that the potential will be staggering.

Industry Leader Interview - Dr Joseph Kim, CEO, Inovio Biomedical
Inovio Biomedical is focused on the design, development, and delivery of DNA vaccines to prevent and treat cancers and infectious diseases. The company's SynCon™ technology enables the design of "universal" vaccines capable of protecting against multiple strains of pathogens such as influenza. Inovio's proprietary electroporation-based DNA vaccine delivery technology has been shown by initial human data to safely and significantly increase gene expression and immune responses. Inovio's clinical programs include HPV/cervical cancer (therapeutic) and HIV vaccines. By leveraging Inovio's technology, CEO Dr. J. Joseph Kim hopes to change the current paradigm of vaccine development, manufacturing and delivery.

News-wire
Our take on a selection of current events in Pharma, Biotech, Devices and Diagnostics.

We at Veracity Health hope that you enjoy this second edition. If you would like to be on our mailing list to receive *Synopsis*, please send us an email. We would certainly appreciate hearing your comments and suggestions for future articles and improvements. Please send these to info@veracityhealth.com.

MRSA – An Expanding Opportunity For Devices, Diagnostics and Pharmaceuticals

Staphylococcus aureus (*S. aureus*) is one of the bacteria most frequently isolated from patients with serious healthcare-associated infections (HAI). Methicillin was introduced in 1959; only two years later, cases of methicillin resistant *S. aureus* (MRSA) were detected. MRSA is the *S. aureus* bacterium that has mutated to become much less susceptible to the methicillin class of antibiotics, which includes methicillin, penicillin and amoxicillin. This bacterium is responsible for causing high rates of dangerous and difficult to treat infections, as well as mortality, especially among those with weakened immune systems. It is now recognized that MRSA infections are a tremendous, and growing, burden for healthcare systems and hospitals, and are associated with significant healthcare costs.

MRSA accounts for between 25-40% of nosocomial S.aureus infections in hospitals

Healthcare-associated MRSA (HA-MRSA) more commonly causes bloodstream, wound site, pneumonia or urinary tract infections. It is now the leading cause of identifiable skin and skin structure infections (SSSIs) seen in US emergency departments. According to the 2007 report of a nationwide survey of 1,237 U.S. healthcare facilities conducted by Association for Professionals in Infection Control and Epidemiology (APIC), MRSA infection was recorded in 46 of 1,000 patients in the US, which is 8-11 times higher than earlier estimates conducted using different methodologies. The report also suggests that MRSA may be the cause of between 48,000 to 119,000 patient deaths in US hospitals each year. MRSA may account for up to 40% of nosocomial *S. aureus* infections in larger hospitals, and up to 25-30% in smaller hospitals. The cost of treating antibiotic-resistant bacteria in the US is estimated to be over $5 billion per year.

Another report from 2007, this time from the CDC, estimated that the number of MRSA infections treated in hospitals doubled nationwide, from approximately 127,000 in 1999 to 278,000 in 2005, while at the same time deaths increased from 11,000 to more than 17,000.

MRSA infection not confined to the hospital setting

New lineages of MRSA, defined as community acquired (CA)-MRSA, have emerged that tend to cause infections in young individuals without risk factors.

Community-based infections on the rise

Current research seems to confirm the possibility that not all *S. aureus* infections originate in the hospital and that the community may be a significant source of infection as well. One study (Miller M, *et al*, 2009) was designed to determine if *S. aureus* colonization is a useful proxy measure to study disease transmission and infection in community settings, and to identify potential community reservoirs.

The researchers randomly surveyed 321 households (914 members) in North Manhattan, collecting nasal swabs and information regarding activity, infections, antibiotic usage, etc. The swabs were typed by pulsed field gel electrophoresis to identify *S. aureus* colonizing strains. The prevalence of *S. aureus* was about 25%; 0.4% tested positive for MRSA, and more than 40% of households were colonized with *S. aureus*. About 24% of households reported serious skin infections. However, there was no statistically significant correlation between the households with *S. aureus* and those with the skin infections.

Researchers concluded that the lack of association between *S. aureus* nasal colonization and serious skin infection meant that further research is needed to explore alternative venues or body sites that may be crucial to transmission. The researchers also drew attention to the apparent role played by antibiotic use.

About 25% of participants reported antibiotic use in the last six months. The data suggest that at least some usage may be unmonitored, given the high levels of self-reported non-prescription antibiotic use. Uncontrolled and perhaps inappropriate use of antibiotics has the potential to eventually increase resistance not only to methicillin, but to other first and second line antibiotics as well. Finally, the magnitude of colonization and infection within the household suggested that households are a substantial community reservoir requiring further study.

Community Associated-MRSA more virulent than hospital-associated infection

CA- and HA-MRSA are still often differentiated based upon detecting MRSA a certain number of hours post-admission. However, the previously cited APIC report suggests that this method of differentiation ignores the fact that many patients are admitted to hospital several times; what is detected as a new case of CA-MRSA, may actually be the result of colonization from an earlier hospital admission.

More importantly, CA-MRSA now appears to be a different, more virulent strain of MRSA. CA-MRSA primarily causes SSSIs and, rarely, necrotizing pneumonia. In 2008, public health officials identified a widespread variant of CA-MRSA, designated as multidrug-resistant USA300. Most of the CA-MRSA strains in the US are of this type, and most carry genes for the Panton–Valentine leucocidin (PVL), whose role in diseases appears to be significant, but is still under debate.

What is of ultimate concern is that both CA- and HA-MRSA strains are now spreading inside the hospital environment. In addition, the emergence of MRSA has been followed by both multi-drug resistant SA and strains of MRSA with high-level resistance to vancomycin (VRSA: vancomycin-resistant *S. aureus*). Fortunately, to date only about a dozen such isolates have been reported.

A global phenomenon

Prevalence of MRSA infection in Portugal and Italy and in Asia reported to be as high as 50%

In the EU, antimicrobial resistance and HAIs, either in combination or separately, constitute a major infectious disease problem, and show signs of becoming more prevalent in the future. An estimated 4 million HAIs and 37,000 deaths annually are thought to be due to *S. aureus* infections. In 2004, the United Kingdom National Audit Office estimated that infections such as MRSA kill 5,000 people each year in the UK and hospital-associated infections cost the National Health Service around £1 billion ($1.6bn) a year. Prevalence varies widely by country: from over 50% in Portugal and Italy, to less than 2% in Switzerland. Most CA-MRSA strains in Europe, rather than belonging primarily to USA300, belong to a variety of clones.

In Asia, health authorities estimate that the overall prevalence may be as high as 50%, soaring to 75% in Hong Kong and 72% in Japan. In Africa, prevalence appears to be around 15% in many hospitals. However, the MRSA numbers are thought to be significantly underreported; so many people die of pneumonia and infection that testing for MRSA is often simply not conducted.

As the threat posed by MRSA grows, healthcare institutions are having to confront thorny issues, including how to successfully avoid, detect and combat MRSA infections. In addition, as of October 2008 the Centers for Medicare and Medicaid (CMS) are no longer paying for hospital-acquired infections; therefore, healthcare facilities will have to either find ways to avoid HAIs, or absorb these potentially staggering costs.

Although pharmaceutical companies have sharply reduced antibiotic research, a number of compounds are either experiencing new life or have been developed

Traditional risk factors for MRSA infections

- *Recent hospitalization*
- *Surgery*
- *Dialysis*
- *Residence in a long-term care facility during the year preceding the finding of MRSA infection*
- *Invasive medical device*
- *History of MRSA infection or colonization*

Most common MRSA clinical problems:

- *Bacteraemia*
- *Staphylococcal pneumonia (+/- Panton-Valentine leucocidin (PVL) toxin)*
- *Osteomyelitis*
- *Abscesses and other complicated SSSIs*
- *Endocarditis*

to combat drug-resistant infections. These include quinopristin-dalfopristin, linezolid, daptomycin, new cephalosporins such as ceftobiprole and ceftaroline. However, most of these new or re-introduced drugs have important limitations, such as toxic side effects, reaching unsatisfactory levels in the blood, or observed resistance by *S. aureus*. In addition, while new antibiotics may work well in the short to medium term, experts say that in the long term it's only a matter of time before *S. aureus* and other bacteria develop resistant strains to the new drugs.
A number of researchers and companies are nevertheless searching for and finding opportunities in the lining of this cloud. The outstanding revenue generating opportunities are apparent across the medical device, diagnostic and pharmaceutical markets and in this article we report and discuss some of the key areas of opportunity ripe for exploitation by those companies which can rapidly innovate and deftly navigate through the regulatory process.

PREVENTION

Hand hygiene---Developing hand washing/sanitizing monitoring systems

Hand hygiene is widely recognised amongst healthcare professionals as of immense importance in combating the spread of infection in the hospital and clinical setting. The transmission of pathogenic organisms by hand is common but nevertheless compliance with directives aimed at improving frequency and thoroughness of handwashing remains problematic. Less than optimal compliance means that there is a market for systems which monitor and provide reminders for patients and staff in hospitals to maintain hand cleanliness. An indication of some of the products recently entering the market or on the verge of entry are shown in Table 1.

Table 1 - Technologies for improving compliance of handwashing

Company	Product/Technology
Healthquest Technologies Safe-Hands Hygiene Monitoring Technology	Microprocessor-controlled non-invasive electronic monitoring of the hospitalized patient to check that hospital staff and visitors are sanitizing hands properly before coming within the Bio-Shield™ area surrounding the patient. At this time, although demonstrations may be arranged, the technology is not yet commercially available. The company is currently seeking venture capital partners, and expects to market the technology by the end of 2010.
Resurgent Health and Medical Resurgent automated hand washing system	Automated hand washing system uses badges and RFID to verify compliance and to automate compliance reporting.
Versus Technology, Inc. Versus Hand Hygiene Compliance solution	Uses soap/gel dispensers equipped with sensors that, when activated, "read" the participant's active ID badge, noting when and where the event is taking place, and allowing hospitals to relate the data to patient care events
XHale, Inc. HyGreen Sensing system	After cleaning hands with alcohol-based sanitizers, healthcare personnel place hands under the HyGreen sensor that detects the alcohol in the sanitizer that they just used. The HyGreen sensor then sends a wireless "all clean" message to a badge worn on the HCP's shirt pocket. A wireless monitor on patient beds searches for the message; if it's absent, the badge vibrates, reminding the wearer to sanitize his hands.

Source: Veracity Health analysis

DIAGNOSTICS

State legislature activity in the USA shows recognition of the need to monitor and ultimately tackle MRSA infection rates. As of the time of writing the situation in the USA showed:

Legislative measures to improve diagnosis TAT (turnaround time) gathering support across USA

States with legislation passed:

- 25 state laws require public reporting of hospital-acquired infec tion rates CA, CO, CT, DE, FL, IL, MD, MA, MN, MO, NJ, NY, NH, OH, OK, OR, PA, RI, SC, TN, TX, VA, VT, WA, WV)
- 2 state laws require confidential reporting of infection rates to state agencies (NE, NV).
- 2 state law permits voluntary public reporting of infection infor mation (AR, AZ).
- 5 states have study laws on public reporting (AK, GA, IN, NM, NC).
- 16 states and D.C. have no laws on public reporting of hospital infections.
- Only 3 states (MT, ND, WY) have not entertained any legislation on the matter.

Legislation, as well as mandatory surveillance, have led to the setting up and implementation of testing programs in major hospitals— a key driver of the diagnostics market. One of the reasons for the attractiveness of using point of care (POC) or rapid tests for MRSA is that the costs of isolation or quarantining of patients who test positive for MRSA infection can be significantly reduced if patients are diagnosed faster and begin to receive the necessary treatments more quickly. In the Netherlands, research has shown that costs of quarantine can be reduced by 80% and in the US studies suggest that 90% of isolation costs can be saved by rapid testing (Bootsma MCJ, et al. "Controlling methicillin-resistant Staphylococcus aureus: Quantifying the effects of interventions and rapid diagnostic testing." Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 5620-5625).

In terms of market development we believe that over the last 2-3 years as new products have entered the market and as legislation has driven infection control practices, the market has evolved into three distinct segments:

Diagnostic testing needs to include the majority of hospital in-patients- not just those considered high risk.

- Surveillance testing
- Diagnostic testing of symptomatic patients and,
- Testing of pre-surgical patients

It is worthy of note here that research in the USA and the UK suggests that *routine* testing of surgical patients and patients in ICU may not be particularly cost effective. It is recommended that screening all hospital patients for MRSA infection is more effective in reducing infection rates, as opposed to purely targeting only high risk patients for screening or placing sole emphasis on the screening/testing of high risk groups.

While that debate rages, nasal, skin and soft tissue, and blood culture tests serve each of the aforementioned market segments. There are several MRSA rapid tests now available; these fall into one of two categories: PCR-based methods or rapid culturing techniques. All tests can detect MRSA directly from the clinical sample within a few hours with good sensitivity and specificity. Rapid testing appears to be a reliable way of demonstrating that a patient is negative for MRSA

Table 2 - Selected MRSA detection tests, launched and/or under development

Company	Product/Technology
3M 3M™ BacLite™ Rapid MRSA Test	April 2007—launched in EU. Culture-based test for the detection of MRSA using clinical specimens provides confirmation of negative results within 5 hours and positive results within 24 hours.
Accelr8 BACcel technology	Accelr8 states that BACcel is the only technology supported by published data to provide same-day analysis of all significant highly drug-resistant bacteria and their particular resistance mechanisms. Sept. 2009—Becton Dickinson declined an option to license the company's rapid bacterial diagnostic system. Accelr8 is continuing its search for other partners for commercialization
AdvanDx Evigene	Qualitative hybridization assay using signal amplification that provides rapid (3 hours) detection of specific gene markers in *S. aureus* and enterococci isolates.
Becton, Dickinson & Company BD GeneOhm™ MRSA Assay	Qualitative *in vitro* diagnostic test to detect MRSA from a nasal specimen. According to the company, the test provides a definitive result in a single assay in less than two hours. BBL™ CHROMagar™ MRSA Qualitative detection of MRSA from nasal swab; test results in 18-24 hours.
bioMérieux NucliSENS EasyQ® MRSA	November 2009—launch of NucliSENS EasyQ MRSA, a real-time amplification assay for the screening of MRSA on bioMérieux's automated NucliSENS® system. The test provides rapid results, with a turnaround time of under three hours.
Bio-Rad Laboratories MRSASelect™ Chromogenic Medium	Chromogenic medium for rapid screening and detection of MRSA colonization. The MRSA*Select* test can identify MRSA carriers in just 18–28 hours using a nasal swab specimen. Originally launched in US in July 2007; was granted clearance for faster interpretation time (18 hours) in July 2008.
Cepheid Xpert™ MRSA/SA Skin and Soft Tissue Infection (SSTI) test	Introduced in US in September 2008; in EU in march 2009. Xpert™ MRSA/SA Nasal is Cepheid's tenth CE IVD test for use on the GeneXpert® System, a leading healthcare associated infection (HAI) molecular testing platform. Cepheid believes that its multiplex MRSA combination SA products for SSTI and blood culture, which are expected to provide the ability to differentiate between methicillin-resistant and methicillin-sensitive Staph infections will enable healthcare practitioners to initiate appropriate treatment measures more rapidly for symptomatic patients.

Source: Veracity Health analysis

infection; however, positive PCR results always need to be confirmed in order to exclude false-positive results.

Outside the USA, Veracity Health believes that the UK market will see significant growth as continued news flow on MRSA, hospital infections such as *C.diff* and government initiatives drive infection control and testing programs. Similarly, initiatives in France should result in stronger growth rates for MRSA testing applications.

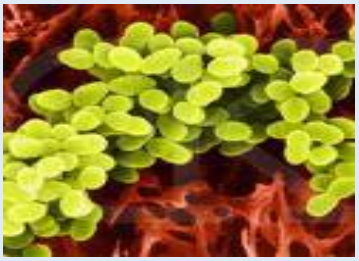
Table 2 lists the main diagnostic tests for MRSA on the market.

We also review some of the more promising tests which will impact the evolution of the market for MRSA diagnostics in Table 3.

Table 3 - A new treatment and novel tests released or pending release for MRSA detection

Company	Product/Technology
Cubist Pharmaceuticals Cubicin® daptomycin for injection	Once daily IV bactericidal antibiotic for treating (at 4mg/kg) complicated SSSI infections caused by susceptible strains of several gram-positive microorganisms, including MRSA. Also approved, at 6mg/kg, for treatment of S. aureus bacteremia, including right-sided infective endocarditis caused by MRSA and MSSA.
Hardy Diagnostics MRSA Latex Test for PBP2	Rapid *in vitro* latex agglutination assay, detecting PBP2' (also called PBP2a) in isolates of *Staphylococcus* as an aid in identifying MRSA. Results in 15 mins.
Invitrogen, with Biosynth AG BCM® MRSA ELF® culture media	Launched in November 2007, with Biosynth AG, a novel, fluorescence-based culture medium for rapid detection of MRSA in healthcare settings. Manufactured and sold by Biosynth under license from Invitrogen's Molecular Probes business unit.
Roche Diagnostics LightCycler MRSA Advanced Test **Thermo Fisher Scientific** Spectra MRSA (marketed through the specialty brand, Remel)	Qualitative *in vitro* test for the detection of nasal colonization with MRSA. April 2009—Roche introduced the test into the EU. Selective chromogenic medium intended for use in the detection of nasal colonization of MRSA. Final results within 24 hours

Source: Veracity Health analysis



THERAPIES

According to the company Tyrx, medical implant related infections and fibrosis add as much as $3.8 billion to annual US healthcare costs. In the US, post-surgical infections following cardiac rhythm management (CRM) implantation cost an estimated $700 million each year.

The company DiFUSION Technologies notes that large studies have reporting a rising incidence—from 2.5% to 13%--of SSSIs within spinal surgery. The company has developed CleanFUZE™, an antimicrobial PEEK spinal interbody cage, to assist surgeons and their patients to avoid these infections.

Table 4 - Medical device /drug convergent technologies targeting MRSA and surgical site infections

Company	Product/Technology
Ceragenix CeraShield™ antimicrobial coatings for medical devices	Currently in development, CeraShield™ technology is designed to prevent bacterial colonization and biofilm development on medical devices. The active ingredient in CeraShield™ is CSA-13, of the Ceragenin™ class of compounds. These are claimed to be rapidly active broad spectrum bactericidal, fungicidal and virucidals with potent activity, even against multidrug resistant strains. Ceragenix holds the worldwide exclusive license from Brigham Young University (Provo, Utah) to develop and commercialize this technology. Ceragenin™ CSA-13 may be incorporated directly into medical devices, coated as CeraShield™ onto medical devices, or used in solution. As of October 2009, Ceragenix had two partners exercising options for exclusive periods to negotiate licensing terms.
DiFUSION Technologies, Inc. CleanFUZE™, an antimicrobial PEEK spinal interbody cage.	January 2009—DiFUSION announced successful completion of a series of laboratory tests of its silver ion-based antimicrobial technology designed to mitigate Surgical Site Infections (SSIs) in spinal surgery. The technology will be incorporated into CleanFUZE. According to DiFUSION Technologies, CleanFUZE™ is capable of stopping biofilm formation in the bone graft site and eliminating 650 types of bacteria, including MRSA, for up to four weeks postoperatively.

Company	Product/Technology
Tyrx, Inc. AIGISRx™ Anti-Bacterial Envelope	Commercially released in June, 2008, AIGISRx™ contains the antimicrobial agents rifampin and minocycline, which have been shown to reduce infection by organisms including MRSA. The "envelope" is intended to securely hold a pacemaker or implantable cardioverter defibrillator (ICD) in order to create a stable environment when implanted in the body. Made of a biocompatible mesh, the envelope is coated with antibiotics that elute within 10 days. The company is currently developing a third-generation, totally resorbable product based on the existing technology behind AIGISRx™. "Orthopedic Implants" bioresorbable antimicrobial polymer. Orthopedic Implants, Tyrx' proprietary bioresorbable polymer, contains minocycline and rifampin, and may be used to coat orthopedic implants with the intent of reducing the potential for infection. Tyrx expects to enter clinical studies with an orthopedic partner during 2010.

Source: Veracity Health analysis

Brief outlines of the activities of these companies in the development of devices and bio-coatings for protecting against, and combating MRSA infection are described in Table 4.

Genetics

In December 2007, a British team from the John Innes Centre in Norwich identified short stretches of DNA that appear to inactivate the genes in bacteria which are responsible for antibiotic resistance. Therefore, they surmised, by putting this genetic information directly into drugs, the 'superbug' bacteria could be blocked from resisting antibiotics. According to researchers, this technology could not only be used to develop new drugs, but could inject new life into existing antibiotics: when combined with this type of genetic decoy, the antibiotic could then be patented as a new drug. A spin-off company, Procarta Biosystems, has been set up to explore commercialization of this genetic decoy technology. The company has developed proprietary transcription factor decoys (TFDs) against the resistance mechanisms of superbugs, including MRSA and VRE (vancomycin-resistant enterococci).

Vaccines

Positive clinical data and safety would open up a significant market for a successful vaccine

In September 2008, a team of vaccine researchers announced that a key to development of an effective vaccine against MRSA hinged upon the so-called 'sticky glue' produced by the bacteria in order to grow as a biofilm. Living in this biofilm protects the bacteria from antibiotics. One type of sticky glue is a complex sugar called PGAG. By chemically manipulating this sugar, variants can be produced which could be used as vaccines. According to researchers, such a vaccine would likely be reserved for those most susceptible to MRSA, being too expensive for general use. If developed along these lines, a vaccine could theoretically be available within six years.

Pharmaceuticals - some signs of the return of the larger players to the market

Large pharma companies have long seemed to be neglectful of the opportunity within the antibiotics market. The market was assumed to be a mature one with limited capacity for growth while costs of development stayed in line with those for more "innovative" treatments.

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Table 5 - Marketed therapies for cSSSI and MRSA

Company	Product/Technology
Basilea Pharmaceuticals	**Ceftobiprole (ZEFTERA™)** Marketed in Canada for the treatment of cSSSI, including non-limb threatening diabetic foot infections without concomitant osteomyelitis and in Switzerland (Zevtera™) for the treatment of cSSTI including diabetic foot infections without concomitant osteomyelitis. It is also approved in Russia, Azerbaijan, Ukraine and Hong Kong. Marketing applications for ceftobiprole are submitted in the EU and several other countries. Marketing delays in the USA due to FDA non-approval relating to concerns about clinical trial audits has led Basilea to seek damages from Johnson & Johnson, its US marketing partner for lost sales.
Cubist Pharmaceuticals	**Cubicin® daptomycin for injection** Once daily IV bactericidal antibiotic for treating (at 4mg/kg) complicated skin and skin structure infections (cSSSI) caused by susceptible strains of several gram-positive microorganisms, including MRSA. Also approved, at 6mg/kg, for treatment of S. aureus bacteremia, including right-sided infective endocarditis caused by MRSA and methicillin susceptible, MSSA strains.
Pfizer	**Zyvox** **Tygacil** Zyvox (linezolid) exclusively targets Gram-positive organisms and is indicated for nosocomial pneumonia and cSSSIs due to methicillin resistant Staphylococcus aureus ("MRSA"). Worldwide sales of Zyvox totaled $1.115 billion in 2008. Zyvox has a stronger brand presence among physicians than the company's broad-spectrum glycycline antibiotic Tygacil (tigecycline IV) which it inherited when it took over the Wyeth business. Tygacil launched in 2005 and had sales of $137 million in 2007, and is a newer product than Zyvox. A concern with Tygacil is its broad applications—it is indicated for cSSSI, including those caused by MRSA, and complicated intra-abdominal infections, but works against both Gram-positive and Gram-negative bacteria. It is thought this could lead to antibacterial resistance. Tygacil is positioned against cephalosporins, penems and quinolones. Tygacil – Phase II for hospital acquired pneumonia and paediatric skin infections Phase III for diabetic foot infection.
Theravance & Astellas	**Vibativ (telavancin)** November 2009—launched in US. Developed to treat cSSSIs caused by susceptible gram-positive bacteria, including MRSA and MSSA strains. Vibativ is a bactericidal, once-daily injectable lipoglycopeptide antibiotic discovered by Theravance.
ViroPharma	**Vancocin Capsules** For treatment of enterocolitis caused by Staph. aureus including methicillin-resistant strains

Source: Veracity Health analysis

New drug treatments need to have superior safety and efficacy over Pfizer's product and be available orally as opposed to IV

However, the market for antibiotics labeled for MRSA is growing rapidly. According to IMS Health, the total United States sales for the four antibiotics labeled for MRSA grew from $778m in 2005 to $1.4bn in 2008. The market is expected to have a CAGR in the region of 7% until 2014. The most widely prescribed antibiotic for treating gram-positive infections is vancomycin, an IV only therapy. Based on the rapid rise of MRSA with reduced susceptibility to vancomycin, newer, more effective IV and orally available antibiotics are expected to increasingly replace vancomycin as the standard treatment for MRSA infections. As there will be a need to move from treating patients in hospital with IV administered drugs to oral drugs as part of recovery in the community, there is a need for effective oral formulations but with improved potency, convenience (e.g. one a day pills) and safety advantages over the current drugs such as Zyvox, the market leader.

Pipeline - Pushing novel antibiotics through to the clinic

In response to these needs, and mindful of the commercial potential, there are some signs that some of the bigger players in the pharma sector are returning to the antibiotics fold. Two factors driving a rethink in strategy are the rise in HAIs, which brings with it a need for new antibiotics to treat serious drug-resistant gram +ve infections, and the premium pricing that can be obtained.

In December 2009, AstraZeneca moved to acquire the French company Novexel (see Table 6) and entered into a collaborative drug development deal with Forest Laboratories. In January 2010 AstraZeneca went as far afield as South Korea to sign a licensing deal to bolster AZ's anti-infectives business. AZ has agreed to fund Korean company CrystalGenomics' R&D efforts for two years while CrystalGenomics develops drug candidates against an unnamed bacterial target. AZ has made public that part of its overall strategy is to build "a leading franchise" in the treatment of infectious diseases.

Table 6 - Novel drug molecules in development for MRSA and acute infections

Company	Product/Technology
Cempra Pharmaceuticals	Fusidic acid (TAKSTA™, CEM-102) - orally active against gram-positive bacteria, including all *S. aureus* strains such as HA-MRSA and CA-MRSA. Oral tablet formulation completed Phase II. Upcoming Phase III trial designed to show non-inferiority to Linezolid in treating ABSSI (acute bacterial skin structure infections). Oral suspension CEM-102 in preclinical studies. Closed $46m Series C financing in May 2009
Cubist Pharmaceuticals	CXA-201—an IV-administered combination of Calixa's anti-pseudomonal cephalosporin CXA-101, and the ß-lactamase inhibitor tazobactam. Cubist announced acquisition of Calixa Therapeutics in December, 2009. CXA-201 is under development as a treatment for serious multi-drug resistant gram-negative bacterial infections. Cubist hopes to move CXA-201 into Phase II clinical studies during 1H10.

Company	Product/Technology
Durata Therapeutics	Dalbavancin—long-acting, injectable, lipoglycopeptide antibiotic. Dalbavancin has produced Phase III results showing efficacy against cSSSIs, and will potentially be a new antibiotic against gram-positive bacteria, including MRSA.
Forest Laboratories & AstraZeneca	Ceftaroline antibiotic August 2009—Forest and AZ entered into collaboration to co-develop and market ceftaroline in all markets outside the US, Canada and Japan. Ceftaroline, acquired through Forest's acquisition of Cerexa in 2007, is Forest's next-generation cephalosporin for treating cSSSIs and community-acquired bacterial pneumonia (CABP). The drug has demonstrated bactericidal activity against a broad range of pathogens, including MRSA and multi-drug resistant Streptococcus pneumonia (MDRSP). Forest expects to file an NDA with the US FDA during 1Q10.
PPD & Janssen	Broad-spectrum fluoroquinolone antibiotic. November 2009—PPD and Janssen Pharmaceutica partner to develop and commercialize antibiotic. PPD will move the compound through Phase II clinical testing. Janssen will then have option to continue development and marketing. Compound demonstrates activity against gram positive and gram negative bacteria and MRSA, and is being developed as both oral and IV therapy for skin and respiratory infections.
Novartis	PTZ-601, a novel broad-spectrum carbapenem-class antibiotic for potentially fatal drug-resistant infections. June 2008—Novartis acquires Protez Pharmaceuticals, gaining the rights to PZ-601 (now called PTZ-601.) Currently in Phase II development against potentially fatal drug-resistant infections, including MRSA and beta-lactamase enterobacteriaceae (ESBL) strains.
Novartis & Paratek Pharmaceuticals	PTK 0796, a first-in-class aminomethylcycline (AMC) October 2009—Paratek and Novartis announced collaboration to develop and commercialize PTK 0796, currently in Phase 3 clinical trials. PTK 0796 is a once-daily, oral and IV broad spectrum antibiotic for single-agent treatment of serious infections such as cSSSI and moderate to severe community acquired bacterial pneumonia with activity against MRSA, multi-drug resistant *Streptococcus pneumoniae* (MDRSP) and vancomycin-resistant enterococci (VRE).
Novexel	SANXL103 - oral antibiotic made up of two streptogramin antibiotics, linopristin and flopristin, which acts by inhibiting bacterial ribosomes. Unaffected by both beta-lactam and macrolide resistance mechanisms Currently in Phase II trials for cSSSI indication Novexel to be acquired by AstraZeneca. Deal expected to be completed in first quarter of 2010 for a cash consideration of $505m. Subsequent to the deal, AstraZeneca and its American partner, Forest Laboratories, entered negotiations culminating in an agreement in which Forest announced it would pay half of the Novexel acquisition cost and co-develop 2 anti-infectives.

Company	Product/Technology
Rib-X Pharmaceuticals, Inc.	Delafloxacin (RX-3341) – Oral and IV formulations of a broad spectrum next generation fluoroquinolone. Radezolid (RX-1741) - novel oral and IV broad spectrum oxazolidinone targeting gram-positive organisms. IV delafloxacin - demonstrated efficacy in a recent Phase 2 clinical trial in complicated skin and skin structure infections (cSSSI) when compared to tigecycline. Radezolid successfully completed two Phase 2 clinical trials: one for community acquired pneumonia and the second for uncomplicated skin and skin structure infections (uSSSI). A co-founder of the company, Thomas Steitz, and a member of the company's scientific advisory board, Dr V Ramakrishnan, shared the Nobel Prize in Chemistry for their work in X-ray crystallography of the ribosome. This expertise underpins the overall thrust of the R&D effort at Rib-X where structure-based drug design utilizing data from studies investigating binding of small molecules to the bacterial ribosome is used to identify promising antibacterial drug candidates.
Sanofi Pasteur, with Syntiron	*Staphylococcus sp*. vaccine to prevent *S. aureus* infections, including MRSA. In pre-clinical stage. December 2009—Sanofi Pasteur obtained exclusive rights from Syntiron to develop and commercialize this vaccine.
The Medicines Company	Oritavancin - a semi•synthetic lipoglycopeptide IV antibiotic currently awaiting EU regulatory approval Program to develop an oral version of oritavancin for the possible treatment of *Clostidium difficile*•related infection. Acquired the Canadian company Targanta Therapeutics for $42m in February 2009. Oritavancin was Targanta's principal lead molecule in clinical trials.
Trius Therapeutics	Torezolid phosphate (second generation oxazolidinone) Trius plans to develop Torezolid to treat multiple clinical indications, including acute bacterial skin and skin structure infections, or ABSSI (a new classification for cSSSI), and other important indications involving infections of the lung, blood and bone, such as community acquired bacterial pneumonia (CABP), hospital acquired pneumonia (HAP), ventilator acquired pneumonia (VAP), bacteremia and osteomyelitis. The company plans to conduct two Phase 3 clinical trials for the treatment of ABSSI. In its first Phase 3 clinical trial, Trius plans to test the oral dosage form of torezolid phosphate. In the second Phase 3 clinical trial, the company plans to start patients on IV therapy, then to transition them to oral therapy. Both trials will be randomized, double-blind studies and will use linezolid as the comparator.

Source: Veracity Health analysis

CrystalGenomics specialises in structural chemoproteomics, which scrutinize the three-dimensional structural mechanisms behind the binding of target proteins and chemicals. Its technology platform is designed to make it easier to convert genomic and proteomic discoveries into drug candidates. The company has already developed a pipeline of preclinical anti-infectives, including novel antibiotics for MRSA.

Companies constantly aware of need to test drug interaction before opening a dedicated factory

Some of the companies with products in the pipeline have received strong backing from mostly private and VC investors.

Novexel, before it was purchased by AstraZeneca, had managed to raise up to €70m in series financing. Cempra Pharmaceuticals, in spite of difficult trading conditions, raised $46m in a Series C financing in May 2009. Trius Therapeutics raised $50 million in venture capital in its first two years from Sofinnova, Kleiner Perkins Caufield & Byers, FinTech Global Capital, InterWest Partners, Prism Venture Works and Versant Ventures.

Pricing could become an Issue

These and the other companies in Table 4 are striving to develop drug candidates which demonstrate potency greater than that of Zyvox, the market leader. What these companies must also do to satisfy governments laboring to contain healthcare costs is to offer up a strong pharmacoeconomic argument to support prescription. Companies will ultimately need to address costs of drug manufacture in order to compete favourably on price. Improved dosing regimens (1 a day tablet as opposed to 2 a day) versus Zyvox (which can cost up to $100 a day, or $1400 for a 14 day antibiotic treatment course) will address not only cost but also compliance issues, and may well afford a better chance of obtaining reimbursement.

Likely there will not be a one-size-fits-all solution to the MRSA problem; instead, treatments will target specific subgroups of patients. For example, should a vaccine against MRSA be successfully developed, it would most likely be used only for those patients with particularly weak immune systems, such as patients undergoing chemotherapy or dialysis. Likewise, patients may have to be given first one new antibiotic, and then be switched to another, in order to effectively treat an infection.

Regardless of the challenges, winning even a modest percentage of this market would be lucrative. Drug resistant ‘superbugs’ are here to stay, and the prevention and treatment of related infections will continue to provide interesting opportunities for astute companies. We will continue to monitor this space and report on developments in future issues of *Synopsis*.

Regenerative Medicine – The Market Impact Of Advances In Stem Cell Technologies

Pfizer provides $100m to stem cell researchers - funds split between UK and USA. laboratories

It makes for good print copy and a great news story sometimes tagged on the end of a nightly news programme – a new "cure" is found for a particular disease. The news fans out spreading hope and with it raised expectations. Timing and space issues do not allow reporters to investigate nor emphasise effectively the true complexities of commercialising promising drug candidates and device technologies. Similarly we rarely hear about the failures of a particular type of therapy – the other side of the coin as it were. This scenario certainly applies to stem cell technology and its place in regenerative medicine. Basic and translational research on stem cell biology has progressed rapidly over the last few years and is a burgeoning field. So much so that a lot of hope is invested in the potential clinical utility of stem cells across a range of illnesses and conditions. Not only hope is being invested in this area however. The large pharma companies have begun to take note and investment is being seen in an attempt to harness the potential in regenerative medicine. For example, in November 2008, Pfizer decided to invest $100m in stem cell research, creating facilities in the US and UK, including hiring 70 scientists to staff the labs.

There is no doubting the fascinating potential for stem cell therapies. Within this article we take the opportunity to highlight the activities of some of the companies that are actively seeking to commercialize stem cell therapies. This is the real thrust of the article. In order to try and provide a balanced view of the potential in the market we will briefly outline some of the challenges we understand there to be with respect to achieving commercialization. An article of this size cannot do true justice nor add sufficient detail to the debate surrounding the use of stem cells in the clinical setting, so we strive directly to inform the reader on commercial activity and, where possible, comment on where we envisage the greatest potential to lie. The lack of primary data dictates that we do not provide a forecast of the market size of either the therapeutic banking nor the cellular therapeutics segments of the stem cell technologies market. Suffice it to say that the fascination with the development of this market ensures that we intend to provide forecasts for these sectors and a more complete analysis in future articles which we will post in Synopsis or on our website www.veracityhealth.com

A quick primer

Characteristics of Embryonic Stem Cells

One of the characteristics of an embryonic stem cell is that it can translate or it can be differentiated into all the various cell types in the human body.

The first few of the early embryonic cells are *totipotent*, meaning that they are each capable of giving rise to an entire organism, including all the cell types that make up the embryo and the body, and all the cell types that make up the extra-embryonic supporting tissues, such as the placenta.

About five to seven days after conception, a zygote will have divided into about one hundred to one hundred and fifty cells. These take the form of a hollow ball called a *blastocyst*, with a mass of undifferentiated cells inside it. These undifferentiated cells are used to generate *embryonic stem cell lines.*

These embryonic stem cells are no longer totipotent, but they are still *pluripotent*, that is, they are capable of differentiating into all the types of cells that

comprise a human being. They cannot form extra-embryonic tissues (such as the placenta), and thus cannot give rise to a foetus.

After the embryonic stem cells have differentiated into the many types of cells that make up a foetus, a child, or an adult, most lose their ability to differentiate further. However, a small number, the *adult stem cells,* retain some ability to differentiate. These *multipotent* cells replenish and repair many of the cells of the body.

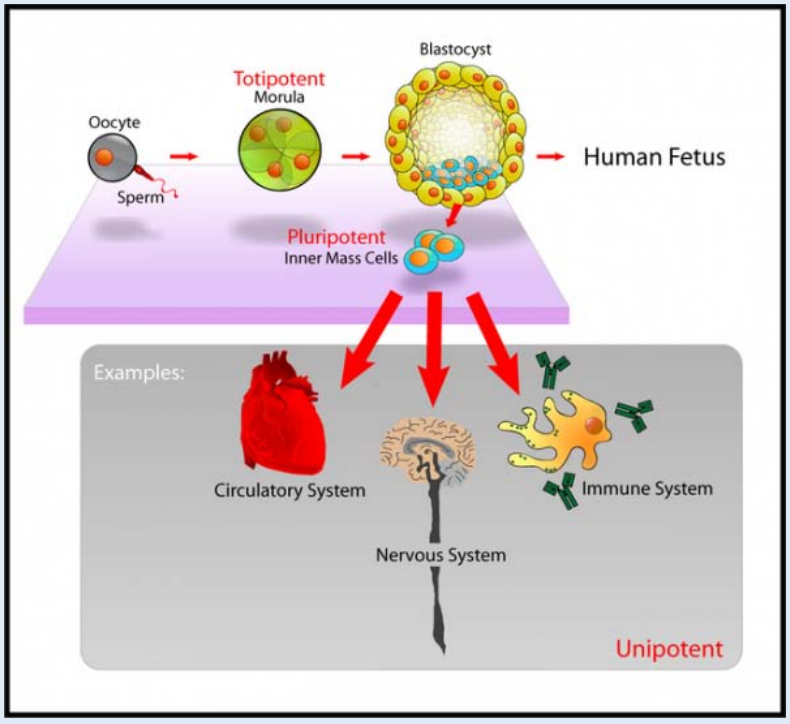
Adult stem cells are difficult to isolate, multiply, and maintain in culture. Embryonic stem cells on the other hand are more easily isolated, multiplied, and maintained in culture.

At least six embryonic sources have been used to establish human pluripotent stem cell lines.

- Traditional human embryonic stem cell (hESC) lines generate from a blastocyst-stage embryo
- hESC lines from human primordial germ cells (destined to become either
- oocytes or sperm cells)
- hESC lines from dead embryos
- hESC lines from genetically abnormal embryos
- hESC lines from single cell embryo biopsy
- hESC lines created via parthenogenesis

All approaches involve isolation of viable cells during an early phase of development, followed by growth of these cells in appropriate culture medium. The pluripotency and rapid proliferation make human stem cells attractive sources for cell therapy.

Figure 1 - Oocyte to Tissue, stages of stem cell development



However, there is a large enough lobby of those opposed to the use of embryonic stem cells derived from human sources in basic research that the opposition on ethical grounds to use such cells in the clinic is seemingly insurmountable. These concerns have led stem cell researchers across the globe to implement basic research programmes aimed at generating stem cells from sources other than embryos.

Nuclear reprogramming is one method of note and developments have advanced considerably since the middle of this decade within this discipline.

Nuclear Reprogramming – a major step forward

Mid 1950s

In the 1950s the British embryologist Dr John Gurdon started his pioneering work in cell biology. Gurdon's early work showed that nuclear transplantation experiments in the frog Xenopus laevis differ entiated cells could be reprogrammed in the egg cytoplasm (nuclear programming). The first step of nuclear reprogramming refers to the erasure of the donor cell's epigenetic pattern following nuclear transfer and the re-establishment of embryonic epigenetic characteristics and gene expression in a cloned embryo. The second step of nuclear repro gramming refers to re-differentiation of cloned embryos from a totipo tent status to a differentiated status for tissue/organ formation during post-implantation development. Genetic information is not lost as the body's different cell types specialise into a range of cells; rather, it is retained in the nuclear reprogramming process.

1977

Ian Wilmut's team at the Roslin Institute, Edinburgh clone Dolly the sheep. Dolly was the first viable offspring ever derived from adult mammalian cells. To achieve their aims, researchers demonstrated that the procedure used was deceptively simple – they removed an unferti lized oocyte (egg cell) from an adult ewe and replaced its nucleus with the nucleus of an adult sheep mammary gland cell. This egg was then implanted in another ewe, and Dolly was the result.

2006/2007

Inducing pluripotency - Pluripotency can be artificially restored to human somatic cells by viral transduction of genes coding for stem cell factors. This process only requires integration of the transcription factors Sox2 and Oct3/4 but the frequency of reprogramming is significantly increased by co-infection with virus coding for KLF4 and c-MYC.

Shinya Yamanaka's group at the Institute for Frontier Medical Sciences, Kyoto in Japan demonstrated the nuclear reprogramming of fully differentiated mouse skin cells into stem cells that can specialize into many fetal and adult types of cells. Yamanaka's team created the first generation of induced pluripotent stem cells (known as iPS cells) by adding four genes normally expressed only in embryos–Oct4, Sox2, c-Myc, and Klf4–to adult skin cells. They also added a drug-resistance gene and put it under the control of a gene, Fbx15, that is typically expressed in embryonic stem cells. The efficiency of the system was low – only about 0.1% of the total cells - the drug-resistant cells– had many characteristics of true embryonic stem cells, but the reprogramming was incomplete. Notably, when iPS cells were added to mouse embryos, no live pups were born (embryonic stem cells added to early-stage

embryos normally contribute to all tissues in live mice).

The Yamanaka group also established iPS cells from adult human dermal fibroblasts by introducing the same four factors. iPS cells are similar to embryonic stem (ES) cells in morphology, proliferation and teratoma formation.
Reactivation of the c-Myc retrovirus in these experiments resulted in an increased tumorigenicity in the chimeras and progeny mice, thus raising considerable fears about the application of the technology for clinical purposes.

2008

Yamanaka's group developed a modified protocol without using the Myc retrovirus. Elimination of c-Myc drastically reduced tumorigenesis, as measured by cancer-related deaths of chimeric mice derived from iPS cells. Using this technique the generation of iPS cells from adult mouse liver and stomach cells was also possible.

Furthermore, Yamanaka was able to generate human iPS cells from adult dermal fibroblasts without c-Myc.

Yamanaka group succeeds in generation of mouse iPS cells without transgene integration into genome by using plasmid DNA.

Improving iPS Cells - Konrad Hochedlinger and his team at Harvard Stem Cell Institute significantly improved the process of generating iPS cells with one simple change to the Yamanaka procedure; his group put the drug-resistance gene under the control of the genes Nanog and Oct4. In gene expression and gene modification studies, the resulting iPS cells showed complete reprogramming, and they were also able to contribute to live mouse births.

While iPS cells will currently be of assistance to disease modelling and drug screening, random integration of genes into skin cells is still seen as capable of presenting an oncogenic risk. Hence this approach constitutes a significant obstacle to using iPS cells therapeutically. The major problem is that while the proof of principle has been demonstrated, the molecular mechanisms by which the programming of pluripotency occurs is little understood. Coupled to this, the low efficiency of the techniques in terms of the number of cells programmed means there is insufficient information, to date, on which genes and which proteins and the concentrations of them which prove critical to ensuring pluripotency.

If cell-based therapy is to reach its full potential, understanding of the cellular capacity for reprogramming is imperative. So too is the need for continued comparison between methods of induction which should allow identification of the "factors" that induce programming.

Current research efforts are seeking not only these answers but also looking at how to remove the need for gene/plasmid vectors for relevant induction factors. In a burgeoning field strategies are also evolving which will lead to generation of genetically unmodified iPS cells or those which are reprogramming factor-free.

The desired outcome is to realize the potential to make reprogrammed iPS cells a source of patient-specific cells for use in medicine, enabling the body to regenerate, repair, replace, and restore diseased or damaged cells, tissues, and organs.

iPS research dictates shift in the market business models

As advances have been seen in generating induced pluripotent cells there is a feeling that the field of regenerative medicine has a clear opportunity to move from embryonic stem cells to iPS cells. This would remove the negative sentiment associated with the ethical fears and controversies and providing a positive push to the market/commercial opportunity.

The potential afforded by advances in iPS technology also supports the assumption that future cell-based therapies will surely benefit from isogenic transplantation (i.e. cells from one patient, reprogrammed and differentiated for transplantation to that patient).

The focus should shift from allogeneic products/treatments to autologous treatments which will be safer and generally more acceptable to patients and society as a whole.

Obama's stem cell stance – Yes We Can

On March 9 2009 President Barack Obama overturned the previous Bush administration's eight-year-old restrictions on federal funding of research involving human embryonic stem cells. In doing so, President Obama paved the way for the National Institutes of Health to introduce new guidelines in the funding of embryonic and non-embryonic stem cell research which allowed US research scientists to use or conduct research on any of the hundreds of stem cell lines which have been cultivated and studied by other groups worldwide. Prior to President Obama's initiative American researchers were restricted to obtaining federal funding relating to work planned on the utilisation of the 21 lines of embryonic stem cells derived before August 9, 2001. With the entry of the US into the "mainstream" of basic stem cell research it is anticipated that the potential for innovation and commercialisation of therapies will be advanced. Time will tell whether the abolition of the ban on US federally funded stem cell research can truly deliver hope rather than confirm hype associated with the view that such research will enhance applications within regenerative medicine.

Analysing comments released by stem cell-focused companies it appears they believe that while funds available to biotechnology remain elusive there seems to be some relaxing of the purse strings due to the more favorable political support of the Obama Administration toward stem cell technology.

Again, scientists and policy makers should be under no illusions that much remains to be learned about the mechanisms by which stem cells repair and regenerate human tissue, the optimal cell types and modes of their delivery, and the safety issues that will accompany their use. As these issues become clearer so the regulatory paths will become smoother, commercialization of the much anticipated cellular therapies occurs and they will enter the clinic.

Over the last few years, international groups have begun demonstrating the potential of stem cells in a number of therapeutic areas. We will review some of these possible applications in this article.

CELL THERAPY IN OPHTHALMOLOGY

Stem cells – targeting corneal blindness

For 15 years Russell Turnbull has been partially blind in one eye after ammonia was deliberately squirted into his eye. The consequences of this mindless attack on Mr Turnbull from Consett, County Durham in the North East of England meant he had to endure continued psychological and physical torment and received constant palliative treatment for a condition called Limbal Stem Cell Deficiency (LSCD). There seemed no end to the turmoil in his life. However, a stem cell treatment developed by a team of scientists and clinicians at NESCI, the North East England Stem Cell Institute (a collaboration between Durham and Newcastle Universities, the Newcastle Hospitals NHS Foundation Trust and other academic and commercial partners), has provided a positive benefit for Mr Turnbull and seven other LSCD patients. This particular treatment involved taking a small amount of stem cells from Mr Turnbull's good eye, cultivating them in a laboratory and then implanting them into his damaged cornea. As a result of the treatment Russell Turnbull stated that the sight through his damaged eye became almost as good as it was prior to the accident and that the treatment had transformed his life. Encouraged by these results there are plans for the NESCI treatment to be made available in other clinics. This is one recent example of the possibilities that lie in stem cell therapies for ophthalmic disorders, especially those involving some degree of corneal damage.

Disease or injury to the cornea can make it go cloudy, leading to impaired vision. The lack of a sufficient supply of donor corneas means that treatment options are limited and this fact drives research into furthering an understanding of the level of potential surrounding the use of stem cells for treatment of corneal damage.

Diseases of the eye affect more than 30m people worldwide and treatments represent a market in excess of $20bn a year

Encouraging news has recently come from a team of researchers located at the University of Cincinnati who implanted human umbilical cord mesenchymal stem cells (UMSCs) which have the ability to become any of a wide range of adult cell types, into mice corneas. The UMSCs survived in mouse corneas for three months with minimal signs of rejection. The findings from the study revealed that the UMSCs appeared to take on the properties of standard corneal cells called keratocytes and that the thickness and transparency of the animals' corneas improved significantly (it should be noted that full transparency was not restored; Winston Kao et al, research presented at the American Society for Cell Biology (ASCB) 49th Annual Meeting, Dec. 5-9, 2009 in San Diego). This and other similar studies suggest that stem cells offer the potential to build new tissue-engineered corneal constructs which will lead to cures for both corneal blindness and visual impairment resulting from scarring following infection and trauma.

Cell therapies chase $4bn Wet AMD application in ophthalmic market opportunity

Globally, age related macular degeneration represents a significant market opportunity due to the size of the patient population and the lack of treatment alternatives

A University of Washington study on Blindness and Blinding Disease in the US (2004) noted that 13,000,000 Americans have signs of wet age-related macular degeneration (AMD), of which over 10,000,000 suffer visual loss and over 200,000 are legally blind from the disease. The occurrence of AMD increases with age: the study concluded that approximately 6,300,000 people are projected to develop AMD in 2030 in the USA alone, compared to 1,700,000 in 1995.

A small number of companies operating in the stem cell space are looking to exploit the significant commercial opportunities that exist for suitable treatments for AMD and retinitis pigmentosa (RP) and some are planning to investigate using stem-cell based treatments for expanded ophthalmic applications. In the short to medium term we expect to see key activity in programmes aimed at providing stem cells to benefit patients suffering from retinal degeneration caused by AMD and RP. Both diseases are characterised by the death of critical photoreceptor cells called rods and cones. Photoreceptor death is due to an abnormality and/or disruption or death of supportive cells called retinal pigment epithelial (RPE) cells.

Our summary of some of the key players in this space is provided in Table 7.

Table 7 - Cellular Therapies under development for ophthalmologic applications

Targeted Opportunity
Current global market for drug treatments for Wet AMD is estimated to reach $4 billion by the end of 2010 There are 3 therapeutics and 2 treatment regimens on the market for treatment of Wet AMD. None of these restore lost vision, they only prevent additional loss of vision • Visudyne - Novartis • Lucentis – Genentech/Roche. For all of 2008, Lucentis sales increased 7%, totaling $875 million vs $815 million for 2007 • Macugen – Pfizer • Laser Treatment • Photodynamic Therapy • No therapy is currently available for Dry AMD
Company + Products/Technology
Advanced Cell Technology **Product** Retinal Pigment Epithelium (“RPE”) Program **Applications** Advanced Cell Technology focuses on human embryonic and adult stem cell technology, and has been granted FDA approval to begin Phase 2 clinical trials for adult stem cell technologies, which are focused on cardiovascular disease and transplants. ACT has prepared its first IND aimed at AMD. Based on its preclinical studies to date, ACT filed its initial IND application in November 2009 utilizing their Retinal Pigment Epithelium (“RPE”) Program for the treatment of macular degeneration. The treatment uses stem cells to re-create retinal pigment epithelium cells that support the photoreceptors needed for vision. RPE are often the first cells to die off in AMD, resulting in loss of vision.
University College London + Pfizer **Product** - **Applications** British scientists have developed the world's first stem cell therapy for age-related macular degeneration (AMD). Under the new treatment, embryonic stem cells are transformed into replicas of the missing cells. They are then placed on an artificial membrane which is inserted in the back of the retina. Surgeons predict it will become a routine, one-hour procedure that will be generally available in six or seven years' time. The treatment involves replacing a layer of degenerated retinal cells with new ones created from embryonic stem cells. It was pioneered by scientists and surgeons from the Institute of Ophthalmology at University College London and Moorfields eye hospital. In April 2009 Pfizer announced its financial backing to assist commercialisation and plans to manufacture the membranes essential for the treatment. In November 2008, Pfizer invested $100m in stem cell research, creating facilities in the US and UK, including hiring 70 scientists to staff the labs.

Company + Products/Technology
StemCells Inc. **Product** Lead product candidate, HuCNS-SC® cells **Applications** HuCNS-SC® cells are highly purified human neural stem cells which can be expanded and banked until they are delivered as patient doses. Preclinical data - studies conducted with the Casey Eye Institute show that, when transplanted into the eye of the RCS (Royal College of Surgeons) rat (a well-established animal model of retinal degeneration), human neural stem cells protect the retina from progressive degeneration and preserve visual function long term as measured by two separate visual tests. The company states that the transplanted cells also exhibited robust, long-term protection of both rod and cone photoreceptors.
EyeCyte **Products** Preparing an IND **Applications** Focused on the use of a patients' blood or bone marrow-derived progenitor cells for the treatment of retinal disease. EyeCyte will employ the properties of these progenitor cells to treat Diabetic Retinopathy as its initial clinical target. Additional vascular and degenerative diseases of the eye will be pursued subsequently, including glaucoma and AMD.

Source: Veracity Health analysis

CELL THERAPY IN NEUROLOGICAL DISORDERS

Targeting Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks the central nervous system. In its early stages, the disease is characterized by intermittent neurological symptoms, called relapsing-remitting MS. During this time, the person will either fully or partially recover from the symptoms experienced during the attacks. Common symptoms are visual problems, fatigue, sensory changes, weakness or paralysis of limbs, tremors, lack of coordination, poor balance, bladder or bowel changes and psychological changes. Within 10 to 15 years after onset of the disease, most patients with this relapsing-remitting MS progress to a later stage called secondary progressive multiple sclerosis. In this stage, they experience a steady worsening of irreversible neurological damage.

Stem cell transplant reverses early-stage multiple sclerosis

In early 2009, Richard Burt and colleagues from Northwestern University's Feinberg School of Medicine reported the results of a small Phase I/II clinical trial investigating the effects of stem cell transplants in 21 patients aged 20 to 53 who had had relapsing-remitting multiple sclerosis. The disease had not responded to at least six months of treatment with interferon beta. The patients had also had MS for an average of five years.

The Feinberg School of Medicine team treated the MS patients with chemotherapy to destroy their immune system. They then injected the patients with their own immune stem cells, obtained from the patients' blood before the chemotherapy, to create a new immune system. The rationale behind this approach was to make the procedure much safer and less toxic than traditional chemotherapy for cancer. After the transplantation, the patient's new lymphocytes or immune cells are self-tolerant and do not attack the immune system.

The procedure, called autologous non-myeloablative haematopoietic stem-cell transplantation, appears to have reversed the neurological dysfunction of early-stage multiple sclerosis in the MS patients studied. Post-treatment the MS patients experienced improvements in areas in which they had been previously affected, including walking, ataxia, limb strength, vision and incontinence. Patients who underwent the stem cell treatment continued to improve for up to 24 months after the transplantation procedure and then stabilized.

After an average follow-up of three years post-transplantation, 17 patients (81 percent) improved by at least one point on a disability scale. The disease also stabilized in all patients. Patients with late-stage MS do not benefit from the procedure.

Other targets for cellular therapy in neurological disorders, where corporate activity has been noted, are in potential treatments for amyotrophic lateral sclerosis, (ALS), traumatic brain injury (TBI), stroke and Parkinson's disease (PD).

Traumatic Brain Injury - Stats

1.4 million people sustain a TBI each year in the United States. Of these,

- 50,000 die;
- 235,000 are hospitalized; and
- 1.1 million are treated and released from an emergency department.

The number of people with TBI who are not seen in an emergency department or who receive no care is unknown.
Direct medical costs and indirect costs such as lost productivity of TBI totaled an estimated $60 billion in the United States in 2000

Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.

Http://www.cdc.gov/NCIPC/tbi/FactSheets/Facts_About_TBI.pdf

Data collated from 20 European countries showed that in Europe there was an aggregate hospitalized plus fatal TBI incidence rate of about 235 per 100,000 population. Prevalence rate data were not reported from any European country. An average mortality rate of about 15 per 100,000 and case fatality rate of about 11 per 100 were derived from country data.

Acta Neurochir (Wien). 2006 Mar;148(3):255-68; discussion 268.

Parkinson's Disease - Statistics

According to available statistics, 1.2 million people in Europe have Parkinson's: approximately 260,000 in Germany; 200,000 in Italy; 150,000 in Spain; 120,000 in UK and 117,000 in France.
In the USA 1 in 272 people have Parkinson's disease, equating to just in excess of 1 million people. It is estimated that 60,000 new PD cases are diagnosed each year in the USA

Amyotrophic Lateral Sclerosis - Statistics

The NIH in the USA estimates that 20,000 U.S. Americans have ALS and 5,000 are diagnosed annually. The ALS Association estimates as many as 30,000 Americans have ALS, at an incidence of approximately 2 per 100,000, with 5,600 new diagnoses annually.
The International Alliance for ALS/MND reports that there are nearly 120,000 cases diagnosed worldwide each year or 328 new cases every day.
Globally the incidence of ALS is 2 per 100,000 of total population, while prevalence is 6 per 100,000 of total population. Research has found that the incidence is higher in people aged over 50 years. Only 10% of cases are familial (inherited) with the remaining 90% sporadic.

The company Brainstem Cell Therapeutics reports there are 100,000 people with ALS in the western world alone at a cost of $1.25bn in the U.S. and $3bn for the western world.
The average life expectancy for ALS is two to five years after diagnosis, although 10% survive 10+ years and 5% will survive 20+ years.

New drug treatment hope for ALS?

The drug IPLEX™ from Insmed was approved in the USA in December 2005 for the treatment of children with growth failure due to severe primary insulin growth factor-I deficiency. IPLEX is a complex of recombinant human insulin-like growth factor-I (rhIGF-I) and its predominant binding protein IGFBP-3 (rhIGFBP-3). Currently IPLEX is being investigated in Myotonic Muscular Dystrophy (MMD) and ALS.

It appears that several European and Australian patients are now securing IPLEX through IDIS Ltd. of Weybridge, UK, the distributor of the drug for countries other than the US and Italy. Some US patients are presently seeking IPLEX from IDIS through shipment to others outside of the US and may then be trans-shipping to the US. The IDIS current estimated quotation is $374 US per vial and patients must use 2-4 vials daily (weight-dependent) for a monthly cost of approximately $22,500 to $45,000 US. As an experimental and trans-shipped drug, no insurance coverage is available through this method. What is interesting with respect to IPLEX and its potential use in treatment of ALS is the treatment costs that some patients are willing to bear. The significant cost of the treatment would deter the majority, if not all, insurance companies from providing coverage but those companies developing stem cell therapies could monitor the situation as it relates to IPLEX.

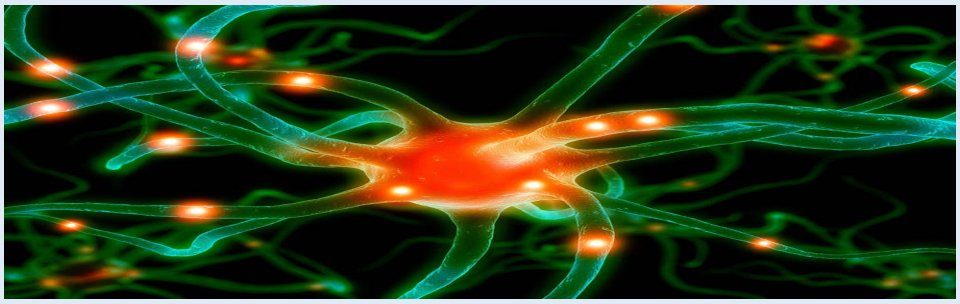


Table 8 - Commercialisation of cell and drug-based treatments for major neurological disorders

Targeted Opportunity
See text
Company + Product/Technology
Geron **Products** Human embryonic stem cell product, GRNOPC1 – Phase I clinical trials commenced in January 2009. FDA has placed trials on hold. January 2010 - announces plans to test GRNOPC1 in Alzheimer's Disease models at the Institute for Brain Aging and Dementia at the University of California, Irvine **Applications** Acute spinal cord injuries and Alzheimer's Disease.

Targeted Opportunity

See text

Company + Product/Technology

NeuroGeneration

Products
Authorised to conduct a Phase II prospective trial designed to assess the safety and efficacy of autologous transplantation of human neural stem cell-derived dopaminergic cells into the affected striatal structures of 15 patients suffering from Parkinson's Disease.
Applications
Parkinson's Disease.
Following an initial needle biopsy-harvesting of neural stem cells and a 6 to 9 months expansion process, cells are characterized and differentiated prior to unilateral injection in the putamen.

Neuralstem Inc.

Products
Amyotrophic Lateral Sclerosis – Filed IND
Traumatic Spinal Cord Injury – Preclinical
Ischemic Spastic Paraplegia – Preclinical
Huntington's Disease – Preclinical
Applications
Neural stem cells for use in ALS, traumatic spinal cord injury, paraplegia, Huntington's disease.
The company's principal product candidate is its spinal cord stem cell line created with its Human Neural Stem Cell technology. The company's technology leverages the capabilities of foetal neural stem cells which it isolates from CNS tissue and then expands each cell in the laboratory up to 60 times ultimately creating a bank of billions of neural stem cells.

Opexa Therapeutics

Products
Adult stem cell technologies
Applications
Develops autologous cell-based therapies for multiple sclerosis, rheumatoid arthritis and diabetes

Q Therapeutics

Products
Q Cells (glial progenitors)
Applications
Q Therapeutics intends to target Q-Cells® for treatment of transverse myelitis, multiple sclerosis (MS), traumatic spinal cord injuries and ALS. With confidence in the capacity of the products to restore neuronal function, future applications could address complications in other diseases, including cerebral palsy, stroke, traumatic brain injury, Parkinson's Disease and Alzheimer's Disease.

Q Therapeutics will also look to provide cells for screening to expedite development of follow-on pharmaceutical products, possibly in-house. Nevertheless the company will seek to offer Q Therapeutics' cells for the screening and development process for promising lead therapeutic candidates showing efficacy in treatment of CNS diseases.

Targeted Opportunity
See text
Company + Product/Technology
Stem Cell Therapeutics **Products** NTx-265 for acute stroke NTx-428 for traumatic brain injury (TBI) NTx-488 for multiple sclerosis **Applications** Drug-based treatments to stimulate stem cells for treatment of a variety of neurological conditions
StemCells Inc. **Products** Proprietary HuCNS-SC®product candidate (purified human neural stem cells) January 2009 - completed Phase I clinical trial of HuCNS-SC cells in Neuronal Ceroid Lipofuscinosis (NCL), also known as Batten's Disease, a brain disorder in children. Data from this study on;y demonstrated the clinical safety and tolerability of the cells. November 2009 – company initiated with the University of California, San Francisco (UCSF) Children's Hospital, a Phase I clinical trial to evaluate the therapeutic potential of StemCells' to treat Pelizaeus-Merzbacher Disease (PMD), a myelination disorder that primarily affects infants and young children. In this trial, patients with a fatal form of PMD will be transplanted with the Company's HuCNS-SC cells to evaluate safety and to explore the ability of the cells to myelinate the patients' nerve axons. **Applications** StemCells Inc., plans to treat neurological, liver and pancreatic conditions with stem cell technology. The conditions they are directly seeking cell therapies for are liver disease, diabetes, Neuronal Ceroid Lipofuscinosis (Batten disease), ALS, disorders of CNS myelination, spinal cord indications, wet AMD and Alzheimer's Disease. StemCells Inc. also sees potential for its technology in the use of HuCNS-SC for high throughput screening of drug targets, toxicology studies in drug development and gene expression profiling.

Source: Veracity Health analysis

First spinal stem cell transplant in 60 year old ALS sufferer

In January 2010 doctors at Emory University in Atlanta, Georgia injected stem cells from 8-week of foetal tissue into the lumbar region of the spinal cord of a 60 year old man who suffers from advanced ALS. This procedure was part of a clinical trial designed to determine the safety of both the transplantation procedure itself and that of the foetal stem cells themselves. At least 12 patients in total are expected to participate in this clinical trial. More precise details of the procedure were given by the company Neuralstem Inc. which provided the stem cells for the study. It was reported that the elderly patient received several injections into the lumbar region of the spinal cord as this is the area that controls leg function. The reason for this strategy lies in the knowledge that most ALS patients first lose muscle function in their legs. The stem cells do not generate motor neurons in the injection site but the aim is to use the stem cells to protect the still-functioning motor neurons in the area.

Transformation of skin cells directly to nerves

Wernig's team "juggle" transcription factor combinations to convert mouse embryonic fibroblasts into functional neurons

Dr Marius Wernig and his group at the Institute for Stem Cell Biology and Regenerative Medicine at Stanford have recently published a paper in Nature in which they describe work confirming their theory that, under the right conditions, a combination of transcription factors could be identified which would allow them to convert mouse embryonic and postnatal fibroblasts into functional neurons *in vitro*. Wernig and his team showed that a combination of only three neural-lineage-specific transcription factors, namely *Ascl1, Brn2 (*also called *Pou3f2*) and *Myt1l* facilitated the conversion of ordinary mouse skin cells to fully functioning induced neuronals which expressed multiple neuron-specific proteins, generated action potentials and formed functional synapses.

Attempts to reproduce the experiment using human cells is proving to be trickier, as might have been anticipated. The induced neuronal cells have been found to have a shorter lifespan than the more primitive stem cells and do not proliferate well. However, this finding adds to the belief that identifying and selecting appropriate combinations of transcription factor cocktails could allow researchers to manipulate nuclear reprogramming and transform skin cells into all cell types. Furthermore Wernig sees potential to bypass transcription factors and search for small molecules or methods to activate the cells. An example of where this might be beneficial, cited by Wernig, is when someone suffers a stroke or other brain lesion, which occasionally leads to an overproliferation of glial cells in the brain. In such circumstances it would be extremely useful clinically to convert those glial cells into neurons.

Direct conversion of fibroblasts to functional neurons by defined factors. Thomas Vierbuchen, Austin Ostermeier, Zhiping P. Pang, Yuko Kokubu, Thomas C. Südhof & Marius Wernig. Nature, advance online publication 27 January 2010

CELL THERAPY IN CARDIOLOGY

The potential of cell transplantation to repair damaged myocardium is attractive and has been widely studied in both experimental and clinical conditions using various cell types. The quest for the ideal cell is still ongoing, as the attributes of the ideal cell and the working mechanism of cell regeneration still remain to be defined.

Current drug treatments for cardiovascular disease provide better outcomes but chronic heart disease still a major killer

According to the American Heart Association (2007 Statistical Update), there were approximately 865,000 cases of acute myocardial infarction (AMI) that occurred in the US in 2004 and approximately 7.9m individuals living in the US that had previously suffered a heart attack. In addition there were more than 452,000 deaths that occurred from various forms of ischaemic heart disease, and 156,000 deaths due directly to myocardial infarction in 2004.

The World Health Report of 2003 published by WHO, contained estimates that of the 16.7m deaths from cardiovascular diseases every year, 7.2m are due to ischaemic heart disease, 5.5m to cerebrovascular disease, and an additional 3.9m to hypertensive and other heart conditions. This particular report also highlighted that a sizeable proportion of the 20m people who survive heart attacks and strokes every year need to receive clinical care which may involve drug or device treatments, all of which ultimately place considerable financial burdens on health-care systems.

Current drug treatment for heart disease include beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors and statins. Surgical treatment op-

tions include the implanting of assistive devices such as pacemakers or defibrillators. In those individuals where the implantation of mechanical ventricular assist devices has been necessary, long term improvement in heart function is observed. The downside to this is the need to all too frequently address complications such as infection and blood clotting.

Ultimately, neither drug nor device treatments restore function to damaged tissue. Thus the unmet need which could be addressed by cell therapies which can repair or regenerate myocardial tissue.

Mesenchymal stem cells show promise in cardiology cell therapy applications

Ischemic heart failure occurs when cardiac tissue is deprived of oxygen. When the ischemic insult is severe enough to cause the loss of critical amounts of cardiac muscle cells (cardiomyocytes), this loss initiates a cascade of detrimental events, including formation of a non-contractile scar, ventricular wall thinning, an overload of blood flow and pressure, ventricular remodeling (the overstretching of viable cardiac cells to sustain cardiac output), heart failure, and eventual death. Restoring damaged heart muscle tissue, through repair or regeneration, therefore represents a fundamental mechanistic strategy to treat heart failure.

A consensus seems to have built up amongst researchers that, among the cells effective in the treatment of heart disease, logistically the easiest to use may be autologous, non-embryonic cells which do not require culturing to obtain a therapeutic dose and can be administered during the same procedure. It is important to consider the need to provide fast acting therapies in such circumstances, which therefore dictates that autologous tissue is preferred over allogeneic tissue. Autologous non-embryonic stem cells may have wider application in catheterisation laboratories. The most extensively studied and characterised cells that have been shown to have some of the above mentioned ideal properties are mesenchymal stem cells (MSCs). MSCs are multipotent, adult stem cells that can expand in cell culture and demonstrate the ability to differentiate into multiple cell phenotypes including vascular endothelial cells and cardiomyocytes as well as bone, cartilage, neuronal and skeletal muscle progenitor cells.

Easily harvested adipose tissue could be alternative to bone marrow as source of multipotent stem cells

Many previous cell therapy trials in patients with AMI have been using mononucleated bone marrow derived cells (BMCs) that consist of a heterogeneous cell population. A small number of these unfractioned BMCs are MSCs. Results of these trials showed an improvement of regional wall motion, global ejection fraction and, in some cases, a reduction of infarct size in the treated group.

Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular progenitor cells, also contains multipotent cell types.

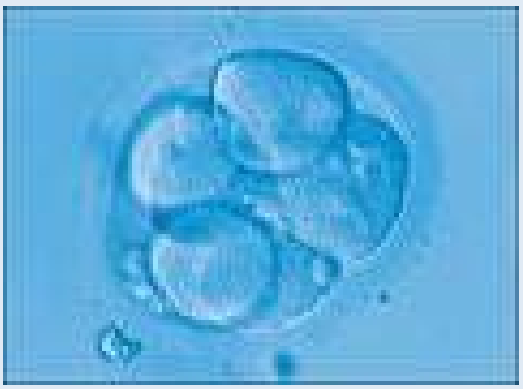
The importance of this development is significant because, in contrast to bone marrow, adipose tissue can be easily and safely harvested in large quantities and with minimal morbidity regardless of the condition of the patient, making it an appealing source for cell therapy. Adipose derived stem cells (ADSCs) are a cell population with properties that are very similar, though not identical, to those of marrow-derived MSCs. These cells have extensive proliferation capacity and are able to differentiate (in cell culture conditions) into osteogenic, chondrogenic, myogenic and neurogenic lineages.

Table 9 - Commercialisation of cell and drug-based treatments for cardiology

Targeted Opportunity See text	
Company	**Product/Technology**
Aastrom Biosciences	**Products** Autologous cell products using the company's Tissue Repair Cell (TRC) technology to harvest bone marrow as source of progenitor and stem cells **Applications** Stem cells for use in cardiac and vascular tissue regeneration
Advanced Cell Technology	**Products** Phase II clinical trials **Applications** Human embryonic and adult stem cells focused on cardiovascular disease and transplants
Athersys	**Products** Collaboration with Angiotech Pharma to develop MultiStem **Applications** Focus on myocardial infarction, peripheral vascular disease and strokes in addition to stem cell transplantation.
Bioheart	**Products** MyoCell – muscle-derived stem cell therapy to restore heart function **Applications** Cardiovascular disease and heart failure
Neostem	**Products** - **Applications** Autologous adult stem cells from bone marrow
Osiris Therapeutics	**Products** Prochymal – Phase III clinical trials for Graft vs Host Disease (GvHD) and Crohn's Disease. Trials suspended Prochymal – heart attack. Uncertainty around this programme. Prochymal – diabetes Chondrogen – Phase I/II for pain/arthritis of the knee **Applications** Adult stem cells from bone marrow for cardiovascular, diabetes, Crohn's Disease and GvHD

Targeted Opportunity	
See text	
Company	**Product/Technology**
ReNeuron Group PLC	**Products** ReN001 – adult stem cells for stroke. In 2009 ReN001 therapy for stroke has received both UK regulatory and conditional ethical approvals for a first-in-man clinical study **Applications** Cellular therapy for stroke patients.
TheraVitae	**Products** VesCell **Applications** The company, based in Thailand, develops stem cell treatments for patients with coronary artery disease and congestive heart failure

Source: Veracity Health analysis



CELL THERAPY IN ORTHOPAEDICS

NuVasive and Orthofix compete against each other with stem cell-based products in the bone graft segment of the orthopaedic market. The value of this market is considered to be in the range of $270 to $300m a year. One of the market leaders Orthofix, envisages potential annual sales of its new Trinity Evolution product at about $100m per year. Trinity Evolution is an allograft of bone containing viable adult stem cells and osteoprogenitor cells within the matrix and a demineralized bone component.

Stem cell therapies could conceivably compete with products in the global $8.1bn spine, $4.85bn trauma and $2.4bn orthobiologics markets segments of the orthopaedics space.

Table 10 - Commercialisation of stem cell therapies for orthopaedic applications

Targeted Opportunity See text	
Company	**Product/Technology**
NuVasive **Products** Osteocel® Plus, an allograft cellular matrix containing viable mesenchymal stem cells. Company claims that it mimics the biologic profile of autograft. Mesenchymal stem cells delivered with , cancellous bone, and demineralized cortical bone to market Osteocel Plus as a unique and complete bone graft substitute. **Applications** To aid fusion in all cervical procedures	
Orthofix **Products** Trinity Trinity® Evolution™ - an allograft of cancellous bone containing viable adult mesenchymal stem cells and osteoprogenitor cells within the matrix and a demineralized bone component. **Applications** Allografts intended for treatment of musculoskeletal defects	

Source: Veracity Health analysis

Cell Therapy for Peripheral Arterial Disease

There are a few programmes aimed at providing stem cell-based therapies to treat peripheral arterial disease.

The most promising pipeline is perhaps the one from Pluristem Therapeutics. This company has some strong IP relating to techniques for harvesting of stem cells.

Table 11 - Commercialisation of stem cell therapies for peripheral arterial disease applications

Company	**Product/Technology**
Athersys Inc **Products** MultiStem **Applications** Peripheral vascular disease	

Source: Veracity Health analysis

Company	Product/Technology
Pluristem Therapeutics **Products** Allogeneic products developed from human placenta. PLX-PAD Also PLX-IBD for inflammatory bowel disease, PLX-MS – multiple sclerosis PLX-BMT - bone marrow transplants PLX-STROKE – ischaemic stroke **Applications** Multiple, including peripheral arterial disease, GI complications, neurodegenerative and cardiovascular	
ReNeuron Group PLC **Products** ReN009 - ReNeuron is developing its ReN009 therapy as a non-patient specific stem cell treatment for late-stage PAD, or critical limb ischaemia, in diabetic patients for whom PAD is a side-effect of their diabetes. **Applications** Cellular therapy for PAD patients.	

Source: Veracity Health analysis

Keeping hope alive - the ideas keep coming

We review here two of a growing number of interesting new developments in the use of stem cells in therapy which captured our attention and which we believe show the possible versatility of the technology and its use in "combination therapies."

Stem Cell therapy + Vaccination - targeting aggressive cancers

In August 2009 a team of Harvard scientists led by Vincent Ho at the Dana-Farber Cancer Institute treated patients suffering from chemotherapy resistant acute myeloid leukemia (AML) with an immune system-stimulating vaccine 30-45 days after a stem cell transplant. The timing of the administration of vaccine was seen to be critical to the success of the combinatorial immunotherapeutic protocol.

In the study, twenty-four AML patients firstly received chemotherapy to reduce the number of diseased hematopoietic cells in their bone marrow. After the course of chemotherapy the patients received an infusion of healthy hematopoietic stem cells from a matched donor. The transplanted cells settled in the patient bone marrow, where they began to regenerate the individual's blood supply, including white blood cells and other agents that constitute the immune system.

Between 30 and 45 days after transplant, 15 of the patients began receiving a cancer vaccine. The administered vaccine was made by surgically removing cancerous or myelodysplastic tissue from patients and genetically altering the diseased cells so they would produce the protein called GM-CSF

(granulocyte/monocyte – colony stimulating factor).

Ten of the participating patients completed the full course of six vaccinations. Of the 10 who received the entire vaccine course, nine remain alive today and are currently in full remission up to four years after treatment. This is a highly encouraging result because it is documented that historically only about 20 percent of similar high-risk AML and myelodysplasia patients who receive a transplant have a life expectancy of perhaps two years.

A further positive outcome of the treatment was the observation that rates of graft versus host disease in the patient cohort were no higher than with stem cell transplants alone. Together, the results from the study suggest that oncologists may be able to safely combine treatments which involve cell therapies to replenish diseased cells with health cells while stimulating the immune systems of patients with relevant vaccines and ultimately strengthen the cancer treatments available for a host of malignancies.

Biologic activity of irradiated, autologous, GM-CSF-secreting leukemia cell vaccines early after allogeneic stem cell transplantation. V Ho, Matthew Vanneman, Tetsuro Sasada, Yoon Joong Kang, Mildred Pasek, Corey Cutler, John Koreth, Edwin Alyea, Stefanie Sarantopoulos, Joseph Antin, Jerome Ritz, Christine Canning, Jeffrey Kutok and Martin Mihm. PNAS, September 15, 2009 vol. 106.

Mesenchymal stem cells and advanced wound care

Jin et al report in Artificial Organs (2008 Dec; 32(12):925-31) the use of bone marrow-derived mesenchymal stem cells seeded onto a collagen-GAG scaffolding matrix to form a dermal patch, which when applied to a deep dermal partial thickness burn (heated brass contact injury at 100°C for 20 seconds) on porcine skin showed significantly better healing, keratinization, wound contraction and increased vascularization over standard treatment protocols. Jin's research suggests that tissue engineered "skin" using bone marrow-derived MSCs can accelerate wound healing in a suitable device matrix and could lead to advances in wound care and graft therapy for burn victims.

Tissue-Engineered Skin Containing Mesenchymal Stem Cells Improves Burn Wounds. Peng Liu, Zhihong Deng, Shufang Han, Tao Liu, Ning Wen, Wei Lu, Xianhui Geng, Sha Huang, and Yan Jin Artif Organs.2008 Dec;32(12):925-31.

Forward investment in stem cell companies will depend on results

In the midst of a severe recession in the West, companies in the pharma and biotech sectors can ill afford negative news regarding drugs or treatments in clinical trials. This fate has befallen companies operating in the stem cell market. In 2009, two high profile companies in the segment, Osiris and Geron, had the misfortune of reporting less than satisfactory trial results. In the case of Osiris it announced that both Phase 3 trials of its product candidate Prochymal for graft versus host disease (GvHD), did not meet their primary endpoints. While subgroup analysis indicated some activity of the stem cell therapy, concerns were raised on the ability of the company to get FDA regulatory approval based on current data. This news came as a reminder to the industry as a whole that systemic stem cell therapy could still be a long way from a clinical reality. The potential problem for Osiris was that Genzyme, its larger biotech partner which paid $130 million upfront for a collaboration might walk away from the deal. These fears arose because a stamp was put on the deal in November 2009 but since then three leading trials of Prochymal have failed: two GvHD trials and a Crohn's disease trial which was

which was abandoned in March 2009. As with many aspects of this business it will be interesting to see what deal activity occurs in the sector in 2010.

Pharma and biotech company interest and importantly further investment in technologies and companies may come in order to take advantage of the use of iPS cells in drug development. Biotechnology and Pharmaceutical companies with their expertise in medicinal chemistry should note the need for small molecule intervention. They should initiate Chemistry R&D Programmes aimed at designing and developing promising drug candidates capable of inducing differentiation of progenitors from definitive ES endoderm. Small molecules are believed to act by affecting key epigenetic modifications and cell signaling pathways.

Stem Cells and Drug Development - improving efficiencies in drug discovery

Scientists at the forefront of research into iPS cells have highlighted the possible importance of the cells in studying the cellular mechanisms behind the onset of a host of diseases. With induced pluripotent cells it is possible to use cells from a person who has one of the hundreds of inherited diseases to study that particular disease. Projects using iPS cells are already being developed to study diseases as varied as motor neuron disease, some psychiatric diseases, and cancer. While small numbers of iPS cells are formed in nuclear reprogramming experiments, iPS cells can form any tissue and multiply many times in culture. It is thought possible to use iPS cells in drug screening and toxicity studies. Some companies with expertise in stem cell technologies are seeking to partner with pharma companies on use of embryonic stem (ES) technologies in drug screening assays.

The company VistaGen for example, utilises human ES cell technology to enable drug screening and toxicity assays to be developed with mature cells expressing the complete set of natural or engineered drug targets. The company states that it “believes that the use of this technology will lead to a higher predictability of a drug's efficacy in clinical trials”. The company offers human ES cell-based screening technology targeting identification of promising small molecules for treatment of a number of mankind’s most critical diseases. VistaGen management feel that analyzing the effects of drugs in cells differentiated from ES cells can provide a more reliable process for developing safe and effective drugs than just relying solely on animal studies. VistaGen states that a “high information content” readout from VistaGen’s ES cell-based drug screening assays provides information not just on drug-to-target binding, but on the broad and complex biological effects of drug candidates. Differentiation of ES cells can be exploited to develop powerful screens for identifying drugs that induce the body's own power of regeneration to repair and activate cells that are needed to treat disorders such as diabetes, cardiovascular and neurodegenerative diseases. Using human ES cells could be considered as an option to address the drug response differences between humans and animals - a key obstacle of conventional drug research and development.

VistaGen also plans to offer its pharma and biotech customers with research tools for neurotransmitter cell signaling and receptor studies using neuronal cell-based assays.

VistaGen hopes to be able to offer clients engineered ES cells to enable high-throughput screening assays of differentiated mature neurons. The mature neurons will then be used to select drug leads for specific neurotransmitters that are important to many CNS disorders.

The company also engineers highly specific, ES cell-based screening assays for drug responses of insulin producing beta-islet cells. These assays enable the search for the biological factors or classical drugs that stimulate the growth and/or prevent the death of beta-islet cells as well as stimulate the production and responses to insulin. VistaGen states that "these proprietary assays will be used by VistaGen and our pharmaceutical partners to develop new drugs to treat Type I and II diabetes and metabolic syndromes. ES and iPS cell technology offers scope for predicting toxicity of drug candidates and reducing dependence on animal models." The animal-based methods used currently by the pharmaceutical industry to predict toxicity are expensive, time-consuming and poorly predictive of human responses. ES and iPS technology could enable researchers to assess how important genetic differences will alter the response to new drugs and thus be useful in assessing pharmacogenomic approaches to therapy.

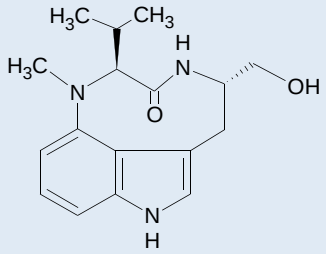
Neuralstem Inc. Is another company seeking to add to its bottom line revenue generation by partnering with pharma and biotech groups in outsourcing their drug screening and drug therapy programmes. With the technology at its disposal Neuralstem Inc. is looking to exploit the benefits in conducting drug screening in neural stem cells, in a similar vein to VistaGen. Neural stem cells are multipotential progenitors of the developing CNS, which differentiate into all three major cell types of the mature CNS--neurons, astrocytes, and oligodendrocytes. The types of neurons arising from an individual neural stem cell depends upon the temporal and spatial cues present in the cell at the time of isolation. Such developmental information is maintained stably throughout long-term passage in culture.

Neuralstem has established a collection of human neural stem cell lines from various areas of developing human CNS. These cells are claimed to provide a renewable source of physiological human neurons and glia. Neuralstem has conducted gene expression profiling and functional assays to demonstrate that these cells contain numerous potential targets, including various voltage-gated ion channels and ligand-gated ion channels in many different subtype compositions. It seems that these stem cells are therefore useful for drug screening aimed at psychiatric diseases. For drug screening aimed at neurodegenerative diseases, it offers several assays suitable as primary or secondary assays. The company also has an internal drug screening project to discover orally active neurogenic drugs that stimulate birth of new functionally active neurons from endogenous neural stem cells in injured adult brain.

Small molecule induction of nuclear reprogramming – novel drug candidates.

There is a need for identification and use of orally active medications which could trigger nuclear reprogramming of endogenous cells. Such therapeutics can act on target cells or their niches *in vivo* to promote cell survival, proliferation, differentiation, reprogramming and homing. There is precedent for this approach and the expansion of the technology would be a significant advance. Being able to reprogram through use of purely chemical or biological therapeutics could provide scope to reduce toxicity and make the process more practical. In 2008, Melton et al (Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2; Nature Biotechnology 26, 1269–1275, 2008 reported the findings from their study on reprogramming of primary human fibroblasts using valproic acid (a histone deacetylase inhibitor). The authors of the study only needed 2 transcription factors, Oct4 and Sox2, to induce nuclear reprogramming in human fibroblasts. They showed that the two factor–induced human iPS cells resembled human ES cells in pluripotency, global gene expression profiles and

epigenetic states. These results support the possibility of reprogramming through the use of new chemical entities which could allay concerns associated with DNA-based approaches such as DNA integration, as well as avoid slow, inefficient and aberrant reprogramming. What this strategy also does is possibly obviate the use of animal products, feeder cell lines and cell extracts.



(-)-Indolactam V

(-)-Indolactam V is an inhibitor of protein kinase C (PKC) isozymes (alpha, beta-I, beta-II, gamma, delta, epsilon, eta, theta). PKC isozymes play a crucial role in cellular signal transduction via the second messenger, 1,2-diacyl-sn-glycerol (DG). Indolactam was identified in a high-content chemical screen as a small molecule inducer of human embryonic stem cell differentiation to functional insulin-secreting beta cells at the definitive endoderm cell stage thereby increasing the number of Pdx1-expressing pancreatic progenitor cells. The Pdx1-expressing cells expressed other pancreatic markers and were shown to contribute to endocrine, exocrine and duct cells, *in vitro* and *in vivo*.

The importance of this is that stepwise differentiation from embryonic stem cells to functional insulin-secreting beta cells may ultimately prove useful for transplantation therapy for diabetics.

Irie, K., Nakagawa, Y., Ohigashi, H. (2004) Indolactam and benzolactam compounds as new medicinal leads with binding selectivity for C1 domains of protein kinase C isozymes. Curr Pharm Des 10: 1371-85.
Chen, S., Borowiak, M., Fox, J.L., Maehr, R., Osafune, K., Davidow, L., Lam, K., Peng, L.F., Schreiber, S.L., Rubin, L.L., Melton, D. (2009) A small molecule that directs differentiation of human ESCs into the pancreatic lineage. Nat Chem Biol 5: 258-65.

It would appear we have only just scratched the surface

Those keenly keeping watch on the scientific and commercial developments in the stem cell therapeutics market receive a vision of great dynamism, endeavour and art in the science especially. The science and the market both are in a good place, a place where positive developments in the next few years could catapult the market to multibillion dollar status. It appears that the research into the potential of stem cell therapies is at a critical juncture. Whether or not market growth is seen very much depends on progress in understanding the cellular mechanisms at play and proving medium to longer term safety of stem cell transplantation. We at Veracity Health have an evolving fascination with the market, in no small way because it requires us to look at a number of different therapeutic areas and markets all at once. For these reasons alone we will endeavour to keep you updated on progress in this sector.

INDUSTRY LEADER INTERVIEW

Dr J Joseph Kim, CEO
Inovio Biomedical

Inovio & DNA Vaccines: Changing the Vaccine Manufacturing Paradigm

In the October issue of *Synopsis*, we asked key opinion leader Dr. Timo Vesikari about the future of egg-based vaccine manufacturing technology. He said that even though egg-based is only used for influenza vaccines, the world needs to break out of that slow technology and make a leap forward in vaccine manufacturing technology.

Inovio Biomedical plans to change this paradigm.

Inovio Biomedical is focused on the design, development, and delivery of a new generation of vaccines, called DNA vaccines, to prevent and treat cancers and infectious diseases. The company's SynCon™ technology enables the design of "universal" vaccines capable of protecting against multiple – including newly emergent, unknown – strains of pathogens such as influenza. Inovio's proprietary electroporation-based DNA vaccine delivery technology has been shown by initial human data to safely and significantly increase gene expression and immune responses. Inovio's clinical programs include HPV/cervical cancer (therapeutic) and HIV vaccines.

Inovio is developing its universal and avian influenza vaccines in collaboration with scientists from the University of Pennsylvania, the National Microbiology Laboratory of the Public Health Agency of Canada, and the NIH's Vaccine Research Center. The company recently welcomed eminent virologist Dr. Stanley Plotkin to its scientific advisory board. Other partners and collaborators include Merck, Tripep, University of Southampton, National Cancer Institute, and HIV Vaccines Trial Network. More information is available at www.inovio.com.

Recent news items about Inovio include:

- November 2009—Inovio announced that its partner, Tripep AB of Sweden, has completed its phase I clinical study establishing the safety and tolerability of its ChronVac-C hepatitis C virus DNA vaccine delivered using Inovio's electroporation technology.
- November 2009—Inovio announced that a combination of its synthetic consensus H1N1, H2N2, H3N2, and H5N1 influenza vaccine candidates achieved protective antibody responses against several different influenza sub-types and strains in ferrets. In addition, ferrets immunized with Inovio's SynCon™ universal flu vaccine combinations were 100% protected against death and sickness in a challenge with the A/H1N1 (2009) swine-origin influenza.
- October 2009—Inovio and the HIV Vaccine Trials Network (HVTN) announced the initiation of a phase I clinical study of Inovio's PENNVAX™-B preventive DNA vaccine delivered using its proprietary electroporation technology. The multi-center study will be conducted at several HVTN clinical sites under a protocol designated HVTN-080.
- August 2009—In *Human Gene Therapy*, the company reported the first human demonstration of significant, persistent antibody response using its electroporation-delivered DNA vaccine.
- July 2009—Inovio reported that its universal dengue DNA vaccine uniquely demonstrates strong immune responses against all four serotypes in preclinical study.

Veracity Health interviewed Dr. J. Joseph Kim on the occasion of his recent trip to Phoenix, Arizona.

Dr. Kim, thank you for agreeing to meet with Veracity Health. Your company, Inovio Biomedical, is working on several projects, including a universal flu vaccine. How far from FDA market approval is that particular product?

Probably, from the pandemic side, in our case it could be less than two years away. During a pandemic, a company only has to successfully complete Phase I safety testing and demonstrate proof of protection in two different animal species. For the traditional approval, all four SynCon™ vaccine components must complete all three phases of clinical testing. If traditional approval were required, a universal flu vaccine would be at least 5-7 years away.

However, the flu vaccine area is in a very fluid situation now because of the pandemic pressure, not just from the health side but also from the government and regulatory angles. The CDC and CHS have been under huge pressure because of the shortage of flu vaccine. The manufacturers promised them, and CDC and CHS in turn promised the US population 150 million doses by the end of October 2009, and the manufacturers delivered less than 25% of it by that time.

There are technologies that make traditional vaccines slightly better, like adjuvants, like GSK is doing outside the US.

In the EU, adjuvants have been used for over ten years, but the US has always said 'no' to combining flu vaccine with adjuvants.

Yes, the US FDA is extremely conservative when it comes to approving a new technology. I think they will eventually come around to the use of adjuvants based on additional safety data. Cervarix (GSK) doesn't use the same adjuvant as is used in the flu vaccine, but they are very close cousins. Recent approval of Cervarix by the FDA demonstrates that they might be warming up (to their thinking) in this area.

There are other pandemic flu vaccines under development which use adjuvants. Are the developers planning to present these to the FDA for consideration?

Yes, and companies such as GSK are leading the way. Actually, the best traditional technology is MedImmune's (AstraZeneca's) FluMist. Using this technology, MedImmune can manufacture 90-100 doses per egg, while the traditional, current swine flu technology can only make 1 dose per egg. FluMist uses a virus engineered for better growth in eggs.

In the long run, there must be a paradigm shift. We're not the first to try to develop a universal flu vaccine—that's been the Holy Grail for flu vaccine companies for years....but it's hard to shift the paradigm when you're making on average $400 million from these cash cow products every year.

Who, or what do you consider represents your greatest competition.... on the flu side?

On the flu side, it's the traditional egg-based technology, because that's tried and true. It's not really competition from the technical or medical side per se, it's the regulatory process and public perception that present the hurdles. And it would take a pandemic to change the paradigm. Without it, it would be a more uphill

battle. In 2008, when we were developing our universal flu DNA vaccine and had the data showing our vaccine's ability to completely protect against the 1918 pandemic flu virus, investors said that the traditional technology was a cash cow and that industry wouldn't go for changing this. Now, everyone can see enough shortcomings of the traditional approach, and we don't need to fight for buy-in to move forward. We are seeking a partnership with one company that would want the whole pie of the next generation of vaccine production, in order to move to that next generation. With this partnership, we can change the paradigm and dominate the future market as we see it developing.

The current pandemic could have been much worse: if the Mexican outbreak had been in July, we'd all have been up the creek, because it takes 6-9 months to develop a flu vaccine. As it was, because it occurred in March, this allowed the CDC to release vaccine strains by early April, only two months behind the normal February release date.

Most government funding is going to the Big Five manufacturers, not so much to companies like Inovio. We have to be more creative in looking for funding. We didn't expect to get this much convincing data when we first set out. We knew it was an ambitious goal: many had tried before to develop a universal flu vaccine. But we knew we had an advantage, and that once we had successfully solved the shortcomings of DNA delivery, and that we were able to use the DNA advantage, which is creating and designing our SynCon™ constructs.

You have, in the past, said that generic companies would have a harder time breaking through into vaccines because of both the drug and the manufacturing facility. Could you elaborate?

Yes, and biosimilars are trying to break into this. The big secret is that biologicals can never be identical. Merck can make ten consecutive product lots in the same facility and they will all be relatively different. So you set the bar where you have some consistency among them, and the manufacturers wink at this, and the FDA winks at this, and as long as they're safe, they're fine.

The Hatch-Waxman law allowed bio-equivalents for chemical drugs. All you had to show was that you were using the same chemicals that act in the same way, in very, very small models, and this is easy to do. But biologicals are all different, if you try to characterize them for long enough.

There has never been a generic vaccine marketed in the US or EU. There have been some made overseas in developing countries like India, Africa, China, but these can never come back into the US or EU because the manufacturers can never prove that these generic vaccines are identical to the originals. On the other hand, you see generic [chemical drug] Zocor made all over the place.

If Inovio were to create a universal flu vaccine, you would not see a challenge from biosimilar companies.

Probably not. We not only control the patent on the design of the vaccine, but also on the delivery methodology: electroporation. They might use another delivery method, but there are only several known ways to deliver DNA: electroporation, lipids, like Vical is doing, and a gene gun. The gene gun was championed by PowderMed, which was purchased by Pfizer for about $400 million three years ago. Since then, we haven't heard much about the gene gun, either because it's

fantastic and they plan to surprise the world, or because it wasn't that successful and it's a small technology that's gotten lost in a big company.

We know, from our own work and that of others, that electroporation has higher utility than the gene gun. The gene gun has limitations on its utility, although its usability is probably similar to that of Inovio's delivery device. You have to coat the DNA with gold particles (and the price of gold has increased four-fold since 2006), and there are limits on how much you can load, and you're shooting the gold particles through the skin into the dermis or muscle.

With regard to cancer vaccines, it is a huge field. On the therapeutic side, Dendreon is the biggest name, and Provenge is likely to be the first product to be approved. But there are huge limits on the usability of that technology. Every patient is a GMP product line, and each site is a production area. The process involves taking blood from the cancer patient and purifying 0.5% of the white blood cells—the antigen-presenting cells. Then you grow these *ex vivo*, load up the antigens as peptides, then put this product back into the patient. The whole process takes two weeks, maybe longer, and is personalized to the patient, so one can only imagine the cost. We could leapfrog this whole process by making a vaccine that can do the production within the patient. This is the potential power of the DNA vaccine.

Do you envision most or all vaccine production eventually going to DNA vaccine technology?

Some economical, very low-cost vaccines may stay where they are. The other question is the pediatric vaccines. The world regulatory agencies have certain safety thresholds for adults, and these are, rightfully so, much stricter and more conservative for babies and children. For these reasons, new vaccine technologies will initially target untreated or undertreated diseases, such as HIV and cancers, until they are proven and fully accepted. The other real opportunities are in the elderly. Most vaccines, especially for flu, do not work well in the elderly. We predict that DNA vaccines could generate better responses in this important population group. Eventually DNA vaccines will be the leading technology for new vaccines.

In the past, the best vaccines were made with live viruses. But there are lots of safety issues with viruses because they can replicate and cause disease. The DNA vaccine technology mimics the live virus vaccines' effectiveness without associated safety concerns: the DNA can't replicate because it can't mutate. So it can't cause disease, and that's the beauty of it.

Our hurdles were to make the DNA vaccine effective—which our studies are proving—and to overcome the delivery problems—which we did with electroporation.

We're continuing to push the advancement of this technology and field. If we're correct, Inovio will own more of this territory, a very hot sector, than Amgen and Genentech did in their monoclonal antibody space. I'm not comparing us to those giants, but we'd have a greater start than they did when they started in that new sector.

I see a similar path going forward. In our case the key was delivery, while for Amgen and Genentech, it was the response in humans. Inovio has the whole package: a fully-integrated platform with optimized content, the SynCon™ vac-

cines, electroporation delivery, formulations and manufacturing. We can pack in more vaccine per volume, and do it better than anyone else in the field. All of these advantages are controlled vertically.

We feel this technology will enable DNA vaccines to become routine, perhaps even the gold standard.

The biggest competitor to DNA vaccine technology is probably some smart post-doc mixing several chemicals with DNA and saying, "Wow, we can mix this and inject it and it gets taken up by your cells even better than electroporation does." The greatest threat therefore is something unknown.

And your greatest hurdle at this time?

Executing our development plans and getting to the clinical results ASAP. We have everything under our control to do this. If the data we expect over the next quarters shows that our technology doesn't work, we'll have only ourselves to blame!

Dr. Kim, thank you for your time!

News-wire

January 27, 2010. Apple's iPad Positioned to Dominate Mobile Healthcare Record Keeping

Steve Jobs unveiled Apple's hotly-anticipated iPad tablet, and the company has been talking to hospitals and physicians about adopting the device for healthcare patient record-keeping. With its impressive array of features, a starting price of $499 (with predictions of the price dropping into the $100-200 range), 10-hour battery life and ease of use, this may be the device that catapults healthcare mobile computing forward. Apple has apparently been letting physicians at Cedars-Sinai test-drive the iPad, with favorable results. But the key question is, will hospital IT departments cozy up to the Apple tablet, when they're accustomed to the Windows operating systems? Also, won't Microsoft follow the Apple tablet with its own version, all nice and compatible with existing hospital systems? Should be interesting to watch.

Big Pharma makes Big Moves into Generics, and in Developing Countries

With a number of blockbusters scheduled to go off-patent within the next five years, Big Pharma companies are scrambling to enrich anemic R&D pipelines. One strategy is to get a piece of the world generics market, a pie that some analysts estimate may reach $93 billion by 2011.

Chris Viehbacher, company shopper extraordinaire and CEO of Sanofi-Aventis, has signed the checks to acquire Zentiva, Kendrick and Medley in 2008 and 2009, as shown in the table below. He is not alone in his shopping spree, though: Pfizer, Novartis and Daiichi Sankyo have all been forming mega-mergers and signing licensing deals as well.

Pfizer has plans to become the number one generics company in Japan. That's a mouthful, given that the company doesn't yet have a foothold in that country. However, apparently Pfizer plans to carve out that foothold by setting up hefty alliances with leading Japanese drugmakers.

However, there is another angle to this story. No longer are the Pharma companies in so-called developing countries staying at home while Big Pharma comes in to dominate markets. These companies are now reaching out and acquiring companies and licensed manufacturing facilities in the US, UK and the EU. For example, Marksans acquired UK-based Relonchem, and with it, a solid track into the UK and EU generics markets. Bangalore-based clinical research organization (CRO) Ecron Acunova, is looking for a mid-sized US CRO, and hopes to sign the deal by late 2010. Ecron already has offices in the US, UK and Russia, as well as an alliance with Tokyo CRO, a Japanese company.

Below are only a few of the mergers, acquisitions and licensing deals which have been closed during the last two years.

Table 12 - M&A Activity in Generics for the period 2008-2009

Company	Year	Action	Investment $US
Daiichi Sankyo	2008	Acquired majority stake in Ranbaxy Laboratories	$5bn
Sanofi-Aventis	2008	Zentiva (Czech Republic)	$2.6bn
Novartis	2009	Acquired specialty generics injectables business of Ebewe Pharma (Austria).	$1.3bn
Pfizer	2009	Signed licensing deals with Indian generics companies Aurobindo Pharma and Claris Lifesciences	Details undisclosed
GlaxoSmithKline	2009	Acquired 19% share in Aspen Pharmacare Holdings (South Africa)	Asset swap arrangement
GlaxoSmithKline	2009	Signed development and marketing deal with India's Dr Reddy for over 100 branded generics	Undisclosed
Sanofi-Aventis	2009	Laboratorios Kendrick (Mexico)	Undisclosed (Kendrick's 2008 sales = $38.3m)
Sanofi-Aventis	2009	Medley (Brazil)	$662m
Marksans Pharmaceutical	2008	UK-based generics company Relonchem	Undisclosed (Relonchem's 2007 sales = $32m)
Hospira	2009	Acquisition of generic injectables pharma business of India-based Orchid Chemicals & Pharmaceuticals	$400m

H1N1 Outbreaks in Long-Term Care Facilities Underscores Importance of Hand Washing

Early data on the H1N1 influenza virus seemed to indicate that adults aged 65 and older were at lower risk of infection, and often had antibodies which offered at least some protection against developing the flu. Therefore this group was placed at a lower priority for vaccination against H1N1. Now, as the pandemic has largely passed and data is coming in, researchers are seeing that elderly populations in long-term care facilities seem to show a higher than expected incidence of H1N1 infection. In the US, where statistics on illness in long-term care facilities are not routinely collected, single incidents of outbreaks in these facilities were reported in New York, Colorado and Maine. Researchers say that these findings again underscore the importance for both healthcare workers and visitors of consistently practicing simple preventive measures such as hand washing.

H1N1 Pandemic: We Were Lucky This Time

Although overall the worldwide reaction to the swine flu pandemic was probably better than expected with regard to rapid development, manufacture and distribution of a vaccine, many researchers say that we were very lucky, because the pandemic could have been much worse. In January 2010 the World Health Organ-

isation estimated that 13,000 people worldwide died due to complications after contracting the H1N1 virus, with most deaths occurring in the Americas. This estimate is on the low side; there are doubtless numerous cases, especially in developing countries, in which deaths were either not recognized as caused by the H1N1 virus, or were simply not recorded as cases.

The mildness of the pandemic was one reason that millions of people adopted a 'wait and see' attitude towards vaccination, despite governments and healthcare professionals urging them to step up for the shot. As a result, a number of countries are now trying to get rid of unused vaccine that they had ordered. France, for example, ordered enough doses to vaccinate every person in the country, but used less than 10% of that supply. The Netherlands, too, used only a fraction of the supply that they had ordered.

Vaccine manufacturers are reluctant to accept return of unused inventory. One CEO advised countries to bear in mind that they clamoured for the vaccine, were given it, were lucky that the pandemic was so mild, and should simply pay for the unused stock. He implied that countries which refuse to pay for unused doses might be put lower on the list, next time there is a pandemic and vaccine is being distributed.

Developments in Diagnostics: Or, You Don't Have to be Big Pharma to Make a Splash in Personalized Medicine

AstraZeneca and Dako Denmark A/S have reported forming an agreement that will further personalized medicine. Under the terms of the agreement Dako will develop diagnostic tests appropriate for pairing with AZ oncology treatments currently in various phases of development. Such tests will help physicians to determine which patients are most likely to respond well to which cancer drugs, thus increasing the probability of a successful outcome for the individual patient, and decreasing the long-term costs associated with fruitless treatments.

It's not only Big Pharma that is capable of working to further the field—and market—of personalized medicine.

Tiny QuantRx Biomedical , with 14 employees, utilizes its patented microarray technology in its key product, a point-of-care (POC) diagnostic reader. The company expects its Q-Reader ™ to be on the market within months. One of the uses is expected to be population-scale typing of the human leukocyte antigen (HLA), which plays an important role in human immune response. An individual's HLA type also signals the ability of that person to respond to a specific vaccine. QuantRx states that its platform technology, with this initial HLA application, could be used in vaccine development and personalized vaccine delivery.

Inverness Medical and Epocal Grow Closer with Distribution Agreement, Buy-Up

Inverness Medical Innovations has announced both a distribution agreement with, and eventual acquisition of, Epocal (Ottawa, Canada). Inverness will distribute Epocal's epoc® hospital POC System for blood gas and electrolyte analysis. Epocal states that the wireless bedside system produces lab-quality results in 30 seconds.

Inverness will be distributing the epoc® System co-exclusively with Epocal worldwide, except in Bhutan, India, Japan, Bangladesh, Nepal and Sri Lanka.

Separate from the distribution agreement, the companies will collaborate to develop additional tests which will expand epoc's menu content. Not surprisingly, it appears that the distribution agreement and close collaboration are but the prelude to an acquisition: Inverness has also inked a deal with Epocal to buy up all of Epocal's issued and outstanding equity securities, a payment that may reach $255 million if certain financial milestones are met.

Abaxis Adds POC CRP Assay to Its Piccolo Xpress™ Analyzer

On January 21, 2010, Abaxis announced that it had received FDA 510k approval of its new C-Reactive Protein (CRP) assay when used with Abaxis' Piccolo Xpress™ POC analyzer. The test, which has been available in the EU and Asia Pacific for several months, will initially be available on Abaxis' MetLyte Plus CRP acute care panel. CRP assays are frequently used in detecting rheumatoid arthritis, but can also be used in the detection of a wide variety of other conditions, including colon cancer, fever due to bacterial infections, atrial fibrillation and osteomyelitis. Abaxis is exploring pairing this CRP assay with other tests in order to arm physicians with an even wider array of POC tests.

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