MEDICAL DEVICE DAILY™

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LIQUID BIOPSY MARKET EXPECTED TO SURGE

Growing evidence supports clinical potential of new cancer tests

1ST OF 2 PARTS

By Amanda Pedersen, Senior Staff Writer

With a market opportunity in the billions (as much as $20 billion by some estimates), diagnostic companies are rushing the liquid biopsy floodgates with new tests designed to make finding and monitoring cancer as easy as a blood draw or urine sample. This week, in a two-part series, *Medical Device Daily* will explore both the business opportunities and the clinical potential of this growing market.

The true clinical impact of this technology remains to be seen and there are some early limitations of these tests that will need to be addressed, but some doctors say liquid biopsies could really transform cancer treatment. To validate the power of

See Liquid Biopsy, page 4

GIVES COMPANY REPOSITIONABLE TAVI

Venus Medtech set to launch cardiac valve product line in China

By Cornelia Zou, Staff Writer

HONG KONG – Aiming to be the first company in China to launch cardiac valve products, China's Venus Medtech (Hang Zhou) Inc. is working to bring advanced European technologies into the country.

German medical device company Transcatheter Technologies GmbH sold its next-generation cardiac valve implantation technology to Venus this

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REGULATORY

Coalition calls on agencies to set aside funds for epidemics

By Mark McCarty, Regulatory Editor

The FDA budget may be stretched thin, but a global health coalition is pushing a recommendation that the agency and other U.S. government agencies set aside a specific percentage of existing funds for programs to battle viral outbreaks, such as the Zika virus.

The Global Health Technologies

See Regulatory, page 6

COULD LEAD TO BETTER INSULIN ABSORPTION

Mexican researchers achieve successful results with novel insulin microcapsule

By Sergio Held, Staff Writer

BOGOTA, Colombia – Researchers in Mexico are developing new microcapsules that would improve the delivery and effectiveness of insulin for diabetes patients.

Researchers at the Instituto Politécnico Nacional de México (IPN) in Mexico City are developing the new microcapsules and have had successful results through in vitro tests and models.

"The project aims at protecting peptides of pharmacological interest such as insulin in its passage through the digestive tract and bring, in this case, the active insulin to the small intestine for absorption," Guillermo Osorio, one of the lead researchers of this project, told *Medical Device Daily*. "We created microcapsules with double emulsions

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IN THIS ISSUE

OTHER NEWS TO NOTE

Illumina Inc., of San Diego, said that it and its subsidiary, **Verinata Health Inc.**, of Redwood City, Calif., filed a patent infringement suit against **Genoma SA**, of Geneva Switzerland, in the Federal Patent Court in Switzerland. Illumina is seeking all available remedies, including damages and injunctive relief. The patents asserted are european patent (CH) 2 183 693 B1, european patent (CH) 0 994 963 B2, european patent (CH) 1 981 995 B1, and european patent (CH) 2 514 842. The patents are directed to using cell-free fetal DNA for non-invasive prenatal testing (NIPT). The suit accuses Genoma's Tranquility NIPT testing service, including its use of next-generation sequencing to analyze cell-free DNA from a sample of maternal blood. Genoma's testing facility in Switzerland also services samples collected from its other labs, including those located in Spain and Italy.

Imaging Advantage LLC (IA), of Phoenix, reported the launch of a machine learning research initiative with faculty members from the Massachusetts Institute of Technology and Harvard Medical School/Massachusetts General Hospital, titled Singularity Healthcare . Singularity is developing an artificial intelligence engine to be incorporated into IA's proprietary exam routing technology, to instantly pre-read digital images and identify potential areas of injury and disease, while continuously learning from IA's expanding database of 7 billion images. The algorithm will be applied before images are routed to one of the 500 board certified radiologists connected in the cloud to IA's platform.

SES SA, of Luxembourg Germany, reported the deployment of Satmed, a satellite-based e-health platform, at the CURE Hospital for Children in Niger, to enhance health care in rural and remote regions in Niger. The Satmed e-health platform was conceived by SES Techcom Services, a subsidiary of SES, and is funded by the Luxembourg Government and the Ministry for Cooperation and Humanitarian Action. The satellite-based communication solution aims to improve public health in developing countries by enabling multiple medical applications and tools to operate collectively on a single platform.

PRODUCT BRIEFS

BD (Becton, Dickinson and Company), of Franklin Lakes, N.J., reported a new line of surgical instrument sterilization containers that are validated for the latest low-temperature sterilization processes.The Genesis low temperature rigid sterilization container system is validated for newer low-temperature sterilization processes and systems from sterilizer manufacturers, including the V-Pro Low Temperature Sterilization Systems from Steris and Sterrad Systems from Advanced Sterilization Products . Low-temperature sterilization is used for instrumentation that cannot withstand the high-temperature and moisture present in traditional steam sterilization practices.

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BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Sarah Cross (Marketing Director), Penney Holland (Web Production Manager)

10 BIGGEST U.S. WINNERS FOR THE WEEK

By Percent		By Dollars	
Hansen Medical	35.18	Intuitive Surgical	13.93
Endologix	11.01	Abiomed	3.61
Tearlab	10.96	Penumbra	3.51
Fluidigm	10.77	Labcorp	2.21
Echo Therapeutics	7.94	Athenahealth	2.08
Bovie Medical	7.65	St. Jude Medical	1.99
Quidel	7.19	Medtronic	1.89
Penumbra	6.83	Heartware Internat	1.82
Spectranetics	5.72	Edwards Lifesci	1.78
Mazor Robotics	5.46	Teleflex	1.67

10 BIGGEST U.S. LOSERS FOR THE WEEK

By Percent		By Dollars	
Transenterix	-64.21	Alere	-6.51
Alere	-13.05	Transenterix	-3.48
Novocure	-11.18	ICU Medical	-2.03
Dehaier Medical	-7.19	Cantel Medical	-1.73
Sunshine Heart	-5.41	Novocure	-1.73
Smith & Nephew	-4.51	Smith & Nephew	-1.56
Stereotaxis	-2.96	Haemonetics	-0.95
Titan Medical	-2.82	Vascular Solutions	-0.52
Haemonetics	-2.78	Conmed	-0.44
Cantel Medical	-2.44	Stryker	-0.40

MDD STOCK REPORT FOR PUBLIC MED-TECH COMPANIES

COMPANY	SYMBOL	CLOSE 4/15	CLOSE 4/22	%CHANGE WK	%CHANGE YTD	VOL (000)
Abbott Laboratories	ABT	43.41	44.08	1.54	-3.34	31612
Abiomed	ABMD	98.22	101.83	3.68	8.79	2843
Accuray	ARAY	6.12	6.13	0.16	-9.33	3104
Agilent Technologies	A	40.91	41.8	2.18	-2.15	7488
Alere	ALR	49.87	43.36	-13.05	27.58	22971
Align Technology	ALGN	73.47	73.87	0.54	11.57	3064
Allscripts Healthcare	MDRX	13.75	13.91	1.16	-10.60	5848
Athenahealth	ATHN	136.23	138.31	1.53	-15.37	1549
Baxter International	BAX	42.69	43.32	1.48	11.90	54418
BD	BDX	159.15	159.88	0.46	3.28	3713
Biolase	BIOL	1.37	1.41	2.92	62.88	90
Boston Scientific	BSX	19.46	19.76	1.54	5.53	42138
Bovie Medical	BVX	1.7	1.83	7.65	-19.05	142
C.R. Bard	BCR	206.79	207.23	0.21	9.16	1893
Cantel Medical	CMN	70.9	69.17	-2.44	14.10	843
Cardiovascular Syst	CSII	13.98	14.72	5.29	-7.54	846
Checkcap	CHEK	2.9255	2.962	1.25	54.79	1
Conmed	CNMD	43.4	42.96	-1.01	-1.48	907
Cynosure	CYNO	44.98	44.84	-0.31	0.69	2273
Dehaier Medical	DHRM	1.724	1.6	-7.19	-23.78	69
Delcath Systems	DCTH	0.341	0.34	-0.29	-31.80	362
Dentsply Internat	XRAY	60.09	60.72	1.05	-1.25	5052
Echo Therapeutics	ECTE	1.26	1.36	7.94	-11.27	113
Edwards Lifesci	EW	106.55	108.33	1.67	34.91	6458
Endologix	ELGX	10.26	11.39	11.01	3.64	5152
Fluidigm	FLDM	9.1	10.08	10.77	-15.82	1123
Haemonetics	HAE	34.2	33.25	-2.78	6.08	2247
Halyard	HYH	31.09	31.78	2.22	-6.94	1369
Hansen Medical	HNSN	3.07	4.15	35.18	31.76	3393
Heartware Internat	HTWR	33.49	35.31	5.43	-33.55	1577
Henry Schein	HSIC	169.98	170.83	0.50	7.45	1465
Hill-Rom Holdings	HRC	53.73	53.86	0.24	11.80	1672
Hologic	HOLX	36.17	37.44	3.51	-6.51	16221
iCAD	ICAD	4.92	5.16	4.88	-4.84	214
ICU Medical	ICUI	105.59	103.56	-1.92	-6.38	551
Idexx Laboratories	IDXX	79.73	81.11	1.73	9.34	4038
Inogen	INGN	48.9	49.64	1.51	21.98	1140
Intersect ENT	XENT	18.69	19.2	2.73	-16.93	690
Intuitive Surgical	ISRG	624.22	638.15	2.23	14.24	2394
Iridex	IRIX	10.2	10.35	1.47	9.80	133
Labcorp	LH	119.56	121.77	1.85	-3.30	6911
Livanova	LIVN	54.9	54.9	0.00	-7.53	1001
Luminex	LMNX	19.93	20.58	3.26	-6.83	877
Masimo	MASI	42.92	43.33	0.96	3.40	1095
Mazor Robotics	MZOR	11.91	12.56	5.46	17.22	342
Medtronic	MDT	77.1	78.99	2.45	0.27	19482
Meridian Bioscience	VIVO	20.67	20.75	0.39	0.73	880
Novocure	NVCR	15.47	13.74	-11.18	-30.81	1143
Nuvasive	NUVA	50.76	51.51	1.48	-6.19	4727
Nxstage Medical	NXTM	15.32	15.85	3.46	-30.08	1649
Orthofix Internat	OFIX	43.95	43.66	-0.66	12.09	597
Penumbra	PEN	51.41	54.92	6.83	-4.46	1249
Quest Diagnostics	DGX	74.45	75.3	1.14	4.65	4756
Quidel	QDEL	17.95	19.24	7.19	-15.33	550
RTI Surgical	RTIX	4.17	4.19	0.48	5.04	636
Smith & Nephew	SNN	34.62	33.06	-4.51	-2.75	1821
Spectranetics	SPNC	16.79	17.75	5.72	11.49	2982
St. Jude Medical	STJ	58.68	60.67	3.39	-5.00	12697
Stereotaxis	STXS	1.69	1.64	-2.96	127.33	341
Steris	STE	71.31	72.93	2.27	-5.35	2068
Strata Skin Sciences	SSKN	0.92	0.93	1.09	-17.12	33138
Stryker	SYK	109.8	109.4	-0.36	18.14	9472
Sunshine Heart	SSH	0.74	0.7	-5.41	-45.19	193
Syneron Medical	ELOS	7.19	7.32	1.81	-6.74	260
Tearlab	TEAR	0.712	0.79	10.96	-48.78	416
Teleflex	TFX	156.91	158.58	1.06	19.34	1114
The Cooper Cos	COO	156.23	157.86	1.04	16.43	1410
Thermo Fisher Sci	TMO	145.34	146.85	1.04	2.46	5564
Titan Medical	TITXF	0.71	0.69	-2.82	-5.33	2350
Transenterix	TRXC	5.42	1.94	-64.21	118.55	36755
Varian Medical	VAR	83.93	85.17	1.48	3.87	3013
Vascular Solutions	VASC	38.02	37.5	-1.37	10.56	664
Wright Medical	WMGI	18.9	19.02	0.63	-21.84	2087
Zeltiq Aesthetics	ZLTQ	29.73	30.39	2.22	4.21	2688
Zimmer Biomet	ZBH	114.03	114.76	0.64	11.16	5832

NOTES

Trading volumes for Nasdaq, Amex and NYSE are recorded as the total number of shares traded (in thousands) on a weekly basis (cumulative Monday through Friday); the weekly and YTD % changes are from IPO completion, where applicable.

Average Percent Change Week: +1.83%

Range: -64.21% to +35.18%; Number Of Companies: 76 (not market weighted)

Average Percent Change YTD: +4.14%

Range: -48.78% to +127.33%; Number Of Companies: 76 (not market weighted)

Liquid Biopsy

Continued from page 1

blood- and urine-based cancer tests, several of the key players in the space presented data at the recent American Association for Cancer Research (AACR) meeting in New Orleans.

Tissue biopsies will continue to be the gold standard approach to diagnosing cancer for at least the next couple of years, oncologist Samuel Klempner told *MDD*, but the sensitivity of some of these liquid-based technologies should not be underestimated. He said the technology is likely to first play a role in how oncologists monitor disease progression and treatment-response early on, especially in rare cancer cases. Klempner, director of precision medicine at the Angeles Clinic and Research Institute who is affiliated with Cedars-Sinai Medical Center, presented a case study at AACR in which he treated a patient with a BRAF-MEK inhibitor for a rare type of colorectal cancer and used Trovagene Inc.'s urine-based Precision Cancer Monitoring (PCM) technology to confirm the presence of the BRAF V600E mutation and then monitor the response to treatment in advance of imaging tests. Klempner also described the case in a report published in *Cancer Discovery*.

Klempner said a tissue biopsy detected the presence of the BRAF mutation and that there are drugs targeting that pathway but this particular form of cancer is not a studied disease indication for those drugs so he was not sure if the BRAF-MEK inhibitor would work against that tumor.

"We were looking for ways to assess whether or not our therapy was working," he said.

Imaging technology such as CT can be used to monitor a patient's response to a therapy, but it doesn't always show evidence of a response early enough. Klempner also noted that there are no blood-based biomarkers for neuroendocrine tumors so Trovagene's urine-based technology offered an ideal solution. The test was able to show the patient responding to the treatment long before any changes could be assessed with imaging technology, he said.

Because this was a one-patient study, Klempner said more rigorous data will need to be collected, ideally in a clinical trial, but so far it seems that the test should play a role in monitoring early disease response, especially in rare cancer cases.

By using a urine-based test rather than a blood-based test, Klempner said his patient benefited from a convenience advantage that he hadn't given much thought to before the study. She has to drive 45 minutes for office visits, which she would have had to do more frequently if he had used a blood-based technology instead of the urine-based test.

Trovagene, of San Diego, said this patient case study shows that as more therapies are designed to target and inhibit specific mutations that are associated with cancer growth, cancers could potentially be treated according to the genomic profile of the tumor, rather than tumor location alone. This is especially important for less common tumor types with limited treatment options, the company said. Trovagene offers both urine- and blood-based BRAF, KRAS and EGFR oncogene mutation assays.

Mark Erlander, chief scientific officer of Trovagene, said the case study provides a good example of how a disease can be classified and treated based on genomic information. "We believe this is the way cancer will be treated in the future," he said.

The combination BRAF-MEK inhibitor therapy is undergoing clinical investigation across multiple tumor types and the information provided by Trovagene's test can be helpful in demonstrating that the treatment regimen is having its intended effect, Klempner said.

There are some limitations of current liquid biopsy technologies that will keep tissue biopsies as the gold standard, at least for a while, Klempner said.

"Tissue allows us to assess multiple genes at the same time whereas most of these blood and urine tests assess one gene at a time," he said. If there are 10 drugs available that might work, it is important to assess all 10 of those target genes and then, after starting treatment, liquid biopsies can be used to monitor its effectiveness.

Another limitation that liquid biopsy companies face, Klempner said, is penetration into the broader oncology market. Overcoming that barrier is a matter of educating the smaller community practitioners about the availability of these tests and how they can be used to improve patient outcomes.

OUT FOR BLOOD

Vortex Biosciences Inc. also presented data at AACR to support the ability of its technology to rapidly collect highly enriched populations of circulating tumor cells (CTCs), undamaged by labels or reagents, for colorectal and prostate cancer research. Previous research demonstrated the performance of Vortex's technology in isolating CTCs in breast and lung cancer research.

Vortex, of Menlo Park, Calif., has developed a fully automated benchtop system called the Vtx-1 for collecting intact CTCs using microfluidic technology. Inside the Vtx-1 chip, unlabeled CTCs in whole blood are trapped in microsale vortices while smaller red and white blood cells pass through. After selective trapping into the microfluidic chambers, CTCs can be flushed and collected into a variety of containers for downstream analysis, the company said.

The ability of the technology to isolate CTCs and ctDNA without killing the cells in the process is important, particularly for personalized medicine applications, Dino Di Carlo, a bioengineering professor at the University of California at Los Angeles and an advisor to Vortex, told *MDD*.

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TAVI

Continued from page 1

week. The newly transferred technology portfolio will be the basis of Venus' next-generation product line, a product line that the company plans to market worldwide.

"All the valve products Venus has developed so far are not repositionable, and the technology Transcatheter Technologies offers precisely solves this problem," Johnson Yang, Venus' marketing director told *Medical Device Daily*.

Under the terms of the agreement, Transcatheter Technologies' two co-founders will assist Venus during the transition and commercialization of the acquired technology. Financial details of the deal were not disclosed.

"Transcatheter Technologies was founded with the goal of making noninvasive heart valve implantation safer for patients. Our agreement with Venus Medtech helps us continue this mission and will fuel the continued development of our next-generation technology platform for the treatment of various structural heart diseases in the Chinese market," said Wolfgang Goetz, co-founder and CEO of Transcatheter Technologies. "Our third-generation transcatheter aortic valve implantation (TAVI) system—Trinity—is designed to be the world's first 'truly repositionable' TAVI system and has already completed two-years of follow-up."

TAVI is a minimally invasive and low-risk procedure for patients with severe aortic stenosis, especially those who are not suitable for open chest surgery.

Trinity TA is the German company's novel transapical aortic valve system that increases the safety and durability of the TAVI. By using this technology, the valve can be precisely positioned, protected from leaflets damage for longer durability while avoiding aortic regurgitation. The long operation time and personnel can also be reduced.

The company also has a Trinity TF product that is the transfemoral version of Trinity TA. Trinity TF is inserted via femoral artery and is catered to patients with large diameter groin vessels.

Traditionally, second-generation TAVI systems cannot be repositioned once they are fully implanted. But Trinity allows cardiologists to fully evaluate the valve's function to determine whether it needs to be repositioned, retrieved or not.

"Certainly, the early clinical results for the Trinity TAVI system have been very impressive," said Christian Hengstenberg, a cardiologist at the German Heart Center in Munich. "Unlike second-generation TAVI systems, the Trinity aortic valve is able to be positioned precisely or repositioned, even after full implantation, in a safe manner."

Hengstenberg's study found that Trinity's novel sealing cuff could avoid paravalvular leakage, a frequent complication of TAVI. The risk of atrio-ventricular block is also significantly reduced due to the supra-annular positioning of the Trinity valve.

Based in Hangzhou City of Zhejiang Province, Venus is one of the few Chinese companies that are developing advanced interventional artificial cardiac valve systems. It is a few months away from getting a CFDA approval for its A-Valve product since it has completed the clinical trials and follow-up of its transcatheter aortic valve and is waiting for the regulator's clearance this year. (See *Medical Device Daily*, Mar. 30, 2016.)

Venus has a significant lead in the Chinese cardiac valve product market. Apart from the aortic valve that is steps away from being approved in China, the company also has its pulmonic valves in clinical trials.

Since the cardiac valve sector is still nascent in the country, and the product development is progressing smoothly, Venus is under no competitive pressure.

Some of its rivals include domestic peer Microport Scientific Corp. (HKG:0853) and multinational device makers such as Edwards Lifesciences Corp. and Medtronic plc. But they're much farther away from completing clinical trials, not to mention launching products.

"For the next year and half, we don't see any competitors in the China market," said Yang.

Venus jointly formed the Cardiac Valve Research Institute in Zhejiang Province with the Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU) last month. The institute is the first in China that focuses on cardiac valves and minimally invasive treatment for heart diseases.

Venus made headlines last month with a $37 million investment from investment bank Goldman Sachs Group Inc. to support the R&D and marketing activities for its cardiac valve products.

"We recently received the support from Goldman Sachs and it has since enhanced our global reputation," said Yang. "There are very few Chinese companies that have the vision and ability to acquire such technologies." //

Regulatory

Continued from page 1

Coalition (GHTC), a D.C.-based group that advocates for U.S. involvement in public health programs in other nations, recently reported that the death toll for diseases such as malaria has ebbed substantially over the past 20 years or so, and pointed out that the volume of U.S. taxpayer dollars toward such programs had doubled between 2000 and 2010. However, the flattening of U.S. funding for the National Institutes of Health, which also doubled in the last decade of the 20th Century, has accompanied a flattening of taxpayer funding for health programs outside the U.S. since 2010.

The GHTC, which is funding in part by the Bill & Melinda Gates Foundation, has made the case that the FDA and other agencies set aside a fixed amount of their annual appropriations toward these international health programs, an argument bolstered in part by the emergence of the Zika virus as the latest in a series of potential epidemics.

Erin Will Morton of the Global Health Technologies Coalition told *Medical Device Daily*, "we don't have a specific figure when we talk about agencies setting aside parts of their budgets," but she added, "I do think it's important that Congress increase its funding across the board" for these causes.

Morton acknowledged the difficulties of the current budget environment, and noted that the Obama administration's sequester proposal, which the GOP-led House of Representatives adopted, was a big impediment to expanded funding of such programs. However, she also stated that the progress made thus far in stanching many communicable diseases in the developing world might be difficult to replicate.

"I think the early progress is sometimes the easy progress," Morton said, which she said is why it is vital that the Congress and the White House "continue to sustain that funding and not risk that backslide. We can't become complacent. We have to continue to think about new tools that might be needed" for Zika, a potential resurgence of Ebola, and other diseases that receive substantially less media coverage.

Morton acknowledged that she is uncertain as to whether other national governments in the developed world have doubled their spending on such programs, explaining, "our primary advocacy focused is the U.S. government," although some coalition members are working with their governments. She said the organization is not ignoring the United Nations or the World Health Organization, pointing out that GHTC recently hosted a webinar addressing non-U.S. revenue streams. "One of the biggest concerns is that if WHO has a fund like that, there has to be fundraising for it," Morton said,

Despite the uncertainty as to whether the doubling of U.S. funding between 2000 and 2010 had any effect on other nations in the developed world, Morton said, "I don't think the U.S. is in a position to take a step back. That role as a leader in funding is setting a precedent" that will prod other nations to follow suit.

Despite that the most recent Ebola break-out seemed to prod little activity in the way of private-sector investment in diagnostics for the virus, Morton said, "the private sector definitely has a role to play" in bringing diagnostics to market for these rapid-emergence pathogens. Getting makers of diagnostics to "work closely with CDC and other agencies ... is the most effective way to get these tools out there," she asserted.

As for whether the FDA premarket review process is a sticking point, Morton said, "we haven't spoken specifically with the FDA about their approval process." She stated further, however, "the bigger take-home message is that we don't know what the next epidemic and outbreak will be," concluding that even the Ebola virus "is not really done, and we will see another outbreak."

SEQUENOM APPEALS TO SCOTUS FOR CERT

San Diego-based Sequenom, Inc., has petitioned the Supreme Court of the United States for a grant of cert for the patent suit between the company and rival Ariosa Diagnostics of San Jose, Ca., a case that would force the Court to revisit its decisions in several recent landmark decisions.

The Court of Appeals for the Federal Circuit ruled last year in favor of Ariosa in *Ariosa v. Sequenom*, but the Federal Circuit passed on the chance to give the case a full, 12-judge hearing toward the end of the year (See *Medical Device Daily*, Dec. 4, 2015.) The appeal for cert was accompanied by a friend-of-the-court briefing penned by David Gass, a partner at Marshall Gerstein & Borun, LLP, on behalf of several trade organizations, including the Biotechnology Innovation Organization (BIO). This briefing made several arguments, including that previous cases decided at the Supreme Court and other courts have erroneously applied the judicial exceptions standards to the patents in question.

The briefing stated that Ariosa offers the high court "an opportunity to discuss the interplay between the judicial exceptions analysis and the preemption concerns that underlie it." Gass wrote that the Supreme Court had not ruled out the use of DNA in *AMP v. Myriad*, the 2013 case that scuttled the patent eligibility of DNA, but that Ariosa does not create any concerns about preemption of other uses of the genetic markers in question, which are used to evaluate the risk of developmental abnormalities.

Gass spoke again with *Medical Device Daily*, and said, "at this stage of the game, industry is trying to persuade the Court that this is an important case and that it affects the U.S. economy" as well as the biotech and diagnostics industries. He said the view that the Court's decisions have made the U.S. patent law landscape "less predictable and less protective than in other countries might be a factor [the justices] would consider."

Gass said some in industry have urged the Court to "exhibit some judicial restraint and let the statute do it's job. I think the Court could frame the [Ariosa] opinion as clarifying Mayo and

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Insulin

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from the water-oil-water type, coated with a layer of whey protein and a polysaccharide with mucoadhesive properties to retard the passage of insulin through the small intestine and enhance absorption."

"The project is still in the laboratory stage," said Osorio. "We have found in in vitro digestion with simulated gastric juice that insulin is released into the intestine with 90 to 95 percent of its activity, so the first objective was achieved, since we are protecting insulin from stomachal pH and of digestive enzymes, releasing insulin in the intestine."

The researchers are now starting to tests the microencapsules in mice "to see the absorption of insulin in the intestine and afterwards, depending on the results, we would move [the test] to rats and finally to clinical trials," said Osorio.

Their aim is to reach clinical trials for microcapsules carrying insulin used for type 1 and type 2 diabetes. They say that this is a more effective delivery method than the commonly used injections.

"When insulin is administered by subcutaneous injection, it goes directly to the peripheral blood circulation, without following the natural metabolic pathway of insulin produced in the pancreas, this being responsible for hypoglycemic episodes in these patients," said Osorio.

"But with the oral administration, [insulin] would be absorbed in the intestine, to go directly to the portal veins and from there to first pass the metabolism in the liver, emulating the natural metabolism of insulin produced in the pancreas and therefore having a better control of glucose levels in blood."

For the time being, the project is being funded by IPN and the Mexican National Council of Science and Technology (CONACyT) and it is unclear how long it will take before it can be commercialized.

"Right now we are in the process of protecting the intellectual property of the project," said Osorio. "We could not answer questions regarding patients, duration of preclinical and clinical trials and whether or not it is possible its commercial exploitation."

A better insulin delivery method that does not rely on injections could be a boon for diabetes patients, particularly in developing markets where access to medicine and sanitation of syringes are significant issues.

According to the World Health Organization (WHO) there are about 422 million diabetes patients in the world, four times as many as the 108 million reported in 1980. On its latest Global Report on Diabetes published this month, the WHO estimated that there were 1.5 million deaths related to diabetes in 2012.

The cost of insulin and the way the market is structured may be a cause for concern.

"The insulin market is dominated by a small number of multinational manufacturers, with a few, smaller producers making up only 4 percent of the market by volume," said the WHO in its report. "While the major cost drivers are hospital and outpatient care, a contributing factor is the rise in cost for analogue insulins which are increasingly prescribed despite little evidence that they provide significant advantages over cheaper human insulins."

Type 1 diabetes patients are unable to produce the insulin that their bodies require and are dependent on regular injections of insulin. Type 2 diabetes patients produce enough insulin, but they are unable to process it as they require.

According to the WHO, Mexico has the highest prevalence of diabetes among the 22 Organization for Economic Cooperation and Development countries.

"There is still some way to go, but the results of the in vitro tests and what has been obtained from biological tests are very encouraging," remarked Osorio. //

Regulatory

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Myriad, and not have to acknowledge they did anything wrong in those cases," Gass commented.

"If the concern is that something already exists in nature, maybe the Court can say with method claims that there is no risk of preemption," Gass mused, but he added that when it comes to claims that cite more abstract exceptions, "maybe they are more concerned about the risk of preemption" of other uses of the underlying law of nature or natural phenomena.

The impact-on-industry argument might seem to rely on the gyrations of the stock market, but Gass replied, "I think the stock market reacts day-to-day, minute-to-minute to all sorts of different news," and that "I don't think patent decisions can be measured as an influence on the market in that respect." He pointed out that venture capital companies, for instance, in the affected life sciences industries are not strongly inclined to issue press releases to explain their investment decisions, but those decisions are nonetheless influenced greatly by how the courts interpret the statute.

A large percentage of recent patent cases at the Supreme Court have yielded anything but a classic 5-4 split, and Gass mused, "it's kind of surprising how unified [the Court] has been." Consequently, he stated, "it doesn't seem like eight versus nine justices will make a difference," should Sequenom win a review.

"One of the things I think was important in the BIO brief was the point that you can't look at diagnostics in a vacuum," Gass stated, arguing that the related discoveries of biomarkers give researchers fodder for additional research in other areas of medical science. He said these patents do not preempt research on those markers in unrelated fields, adding, "I think that's an important issue" for the Supreme Court to consider. //

Liquid Biopsy

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CTC enrichment technologies have been limited by complex sample processing, poor scalability, low sample purity, reliance on cell surface proteins for isolation and dilute output volumes that require additional cell concentration steps, according to the company.

Gene Walther, CEO of Vortex, told *MDD* that the technology could potentially help scientists advance cancer research and accelerate the development of new diagnostics and therapeutics.

Another study added validation to Berlin-based Epigenomics AG's panel of blood-based DNA methylation biomarkers for the detection of lung cancer. The FDA recently approved Epigenomics' Epi Procolon liquid biopsy test. (See *Medical Device Daily*, April 14, 2016.)

Epigenomics CEO Thomas Taapken told *Medical Device Daily* that lung cancer is the second area of focus for the company now that it has FDA approval for its colorectal cancer test.

"To develop blood-based tests for cancer is a very important task and while there are many companies working on this, there are not so many out there that have been doing this on the basis of a proprietary set of biomarkers and that is maybe the biggest differentiating factor we have," he said. "What we have is a platform that allows us to go after several cancerous diseases without having to enter what could become a commodity market."

In lung cancer, the company has not yet done any major clinical studies and the data presented at AACR is considered validation research that was completed on about 116 patients, some healthy patients, some with lung cancer and some with non-malignant tumors.

Lung cancer is an interesting application for liquid biopsy, Taapken said, because of the new U.S. recommendation to screen high risk patients (those with a long history of smoking) annually with low-dose CT scans starting at age 50.

The problem with that screening method, he said, is that it uses radiation and also results in a high percentage of false positives. Low-dose CT typically produces positive results about 27 percent of the time and not all of those cases are true positives, he said.

"You cannot have millions of people screened and then have every third patient undergo a tissue biopsy," Taapken said. "That is where liquid biopsy tests come into play. We are trying to develop a test that will help those positively tested patients after low-dose CT screening to confirm or rule out the presence of lung cancer."

If the liquid biopsy confirms the low-dose CT positive, the patient would then be referred for a tissue biopsy. **//**

FINANCINGS

Baxter International Inc., of Deerfield, Ill., and **Baxalta Inc.**, of Bannockburn, Ill., said that Baxter has commenced an offer to exchange up to 12.8 million shares of Baxalta common stock that are currently owned by Baxter, which represents approximately 1.9 percent of the outstanding common stock of Baxalta, for shares of Baxter common stock that are validly tendered and not validly withdrawn in the exchange offer. Following the completion of the exchange offer, if Baxter disposes of all of the remaining shares of Baxalta common stock held by it in the exchange offer, Baxalta will be wholly independent from Baxter, except that certain agreements between Baxter and Baxalta will remain in place. Baxter stockholders have the option to exchange all, some or none of their shares of Baxter common stock for shares of Baxalta common stock, subject to proration. Tendering Baxter stockholders are expected to receive approximately $107.52 of Baxalta common stock for every $100 of Baxter common stock tendered and accepted in the exchange offer. Baxter will determine the ratio at which shares of Baxter common stock and Baxalta common stock will be exchanged by reference to the simple arithmetic average of the daily volume-weighted average prices of shares of Baxter common stock and Baxalta common stock on the New York Stock Exchange over a three consecutive trading day averaging period ending on and including the second trading day preceding the expiration date of the exchange offer. The number of shares of Baxter common stock that will be accepted in the exchange offer will depend on the final exchange ratio and the number of shares of Baxter common stock tendered. Baxter currently holds 30,506,097 shares of Baxalta common stock, which represents approximately 4.5 percent of the outstanding common stock of Baxalta. If Baxter does not exchange all of the shares of Baxalta common stock owned by it in the exchange offer, Baxter intends to, prior to or following the completion of the exchange offer, make a contribution to Baxter's U.S. pension fund or distribute as a special dividend to all Baxter stockholders, on a pro rata basis, some or all of its remaining shares of Baxalta common stock. If Baxalta's proposed merger with Shire plc is consummated, each share of Baxalta common stock will be converted into the right to receive both $18 in cash and 0.1482 of an American Depositary Share of Shire.

NEUROLOGY EXTRA

Keeping you up to date on recent developments in neurology

By Omar Ford, Staff Writer

Researchers propose mapping neurons to improve Parkinson's

Because billions of neurons are packed into our brain, the neuronal circuits that are responsible for controlling our behaviors are by necessity highly intermingled. This tangled web makes it complicated for scientists to determine exactly which circuits do what. Now, using two laboratory techniques pioneered in part at Caltech, Caltech researchers have mapped out the pathways of a set of neurons responsible for the kinds of motor impairments — such as difficulty walking — found in patients with Parkinson's disease. The work was published in the journal *Neuron*. In patients with Parkinson's disease, gait disorders and difficulty with balance are often caused by the degeneration of a specific type of neuron — called cholinergic neurons — in a region of the brainstem called the pedunculopontine nucleus (PPN). Damage to this same population of neurons in the PPN is also linked to reward-based behaviors and disorders, such as addiction. Previously, researchers had not been able to untangle the neural circuitry originating in the PPN to understand how both addictions and Parkinson's motor impairments are modulated within the same population of cells. Furthermore, this uncertainty created a barrier to treating those motor symptoms. After all, deep brain stimulation--in which a device is inserted into the brain to deliver electrical pulses to a targeted region — can be used to correct walking and balance difficulties in these patients, but without knowing exactly which part of the PPN to target, the procedure can lead to mixed results.

Genes behind well-being, depression and neuroticism, discovered

An international group of more than 190 scientists who analyzed the genomes of 298,420 individuals have found genetic variants that may influence our sense of well-being, depression and neuroticism. The study, to be published April 18 by the *journal Nature Genetics*, is one of the largest genomic studies to date on behavioral genetics. The scientists found three genetic variants associated with "subjective well-being" — how happy or satisfied a person reports feeling about his or her life — based on an analysis of roughly 300,000 people. The researchers also found two genetic variants associated with depressive symptoms, based on an analysis of nearly 180,000 people, and 11 genetic variants associated with neuroticism, based on an analysis of 170,000 people. The depression results were replicated through an analysis of another sample of nearly 370,000 people. The study also found that subjective well-being, neuroticism and depression are predominantly influenced by the same set of genes. The scientists said this finding indicates that researchers may want to consider studying these traits jointly for future work The interdisciplinary team — which included medical researchers and psychologists — also studied whether the genetic variants that they had identified overlap with genetic variants associated with other diseases and disorders, including Alzheimer's disease, anxiety disorders, autism spectrum disorder, bipolar disorder and schizophrenia. The strongest link was with anxiety disorders. The researchers also found the genetic variants tied to subjective well-being, depression and neuroticism moderately overlap with the variants that are associated with schizophrenia and bipolar disorder. Because the study has found some of the first genetic variants associated with well-being, depression and neuroticism, it is too soon to draw conclusions about how the genes affect biological mechanisms. The scientists issued several cautions for interpreting the results of their study.

Plasma levels could leave clues for Alzheimer's

A Center for Healthy Brain Aging (CHeBA) paper published in Current Alzheimer Research presents the first detailed study of the relationship between plasma levels of two amyloid beta peptides (Aβ1-40 and Aβ1-42), brain volumetrics (measures studying the size of brain, which shrinks with Alzheimer's disease) and cognitive performance in an investigation of the usefulness of plasma levels as a biomarker for Alzheimer's disease (AD). Lead author on the paper and head of CHeBA's Proteomics Group at the University of New South Wales, Anne Poljak, said that since amyloid beta (Aβ) peptides are the main component of the amyloid plaques found in Alzheimer patients' brains, changes in levels of Aβ in blood plasma may provide a biomarker for detecting increased risk or early diagnosis of disease. The study examined age-matched cognitively normal controls (n=126), individuals with amnestic mild cognitive impairment (aMCI, n=89) from CHeBA's Sydney Memory & Ageing Study, as well as individuals with Alzheimer's disease (AD, n=39). Plasma levels of the two peptides and the Aβ1-42/1-40 ratio were lower in aMCI and Alzheimer's disease than in cognitively normal controls, and lower levels of Aβ1-42 were associated with lower global cognition and hippocampal volume and higher levels of white matter hyperintensities

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(which are believed to contribute to Alzheimer's disease). A genetic component was also identified, with associations between Aβ1-40 and cognitive and brain volume measures predominantly observed in individuals carrying the ε4 allele, while the opposite was observed in non-carriers. Longitudinal analysis revealed greater decline in global cognition and memory for the highest quintiles of Aβ1-42 and the ratio measure.

Wrist watch helps improve patient's lives with Parkinson's Disease

A new tool that resembles a wristwatch could improve the quality of life for patients with Parkinson's disease and better inform neurologists who treat them. A Cedars-Sinai research team is one of the first in the nation to test the Personal Kinetigraph (PKG) data logger, which tracks the movements of Parkinson's patients every two minutes over a period of six to 10 days. The information enables neurologists to generate reports showing the fluctuations of Parkinson's symptoms throughout the day and the timing of when patients take their medication. Researchers said the device could be a game changer for the treatment of patients with advanced Parkinson's disease by providing an objective record of movement fluctuations. The information can enhance doctors' understanding of the nature and progression of the brain disorder, which progressively affects a person's ability to control body movements. Up to 60,000 new cases are diagnosed each year. The small gadget – the size, weight and shape of a wristwatch – also vibrates to remind patients to press a button indicating that they have taken medication prescribed to reduce their body movements.