



ALLIANCE<sub>for</sub>  
*Regenerative Medicine*

**2016**

## *Annual Data Report*

*on gene and cellular therapies and the regenerative medicine sector*



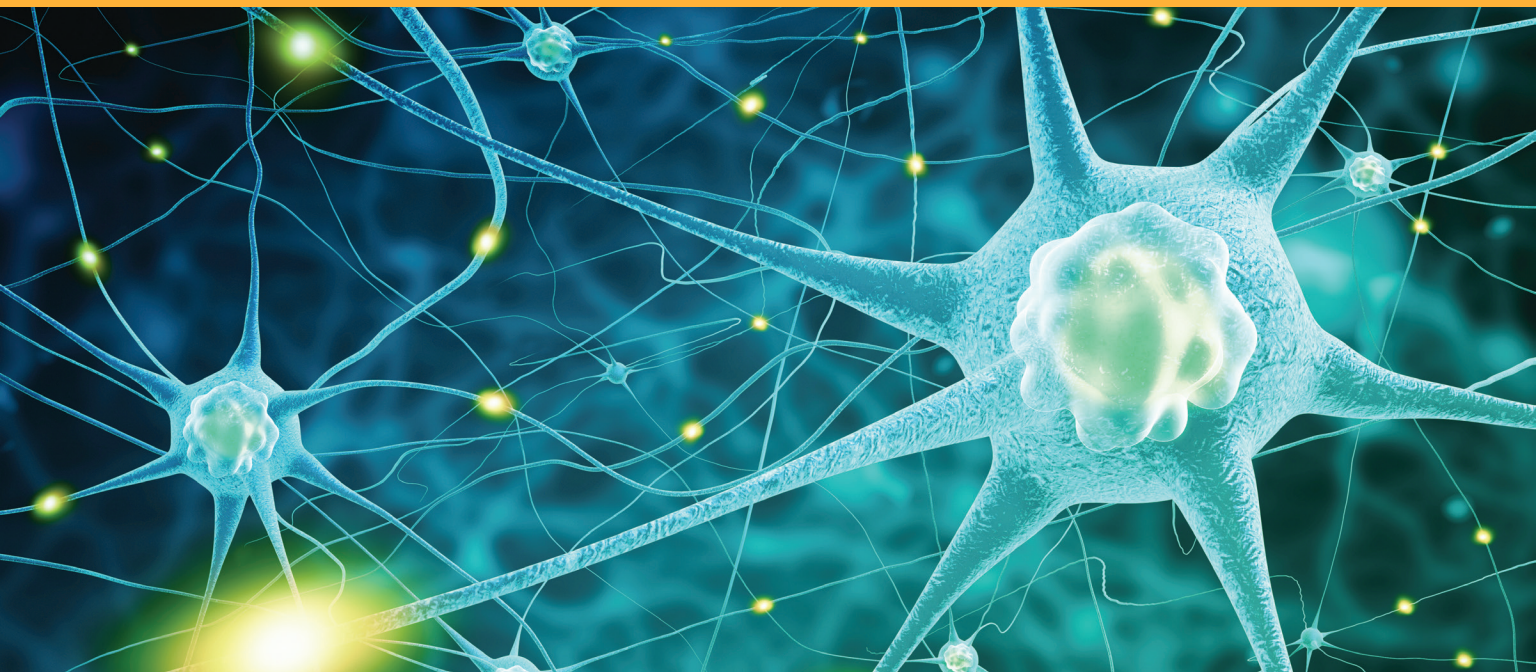
# ALLIANCE<sup>for</sup> *Regenerative Medicine*

***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.***

***[alliancerm.org](http://alliancerm.org)***

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# Chairman's Note

This is a very exciting time to be part of the regenerative medicine sector as we continue to see signs that we truly are at an inflection point for this industry. Companies in this space continue to introduce novel therapies that are progressing through the clinic and beginning to demonstrate true therapeutic potential in areas of significant unmet medical need, especially in rare genetic diseases and oncology. Progress rarely occurs without some setbacks, however, and a few companies are experiencing the challenges typically associated with the uncertainty of outcomes in the therapeutic development paradigm. In the midst of these ups and downs, we're hopeful that we will soon see the first approvals of CAR-T therapies, *in vivo* gene therapy, as well as a steady stream of positive Phase III results for cell and gene therapies alike. We also anticipate continued progress in the tissue engineering sector with a variety of applications advancing through the clinic. These developments will lead to even larger capital investments and attract partnership interests from pharma and large cap biotech companies.

At the Alliance for Regenerative Medicine (ARM), we continue our efforts to advocate for this developing space, especially when it comes to issues related to the regulatory framework, reimbursement and market access and capital formation.

Passage of the 21st Century Cures Act in late 2016 was a major win for this industry, and ARM played an important leadership role in bringing together many key stakeholders to ensure the legislation accelerates development of regenerative medicine therapies and optimizes the approval pathway while maintaining FDA's high product approval standards.

On the reimbursement front, ARM continues to lead discussions focused on the value and adoption of future gene and cell therapies through introduction of a three-part white paper series aimed at helping to prepare our healthcare reimbursement system to evolve and accommodate these transformative therapies through implementation of new payment methodologies.

In addition, ARM continues to raise the profile of public and private companies within the institutional and investor community and government agencies via key investor outreach and engagement, targeted events, discussions and investment policy initiatives.

In further support of our efforts to address the regulatory, reimbursement, capital formation and communication needs of this industry, as Chairman of the Board of Directors, my priorities for the coming year are:

- To facilitate the selection and integration of a new ARM CEO to the organization;
- To champion the efforts of the international Standards Coordinating Body for regenerative medicines (SCB), launched at the outset of this year, to efficiently and effectively advocate for sector standards development with the goal of accelerating product development and scalability, and streamlining regulatory submission review and approval;
- To support the launch of the ARM Foundation, the mission of which is to serve as the educational and central information resource on all issues fundamental to the clinical and commercial success of gene and cell therapies, tissue-engineered products and other regenerative medicine treatments;
- To ensure the efforts of our staff and member committees are addressing the needs of each technology sector within a global healthcare environment, including advocating for language that ensures gene therapy products are eligible for the regenerative advanced therapies designation outlined in the 21st Century Cures Act, and advancing proposals that promote enactment of payment reforms that facilitate development of and patient access to regenerative medicine products.

On behalf of the Alliance for Regenerative Medicine, I'd like to thank you for your many contributions and continued support.



Robert A. Preti, Ph.D.  
Chairman, Alliance for Regenerative Medicine  
President, PCT, a Caladrius Company  
CTO & SVP, Manufacturing & Technical Operations, Caladrius Biosciences

# Global Landscape

**772+**

Regenerative Medicine Companies Worldwide,  
Including Gene and Cell Therapies

**219**

Europe  
& Israel

**122**

Asia

**399**

North  
America

**13**

South  
America

**1**

Africa

**18**

Australia &  
New Zealand

# Industry Overview

The year saw intensifying dialogue on how to assess the value of and properly price therapeutics poised to cure diseases with a single dose, thus making drug pricing the major health care story of 2016. Stakeholders in the regenerative medicine space are preemptively laying the groundwork for the day when more of these products are approved and discussion of their cost-benefit analysis surfaces. Leading this charge, the Alliance for Regenerative Medicine published a white paper in *IN VIVO* that established a framework to guide future conversations.

As 2016 drew to a close, the U.S. Congress enacted the 21st Century Cures Act, which contains several provisions aimed at expediting the approval of advanced therapy products, including a designated pathway for regenerative advanced therapies (RAT). Drugs may qualify for the RAT designation if they are intended to treat or cure serious, life-threatening conditions, and if preliminary clinical evidence indicates the drug has the potential to address unmet medical needs. Further, FDA reorganized in October 2016, creating the Center for Biologics Evaluation and Research Office of Tissues and Advanced Therapies (CBER-OTAT), to consolidate and streamline its departments in an effort to make reviews of advanced regenerative medicine candidates more efficient.

On the European regulatory front, the European Medicines Agency issued an action plan that provides regulatory and scientific support for Advanced Therapy Medicinal Products (ATMPs), and prioritizes solutions that can be implemented quickly.

With these recent regulatory advances, combined with a new U.S. president and a new FDA commissioner, 2017 may see further acceleration in the approval process, especially for drugs intended to treat rare diseases.

In the clinical trials arena, 2016 was an exciting time for regenerative medicine companies seeking to advance their clinical programs. There were 21% more trials underway by year-end 2016 than the previous year, with 68% moving into either Phase II or III. Fate Therapeutics, Sangamo Therapeutics, Spark Therapeutics, Kiadis Pharma, Kite Pharma and many others had their therapies progress into Phases I and I/II for a variety of indications including cytomegalovirus, beta thalassemia, hemophilia B and a wide range of oncology indications. Phase II starts included Caladrius Biosciences and Argos Therapeutics, to name a few. Companies with more advanced therapies – BioCardia, Adaptimmune, bluebird bio and others – initiated Phase III studies in 2016 for beta thalassemia, congestive heart failure, diabetic neuropathy and cancer indications.

Deal making in regenerative medicine was as strong as ever in 2016, with some notable strategic alliances, both cross-industry and industry-academia. Big pharma companies Allergan and Pfizer acquired cell- and gene therapy-focused biotechs in 2016. Nine regenerative medicine companies made initial public offerings during the year, including CRISPR Therapeutics, Editas Medicine and Intellia Therapeutics, all focused on gene-editing. There were a number of innovative early-stage financings as well, with December's \$225 million deal between Bayer and Versant Ventures to form BlueRock Therapeutics, a next-gen stem cell play, being the biggest Series A closed in 2016.

2016 saw an ever-increasing pace of scientific advancement coupled with high expectations for novel therapies from the cell and gene therapy and tissue regeneration sectors. Investors and pharma alike continued to show interest in partnerships and investment in the sector, and we look forward to continuing our analysis of regenerative medicine and advanced therapies throughout 2017.

– Patricia Reilly  
Vice President, Intelligence Alliances

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

Informa Business Intelligence,  
Pharma and Healthcare



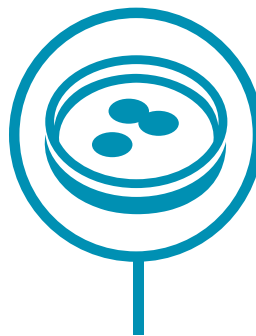
## Global Financings: 2016



TOTAL GLOBAL  
FINANCINGS  
**\$5.22 Billion**



GENE & GENE-MODIFIED  
CELL THERAPY  
**\$2.73 Billion**



CELL THERAPY  
**\$2.97 Billion**



TISSUE  
ENGINEERING  
**\$461 Million**

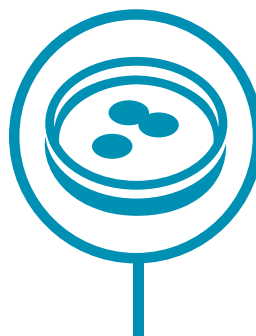
## EU Financings: 2016



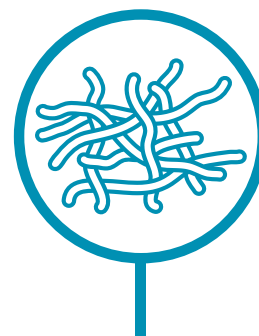
TOTAL EU  
FINANCINGS  
**\$1.06 Billion**



GENE & GENE-MODIFIED  
CELL THERAPY  
**\$353 Million**



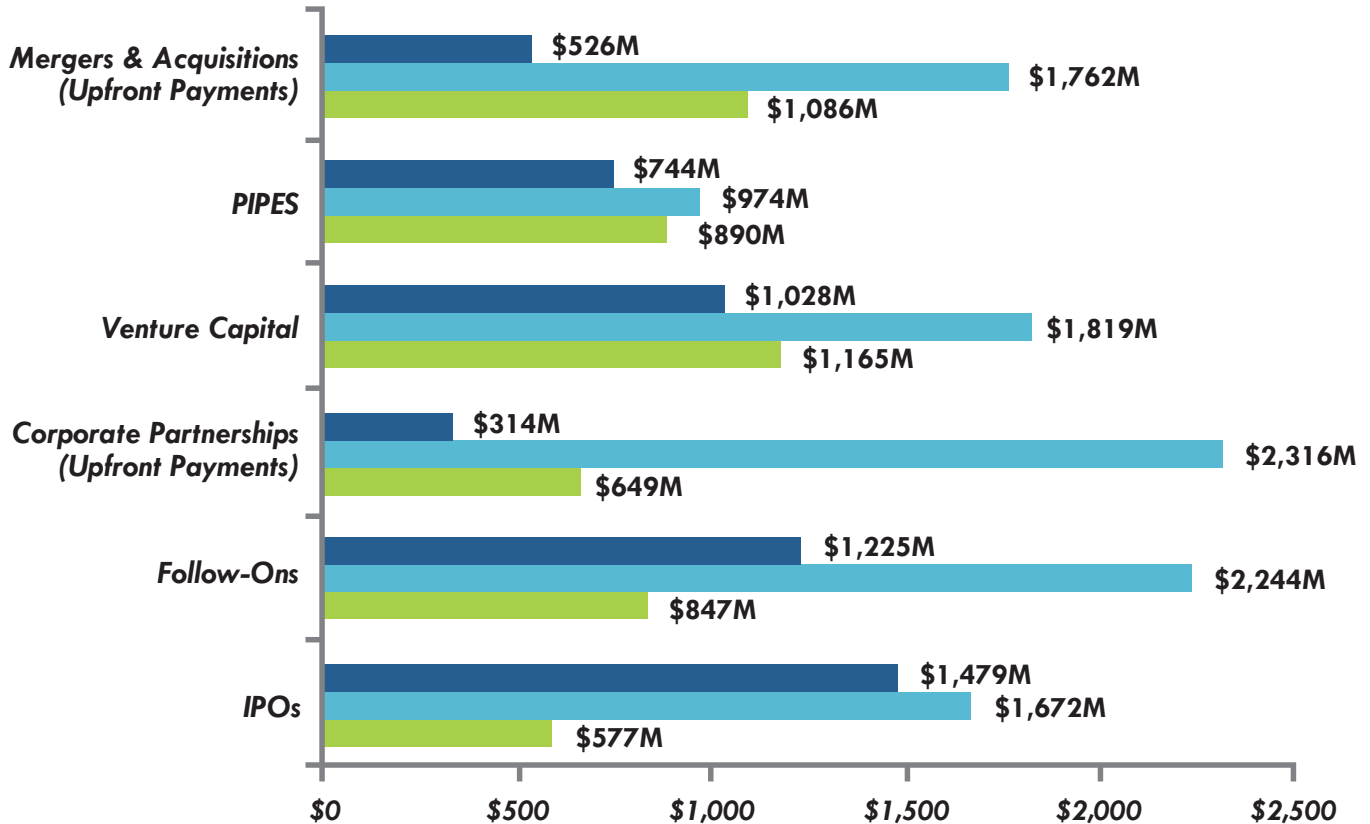
CELL THERAPY  
**\$571 Million**



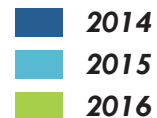
TISSUE  
ENGINEERING  
**\$209 Million**

*\*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 Global Financings by Type, by Year



### Key





## Examples of Key Financings: 2016

### IPOs

- **Intellia Therapeutics IPO raises \$124.2M** – May 11, 2016
- **Editas Medicine IPO raises \$108.6M** – February 8, 2016
- **AveXis, Inc. IPO raises \$95M** – February 10, 2016
- **Audentes Therapeutics IPO raises \$85.1M** – August 20, 2016
- **CRISPR Therapeutics IPO raises \$56M** – October 18, 2016
- **GenSight Biologics IPO raises €45.2M on Euronext Paris Stock Exchange** – August 11, 2016
- **TiGenix US IPO raises \$35.7M** – December 20, 2016
- **MaxCyte, Inc. IPO raises \$14.2M on London Stock Exchange** – March 29, 2016
- **GCellect Biotechnology Ltd. IPO raises \$8.4M** – August 3, 2016

### Corporate partnerships, acquisitions and other financings

- **Biogen & UPenn enter into \$2B collaboration on multiple gene therapy programs, upfront payment of \$20M** – May 16, 2016
- **Pfizer acquires Bamboo Therapeutics in \$645M deal, with \$150M upfront** – August 1, 2016
- **Adaptimmune & GSK expand immunotherapy collaboration to \$500M from \$300M** – February 2, 2016
- **bluebird bio & Medigene establish \$1B+ strategic TCR immunotherapy R&D collaboration & licensing agreement, \$15M upfront** – September 29, 2016
- **Baxalta signs \$1.7B agreement with Precision Biosciences, Inc., \$105M upfront** – February 25, 2016
- **Juno Therapeutics acquires AbVitro in \$123.9M deal for next-generation single-cell sequencing platform** – January 11, 2016
- **Regeneron signs agreement with Intellia Therapeutics to develop CRISPR/Cas therapeutics, \$75M upfront** – April 11, 2016
- **Takeda & TiGenix enter into €355M licensing agreement for ex-U.S. rights to Cx601, €25M upfront to TiGenix** – July 5, 2016
- **Healios K.K. & Athersys enter into \$240M partnership for treatment of stroke using Athersys MultiStem Therapy, \$15M upfront** – January 8, 2016
- **Allergan acquires LifeCell regenerative medicine business unit from Acelity in \$2.9B cash deal** – December 20, 2016
- **Celgene & Evotec enter into \$250M exclusive iPSC R&D collaboration, Evotec to receive \$45M upfront** – December 15, 2016
- **Bayer & Versant Ventures launch iPSC therapy company BlueRock Therapeutics with \$22M SeriesA Financing** – December 12, 2016
- **Celgene exercises \$50M option with Juno for CD19 program outside North America and China** – April 11, 2016
- **Regeneron and Adicet Bio enter into licensing agreement to develop next-generation engineered immune cell therapeutics, \$25M upfront** – August 2, 2016
- **Spark Therapeutics enters into licensing agreement with Selecta Biosciences, \$10M upfront** – December 5, 2016

# Sector Commentary: What 2017 Will Mean for Cell & Gene Therapies



Usman "Oz" Azam  
President & CEO  
Tmunity Therapeutics, Inc.

*The cell and gene therapy sectors are expecting several significant clinical data events in 2017. What impact will positive results have on the sector as a whole and what is the next step in demonstrating clinical utility of these novel technologies?*

I am very optimistic that both in cell and gene therapies, there will be continuing momentum of credible and compelling data emerging that continues to demonstrate the positive benefit-to-risk ratios of these individualized therapies. CAR-T therapies will lead the way with the first waves of approvals in the U.S., but I believe we will begin to see emergence of human data in novel, second-generation CAR-T programs and progress in gene therapy registration study data. – UA



David Chang, MD, Ph.D.  
EVP R&D and Chief Medical Officer  
Kite Pharma

There are already some early clinical experiences coming from Phase I studies that suggest that you can achieve complete responses with a cell therapy in oncology. Some of these complete responses are very long lasting, so much so that the word 'cure' — even in the refractory setting — is being mentioned. Going forward, this industry will need to demonstrate long-term durability to really justify the benefit of cell therapy. Once we can do that, I think the whole field will open up because it's something that no other therapy, and certainly no other sector, has been able to achieve. – DC

It's clear that for many of the autologous products that have reported clinical data, the results are encouraging. I believe the next step is showing how that data translates into a path for effectively treating solid tumors using CAR-T or cell therapy technology. In the allogeneic space, I think we have to show that moving to the convenience of an allogeneic approach — something we think will enable broader utility for patients — will be efficacious, safe and durable. – BS



Barbra Sasu, Ph.D.  
VP, Allogeneic CAR T Platform  
Pfizer

Clinical successes float a lot of boats. The industry rallies around these successes to reinforce the clinical benefit of truly transformative and presumptively durable medicines, and will be buoyed by the continually improving patient risk profiles and outcomes as we learn more about mechanisms of action. – PV

*How is your organization thinking about reimbursement and market access?*

We are actively involved in developing and beginning to execute our reimbursement and commercialization strategies. While the key drivers in setting the value of any new treatment are the clinical benefit and the stability of the response, I think we have an opportunity to educate payers ahead of any significant clinical data about what the technology is, how it's innovative, and what the potential benefit is to the patient. – DC

Our initial focus has been on understanding and gaining confidence in our intended drug profile. Is it a bridge to transplant or is it a standalone therapy that replaces a transplant? Those profiles will position very differently and will determine what kind of reimbursement we think would be appropriate. In sum, we feel that for transformative medicines, there will be a path to ensuring patients receive medicines they need. – BS

While we see reimbursement and access as critical long-term goals and outcomes, we think the market is best served today by focusing on safety and efficacy. As we continue to demonstrate that these therapies can be transformative, reimbursement and market access will follow as a consequence. – PV

*(Continued on page 9)*



Phil Vanek, Ph.D.  
GM, Cell Therapy Growth Strategy  
GE Healthcare

(Continued from page 8)

Due to the breakthrough nature of these therapies, and the fact that we're serving patient populations that are in desperate need, we have an opportunity to have a dialogue around reimbursement that others may not. It really is a value story—the question is not what can you charge, but what should you charge? We have a responsibility to engage with the agencies and the payers that are ultimately going to make reimbursement decisions in the same way that we engage regulators, which is with openness, trust, transparency and creativity. — JW

## **What opportunities do you see for companies in the cell and gene therapy sector in the year ahead? Challenges?**



Jeffrey Walsh  
Chief Financial & Strategy Officer  
bluebird bio

At Tmunity, we are currently thinking about the landscape of T cell engineering in areas beyond oncology—in autoimmune diseases, for example. As we continue to evolve and prepare to enter new indications and markets, the need for clinical outcomes data at the provider and patient levels will become even more critical than it has been to date. As an industry, I believe our opportunities are in continuing the quest to make cell and gene therapies accepted as 'standard of care,' and to be considered equal to small molecule and biologic therapies. Our challenges will be to improve the safety profile of the innovative therapies we are all wishing to bring to patients, as well as ensuring a focus on reducing the cost of goods to make these products accessible and affordable, globally. — UA

2017 will be a very pivotal and important year for the entire cell and gene therapy field. We are beginning to see new waves of cell therapy now being scrutinized by the regulatory agencies where the outcome of the review very well may set the standard for how the benefit-risk of cell therapies will be assessed and for the level of science-based rationale that will be required of companies in this space going forward. What drives the value of the therapies we're developing is the impact that we can make for patients. This is still a very nascent field, but the opportunities are great for cell and gene therapies to address unmet needs or targets that are not 'drugable'. Our objective as an industry should be to work together to realize the opportunities that the science is providing into something we can clinically demonstrate and bring a product forward. — DC

This is a truly novel field of medicine. I don't know what it's going to look like in five years, but it's worth doing the work. As a case in point, consider immunotherapy five years ago, and the difference those advances have made in the lives of cancer patients. It's hard to think about oncology going forward without immunotherapy, and maybe cell therapy will similarly help re-shape the oncology treatment landscape. — BS

The sky's the limit. We'll continue to see technologies evolve to meet the needs of the market, both on the therapeutic and manufacturing side. We should continue to see improved therapies with fewer side effects, more solid tumor progress, new manufacturing tools, and a more integrated clinical and manufacturing workflow. — PV

# Sector Commentary: Gene Editing



Nesson Bermingham, Ph.D.  
Chief Executive Officer,  
President & Founder  
Intellia Therapeutics

**Gene editing technologies, including CRISPR/Cas, ZFN and TALENs are providing powerful new tools to manipulate and correct genetic sequences; what and how long will it take until we see robust and meaningful clinical results?**

CRISPR/Cas9 hold the promise for a new era in therapeutics providing patients with a potential curative therapy that targets the direct driver of a disease at the DNA level. In combination with developments in bioinformatics, sequencing and molecular biology, CRISPR Cas9 has the potential to drive a truly personalized approach in addressing patients' specific genetically based diseases and a medical revolution in the near future. Medicine has not yet caught up to the genomics revolution that has taken place over the last two decades. What has been missing is a molecular tool to allow us to interrogate the genomic data rapidly moving into therapeutic application and act on it to elicit a therapeutic effect. CRISPR/Cas9 is the first viable tool not only to enable us to explore and interrogate the genome but also to provide us with the drug to repair the genome in diseases where limited treatment options are available for patients today. One can envision a time in the not-too-distant future when a patient presents with a genetic disease. Her genome is sequenced and a genome-editing drug is custom made, targeted to her specific genetic sequence. The patient is subsequently treated and potentially cured, all done in a cost-effective manner and easily applied on a global basis within the existing medical structure. — NB



Alexandra Glucksmann, Ph.D.  
Chief Operating Officer  
Editas Medicine

Genome editing techniques have shown enormous potential in revolutionizing our approach to research, but to really have an impact, they must show therapeutic effect in the clinic. Today, the rationale is all there—in our understanding of the genetic cause of many diseases, the identification of targets relevant to those diseases, the technical ability to correct those targets at the molecular level, and our understanding of the anticipated biologic effect of editing certain targets. The proof will be whether we can deliver these molecular editing machineries to the different parts of the body where the editing activity is needed, or in the case of *ex vivo*, if we can edit the cells to have a therapeutic effect once placed back in the body.



Sandy Macrae  
President and CEO  
Sangamo Therapeutics

Clinical studies for genetic diseases are carried out with affected patients. This allows the researchers to get a both a safety and an efficacy readout. I anticipate that we will get such readouts in the coming years. If the results from these studies demonstrate positive clinical impact, I believe success will lead to more success, more excitement and more investment in the field. At the end of the day, what keeps me up at night is not the technology *per se*, but making sure we gain the best understanding of the diseases we are trying to address, show the technology has the clinical effect that we want it to, and develop innovative therapies to treat these diseases where no other therapy is available. — AG

Meaningful clinical trial results are coming soon. 2017 is an historic year for genome editing as Sangamo will conduct the first ever *in vivo* genome editing clinical trials, for three of our therapeutic programs, using zinc finger nuclease (ZFN) technology. Preclinical data for Sangamo's ZFN-mediated genome editing programs have been reviewed by advisory bodies such as the NIH Recombinant Advisory Committee (RAC), and the U.S. Food and Drug Administration (FDA) has granted clearance for investigational new drug application clearance for each of our three *in vivo* genome editing clinical development programs. — SM

(Continued on page 11)

# Sector Commentary: Gene Editing

(Continued from page 10)

## **What types of indications will likely be the first to be addressed with a therapy utilizing genome editing?**

Given the types of editing one can do with CRISPR-based approaches, we're seeing companies focused on diseases where a single, genetic mutation is present, including sickle cell disease, leber congenital amaurosis (LCA), cystic fibrosis, and blood-based diseases, such as beta thalassemia. At Intellia, we're pursuing rare conditions such as Alpha-1 Antitrypsin, Amyloidosis of the Transthyretin (TTR), and other Inborn Errors of Metabolism (IEM). Additionally, CRISPR hold significant promise with DNA-based infectious diseases such as HIV and hepatitis B, which affects more than 300 million people globally. GIVEN ITS UNIQUE ABILITY TO TARGET MULTIPLE REGIONS OF THE GENOME, IN TIME, WE BELIEVE, THIS APPROACH MAYBE APPLICABLE TO MORE COMPLEX DISORDERS SUCH AS NEURODEGENERATIVE DISEASES. – NB

Editas is applying the CRISPR technology in ophthalmology, in hemoglobinopathies, such as Beta thalassemia and sickle cell disease, and in oncology through our partnership with Juno. Additional research programs in our pipeline include genetic diseases, such as Duchene muscular dystrophy, cystic fibrosis and Alpha-1 antitrypsin deficiency. – AG

Sangamo is developing genomic therapies using ZFN technology to address unmet medical needs in monogenic diseases. We are focusing especially on diseases where ZFN-mediated genome editing has the potential to achieve long lasting therapeutic outcomes, or even cures, with a single administration. In 2017, Sangamo will enroll Phase 1/2 clinical trials evaluating ZFN-mediated genome editing therapies as treatments for hemophilia B, MPS I and MPS II. These three studies are the first ever *in vivo* genome editing clinical trials. We will report data from the three studies once we have gathered sufficient information to understand clinical relevance, which we expect will be early 2018, but perhaps as soon as late this year. – SM

## **What impact, if any, will the National Academy of Science (NAS) report on human genome editing have on companies and technologies in the sector?**

When you think about the questions being addressed in the NAS report, there were some important determinations made for science, the genome-editing industry and healthcare community at large. First, the NAS determined that the existing regulatory framework in place is well established and prepared to handle the oversight of genome editing. Second, the NAS confirmed their position that the genome editing industry can proceed with somatic cell research to create medicines for patients using the breakthrough technology, CRISPR/Cas9. Third, with regard to heritable germline genome editing, the NAS will allow it, but it will be permitted only within a robust and effective regulatory framework, and though meeting 10 key requirements, including the absence of reasonable medical alternatives, and comprehensive multi-generational follow-up study. Finally, there is an opportunity to engage in public discussion with global stakeholders around clinical trials, ethical considerations, safety and risk benefit, and education. This dialogue and input will hopefully create a broader acceptance of this important technology, which has the capacity to revolutionize medicine. – NB

Important for all us advancing novel therapies, the NAS report stated that the appropriate regulatory framework and regulatory bodies that are pro-patient and pro-innovation are already in place in the U.S. We, at Editas, also believe that we have an obligation to both the patients and the technology to use it in a responsible way with the goal of making transformative medicines to treat patients with severe diseases. – AG

# 804

Clinical trials underway  
by year-end 2016

631 in 2015

**Ph. I: 261**

(192 in 2015)

**Ph. II: 475**

(376 in 2015)

**Ph. III: 68**

(63 in 2015)

**21% growth over 2015**

## Worldwide Clinical Trials by Technology Type: 2016

### Gene Therapy & Gene-Modified Cell Therapy

**Total: 425**

Ph. I: 161

Ph. II: 233

Ph III: 31

### Cell Therapy

**Total: 533**

Ph. I: 160

Ph. II: 330

Ph III: 43

### Tissue Engineering

**Total: 20**

Ph. I: 6

Ph. II: 12

Ph III: 2

## EU Clinical Trials by Technology Type: 2016

### Total

**Total: 238**

Ph. I: 56

Ph. II: 163

Ph III: 19

### Gene Therapy & Gene-Modified Cell Therapy

**Total: 119**

Ph. I: 33

Ph. II: 76

Ph III: 10

### Cell Therapy

**Total: 162**

Ph. I: 37

Ph. II: 113

Ph III: 12

### Tissue Engineering

**Total: 4**

Ph. I: 0

Ph. II: 4

Ph III: 0

\* Total number of clinical trials represents sector-wide figures; please note that products employing cell-based immunotherapy are accounted for in both the gene therapy & gene-modified cell therapy and cell therapy sectors. As a result, the total number of clinical trials does not equal the sum of the trials within the individual technology groups.

## Current Clinical Trials by Therapeutic Category: Year-End 2016

- Approx. 47% of current clinical trials are in oncology
- More than one in 10 are in cardiovascular



### Examples of Major Milestones and Key Data Events: 2016

#### Cell-based immuno-oncology programs

- Kite Pharma files first US CAR-T therapy BLA submission for KTE-C19, investigational anti-CD19 CAR-T Therapy for treatment of relapsed/refractory aggressive b-cell non Hodgkin lymphoma – *December 4, 2016*
- Novartis reports positive data from pivotal trial of CTL019 CAR-T cell therapy for treatment of r/r ALL, the first global CAR-T therapy trial – *December 4, 2016*

#### Gene therapy programs

- Spark Therapeutics announces positive Phase III data for voretigene neparvovec to treat inherited retinal disease – *August 10, 2016*
- BioMarin announces positive interim results from Ph I/II trial of BMN 270 gene therapy for treatment of severe hemophilia A – *July 27, 2016*
- GSK's ex vivo stem cell gene therapy Strimvelis receives European Marketing Authorization to treat very rare disease ADA-SCID – *May 27, 2016*

#### Cell-based therapy programs

- Vericel's MACI, the first autologous cellularized scaffold, approved by FDA for the repair of cartilage defects of the knee – *December 13, 2016*
- ReNeuron announces positive results in Ph II trial of CTX cell therapy in patients with stroke disability – *December 5, 2016*
- TiGenix announces positive 52-week results in Phase III trial of Cx601 in complex perianal fistulas in Crohn's disease patients – *March 7, 2016*
- Mesoblast licensee JCR Pharmaceuticals launches allogeneic cell therapy product TEMCELL in Japan for treatment of acute GvHD – *February 24, 2016*





Robert A. Preti, Ph.D.  
President, PCT, a Caladrius Company  
CTO & SVP,  
Manufacturing & Technical Operations,  
Caladrius Biosciences



Barbra Sasu, Ph.D.  
VP, Allogeneic CAR T Platform  
Pfizer



Ryan Scanlon  
Business Head, Viral Gene Therapy  
Lonza Pharma & Biotech



Phil Vanek, Ph.D.  
GM, Cell Therapy Growth Strategy  
GE Healthcare

*As several autologous cell-based therapies enter late-stage development, do the manufacturing and industrial infrastructures exist to support the expected demand for these products?*

While the infrastructure for patient-specific or off-the-shelf cell therapy products is currently adequate for launch of these exciting therapies, the industry's wide scale manufacture and distribution is currently only in its formative stages. Generally, companies currently developing such infrastructure are doing so based on the current state of our highly manual, often only "functionally closed" processes which require stringently controlled clean room environments and the adaptation of existing infrastructure, built for related but different industries. Therefore, individual companies must work to develop a business model in the short term that is appropriate to meet with the demands associated with each product's unique Target Product Profile, and in the mid- to long-term, anticipate and invest accordingly to adjust the manufacturing and delivery paradigm to provide for scalability and sustainability throughout the commercial life of the product. – RP

In our experience, current manufacturing capabilities are scaled to meet the needs of autologous products. As Pfizer is developing allogeneic cell-based therapies, it is difficult for us to comment on the capabilities of autologous. However, our goal at Pfizer is to be able to use all the cells from a donation of one of our healthy donors for development of our allogeneic products, and to do that, we'll need to continue to scale up our manufacturing process over time. This may require custom machinery, working with multiple partners, coming up with different solutions for different parts of the process, and eventually having a closed system featuring all those components.

To succeed, I believe access to raw materials will be a significant issue industry-wide. Some of the currently used critical reagents are controlled by a single party or parties or aren't generally available enough to the point that lack of access may become rate limiting to production. The industry is faced with either developing a path forward to use existing reagents or using alternative reagents. – BS

The mammalian bioprocessing industry has established a fantastic set of industrial equipment, single-use technologies and facility designs. The biological processes involved with manufacturing viral vector *in vivo* gene therapies need to be improved to meet these modern standards. – RS

Two years ago, we commented on the need for new built-for-purpose unit operations in manufacturing that are operationally closed, physically linked and digitally connected across the workflow, and we've watched the industry slowly make progress toward those goals. We were also looking at how a completed manufacturing workflow could "plug in" to a clinical practice such that we could improve patient safety and better connect the practitioner to the producer. While we've watched the industry slowly make progress toward those goals, we're now looking at challenges such as zero-defect manufacturing and supply chain management as the next area to tackle. – PV

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# Sector Commentary: Manufacturing and Infrastructure in Cell & Gene Therapy

*(Continued from page 15)*

***At what phase in the product development process should companies begin thinking about manufacturing and infrastructure needs to support future commercialization?***

This thinking should start immediately and develop into an adaptive planning mode, at whatever phase of development a company's products may be, and certainly once some clinical data is available. Companies must start with a Target Product Profile that will provide the lens through which decisions about manufacturing improvements and infrastructure scenarios must be considered. – RP

Successful manufacturing is key from the onset of the project and it's something companies working in CAR-T should focus on early in the development process. Upon Pfizer's entering into our development collaboration with Collectis, our research and pharmaceutical science teams collaborated to build a cell engineering facility where we are working together to understand and address our near and longer term manufacturing and infrastructure needs. – BS

Even before they file an IND, companies should have a plan to use a GMP process for Phase 1 supply that establishes a foundation from which it can be further optimized for commercial viability. Gene therapies, in particular, offer exciting potential for relatively quick clinical timelines into a pivotal trial and then subsequently to market. However, we believe that establishing CMC should be a critical component of a company's commercialization strategy very early because switching to a new process halfway through can lead to a lengthy and costly bridging and comparability effort. Also, properly characterizing and validating the manufacturing process and analytical methods before a BLA submission can take up to 2 years, so planning for these activities early is critical to prevent a launch from being delayed. – RS

***How is your company planning to address the requirements of scalable and sustainable manufacturing systems and process development in this sector? Or if more applicable, how does your organization help companies in this sector address these requirements?***

PCT is a contract development and manufacturing company that supports the advancement of our partners' products by mitigating the risks of product development and by providing efficient, custom manufacturing solutions. – RP

Lonza helps customers optimize, scale-up and modernize, and in some cases, replace their existing processes. We are committed to investing in process technology and scalable platforms so we can help unlock the potential of markets that need very large volumes of product. Through our partnership with Massachusetts Eye & Ear, Lonza is working to develop next generation types of synthetic AAV viral vectors that have the potential to be more effective at gene transfer, address pre-existing immunity challenges, and are easier to produce. – RS

GE Healthcare views the cell therapy manufacturing space as an interoperable ecosystem involving multiple stakeholders (clinicians, scientists, process engineers, regulators, payers, etc). As such, we try to balance the development of standardized manufacturing tools and environments to the myriad cell types and indications being addressed in the cell and gene therapy field. This enables us to provide enough flexibility to produce a therapy safely, yet scalable enough to satisfy the broader needs of the industry. – PV

***What steps are you taking to ensure your quality systems and personnel are equipped to support commercialization of your product?***

Our manufacturing operations team at PCT is building commercial grade quality systems and physical infrastructure. Upgrades to the clinical quality and operational systems will soon be complete, and we will be ready to launch commercial product from our east coast location, located in Allendale, NJ. We are also expanding to full-scale commercial capacity to meet with our current and future clients' needs, and expect to be up and running in 2018. – RP

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# Sector Commentary: Manufacturing and Infrastructure in Cell & Gene Therapy

(Continued from page 16)

Having a quality system and personnel equipped to support the manufacturing process through commercialization are key to any development program. We are currently innovating our manufacturing process, which includes production, processing and QC, at a dedicated cell engineering facility. While there aren't many precedents out there to follow, we're learning what we can from the literature, from the direction people and companies active in the space have taken, and the experiences of our partner, Cellectis, to build a custom approach for our allogeneic portfolio, all the while ensuring the integrity of that approach. – BS

At our new state-of-the-art viral gene therapy facility in the Houston area, which will be coming on-line later in 2017, we are installing and implementing well-established Lonza Biologics quality and compliance systems. In addition, we are partnering with many of our customers planning for commercialization to engage with FDA for guidance on specific process and product situations. – RS

As a healthcare company, we recognize that quality is at the heart of patient safety and wellbeing. One area of particular interest to us is integrating all the disparate quality, clinical scheduling, enterprise management, and distribution toolboxes that exist today to make the process more seamless from vein to vein. That activity will require great digital infrastructure, standards, and new ways of interacting with technology – all things that are in GE's DNA. – PV

## ***How are you addressing logistics around delivery of cell and gene therapies to patients?***

The infrastructure to support delivery of cell and gene therapies to patients requires information systems, transportation carriers, coordination with multiple stakeholders, and transport packages. We have transported over 15,000 products in our lifetime as a company, and have found over the years that the infrastructure is increasingly able to handle these products and their specific requirements. – RP

Our allogeneic product portfolio is intended to be off-the-shelf, and as a result, logistics become a little less challenging than for companies whose products require significant consideration of timelines for delivery. We intend that our products will be shipped in vapor phase liquid nitrogen, so our biggest challenge is ensuring each and every stakeholder involved with the cold chain logistics surrounding our products is very clear on storage, handling and thawing conditions. – BS

GE plays a big role in global logistics management – from aviation, to rail transportation, to infrastructure to digital platforms. We can leverage these broad capabilities to address unmet needs in the cell and gene therapy space. The investment from GE Ventures in collaboration with Mayo Clinic to create Vitruvian Networks takes us a step closer to realizing the digital interconnectedness of the manufacturing and clinical environment. – PV



## Overarching strategic 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 2017

### **Advocate for clear, predictable and harmonized regulatory and review pathways**

- Serve as an industry resource for implementation of the 21st Century Cures Act enacted in late 2016, work toward inclusion of gene therapy in the Regenerative Advanced Therapies designation, and represent sector interests in PDUFA reauthorization discussions.

### **Enable market access and value-based, favorable reimbursement policies**

- Continue to evaluate new reimbursement models, and further education and engagement with payer community, policymakers and other key constituent groups in the U.S. and Europe to advance proposals that support appropriate value, price, access, funding and reimbursement of regenerative medicine products.

### **Facilitate sustainable access to capital and identify sources of potential public funding**

- Continue to raise the profile of public and private companies within the institutional investor community and government agencies, via key investor outreach and engagement; targeted roundtable events and panel discussions; education efforts; and investment policy initiatives.

### **Address industrialization and manufacturing hurdles, develop and establish industry-wide standards**

- Establish the Standards Coordinating Body to support the development, communication and implementation of technical, process development and manufacturing scalability standards for gene therapy, cell therapy and other regenerative medicines.

### **Conduct key stakeholder outreach, communication and education**

- Continue to position ARM as the global go-to information resource for all key stakeholders, and continue to provide relevant and timely information and commentary on global sector data and performance metrics.

# ARM Regulatory & Legislative Focus Areas: 2017

**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.

- Conduct formal analysis of payment models to facilitate access and adoption; identify pros and cons of different models and advocate specific proposals to support appropriate value, price, access, funding, and reimbursement of regenerative medicine products.
- Outreach to U.S. CMS, private payers and EU HTA bodies, reimbursement agencies, and other stakeholders. Ensure proposals for ACA repeal and Medicaid reform appropriately support reimbursement for regenerative medicine products.

**U.S. regulatory issues** – Advocating for ARM's provisions to be included in congressional efforts to continue to streamline the drug development and review process. This includes:

- Building upon new language from the 21st Century Cures Act that established a new Regenerative Advanced Therapy designation and optimizes a pathway to market for regenerative medicine products, ARM will advocate for language ensuring that gene therapy products are eligible for the new designation.
- Developing policy and advocacy approach regarding early access to unapproved products.
- Supporting a modified role for the NIH-Recombinant DNA Advisory Committee (RAC) to ensure the oversight of gene therapy clinical trials is streamlined.
- Continuing to comment on and help shape FDA's draft guidance on minimal manipulation and homologous use of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

**Gene editing & related bioethics issues** – Continuing to work closely with the National Academy of Sciences (NAS) to provide a detailed industry perspective on the state of commercialization of somatic cell gene editing technologies and ensure no barriers are imposed regarding use of gene editing for somatic cell gene therapy products.

**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.

**European regulatory issues** – Providing 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); and hospital exemption policy development.



# 21st Century Cures Act

**The 21st Century Cures Act, which was signed into law on December 13, 2016, introduced, for the first time in the U.S., a specific Regenerative Advanced Therapies (RAT) product designation, as well as regenerative medicine-specific language intended to optimize the U.S. Food and Drug Administration's (FDA) approval pathways for regenerative medicine products, without reducing the agency's high approval standards for product safety and efficacy.**

This specific acknowledgement of the potential of these technologies to treat, modify, reverse or cure serious or life-threatening diseases and conditions provides regenerative medicine and advanced therapy product sponsors with key benefits, including:

- Guaranteed interactions with FDA
- Eligibility for priority review and accelerated approval
- Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval studies, pending agreement and approval from FDA


The bill also directs FDA to work with sector stakeholders to identify ways to develop standards that aid in product development and evaluation, which ARM has asserted is essential to commercialization efforts and sector advancement.

On January 18, 2017, ARM facilitated creation of the international Standards Coordinating Body for regenerative medicines (SCB), a public-private partnership for coordinating, prioritizing and supporting standards that advance process, measurement and analytical techniques to support the global availability of products across the gene and gene-modified cell therapy, cell therapy, cell-based drug discovery, tissue engineering and biomaterials sectors.

Prior to the Act's passing, ARM engaged in years-long legislative dialogue with bipartisan congressional offices, FDA, the White House, patient advocacy organizations, media, industry trade associations, and other organizations to advocate for:

- Explicit recognition of the therapeutic potential of regenerative medicine and advanced therapy products
- Optimized approval pathways that help safe and effective regenerative medicine and advanced therapy products reach patients as soon as possible
- High FDA product approval standards while opposing proposals that would weaken FDA standards or not fully ensure that safe and effective products reach the market
- Federal support for efforts to increase standards across the regenerative medicine and advanced therapies sector

ARM supports the provisions within the 21st Century Cures Act because they address each of these objectives. On February 2, 2017, ARM hosted a webinar titled, “Understanding the 21st Century Cures Act for Cell & Gene Therapies.” During the one-hour live event, Michael Werner, Executive Director for ARM was joined by Director Wilson Bryan and Deputy Director Rachael Anatol of the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies (OTAT), and Anne-Virginie Eggimann, Vice President of Regulatory Science for bluebird bio, to highlight several of the Act's regenerative advanced therapies-related provisions and describe how they affect companies in the cell and gene therapies sector.

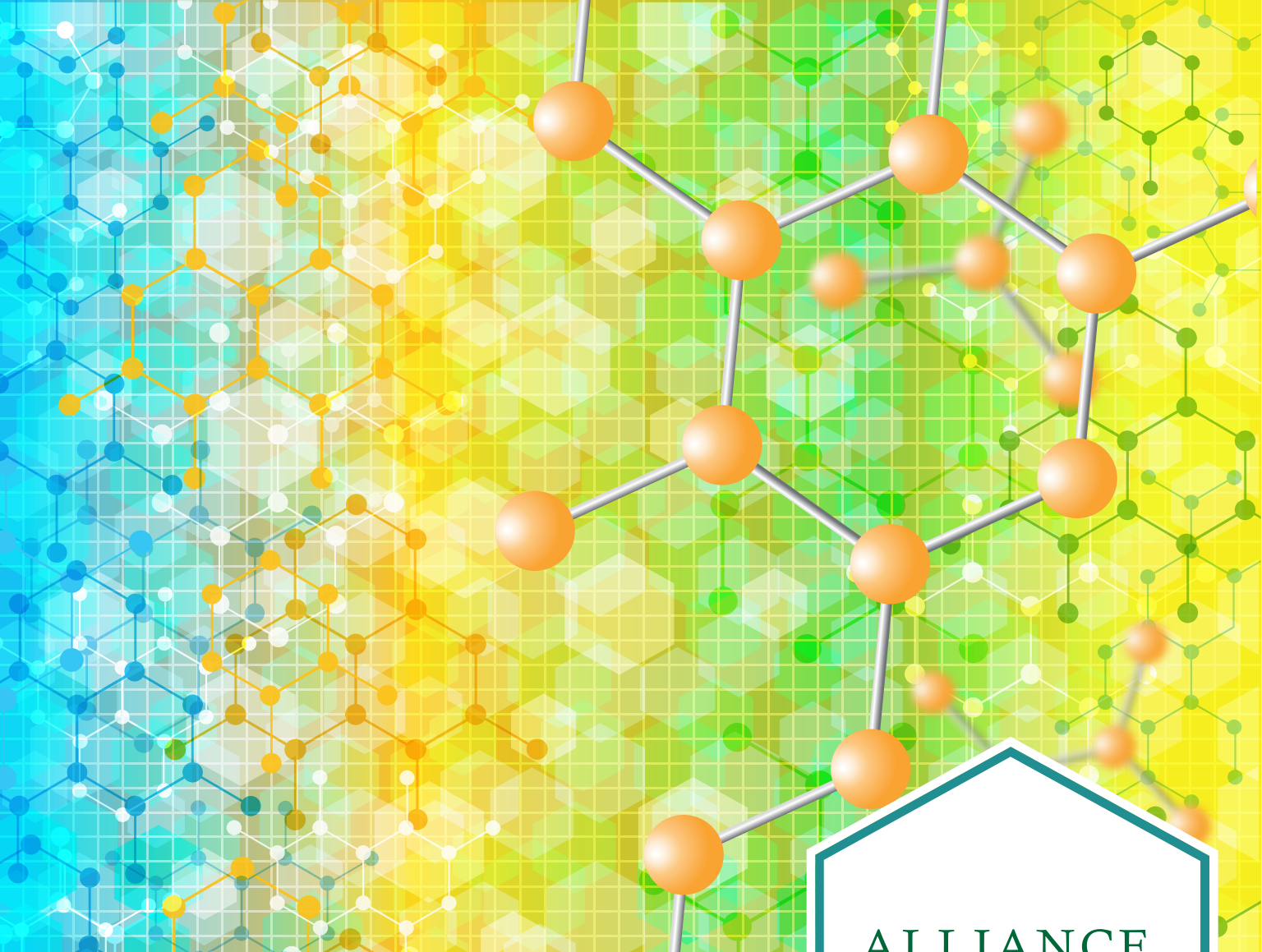


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