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Features

Buoyed by *In Vitro* Data, UCLA Researcher Says Stem Cell-Based RNAi Rx May Fight HIV

Many academic and private-sector RNAi researchers believe that HIV is one of the most promising targets for RNAi-based therapeutic intervention. One of these is Irvin Chen, director of the UCLA AIDS Institute, who has recently begun testing a stem cell-based RNAi treatment in monkeys, and presented *in vitro* data at the first meeting of the Oligonucleotide Therapeutics Society last week in New York City.

However, Chen conceded that the approach faces significant hurdles, including the prerequisite to destroy a patient's existing stem cell population through radiation therapy — a risky proposition for individuals with HIV because it could sap their already-weakened immune system.

"I think that RNAi is going to be a good approach for HIV disease," Chen told *RNAi News* this week. "We have a very discrete target, the virus, and either directly targeting the virus itself or … knocking out a co-receptor for HIV-1 … will be a very effective means of preventing HIV replication.

"RNAi [also] can be administered through a gene-therapy approach via reconstitution of the hematopoietic system," Chen continued. "Since in advanced HIV disease the immune system is wreaked, [this gene therapy approach allows you] to create a new immune system while at the same time protecting those cells from HIV infection."

This gene therapy approach "allows you] to create a new immune system while at the same time protecting those cells from HIV infection."

According to Chen, the approach he is taking, which he said is a proof-of-concept study, involves treating a rhesus macaque with cytokines that increase levels of stem cells in the blood. "Basically, [the treatment] mobilizes stem cells from the bone marrow so that they appear in the blood," he explained. "Then, you can harvest those stem cells, purify them, put in whatever gene therapy reagent you want, say a vector expressing RNAi, and infuse those back into a patient" intravenously.

The vector Chen is using expresses an siRNA against CCR5, a co-receptor essential for replication in about 95 percent of all HIV-1 strains, he said. "Experiments [on the importance of CCR5] have already been done in nature — there are people that are naturally resistant to HIV because they lack CCR5. They can't be infected at all by those strains of HIV that use the co-receptor."

He added that HIV-infected people who are CCR5 heterozygous don't experience as rapid a progression to full-blown AIDS as individuals with normal CCR5 genotypes. "Even though they only have half as much CCR5 on their T-cells as other people, these individuals show much delayed progression to AIDS."

Chen noted that his approach faces some big hurdles, including the prerequisite ablation of a patient's stem cell population. "The patients need to be treated with drugs or radiation to suppress the existing hematopoietic cells that are in the body as much as possible," he said. "If you don't get rid of the existing hematopoietic cells, the new stem cells that you put in don't seem to take very well.

"Treatments like that are going to be tough to do for HIV patients who are already immunosuppressed to begin with," Chen added. "But at the moment at least, that's the best way to get stem cells into people [and] in the future I think we're going to see other ways without such dramatic measures."

Additionally, there is the problem of HIV's ability to mutate and become immune to treatment. However, Chen believes that "if you can reduce the population of viruses to such a low level that even if you do get mutations, it's unlikely you'll get a virus carrying that mutation within your population.

"Basically, [the treatment] mobilizes stem cells from the bone marrow so that they appear in the blood. Then, you can harvest those stem cells, purify them, put in whatever gene therapy reagent you want, say a vector expressing RNAi, and infuse those back into a patient" intravenously.

"That's the way all HIV drugs work now — there's always the chance of mutation, but if you can reduce the viral load in the body to … a low level that the chances of the mutation occurring within the remaining viruses is low," he said.

At the Oligonucleotide Therapeutics Society meeting, Chen presented *in vitro* data showing that his approach could be used to make human T-cells resistant to HIV infection. He also noted that about four weeks ago he and his colleagues, which include California Institute of Technology President and Nobel Laureate David Baltimore, began non-human primate experiments.

He said that he expects to see data from the monkey work in a few months "because we have to wait for their immune systems to fully restore after the [stem cell] transplant" before they can be evaluated to see if they are expressing CCR5.

"If we do see a reduction, the next step would be to challenge these animals with SIV" to see if they are resistant, he said.

— *Doug Macron* (dmacron@genomeweb.com)

RNAi Startup Believes siRNAs Can Treat Extremely Rare Skin Disorder

As interest in the RNAi drugs sector grows, so does the number of companies entering the playing field. The newest entrant is Santa Cruz, Calif.-based TransDerm, which, with the help of a nonprofit consortium, some well-known academic centers, and a former employer, is trying to use siRNAs to develop therapeutics for an extremely rare skin disorder.

The four-person company was co-founded late last year by CEO Roger Kaspar, who previously served as vice president of biology for Somagenics, a startup focused on developing siRNA libraries and a novel antisense-related gene-silencing technology called RNA lassos (see *RNAi News, 4/30/2004*).

TransDerm's primary goal, according to Kaspar, is to develop delivery approaches for nucleic acid-based treatments for pachyonychia congenita, a rare autosomal disorder characterized by hypertrophic nail dystrophy and focal palmoplantar keraderma with blisters.

While at Somagenics, Kaspar participated in a symposium sponsored by the International Pachyonychia Congenita Consortium "where a group of physicians and scientists that all had different skills were brought together with the idea of trying to figure out how to come up with a therapeutic as quickly as possible for PC," he told *RNAi News* this week.

"One thing led to another and finally I told them, 'If you want to put up some money, we'll start a company [with] goals aligned with your goals for the initial couple of years.'"

The investigators sought Kaspar's and Somagenics' help with their PC project, "and I told them I was happy to help … but I couldn't help them the way they wanted me to" given that Somagenics was focused on more widespread diseases such as HIV and hepatitis C.

"One thing led to another and finally I told them, 'If you want to put up some money, we'll start a company [with] goals aligned with your goals for the initial couple of years,'" Kaspar said. An undisclosed angel investor then provided the funding necessary to get TransDerm up and running, and "that's how the whole thing started."

The investor "is basically [a group] that's very interested in seeing a therapeutic be brought to clinic, [and who] realized that it's such a rare disorder — there's only several hundred patients that have been identified worldwide — that if they didn't do something, it was unlikely the NIH or some big company would pick up on this," Kaspar said.

"And yet, this disease is a great disease [for therapeutic intervention] because the molecular targets are well-defined and it [affects] the skin, which is fairly accessible," he added.

During a poster session at the first meeting of the Oligonucleotide Therapeutics Society in New York City last week, Kaspar presented *in vitro* data on the use of siRNAs to inhibit the mutant genes responsible for PC. Also contributing to the poster data were researchers from Ninewells Medical School in the UK, Rockefeller University, and Johannes Gutenberg-Universitat in Germany.

According to the poster, PC is caused by mutations in genes encoding keratin 6a or keratin 16, "including several recurrent mutations at the N171 site of K6a, which can be deleted (K6a 171del) or mutated at a single nucleotide resulting in an amino acid change (N171K)."

Kaspar and his colleagues demonstrated that a fusion protein comprising "wild-type K6a and YFP reporter results in keratin filaments in transfected human PLC and keratinocyte cells as assayed by fluorescence microscopy. Similar constructs containing the N171K or 171del mutations result in keratin aggregates," the poster notes.

The researchers designed siRNAs to target the mutation sites, and co-transfected them with K6a/YFP constructs (wild-type, N171K, or 171del) into 293 FT cells, the poster states. They found that the inhibitors preferentially targeted mutant K6a mRNA.

Additionally, the researchers saw that K6a mutation-specific siRNAs were able to "rescue aberrant keratin filaments in cells co-transfected with a mixture of K6a-wt/YFP and K6a-mut/YFP plasmids," suggesting that "siRNAs can discriminate single [nucleotide] mutations … [and] that 'designer siRNAs' may allow effective treatment of a host of genetic disorders including PC."

PC is a "dominant-negative disorder, so there's a copy of a bad gene and a copy of a good gene," Kaspar explained. Based on the data thus far, "we think we can knock down the bad gene without affecting the good gene."

He noted that he has also conducted follow-on work using "we call a dominant-negative tissue culture model where we introduce a mixture of the wild-type and mutant [K6a], and both of these are fused to a reporter gene. If we put both of them in [the model], it screws up the keratin filaments. But if we put both of them in the presence of [the siRNA] … the mutant form … is knocked down and only the wild-type is left, and you get very nice keratin filament structures being formed."

With these data in hand, Kaspar said TransDerm is working with Stanford University researcher Chris Contag to test the siRNAs in mice and begin tackling the delivery issue.

"We have a couple of different [delivery] methods" being tested, Kaspar said. "The most direct is just to do intradermal injections. We're also working [in collaboration with Somagenics] on what we call a 'gene cream,' which is a formulation where we introduce our siRNAs or reporter genes and then rub this onto shaved skin of mice. It works pretty well and is obviously something we're interested in making work even better."

He noted that since one of the biggest hurdles PC patients face is walking due to foot pain, TransDerm is initially working on a treatment that can be applied directly to the soles of the feet.

While this work progresses, Kaspar said, TransDerm is trying to schedule a pre-investigational new drug application meeting with US regulators "to find out exactly what they'll require of us to use these things in patients."

He noted that TransDerm is part of the International Pachyonychia Congenita Consortium and collaborates with nonprofit organization PC Project, which is expected to help the company find and enroll patients in a possible clinical trial.

Aside from PC, Kaspar expects that TransDerm's technology could apply to a number of disorders.

"There are about 10,000 different congenital disorders in man, and about 20 percent of them involve the skin," he said. "If we can knock down any gene specifically, which from our tissue culture experiments and early animal work [looks possible], there is a tremendous number of disorders we could go after that are caused by a single gene. Then there are multi-factorial [diseases] such as psoriasis or atopic dermatitis that ought to be amenable to these types of treatments."

— *Doug Macron* (dmacron@genomeweb.com)

Brown's Bharat Ramratnam on RNAi-Based Microbicides as HIV Treatments

Bharat Ramratnam
Assistant professor of medicine
Brown Medical School

At A Glance

Name: Bharat Ramratnam

Position: Assistant professor of medicine, Brown Medical School

Background: MD, Brown Medical School — 1993

AB, chemistry, Brown University — 1989

After receiving his undergraduate and medical degrees from Brown, Bharat Ramratnam went on to conduct his postdoctoral work at the Aaron Diamond AIDS Research Center at Rockefeller University. He made his way back to Rhode Island, however, where he now divides his time between doing laboratory research and practicing medicine.

Recently, he spoke with *RNAi News* about his work in the HIV field and how RNAi is playing a role.

Could you give an overview of your lab and your medical practice?

Our medical practice is consigned to HIV-infected individuals in Rhode Island and Southeastern Massachusetts. The take-home message is that people are still getting infected, and they're still getting infected despite increased education on the things that people need to do to prevent being infected. People are being infected mostly through heterosexual sex is what we're finding here, though homosexual sex also continues to be a risk factor — but the rates have increased for women getting infected.

This has lead to our interest in novel microbicides — agents that can be applied to mucosal surfaces and thereby prevent a person from being infected by a viral pathogen such as HIV. But if you also look at other viral pathogens that are sexually transmitted, whether it be herpes or human papillomavirus, the same principles apply: we need locally acting drugs that can prevent the transmission of these viruses during sexual intercourse. That is really where our interest in RNAi is right now — to see if RNAi can provide a platform to provide these drugs.

Given your postdoc work and your experience there, you've been working in the HIV field for quite a while. When did RNAi enter the picture?

RNAi entered the picture just three or four years ago. The publications [at that time] and indeed our own work were on using RNA interference towards a potential genetic therapy — that is, transducing lymphocytes and introducing this into the whole body in infected individuals to see whether or not viral transcription could be decreased. This sort of approach, unless there is a major advance in gene therapy, is not something that is going to be doable in the next few years or months. So that is what made us change our focus to see whether short interfering RNAs can be formulated and taken up by mucosal surfaces, and in that way, if they could be used to degrade proteins that are necessary for the transmission of viral pathogens.

The gene therapy work, is that going forward in any respect?

With respect to HIV and our use of RNAi, we've shifted completely to a microbicidal approach and none on

gene therapy.

So where are you in the microbicide development effort?

Well, there are a few challenges. Curiously enough, the easiest thing to do is to select targets, and that is the hardest thing to do when you're thinking about HIV-1-specific gene therapy by RNAi because if you're choosing a viral target, I'm not convinced that there is any one that would be a drug target useful for each and all infected individuals. Say you had in your mind that you were going to degrade tat using RNA interference; just the genetic variation in tat across different patients, different clades, different continents is so large that it's going to take [a tremendous amount] of time to come up with one siRNA molecule that is going to effectively target all these different kinds of tats. The challenge is actually much [greater] because if you just degrade tat, as we've shown, you're going to have escape mutations emerge, and you're going to have viral strains that have mutated to render the siRNA useless. So you have to go for quite a few targets.

Whereas for the microbicide work, CCR5 is a perfect example of one target that a human can do without that, if we are able to downregulate on mucosal surfaces, could serve as a potent microbicidal preventative strategy. New knowledge is emerging about herpes co-receptors, and the same sort of principles apply there: if we can design an siRNA molecule against one of these entry molecules that are specific for herpes, then you could make an enormous impact not only for herpes, but [HIV as well.] … Those people infected by herpes secret larger amounts of [HIV] virus, they're more infectious, those people that are HIV-positive, if they get herpetic lesions, the course is worse. All these viruses live in this ecosystem and they help each other out. In the end they can hurt the overall epidemic.

So at this point do you have an siRNA formulation?

We've gotten proof of principle with liposomal formulations, but now we're working with different academic enterprises and a few commercial enterprises to formulate them as microcapsules and sustained-release rings, but that work is still all in the very preliminary stages and we have no results as to whether that will be successful or not.

Have you tried the liposomal formulations *in vivo*?

We've tried the liposomal formulations *in vivo* and we do see uptake and we do see knockdown of targeted genes.

What kind of animal?

Rodents. We're just beginning macaque work at the New England Primate Center with a liposomal formulation.

You talked about gene therapy being pretty down-the-road kind of stuff. Where do you see an HIV microbicide in terms of a timeline?

I think the most important roadblock is proof of principle in macaques. If there is convincing data that siRNA can indeed knock down CCR5, and the kinetics and potency of knockdown are sufficient to prevent vaginal virus transmission, then it really eases the next steps, which would be preclinical safety [and[phase I safety studies in humans. That also is a long process, but here I don't think we need a major technological advance such as in gene therapy to see this go into humans. We have all the tools now, and I'm confident that we will be able to formulate these molecules just with the knowledge we have now.

A big hurdle to [an HIV microbicide] would be compliance issues. Do you have any sense of how long the prophylactic effect might be sustained?

This is a complicated question because it not only depends upon your formulation — the stability of the siRNA molecules — but the turnover kinetics of whatever your target is going to be. So we have no *in vivo* data yet on CCR5, but the macaque studies will hopefully provide that.

You mentioned your collaborating with different people. Can you comment on who?

Right now, I don't think I have their permission to say who they are.

But they are both academic and industry?

Yes. And we're getting very strong industry support, which is a very nice thing.

Thus far we've been talking about microbicides, but what we're essentially talking about is transient mucosal gene therapy. Transient because we expect the siRNA effect to wear off after either it is destroyed or the gene target turns over. Gene therapy because it is gene therapy — we're silencing a gene. We don't need a viral vector to do this, but if you look at the types of diseases that this could have a potential impact on, an obvious one is inflammatory bowel disease.

We have very nice data in a murine model showing that we could potentially knock down inflammatory mediatorsl. The next step, of course, is to see in inflammatory bowel disease whether such knockdown would impact disease severity.

What targets are you looking at?

The obvious targets in IBD that most people agree on are things such as TNF-alpha and NF-kappa B, for which there are already existing therapies but which are systemic. This would allow a localized anti-cytokine therapy. And that is the sort of disease that an siRNA drug is going to be ideal for.

Is that indication something you are actively pursuing?

Yes. And for [this] we also have strong commercial backing. We are needing milligram quantities of siRNA. And another thing we haven't talked about is that there are a lot of people out there who are accumulating expertise on the structural modifications, the chemical modifications, that could potentially render an siRNA molecule more stable, more potent. That field of study, which we're not directly involved in but [for which we] are tapping into the expertise of our collaborators, is going to be extremely important, as well, as we decide what form of siRNA to formulate.

People in the News

Andrew von Eschenbach has been named acting commissioner of the **US Food and Drug Administration** following the resignation of former commissioner **Lester Crawford** last week.

Von Eschenbach has been director of the **National Cancer Institute**, part of the **National Institutes of Health**, since January 2002. Before that, he worked as a doctor and executive at the **M D Anderson Cancer Center** in Houston. Von Eschenbach has said that he intends to act as both head of the FDA and director of NCI.

The appointment ends the tenure of Crawford who resigned last Friday.

Crawford, a veterinarian and expert on food safety, was named deputy commissioner of the agency in early 2002 before his tenure as acting commissioner began last year.

In a message to colleagues, Crawford cited his age — 67 — as a factor in his decision to step aside.

Douglas Throckmorton has been named deputy director of the **Center for Drug Evaluation and Research** by the FDA. Throckmorton joined the FDA in 1997 and has been acting deputy director of CDER since May 2004.

Before joining the FDA, Throckmorton practiced medicine and held academic appointments at the **Medical College of Georgia** and the **VA Medical Center** in Augusta, Ga.

Walter Narajowski has been named president and CEO of **Pathways Diagnostics**, the assay development company said this week. He will also join the firm's board of directors.

Narajowski was formerly the vice president and general manager of **Focus Diagnostics'** infectious disease reference lab. Prior to Focus, Mr. Narajowski spent over 20 years at **Abbott Laboratories**, where he was most recently vice president and general manager of critical care products and vice president and general manager of the infusion pump business.

Narajowski holds an MS in bioengineering from the **University of Utah** and a BSc in electrical engineering from **Illinois Institute of Technology**.

Assay Designs has appointed **Gustavo Salem** as its new president and CEO, the Ann Arbor, Mich.-based biotech firm said last week.

Prior to joining Assay Designs, Salem held a variety of positions at **Bio-Rad Laboratories**, including division manager of protein separations and business unit manager for biomaterials. Prior to this, he held a series of sales and marketing positions at **PerSeptive Biosystems, Beckman Instruments**, and **Amersham**.

IP Update

Title: *Nucleic Acid-Mediated Inhibition of Enterococcus Infection and Cytolysin Toxin Activity*

Number: 20050209182

Filed: Dec. 14, 2004

Lead Inventor: David Morrissey, Sirna Therapeutics

According to the patent application's abstract, the invention "relates to nucleic acid aptamers that bind to bacterial proteases such as CylA and methods for their use alone or in combination with other therapies, such as antibiotics. Also disclosed are nucleic acids such as siRNA, antisense, and enzymatic nucleic acid molecules that can modulate the expression of CylA genes. The compounds and methods of the invention are expected to inhibit enterococcus infection and cytolysin activity," the abstract notes.

Title: *RNA Interference-Mediated Inhibition of Hepatitis C Virus Expression Using Short Interfering Nucleic Acid*

Number: 20050209180

Filed: Sept. 15, 2004

Lead Inventor: Vasant Jadhav, Sirna Therapeutics

"This invention relates to compounds, compositions, and methods useful for modulating HCV gene expression using short interfering nucleic acid molecules," the patent application's abstract states. "This invention also relates to compounds, compositions, and methods useful for modulating the expression and activity of other genes involved in pathways of HCV gene expression and/or activity by RNA interference using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid, short interfering RNA, double-stranded RNA, microRNA, and short hairpin RNA molecules and methods used to modulate the expression of HCV genes."

Title: *RNA Interference-Mediated Treatment of Alzheimer's Disease Using Short Interfering Nucleic Acid*

Number: 20050209179

Filed: June 25, 2004

Lead Inventor: James McSwiggen, Sirna Therapeutics

"This invention relates to compounds, compositions, and methods useful for modulating beta-secretase, amyloid precurson protein, PIN-1, presenillin 1, and/or presenillin 2 gene expression using short interfering nucleic acid molecules," the patent application's abstract states. "This invention also relates to compounds, compositions, and methods useful for modulating the expression and activity of other genes involved in pathways of BACE, APP, PIN-1, PS-1, and/or PS-2 gene expression and/or activity by RNA interference using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules,

such as short interfering nucleic acid, short interfering RNA, double-stranded RNA, microRNA, and short hairpin RNA molecules and methods used to modulate the expression of BACE, APP, PIN-1, PS-1, and/or PS-2 genes."

Title: *RNA Interference-Mediated Inhibition of 11Beta Hydroxysteriod Dehydrogenase-1 Gene Expression*

Number: 20050208658

Filed: Nov. 19, 2004

Inventor: Thomas Castonguay, University of Maryland

According to the patent application's abstract, the invention relates "to compositions comprising double stranded RNA capable of inhibiting the expression of the gene encoding 11beta HSD-1, and methods of using the compositions in therapeutic, prophylactic, and research methods."

Title: *Methods and Apparatus for Determination of RNAi Cell Transfection Effects by Multiple Gene Expression Analysis on Microarrays*

Number: 20050208518

Filed: Nov. 12, 2004

Lead Inventor: Francoise de Longueville, Eppendorf Array Technologies

"The invention provides a tool and a method for the easy interpretation of the changes occurring in a cell, being a three dimensional complex and control system when transfected by RNAi," the patent application states. "The method is based on the analysis of a limited number of data obtained by quantifying the intensity of the signals present on spots distributed in a two dimensional surface. The invention allows to observe the effects of the presence of a particular RNAI on the cells main vital cellular functions together with the possible side or deleterious effects resulting from the transfection process or to the presence of the RNAi in a cell," the abstract adds. "The invention also provides a method for the determination of change in the three dimensional status of a cell, wherein an array containing nucleic acids or proteins belonging to or being representative for at least 5 vital cellular functions together with 3 deleterious functions."

Strands

GE Healthcare to Manufacture miRNA Arrays for Ambion on CodeLink Chips

GE Healthcare will manufacture microRNA microarrays on its CodeLink platform for Ambion, the companies said today.

These arrays, called mirVana miRNA microarrays, include a panel of known human, mouse, and rat miRNAs, as well as Ambion's "proprietary" and "non-published" microRNAs, called Ambi-miRs. Ambion will market the arrays, according to a company spokesperson.

Financial terms of the deal were not disclosed.

Sirna Stands to Gain $250M from Allergan in AMD Drug Pact …

Sirna Therapeutics stands to pocket $250 million in milestone and other payments as part of a deal with Allergan to develop an RNAi-based therapeutic for age-related macular degeneration and discover and develop other RNAi-based drugs against gene targets developed by Allergan for ophthalmic diseases, the companies said this week.

Terms of the alliance call for Sirna to receive an initial payment of $5 million and be eligible for development milestones of up to $245 million in addition to research funding and royalties on the worldwide sales of products resulting from the collaboration, the companies said in a statement. Sirna said it will also receive contract manufacturing revenues.

Allergan will assume all development and future commercialization responsibilities for the AMD drug, Sirna-027, which is currently in Phase I studies, and will bring to the alliance its ocular drug-delivery technologies, the firms said. Sirna will develop optimized lead compounds against Allergan's identified gene targets and Allergan will be responsible for all pre-clinical, clinical, and commercialization activities for those compounds.

The companies will form a Joint Steering Committee to oversee the research and move Sirna compounds through Allergan's discovery and development pipeline, the partners said.

… and Wins UK Patent Covering siRNA-Based Gene Expression Inhibition

Sirna Therapeutics said this week that it has been issued a UK patent covering RNAi-mediated inhibition of gene expression using siRNAs.

According to the company, the patent claims are not limited to a specific to an siRNA sequence or structure, and broadly cover any siRNA molecule which targets conserved sequences within a virus or a gene.

Sirna noted that the patent — No. GB 2396616 — covers the development of siRNA drugs in areas such as hepatitis C and HIV, as well as respiratory syncytial virus, influenza virus, bird flu virus, and severe acute respiratory syndrome — three indications that rival Alnylam Pharmaceuticals is pursuing.

The patent is entitled, "RNA Interference Mediated Inhibition of Gene Expression Using Short Interfering

Nucleic Acid."

Amaxa to Optimize Nucleic Acid Technology Using ATCC Cell Lines

Amaxa said this week that it has signed a deal under which it will develop and optimize protocols for its nucleofector nucleic acid transfer technology using cell lines from the American Type Culture Collection.

"It is our goal to enable our customers to genetically manipulate the cell types they consider the best experimental model," Rainer Christine, CEO of Amaxa, said in a statement. "In looking for a partner, we needed a large collection of cell lines that came with reliable authentication. ATCC was the obvious choice."

Additional terms of the arrangement were not disclosed.

FDA Lifts Hold on CytRx ALS Drug, Grants Fast Track Status

CytRx said last week that US regulators have lifted a hold on a phase II clinical trial of the company's investigational small molecule amyotrophic lateral sclerosis arimoclomol.

As a result, CytRx said it has begun the phase II trial, and patient enrollment has commenced at several sites.

CytRx also announced this week that the US Food and Drug Administration has granted fast track status to arimoclomol. According to the company, the designation allows for scheduled meetings seeking FDA input into development plans, the option of submitting a new drug application in sections rather than submitting all components simultaneously, and the option of requesting evaluation of studies using surrogate endpoints.

ABI, Promega Settle Litigation Over PCR Technology

Applied Biosystems said this week that it has settled its litigation with Promega over PCR technology.

Promega originally sued Hoffman-La Roche and Applera in the US District Court for the Eastern District of Virginia on behalf of the US government but the court dismissed the company's amended complaint with prejudice a year ago. Both Promega and Applera filed appeals at the time, which they have now withdrawn.

Promega's suit was based on the False Claims Act, also known as the Informer's Act or the Qui Tam Statute, which allows a private person to sue a person or company that knowingly submits false bills to the federal government.

Following the settlement, Promega can now negotiate a license to Roche's PCR patents with ABI, the exclusive licensor of the patents for life science research and applied fields, according to ABI.

Earlier in the month, Promega settled its PCR-related litigation with Roche.

Qiagen to Acquire PCR-based Dx Maker Shenzhen PG Biotech

Qiagen said this week it plans to acquire Chinese molecular diagnostics company Shenzhen PG Biotech for

$14.5 million in cash.

Under the terms of the agreement, which is pending Chinese government approval and subject to certain closing conditions, Qiagen will acquire all outstanding shares of Shenzhen-based PG Biotech. More than half of the company's shares are currently held by state-owned institutions. Depending on the date of the closing, Qiagen expects the acquisition to contribute $6millionn to $7 million in sales over 12 months.

PG Biotech, which has a staff of 120, with a "substantial number" in research and development, according to Qiagen, provides PCR-based molecular diagnostic assays in China. The company has more than ten assays approved by the Chinese State Food and Drug Administration, including assays for pathogens such as SARS, HBV, HPV, *Mycobacterium tuberculosis, Neisseria,* and *Chlamydia.* In addition, PG Biotech provides assays for import/export controls and quarantine testing, and is developing panels for disease profiles. Qiagen said PG Biotech's business profile is "comparable" to that of Artus, which the company acquired earlier this year.

This is not Qiagen's first foray in to the Chinese market: in June, the company acquired nucleic acid reagent provider Tianwei Times. Qiagen also opened an office in Shanghai this year and strengthened its distribution channels with Gene Company.

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