



ALLIANCE_{for}
Regenerative Medicine

2015

Annual Data Report

on gene and cellular therapies and the regenerative medicine sector

The background of the slide features a complex, stylized molecular structure in shades of light blue. It consists of various interconnected circles and spheres of different sizes, some with white outlines, creating a network-like pattern that resembles a chemical or biological structure. The overall aesthetic is clean and scientific.

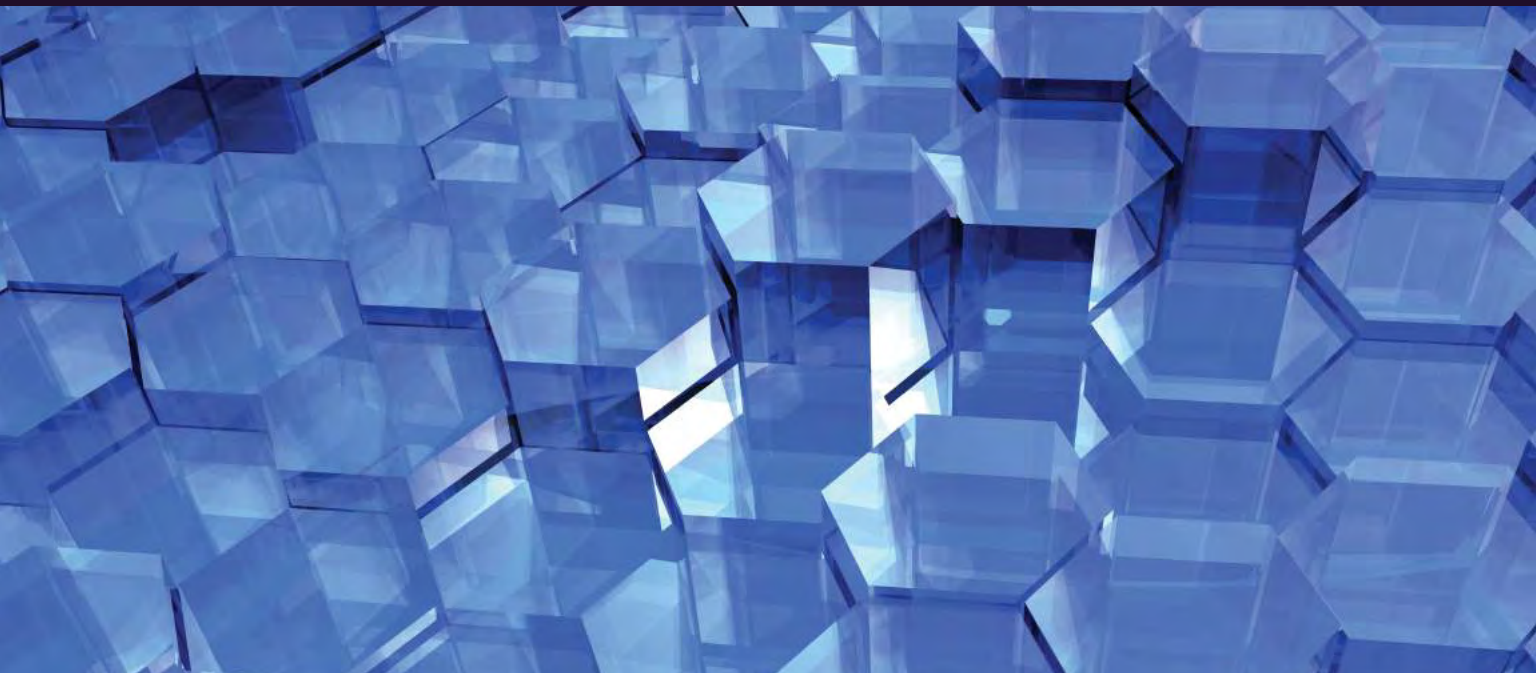
ALLIANCE for *Regenerative Medicine*

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

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Industry Overview

672+

Regenerative Medicine Companies Worldwide,
Including Gene and Cell Therapies

185

Europe
& Israel

112

Asia

349

North
America

10

South
America

1

Africa

15

Australia &
New Zealand

Industry Overview

Key companies working in cellular, gene and other regenerative medicine breakthroughs experienced an outstanding year in this expanding and transformative area of the biotech industry. New IPOs, M&As, financing rounds, dealmaking and partnerships continued in a steady growth pattern throughout 2015 with large investments by leading biopharma companies, including Eli Lilly, BMS, AstraZeneca, Sanofi and Biogen in a wide variety of gene and cell therapies. This year also saw numerous partnerships among regenerative medicine companies themselves, including Juno with Fate Therapeutics and Editas Medicine, and bluebird with Five Prime and Kite Therapeutics.

Gene editing technologies had some of the highest deal values of the year. CRISPR Therapeutics and Vertex signed a \$2.6 billion four-year agreement to use CRISPR-Cas9 to attack genetic defects in cystic fibrosis and sickle cell disease, among others. Cellectis' news that its allogeneic TALEN gene-edited CAR-T immunotherapy put a patient with ALL into remission no doubt encouraged Pfizer and Servier to morph their existing deals with the company into exclusive global license and collaboration agreements worth a potential \$3.8 billion. Voyager also closed a sizeable deal with Genzyme with the potential for \$845 million, looking at therapies in neurological diseases, while uniQure's deal with BMS for up to \$2.3 billion will concentrate on cardiovascular targets.

One of the largest cell therapy deals was a 10-year agreement reached between Juno and Celgene for immunotherapeutics. Worth \$1 billion, it centers on research in oncology and autoimmune diseases, based on Juno's expertise in TCR and CAR-T therapies. Kite Pharma and Alpine Immune Sciences entered into a \$535 million agreement in which Alpine will license their transmembrane immunomodulatory protein technology that Kite will use to enhance their CAR-T and TCR therapies targeting the immune synapse and the tumor microenvironment.

Clinical optimism and success was noteworthy this year with gene and cell therapies moving more rapidly into the clinic. Mesoblast had multiple clinical trial announcements, reporting positive Phase II trial results from its allogeneic cell therapy product for diabetes and chronic kidney disease, and moved into Phase III with allogeneic MPCs for several indications. uniQure revealed promising trial data in a small gene therapy trial of MPSIIIB patients as well as preliminary data from the Phase I/II in hemophilia B. Adaptimmune, Celldex Therapeutics and Kite Pharma all announced they had moved into Phase I/II studies for different forms of cancer. Biomarin initiated a Phase I/II trial using its investigational gene therapy for the treatment of patients with hemophilia A. However, despite overall positive results for its Phase I/II beta-thalassemia gene therapy, bluebird bio reported that a subset of patients with a more severe gene mutation didn't respond to treatment. Additional clarity to come in 2016 as the company treats more patients and longer follow-up data is made available.

As we move into 2016, companies involved in regenerative medicine continue to sustain elevated interest from investors of all types. It is an exciting field to watch as deals and agreements could potentially increase in both number and value, eclipsing results from 2015. We look forward to the continuing pace of discovery and development in this area and the implementation of collaborations to move greater disease understanding forward.

– Patricia Reilly
Executive Director – Medtrack

– Nancy Dvorin
Managing Editor – IN VIVO, Start-Up and Medtech Insight

Informa Business Intelligence,
Pharma and Healthcare



Financings



Total Financings:
\$10.8 Billion 2015
 Up 106% compared to 2014



Gene & Gene-Modified Cell Therapy: **\$6.8 Billion 2015**
 Up 84% compared to 2014



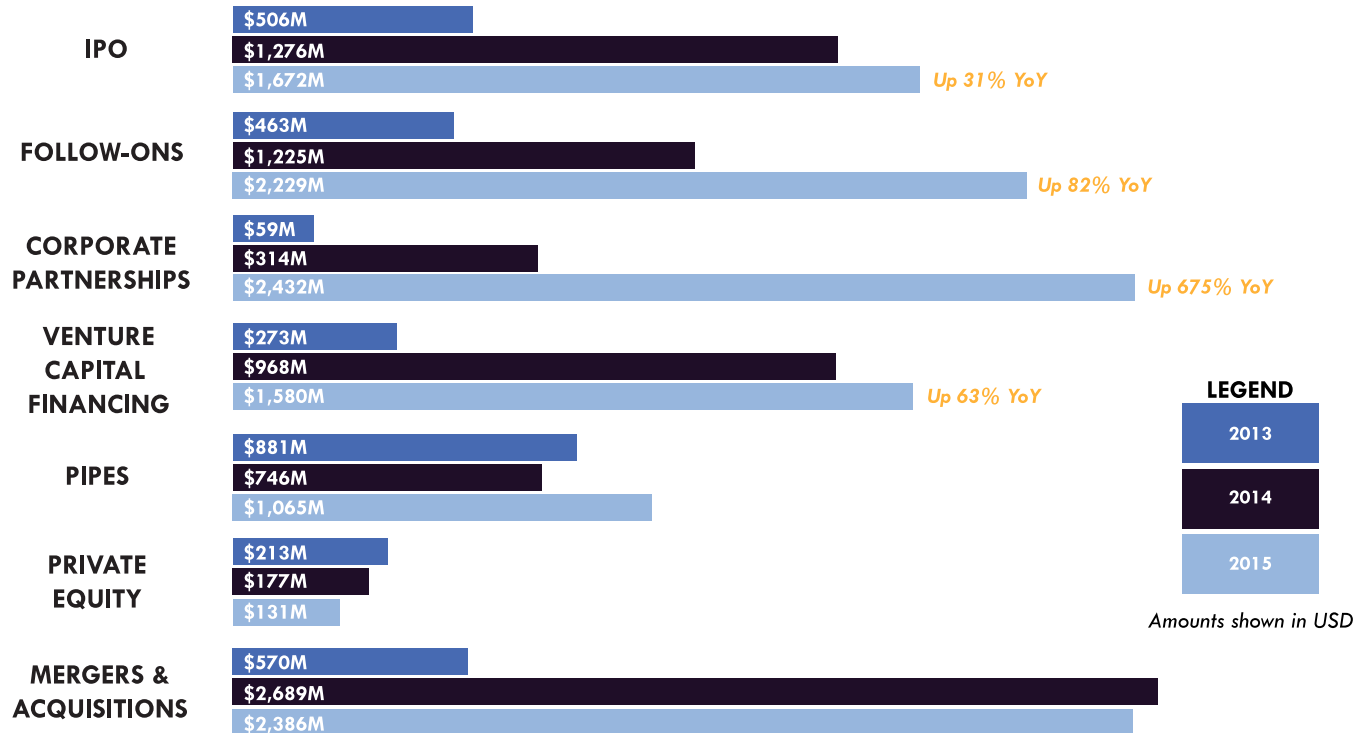
Tissue Engineering: **\$806.8 Million 2015**
 Up 175% compared to 2014



Cell Therapy: \$7.0 Billion 2015
 Up 104% compared to 2014

**Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.*

Total financings by type: by year



Examples of key corporate partnerships: 2015

Celgene and Juno announce 10-year collaboration (with initial payment of \$1B) to advance immunotherapies for cancer and autoimmune diseases

June 29, 2015

Vertex Pharmaceuticals and CRISPR Therapeutics establish 4-year collaboration (valued at \$2.6B, \$105M upfront) to discover and develop new treatments for genetic disease

October 26, 2015

uniQure N.V. and Bristol-Myers Squibb enter into exclusive strategic collaboration (valued at \$2.3B, \$100M upfront) to develop gene therapies for cardiovascular disease

May 26, 2015

Voyager Therapeutics signs agreement (valued at \$845M, \$100M upfront) with Genzyme for CNS disorder gene therapies

February 11, 2015

Amgen and Kite Pharma enter strategic cancer immunotherapy collaboration (valued at \$1.1B, \$60M upfront) to advance CAR-T cell therapies

January 5, 2015

Examples of key IPOs: 2015

- NantKwest, Inc. closes \$238.3M IPO – July 31, 2015
- Cellectis IPO raises \$228M to advance its CAR-T pipeline – March 25, 2015
- Adaptimmune closes \$191.3M IPO – May 11, 2015
- Spark Therapeutics IPO raises \$185.2M in IPO – February 4, 2015
- REGENXBIO closes \$159.4M IPO – September 22, 2015
- Aduro Biotech closes \$136.9M IPO – April 20, 2015
- Celyad SA raises \$100.1M with NASDAQ IPO – June 19, 2015
- Voyager Therapeutics closes \$80.5M IPO – October 12, 2015

Partnering & Dealmaking Environment

Key Trends in Partnering & Dealmaking in 2015:

- In 2015 in this sector, there were numerous deals with \$50M+ upfront payments, signaling a major commitment on behalf of large pharma and large-cap biotech to fund clinical development.
- Such activity also demonstrates confidence in the commercial potential of cellular, gene and other regenerative medicines.
- While the broad IPO and follow-on market declined towards the end of 2015, the overall sector performance for the year significantly surpassed that of previous years, enabling many companies to raise funds to support their clinical programs.

From our vantage point, large biopharma's interest in the transformative potential of gene therapy has continued to increase over the past year and we are optimistic that it will translate into more collaborations driving towards the development of innovative therapies to help patients in need. – Jeff Goater, Chief Financial Officer, Voyager Therapeutics



Jeff Goater
Chief Financial Officer
Voyager Therapeutics, Inc.

Fujifilm feels strongly that regenerative medicine is poised to deliver revolutionary therapies to treat a wide range of serious medical disorders such as macular degeneration, Parkinson's disease and heart disease, and that patients will greatly benefit from the scientific progress and investment being made in this area now.

It is for these reasons that in 2015 Fujifilm Holdings decided to acquire Cellular Dynamics International (CDI), the global leader in providing high-quality, fully-functional human cells derived from iPSCs. The combination of CDI's expertise in stem cell biology, and Fujifilm's diverse array of manufacturing technologies, will accelerate the development of cellular therapies that are desperately needed by patients around the world. – Kaz Hirao, CEO, Cellular Dynamics International (a FUJIFILM company)



Kaz Hirao
CEO
Cellular Dynamics International
(a FUJIFILM Company)



Partnering & Dealmaking Environment



Usman (Oz) Azam
Global Head,
Cell & Gene Therapies Unit
Novartis

Partnering and dealmaking was up significantly in 2015 compared to previous years, with corporate partnership upfront payments up 675% YoY. In your view, what technology development or change accounts for this?

There has been unprecedented growth and activity across the entire field of regenerative medicine, and I believe the increase in partnering is a reflection of this. From the bench to the clinic, collaboration has always been an essential part of drug development, be it small molecular or biologics, so it's not surprising to see partnering play an increasing role in this space. – UA

Has there been a shift in the perception of the commercial potential of gene & cell therapies? If so, would you say this has been a sudden change, or one that's been gradually developing over the past few years?

While the promise of cell and gene therapies has existed for decades, perceptions are formed by evidence, and recently have we seen an explosion of compelling clinical trial data across the field. These results have ignited a belief that cell and gene therapies hold the potential to be the next transformative pillar of medicine. – UA

What do you feel accounts for the uptick in partnering and dealmaking activity in this sector in 2015, while M&A activity has remained relatively flat (even decreased) compared to 2014?

As new science and technologies emerge, there are complex ecosystems which need to be established to support them. This was certainly true for cell and gene therapy based companies in 2015. Collaboration plays a central role in the value creation chain as nascent companies establish their infrastructure, whereas M&A activity tends to occur a bit further downstream at an inflection point. – UA

Would you say your company is looking to build value in this sector through developing internal or external RM/AT programs? Or a combination of both?

Within Novartis, we have embraced a mindset that enables us to seamlessly source, process and deliver cell therapies to clinical trial patients. To achieve this, we strike a balance between ensuring we have the right internal capabilities and talent while working in close collaboration with our partners. – UA

Europe's Regenerative Medicine & Advanced Therapy Sector



André Choulika
Chairman & CEO
Collectis

Looking back on 2015, how would you characterize the current state of the RM/AT sector in Europe?

Europe is making great advances as most of breakthrough innovations came also from Europe. At Collectis, we believe that advanced therapies are leading the way. – AC

The sector has been greatly developing and closely watching the leading company's clinical progress. European companies have ambitious development plans with real innovative approaches, however the European investors have been very cautious pushing these companies to seek fresh investment in US and in some cases in Asia. – CH



Christian Homsy
CEO
Celyad

We notice that the field of regenerative medicine is getting more traction. The industry is accelerating, with more and more clinical trials being initiated and products now steadily reaching the market, gradually making it an established technology. Several companies have been able to strengthen their financial position through listings on Euronext and Nasdaq in the past year and new initiatives have surfaced, increasing awareness among investors. The progress made in the last years indicates that the next big opportunity for the pharmaceutical industry in the coming years could be in the field of regenerative medicine. – TL

What were your company's or organization's topmost priorities for 2015 and how did you address those?

Our top priorities for 2015 included building a viable manufacturing run for UCART19, which we have achieved, delivering a first proof-of-concept in a first patient case, which we have achieved, as well as filing a clinical trial authorization for UCART19, which we have achieved as well. – AC



Thomas Lienard
Chief Business Officer
Bone Therapeutics

In 2015, Celyad's two top priorities were: (i) to set the foundations to support the operational challenges triggered by the upcoming clinical results of its European Phase III trial in ischemic heart failure (we also received IND clearance from the U.S. FDA for the clinical testing of C-Cure cardiopoietic cells delivered via our proprietary intra-myocardial injection catheter (C-Cathez) in the future Phase III Heart Failure Trial (CHART-2) in the U.S.); (ii) and to diversify our cell therapy portfolio which was achieved through the acquisition of CAR T-cell based immuno-therapy assets. We have also succeeded in consolidating our cash position with USD 100.1 million raised through our IPO on Nasdaq. This operation enables us to finance our development programs until 2017 and has considerably increased our visibility on the U.S. market. Celyad has also reinforced its management team with the appointment of seasoned executives that will help driving the growth and evolution of the Company. – CH

(continued on page 9)

Europe's Regenerative Medicine & Advanced Therapy Sector

(continued from page 8)

Our topmost priority in 2015 was strengthening the financial position of the company. We completed a successful Initial Public Offering in February 2015. We raised €37 million, an amount sufficient to fuel our clinical program for a period of approximately three years. In 2015, we also focused on advancing our pivotal Phase III trials and our allogeneic program that was kicked-off in 2014. Important safety results and first efficacy results, obtained during 2015, increase our confidence that we will be able to maximize the potential of our allogeneic platform. – TL

Would you say the financing environment for RM/AT sector improved in 2015? Can you comment on your outlook for 2016?

The first half of 2015 was a good financing environment, however, in the second half of 2015, the markets completely shut down. We were pleased to have completed our U.S. IPO in March, with \$228M in net proceeds. There are many great companies out there in the starting blocks now, waiting to go public, but it has not been easy. Funding always goes hand-in-hand with clinical data. Gene editing is just beginning to come into the clinic now, and what we have seen pre-clinically shows great promise and hopefully we will see some scientific breakthroughs soon. – AC

The first half of 2015 was a great opportunity for biotech companies to raise money, and several European cell therapies have taken advantage of the investor appetite and enthusiasm during this period. With the recent changes in the macroeconomic environment (oil price, China's slowing growth, etc.), while many still believe cell therapy is closer to becoming a reality, investors became cautious and increasingly sought data proof points. 2016 is going to be a pivotal year for companies to further build on the progress of their clinical activities. – CH

2015 was certainly another strong year with an increased interest of U.S. investors in European RM companies. For 2016, we will have to see down which road the general market takes us. Many value inflection points lie ahead for companies in our industry, and we remain positive for 2016. – TL

Can you please provide insight as to the major clinical progress or technical developments you're anticipating in 2016?

Celyad is looking for two major events in 2016. The first being the results from CHART-1, our European Phase III trial in ischemic heart failure, by mid-2016. This will be an important milestone for Celyad toward registration, and should we achieve positive results, the first cell therapy for ischemic heart failure. The second is the completion of the U.S. Phase I trial of our lead product NKG2D CAR T-Cell that is currently enrolling. – CH

In 2016 we intend to further validate our allogeneic platform with efficacy results in different indications. Another major development will be the preparation of our clinical trials in the U.S., which will be initiated upon receiving FDA approval. – TL

631

Clinical trials
underway by
year-end 2015

Ph. I: 192
Ph. II: 376
Ph. III: 63

Clinical Trials by Therapeutic Category: Year-End 2015

- More than 40% of current clinical trials are in oncology
- More than 12% are in cardiovascular



Major Clinical Milestones & Key Data Events

Cell-based immuno-oncology:

- In separate trials, Juno's investigational CAR T-Cell product candidates JCAR015 & JCAR014 demonstrate encouraging clinical responses in patients with relapsed or refractory lymphoblastic leukemia – Dec 7, 2015
- Kite Pharma receives FDA Breakthrough Therapy designation for KTE-C19 for treatment of refractory, aggressive non-Hodgkin Lymphoma – Dec 7, 2015
- Novartis releases new CTL019 phase II data demonstrating 93% complete remission in pediatric patients with relapsed/refractory acute lymphoblastic leukemia – Dec 7, 2015
- Great Ormond Street Hospital announces world's first use of gene-edited immune cells to treat 'incurable' acute lymphoblastic leukemia in one-year-old child, using Cellectis' TALEN gene edited allogeneic UCART19 product candidate – Nov 5, 2015

Gene therapy programs:

- Sangamo BioSciences announces FDA clearance of IND application for SB-FIX, the first in vivo protein replacement platform for treatment of hemophilia B – Dec 1, 2015
- Spark Therapeutics announces positive top-line results from pivotal phase III trial of SPK-RPE65 for genetic blinding conditions – Oct 5, 2015
- uniQure announces topline results from phase I/II trial in Sanfilippo B syndrome in patients treated with novel gene therapy, AMT-110 – Sept 19, 2015
- Dimension Therapeutics, Inc. announces FDA Fast Track designation for lead candidate DTX101 in patients with hemophilia B – Sept 17, 2015
- Audentes Therapeutics, Inc. receives orphan drug designation from the U.S. & EU's EMA for AT001 for treatment of x-linked myotubular myopathy – Aug 26, 2015
- Baxalta reports continued progress on Phase I/2 clinical trial of BAX335, investigational gene therapy treatment for hemophilia B – June 24, 2015
- GSK, Fondazione Telethon and Ospedale San Raffaele submit applications to EMA for gene therapy to treat rare immunodeficiency disease ADA-SCID – May 5, 2015

Cell therapy programs:

- U.S. FDA grants orphan drug designation to Pluristem's PLX-PAD cells for treatment of severe preeclampsia – Dec 31, 2015
- Mesoblast Limited licensee JCR Pharmaceuticals Co. Ltd. – first allogeneic regenerative medicine to receive full approval in Japan – Sept 17, 2015
- TiGenix announces Cx601 meets primary endpoint in pivotal phase III ADMIRE-CD trial in Crohn's patients with complex perianal fistulas – Aug 23, 2015
- U.S. FDA grants Fast Track designation to ReNeuron's retinitis pigmentosa cell therapy candidate – May 22, 2015
- The European Commission approves Chiesi's autologous stem cell product Holoclar for the treatment of patients with severe cornea damage – Feb 20, 2015

CAR-T & Adoptive T-Cell Therapies



Usman (Oz) Azam
Global Head,
Cell & Gene Therapies Unit
Novartis

In your view, what will drive investor and commercial interest in CAR-T and adoptive T-cell therapies, other than positive clinical data? What other drivers will contribute to its success in the next one to two years?

Compelling clinical data is of course the most important driver, but beyond that, I expect that investors will be looking carefully at manufacturing and distribution capability. The production of these new therapies requires an entirely new supply chain and those who are able to deliver GMP quality production will be very attractive from an investor's perspective. – UA

A fundamental belief at Juno is that, while the early results of CAR-T therapy are highly encouraging, we can improve on them. We are executing on our strategy to develop “best-in-class” therapies by developing “best-in-class” technologies that we believe will set the standard for efficacy, safety and manufacturability. – HB



Hans Bishop
CEO & President
Juno Therapeutics

What clinical progress can we expect from your company in the near term?

CTL019 is our lead program, and it is currently in Phase II development in pediatric relapsed/refractory acute lymphoblastic leukemia (r/r ALL) and diffuse large B cell lymphoma (r/r DLBCL). Novartis is aiming to file a BLA with the US FDA for CTL019 in pediatric r/r ALL in early 2017. – UA

Juno is making significant advances with our CD19-directed program and we are actively developing go-to market strategies in acute lymphoblastic leukemia, non-Hodgkin Lymphoma, and chronic lymphocytic leukemia. We are also evaluating CAR-T therapy for other hematologic cancers, including multiple myeloma. In addition, we will be in the clinic in 2016 with four novel targets against a range of solid organ cancers. – HB

In your view, what are the main challenges for this sector (regulatory, reimbursement, infrastructure, international harmonization, manufacturing, etc.) and how is your company addressing those?

As I mentioned, high-quality, consistent GMP level manufacturing is one of the most significant challenges. It's an area in which Novartis has invested heavily and is very well positioned. In late 2012, Novartis purchased from Dendreon Corporation the first FDA-approved GMP quality site for a cell therapy, which has a strong foundation for implementing the CTL019 manufacturing process and supporting its clinical supply and approval timelines. The facility space and infrastructure can accommodate additional future cell and gene production activities. – UA

There are parallels with the first decade of antibody therapeutics. We expect to see a fast pace of innovation in a number of areas, including a better understanding of T cell biology that will lead to improved efficacy and safety, a broader range of diseases that these therapies can address and fundamental changes in manufacturing technologies to make these products. Our challenge is to set the pace of these innovations. – HB

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CAR-T & Adoptive T-Cell Therapies

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What is the potential for this technology's use in solid tumors and why?

We are working in close collaboration with our partners at the University of Pennsylvania who are advancing exploratory trials of CTL019 and other CAR-T therapies in a variety of solid tumors. Indications include mesothelioma, pancreatic cancer, ovarian cancer and glioma. Solid tumors present a more challenging target for CAR-Ts than hematologic malignancies; however, there may be opportunities to target solid tumors with combinations of CAR-Ts and other therapies. There's active research in this space, but it is still early days. – UA

Evidence from the clinic, including with checkpoint inhibitors, demonstrates that T cells can kill solid tumors. There are a number of hurdles that are different than blood cancers, but we believe fundamentally in the potential of this technology in solid tumors, and we are investing in technologies and product candidates that we hope will benefit patients with these cancers. – HB

What are you most optimistic about as we move into 2016?

Every day I am struck by the dedication of the associates who work in our Novartis Cell & Gene Therapies Unit. As I think about their passion for bringing new therapies to patients who have exhausted all other treatment options, I am more than inspired, I'm humbled. Thanks to them, I'm truly optimistic about what we can achieve for patients in 2016 and beyond. – UA

Looking back in 2015, clinical data with CAR-T cells and TCRs developed in a very positive way. The long-term goal of company is to develop curative therapies in a range of different diseases. In 2016, we look forward to another year of positive developments that support T cell therapy as a third pillar of medicine. - HB



Gene Editing Technologies



André Choulika
Chairman & CEO
Collectis

2015 was a tremendous year for gene editing technology - in your view, what accounts for this excitement and what does that mean for your company?

Gene editing has been an ongoing revolution for many years, with TALEN as the main driver. These days, with the extensive coverage on nuclease technologies and their ease of use, the topic is widely discussed. This is great news for the gene editing space in general, as this will open the public's mind towards a new era of fighting disease. With more and more scientists working on gene editing around the globe, we will hopefully see more viable targets to go after, as there is a huge unmet medical need in genetically-based diseases. – AC

The excitement is driven by the vast potential to actually solve so many serious problems that have proven otherwise impossible. For our company, the broad market interest has made it much easier for us access the information, technology, talent and capital needed to explore new opportunities that exploit the power of our unique editing platform. – MK



Matthew Kane
CEO
Precision BioSciences

For those of us at Sangamo, it's very rewarding to see a growing realization of the potential therapeutic applications of modifying the genome and the possibility of using a precise and efficient method, such as ZFNs, to develop long-lasting and potentially curative therapeutics for human disease.

Over the past several years, Sangamo has been developing therapeutic applications of its zinc finger nuclease (ZFN) mediated genome editing technology. In our HIV program we have treated more than 80 subjects with ZFN-edited T-cells. The modified cells have durably engrafted and been well tolerated in all subjects. In multiple clinical studies we have demonstrated functional control of viral load and reduction of viral reservoir in treated subjects. We also have an open trial of the same approach in hematopoietic stem cells and are beginning clinical studies of the first *in vivo* applications of genome editing to evaluate our ZFP Therapeutics for hemophilia B and MPS I. – GN

In your view, what are the main challenges for this sector (regulatory, reimbursement, infrastructure, international harmonization, manufacturing, etc.) and how is your company addressing those?

We want to manage expectations that while the latest technologies have made significant advancements in making gene editing easier, we need to focus on safety and precision of the technology. There is also the huge question of delivery mechanisms – how easy is it to deliver, to vectorize the technology and how it fits in manufacturing processes. Another challenge is manufacturing – while you can get great results in a laboratory, translating these results into a large-scale production process is an entirely different and more challenging hurdle. Collectis has made great advances in building a manufacturing process for our gene-edited living cell product, UCART19, a TALEN gene-edited, allogeneic CAR T-cell product candidate designed to target the CD19 antigen in ALL and CLL patients. – AC

A key challenge for the sector involves the identification of the right application for the right editing platform and then marrying that to the right ancillary technologies and right expertise to best position the product for success. – MK

All of the issues mentioned are important challenges that must be included in discussions surrounding the commercialization of genome editing technology. We have worked closely with the regulatory agencies to develop the appropriate assays to assess specificity and safety of the technology as we have brought programs into clinical development. While we currently use contract manufacturing organizations for our clinical manufacturing, Sangamo has established delivery and manufacturing as a core competency; we have hired the necessary personnel to continue to develop and evolve our manufacturing capabilities. – GN



Geoff Nichol
EVP, R&D
Sangamo BioSciences

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Gene Editing Technologies

(continued from page 14)

As the developer of an enabling platform, are you anticipating working with partners in the application of genome editing technology to address therapeutic needs?

We are already working with great partners, Pfizer and Servier, on bringing our lead product candidates to the market and through this experience we will have a superb learning curve that will teach us how to speed up the development and commercialization of our wholly owned product candidate pipeline. – AC

Absolutely, and not just to address therapeutic needs. We anticipate (and are already) working with partners to develop editing products across the life sciences. This demands that we operate with a collaborative mindset and are always looking to work with other groups that possess critical expertise or technology in a given product area. – MK

Yes, we have already established collaborations for therapeutic applications of our technology with Biogen in hemoglobinopathies, such as sickle cell disease and beta-thalassemia, and with Shire in Huntington's disease. We will also evaluate collaboration opportunities for our HIV program as well as the application of our ZFN technology in T-cell immunotherapies. – GN

What are the major technical issues involved with genome editing, and how is your company addressing those?

After nearly two decades of gene editing, a few nuclease platforms successfully transitioned from research laboratory to industrial and therapeutic products. That is the main challenge, along with manufacturing and delivery mechanism. We believe the initial applications of the new wave of gene editing programs will focus on *ex vivo* gene editing or easy-to-reach organs, such as the eye, for example. – AC

The major technical issues vary significantly between the various editing platforms. At Precision, the technical challenges we focus on are highly specific to optimizing the particular genome-edited products in our pipeline. – MK

The major technical issues with genome editing involve the ability to efficiently target the desired modification to the precise site in the genome with the degree of specificity required for the development of human therapeutics. We also have to safely and effectively deliver these therapeutics to patients. Our technology has certain advantages over other technologies that have thus far only been used in research. ZFPs are human proteins whose function is to accurately bind DNA sequences and they have evolved with our complex genomes. We have been developing our ZFN platform over the years to the extent that we can efficiently target any site in the genome that we choose, with singular specificity.

With our large archive of ZFN modules and industrialized process, we can also move rapidly from selection of a target site to a clinical lead. We continue to research and develop multiple delivery strategies for our *ex vivo* and *in vivo* genome editing applications. We are evaluating both mRNA and viral vector-based delivery to ensure that the safest and most effective delivery method is used based on the ZFN-editing application and the characteristics of the specific disease that we want to treat. – GN

What are you most optimistic about as we move into 2016?

We are excited to see more viable diseases to go after with gene editing. We'd like to see new technologies receive funding which, to us, is a validation of the gene editing space in general and we are excited to see more initial clinical data. – AC

Breadth and depth. We are optimistic that genome editing will be successfully applied to a far broader array of applications in 2016 and that we'll see a number of programs make significant steps forward in development. – MK

We are very excited about the initiation of the Phase 1/2 clinical trials of our SB-FIX hemophilia B program and our SB-318 MPS I program, which will be the first *in vivo* genome editing clinical trials in humans. We are also very optimistic about demonstrating the potential for therapeutic genome editing, as this, and several other programs, progress through clinical studies. – GN

ARM Strategic Priorities 2016

Overall guiding objectives:

- Drive credible regulatory, scientific and policy advancement
- Maximize access and reimbursement for disruptive innovations
- Enable sustainable capital and funding formation

Key strategic priorities in 2016:

- Educate and engage payer community, policymakers and other key constituent groups in the U.S. and Europe regarding new reimbursement models.
- Establish the Standards Coordinating Body to support the development, communication and implementation of technical and process standards for gene therapy, cell therapy and other regenerative medicines.
- Achieve greater international regulatory harmonization, enabling evaluation of proposals to form a framework for new sector-specific policy initiatives.
- Identify and define process development and manufacturing scalability challenges in key disciplines, incorporating ongoing technology advancements and the need for comparability.
- Continue to raise the profile of public and private companies within the institutional investor community, via key investor outreach and engagement; targeted roundtable events and panel discussions; education efforts; and investment policy initiatives.
- Continue to position ARM as the global go-to information resource for all key stakeholders. Via our data partnership with Informa, this includes the collection and dissemination of global sector data and performance metrics: total financings, dealmaking and partnerships, clinical trials, key data events and more.
- Build out educational resources for the patient and patient advocacy community, including information related to the promise and potential of gene therapy, cell therapy and other forms of regenerative medicine on various diseases and disorders.

ARM Regulatory & Legislative Focus Areas

Global reimbursement issues – advancing specific proposals to promote coverage, coding and payment policies that facilitate development of and patient access to gene and cellular therapies and other regenerative medicine products.

- Identifying potential policy and legal impediments to coverage and reimbursement
- Conducting formal analysis of payment models to facilitate access and adoption
- Outreach to U.S. CMS, private payers and EU HTA bodies and reimbursement agencies

Advocating for ARM's provisions to be included in congressional efforts to streamline the drug development and review process. This includes:

- Standards Coordinating Body – In January 2016, U.S. Senator Tammy Baldwin introduced the “Advancing Standards in Regenerative Medicine Act,” directing the FDA to work with stakeholders to facilitate the establishment of a public-private Standards Coordinating Body (SCB) in Regenerative Medicine.
- A modified role for the NIH-Recombinant DNA Advisory Committee (RAC) to ensure the oversight of gene therapy clinical trials is streamlined.
- Combination products - ARM advocates for reforms to streamline the review process for combination products or other situations when more than one review center at FDA is involved in product evaluation and review.
- Potential new pathway to market - In order to improve the efficiency of the approval pathway for regenerative medicine and advanced therapies products, ARM advocates the FDA designate certain regenerative medicine / advanced therapy products as “Qualified Regenerative Medicine Products” (QRMP), intended for serious and life-threatening diseases with currently no available treatment options. The FDA would meet with the QRMP sponsors to discuss expedited review options. ARM is working with policymakers on other potential pathways as well.

Gene editing & related bioethics issues - ARM is working closely with the National Academy of Sciences (NAS), providing a detailed industry perspective on the state of commercialization of somatic cell gene editing technologies. This information will be included in their upcoming consensus report to be released by EOY 2016.

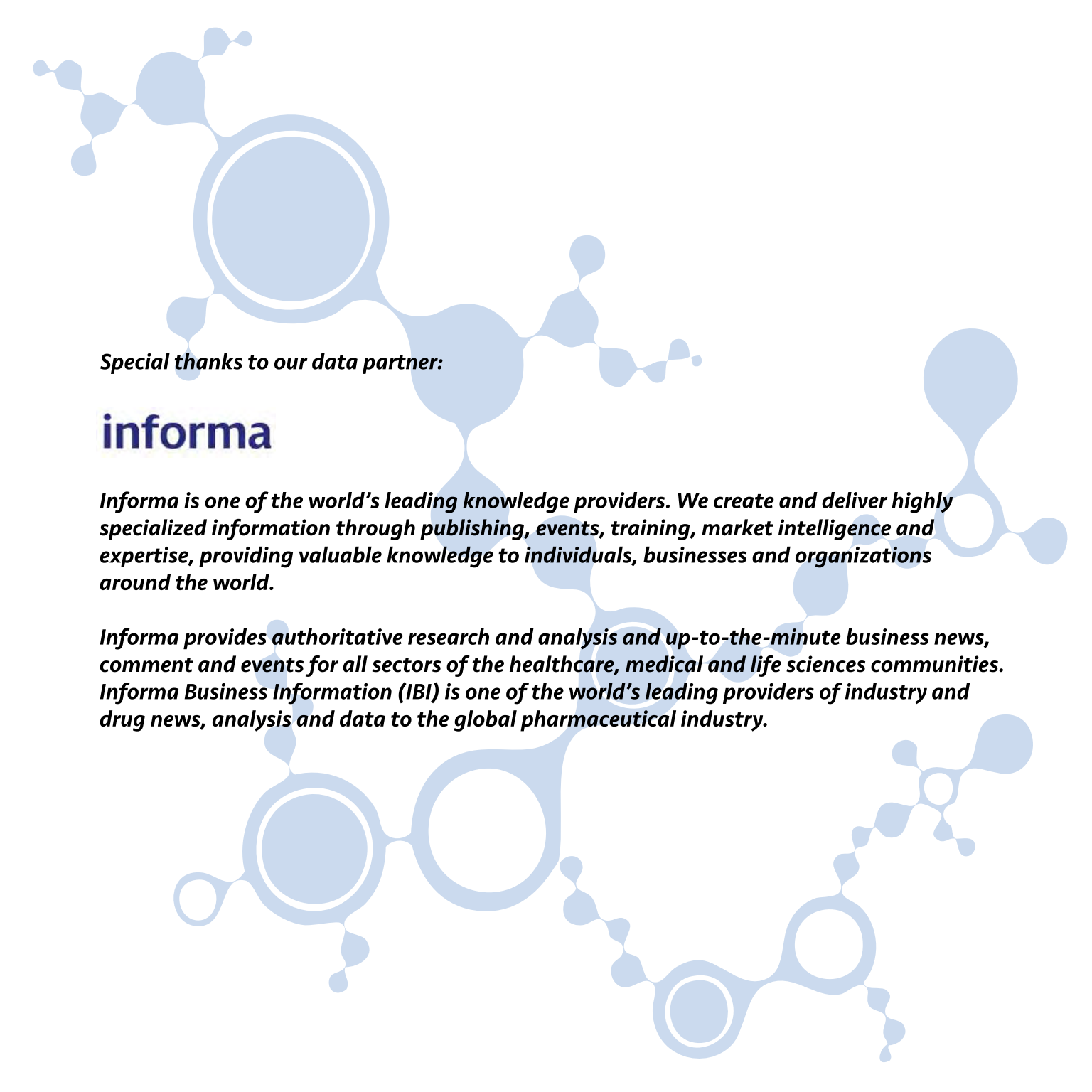
PDUFA reauthorization recommendations – The current Prescription Drug User Fee Act (PDUFA) version V is set to expire in 2017.

- ARM has submitted comments advocating for the Standards Coordinating Body, QRMP designation and improved coordination and communication among FDA review centers.
- ARM continues to develop other policy recommendations for inclusion in PDUFA discussions.

ARM will comment on and help to shape FDA's draft guidance on minimal manipulation and homologous use. ARM will also present at the FDA public meeting Spring 2016.

International regulatory convergence – working to establish and maintain a predictable and efficient regulatory review and approval process in the U.S. and EU to promote greater international harmonization.

Input to the EU public consultations on gene therapy medicinal products (quality, non-clinical and clinical aspects); GMP to ATMPs; the new Priority Medicines Scheme (PRIME).



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The logo is a circular emblem with a white center and a dark blue outer ring. It is positioned in the lower right quadrant of the page, overlapping the dark blue background. The text inside the circle is centered and reads "ALLIANCE for Regenerative Medicine".

ALLIANCE^{for}
Regenerative Medicine

Alliance for Regenerative Medicine

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