Developing Novel Therapies and Unique Delivery Methods to Improve Treatment for Bleeding Crises, Leukemia: Program

This session looks at a number of new therapies and delivery methods, from early studies to Phase III trials. Research to be presented during this briefing adds to the growing body of evidence that gene therapy and emerging drug delivery methods hold promise for patients with various forms of blood diseases.

Allan Doctor, et al.

1027 Erythromer (EM), a Nanoscale Bio-Synthetic Artificial Red Cell: Proof of Concept and *In Vivo* Efficacy Results

Conclusion: The ErythroMer prototype has passed rigorous initial *ex vivo* and *in vivo* "proof of concept" testing and bench testing, which suggests this design surmounts prior challenges (by HBOCs) in emulating normal RBC physiologic interactions with O2 and NO. In models of major bleeding/anemia, EM reconstitutes normal hemodynamics and O2 delivery, observed at the system, tissue, and cellular level. EM potential for extended ambient dry storage has significant implications for portability and use. Next steps include formulation scaling, detailed study of pharmacokinetics, biodistribution and safety, as well as evaluation in large animal models of hemorrhagic shock.

ASH Press Release: Researchers have developed the first artificial red blood cells designed to emulate vital functions of natural red blood cells. If confirmed safe for use in humans, the nanotechnology-based product could represent an innovative alternative to blood transfusions that would be especially valuable on the battlefield and in other situations where donated blood is difficult to obtain or store. The artificial cells, called ErythroMer, are designed to be freeze-dried, stored at ambient temperatures, and simply reconstituted with water when needed.

"One key goal is to advance field resuscitation of civilian trauma victims in remote settings and soldiers who are wounded in austere environments without access to timely evacuation," said lead study author Allan Doctor, MD, of Washington University in Saint Louis. "ErythroMer would be a blood substitute that a medic can carry in his or her pack and literally take it out, add water, and inject it. There are currently no simple, practical means to bring transfusion to most trauma victims outside of hospitals. Delays in resuscitation significantly impact outcomes; it is our goal to push timely, effective care to field settings."

Proof-of-concept studies in mice, conducted in partnership with Greg Hare MD, PhD, at the University of Toronto, demonstrate that the artificial cells capture oxygen in the lungs and release it to tissues — the main functions of red blood cells — in a pattern that is indistinguishable from that seen in a control group of mice injected with their own blood. In rats, ErythroMer effectively resuscitated animals in shock following acute loss of 40 percent of their blood volume.

The donut-shaped artificial cells are formulated with nanotechnology, in partnership with Dipanjan Pan, PhD, at the University of Illinois at Urbana-Champaign, and are about one-fiftieth the size of human red blood cells. A special lining encodes a control system that links ErythroMer oxygen binding to changes in blood pH, thus enhancing oxygen acquisition in the lungs and then dispensing oxygen in tissues with the greatest need. Tests show ErythroMer matches this vital oxygen binding feature of human red blood cells within 10 percent, a level the researchers say should be sufficient to stabilize a bleeding patient until a blood transfusion can be obtained.

So far, tests suggest ErythroMer has overcome key barriers that halted development of previous blood substitutes, including efficacy and blood vessel narrowing. The team's next steps are testing in larger animals, ongoing safety assessment, optimizing pharmacokinetics, and ultimately conducting in-human clinical trials. The researchers are also pursuing methods for scaling up production. If further testing goes well, they estimate ErythroMer could be ready for use by field medics and emergency responders within 10-12 years.

ErythroMer development has been supported by the Children's Discovery Institute at Washington University and St. Louis Children's Hospital, the Skandalaris Center at Washington University and the BioSTL Fundamentals Program.

Allan Doctor, MD, Washington University in St. Louis, will present this study during an oral presentation on Monday, December 5 at 4:30 p.m. in Ballroom 20D of the San Diego Convention Center.

Webcast:

Katherine A. High et al.

3: Updated Interim Data from SPK-9001 Phase 1/2 Trial Hemophilia B

Conclusion: As of 8/4/2016, we report the highest and most consistent levels of sustained vector-derived FIX:C following FIX gene transfer. Levels of FIX:C achieved by SPK-9001 permitted termination of prophylaxis, prevention of bleeding, and nearly complete cessation of factor use. Despite the heterogeneity in subjects with respect to presence and extent of hemophilic arthropathy, age, and co-morbidities,

consistency of transgene expression and clinical outcomes have been observed in all participants studied to date. A vector dose of 5x1011vg/kg is the lowest dose currently reported in hemophilia gene transfer trials; the absence of any observed CD8+ T cell immune response supports the hypothesis that lowering the dose can reduce or eliminate the risk of a capsid-specific immune response and maximize efficacy. In summary, preliminary data suggest SPK-9001 safely and consistently produces sustained elevation in FIX:C levels sufficient to prevent spontaneous hemarthroses without the need for factor consumption or immunosuppression.

ASH Press Release: Preliminary data from an ongoing Phase I/II trial suggest that patients with hemophilia B, who are born unable to produce the blood-clotting protein factor IX (FIX), began producing FIX at sufficient levels after receiving a single infusion of an investigational gene therapy product called SPK-9001. The results show the highest and most consistent levels of FIX production of any gene therapy tested to date, according to the researchers.

FIX is crucial to the formation of blood clots and prevention of life-threatening uncontrolled bleeding. This ongoing trial involves nine previously treated adult patients with a baseline FIX of less than 2 percent, which is considered extremely deficient. As of the November 30, 2016, data cut off, seven of the nine patients who have progressed to at least 12 weeks post-vector administration showed FIX levels in the range of 12-46 percent with a mean steady-state level greater than 28 percent, a range the researchers say is close enough to normal (at least 50% in healthy adults). Maintaining a minimum level of 12 percent is considered necessary to prevent minor, chronic bleeding in the joints, a common cause of disability in patients with hemophilia.

SPK-9001 uses an inactive virus to deliver into a patient's cells a small section of DNA that, when stabilized in the patient's own liver cells, allows the body to produce FIX. Current standard of care for hemophilia B requires patients to self-administer intravenous infusions of laboratory-produced FIX at regular intervals, typically one to two times a week. A key downside of this standard regimen is that it causes FIX levels to fluctuate widely, and patients may need to limit their activities to avoid breakthrough bleeding when their FIX levels are low.

The FIX levels achieved with SPK-9001 to date in this study have been sufficient to allow patients to engage in normal daily activities without the need for FIX infusions. Eight of the infused patients have required no factor IX concentrates to prevent or control bleeding events since the day after vector administration. One participant with severe joint disease self-administrated a precautionary infusion two days after administration of SPK-9001 for a suspected ankle bleed and again at week 35 post the data cut-off date and despite a factor IX activity level of 36, for a suspected knee bleed. In addition, six patients reported increased physical activity and improved quality of life.

"One of the potential innovations with a gene therapy for hemophilia B, compared to factor IX infusions, is that once an individual establishes a stable factor activity level, then they may remain at that level for an extended time," said Katherine A. High, MD, of Spark Therapeutics, Inc. in Philadelphia. "At the factor IX levels seen in this study, most normal activities of daily living should be open to people with

hemophilia. It could be a potential paradigm shift in the treatment of hemophilia."

Two participants recently suffered an autoimmune response and were put on corticosteroids. Despite the immune response and decline in FIX activity level, these two participants have not had any bleeds or required replacement FIX. The researchers will continue to track patient outcomes for at least five years.

Funding for the study was provided by Spark Therapeutics and Pfizer, Inc.

Katherine A. High, MD, Spark Therapeutics, Inc., Philadelphia, will present this study during the ASH press conference. Lindsey A. George, MD, Department of Pediatrics, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, will present this study during the Plenary Scientific Session on Sunday, December 4 at 2:00 p.m. in Hall AB of the San Diego Convention Center.

Webcast:

Caroline E. Hansen,et al.

81 Leveraging the Contractile Force of Platelets for Targeted Factor VIII Delivery in Hemophilia with Inhibitors

Conclusion: These microcapsules use platelets from the patient to target and deliver encapsulated FVIII – a new paradigm in targeted drug delivery. *In vitro* experiments show this technology increases FVIII efficacy for hemophilia A patients with inhibitors due to shielding from neutralizing antibodies. Current work evaluating localized thrombin generation due to the FVIII loaded microcapsules and the effect of platelet contraction force via pharmacologic agents such as blebbistatin, ROCK, and myosin inhibitors are ongoing.

ASH Press Release: A new drug delivery technology uses the body's natural processes to supply the blood-clotting protein factor VIII (FVIII) directly to the site of a developing clot to stop bleeding in patients with hemophilia A. The approach, in which small amounts of FVIII are encased within microscopic capsules that are injected into the bloodstream, could significantly improve outcomes for the approximately 30 percent of patients with severe hemophilia A in which direct infusion of FVIII triggers an immune response.

People with hemophilia A do not produce FVIII, a protein necessary for forming blood clots, putting them

at risk of dangerous uncontrolled bleeding. The standard treatment for these patients is intravenous infusion of FVIII; however, if the patient's immune system attacks the infused FVIII, the drug's effectiveness is greatly reduced. These patients often require several infusions a day to control a single bleeding event.

In vitro experiments show the new microcapsules act as a shield that allows the FVIII payload to fly under the immune system's radar and potentially stem bleeding with only one or two injections. In addition, the microcapsules are designed to go directly to the site where FVIII is needed by hitchhiking on platelets, cell fragments present in blood that play a key role in clot formation.

"This is a completely new way to target delivery of a biologic drug, capitalizing on the natural functions of cells that are already in your body," said Caroline E. Hansen, a graduate student in the laboratory of bioengineer and pediatric hematologist Wilbur A. Lam, MD, PhD, of the Georgia Institute of Technology and Emory University in Atlanta. "We're utilizing platelets' natural behavior to accomplish targeting and delivery. Because platelets are so heavily relied upon in the clot formation process, they could actually carry these microcapsules to the forming clot or the site of injury."

After binding to platelets and traveling to a forming clot, the microcapsules are designed to burst open, releasing FVIII. This bursting occurs when platelets join a clot and contract. The FVIII then stimulates the formation of fibrin at the site, creating a mesh network that holds the blood clot together.

The researchers recently tested their microcapsules in laboratory experiments that model sites of blood vessel injuries, comparing the amount of fibrin formed when FVIII was delivered via microcapsules versus traditional systemic infusions. They found that the microcapsules resulted in 2.7 times as much fibrin formation compared to a systemic FVIII infusion when immune antibodies were present, a test that mimicked what happens when FVIII infusions trigger an immune response in a person with hemophilia A.

After further examination of how the microcapsules influence the formation of fibrin, the team plans to test the microcapsules in mouse models.

Funding for the study was provided by the NIH (U54HL112309) and the NSF (1150235).

Caroline E. Hansen, BS, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta will present this study during an oral presentation on Saturday, December 3 at 10:00 a.m. in Room 28ABCD of the San Diego Convention Center.

Webcast:

Jeffrey E. Lancet, et al.

906 Survival Following Allogeneic Hematopoietic Cell Transplantation in Older High-Risk Acute Myeloid Leukemia Patients Initially Treated with CPX-351 Liposome Injection Versus Standard Cytarabine and Daunorubicin: Subgroup Analysis of a Large Phase III Trial

Conclusion: An exploratory analysis from this phase III study demonstrated that CPX-351, compared with standard cytarabine and daunorubicin, resulted in better outcomes after allogeneic HCT in older patients with high-risk AML, including 53% fewer deaths within 100 days of transplant. These results suggest that CPX-351 may provide an effective bridge to successful transplant for a very poor-risk subgroup of AML patients.

ASH Press Release:

A new analysis shows older patients with acute myeloid leukemia (AML) survived longer after receiving an allogeneic stem cell transplant if they were first treated with the experimental chemotherapy delivery method known as CPX-351 instead of the standard “7+3” administration of chemotherapy drugs cytarabine and daunorubicin. Researchers say the findings are encouraging for improving survival among high-risk AML patients who currently have limited treatment options and poor survival rates.

The new study is a subgroup analysis of a large Phase III randomized controlled trial completed earlier this year that found CPX-351 nearly doubled overall survival compared to the 7+3 regimen. The researchers examined survival and other health outcomes among trial participants who received chemotherapy and then hematopoietic stem cell transplantation, a treatment that provides healthy replacement stem cells to the bone marrow to better equip patients to fight the disease on their own.

Of 309 total trial participants, 91 received an allogeneic stem cell transplant, including 52 in patients who received CPX-351 compared with 39 in patients receiving 7+3. CPX-351-treated patients were also more likely to undergo transplantation while in a remission state (75% of CPX-351 vs. 62% of 7+3). In the first 100 days after transplantation there were 53 percent fewer deaths among patients receiving CPX-351 compared with those receiving 7+3 therapy.

The active ingredients of CPX-351 are the same as those in the 7+3 regimen, but in contrast to 7+3 in which cytarabine and daunorubicin are delivered separately, CPX-351 encapsulates the drugs into a single delivery vehicle in a fixed synergistic molar ratio.

“The two drugs together are delivered to the cell in the proper synergistic ratio that optimizes the cell-killing ability of these two drugs,” said lead study author Jeffrey E. Lancet, MD, of the Moffitt Cancer Center in Tampa, Fla. “We think that by doing this, we can improve delivery to the cancer cells at the proper ratio.”

The trial focused on the group of AML patients considered at high risk; all participants were older than 60 and had AML related to prior chemotherapy, AML arising from MDS, or AML MDS-related cytogenetic abnormalities.

The study was funded by Celator Pharmaceuticals, Inc., a subsidiary of Jazz Pharmaceuticals plc.

Jeffrey E. Lancet, MD, Department of Malignant Hematology, Moffitt Cancer Center, Tampa, Fla., will present this study during an oral presentation on Monday, December 5 at 4:00 p.m. in San Diego Ballroom AB of the Marriott Marquis San Diego Marina.

Webcast:

Terry J. Fry, et al.

650: MRD Negative Complete Remissions Following Anti-CD22 CAR in Children and Young Adults with Relapsed/Refractory ALL

Conclusion: This first-in-human anti-CD22 CAR T-cell therapy is safe, feasible and clinically active in patients with leukemia who have undergone prior CAR therapy. MRD negative complete remissions were seen in patients who were both CAR-naïve or had previously been treated with anti-CD19 CAR and were CD19 negative. Accrual is ongoing.

ASH Press Release: Children and young adults with relapsed or refractory ALL who receive chimeric antigen receptor (CAR) T-cell therapy targeting CD22, a protein found on the surface of leukemic cells, appear to mount a clinical response and, in some cases, achieve remission. Researchers from the Pediatric Oncology Branch of the National Cancer Institute of the National Institutes of Health genetically altered patients' own T cells to track down and kill cancer cells expressing CD22. The study — the first to evaluate CAR targeting CD22 in humans — also gives a first glimpse into how patients who already received CAR-T therapy directed at a different antigen, CD19, might fare when given a second immunotherapy.

Data are presented for 16 patients who received the new anti-CD22 therapy. One of the six patients treated at a lower dose initially set by the U.S. Food and Drug Administration (FDA) and other agencies attained remission. The majority – eight of 10 – participants treated at a higher dose level (a dose comparable to that used by current CD19 CAR programs) attained a complete remission without evidence of residual disease after one month of their infusion. There have since been relapses among six out of nine patients who achieved remission, the majority of which are due to drops in CD22 expression on the cells, which has similarly been observed with CD19 CAR therapy. So far, one patient remains in remission beyond one

year.

“We’ve been able to show that you can give a second CAR therapy that is directed against a different antigen and have it be safe and effective,” said study author Terry J. Fry, MD, of the Center for Cancer Research, National Cancer Institute in Bethesda, MD.

Dr. Fry said this adds to the notion that a single antigen-directed CAR immunotherapy probably won’t be sufficient for long-term durable remissions in many patients and points to the potential for targeting multiple cancer-related proteins (also called bispecific targeting).

Participants in this Phase 1 trial had relapsed or treatment-resistant ALL and were either CAR naïve or previously treated with anti-CD19 CAR T cells and/or blinatumomab therapy and some who became resistant to CD19 CAR due to loss of CD19. The patients, ranging in age from 7– 22 years old, all had CD22+ ALL and had previously undergone at least one allogeneic stem cell transplant. A majority of participants (11 out of 16) had relapsed after receiving anti-CD19 CAR T cell before entering the trial. Researchers collected T cells from eligible patients and modified them to recognize and bind to CD22. Patients then received an infusion of their own modified cells and were evaluated for response and adverse effects after an average of 28 days.

The primary adverse event was cytokine release syndrome, a common, potentially dangerous reaction to this type of infusion, which Dr. Fry reports was mild in all cases; fever and low blood pressure were the main symptoms. There was one death due to sepsis that occurred after resolution of cytokine release syndrome.

While the trial is continuing to accrue patients, these early results raise new questions about how anti-CD22 CAR therapy might best be used; for example, if it is better to wait for relapse after initial CAR therapy or preempt it by co-treating it. Dr. Fry and his team plan to investigate the combined use of anti-CD19 and CD22 CAR targeting approaches with the hypothesis that this will increase the likelihood of sustained remission.

This study was funded by the National Institutes of Health.

Terry J. Fry, MD, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Md., will present this study during the ASH press conference. Nirali N. Shah, MD, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Md., will present this study during an oral presentation on Monday, December 5 at 7:15 a.m. in Room 6CF of the San Diego Convention Center.

Webcast: