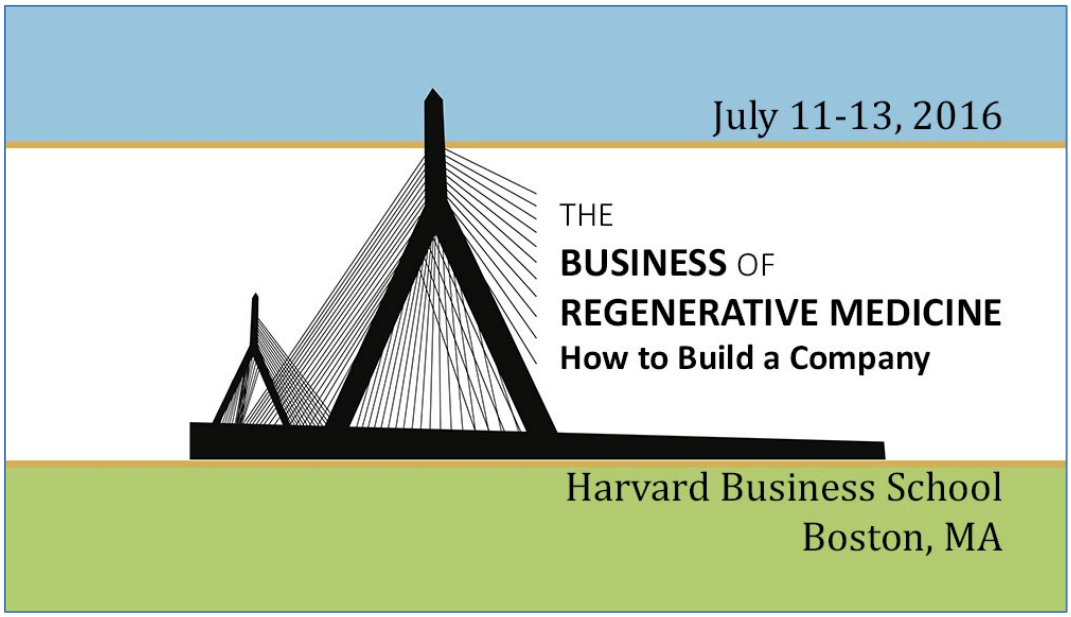
PROCEEDINGS OF



Prepared by:
Jack Kreiger
Sasan Jalili Firoozinezhad
Susan Kennedy

Conference hosted by

HSCI HARVARD STEM CELL INSTITUTE
1000 scientists. One goal. Discovering cures.

and co-organized by

CCRM Commercializing Living Therapies

Case Western Reserve University | National Center for Regenerative Medicine

Georgia Tech | Parker H. Petit Institute for Bioengineering and Bioscience

PROGRAM SPONSORS

Start-Up Level

ThermoFisher SCIENTIFIC

SOLIDGT

WSGR

Accelerator Level

Georgia Tech Parker H. Petit Institute for Bioengineering and Bioscience

semma THERAPEUTICS

GE Healthcare

Concept Level

Histogenics

gsk

Endorsing Level

MassBio
MASSACHUSETTS BIOTECHNOLOGY COUNCIL

MASSACHUSETTS LIFE SCIENCES CENTER
Investing in the State of Innovation

termis

MSCRF
Maryland Stem Cell Research Fund

PROGRAM | BUSINESS OF REGENERATIVE MEDICINE: *How to Build a Company*

MONDAY
July 11, 2016

Aldrich Hall, Room 111

9:30 am	**WELCOME**	**Martin J. Walsh,** Mayor, City of Boston	**Introduction: Brock Reeve**
10:00 – 11:00 am	**KEYNOTES: STATE OF THE FIELD** **SCIENCE** **BUSINESS**	 **Leonard Zon** - HSCI **Reni Benjamin**- Raymond James	
11:00 am – 12:30 pm	**BIOPHARMA**	Sanofi **Sridaran Natesan** Kohlberg & Company **Scott Bruder** Thermo Fisher Scientific **Amy Butler** GE Healthcare **Phil Vanek** GSK **Sven Kili** Biogen **Chris Henderson**	**Moderator: Brock Reeve**
12:30 – 1:30 pm	**LUNCH**		
1:30 – 2:00 pm	**REMARKS**	Harvard Innovation Lab and Life Lab **Neal Doyle** and **Alice Ly**	
2:00 – 3:30 PM	**MANUFACTURING SOLUTIONS FOR CELL/GENE THERAPY**	Cell Manipulation Facility at DFCI **Jerome Ritz** Rooster Bio **Jon Rowley** PCT, a Caladrius Company **Robert Preti**	**Moderator: Robert Guldberg**
3:30 – 4:00 pm	**BREAK**		
4:00 – 5:00 pm	**NATIONAL MANUFACTURING PROGRAMS**	Cell and Gene Therapy Catapult (UK) **Keith Thompson** Cell Manufacturing Consortium **Krishnendu Roy** Centre for Commercialization of Regenerative Medicine-Toronto **Michael May**	**Moderator: Robert Guldberg**
5:00 – 6:00 pm	**REGULATION AND REIMBURSEMENT**	University College London **Chris Mason** Human Longevity Institute **Sally Howard**	**Moderator: Arnold Caplan**
6:00 – 7:30 pm	**RECEPTION**	Harvard Business School – Chao Center, Yi Ren Room	

TUESDAY **July 12, 2016**	**Aldrich Hall, Room 111**		
	Case studies at Harvard Business School: *What it takes to build a company with the rationale for investing probed by mini-panel of scientist/clinician/VC/regulator.*		
			Moderator: Jonathan Gertler
8:30 – 10:00 am	**CELL/GENE THERAPY**	Histogenics (public) **Adam Gridley** Amasa (private) **Khalid Shah**	**Response/critique panel:** **Jens Eckstein|** **Reni Benjamin|Jim Geraghty**
10:00 -10:30 am	**BREAK**		
			Moderator: Jonathan Gertler
10:30 am – 12:00 pm	**CELL/GENE THERAPY (cont'd)**	Semma (private) **Robert Millman** NeuralStem (public) **Richard Garr**	**Response/critique panel:** **Jens Eckstein|Chris Mason |** **Neil Littman**
12:00 – 1:00 pm	**LUNCH**		
1:00 – 1:30 pm	**REMARKS**	Solid Biosciences | Solid GT **Ilan Ganot**	
			Moderator: Jonathan Gertler
1:30 – 3:00 pm	**TOOLS/BIOENGINEERING**	Emulate (private) **Geraldine Hamilton** Organovo (public) **Keith Murphy**	**Response/critique panel:** **Scott Bruder|** **Reni Benjamin|Amir Nashat**
3:00 – 3:30 pm	**BREAK**		
			Moderator: Jonathan Gertler
3:30 – 5:00 pm	**TOOLS/BIOENGINEERING (cont'd)**	Iviva (private) **Harald Ott** Biostage [formerly HART] (public) **David Green**	**Response/critique panel:** **Rich Lee|Scott Bruder|** **Amir Nashat**
6:00 – 8:30 pm	**DINNER** *Creating and Implementing Breakthrough Technologies*	**Robert Langer**, MIT Harvard Business School – Spangler Center-Williams Room	**Introduction: Brock Reeve**

Morning and afternoon panels of experts include:

Reni Benjamin (Raymond James)
Jens Eckstein (SR One)
Richard Lee (HSCI)
Chris Mason (UCL)
Jonathan Gertler (Back Bay Life Science Advisors)
Scott Bruder (Kohlberg & Company)
Jim Geraghty (Third Rock Ventures)
Neil Littman (CIRM)
Amir Nashat (Polaris Ventures)

WEDNESDAY **July 13, 2016**	**Aldrich Hall, Room 111**		
8:30 – 10:00 am	**LESSONS FROM THE PAST**	Introduction **Arnold Caplan** *on* Organogenesis **Chris Gemmiti** *on* Genzyme **Sven Kili**	**Moderator:** **Arnold Caplan**
10:00 – 10:30 am	**BREAK**		
10:30 am – 12:00 pm	**NEW BUSINESS AND FINANCING MODELS** *State of the economy and implications for financial structures* *Alternative financing models* *Buying Cures vs. Renting Health; New Approaches to Financing Transformative Medicine*	Harvard Business School **William Sahlman** Harvard University-Advanced Leadership Initiative **Robert Palay** MIT Sloan School of Management **Andrew W. Lo**	**Moderator:** **Michael May**
12:00 – 1:00 pm	**LUNCH**		
1:00 – 2:00 PM	**PLENARY**	GE Ventures & healthymagination **Sue Siegel**	**Introduction:** **Brock Reeve**
2:00 PM	**ADJOURN**		

#BRM2016 @HarvardStemCell

SUMMARY of PROCEEDINGS

The Business of Regenerative Medicine Course 2016, jointly organized by the Harvard Stem Cell Institute, Case Western Reserve University, the Petit Institute for Bioengineering and Bioscience at Georgia Tech, and the Centre for the Commercialization of Regenerative Medicine, brought together leaders in regenerative medicine from a broad range of industrial and academic organizations. The 3-day course utilized a series of invited talks, case studies, panel discussions, and networking events to foster discussion of the regenerative medicine industry's major challenges—many issues ultimately related to risk and profitability. In discussing how to de-risk individual companies and the industry at-large, several themes emerged regarding key strategies. These strategies address technological, regulatory, financial, and organizational risks.

Technologically, there are critical knowledge gaps in cell therapy and its manufacturing processes, including defining mechanisms of action (MOA), identifying Critical Quality Attributes (CQA), growing and re-engineering billions of cells reproducibly, evaluating CQAs in-line with manufacturing processes, and maintaining cold supply chains. Whether first-to-market companies adopt a centralized hub-and-spoke manufacturing model or a distributed alternative may strongly influence the practices of companies entering later. Strategic partnerships have emerged to overcome critical knowledge gaps too large for individual companies to address. In public-private partnerships such as the UK's Cell and Gene Therapy Catapult, USA's National Cell Manufacturing Consortium, and Canada's Centre for Commercialization of Regenerative Medicine (CCRM), governments are investing in de-risking the industry to reap long-term societal benefits from the realization of a sustainable cell therapy industry. Additionally, cell therapy companies have incentives to form non-competitive industrial collaborations because such partnerships increase the entire industry's probability of success. The final strategy for mitigating technological risk is for companies to focus their pipeline technologically yet take multiple "shots on goal" clinically. In other words, focus on one platform, apply it to multiple clinical indications, and foster an ability and willingness to change direction as clinical data emerge.

Regulatory risk can be managed by three strategies. Firstly, companies should engage in early and frequent conversation with the FDA, since the regulatory territory is largely uncharted. Secondly, clinical trials should incorporate wisdom from past failures. Medical science teams should utilize adaptive design, initially focus on narrow well-defined patient segments before expanding outward, carefully select comparators, and, whenever possible, measure biomarkers that serve as reliable surrogate endpoints. Lastly, companies should consider regulatory paths that accelerate time-to-market, either using Dr. Chris Mason's hybrid Japan-US/EU model (discussed below) or the FDA's expedited programs that, like the Orphan Drug route, provide term-limited protection against competition.

Four strategies emerged for mitigating financial risk. Raising capital whenever possible, not just when needed, protects new ventures against unexpected, unfavorable economic conditions. By conducting R&D in academia as long as possible, new ventures may acquire non-dilutive capital through grants and postpone the decision-making involvement and shorter term focus that can accompany VC funding. Lastly, companies can increase investor confidence by demonstrating commercial viability of their cell therapy on a small or narrow indication first. If a new venture can't succeed on a small scale then it probably can't succeed on a large scale.

Regarding organizational risk, the following adage emerged from the sessions: the management team is more important than the particular technology. The best management teams have complementary strengths, passionate belief in the mission, willingness to pivot, and track records of execution.

The second major challenge facing the regen med industry is how to ensure profitable and sustainable reimbursement. This is accomplished by several means: demonstrating dramatic advancement in efficacy, lowering costs of goods and supplies (COGS), garnering health economic data, and protecting against competition. Opportunities for lower costs include scaling manufacturing and optimizing manufacturing processes, improving reproducibility, and earning approval of allogeneic "off-the-shelf" therapies which yield many doses per donor. Garnering health economic data enables fact-based price negotiation with medical payers. Strategies for acquiring this data prior to US/EU marketing include tracking phase I patients long-term or acquiring term-limited marketing authorization in Japan prior to completion of US/EU pivotal studies. Lastly, Orphan Drug designation and related high-need regulatory pathways provide additional protection of profits against competition.

For more detailed summaries of individual talks and panel discussions, please refer to the sections below, summarized in chronological order.

KEYNOTES: STATE OF THE FIELD

Leonard Zon [Harvard Stem Cell Institute]

Reviewing the "state of the science", Leonard Zon introduced the notion of using reprogrammed (iPS) cells from patients, or "disease in a dish", as a cutting-edge, stem cell-based strategy that is being applied to the developing field of personalized medicine. This "virtual clinical trial" strategy allows researchers to study efficacy and safety of new therapeutics by using an individual patient's cells in vitro, and to discover new therapeutics for various diseases such as neuropsychiatric disorders (e.g. Alzheimer's disease, Parkinson's disease) and neuromuscular diseases (e.g. spinal muscular atrophy).

iPS cells could also be used therapeutically, for example, as a source to generate hematopoietic stem cells (HSCs). Although HSCs have been used clinically to reconstitute the bone marrow, half of all patients lack a matched donor marrow. iPSC-derived HSCs hold great promise for treating such patients; however, our understanding of the pathways involved in HSC formation is incomplete. Current knowledge of in vitro differentiation of iPSCs to HSCs remains incomplete. Despite considerable effort at guiding differentiation using embryonic morphogens, so far no group has achieved the production of HSCs in vitro. Among different strategies, transcription factors could be used to drive the re-specification of iPSCs to HSCs.

iPS cells can also be used for generating retinal pigment epithelium (RPE) cell sheets for age-related macular degeneration (AMD) patients. Both HLA-matched allogeneic iPSCs and autologous iPSCs could be used for RPE transplantation, although the allogeneic cells have greater commercialization potential because of their inherent cost advantage.

iPSC derived dopaminergic neurons are potential therapeutic cells for Parkinson's disease (PD); in late 2017 a phase I clinical trial will begin in 10 mid-stage PD patients.

Reni Benjamin [Raymond James]

Reviewing the "state of the industry", Reni Benjamin showed there is high fundamental demand as investors are interested in regenerative medicine due to an aging population, increase of chronic diseases, pharmaceutical companies cutting back on R&D, pharmaceutical patents expiring, improved regulatory conditions, and more efficient design of clinical trials.

Benjamin also discussed risks, pointing out that lack of clarity creates uncertainty which leads to manufacturing, regulatory, clinical, and financing issues. He mentioned that binary regulatory risk (i.e. approved/not approved) is a major preventive force; that management trustworthiness is a perceived risk to investors; and that creating value and capturing value are two distinct processes.

Important lessons in developing a good regen med business include: 1) ignoring the noise and focusing on the fundamentals, 2) being realistic about valuations, 3) raising capital when you can, not when you have to, 4) watching the markets closely and understanding your position in the cycle, 5) "taking multiple shots on goal" by diversifying potential indications of one product, 6) being objective and avoiding drinking your own Kool-Aid , and 7) listening carefully to the critics of your plan.

GSK [Sven Kili]

GlaxoSmithKline has several gene therapy products in the pipeline. Most notably, their autologous stem cell gene therapy for Immunodeficiency due to Adenosine Deaminase Deficiency (ADA-SCID) completed its pivotal clinical study GSK2696273. Current treatment options for ADA-SCID include bone marrow transplantation, which has a 60-90% survival rate but also a significant risk of graft-versus-host disease, and enzyme replacement therapy (ERT), which presents a 78% survival rate but requires constant administration. GSK's stem cell gene therapy is a single use solution that involves transduction of autologous CD34+ hematopoietic stem cells followed by intravenous infusion. Clinical trials produced exciting results, including 100% survival past 7 years (versus 86% for matched siblings), 7-fold increase in T cell count and 3-fold reduction in the rate of severe infection compared to baseline, and no incidence of leukemia which would be indicative of cancerous mutation of product. Thus, GSK2696273 represents the first autologous stem cell product to be recommended for marketing approval anywhere in the world and received orphan drug status for ADA-SCID. GSK will initially manufacture non-cryopreserved cells before considering single-site manufacturing of a cryopreserved product. Although sales potential in ADA-SCID is low (25 patients p.a.in US/Europe, or £5-10M market), GSK's strategy is to develop mastery by treating a small patient population to establish confidence in the commercial model of stem cell gene therapies. To that end, GSK also partnered with San Raffaele Telethon Institute for Gene Therapy to develop therapies targeted at other rare genetic blood diseases. Clinical trials are underway for beta-thalassemia and metachromatic leukodystrophy, which has produced exciting functional and survival results to-date.

Biogen [Chris Henderson]

Biogen is investigating regenerative approaches to treating nerve and muscle pathologies. Biogen's research strategy is parsed across vertical segments such as ALS and Parkinson's Disease and horizontal segments such as gene therapy, epigenetics, and demyelination that cut across all verticals. Although there aren't identical characteristics between neurodegenerative diseases, Biogen is focused on understanding commonalities that could be targeted by single agents. Moreover, Biogen's strategy involves identifying therapeutic targets at multiple points in the major neurodegenerative pathways and thereby developing complementary therapies. Dr. Henderson (VP of Neurology) believes that large pharma's lack of interest in regen med at large may be due to lack of robustness and reproducibility of results to-date.

Thermo Fisher [Amy Butler]

Thermo Fisher is positioning itself as a supplier of consumables to support a cell therapy market segment that has experienced 4 to 6-fold increases in clinical trials and investments, respectively, in the last 5 years. Thermo Fisher plans to target all levels of the cell therapy value chain, including cell collection, cell processing, and cell distribution. The predominance of autologous versus allogeneic therapies will be a key driver of Thermo Fisher's strategy because of their dramatically different manufacturing and consumable needs. Timing of investment is also critical because of the tradeoff between growth rate and investor optimism.

GE Healthcare/Cell Therapies [Phil Vanek]

GE Healthcare operates in 5 major healthcare-related markets, including research tools, bioprocessing, diagnostics, medical imaging, and cell therapies. With FDA approvals on the horizon, estimates indicate the emergence of a multi-billion dollar cell therapy market requiring 1000s or 100,000s of doses per year in the coming decade. Scaling production will require innovation in manufacturing infrastructure and workflows. GE's value proposition is to provide product and service solutions throughout a "vein to vein" value chain that make cell therapies cost-effective for reimbursement. GE plans to leverage its growing Digital division to integrate all phases of the cell therapy workflow, including initial patient engagement, manufacturing, and dose administration. A key trend affecting GE's strategy is how the convergence of clinical and manufacturing sites may affect the cell manufacturing paradigm. For example, will cell therapy companies build distributed, combined manufacturing-clinical centers, like Novartis's strategy, or hub-and-spoke systems in which centralized manufacturing centers serve networks of clinics?

Kohlberg and Company [Scott Bruder]

Dr. Scott Bruder described the evolution of the regenerative medicine industry through the lens of his personal career path. One particularly important trend beginning in the late 2000s was the cautious attitude adopted by large multinational healthcare companies, particularly the desire to mitigate risk by waiting until later stages of FDA trials to acquire products or companies, albeit at higher prices. Effectively, innovation in regenerative therapies has been outsourced to new ventures. Dr. Bruder advised that new ventures choose therapies that satisfy the least rigorous indication-specific performance criteria, in order to mitigate risk and shrink the time horizon of approval/revenue in an environment where the financial burn rate is often commercially fatal. Regenerative medicine competes for healthcare expenditure against other key technologies like small molecules, and those competitors have faster time horizons. Dr. Bruder also emphasized that metrics for success vary dramatically across stakeholders such as entrepreneurs, venture capitalists, clinicians, and shareholders.

Panel Discussion

Disparate topics were covered during Q&A with the biopharma panel.

Question: How does large pharma view the promise of organ-on-chip technologies to improve the economics of drug discovery?
Answer: Attaining accuracy to human disease conditions in organ-on-chip systems is critical to generate useful data and thereby decrease costs associated with failed drugs.

Question: What's the likely delivery model of cell therapies?
Answer: Although distributed and centralized manufacturing models are being pursued separately, a large company needs to commit completely to one approach to proceed with product launch and capturing market share. To profit, companies invested in manufacturing must scale so that a variety of different therapies can be processed within the same manufacturing model.

Question: How does large pharma fit into the regenerative medicine picture?
Answer: The small molecule blockbuster days are gone. Partnerships between large pharma and small regen med companies can leverage the reach and established personal relationship of large pharma and the deep knowledge of small companies. Both parties stand to gain financially.

Question: What lessons emerge from Juno's CAR-T trial halt?
Answer: Unexpected things will happen in human trials of regen med therapies, so don't throw out the baby with the bathwater. The industry must continue investigating key biological mechanisms and be proactive with patient follow-up. Moreover, the Juno case demonstrates that social media may exacerbate investor groupthink.

Question: Are platform technologies a good strategy?
Answer: Many on the panel believe mastering smaller diseases or patient segments with bundled, complementary products is a strong strategy that may reveal best practices and demonstrate viability of regenerative medicine's commercial model. Such a strategy stands in opposition to investors, who typically push for targeting larger markets.

Manufacturing Solutions for Cell and Gene Therapy

Cell Manufacturing Facility at Dana-Farber Cancer Institute [Jerome Ritz]

DFCI's Cell Manipulation Core Facility focuses on providing cost-effective manufacturing support for early-phase clinical trials rather than late-stage manufacturing. As such, they are currently supporting 4 stem cell gene therapy trials and 1 CAR-T trial using a variety of autologous and allogeneic cell products. The facility provides services throughout the cell

therapy workflow, including product manufacturing under GMP conditions, sample banking and inventory, information systems and data management, quality control and assurance, and regulatory affairs. Longitudinal tracking and custody of samples is crucial and will present bigger challenges for scaled-out manufacturing organizations in the future. As an academic center the CMCF provides a critical transition point between the research labs and commercial entities who can conduct the Phase III and later clinical studies.

Rooster Bio [Jon Rowley]

Rooster Bio's value proposition is to enable MSC therapy companies to create more cells faster per unit price, with the overall goal of decreasing cost so that cell therapy companies can price their products at levels reasonable for reimbursement. Currently, producing lot sizes of 1 trillion cells using suspension bio-reactors costs ~$10k, which corresponds to a $100k reimbursement price assuming typical 90% margin. Rooster Bio seeks to disrupt key cost drivers and industry bottlenecks to maximize viability of new ventures and regen med overall. The company will sell platforms including cells and tools that enable massive cell expansion. Consistent with the challenges facing all cell therapy companies, Rooster is particularly focused on characterizing key quality attributes of MSCs. Extrapolating Arnold Caplan's emphasis on the context-specific behavior of MSCs in vivo, one future challenge for Rooster may be identifying the extent to which quality metrics cut across indications or need to be indication-specific.

PCT [Robert Preti]

PCT's mission is to provide manufacturing platforms and services to clients commercializing cell therapies. PCT focuses on providing closed, automated cGMP infrastructure and operations, and developing "future state" manufacturing processes. They believe Manufacturing-as-Service will prevail as the cell therapy manufacturing model because building in-house may prove too costly for individual companies. Their goal is deliverability: producing consistently high quality product that meets demand over the lifetime of the product and at reasonable cost of goods (COGS). Key to deliverability is carefully watching market trends and the technological choices of potential clients, and taking clues from their choices. PCT partnered with Hitachi (20% equity stake in PCT) to increase its global reach.

To enable commercial sustainability, PCT is focused on dramatically reducing COGS by limiting idle manufacturing capacity, which is driven by uncertain market demand, labor intensity, and complexity of scheduling. To reduce impact of idle capacity, PCT employs modular, compartmentalized design to incorporate multiple products and multiple clients. As such, PCT may maintain stability in the face of possible failure of any individual client or product.

Panel Discussion

COGS related to manufacturability is one major reason that large pharma hasn't invested in cell therapy. Moving forward, pharma companies could help enable confident, large investment in the nascent industry.

Defining CQAs—critical to commercialization and manufacturability—is difficult given that cell therapy MOAs are largely unknown. Further, evaluating cell quality after freezing is a problem that must be addressed before completion of clinical trials. However, the science investigating cryopreservation is ambiguous and in progress. Dr. Krish Roy, head of MC3M (see below), believes that clinical trials must mirror the expected commercial manufacturing process before approval, ideally incorporating the full value chain methodology into phase I trials. He believes quality should be addressed by iterating phase I trials before advancing to phase II and beyond.

Cell and Gene Therapy Catapult [Keith Thompson]

Funded by the UK government's innovation agency, The Cell and Gene Therapy Catapult's mission is to create an advantageous business environment for the UK's cell and gene therapy industry and bridge the gap between government, academia, and businesses. Catapult worked with ReNeuron, Athersys, and Asterias to solve specific commercialization challenges facing their cell therapy products in development. Catapult is currently building a £55M large-scale cell manufacturing center in Stevenage to provide cell manufacturing facilities and solutions, and thereby enable clients to focus on their own core strengths rather than industry-wide issues such as GMP processes. Rationale for this massive investment include providing sufficient scale for late-stage and in-market supply of cells, removing the capital investment risk for cell/gene therapy companies, anchoring long-term growth to licensed manufacturing within the facility, and testing a novel business model. Catapult markets a four-part value proposition to potential users/customers: excellent supply chain, growth designed to meet needs, control over manufacturing strategy such as material flows, and world-class expertise.

National Cell Manufacturing Consortium and the Marcus Center for Cell Therapy Characterization and Manufacturing [Krishnendu Roy]

The National Cell Manufacturing Consortium gathered several dozen stakeholders in cell therapy across governmental, academic, clinical, and industrial organizations to create an industry-driven 10 year road map. The primary objective of the Consortium is to de-risk the cell therapy industry using the impending Marcus Center for Cell Therapy Characterization and Manufacturing (MC3M) to address several key challenges: process reproducibility, measuring cell quality in-line during cell manufacturing, growing billions of cells while maintaining safety and potency, predicting safety and potency for specific indications or patients, storing and transporting doses, lowering costs to enable feasible reimbursement, and training a cell manufacturing workforce. MC3M will focus especially on identifying Critical Quality Attributes (CQA) using a big data approach—rather than a hypothesis-driven approach—and developing sensors and potency/safety assays for in-line quality assurance measurements. Specifically, MC3M sees promise in imaging-based sensors and organ-on-chip potency assays. The Center will be run by Georgia Tech's Petit Institute for Bioengineering and Bioscience, which has a budget of $23M for the project.

Centre for Commercialization of Regenerative Medicine [Michael May]

CCRM's mission is to create sustainable health and economic impact by creating a regenerative medicine ecosystem that agglomerates academic researchers, companies, and investors. CCRM is particularly focused on addressing manufacturing challenges in order to enable scaling up/out, lower costs of cell therapies for reimbursement, and create advanced manufacturing jobs that stay in Canada. Commercial opportunity exists in addressing major technological challenges in cell manufacturing, including automation, parallelization of patient samples, and real-time quality analysis. Accordingly, GE invested $40M to partner with CCRM to tackle these workflow gaps and develop new tools, devices, reagents, and data analytical systems. CCRM invests in companies in the Phase I/II translational "sweet spot" to maximize its impact by increasing probability of success. CCRM's new regen med cluster at MaRS Ontario will physically unite its programs by providing 40,000 sq ft of space such as cleanrooms and co-localization with the University Health Network for clinical trials. Major challenges facing CCRM's model of academic-industry partnership include the rapid pace of industry and managing differing budget cycles, missions, and understanding of manufacturing.

Chris Mason [University College London and AvroBio]

Cell and gene therapies are poorly suited for traditional regulatory pathways, which were optimized for small molecules. Cell/gene therapy ventures face higher risk because reimbursement is uncertain even after marketing approval. To be reimbursed, expensive therapies must demonstrate a step change in outcomes compared to alternatives.

The U.S. FDA has taken modest measures to expedite cell/gene therapies through programs such as Fast Track, Breakthrough Therapy Program, Priority Review, and Accelerated Approval for products that address serious conditions, unmet medical needs, and have justifiable risk-to-benefit ratio. Approval through these programs requires transformative, durable changes in patient outcomes while offering the benefit of smaller sized trials and a two-step process (first-in-man then pivotal).

Japan's regulatory environment is more funding-friendly than other countries in part because regulation and reimbursement are directly linked, thus stabilizing the goal post. Japan has a large $500B healthcare market with universal adoption due to nationalized healthcare. The country has changed the paradigm for cell/gene therapy by shortening the time-to-market-authorization. Clinical trials must confirm safety and predict likely efficacy, then the product is given term-limited (7 year) conditional marketing authorization. Indefinite marketing authorization requires re-application using efficacy and safety data from post-launch trials. For example, Terumo's HeartSheet gained conditional approval at $120k reimbursement after showing safety and a hint of efficacy. For indefinite authorization, they must show 60 cases of efficacy and complete a study (n=120) showing superiority compared to existing alternatives. The Japanese model expedites the path to revenue, which is critical to survival of new ventures. However, one challenge for post-marketing trial enrollment is that patients want the experimental therapy not the control.

Mason proposes that regen med companies adopt a hybrid regulatory strategy. First, conduct first-in-man clinical trials in the EU/US. Then perform a small "bridging study" in Japan while manufacturing in the EU/US. Gain conditional approval from Japan and launch into the Japanese. In parallel, conduct pivotal clinical trials in EU/US. As such, the company will gain earlier revenue from Japanese reimbursement, clinical data and experience, and health economic data critical to reimbursement negotiations in EU/US.

Appropriate pricing is another major challenge with cell/gene therapies and their reimbursement. How do you price a supposedly curative therapy? For most products in development, the efficacy and durability are unknown and there few cases to benchmark against (e.g. Sovaldi for hepatitis C). Is the best reimbursement scheme all-up-front payment, payment for performance, annuities, or some other option? One solution is proposed by Dr. Andrew Lo during his talk (see below).

Sally Howard [Human Longevity Institute]

Howard talked about the USA FDA Biologics Framework options for a faster than normal approval process, including fast track accelerated approval, breakthrough designation, and priority review under FDASIA that leads to expedited approval for unmet medical need related to serious or life threatening conditions. This involves collapsing Phase 1 and Phase 2. Half the novel new drug approvals in 2014 used an accelerated pathway.

Other countries approaches include Japan's seven-year conditional approval for regenerative medicine based upon evidence of safety and preliminary efficacy. In Europe, there is an adaptive pathways pilot, similar to US for expedited approval, specifically for unmet medical need. This leads to conditional approval for narrower population and continued study by the sponsor for safety and efficacy before expansion to larger populations.

Howard discussed the REGROW bill for conditional approval when there is preliminary clinical evidence for safety and reasonable expectations for efficacy. The bill would allow five years to file the 351 application demonstrating potency,

purity, safety, and efficacy. The drugs would be on the market without Phase 3 trials. She said ARM and patient advocacy groups oppose the bill, which will most likely not be passed.

Howard talked about the future regulatory framework. She advised companies to start the conversation with the FDA and continue pressure on CBER to use expedited pathways. In general, there is unease about marketing products without substantial evidence of safety and efficacy, except in indications with unmet need and highly negative outcomes.

Case Studies | Cell and Gene Therapy

Histogenics [Adam Gridley]

Adam Gridley introduced the "NeoCart®" product as a novel innovative therapy that creates new knee cartilage using autologous chondrocytes, scaffolding materials, bioengineering processes and related bioadhesives. NeoCart® targets active and athletic adults with cartilage injury who are not candidates for total knee replacement surgery.

Gridley believes that an ideal cartilage therapy is a combination of biologic and engineered components. NeoCart® provides a therapy with improved efficiency, accelerated patient recovery (i.e. quick and easy process, less rehabilitation and less pain medication), straightforward surgery and positive safety profile.

In clinical trials, the 1-year primary endpoint for BLA filing under Special Protocol Assessment (SPA) is knee pain and function. Their phase 3 clinical trial is currently enrolling under a SPA with the FDA and the company anticipates FDA approval in 2018. In phase 2, NeoCart® patients demonstrated significant efficacy over standard of care, with improved pain/function metrics.

The commercialization strategy of the company is based on small investment (scalable US commercial infrastructure for NeoCart®), specialty US sales force targeting 4,000 to 5,000 orthopedic surgeons, and selectively evaluating commercialization opportunities outside the US.

Gridley believes that the success of Histogenics and regen med companies in general requires more capital, ability to find investors who believe in regen med, ability to pivot, close partnership with the FDA to define endpoints and manufacturing criteria, manufacturing leadership that can accommodate inevitable changes to bioprocess, and early consideration of commercial scaling, logistics, and value to payers and patients.

Amasa Technologies [Khalid Shah]

Amasa aims to commercialize engineered cell based therapeutics to treat cancer patients with the greatest unmet need. Their initial focus is on glioblastoma (GBM) grade IV which has a median survival of 12-18 months after diagnosis. About 70% of patients get tumor resection followed by radiotherapy and chemotherapy which huge side effects. In an effort to develop local therapies, Amasa engineered MSCs to induce apoptosis in tumor cells. To do so, MSCs expressing apoptotic (S-TRAIL) or oncolytic (oHSV-TRAIL) ligands are encapsulated in a synthetic hyaluronic acid-based ECM to increase MSC survival. The main target of this therapy is resected tumors. After performing MRI and stratifying patients, MSCs (from engineered GMP cell bank) are mixed with ECM gels and are implanted in the resection cavity following tumor resection. Treatment is followed-up by MRI and PET imaging.

Amasa has raised over $1.5M and hope to raise an additional $15 M to complete phase I/IIa trial by next year. Ongoing challenges to commercialization are determining the final product (drug vs. kit), reimbursement, physician training, and understanding the product liability.

Panel discussion largely covered two major topics: 1) GBM as a difficult indication, and 2) funding strategy. Historically, GBM was described as a graveyard for many therapeutic approaches, and the panel suggests doing more academic

clinical research to better understand the science of Amasa's approach, before seeking VC funding. Otherwise, Amasa may have to choose between treating GBM and building a viable company by targeting lower hanging fruit. Because Amasa's phase 1 trial is risky due to many steps and factors, Reni Benjamin emphasized the need to demonstrate efficacy in addition to safety, to inspire investor confidence. Angel investors or non-profit foundations could be serve as the financial bridge that funds the next clinical trial that in turn generates VC investment.

Semma Therapeutics [Robert Millman]

Islet transplantation from organ donors was shown to cure type 1 diabetes, providing a proof of concept for cell therapies for type 1 diabetes. However, transplantation of donor islets requires life-long immunosuppression and does not provide sufficient numbers of cells. Thus, Semma is commercializing allogeneic stem cell-derived islets. Their cell therapy is in preclinical development and phase 1/2 clinical trials. Semma has acquired Cytosolv, who provides world-class device engineering and focuses on cell immunoprotection. This device is based on microencapsulation using alginate and other polymers. Semma's commercial goal is 2-3 year survival of the iPSC-derived islet grafts, with hopes of longer survival.

Semma's current challenges include shelf life and cost of the product, limited suitable toxicology and efficacy models, identifying a delivery method which not only prevents cell/graft rejection but also allows sufficient function (parallel paths to clinic including autologous iPSC and allogeneic cells+immunosuppression), manufacturing complex cellular products, and sourcing regulatory-compliant ESCs or iPSCs.

One major concern voiced by the panel was Semma's main competitor, Viacyte. Because Viacyte is likely to be first-in-class, Semma is faced with the challenge of demonstrating best-in-class performance.

NeuralStem [Richard Garr]

NeuralStem has ongoing clinical trials at UCSD for chronic spinal cord injury (SCI) and ALS, using a hippocampal neuronal product that is composed of half neurons and half glia. NeuralStem's major scientific challenges are that neurodegenerative endpoints are soft, hard-to-track, and highly variable, and there are no strong biomarker surrogates. Selection of chronic over acute SCI provides a commercialization advantage because chronic SCI patients do not improve without treatment, whereas acute cases present confounding variables and complicate evaluation of success.

They are not interested in VC funding, but rather acquired pre-competitive funding and solidified public-private partnerships to identify new biomarkers in neurodegenerative diseases.

Remarks | Solid Biosciences (Ilan Ganot)

Duchenne muscular dystrophy (DMD) affects 300,000 patients worldwide with a disease burden of $10B. Led by Ilan Ganot, the father of a DMD patient, Solid Biosciences has the singular mission of improving lives of DMD patients. They are solely focused on DMD and, uniquely, are modality-agnostic. Their multiple focus areas include corrective therapies (e.g. gene therapy), modifying therapies, assistive devices (e.g. exoskeletons), and disease understanding (e.g. biomarker identification). Pre-clinical studies using their dystrophin gene therapy product showed muscle force restoration and gait improvement in DMD models in mice and dogs; plans for clinical studies are in process. Manufacturing scale-up looms as a commercial challenge.

The company has raised $65M to-date, thanks in part to Ilan Ganot's strong investor connections developed during his tenure at JP Morgan.

Emulate Biosciences [Geraldine Hamilton]

3D in vitro models of organs and disease are not easily or cost-effectively scaled up to pharma workflow. Moreover, expensive and time-intensive in vivo studies often cannot reflect human responses in a robust and efficient manner (less than 8% of drugs will make it to patients). Emulate is developing and commercializing organ-on-chip (OOC) systems as pre-clinical testing models for pharma. They have received funding from various sources in academia (Wyss Institute), electronics (Sony), pharma (Merck, Pfizer), and government (DARPA: $37M).

In theory, human cell-based OOC systems enable cheaper and faster identification of mechanisms of action and biomarkers of efficacy/safety, compared to animal models. Geraldine Hamilton emphasized that getting pharma to adopt OOC systems is difficult and requires demonstration that using OOC enables different and superior decision making about drug candidates compared to alternative test-beds.

For DARPA, Emulate linked 10 different OOC chips as a model of the whole body. From the studies, Emulate developed useful new instrumentation that makes their systems more ready-to-use in pharma labs. In parallel new instrumentations are being developed to allow the devices to be automatic (plug & play) and simple, without using of pumps and tubes that cause problems in the scale-up of microfluidics systems. OOC systems are expected to get into market in 2017.

The panel praised Emulate for its acquisition of $37M of non-dilutive funding from DARPA, followed by $57M in Series A/B VC rounds. The panel discussion revealed more specifics about Emulate's business model. They will send OOC chips and instruments to pharma companies pro bono but will own the software and data. Because they have no extensive cell isolation knowledge in-house, they formed partnerships to acquire iPSCs and will perform extensive quality control in-house.

Organovo [Keith Murphy]

Organovo, founded in 2007, in-licensed 3D bioprinting technology from the University of Missouri. Subsequently, the company started commercial-grade Novogen Bioprinters and custom tissue development service in 2010 and expanded their facility in San Diego (>36000 square feet) in 2014. Organovo launched ExVive3D liver tissues for use in pediatric toxicology in 2014. Keith Murphy noted the company completed a $46.6 M initial public offering (IPO) and listed on the NYSE in 2013, after starting from $3M angel funding.

Organovo's focus is on using bioprinted systems to evaluate preclinical safety in healthy tissue or model various diseases (e.g. liver fibrosis) to study drug efficacy. They are able to generate fully human multicellular functional structures which could be used instead of non-reliable 2D models and without reliance on animal models. Organovo has demonstrated the value of their system by retrospectively analyzing drugs that failed in humans after not sounding alarms in old in vitro models.

Iviva Medical [Harald Ott]

Harald Ott believes that organ replacement products represent fundable projects. End-stage renal disease (ESRD) treatment cost is expensive for patients. Hemodialysis (HD) has a relatively high death rate and only provides minimal kidney function. Iviva's goal is engineer human kidneys. To accomplish this aim, iPS cells are generated from patient blood after HD, differentiated to progenitors, seeded on acellular porcine kidney scaffolds, and matured in bioreactors. The science is early stage and pre-clinical large animal studies are ongoing.

Despite great laboratory success so far, Iviva still needs to address major challenges such as defining a clear business model, reducing the bioprocessing time to a scale fast enough to treat patients, unclear regulatory pathway, gathering

multidisciplinary expertise, and transitioning from lab-scale to industrial manufacturing techniques. Nevertheless, the project is aided by similarly high but distinct hurdles facing the alternative therapies, xenotransplantation and tolerance.

The panel elaborated on additional challenges facing Iviva. One major technical hurdle is that the kidney has multiple divergent maturation/differentiation steps that may not be fully realized by one batch of iPS cells. The panel questioned whether at this stage Iviva should be a company or remain purely academic. Industrial pace could help accelerate progress compared to academia; alternatively, the pressure to earn revenue could drive the project down a fruitless path.

Biostage [David Green]

Biostage is commercializing an esophageal transplant engineered from AD-MSCs seeded on a fiber-based esophageal scaffold and grown in a bioreactor. In vivo, a new esophagus grows over the scaffold and later the scaffold is removed endotracheally.

David Green presented 8 major pieces of advice for regen med companies to win for patients and investors. 1) Target life-threatening diseases to earn compassionate-use designation by FDA and create a strong mission for employees, 2) acquire human efficacy data early to avoid late-stage risk of failure, 3) focus on the mission not the specific product, and pivot when necessary, 4) target orphan indications to speed path to market and protect against competition, 5) target pediatric indications and then adult indications, 6) be lean with respect to costs, 7) incubate longer in academia to preclude late funding rounds that dilute ROI of original investors, and 8) go public to improve the CEO's bargaining power.

Keynote | "Creating and Implementing Breakthrough Technologies"

Robert Langer [Massachusetts Institute of Technology]

Lessons from the Past

Osiris [Arnold Caplan, Case Western]

Caplan discussed lessons learned from the past related to cell-based theories and beyond. Breakthroughs take a long time to come to fruition (average of 20 years). Lessons learned include: founding scientists should not be CEOs, scientists belong on SABs not BODs, the quality of management rather than quality of the technology determines success of the company, new technologies need proof-of-concept clinical trials ASAP, honesty is the best policy, and strategic planning, milestone goals, and market awareness are the only way to turn technology into products. We are at the end of the beginning phase of regenerative medicine. The next five to ten years are particularly important for the industry.

Organogenesis [Chris Gemmiti, *formerly Organogenesis*, currently Wyss Institute]

Organogenesis began as a spin out from MIT in 1985 as an early pioneer in tissue engineering, with the product Apligraf as the first FDA-approved allogeneic cell therapy effective in the treatment of venous leg ulcers and diabetic foot ulcers. Gemmiti discussed different phases of the company (1.0, 2.0, 3.0) and the lessons learned throughout the hype cycle.

During the transition from 1.0 to 2.0, the company went from a market cap of $1B in 1997 to bankruptcy in 2002. Their initial product was not commercially viable. Great science does not always mean great business. As a result of

reorganizing and refocusing, the company emerged from bankruptcy and, by 2010, revenues were greater than $100M with more than 500 employees. They introduced Gintuit in 2012 for soft tissue regeneration.

Gemmiti discussed key lessons were learned from stage 1.0 to 2.0. The innovation pipeline had too many disparate therapeutic areas. The company was run like an academic organization--not an efficient business model. The change in 2.0 was to focus on select therapeutic areas, the industry, and public expectations. The staff devoted itself to reimbursement. The shelf life changed from 3 days in phase 1.0 to 10 days in 2.0. The manufacturing became more reliable, moving from manual processes in 1.0 to scalable semi-automated in 2.0. The commercialization strategy changed from the use of Novartis' sales and marketing channel that was focused on plastic surgeons, to a consultative approach and focus on vascular surgeons and podiatrists.

The company next went from a pragmatist view in 2.0 to a wound healing therapeutics focus in 3.0. This started in 2014 with CMS slashing reimbursement of Apligraf by 40% that resulted in a reduction in revenue and significant layoffs. Gintuit was removed from the market. The company focused on wound healing with an acquisition of Dermagraft in 2014 and the Puraply, a cellular collagen biomaterial product. This product was re-launched in 2015.

Gemmiti offered several pieces of counsel. Understand that a therapeutic focus leverages manufacturing infrastructure and commercial investment. Be aware that reimbursement policy can change abruptly, and show significant clear health economic benefits. Plan on failure and unforeseen circumstances. Promote a strong culture. Do what you think in right. Most therapies are expensive, so efficacy must justify investment. Partnerships and the board of directors are opportunities that allow companies to better equip for the future.

Genzyme [Sven Kili, *formerly Genzyme*, currently GSK]

Kili was an orthopedic surgeon focused on sports medicine before he joined Genzyme to oversee clinical research and medical affairs. Kili talked about lessons learned on three products: Epicel, Carticel and MACI.

Epicel (cultured epidermal autographs) was a leading edge solution for deep dermal or full thickness burns device approved for humanitarian use (not for profit).. There was a slim chance of survival for patients with greater than 30% body area burned. The product had a shelf life of 24 hours which impacted the financial viability of the product as last-minute airplane based transport is inherently expensive.

Carticel, a two-step treatment for cartilage repair, was tested in humans in 1987, launched in 1995 by Genzyme, with FDA guidelines in 1996. Carticel was approved for safety and efficacy in 2005.

There was a small German company working on ACI to MACI technology. The treatment was Carticel in the USA and MACI for rest of the world. The Summit trial in 2008 found MACI (covers 3-20 cm2) worked significantly better than microfracture (covers up to 4 cm2) for treating cartilage lesions. In 2013, MACI was approved as combined ATMP (Advanced Therapy Medicinal Product). Sanofi purchased Genzyme and divested the cell therapy initiative.

Major challenges in this space include finding patients with isolated injury, determining outcomes and the goal of the therapy, regulatory issues, and reimbursement.

Lessons learned include improving COGS and the clinical trials design (adaptive design and real world applicability), understanding regulatory changes (more effective endpoints and ability to pivot to other indications), collaborating early, educating stakeholders, acquiring supportive financing, engaging medical payers early, focusing on the patient, and identifying the real medical need.

William Sahlman [Harvard Business School]

Sahlman opened with an overview of the state of US health and healthcare. Although healthcare spend is 18% of GDP, 2x higher than average developed countries, quality is mostly mediocre. There are issues with the fee-for-service paradigm, the ACA reform of access to health insurance versus access to affordable health, and Medicare liabilities greater than $30T. Massive increases in insurance costs threaten scientific progress.

Salhman discussed the entrepreneurial process. All new ventures begin as hypotheses, with high uncertainty. Entrepreneurs acquire financial, human and other resources to run experiments. Investors give enough money to run sensible experiments. Experiments produce value-changing information as stepping-stones to the next experiment. Money is time. Buy time to produce information.

With the venture capital process, great people with outstanding ideas are backed with money to run structured experiments that reveal information about the team, the competition, and the opportunity.

With the entrepreneurial process of risk and reward management, pick the opportunity with upside, discover the shape of the uncertainty curve, and change the odds and payoffs. Value is a function of expected cash, risk and time. Value inflection points are significant changes in expected cash, risk and/or time. Everyone creates value. Entrepreneurs are in the sales business and constantly selling.

Key financing rules include raising money when you can, not raising money when you cannot, and not running out of capital.

Tackle risk by execution. Execution trumps technology every time. All the companies that lost money in which Sahlman had been involved had the idea but someone else did the execution.

Money is time. VC may not be the best model for life sciences as the milestones are difficult to predict and picking the right investor to stick with it for the long run is a challenge. Cash management is the most important. Spend current financing as though it's the last money you will ever have. Plan for economic downturn, buy insurance, and raise more money than needed. The best money comes from customers not investors.

Robert Palay [*formerly Cellular Dynamics*, currently Harvard University, Advanced Leadership Initiative]

Palay is currently a 2016 Harvard Advanced Leadership Fellow. His entrepreneurial background includes CEO at Cellular Dynamics (stem cell company), Nimble Gen systems (gene chip company), and Tactics II Group. Palay talked about financing alternatives for regenerative medicine companies. Great regenerative medicine companies have a large market opportunity, strong management team, cutting edge technology, and capital. Capital is a commodity. There are four options for raising money in order of preference: gifts, sales/revenue, loans, and equity. Palay recommends pursuing all four options simultaneously. For founders, equity is the least attractive option.

Gifts are dollars with no expectations in return. Sources of gifts include academic institutions, relatives, and friends. Grants are not gifts but instead revenue bearing contracts. Gifts are the best option for founders, but highly unlikely.

Sales/Revenue means the company receives payment for product or services. Sources of sales/revenue include grants (government, foundations) and customers (pharmaceutical, biotech, academic, consumers). Customers validate business models for investors.

With loans, the lender advances principal dollars and the company makes promises. Sources include economic development loans (government), venture lenders, and royalty (IP) lenders.

With equity, the company sells stock in exchange for percent ownership in the company. Different types of equity include common and preferred stock. The sources of equity include: direct investment, strategic investors, venture capital firms, public equity, and hybrids.

With direct investment the company sells stock directly to individual "angel" investors. The strategic investor option involves the company selling stock to participants in the industry who are motivated by factors beyond purely financial ones. The company can sell stock to financial investors, such as VCs. There are also hybrid models led by non-traditional VCs, who may have more flexible criteria and time horizons.

Andrew Lo [Massachusetts Institute of Technology]

Andrew Lo proposes a new healthcare financing vehicle based on healthcare loans (HCLs) that would broaden access to curative therapies, incentivize development of curative vs. incremental therapies, and allow payers to link their payments to value received and realized health benefits.

Central to the problem of rising costs of U.S. healthcare is the question: what is the monetary value of human life? In many other facets of society besides healthcare, this question has been answered on the policy level. For example, the U.S. Department of Transportation says the economic value of a statistical life (VSL) is $9.1M. Can society afford breakthrough therapies? In the current healthcare system, the answer is apparently "no." Take the hepatitis C drug, Sovaldi, as an example. The reimbursement price is only $84k even though the drug precludes the need for liver transplantation, which costs $580k. What's more, Sovaldi's supplier, Gilead, has been accused of price gouging.

Lo believes more efficient financing mechanisms can help reduce costs, irrespective of who pays, and increase availability. In the current paradigm, co-pays are prohibitive for individual patients, and insurers are de-incentivized to pay for curative therapies because of the risk that policyholders will switch payers and, by extension, transfer their lifetime health benefits of curative treatment. Lo's solution is to pay via HCLs, debt obligations that amortize prices over longer time periods of payment and that follow patients from payer to payer. In parallel, he proposes enactment of legislation that prohibits insurance providers from denying coverage on the basis of pre-existing HCLs. Applying common financial engineering techniques and portfolio theory would enable creation of a healthcare credit market analogous to the many other consumer loan markets in existence. Taxpayers would pay in the very long run; insurers in the long run, and patients, families, and foundations in the short run.

Lo also discussed public-private pooling of funds as emerging alternatives to financing the development of therapies. Examples include California Institute of Regenerative Medicine, London Mayor Mega Fund, UBS Wealth Management Fund, and Mass Health funding Hepatitis C drug. He posited that finance isn't necessarily a zero-sum game and that large scale finance can do good for all stakeholders.

Plenary – GE Ventures (Sue Siegel and Amy DuRoss)

Disruption happens in any industry. Companies have to innovate and recreate no matter what size they are to avoid the effect of disruption. As an example, **Susan Siegel** talked about the restructuring at GE with reductions in the financing business and sale of the appliance division.

The healthcare business models are changing: centralized to distributed, fixed costs to fexible (CAPEX to OPEX), and static to connected. Newer models include X-as-a-service with pay-as-you-go and subscription payment models. Geographic convergence with emerging nations is a huge disruption.

Non-traditional players are entering the healthcare ecosystem such as Verizon with changes in broadband, increasing mobile, enabling faster access to information. Siegel discussed building partnerships and collaborative networks along

with platforms, networks and orchestration. Network orchestrators receive strong market multiples. She talked about average multiplier (price to revenue ratio) for example S&P companies in 2013: asset builder 2.0X (e.g. Walmart, Ford), service provider 2.6X (PWC, United Healthcare), technology creator 4.8X (Amgen, Oracle), and network orchestrator 8.2X (Airbnb, Uber, Amazon).

GE Ventures provides access to alternative growth models through key initiatives: Catalyst, Venture Investing, New Business Creation, Licensing, and Healthy-Imagination. GE Ventures is focused on software, healthcare, energy and advanced manufacturing and enterprise solutions.

The healthcare investment themes include entry into new markets and innovations, building ecosystems and partnerships. GE Ventures healthcare investments include digital health, precision medicine and image-guided procedures. With new business creation, GE Ventures enters new markets, enables GE business, and maximizes GE assets.

Amy DuRoss talked about the issues of scaling and commercializing cell therapy solutions. Cell therapy products are potentially curative but are expensive and complex. There is a multi-billion dollar opportunity for cost and quality improvement. Amy talked about the launch of Vitruvian Networks, a GE Ventures funded network orchestrator and independent platform company focused on accelerating access to cell and gene therapies through advanced, cloud-ready software systems and manufacturing services. The company offers an end-to-end solution that includes integrated software, analytics and manufacturing services. Their Atlas Software Platform will focus on cloud and mobile first. The sales model will be business-to-business and will provide multiple revenue stream opportunities. With Vitruvian and other investments, GE is playing a leadership role in the disruption of the cell-based therapy market.

During the subsequent Q&A discussion, Arnold Caplan expressed belief that GE is well positioned to fill an informational need in MSC therapy with the data capture system and database of outcomes. Looking ahead, the clinic-centric healthcare paradigm could be disrupted by digital/mobile healthcare for non-acute issues.

How to Build a Company was the 9th program in this series organized and managed collaboratively by HSCI, Case Western Reserve University, Centre for the Commercialization of Regenerative Medicine (Toronto), and the Parker H. Petit Institute for Bioengineering and Bioscience at Georgia Tech.

Next year's event will be hosted in July, 2017, in Toronto by the
Centre for the Commercialization of Regenerative Medicine.