HELLENIC SOCIETY
GENE THERAPY AND
REGENERATIVE MEDICINE
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Under the Auspices of

7th Congress of the Hellenic Society of Gene Therapy and Regenerative Medicine

May
24 | 26
2024

Aristotle
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FINAL PROGRAM
PROCEEDINGS BOOK

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Welcome note

Dear Colleagues,

*On behalf of the **Organizing and Scientific Committees**, it is with great pleasure that I welcome you to the forthcoming **7th Annual Meeting of the Hellenic Society of Gene Therapy and Regenerative Medicine**, which will be held in **Thessaloniki, Greece** on **May 24-26, 2024**. The Board of Directors of the HSGTRM is pleased to announce that we are organizing a live Meeting this year with physical presence of all speakers and participants! We envisage a forum that will provide ample opportunities to meet and interact with distinguished scientists, researchers as well as distinguished experts from Greece and Europe, and promote a high level of networking.*

*The meeting will cover diverse aspects in the field of **Gene & Cell Therapy and Regenerative Medicine**, including pluripotent stem cell disease modeling, exosome therapeutics, regenerative perspectives of cord blood banks, clinical progress and challenges of gene therapy & gene editing, and updates on CAR-T and non-engineered T-cell targeting of malignancies and viruses. The educational program comprises lectures on state-of-the-art tools and approaches aiming to overcome current barriers and enable successful data analysis and management. Keynote lectures will be delivered by renowned international Faculty, while fruitful discussions are expected to be stimulated that will keep professionals up to date on issues related to Gene therapy, Regenerative medicine and the regulatory framework of Advanced Therapies. In addition, the oral and poster sessions will give the opportunity to young scientists and junior faculty to present their research and interact productively with their peers.*

The meeting is intended to bring together relevant field experts, scientists, clinicians, industry representatives, postdoctoral fellows, and research students, providing them with opportunity to report, present, share, and discuss scientific advancements, remaining issues and future challenges in the field!

I am looking forward to meeting you all in Thessaloniki and to joining fruitful discussions!

Sincerely,

Rebecca Matsas
President of Board of Directors
and Organizing Committee

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General Information

The **7th Congress of the Hellenic Society of Gene Therapy and Regenerative Medicine** will take place at the Aristotle University Research Dissemination Center in Thessaloniki, Greece, on **May 24-26, 2024**. The Congress will be held only with physical presence of all participants, Speakers, Chairs and Delegates.

Registration

In order to register for the **7th Congress of the Hellenic Society of Gene Therapy and Regenerative Medicine**, please visit the Congress website www.hsgtrm2024.gr and fill in the Registration Form.

Category	NON MEMBERS of the HSGTRM	MEMBERS of the HSGTRM
Doctors	140 €	120 €
Biologists, Biochemists, other Medical Professionals	80 €	60 €
Doctors in Residency, Postdoctoral Fellows	80 €	50 €
Nurses, Technologists	40 €	-
Undergraduate Students, Postgraduate Students, PhD Students	Free Participation	Free Participation

** The above costs are subject to VAT 24%.*

Registration includes:

• Entrance in the Exhibition Area and Attendance of the Congress

• Certificate of Attendance

Congress Secretariat

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Acknowledgements

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Acknowledgements

We would like to warmly thank the following sponsors:

PROGRAM

Friday, 24 May 2024

08.00-09.00 **Working Group: Gene Therapy**
Chair: **Stylianos Michalakis**

09.00-11.00 **Educational I: The Researcher's Toolkit**
Chairs: **Maria Gaitanou, Era Taoufik**

09.00-09.30 **Functional enrichment analysis of genomics & transcriptomics datasets using multiple sources: the Flame 2.0 enrichment analysis pipeline**
Fotis Baltoumas

09.30-10.00 **Proteomics**
Martina Samiotaki

10.00-10.30 **Fine-Tuning the Future: Precision Editing Methods as Pioneering Therapeutic Strategies**
Carsten W. Lederer

10.30-11.00 **From Data to Discoveries: AI-powered Strategies**
Grigorios Georgolopoulos

11.00-11.30 **Coffee break**

11.30-13.00 **Educational II: From Cellular Models to Advanced Therapeutics**
Chairs: **Maria Roubelakis, Rebecca Matsas**

11.30-12.00 **Neurodegenerative disease modeling using induced neural-stem cells**
Spyros Petrakis

12.00-12.30 **Cardiac stem cells in vitro and in vivo**
Konstantinos Hatzistergos

12:30-13:00 **Strategic Planning for Clinical Trials with ATMPs**
Evangelia Yannaki

13.00-14.15 **Lunch break**

Friday, 24 May 2024

14.15-15.15 **Session 1: New Medications, Novel Insights**

Chairs: **Chrysavgi Lalayanni, George Vassilopoulos**

14:15-14.45 **The changing Multiple Myeloma treatment algorithm in the era of CAR T cells and bispecific Abs**
Eirini Katodritou

14:45-15.15 **Spinal muscular atrophy gene therapy: real word evidence and dilemmas**
Vasileios Kimiskidis

15.15-15.30 **Short break**

15.30-17.30 **Session 2: iPSC models of brain physiology and disease**

Chairs: **Rebecca Matsas, Achilleas Gravanis**

15.30-16.00 **High Definition Disease Modelling: Stem Cell and Organoid Epigenetics**
Nicolo Caporale

16.00-16.30 **Harnessing human iPSC models of neurodegeneration to exploit neurotrophin potential of novel pharmacological agents**
Ioannis Charalampopoulos

16.30-17.00 **RNA metabolism & editing dysfunctions in Parkinson's disease**
Era Taoufik

17.00-17.30 **Bioengineering of a human innervated and vascularized cardiac muscle organoids**
Maria Patapia Zafeiriou

17.30-18.00 **Coffee break**

18.00-19.30 **Special Lectures I & II**

Chairs: **Helen Papadaki, Stylianos Michalakis**

18.00-18.45 **Experimental Disease Modeling and Gene Therapy Approaches for children with Severe Congenital Neutropenia**
Julia Skokowa

18.45-19.30 **Liver-directed gene therapy for inherited metabolic diseases**
Nicola Brunetti-Pierri

19.30 **Welcome reception**

Saturday, 25 May 2024

08.30-09.00 **Working group: "Cell Therapy"**
Chair: **Helen Papadaki**

09.00-10.30 **Session 3: Regenerative perspectives of Cord Blood banks**
Chairs: **Helen Papadaki, Damianos Sotiropoulos**

09.00-09.30 **The Haplo-iPS COST Action. Challenges and perspectives**
Anna Veiga

09.30-10.00 **Public Cord Blood Banks as a source for clinical grade iPSCs and other applications beyond transplantation**
Ana Belen Alvarez-Palomo

10.00-10.30 **Optimization of methods for generation of iPSCs from umbilical cord and other sources for clinical usage**
Angel Raya

10.30-11.00 **Coffee break**

11.00-13.00 **Session 4: The next wave of cancer immunotherapy**
Chairs: **Christos Georgiadis, Anastasia Papadopoulou**

11.00-11.30 **Cancer-associated fibroblasts and their impact on cancer development and therapy**
Vasiliki Koliariaki

11.30-12:00 **iNKT Cells: A new horizon in CAR-based cancer immunotherapy**
Anastasios Karadimitris

12.00-12:30 **Plasmacytoid Dendritic Cells as Next-Generation Cell-Based Therapeutics**
Iulia Diaconu

12.30-13:00 **Improvement of chimeric antigen receptor redirected T and NK cells in refractory malignancies by metabolic rewiring**
Ignazio Caruana

13.00-14.20 **Lunch break and Poster Presentation**

P1. **MIRK/DYRK1B KINASE IS INVOLVED IN NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS**

A. Nalmpanti[1], N. Kokkorakis[1], L. Zagoraiou[2], R. Matsas[1], M. Gaitanou[1]
[1]*Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute,* [2]*Center of Basic Research, Biomedical Research Foundation of the Academy of Athens, Greece*

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P2. CORRECTION AND INTEGRITY OF DUPLEX BASE EDITING FOR FETAL HEMOGLOBIN INDUCTION IN Β-HEMOGLOBINOPATHIES

N.Y. Papaioannou[1], P. Patsali[1], J. Klermund[2,3], P.L. Papasavva[1], L. Koniali[1], B. Naiisseh[1], S. Christou[4], M. Sitarou[5], M. Kleanthous[1], T. Cathomen[2,3,6], C.W. Lederer[1]

[1]Department of Molecular Genetics Thalassemia, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, [2]Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, Freiburg, Germany, [3]Center for Chronic Immunodeficiency (CCI), Medical Center – University of Freiburg, Freiburg, Germany, [4]Thalassemia Center, State Health Services Organization of Cyprus, Nicosia, Cyprus, [5]Thalassemia Center, State health Services Organization of Cyprus, Larnaca, Cyprus, [6]Faculty of Medicine, University of Freiburg, Freiburg, Germany

P3. PROCESS DEVELOPMENT FOR GMP-COMPLIANT PRODUCTION OF ADIPOSE-DERIVED MESENCHYMAL STROMAL CELLS AS OSTEOARTHRITIS TREATMENT

M. Kontou, M. Gjika, L.-M. Gkouma, E. Simantirakis, C. Fatouros

Theracell Laboratories IKE, Koropi, Attiki, Greece

P4. THE ROLE OF GEMC1 AND MCIDAS TOWARDS CELLULAR REPROGRAMMING TO EPENDYMAL LINEAGE

G. Kritikos[1], D. Korrou-Karava[1], K. Kaplani[1], St. Vassalou[1], M.E. Lalioti[1], G. Lokka[1], E. Parlapani[1], M. Kanellopoulou[1], Z. Lygerou[2], St. Taraviras[1]

[1]Department of Physiology, Medical School, University of Patras, [2]Department of General Biology, Medical School, University of Patras, Greece

P5. SINGLE NUCLEUS RNA SEQUENCING ANALYSIS COMBINED WITH IN VITRO VALIDATION IN ENGINEERED DOPAMINERGIC NEURONS REVEALS ASPECTS OF IDIOPATHIC PARKINSON'S DISEASE PATHOLOGY

G. Katsanopoulou[1,#], S. Notopoulou[1,2,#] , G. Gavriilidis[1], F. Psomopoulos[1], S. Petrakis[1]

[1]Institute of Applied Biosciences, CERTH, Thessaloniki, Greece, [2]School of Medicine, Aristotle University of Thessaloniki, Greece

[#]Contributed equally

P6. UNRAVELING THE ROLE OF MCIDAS IN MULTICILIOGENESIS AND E2 EPENDYMAL CELL GENERATION

A. Chantzara[1], G. Lokka[1], K. Kaplani[1], I. Papadionysiou[1], M. Mpakogianni[1], M.E. Lalioti[1], M. Panagopoulou[1], Z. Lygerou[2], S. Taraviras[1]

[1]Laboratory of Physiology, Medical School, University of Patras, Greece, [2]Laboratory of General Biology, Medical School, University of Patras, Greece

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P7. GENERATION OF INSCS FROM PATIENTS WITH FAMILIAL PARKINSON'S DISEASE FOR PERSONALIZED DISEASE MODELING

S. Notopoulou[1], M. Peitz[2], L. J. Flitsch[2], L. Stefanis[3], G. Xiromerisiou[4], N. Grigoriadis[5], S. Petrakis[1]

[1]Institute of Applied Biosciences, CERTH, Thessaloniki, Greece, [2]Institute of Reconstructive Neurobiology, Life & Brain Center, University of Bonn Medical Center, Bonn, Germany, [3]1st Department of Neurology, Aiginition University Hospital, National and Kapodistrian University of Athens, Athens, Greece, [4]Department of Neurology, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece, [5]2nd Department of Neurology, MS Center, School of Medicine, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

P8. INTEGRATION OF DIVERSE PLATFORMS TO DEFINE LOCAL MECHANISMS AND LONG-RANGE SIGNALS THAT MEDIATE INTER-ORGAN COMMUNICATION AFTER INJURY AND DURING REGENERATION

E. Kotzairaki, A. Theodoridi, D. Grivas, D. Karampela, G. Louridas, K. Vekrellis, M. Pantazopoulou, A. Delis, S.N Pagakis, E. Athanasiadis, E. Xingi, D. Thomaidou, D. Beis, S. Psarras, V. Tsata

Center of Basic Research, Biomedical Research Foundation Academy of Athens, Greece

P9. COMPARISON OF UMBILICAL CORD BLOOD DERIVED PLATELET CONCENTRATE GEL WITH AUTOLOGOUS PLATELET CONCENTRATE GEL FOR THE TREATMENT OF CHRONIC DIABETIC FOOT ULCER

I. Gontika[1*], G. Tzouliadakis[2*], N. Kontopodis[2], E. Fragiadaki[1], K. Boura[1], C. Chronis, C. Ioannou[2#], H.A. Papadaki[1#]

[1]Public Cord Blood Bank of Crete, Department of Haematology, University Hospital of Heraklion and University of Crete, Greece, [2]Vascular Surgery Unit, Department of Cardiothoracic and Vascular Surgery, University Hospital of Heraklion and University of Crete, Greece

** Both authors have contributed equally to this work*

 # Both authors have contributed equally to this Work

P10. AN ARTIFICIAL NEURAL NETWORK FOR VIRTUALLY INCREASING THE SAMPLE SIZE OF CLINICAL STUDIES

A. Nikolopoulos[1,2], V.D. Karalis[1,2]

[1]Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Greece, [2]Institute of Applied and Computational Mathematics, Foundation of Research and Technology Hellas (FORTH), Greece

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P11. IS THE AMAZING REGENERATIVE ABILITY OF AUTOLOGOUS ADMINISTRATED FIBROBLASTS DISPUTABLE?

I. Karchilaki[1], A. Katseli[2], I. Anastasiou[3], G. Topakas[1], C. Tsirligkani[1], D. Kapnias[2], N. Kikas[2], G. Zografos[2], N. Tentolouris[3], G. Paterakis[1]
[1]Immunology and National Histocompatibility Department, 'G. Gennimatas' General Hospital, Athens, Greece, [2]3rd Department of Surgery, 'G. Gennimatas' General Hospital, Athens, Greece, [3]1st Department of Propaedeutic Clinic of Athens Univercity, "Laiko", General Hospital, Athens, Greece

14:20-16:00 Oral Presentations (1-10)

Chairs: **Era Taoufik, Florentia Papastefanaki**

1. **UNVEILING THE NEUROREGENERATIVE PROPERTIES OF THE PAN-NEUROTROPHIN P75 RECEPTOR IN MOUSE AND HUMAN NEURAL STEM CELLS: A NOVEL PERSPECTIVE ON ALZHEIMER'S DISEASE PATHOLOGY**

M.A. Papadopoulou[1,2], K. Chanoumidou[1,2], I. Charalampopoulos[1,2]
[1]Department of Pharmacology, Medical School, University of Crete, Heraklion, Greece, [2]Institute of Molecular Biology & Biotechnology (IMBB), Foundation for Research and Technology Hellas (FORTH), Heraklion, Greece

2. **DYNAMIC LINKS BETWEEN THE CARDIAC INTERMEDIATE FILAMENTS OF THE CYTOSKELETON AND NUCLEOSKELETON FOR PROPER CARDIOMYOCYTE DIFFERENTIATION, MATURATION AND REPROGRAMMING**

M. Tsikitis[1], A. Diokmetzidou[1], P. Kolovos[2], G. Vatsellas[1], Y. Capetanaki[1]
[1] Center of Basic Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece, [2]Democritus University of Thrace, School ofMolecular Biology and Genetics, Alexandroupolis, Greece

3. **NOVEL CHEMICAL COMPOUND PROTECTS PATIENT-DERIVED NEURONS FROM CELL DEATH IN SCA1**

K. Pliatsika[1,2], I. Gkekas[1,2], S. Mylonas[3], S. Katsamakas[4], P. Pechlivani[1], A. Axenopoulos[3], L.J. Flitsch[5], B. van de Warrenburg[5], K. Xanthopoulos[2], P. Darras[3], M. Peitz[5], S. Petrakis[1]
[1]Institute of Applied Biosciences (INAB), Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece, [2]Department of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3]Information Technologies Institute (ITI), Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece, [4]Institute of Chemical Biology, National Hellenic Research Foundation, Athens, Greece, [5]Institute of Reconstructive Neurobiology, Life & Brain Center, University of Bonn Medical Center, Bonn, Germany, [6]Department of Neurol-

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ogy, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands

4. **CONTROL IPSC-DERIVED ASTROCYTES RESCUE P.A53T-ASYN PATIENT-IPSC-DERIVED NEURONS FROM PARKINSON'S DISEASE-RELATED PATHOLOGY**

O. Apokotou[1], C. Paschou[2], A. Kollias[2], K. Charmpi[2], S. Dede[1,4], M. Samiotaki[3], E. Taoufik[2], C. Zurzolo[4], R. Matsas[2], F. Papastefanaki[1,2]
[1]Human Embryonic and Induced Pluripotent Stem Cell Unit, Hellenic Pasteur Institute, Athens, Greece, [2]Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute, Athens, Greece, [3]Institute of Bioinnovation, Biomedical Sciences Research Center "Alexander Fleming", Vari, Greece, [4]Membrane Traffic and Pathogenesis, Cell Biology and Infection Department, Institut Pasteur Paris, France

5. **NR5A2 REGULATES HYPOXIA RESPONSE AND METABOLISM IN NEURAL CELLS: IMPLICATIONS FOR NERVOUS SYSTEM-RELATED DISEASES**

<u>D. Gkikas</u>[1], P. Milioti[1], E. Markidi[1], A. Nomikou[1], A. Stergiopoulos[1], I. Rozani[1], V. Kaltezioti[1], G. Vatselas[1], D. Valakos[1], P. Politis[1]
[1]Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

6. **DHS ANALYSIS TO STUDY THE EPIGENETIC MECHANISMS BEHIND DEDIFFERENTIATION OF ADIPOCYTE LIKE CELLS TO MESENCHYMAL STEM/STROMAL CELL CELLS WITHOUT GENE EDITING**

S.M. Giatro[1], G. Georgolopoulos[2], O. Trohatou[1,3], J. Halow[2], F. Neri[2], M. Diegel[2], D. Dunn[2], D. Bates, R. Sandstrom[2], J. Stamatoyannopoulos[2], M. Roubelakis[1,3]
[1]Laboratory of Biology, Medical School, National and Kapodistrian University of Athens, [2]Altius Institute for Biomedical Sciences, Seattle, USA, [3]Cell and Gene Therapy Laboratory, BRFAA

7. **INHIBITION OF HIF-1α PROLONGS THE CARDIOMYOCYTE REGENERATIVE WINDOW IN NEONATAL MICE**

A.Daiou, E. Kotelli, D. Skarpari, K.E. Hatzistergos
Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece

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8. **THE SIGNIFICANCE OF HLA PHYLOGENETICALLY RELATED COUNTRIES IN THE CREATION OF IPSC HAPLOBANKS AGAINST THE REGIONAL HLA HETEROGENEITY**

H. Latsoudis[1,2*], I. Vasilopoulou[2*], I. Mavroudi[2], A. Xagorari[3], T. Chatzistamatiou[4], E.F. Sarri[4], D. Papaioannou[3], I. Gontika[2], I. Fragiadaki[2], D. Sotiropoulos[3], C. Stavropoulos-Giokas[4], A. Spyridonidis[5], M. Smaili[5], A. Manolis[6], J. Sauter[7], A.H. Schmidt[7], P. Costeas[8], H.A. Papadaki[2]
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**equal contribution*

9. **DECIPHERING AND TARGETING EARLY SYNAPTIC DYSFUNCTION IN PRE-CLINICAL MODELS OF FAMILIAL PARKINSON'S DISEASE**

E.K. Akrioti[1], K. Segklia[1], P. Chandris[1], K. Charmpi[1], A. Stavrou[1], O. Apokotou[1,2], F. Papastefanaki[1,2], P. Koutsoudaki[3], S. Chavaki[3], S. Lipton[4], R. Matsas[1], E. Taoufik[1]
[1]Laboratory of Cellular & Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute, Athens, Greece, [2]Human Embryonic and Induced Pluripotent Stem Cell Unit, Hellenic Pasteur Institute, Athens, Greece, [3]Laboratory of Histology-Embryology, Medical School, NKUA, Athens, Greece, [4]Scripps Research & UC San Diego, Neurodegeneration New Medicines Center, US

10. **STUDYING GLUCOSE NEUROTOXICITY IN A HUMAN IPSC-BASED MODEL TO UNRAVEL THE THERAPEUTIC BENEFITS OF P75NTR TARGETING**

K. Chanoumidou[1,2], I. Zota[1], M. Papadopoulou[1,2], I. Charalampopoulos[1,2]
[1]School of Medicine, University of Crete, Greece, [2]Institute of Molecular Biology and Biotechnology of the Foundation for Research and Technology Hellas (IMBB-FORTH)

Saturday, 25 May 2024

16.00-17.30 **Session 5: Gene therapy delivery modules**

Chairs: **Carsten W. Lederer, Maria Roubelakis**

16.00-16.30 **Engineering of extracellular vesicles for efficient intracellular delivery of nucleic acid-based therapeutics**
Pieter Vader

16.30-17:00 **Novel non-VSVG LV pseudotyped vectors in beta-thalassemia gene therapy**
Nicholas Anagnou

17.00-17:30 **Pioneering strategies in AAV capsid engineering for safer and broadly applicable gene therapies**
Kleopatra Rapti

17.30-18.00 **Coffee break**

18.00-19.30 **Special Lectures III & IV**

Chairs: **Rebecca Matsas, Maria Roubelakis**

18.00-18.45 **The Hellenic DNA project**
John Stamatoyannopoulos

18.45-19:30 **The Greek Genome project**
Dimitrios Thanos

19.30-20.30 **General assembly**

Sunday, 26 May 2024

08.30-09.00 Working group: "Regenerative Medicine"
Chair: **Achilleas Gravanis**

09.00-10.00 Session 6: AAV-mediated in vivo gene therapy session
Chairs: **Takis Athanasopoulos, George Vassilopoulos**

09.00-09.30 **AAV gene therapy for cardio-pulmonal diseases**
Olympia Bikou

09.30-10.00 **Update on AAV gene therapy**
Stylianos Michalakis

10.00-10.30 Coffee break

10:30-12:00 Oral Presentations (11-19)
Chairs: **Nikoleta Psatha, Konstantinos Hatzistergos**

11. **UNLOCKING HLA-G: PRECISION EPIGENOME EDITING FOR IMMUNOMODULATION**
P. Simonopoulos[1,2], P. Christofi[1,3], V. Papageorgiou[1,4], K. Boufidou[1,4], A. Galanis[2], I. Sakellari[1], N. Psatha[4], E. Yannaki[1,5], A. Papadopoulou[1]
[1]Gene and Cell Therapy Center, Hematology Department – Hematopoietic Cell Transplantation Unit, "George Papanikolaou" Hospital, Thessaloniki, Greece, [2]Department of Molecular Biology and Genetics, Faculty of Health Sciences, Democritus University of Thrace, Alexandroupoli, Greece, [3]Institute of Cell Therapy, University of Patras, Rio, Greece, [4]Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece, [5]Department of Medicine, Division of Hematology, University of Washington, Seattle, USA

12. **RECOMBINANT AAV CAPSIDS AS A NOVEL VACCINE PLATFORM**
C. Kooyman[1], S. Babutzka[1], L. Zobel[1], M. Diedrichs-Möhring[1], M. Gehrke[1], G. Wildner[1], H. Ammer[2], S. Michalakis[1]
[1]Department of Ophthalmology, University Hospital, LMU Munich, Munich, Germany, [2]Department of Veterinary Sciences, LMU Munich, Munich, Germany

Sunday, 26 May 2024

13. GENETIC MODIFICATION OF HEMATOPOIETIC STEM CELLS (HSCs) AS A TREATMENT OF FRIEDREICH'S ATAXIA

C. Beta[1,2], C. Piperidou[1,2], A. Iordanidou[1,2], T. Intzou[1,2], K. Boufidou[2], A. Papadopoulou[2], I. Sakellari[2], N. Psatha[1], E. Yannaki[2,3]

[1]Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Greece, [2]Gene and Cell Therapy Center, Hematology Department, "G. Papanikolaou" General Hospital, Thessaloniki, Greece, [3]University of Washington, Seattle

14. PRECLINICAL VALIDATION OF CRISPR/CAS GENOME EDITING APPROACHES AS ADVANCED THERAPY FOR HBB$^{IVSI-110(G>A)}$ THALASSEMIA

P. Patsali[1], C.G. Constantinou[1], K. Paschoudi[2,5], N. Papaioannou[1], B. Naiisseh[1], P.L. Papasavva[1], P. Christofi[2,5], S. Christou[6], M. Sitarou[6], A. Pirovolaki[6], M. Hadjigabriel[6], T. Athanasopoulos[7], C. Mussolino[3,4], T. Cathomen[3,4], M. Kleanthous[1], N. Psatha[2], E. Yannaki[5], C.W. Lederer[1]

[1]Department of Molecular Genetics Thalassamia, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, [2]School of Biology, Department of Genetics, Development and Molecular Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3]Center for Chronic Immunodeficiency, Medical Center – University of Freiburg, Freiburg, Germany, [4]Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, Freiburg, Germany, [5]Gene and Cell Therapy Center/Hematology-Hematopoietic Cell Transplantation Unit, G. Papanikolaou Hospital, Thessaloniki, Greece, [6]Thalassaemia Centre, Cyprus Ministry of Health, Cyprus, [7]Gene & Cell Ltd, London, United Kingdom

15. GENERATION OF AN 'OFF-THE-SHELF' FOAMY VIRUS GENE-MODIFIED CD16-CR T CELL PRODUCT FOR THE TREATMENT OF HEMATOLOGICAL AND SOLID TUMOUR MALIGNANCIES

I. Lazana[1,2], E. Simantirakis[1], M. Daniil[1], E.Kourous[1], G. Vassilopoulos[1,3]

[1]Cell and Gene Therapy Lab, Biomedical Research Foundation of the Academy of Athens, Athens, Greece, [2]Haematology department, General University Hospital 'Attikon', Athens, Greece, [3]Haematology department, Larissa General University Hospital, Larissa, Thessaly, Greece

Sunday, 26 May 2024

16. **BASE EDITING TO INSTALL THE HB G-MAKASSAR IN CD34+ CELLS FROM SCD PATIENTS EFFICIENTLY IMPROVES THE DISEASE PHENOTYPE**
K. Paschoudi[1,2], M. Giannaki[2], C. Li[3], A. Georgakopoulou[3], I. Mavrikou[2], Z.M. Sgouromalli[1,2], I. Kalousis[1,2], E. Vlachaki[4], I. Sakellari[5], A. Papadopoulou[2], N. Psatha[1], A. Lieber[3], E. Yannaki[2,3,5]
[1]Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Greece, [2]Gene and Cell Therapy Center, Hematology Department, "G. Papanikolaou" General Hospital, Thessaloniki, Greece, [3]University of Washington, Seattle, [4]Hematology Department, "Hippokration" General Hospital, Thessaloniki, Greece, [5]Hematology Department, "G. Papanikolaou" General Hospital, Thessaloniki, Greece

17. **IDENTIFICATION OF NOVEL γ-GLOBIN REPRESSORS THROUGH A CUSTOM CRISPR KNOCKOUT SCREEN AND VALIDATION OF THESE REPRESSORS FOR THE TREATMENT OF β-HEMOGLOBINOPATHIES**
S. Özkaramehmet, A. Demetriadou, P. Patsali, M. Xenophontos, C. Stephanou, P. Kountouris, M. Kleanthous, M. Phylactides, C.W. Lederer
Molecular Genetics Thalassaemia Department, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

18. **THE SMALL MOLECULE UM171 AS A POTENTIAL NOVEL, FETAL HEMOGLOBIN INDUCERFOR THE TREATMENT OF β-HEMOGLOBINOPATHIES**
I. Vallianou[1], G. Bolis[1], A. Georgakopoulou[2], P. Christofi[1,3], E. Katsantoni[4], I. Sakellari[1], N. Psatha[2], E. Yannaki[1,3]
[1]Gene and Cell Therapy Unit, George Papanikolaou Hospital, Thessaloniki, Greece, [2]Department of Medicine, University of Washington, Seattle, [3]Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University, Thessaloniki, Greece, [4]Biomedical Research Foundation, Academy of Athens, Athens, Greece

19. **EPIGENOME EDITING RESULTS IN EFFICIENT HBF REACTIVATION IN CD34+ CELLS OF PATIENTS WITH BETA-THALASSEMIA**
K. Paschoudi[1,2], I. Kalousis[1,2], F. Papadopoulos[1,2], Z.M. Sgouromalli[1,2], D. Grigoriou[1,2], M. Koutra[3], A. Papalexandri[3], I. Sakellari[3], E. Yannaki[2,4], N. Psatha[2]
[1]Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Greece, [2]Gene and Cell Therapy Center, Hematology Department, "G. Papanikolaou" General Hospital, Thessaloniki, Greece, [3]Hematology Department, "G. Papanikolaou" General Hospital, Thessaloniki, Greece, [4]University of Washington, Seattle

Sunday, 26 May 2024

12.00-13.00 **Special Lecture V**

Chairs: **Rebecca Matsas, Achilles Anagnostopoulos**

Neural stem cells: from bench to bedside for treatment of neurological diseases
Angelo-Luigi Vescovi

13.00-14.00 **Light Lunch**

14.00-15.30 **Session 7: CAR-T From bench to bedside**

Chair: **Evangelia Yannaki**

14.00-14.30 **GD2 CAR T-Cell Therapy: A Breakthrough in Neuroblastoma Research**
Francesca Del Bufalo

14.30-15.00 **The first in man base edited CAR7 for T-ALL**
Christos Georgiadis

15.00-15.30 **Current experience and perspectives in Greece**
George Karavalakis

15.30-16.30 **Awards - Concluding remarks and meeting closing**

Chairs: **Rebecca Matsas, Evangelia Yannaki, Minas Yiangou**

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Τρόπος διάθεσης: Περιορισμένη ιατρική συνταγή. Η έναρξη της θεραπείας γίνεται σε νοσοκομείο και μπορεί να συνεχίζεται εκτός νοσοκομείου υπό την παρακολούθηση ειδικού ιατρού.

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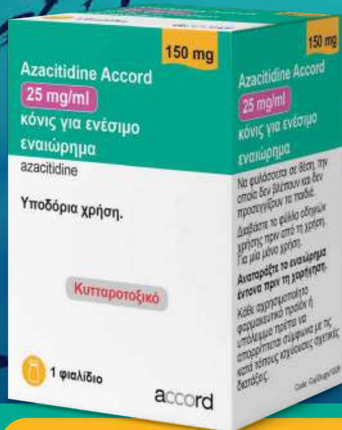

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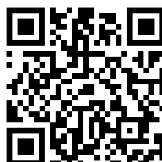

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Βιβλιογραφία: 1. REBLOZYL®, Περίληψη Χαρακτηριστικών του Προϊόντος, 03/2024 **2.** Cappellini MD et al, A phase 3 trial of Luspatercept in Patients with Transfusion-Dependent b-Thalassemia; N Engl J Med 2020; 382: 1219-31. DOI: 10.1056/NEJMoa1910182 **3.** Fenaux P et al, Luspatercept in Patients with Lower-Risk Myelodisplastic Syndrome; N Engl J Med 2020; 382: 140-51. DOI: 10.1056/NEJMoa1908892 **4.** Taher AT et al, Luspatercept for the treatment of anaemia in Non-Transfusion-Dependent b-Thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial. Lancet Haematol. 2022;9(10):e733-e744. **5.** Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402:373-385

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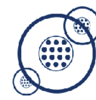

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Achilles Anagnostopoulos	Chief Scientific Director, TheraCell Laboratories, Athens, Greece
Nicholas Anagnou	MD, PhD, Professor of Biology, University of Athens School of Medicine and Head, Laboratory of Cell and Gene Therapy, Foundation for Biomedical Research of the Academy of Athens (IIBEAA), Athens, Greece
Takis Athanasopoulos	CEO & Founder Gene & Cell Ltd: A London-based CGT Consulting Firm, London, UK
Fotis Baltoumas	Post-doctoral Researcher, Bioinformatics & Integrative Biology Lab, Institute for Fundamental Biomedical Research, Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece
Olympia Bikou	MD, Cardiologist, Physician Scientist, Department of Medicine I, LMU University Hospital, Munich, Germany
Nicola Brunetti-Pierri	Professor of Pediatrics, University of Naples "Federico II", Naples, Italy and Principal Investigator, Telethon Institute of Genetics and Medicine, Pozzuoli, Italy
Nicolo Caporale	MD, PhD University of Milan, Human Technopole, Milan, Italy
Ignazio Caruana	PhD, Laboratory for Cell and Gene Therapy, Department of Paediatric Haematology, Oncology and Stem Cell Transplantation - University Hospital of Würzburg, Würzburg, Germany
Ioannis Charalampopoulos	PhD, Professor of Pharmacology, Medical School, University of Crete & Researcher at the Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology Hellas (FORTH), Heraklion, Crete, Greece
Franscesca Del Bufalo	MD, PhD, Scientist Pediatric Hematology Oncology, Ospedale Pediatrico Bambino Gesù of Rome, Rome, Italy
Iulia Diaconu	Chief Scientific Officer, Unikum Therapeutics Copenhagen, Denmark
Maria Gaitanou	Researcher, Assistant Professor Level, Laboratory of Cellular and Molecular Neurobiology, Department of Neurobiology, Hellenic Pasteur Institute, Athens, Greece
Christos Georgiadis	PhD, Senior Research Fellow UCL Great Ormond street Institute of Child Health, Zayed Centre for Research into Rare Disease, London, UK
Grigorios Georgolopoulos	PhD, Bioinformatics Team Leader, Genevia Technologies Oy, Tampere, Finland

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Achilleas Gravanis	Professor of Pharmacology, School of Medicine University of Crete and IMBB-FORTH, Heraklion, Crete, Greece; Affiliated Research Professor, Center of Drug Discovery, Northeastern University, Boston, MA, USA
Konstantinos Hatzistergos	PhD, Associate Professor, School of Biology, Aristotle University of Thessaloniki, Greece, Voluntary Assistant Professor, Interdisciplinary Stem Cell Institute, Miller School of Medicine, University of Miami, USA
Anastasios Karadimitris	PhD, MRCP, FRCPath Professor, Langmuir Chair in Haematology and Consultant Haematologist Co-Director, Centre for Haematology Director, Hugh and Josseline Langmuir Centre for Myeloma Research Centre for Haematology, Department of Immunology and Inflammation Imperial College London Department of Haematology Hammersmith Hospital, Imperial College Healthcare NHS Trust Du Cane Road, London, UK
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Carsten W. Lederer	PhD, Senior Scientist, Associate Professor and Head of Department, Molecular Genetics Thalassaemia Department, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus
Rebecca Matsas	PhD, Research Director, Laboratory of Cellular and Molecular Neurobiology - Stem Cells, Department of Neurobiology, Hellenic Pasteur Institute, Athens, Greece
Stylianos Michalakis	Professor, Department of Ophthalmology, University Hospital, LMU, Munich, Germany
Helen Papadaki	MD, PhD, Professor of Haematology, University of Crete School of Medicine, Head of the Department of Haematology, University Hospital of Heraklion, Heraklion, Crete, Greece
Anastasia Papadopoulou	PhD, Biochemist, Production Manager, Gene and Cell Therapy Center, Hematology - HCT Unit, "G. Papanikolaou" Hospital, Thessaloniki, Greece

Chairs - Speakers

Florentia Papastefanaki	PhD, Staff Research Scientist, Laboratory of Cellular and Molecular Neurobiology – Stem Cells, Head Human Embryonic and Induced Pluripotent Stem Cell Unit, Hellenic Pasteur Institute, Athens, Greece
Spyros Petrakis	Researcher, Institute of Applied Biosciences/Centre for Research and Technology Hellas (INAB/CERTH), Thessaloniki, Greece
Nikoleta Psatha	PhD, Assistant Professor, Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, Greece
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Chairs - Speakers

George Vassilopoulos	MD, PhD, Professor of Hematology - Internal Medicine, University of Thessalia, University Hospital of Larissa, Group Leader, Laboratory of Cell and Gene Therapy, Foundation for Biomedical Research of the Academy of Athens (IIBEAA), Athens, Greece
Anna Veiga	HaploiPS COST Action Chair. Barcelona Stem Cell Bank Director. Regenerative Medicine Programme. IDIBELL Barcelona, Spain
Angelo-Luigi Vescovi	Professor of Cell Biology, Director of Research Hospital Casa Sollievo Della Sofferenza, Rome, Italy, University of Milan Bicocca, Italy
Evangelia Yannaki	Director, Gene and Cell Therapy Center, Hematology Department-HCT Untit, "G. Papanikolaou" Hospital, Thessaloniki, Greece; Affiliate Professor, University of Washington, Seattle, USA
Minas Yiangou	Professor of Immunobiology & Molecular Biology, Aristotle University of Thessaloniki, Greece
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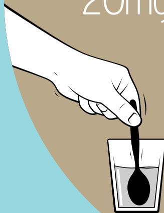

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Βιβλιογραφία: **1.** U1.Lancet JE et al. J Clin Oncol 2018;36(26): 2684-92; **2.** Lin TL et al. Blood Adv 2021;5(6):1719-28; **3.** Lancet JE et al. Lancet Haematol 2021;8(7):e481-91 ; **4.** Vyxeos Liposomal® Περίληψη Χαρακτηριστικών του Προϊόντος

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** Μεγαλύτερη συνολική επιβίωση σε σύγκριση με τη συμβατική χημειοθεραπεία (7+3/5+2 κυταραβίνη+δαουνορουβικίνη αντίστοιχα) σε ασθενείς με υψηλού κινδύνου οξεία μυελογενή λευχαιμία (high-risk AML).

Περαιτέρω πληροφορίες διατίθενται από τη Γένεσις Φάρμα Α.Ε

Τρόπος Διάθεσης: Με περιορισμένη ιατρική συνταγή: Μόνο για Νοσοκομειακή Χρήση.

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Μεγαλύτερη συνολική επιβίωση σε σύγκριση με τη συμβατική χημειοθεραπεία στους ασθενείς με υψηλού κινδύνου* Οξεία Μυελογενή Λευχαιμία[2,4-6]**

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Βιβλιογραφία: **1.** U.S. Food and drug administration 2017. FDA news release: FDA approves first treatment for certain types of poor-prognosis acute myeloid leukemia. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-certain-types-poor-prognosis-acute-myeloid-leukemia. Last accessed JUN 2023; **2.** Lancet JE et al. J Clin Oncol 2018;36(26): 2684-92; **3.** Talati C, Lancet JE. Future Oncol 2018;14(2):1147-54; **4.** Lin TL et al. Blood Adv 2021;5(6):1719-28; **5.** Vyxeos Liposomal® Περίληψη Χαρακτηριστικών του Προϊόντος; **6.** Lancet JE et al. Lancet Haematol 2021;8(7):e481-91.

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ORAL ABSTRACTS

ORAL PRESENTATIONS

1. UNVEILING THE NEUROREGENERATIVE PROPERTIES OF THE PAN-NEUROTROPHIN P75 RECEPTOR IN MOUSE AND HUMAN NEURAL STEM CELLS: A NOVEL PERSPECTIVE ON ALZHEIMER'S DISEASE PATHOLOGY

M.A. Papadopoulou[1,2], K. Chanoumidou[1,2], I. Charalampopoulos[1,2]
[1]Department of Pharmacology, Medical School, University of Crete, Heraklion, Greece, [2]Institute of Molecular Biology & Biotechnology (IMBB), Foundation for Research and Technology Hellas (FORTH), Heraklion, Greece

Aim: The pan-neurotrophin p75 receptor (p75NTR) is a member of the TNF receptors superfamily with pleiotropic expression in neural tissue and multifaced regulatory functions, ranging from neuronal differentiation to cell death. Many studies have shown that p75NTR is upregulated by a variety of pathological insults such as brain injury and neurodegenerative conditions (Ibanez & Simi, 2012). The altered expression profile combined with its controversial signaling, acting as pro-apoptotic and/or pro-survival mediator, makes p75NTR an appealing target in neurotherapeutics. A plethora of experimental results, have implicated p75NTR in Alzheimer's Disease (AD) onset and progress,while its contribution to adult hippocampal neurogenesis, which drops sharply in AD, remains poorly understood. Contradictory evidence in mouse model studies suggests either a pro-neurogenic or an anti-neurogenic effect of p75NTR (Catts 2008; Bernabeu-Longo 2010). There are also no clues, addressing its function in human neural stem cells (hNSCs). Based on this knowledge, we now investigate p75NTR role in rodent and human neurogenesis under physiological and AD-related conditions.

Materials and Methods: In order to study the adult hippocampal neurogenesis in mice, we performed BrdU injections for detection of proliferation and immunohistochemistry analyses for key neurogenic markers in p75KO, 5xFAD and 5xFAD_p75KOmiceof different ages. We have also generated NSCs from human iPSCs and examined the activity of p75NTR signaling with co-immunoprecipitation and WesternBlot analysis. Furthermore, with apoptosis and proliferation assays as well, we investigated p75NTR contribution to hNSCs survival under treatments with Aβ-peptides (AD condition).

Results: p75 KO mice at 2 months old age exhibit decreased NSCs proliferation and attenuated neuronal differentiation in the dentate gyrus, as shown with immunohistochemistry analysis for DCX and NeuN as well as with an RNA sequence for differential gene expression, revealing key neurogenic properties. A newly formed 5xFAD-p75KOmodel depicts a decreased number of proliferative NSCs showing the significance of p75NTR in neurogenic procedures, even in an AD background. Furthermore, p75NTR signaling is active in hNSCs and regulates survival in the presence of Aβ peptides indicating its involvement in the neurogenic deficits reported in human AD.

Conclusions: The present study demonstrates the expression and activity of p75NTR in neurogenesis phenomenon, both in mouse and human cells, emphasizing on its role in AD neurogenic deficits. Our results from p75KO and 5xFAD animals suggest receptor's requirement for intact neurogenesis in rodents, even in an AD background. Configuration of p75NTR sig-

naling in NSCs and its pharmacological targeting will enable the enhancement of the endogenous regeneration against AD.

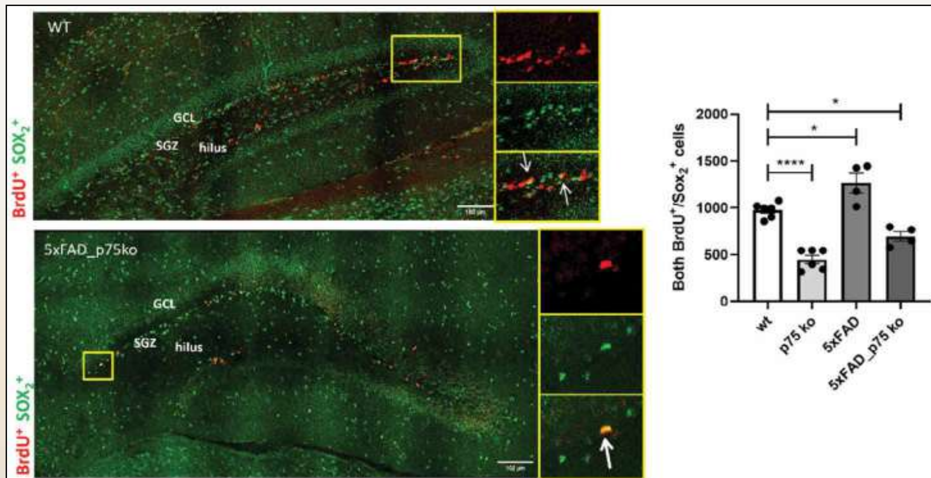

Figure. Quantification for BrdU (red) and SOX_2 (green) positive cells in DG of WT and 5xFAD_p75KOmice of 2-months-old, showing reduction in the number of proliferating NSCs (N=6 or 4, one way ANOVA; p****<0,0001, p*<0,05).

Funding: *European Innovation Council SoftReach ID:101099145*

2. DYNAMIC LINKS BETWEEN THE CARDIAC INTERMEDIATE FILAMENTS OF THE CYTOSKELETON AND NUCLEOSKELETON FOR PROPER CARDIOMYOCYTE DIFFERENTIATION, MATURATION AND REPROGRAMMING

M. Tsikitis[1], A. Diokmetzidou[1], P. Kolovos[2], G. Vatsellas[1], Y. Capetanaki[1]
[1] Center of Basic Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece, [2]Democritus University of Thrace, School ofMolecular Biology and Genetics, Alexandroupolis, Greece

Accumulating evidence suggests that mechanical forces are integral to the commitment and differentiation of cardiac stem cells. Studies have proposed that the cytoskeleton and specifically the desmin intermediate filament (IF) network and its association with nuclear lamins through the LINC complex, link the contractile apparatus to both the extracellular and nuclear matrix, thus regulating trafficking processes and mechanotransduction during development and adulthood, governing myocyte homeostasis and survival. Desmin, in addition to being one of the earliest myogenic markers both in heart and somites (Kuisk I. et al. *Dev. Bio.* 1996), regulates nuclear shape and positioning

ORAL PRESENTATIONS

(Ralston E. et al. *Journal of cellular physiology* 2006, Shah S.B. et al. *Biophys J* 2004), as well as the expression of myogenic (MyoD, Myogenin) (Li H. et al. *JCB* 1994) and cardiogenic (MEF2, Nkx2.5) transcription regulators, during embryonic stem cell differentiation (Kuisk I. et al. *Dev. Bio.* 1996). Consistent with the above findings, desmin deficiency has negative impact in the proper regeneration of skeletal muscle cells by hematopoietic stem cells (Camargo FD et al. *Nat. Med.* 2003). Despite these overwhelming data linking desmin to the establishment and maintenance of myogenesis and cardiogenesis, the precise underlying mechanisms remain elusive. To dissect the exact mechanism of cardiogenic regulation we took advantage of the fibroblast-to-cardiomyocyte direct reprogramming, where fibroblasts trans-differentiate into functional induced cardiomyocytes (iCM) through ectopic expression of three transcription factors, GATA4, Mef2C and Tbx5 (GMT) (Ieda M. et al. *Cell* 2010). We hypothesized that desmin could enhance the reprogramming of fibroblasts into cardiomyocytes. Indeed, we have found that expression of desmin together with the GMT factors increases reprogramming by 40-60%. Involvement of a cytoskeletal protein such as desmin in cell differentiation and potentially regeneration, raises intriguing questions and exciting possibilities. To unravel the mechanism of this enhancement we focused on desmin serving as direct mechanotransducer (through the LINC complex) to chromatin. Toward this goal, we investigate the changes of the genetic profile induced by the GMT cocktail during reprogramming in the presence or absence of desmin. RNA sequence analysis has shown that the Notch developmental pathway is regulated by desmin. With the use of Chromosome Conformation Capture, Hi-C and ChIP-sequence analysis, we demonstrated the importance of desmin cytoskeleton on the genome 3D organization. In addition, we show that desmin is expressed in most of the cardiac progenitor cells population declaring its role in proper cardiac formation. Moreover, immunofluorescence, calcium influx and electron microcopy studies establish desmin as a major player for cardiac maturity, a critical subject in cardiac regenerative medicine, since its absence substantial reduces expression and proper localization of cardiac specific proteins, delays myofibril formation and impairs function of the induced cardiomyocytes driving most of them to senescence. All the above data will be presented.

ORAL PRESENTATIONS

3. NOVEL CHEMICAL COMPOUND PROTECTS PATIENT-DERIVED NEURONS FROM CELL DEATH IN SCA1

K. Pliatsika[1,2], I. Gkekas[1,2], S. Mylonas[3], S. Katsamakas[4], P. Pechlivani[1], A. Axenopoulos[3], L.J. Flitsch[5], B. van de Warrenburg[5], K. Xanthopoulos[2], P. Darras[3], M. Peitz[5], S. Petrakis[1]
[1]Institute of Applied Biosciences (INAB), Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece, [2]Department of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3]Information Technologies Institute (ITI), Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece, [4]Institute of Chemical Biology, National Hellenic Research Foundation, Athens, Greece, [5]Institute of Reconstructive Neurobiology, Life & Brain Center, University of Bonn Medical Center, Bonn, Germany, [6]Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands

Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease which belongs to the group of polyglutamine (polyQ) disorders. It is characterized by progressive degeneration that mainly affects the Purkinje cells of the cerebellum. SCA1 is caused by CAG repeat expansions in the *ATXN1* gene and is associated with an abnormally large polyglutamine tract in the encoded ataxin-1 (ATXN1) protein. The mutant protein forms toxic oligomers which slowly aggregate into larger insoluble inclusions within the nucleus. These aggregates correlate with disease progression and the age of the patient. The AXH domain of ATXN1 is suggested to play a very critical role in the aggregation of mutant ATXN1. Currently, there is no treatment available for SCA1 and the disease leads to death within 10 to 30 years from the onset of symptoms.

Despite significant studies in SCA1 modeling, a reliable cell model is still missing. Here, we present the generation of a patient-derived neuronal cell model, partially retaining the aging signature of the donor. To this end, peripheral blood mononuclear cells (PBMCs) from a SCA1 patient were directly trans-differentiated into induced neural stem cells (iNSCs). Reprogramming was implemented using non-integrating Sox-2 and c-Myc Sendai viruses. The generated iNSCs exhibit neural stem cell properties, including the expression of neural markers, self-renewal and differentiation ability into neurons.

This patient-derived cell model served as a platform to evaluate the effect of a previously identified novel chemical compound in SCA1 neurons. Using artificial intelligence (AI), we previously identified compounds binding to the AXH domain of ATXN1. Following in vitro experimental validation, we identified a compound that inhibits AXH dimerization and effectively suppresses the aggregation of mutant ATXN1. Further testing of this compound in patient-derived neurons demonstrated a marked decrease in programmed cell death (apoptosis) in SCA1 neurons. By utilizing SCA1-iNSCs for disease modeling and compound testing, our research provides a strong basis for establishing a drug-based therapeutic intervention for SCA1.

ORAL PRESENTATIONS

4. CONTROL IPSC-DERIVED ASTROCYTES RESCUE P.A53T-ASYN PATIENT-IPSC-DERIVED NEURONS FROM PARKINSON'S DISEASE-RELATED PATHOLOGY

O. Apokotou[1], C. Paschou[2], A. Kollias[2], K. Charmpi[2], S. Dede[1,4], M. Samiotaki[3], E. Taoufik[2], C. Zurzolo[4], R. Matsas[2], F. Papastefanaki[1,2]

[1]Human Embryonic and Induced Pluripotent Stem Cell Unit, Hellenic Pasteur Institute, Athens, Greece, [2]Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute, Athens, Greece, [3]Institute of Bioinnovation, Biomedical Sciences Research Center "Alexander Fleming", Vari, Greece, [4]Membrane Traffic and Pathogenesis, Cell Biology and Infection Department, Institut Pasteur Paris, France

Aim of Study: Parkinson's disease (PD), the second most common neurodegenerative disorder is characterized by progressive loss of midbrain dopaminergic neurons resulting in motor and non-motor symptoms. The histopathological disease hallmark is the presence of intraneuronal protein inclusions of α-synuclein, termed Lewy bodies and Lewy neurites. Approximately 10% of PD cases are associated with mutations in specific genes, such as the p.A53T α-synuclein (αSyn) mutation (G209A in the SNCA gene) that causes a familial form of PD with early onset and severe phenotype. Despite intensive research, PD is still incurable. While neuron-intrinsic dysfunction has been extensively studied, research on the role of astrocytes, the most abundant cells in the human brain, has lagged behind, regardless of their critical roles in maintaining neuronal health and their capacity to exert neuroprotective or neurotoxic effects upon disease.

Methods: To investigate the impact of p.A53T-αSyn on astrocytes and their contribution in neuronal pathology in PD, we differentiated patient-derived induced pluripotent stem cells (iPSC) to ventral midbrain astrocytes and studied them separately and in a co-culture system with dopaminergic neurons from the same pool of iPSCs.

Results: PD iPSC-derived astrocytes displayed cell-intrinsic pathological phenotypes such as intracellular protein aggregates, including accumulation of pathological phospho(Ser129) αSyn, and dysregulation of Ca^{2+} homeostasis. Proteomic analysis revealed perturbed protein catabolic processes, autophagy, and endocytosis, with dysregulation of lysosomal properties and the mammalian target of rapamycin (mTOR) pathway. Furthermore, iPSC-derived dopamine neurons co-cultured with PD astrocytes displayed exacerbated neurodegenerative phenotypes, such as compromised neuronal viability and neurite outgrowth, Lewy-related pathology as well as defective synaptic connectivity and Ca^{2+}oscillations. Notably, neurodegeneration was reversed by control astrocytes, at least partially, due to their capacity to uptake and resolve neuronal aSyn aggregates – a process impaired in PD astrocytes.

Conclusions: Our findings underscore a critical impact of the p.A53T-αSyn mutation in astrocytic proteostasis and clearance mechanisms, rendering astrocytes important contributors to PD neuropathology. This study also highlights a remarkable ability of healthy astrocytes in rescuing neurodegeneration of p.A53T-αSyn neurons. These results provide valuable insights into potential disease targets for the development of novel PD therapeutics.

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This work is funded by the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "1st Call for H.F.R.I. Research Projects to support Faculty members and Researchers and the procurement of high-cost research equipment" (Project 1019-DiseasePhenoTarget).

5. NR5A2 REGULATES HYPOXIA RESPONSE AND METABOLISM IN NEURAL CELLS: IMPLICATIONS FOR NERVOUS SYSTEM-RELATED DISEASES

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Metabolic regulation in the nervous system plays a pivotal role in orchestrating neuronal function and maintaining cellular homeostasis. Utilizing our RNAseq data from gain- and loss-of-function studies of embryonic neural tissue and neuronal cells, we demonstrate that the nuclear receptor NR5A2 regulates hypoxia response, glycolysis, and fatty acid metabolism. Consistently, we have previously shown that NR5A2 inhibits the proliferation and growth of glioblastoma cells and tumors, respectively. Here, we elucidate a novel mechanism whereby NR5A2 functions as a potent suppressor of HIF-1α (Hypoxia-Inducible Factor 1-alpha), independent of prolyl hydroxylase (PHD)-mediated inhibition. This repression of HIF-1α by NR5A2 leads to the downstream inhibition of the genes that are direct targets of HIF-1α and code for proteins that are crucial players in metabolic pathways such as glycolysis, fatty acid and glutathione metabolism, thereby reshaping the metabolic landscape within neural and glioblastoma cells. This mechanism could also contribute to the antiproliferative, antigliogenic, and anti-tumorigenic properties of NR5A2 in the context of GBM and neural/stem progenitor cells. Notably, pharmacological activation of NR5A2 using DLPC (Dilauroylphosphatidylcholine), a well-established agonist, mirrors the anti-tumorigenic effects observed with NR5A2 overexpression. These data highlight DLPC as a promising therapeutic molecule for glioblastoma multiforme, a very aggressive malignancy of the central nervous system. Overall, our study uncovers a link between NR5A2-mediated metabolic regulation, neuronal development, and inhibition of glioblastoma tumor progression. These observations suggest that NR5A2 and its agonists could be used as potential therapeutic targets for nervous system malignancies and/or other nervous system-related diseases.

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6. DHS ANALYSIS TO STUDY THE EPIGENETIC MECHANISMS BEHIND DEDIFFERENTIATION OF ADIPOCYTE LIKE CELLS TO MESENCHYMAL STEM/STROMAL CELL CELLS WITHOUT GENE EDITING

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Background: In our previous studies, we investigated the plasticity of amniotic fluid mesenchymal stem cells (AF-MSCs) based on their differentiation and dedifferentiation potential *in vitro.* We proved that adipocyte-like (AL) cells derived from AF-MSCs can regain, under certain culture conditions, a more primitive phenotype through the process of dedifferentiation. Dedifferentiated AL cells (DAF-MSCs), gradually lost the expression of adipogenic markers and obtained similar morphology and differentiation potential to AF-MSCs, together with regaining the pluripotency marker expression.
Aim: The aim of the present study was to compare the chromatin accessibility profiles of AF-MSCs, AL and DAF-MSCs and associate these to expression changes in order to gain insights into the underlying mechanisms of differentiation and dedifferentiation.
Methodology: To this end, we performed Dnase I sequencing to profile the accessible chromatin and identify active regulatory DNA elements.
Results: In order to quantify the degree of similarity of the accessible regions between AF-MSCs, AL cells and DAF-MSCs, we computed the fraction of shared peaks. This revealed that DAF-MSC peaks shared more similarities with AF-MSC than with AL peaks (61.7% and 50.9%, respectively). Genic annotation of peaks revealed a higher frequency of accessible promoters in the unique AL peaks compared to unique AF-MSC and DAF-MSC peaks. We then performed transcription factor binding motif enrichment analysis in order to delineate the upstream transcriptional regulators acting through the accessible elements. We discovered that AF-MSCs, compared to AF-MSCs and AL, exhibit robust enrichment for stem cell-related transcription factors such as the Activator protein-1 (*AP1*) family which includes proteins such as *c-JUN*, known as a promoter of self-renewal (log2-fold change 1.92), and significant enrichment for the *POU* domain of octamer-binding transcription factor 4 (*OCT4)* (log2-fold change 1.19). The DAF-MSC motifs with the highest fold change compared to AF-MSCs and AL, were associated with stem cell transcription factors, including the OneCut Homeobox family, *DUX4* (Double-homeobox 4), *PAX3* and *PAX7* (paired-box gene 3&7). The *AP1* motif was highly downregulated in DAF-MSCs (log2-fold change -0.23) exhibiting a potential limitation for self-renewal. In contrast, enrichment of the *POU* domain of *OCT4* was observed in DAF-MSCs compared to AL (log2 fold change 1.18). Transcription factors with clear association with adipocytes were not detected in the DAF-MSCs, indicating successful dedifferentiation; however, *CEBPa* (CCAAT/enhancer-binding protein-alpha), a major adipocyte related transcription factor was highly enriched (log2-fold change 1.54) in AL samples. Finally, in order to link chro-

matin accessibility to gene expression changes we performed promoter-specific differential chromatin accessibility analysis. We identified 16 gene promoters with high statistical significance and fold change (adjusted p-value<0.05 and log2-fold change>1) shared between AF-MSCs and DAF-MSCs, and 10 shared between AL and DAF-MSCs.

Conclusions: Overall, motif enrichment indicated a degree of heterogeneity between DAF-MSCs and AF-MSCs; however, the functional similarity and the primitive phenotype were evident. AL cells exhibited a preadipocyte profile and a more differentiated state, also supported by a high promoter frequency. In addition, promoter accessibility analysis indicated high similarity between DAF-MSCs and AF-MSCs. Our current studies focus on further analysis of the functional implications of the differentially accessible regions that may indicate regulatory regions and transcripts.

7. INHIBITION OF HIF-1α PROLONGS THE CARDIOMYOCYTE REGENERATIVE WINDOW IN NEONATAL MICE

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Introduction: Heart disease represents a significant challenge in global health, persisting as the primary cause of morbidity and mortality worldwide. Unlike some organisms which retain lifelong ability to regenerate their myocardium, mammals exhibit a limited cardiac regenerative capacity restricted to the first three days of postnatal life, beyond which this ability diminishes. Recent studies propose a potential mechanism, wherein shifting cardiomyocyte metabolism toward glycolysis, facilitated by the stabilization of the transcription factor Hypoxia Inducible Factor-1α (HIF-1α) through transient exposure to hypoxia, mayinduce cardiomyocyte proliferation and regeneration in the postnatal mammalian heart. However, the exact role of hypoxia and HIF-1αin mammalian heart development and regeneration remains controversial.

Aim: To explore the involvement of hypoxia and HIF-1α in the development and regeneration of the mammalian heart.

Materials and Methods: The role of hypoxia and HIF-1α in the developing mouse heart was investigated by subjecting BALB/c dams to timed pregnancies, followed by intraperitoneal injections of the hypoxia marker Pimonidazole on embryonic days (E)9.5 (n=3), E10.5 (n=3), E14.5 (n=4), and E18.5 (n=4). To investigate therole of hypoxia and HIF-1α in postnatal cardiomyocyte regeneration, one- (P1) and seven-day-old (P7) BALB/c pups of both sexes were randomized to sham or cryoinjury-induced heart regeneration, followed by daily subcutaneous injections of either PBS (Ctrl), the HIF-1α inhibitor YC-1, or the HIF-1α inducer $CoCl_2$, for seven days (n=6-8/group). Cardiomyocyte proliferation was examined using confocal immunofluorescence analysis after co-immunostaining for the mitotic marker Serine-10 phos-

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phorylated Histone H3 (PH3) and the cardiomyocyte-specific marker Pericentriolar Material-1 (PCM1). Subsequently, both the mitotic cardiomyocytes ($PH3^+/PCM1^+$), and non-cardiomyocytes ($PH3^+/PCM1^-$) indices were quantified. Additionally, the levels of hypoxia and HIF-1α stabilization were evaluated with Pimonidazole and anti HIF-1α confocal immunofluorescence, respectively.

Results: Confocal microscopy analysis revealed persistent, nuclear HIF-1αimmunoreactivity in >95% of fetal and neonatal cardiomyocytes. Interestingly, pimonidazole adducts co-localized completely with nuclear HIF-1α in E9.5 and E10.5 hearts, while in the E14.5 myocardium, pimonidazole was restricted to a subset of HIF-1α$^+$ cardiomyocytes before becoming fully extinguished by E18.5. These observations suggest that cardiac HIF-1α activity becomes oxygen-independent from E14.5 onwards in the mouse heart. Importantly, most $PH3^+$ cardiomyocytes exhibited nuclear HIF-1α immunoreactivity in neonatal hearts but not in fetal hearts. Furthermore, the proliferative capacity of neonatal cardiomyocytes significantly declined in P7 compared to P1 mice ($p<0.0001$), indicating that sustained HIF-1α activity may impede postnatal cardiomyocyte proliferation and regeneration. Consequently, inhibition of HIF-1α with YC-1 in P7 cryoinjured mice led to a marked increase in the number of $PH3^+$mitotic cardiomyocytes and non-cardiomyocytes compared to controls ($p<0.0001$), whereas this effect was reversed when HIF-1α was stabilized with $CoCl_2$. Notably, the distribution of $PH3^+$ mitotic cardiomyocytes and non-cardiomyocytes was uniform across apex, border, and remote zones ($p=0.0647$).

Conclusions: Our findings highlight an oxygen-independent mechanism of HIF-1α activation in the developing and regenerating mouse heart. Inhibiting HIF-1α extends the cardiac regenerative window, shedding light on mammalian cardiac regenerative biology. These findings open promising avenues for developing HIF-1α-targeted therapeutic interventions in heart disease.

8. THE SIGNIFICANCE OF HLA PHYLOGENETICALLY RELATED COUNTRIES IN THE CREATION OF IPSC HAPLOBANKS AGAINST THE REGIONAL HLA HETEROGENEITY

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Background/Objectives: The molecular complexity and geographic diversity of Human Leukocyte Antigens (HLA) genes pose a major determinant for donor-recipient matching during allogeneic hematopoietic stem cell transplantation (HSCT). HSCs derived from induced pluripotent stem cell lines (iPSC) with homozygous HLA haplotypes (haplolines) might represent an alternative solution. There is an ongoing effort to use banked Cord Blood Units (CBUs) from different populations as a source of haplolines to cover a reasonable percentage of the target population. In the context of global initiatives, we aim to create a Greek iPSC haplobank by combining donor data from public CB banks of Greece and Cyprus.

Methods: The size of the iPSC haplobank required to cover the HLA matching needs of the Greek population was calculated using the estimated haplotypes from the 3,012 Greek CBUs (total n=79,701 CBUs & BMDs) typed for HLA-A, -B and -DRB1 with 2nd field NGS. The number of haplolines providing maximum coverage (probability of zero mismatches) was estimated using an in-house iterative algorithm. Matching coverage was based on the concordance of HLA alleles of the estimated homozygous haplotypes with at least one of the two alleles matched. To investigate the probability of improvement in matching coverage, we combined the Greek CBUs with 2,843 CBUs (total n=98,998 CBUs & BMDs) from the Greek-Cypriot population. The coverage of the combined iPSC haplobank (n=5,855) was re-estimated against the 10 most frequent total Greek haplotypes.The genetic distances were calculated by Prevosti's metric and the HLA genetic divergence or resemblance was graphically displayed in a cluster-map .

Results: 9,567 HLA haplotypes were estimated for the total Greek cohort (n=79,701) with 4 haplotypes at frequency ≥1%. In total, 100 and 463 CBUs haplolines cover 65.83% and 88.68% of the Greek population, respectively. Among the 3,012 CBUs, 5 samples were homozygous for 4 haplotypes with 3 being present within the top 10 common providing a cumulative coverage of 11.31% (vs. the estimated 27.46%). Even though the combined panel of 10 homozygous Greek and Greek-Cypriot CBUs didn't improve the cumulative percentage of total Greek HLA-matched individuals (26.61%), it provided additional candidates as source cells for the iPSC haplobank. Specifically, two extra homozygous haplotypes increased the number of haplolines to 5 (out of total 11) and the respective cumulative matching coverage to 13.78%. Moreover, the two haplolines significantly improved the coverage of the Greek regional heterogeneity since A*33:01~B*14:02~DRB1*01:02 is the top haplotype in Crete (1.44%) and A*02:01~B*44:05~DRB1*16:01 is highly expressed in Crete (0.59%) and Northern Greece (0.25%). Based on these results, we estimated the genetic distances between Greece and 11 representative European populations (10.000 samples each) from the DKMS registry. We are currently exploring the significance of combining HLA phylogenetically closer populations, i.e. Romania (GD=0.479), Italy (GD=0.467) and Turkey (GD=0.453), with the Greek cohort to

create a more efficient Greek haplobank.

Conclusion: These results not only verify the importance of establishing iPSC repositories from individuals homozygous for frequent HLA haplotypes, but also highlight the significance of sharing haplolines with HLA phylogenetically close populations in order to cover the Greek HLA diversity.

9. DECIPHERING AND TARGETING EARLY SYNAPTIC DYSFUNCTION IN PRE-CLINICAL MODELS OF FAMILIAL PARKINSON'S DISEASE

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Alpha-synuclein (αSyn) is a highly expressed and conserved presynaptic protein, which has been tightly linked to Parkinson's disease (PD). Synaptic dysfunction is considered to be an early yet progressive pathological feature in PD, with the triggering mechanisms remaining undefined. This study analyzes how the G209S pathogenic mutation in the synuclein gene, and its aberrant protein product p. A53TαSyn protein disrupts synapse formation and function, even at early stages of neuronal differentiation. Herein, a transgenic mouse model expressing the human p.A53T-αSyn in brain neurons under the control of the PrP promoter (Prnp-SNCA*A53T), alongside with human-derived neurons bearing the p.A53T mutation are employed.Proteomic analysis of synaptosomes from different brain regions of 6-month-old mice reveals dysregulation of presynaptic proteins primarily associated with synaptic vesicle trafficking while imaging analysis of the p.A53T synapse structure demonstrates diminished number of synaptic vesicles and impairment of PSD formation, prior to αSyn aggregation. In compliance, the cortical and hippocampal expression of the vesicular glutamate transporter protein vGLUT1 and the neurotransmitter GABA is impaired long before the reduction of dopaminergic neurons in the substantia nigra. Moreover, immunocytochemical assessment of mouse and human p.A53T-αSyn neurons unveils aberrant connectivity, alterations in the numbers of excitatory and inhibitory synaptic contacts, and a largely compromised network. The early appearance of these defects is further reinforced by the partial inability of p.A53T neurons to form artificial synapses. Notably, the administration of dual-allosteric NMDAR antagonists, Memantine and Nitrosynapsin, potentially reverses the observed synaptic dysfunction. The cellular and molecular analyses of the *in vitro* p.A53T-αSyn pre-clinical systems are complemented by longitudinal electrophysiological studies using a multi-electrode array system to record neural network activity and synaptic functionality. Altogether, our approach provides spatiotemporal evidence of early synaptic dysfunction as a key aspect of p.A53T-

αSyn pathology, which can be reversed by the use of neuromodulatory agents.

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10. STUDYING GLUCOSE NEUROTOXICITY IN A HUMAN IPSC-BASED MODEL TO UNRAVEL THE THERAPEUTIC BENEFITS OF P75NTR TARGETING

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The energy demands of the brain are primarily met by glucose. Neuronal glucose uptake is insulin independent and depends on the extracellular concentration. Therefore, glucose concentration should be tightly regulated to maintain brain homeostasis since persistent episodes of high glucose, a common feature of Diabetes Mellitus, cause complications including neuronal damage and inflammation. To date, most studies address glucose neurotoxicity in animal diabetic models. Here, we aim to study the neurological manifestations of high glucose in a human iPSC – based model with emphasis on the role of p75 neurotrophin receptor ($p75^{NTR}$). $p75^{NTR}$ belongs to the TNF-receptor superfamily and signals apoptosis in different settings. We use mono- and co-cultures of human iPSC-derived neurons and astrocytes in 2D and porous collagen scaffolds based- 3D conditions to investigate the involvement of $p75^{NTR}$ signaling in the direct and inflammation-mediated effects of hyperglycemia on neurodegeneration. Our RNA-seq analysis of the hyperglycemic neurons provided insights into the de-regulated processes of the cells including cell cycle progression, DNA damage response and cellular stress. In agreement, *in vitro* experiments showed that high glucose triggers neuronal cell death in a dose-dependent manner accompanied by an up-regulation of $p75^{NTR}$ expression. Inhibition of $p75^{NTR}$ activity rescues neuronal cell death highlighting $p75^{NTR}$ as a mediator of glucose neurotoxicity. Furthermore, we found that high glucose down regulates key synaptic proteins in neurons indicating a deregulation of synaptic plasticity. Intriguingly, high glucose does not show any effect on iPSC-derived astrocyte survival or activation in

contrast to previous findings in rodents. This finding suggests that microglia is probably the primary source of inflammation that is reported in rodents and human patients in hyperglycemic condition. Collectively, our study provides insights into the brain deficits caused by hyperglycemia and suggests the therapeutic potential of $p75^{NTR}$ targeting.

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11. UNLOCKING HLA-G: PRECISION EPIGENOME EDITING FOR IMMUNOMODULATION

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Background: Human leukocyte antigen G (HLA-G) is a crucial immunomodulatory molecule expressed during pregnancy, that orchestrates maternal-fetal tolerance by shielding the semi-allogeneic embryo from immune rejection. However, HLA-G is epigenetically silenced post-birth, marking a significant transition in immune regulation. Recently, epigenome editing has emerged as a promising strategy to rewrite the epigenetic landscape and modulate gene expression, without altering the DNA sequence.
Aim: In these preliminary studies we aimed to reactivate the developmentally silenced HLA-G gene by epigenome editing to exploit its immunomodulatory capacity for therapeutic purposes. More specifically, our first objective was to identify the optimal epigenome editor in terms of effector module and target sequence, by assessing combinations of four different CRISPR activators (CRISPRa) and four distinct HLA-G cis-regulatory sequences. Additionally, we sought to evaluate whether HLA-G activation confers immunosuppressive function.
Methods: We identified two promoter-like regions (PR1, PR2) and two enhancer-like signature regions (ER1, ER2) based on chromatin accessibility and post-translational histone modification signatures (as per the ENCODE Registry of candidate cis-Regulatory Elements-cCREs). Twenty non-overlapping guide RNAs (gRNAs) were designed to target these regions (5 gRNAs per cCRE), and four CRISPRa systems (EpiEditors) were developed, each expressing a nuclease-deficient Cas9 (dCas9) fused to a transcription activator (VPR, MSK1, p300, or SUNTAG). The 20 gRNAs were delivered by lentiviral vectors, either as a pooled library or individually, into K562 cells expressing the EpiEditors and HLA-G expression was measured by flow cytometry. Cells expressing the EpiEditor, but no gRNA served as negative controls.

Results: Combining the dCas9/VPR EpiEditor with a gRNA pool, targeting one of the promoter-like regions (HLA-G^{PR1}) significantly tuned the expression of HLA-G compared to empty-vector controls (13.26% vs 0.17%, p=0.001). However, none of the MSK1, p300, SUNTAG EpiEditors, and none of the PR2, ER1, or ER2 genomic targets in conjuction with HLA-G^{PR1}, elicited discernible activation of HLA-G expression, thus suggesting that PR1 likely governs HLA-G silencing. Subsequent analysis, with the 5 individual gRNAs targeting HLA-G^{PR1}, identified two highly effective gRNAs, with one demonstrating superior efficacy compared to empty-vector controls (31.75% vs 0.73%, p=0.005). Notably, immunomagnetically enriched HLA-G+^{PR1}-epigenetically edited K562 cells significantly inhibited the cytotoxic activity of T cells compared to wild type K562 cells (% lysis at 40:1 ratio: 14.5±2.53 vs 45.5±1.5, respectively, p=0.004), confirming the immunosuppressive potential of HLA-G.
Conclusions: Overall, we have identified key genomic elements regulating the HLA-G expression and demonstrated the feasibility of reactivating HLA-G through CRISPR-mediated epigenomic editing, resulting in robust immunosuppression. This approach presents a novel strategy with therapeutic potential for leveraging HLA-G in various clinical scenarios, including mitigating Graft-versus-Host (GvH) and Host-versus-Graft (HvG) complications post-transplantation.

12. RECOMBINANT AAV CAPSIDS AS A NOVEL VACCINE PLATFORM

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Purpose: Adeno-associated viruses (AAVs) are widely explored as vectors in the field of gene therapy. However, their versatility allows them to be further used in unconventional applications. The COVID-19 pandemic exposed an unmet medical need for the rapid and large-scale development of novel vaccines, sparking interest in alternative avenues for antigen delivery in vaccine development. One such avenue is utilizing the highly versatile AAV capsid, which presents several advantages over conventional peptide-based vaccines, including high stability, ease of manipulation, and inherent interaction with the immune system.
Methods: To explore the potential of this platform, we developed an AAV capsid-based vaccine against COVID-19 as a model disease. We genetically introduced immunogenic peptide insertions of approximately 200 amino-acidresiduesof the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein on the surface-exposed loop IV of AAV2 and AAV9, resulting in recombinant AAV capsids (AAV2-RBD and AAV9-RBD, respectively) that presents the immunogenic antigen 60 times on its surface. Empty virus-like particles (VLPs) without a vector genome were produced and administered subcutaneously in adult rabbits. Serum was taken 30 days after injection and analyzed for specific IgG and IgM titers against the presented antigen.

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Results: Engineered AAV2-RBD and AAV9-RBD could be produced and purified by standard methods as full or empty VLPs. Full particles carrying aeGFP-expressing genome showed higher transduction levels on ACE2-overexpressing cell lines confirming that the modification endowed the AAVs with this SARS-CoV-2-like property. In rabbits, subcutaneous VLP injections elicited a strong immune response, resulting in a high titer of specific neutralizing IgG antibodies. Furthermore, serum of individuals vaccinated with the Comirnaty® mRNA-based vaccine also showed neutralization capacity against the VLPs. Finally, these VLPs also triggered a strong cellular immune response in peripheral blood mononuclear cells of individuals previously infected with SARS-CoV-2 and/or vaccinated with mRNA-based vaccines. **Conclusions:** These results show a promising method of inducing a strong immune response using the AAV capsid as an immunogenic scaffold. This method circumvents the need for delivery of a transgene cassette to deliver antigen information, reducing the risk of potentially pathogenic intracellular processes and instead leading to a rapid immune response. Therefore, this approach could be implemented as a next-generation vaccine development platform against diseases where traditional vaccination attempts have been thus far unsuccessful.

13. GENETIC MODIFICATION OF HEMATOPOIETIC STEM CELLS (HSCs) AS A TREATMENT OF FRIEDREICH'S ATAXIA

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Background: Friedreich's Ataxia (FRDA) is an autosomal recessive, multisystemic disease primarily affecting the CNS and the heart, resulting from reduced frataxin (FXN) expression, a mitochondrial protein involved in iron-sulfur cluster biogenesis and cell metabolism. FRDA arises from an unstable expansion of a GAA-trinucleotide repeat located in intron 1 of the FXN locus. As a monogenic disease, FRDA is an ideal candidate for gene therapy (GT). However, results from preclinical studiesare suboptimal, as they mostly focus on repairing either the CNS or the heart by in vivo delivery of tissue-tropic adeno-associated viral vectors (AAVs) encoding the FXN gene and carrying potent enhancers. The latter along with the high AAV doses required for achieving a therapeutic effect, have been associated with safety concerns. Recently, unmanipulated allogenic or lentiviral-vector (LV) genetically-engineered autologous HSCs, have shown efficacy in treating neurodegenerative diseases through their differentiation to macrophages/microglia or/and cross correction by delivering organelles carrying the functional proteinsto the diseased cells via tunneling nanotubes. Additionally, the abundance and systemic distribution of erythroid cells was recently harnessed for high-level production of therapeutic proteins through genetically modified HSCs, in a non-hemato-

poietic disease context. Therefore, LV gene therapy with FXN-expressing HSCs could target FRDA through multiple pathways, including differentiation of HSCs into microglia/macrophages, mature erythrocytes and cross-correction.
Aims: Correcting the FRDA phenotype through ex vivo LV-HSC genetic modification could address GT limitations inherent in AAVs, providing systemic frataxin delivery. In this stage of our studies, we explore the delivery of non-toxic FXN expression and release by erythrocytes following genetic modification of HSCs.
Methods: To fine-tune FXN expression, we performed a data-driven evaluation of several erythroid enhancers with differential activity. Based on these results, we produced three FXN-expressing LVs, two carrying recently identified, erythroid enhancers (cis-regulators of PVT1 and PPARA) and one carrying the uLCR prototype enhancer. The new FXN-vectors were assessed both in immortalized erythroid (HUDEP-2) and erythroleukemia cell lines (K562) and in CD34+ cells isolated from healthy donors. A variety of functional parameters such as cell proliferation/viability, ROS, clonogenicity, differentiation capacity and morphology, were employed to investigate potential cytotoxicity.
Results: In cell lines, FXN expression increased 5-25 fold above the levels of untransduced cells with uLCR achieving the greatest fold-change with no adverse impact observed on cell phenotype or proliferation. In CD34+ cells, the three vectors significantly increased FXN expression (4.5to100-fold vs control) in a vector copy number (VCN)-dependent manner. Interestingly, the PVT1-vector led to the highest absolute FXN expression, while PPARA yielded the highest FXN expression post vcn normalization. PVT1-transfected cells also demonstrated increased intracellular FXN at day 14 of EC and elevated FXN release into the medium at day 18. Crucially, despite the substantially elevated FXN expression, genetically modified HSPCs exhibited normal clonogenic capacity and ex vivo differentiation ability with unaffected morphology, proliferation, viability, oxidative stress, suggesting absence of cytotoxicity.
Conclusions: Overall, our results suggest that LV-FXN expression in HSPCs is feasible, non-cytotoxic, and holds promise as a safe, efficient GT for FRDA. These viral vectors are currently being evaluated in FRDA animal models.

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14. PRECLINICAL VALIDATION OF CRISPR/CAS GENOME EDITING APPROACHES AS ADVANCED THERAPY FOR HBB$^{IVSI-110(G>A)}$ THALASSEMIA

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Aim of the study: β-Thalassemia, a global single-gene disorder, is caused by deficient β-globin production, with the prevalent mutation HBB$^{IVSI-110(G>A)}$ creating an aberrant intronic splice site. This mutation has a high carrier frequency in Cyprus (76%) and many EU countries (>20%). A mutation-specific gene therapy has been developed using two approaches: a DSB-dependent approach with CRISPR/Cas9 RNA-guided nuclease (IVSI-110 RGN) and a DSB-independent approach with a nearly PAM-less SpG Adenine Base Editor (SpG7 ABE). Both methods disrupt HBB$^{IVSI-110}$ abnormal splicing elements, achieving clinically relevant efficiencies in patient-derived HSCs in vitro. IVSI-110 RGN introduces indels via the non-homologous end joining repair mechanism, while SpG7 ABE uses targeted base (T>C) substitutions.

The project aims to advance these methods by conducting preclinical evaluations of edited cells both in vitro and in vivo using chimeric NBSGW mice, specifically engineered to facilitate human HSC engraftment without irradiation. The primary objective is to confirm the therapy's readiness for clinical trials, focusing on efficacy, safety, and the long-term repopulation (LTR) potential of modified cells. Additionally, the study seeks to compare the mutation-specific approach with a universal therapy targeting the erythroid BCL11A enhancer element for HbF induction (sg1617 RGN), recently FDA-approved as the first CRISPR therapy for sickle cell disease.

Methodology: RGNs and ABE were delivered via nucleofection to mobilized HBB$^{IVSI-110}$ patient-derived HSCs as ribonucleoprotein complexes(RNPs) and in vitro transcribed mRNAs, respectively. The therapeutic potential was evaluated in vitro through induced erythroid differentiation (ED) cultures, assessing correction at DNA(on- and off-targeting, Sanger sequencing), protein(RP-HPLC), and late-stage ED levels(flow cytometry), as well as clonogenic assays forerythroid and myeloid lineage potential. In vivo assessment involved xenotransplantation in NBSGW mice to evaluate LTR potential 16 weeks post-transplantation(flow cytometry).

Results: Overall, both mutation-specific genome editors let to high on-targeting (IVSI-110 RGN

85%; SpG7 ABE (T>C): IVSI-106 and -108: ~40%; -109: ~18%) with undetected off-targeting, and moderate disrutprion of erythroid BCL11A enhancer element(sg1617 RGN: ~40%). RP-HPLC analysis of the in-vitro ED cultures, showed significant increase of HBB/HBA ratios to normal levels (0.9-1) in IVSI-110 RGN- and SpG7 ABE-genome edited cellsand a significant increase of HBG/HBA ratios in the sg1617 RGN edited population (~0.51) relative to UT control (HBB/HBA: ~0.39; HBG/HBA: ~0.27). There was a clear correction of late-stage erythroid differentiation in the mutation-specific edited populations,while genome editing didn't affect erythroid and myeloid lineage potential of HSCs. Analysis of BM chimerism in xenotransplanted NBSGW mice showed high engraftment for all samples (hCD45+: 65% and hCD34+ves: ~6.5%). When comparing genome editing levels between BM bulk inputs and primary recipient BM cells, a 50% reduction was observed in IVSI-110 RGN, while sg1617 RGN showed consistent levels, and SpG7 ABE demonstrated a 20% increase.
Conclusions: Even though, analysis of the biosafety of the genome editing tools is still in progress, the current data indicates ABE SpG7 as the most promising approach for clinical application, since therapeutic levels were achieved while the erythroid and myeloid-lineage and LTR capacity of the edited HSC population was maintained.

15. GENERATION OF AN 'OFF-THE-SHELF' FOAMY VIRUS GENE-MODIFIED CD16-CR T CELL PRODUCT FOR THE TREATMENT OF HEMATOLOGICAL AND SOLID TUMOUR MALIGNANCIES

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Introduction: Novel approaches, such as the use of Fc gamma chimeric receptor (Fcγ-CR)-T cells have expanded the applicability of cell therapies in both solid and liquid tumours with the added benefit of tackling some of the hurdles associated with CAR-T therapies. Previous studies have generated Fcγ-CR-T cells from autologous cells, which carry several limitations (prolonged production time, costly, manufacturing failure), whereas the use of Lentiviral vectors (LV) is endowed with extra limitations (packaging limits and mutagenesis risk). Our group has developed an in-house Fcγ-CR-T cell product, using a safer to LV, foamy virus (FV) vector.
Materials: We constructed FV vectors expressing the CD16 V158, which has higher Fc binding, and purchased 2nd generation LV vector backbones. T cells were isolated from healthy donors, activated by CD3/CD28 beads and transduced with CD16-CR, LV or FV vectors. Transduction efficiency was assayed by flow cytometry (FCM) on day 3. The human cell lines Raji, Panc01 and DLD-1 were used for functional assays, in the presence of the antibodies (Abs) Rituximab and Cetuximab, respectively. The CR's Ab-binding capacity was assessed, as well as the cell aggregation promoted by the binding of the Ab to the CR. Their cytotoxic effect

was evaluated against the CFSE-labelled Raji or DLD-1 or Panc01 cells at different ratios (5:1, 10:1) for 18 hours, in the presence of Rituximab (0.1ug/ml) or Cetuximab (0.1ug/ml), respectively. The % of live cells was assessed by flow cytometry and calculated as: [1-live targets (sample)/live targets (control)]x100.

Results: Transduction efficiency ranged from 58.3-69.2% with FV vectors (MOI 3-5) and 85.2-85.9% with LV vectors (MOI 10-20). The median Ab-binding capacity of FV-CD16-CRs was determined to be 68.7% and 71.3%, (n=3) for Rituximab and Cetuximab, respectively, whereas that of LV-CD16-CRs was 72.1 and 76.5, (n=3), respectively. Cell aggregation of effector and target cells was: (i) 32%, 39% and 36% for FV-CD16-CRs and (ii) 26%, 31% and 29% for LV-CD16-CRs, coated with Rituximab and Cetuximab, respectively, and it was specific for the Raji, DLD-1 and Panc01 cells, respectively. Next, we assessed whether CD16-CR-T cells were able to kill target cells in the presence of specific antibodies. Results showed that the FV-CD16-CR-induced % cell lysis was: (i) 26.3% and 51.5%, (ii) 41.5% and 57.7% and (iii) 39.4% and 57.3% at 5:1 and 10:1 ratio, in the presence of Rituximab and Raji cells, Cetuximab and DLD1 cells and Cetuximab and Panc01 cells, respectively. For LV-CD16-CRs the respective % lysis was comparable. More importantly, this lysis was shown to be specific (no lysis noted with untransduced T cells) and significantly lower in the absence of the antibodies.

Conclusion: Our group has developed for the first time a FV vector for the generation of CD16-CR-T cells, with an efficient gene transfer to human T cells and with potent *in vitro* cytotoxic properties, similar to their LV-derived counterpart. Overall, we provide a proof of concept that allogeneic, in-house Fcγ-CR-T cells derived from a non-pathogenic viral backbone such as the FV, could be a safe, efficient and affordable alternative to LV-derived vectors for immunotherapy.

16. BASE EDITING TO INSTALL THE HB G-MAKASSAR IN CD34+ CELLS FROM SCD PATIENTS EFFICIENTLY IMPROVES THE DISEASE PHENOTYPE

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Background: The evolution of gene therapy has opened up new avenues for treating sickle-cell disease (SCD). These include gene addition, introducing anti-sickling β- or γ-globin genes to hinder HbS polymerization or genome editing approaches to reactivate the developmentally silenced fetal hemoglobin (HbF). However, merely expressing or reactivating anti-sickling globins doesn't address the presence of endogenous

β^s-globin, which can still compete for incorporation into the hemoglobin tetramer, limiting the overall therapeutic efficacy. Moreover, both gene addition and genome editing raise safety concerns such as the potential induction of insertional mutagenesis and genomic translocations, respectively. Recently developed base editors (BE) offer a higher safety profile compared to traditional gene editing methods, by avoiding the induction of double-strand breaks and minimizing the risks of both off-target and on-target effects. BEs can induce site-specific A>G conversions facilitating the in-situ conversion of the SCD pathogenic codon (valine, CAC) to a non-pathogenic variant of β-globin, Hb G-Makassar (HBBG-Makassar). This conversion results to the elimination of HbS which consequently prevents hemoglobin polymerization and ameliorates the disease symptoms.

Aim: The aim of this study was to develop an in vivo applicable tool for the introduction of the A>G G-Makassar mutation in SCD-donor derived CD34+ cells using a non-integrating HDAd5/35++ vector expressing a highly efficient adenine base editor (ABE8e). To further expand the transduced cells, our vector contained also an mgmt^{P140K} gene allowing for enrichment of edited cells after O^6BG/BCNU treatment.

Methods: Following 48-hour transduction with HDAd 5/35+ Makassar vector, SCD CD34+ cells were treated or not, with 50μMO^{6}BG & 35μM BCNU and seeded in erythroid differentiation (ED) medium and in methyl cellulose culture. During erythroid differentiation, cell growth and morphology were assessed. Differentiation/maturation and reactive oxygen species (ROS) levels were evaluated by flow cytometry. A sickling assay using sodium metabisulfite provided the percentage of sickling.

Results: The introduction of A>G G-Makassar mutation coupled with O6BG/BCNU to select for transduced cells, significantly improved the cells' growth rate (fold expansion: 10±0.1 versus 4.81±0.21 control group, $p=0.009$) as well as clonogenic capacity ($p<0.05$). The increased production of G-Makassar β-globin led to significant reduction of ROS levels in GlyA+ cells, a hallmark of SCD (MFI: 3783±242 versus 12220±1729 control group, $p=0.008$) and corrected the morphology of patients' erythroid cells in cytospins. The improved phenotype was also manifested as significantly increased percentage of terminal differentiated erythroid cells (%GlyA+/NucRed- cells) ($p=0.01$) and decreased sickling of the transduced/selected cells (% sickling: 19.74 ±3.59% versus 48.95±3.44% control group, $p=0.004$).

Conclusion: Overall, we present an alternative, effective method of precise genome editing for SCD by indirect repair of the causal mutation using an HD Ad5/35++-BE, thus potentially overcoming critical obstacles to clinical translation of gene editing for sickle cell disease.

ORAL PRESENTATIONS

17. IDENTIFICATION OF NOVEL γ-GLOBIN REPRESSORS THROUGH A CUSTOM CRISPR KNOCKOUT SCREEN AND VALIDATION OF THESE REPRESSORS FOR THE TREATMENT OF β-HEMOGLOBINOPATHIES

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Introduction: Haemoglobinopathies, a group of conditions affecting haemoglobin, result from mutations in the HBB gene, leading to prevalent monogenic disorders such as β-thalassaemia and sickle cell disease. Reactivating the γ-globin gene for fetal haemoglobin (HbF) production emerges as a promising therapeutic strategy. However, current gene therapy approaches face limitations in terms of risks, costs, and accessibility. Additionally, pharmacologically targeting key regulators BCL11A and LRF (ZBTB7A) proves challenging due to their involvement in the regulation of non-erythroid genes. Identifying new factors amenable to pharmacological control is crucial for effective treatment of β-haemoglobinopathies.

Materials & Methods: Building on a prior custom CRISPR/Cas9 knockout screen targeting 293 genes, this study focuses on validating candidate genes associated with the screening phenotype, specifically HbF upregulation. Two candidate genes were selected for in-depth investigation. CRISPR/Cas-mediated knockouts were conducted through lentiviral transduction and nucleofection with ribonucleoproteins.

hCD34+ cells were isolated from peripheral blood using magnetic-activated cell sorting. Nucleofections involved two single and one double nucleofection per candidate gene, aiming to enhance disruption efficiency. Nucleofected cells were expanded, and erythroid differentiation spanned 11 days, with cell collection on the final day. HPLC analysis was used for assessing the levels of globins in the samples. Furhter, the HPLC analysis was quantified in order to detect the ratios of β/α and (Gγ+Aγ)/α.

Results: The CRISPR/Cas-mediated knockdown of Gene A demonstrated a more pronounced upregulation of γ-globin compared to Gene B. Remarkably, employing a double nucleofection strategy for both Gene A and Gene B resulted in a more significant increase in γ-globin levels compared to the individual knockdowns. The observed increase in γ-globin levels with the double nucleofections highlights the potential for independent contributions of Gene A and Gene B to γ-globin regulation. Further dissection of their individual mechanisms is necessary for a comprehensive understanding of their roles in γ-globin modulation.

Discussion & Conclusions: This project lays the groundwork for potentially validating new HbF regulators identified through a CRISPR-knockout screen. Ongoing investigations into the mechanisms of Gene A and Gene B, particularly their impact on HbF upregulation in hCD34+ cells, hold promise for identifying novel therapeutic targets. The outcomes may contribute to innovative strategies in treating β-haemoglobinopathies, offering significant advancements in genetic therapies for these inherited monogenic disorders.

ORAL PRESENTATIONS

18. THE SMALL MOLECULE UM171 AS A POTENTIAL NOVEL, FETAL HEMOGLOBIN INDUCERFOR THE TREATMENT OF β-HEMOGLOBINOPATHIES

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Aim of the study: A considerable interest has been generated for developing therapeutic strategies for hemoglobinopathies through fetal hemoglobin (HBF) induction, as the increased production of HbF can ameliorate the severity of β-hemoglobindisorders. These strategies involve either drug modulation or gene therapy. The small molecule UM171, has been shown to expand hematopoietic stemcells (HSCs) ex vivo while restricting their differentiation by targeting the Lysine-Specific Histone Demethylase (LSD1)-CoREST complex. In a different context, LSD1 inhibitors were shown to induce HBF expression with comparable activity to decitabine, a powerful pharmacological HBF inducer. Based on this evidence, we aimed to explore any possible interconnection of UM171 and HbF induction.
Methods: CD34+ cells derived from mobilized peripheral blood of healthy or thalassemic donors were expanded in the presence of escalating concentrations of UM171 (35-250nM) for 7 days and then cultured towards erythroid differentiation in medium supplemented with erythropoietin. The effect of UM171 on the expression of erythropoiesis-associated genes was assessed by qPCR arrays. The phenotype of early- and late-stage differentiation erythroid cells and HbF levels were assessed by flow cytometry. LSD1 protein expression was evaluated by Western blot analysis.
Results: As expected, UM171 significantly expanded primitive subsets of human HSCs (CD34+/CD38-, CD34+/CD38-/CD90+, CD34+/CD45RA-/CD133+) on day 7 over their input on day 0 and as compared to the control (DMSO) ($p<0.001$). Targeted mRNA analysis showed that UM171 significantly down-regulates master transcription factors and genes regulating erythropoiesis including *GATA1, KLF1, LMO2, E2F4* (p≤0018) and *PKLR* (p≤0.045). UM171 also repressed erythroid markers such as CD36 and CD105 (ENG, endoglin) (p≤0.03). Consequently, UM171 treatment of CD34+ cells delayed their erythroid differentiation at an early time point (day 4 of erythroid differentiation culture), as compared to DMSO control in terms of CD235a and CD71 expression (CD235a%: 2.90±0.63 vs 14.23±1.62, p<0.0001, respectively / CD71%: 5.8±0.3 vs 42.4±2.2, p=0.045, respectively), although by the end of the erythroid differentiation culture, the expression levels did not differ over control. Cytospin preparations verified the delayed erythroid differentiation of the UM171-treated cells over control cells, displaying predominance of early proerythroblasts. Interestingly, UM171 induced HbF expression both in healthy and thalassemic erythroid cells vs the DMSO control (CD34+ thalassemic UM171: 57.6% DMSO: 37.3%, p=0.068 and CD34+ normal UM171: 17.8%, DMSO: 4.2 %, p=0.016). Mechanistically,

the HbF increase was associated with inhibition of LSD1 by UM171, as it was implicated by the decreased LSD1 protein expression levels in the UM171-treated cells.
Conclusions: Our findings provide preliminary evidence supporting UM171 as a potent HbF inducer in addition to its capacity to maintain the HSC phenotype during ex vivo expansion. Although further studies are needed to fully elucidate the molecular mechanism involved, our data implicate that UM171 as monotherapy or in the context of gene therapy, could play an essential role in the treatment of hemoglobinopathies.

19. EPIGENOME EDITING RESULTS IN EFFICIENT HBF REACTIVATION IN CD34+ CELLS OF PATIENTS WITH BETA-THALASSEMIA

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Background: Significant progress in the field of genome editing has recently enabled the development of innovative gene therapy strategies including the targeted correction of point mutations or the introduction of disease-modulatory mutations. In beta-hemoglobinopathies specifically, perturbation of fetal hemoglobin (HbF)-transcription modulators via genome editing has enabled the therapeutic reactivation of gamma globin. Despite the successful preclinical and clinical application of such methods so far, limitations related to the induction of genomic double strand breaks still exist. Recently, the development of less invasive, custom-designed epigenome editors (epi-editors) has allowed the introduction of specific epigenetic alterations to tightly regulate gene expression, without affecting genome integrity.
Aim: The scope of the current study was to assess the safety and efficacy of the HbF reactivation in human primary cells, mediated by novel epigenome editing tools.
Methods: Initially, a HUDEP-2 cell line stably expressing a deactivated Cas9 protein (dCas9) fused with the Krüppel-associated box (KRAB) effector domain, was established. Subsequently, single guide RNAs (gRNAs) were designed targetingcis-regulatory elements of three genes—LRF, BCL11A, and ZNF410—known askey HbF-suppressors. Following transduction with each lenti-gRNA vector, the growth rate and the HbF levels of the HUDEP-2-dCas9-KRAB cells were assessed at different time points. Toconfirm the safety and efficacy of the approach in human primary cells, an all-in-one lenti-viral vector was generated containing both the dCas9-KRAB domain and the most effective gRNA. After transduction, CD34+ cells from normal and thalassemic donors, were differentiated ex vivo towards the erythroid and granulocytic-monocytic lineage in suspension or semi-solid cultures. Clonogenic capacity was assessed 14-days post

transduction. During ex vivo differentiation cell proliferation, cell differentiation and maturation, oxidative stress and HbF levels were evaluated.

Results: Combining dCas9-KRAB with the respective gRNAs led to efficient suppression of *ZNF410*, *LRF* and *BCL11A* expression that was translated into significantly increased gamma globin levels within the transduced populations. Among the three targeted transcription factors (TFs), epigenetic silencing of *ZNF410* induced higher levels of HbF+ cells over the other two TFs (ZNF410: 36±5.6%, LRF: 31.8±2.11%, BCL11A: 25.7±2.07% versus 16±2.5% HbF+ cells in the control group, $p \leq 0.05$). In subsequent experiments in primary cells, we designed and generated an all-in one lenti-vector, carrying both the dCas9-KRAB effector and the most effective gRNA targeting the *ZNF410* promoter. Epigenomic suppression of *ZNF410* in both normal and thalassemic CD34+ cells, using the all-in one lenti-vector had no effect on cell proliferation, clonogenic capacity or the differentiation/maturation process. Importantly, the *ZNF410* epigenetic silencing increased the percentage of HbF+ at the end of the erythroid differentiation in both normal (%HbF+ cells: 61.4±0.56% versus 48.1±2.2%, $p=0.004$ in the control group) and thalassemic cells (%HbF+ cells: 29.05±1.25% versus 15.3±3.4% in the control group). Additionally, the HbF reactivation in thalassemic group resulted in reduced oxidative stress (ROS MFI: 4807±110 versus 5697±192.5 in the control group).

Conclusions. Overall, our findings indicate for the first time the feasibility of the epigenetically mediated suppression of gamma globin regulators leading to efficient HbF induction both in normal donor and beta-thalassemia patient derived cells, without apparent toxicity.

POSTER ABSTRACTS

POSTERS

P1. MIRK/DYRK1B KINASE IS INVOLVED IN NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neurons (MNs) degeneration.

Aim: Here, we used SOD1^{G93A} mice to investigate the role of Mirk/Dyrk1B kinase in ALS. We previously demonstrated that in the embryonic chick spinal cord (SC), Mirk/Dyrk1B regulates the generation and survival of MNs and V2A interneurons and additionally affects the LMCm motor column which innervates ventrally the muscles of the limbs. Notably, MNs and V2A are firstly affected in the spinal cord of SOD1^{G93A} mice.

Methods: To investigate Mirk/Dyrk1B function, we developed a primary culture protocol enriched for spinal MNs (SpMNs) isolated from E12.5 mouse SC.

Results: We revealed that SpMNs derived from E12.5 SOD1^{G93A} mice exhibit significantly shorter and fragmented axons compared to WT, indicating an early axonopathy. Dyrk1B pharmacological inhibition by AZ191 increased the axonal length of both E12.5 WT and SOD1^{G93A} and rescued the axonal phenotype of SOD1^{G93A}SpMNs. Moreover, AZ191 inhibitor reduced the apoptosis of SOD1^{G93A}SpMNs, suggesting a neurotrophic and anti-apoptotic effect following Dyrk1B inhibition. Finally, in the lumbar SC of P140 SOD1^{G93A} mice (late-stage of the disease), where neuroinflammation is prominent, Dyrk1B is expressed by an increased number of astrocytesand microglia by 3.84-fold and by 8.45-fold respectively, implicating thus Dyrk1B in neuroinflammation.

Conclusions: Our results render Mirk/Dyrk1B a potential drug target in ALS.

P2. CORRECTION AND INTEGRITY OF DUPLEX BASE EDITING FOR FETAL HEMOGLOBIN INDUCTION IN B-HEMOGLOBINOPATHIES

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Introduction/Aim: Beta-haemoglobinopathies are the most common monogenic diseases. Of these, β-thalassemia results from decreased (β$^+$) or absence (β^0) of β-globin chain pro-

duction, causing hemolysis and ineffective erythropoiesis. Elevated γ-globin levels, the fetal hemoglobin (HbF, $\alpha_2\gamma_2$), confer major clinical benefits in β-thalassemic patients. Recent research demonstrates that targeting β-thalaseemia modifiers such as *BCL11A* and *HBG* genes, enhances γ-globin expression. Genome editing tools show therapeutic promise such as base editors (BEs) which are safer and likely more efficient than traditional DSB-dependent CRISPR/Cas technology. However, safety concerns regarding chromosomal aberrations still remain a risk. The project aims to adopt BEs for simultaneously editing both *BCL11A* erythroid enhancer and *HBG* promoter for correspondingly increased clinical potential and investigate the potential of genomic alterations using CAST-Seq analysis.
Methods: In this study, the HUDEP-2 cell-line and patient-derived $CD34^+$ cells were used. Cells were nucleofected with three different guide RNAs (gRNAs) for single or double target editing. Editing efficiency and functional studies at the DNA, RNA, and protein level were conducted. Lastly, CAST-Seq analysis was performed, for the assessment of chromosomal aberrations.
Results: A successful double base editing protocol was established resulting in high editing efficiency after targeting both *BCL11A* and *HBG* loci. Our study reveals that multiplex base editing of both *BCL11A* enhancer and *HBG* promoter (2xBE) in patient-derived $CD34^+$ cells induces robust γ-globin and HbF induction reaching to 56.86% HbF increase, indicating a potential therapeutic benefit of 2xBE approach. Our study shows that single and, most importantly, double base editing offers a safe editing option, resulting in a low incidence of genomic alterations in these therapeutically relevant target loci.
Conclusions: In this pioneering study we demonstrate the effectiveness of multiplex base editing targeting both, *BCL11A* and *HBG*loci. This approach induces potent fetal hemoglobin with negligible chromosomal aberrations, highlighting the therapeutic potential and safety benefits.

P3. PROCESS DEVELOPMENT FOR GMP-COMPLIANT PRODUCTION OF ADIPOSE-DERIVED MESENCHYMAL STROMAL CELLS AS OSTEOARTHRITIS TREATMENT

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Purpose of the study: Osteoarthritis (OA) is a degenerative disease of the joint affecting more than 240 million people worldwide. In OA, cartilage tissue degrades over time leading to chronic pain, joint stiffness and eventually disability. The pathogenesis of OA is linked to synovitis and chronic low-grade inflammation fueling a vicious cycle of cartilage damage. Adipose-derived Mesenchymal Stromal Cells (ADMSCs) hold great potential as a treatment for OA and other maladies and have been used in many clinical trials but also as unproven therapies globally. ADMSCs are considered to possess immunomodulatory properties acting in a paracrine fashion in the damaged joint by producing various growth factors and cytokines which induce local tissue repair and cartilage regrowth, leading to functional improvement. The purpose of Theracell Laboratories was to develop a GMP-compliant process for an

autologous MSC advanced therapy medicinal product (ATMP), using a minimally invasive lipoectomy as starting material while the final product is tested by a variety of assays (matrix approach) to ensure identity, safety and quality.

Methodology: For each batch produced, ~1 gr of adipose tissue was obtained by lipoectomy without hospitalization, after patient's informed consent, and was collagenase-digested. ADMSCs were isolated and cultured for two weeks using RUO or GMP-grade materials, employing either open-system adherent Cell Factory 2D culture or alternatively, the automated closed-system NANT-XL Bioreactor with its single-use cartridges. Upon harvesting of final product, flow cytometry was performed for the classical ISCT minimal criteria markers CD73/CD90/CD105. Trilineage differentiation capacity was demonstrated by Alcian Blue staining (chondrocytes), Alizarin Red (osteoblasts) and Oil Red O (adipocytes) after culture of ADMSCs in appropriate differentiation media. To probe functionality regarding the purported Mechanism of Action in OA, relevant potency assays were developed, including detection of IFNγ-inducible markers like HLA-DR, CD40 and IDO1 ("licensed" phenotype) by antibody staining or detection of secreted factors by ELISA, like IL-6 and TGFβ.

Results: After 2 weeks of culture the ADMSC cell yield was typically more than 50e-6. Cell duplication time was reduced from a mean of 2 days with RUO media to less than 24h when GMP-grade media were used, while trilineage differentiation potential was maintained. Furthermore, identity was verified by FACS for the expression of the ISCT minimal MSC markers. After licensing, ADMSCs began expressing HLA-DR ranging from 10-80% and CD40 ranging from 5% -100% positive cells. IDO1 intracellular expression peaked after 48h post-stimulation reaching 100% positivity. Absence of microbial contamination was verified for both the open-system and the bioreactor produced batches.

Conclusions: In summary, a robust GMP compliant process was developed for ADMSCs manufacturing resulting in high cell yield and rapid population doubling time. Produced cells satisfied all minimal ISCT criteria for MSCs. After licensing, ADMSCs expressed potency markers like HLA-DR, CD40 and IDO1 and secreted immunomodulatory factors. A matrix approach for Quality Control testing of the final product has been developed and an automated bioreactor system has been tested and its protocol was optimized. This paves the way for clinical translation of ADMSCs from a Greek biotech.

P4. THE ROLE OF GEMC1 AND MCIDAS TOWARDS CELLULAR REPROGRAMMING TO EPENDYMAL LINEAGE

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Hydrocephalus is a neurological condition which often results from impaired cerebrospinal

fluid (CSF) clearance, caused by either genetic mutations or environmental factors, like infections. Consistent findings in the disease are defects in multiciliated ependymal cells, which are ciliated-epithelial cells lining the brain ventricles, regulating CSF circulation and brain homeostasis. Current treatments involve repeated surgical procedures such as shunt placement or endoscopic third ventriculostomy (EVT), which only temporarily relieve the disease's symptoms. Therefore, there's a pressing need for more effective therapies.
In response to the increasing necessity of developing efficient therapeutic strategies, pluripotent stem cells have been characterised by researchers for their pluripotency and ability to differentiate into a desired cellular lineage by the method of reprogramming. However, direct reprogramming enables the cell fate conversion from one lineage into another without transitioning through an intermediate pluripotent state. In this respect, the reprogramming capacity of differentiated resident cells at the site of damagehas started to be exploited in the field of regenerative medicine. Astrocytes occupy a large area on the brain cortex and are activated during brain injury and in hydrocephalus, creating a protective barrier between the brain ventricles and the CSF, rendering them an ideal cell population for reprogramming. The effectiveness of reprogramming depends greatly on the choice of pioneer factors associated with the desired cell type. Our laboratory has extensively characterised GemC1 and Mcldas as the earliest factors to contribute to the fate commitment of neural progenitor cells towards the ependymal lineage. Our objective is to decipher the role of GemC1 and Mcldasin reprogramming of mouse embryonic stem cells (mESCs) and astrocytes into ependyma. Our results reveal that both GemC1 and Mcldas promote the early steps of differentiation towards ependyma of both mESCs and murine astrocytes. More specifically, overexpression experiments showed that Mcldas and GemC1 upregulate the expression of different ependymal markers (p73, Pericentrin, acetylated α-tubulin), revealing that both factors can induce the differentiation of mESCs towards the ependymal lineage. In addition, after lentiviral infection of isolated murine cortical astrocytes with lentiviral vectors encoding Mcldasor GemC1, it was observed that these cells exhibited fate alteration competency from an early timepoint. Our study shows that both factors were capable of downregulating the astrocytic characteristics in transduced astrocytes and upregulating early ependymal markers. At a later timepoint, it was detected that Mcldas can more efficiently induce the reprogramming of those murine astrocytes to the ependymal lineage, compared to GemC1, based on the generation of multiple centrioles, a unique characteristic of the ependymal cells. Finally, live imaging analysis revealed that the Mcldas-transduced reprogrammed astrocytes acquired functional motile cilia. Overall, our results show that direct reprogramming towards the ependymal lineage mediated by Mcldas and GemC1 expression could provide new evidence for the creation of new therapeutic approaches against neurological disorders such as hydrocephalus.

POSTERS

P5. SINGLE NUCLEUS RNA SEQUENCING ANALYSIS COMBINED WITH IN VITRO VALIDATION IN ENGINEERED DOPAMINERGIC NEURONS REVEALS ASPECTS OF IDIOPATHIC PARKINSON'S DISEASE PATHOLOGY

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The number of cases of Idiopathic Parkinson's disease (IPD) has doubled in the past 25 years, with this increase expected to continue its rapid incline, as the population ages. During the disease's onset, a variety of clinical symptoms gradually arise, including both motor and non-motor, the latter manifesting earlier, before an observation of the motor symptoms or an exact diagnosis can be made. Nonetheless, our understanding of the exact molecular mechanisms associated with the generation and progression of this disease has yet to be fully understood. To gain detailed insights into IPD cellular pathology,we utilized a publicly available dataset and analyzed 41,435 single-nuclei transcriptomes of post-mortem midbrain fromIPD patients (*n=6*) and healthy donors (*n=5*). Overall, alteration in a plethora of subtypes was observed, with oligodendrocytes, microglia, and dopaminergic neurons (DaNs) being the more substantial ones. Differential analysis of activated transcription factors revealed dysregulation of dopaminergic-related TFs in IPD samples, with *NR4A2* being one of the most evident ones. Similarly, Trail and p53 pathways were significantly altered, indicating a malfunction in pathways associated with cell death. To validate these results *in vitro*, we generated anIPD-like cellular model of human DaNs that inducibly expressed the *EYFP-SNCA WT* transgene. Specifically, human neural progenitor cells (hNPCs) were stably transfected with the TetOnEYFP-SNCA WT cassette and directly differentiated into midbrain dopaminergic neurons. Interestingly, the generated DaNs exhibited high levels of tyrosine hydroxylase (*TH*), dopamine transporter (*SLC6A3*), and vesicular monoamine transporter 2 (*SLC18A2*). Additionally, they were characterized by the absence of lipoprotein lipase (*LPL*) and the increased expression of Aldehyde Dehydrogenase 1(*ALDH1A1*), a pattern specific to IDP-prone DaNs. After inducible expression of *EYFP-SNCA WT* for 5 days, DaNs exhibited a significant activation of apoptosis as well as impairment in the patterns of transcription factors involved in dopaminergic neuron maintenance, particularly that of *NR4A2*, which was also found to be dysregulated in our computational analysis. Our findings propose a potent workflow where a combination of snRNA seq technology along with *in vitro* validation in a cellular model might reveal crucial aspects of IPD pathology.

POSTERS

P6. UNRAVELING THE ROLE OF MCIDAS IN MULTICILIOGENESIS AND E2 EPENDYMAL CELL GENERATION

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Ependymal cells (ECs) are ciliated epithelial glial cells developed from radial glia, lining the brain ventricles. Multiciliated ECs are the larger population of ECs and play a crucial role in cerebrospinal fluid flow, while their absence is related to neurodevelopmental conditions, such as hydrocephalus. A very rare subpopulation of ECs is E2 cells, which have only two large basal bodies bearing two cilia. Due to their rarity, their function and origin remains unknown. The commitment of cells towards the ependymal lineage is mediated by a strictly regulated molecular pathway that coordinates the generation of multiple basal bodies and ciliogenesis. McIdas has been identified as a crucial regulator of multiciliogenesis in different organisms and systems. Our data provide evidence that upon McIdas deletion, progenitor cells commit to the EC fate, as they still express p73 and Foxj1, both necessary for differentiation and maturation to EC lineage. However, they are unable to produce multiple basal bodies and thus multiciliated ECs are not generated, leading to hydrocephalus development in McIdas mutants. Instead, a larger number of biciliated cells, showing characteristics of E2 ECs, such as two large basal bodies bearing only two cilia, are generated, indicating that McIdas is implicated in their formation. In conclusion, although McIdas is not required for the progenitors' commitment towards the EC fate, it is critical in regulating the early stages of multiciliogenesis, and therefore affects the balance between multiciliated and biciliated EC subpopulations. Such insights into the specific mechanisms governing multiciliogenesis set the foundation to genetically modify E2 ECs to differentiate to multiciliated ECs. This could potentially result in restoration of ciliary function within the brain ventricles, offering new avenues for hydrocephalus treatment strategies.

POSTERS

P7. GENERATION OF INSCS FROM PATIENTS WITH FAMILIAL PARKINSON'S DISEASE FOR PERSONALIZED DISEASE MODELING

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Parkinson's disease (PD) is the fastest-growing neurological disease, affecting approximately 10 million people worldwide. Distinct types of PD emerge due to aging, genetic mutations or environmental factors, with each one exhibiting heterogeneity in the age of onset and symptom progression. However, all patients rely on a uniform treatment, levodopa re-adjustment, which has also remained the same for decades. A critical barrier to the development of efficient therapies may be the lack of disease-relevant models, representative of each type of PD. Here, we describe the generation of cellular models from patients with a familial form of PD caused by the p.*A53T* mutation in the *SNCA* gene. Peripheral blood mononuclear cells (PBMCs) of p.*A53T* mutation carriers (n=3) and age/sex-matched controls (n=3) were infected with non-integrating Sendai viruses (SeVs) expressing *c-Myc* and *Sox2* and trans-differentiated into induced neural stem cells (iNSCs). Due to this direct cell-fate transition, iNSCs partially maintain the epigenetic profile and the biological age of donors. Reprogramming factors were subsequently removed, resulting in transgene-free iNSCs and thus, eliminating the risk of tumorigenesis. In general, the reprogramming protocol is rapid, resulting in high numbers of iNSCs in less than three months and efficient, as cells can be differentiated into neuronal populations. A detailed characterization of the generated cell lines will reveal the differentiation potential into midbrain dopaminergic neurons, the PD-prone neuronal population. Additionally, several tests will assess epigenetic profile, thus an approximate age of cells. Importantly, iNSCs can be used for the *in vitro* personalized modeling of PD in human patients and the identification of new therapeutic targets.

P8. INTEGRATION OF DIVERSE PLATFORMS TO DEFINE LOCAL MECHANISMS AND LONG-RANGE SIGNALS THAT MEDIATE INTER-ORGAN COMMUNICATION AFTER INJURY AND DURING REGENERATION

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A plethora of clinical studies have described how disorders of the brain and/or heart affect

the other organ. However, our inability to explain the molecular mechanisms that regulate such inter-organ communication in both homeostatic and post-traumatic conditions is a major obstacle to effective disease prognosis and treatment.
In this study, we use the zebrafish as a model organism due to its excellent regenerative capacity for several organs, including the brain and heart. With an integrative approach that combines i) different models of brain (stab lesion) and heart injury (cryoinjury and chemogenetic ablation), ii) advanced imaging techniques in combination with tissue clearing, iii) transcriptome analysis (RNAseq), and iv) diverse functional readouts, we aim to map cellular responses in the respective organ and isolate candidate signaling molecules. To further identify mediators of intra-organ communication, we investigate brain and heart exosomes under homeostatic and post-injury conditions. The role of candidate signaling molecules that are currently identified via RNA sequencing and the characterisation of exosome cargo, are functionally verified i) *in vitro* in primary cultures of adult mouse cardiac fibroblasts and neonatal cardiomyocytes and ii) by generating novel zebrafish transgenic lines that allow for tissue-specific manipulation.
We propose that identifying the mechanisms underlying brain-heart interactions in zebrafish could reveal targets for reprogramming homologous pathways in mammals with implications for regenerative medicine.

P9. COMPARISON OF UMBILICAL CORD BLOOD DERIVED PLATELET CONCENTRATE GEL WITH AUTOLOGOUS PLATELET CONCENTRATE GEL FOR THE TREATMENT OF CHRONIC DIABETIC FOOT ULCER

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Aim of this study is to compare the healing capacity of platelet concentrate (PC) gel derived from Umbilical Cord Blood (UCB) units unsuitable for transplantation versus the respective derived by autologous Peripheral Blood (PB), in patients with chronic diabetic foot ulcer. The study has been approved by the Scientific and Ethics Committee of the University Hospital of Heraklion (716/13-07-2022).
Method: Until now, eight patients have completed the study protocol. The patients were distributed in two groups. Patients in group A *(n = 4)* received autologous PC gel while patients in group B *(n = 4)* received UCB derived PC gel. The rate index of ulcer reduction parameters (perimeter, area, diameter) was evaluated using the noncommercial software "ARCHYTAS" and 2D digital planimetry based on the digital images of the ulcers in defined time-points.

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In this study we report healing rates taking into account reduction of the ulcer size parameters during the last 2 gel applications. We also evaluated the levels of the growth factors Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), and Platelet-Derived Growth Factor -BB (PDGF/BB) in the UCB-derived PC gel and autologous PC gel, using commercially available ELISA kits Statistical analysis was performed by

Results: We found that the UCB-derived PC gel displays at least similar ulcer healing capacity compared to autologous PC. In particular, the average percentage rate index for the area of the ulcer were 7,26% for group A and 8,9% for group B (p=0,4857), for the diameter were 15,5% and 29,8% respectively (p=0,3714), while for the perimeter were 16% and 29,3% respectively (p=0,3471).The concentration of the VEGF is statistically higher in UCB than in PB (P=0.0328). The concentration of the PDGF/BB in autologous PB PC is higher than in UCB PC (P=0.0096). No significant differences were found in EGF levels.

Conclusion: So far we have shown that the ulcer healing capacity of the UCB PC gel is equal to that of the autologous PC gel. Therefore, we have shown that the unsuitable for transplantation UCB units can be successfully used in this generative medicine application, enhancing further the value of this important biologic material.

P10. AN ARTIFICIAL NEURAL NETWORK FOR VIRTUALLY INCREASING THE SAMPLE SIZE OF CLINICAL STUDIES

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Purpose of the study: Determining the appropriate sample size is of pivotal concern in clinical studies, since small sample sizes may be incapable of detecting true effects (Wang et al, 2020). Not only does sample size impact accuracy and reliability, but it also directly influences the associated costs and time investments in a clinical trial, not to mention the ethical concerns that arise because of the participation of humans. Data augmentation emerges as a pivotal technique in this context, facilitating the generation of synthetic replicas of existing datasets through utilization of previously collected data (Papadopoulos et al., 2023). This study introduces a novel approach aimed at diminishing sample size requirements in clinical trials through the utilization of Artificial Neural Networks (ANNs). The primary objective of this investigation is to illustrate how artificial intelligence techniques can be employed to generate "virtual patients", thus reducing reliance on real patient data and offering a potential solution to the challenges associated with small sample sizes and human exposure in clinical research settings.

Methodology: Monte Carlo simulations served as the basis for generating random normal distributions representing two extensive patient populations, each comprising 10,000 individuals undergoing distinct interventions: treatment A and treatment B. Subsequently, the

distributions underwent preprocessing, involving standardization (z-scores). Following the conventional clinical trial methodology, a small sample size (consisting of either 50 or 100 patients) was randomly selected, whereupon ANNs were applied, leveraging information extracted from this subset. Statistical analysis followed, utilizing the classical t-test to compare the two interventions (A and B). Then, a comparative analysis was conducted between the outcomes obtained from the "virtual patients", the sampled subset, and the original (large) population. A novel evaluation metric termed "similarity" was introduced to capture the correspondence between the statistical results derived from: a) the population versus the sample and b) the population versus the generated population. Multiple scenarios were meticulously developed and evaluated, encompassing diverse real-world scenarios such as variations in the mean difference between the populations and fluctuations in measurement variability.
Results: Across all tested scenarios, the integration of the ANNs and the corresponding generated population consistently yielded superior outcomes compared to those obtained from the sampled subset. It is worth mentioning that the t-test evaluation demonstrated a higher rate of success or an equal one for the generated population relative to the population. The 0.5% sampling strategy exhibited more favorable outcomes compared to the 1% sampling approach. Finally, the 0.5% sampling exhibited a smaller maximum absolute difference between the means of the generated populations and the populations (0.06 units) compared to the 1% sampling (0.18 units).
Conclusion: The present study exhibits a pioneering initiative leveraging artificial intelligence within the realm of clinical trials by harnessing the power of ANNs to generate virtual subjects, thereby mitigating the necessity for human participation. This methodology holds immense potential across various ways in clinical settings, offering compelling advantages such as substantial cost savings, resource efficiency, accelerated completion, ethical considerations, feasibility, enhanced participant diversity, precision in estimates, and flexibility in design.

P11. IS THE AMAZING REGENERATIVE ABILITY OF AUTOLOGOUS ADMINISTRATED FIBROBLASTS DISPUTABLE?

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The Purpose of this Study: The administration of autologous fibroblasts in ulcers of diabetic foot patients does not have successful healing results in certain cases. This fact prompted us to investigate the reasons. We suspected two causes might be responsible which either co- exist or stand separately: a) There was not proper elimination of microbiological load in the area of ulcer and b) Unsatisfactory regulation of glucose level.

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Patients and Method: We selected 12 (among 178) patients whose the process of their ulcers' healing was very slow or somehow has started and then stopped. The patients were re-examined thoroughly by their physicians and our suspicions were verified: 5 patients had insufficient regulation of blood glucose (they constituted the group "bad regulation"), 4 had chronic infection (the group "infection") of their ulcers which demanded special care and 3 combined the two mentioned above statuses ("combined statuses"). After a considerable period of time the caring doctors managed to have results in the normal level. Then we followed the procedure which we described in two previous studies published. (Burn 33(6)791-2, 2007 and British Journal of Medicine and Medical Research, 3(4):1507-1516, 2013).

In brief: We took a small biopsy of healthy tissue from each patient, we isolated the fibroblasts and we cultured them for approximately 25 to 30 days. Then we injected the produced cells in the edge of the ulcers' surrounding healthy tissue.

Results: The attempt succeeded for 4 in 5 patients from the group "bad regulation", 3 in 4 from the group "infection" and 1 in 3 from the group "combined statuses". Comparing the healing's rate of the rest patients with the healing's rate of patients without problems during the process, we did not find any difference.

Conclusions: Although we had four failures among (12), we believe that the healing power of fibroblasts is undisputable after the control of the glucose regulation and the treatment of infection. We attribute the failures to the style of life of the patients. In support of the above we are presenting additionally, three diabetic patients who underwent kidney transplantation, under immunosuppressive therapy. We must emphasize that bibliography maintains that efforts to cure such patients' ulcers are in vain. Despite the disappointing prognosis our patients were cured.

Diabetic patient immunosuppressive after kidney transplantation

LECTURES’ ABSTRACTS

LECTURES

FUNCTIONAL ENRICHMENT ANALYSIS OF GENOMICS & TRANSCRIPTOMICS DATASETS USING MULTIPLE SOURCES: THE FLAME 2.0 ENRICHMENT ANALYSIS PIPELINE

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Functional enrichment analysis is the process of identifying the most over-represented biological functions, pathways, diseases, or phenotypes where groups of genes or proteins are involved. This type of analysis can aid researchers in revealing biological insights from genomics and transcriptomics experiments, and interpreting gene lists of interest in a biologically meaningful way. To this end, several applications have been developed, enabling the annotation of gene and protein datasets. However, most of the currently available enrichment tools and services are limited to very specific sets of organisms and annotation sources; at the same time, each tool presents its result in vastly different formats, making the comparison and testing of different enrichment methods more difficult. Flame (v. 2.0) is a web tool which offers a combinatorial approach through merging and visualizing results from multiple functional enrichment applications while also allowing various flexible input options. In its current version, Flame supports functional enrichment annotation for more than 14,000 different organisms, using resources such as Gene Ontology, metabolic pathways and disease databases, and allows for the generation of interactive visualization schemes for the advanced analysis and interpretation of biomedical data.

PROTEOMICS

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The proteome is the link between genotype and phenotype and its determination provides understanding of processes governing health and disease. Mass spectrometry-based proteomics is today the primary method used for the characterization of the proteome. An overview of the latest developments in the field of quantitative bottom-up proteomic approaches will be presented in respect of sensitivity, speed, robustness, and proteome coverage. Analysis of how to characterize protein posttranslational modifications will be discussed as mass spectrometry is the most powerful tool for this. Finally, the major technological advances permitting single-cell proteomics analyses together with potential applications will be presented.

LECTURES

FINE-TUNING THE FUTURE: PRECISION EDITING METHODS AS PIONEERING THERAPEUTIC STRATEGIES

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A growing molecular tool kit comprising classical genome editors based on DNA double-strand breaks and DSB-independent DNA editors is revolutionizing therapy development. As the first approved products enter the market, discovery and design point the way forward with new molecular and delivery approaches for higher efficiency and safety. Progress is particularly swift for readily accessible cells and tissues, which often showcase new technologies. The present talk touches on some corresponding results of our department and on the latest achievements and trends in gene editing for the therapy of human diseases

FROM DATA TO DISCOVERIES: AI-POWERED STRATEGIES

Grigoris Georgopoulos
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We live in the era of big data, where advances in genome sequencing technologies have enabled the generation of vast biological data at a fraction of the cost. However, it is impossible to parse such an amount of data relying solely on human capabilities. Recent advances in artificial intelligence have empowered algorithms with the ability to parse and extract meaningful information and patterns from massive data sets. Although the field of gene therapy has been since its inception at the forefront of precision medicine, we are now falling behind in leveraging advances in other fields. In this lecture we will review examples of how artificial intelligence has been transforming fields tangential to gene therapy such as genomics, cell biology, structural biology, drug discovery and precision medicine. Additionally, we will learn how to explore databases hosting a wealth of data critical to the field of gene and cell therapy enriching our understanding of key biology mechanism underpinning the development of advanced medicinal products.

NEURODEGENERATIVE DISEASE MODELING USING INDUCED NEURAL-STEM CELLS

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Since the development of the reprogramming technology by Prof. Dr. Yamanaka, researchers can reprogram terminally-differentiated somatic cells into induced pluripotent stem cells (iPSCs). These cells are generated by the forced expression of specific transcription factors

and can be differentiated into patient-specific neurons for modeling of human neurodegenerative diseases. The process for the generation of iPSC-derived neurons is laborious and demanding but is constantly optimized in order to increase the reliability of the cell models. A problem in iPSC-derived neurons is their partial developmental reset into an embryonic stage. This event may affect the detection of disease-specific phenotypes as the resulting neurons may not display aging-associated characteristics of neurodegeneration. An alternative approach is the direct trans-differentiation of easily accessible peripheral blood mononuclear cells (PBMCs) into induced neural stem cells (iNSCs), bypassing the intermediate step of iPSCs. These cells partially retain the aging signature of the donor, can be expanded into large numbers and may differentiate into various neuronal subtypes for disease modeling. Most importantly, iNSCs may serve as a platform for the development of drug-based therapeutic interventions against neurodegeneration.

CARDIAC STEM CELLS IN VITRO AND IN VIVO

Konstantinos Hatzistergos

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Traditionally, the regenerative capacity of the heart has been viewed as limited; however, emerging research has challenged this notion, revealing dynamic processes that offer new avenues for therapeutic intervention. Here, we present an overview of current knowledge on the developmental and regenerative biology of the heart, supplemented by recent insights gleaned from our laboratory, which illuminate novel developmental mechanisms and their potential therapeutic implications. Emphasis is placed on the role of neural crest cells, an embryonic lineage of migratory multipotent cells. Our laboratory recently identified in mice a novel «niche» of neural crest-derived, bipotent neuromyocardiogenic progenitors in the inflow tract that persist into postnatal life. Furthermore, by developing innovative pluripotent stem cell-based models of human development, we offer new insights into the developmental origins of this lineage in humans and discuss its potential role in cardiomyocyte development and regeneration.

THE CHANGING MM TREATMENT ALGORITHM IN THE ERA OF CAR T CELLS AND BISPECIFIC ABs

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Hematologist, Director, Head of Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece

Since the naked anti-CD38 antibodies have become the new backbone of first-line therapy

in transplantation eligible and -ineligible Multiple myeloma (MM) patients, most myeloma patients become triple class exposed (TCE) or refractory in earlier lines. This has enhanced the need of exploring for new targets of immunotherapy. T cell–redirecting therapies with genetically engineered chimeric antigen receptor T-cells (CAR-T) and T-cell–engaging bispecific antibodies (BsAbs) currently comprise the most exciting new developments in cancer immunotherapy and have changed the treatment paradigm for MM.
Two CAR-T products targeting B-cell maturation antigen (BCMA) (cilta-cel and ide-cel) and two BsABs targeting BCMA (teclistamab) and GPRC5D (talquetamab), respectively, have been approved for the treatment of TCE MM patients beyond third line. Both T-cell redirecting therapies significantly improve response rates and survival parameters compared to standard of care approach, therefore, they have been incorporated in the treatment algorithm of relapsed/refractory multiple myeloma and they are currently investigated in earlier lines of anti-myeloma therapy. Anti-BCMA CAR-Ts perform better, and they should probably be given before anti-BCMA BiAbs to obtain their best efficacy. However, the optimal sequencing has not been determined yet, and it depends on several patients and disease factors, drug availability, preparation restrictions and cost.

HIGH DEFINITION DISEASE MODELLING: STEM CELL AND ORGANOID EPIGENETICS

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The development of the human brain relies on a precise sequence of spatio-temporally organized events and is susceptible to both genetic alterations and environmental insults which can disrupt its underlying process and trigger neurodevelopmental disorders. Extensive evidence shows that the etiopathogenesis of neurodevelopmental disorders (NDDs) is heterogeneous, spanning a spectrum from rare, highly penetrant monogenic variants to the complex architecture of individual polygenic loads in common variants that can increase susceptibility to environmental factors or themselves trigger neurodivergent phenotypes.
Amongst the most relevant exogenous factors identified to play detrimental effects on neurodevelopment are endocrine disrupting chemicals, pervasive compounds that alter endocrine signalling.
Yet our ability to make the genetic and environmental basis of human neurodiversity experimentally tractable at scale has been hampered until recently by the complexity of the underlying architectures and the dearth of physiopathologically meaningful models that could be scaled to epidemiological significance.
Pluripotent stem cells-derived brain organoids have been transforming the field through the unprecedented opportunity to link clinical phenotypes, epidemiological traits and molecular endophenotypes by replaying neurodevelopmental processes in vitro. Against this backdrop, single cell omics methodologies enable to delve into the cell type-specific dynamics underly-

ing normotyopical and neurodiverse brain development, promising to unravel the molecular basis of the developmental pathogenesis of NDDs across the complex and broad spectrum of polygenic loads and environmental factors that contribute to their onset.
Our work focuses on the paradigm of endocrine disruptors on human neurodevelopment and the rise of atlasing efforts as key resources for causal inference.

HARNESSING HUMAN iPSC MODELS OF NEURODEGENERATION TO EXPLOIT NEUROTROPHIN POTENTIAL OF NOVEL PHARMACOLOGICAL AGENTS

Ioannis Charalampopoulos
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The emerging technology of human induced Pluripotent Stem Cells (hiPSCs) and their utilization to model Central Nervous System diseases, is providing an important research tool for deciphering the pharmacological actions of novel drugs and testing their effects on human neural tissue. Our research approach is focusing on the construction of 2D/3D neuronal circuits of hiPSC-derived neurons, astrocytes and oligodendrocytes, under physiological or pathological conditions, in order to investigate the biological role of neurotrophins and their receptors, and furthermore, to explore the effects of newly synthesized neurotrophin analogs on neurodegenerative disorders, like Alzheimer's Disease (AD), Diabetes Mellitus or Spinal Cord Injury (SCI). More specifically, upon development of novel selective agonists for TrkB and p75 neurotrophin receptors, mimicking BDNF actions, we are now evaluating their neuroprotective and neurogenic properties on hiPSCs, derived from healthy donors or AD patients, after their differentiation to Neural Stem Cells (NSCs), mature neurons, astrocytes or oligodendrocytes. Additionally, we investigate their neuroprotective and anti-inflammatory effects on a hyperglycemia model, focusing on the role of p75NTR-dependent effects. Finally, we aim to use 3D collagen scaffolds as carriers of hiPSC-derived NSCs in order to implant them on SCI mouse models, revealing their regenerative capacity on brain trauma.

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LECTURES

RNA METABOLISM & EDITING DYSFUNCTIONS IN PARKINSON'S DISEASE

Era Taoufik
Neuroimmunologist, Principal Investigator, Hellenic Pasteur Institute, Athens, Greece

PD and related synucleinopathies are incurable neurodegenerative disorders associated with alpha-synuclein (αSyn) pathology. Substantial evidence ties αSyn to Parkinson's disease (PD): the protein is the principal constituent of Lewy bodies (LB), the histopathological hallmark of the pathology; variation at its locus is the major genetic risk factor for sporadic disease; point mutations and multiplications of the locus cause familial forms of the disease. Therefore, it is not surprising that the molecular basis of PD has been tightly coupled to αSyn, with the main focus being around protein aggregation processes and factors that affect its conformational states. Today, we know that different αSyn species can activate, regulate and affect core cellular processes, including mRNA metabolic pathways, through numerous RNA-binding proteins (RBPs), ribosomal subunits and spliceosome components, and RNA editing mechanisms. We exploit advanced imaging, omics and computational analyses of mouse and human-based cellular models of α-Synucleinopathy, to reveal and characterize in depth how αSyn can modify the nature, localization, regulatory potential, stability and plasticity of mRNAs in specific neuronal compartments in health and disease. Our approach provides new knowledge on how a small neuronal protein has such a detrimental effect in a plethora of cellular processes through core RNA metabolic pathways.

BIOENGINEERING OF A HUMAN INNERVATED AND VASCULARIZED CARDIAC MUSCLE ORGANOID

Maria Patapia Zafeiriou
PhD, Group leader 3D excitable cell networks Department of Pharmacology and Toxicology, University Medical Center Goettingen, Germany

Although brain and heart are two organs with very different architectures and functions, they both depend on well-orchestrated electrically excitable cell networks. The coordinated activation of the excitable cells in the individual organ as well as the communication between brain and heart are essential for life. Imbalance of network excitability can lead to epilepsy in the brain and arrhythmias in the heart and on some occasions, these are fatally linked (sudden cardiac death under epilepsy, SUDEP). To study the communication of human autonomic neurons with cardiac cells, we generate a novel iPSC derived autonomically innervated and vascularized cardiac muscle organoid. The model is generated by fusion of an autonomic neuronal organoid enriched in sympathetic neurons (SNO) with engineered human myocardium (EHM). The co-development of autonomic neurons and vessels in this model offers the opportunity to study guidance cues dictating neuro-vascular network architecture. Light stimulation of optogenetic SNO fused with wild-type EHM resulted in a significant beating rate increase, providing proof for functional connectivity between sympathetic neurons

and pacemakers/cardiomyocytes. The modular nature of this model allows for mix&match tissues consisting of mutant and isogenic components. Such experiments can delineate the individual contribution of autonomic neurons and cardiac cells to neuro-cardiac pathologies.

EXPERIMENTAL DISEASE MODELING AND GENE THERAPY APPROACHES FOR CHILDREN WITH SEVERE CONGENITAL NEUTROPENIA

Julia Skokowa

MD, Ph.D., Head, Division of Translational Oncology, Department of Oncology, Hematology, Clinical Immunology and Rheumatology, Head, Reference Laboratory, Severe Chronic Neutropenia International Registry Europe, Founding Director, Gene and RNA Therapy Center, University Hospital Tübingen, Germany

Patients with severe congenital neutropenia (CN), an inherited pre-leukemia bone marrow failure syndrome, suffer from severe bacterial infections, usually beginning shortly after birth. In addition to impaired granulopoiesis, patients with CN are at risk of hematological malignancies including myelodysplastic syndrome, acute myeloid leukemia and, rarely, chronic myelomonocytic leukemia, acute lymphoblastic leukemia or bi-phenotypic leukemia. Most patients with CN respond to daily subcutaneous injections of rhG-CSF. However, some do not, even at doses of up to 50 µg/kg/d. Some patients continue to have frequent infections despite rhG-CSF therapy, and some, particularly in adolescence and adulthood, experience severe bone pain with rhG-CSF, leading to treatment withdrawal and high risk of subsequent serious infections. G-CSF therapy does not cure CN, and the only potentially curative treatment is allogeneic hematopoietic stem cell (HSC) transplantation, which, despite its benefits, still has a high mortality rate and severe side effects. There is an unmet need for an alternative curative treatment option for patients with CN. I will review recent efforts by our group and others to establish experimental disease modelling and clinical gene editing approaches aimed at correcting CN-associated mutations or inhibiting mutated genes in patients' hematopoietic stem and progenitor cells *ex vivo*, followed by autologous transplantation of edited cells. Some of the approaches, including the newly established safe inhibition of *ELANE* mRNA expression by targeting the gene promoter with two Cas9 nickase proteins, may be applicable to many other bone marrow failure syndromes. I will also discuss important safety considerations, desirable therapeutic thresholds and patient selection criteria that are particularly important for gene therapy in patients with pre-leukemic bone marrow syndromes.

LECTURES

LIVER-DIRECTED GENE THERAPY FOR INHERITED METABOLIC DISEASES

Nicola Brunetti-Pierri
Professor of Pediatrics, University of Naples "Federico II", Naples, Italy and Principal Investigator, Telethon Institute of Genetics and Medicine, Pozzuoli, Italy

Inherited metabolic diseases (IMD) are disorders affecting human biochemical pathways and represent attractive targets for gene therapy because of their severity, high overall prevalence, lack of effective treatments, and possibility of early diagnosis through newborn screening. The liver is a central organ involved in several metabolic reactions and is a favorite target for gene therapy in many IMD. Adeno-associated virus (AAV) vectors have emerged in the last years as the preferred vectors for in vivo gene delivery. Gene replacement strategies are aimed either at correcting liver disease or providing a source for production and secretion of the lacking enzyme for cross-correction of other tissues. A number of preclinical studies have been conducted in the last two decades and, for several diseases, gene therapy has reached the clinical stage. In my talk, our experience on two ongoing clinical gene therapy trials for IMD and I will highlight current obstacles and future strategies to overcome them.

GENERATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS FROM HAPLO-SELECTED CORD BLOOD SAMPLES (CA21151)

Anna Veiga
Haploi PS COST Action Chair, Barcelona Stem Cell Bank Director, Regenerative Medicine Programme, IDIBELL Barcelona, Spain

There is a critical need worldwide for tissue for transplantation in patients with organ failure and with degenerative diseases with no treatments available. The generation of human induced pluripotent stem cells (hiPSC) offers a unique opportunity to obtain an unlimited supply of specialized cells. An alternative to the use of patient-specific hiPSC would be an hiPSC collection from healthy donors that could be expanded and differentiated to treat different patients.

HAPLO-iPS aims to create a collaborative network to provide a framework for hiPSC generation of hiPSC homozygous for frequent HLA haplotypes, compatible with a significant percentage of the population to be used for cell therapy clinical trials, and to collect a data collection system for such lines and all the associated data. This network involves key stakeholders such as hiPSC generation/banking centers, cord blood banks, manufacturing centers compliant with Good Manufacturing Practices (GMP), immunology experts, chemistry and manufacturing controls professionals, regulatory bodies, national agencies, and ethics experts. The approach to this challenge involves networking among stakeholders, sharing knowledge, standardizing methodologies, and developing an educational training program for researchers. HAPLO-iPS also promotes the participation of researchers from less research-intensive countries, as a significant percentage of the members come from these countries.

LECTURES

PUBLIC CORD BLOOD BANKS AS A SOURCE FOR CLINICAL GRADE IPSCS AND OTHER APPLICATIONS BEYOND TRANSPLANTATIONS

Ana Belen Alvarez-Palomo
PhD in Biochemistry, Senior Researcher, Cell Therapy Service Blood and Tissue Bank (Barcelona), Leader of the iPSC-derived Advanced Therapies group, Barcelona, Spain

Cord Blood contains a particular set of cells and components of great interests beyond the well-established hematopoietic stem cell transplantation. One of the uses is to be a source of starting material for making induced pluripotent stem cells (iPSC), which in turn can be used for therapeutic cell products in regenerative medicine and immunotherapies. Allogeneic approaches to iPSC-derived therapies based on HLA matching require HLA-homozygous donors for greater population matching. Cord blood banks offer high numbers of HLA-typed, clinically procured, young cells where to find the right donors for iPSC derivation. Moreover, cord blood plasma, platelets and erythrocytes are finding new fascinating applications in medicine like regeneration of wounds in cornea and skin, or transfusion of premature new-borns. Also, mesenchymal stem cells from umbilical cord Wharton's jelly are showing impressive results in clinical trials like treatment of graft-vs-host disease after hematopoietic transplantation. New Applications are bringing on the Cord Blood Bank 2.0.

CANCER-ASSOCIATED FIBROBLASTS AND THEIR IMPACT ON CANCER DEVELOPMENT AND THERAPY

Vasiliki Koliaraki
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Cancer-associated fibroblasts (CAFs) are a major component of solid tumors, including colorectal cancer (CRC). They play a critical role in cancer development, progression, and response to therapy, through reciprocal interactions with cancer cells and the tumor microenvironment. As such, CAF targeting is considered a promising therapeutic strategy either alone or in combination with standard therapy. However, CAFs constitute a heterogenous group of cells, whose functions depend on their origin, location in the tissue/tumor, and microenvironmental milieu. To delineate fibroblast heterogeneity, activation, and functions in colorectal cancer, we employ mouse models, high-throughput single-cell transcriptomics, and 3D co-culture assays. Our results show significant similarities in fibroblast reprogramming between tissue regeneration and early adenomas, while bona fide CAFs are specifically found in metastatic tumors. In addition, there is an enrichment in endothelial cells and vascular CAFs during early carcinogenesis, which can be further divided into distinct subsets, indicating diverse activation patterns and functions. In my talk, I plan to show how a deeper insight into stromal cell biology and the evolving tumor microenvironment is essential for the identification of new targeted anti-cancer approaches.

LECTURES

iNKT CELLS: A NEW HORIZON IN CAR-BASED CANCER IMMUNOTHERAPY

Anastasios Karadimitris
PhD, MRCP, FRCPath Professor, Langmuir Chair in Haematology and Consultant Haematologist Co-Director, Centre for Haematology Director, Hugh and Josseline Langmuir Centre for Myeloma Research Centre for Haematology, Department of Immunology and Inflammation Imperial College London Department of Haematology Hammersmith Hospital, Imperial College Healthcare NHS Trust Du Cane Road, London, UK

We develop iNKT cells, a rare subset of T cells characterised by a stereotypical TCR, and restricted by the glycolipid-presenting, MHC-like molecule CD1d as a platform for immunotherapy of blood cancers. iNKT cells have features of both innate and adaptive immunity and possess effector as well as immunoregulatory activity. Their notable direct and indirect anti-tumour activity is mediated by CD1d-dependent and -independent mechanisms, including direct killing of tumour cells, antigen presenting cell (APC) maturation and activation of tumour-specific T and NK cells. I will present published and unpublished pre-clinical data demonstrating that these inherent anti-tumour properties make iNKT cells a more effective platform than conventional T cells for chimaeric antigen receptor (CAR) immunotherapy of blood cancers. As well CARs, we develop and equip iNKT with additional anticancer modules such as novel iNKT-specific engagers, TCRs and NKG2D amplifiers. I will also discuss the potential of iNKT cells sourced from alternative sources and progress towards their clinical development as an allogeneic, 'off-the-shelf', immunotherapeutic platform.

PLASMACYTOID DENDRITIC CELLS AS NEXT-GENERATION CELL-BASED THERAPEUTICS

Iulia Diaconu
Chief Scientific Officer, Unikum Therapeutics Copenhagen, Denmark

Plasmacytoid dendritic cells (pDCs), known as type I interferon producing cells, play a pivotal role as key orchestrators of the immune response. pDCs are renowned for their robust production of Interferon alpha (IFNa), along with secretion of inflammatory cytokines and direct effector functions.

Despite their critical functions, the therapeutic potential of pDCs in cancer has been hindered by several challenges. Notably, their scarcity in circulation, high fragility during laboratory handling, and resistance to genetic modification have posed significant obstacles for adoptive cell therapy development.

A groundbreaking advancement has been achieved through the generation of human pDC-like cells from hemopoietic stem and progenitor cells (HSPCs) at clinically relevant scales. This novel method has been further refined to incorporate lentiviral gene transfer for genetic engineering, culminating in the development of a Programmable Immune Regulatory Cell (PIRC) therapy platform.

UNIKUM Therapeutics has pioneered this technology to create an oncology pDC-like PIRC cell therapy program, uniquely designed for antigen-triggered activation leading to a local, acute release of IFNs, direct cytotoxicity against tumor cells, and facilitation of immune cell recruitment within the tumor microenvironment. This approach promises a new era in immunotherapy, offering a promising avenue for targeted and potent immune-based cancer treatments.

ENGINEERING OF EXTRACELLULAR VESICLES FOR EFFICIENT INTRACELLULAR DELIVERY OF NUCLEIC ACID-BASED THERAPEUTICS

Pieter Vader

PhD, Associate Professor, CDL Research & Department of Experimental Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

Extracellular vesicles (EVs) play a pivotal role in intercellular communication through functional transfer of bioactive cargo, including nucleic acids. Despite increasing interest in EV-mediated nucleic acid transfer, understanding of the pathways and mechanisms regulating EV-mediated nucleic acid delivery is limited. Here, we show a CRISPR/Cas9-based reporter system that allows the study of EV-mediated RNA transfer at single-cell resolution. We employed this system to compare the delivery efficiency of EVs to clinically approved state-of-the-art lipid nanoparticles and found that EVs delivered RNA several orders of magnitude more efficiently than these synthetic systems.

To overcome challenges related to the difficulty of RNA loading into EVs, we prepared EV-liposome hybrid nanoparticles and evaluated them as siRNA delivery systems in terms of cellular uptake, toxicity, and gene-silencing efficacy. We show that hybrids combine benefits of both synthetic and biological drug delivery systems and might serve as future therapeutic carriers of siRNA.

Finally, we show how we developed EVs as delivery vehicles for CRISPR RNPs.

PIONEERING STRATEGIES IN AAV CAPSID ENGINEERING FOR SAFER AND BROADLY APPLICABLE GENE THERAPIES

Kleopatra Rapti

PhD, Department of Infectious Diseases, Section Viral Vector Technologies Bioquant, Heidelberg University Hospital, Heidelberg, Germany

Adeno-associated viruses (AAV) have emerged as a leading gene therapy vector in multiple clinical trials and several approved gene therapies to treat human diseases, such as hemophilia and Leber's congenital amaurosis. AAV vectors are safe and effective in sustaining robust and long-term transgene expression. Their broad but also distinct tropism allows targeting of multiple tissues. However, they display immunogenicity, albeit low, and at higher dosages moderate to high toxicity. This has raised concerns about their safety and the need

for improved efficiency and specificity. Furthermore, the presence of pre-existing anti-AAV antibodies in the human population excludes a significant proportion of patients (up to 50%) from receiving therapeutic natural AAV vectors. Fortunately, AAVs are amenable to capsid engineering, which improves several of their properties, and thereby enriches the arsenal of natural AAV serotypes. This typically consists of either rational design or the generation of randomized libraries and subsequently the enrichment of potent variants from such libraries through directed evolution by applying selection pressure for the desired properties. Finally, these variants need to be further validated in animal disease models. Recent advances in next-generation sequencing techniques have contributed immensely toward this goal, as they allow the inspection of the complete library, rather than some variants. The continuing improvement of AAV vectors to minimize their limitations can build a strong foundation for the successful and safe treatment of multiple diseases.

AAV GENE THERAPY FOR CARDIO-PULMONAL DISEASES

Olympia Bikou
MD, Cardiologist, Physician Scientist, Department of Medicine I, LMU University Hospital, Munich, Germany

While the gene therapy field has immensely evolved celebrating clinical successes, none of the current approved products for clinical use target cardiac and pulmonary vascular disease. The efficacy of the gene therapeutic approaches, attributed both to the delivery methods and the vectors being used, are in the center of further optimization and scientific research. A bottleneck in the test of new gene therapeutic approaches is the pre-clinical testing in large animal models, that successfully imitate the human disease.
New discoveries in the field, addressing the aforementioned issues will be enlightened. Specifically, new results on the use of heart pumps for efficient cardiac gene delivery as well as new aerosolization techniques for treating pulmonary vascular diseases hold evident promise for the future. Furthermore, the use of pre-clinical models and oligonucleotide approaches for efficiently treating cardio-pulmonal vascular diseases is in focus of current research, paving the way for successful new clinical trials.

UPDATE ON AAV GENE THERAPY

Stylianos Michalakis
Professor, Department of Ophthalmology, University Hospital, LMU, Munich, Germany

With the advent of efficient gene therapy vectors based on non-pathogenic recombinant adeno-associated viruses (AAV), it is now possible to develop potentially curative therapeutic approaches for previously incurable diseases. Since 2012, eight AAV-based gene therapies have been approved in the EU, the UK, the US and Canada. In my talk, I will give an introduc-

tion to the biology of AAV and discuss current therapeutic approaches using AAV-based vectors. I will provide an overview of current AAV gene therapy products and discuss approaches for gene therapy of inherited and acquired diseases currently in clinical development. I will then highlight key unmet needs and introduce new technologies under development to address remaining challenges.

NEURAL STEM CELLS: FROM BENCH TO BEDSIDE FOR TREATMENT OF NEUROLOGICAL DISEASES

Angelo-Luigi Vescovi
Professor of Cell Biology, Director of Research Hospital Casa Sollievo Della Sofferenza, Rome, Italy, University of Milan Bicocca, Italy

The dogma that the adult mammalian brain was incapable of neurogenesis was challenged when Joseph Altman hypothesized the new neural cells could be generated well into adulthood in the brain. This presentation describes a scientific, professional journey, from the initial discovery of multipotent neural stem cells (NSCs) in the rodent's brain in the early 90s, through the isolation of human NSCs from the fetal brain, the unravelling of their critical physiological properties and their harnessing to establish reproducible cell therapy drug preparations. A synoptic description will follow on the use of these cell drugs to implement phase 1 clinical trials in neurological disorders, that is their intraspinal transplantation for the experimental therapy of ALS[1] and intracerebroventricular injection in patients with secondary progressive multiple sclerosis[2]. An important ramification of these findings was the discovery in 2003 that the most aggressive, incurable tumor of the CNS, glioblastoma, originates from transformed cells with NSCs properties. A brief comment on this subject and a synthetic discussion of data from a successful phase 1 trial on recurrent glioblastomas using an NSCs pro-differentiation protein, BMP4, will be presented.

1. European Clinical Trials Database (EudraCT, 2009-014484-39) and ClinicalTrials.gov (NCT01640067)
2. European Clinical Trials Database (EudraCT, 2015-004855-37) and ClinicalTrials.gov (NCT03282760)

GD2 CAR T-CELL THERAPY: A BREAKTHROUGH IN NEUROBLASTOMA RESEARCH

Francesca Del Bufalo
MD, PhD, Scientist Pediatric Hematology Oncology, Ospedale Pediatrico Bambino Gesù of Rome, Rome, Italy

Immunotherapy has achieved remarkable clinical success in the treatment of several haematological malignancies, and more advanced approaches are under evaluation to further improve outcomes. Yet the translation of similar approaches to solid tumours has faced multiple challenges. At the Bambino Gesù Children's Hospital we obtained promising results with the use of third-generation (CD28-4.1bb), GD2-directed CAR T cells for the treatment of chil-

dren with relapsed/refractory neuroblastoma and the updated results of the phase I/II clinical trial and the subsequent expanded cohort will be presented.

FIRST-IN-MAN BASE-EDITED BE-CAR7 CELLS FOR T-ALL

Christos Georgiadis
PhD, Senior Research Fellow UCL Great Ormond street Institute of Child Health, Zayed Centre for Research into Rare Disease, London, UK

'Off-the-shelf' chimeric antigen receptor (CAR) T cells generated using CRISPR-Cas9 to overcome HLA barriers have previously been deployed against B-cell childhood leukaemia. Novel CRISPR-guided cytidine deaminases can instead enable direct disruption of gene expression across multiple sites without DNA breaks, mitigating translocation risk and other chromosomal aberrations.
'Universal', off-the-shelf CAR T cells (BE-CAR7) were generated using a semi-automated compliant process from allogeneic healthy donor apheresis. Codon-optimised base-editor (coBE) mRNA was used for the multiplexed inactivation of T-cell receptor αβ chain (limiting graft-versus-host disease), CD52 (protecting from pre-conditioning serotherapy) and CD7 (resisting fratricide), and cells were next transduced with a lentivirus to express a CAR against CD7 (CAR7), a protein expressed by T-cell acute lymphoblastic leukaemia (T-ALL).
A Phase 1 trial investigating feasibility and safety of BE-CAR7 cells in R/R paediatric T-ALL was initiated at Great Ormond Street Hospital. The first patient, aged 13, who had relapsed T-ALL after allogeneic stem-cell transplantation (allo-SCT), achieved molecular remission within 28 days of infusion of a single BE-CAR7 dose prior to receiving reduced-intensity (non-myeloblative) allo-SCT, with successful immunological reconstitution and ongoing leukaemic remission. The study has demonstrated feasibility of 'off-the-shelf' base-edited CAR7 T cells with recruitment ongoing for treatment of patients with relapsed T-ALL.

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