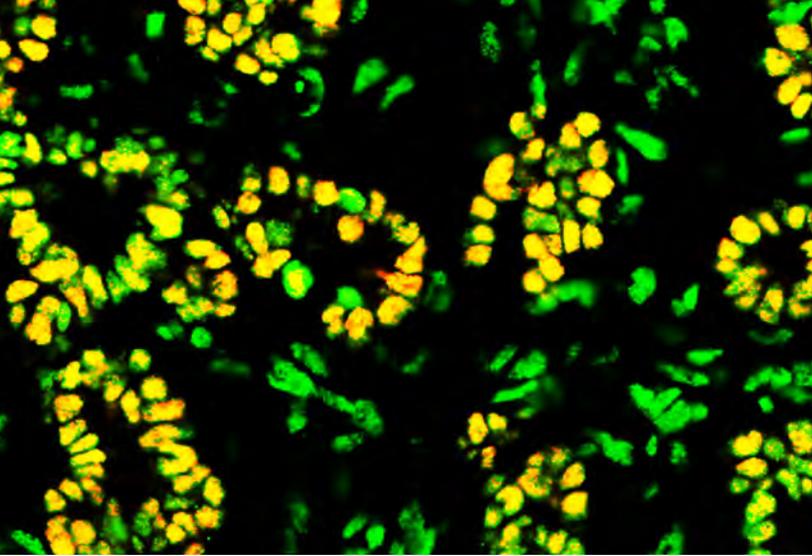


## Pharma and Biotech Survey Alliance for Regenerative Medicine

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The Alliance for Regenerative Medicine (ARM)'s Science and Technology Committee began a project in the summer of 2013 to survey the R&D, product development and business development leadership in top pharma and biotech companies regarding their strategic perspectives of regenerative medicine. This summary reports the results of that survey.

The primary objective of the survey was to engage pharma and biotech executives to speak candidly and openly about their views of the sector – highlighting opportunities and the therapeutic potential of the technologies while also addressing concerns regarding major regulatory and commercial hurdles yet to be overcome. The survey covered the following discussion topics:

- What is the pharma and large-cap biotech strategic perspective on regenerative medicine?
- Where and how is pharma investing in regenerative medicine?
- How are pharma and large-cap biotech companies organized to pursue regenerative medicine?
- What do pharma and large-cap biotechs view as the major therapeutic opportunities in regenerative medicine?
- What are pharma and large-cap biotech companies' major concerns regarding the sector?

The majority of interviews were conducted by members of ARM's Science and Technology committee who have the industry experience and technical background to put responses in the proper context. Some of the companies provided several individuals to respond to the survey while others had a single point of contact.

The summary that is provided herein is a compilation of their responses that provides an unprecedented look into the thought process used by large companies to evaluate regenerative medicine opportunities. Each subsection below summarizes the responses received from a representative cross section of the respondents. To further illustrate the findings, an even sampling of quotes were selected from each of the interviewees and incorporated into the summary. These survey responses have been kept anonymous.

SURVEY RESPONDENTS = 16

- |               |                        |                     |                  |
|---------------|------------------------|---------------------|------------------|
| • Allergan    | • Boehringer Ingelheim | • Johnson & Johnson | • Pfizer         |
| • Amgen       | • Celgene              | • Merck Serono      | • Roche          |
| • Baxter      | • Eli Lilly            | • Novartis          | • Sanofi Genzyme |
| • Biogen Idec | • GSK                  | • Novo Nordisk      | • Shire          |

# How Pharmaceutical and Large-Cap Biotech Companies Define Regenerative Medicine

To begin the interview process, the first topic discussed was focused around the definition of regenerative medicine and what technology types both ARM and the interviewees consider to be part of this discipline. This was an important first step as ARM represents a broad range of technologies within the membership of the organization, and several of the interview questions were specific to technology subsectors such as cell therapies, gene therapies, tissue engineered products and others. As a point of context, below is ARM's definition of regenerative medicine along with the descriptions of regenerative medicine from several of the participating companies.

## ARM Definition of Regenerative Medicine:

*Regenerative medicine represents a new paradigm in human health with the potential to resolve unmet medical needs by correcting the underlying causes of disease via tissue regeneration or replacement. This includes biologics or drugs controlling pathways regulating tissue regeneration, as well as synthetic or natural scaffolds for tissue engineering. Regenerative medicine research translates fundamental knowledge in biology, chemistry and physics into materials, devices, systems and a variety of therapeutic strategies, which augment, repair, replace or regenerate organs and tissue. Our broad definition also includes gene therapy if genes are being delivered in vivo or ex vivo to modify a cell for a specific therapeutic objective.*

## Regenerative Medicine Descriptions from Interviewed Companies:

*"Our working definition of regenerative medicine includes a broad range of products that leverage the body's intrinsic abilities to heal itself."*

*"Regenerative medicine is the use of cells or entities that stimulate cells to repair or replace damaged tissues."*

*"We define regenerative medicine broadly. We include all technologies that are regenerative including cells, antibodies, gene therapies, small molecules, biologics, biomaterials, etc. Our company also considers stem cells for drug screening and safety toxicology testing as regenerative medicine. Immunotherapy is not positioned within our regenerative medicine group."*

*"Our team views 'cell-based immunotherapy' as regenerative medicine with a large focus on oncology."*

*"Regenerative medicine is anything that results from manipulation of stem cells."*

*"Regenerative medicine is putting tissues or cells into organism to regenerate. We do not consider gene therapy and small molecules in our definition of regenerative medicine, but these technologies could have much lower price points than cell therapies. We think cell-based therapies will be the majority of regenerative medicine."*

*"Regenerative medicine is more oriented toward cell-based materials and products for renewal or repair."*

*"Within our venture group we don't have a specific definition, but from our understanding it can include a range of technologies including small molecules, biomaterials, cell-based therapies and stem cells. We would also include gene therapy."*

*"Regenerative medicine means any therapy that will repair or restore cells and physiology leading to improved function."*

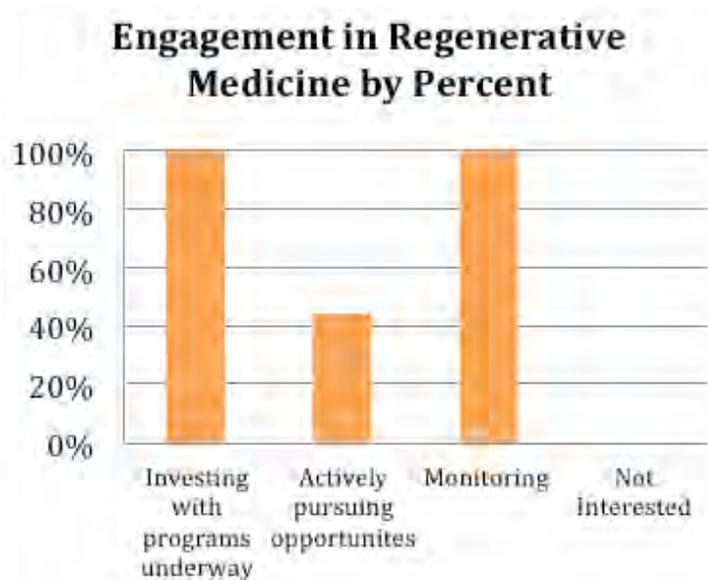
*"We view the field of regenerative medicine in the same way ARM does. In fact, our group was part of the team that came up with ARM's definition of regenerative medicine."*

While the majority of respondents defined regenerative medicine along the same lines as ARM, as expected some considered cellular therapies to address diseases which do not require 'reconstruction' of tissue (such as immunotherapy) to fall outside of a traditional definition. This distinction had no bearing on their overall view of the sector in terms of strategic outlook and what they considered to be advanced or next-generation therapies.

# The Pharmaceutical and Large-Cap Biotech Perspective on Regenerative Medicine

A central question small- and mid-cap regenerative medicine companies are seeking to answer is if the larger, established biotech and pharma companies view the sector as a strategic investment opportunity? How are they organized, if at all, to pursue opportunities in this industry? Do they have teams and strategies already in place? Are they investing in regenerative medicine and if so, in what technologies and disease indications? Do they see regenerative medicine technologies as potential billion dollar products? And, when will competition among pharma and large-cap biotechs for regenerative medicine development programs and therapies begin to escalate, similar to what we witnessed around monoclonal antibody technologies beginning in the late 1990s and early 2000s?

Most followers of the regenerative medicine sector are familiar with the few noteworthy partnerships with large pharma: Pfizer's investment in Athersys' MultiStem therapy for ulcerative colitis, Cephalon's (now Teva's) investment in Mesoblast focused on their MSC program to treat congestive heart failure and United Healthcare's collaboration with Pluristem. We also observed Celgene's bet on bluebird bio and Tengion and Boehringer Ingelheim and Shire's investment in Promethera, but what about the others? Where are they focused and when will they be investing? Here are some of the responses:



What the interviews revealed is both informative and encouraging – of the sixteen companies interviewed, each of them is investing in some aspect of regenerative medicine and view the sector as a potential paradigm shift in the development of breakthrough medicines. One hundred percent of the companies interviewed also indicated that they are closely monitoring both preclinical and clinical stage technologies – 40% of these companies are in active pursuit of therapeutic opportunities. In addition to having some level of investment in the industry, a recurring message that echoed throughout each interview is that pharma does not want to miss this opportunity, and they are monitoring the space diligently and methodically assessing the key questions to commercialize and bring these products to market. Lastly, not one company representative stated that they were not interested in this field.

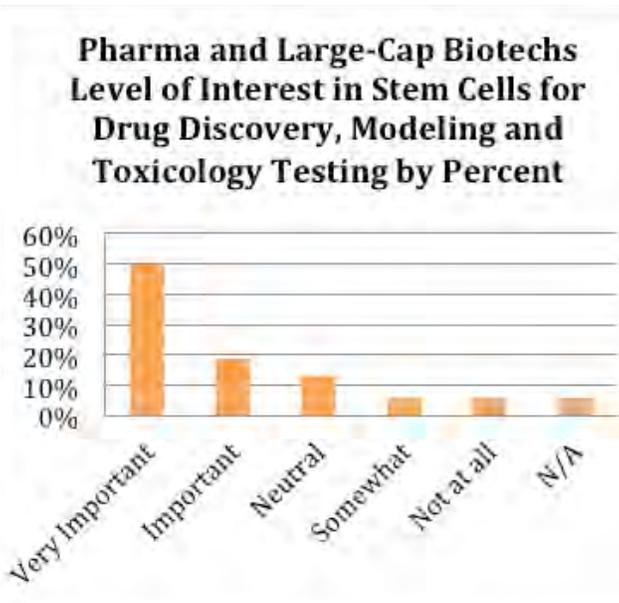
*"We are actively looking for a partner in the cell therapy business and are open to any relationship from partnership to divestiture."*

*"We realize it's a frontier technology beyond a five year time horizon and we don't want to miss the boat. Our company is engaged in various levels and resources are internally devoted."*

*"We are engaged in the Alliance for Regenerative Medicine because we want expertise, we want to be at the right place at the right time."*

## Where is Pharma Investing?

It was not surprising to find a wide range of opinions around what technologies pharma views as regenerative medicine (i.e., cell-based therapies, gene modified cell therapies, gene therapies, scaffolds and biomaterials, the use of small molecules and proteins for endogenous repair and the use of stem cells for drug discovery, modeling and toxicology testing). All of those interviewed, however, agreed that stem cells and regenerative cell-based therapies are in fact regenerative medicine. Of the interviewed companies 88% considered the use of stem cells for disease modeling, drug discovery and toxicology testing as regenerative medicine and of those companies, 64% are actively working with stem cells as key drug discovery tools. Several of those companies mentioned that stem cells represent a paradigm shift in drug discovery.



*"We view iPSCs as very important tools for modeling monogenic diseases."*

*"iPSCs for drug discovery, toxicology and modeling is our core focus in regenerative medicine. This technology not only enhances drug discovery, it is a paradigm shift in drug discovery."*

*We're getting more used to using stem cells for modeling and discovery. We have a group that's very focused on genetics and genetic variants that cause disease. For this group cellular models make a lot of sense."*

*"Stem cells are a tremendous resource for high-throughput screening and toxicology testing, they allow for efficient screening and it gets around animal models."*

*"Our team is a major proponent of stem cells for drug discovery, modeling and toxicology studies."*

*"We use iPSCs and embryonic stem cells for modeling disease. High throughput screening is also fantastic use for these cells."*

On the therapeutic front, 69% of the companies have already invested in cellular based regenerative medicine products and five of them had made or were making investments in gene-modified cell therapies.

Beyond cell-based therapies, the interviews revealed a core group of pharma and large-cap biotechs, especially those focusing on specific neurodegenerative disease indications, to have teams of cellular biologists in place studying endogenous stem cell microenvironments. The common goal of these groups is to discover small molecules and/or biologics that can activate dormant cells and down regulated cellular pathways, thus restoring the body's natural ability to regenerate certain tissues.

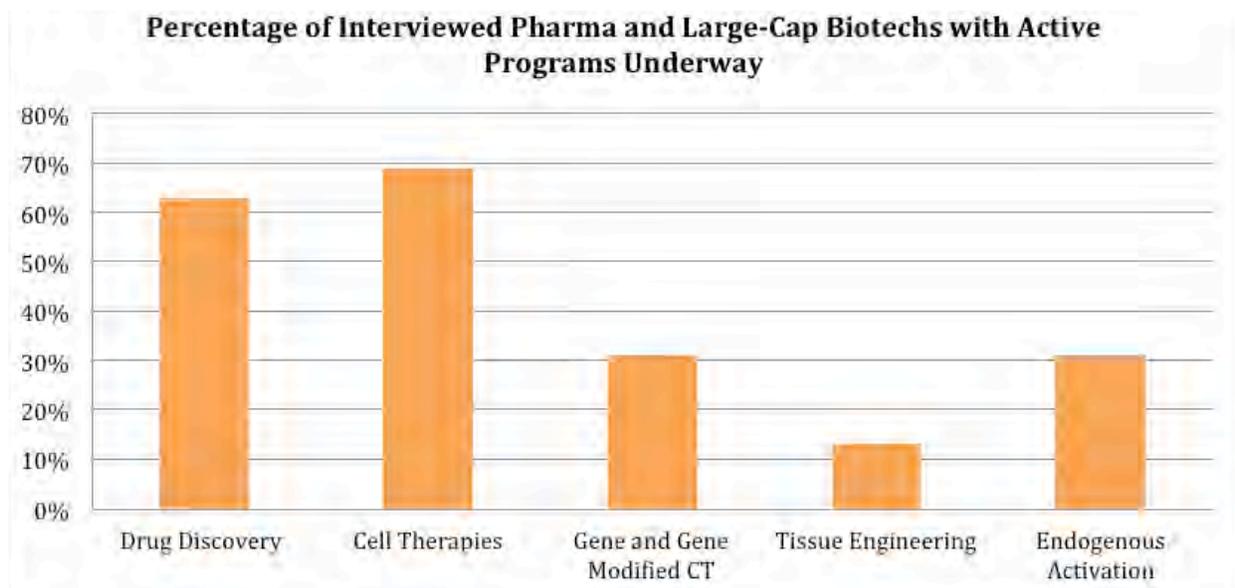
Tissue engineered products and technologies, while recognized as an area of huge potential for regenerative medicine, was seen as less of a strategic priority with only 13% of the companies viewing this as a core part of their regenerative medicine strategy. (It is important to note here that the device and orthopedic companies that are active in the tissue engineering space were not asked to participate in this initial survey.) On the contrary, 56% of the companies surveyed expressed moderate to significant interest in combination products that include a tissue engineered scaffold/device component.

*"We are not currently interested in devices alone. Combination products are a future area of interest."*

*"We're just beginning to understand the potential for regeneration. As this unfolds the potential for endogenous repair is going to accelerate."*

*"We would like to invest early, close to proof of concept. We will continue to invest in the areas of stem cells, gene therapy and other regenerative medicine venture investments."*

*"Our internal investment in regenerative medicine is probably upward of 10% of the overall R&D budget."*



These findings indicate that pharma is actively involved and already investing in the field of regenerative medicine on a variety of levels. The interviews also illustrated that pharma seems to agree that the industry is on the cusp of a strategic inflection point driven by an increased volume of efficacy data, a paramount requirement for pharmaceutical investment. With an increased number of companies entering mid-late stage clinical trials and several major trials expected to read out in 2014, the tipping point may be just over the horizon.

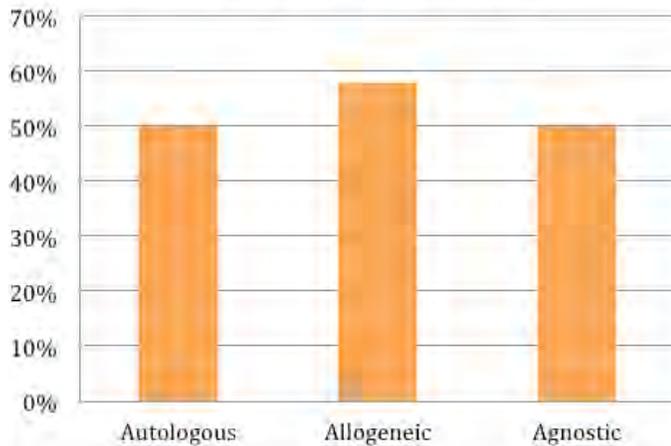
In January 2014 the industry witnessed Johnson & Johnson's \$12.5 million upfront investment in Capricor with up to \$325 million in additional payments. That was followed by Biogen Idec's \$20 million dollar upfront investment in Sangamo BioSciences with up to \$300 million in payments tied to development, regulatory, commercialization and sales milestones - two hopeful signs of pharma and large-cap biotechs' growing commitment.

*"We believe that regenerative medicine is at a critical juncture - similar to the position of monoclonal antibodies in the mid to late 90s."*

## Autologous vs. Allogeneic Cells as Therapeutic Modalities

Within the regenerative medicine industry there has been a great deal of debate over the years around which type of cell therapy will emerge clinically and commercially in the near future – autologous or allogeneic. Perhaps the more likely outcome is that both will find their niche, even within specific therapeutic areas where unique patient requirements may make one of these approaches better suited to a particular patient than the other. How much of an impact will scalability, logistics, shelf life or immune concerns play into the development and adoption of these technologies? People have speculated that large pharma may have a preference for the off-the-shelf stem cell approach (allogeneic) as this business model and cell type fits more within pharma's traditional approach to develop a scalable, low-cost product. The responses from the interviews were diverse and open-minded. Very few of the companies interviewed had a strong preference toward one model versus the other, despite the logistical challenges and potentially higher costs linked to patient-specific or autologous cellular therapeutics. Of the 16 companies interviewed, 50% of them are already investing in patient-specific autologous cellular therapies. Investment in off-the-shelf allogeneic cell therapies was virtually the same with 56% of the participants declaring projects and investments under way. The findings clearly illustrate that, for the most part, pharma does not believe there is a dominant technology. This was evident as 50% of the participants stated that their company remains agnostic toward the two therapeutic modalities. Pharma and large cap biotechs also did not view immune response issues surrounding the off-the-shelf allogeneic model to be a major concern, just as they didn't see manufacturing and/or logistical concerns around autologous technologies to be of high concern. What pharma is once again most interested in is the clinical data. Lastly, the interviews concluded that there will be success and failures with both technology types and neither should therefore be ruled out or considered superior until more clinical data is available.

### Percentage of Companies Focused on Investing or Developing Autologous and Allogeneic Cell Therapies



*"We are working with both autologous and allogeneic stem cells - clinical data will be what's most important."*

*"The most successful products to date have been autologous and though they are very challenging, manufacturing costs amongst other challenges, we think they are very promising."*

*"The most promising cell types are allogeneic MSCs and ESCs."*

*"Autologous is difficult because of logistical challenges but at the end of the day it's all manageable if it can impact patients."*

*"We are actively working in the area of allogeneic stem cell therapy for the treatment of diabetes."*

*"Personalized autologous therapies are our core focus."*

*"We have some concerns about autologous therapies because of manufacturing and logistics. But there is also concern about allogeneic as there could be an immune response – this seems to be getting less risky. We will certainly look at all different approaches."*

*"Autologous versus allogeneic is a tough question...historically there has been concerns around using non-autologous systems but proof is in the data – relatively agnostic. Unmet medical needs are wide open for autologous products."*

*"Autologous is difficult because of logistical challenges but at the end of the day it's all manageable if it can impact patients."*

## How Are Pharma and Large-Cap Biotech Companies Organized to Pursue Regenerative Medicine?

The interviews focused on how the leading pharmaceutical companies are organized internally to monitor, discover, develop and invest in regenerative medicine.

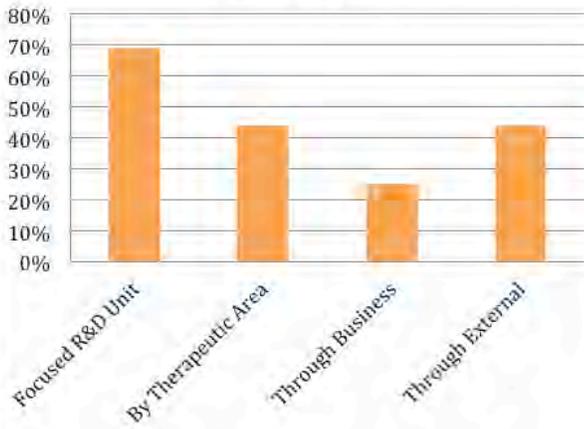
Organizational strategies within the 16 pharmaceutical companies interviewed were, by in large, led by four major divisions or teams:

1. Focused R&D units
2. Disease teams or therapeutic divisions
3. Business development teams
4. Venture groups focused on external investments outside the company's core areas of expertise

Of the four major group types, the most common organizational structure was through vertically integrated regenerative medicine R&D units. The interviews revealed that 69% of the companies already have regenerative medicine focused teams established, each with unique strategies and therapeutic targets. The second most common organizational structure was found to be directly through therapeutic divisions. In other words, it is the responsibility of a disease specific team, i.e., the diabetes team, to identify regenerative medicine opportunities and/or develop technologies within that corresponding therapeutic area. Only 25% of the companies interviewed are predominantly relying on their business development teams or venture divisions to pursue regenerative medicine opportunities. In contrast, more of the companies have employed in-house regenerative medicine executives that are charged with the responsibility to identify investment opportunities and steer the strategic direction for the company. Lastly, of the companies interviewed, 44% have already invested in public and/or private regenerative medicine companies.

What this indicates is that pharma's perspective on regenerative medicine is maturing and shifting from a predominantly venture group and/or business development focus, to a more integrated approach with formal research and clinical development teams in place. Moreover, the findings support that pharma is beginning to look at the leading regenerative medicine therapeutic companies as viable investment opportunities with bets placed by 44% of the companies interviewed.

**How Pharma and Large-Cap Biotechs are Organized to Pursue Regenerative Medicine by Percent**



*"We look at regenerative medicine technologies carefully within disease areas we're interested in, looking carefully at what clinical data will read out over the next several years."*

*"When we decided to enter the regenerative medicine space, we created a division to strategically assess and enter the market. We have also invested in regenerative medicine companies and therapeutic initiatives."*

*"Our venture fund is a strategic fund which invests in areas that the company has not yet accessed. Regenerative medicine and cell therapy were two areas we were interested to enter, gain experience and know how."*

*"The company itself has a research arm, a licensing arm and a venture arm. All three are involved in regenerative medicine."*

External regenerative medicine partnerships were also highly common among the participating companies. Several of them considered partnerships a critical component of success within the regenerative medicine industry. Pharma generally agreed that they are not experts in cell-based therapies and must rely on the experts in industry and academia to successfully co-develop regenerative medicine products.

One of the only major differences between the biotechs and pharma companies surveyed was that large-cap biotechs expressed a deeper understanding around the opportunities and challenges pertaining to the development of cell-based technologies. Several of the biotechs interviewed even seemed somewhat dismissive of the challenges that surfaced in developing, commercializing and marketing first generation cell therapy products. They expressed less need for external partnerships to gain expertise in this sector than large pharma.

Overall though, 69% of the companies have external partnerships in place to accompany internal efforts. Only 25% of the companies have internal efforts underway without external partners. Further discussion of these external partnerships showed that pharma is working with a variety of external groups including academic research institutions and hospitals, a variety of regenerative medicine tool and discovery companies, research foundations and therapeutic companies in both preclinical and clinical stages of development.

The common message that resonated through the majority of interviews was that pharma cannot do this alone and will need to rely on a variety of external partners to advance their regenerative medicine programs.

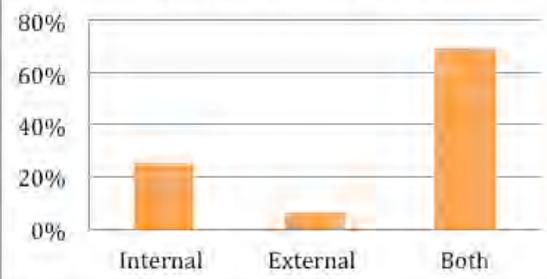
*"In the next 5-10 years a lot will be done here through external partnerships. Our expertise is regulatory, manufacturing and commercialization, the rest will be done with partners."*

*"Our company is tracking stem cell partnerships through science focus groups and companies in areas of interest. We've also in-licensed technology from universities and we're funding research projects at several external academic partner laboratories."*

*"We have several validated programs with academic labs. It's important for an independent entity to look at the data."*

*"Most of our effort in regenerative medicine would be through partnerships... we want to be working with the experts."*

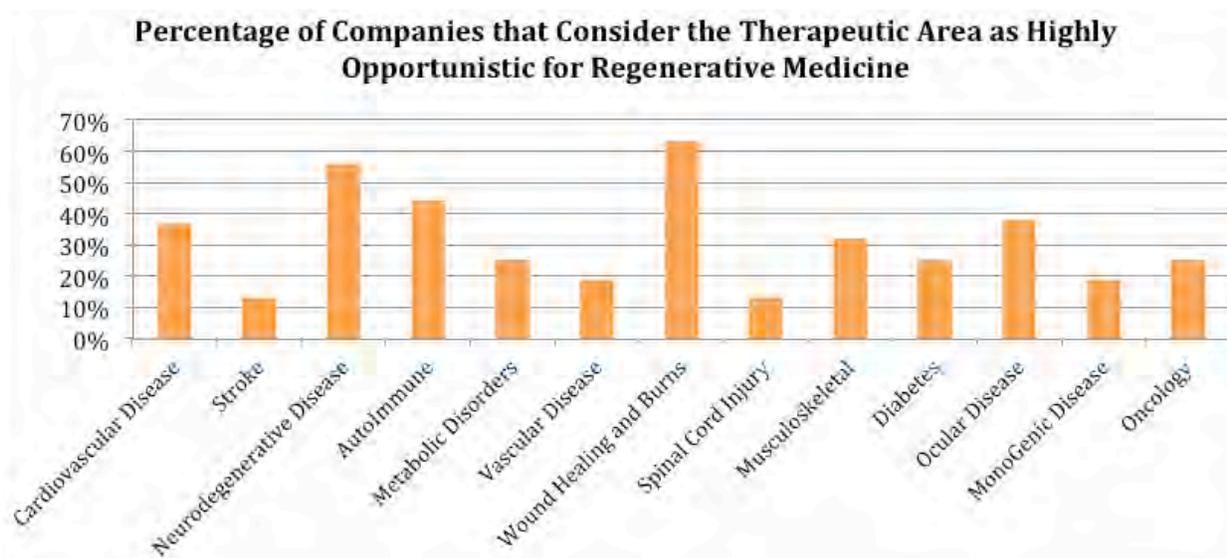
**Percentage of Interviewed Companies with Internal and External Partnership**



## Where Pharma Sees Major Therapeutic Opportunities

During each interview, significant time was spent discussing the therapeutic opportunities and the potential of regenerative medicine as a technology discipline. The goal was to truly understand where pharma views the greatest opportunities to exist. To accomplish this, each interview was initiated by emphasizing to the interviewee that ARM has found regenerative medicine to involve many different therapeutic areas, including oncology, cardiovascular, neurology, orthopedic, ocular, wound repair, organ replacement/regeneration, rare monogenic diseases (across multiple TAs) and many others. We then asked each of the interviewees what specific therapeutic indications (not just those within their company's focus) they believe will have the most impact in the next five years and subsequently, the next 5-10 years and beyond.

The responses were overall quite similar. It is important to note though, that the participants often mentioned that their responses might be biased due to their therapeutic area of expertise and lack of knowledge around regenerative medicine advancements in indications outside of their specific area of focus.



### Here and Now Opportunities

The majority of participants, 63%, stated that regenerative medicine technologies for wound healing are here now and will continue to constitute the nearest term therapeutic opportunity. Other therapeutic areas just over the horizon included cell-based therapies for musculoskeletal conditions, bladder and autoimmune disorders such as GvHD and Crohn's Disease, adoptive T-Cell therapies to treat hematological malignancies and gene therapy.

### Near-Term Opportunities

In the near term -- within the next five years -- treating cardiovascular and ischemic related diseases with autologous and allogeneic stem cell based technologies received the most comments from the participants.

The thoughts around these technologies, however, were mixed in terms of the potential for breakthrough therapies. Several of the companies strongly believed that cell therapies for cardiovascular disease represent the most opportunistic near term therapeutic application for regenerative medicine, whereas others expressed skepticism around the potential impact and efficacy of the technologies in clinical development. All participants agreed, however, that the likelihood of new safety issues arising was relatively small. It will be the Phase II/III data and a clearer understanding of dose ranges and potency that will determine how impactful these technologies will be, and what role they will play in the future of medicine.

With that being said, 2014 and 2015 will be a pivotal period in the evolution of the industry as several of the major public regenerative medicine companies targeting heart disease will be reporting out mid- to late-stage clinical trial results. These companies include: Aastrom, Amorceyte, Athersys, Baxter, Capricor, Cardio3 BioSciences, Cytori, Intrexon, Juventas,, Mesoblast and Neostem. Positive clinical data readouts over the next two years will be vital for the continued support of the industry and to galvanize the interest of big pharma.

Cytori's Phase II trial results will most likely read out in the first half of this year. Shortly thereafter Athersys is expected to publish Phase II data on both their ischemic stroke trial and Phase II data on their Ulcerative Colitis trial (Pfizer partnership). Amorceyte (a NeoStem company) is likely to publish Phase II results for the use of AMR001 cells for myocardial infarction in the third quarter of 2014 and lastly, Juventas' Phase II gene therapy trial is expected to be complete this year as well. If these trials go as planned and the data readouts are positive, we may very well witness an increase of interest around the field of regenerative medicine.

Interviewees also clearly identified cell and gene based therapies for ocular diseases, such as age-related macular degeneration, to be a near term opportunity for the field. Each of the six companies engaged in this space considered ocular disease to be a key therapeutic opportunity for regenerative medicine and strongly believed that these technologies will show clear clinical efficacy and could represent a major advancement in standard of care.

*"Most promising areas of regenerative medicine include the ischemic space/cardiovascular, autoimmune/UC/IB/GVHD, skin and musculoskeletal related injury and disease."*

*"In the next five years we will see progress in the areas of oncology and cardiovascular. The cardio space will see the most progress in the next 10 years."*

*"Mesenchymal stem cell trials for GvHD, cardiovascular and other indications will read out - potentially transformative one way or the other. Regardless, they will definitely be safe and find their place in medicine. The skin is where cell based therapy is now."*

*"The most promising areas for regenerative medicine in the next 5-10 years include cardiovascular, ischemia and immunology."*

Another disease area that garnered interest of big pharma is the monogenic disease space. Of the three pharma companies that expressed significant interest in monogenic disease, they each believed that this area of regenerative medicine is a wide-open opportunity and achievable in the near term. The companies are primarily developing gene-modified cell therapies to target a variety of monogenic rare diseases. The companies focused on these opportunities saw potential for these therapies since the mechanism of action is clear - a single nucleotide mutation resulting in the manifestation of the disease.

In addition to a straightforward mechanism of action, targeting rare diseases allows for a less risky test bed for the platform technology as the regulatory pathway is significantly faster and patient enrollment is much easier in many orphan/rare diseases. Lastly, it was stated that targeting rare diseases with lower regulatory boundaries first, allows the companies to work through the CMC issues before scaling the technology platforms for larger disease indications with higher risk.

*"The disease area that holds the greatest promise is the monogenic disease space."*

*"We have a large effort currently taking place in gene-modified HSCs for several rare diseases. Focusing on rare diseases allows us to test transformative platforms on small patient groups with lower regulatory boundaries."*

*"We believe that monogenic disease is where you can focus and be successful because there's no other therapeutic option. We can also be successful in this are because the MOA is 100% clear. Large indications are tough because we don't really understand the disease."*

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## Long-Term Opportunities

Neurodegenerative diseases were viewed as a longer-term opportunity for regenerative medicine, especially as several of these indications affect millions and treatment options are highly limited. In ALS for example, currently available treatments do not actually treat ALS, but instead attempt to alleviate the disruptive and debilitating side effects of the disease. An advanced cell therapy with the ability to excrete factors that induce preservation of neurons and stimulation of their growth represents a tremendous unmet medical need and opportunity for the pharmaceutical industry. The situation is similar for spinal cord injury where treatment is currently limited to anti-inflammatory agents within eight hours of the injury, surgical implants for the stabilization of the spinal cord and intensive rehabilitation to help maintain strength. Additional diseases such as Alzheimer's and Parkinson's represent indications with tremendous unmet medical need as well. However, these diseases are complicated and still not completely scientifically understood. Below are a series of quotes from the respondents relating to the field's long-term opportunities:

*"Pancreas is going to be big – should be a huge priority for the field. Eye is a promising area...bladder is now."*

*"Most promising regenerative medicine therapies in our opinion are those that offer trophic support for at risk cells such as axons; allowing those at risk cells and tissue to function better. The low hanging fruit is not cell replacement but cellular support."*

*"Neuro or tissue degenerative diseases where cells are lost, such as eye diseases, are therapeutic areas that hold the greatest promise for regenerative medicine."*

*"Cell-based treatment of neurological disease represent the highest risk to return ratio."*

*"The next five years is really all about modeling but the low hanging fruit is eye, ear and kidney."*

*"Disease areas that hold the greatest promise include monogenic diseases, genetic diseases and neurologic diseases."*

*"In 10 years we will crack diabetes. This is a major area of interest."*

While the majority of technology discussions for other indications were around cell-based therapies, pharma expressed a high level of interest in the discovery of small molecules and proteins, through stem cell models, for endogenous neural repair.

Additionally, the interviews revealed interest around the use of neural stem cell and progenitor derived cells for treatment of neurological indications such as Alzheimer's, Parkinson's, ALS and spinal cord injury to name a few. Even though the mechanism of action is not as well defined for many of these technologies and clinical trials are still in early to mid-stage, the use of cells as support platforms to aid in remyelination or regeneration of neuronal cells is an exciting area.

The companies investing in this area of research continually emphasized the importance of creating models to study the science of neural stem cell niches. They noted that understanding these complex microenvironments will be the key to understanding these diseases and treating them early in the disease onset. Furthermore, 19% of the interviewed companies disclosed having in-house stem cell biologists studying the microenvironments and niches of neural stem and progenitor cells to better understand cellular pathways, hoping to identify compounds that up or down regulate these pathways – ultimately resulting in neural tissue regeneration and protection.

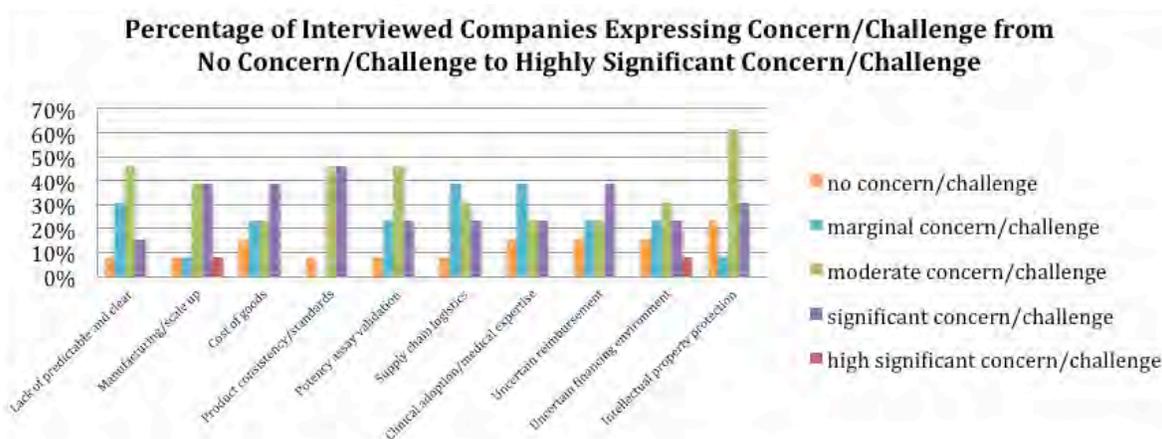
Diabetes did not receive an overwhelmingly high amount of responses, however, the 25% of companies that viewed diabetes as a major opportunity for regenerative medicine were extremely passionate about their reply and highly committed to the therapeutic area. The companies interested in targeting diabetes also stated that despite the difficulty in understanding the science behind the disease, they believe that there will be a major breakthrough within the next 10 years and the opportunities to treat the disease with regenerative therapies for beta cells and other insulin regulating mechanisms will be tremendous. The dominant technology strategy for each of the four companies was predominantly cell-based, testing a variety of multipotent and pluripotent cell types, both PSCT and OTSCT. Additionally, there was interest expressed in possible gene therapies for diabetes. It should be known that all of this work is in research and preclinical stages of development. Lastly, diabetes, of the various therapeutic areas mentioned, seemed to be the furthest from significant clinical breakthroughs.

# What does Pharma See as the Major Challenges?

Many executives, investors and other regenerative medicine professionals are wondering what pharma views as the major concerns and challenges facing the field of regenerative medicine - especially in areas of clinical development, commercialization and market adoption. The respondents were specifically asked if there are any particular areas hindering pharma's willingness to become substantially involved in developing and funding regenerative medicine technologies. To better understand the concerns, a quantitative survey was conducted on each of the participants, followed by a lengthy conversational interview to discuss the level of concern around the following 10 areas: 1) regulation 2) manufacturing and scale-up 3) cost of goods 4) product consistency and standards 5) potency assay validation 6) supply chain logistics 7) clinical adoption/medical experience 8) uncertain reimbursement environment 9) uncertain financing environment 10) intellectual property protection. Below is the detailed look at the quantitative data and comments followed by a brief interpretation and analysis.

## Lack of Predictable and Clear Regulatory Guidance

Of the 10 areas examined, the lack of predictable and clear regulatory guidance received the lowest amount of concern from the participants – indicating that these companies feel that regenerative medicine products have the ability to succeed within current regulatory constructs. Seventy-one percent of the participants agreed that the lack of predictable and clear regulatory pathways is merely a marginal-to-moderate concern. Only 15% viewed regulatory pathways as a significant concern (again, the lowest of any of the categories), and none of the companies considered the regulatory landscape to be a highly significant concern or challenge. The remaining 8% considered this to be of no concern whatsoever. After discussing the subject matter with each of participants, the overarching message was consistent -- regenerative medicine technologies will progress through more complicated regulatory pathways when compared to traditional drugs and proteins. This is especially the case for cell-based technologies and combination products with engraftment capabilities. However, they also emphasized that regulatory expertise is a core competency amid big pharma and something that it viewed will not be an impediment to success.



Of perhaps greater concern is the disparity in regulatory requirements between countries, or in other words, the lack of global regulatory harmonization. Several respondents mentioned that this could add considerable financial burden, limiting the number of markets they can target and the quality of trials they can conduct. What this implies is if a regulatory path is clear, and a company can achieve relevant Phase II clinical endpoints, then differences in regulatory regimes will not dissuade a pharma company from investing. As echoed by several of the participants, the regulatory path will either prove that the technology is worthy of commercialization or not.

*"Cost of goods is a very low concern. Scientific and technical challenges must be determined up-front. Safety and efficacy defines the risk benefit. Regulatory pathway defines if the technology can be successful."*

*"The key questions we're considering are mostly centric around business models and regulatory pathways."*

*"Disagreement amongst regulatory agencies adds to the challenge."*

*"Lack of geographic harmonization is not a unique issue and true of all drug development."*

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## Manufacturing and Scale-Up

The common message from the participants around manufacturing and scale-up was that cell-based therapeutics, combination products and other advanced therapies will be more complex in manufacturing design than current drugs, and therefore, will confront significant development challenges. However, these are engineering questions that companies will undoubtedly solve; similar to the way manufacturing and scale-up challenges were solved for biotechnology products such as proteins and antibodies in the early- to mid-1990s. When looking at the numbers, 78% of the participants stated that manufacturing and scale-up of regenerative medicine technologies would be a moderate to significant challenge. Only 6% viewed scale-up to be a highly significant concern while on the other end of the spectrum a mere 16% viewed this to be a non-issue or marginal concern. By studying the numbers, one can conclude that scale-up and manufacturing is a potential core issue, but as mentioned above, there is more to it than that. Several of the participants stressed that manufacturing and scale-up is something we should not be hung up on as an industry – it represents a healthy challenge and something we will solve. Lastly, those that viewed scale-up and manufacturing to be a non-issue or marginal concern were not developing cell therapies, and were primarily focused on small molecule and biologic based approaches to regenerative medicine with scale-up systems in place.

*“People over estimate CMC as an issue. Although it is a significant hurdle, we believe if the therapy shows a significant benefit and the data is robust, companies will figure out how to address CMC issues. Science is the main challenge.”*

*“We manufacture all of our products on our own, but we don’t have any cell therapy manufacturing capabilities.”*

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## Cost of Goods

After reviewing the interviews and the quantitative results it was evident that a fair amount of disparity existed around the level of concern regarding cost of goods for regenerative medicine therapies. Despite the range of concerns, 61%, of the participants responded within the no concern to moderate concern brackets – a positive sign for the regenerative medicine industry. The remaining 39% viewed cost of goods to be a significant concern. The phone interviews helped elaborate on the disparity and further articulate the scenarios where cost of goods became a significant issue. It is reasonable to expect that the interviewees would respond that autologous cell therapies represent the area of highest concern in terms of a commercial model, but that was not necessarily the case. What the concern really depended on was not simply the cost of manufacturing the product, but the cost of manufacturing the product when juxtaposed to existing product competition within therapeutic areas. To help illustrate this point, several of the companies developing gene-modified autologous cell therapies (a personalized product with high development costs) for rare monogenic diseases, did not view cost of goods to be a significant concern as there are very few, if any, therapeutic alternatives. Essentially, the more wide open the market, the less concern there was around cost of goods. Pharma is highly aware of the costs associated with advanced regenerative medicine therapies and is therefore looking at technologies that have the opportunity to offer substantial benefit over current treatment options.

*“Development costs and unproven business models are not major concerns. Areas of high concern include lack of standards and geo regulatory harmonization.”*

*“We want to use regenerative medicine technologies where there is clear benefit over drugs on the market.”*

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## Product Consistency and Standards

Results from the quantitative survey and the personal interviews revealed that product consistency and lack of standards is possibly the single greatest challenge facing the field. Of the companies interviewed 93% rated this to be area of moderate-to-significant concern. The interviews also illustrate how young the regenerative medicine industry still is, despite the excitement and number of companies in the space and that time is still needed for the industry to mature and become more standardized. It should be noted that ARM is currently tracking 190 regenerative medicine therapeutic companies developing 320+ products and sponsoring approximately 240 trials. It was mentioned by several participants however, that the issue around standards has improved when compared to 10 or even five years ago.

*"Lack of standards has been problematic, but the situation is improving."*

*"Areas of high concern include lack of standards and geo regulatory harmonization."*

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## Potency Assay Validation

The quantitative survey revealed 43% of participants found potency assay development to be a more than moderate concern. Additionally, potency assay validation was often the first challenge or concern mentioned during the interviews. These top of mind concerns mirror where we are as an industry, and may be especially reflective of the clinical development challenges facing the leading companies – many of which are now moving past safety trials and entering later stage efficacy and dosing trials. Potency assay validation is a here-and-now issue and something with which pharma is grappling with. The good news is that no companies viewed potency assay validation as a highly significant concern and only 23% considered this to be a significant concern. Instead, potency assay validation is considered to be a somewhat new and unique issue that cell-based regenerative medicine companies are actively facing. This is not an area overlooked by the community. ARM's Science and Technology Committee serves as one example where a group of industry professionals have identified this as a core issue facing regenerative medicine companies and implemented efforts to mitigate these concerns.

*"Potency assay development and validation is an issue. Cell characterization on the other hand is getting much better with a pretty good roadmap at this time."*

*"Potency assay development and validation is also very difficult as it's hard to say that a given marker indicates a particular clinical outcome."*

*"Potency assay development and validation is a concern – it's a necessity for the end-user and of course important from a regulatory standpoint."*

*"Dosing of cell therapies is an area of concern."*

*"Cell characterization is not as risky as cell potency as it's more objective."*

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## Supply Chain Logistics

For the most part, supply chain logistics were not considered to be a significant or highly significant challenge facing the field. In fact, the majority of participants, 77%, considered supply chain logistics to be a moderate concern or less. A handful of participants mentioned that shipping and storage of cell-based therapies will be significantly more challenging than shipping and storage of chemical and protein-based drugs. Several participants additionally mentioned that with recent advances in quality control systems and the available expertise from supply chain focused service partners, supply chain and logistical concerns will not be a major hurdle for regenerative medicine technologies. Regardless, supply chain logistics is something that should not be dismissed and will be a marginal to moderate challenge facing the field.

*"Cells will be the 'easy' part – the engineering and delivery will be the complex part."*

*"Scalability, development costs, risk of lot failure, unproven business models and COGs are concerns. Other logistical challenges include shipping conditions for live cells."*

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## Clinical Adoption and Medical Expertise

Fifty-four percent of respondents believed that clinical adoption and medical expertise is a marginal concern or less than marginal concern. Of the remaining survey participants, 23% considered clinical adoption to be a moderate concern and another 23% declared it a significant concern. None of the participants considered this to be a highly significant concern.

Throughout the discussions it became evident that the companies which expressed the highest level of concerns related to medical acceptance were those with cell therapy products currently on the market, indicating that first generation products faced more clinical adoption issues than expected. The discussions also accentuated the importance of medical education for regenerative medicine and how educating the medical community can and will influence the adoption of future therapies.

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## Uncertain Reimbursement Environment

Throughout the interviews, pharma consistently mentioned that reimbursement is a challenge, but not one specific to regenerative medicine. Of course companies developing more expensive regenerative medicine therapeutics will feel the pressure, as third- party payers will demand a high clinical benefit to justify the costs. More importantly though, the level of challenge around reimbursement is comprised of many parts, that being the intersection of the disease indication being approached, existing products on the market, cost of the proposed regenerative medicine product and the level of clinical benefit achieved – among others. When taking this into consideration, the disparity in responses makes complete sense. Companies focusing on indications such as diabetes, incurable neurological disorders, rare diseases or other indications with a high level of unmet medical need displayed less concern around reimbursement than companies targeting therapeutic areas with higher product competition, i.e., wound healing and orthopedic conditions. Of the participants, 15% considered reimbursement to be no concern or challenge; 23% marginal concern or challenge; 23% moderate concern or challenge and 39% considered this to be a significant concern or challenge.

*“Reimbursement would be layered in the discussion very early and more and more so that is the case. Public perception is not an issue. Scale-up and manufacturing is a secondary situation.”*

*“Cell-based products are very expensive and need to demonstrate significant impact of therapy for reimbursement.”*

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## Uncertain Financing Environment

The question around finance and access to capital yielded a high amount of variability in responses, both positive and negative. Surprisingly, 23% of the participants claimed that the uncertain financing environment is of no concern, while on the contrary, 23% considered this to be a significant challenge. An additional 8% stated that the financing environment is a highly significant concern – this was the only category to receive responses in the highly significant concern bracket aside from scale-up and manufacturing. Lastly, 23% of participants considered the uncertain financing environment to be a marginal issue. Despite the variation gathered from the quantitative survey, the comments made throughout the interviews were quite homogenous. Each of the 16 companies interviewed mentioned that lack of access to capital is causing companies to run scaled-down, inadequately powered clinical trials with poorly understood endpoints – a major concern of pharma. Small-cap companies struggling to run high quality clinical trials due to lack of capital was the most frequently mentioned concern. Several participants even mentioned that the science and technology behind many of the regenerative medicine companies may in fact be sound, but, without well-designed trials generating quality clinical data, it will be very difficult for pharma to measure the opportunity and the clinical value of these technologies. The bottom line message is that the lack of access to capital may be forcing companies to run poorly designed clinical trials, therefore resulting in questionable clinical data – the single most influential factor for pharmaceutical investment.

*"We always focus on data and our strategy evolves based on the data."*

*"The finance environment is very difficult. It's causing companies to run poor trials with poor clinical endpoints."*

*"We look at it carefully within disease areas we're interested in. Looking carefully at what clinical data will read out over the next several years."*

*"Companies are going to reinvest once they see clinical success and marketed products. Mechanism of action is important but not critical, we've had products on the market without knowing the mechanism of action."*

*"Government funding would help get small companies through some of the valleys. There are lots of gaps in the preclinical work, early trial and experiments due to shoestring budgets."*

*"Clinical data will be what's most important."*

## Final Thought

Perhaps the most important insight gained from this report is that there is no longer any doubt that large pharma and large-cap biotechs are actively engaged in building out their knowledge base in regenerative medicine and advanced therapies. As one would expect, some are more advanced and contributing significant resources while others are taking a far more cautious approach. Regardless of how convincing pharma and biotech execs may be when they describe their strong commitments to these technologies, the truth will be revealed through the investments and partnerships they may or may not undertake in the next 2-3 years. Hopefully these deals will materialize, providing much needed resources to fund clinical development and commercialization.

## About the Alliance for Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is a Washington, DC-based multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine. ARM also works to increase public understanding of the field and its potential to transform human healthcare, providing business development and investor outreach services to support the growth of its member companies and research organizations. Prior to the formation of ARM in 2009, there was no advocacy organization operating in Washington, DC to specifically represent the interests of the companies, research institutions, investors and patient groups that comprise the entire regenerative medicine community. Today ARM has more than 155 members and is the leading global advocacy organization in this field.

## About ARM's Science and Technology Committee

ARM's Science and Technology (S&T) Committee is co-chaired by Dolores Baksh, Director, R&D, Organogenesis; Bob Deans, EVP, Regenerative Medicine, Athersys and Bob Preti, President and CSO, PCT. This Committee serves as a forum for ARM members to exchange ideas, information and data on different science and technology issues within the regenerative medicine field. One of the principal responsibilities of the committee is to consider issues relating to process and research standards in the context of regulatory science that could be adopted by the industry after consultation with other interested and qualified organizations and the appropriate federal agencies.

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

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