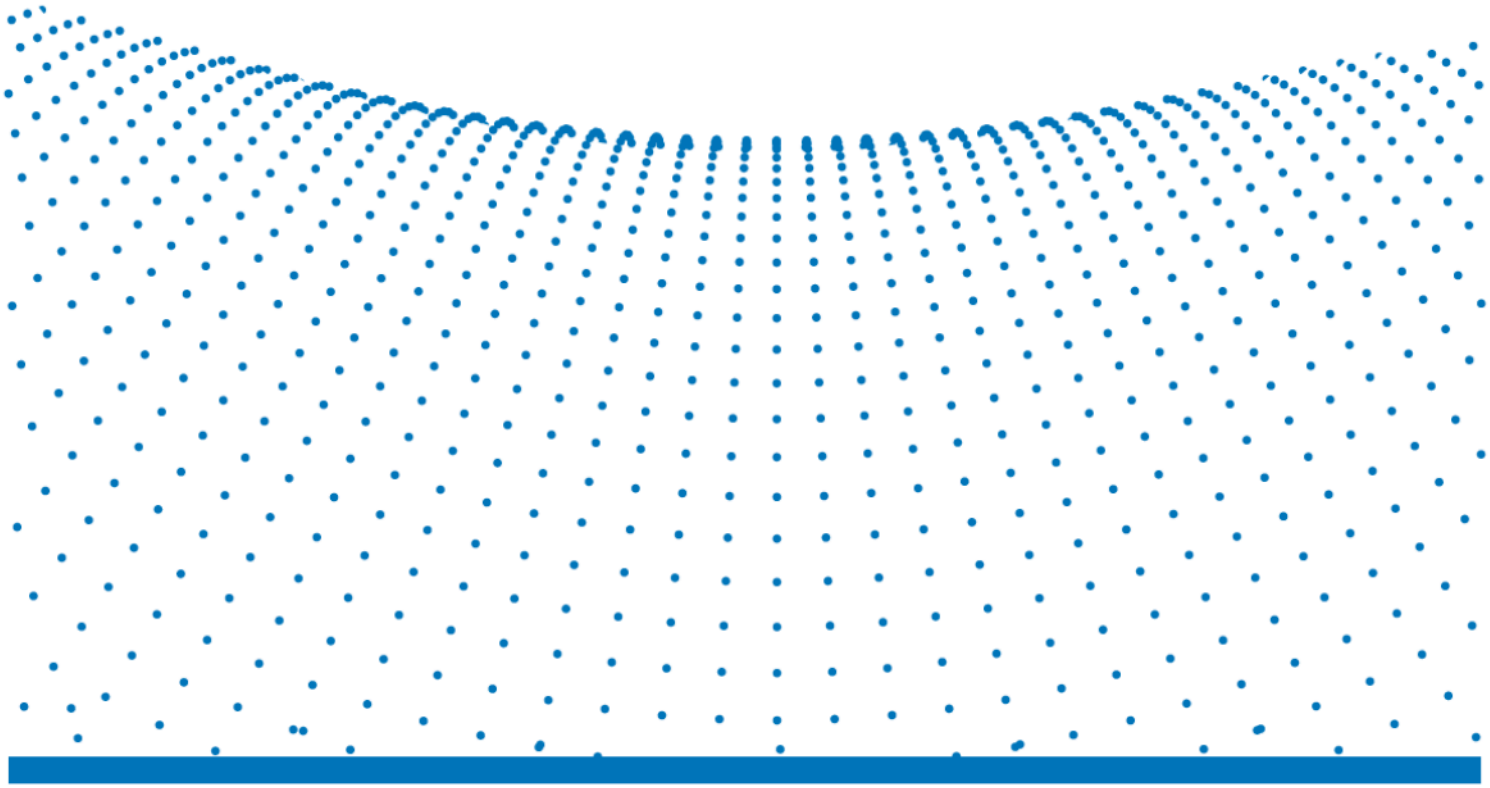
10 Years Experience With Advanced Therapy Medicinal Products: Past, Present and Future

November 10th, 2017
Istituto Superiore di Sanità
Aula Pocchiari – Roma - Italy



OVERVIEW

Advanced Therapy Medicinal Products (ATMP) represent significant tools for efficacious treatments in patients suffering for diseases with limited or absent therapeutic options.

ATMP represent a field where Italian research and development generated excellent results.

Italy is now leader in Europe, since three ATMP out of the four available at present on the European market have been completely developed by Italian researchers and are produced in Italy. Among those, the first market-authorized ATMP based on stem cells.

Those ATMP that successfully made it to market are only a part of the many that are being developed and produced for clinical trials, mainly by academic entities and frequently supported by charities or public resources.

Since the very beginning of the ATMP development, all the Italian production entities have complied with applicable regulatory requirements and are regularly controlled by Italian Competent Authorities, as it is of paramount importance that ATMP development is done in compliance with regulatory requirements.

Starting from the 10th Anniversary of European Regulation 1394/2007, this meeting aims at describing the present situation for ATMP development and production in Italy and abroad, focusing on the experience of Italian academic as well as industrial ATMP production entities as compared with some selected international research and corporate institutions in USA, Europe and Asia.

PROGRAM

8.30 Registration
8.50 Introduction: M. Dominici (UNIMORE, ISCT Chair Advisory Board), M.C. Galli (ISS), F. Moretti (ISS; A_IATRIS)

Session 1: ATMP Manufacturing: The Academic Perspective
(2007-2017 ten years of ATMP EU Regulation: academic/hospital cell factories experiences)

- Progenitor Cells
Moderator: M. Dominici

9:00 Keynote Lecture: The Evolution of Academic Cell Therapy – From Cowboys to Executives
EM. Horwitz - USA
9:30 Focusing on MSC
R. Giordano - Italy
9:45 Human Platelet Lysate In Mesenchymal Stromal Cell Expansion According to a GMP Grade Protocol: a 360° Overview with Open Issues
V. Becherucci - Italy
10:00 Human Neural Stem Cells for Neurodegenerative Diseases Treatment
M. Gelati - Italy
10:15 Critical Aspects in Processing Development & GMP
M. Dieci - Italy

10:30 Coffee break

- Immune Cells
Moderator: F. Moretti

11:00 Keynote Lecture: Translating Laboratory Research into Effective Cell Therapy for Cancer
D. Campana - Singapore
11:30 Dendritic Cell Immunotherapy in Glioblastoma Patients
S. Frigerio - Italy
11:45 Cytokine Induced Killer (CIK) cells with CD19 Chimeric Antigen Receptor (CAR) for Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL)"
G. Gaipa - Italy
12:00 CIK Cells for Clinical Use
M. Introna - Italy
12:15 Dendritic Cell Therapeutic Vaccines at IRST: a Journey from Yesterday to Tomorrow
A. Riccobon & M. Petrini - Italy
12:30 IFN-DC: a New Advanced Therapy Medicinal Product Produced at the ISS GMP Facility "FaBioCell" for the Development of Combination Therapies of Cancer
C. Rozera & F. Belardelli - Italy

12:45 Discussion

13:00 Lunch break

Session 2: ATMP Manufacturing: pharma and competent authority perspective
Moderator: M.C. Galli

14:00 Keynote Lecture: Cell and Gene Therapy: the Emergent Value for Patients
M. Forte - Belgium
14:20 Centre for Cell Gene & Tissue Therapeutics – what is special about us?
C. Carvalho - UK

14:40 Coffee break

15:00 The MolMed experience
C. Bordignon - Italy
15:15 Role of pharmaceutical industry in development and commercialization of ATMPs
G. Iotti - Italy
15:45 Hospital exemption: Italian current and future directions
G. Pantè - Italy

16:05 **ROUND TABLE (with speakers and audience on preselected issues)**

Moderators: M. Dominici, M.C. Galli, F. Moretti

17:00 Conclusions

Meeting Co-Chairs
Maria Cristina Galli, Centro Nazionale per il Controllo e la Valutazione dei Medicinali, ISS, Roma
Massimo Dominici, Università di Modena e Reggio Emilia, Modena e ISCT, Vancouver, Canada
Franca Moretti, Servizio Coordinamento e Supporto alla Ricerca, ISS e A_IATRIS, Roma

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Session I
ATMP Manufacturing: The Academic Perspective
Progenitor Cells

THE EVOLUTION OF ACADEMIC CELL THERAPY – FROM COWBOYS TO EXECUTIVES

Edwin M. Horwitz[1,2]
[1]*Professor of Pediatrics and Medicine, The Ohio State University College of Medicine*
[2]*ISCT Advisory Board Member*

In the American parlance, the cowboy represents the unruly frontier man of seeking to tame the wild as American grew westward. The toughest cowboys may have been admired of feared, but always respected. The executive is the modern business leader who plans, talks, manages, and sells ideas to advance the goals of an organization. At the beginning of my career, there were few rules, beyond fundamental ethical standards; the smartest, most hard working, greatest risk takers were leading small teams, pushing the edge of possible, seeking new discoveries in cell therapy-much like a modern day cowboy. Today, the rapid scientific advances have led academia to adopt a more traditional industry structure, with large multifaceted programs led by a director-much like a business executive. Moreover, the pharmaceutical industry has emerged as an essential partner to academia bringing discoveries to mild-level clinical trials and beyond. Despite this wonderful evolution of purely academic research into academic-industry partnership, universities remain the fertile ground where new ideas are born. Without academic research, the entire enterprise of biologically based advanced therapies would falter. While the playing field continues to evolve, academic research remains the heart and soul of improved therapy for patients.

MSC: THE THINGS WE KNOW NOW

R. Giordano, L. Lazzari, T. Montemurro, M. Viganò, C. Lavazza, S. Budelli, M. Barilani, S. Savelli.
Center of Regenerative Medicine – Cell Factory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

After 10 years from the implementation of the European Regulation on advanced therapy medicinal products (ATMPs), we gained an increasingly stimulating perspective on the possibility to deliver them to patients, especially those affected by still unmet clinical needs. Among ATMPs, mesenchymal stem/stromal cells (MSC) are the most extensively studied and clinically tested so far. Despite several initial definitions and hypotheses on their putative mechanism/s of action were rejected or partially revised, the information obtained in the last 10 years has in part confirmed their therapeutic potential, particularly when used as immune–modulator drug. All this information has a critical influence on the identity definition of MSC, their required profile in different clinical contexts and therefore the specifications for their quality control and release and the development of specific potency assays. Even the MSC nomenclature has been extensively discussed together with the need of more specific parameters for their definition. In my presentation I will briefly review the state-of-the-art in the field of the therapeutic applications of MSC from the point of view of a pioneer developer of ATMPs in Italy, Europe.

HUMAN PLATELET LYSATE IN MESENCHYMAL STROMAL CELL EXPANSION ACCORDING TO A GMP GRADE PROTOCOL: A 360° OVERVIEW WITH OPEN ISSUES

V. Becherucci[1], L. Piccini[1], V. Gori[1], S. Bisin[1], B. Bindi[1], R. Ceccantini[1], P. Pavan[1], V. Cunial[1], F. Gentile[1], E. De Rienzo[1], E. Allegro[1], S. Ermini[1], F. Brugnolo[1], G. Astori[2], F. Bambi[1].
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The use of platelet lysate (PL) for the ex vivo expansion of mesenchymal stromal cells (MSC) was initially proposed by Doucet al al. since 2005 (1), as an alternative to animal serum. Moreover, regulatory authorities discourage the use of foetal bovine serum (FBS) or other animal derivatives, to avoid risk of zoonoses and xenogeneic immune reactions (2). Many studies investigated PL composition, discovering the presence of a wide number of of growth factors and bioactive molecules, such as bFGF, EGF, VEGF, IGF1, TGF β, released by α granules after platelet rupture, but there are still some open issues to define the product itself (3) (4) (5). For example, even if several studies already demonstrated that the final concentration of cytokines and growth factors presents in PL and eventually affecting both functional and phenotypic properties of MSCs is strictly correlated to the preparation method, (6, 7, 8, 9, 10), there is still a lack of consensus about the standardization of the method(s) used for PL production. Also the classification of PL as blood component for non-transfusion use is still being discussed. As an authorized cell factory (Cell Factory Meyer, Meyer Children's Hospital, Florence), we propose our experience using PL for the ex vivo culture of bone marrow derived mesenchymal stromal cell, according to a GMP grade protocol. We also discuss and propose a release criteria for PL, testing and comparing surface marker expression, immunomodulatory and differentiation potential and telomere length of the same bone marrow derived MSC, cultured in the presence of PL or FBS.

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HUMAN NEURAL STEM CELLS FOR NEURODEGENERATIVE DISEASES TREATMENT

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Amyotrophic Lateral Sclerosis (ALS) is an incurable disease that targets motor neurons (MNs) in the primary motor cortex, brainstem and spinal cord. The mechanisms of the inherent neurodegenerative process are still largely unknown Human neural stem cells (hNSCs) represent a potential therapeutic option for ALS. Their inherent functional plasticity allows hNSCs to carry out a plethora of healing actions, spanning the replacement of dead cells, immunomodulation, anti-inflammatory, trophic, homeostatic, scavenging and toxicity-blunting effects. Following non clinical and pre-clinical studies, we established a cGMP protocol that allows the establishment of continuous, stable, plentiful and standardized hNSCs lines. Indeed, those hNSCs have been used in a Phase I clinical trial (EudraCT 2009-014484-39) in which 18 ALS patients received multiple grafts of these cells. The trial was completed successfully, follow up exceeding four years landmark. hNSCs induced no severe adverse events and were associated with a transitory improved neurological function in 50% of patients. We are now planning a Phase II clinical trial on ALS and a Phase I trial on multiple sclerosis patients is currently ongoing.

CRITICAL ASPECTS IN PROCESSING DEVELOPMENT & GMP VALIDATION

Marco Dieci
Ospedale Pediatrico Bambino Gesù, Roma

The critical aspects identified during Processing Development & GMP Validation can be reduced with the implementation of several assets, such as knowledge, skills and good management, but the great variability of the process generates itself a high possibility of failure. One critical aspect that can support and increase the success rate when in stream is the design of a facility able to cover the differences generated by Gene and Cell production.

Session I
ATMP Manufacturing: The Academic Perspective
Immune Cells

TRANSLATING LABORATORY RESEARCH INTO EFFECTIVE CELL THERAPY FOR CANCER

Dario Campana
Yong Loo Lin School of Medicine, National University of Singapore

The inherent specificity of immune cells, and their capacity for cell killing suggest that they could be used as "living drugs" to treat cancer. Early evidence from allogeneic hematopoietic stem cell transplantation in patients with leukemia indicated that donor T and natural killer (NK) cells significantly contributed to suppressing relapse post-transplant. More recently, administration of autologous T cells induced to express anti-CD19 chimeric antigen receptors (CARs) ex vivo have been shown to exert potent anti-tumor activity in patients with CD19+ B-cell malignancies.

Widening the range of targetable tumors is critical to move this promising field forward. To overcome the need of developing an individual CAR for each tumor target, we developed a CD16V-41BB-CD3z receptor which endows T cells with antibody-dependent cell cytotoxic capacity. Moreover, methods to expand and genetically engineer NK cells have been established and validated in a clinical-grade setting. These and other new immune cell therapy approaches are being explored with the vision of building an array of immunotherapeutic options that can complement, and ultimately replace, standard therapy of cancer.

DENDRITIC CELL IMMUNOTHERAPY IN GLIOBLASTOMA PATIENTS

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Unità Produttiva per Terapie Cellulari Neurological Institute C. Besta Foundation Milan, Italy

The "Unità Produttiva per Terapie Cellulari" (UPTC) is the Cell Factory of Neurological Institute C. Besta Foundation of Milan. Since 2010, UPTC has been involved in the production of autologous Dendritic Cells (DCs) pulsed with tumor antigens for the treatment of glioblastoma (GBM)-affected patients: to date 83 patients received immunotherapy.

Our method to produce DCs is safe and highly reproducible and permits routine generation of large number of cells that fulfill all requirements for in vivo use in immunotherapy: DCs phenotype showed upregulation of maturation markers (CD80,CD83,CD86); potency test (Mixed Lymphocyte Reaction) demonstrated that all batches were able to induce lymphocyte responses; cells maintained a high percentage of viability also after cryopreservation (mean ±SD: 94.6%±2.9%).

Two protocols for GBM immunotherapy are presently ongoing. DENDR1 is a two phase study with Simon design, testing safety and efficacy of DCs administration in the context of the standard treatment for GBM. Results of the first phase allow the passage to phase II and show that the increased number of NK cells in peripheral blood may be associated to prolonged survival. DENDR-STEM is a new study based on the treatment of recurrent GBM patients with DCs loaded with a lysate from cancer stem-like cells rather than whole tumor lysate. Enrollment started recently, no patient has yet been treated.

CYTOKINE INDUCED KILLER (CIK) CELLS WITH CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) FOR RELAPSED/REFRACTORY B-CELL PRECURSOR ACUTE LYMPOBLASTIC LEUKEMIA (BCP-ALL)

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BCP-ALL is a malignant disorder with a long-term remission of less than 50% of adult patients and of nearly 80% of children. Adoptive transfer of engineered CAR-T cells has shown striking responses in highly refractory diseases. Unmodified CIK cells have demonstrated a high profile of safety in ALL patients. We performed a genetic modification that confers ectopic expression of the anti-CD19 CAR on the donor-derived CIK cells. The resulting CAR binds the CD19 antigen on BCP-ALL extracellular antibody domain, thereby activating a potent cytotoxic response.

GMP-grade validation of the manufacturing process was performed in the academic cell factory Laboratorio Stefano Verri. Allogeneic peripheral blood mononuclear cells (PBMCs) were isolated and modified with simultaneous electro-transfer of the Sleeping Beauty (SB) GMP-grade DNA plasmids CD19.CAR/pTMNDU3 and pCMV-SB11 using 4D-Nucleofector (Lonza) and then expanded for 18-21 days according to a well-established CIK-expansion protocol demonstrating the feasibility and reproducibility of the process.

These results represent solid bases for the application of this platform in a up-coming Phase I-IIa clinical trial (sponsored by Fondazione Tettamanti) for adult and pediatric patients with relapsed/refractory BCP-ALL after hematopoietic stem cell transplantation (HSCT) aiming at assessing the feasibility and safety of a single dose of allogeneic (donor-derived) CARCIK-CD19 cells.

CIK CELLS FOR CLINICAL USE

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CIK (Cytokine Induced Killer) cells are T-EMRA lymphocytes obtained following 21 days expansion in vitro by addition of anti-CD3 monoclonal antibody, interpheron gamma and IL-2.

CIK cells have been demonstrated able to destroy tumoral cells via non-specific and non-restricted HLA recognition, but rather via NK-like mechanism. Moreover CIK cells have been shown able to infiltrate tumors in several experimental models. Finally, and more interestingly, CIK cells appear almost devoid of Graft-versus-Host activity. As a consequence, we developed a phase I study and a subsequent phase II study to treat leukemia patients relapsed of disease after allogeneic bone marrow transplantation with donor derived CIK cells. CIK cells have been produced in our academic cell factory which has been authorized by AIFA to operate according to GMP laws. Clinical data will be shown together with new future planned studies as well as technical innovations to improve safety and management of the cell productions.

DENDRITIC CELL THERAPEUTIC VACCINES AT IRST: A JOURNEY FROM YESTERDAY TO TOMORROW

A. Riccobon, M. Petrini, L. Fiammenghi, A. Granato, E. Pancisi, V. Soldati, S. Cassan, L. Ridolfi, F. De Rosa, C. Piccinini, G. Gentili, R. Ridolfi, M. Guidoboni
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The Somatic Cell Therapy Laboratory of IRST IRCCS was first authorized on April 27, 2012 to produce an advanced therapy medicinal product (ATMP) consisting of autologous dendritic cells pulsed with autologous tumour homogenate, exclusively employed within clinical trials in patients with solid tumors.

The first study on advanced melanoma patients dates back to 2001. Since 2006 ATMP manufacturing must be GMP-compliant: however, the production continued under a transitory regimen until the 2012 authorization. Clinical trials on patients affected by other cancers have been conducted since 2016.

81 patients with metastatic melanoma have been treated with our ATMP. Of these, two patients obtained a complete response, two a partial response, and other 23 a stable disease; median overall survival was 11.4 months. The toxicity was generally mild and the majority of evaluable patients developed a significant antitumor immune response after treatment.

Additional 38 patients have been enrolled in the currently active clinical trials. Two of these are directed to melanoma, a third to resected stage IV colorectal cancer, and the last one to advanced renal cell carcinoma.

Further clinical development of our product are now being planned both in other cancers and in combination with immune checkpoint inhibitors.

IFN-DC: A NEW ADVANCED THERAPY MEDICINAL PRODUCT PRODUCED AT THE ISS GMP FACILITY "FABIOCELL" FOR THE DEVELOPMENT OF COMBINATION THERAPIES OF CANCER

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Dendritic cells (DC) have been used in clinical trials of cancer immunotherapy for 20 years, but the clinical responses have been sporadic so far. Critical issues remain the identification of optimal methods for preparing DC-based vaccines and of criteria for consistency/potency of these cell products. We developed a method for generation of a novel type of DC by in vitro treatment of monocytes with GM-CSF and IFN-a (IFN-DC). IFN-DC are highly efficient in internalizing tumor antigens, developing cytotoxic T and NK cell antitumor responses and inducing antitumor activity in preclinical models. IFN-DC prepared under GMP conditions at the ISS facility FaBioCell were successfully used in a phase I clinical trial in patients with advanced melanoma treated with dacarbazine (J. Trasl. Med., 13:464-71,2015). We have then started another clinical trial based on "in situ vaccination" by intratumoral injection of low-dose anti-CD20 antibody, followed by IFN-DC in patients with advanced follicular lymphoma (FL) relapsing after at least two lines of therapy. Seven patients have been treated so far. The treatment was well tolerated, with evidence of complete responses in some patients. These results suggest that IFN-DC immunotherapy is safe and capable of inducing systemic antitumor responses, opening promising perspectives in combinatorial immunotherapy regimens.

Session II
ATMP Manufacturing:
pharma and competent authority perspective

CELL AND GENE THERAPY: THE EMERGENT VALUE FOR PATIENTS

Miguel Forte[1,2]
[1]*CEO Zelluna Immunotherapy*
[2]*CCO and Chair of Commercialization Committee, ISCT*

Cell and gene therapy is delivering unprecedented value to patients. From regenerative approaches in tissue repair to near cure in some genetic diseases or until now hopeless cancer, cell and gene therapy is changing medicine.

Nevertheless, this exciting perspective is still faced with multiple challenges. In manufacturing and process development, reproducible product characterization, comparability and sensible potency assays are key. Pre-clinical research is being reconsidered to deal with complex and living products. Clinical development, from proof-of-concept to registration, is facing challenges of feasibility on top of clinical evidence generation. Regulators and decision makers, supporting innovation, are having to learn news ways to assess data and approach reimbursement.

Over the last 10 years, with a clear acceleration recently, the field has evolved from a curiosity to a vibrant biotech area. The clinical data is exciting, the manufacturing is becoming more cost-effective and viable with multiple players providing new solutions. The community, from investors to patients have understood that cell and gene therapy products are a reality. Competition is mounting, we know that the question is no longer if we have products but which will be the ones with a competitive advantage. The value proposition for patients will continue to increase.

CENTRE FOR CELL GENE & TISSUE THERAPEUTICS – WHAT IS SPECIAL ABOUT US?

Carla Carvalho
Centre for Cell Gene & Tissue Therapeutics (CCGTT), London, UK

The Centre for Cell Gene & Tissue Therapeutics (CCGTT) is an academic facility for the manufacture of Advanced Therapy Medicinal Products (ATMPs) in the UK. We are licensed by the UK MHRA and HTA for the procurement, production and storage of human cells & tissues for therapy and ATMP manufacture and incorporate the University College London (UCL) /Royal Free Hospital (RFH) BioBank.

This special link with the RFH, a teaching hospital, UCL and the Biobank, which stores both therapeutic and non-therapeutic research samples for clinical trials and collaborative projects as a resource across UCL Partners, exposes us to world class R&D projects.

Most of these focus on the development of cell and tissue medicines for immunotherapy and transplantation and range from basic science to regeneration of human 3-D tissue scaffolds all with a significant translational component.

It is this translational work carried out across all aspects of development of the product, from engineering and validation through to GMP production, that allows us to establish a successful bridge between the academic world and industry.

I will explain how these collaborations came about and how they work in more detail during this presentation.

ROLE OF PHARMACEUTICAL INDUSTRY IN DEVELOPMENT AND COMMERCIALIZATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

Giorgio Iotti
Chiesi Farmaceutici S.p.A.

The introduction of ATMP regulation opened a new field for the pharmaceutical industry.

Holoclar® (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is the first stem cell-based product approved in Europe. The partnership between academia and industry, with the creation of the spinoff company Holostem, has been a key factor in the achievement of this milestone.

ATMPs represent promising approaches to target potentially incurable diseases and are characterized by highly specific aspects.

Such therapies are often initially tested and produced in academic laboratories and the technology is up-scaled to industry grade standards relatively late during development. Manufacturing solutions to maximize cost effectiveness are key as many methods currently require significant operator-based interventions.

Furthermore, ATMPs can be manufactured in a small number of specialized facilities and the final products administered to patients in highly equipped clinical centers, underlying the importance of optimization of the supply chain.

Treatment typically requires a single administration with long-lasting therapeutic effects and the reimbursement process must be adapted to this characteristic.

From an industry perspective, key elements for the success of ATMPs represent the collaboration with world-class research groups together with early and regular dialogue with regulatory and reimbursement authorities.