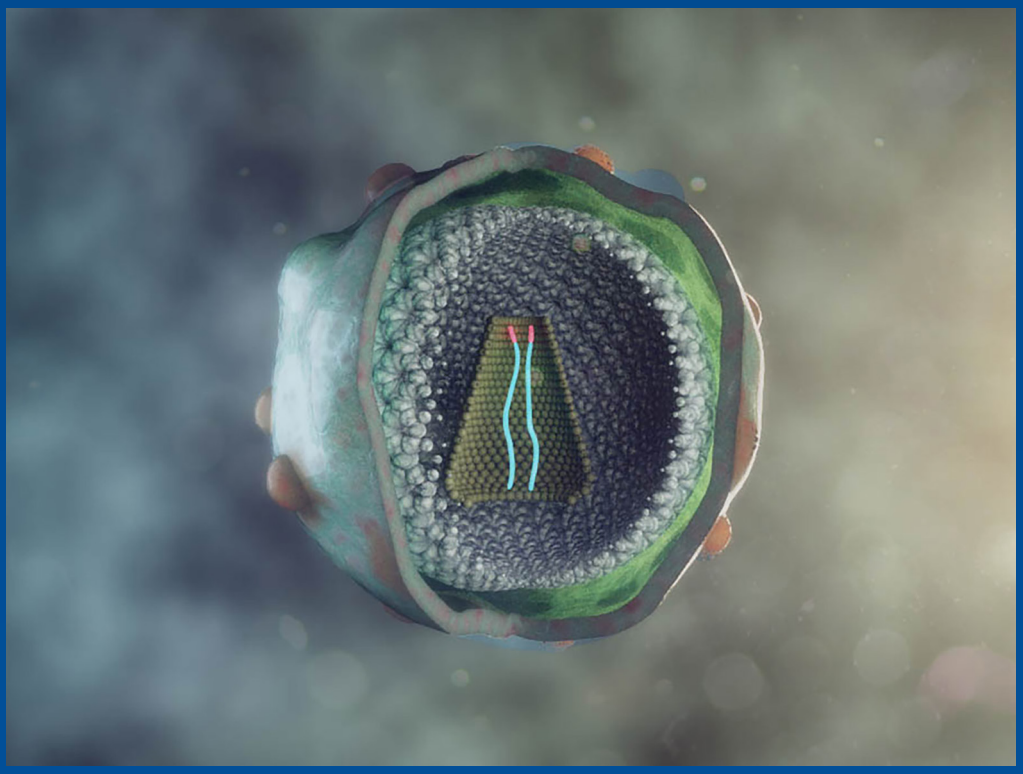
Fondazione Telethon

XIX Scientific Convention

March 13-15, 2017
Riva del Garda (TN) – Palazzo dei Congressi



FONDAZIONE
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XIX SCIENTIFIC CONVENTION

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Palazzo dei Congressi

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PROVINCIA
AUTONOMA
DI TRENTO

Front cover: 3D reconstruction of the viral vector with the normal copy of the ADA gene.

In May 2016 the first ex vivo gene therapy in the world was approved, under the brand name Strimvelis, developed through the collaboration between Fondazione Telethon, Ospedale San Raffaele and GlaxoSmithKline for the treatment of patients with the congenital immunodeficiency ADA-SCID for whom no suitable HLA-matched related stem cell donor is available.

Immagine di copertina: Ricostruzione 3D del vettore virale contenente la copia corretta del gene ADA.

Nel maggio del 2016 è stata approvata con il nome di Strimvelis la prima terapia genica ex vivo al mondo, sviluppata grazie alla collaborazione tra Fondazione Telethon, Ospedale San Raffaele e GlaxoSmithKline per il trattamento dei pazienti affetti dall'immunodeficienza congenita ADA-SCID per i quali non è disponibile un donatore di cellule staminali adeguato.

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Fondazione Telethon would like to express its gratitude to those who, through their generosity, have made it possible to hold the XIX Scientific Convention

RINGRAZIAMENTI

La Fondazione Telethon desidera esprimere la propria gratitudine a coloro che, con la loro generosità, hanno contribuito a rendere possibile la XIX Convention Scientifica

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SCIENTIFIC PROGRAM

Monday, 13th March 2017

10.00 – 14.00 *Registration and poster setting up*

14.00 – 14.30 **Welcome and Opening address**
Lucia Monaco, Fondazione Telethon, Milan

14.30 – 15.00 **OPENING LECTURE** *(Talk 1)*
Yann Le Cam – EURORDIS, France

15.00 – 17.00 **PLENARY SESSION - Neurodevelopmental disorders: from molecular mechanisms to therapeutic inroads**
Chairpersons: Enrico Cherubini, EBRI, Rome and Claudia Bagni, Università di Roma Tor Vergata, Rome

Synaptic dysfunctions leading to intellectual disabilities in Autism Spectrum Disorders
Enrico Cherubini, European Brain Research Institute (EBRI), Rome *(Talk 2)*

Fragile X Syndrome and Autism: the molecular mechanisms underlying brain plasticity and therapy *(Talk 3)*
Claudia Bagni, Tor Vergata University, Rome and University of Lausanne, Switzerland

Integrating 2D and 3D patient-specific models for the molecular elucidation of Williams and 7q11.23 microduplication syndromes *(Talk 4)*
Giuseppe Testa, Istituto Europeo di Oncologia, Università degli Studi di Milano, Milan

Protein substitution therapy: an innovative approach to treat CDKL5 disorder
Elisabetta Ciani, University of Bologna, Bologna *(Talk 5)*

Drug repurposing in neurodevelopmental disorders as a faster track from mouse models to clinical trials: the case of Down syndrome *(Talk 6)*
Laura Cancedda, Dulbecco Telethon Institute, Istituto Italiano di Tecnologia, Genoa

17.00 – 17.30 *Coffee break*

17.30 – 20.00 **POSTER SESSIONS - 1 & 2**

20.00 – 21.00 *Welcome buffet*

Tuesday, 14th March 2017

08.30 – 09.00 *Registration and poster setting up*

09.00 – 11.00 **PLENARY SESSION - Share for Rare**
Clinical data, biological samples and research results to fight genetic diseases
Chair: William A. Gahl, National Human Genome Research Institute (NHGRI), NIH, Bethesda, USA

09.00 – 09.30 **The NIH Undiagnosed Diseases Program, Network, and Network International**
William A. Gahl, NHGRI, NIH, Bethesda, USA *(Talk 7)*

09.30 – 10.00 **Telethon Undiagnosed Disease Program**
Vincenzo Nigro, Tigem, Pozzuoli (Naples) *(Talk 8)*

10.00 – 10.20 **Telethon Network of Genetic Biobanks: sharing of human biological material for research**
Mirella Filocamo, Istituto Giannina Gaslini, Genoa *(Talk 9)*

10.20 – 10.40 **Cross-Cutting bottlenecks and solutions in rare diseases research**
Hanns Lochmüller, Newcastle University, Newcastle upon Tyne, UK *(Talk 10)*

10:40 – 11:00 **Discussion**

11.00 – 11.30 *Coffee break*

11.30 – 12.30 **ROUND TABLE - Ethical, legal and social implications (ELSI) in resource sharing**

Moderators: Yann Le Cam, EURORDIS, Domenica Taruscio, Istituto Superiore di Sanità

11:30 – 11:45 **Practical implications for researchers under the new EU "General Data Protection Regulation"**
Marta Tomasi, University of Trento, Trento *(Talk 11)*

11:45 – 12:30 **Discussion**
Yann Le Cam, Domenica Taruscio, Marta Tomasi, William A. Gahl, Vincenzo Nigro, Mirella Filocamo, Hanns Lochmüller, Sharon Terry

12.30 – 13.30 *Buffet lunch*

13.30 – 15.00 **PLENARY SESSION - Fondazione Telethon and clinical trials**

Chair: Luigi Naldini, San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), San Raffaele Scientific Institute Vita Salute San Raffaele University, Milan

Gene therapy clinical trial for mucopolysaccharidosis type VI
Nicola Brunetti Pierri, Tigem, Pozzuoli (Naples) *(Talk 12)*

Hematopoietic stem cell gene therapy for inborn errors: from clinical studies to approved drugs
Alessandro Aiuti, SR-Tiget, San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan *(Talk 13)*

Gene therapy for beta-thalassemia: initial results from TIGET BTHAL clinical trial
Giuliana Ferrari, SR-TIGET, Scientific Institute San Raffaele and Vita-Salute San Raffaele University, Milan *(Talk 14)*

15.00 – 16.30 **PLENARY SESSION - Preclinical approaches to correct neurological defects**
Chair: Joel Gottesfeld – The Scripps Research Institute, La Jolla, USA

CNS therapy for Lysosomal Storage Disorders
Alessandro Fraldi, Tigem, Pozzuoli (Naples) *(Talk 15)*

Lysosomal Storage Disorders: modeling the disease complexity to refine gene and cell therapy treatment strategies
Angela Gritti, SR-Tiget, San Raffaele Scientific Institute, Milan *(Talk 16)*

GLUT1 deficiency syndrome: biochemical basis of the neurologic defect and possible therapeutic approaches in preclinical models
Maurizio Crestani, University of Milan, Milan *(Talk 17)*

Novel therapeutic strategies for hereditary Cerebral Cavernous Malformations
Elisabetta Dejana, Fondazione Istituto Firc di Oncologia Molecolare, Milan *(Talk 18)*

16.30 – 17.00 *Coffee break*

17.00 – 18.30 **POSTER SESSION - 3**

18.30 – 19.30 ***SCIENCE AND MEDIA: DISSEMINATION OF RESEARCH*** *(Talk 19)*

Guglielmo Lorenzo, Content Manager of Fondazione Telethon will give an introduction, after which Annamaria Zaccheddu, Fondazione Telethon, will lead the discussion with two science communication professionals.

Wednesday, 15th March 2017

09.00 – 11.00 **PARALLEL SESSIONS**

A. From molecular insights to development of therapeutic approaches in amyloidosis
Chairpersons: Giaolo Merlini, Policlinico San Matteo, University of Pavia, Serena Carra, Università degli Studi di Modena e Reggio Emilia, Modena

Unfolding amyloid diseases: challenges and advances *(Talk 20)*
Giampaolo Merlini, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia

Transthyretin related amyloidosis: toward a proper therapy based on the right target
Vittorio Bellotti, University of Pavia, Pavia, University College London, London *(Talk 21)*

From protein structure to novel therapeutics against gelsolin amyloidosis
Matteo de Rosa, CNR, Milan *(Talk 22)*

Defining common pathogenic mechanisms elicited by amyloids in the central nervous system
Emiliano Biasini, Dulbecco Telethon Institute (DTI), Center for Integrative Biology (CIBIO), University of Trento, Italy *(Talk 23)*

Molecular chaperones and protein aggregation: from cellular function to disease
Serena Carra, Università degli Studi di Modena e Reggio Emilia, Modena *(Talk 24)*

B. Translational research in muscle diseases: From biology to bedside

Chairpersons: Petra Kaufman, National Institutes of Health, Bethesda, USA,

Irene Bozzoni, Sapienza University of Rome, Rome

RNA-based studies of Duchenne Muscular Dystrophy: post-transcriptional control and role of non-coding RNAs in normal and dystrophic muscle development
Irene Bozzoni, Sapienza University of Rome, Rome *(Talk 25)*

Transcriptional regulation of muscle metabolism in response to physical exercise
Andrea Ballabio, Tigem, Pozzuoli (Naples) *(Talk 26)*

Framing clinical and pathological variability of muscle disorders and genetic heterogeneity: nosography, registries and molecular targets
Giacomo Comi, Università degli Studi di Milano, Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milan *(Talk 27)*

Setting the stage for successful trials in muscle disease
Petra Kaufmann, Petra Kaufmann, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda (USA) *(Talk 28)*

11.00 – 11.30 *Coffee break*

11.30 – 13.00 **PARALLEL WORKSHOPS**

A. Data Management *(Talk 29)*

11.30 – 12.30 **Introduction to *-omics* data management in life sciences**
Diego Di Bernardo, Tigem, Pozzuoli (Naples)

Transcriptomics data:

How to submit transcriptomic data to the Gene Expression Omnibus database
Annamaria Carissimo, Tigem, Pozzuoli (Naples)

How to access and analyse transcriptomics data via interactive web tools: GEO2R and GEO Profiles
Rossella De Cegli, Tigem, Pozzuoli (Naples)

Genomics data:

Online repositories of sequencing data: The European Nucleotide Archive and the European Genome-Phenome Archive
Margherita Mutarelli, Tigem, Pozzuoli (Naples)

12.30 – 13.00 **The Telethon-CINECA Genomics Repository**
Mattia D'Antonio, Cineca, Rome

B. Clinical Development and enabling Regulatory Steps *(Talk 30)*

Filling the gap: what I need to know, plan and do to enter into the clinics
Stefano Zancan, Fondazione Telethon, Milan

How to obtain ODD and Scientific Advice at EMA
Michela Gabaldo, Fondazione Telethon, Milan

13.00 – 13.30 **LATE BREAKING NEWS**

Original research article
Citron Kinase deficiency leads to chromosomal instability and TP53-sensitive microcephaly. Cell Reports, February 14, 2017
Federico Bianchi, University of Turin

Consensus Report
Human genome editing: Science, ethics, and governance.
National Academy of Sciences and National Academy of Medicine. nationalacademies.org/gene-editing

Luigi Naldini, San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), Vita Salute San Raffaele University, Milan

13.30 **CLOSING REMARKS**

13 MARZO 2017

10.00 – 13.45 *Registrazione dei partecipanti e ritiro cuffie per traduzione simultanea*

14.00 - 15.00 **SESSIONE PLENARIA (Sala 1000, traduzione simultanea in italiano)**

Benvenuto e apertura dei lavori
Lucia Monaco, Fondazione Telethon

Opening Lecture
Yann Le Cam, Eurordis

15.00 - 17.30 **WORKSHOP CON LE ASSOCIAZIONI (Sala 300, lingua italiana)**
Moderatore: Alessia Daturi, Fondazione Telethon

15.00 - 16.00 **I registri di patologia: diversi modelli possibili**
I registri di patologia: uno strumento prezioso per la ricerca ed i pazienti
Anna Ambrosini, Fondazione Telethon
RegistRare : la nuova Piattaforma nazionale dedicata ai registri di patologie rare
Domenica Taruscio, Centro nazionale malattie rare, ISS – Istituto Superiore di Sanità
L'esperienza di un'Associazione
Piero Santantonio, Mitocon Onlus

16.00 - 16.30 **Una nuova Unità per i pazienti**
Dalla voce dei pazienti ad una nuova visione
Anna Maria Cazzato, Alessia Daturi, Fondazione Telethon

16.30 - 17.20 **Discussione**

17.20 - 17.30 **Saluti finali**
Omero Toso, vice Presidente Fondazione Telethon

17.30 – 18.00 *Coffee break*

18.00 - 20.00 **SESSIONE POSTER: Incontro con i Ricercatori (Palameeting)**

20.00 - 21.00 *Buffet di benvenuto*

14 MARZO 2017

08.30 – 09.00 *Ritiro cuffie per traduzione simultanea*

09.00 - 11.00 **SESSIONE PLENARIA (Sala 1000, traduzione simultanea in italiano)- *Share for rare:* la condivisione di dati, campioni biologici e risultati scientifici nella lotta alle malattie genetiche**

Moderatore: William A. Gahl, National Human Genome Research Institute, NIH

09.00 - 09.30 **Il programma NIH per le malattie non diagnosticate**
William A. Gahl, National Human Genome Research Institute, NIH

09.30 - 10.00 **Il programma Telethon per le malattie non diagnosticate**
Vincenzo Nigro, Tigem

10.00 - 10.20 **Il Network Telethon per le biobanche genetiche: condivisione di materiali biologici per la ricerca**
Mirella Filocamo, Istituto G. Gaslini

10.20 - 10.40 **Problematiche trasversali e soluzioni nella ricerca per le malattie rare**
Hanns Lochmüller, Università di Newcastle

10:40 - 11:00 **Discussione**

11.00 – 11.30 *Coffee break*

11.30 - 12.30 **TAVOLA ROTONDA (Sala 1000, traduzione simultanea in italiano) - Il punto di vista ELSI (Ethical, legal and social implications) nella condivisione dei dati**

Moderano: Yann Le Cam, EURORDIS e Domenica Taruscio, Istituto Superiore di Sanità

Intervengono: Yann Le Cam, Domenica Taruscio, Marta Tomasi, William Gahl, Vincenzo Nigro, Mirella Filocamo, Hanns Lochmuller , Sharon Terry

11:30 - 11:45 **Implicazioni pratiche per la ricerca scientifica alla luce del nuovo Regolamento generale UE sulla protezione dei dati**
Marta Tomasi, Università di Trento

11:45 - 12:30 **Discussione**

12.30 – 13.30 *Pranzo*

14.15 *Partenza navetta per Verona aeroporto e stazione FS*

Talk 1

OPENING LECTURE

Yann Le Cam, EURORDIS

Yann Le Cam is a patient advocate who has dedicated 25 years of professional and personal commitment to health and medical research non-governmental organisations in France, Europe and the United States in the fields of cancer, HIV/AIDS and rare diseases.
He has three daughters, the eldest of whom is living with cystic fibrosis. Yann is one of the founders of EURORDIS in 1997 and the organisation's Chief Executive Officer since 2001.
He has participated in the revision and adoption of European regulations that impact the lives of rare disease patients, including the EU Regulation on orphan medicinal products.
He was one of the first patient representatives appointed to the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA), where he served for 9 years and was its vice-chair for 6 years. He served on the Management Board and Executive Committee of the French HTA agency for 5 years, on the DIA Advisory Committee Europe for 3 years.
He was the Vice Chairman of the EU Committee of Experts on Rare Diseases (EUCERD) from 2011 to July 2013, and he is nominated on the current Commission Expert Group on Rare Diseases.
Yann Le Cam is also a member of- and immediate past Chair of the Therapies Scientific Committee of IRDIRC (the International Rare Diseases Research Consortium).
In June 2016, Yann Le Cam was elected to the Management Board of the European Medicines Agency.

Talk 2

Synaptic dysfunctions leading to intellectual disabilities in Autism Spectrum Disorders

Enrico Cherubini, European Brain Research Institute (EBRI), Rome, Italy

Single mutations in genes encoding for synaptic proteins account for intellectual disabilities observed in neuro-developmental disorders including Autism Spectrum Disorders (ASD). Although rare, these forms of Autism, often associated with other comorbid conditions, point to synapses as possible sites of origin. Here, we used an electrophysiological approach to study, in an animal model of ASD, how changes in synaptic functions affect neuronal circuits leading to an excitatory/inhibitory (E/I) unbalance. A proper E/I balance is essential for nearly all brain functions, including representation of sensory information, and cognitive processes.
We used transgenic mice carrying the R451C mutation of the gene encoding for neuroligin 3 ($NL3^{R451C}$ knock-in mice), found in few families with children affected by ASD, or devoid of NL3 (NL3 knock-out mice). Neuroligins are postsynaptic adhesion molecules, that by interacting with their presynaptic partners neurexins ensure the cross talk between the post and presynaptic specializations and synaptic stabilization.
We found that in layer IV spiny neurons of the barrel cortex of $NL3^{R451C}$ mutant mice, the probability of GABA release from PV-expressing basket cells, responsible for controlling *via* feed-forward inhibition thalamo-cortical inputs, is severely impaired. In addition, in preliminary experiments, we observed that $NL3^{R451C}$ knock-in and NL3 knock-out mice are unable to undergo STDP, a particular form of associative type of learning, crucial for information coding, consisting in bidirectional modifications of synaptic strength which relies on the temporal order of presynaptic and postsynaptic spiking in the hippocampus. Precise spike timing is critically important for oscillatory activity known to play a crucial role in high cognitive functions.

Talk 3

Fragile X Syndrome and Autism: the molecular mechanisms underlying brain plasticity and therapy

Claudia Bagni[1,2], Laura Pacini[1], Giorgia Pedini[1], Laura D Andrea[1], Eleonora Rosina[1], Giulia Cencelli[1], Anastasia De Luca[1], Veronica Nobile[3], Federica Palumbo[3], Pietro Chiurazzi[3], Giovanni Neri[3], Elisabetta Tabolacci[3]

[1] Tor Vergata University, Department of Biomedicine and Prevention, Rome, Italy
[2] University of Lausanne, Department of Fundamental Neuroscience, Lausanne, Switzerland
[3] Università Cattolica del Sacro Cuore, Rome, Italy

One fourth of the population is estimated to be affected by a mental or behavioural disorder, including schizophrenia (SCZ), autism spectrum disorder (ASD) and intellectual disability (ID). These pathologies are typically associated with disturbed early neurodevelopment.
The Fragile X Syndrome (FXS) is the most frequent form of inherited intellectual disability and is also linked to other neurologic and psychiatric disorders. FXS is caused by a triplet expansion that inhibits expression of the FMR1 gene; the gene product, FMRP, regulates mRNA metabolism in the brain and thus controls the expression of key molecules involved in receptor signaling and spine morphology. While there is no definitive cure for FXS yet, the understanding of FMRP function has paved the way for rational treatment designs that could potentially reverse many of the neurobiological changes observed in FXS.
We will discuss how using mouse and fly models as well patients' cells, we identified crucial FMRP-mediated mechanisms involved in regulating gene expression during development and how, tackling nuclear and synaptic pathways, specific pharmacological therapies could ameliorate FXS.

Talk 4

Integrating 2D and 3D patient-specific models for the molecular elucidation of Williams and 7q11.23 microduplication syndromes

Giuseppe Testa, Istituto Europeo di Oncologia, Università degli Studi di Milano, Milan, Italy

The *in vitro* recapitulation of human development, largely propelled by cell reprogramming, is transforming medicine by making genetic variation and disease predisposition experimentally tractable. This is especially true for disorders of the nervous system, for which cell reprogramming is particularly relevant due to the inaccessibility of relevant tissues, and whose main disease-associated genes are strongly enriched for transcription factors and chromatin regulators. Transcriptional and chromatin dysregulation is thus a privileged entry point into the mechanistic underpinnings of neurodevelopmental conditions, yielding relatively rapid molecular insight for bridging genetic or environmental lesions to in vivo phenotypes. I will discuss novel insights from an integrated platform of 2D and 3D stem cell-based models of neural development that we have applied to the mechanistic dissection of the symmetrical copy number variations (CNV) causing Williams and 7q.11 microduplication syndromes.

Talk 5

Protein substitution therapy: an innovative approach to treat CDKL5 disorder

Elisabetta Ciani, Dipartimento di scienze biomediche e neuromotorie, University of Bologna, Bologna, Italy

No therapies are presently available for the improvement of the neurological phenotypes associated with CDKL5 disorder. Since mutations in the CDKL5 gene lead to a lack of functional CDKL5, delivery of a functional CDKL5 protein into the brain represents the best therapeutic approach. It has been discovered that certain proteins and peptides exhibit the unique property of efficient translocation across cell membranes. This unique translocation is usually due to the presence of a Protein Transduction Domain (PTD) in these molecules. The HIV-1 Transactivator of Transcription (TAT) protein is the best characterized viral PTD containing protein. Earlier experiments with the TAT-PTD protein domain demonstrated successful transduction of high molecular weight proteins into the mouse brain. Importantly, no toxic effects or immunogenicity problems of the TAT-PTD have been reported so far.
Our study provides novel evidence that the innovative approach, named protein substitution therapy, aimed at compensating for the lack of CDKL5 function by targeting a functional recombinant CDKL5 protein into the brain, is

feasible. To deliver an active CDKL5 into the nervous system and within brain cells, we constructed a TAT-CDKL5 fusion protein using a modified HIV protein transduction domain TAT as a delivering moiety. We demonstrated that TAT-CDKL5 fusion proteins can be delivered into cells and retain CDKL5 activity after internalization. When administrated in vivo, TAT-CDKL5 fusion protein was able to cross the blood brain barrier and diffuse into the brain. Finally, we treated Cdkl5 knockout mice with TAT-CDKL5 protein and showed that neurobiological and neurobehavioral defects underwent an improvement, in several cases bringing brain development and behavior up to wild-type levels.
Such promising results strengthen the idea that a protein substitution therapy with TAT-CDKL5 fusion protein may be successfully developed for CDKL5 patients.

Talk 6

Drug repurposing in neurodevelopmental disorders as a faster track from mouse models to clinical trials: the case of Down syndrome

Laura Cancedda, Dulbecco Telethon Institute, Istituto Italiano di Tecnologia, Genoa, Italy

Neurodevelopmental disorders (ND) are chronic psychiatric conditions with different etiologies, but most share intellectual disability. Currently, treatment options are very limited, and early educational intervention is the cornerstone for the management of cognitive impairment in most ND. Among ND,
Down syndrome (DS) represents the leading cause of genetically-defined intellectual disability. Interestingly, a number of mouse models of DS are currently available and basic research has provided insights on possible molecular targets for pharmacological therapy aimed at treating cognitive impairment in these mice. Nevertheless, developing new drugs able to act on newly discovered molecular targets is an extremely long, risky and expensive process that proves unsuccessful in most cases, especially for brain disorders. In this context, identifying new therapeutic indications for already existing and clinically used drugs (drug repurposing) may strongly reduce the time, risks and costs associated to classical drug discovery, leading to a faster track from the laboratory benches to the bedsides in the clinics. Here, we summarize recent finding from our laboratory on DS mouse models and we discuss the possibility of drug repurposing to recover cognitive deficits in DS mice in the view of potential translational applications in the near future.

Talk 7

The NIH Undiagnosed Diseases Program, Network, and Network International

William A. Gahl, Clinical Director, National Human Genome Research Institute (NHGRI), NIH, Bethesda, MD, USA

The inability of some seriously and chronically ill individuals to receive a definitive diagnosis represents an unmet medical need. In 2008, the NIH Undiagnosed Diseases Program (UDP) was established to provide answers to patients with mysterious conditions that long eluded diagnosis and to discover novel pathways and new cell biology. Patients admitted to the NIH UDP undergo a five-day hospitalization with extensive clinical evaluations. Genetic studies include commercially available testing, single nucleotide polymorphism analysis, and family exomic sequencing studies. Selected gene variants are evaluated by collaborators using informatics, *in vitro* cell studies, and functional assays in model systems (fly, zebrafish, worm, or mouse). Nearly 1000 patients with mysterious diseases have been evaluated in this manner. The UDP has recently expanded to a national Undiagnosed Diseases Network (UDN), with six additional clinical sites, a coordinating center, two sequencing centers, a metabolomics core, a model organisms core, and a biorepository center. In addition, the Undiagnosed Diseases Network International (UDNI) was recently established for the sharing of phenotypic and sequence data across the world. The expectation is to achieve more rare disease diagnoses and to find second cases of unique human disorders, linking phenotype and genetic variant in the discovery of new diseases. In addition, individuals well phenotyped by undiagnosed diseases programs provide a basis for identifying new pathways and druggable targets in humans.

Talk 8

Telethon Undiagnosed Disease Program

Vincenzo Nigro

Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (Naples), Italy

In 2016, Telethon has launched the first Undiagnosed Diseases Program (UDP) in Italy, a pilot program aimed at clinical and genetic analysis of pediatric patients with complex phenotype that cannot be attributed to a known condition.
The pilot program will allow us to create also in Italy a standardized strategy for the definition of new rare undiagnosed diseases with childhood-onset and the discovery of new genes using next generation sequencing. The findings will lead to a better understanding of the disease, earlier diagnosis and to make possible the genetic counseling of families. In the coming years, this will lead to do scientific research and to test and develop new targeted therapies.
From April 2016, physicians are able to candidate patient's disorders through a specifically developed web tool. The program is centered at the Telethon Institute of Genetics and Medicine -TIGEM- (Pozzuoli) where NGS activities converge. Patients with unrecognizable genetic syndromes undergo an initial clinical evaluation by one of clinical partners of the program and selected cases are then discussed in plenary sessions with all the clinicians and researchers of the Telethon UDP. The cases are placed in order of priority based on several criteria, including the severity of the case and the negativity to a number of genetic testing. Selected cases are recruited for exome analysis or genome of the entire family Whole exome target enrichment is performed by SureSelect Clinical Research Exome 54Mb at 150x2 nt, with an average coverage of 250x. Proband has a stronger coverage (>25Gb), while parents are run separately using a separate flow cell.
The results are shared and compared with those produced by analogues of international sequencing projects to recognize more patients with the same genetic disease, through the adoption of international standardized instruments as Phenotips and Phenome Central. The first patients have been evaluated starting May 2016. At January 31 2017, the registered physicians were 105, about 210 new cases were discussed by our clinical team, 80 families have been sequenced, 66 cases are now under different phases of procedure (bioinformatics analysis or in validation), 14 cases have already received an official clinical report (Italian Health system). The Italian Telethon UDP team is part of an international UD network that includes the UDP of the USA projects, Japan, Australia, etc.

Talk 9

Telethon Network of Genetic Biobanks: sharing of human biological material for research

Mirella Filocamo, Coordinator of the "Telethon Network of Genetic Biobanks" project Istituto Giannina Gaslini, Genoa, Italy

Easy access to well annotated and properly preserved samples is a key prerequisite for biomedical research, particularly in the field of the – often neglected - rare diseases, as they affect a limited number of individuals (6-8% of the population worldwide).
In this context, Genetic Biobanks (GBs) have been recognised as critical resources for samples and data collected, stored, processed, and distributed in an appropriately governed and managed system.
Recent advances in molecular biology and genetics have resulted in a concomitant increase in the demand for samples and data, and have contributed to raise the awareness of the importance of coordinated biobanking activity through the creation of networks.
The need for networking well established and managed GBs was recognised in 2008 by the Telethon Foundation, which has financially supported the project entitled "Telethon Network of Genetic Biobanks" (TNGB).
Currently, TNGB is composed of 11 Italian non-profit repositories and stores more than 90,000 biological samples representing approximately 850 distinct rare genetic diseases.
One of the primary objectives of the project was to interconnect already well-established Italian GBs, most of which have been operating since the 1970s - 1980s, through a unique and centrally coordinated IT infrastructure designed to (i) centralise very rare samples and data; (ii) standardise and harmonise the procedures; (iii) minimise biases that might arise from heterogeneity in sam-

ple quality; (iv) develop a common sample access policy based on predefined criteria. Responsibilities for harmonisation and standardisation – with regard to the collection, preparation, transport, storage, and distribution of samples – have been shared by all partners and are stated in the TNGB Charter.
Another central aim of TNGB has always been to promote Biobank services within RD-Patient Organisations (POs), with the goal of fostering their active participation and sharing benefits with them in terms of research findings. To make this strategy practical, a representative of the RD-POs was invited to join the TNGB Advisory Board since the conception of the TNGB and to contribute to its development.
The interaction with PO members has been an effective way for patients to be actively involved in drafting TNGB policies and in sharing their perspectives on procedures that can have ethical, legal and social implications such as transparency, informed consent, privacy, sample use and transfer, data sharing, and return of results.
This presentation will focus on the 10-year experience of the TNGB and on the results in the field of RDs obtained from the distribution service of many thousand samples that has led to more than 500 scientific publications.
Rete Telethon di Biobanche Genetiche: distribuzione di campioni biologici umani per la ricerca biomedica

Talk 10

Cross-Cutting bottlenecks and solutions in rare diseases research

Hanns Lochmüller, Newcastle University, Newcastle upon Tyne, UK

Talk 11

Practical implications for researchers under the new EU "General Data Protection Regulation"

Marta Tomasi, University of Trento, Trento, Italy

The use of personal data and the possibility of sharing them are critical features to ensure the quality and reliability of contemporary scientific research. The new Regulation [European Union (EU)] 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data [general data protection regulation (GDPR)], repealing Directive 95/46/EC, aims at harmonising the rules for the protection of individuals' privacy rights and freedoms. The presentation aims to provide a general overview of some of the new rules relating to the processing of personal health or genetic data and to the possibility of sharing them. A focus will be made on the specific Italian regulations on the matter, in order verify their degree of compliance with the new EU setting to be enforced in May 2018.

Talk 12

Gene therapy clinical trial for mucopolysaccharidosis type VI

Nicola Brunetti-Pierri[1,2], Stefano Zancan[3], Rita Ferla[1,2], Marialuisa Alliegro[1,2], Mafalda Graziano[1,2], Valentina Pecorella[1,2], Giancarlo Parenti [1,2], Simona Fecarotta[2], Roberto Della Casa[2], Hatice Serap Sivri[4], Ans Van Der Ploeg[5], Generoso Andria[2], Alberto Auricchio[1,2].

[1] Telethon Institute of Genetics and Medicine, Pozzuoli, Naples, Italy
[2] Department of Translational Medicine, Federico II University, Naples, Italy
[3] Fondazione Telethon, Roma, Italy
[4] Section of Metabolic Disorders, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey
[5] Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus Medical Center, University Hospital, Rotterdam, The Netherlands

Mucopolysaccharidosis type VI (MPSVI) or Maroteaux-Lamy syndrome is a rare lysosomal storage disorder caused by arylsulfatase B (ARSB) deficiency that results in the accumulation of dermatan sulfate (DS) in multiple tissues and organs without primary brain involvement. Enzyme replacement therapy (ERT) is the standard treatment for MPSVI. However, it requires weekly intravenous infusions of costly enzyme that has limited efficacy. We have shown that a single intravenous injection of an adeno-associated viral (AAV) vector 8 expressing ARSB from a liver-specific promoter results in significant biochemical, pathological and functional improvement in MPSVI rats and cats. ARSB expression and DS clearance were sustained long-term for at least 6 years after vector administration in cats. In addition, we have shown in a MPSVI mouse model that a single administration of high-dose AAV8 vector results in therapeutic efficacy similar to weekly infusions of the recombinant enzyme. Based on these promising pre-clinical data, we are developing a liver-directed gene therapy clinical trial to investigate the safety and efficacy of a single intravenous administration of AAV8 in MPSVI patients. This phase I/II clinical trial is designed as an open label dose escalation study and will be carried out as a multi-center trial. Primary objectives of the trial are to evaluate the safety of the AAV whereas clinically relevant biochemical endpoint will be evaluated to investigate efficacy. In preparation for the trial, we evaluated in a multiethnic cohort of MPSVI patients the prevalence of neutralizing antibodies (Nab) to AAV8 which will affect the efficacy of gene transfer. Pre-existing Nab to AAV8 were undetectable in 19/33 (58%) patients who can be enrolled in the trial. In conclusion, the preclinical data in large and small animal models support the potential of AAV8 for liver-directed gene therapy of MPSVI and significant progress has been achieved in the production of the clinical grade vector, design of the clinical protocol and submission of the regulatory documents required to perform a clinical gene therapy trial.

Talk 13

Hematopoietic stem cell gene therapy for inborn errors: from clinical studies to approved drugs

MP Cicalese[1,2], F. Fumagalli[1,3], F. Ferrua[1,2], V. Calbi[1,2], F. Barzaghi[1,2], M. Migliavacca[1,2], A. Assanelli[4], L. Lorioli[1,2], S. Giannelli[1], F. Dionisio[1], I. Brigida[1], F. Salerio[1], S. Acquati[1], D. Redealli[1], V. Attanasio[1], N. Carriglio[1], R Jofra Hernandez[1], F. Morena[5], S. Martino[5], M. Sarzana[1,2], F. Ciotti[1,2], M. Casiraghi[1,2], G. Antonioli[1,2], S. Darin[1,2], C. Fossati[1], A. Corti[1], L. Castagnaro[1], M. Facchini[1], P. Cristofori[1], S. Zancan[1], M. Gabaldo[1], M. Sessa[1], MG Natali Sora[3], ME Bernardo[1,2], A. Biffi[1,2*], F. Ciceri[4,6], L. Naldini[1,6], A. Aiuti[1,2,6]

[1]San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), San Raffaele Scientific Institute Milan, Italy [2]Pediatric Immunohematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy
[3]Neurology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy
[4]Haematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy [5]Department of Chemistry, Biology and Biotechnologies, University of Perugia, Perugia, Italy
[6]Vita-Salute San Raffaele University Milan, Italy
*Present address: Gene Therapy Program Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Pediatric Oncology, Boston, MA, USA

Hematopoietic stem cell (HSC) gene therapy has become in the recent years an attractive therapeutic strategy for inherited genetic disorders, offering several potential advantages over allogeneic HSC transplantation. Since year 2000, SR-TIGET has treated with ex vivo HSC-GT more than 40 patients affected by adenosine deaminase (ADA)-severe combined immunodeficiency (SCID), Wiskott-Aldrich Syndrome (WAS) and Metachromatic Leukodystrophy (MLD). Prior to GT patients received a chemotherapy conditioning to favour HSC engraftment. The intensity and type of conditioning was tailored to take in account the disease biology as well as the degree of chimerism needed[1].
SR-TIGET established dedicated infrastructures to provide the necessary regulatory experience and collect the high quality data including: (i) a Good Laboratory Practice (GLP) test facility for preclinical studies[2,3], (ii) a Pediatric Clinical Research Unit with a multidisciplinary clinical team and the TIGET clinical trial office (TCTO), and (iii) a vector integration Core Unit to perform genome-wide profiling of vector integration sites. The agreement signed by the Telethon Foundation, the San Raffaele Hospital and GlaxoSmithKline (GSK) in 2010, provided the economic resources, the expertise and the infrastructures required to complete clinical development, establish pharmaceutical production, and prepare for the launch of new medicinal products [4].
Outcome results of the first 18 ADA-SCID patients treated with gene therapy showed 100% survival with improved metabolic functions and immune recovery in most patients, leading to reduction in infections, in the absence of leukemic transformation[5]. In 2016 the European Commission granted market

approval for ex-vivo HSC gene therapy to GSK for the treatment of ADA-SCID patients without a suitable HLA-matched related donor, under the name of Strimvelis™. A long term prospective observational study is being implemented by GSK in accordance with EMA recommendations to monitor the long-term risks and persistence of efficacy of ADA-SCID gene therapy.
The TIGET-WAS gene therapy clinical trial has completed enrollment of the 8 foreseen patients[6]. Robust, persistent engraftment of Lentiviral vector (LV)-transduced cells and WAS protein expression was restored in most platelets and lymphocytes. Updated clinical results show improvement in immune functions and platelet counts, with reduction in severe infections and severe-moderate bleeding episodes and improvement of eczema (Ferrua, Cicalese, et al., ESID 2016).
A recent ad hoc analyses was performed on the first nine children with the diagnosis of an early-onset MLD patients who received LV-mediated HSC gene therapy[7]. A progressive reconstitution of Arysulfatase A activity in circulating haemopoietic cells and in the cerebrospinal fluid was documented in all patients. Eight patients, 7 of whom received treatment when presymptomatic, showed prevention of disease onset or halted disease progression compared with historical untreated control patients with early-onset disease[8].
Long-term follow up of treated patients is ongoing with no evidence of abnormal clonal proliferations in these trials. GSK, San Raffaele Hospital and Telethon are now working to make gene therapy for MLD and WAS an approved treatment available for patients. These results will pave the way for the application of HSC-GT in a wider spectrum of genetic disorders with unmet medical need.
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Talk 14

Gene therapy for beta-thalassemia: initial results from TIGET-BTHAL clinical trial

Giuliana Ferrari

SR-TIGET, Scientific Institute San Raffaele and "Vita-Salute" San Raffaele University, Milan, Italy

Severe beta-thalassemia (BTHAL) is a congenital anemia caused by reduced or absent production of the beta-globin chain of adult hemoglobin. It is a heterogeneous disorder and more than 200 mutations in the beta globin gene locus have been described causing a BTHAL phenotype. Patients present severe anemia, stigmata of chronic hemolysis, hepatosplenomegaly, skeletal abnormalities and complications related to iron overload such as cardiopathies, hepatic dysfunction and endocrine disorders.
Treatment of BTHAL is essentially supportive with lifelong transfusions combined with iron chelation therapy to reduce hemosiderosis, that is ultimately fatal if not treated. Optimal clinical management have greatly improved survival and quality of life converting a previously fatal disease into a chronic, progressive disease with a life expectancy into adulthood. Indeed, BTHAL remains a challenge in developing countries where children have poor access to blood products and iron chelating drugs, resulting in a life expectancy below 20 years of age. At present, the only curative approach is represented by allogeneic bone marrow transplantation with the probability to find a matched donor of about 30%. Thus, most of the patients will not have access to a suitable donor.
Gene therapy, based on the autologous transplantation of hematopoietic stem cells (HSC) engineered by a lentiviral vector expressing a transcriptionally regulated beta-globin gene, represents a cure for all patients, regardless of donor availability and free from transplant related immunological complications such as graft rejection and GVHD. Our contribution to this field was devoted to the clinical development of a gene therapy protocol based on high-titer vector GLOBE, use of G-CSF and plerixafor as source of HSC and a conditioning regimen based on treosulfan and thiotepa favoring efficient engraftment of corrected cells with reduced toxicity. On the basis of extensive efficacy and safety preclinical studies the clinical trial TIGET BTHAL (NCT02453477) was approved and started in 2015. The clinical protocol will treat 10 patients: 3 adults followed by 7 minors, with a staggered enrolment strategy based on evaluation of safety and preliminary efficacy in adult patients by an independent data safety monitoring board before inclusion of pediatric subjects. The chosen route of administration of gene-modified cells is intraosseous in the posterior-superior iliac crests, bilaterally, with the aim of enhancing engraftment and minimizing first-pass intravenous filter. As of February 2017, seven patients with different genotypes ($^{0}/^{0}$, $^{+}/^{+}$ and $^{0}/^{+}$) have been treated with GLOBE-transduced $CD34^{+}$ cells at a dose of $>16x10^{6}$ cells/kg (max. $19.5x10^{6}$ cells/kg) and a vector copy number/cell ranging from 0.7 to 1.5. The procedure was well tolerated by all patients, with no product-related adverse events. Multilineage engraftment of gene-marked cells was observed in all tested peripheral blood and bone marrow samples. Polyclonal vector integrations profiles have been detected in the first tested 3 patients, with thousands of unique integration sites and no evidence of clonal dominance. The vector integrated with the expected genomic distribution, with the same top-targeted genes detected in other trials with LVs. So far, the clinical outcome indicates reduction in transfusion requirement in adult patients and greater clinical benefit in younger patients.

Talk 15

CNS therapy for Lysosomal Storage Disorders

Nicolina Cristina Sorrentino, Teresa Giuliano, Irene Sambri, Yulia Ezhova, Vincenzo Cacace, Veronica Maffia, Sandra Strollo, Elvira De Leonibus and Alessandro Fraldi

Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (Naples), Italy

Email: fraldi@tigem.it

Lysosomal storage disorders (LSDs) are severe childhood conditions (incidence: 1/5,000) caused by inherited defects of lysosomal function and often characterized by a neurodegenerative course. There is no cure for the central nervous system (CNS) pathology in these diseases. The overall goal of our projects is to develop minimally invasive therapies that efficaciously treat the CNS and that can lead, therefore, to curative protocols for LSD patients.
Developing AAV-mediated gene therapy approaches to treat CNS in LSDs
We are developing and testing adeno-associated virus (AAV)-mediated gene transfer therapies for different LSDs, including the mucopolisaccharidosis type IIIA (MPS-IIIA), one of the most common and severe forms of neurodegenerative LSDs. Some of these strategies are based on intrathecal delivery of AAV serotype 9 bearing modified versions of lysosomal enzymes with enhanced therapeutic potential. Modifications that increase enzyme secretion efficiency have been already identified and are being used in our approaches; other modifications will be generated by molecular evolution methods. We are also testing the therapeutic potential of a gene transfer strategy based on the systemic delivery of AAV serotype 8 to target the liver and convert it into a factory organ for lysosomal enzymes engineered to cross the blood-brain barrier and target the brain. This approach has been successfully tested in MPS-IIIA mice and is now being tested in a dog model of MPS-IIIA and in other animal models of MPSs.
Targeting downstream pathogenic pathways in neurodegenerative LSDs
Understanding cascade of events consequent to lysosomal dysfunction

makes it possible to develop new therapies for LSDs. Data in our laboratory revealed a disease-relevant link between lysosomal dysfunction and defective neuronal proteostasis. Alpha-synuclein and CSP-alpha are two presynaptic chaperones involved in maintaining normal proteostasis at nerve terminals during synaptic activity. We demonstrated that in LSDs lysosomal dysfunction causes amyloid aggregation of alpha-synuclein and increased proteasomal degradation of CSP-alpha. These events lead to a concurrent loss of these two chaperones at nerve terminals that disrupts presynaptic proteostasis and function, thus initiating neurodegeneration. Building upon these findings we are exploring the possibility to slow down neurodegenerative processes in LSDs re-establishing the physiological levels of CSP-alpha and alpha-synuclein at nerve terminals. We are also evaluating the overall impact of lysosomal dysfunction on the neuronal proteome in order to unveil other neurodegenerative-relevant alterations of neuronal proteostasis, which might be targeted for therapeutic purposes. Overall, the expected outcome of these projects is to develop drug-based protocols for the CNS treatment in LSDs.

Talk 16

Lysosomal Storage Disorders: modeling the disease complexity to refine gene and cell therapy treatment strategies

Angela Gritti

San Raffaele Scientific Institute, San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Milan, Italy

Lysosomal storage disorders (LSD) are a heterogeneous group of inherited diseases caused by the deficiency in one or more lysosomal proteins. Pathology results from the progressive accumulation of unprocessed substrates (primary damage) and a plethora of secondary events that differently affect major cell types in the central nervous system (CNS; in >70% of LSD), peripheral nervous system (PNS) and periphery. Defects in the lysosomal enzymes arylsulfatase A (ARSA), ß-galactocerebrosidase (GALC) and ß-N-acetylhexosaminidase (ß-Hex) lead to metachromatic leukodystrophy, globoid cell leukodystrophy and GM2 gangliosidosis, respectively. Several therapeutic approaches provide various degree of correction of the biochemical and clinical-pathological phenotype in these LSD. However, none of them is able to arrest the disease, neither in animal models nor in clinical testing, failing to address the complex multi-organ pathology and to provide effectual enzymatic reconstitution of CNS tissues. Based on these observations, it is expected that novel combinatorial strategies that could ensure therapeutic levels of functional lysosomal enzymes at all affected tissues and organs with an appropriate timing would become of increasing interest in the perspective of clinical development. Our long-term goal is to enhance and complement the unique treatment modality provided by *in vivo* and *ex vivo* gene therapy (GT; i.e. the advantages of enzyme overexpression in specific cell types and the widespread enzyme biodistribution) to develop innovative and safer combined therapeutic strategies addressing the specific requirements posed by these severe LSD that still lack effective curative options. To pursue this goal, a better understanding of the pathogenic events underlying disease onset/progression (e.g. early impairment of organelle-specific intracellular function; altered cell signaling, autophagy defects) and of the therapeutic mechanisms of disease correction upon GT (e.g. enzyme trafficking and cross-correction) is required. Importantly, these issues have to be addressed *in vivo* using appropriate animal models, and *in vitro* using cell types that are mainly affected by the disease (e.g. neural progenitors, neurons and oligodendroglial cells). To this end, we take advantage of relevant murine and human experimental models, including the neural derivatives of patient-specific induced pluripotent stem cells (iPSCs), which offer an unprecedented opportunity to recapitulate the LSD CNS pathology *in vitro* and, in the long-term, may provide an autologous cell source for ex-vivo GT therapies. Here, we will discuss the most recent findings related to this research activity.

Talk 17

GLUT1 deficiency syndrome: biochemical basis of the neurologic defect and possible therapeutic approaches in preclinical models

Raffaella Longo[1], Monica Zocchi[1], Alessandra Ferrari[1], Darryl C. De Vivo[2], Maurizio Crestani[1]

[1]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy
[2]The Neurological Institute, Columbia University Medical Center, New York, NY, USA

Introduction and preliminary results - Glucose transporters belong to a family of membrane proteins facilitating glucose entry across the plasma membrane. GLUT1 Deficiency Syndrome (GLUT1 DS) is a genetic disorder caused by mutations of GLUT1 gene (*SLC2A1*), a transporter allowing glucose to cross the blood-brain barrier, thus providing energy substrates for the brain. Carriers of this mutation display hypoglycorrhachia and various neurological disorders including infantile onset of epileptic encephalopathy refractory to anticonvulsants, motor developmental delays and cognitive impairment. The only therapeutical option is the ketogenic diet (KD), a tight dietary regimen rich in fat that boosts the hepatic synthesis of ketone bodies, the alternative source of energy for the brain. Since ketogenic diet limits the choice of ingredients, compliance is often difficult to achieve. Ketone bodies synthesis occurs mainly in the liver as a result of surplus production of acetyl-CoA deriving from fatty acid β-oxidation. Peroxisome proliferator activated receptor α (PPARα) is the master regulator of these metabolic pathways that are typically active during the fasted state in the liver and it has been shown that the PPAR ligand bezafibrate induces ketone bodies synthesis in humans (Tremblay-Mercier et al., 2010). Moreover, fibroblast growth factor 21 (FGF21) also regulates the ketogenic program in the liver (Badman et al, 2007) and its analogue LY2405319 in obese subjects increases levels of β-hydroxybutyrate, the major ketone body. Our laboratory and other investigators demonstrated that administration of PPARα ligands to C57BL/6J mice increases hepatic expression of genes involved in ketogenesis and of FGF21.
Aim of the project - The aim of this project is to test whether the PPAR agonist Wy14,643 improves ketone body availability and neurological aspects of this disease in *Glut1* heterozygous mice (*Glut1*$^{+/-}$), a model resembling GLUT1 DS.
Results - *Glut1*$^{+/-}$ mice showed lower Rotarod performance compared to WT mice at 16 weeks of age, thus confirming that at this age motor coordination is compromised. At the end of treatments, Rotarod test did not show differences between the groups. Yet, Wy14,643 treated mice displayed same performances before and after treatment, whereas mice treated with vehicle or KD showed decreased performance before and after treatment. Liver gene expression showed a strong upregulation of β-oxidation and ketogenic pathways in the group of mice treated with Wy14,643.
Conclusions - The PPARα agonist Wy14,643 induced the ketogenic pathway in the liver. Wy14,643 treatment might protect mice from deterioration of the neurologic phenotype. Treatment of 16 weeks old *Glut1*$^{+/-}$ mice with PPAR ligands does not yield amelioration in motor coordination as these mice are already compromised. We envisage that therapeutic intervention at earlier age may yield the beneficial effects of PPAR ligands in preventing the onset of neurologic disorders of GLUT1 DS. [*Telethon Exploratory project GEP14129*]

Talk 18

Novel therapeutic strategies for hereditary Cerebral Cavernous Malformations

Elisabetta Dejana, Maria Grazia Lampugnani and Matteo Malinverno

FIRC Institute of Molecular Oncology, Milan, Italy

Cerebral cavernous malformations (CCMs) are capillary-venous malformations mostly located in the central nervous system. These vascular malformations may cause microbleeds leading to epileptic seizures and cerebral haemorrhages. . The familial form of CCM has an overall prevalence of <1/10,000 and is characterized by the presence of multiple CCM lesions that increase in number and size during patients' life and cause recurrent cerebral hemorrhag-

es. Familial CCM is due to loss of function mutations in any one of three related genes called CCM1 (or Krit), CCM2 (malcavernin, OSM, MGC4607), and CCM3 (or PDCD10). Remarkably, the morphology and specific brain localization is comparable in the three types of CCM loss of function mutations.
Effective medical treatment that may limit disease progression is dearly needed, as available curative therapy is limited to surgical lesion eradication or stereotactic radiosurgery. Open skull surgery is currently applied to selected symptomatic lesions only (after hemorrhage or symptomatic lesion growth), but it is highly invasive with, at times, significant complications and unproven long-term benefit. Also, neither surgery nor radiotherapy can cure multiple lesions throughout the brain and spinal cord in CCM cases. Despites many research efforts, an effective medical therapy for this disease is still missing
A prerequisite for the definition of a pharmacological intervention is the detailed knowledge of the signaling pathways that induce the functional and morphological alteration of the vessels. We created experimental mouse models of the disease inactivating anyone of the three CCM genes in a Tamoxifen inducible and EC specific way. The cavernomas grew quite rapidly in the mouse and acquired features similar to those described in man. We found that ECs lining the cavernomas present different features than the surrounding ECs. More specifically, these cells showed a mixed phenotype combining both endothelial and mesenchymal/stem cell features and markers, in a way similar to endothelial-to-mesenchymal transition (EndMT). This switch in phenotype followed a precise kinetics. It was mediated first by induction of canonical Wnt signaling followed by Smad activation induced by TGF beta and BMP activation of the cells. Through an *in vitro* screening assay on brain derived ECs we could select drugs able to revert EndMT induced by abrogation of anyone of the three CCM proteins both *in vitro* and *in vivo*. This effect was accompanied by a significant inhibition of cavernoma onset and progression in *in vivo* CCM models. Overall these studies open new pharmacological perspectives in the pharmacological treatment of CCM.

Talk 19

Science and media: dissemination of research

Guglielmo Lorenzo, Content Manager of Fondazione Telethon will give an introduction, after which Annamaria Zaccheddu, Fondazione Telethon, will lead the discussion with two science communication professionals.

Each researcher is potentially a promoter of scientific information, and the means of communication can be diverse.
How can results be disclosed in an editorial meeting? What makes science newsworthy? Is it possible to raise the interest of the general public without being too technical?
An encounter between researchers and journalists with the aim to get to know each other and work together in effective ways.

Talk 20

Unfolding amyloid diseases: challenges and advances

Giampaolo Merlini

Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, Pavia
Department of Molecular Medicine, University of Pavia

Amyloidoses are a group of complex diseases caused by tissue deposition of misfolded proteins, as fibrillary aggregates, that results in progressive organ damage and dysfunction. The conversion of peptides or proteins from their soluble functional states into highly organized fibrillar aggregates is a complex process involving key players from the intracellular protein quality control system, extracellular chaperones and matrix components, proteases, and other cofactors. The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that involve proteotoxicity and mass action. Advances have been made during the last decade in deciphering the molecular mechanisms that have led to the development of novel drugs targeting specific steps of the amyloid cascade. Most of these diseases are rare, and the knowledge of the natural history is scarce making mandatory the establishment of disease registries. Due to the progressive nature of the disease, early diagnosis, preferably based on biomarkers, is the key to effective treatment, reversal of organ damage and extended survival. The diagnostic process requires advanced technologies, such as mass spectrometry. The most impressive therapeutic results have been achieved, so far, through the suppression of the synthesis of the amyloid protein precursor, resulting in full recovery of organ dysfunction and long-term survival. Additional approaches have been recently developed and ultimately, amyloid diseases will be treated with combination therapy including cytotoxic, targeted, and immunologic approaches that reduce protein precursor production, prevent aggregation, and induce fibril resorption.

Talk 21

Transthyretin related amyloidosis: toward a proper therapy based on the right target

Vittorio Bellotti

[1]Department of Molecular Medicine, Institute of Biochemistry, University of Pavia, Pavia
[2]Wolfson Drug Discovery Unit, Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, University College London, London

Dissociation of the native transthyretin (TTR) tetramer is widely accepted as the critical step in TTR amyloid fibrillogenesis. It is modelled by exposure of the protein to non-physiological low pH *in vitro* and is inhibited by small molecule compounds, such as the drug tafamidis. We have recently identified a new mechano-enzymatic pathway of TTR fibrillogenesis *in vitro*, catalyzed by selective proteolytic cleavage, which produces a high yield of genuine amyloid fibrils. This pathway is efficiently inhibited only by ligands that occupy both binding sites in TTR. Tolcapone, which is bound with similar high affinity in both TTR binding sites without the usual negative cooperativity, is therefore of interest. Here we show that TTR fibrillogenesis by the mechano-enzymatic pathway is indeed more potently inhibited by tolcapone than by tafamidis but neither, even in large molar excess, completely prevents amyloid fibril formation. In contrast, mds84, the prototype of our previously reported bivalent ligand TTR 'superstabiliser' family, is notably more potent than the monovalent ligands and we show here that this apparently reflects the critical additional interactions of its linker within the TTR inner central channel.

Talk 22

From protein structure to novel therapeutics against gelsolin amyloidosis

Matteo de Rosa

Istituto di Biofisica – CNR, Milan, Italy

Mutations in gelsolin protein are responsible for a systemic amyloidosis first described in 1969. Until recently, the disease was associated with only two substitutions of the same residue (D187 to either N or Y), leading to the impairment of a regulatory calcium binding site. Novel interest arose in 2014 when the N184K and G167R variants of the protein were identified as the etiological agents of a novel kidney-localized amyloidosis.
Although both forms of gelsolin related amyloidosis are very rare, they are serious diseases, disabling and life threatening as they lead to a slowly progressive polyneuropathy, sight disability and eventually to death due to cerebral haemorrhage or kidney failure. Currently, there are no drugs against gelsolin amyloidosis, moreover the molecular determinants responsible for the disease are only partially characterized.
We apply an integrated approach of several state of the art structural, biophysical and biochemical methods to understand the impact of the mutations on protein fold and dynamics, deciphering the pathological mechanism at molecular level. So far, we focused on the novel variants responsible for the renal form of the disease and we recently obtained high-resolution structures for both of them. Our 3D structural analysis of the two variants has driven a computer-aided drug discovery search for new synthetic small molecules able to bind gelsolin and help to prevent its aggregation.

Talk 23

Defining common pathogenic mechanisms elicited by amyloids in the central nervous system

Emiliano Biasini

Dulbecco Telethon Laboratory of Prions & Amyloids, Center for Integrative Biology (CIBIO), University of Trento, Italy
email: biasinie@gmail.com

Several age-related disorders are associated with a change in the shape of specific proteins, and their consequent accumulation in brain tissues as amyloids. These "misfolded" isoforms are thought to be primarily responsible for the molecular, cellular and functional abnormalities underlying a wide variety of neurodegenerative syndromes, such as Alzheimer, Parkinson and amyotrophic lateral sclerosis. In contrast to the original view of these pathologies as clinically-unrelated conditions, an increasing number of mechanistic connections have emerged over the past decade. These include stress of the protein synthesis machinery, activation of specific neurotoxic signaling pathways, and the auto-catalytic propagation of amyloidogenic proteins in different brain areas, which could possibly explain the inevitable progression of these diseases. Understanding such connections have direct relevance for therapy, as interventions targeting common molecular pathways could lead to novel pharmacological strategies for several neurological disorders.
We have been interested to characterize the function of the cellular prion protein (PrP^C), a cell-surface glycoprotein already known to play a central role in transmissible neurodegenerative conditions called prion diseases. Emerging evidence suggests that PrP^C may act across different brain disorders by binding to a variety of misfolded proteins, and activating a specific neurotoxic signaling cascade leading to synaptic dysfunction and neuronal death. Here, we will present an overview of our current efforts to identify and characterize novel pharmacological agents targeting PrP^C in different pathological contexts.

Talk 24

Molecular chaperones and protein aggregation: from cellular function to disease

Serena Carra

Università degli Studi di Modena e Reggio Emilia, Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Modena, Italy
e-mail: serena.carra@unimore.it

Stress granules (SGs) are membraneless ribonucleoprotein particles that assemble when translation is inhibited and serve to store and protect messenger RNAs from degradation upon stress (Kedersha and Anderson, 2002). SGs contain RNA-binding proteins (RBPs), including TDP-43, FUS, hnRNPA1, TIA-1 that are characterized by the presence of prion-like or low complexity domains (LCDs). LCDs confer to these proteins the ability to rapidly self-assemble and concentrate in discrete foci in the cells via a process of liquid-liquid-phase separation (LLPS). LLPS has recently emerged as an essential process that drives the assembly of nucleoli, Cajal bodies, paraspeckles, DNA damage-repair sites and SGs (Hyman et al., 2014; Aguzzi and Altmeyer, 2016).
Over the past 5 years, genetic and experimental evidence suggest that SGs play a central role in the pathogenesis of Alzheimer's disease, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and inclusion body myopathy. In fact, these neurodegenerative diseases are all characterized by the accumulation of fibrillary (amyloid-like) deposits enriched for RBPs such as e.g. TDP-43, FUS, hnRNPA1 (Kim et al., 2013; Patel et al., 2015). Moreover, inherited forms of ALS, FTD and myopathy are caused by missense mutations in the genes encoding for TDP-43, FUS and hnRNPA1. Wildtype TDP-43, FUS and hnRNPA1 form, via LLPS *in vitro*, liquid-like dynamic droplets that are unstable and slowly mature into more solid hydrogels. Intriguingly, the disease-linked mutations of these RBPs all accelerate the conversion from a liquid-like to a solid aggregated state (Molliex et al., 2015; Murakami et al., 2015; Patel et al., 2015). In addition, mutations in VCP/p97, which are associated with ALS, FTD and myopathy also impair the autophagic clearance of SGs. Combined these findings support the interpretation that the pathological inclusions observed in the patients may arise from the aberrant conversion of physiological SGs into fibrils. But what drives the conversion of physiological SGs into aberrant aggregates? We showed that liquid-like SGs can sequester misfolded proteins, which promote an aberrant conversion of liquid SGs into solid aggregates. Importantly, we identified a specific protein quality control process that prevents the accumulation of misfolding-prone proteins in SGs and, by doing so, maintains SG dynamic state. This quality control process has been referred to as granulostasis and it relies on the action of the HSPB8-BAG3-HSP70 complex of molecular chaperones (Ganassi et al., 2016).
Molecular chaperones are emerging as key players that control the composition and reversibility of "physiological" aggregates, thereby preventing age-related diseases and ensuring healthy aging.
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Talk 25

RNA-based studies of Duchenne Muscular Dystrophy: post-transcriptional control and role of non-coding RNAs in normal and dystrophic muscle development

Irene Bozzoni

Department of Biology and Biotechnology Charles Darwin, Sapienza University of Rome, Rome, Italy
email: irene.bozzoni@uniroma1.it

It is well known that Duchenne patients with similar deletions can display disparate phenotype, probably due to either different extension in flanking introns, that could have a diverse impact on splicing mechanisms, or mis-regulation of factors directly involved in DMD pre-mRNA splicing. For this reason we have recently started to analyse cellular factors that, by controlling dystrophin splicing, can become new therapeutic targets for Duchenne muscular Distrophy. Indeed in one case of study we have found that the lack of a specific splicing enhancer isoform (Celf2a) contributes to natural exon 45 skipping and recovers dystrophin synthesis in a genetic DMD delta 44 background (Martone et al., 2016). Notably, delta 44 fibroblasts derived from this patient and reprogrammed into induced Pluripotent Stem (iPS) cells re-acquire the ability to produce Celf2a suggesting that the absence of this protein is not due to specific mutations but to epigenetic regulation, that is lost during reprogramming.
The chromatin structure of the Celf2a gene is under investigation as well as the presence of transcripts around the Celf2a locus in order to check whether antisense, overlapping or enhancer RNAs enter the regulatory pathway of Celf2a expression.
With the idea that DMD therapeutic interventions could be potentiated by joining different types of treatments such as exon skipping and control of splicing factors (through genetic and pharmacological approaches) the first round of pharmacological treatments (epidrugs) for interfering with Celf2a expression is ongoing.
The second line of activity aims to get new insight into the Duchenne pathology. High-throughput transcriptome analysis has revealed that the mammalian

genome is pervasively transcribed into many different complex families of RNAs. Among them two novel classes of non-canonical RNAs, long non coding RNAs and circular RNAs, are emerging as crucial players in the control of differentiation and development; their deregulation has also been linked to several inherited and acquired disorders. Several interesting examples will be presented indicating a crucial role of these molecules in the control of muscle homeostasis. These novel RNAs should constitute a vast and largely unexplored territory for the development of novel therapeutics and diagnostics.

Talk 26

Transcriptional regulation of muscle metabolism in response to physical exercise

Andrea Ballabio
Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (Naples), Italy

Previous studies in our lab have led to the identification of a lysosomal gene network and of a master gene, TFEB, which regulates lysosomal biogenesis and autophagy. The activity of TFEB is controlled by the mTORC1 kinase complex and by the phosphatase calcineurin, through a lysosomal signaling pathway. This mechanism plays an important role in the response to starvation and is deregulated in cancer. Recently, we discovered that TFEB also plays a crucial role in the control of the metabolic response to physical exercise. Indeed, TFEB translocates into the myonuclei during physical activity and regulates glucose uptake and glycogen content by controlling expression of glucose transporters, glycolytic enzymes, and pathways related to glucose homeostasis. In addition, TFEB induces the expression of genes involved in mitochondrial biogenesis, fatty acid oxidation, and oxidative phosphorylation. This coordinated action optimizes mitochondrial substrate utilization, thus enhancing ATP production and exercise capacity. Thus, by controlling metabolic flexibility in muscle during exercise TFEB acts as a critical mediator of the beneficial effects of exercise on metabolism.

Talk 27

Framing clinical and pathological variability of muscle disorders and genetic heterogeneity: nosography, registries and molecular targets

Giacomo P. Comi

Università degli Studi di Milano, Fondazione I.R.C.C.S. Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Genetic heterogeneity has long been known as a common feature in almost every field of human inherited disorders, and this was particularly true for the diversity among disorders affecting skeletal muscle tissue, such as congenital myopathies, congenital muscular dystrophies, limb-girdle muscular dystrophies and muscular dystrophies in general, congenital myasthenia syndromes as well as mitochondrial myopathies. Furthermore clinical heterogeneity of diseases associated with different mutations in the same gene was known to expand the range of possibility, further modulated by so-far relatively undetermined modulator genes. The classification of a suspected genetic muscle disorder based on the presence of a certain pattern of clinical features (e.g. inheritance, age of onset, progression rate, affected muscle groups, and extra-muscular involvement), histological characteristic and ultrastructural abnormalities, variation of expression and/or function of certain muscle proteins and specific gene findings, secured the diagnostic process in subspecialties expert centers. As expected, massive parallel sequencing and other NGS techniques are exponentially dilating our current classification, blurring boundaries among splitted forms and are posing several challenges to our understanding of muscle pathology. These challenges range from deep haplotyping, to data management and interpretation, to the need of validation sources, to genotypic-phenotipic matching on a global scale, to the building of essential registry dense of prognostic data related to pivotal aspects of clinical outcome. Registries and clinical studies have already provided essential data regarding the natural history of DMD, SMA and some lysosomal disorder. This knowledge finally resulted in the validation of the first disease modifying drugs for these disorders. In this unprecedented era, the diversity of myopathology should be mastered in order to expand our repertoire of reachable therapeutic targets.

Talk 28

Setting the stage for successful trials in muscle disease

Petra Kaufmann

Office of Rare Diseases Research and Division of Clinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health. Bethesda, MD (USA)

Despite great advances in our understanding of the underlying genetic etiology and diseases biology, many muscle diseases remain without an effective treatment. Moreover, the therapeutics development process often takes over a decade, and requires significant resources. This presentation reviews some of the recent developments in the treatment of Duchenne Muscular Dystrophy, and discusses what lessons might be learned that could help accelerate future programs aimed at bringing discoveries all the way to approved therapeutics. Specific opportunities to be discussed in this presentation include the use of robust biomarkers and clinical endpoints in the therapeutics development process, and the role of strong partnerships that maximize among stakeholders the harmonization and sharing of information and data.

Talk 29

Workshop Data Management
Introduction to *-omics* data management in life sciences
How to submit transcriptomic data to the Gene Expression Omnibus database
How to access and analyse transcriptomics data via interactive web tools: GEO2R and GEO Profiles Online repositories of sequencing data: The European Nucleotide Archive and the European Genome-Phenome Archive

Diego Di Bernardo, Annamaria Carissimo, Rossella De Cegli, Margherita Mutarelli

Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (Naples), Italy

Research data management is "the active management and appraisal of data over the lifecycle of scholarly and scientific interest." Nowadays most journals and granting agencies require that the underlying data are made available to the public in a standard compliant format. The workshop will introduce data management in life sciences and what it means in practice using "hands-on" examples focused on transcriptomics and genomic data. The workshop will also introduce the Telethon-CINECA Genomics Repository.

The Telethon-CINECA Genomics Repository

Mattia D'Antonio

Cineca, Rome, Italy

How to use the Telethon Genomics Repository implemented in CINECA to store raw data, metadata and analysis results. The access to the platform will be discussed from different points of view: web interface, REST APIs, iRODS.

Talk 30

Clinical Development and enabling Regulatory Steps
Filling the gap: what I need to know, plan and do to enter into the clinics
How to obtain ODD and Scientific Advice at EMA

Stefano Zancan, Michela Gabaldo

Fondazione Telethon, Milan

How to overcome clinical translation bottlenecks and successfully enter into clinics managing the regulatory steps enabling the clinical start and the funding requirements both at National and Central (EMA) level.

V CONVEGNO DELLE ASSOCIAZIONI AMICHE
PRESENTAZIONI ORALI

I registri di patologia: diversi modelli possibili

I registri di patologia. Uno strumento prezioso per la ricerca ed i pazienti

Anna Ambrosini

Fondazione Telethon e Associazione del Registro dei pazienti con malattie neuromuscolari

Nell'ambito delle malattie rare, i registri di patologia costituiscono uno strumento fondamentale per lo sviluppo della ricerca clinica e per l'implementazione della gestione di cura dei pazienti contribuendo la miglioramento della loro qualità di vita. Questo perché consentono di raccogliere in maniera accurata e a lungo termine di dati clinici rilevanti, dando accesso agli specialisti ad informazioni che riguardano le condizioni reali dei pazienti. Maggiori sono i dettagli a disposizione – che devono essere raccolti con criteri standardizzati e omogenei con quelli adottati anche a livello internazionale – maggiori sono le probabilità di aumentare le conoscenze sulla patologia e di disegnare uno studio clinico di successo.
Il Registro italiano dei pazienti neuromuscolari (www.registronmd.it) è basato su un'alleanza tra associazioni di pazienti – ACMT-Rete, Aisla, Asamsi, Famiglie Sma, Uildm – e Fondazione Telethon, formalizzata legalmente dalla costituzione dell'Associazione del Registro. L'obiettivo principale è quello di raccogliere dati anagrafici, genetici e clinici di pazienti con malattie neuromuscolari, conservati in specifici database per ordinare e aggiornare queste informazioni, renderle disponibili ai ricercatori impegnati nella ricerca di nuove terapie e facilitare l'arruolamento di pazienti nei trial clinici.
La scheda di registrazione è accessibile online e può essere compilata direttamente dal paziente, o da suoi famigliari in caso di minori, consentendo loro di sentirsi coinvolti in prima persona e avere accesso ad informazioni che li riguardano direttamente. Dati accurati di clinica e genetica sono raccolti dalla rete dei centri clinici, i quali accedono al registro attraverso codici personalizzati. I dati sono depositati in un database tramite una procedura che tutela la privacy e la sicurezza, e la consultazione delle informazioni da parte di ricercatori o altri utenti è regolata da un comitato indipendente. L'aumento di complessità degli ultimi anni delle diverse tipologie di registro e il fondamentale coinvolgimento dei clinici nella raccolta dei dati hanno generato la necessità di elaborare una governance più articolata, in cui tutti gli attori coinvolti siano rappresentati, garantendo trasparenza al processo di gestione e accesso ai dati.
Grazie a questo strumento, che sarà costantemente aggiornato, i medici impegnati nella pianificazione di sperimentazioni cliniche saranno anche in grado di contattare nel minor tempo possibile, tramite il Responsabile del Registro, tutti i pazienti potenzialmente idonei agli studi in preparazione. Ad oggi il Registro è già stato usato con successo per l'inserimento di pazienti in trial internazionali sulla distrofia muscolare di Duchenne e sulla atrofia muscolare spinale e per effettuare studi sugli standard di cura respiratori a livello nazionale. Altri database attivi sulla piattaforma del Registro neuromuscolare riguardano le seguenti patologie: malattia di Charcot-Marie-Tooth, malattia di Kennedy, glicogenosi muscolari, polineuropatia da amiloidosi della transtiretina.

RegistRare: la nuova Piattaforma nazionale dedicata ai registri di patologie rare

D. Taruscio, C. Carta, P. Torreri

Centro nazionale malattie rare, Istituto Superiore Sanità

In linea con quanto raccomandato a livello europeo, partendo dall'esperienza nel settore dei registri e riconoscendo il ruolo centrale dei pazienti, il Centro Nazionale Malattie Rare, si propone di sviluppare una piattaforma italiana per la raccolta dei dati sulle malattie rare.
RegistRare nasce per rispondere all'esigenze emerse in anni di collaborazione con il mondo associativo e si propone come la nuova Piattaforma web Nazionale dedicata a Registri di Patologie Rare.
Nell'ambito di questo progetto le Associazioni di pazienti che ne faranno richiesta, dopo un preliminare studio di fattibilità specifico per ogni contesto, potranno sviluppare in maniera rapida ed efficace, collaborando attivamente con i clinici di riferimento, il proprio Registro di patologia.
Principali obiettivi di tale piattaforma sono fornire un punto di accesso centrale alle informazioni sui registri di pazienti affetti da malattie rare, creando nuovi registri di patologia specifica e sostenendo quelli esistenti in vista della loro interoperabilità, fornendo gli strumenti informatici necessari per mantenere la raccolta dei dati.
Per approfondire le conoscenze epidemiologiche e cliniche su malattie rare, considerato il limitatissimo numero di casi, lo strumento scientificamente più idoneo è quello di un registro che possa raccogliere dati epidemiologici e clinici dei pazienti. Ciò consentirà di effettuare analisi statistiche, epidemiologiche e di correlazione genotipo-fenotipo che saranno alla base di un notevole approfondimento delle conoscenze cliniche, scientifiche e terapeutiche. Attraverso la creazione di registri di patologia sarà anche possibile conoscere in maggior dettaglio i fattori che condizionano la storia naturale delle varie malattie, o raffrontare ed analizzare l'impatto delle diverse opzioni terapeutiche, o trattamenti disponibili.
La raccolta dei dati presso un'istituzione pubblica quale l'Istituto Superiore di Sanità è, per le parti coinvolte, garanzia di imparzialità, correttezza istituzionale ed aderenza alle norme e leggi vigenti.
Tale progetto ha caratteristiche eminentemente scientifiche e di ricerca e non si propone di sostituirsi o di competere con le strutture regionali e nazionali di rilevamento dei dati sulle malattie rare. In aggiunta, non è uno strumento di farmacovigilanza né si propone di sostituirsi agli strumenti di farmacovigilanza istituzionali.

L'esperienza di un'Associazione

Piero Santantonio

Mitocon Onlus

I registri sono anzitutto una esperienza di condivisione, perché sono un potente strumento che richiede una forte collaborazione tra molti centri e molti soggetti. E' poi un'esperienza contagiosa, perché quando finalmente si hanno a disposizione tanti dati su delle patologie rare fioriscono idee che è poi difficile riuscire a frenare. Le associazioni dei pazienti possono fare molto in questo ambito perché hanno la forza di far andare d'accordo tutti i soggetti che collaborano. Mitocon ha sostenuto e sostiene anche finanziariamente il Registro Clinico che il Registro dei pazienti. Il primo contiene dati sanitari ed è compilato dai medici di riferimento ed è uno strumento fondamentale ed indispensabile per conoscere meglio le malattie. Il secondo è compilato dai pazienti ed è uno strumento importantissimo per sapere come vivono e quali bisogni hanno i pazienti.
Su entrambi i fronti in questo periodo Mitocon è attiva nel supportare le collaborazioni internazionali per la realizzazione di registri globali, dove mettere insieme il patrimonio di dati clinici e personali di tutto il mondo.

Una nuova Unità per i pazienti

Dalla voce dei pazienti ad una nuova visione

Anna Maria Cazzato, Alessia Daturi
Fondazione Telethon

Fondazione Telethon ha creato al proprio interno un gruppo di lavoro espressamente dedicato allo sviluppo e alla gestione di progetti, sia nuovi sia preesistenti, dedicati alla comunità di pazienti. L'obiettivo dell'unità è quello di porsi "in ascolto" dei pazienti, conoscerne i bisogni e dare vita a attività e programmi condivisi con essi.
Ad oggi le attività dell'Unità sono:

- Info_rare: un servizio di consulenza on line che fornisce informazioni sulle malattie genetiche rare, sulla presa in carico dei pazienti e sugli avanzamenti della ricerca.
- Rete delle Associazioni amiche: ne fanno parte organizzazioni senza scopo di lucro che si occupano di una o più malattie genetiche e che condividono con Fondazione Telethon un unico obiettivo, far progredire la ricerca scientifica verso la terapia e, al contempo, elevare la qualità della vita dei pazienti e delle loro famiglie.
- Come a casa: un progetto finalizzato a rendere realmente fruibili le terapie identificate da Fondazione Telethon, attraverso un supporto alle famiglie di tipo logistico, organizzativo, psicologico e di mediazione.
- Volontariato: un progetto che mira alla costruzione di una rete di volontari dell'accoglienza nell'area milanese, per creare relazioni e incontri con le famiglie nella fase delicata del trattamento.

Share for rare: la condivisione di dati, campioni biologici e risultati scientifici nella lotta alle malattie genetiche

Il programma UDP dell'NIH, il network nazionale ed internazionale

William A. Gahl, direttore dell'Istituto Nazionale di Ricerca sul Genoma Umano (NHGRI), NIH, Bethesda, MD, USA

Per i pazienti con malattie croniche e gravi, l'impossibilità di ricevere una diagnosi definitiva rappresenta un'importante questione medica. Nel 2008 è stato lanciato il programma Undiagnosed Diseases Program (UDP) dell'NIH per fornire risposte a pazienti con condizioni cliniche misteriose che sfuggono alla diagnosi e per scoprire nuovi *pathway* biologici e cellulari. I pazienti ammessi al programma UDP-NIH sono sottoposti ad una ospedalizzazione di cinque giorni per un'estensiva valutazione clinica. Analisi genetiche alle quali i pazienti sono sottoposti comprendono i principali test commerciali, analisi di polimorfismi a singolo nucleotide (SNP) e l'analisi dell'esoma nell'ambito familiare. Varianti geniche selezionate vengono valutate da collaboratori del programma mediante l'utilizzo di analisi bioinformatiche, studi cellulari *in-vitro*, e saggi funzionali in organismi modello (Drosophila, zebrafish, C. elegans o modelli murini). Con questa procedura sono stati valutati circa 1000 pazienti con malattie misteriose. L'UDP si è recentemente ampliato in una rete nazionale statunitense, Undiagnosed Diseases Network (UDN) con sei centri addizionali, un centro di coordinamento, due centri di sequenziamento, un centro di analisi metabolomiche, uno per gli organismi modello ed un bio-repository. Inoltre è stata recentemente costituita la rete internazionale, Undiagnosed Diseases Network International (UDNI), per la condivisione in tutto il mondo di dati fenotipici e di sequenze. L'obiettivo è quello di raggiungere più diagnosi di malattie rare ed identificare dei "second cases" di malati rari o unici nel mondo mediante l'associazione del fenotipo e delle varianti geniche nella scoperta di nuove malattie. In aggiunta, individui il cui fenotipo è ben caratterizzato dai programmi UDP, forniscono le basi per l'identificazione di nuovi pathway e target cellulari o molecolari per il disegno di farmaci.

Il programma Telethon per le malattie non diagnosticate

Vincenzo Nigro

Istituto Telethon di Genetica e Medicina (Tigem), Pozzuoli (Napoli)

Nel 2016, Telethon ha lanciato il primo programma per le malattie non diagnosticate (UDP) in Italia, un programma pilota che mira ad un'analisi clinica e genetica dei pazienti pediatrici senza diagnosi, con sindromi complesse senza nome. Il programma pilota ci consentirà di creare in Italia la strategia idonea per la definizione di nuove malattie rare non diagnosticate ad insorgenza infantile e la scoperta di nuovi geni usando la next generation sequencing. Le scoperte porteranno ad una migliore conoscenza della malattia, a diagnosi più precoci e renderanno possibile la consulenza genetica nelle famiglie. Nei prossimi anni, questo porterà a fare ricerca scientifica ed a testare e sviluppare nuovi trattamenti terapeutici mirati.
Da aprile 2016, i medici sono in grado di proporre casi clinici attraverso uno strumento web appositamente sviluppato. Il programma ha la sede centrale presso l'Istituto Telethon di Genetica e Medicina -TIGEM- (Pozzuoli) dove le attività di coordinamento e di sequenziamento convergono.
I pazienti con sindrome genetica non riconoscibile sono sottoposti ad una prima valutazione clinica da uno dei tre partner clinici del programma ed i casi selezionai sono poi discussi in sessioni plenarie con tutti i ricercatori del Telethon UDP. I casi sono collocati in ordine di priorità in base a diversi criteri, tra cui la severità del caso e la negatività ad una serie di test genetici. I casi selezionati vengono reclutati per l'analisi dell'esoma o del genoma dell'intera famiglia.
I risultati sono condivisi e confrontati con quelli prodotti da analoghi progetti di sequenziamento internazionali per riconoscere ulteriori pazienti con la stessa malattia genetica, attraverso l'adozione di strumenti standardizzati internazionali come Phenotips e Phenome Central. L'attività di reclutamento è iniziata nell'aprile 2016. La squadra Telethon UDP italiana è parte di un network internazionale che comprende i progetti UDP di Stati Uniti, Giappone, Australia, ecc.

Rete Telethon di Biobanche Genetiche: distribuzione di campioni biologici umani per la ricerca biomedica

Mirella Filocamo, Coordinatore del progetto "Telethon Network of Genetic Biobanks"

Istituto G. Gaslini, Genova

L'accesso a campioni biologici, ben conservati e associati a dati clinici/biologici/genetici, è un prerequisito importante per la ricerca biomedica, in particolare per lo studio di malattie rare che, colpendo un limitato numero di persone (6-8% della popolazione mondiale), rendono difficile reperire campioni biologici in quantità statisticamente significativa per un progetto di ricerca.
In questo ambito, le Biobanche Genetiche rappresentano una risorsa inestimabile, poiché mettono a disposizione un grande numero di campioni e dati che vengono raccolti, processati, conservati e distribuiti per diagnosi e/o ricerca attraverso un sistema disciplinato e standardizzato che garantisce il buon uso del materiale biologico, la tutela della riservatezza e dei diritti delle persone e, allo stesso tempo, la qualità del campioni.
In questi ultimi anni, l'avanzamento della ricerca e delle tecnologie applicate alla genetica, ha portato a un crescente aumento della richiesta di campioni e dati, e alla concomitante necessità di mettere in rete le biobanche esistenti per creare "network" di biobanche.
Nasce così nel 2008, nell'ambito di un progetto Telethon, la prima rete italiana di biobanche genetiche "Telethon Network of Genetic Biobanks" (TNGB), che è attualmente composta da 11 biobanche (alcune operative già dagli anni '70-'80) e che conserva oltre 90.000 campioni per circa 850 diverse malattie rare.
La rete TNGB, ora al 10º anno di attività, ha raggiunto importanti obbiettivi principalmente grazie all'adozione e alla condivisione di un'infrastruttura informatica, coordinata centralmente, che ha permesso: (i) la centralizzazione di campioni rari e la creazione di un catalogo condiviso costantemente aggiornato e disponibile online; (ii) lo sviluppo di procedure operative standard per garantire la qualità dei campioni; (iii) la definizione di politiche condivise per regolare l'accesso ai campioni a garanzia della trasparenza e dell'imparzialità.
Un altro importante obiettivo di TNGB è stato da sempre la promozione dei servizi delle biobanche nell'ambito delle Associazioni di Pazienti allo scopo di aumentare i livelli di conoscenza, fiducia e interesse, e nello stesso tempo, di coinvolgere le Associazioni nell'elaborazione di procedure con implicazioni etiche, giuridiche e sociali, quali, trasparenza delle attività, privacy, consenso e informativa, uso e trasferimento di campioni e dati, restituzione dei risultati.
Tutte queste attività sono state rese possibili anche dalla costante partecipazione di un rappresentante delle associazioni all' Organo Consultivo del TNGB ("Advisory Board"), sin dalla sua istituzione.
Questa presentazione ha lo scopo di riportare l'esperienza di 10 anni di attività della rete TNGB e di presentare alcuni risultati ottenuti grazie al servizio di distribuzione di diverse migliaia di campioni che ha prodotto oltre 500 pubblicazioni scientifiche.

Problematiche trasversali e soluzioni nella ricerca per le malattie rare

Hanns Lochmüller, Università di Newcastle, Newcastle, UK

TAVOLA ROTONDA - Il punto di vista ELSI (Ethical, legal and social implications) nella condivisione di dati e materiali biologici

Implicazioni pratiche per la ricerca scientifica alla luce del nuovo Regolamento generale UE sulla protezione dei dati

Marta Tomasi, Università di Trento, Trento

L'impiego di dati personali e la possibilità di condividerli e renderli accessibili rappresentano alcune delle caratteristiche che garantiscono oggi la qualità e l'affidabilità della ricerca scientifica. Il nuovo Regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (Regolamento generale sulla protezione dei dati), che abroga la direttiva 95/46/CE, mira a realizzare un'armonizzazione delle regole per la protezione dei diritti e delle libertà relative alla privacy degli individui. Si ritiene opportuno fornire un quadro generale delle nuove regole introdotte in riferimento al trattamento di dati relativi alla salute e, nello specifico, di dati genetici e alla possibilità di condividerli. Un focus specifico riguarderà la normativa italiana in materia, al fine di verificare il suo livello di adeguatezza rispetto al nuovo quadro europeo che diverrà pienamente efficace a partire dal mese di maggio 2018.

GENETIC BIOBANKS

#1 – FTP17Y01

DEVELOPING AN INTERNATIONAL NETWORK OF RARE DISEASE BIOBANKS WITHIN THE RD-CONNECT/EUROBIOBANK PLATFORM

SVILUPPO DI UNA RETE INTERNAZIONALE DI BIOBANCHE SULLE MALATTIE RARE ATTRAVERSO LA PIATTAFORMA RD-CONNECT / EUROBIOBANK

Chiuhui Mary Wang

Fondazione Telethon *Years:* **6** *Starting:* **2012**

#2 – GTB12001

TELETHON NETWORK OF GENETIC BIOBANKS

RETE TELETHON DI BIOBANCHE GENETICHE

Coordinator **Mirella Filocamo**
Partner Chiara Baldo, Stefano Goldwurm, Alessandra Renieri, Elena Pegoraro, Maurizio Moggio, Marina Mora, Giuseppe Merla, Luisa Politano, Barbara Garavaglia, Luca Sangiorgi

Centres: **11** *Years:* **5** *Starting:* **2013**

NEUROMUSCULAR DISEASES

#3 – GGP14037

A MITOCHONDRIAL THERAPY FOR MUSCULAR DYSTROPHIES

UNA TERAPIA MITOCONDRIALE PER LE DISTROFIE MUSCOLARI

PI **Paolo Bernardi**

Centres: **1** *Years:* **2** *Starting:* **2014**

#4 – GGP14202

MANIPULATING AUTOPHAGY IN MUSCLE DISEASES

MODULAZIONE DELL'AUTOFAGIA NELLE MALATTIE MUSCOLARI

Coordinator **Francesco Cecconi**
Partner Paolo Bonaldo

Centres: **2** *Years:* **2** *Starting:* **2014**

#5 – GGP11185

THE INTRACELLULAR CONTROL OF THYROID HORMONE SIGNALING IN MUSCLE STEM CELLS AND IN DUCHENNE MUSCULAR DYSTROPHY

IL CONTROLLO INTRACELLULARE DELL'ORMONE TIROIDEO NELLE CELLULE MUSCOLARI STAMINALI E NELLA DISTROFIA MUSCOLARE DI DUCHENNE

PI **Domenico Salvatore**

Centres: **1** *Years:* **3** *Starting:* **2011**

#6 – GGP13013

MODULATION OF DYSTROPHIC MICROENVIRONMENT TO IMPROVE STEM CELL-MEDIATED THERAPY

MODULAZIONE DEL MICROAMBIENTE DISTROFICO PER MIGLIORARE LA TERAPIA CELLULARE MEDIATA DA CELLULE STAMINALI

PI **Antonio Musarò**

Centres: **1** *Years:* **3** *Starting:* **2013**

#7 – GGP13165

ROLE OF THE BROMODOMAIN PROTEIN BRD4 IN THE TRANSCRIPTIONAL REGULATION OF PRO-ATROPHIC GENES, IN THE MOUSE MODEL OF DUCHENNE MUSCULAR DYSTROPHY

RUOLO DELLA BROMODOMAIN PROTEIN BRD4 NELLA REGOLAZIONE TRASCRIZIONALE DI PROTEINE PRO-ATROFICHE NELLA DISTROFIA MUSCOLARE DI DUCHENNE

PI **Giuseppina Caretti**

Centres: **1** *Years:* **1** *Starting:* **2013**

#8 – GGP13233

PROTEIN KINASE C THETA AS A NOVEL MOLECULAR TARGET TO COUNTERACT INFLAMMATION IN MUSCULAR DYSTROPHY

LA PROTEINCHINASI C TETA COME NUOVO POSSIBILE BERSAGLIO TERAPEUTICO PER CONTRASTARE LA RISPOSTA INFIAMMATORIA NELLA DISTROFIA MUSCOLARE

PI **Marina Bouchè**

Centres: **1** *Years:* **3** *Starting:* **2013**

#9 – GGP14073

INNOVATIVE THERAPEUTIC STRATEGY FOR DUCHENNE MUSCULAR DYSTROPHY BY AAV MEDIATED DELIVERY OF ARTIFICIAL TRANSCRIPTION FACTOR GENES

STRATEGIA TERAPEUTICA INNOVATIVA PER LA CURA DELLA DISTROFIA MUSCOLARE DI DUCHENNE, BASATA SULL'USO DI FATTORI TRASCRIZIONALI ARTIFICIALI VEICOLATI NEL MUSCOLO DA VETTORI VIRALI ADENO-ASSOCIATI

Coordinator **Nicoletta Corbi**
Partner Elisabetta Mattei

Centres: **2** *Years:* **2** *Starting:* **2014**

#10 – GGP15022

ROLE OF HDAC4 IN MUSCULAR DYSTROPHY AND REGENERATION

RUOLO DI HDAC4 NELLA DISTROFIA E NELLA RIGENERAZIONE MUSCOLARE

PI **Viviana Moresi**

Centres: **1** *Years:* **2** *Starting:* **2016**

#11 – GGP16191

A NOVEL IN VITRO DUCHENNE MUSCULAR DYSTROPHY CARDIOMYOPATHY MODEL: HUMAN IPSC-DERIVED CARDIOMYOCYTES FOR MECHANISTIC STUDIES

UN NUOVO MODELLO IN VITRO, BASATO SU CARDIOMIOCITI DERIVATI DA CELLULE IPS, PER STUDIARE I MECCANISMI DELLA CARDIOMIOPATIA ASSOCIATA ALLA DISTROFIA MUSCOLARE

Coordinator **Cecilia Ferrantini**
Partner Leonardo Sacconi

Centres: **2** *Years:* **2** *Starting:* **2016**

#12 – GGP16213

RNA-BASED STUDIES OF DUCHENNE MUSCULAR DYSTROPHY: POST-TRANSCRIPTIONAL CONTROL AND ROLE OF NON CODING RNAS IN NORMAL AND DYSTROPHIC MUSCLE DEVELOPMENT

STRATEGIE BASATE SULL'RNA PER LA CURA DELLA DISTROFIA MUSCOLARE DI DUCHENNE: MODULAZIONE DELLO SPLICING DELL'RNA DELLA DISTROFINA E RUOLO DI RNA NON CODIFICANTI NELLO SVILUPPO MUSCOLARE NORMALE E DISTROFICO

PI **Irene Bozzoni**

Centres: **1** *Years:* **3** *Starting:* **2016**

#13 – GUP11011

EVALUATION OF BONE TURNOVER, BONE METABOLISM, BONE DENSITY, AND FRACTURES IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY AND POSSIBLE SIDE EFFECTS OF LONG-TERM CORTICOSTEROID THERAPY (BON-DMD)

VALUTAZIONE DI TURNOVER OSSEO, METABOLISMO OSSEO, DENSITÀ OSSEA E FRATTURE NEI BAMBINI AFFETTI DA DISTROFIA MUSCOLARE DI DUCHENNE, E DEI POSSIBILI EFFETTI DI UNA TERAPIA STEROIDEA CRONICA

PI **Maria Luisa Bianchi**

Centres: **1** *Years:* **3** *Starting:* **2012**

#14 – GUP15011

LONG TERM NATURAL HISTORY IN DUCHENNE MUSCULAR DYSTROPHY

STORIA NATURALE A LUNGO TERMINE DELLA DISTROFIA MUSCOLARE DI DUCHENNE

Coordinator **Eugenio Maria Mercuri**
Partner Angela Lucia Berardinelli, Luisa Politano, Giovanni Baranello, Adele D'amico, Giacomo Pietro Comi, Antonella Pini, Roberta Battini, Ksenija Gorni, Sonia Messina, Claudio Bruno, Elena Pegoraro, Sandra Gandossini, Federica Ricci

Centres: **14** *Years:* **3** *Starting:* **2016**

#15 – GUP15021

USEFUL: USER-CENTRED ASSISTIVE SYSTEM FOR ARM FUNCTIONS IN NEUROMUSCULAR SUBJECTS

USEFUL: SISTEMA ASSISTIVO CENTRATO SULL'UTENTE PER IL SUPPORTO DELLE FUNZIONI DEL BRACCIO IN SOGGETTI AFFETTI DA PATOLOGIE NEUROMOSCOLARI

Coordinator **Alessandra Laura Giulia Pedrocchi**
Partner Maria Grazia D'angelo, Franco Molteni

Centres: **3** *Years:* **2** *Starting:* **2016**

#16 – TCP13007

MECHANISMS OF FIBROSIS IN MUSCULAR DYSTROPHIES

MECCANISMI CHE CONTROLLANO LA FIBROSI NELLE DISTROFIE MUSCOLARI

PI **Stefano Augusto Maria Biressi**

DTI *Years:* **5** *Starting:* **2014**

#17 – GUP13012

PHENOTYPIC AND MOLECULAR CHARACTERIZATION OF FSHD FAMILIES: A SYSTEMATIC APPROACH TOWARDS TRIAL READINESS

CARATTERIZZAZIONE CLINICA E MOLECOLARE DI FAMIGLIE FSHD COME PRESUPPOSTO PER VALUTARE L'EFFICACIA DI TERAPIE

Coordinator **Rossella Ginevra Tupler**
Partner Emiliano Giardina, Tiziana Mongini, Maurizio Moggio, Corrado Angelini, Lucio Santoro, Gabriele Siciliano, Marina Mora, Enzo Ricci, Carmelo Rodolico, Antonio Di Muzio, Angela Lucia Berardinelli, Massimiliano Filosto, Gaetano Nicola Vattemi, Giovanni Antonini

Centres: **15** *Years:* **3** *Starting:* **2014**

#18 – TCR13001

POLYCOMB REPRESSIVE COMPLEX 1 PROVIDES A MOLECULAR EXPLANATION FOR REPEAT COPY NUMBER DEPENDENCY IN FSHD MUSCULAR DYSTROPHY.

PRC1 FORNISCE UNA SPIEGAZIONE MOLECOLARE PER LA DIPENDENZA DAL NUMERO DI REPEATS NELLA DISTROFIA MUSCOLARE FSHD

PI **Davide Gabellini**

DTI *Years:* **3** *Starting:* **2013**

#19 – GUP11006

GENETIC DIAGNOSIS OF ITALIAN LGMD PATIENTS BY NGS TECHNOLOGY

DIAGNOSI GENETICA DEI PAZIENTI ITALIANI CON DISTROFIA MUSCOLARE DEI CINGOLI BASATA SU SEQUENZIAMENTO DI PROSSIMA GENERAZIONE (NGS)

PI **Vincenzo Nigro**

Centres: **1** *Years:* **3** *Starting:* **2012**

#20 – GGP15140

SMALL MOLECULES TO RESCUE FOLDING-DEFECTIVE SARCOGLYCANS: IN VIVO ASSESSMENT OF NOVEL THERAPEUTIC STRATEGIES

USO DI PICCOLE MOLECOLE PER IL RECUPERO DI SARCOGLICANI CON DIFETTI DI RIPIEGAMENTO: VALUTAZIONE IN VIVO DELL'EFFICACIA DI NUOVE STRATEGIE TERAPEUTICHE

PI **Dorianna Sandonà**

Centres: **1** *Years:* **3** *Starting:* **2015**

#21 – GUP13004

COMPLETE MOLECULAR CHARACTERIZATION OF PATIENTS AFFECTED BY CONGENITAL MUSCULAR DYSTROPHIES WITH ALPHA-DYSTROGLYCAN DEFECT USING NEXT GENERATION SEQUENCING STRATEGIES

COMPLETA CARATTERIZZAZIONE GENETICA DI PAZIENTI AFFETTI DA DISTROFIA MUSCOLARE CONGENITA CON DIFETTO DI GLICOSILAZIONE DELL'ALFA-DISTROGLICANO APPLICANDO STRATEGIE DI NEXT-GENERATION SEQUENCING

Coordinator **Adele D'Amico**
Partner Eugenio Maria Mercuri, Guja Astrea, Sonia Messina, Claudio Bruno, Elena Pegoraro, Angela Lucia Berardinelli, Giacomo Pietro Comi, Marina Mora, Antonella Pini, Luisa Politano, Federica Ricci

Centres: **12** *Years:* **2** *Starting:* **2014**

#22 – GGP12024

ROLE OF JAB1 IN THE CONTROL OF NERVE DEVELOPMENT AND REPAIR: IMPLICATION IN THE PATHOGENESIS OF MEROSIN DEFICIENT CONGENITAL MUSCULAR DYSTROPHY (MDC1A)-ASSOCIATED HEREDITARY NEUROPATHIES

RUOLO DI JAB1 NEL CONTROLLO DELLO SVILUPPO E RIGENERAZIONE DEL NERVO PERIFERICO: IMPLICAZIONE NELLA PATOGENESI DELLE NEUROPATIE EREDITARIE ASSOCIATE ALLA DISTROFIA MUSCOLARE CONGENITA (MDC1A)

PI **Stefano Carlo Previtali**

Centres: **1** *Years:* **3** *Starting:* **2013**

#23 – TCP12001

DISSECTING THE MOLECULAR BASIS OF SEPN1-RELATED-MYOPATHIES

ANALISI DELLE BASI MOLECOLARI DELLE MIOPATIE CORRELATE A SEPN1

PI **Ester Zito**

DTI *Years:* **5** *Starting:* **2012**

#24 – GGP13213

ALTERED CALCIUM HANDLING IN CENTRAL CORE DISEASE AND MALIGNANT HYPERTHERMIA: UNDERSTAND MOLECULAR MECHANISMS AND GENETIC BACKGROUND TO DEVELOP INNOVATIVE THERAPEUTIC INTERVENTIONS.

MIOPATIA CENTRAL CORE E IPERTERMIA MALIGNA: COMPRENDERNE I MECCANISMI MOLECOLARI E LE BASI GENETICHE PER SVILUPPARE TERAPIE FARMACOLOGICHE INNOVATIVE.

Coordinator **Feliciano Protasi**
Partner Carlo Reggiani, Vincenzo Sorrentino

Centres: **3** *Years:* **3** *Starting:* **2013**

#25 – GGP14003

JP45 A FUNCTIONAL MODIFIER IN RYANODINOPATHIES

JP45 UN MODULATORE DEL FENOTIPO CAUSATO DA MUTAZIONI DEL GENE CODIFICANTE IL RECETTORE DELLA RIANODINA DEL MUSCOLO SCHELETRICO (RIANODINOPATIE)

PI **Francesco Zorzato**

Centres: **1** *Years:* **2** *Starting:* **2014**

#26 – GGP16026

TARGETING MITOCHONDRIA IN MYOPATHIES WITH RYR1 AND MICU1 MUTATIONS

I MITOCONDRI COME BERSAGLIO NELLE MIOPATIE CON MUTAZIONI NEI GENI RYR1 E MICU1

Coordinator **Gyorgy Szabadkai**
Partner Anna Raffaello

Centres: **2** *Years:* **3** *Starting:* **2016**

#27 – GGP14096

PRECLINICAL EVALUATION OF PHARMACOGENETICS AND NEW THERAPEUTIC OPTIONS IN NONDYSTROPHIC MYOTONIAS TOWARD PERSONALIZED MEDICINE

VALUTAZIONE PRECLINICA DI FARMACOGENETICA E NUOVE OPZIONI TERAPEUTICHE NELLE MIOTONIE NON-DISTROFICHE VERSO UNA MEDICINA PERSONALIZZATA

PI **Diana Conte Camerino**

Centres: **1** *Years:* **3** *Starting:* **2014**

#28 – GGP14092

SKELETAL MUSCLE AND CIRCULATING MICRORNAS IN MYOTONIC DYSTROPHY TYPE 1

RUOLO DEI MICRORNA NEL MUSCOLO SCHELETRICO E NEL SANGUE CIRCOLANTE DEI MALATI DI DISTROFIA MIOTONICA DI TIPO 1

Coordinator **Fabio Martelli**
Partner Germana Falcone

Centres: **2** *Years:* **3** *Starting:* **2014**

#29 – GUP15004

CLINICAL EFFICACY OF NIV AND MODAFINIL ON EXCESSIVE DAYTIME SLEEPINESS: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL IN DM1

EFFICACIA CLINICA DELLA VENTILAZIONE NON INVASIVA E DEL MODAFINIL SULLA ECCESSIVA SONNOLENZA DIURNA: STUDIO MULTICENTRICO, RANDOMIZZATO, IN DOPPIO-CIECO, PLACEBO-CONTROLLATO NELLA DISTROFIA MIOTONICA DI TIPO 1 (DM1)

Coordinator **Valeria Sansone**
Partner Lino Nobili, Roberto Massa, Fabio Placidi

Centres: **4** *Years:* **2** *Starting:* **2016**

#30 – GEP14049

PATIENTS DERIVED CELLULAR MODELS TO INVESTIGATE THE PATHOGENESIS AND TO DEVELOP THERAPIES FOR HUMAN DISORDERS CAUSED BY ACID CERAMIDASE DEFICIENCY.

MODELLI CELLULARI PAZIENTE-SPECIFICI PER LO STUDIO DELLA PATOGENESI E LO SVILUPPO DI TERAPIE NELLE MALATTIE UMANE CAUSATE DA DEFICIT DI CERAMIDASI ACIDA.

PI **Dario Ronchi**

Centres: **1** *Years:* **1** *Starting:* **2015**

#31 – GGP15001

THE HSPB2-HSPB3 COMPLEX: UNRAVELING NEW FUNCTIONS THAT AFFECT NUCLEAR HOMEOSTASIS AND THEIR IMPLICATION IN NEUROMUSCULAR AND MUSCULAR DISEASES.

IL COMPLESSO HSPB2-HSPB3: STUDIO DI NUOVE FUNZIONI CHE INFLUENZANO L'OMEOSTASI NUCLEARE E DELLA LORO IMPLICAZIONE IN MALATTIE NEUROMUSCOLARI E MUSCOLARI.

PI **Serena Carra**

Centres: **1** *Years:* **2** *Starting:* **2015**

#32 – GGP14039

MOTOR NEURON DEGENERATION IN SPINAL AND BULBAR MUSCULAR ATROPHY: MOLECULAR APPROACHES TO COUNTERACT MUTANT ANDROGEN RECEPTOR NEUROTOXICITY

DEGENERAZIONE DEI MOTONEURONI NELLA ATROFIA MUSCOLARE SPINALE E BULBARE. APPROCCI MOLECOLARI PER CONTRASTARE LA NEUROTOSSICITÀ DEL RECETTORE DEGLI ANDROGENI MUTATO

PI **Angelo Poletti**

Centres: **1** *Years:* **3** *Starting:* **2014**

#33 – GUP15009

CLINICAL NETWORK AND REGISTRY FOR TRIAL READINESS IN SPINAL AND BULBAR MUSCLE ATROPHY

RETE CLINICA E REGISTRO DI MALATTIA PER LA PREPARAZIONE A TRIAL CLINICI NELLA ATROFIA MUSCOLARE BULBO-SPINALE

Coordinator **Caterina Mariotti**
Partner Davide Pareyson, Gianni Soraru', Mario Sabatelli

Centres: **4** *Years:* **3** *Starting:* **2016**

#34 – TCP12013

TARGETING AKT SIGNALING IN MUSCLE TO IDENTIFY NEW THERAPEUTIC STRATEGIES FOR SPINAL AND BULBAR MUSCULAR ATROPHY

RUOLO DEI SEGNALI INTRACELLULARI ATTIVATI NEL MUSCOLO DALLA CINASI AKT NELLA PATOGENESI DELLA ATROFIA MUSCOLARE SPINALE E BULBARE

PI **Maria Pennuto**

DTI *Years:* **5** *Starting:* **2013**

35 – GGP13081

RELEVANCE OF THE AXONAL SMN PROTEIN (A-SMN) FOR SPINAL MUSCULAR ATROPHY: NOVEL CELL MODELS, TRANSGENIC MICE AND THERAPEUTIC APPROACHES

IMPORTANZA DELLA PROTEINA A-SMN O SMN ASSONALE NELL'ATROFIA MUSCOLARE SPINALE: NUOVI MODELLI CELLULARI, TOPI TRANSGENICI E TERAPIE GENICHE

Coordinator **Denise Locatelli**
Partner Enrico Garattini, Ferdinando Di Cunto

Centres: **3** *Years:* **3** *Starting:* **2013**

36 – GGP13147

A DROSOPHILA MODEL FOR SPINAL MUSCULAR ATROPHY (SMA): IDENTIFICATION AND CHARACTERIZATION OF SMN INTERACTORS AND PHENOTYPIC MODIFIERS

IL MOSCERINO DELLA FRUTTA COME MODELLO PER SMA: IDENTIFICAZIONE E CARATTERIZZAZIONE DI INTERATTORI E MODIFICATORI DELLA PROTEINA SMN

PI **Grazia Daniela Raffa**

Centres: **1** *Years:* **2** *Starting:* **2013**

37 – GGP14025

PEPTIDE-CONJUGATED MORPHOLINO FOR TREATMENT OF SPINAL MUSCULAR ATROPHY

MORFOLINO CONIUGATO CON PEPTIDI PER IL TRATTAMENTO DELL'ATROFIA MUSCOLARE SPINALE

PI **Monica Nizzardo**

Centres: **1** *Years:* **3** *Starting:* **2014**

38 – GGP14095

REGULATION OF SMN2 SPLICING AND EXPRESSION IN SPINAL MUSCULAR ATROPHY

REGOLAZIONE DELLO SPLICING E DELL'ESPRESSIONE DEL GENE SMN2 NELL'ATROFIA MUSCOLARE SPINALE

PI **Claudio Sette**

Centres: **1** *Years:* **3** *Starting:* **2014**

39 – GSP13002

DEVELOPMENT OF AN ITALIAN CLINICAL NETWORK FOR SPINAL MUSCULAR ATROPHY

CREAZIONE DI UNA RETE CLINICA ITALIANA PER L'ATROFIA MUSCOLARE SPINALE (SMA)

Coordinator **Eugenio Maria Mercuri**
Partner Enrico Silvio Bertini, Roberta Battini, Angela Lucia Berardinelli, Claudio Bruno, Maria Grazia D'angelo, Ksenija Gorni, Tiziana Mongini, Giovanni Baranello, Elena Pegoraro, Luisa Politano, Sonia Messina, Antonella Pini

Centres: **13** *Years:* **2** *Starting:* **2014**

40 – GGP16203

IDENTIFICATION OF NEW DRUGGABLE TARGETS AND POTENTIAL THERAPEUTIC COMPOUNDS FOR SPINAL MUSCULAR ATROPHY, USING A C.ELEGANS MODEL OF NEURODEGENERATION

IDENTIFICAZIONE DI NUOVI TARGET FARMACOLOGICI E DI POTENZIALI FARMACI PER L'ATROFIA MUSCOLARE SPINALE UTILIZZANDO UN MODELLO DI NEURODEGENERAZIONE IN C. ELEGANS

PI **Elia Di Schiavi**

Centres: **1** *Years:* **3** *Starting:* **2016**

41 – GUP15014

OBSERVATIONAL LONGITUDINAL STUDY OF GROWTH PATTERNS, BODY COMPOSITION, ENERGY EXPENDITURE AND DIETARY INTAKE IN ITALIAN INFANTS AND CHILDREN WITH SPINAL MUSCULAR ATROPHY TYPE I AND II.

STUDIO OSSERVAZIONALE LONGITUDINALE DI PATTERN DI CRESCITA, COMPOSIZIONE CORPOREA, DISPENDIO ENERGETICO E CONSUMI ALIMENTARI IN BAMBINI ITALIANI CON ATROFIA MUSCOLARE SPINALE TIPO I E II

Coordinator **Simona Bertoli**
Partner Enrico Silvio Bertini, Giovanni Baranello, Marina Pedemonte, Caterina Agosto

Centres: **5** *Years:* **3** *Starting:* **2016**

42 – GGP12017

PHOSPHOLIPID METABOLISM AND MEMBRANE TRAFFICKING IN THE PATHOGENESIS OF CHARCOT-MARIE-TOOTH NEUROPATHIES

RUOLO DEI FOSFOLIPIDI E DEL TRAFFICO DI MEMBRANA NELLA PATOGENESI DELLE NEUROPATIE DI CHARCOT-MARIE-TOOTH

PI **Alessandra Bolino**

Centres: **1** *Years:* **3** *Starting:* **2013**

43 – GGP14040

ROLE OF PROSTAGLANDIN D2 SYNTHASE IN PNS MYELINATION AND REMYELINATION

RUOLO DELLA PROSTAGLANDINA D2 SINTASI NELLA MIELINIZZAZIONE E NELLA RIMIELINIZZAZIONE

PI **Carla Taveggia**

Centres: **1** *Years:* **3** *Starting:* **2014**

44 – GGP15012

MODULATING NEUREGULIN-1 SIGNALS TO TREAT HEREDITARY DEMYELINATING NEUROPATHIES

MODULAZIONE DELLA NEUREGULINA 1 COME APPROCCIO TERAPEUTICO PER IL TRATTAMENTO DI NEUROPATIE EREDITARIE DEMIELINIZZANTI

Coordinator **Carla Taveggia**
Partner Alessandra Bolino, Stefano Carlo Previtali, Maurizio D'antonio

Centres: **4** *Years:* **3** *Starting:* **2016**

45 – GGP14147

PROTEIN MISFOLDING IN CHARCOT-MARIE-TOOTH DISEASE: TOWARDS THE DEVELOPMENT OF A THERAPEUTIC STRATEGY TARGETING THE UNFOLDED PROTEIN RESPONSE

SCORRETTO RIPIEGAMENTO DELLE PROTEINE NELLA MALATTIA DI CHARCOT-MARIE-TOOTH: VERSO LO SVILUPPO DI UNA STRATEGIA TERAPEUTICA CHE MODULI LA RISPOSTA ALLE PROTEINE NON NATIVE

PI **Maurizio D'Antonio**

Centres: **1** *Years:* **3** *Starting:* **2014**

46 – GUP13006

CMT NATIONAL REGISTRY: TOWARDS DEFINITION OF STANDARDS OF CARE AND CLINICAL TRIALS

REGISTRO NAZIONALE CMT: VERSO LA DEFINIZIONE DEGLI STANDARD DI CURA E LE SPERIMENTAZIONI CLINICHE

Coordinator **Davide Pareyson**
Partner Angelo Schenone, Gian Maria Fabrizi, Stefano Carlo Previtali, Isabella Allegri, Luca Padua, Lucio Santoro, Aldo Quattrone, Giuseppe Vita, Isabella Moroni

Centres: **10** *Years:* **2** *Starting:* **2014**

47 – GGP12269

A MIMETIC PEPTIDE RESTORES CONNEXIN 32 HEMICHANNEL GATING INHIBITED BY THE R220X MUTATION THAT CAUSES CHARCOT-MARIE-TOOTH DISEASE.

UN PEPTIDE MIMETICO RIPRISTINA IL GATING DEGLI EMICANALI DI CONNESSINA 32 INIBITO DALLA MUTAZIONE R220X CHE CAUSA LA MALATTIA DI CHARCOT-MARIE-TOOTH.

PI **Mario Bortolozzi**

Centres: **1** *Years:* **3** *Starting:* **2013**

48 – GGP16037

CHARCOT-MARIE-TOOTH TYPE 2B: ROLE OF THE RAB7 GTPASE AND OF RAB7 INTERACTING PROTEINS

CHARCOT-MARIE-TOOTH TYPE 2B: RUOLO DELLA GTPASI RAB7 E DEI SUOI INTERATTORI

Coordinator **Cecilia Bucci**
Partner Lucio Santoro, Stefano Carlo Previtali

Centres: **3** *Years:* **3** *Starting:* **2016**

49 – GUP15010

TTR-FAP ITALIAN REGISTRY: A COLLABORATIVE NETWORK FOR DEFINITION OF NATURAL HISTORY, PSYCHOSOCIAL BURDEN, STANDARDS OF CARE AND CLINICAL TRIALS

REGISTRO NAZIONALE TTR-FAP: RETE COLLABORATIVA MULTICENTRICA PER LA DEFINIZIONE DELLA STORIA NATURALE, DEGLI STANDARD DI CURA, DEL CARICO E DEI BISOGNI DEI PAZIENTI E DELLE SPERIMENTAZIONI CLINICHE

Coordinator **Giuseppe Vita**
Partner Giampaolo Merlini, Lorenza Magliano, Mario Sabatelli, Marina Grandis, Gian Maria Fabrizi, Davide Pareyson, Lucio Santoro, Alessandro Mauro

Centres: **9** *Years:* **2** *Starting:* **2016**

50 – GUP13013

BUILDING A NATION-WIDE ITALIAN COLLABORATIVE NETWORK FOR MUSCLE GLYCOGENOSES: REGISTRY AND NATURAL HISTORY

SVILUPPO DI UNA RETE COLLABORATIVA ITALIANA PER LA RACCOLTA DEI PAZIENTI CON GLICOGENOSI MUSCOLARI: CREAZIONE DI UN REGISTRO NAZIONALE E STUDIO DELLA STORIA NATURALE DELLE MGSD

Coordinator **Antonio Toscano**
Partner Tiziana Mongini, Corrado Angelini, Claudio Bruno, Maurizio Moggio, Gabriele Siciliano, Paola Tonin, Lorenzo Maggi, Andrea Martinuzzi, Massimiliano Filosto, Serenella Servidei, Maria Alice Donati, Bruno Bembi

Centres: **13** *Years:* **2** *Starting:* **2014**

51 – GGP14192

IDENTIFICATION OF NEW THERAPEUTIC AGENTS FOR THE TREATMENT OF GLYCOGENOSIS TYPE 2 DUE TO THE COMMON SPLICING MUTATION C.-32-13T>G

IDENTIFICAZIONE DI NUOVE TERAPIE PER IL TRATTAMENTO DELLA GLICOGENOSI DI TIPO 2 DOVUTA A UN DIFETTO DI SPLICING

Coordinator **Emanuele Buratti**
Partner Andrea Elena Dardis

Centres: **2** *Years:* **3** *Starting:* **2014**

52 – TGM16YMT11

NOVEL THERAPEUTIC APPROACHES FOR POMPE DISEASE

NUOVE STRATEGIE TERAPEUTICHE PER LA MALATTIA DI POMPE

PI **Giancarlo Parenti**

TIGEM **2016 - 2021**

53 – GGP15051

GENE THERAPY AND LONG TERM EVALUATION OF DIFFERENT DIETARY REGIMENS IN A GLYCOGEN STORAGE DISEASE TYPE III KO MOUSE MODEL

TERAPIA GENICA E VALUTAZIONE A LUNGO TERMINE DI DIFFERENTI REGIMI DIETETICI NEL MODELLO MURINO KNOCKOUT PER LA GLICOGENOSI DI TIPO III

PI **Giacomo Pietro Comi**

Centres: **1** *Years:* **3** *Starting:* **2015**

54 – GGP14066

CLINICAL, MOLECULAR AND PATHOGENETIC STUDIES OF NEUTRAL LIPID STORAGE DISEASE (NLSD)

STUDIO DEGLI ASPETTI CLINICI E PATOGENETICI DELLE SINDROMI DA ACCUMULO DI LIPIDI NEUTRI (NLSD)

Coordinator **Marcello Arca**
Partner Elena Maria Pennisi, Daniela Tavian, Antonio Musaro', Corrado Angelini

Centres: **5** *Years:* **3** *Starting:* **2015**

55 – GGP14187

MITCARE-2

MITCARE-2

Coordinator **Luca Scorrano**
Partner Valerio Carelli, Paolo Bernardi, Leonardo Salviati

Centres: **4** *Years:* **3** *Starting:* **2014**

56 – GGP13222

PATHOGENESIS OF PRIMARY AND SECONDARY COENZYME Q DEFICIENCY

PATOGENESI DEL DEFICIT PRIMARIO E SECONDARIO DI COENZIMA Q

PI **Leonardo Salviati**

Centres: **1** *Years:* **3** *Starting:* **2013**

57 – GGP15041

MITMED CONSORTIUM: FROM THE IDENTIFICATION AND CHARACTERIZATION OF NUCLEAR GENES RESPONSIBLE FOR HUMAN MITOCHONDRIAL DISORDERS TOWARDS POTENTIAL THERAPEUTIC APPROACHES IN EXPERIMENTAL MODELS

CONSORZIO MITMED: DALL'IDENTIFICAZIONE E CARATTERIZZAZIONE DI GENI NUCLEARI RESPONSABILI DI MALATTIE MITOCONDRIALI VERSO POTENZIALI APPROCCI TERAPEUTICI IN MODELLI SPERIMENTALI

Coordinator **Daniele Ghezzi**
Partner Rodolfo Costa, Claudia Donnini

Centres: **3** *Years:* **3** *Starting:* **2015**

NEUROLOGICAL DISEASES

#59 – GGP13097

ISOLATED DOMAINS OF AMINOACYL TRNA SYNTETHASES AS A NOVEL THERAPEUTIC TOOL FOR MT TRNA MUTATION ASSOCIATED DISEASE

RUOLO TERAPEUTICO DELLE AMINOACIL TRNA SINTETASI NELLE MALATTIE DA MUTAZIONI DEI TRNA MITOCONDRIALI

PI **Giulia D'amati**

Centres: **1** *Years:* **2** *Starting:* **2013**

#60 – GEP14134

MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS: STUDY OF MLC MOLECULAR PATHOGENESIS AND IDENTIFICATION OF POTENTIAL THERAPEUTIC TARGETS USING ASTROCYTES DERIVED FROM PATIENT INDUCIBLE PLURIPOTENT STEM CELLS.

LEUCOENCEFALOPATIA MEGALENCEFALICA CON CISTI SUBCORTICALI: STUDIO DELLA PATOGENESI MOLECOLARE E IDENTIFICAZIONE DI BERSAGLI TERAPEUTICI MEDIANTE LA GENERAZIONE DI ASTROCITI DIFFERENZIATI DA CELLULE STAMINALI PLURIPOTENTI INDOTTE DERIVATE DA PAZIENTI.

PI **Elena Ambrosini**

Centres: **1** *Years:* **1** *Starting:* **2015**

#61 – GGP13055

NEW APPROACHES TO THE MOLECULAR PATHOGENESIS OF CCHS: IMPLICATIONS FOR THERAPEUTIC STRATEGIES

STUDIO DEI MECCANISMI MOLECOLARI NELLA PATOGENESI DELLA SINDROME DI ONDINE PER LO SVILUPPO DI NUOVE STRATEGIE TERAPEUTICHE

PI **Diego Maria Michele Fornasari**

Centres: **1** *Years:* **2** *Starting:* **2013**

#62 – GEP13109

A NOVEL STRATEGY TO DELIVER GLUCOSE TO THE BRAIN UNDER CONDITIONS OF GLUCOSE TRANSPORTER DEFICIENCY

INDIVIDUAZIONE DI UNA TERAPIA FARMACOLOGICA PER LA MALATTIA DI DE VIVO O SINDROME DA DEFICIT DEL TRASPORTATORE DEL GLUCOSIO

PI **Maurizio Balestrino**

Centres: **1** *Years:* **1** *Starting:* **2014**

#63 – GEP14129

NOVEL PHARMACOLOGICAL APPROACHES TO INCREASE KETONE BODIES AVAILABILITY IN GLUT1 DEFICIENCY SYNDROME

NUOVI APPROCCI FARMACOLOGICI PER AUMENTARE I LIVELLI DI CORPI CHETONICI NEI PAZIENTI CON DEFICIT DEL TRASPORTATORE GLUT1

PI **Maurizio Crestani**

Centres: **1** *Years:* **1** *Starting:* **2015**

#64 – GGP16072

HEREDITARY SPASTIC PARAPLEGIA: INVESTIGATIONS ON THE REGULATION OF SPASTIN PROTEIN MEDIATED BY THE KINASE HIPK2 IN PROLIFERATING CELLS AND IN NEURONS

PARAPLEGIA SPASTICA EREDITARIA: INDAGINE SULLA REGOLAZIONE DELLA PROTEINA SPASTINA DA PARTE DELLA CHINASI HIPK2 IN CELLULE PROLIFERANTI E NEI NEURONI

PI **Cinzia Rinaldo**

Centres: **1** *Years:* **1** *Starting:* **2016**

#65 – GGP12059

RNA:RNA INTERACTIONS CONTROL THE ATM ACTIVATION AT INDIVIDUAL GENOMIC SITES

INTERAZIONI RNA:RNA CONTROLLANO L'ATTIVAZIONE DI ATM A SINGOLI SITI GENOMICI

PI **Fabrizio D'Adda di Fagagna**

Centres: **1** *Years:* **3** *Starting:* **2012**

#66 – GGP12171

MEC1/ATR MEDIATED CANONICAL AND NON-CANONICAL MODE OF MAINTAINING GENOME STABILITY

SISTEMI MODELLO PER IDENTIFICARE GENI E FATTORI NEI PROCESSI MOLECOLARI DIFETTIVI NEI PAZIENTI CON ATASSIA TELANGECTASIA

PI **Marco Foiani**

Centres: **1** *Years:* **3** *Starting:* **2012**

#67 – GGP13071

ATM DEPENDENT CONTROL OF CELL METABOLISM IN ATAXIA-TELANGIECTASIA DISEASE

CONTROLLO DEL METABOLISMO CELLULARE DA PARTE DI ATM NELL'ATASSIA-TELANGECTASIA

PI **Vincenzo Costanzo**

Centres: **1** *Years:* **3** *Starting:* **2013**

#68 – GGP14164

DETERMINANTS OF NEURODEGENERATION IN ATAXIA TELANGIECTASIA

DETERMINANTI DELLA NEURODEGENERAZIONE NELL'ATASSIA TELANGECTASIA

Coordinator **Domenico Delia**
Partner Lorenzo Magrassi

Centres: **2** *Years:* **3** *Starting:* **2014**

#69 – GGP16015

EXCITATORY/INHIBITORY UNBALANCE IN ATAXIA TELANGIECTASIA AND PERSPECTIVE THERAPEUTICAL INTERVENTIONS

SBILANCIATO RAPPORTO TRA ECCITAZIONE E INIBIZIONE NELL'ATASSIA TELANGECTASIA E PROSPETTIVE D'INTERVENTO TERAPEUTICO

PI **Flavia Antonucci**

Centres: **1** *Years:* **2** *Starting:* **2016**

#70 – GGP15004

RNA THERAPEUTICS FOR FRIEDREICH'S ATAXIA

TERAPIA A BASE DI RNA PER LA ATASSIA DI FREIDREICH

Coordinator **Stefano Gustincich**
Partner Antonello Mallamaci, Ivano Condò

Centres: **3** *Years:* **2** *Starting:* **2015**

#71 – GEP14096

ROLE OF ANO10 IN SPINOCEREBELLAR ATAXIA

RUOLO DELLA PROTEINA ANO10 NELL'ATASSIA SPINOCEREBELLARE

PI **Luis Juan Vicente Galietta**

Centres: **1** *Years:* **1** *Starting:* **2015**

#72 – GGP12217

SPINOCEREBELLAR ATAXIA TYPE 28: CELLULAR AND ANIMAL MODELS TO UNRAVEL THE PATHOGENESIS AND TO IDENTIFY POTENTIAL THERAPEUTIC TARGETS

ATASSIA SPINOCEREBELLARE TIPO 28 (SCA28): MODELLI CELLULARI E ANIMALI PER IDENTIFICARE I MECCANISMI PATOGENETICI ED I POTENZIALI BERSAGLI TERAPEUTICI

Coordinator **Alfredo Brusco**
Partner Filippo Tempia

Centres: **2** *Years:* **3** *Starting:* **2012**

#73 – TGM16YMT12

ONE PROTEIN COMPLEX, TWO DISEASES: THE MITOCHONDRIAL MAAA INVOLVEMENT IN NEURODEGENERATION

UN COMPLESSO PROTEICO PER DUE MALATTIE: LA NEURODEGENERAZIONE ASSOCIATA ALLA PROTEASI MITOCONDRIALE MAAA

PI **Giorgio Casari**

TIGEM **2016 - 2021**

#74 – GGP14225

TRANSLATING MOLECULAR PATHOLOGY INTO A THERAPEUTIC STRATEGY IN SCA38, A NEWLY IDENTIFIED FORM OF SPINOCEREBELLAR ATAXIA

DAI MECCANISMI PATOGENETICI ALLA TERAPIA DELLA SCA38, UNA NUOVA FORMA DI ATASSIA AUTOSOMICA DOMINANTE

Coordinator **Barbara Borroni**
Partner Alfredo Brusco, Donatella Caruso, Loredana Boccone, Filippo Tempia

Centres: **5** *Years:* **3** *Starting:* **2014**

#75 – GGP12220

PURKINJE CELL DEGENERATION IN MARINESCO-SJOGREN SYNDROME: ROLE OF CELL STRESS, ALTERATIONS OF PROTEOSTASIS AND CALCIUM HOMEOSTASIS

RUOLO DELLO STRESS CELLULARE, PROTEOSTASI E OMEOSTASI DEL CALCIO NELLA DEGENERAZIONE DELLE CELLULE DEL PURKINJE NELLA SINDROME DI MARINESCO-SJOGREN

Coordinator **Michele Sallese**
Partner Roberto Chiesa

Centres: **2** *Years:* **3** *Starting:* **2013**

#76 – GGP16029

MITOCHONDRIAL CA+2 UPTAKE IN THE PATHOGENESIS OF FAMILIAL ALZHEIMER'S DISEASE

L'ACCUMULO MITOCONDRIALE DI CALCIO NELLA PATOGENESI DELLE FORME FAMILIARI DELLA MALATTIA DI ALZHEIMER

Coordinator **Rosario Rizzuto**
Partner Tullio Pozzan

Centres: **2** *Years:* **3** *Starting:* **2016**

#77 – TCP14009

DEFINING THE ROLE OF THE CELLULAR PRION PROTEIN AT THE INTERSECTION OF SEVERAL NEURODEGENERATIVE DISEASES

STUDIO DEL RUOLO DELLA PROTEINA PRIONICA CELLULARE IN DIFFERENTI MALATTIE NEURODEGENERATIVE

PI **Emiliano Biasini**

DTI *Years:* **5** *Starting:* **2015**

#78 – GGP13005

ANALYSIS OF LYN CORE SIGNALING MACHINERY IN NEUROACANTHOCYTOSIS

ANALISI FUNZIONALE DEL SISTEMA LYN RELATO NELLA NEUROACANTOCITOSI

PI **Lucia De Franceschi**

Centres: **1** *Years:* **3** *Starting:* **2013**

#79 – GGP15225

A NEW EXPLOITATION OF A TETRACATIONIC-PORPHYRIN ABLE TO REDUCE PRPC AND TO INHIBIT PRPSC REPLICATION: CHARACTERIZATION OF THE MECHANISM OF ACTION AND PRECLINICAL STUDIES IN MOUSE MODELS OF GENETIC PRION DISEASE

UNA NUOVA APPLICAZIONE DI UNA PORFIRINA TETRACATIONICA CAPACE DI RIDURRE PRPC E INIBIRE LA REPLICAZIONE DI PRPSC: CARATTERIZZAZIONE DEL MECCANISMO D'AZIONE E STUDI PRECLINICI IN MODELLI MURINI DI MALATTIE DA PRIONI DI ORIGINE GENETICA

Coordinator **Roberto Chiesa**
Partner Stefano Banfi, Giovanna Musco

Centres: **3** *Years:* **3** *Starting:* **2015**

#80 – GGP12122

IMPACT OF REDUCED GLIAL-DERIVED CHOLESTEROL IN HUNTINGTON'S DISEASE

IMPATTO DELLA MINOR PRODUZIONE DI COLESTEROLO DI ORIGINE GLIALE NELLA MALATTIA DI HUNTINGTON

PI **Elena Cattaneo**

Centres: **1** *Years:* **2** *Starting:* **2012**

#81 – GGP13053

ROLE OF ADAM10 IN HUNTINGTON'S DISEASE

IL RUOLO DI ADAM10 NELLA MALATTIA DI HUNTINGTON

PI **Chiara Zuccato**

Centres: **1** *Years:* **2** *Starting:* **2013**

#82 – TCP13013

DISSECTING THE MOLECULAR FUNCTION OF MUTANT HUNTINGTIN WITH STEM CELLS

CARATTERIZZARE LE ALTERAZIONI MOLECOLARI ASSOCIATE ALLA MALATTIA DI HUNTINGTON USANDO CELLULE STAMINALI.

PI **Graziano Martello**

DTI *Years:* **5** *Starting:* **2013**

#83 – TCP15011

ROLE OF THE COILED-COIL STRUCTURE OF THE HUNTINGTIN PROTEIN IN THE INTERCELLULAR PROPAGATION OF POLYQ AGGREGATES

RUOLO DELLA STRUTTURA COILED-COIL DELLA PROTEINA HUNTINGTIN NELLA PROPAGAZIONE INTRACELLULARE DEGLI AGGREGATI POLYQ

PI **Luana Fioriti**

DTI *Years:* **5** *Starting:* **2016**

84 – GGP16234

IMPLEMENTATION OF HUMAN NEURONAL CULTURES AND MOUSE MODELS OF PANTOTHENATE KINASE 2 DEFICIENCY TO INVESTIGATE PATHOGENIC MECHANISMS OF IRON-RELATED NEURODEGENERATION AND EVALUATE COENZYME A THERAPEUTIC EFFICACY

SVILUPPO DI MODELLI DI CELLULE NERVOSE UMANE E DI MODELLI MURINI DEFICITARI DI PANTOTENATO KINASI-2, PER LO STUDIO DEI MECCANISMI PATOGENETICI DI NEURODEGENERAZIONE DA ACCUMULO DI FERRO E PER VALUTARE L'EFFICACIA TERAPEUTICA DELLA SUPPLEMENTAZIONE DI COENZIMA A

Coordinator **Sonia Levi**
Partner Vania Broccoli, Stefano Taverna, Valeria Tiranti

Centres: **4** *Years:* **3** *Starting:* **2016**

85 – GGP15167

ANALYSIS OF NEURONAL ALTERATIONS ASSOCIATED TO PARK2 MUTATIONS AND THEIR RESCUE BY GENETIC AND PHARMACOLOGICAL THERAPIES TARGETING KAINATE RECEPTORS

ANALISI DELLE ALTERAZIONI NEURONALI ASSOCIATE A MUTAZIONI DEL GENE PARK2 E POSSIBILI TERAPIE GENETICHE E FARMACOLOGICHE MIRATE ALLA MODULAZIONE DEL RECETTORE DEL KAINATO

Coordinator **Andrea Ciammola**
Partner Maria Passafaro

Centres: **2** *Years:* **3** *Starting:* **2015**

86 – GGP12237

FUNCTION AND DYSFUNCTION OF THE PARKINSON'S DISEASE KINASE LRRK2 AT THE PRE-SYNAPTIC SITE

FUNZIONE E DISFUNZIONE A LIVELLO PRESINAPTICO DI LRRK2, UNA PROTEINA CHINASI ASSOCIATA ALLA MALATTIA DI PARKINSON

Coordinator **Elisa Greggio**
Partner Giovanni Piccoli, Franco Onofri, Michele Morari

Centres: **4** *Years:* **3** *Starting:* **2012**

87 – TCP14005

PARKINSON'S DISEASE AT THE SYNAPTIC SITE: SHORT AND LONG TERM IMPACT OF PATHOLOGICAL LRRK2 KINASE ACTIVITY

IL MORBO DI PARKINSON A LIVELLO PRESINAPTICO: IMPATTO A BREVE E LUNGO TERMINE DELL'ATTIVITÀ CHINASICA DI LRRK2

PI **Giovanni Piccoli**

DTI *Years:* **5** *Starting:* **2015**

88 – TGM16YMT06

DEVELOPMENT OF NEW THERAPEUTIC STRATEGIES FOR PARKINSON'S DISEASE

EFFETTI DELL'INIBIZIONE DELLA CALCINEURINA IN FORME GENETICHE DI MORBO DI PARKINSON CAUSATE DALLA MUTAZIONE G2019S IN LRRK2

PI **Michael Decressac**

TIGEM **2016 - 2021**

89 – GGP12115

MUTANT PRION PROTEIN IMPAIRS DELIVERY OF VOLTAGE GATED CALCIUM CHANNELS TO THE PRESYNAPTIC MEMBRANE: MECHANISMS OF NEUROTOXICITY AND POTENTIAL THERAPEUTIC STRATEGIES

LA PROTEINA PRIONICA MUTATA IMPEDISCE L'INSERZIONE DI CANALI AL CALCIO VOLTAGGIO-DIPENDENTI NELLA MEMBRANA PRESINAPTICA: ANALISI DEI MECCANISMI DI NEUROTOSSICITÀ E POTENZIALI STRATEGIE TERAPEUTICHE

Coordinator **Michela Matteoli**
Partner Roberto Chiesa

Centres: **2** *Years:* **3** *Starting:* **2013**

90 – GSP14001

FATAL FAMILIAL INSOMNIA: PREVENTIVE TREATMENT WITH DOXYCYCLINE OF AT RISK INDIVIDUALS

INSONNIA FATALE FAMILIARE: TRATTAMENTO PREVENTIVO CON DOXICICLINA IN SOGGETTI A RISCHIO GENETICO DI MALATTIA

Coordinator **Gianluigi Forloni**
Partner Benedetto Ignazio Roiter, Fabrizio Tagliavini

Centres: **3** *Years:* **3** *Starting:* **2015**

91 – GGP13033

ROLE OF THE NOVEL PRESYNAPTIC PROTEIN PRRT2 IN NEURONAL PHYSIOLOGY AND IN THE PATHOGENESIS OF PAROXYSMAL NEUROLOGICAL DISORDERS

RUOLO DELLA PROTEINA PRESINAPTICA PRRT2 NELLA FISIOLOGIA NEURONALE E NELLA PATOGENESI DEI DISORDINI PAROSSISTICI DEL SISTEMA NERVOSO

Coordinator **Fabio Benfenati**
Partner Federico Zara, Flavia Valtorta

Centres: **3** *Years:* **3** *Starting:* **2013**

92 – GGP15229

DELINEATING THE MOLECULAR PATHWAY AND PATHOGENIC MECHANISM UNDERLYING AUTOSOMAL DOMINANT LATERAL TEMPORAL EPILEPSY (ADLTE)

DETERMINAZIONE DEI MECCANISMI MOLECOLARE E PATOGENETICO CHE DETERMINANO L' EPILESSIA TEMPORALE LATERALE AUTOSOMICA DOMINANTE (ADLTE)

Coordinator **Carlo Nobile**
Partner Federico Zara

Centres: **2** *Years:* **3** *Starting:* **2015**

93 – GGP12147

THE ROLE OF NEURONAL NICOTINIC RECEPTORS IN THE PATHOGENESIS OF AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY (ADNFLE): A STUDY ON WILD-TYPE AND CONDITIONAL TRANSGENIC MICE EXPRESSING THE BETA2-V287L SUBUNIT

RUOLO DEI RECETTORI NICOTINICI NELLA PATOGENESI DELL'EPILESSIA NOTTURNA AUTOSOMICA DOMINANTE DEL LOBO FRONTALE (ADNFLE): UNO STUDIO SU TOPI CON ESPRESSIONE CONDIZIONALE DELLA SUBUNITÀ ß2-V287L

PI **Andrea Becchetti**

Centres: **1** *Years:* **3** *Starting:* **2012**

#94 – GGP13200

IN-DEPTH CLINICAL AND GENETIC STUDY OF FAMILIAL AND SPORADIC PATIENTS WITH NOCTURNAL FRONTAL LOBE EPILEPSY (NFLE): IDENTIFICATION OF NEW GENES BY WES IN 192 CASES NEGATIVE FOR MUTATIONS IN THE NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR SUBUNITS GENES

STUDIO CLINICO E GENETICO DI CASI SPORADICI E FAMILIARI DI EPILESSIA FRONTALE NOTTURNA (EFN)

Coordinator **Paolo Tinuper**
Partner Tommaso Pippucci

Centres: **2** *Years:* **3** *Starting:* **2014**

#95 – GEP14137

STRUCTURAL AND FUNCTIONAL STUDIES OF HCN1 CHANNEL MUTATIONS CAUSING EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY

STUDIO STRUTTURALE E FUNZIONALE DELLE MUTAZIONI DEI CANALI HCN1 RESPONSABILI DI ENCEFALOPATIA EPILETTICA INFANTILE PRECOCE

PI **Anna Moroni**

Centres: **1** *Years:* **1** *Starting:* **2015**

#96 – GGP15113

GENOTYPE-PHENOTYPE CORRELATIONS, NOVEL PATHOGENETIC MECHANISMS, AND PILOT CLINICAL STUDIES IN NEONATAL EPILEPSIES ASSOCIATED TO MUTATIONS IN THE KCNQ2/3 POTASSIUM CHANNEL GENES

CORRELAZIONI GENOTIPO-FENOTIPO, NUOVI MECCANISMI PATOGENETICI, E STUDIO CLINICO PILOTA NELLE EPILESSIE NEONATALI ASSOCIATE A MUTAZIONI NEI GENI KCNQ2/3 CODIFICANTI PER CANALI DEL POTASSIO

Coordinator **Maurizio Taglialatela**
Partner Pasquale Striano

Centres: **2** *Years:* **3** *Starting:* **2015**

#97 – GGP13034

MODELLING ETIOPATHOGENESIS OF THE FOXG1 DUPLICATION-LINKED VARIANT OF WEST SYNDROME

MODELLAMENTO DELLA EZIOPATOGENESI DELLA SINDROME DI WEST ASSOCIATA A DUPLICAZIONE DEL GENE FOXG1

Coordinator **Antonello Mallamaci**
Partner Pasquale Striano, Yuri Bozzi

Centres: **3** *Years:* **3** *Starting:* **2013**

#98 – GGP14198

DISSECTING THE ARISTALESS-RELATED HOMEOBOX EPILEPSY PATH TO FIND DRUGGABLE TARGET MOLECULES

ANALISI DELLA FUNZIONE DEL GENE ARISTALESS-RELATED HOMEOBOX NELL'EPILESSIA E IDENTIFICAZIONE DI BERSAGLI MOLECOLARI A SCOPO TERAPEUTICO

PI **Maria Giuseppina Miano**

Centres: **1** *Years:* **3** *Starting:* **2014**

#99 – GGP12265

ROLE OF DYSREGULATED ASTROCYTE-GABAERGIC INTERNEURON INTERACTIONS IN THE CONTROL OF SEIZURES IN MONOGENIC MODELS OF EPILEPSY

RUOLO DELLE INTERAZIONI TRA ASTROCITI ED INTERNEURONI NEL CONTROLLO DELLE CRISI EPILETTICHE IN MODELLI DI MALATTIE NEUROLOGICHE MONOGENICHE ASSOCIATE AD EPILESSIA

Coordinator **Giorgio Carmignoto**
Partner Marco De Curtis, Gian Michele Ratto

Centres: **3** *Years:* **3** *Starting:* **2012**

#100 – GGP14234

FAMILIAL HEMIPLEGIC MIGRAINE MECHANISMS

MECCANISMI DELL'EMICRANIA EMIPLEGICA FAMILIARE

PI **Daniela Pietrobon**

Centres: **1** *Years:* **3** *Starting:* **2015**

#101 – GGP16083

IMPAIRMENT OF GABAERGIC SIGNALING AND SYNAPTIC PLASTICITY AS KEY DETERMINANTS FOR NEURODEVELOPMENTAL DISORDERS: A STUDY FROM NL3R451C KNOCK-IN MICE, AN ANIMAL MODEL OF AUTISM

LE SINAPSI GABAERGICHE COME POSSIBILE BERSAGLIO DEI DISTURBI DELLO SPETTRO AUTISTICO: STUDIO SU TOPI TRANSGENICI PORTATORI DELLA MUTAZIONE UMANA R451C DELLA NEUROLIGINA 3

Coordinator **Enrico Cherubini**
Partner Andrea Barberis

Centres: **2** *Years:* **3** *Starting:* **2016**

#102 – GGP11188

ROLE OF ASTROCYTIC INWARDLY-RECTIFYING K+ CHANNELS IN THE PATHOGENESIS OF AUTISM SPECTRUM DISORDERS WITH SUSCEPTIBILITY TO SEIZURES (AUTISM-EPILEPSY PHENOTYPE)

RUOLO DEI CANALI RETTIFICATORI DI INGRESSO DEL K ASTROCITARI NELLA PATOGENESI DEI DISTURBI DELLO SPETTRO AUTISTICO CON SUSCETTIBILITÀ ALLE CRISI EPILETTICHE (FENOTIPO AUTISMO-EPILESSIA)

Coordinator **Federico Sicca**
Partner Mauro Pessia, Elena Ambrosini

Centres: **3** *Years:* **3** *Starting:* **2011**

#103 – GGP13145

ACTIVATION OF 5-HT7 RECEPTORS FOR SEROTONIN RESCUES HIPPOCAMPAL SYNAPTIC PLASTICITY, DENDRITE MORPHOLOGY, LEARNING AND BEHAVIOR IN A MOUSE MODEL OF FRAGILE X SYNDROME.

L'ATTIVAZIONE DI RECETTORI 5-HT7 PER LA SEROTONINA CORREGGE ALTERAZIONI NELLA PLASTICITÀ SINAPTICA, NELLA MORFOLOGIA DENDRITICA, NELL'APPRENDIMENTO E NEL COMPORTAMENTO IN UN MODELLO MURINO DELLA SINDROME DEL CROMOSOMA X FRAGILE.

Coordinator **Lucia Ciranna**
Partner Maria Vincenza Catania, Marcello Leopoldo

Centres: **3** *Years:* **3** *Starting:* **2013**

#104 – GGP14181

DROSOPHILA MELANOGASTER AS A MODEL TO STUDY THE ROLE OF THE FRAGILE X MENTAL RETARDATION PROTEIN IN THE GENOME STABILITY PATHWAY MEDIATED BY PIRNAS

DROSOPHILA MELANOGASTER COME MODELLO PER STUDIARE IL RUOLO DELLA PROTEINA FMRP, COINVOLTA NELLA SINDROME DELL'X FRAGILE NELLA STABILITÀ GENOMICA MEDIATA DAI PIRNA

PI **Maria Giuseppina Bozzetti**

Centres: **1** *Years:* **3** *Starting:* **2014**

#105 – GGP15257

EPIGENETIC AND SYNAPTIC MECHANISMS AFFECTED IN FRAGILE X SYNDROME

MECCANISMI EPIGENETICI E SINAPTICI ALLA BASE DELLA SINDROME X FRAGILE

Coordinator **Claudia Bagni**
Partner Elisabetta Tabolacci

Centres: **2** *Years:* **2** *Starting:* **2015**

#106 – GGP12097

ANALYSIS OF NEURONAL ALTERATIONS ASSOCIATED TO TM4SF2 MUTATIONS AND THEIR RESCUE BY GENETIC AND PHARMACOLOGICAL THERAPIES

ANALISI DELLE ALTERAZIONI NEURONALI ASSOCIATE A MUTAZIONI NEL GENE TM4SF2 A RESCUE MEDIANTE TERAPIE GENETICHE E FARMACOLOGICHE

Coordinator **Maria Passafaro**
Partner Patrizia D'adamo

Centres: **2** *Years:* **3** *Starting:* **2012**

#107 – GGP12126

ROLE OF RHO FAMILY GTPASES DURING NEURONAL DEVELOPMENT

RUOLO DELLE GTPASI DELLA FAMIGLIA RHO DURANTE LO SVILUPPO NEURONALE

PI **Ivan De Curtis**

Centres: **1** *Years:* **3** *Starting:* **2012**

#108 – GGP15096

UNDERSTANDING AND CORRECTING SETD5 HAPLOINSUFFICIENCY LEADING TO INTELLECTUAL DISABILITY

STUDIO E CORREZIONE DELL'APLOINSUFFICIENZA, LEGATA ALLA DISABILITÀ MENTALE, DEL GENE SETD5

Coordinator **Alessandro Sessa**
Partner Alessio Zippo, Massimiliano Andreazzoli

Centres: **3** *Years:* **3** *Starting:* **2015**

#109 – GEP14115

THE CHROMATIN BASIS OF NEUROLOGIC DYSFUNCTION IN THE SWI/SNF-RELATED AUTISM SYNDROME

LE BASI EPIGENETICHE DELLE ALTERAZIONI NEUROLOGICHE NELLA SINDROME AUTISTICA CORRELATA AL COMPLESSO SWI/SNF

PI **Giuseppe Testa**

Centres: **1** *Years:* **1** *Starting:* **2015**

#110 – GGP16131

NEURONAL DYSFUNCTIONS UNDERLYING PHELAN-MCDERMID SYNDROME AND THEIRS RESCUE BY GENETIC AND PHARMACOLOGICAL MODULATION OF MGLU5 SIGNALING

MODULAZIONE GENETICA E FARMACOLOGICA DEL RECETTORE MGLU5 PER MIGLIORARE I DIFETTI NEUROLOGICI NELLA SINDROME DI PHELAN-MCDERMID

Coordinator **Chiara Verpelli**
Partner Alessandro Tozzi

Centres: **2** *Years:* **3** *Starting:* **2016**

#111 – GGP13187

UNRAVELLING THE RETT SYNDROME: EFFECTS OF MECP2 MUTATIONS ON SYNAPTIC FUNCTION

CAPIRE I MECCANISMI CELLULARI ALLA BASE DELLA SINDROME DI RETT

Coordinator **Gian Michele Ratto**
Partner Laura Cancedda, Claudia Lodovichi, Carlo Sala

Centres: **4** *Years:* **3** *Starting:* **2013**

#112 – GGP14074

NEW STRATEGIES TO TARGET HYPER-EXCITABILITY IN RETT SYNDROME

NUOVE STRATEGIE PER CONTRASTARE L'IPER-ECCITABILITÀ PROPRIA DELLA SINDROME DI RETT

PI **Elena Battaglioli**

Centres: **1** *Years:* **3** *Starting:* **2015**

#113 – GGP15098

MECHANISMS UNDERLYING CDKL5 DISORDER FOR THE DESIGN OF TARGETED INTERVENTIONS

MECCANISMI ALLA BASE DEL DISORDINE CDKL5 PER LA RICERCA DI STRATEGIE TERAPEUTICHE MIRATE

Coordinator **Elisabetta Ciani**
Partner Charlotte Kilstrup-Nielsen, Maurizio Giustetto, Tommaso Pizzorusso

Centres: **4** *Years:* **3** *Starting:* **2015**

#114 – GGP13060

RING 14 SYNDROME: TOWARD A DETAILED GENOTYPE-PHENOTYPE CORRELATION

RING 14 SYNDROME: TOWARD A DETAILED GENOTYPE-PHENOTYPE CORRELATION

PI **Orsetta Zuffardi**

Centres: **1** *Years:* **2** *Starting:* **2013**

#115 – GGP13231

AN INTEGRATED STRATEGY TO FUNCTIONALLY DISSECT THE GENETIC AND EPIGENETIC MECHANISMS UNDERLYING KABUKI SYNDROME

UNA STRATEGIA INTEGRATA PER COMPRENDERE I MECCANISMI GENETICI ED EPIGENETICI ALLA BASE DELLA SINDROME KABUKI

Coordinator **Giuseppe Merla**
Partner Stefano Casola, Giuseppe Testa

Centres: **3** *Years:* **3** *Starting:* **2014**

#116 – GGP15110

BRIDGING TIMOTHY SYNDROME CAV1.2 CALCIUM CHANNEL MUTATIONS (TS1 AND TS2) TO AUTISM SPECTRUM DISORDERS

EFFETTI DELLE MUTAZIONI DEI CANALI DEL CALCIO CAV1.2 DELLA SINDROME DI TIMOTHY (TS1 E TS2) SUI DISTURBI DELLO SPETTRO AUTISTICO

PI **Emilio Carbone**

Centres: **1** *Years:* **3** *Starting:* **2015**

#117 – GEP13056

FUNCTIONAL ROLE OF EZH2 MUTATIONS IN WEAVER SYNDROME

RUOLO FUNZIONALE DI PROTEINE EZH2 MUTATE NELLA SINDROME DI WEAVER

PI **Giuseppina Caretti**

Centres: **1** *Years:* **1** *Starting:* **2014**

#118 – GEP13105

NEURODEVELOPMENTAL ALTERATIONS IN WEAVER SYNDROME: A CELL REPROGRAMMING-BASED APPROACH TO THE ELUCIDATION OF EPIGENETIC DISEASE MECHANISMS

SINDROME DI WEAVER: NUOVE TECNOLOGIE DI RIPROGRAMMAZIONE CELLULARE PER LO STUDIO DEI MECCANISMI PATOGENETICI ALL'ORIGINE DI QUESTA MALATTIA

PI **Giuseppe Testa**

Centres: **1** *Years:* **1** *Starting:* **2014**

#119 – GEP14118

IDENTIFICATION OF GENES FOR AICARDI SYNDROME BY EXOME SEQUENCING

IDENTIFICAZIONE DEL GENE PER LA SINDROME DI AICARDI ATTRAVERSO IL SEQUENZIAMENTO DELL'ESOMA.

PI **Federico Zara**

Centres: **1** *Years:* **1** *Starting:* **2015**

#120 – GGP13146

CLINICAL, GENETIC AND FUNCTIONAL STUDIES ON JOUBERT SYNDROME AND RELATED DISORDERS: A MODEL TO UNDERSTAND THE COMPLEXITY OF CILIOPATHIES

STUDI CLINICI, GENETICI E FUNZIONALI SULLA SINDROME DI JOUBERT PER COMPRENDERE LE CILIOPATIE

Coordinator **Enrico Silvio Bertini**
Partner Enza Maria Valente, Giangiacomo Consalez

Centres: **3** *Years:* **3** *Starting:* **2013**

#121 – GGP12095

IDENTIFICATION OF THERAPEUTIC TARGETS IN PRIMARY MICROCEPHALY THROUGH THE ANALYSIS OF THE CIT-K/ASPM PATHWAY

IDENTIFICAZIONE DI TARGET TERAPEUTICI NELLA MICROCEFALIA PRIMARIA ATTRAVERSO L'ANALISI DELLA VIA CIT-K/ASPM

PI **Ferdinando Di Cunto**

Centres: **1** *Years:* **3** *Starting:* **2012**

#122 – GEP14131

CLINICAL FINDINGS IN MOWAT-WILSON SYNDROME: A STUDY OF 80 PATIENTS

CORRELAZIONE GENOTIPO-FENOTIPO E RISONANZA MAGNETICA CEREBRALE NELLA SINDROME DI MOWAT-WILSON DA MUTAZIONE DI ZEB2: CREAZIONE DI UN DATABASE INTERNAZIONALE E APERTURA A STUDI FUTURI SUL RUOLO DEL GENE ZEB2 NELLO SVILUPPO DELL'ENCEFALO UMANO

PI **Livia Garavelli**

Centres: **1** *Years:* **1** *Starting:* **2015**

#123 – GEP14089

NGS TECHNIQUES TO EXPLORE UNUSUAL TCF4 MUTATIONS AND GENETIC HETEROGENEITY IN PATIENTS WITH PITT-HOPKINS SYNDROME PHENOTYPE

APPLICAZIONE DELLE TECNICHE DI SEQUENZIAMENTO DI NUOVA GENERAZIONE PER LA RICERCA DI MUTAZIONI ATIPICHE DEL GENE TCF4 E DI ETEROGENEITÀ GENETICA NELLA SINDROME DI PITT-HOPKINS

PI **Marcella Zollino**

Centres: **1** *Years:* **1** *Starting:* **2015**

#124 – GGP14005

SAMHD1, A NEW REGULATOR OF DNA REPLICATION INVOLVED IN AICARDI-GOUTIÈRES SYNDROME

SAMHD1, UN NUOVO REGOLATORE DELLA SINTESI DEL DNA IMPLICATO NELLA SINDROME DI AICARDI-GOUTIÈRES

PI **Chiara Rampazzo**

Centres: **1** *Years:* **2** *Starting:* **2014**

#125 – GGP15227

CROSSTALKS BETWEEN DNA DAMAGE RESPONSE AND RETROELEMENTS ACTIVITY IN THE PATHOGENESIS OF AICARDI-GOUTIÈRES SYNDROME

CONNESSIONI TRA RISPOSTA A DANNI AL DNA E ATTIVITÀ DEI RETROELEMENTI NELLA PATOGENESI DELLA SINDROME DI AICARDI-GOUTIÈRES

PI **Marco Muzi Falconi**

Centres: **1** *Years:* **3** *Starting:* **2015**

#126 – TGT16D03

THE AICARDI-GOUTIÈRES SYNDROME – FROM NUCLEIC ACID SENSING TO DISEASE MODELLING

IL SINDROME DI AICARDI-GOUTIÈRES – DAL RICONOSCIMENTO DEGLI ACIDI NUCLEICI AD UN MODELLO DI MALATTIA

PI **Anna Kajaste Rudnitski**

SR-TIGET **2016 - 2021**

#127 – GGP14211

PHENOTYPIC RESCUE OF THE DIGEORGE SYNDROME PHENOTYPE IN MOUSE MODELS

SINDROME DI DIGEORGE: APPROCCI TERAPEUTICI NEL MODELLO MURINO

PI **Antonio Baldini**

Centres: **1** *Years:* **3** *Starting:* **2015**

#128 – GGP12149

SHORT- AND LONG-TERM EFFECTS OF NEONATAL PHARMACOTHERAPY WITH A SELECTIVE GAMMA-SECRETASE INHIBITOR ON HIPPOCAMPAL DEVELOPMENT IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME

EFFETTI A BREVE E LUNGO TERMINE DI UNA FARMACOTERAPIA NEONATALE CON UN INIBITORE SELETTIVO DELLA GAMMA-SECRETASI SULLO SVILUPPO DELL'IPPOCAMPO NEL MODELLO MURINO DI SINDROME DI DOWN TS65DN

Coordinator **Renata Bartesaghi**
Partner Laura Calza', Jacopo Magistretti

Centres: **3** *Years:* **3** *Starting:* **2012**

#129 – GGP15043

NEUROTROPHIC TREATMENT TO RESCUE SYNAPTIC PLASTICITY AND COGNITIVE FUNCTIONS IN A MOUSE MODEL OF DOWN SYNDROME

TRATTAMENTO NEUROTROFICO PER RISTABILIRE LE FUNZIONI DI PLASTICITÀ SINAPTICA E COGNITIVE IN UN MODELLO MURINO DI SINDROME DI DOWN

PI **Andrea Contestabile**

Centres: **1** *Years:* **3** *Starting:* **2015**

#130 – TCP15021

ROLE OF INTRACELLULAR CHLORIDE ACCUMULATION IN DOWN SYNDROME PHYSIOPATHOLOGY

RUOLO DELLA ACCUMULAZIONE DI CLORO INTRACELLULARE NELLA FISIOPATOLOGIA DELLA SINDROME DI DOWN

PI **Laura Cancedda**

DTI *Years:* **5** *Starting:* **2016**

#131 – GEP13004

BRAIN MAPPING OF THE CORTICAL REPRESENTATION OF FACIAL MOVEMENTS IN PATIENTS WITH CONGENITAL FACIAL PALSY UNDERGOING SURGICAL PROCEDURES OF FACIAL ANIMATION

STUDIO DEI MECCANISMI DI CONTROLLO CEREBRALE DEI MOVIMENTI FACCIALI IN PAZIENTI CON SINDROME DI MOEBIUS DOPO L'INTERVENTO DI ANIMAZIONE FACCIALE

PI **Luigi Cattaneo**

Centres: **1** *Years:* **1** *Starting:* **2014**

#132 – GGP13022

EXPLOITING NEURAL STEM CELL-TARGETED MOUSE MODELS FOR IMPROVING THE UNDERSTANDING OF THE PATHOGENETIC MECHANISMS UNDERLYING TUBEROUS SCLEROSIS COMPLEX AND DEVELOPING NOVEL THERAPEUTIC APPROACHES

NUOVI MODELLI ANIMALI DI SCLEROSI TUBEROSA PER MIGLIORARE LA COMPRENSIONE DEI MECCANISMI PATOGENETICI E SVILUPPARE NUOVI APPROCCI TERAPEUTICI

Coordinator **Rossella Galli**
Partner Pietro Luigi Poliani

Centres: **2** *Years:* **3** *Starting:* **2013**

#133 – GGP14265

BAZ1B AND GTF2I DOSAGE CONTROLS THE TRANSCRIPTIONAL PROGRAM OF CELL TYPES AFFECTED IN WILLIAMS-BEUREN AND 7Q11.23 MICRODUPLICATION SYNDROME PATIENTS

IL DOSAGGIO GENICO DI BAZ1B E GTIF2I CONTROLLA IL PROGRAMMA TRASCRIZIONALE DI TIPI CELLULARI ALTERATI IN PAZIENTI AFFETTI DA SINDROME DI WILLIAMS-BEUREN O DA SINDROME DA MICRODUPLICAZIONE DELLA REGIONE 7Q11.23

Coordinator **Giuseppe Testa**
Partner Giuseppe Merla

Centres: **2** *Years:* **3** *Starting:* **2015**

#134 – GEP14102

THERAPEUTIC POTENTIAL OF CERULOPLASMIN ADMINISTRATION IN ACERULOPLASMINEMIA

POTENZIALE TERAPEUTICO DELLA SOMMINISTRAZIONE DI CERULOPLASMINA IN ACERULOPLASMINEMIA

PI **Massimo Alessio**

Centres: **1** *Years:* **1** *Starting:* **2015**

#135 – GEP14076

A DROSOPHILA MODEL FOR STUDYING NEUROLOGICAL DEFECTS ASSOCIATED WITH CONGENITAL DISORDER OF GLYCOSYLATION TYPE IIE

LA DROSOPHILA COME SISTEMA MODELLO PER LO STUDIO DEI DIFETTI NEUROLOGICI ASSOCIATI ALLA MALATTIA COG7-CDG

PI **Maria Grazia Giansanti**

Centres: **1** *Years:* **1** *Starting:* **2015**

#136 – GEP14141

MOLECULAR AND CELLULAR UNDERPINNINGS OF THE NEUROLOGICAL PHENOTYPES ASSOCIATED TO MITOCHONDRIAL CITRATE CARRIER (SLC25A1) DEFICIENCY

BASI MOLECOLARI E CELLULARI DEL FENOTIPO NEUROLOGICO ASSOCIATO AL DIFETTO DEL CARRIER MITOCONDRIALE DEL CITRATO (SLC15A1)

PI **Luigi Palmieri**

Centres: **1** *Years:* **1** *Starting:* **2015**

#137 – GGP13149

A TRIVALENT URICOLYTIC PREPARATION FOR THE ENZYMATIC THERAPY OF HPRT DEFICIENCY AND LESCH-NYHAN DISEASE

UN PREPARATO URICOLITICO TRIVALENTE PER LA TERAPIA ENZIMATICA DELLA CARENZA DI HPRT E DELLA MALATTIA DI LESCH-NYHAN.

Coordinator **Riccardo Percudani**
Partner Maria Pia Rastaldi

Centres: **2** *Years:* **3** *Starting:* **2013**

#138 – TGM16YMT04

DEVELOPING AAV-MEDIATED GENE THERAPY APPROACHES TO TREAT CNS IN LSDS

SVILUPPO DI APPROCCI DI TERAPIA GENICA MEDIATA DA AAV PER IL TRATTAMENTO DELLA PATOLOGIA NEUROLOGICA IN LSDS

PI **Alessandro Fraldi**

TIGEM **2016 - 2021**

#139 – TGM16YMT05

TARGETING DOWNSTREAM PATHOGENIC PATHWAYS IN NEURODEGENERATIVE LSDS

"TARGETING" DEI PROCESSI PATOGENETICI A VALLE DELLA DISFUNZIONE LISOSOMIALE NELLE LSD NEURODEGENERATIVE.

PI **Alessandro Fraldi**

TIGEM **2016 - 2021**

#140 – TGT16D02

LYSOSOMAL STORAGE DISORDERS (LSD) - MODELING THE DISEASE COMPLEXITY TO REFINE GENE/CELL THERAPY TREATMENT STRATEGIES

MALATTIE DA ACCUMULO LISOSOMIALE (LSD) - MODELLARE LA COMPLESSITA' DELLA PATOLOGIA PER OTTIMIZZARE STRATEGIE DI TERAPIA GENICA E CELLULARE

PI **Angela Gritti**

SR-TIGET **2016 - 2021**

#141 – GEP13108

IN VITRO FEASIBILITY STUDY OF A PROTEIN REPLACEMENT THERAPY FOR METHYLMALONIC ACIDEMIA WITH HOMOCYSTINURIA CBLC TYPE: DELIVERY OF RECOMBINANT HUMAN MMACHC PROTEINS INTO PRIMARY FIBROBLASTS FROM CBLC PATIENTS

STUDIO DI FATTIBILITÀ PER LO SVILUPPO IN VITRO DI UNA TERAPIA ENZIMATICA SOSTITUTIVA MIRATA AL TRATTAMENTO DELL'ACIDURIA METILMALONICA CON OMOCISTINURIA DI TIPO CBLC

PI **Laura Tinti**

Centres: **1** *Years:* **1** *Starting:* **2014**

#142 – GGP13183

ENLIGHTENING MOLECULAR MECHANISMS OF ABNORMAL CEREBELLUM DEVELOPMENT IN MOUSE MODELS OF HUMAN NIEMANN-PICK C 1 DISEASE: THE EFFICACY OF HYDROXYPROPYL-BETACYCLODEXTRIN IN CORRECTING THE PHENOTYPE

STUDIO DEI MECCANISMI MOLECOLARI ALLA BASE DELLE ANOMALIE DELLO SVILUPPO DEL CERVELLETTO NELLA MALATTIA DI NIEMANN PICK C1: EFFICACIA DELLA CICLODESTRINA NEL CONTRASTARE I SINTOMI DELLA MALATTIA

PI **Maria Teresa Fiorenza**

Centres: **1** *Years:* **2** *Starting:* **2013**

OTHER GENETIC DISEASES

#143 – TGM16YINST

TIGEM INSTITUTE OVERVIEW

OVERVIEW DELL'ISTITUTO TELETHON DI GENETICA E MEDICINA (TIGEM)

Andrea Ballabio

TIGEM **2016 - 2021**

#144 – TGT16YINST

SR-TIGET INSTITUTE OVERVIEW

OVERVIEW DELL'ITITUTO SAN RAFFAELE TELETHON PER LA TERAPIA GENICA (SR-TIGET)

Luigi Naldini

SR-TIGET **2016 - 2021**

#145 – TGT16B01

SAFETY AND EFFICACY OF LENTIVIRAL VECTOR BASED HEMATOPOIETIC STEM CELL GENE THERAPY IN PATIENTS AND PRECLINICAL MODELS

STUDI DI BIOSICUREZZA ED EFFICACIA DELLA TERAPIA GENICA BASATA SU CELLULE STAMINALI EMATOPOIETICHE E VETTORI LENTIVIRALI IN SPERIMENTAZIONI CLINICHE E MODELLI PRECLINICI

PI **Eugenio Montini**

SR-TIGET **2016 - 2021**

#146 – TGT16C01

EFFICIENT EX VIVO ENGINEERING AND EXPANSION OF HIGHLY PURIFIED HUMAN HEMATOPOIETIC STEM/PROGENITOR CELL POPULATIONS FOR GENE THERAPY

INGEGNERIZZAZIONE GENETICA ED ESPANSIONE DI CELLULE STAMINALI EMATOPOIETICHE ALTAMENTE PURIFICATE PER LA TERAPIA GENICA

PI **Bernhard Gentner**

SR-TIGET **2016 - 2021**

#147 – TGT16C03

MECHANISMS OF ENHANCED HEMATOPOIETIC STEM CELL TRANSDUCTION AND NUCLEIC ACID SENSING

MECCANISMI DI EFFICIENTE TRASDUCZIONE E DI RICONOSCIMENTO DEGLI ACIDI NUCLEICI NELLE CELLULE STAMINALI EMATOPOIETICHE

PI **Anna Kajaste Rudnitski**

SR-TIGET **2016 - 2021**

#148 – TGT16E06

USE OF MSC TO OPTIMIZE TRANSPLANTATION OUTCOME OF GENE EDITED-HSC

UTILIZZO DELLE CELLULE STROMALI MESENCHIMALI PER OTTIMIZZARE L'OUTCOME DEL TRAPIANTO DI CELLULE STAMINALI EMATOPOIETICHE EDITATE

PI **Maria Ester Bernardo**
Co-PI Alessandro Aiuti

SR-TIGET **2016 - 2021**

#149 – TGT16F01

MECHANISTIC PRINCIPLES OF PERMANENT EPIGENETIC SILENCING AND THEIR EXPLOITATION TO IMPROVE TARGETED EPIGENETIC EDITING.

MECCANISIMI DI SILENZIAMENTO EPIGENETICO E LORO UTILIZZO PER MIGLIORARE L'EDITING EPIGENETICO MIRATO.

PI **Angelo Lombardo**

SR-TIGET **2016 - 2021**

#150 – TGT16F04

GENOMIC MECHANISMS OF HUMAN MYELOPOIESIS: IMPLICATIONS FOR BONE MARROW RECONSTITUTION AFTER GENE THERAPY

MECCANISMI GENOMICI DELLA MIELOPOIESI NELL'UOMO: IMPLICAZIONI PER LA RICOSTITUZIONE DEL MIDOLLO OSSEO DOPO TERAPIA GENICA

PI **Renato Ostuni**

SR-TIGET **2016 - 2021**

#151 – TGT16G03

INNOVATIVE STRATEGIES TO PROMOTE AG-SPECIFIC TOLERANCE

SVILUPPO DI STRATEGIE INNOVATIVE PER LA PROMOZIONE DI TOLLERANZA IMMUNOLOGICA ANTIGENE-SPECIFICA

PI **Eugenio Montini**
Co-PI Andrea Ditadi, Angelo Lombardo

SR-TIGET **2016 - 2021**

#152 – TGM16YCBDM02

PHOSPHOINOSITIDES AND THE GOLGI COMPLEX: THE ROLE OF ER-GOLGI CONTACT SITES

FOSFOINOSITIDI E L'APPARATO DEL GOLGI: RUOLO DEI SITI DI CONTATTO RETICOLO ENDOPLASMATICO-GOLGI.

PI **Maria Antonietta De Matteis**

TIGEM **2016 - 2021**

#153 – GSP15001

TELETHON UNDIAGNOSED DISEASE PROGRAM (UDP) 2016-2018

PROGRAMMA TELETHON PER LE MALATTIE SENZA DIAGNOSI 2016-2018

Coordinator **Vincenzo Nigro**
Partner Bruno Dallapiccola, Angelo Selicorni, Nicola Brunetti Pierrii

Centres: **4** *Years:* **3** *Starting:* **2016**

#154 – TGM16YGM02

SYSTEMATIC SEARCH FOR MICRORNAS THAT PLAY A ROLE IN PHOTORECEPTOR DEGENERATION

IDENTIFICAZIONE DI MICRORNA COINVOLTI NEI PROCESSI DI DEGENERAZIONE RETINICA

PI **Sandro Banfi**

TIGEM **2016 - 2021**

#155 – TGM16YGM02I

MIR-204/211 IN EYE DEVELOPMENT AND DISEASE: AN INTRICATE RELATIONSHIP

MIR-204/211 NELLO SVILUPPO E MALATTIE DELL'OCCHIO: UN'INTRICATA RELAZIONE

PI **Ivan Conte**

TIGEM **2016 - 2021**

#156 – TGM16YMT01

LARGE GENE TRANSFER TO THE RETINA

TRASFERIMENTO DI GENI DI GRANDI DIMENSIONI ALLA RETINA

PI **Alberto Auricchio**

TIGEM **2016 - 2021**

#157 – GGP15114

COMPREHENSIVE ANALYSIS OF THE MOLECULAR PATHOGENESIS OF GYRATE ATROPHY TOWARDS THE RATIONALIZATION AND THE OPTIMIZATION OF THE THERAPY WITH VITAMIN B6

STUDIO DELLA PATOGENESI MOLECOLARE DELL'ATROFIA GIRATA COME BASE PER LA RAZIONALIZZAZIONE E OTTIMIZZAZIONE DELLA TERAPIA CON VITAMINA B6

Coordinator **Barbara Cellini**
Partner Leonardo Salviati

Centres: **2** *Years:* **3** *Starting:* **2016**

#158 – GGP15091

EXTENDING THE OPTIC ATROPHY 1 DEPENDENT CRISTAE REMODELING: FROM MODELS TO A THERAPY OF AUTOSOMAL DOMINANT OPTIC ATROPHY

IL RIMODELLAMENTO DELLE CRISTE CONTROLLATO DA OPA1: DAI MODELLI ALLE BASI PER LA TERAPIA DELL'ATROFIA OTTICA DOMINANTE

PI **Luca Scorrano**

Centres: **1** *Years:* **3** *Starting:* **2015**

#159 – GGP16010

CONE DYSTROPHIES AND RETINAL DEGENERATION FROM PROTEIN STRUCTURES TO BIOLOGICAL NETWORKS. TOWARD THE DESIGN OF THERAPEUTIC MOLECULES

DISTROFIE DEI CONI E DEGENERAZIONE RETINICA, DALLA STRUTTURA DELLE PROTEINE ALLE RETI BIOLOGICHE. VERSO L'IDENTIFICAZIONE DI NUOVE MOLECOLE TERAPEUTICHE

Coordinator **Daniele Dell'Orco**
Partner Mario Milani, Lorenzo Cangiano

Centres: **3** *Years:* **3** *Starting:* **2016**

#160 – GGP11210

INTEGRATED IN SILICO, IN VITRO, AND IN VIVO STUDIES TOWARDS THE DESIGN OF MOLECULES WITH THERAPEUTIC POTENTIAL FOR RETINITIS PIGMENTOSA

STUDI INTEGRATI IN SILICO, IN VITRO ED IN VIVO VERSO LA PROGETTAZIONE DI POTENZIALI AGENTI TERAPEUTICI PER LA RETINITE PIGMENTOSA

Coordinator **Francesca Fanelli**
Partner Valeria Marigo

Centres: **2** *Years:* **3** *Starting:* **2011**

#161 – GGP14022

DEVELOPMENT AND IMPLANT OF THE PHOTOVOLTAIC ARTIFICIAL RETINA IN THE PIG WITH PHOTORECEPTOR DEGENERATION: TOWARDS THE HUMAN PHASE-1 EXPERIMENTATION

SVILUPPO ED IMPIANTO DELLA RETINA ARTIFICIALE FOTOVOLTAICA NEL MAIALE CON DEGENERAZIONE DEI FOTORECETTORI: ULTIMO STADIO VERSO LA SPERIMENTAZIONE NELL'UOMO

Coordinator **Grazia Pertile**
Partner Fabio Benfenati

Centres: **2** *Years:* **2** *Starting:* **2014**

#162 – GGP14180

EXPLORING PEDF AS THERAPEUTIC AGENT FOR RETINITIS PIGMENTOSA

IL PEDF COME AGENTE TERAPEUTICO PER LA RETINITE PIGMENTOSA

PI **Valeria Marigo**

Centres: **1** *Years:* **3** *Starting:* **2014**

#163 – TGM16YMT02

TRANSCRIPTIONAL REPRESSION AND GENOME EDITING FOR AUTOSOMAL DOMINANT RP

REPRESSIONE TRASCRIZIONALE E GENOME EDITING PER LA RETINITE PIGMENTOSA AUTOSOMICA DOMINANTE

PI **Enrico Surace**

TIGEM **2016 - 2021**

#164 – GGP13114

INNER EAR CONNEXINS: ROLE IN HEARING ACQUISITION AND DFNB1 PATHOPHYSIOLOGY

PATOGENESI DELLA SORDITÀ EREDITARIA: RUOLO DELLE CONNESSINE NELL'ORECCHIO INTERNO PER LO SVILUPPO DEL SENSO DELL'UDITO

PI **Fabio Mammano**

Centres: **1** *Years:* **3** *Starting:* **2013**

#165 – GGP13177

RESCUE OF DIAMOND-BLACKFAN ANEMIA HAPLOINSUFFICIENCY BY KNOCK-UP OF THE DEFICIENT PROTEIN

CORREZIONE DELLA CARENZA DI GLOBULI ROSSI NELL'ANEMIA DI DIAMOND-BLACKFAN TRAMITE UNA NUOVA TECNICA MOLECOLARE A BASE DI RNA

Coordinator **Irma Dianzani**
Partner Fabrizio Loreni

Centres: **2** *Years:* **3** *Starting:* **2013**

#166 – GGP11076

TNEW PHARMACOLOGICAL TARGETS IN FANCONI ANEMIA

NUOVI BERSAGLI FARMACOLOGICI NELL'ANEMIA DI FANCONI

Coordinator **Adriana La Volpe**
Partner Maria Ciaramella, Anna Savoia

Centres: **3** *Years:* **3** *Starting:* **2012**

#167 – GGP14285

THE METABOLIC ABNORMALITY OF HEREDITARY HEMOCHROMATOSIS: MECHANISMS AND CONSEQUENCES OF HEPCIDIN DEFICIENCY ON GLUCOSE HOMEOSTASIS AND INSULIN SIGNALING

ANOMALIE E ADATTAMENTO METABOLICO NELL'EMOCROMATOSI EREDITARIA: MECCANISMI E CONSEGUENZE DELLA CARENZA DI EPCIDINA

PI **Antonello Pietrangelo**

Centres: **1** *Years:* **3** *Starting:* **2014**

#168 – GGP12025

HEMOCHROMATOSIS: FROM GENES TO CLINICS AND BACK

EMOCROMATOSI: DAI GENI ALLA CLINICA E RITORNO

PI **Clara Camaschella**

Centres: **1** *Years:* **3** *Starting:* **2012**

#169 – GGP15064

NOVEL PHARMACOLOGIC APPROACHES TO HEPCIDIN GENETIC DISORDERS

NUOVI APPROCCI FARMACOLOGICI PER DISORDINI GENETICI DELL'EPCIDINA

Coordinator **Paolo Arosio**
Partner Laura Silvestri

Centres: **2** *Years:* **2** *Starting:* **2016**

#170 – GGP14042

INSTALLING FVIII-SPECIFIC TOLERANCE IN HEMOPHILIA A VIA TRYPTOPHAN CATABOLITES AND ARYL HYDROCARBON RECEPTOR (AHR) ACTIVATION

INDUZIONE DELLA TOLLERANZA VERSO LA PROTEINA RFVIII NELL'EMOFILIA A ATTRAVERSO METABOLITI DEL TRIPTOFANO E L'ATTIVAZIONE DEL RECETTORE AHR

PI **Francesca Fallarino**

Centres: **1** *Years:* **2** *Starting:* **2014**

#171 – TGT16YD04

LIVER-DIRECTED GENE THERAPY FOR HEMOPHILIA WITH LENTIVIRAL VECTORS

TERAPIA GENICA DIRETTA AL FEGATO PER L'EMOFILIA CON VETTORI LENTIVIRALI

PI **Luigi Naldini**
Co-PI Alessio Cantore

SR-TIGET **2016 - 2021**

#172 – GGP14190

DEVELOPMENT OF A RNA-BASED THERAPEUTIC APPROACH FOR HEMOPHILIA B CAUSED BY EXON-SKIPPING MUTATIONS

SVILUPPO DI UN NUOVO APPROCCIO TERAPEUTICO PER L'EMOFILIA B CAUSATA DA MUTAZIONI CHE CAUSANO SALTO DELL'ESONE MEDIANTE MODULAZIONE DEL PROCESSAMENTO DI RNA MESSAGGERO

Coordinator **Mirko Pinotti**
Partner Franco Pagani

Centres: **2** *Years:* **2** *Starting:* **2014**

#173 – GGP13246

POST GWAS FUNCTIONAL CHARACTERIZATION OF BCL11A LOCUS TOWARD THE DEVELOPMENT OF A TREATMENT FOR ß-THALASSEMIA

CARATTERIZZAZIONE FUNZIONALE DEL GENE BCL11A, VOLTA ALLO SVILUPPO DI UNA NUOVA TERAPIA PER LA CURA DELLA BETA-TALASSEMIA

Coordinator **Manuela Uda**
Partner Paolo Moi, Andrea Angius

Centres: **3** *Years:* **2** *Starting:* **2013**

#174 – GGP14065

VALIDATION OF THE HUMAN DELTA GLOBIN GENE AS A THERAPEUTIC TARGET FOR BETA THALASSEMIA AND SICKLE CELL DISEASE

VALIDAZIONE DEL GENE DELTA GLOBINICO UMANO QUALE TARGET TERAPEUTICO PER LA BETA TALASSEMIA E L'ANEMIA FALCIFORME

PI **Maria Serafina Ristaldi**

Centres: **1** *Years:* **3** *Starting:* **2014**

#175 – TGT16A03

REGULATION OF HEMATOPOIESIS IN NORMAL AND STRESSED CONDITIONS

REGOLAZIONE DELL'EMATOPOIESI IN CONDIZIONI NORMALI E DI STRESS

PI **Giuliana Ferrari**

SR-TIGET **2016 - 2021**

#176 – TGT16A04

RESTORATION OF HEMATOPOIESIS FOLLOWING GENE CORRECTION IN BETA-THAL

STUDIO DELL'EMATOPOIESI IN SEGUITO ALLA TERAPIA GENICA IN BTHAL

PI **Giuliana Ferrari**

SR-TIGET **2016 - 2021**

#177 – TGT16E05

HSPC AGING IN PHYSIOLOGY AND DISEASE

INVECCHIAMENTO CELLULARE EMATOPOIETICO IN CONDIZIONI FISIOLOGICHE E PATOLOGICHE

PI **Raffaella Di Micco**

SR-TIGET **2016 - 2021**

#178 – GGP13082

COMBINING NEXT GENERATION SEQUENCING WITH CLINICAL STUDIES TO UNRAVEL NOVEL INHERITED THROMBOCYTOPENIAS AFFECTING HALF OF THE PATIENTS

IDENTIFICAZIONE DI NUOVI GENI COINVOLTI NELL'INSORGENZA DI PIASTRINOPENIE EREDITARIE TRAMITE TECNOLOGIE DI SEQUENZIAMENTO DI ULTIMA GENERAZIONE

Coordinator **Marco Seri**
Partner Patrizia Noris, Anna Savoia

Centres: **3** *Years:* **2** *Starting:* **2014**

#179 – GGP15063

PLATELET TYPE-VON WILLEBRAND DISEASE: A RARE, UNDERDIAGNOSED, INHERITED BLEEDING DISORDER. STUDIES TO IMPROVE THE DIAGNOSIS AND TO UNDERSTAND THE MECHANISMS OF PLATELET DYSFUNCTION AND MACROTHROMBOCYTOPENIA

LA MALATTIA DI VON WILLEBRAND - PLATELET TYPE: UN RARO DISORDINE EMORRAGICO EREDITARIO SPESSO NON DIAGNOSTICATO. STUDI PER MIGLIORARE LA DIAGNOSI E PER COMPRENDERE I MECCANISMI DELLA DISFUNZIONE PIASTRINICA E DELLA MACROTROMBOCITOPENIA

PI **Paolo Gresele**

Centres: **1** *Years:* **3** *Starting:* **2016**

#180 – GGP14144

CRYOPYRIN ASSOCIATED PERIODIC SYNDROMES (CAPS): INVESTIGATIONS ON PATIENTS BLOOD CELLS AND IN A KNOCK-IN MOUSE MODEL TO EXPLOIT NOVEL APPROACHES FOR THE MODULATION OF THE NLRP3 INFLAMMASOME

SINDROME PERIODICA ASSOCIATA A DEFICIT DI CRIOPIRINA (CAPS): STUDI SU CELLULE PRIMARIE DI PAZIENTI E SU UN MODELLO ANIMALI PER IDENTIFICARE NUOVI APPROCCI TERAPAUTICI PER LA MODULAZIONE DEL NLRP3 INFLAMMASOMA

Coordinator **Marco Gattorno**
Partner Anna Rubartelli

Centres: **2** *Years:* **3** *Starting:* **2014**

#181 – GGP15241

GENETICS, PHYSIOPATHOLOGY AND THERAPEUTIC OPTIONS IN A NOVEL MONOGENIC MULTISYSTEM INFLAMMATORY DISORDER DUE TO DNASE II DEFICIENCY

STUDIO DI UNA NUOVA MALATTIA INFIAMMATORIA MULTISISTEMICA LEGATA A MUTAZIONE DELLA DESOSSIRIBONUCLEASI II: DALLA FISIOPATOLOGIA ALLO SVILUPPO DI NUOVE OPZIONI TERAPEUTICHE

Coordinator **Alberto Tommasini**
Partner Marco Gattorno

Centres: **2** *Years:* **3** *Starting:* **2015**

#182 – TGT16F03

DEVELOPMENT OF NEW TECHNOLOGIES TO PROMOTE THYMIC REGENERATION FOR THE TREATMENT OF PRIMARY IMMUNODEFICIENCIES

SVILUPPO DI TECNOLOGIE INNOVATIVE PER PROMUOVERE LA RIGENERAZIONE TIMICA PER IL TRATTAMENTO DI IMMUNODEFICIENZE PRIMARIE

PI **Marita Bosticardo**

SR-TIGET **2016 - 2021**

#183 – GGP16003

THE CILIOPATHY-RELATED TRAFFIC MACHINERY: A NEW PLAYER IN IMMUNE SYNAPSE ASSEMBLY IN T LYMPHOCYTES AND A DISEASE TARGET IN COMMON VARIABLE IMMUNODEFICIENCY (CVID)

IL MACCHINARIO DI TRASPORTO IMPLICATO NELLE CILIOPATIE: UN NUOVO PROTAGONISTA NELL'ASSEMBLAGGIO DELLA SINAPSI IMMUNOLOGICA NEI LINFOCITI T E UN BERSAGLIO DI MALATTIA NELL'IMMUNODEFICIENZA COMUNE VARIABILE

PI **Cosima T. Baldari**

Centres: **1** *Years:* **3** *Starting:* **2016**

#184 – GGP15109

X-LINKED CHRONIC GRANULOMATOSIS: MOLECULAR AND CELLULAR MECHANISMS UNDERLYING INTESTINAL INFLAMMATION

X-GRANULOMATOSI CRONICA: MECCANISMI MOLECOLARI E CELLULARI RESPONSABILI DELLA INFIAMMAZIONE INTESTINALE

Coordinator **Barbara Cassani**
Partner Andrea Finocchi

Centres: **2** *Years:* **3** *Starting:* **2015**

#185 – TGT16YA06

XCGD HUMAN CD34+ CELLS TRANSDUCED WITH LENTIVIRAL REGULATED VECTOR DISPLAY RESTORED GP91PHOX EXPRESSION IN MYELOID CELLS IN VIVO

CELLULE UMANE XCGD CD34 + TRASDOTTE CON UN VETTORE LENTIVIRALE REGOLATO MOSTRANO RIPRISTINO DELL'ESPRESSIONE DI GP91PHOX NELLE CELLULE MIELOIDI IN VIVO

PI **Alessandro Aiuti**

SR-TIGET **2016 - 2021**

#186 – TGT16E04

ADVANCED GENETIC ENGINEERING OF HEMATOPOIESIS FOR THE TREATMENT OF INHERITED DISEASES

MANIPOLAZIONE GENETICA AVANZATA DELL'EMATOPOIESI PER IL TRATTAMENTO DI MALATTIE EREDITARIE

PI **Luigi Naldini**

SR-TIGET **2016 - 2021**

#187 – GGP13155

A NOVEL AID STRUCTURE PROVIDING NEW INSIGHT INTO HIGM2

NUOVA LUCE SUL GENE AID E LA SINDROME DI IMMUNODEFICIENZA CON IPER-IGM DI TIPO II

PI **Kerstin Maike Schmitz**

Centres: **1** *Years:* **2** *Starting:* **2013**

#188 – GGP15209

EXPLORING THE PATHOGENETIC BASIS OF ICF SYNDROME WITH HUMAN INDUCED PLURIPOTENT STEM CELLS

STUDIO DELLA PATOGENESI DELLA SINDROME ICF ATTRAVERSO L'USO DI CELLULE STAMINALI PLURIPOTENTI INDOTTE UMANE

PI **Maria R. Matarazzo**

Centres: **1** *Years:* **3** *Starting:* **2015**

#189 – GGP16252

SAP-MEDIATED DGKA INHIBITION TRIGGERS A NOVEL CELL FATE SWITCH IN ANTIGEN-ACTIVATED T CELLS: IMPLICATIONS FOR XLP1 THERAPY

L'INIBIZIONE DI DGK-ALFA È UN REOSTATO CHE DETERMINA IL DESTINO CELLULARE DEI LINFOCITI T ATTIVATI: IMPLICAZIONI PER LA TERAPIA DI XLP1

Coordinator **Andrea Graziani**
Partner Gianluca Baldanzi

Centres: **2** *Years:* **3** *Starting:* **2016**

#190 – TGT16E02

TARGETED GENOME EDITING IN RECOMBINATION ACTIVATING GENE 1 (RAG1): A PRECISE CORRECTION OF THE GENETIC DEFECT IN HUMAN SCID

TERAPIA PER IL TRATTEMENTO DI IMMUNODEFICIENZE COMBINATE SEVERE CAUSATE DA MUTAZIONI NEL GENE RAG1 MEDIANTE GENE EDITING

PI **PI** **Anna Villa**

SR-TIGET **2016 - 2021**

#191 – TGT16C04

A HUMAN PLURIPOTENT STEM CELLS-BASED PLATFORM TO MODEL PHYSIOLOGICAL AND DISEASED HSC DEVELOPMENT

USO DI CELLULE STAMINALI PLURIPOTENTI UMANE PER MODELLARE LO SVILUPPO FISIOLOGICO E PATOLOGICO DELLE CELLULE STAMINALI EMATOPOIETICHE.

PI **Andrea Ditadi**

SR-TIGET **2016 - 2021**

#192 – TGT16YA01

GENE THERAPY FOR INHERITED DISEASES: FROM EXPERIMENTAL TRIALS TO MARKET REGISTRATION

LA TERAPIA GENICA APPLICATA A MALATTIE EREDITARIE: DAGLI STUDI CLINICI SPERIMENTALI ALLA REGISTRAZIONE

PI **Alessandro Aiuti**

SR-TIGET **2016 - 2021**

#193 – TGT16E03

TARGETED GENE CORRECTION IN T CELLS AND HEMATOPOIETIC STEM/PROGENITOR CELLS FOR THE TREATMENT OF PRIMARY IMMUNODEFICIENCIES

CORREZIONE GENICA MIRATA DI CELLULE T E STAMINALI/PROGENITRICI EMATOPOIETICHE PER IL TRATTAMENTO DELLE IMMUNODEFICIENCE PRIMARIE

PI **Pietro Genovese**
Co-PI Anna Villa

SR-TIGET **2016 - 2021**

#194 – GGP14281

PLASMACYTOID DENDRITC CELLS FUNCTIONS AND AUTOIMMUNITY IN WISKOTT-ALDRICH SYNDROME

CELLULE DENDRITICHE PLASMACITOIDI E INTERFERONE DI TIPO PRIMO NELLO SVILUPPO DEI FENOMENI AUTOIMMUNI NELLA SINDROME DI WISKOTT-ALDRICH

PI **Federica Benvenuti**

Centres: **1** *Years:* **3** *Starting:* **2015**

#195 – TGT16B02

HSPC BIOLOGY: IN VIVO CLONAL TRACKING AND LINEAGE MODELING

TRACKING CLONALE DELLE CELLULE STAMINALI E DEI PROGENITORI EMATOPOIETICI IN VIVO IN ESSERI UMANI.

PI **Alessandro Aiuti**

SR-TIGET **2016 - 2021**

#196 – GEP14111

ROLE OF UNPRENYLATED 2',3'-CYCLIC-NUCLEOTIDE 3'-PHOSPHODIESTERASE IN THE MOLECULAR MECHANISMS RESPONSIBLE FOR NEUROINFLAMMATION AND NEUROLOGICAL IMPAIRMENTS IN MEVALONATE KINASE DEFICIENCY

RUOLO DELLA DIFETTIVA PRENILAZIONE DELLA 2',3'- NUCLEOTIDE CICLICO 3'-FOSFODIESTERASI NEI MECCANISMI MOLECOLARI RESPONSABILI DELLA NEUROINFIAMMAZIONE E DELLE ALTERAZIONI NEUROLOGICHE NELLA SINDROME DA DEFICIT DI MEVALONATO CHINASI

PI **Maurizio Bifulco**

Centres: **1** *Years:* **1** *Starting:* **2015**

#197 – GGP16277

TARGETING LIPIDS IN CLN8-ASSOCIATED NCL DISEASES: STRUCTURAL AND FUNCTIONAL INTERACTION OF CLN8 WITH VESICLE-ASSOCIATED MEMBRANE PROTEIN-ASSOCIATED PROTEIN A (VAPA), AND GENOTYPE-PHENOTYPE CORRELATIONS

RUOLO DEI LIPIDI NELLE PATOLOGIE NCL ASSOCIATE A CLN8: INTERAZIONI STRUTTURALI E FUNZIONALI DEL CLN8 CON LA PROTEINA VESCICOLARE DI MEMBRANA-ASSOCIATA ALLA PROTEINA A (VAPA) E CORRELAZIONI GENOTIPO-FENOTIPO

Coordinator **Patrizia Guarneri**
Partner Alessandro Prinetti

Centres: **2** *Years:* **3** *Starting:* **2016**

198 – GGP12108

PHARMACOLOGICAL CHAPERONES TO CURE GENETIC DISEASES: DEVELOPMENT OF DRUGS AND IDENTIFICATION OF NEW TARGETS

CHAPERONE FARMACOLOGICI PER LA CURA DI MALATTIE GENETICHE: SVILUPPO DI NUOVI FARMACI E INDIVIDUAZIONE DI BERSAGLI

Coordinator **Maria Vittoria Cubellis**
Partner Giuseppina Andreotti

Centres: **2** *Years:* **3** *Starting:* **2012**

199 – GGP14028

CELL THERAPY FOR CRIGLER-NAJJAR TYPE I SYNDROME USING HUMAN ADULT LIVER STEM CELLS

TERAPIA CELLULARE PER LA SINDROME DI CRIGLER-NAJJAR DI TIPO I CON CELLULE STAMINALI EPATICHE UMANE

Coordinator **Fiorella Altruda**
Partner Giovanni Camussi

Centres: **2** *Years:* **3** *Starting:* **2014**

200 – GEP15086

RESCUE OF FANCONI BICKEL SYNDROME BY TARGETING GLUCOSE TRANSPORT IN THE RENAL PROXIMAL TUBULE

GUARIRE LA SINDROME DI FANCONI-BICKEL RIPRISTINANDO IL METABOLISMO DEL GLUCOSIO NEL TUBULO PROSSIMALE DEL RENE

PI **Francesco Trepiccione**

Centres: **1** *Years:* **1** *Starting:* **2016**

201 – TGM16YMT08

METABOLIC DIVERSION TOWARDS NON-TOXIC METABOLITES FOR THERAPY OF PRIMARY HYPEROXALURIA TYPE 1

ATTIVAZIONE DI PATHWAYS ALTERNATIVI PER LA PRODUZIONE DI METABOLITI NON-TOSSICI PER LA TERAPIA DELLE IPEROSSALURIE

PI **Nicola Brunetti Pierri**

TIGEM **2016 - 2021**

202 – GGP14125

RENAL DISEASE IN GENETIC LCAT DEFICIENCY: FROM PATHOGENESIS TO THERAPY

MALATTIA RENALE NEL DEFICIT DI LCAT: DALLA PATOGENESI ALLA TERAPIA

PI **Laura Calabresi**

Centres: **1** *Years:* **2** *Starting:* **2014**

203 – TGT16B03

MODELING AND UNDERSTANDING OF GENETICALLY MODIFIED SYSTEMS AS A WHOLE

MODELLAZIONE E COMPRENSIONE DEL SISTEMA GENETICAMENTE MODIFICATO NEL SUO INSIEME

PI **Eugenio Montini**

SR-TIGET **2016 - 2021**

204 – TCR14001

MURINE UMBILICAL CORD BLOOD LEADS TO LONG-TERM MULTILINEAGE ENGRAFTMENT AND REVERSES CLINICAL FEATURES FOLLOWING NEONATAL TRANSPLANTATION IN THE MPS I MODEL.

IL SANGUE DEL CORDONE OMBELICALE MURINO GARANTISCE UN RIPOPOLAMENTO EMATOPOIETICO A LUNGO TERMINE E RISOLVE LE MANIFESTAZIONI CLINICHE DEL MODELLO DI MPS I A SEGUITO DI TRAPIANTO IN EPOCA NEONATALE.

PI **Marta Serafini**

DTI *Years:* **2** *Starting:* **2014**

205 – TGM16YMT10

GENE THERAPY OF MUCOPOLYSACCHARIDOSIS TYPE VI

TERAPIA GENICA DELLA MUCOPOLISACCARIDOSI DI TIPO VI

PI **Alberto Auricchio**

TIGEM **2016 - 2021**

206 – GGP14002

AN ALPHA?-CRYSTALLIN DERIVED PEPTIDE TO FACE THE MOST FREQUENT WILSON DISEASE-CAUSING ATP7B MUTATION

UN PEPTIDE DELLA PROTEINA ALPHAB-CRISTALLINO PER CONTRASTARE LA MUTAZIONE DI ATP7B PIÙ FREQUENTEMENTE CAUSA DELLA MALATTIA DI WILSON

PI **Stefano Bonatti**

Centres: **1** *Years:* **3** *Starting:* **2014**

207 – TGM16YCBDM09

IDENTIFICATION AND THERAPEUTIC TARGETING OF NEW MOLECULAR PATHWAYS IN WILSON DISEASE

IDENTIFICAZIONE E TARGETING TERAPEUTICI DI NUOVI PATHWAYS MOLECOLARI COINVOLTI NELLA MALATTIA DI WILSON

PI **Roman Polishchuk**

TIGEM **2016 - 2021**

208 – TGM16YCBDM04

TRANSCRIPTIONAL REGULATION OF THE LYSOSOMAL AUTOPHAGIC PATHWAY

REGOLAZIONE TRASCRIZIONALE DELL'AUTOFAGIA E DEL LISOSOMA

PI **Andrea Ballabio**

TIGEM **2016 - 2021**

209 – TGM16YCBDM05

GENERATION OF A LYSOSOMAL STORAGE DISORDER CRISPR BIOBANK FOR THE STUDY OF LYSOSOMAL STORAGE DISORDERS

LYSOSOMAL STORAGE DISORDER CRISPR BIOBANK: UNA NUOVA RISORSA NELLO STUDIO DELLE LSDS.

PI **Andrea Ballabio**

TIGEM **2016 - 2021**

210 – TGM16YGM06

HIGH CONTENT IMAGING APPROACHES TO IDENTIFY COMPOUNDS INDUCING CLEARANCE IN MUCOLIPIDOSIS TYPE IV

UN APPROCCIO DI HIGH CONTENT IMAGING PER IDENTIFICARE COMPOSTI IN GRADO DI RIDURRE L'ACCUMULO DI SOSTANZE TOSSICHE IN CELLULE DI MUCOLIPIDOSI DI TIPO IV

PI **Diego Medina**

TIGEM **2016 - 2021**

211 – TGT16G01

NOVEL STRATEGIES TO GENERATE TOLEROGENIC DC FOR AG-SPECIFIC IMMUNOTHERAPY

NUOVE STRATEGIE PER GENERARE DC TOLLEROGENICHE FINALIZZATE ALL'IMMUNOTERAPIA ANTIGENE-SPECIFICA

PI **Silvia Gregori**

SR-TIGET **2016 - 2021**

212 – TGT16G02

IN VIVO INDUCTION OF ANTIGEN-SPECIFIC TOLERANCE BY HEPATOCYTE-TARGETED GENE TRANSFER

TRASFERIMENTO GENICO IN VIVO DIRETTO AGLI EPATOCITI PER L'INDUZIONE DI TOLLERANZA IMMUNOLOGICA ANTIGENE-SPECIFICA.

PI **Silvia Gregori**
Co-PI Andrea Annoni

SR-TIGET **2016 - 2021**

213 – TGT16YA05

GENE THERAPY OF TYPE I MUCOPOLYSACCHARIDOSIS (MPS-IH)

TERAPIA GENICA DELLA MUCOPOLISACCARIDOSI DI TIPO I (MPS-IH).

PI **Alessandro Aiuti**

SR-TIGET **2016 - 2021**

214 – GGP14106

IMPROVING MC4R SIGNALING VIA ISOFORM SELECTIVE PI3K TARGETING TO FIGHT MELANOCORTIN OBESITY SYNDROME

COMBATTERE L'OBESITÀ GENETICA INDOTTA DA MUTAZIONI DI MC4R ATTRAVERSO LA MODULAZIONE DELLA SEGNALAZIONE RECETTORIALE

PI **Emilio Hirsch**

Centres: **1** *Years:* **3** *Starting:* **2014**

215 – GGP12047

MELUSIN GENE THERAPY: A POSSIBLE APPROACH TO PREVENT CARDIOMYOPATHY

MELUSINA COME AGENTE DI TERAPIA GENICA: UN NUOVO APPROCCIO PER CONTRASTARE LE CARDIOMIOPATIE

PI **Mara Brancaccio**

Centres: **1** *Years:* **2** *Starting:* **2012**

216 – GGP12282

MYOPALLADIN IN DILATED CARDIOMYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY

LA MIOPALLADINA NELLA CARDIOMOPATIA DILATATIVA E NELLA DISTROFIA MUSCOLARE DEI CINGOLI

Coordinator **Marie-Louise Bang**
Partner Vincenzo Nigro, Marco Linari

Centres: **3** *Years:* **3** *Starting:* **2012**

217 – GGP13162

HYPERTROPHIC CARDIOMYOPATHY CAUSED BY MUTATIONS IN THE THIN FILAMENT REGULATORY PROTEINS OF THE SARCOMERE

CARATTERISTICHE CLINICHE E BIOFISICHE DELLA CARDIOMIOPATIA IPERTROFICA ASSOCIATA A UN DIFETTO GENETICO DELLE PROTEINE REGOLATORIE DEL FILAMENTO SOTTILE

Coordinator **Corrado Poggesi**
Partner Leonardo Sacconi

Centres: **2** *Years:* **2** *Starting:* **2013**

218 – GGP11141

MUTATIONS OF CARDIAC CALSEQUESTRIN AND CARDIAC ARRHYTHMIAS: NOVEL INSIGHTS ON PATHOGENESIS AND THERAPY

MUTAZIONI DEL GENE CASQ2 (CALSEQUESTRINA) ED ARITMIE CARDIACHE: APPROCCIO SPERIMENTALE ALLA PATOGENESI E TERAPIA

Coordinator **Silvia Giuliana Priori**
Partner Pompeo Volpe, Feliciano Protasi

Centres: **3** *Years:* **3** *Starting:* **2011**

219 – GGP11224

NOVEL OPTOGENETIC APPROACH TO INVESTIGATE ARRHYTHMOGENESIS IN DOMINANT CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

NUOVO METODO PER LO STUDIO DELLE ARITMIE CATECOLAMINERGICHE FAMILIARI BASATO SULL'USO DI PROTEINE FOTOATTIVATE

PI **Marco Mongillo**

Centres: **1** *Years:* **3** *Starting:* **2012**

220 – GGP16001

CONTRIBUTION OF LIPIDS AND THEIR OXIDIZED METABOLITES ON ARRHYTHMOGENIC CARDIOMYOPATHY PATHOGENESIS

CONTRIBUTO DEI LIPIDI E DEI LORO METABOLITI OSSIDATI NELLA PATOGENESI DELLA CARDIOMIOPATIA ARITMOGENA

Coordinator **Giulio Pompilio**
Partner Alessandra Rossini, Alberto Corsini

Centres: **3** *Years:* **3** *Starting:* **2016**

221 – GGP13167

ARTERIAL TORTUOSITY SYNDROME: A VITAMIN C COMPARTMENTATION DISEASE?

SINDROME DELLE ARTERIE TORTUOSE: UN PROBLEMA NEL METABOLISMO DELLA VITAMINA C?

PI **Marina Colombi**

Centres: **1** *Years:* **2** *Starting:* **2013**

222 – GGP14149

NOVEL THERAPEUTIC INTERVENTIONS FOR CEREBRAL CAVERNOUS MALFORMATIONS

NUOVE TERAPIE FARMACOLOGICHE PER LA CURA DELLE MALFORMAZIONI CAVERNOSE CEREBRALI

PI **Elisabetta Dejana**

Centres: **1** *Years:* **3** *Starting:* **2014**

223 – GGP15219

OXIDATIVE STRESS AND CEREBRAL CAVERNOUS MALFORMATIONS (CCM): FROM DISEASE MECHANISMS TOWARD PREVENTION AND TREATMENT

STRESS OSSIDATIVO E MALFORMAZIONI CAVERNOSE CEREBRALI (CCM): DALLA COMPRENSIONE DEI MECCANISMI DELLA MALATTIA VERSO GLI APPROCCI TERAPEUTICI

Coordinator **Saverio Francesco Retta**
Partner Lorenza Trabalzini, Paolo Pinton

Centres: **3** *Years:* **3** *Starting:* **2015**

224 – GGP13036

THALIDOMIDE FOR THE TREATMENT OF SEVERE RECURRENT EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA: CLINICAL TRIAL ON THE EFFICACY OF ORAL ADMINISTRATION AND "IN VITRO" STUDY OF A NEW DRUG FORMULATION FOR A TOPICAL EFFECT

TRATTAMENTO CON TALIDOMIDE DEL SANGUINAMENTO NASALE SEVERO RICORRENTE NELLA TELEANGECTASIA EMORRAGICA EREDITARIA: STUDIO CLINICO SULL'EFFICACIA DELLA SOMMINISTRAZIONE ORALE E STUDIO "IN VITRO" DI UNA NUOVA FORMULAZIONE DEL FARMACO PER USO LOCALE

Coordinator **Rosangela Invernizzi**
Partner Paolo Colombo

Centres: **2** *Years:* **2** *Starting:* **2013**

225 – GGP13002

ENGINEERED T REGULATORY CELLS TO CONTROL THE IMMUNE-INFLAMMATORY RESPONSE AND THE ACCELERATED ONSET OF ATHEROSCLEROSIS IN FAMILIAL HYPERCHOLESTEROLEMIA

UTILIZZO DI LINFOCITI T INGEGNERIZZATI NELL'IPERCOLESTEROLEMIA FAMILIARE

Coordinator **Giuseppe Danilo Norata**
Partner Massimo Locati

Centres: **2** *Years:* **3** *Starting:* **2013**

226 – GGP15275

DRUG TESTING FOR LIVER DISEASE IN ALPHA-1 ANTITRYPSIN DEFICIENCY BY A LARGE-SCALE PATIENT-SPECIFIC HIPS CELLS LIBRARY

SVILUPPO DI FARMACI PER MALATTIE EPATICHE CAUSATE DA DEFICIENZA DI ALFA1-ANTITRIPSINA MEDIANTE UNA LIBRERIA DI CELLULE PLURIPOTENTI INDOTTE PAZIENTE-SPECIFICHE

PI **Nicola Elvassore**

Centres: **1** *Years:* **2** *Starting:* **2016**

227 – TGM16YCBDM08

CFTR AND ANOCTAMINS AS TARGETS IN CYSTIC FIBROSIS AND OTHER GENETIC DISEASES

CFTR E ANOCTAMINE, BERSAGLI TERAPEUTICI NELLA FIBROSIS CISTICA E IN ALTRE MALATTIE GENETICHE

PI **Luis Juan Vicente Galietta**

TIGEM **2016 - 2021**

228 – TGM16YGM03

SINGLE CELL SEQUENCING TO ELUCIDATE DISEASE GENE FUNCTION AND TO IDENTIFY THERAPEUTIC MOLECULES.

L'ANALISI TRASCRIZIONALE IN SINGOLA CELLULE PER LO STUDIO DEI GENI MALATTIA E PER L'IDENTIFICAZIONE DI TERAPIA MOLECOLARI.

PI **Diego Di Bernardo**

TIGEM **2016 - 2021**

229 – GGP15171

DISCOVERING MOLECULAR DEFECTS OF SEVERE GUT DYSFUNCTION: NEW ABNORMALITIES UNDERLYING CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (CIPO)

IDENTIFICAZIONE DI DIFETTI MOLECOLARI NELLE SEVERE DISFUNZIONI INTESTINALI: NUOVE ANOMALIE ALLA BASE DELLA PSEUDO-OSTRUZIONE INTESTINALE CRONICA (POIC)

PI **Roberto De Giorgio**

Centres: **1** *Years:* **3** *Starting:* **2015**

230 – GGP13227

GAIN-OF-FUNCTION MUTATIONS OF THE V2 VASOPRESSIN RECEPTOR IN NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS (NSIAD): MOLECULAR CHARACTERIZATION AND IN SILICO IDENTIFICATION OF POTENTIAL THERAPEUTIC AGENTS

MUTAZIONI ATTIVANTI DEL RECETTORE V2 DELLA VASOPRESSINA NELLA SINDROME NEFROGENICA DA ANTIDIURESI NON APPROPRIATA (NSIAD): CARATTERIZZAZIONE MOLECOLARE E IDENTIFICAZIONE IN SILICO DI NUOVI AGENTI TERAPEUTICI

Coordinator **Susanna Cotecchia**
Partner Francesca Fanelli

Centres: **2** *Years:* **3** *Starting:* **2013**

231 – GGP14127

A SPECIFIC NANOBODY PREVENTS AMYLOIDOGENESIS OF D76N ß2-MICROGLOBULIN IN VITRO AND MODIFIES ITS TISSUE DISTRIBUTION IN VIVO

UNO SPECIFICO NANOBODY È IL PIÙ POTENTE INIBITORE DELLA AMILOIDOGENESI DELLA VARIANTE PATOLOGICA DELLA BETA 2-MICROGLOBULINA UMANA

PI **Vittorio Bellotti**

Centres: **1** *Years:* **2** *Starting:* **2014**

232 – GEP15070

CHARACTERIZATION OF RECENTLY IDENTIFIED GELSOLIN VARIANTS RESPONSIBLE FOR A NOVEL RENAL AMYLOIDOSIS AND IN SILICO SCREENING OF DRUG CANDIDATES

CARATTERIZZAZIONE DI MUTANTI DELLA GELSOLINA RESPONSABILI DI UNA NUOVA AMILOIDOSI RENALE E RICERCA DI NUOVI FARMACI

PI **Matteo De Rosa**

Centres: **1** *Years:* **1** *Starting:* **2016**

233 – GGP12008

MOLECULAR MECHANISMS OF TRANSPORT, SMALL LIGAND MODULATION, AND SUBUNIT INTERACTION OF CHLORIDE TRANSPORTING CLC PROTEINS INVOLVED IN HUMAN GENETIC DISEASES

MECCANISMI MOLECOLARI RIGUARDANTI IL TRASPORTO, LA REGOLAZIONE DA PARTE DI PICCOLI LIGANDI E L'INTERAZIONE CON ALTRE SUBUNITÀ DELLE PROTEINE CLC COINVOLTE IN MALATTIE GENETICHE UMANE

PI **Michael Pusch**

Centres: **1** *Years:* **3** *Starting:* **2012**

234 – TCP14008

FUNCTIONAL AND STRUCTURAL STUDIES OF HUMAN CLC CHLORIDE PROTEINS INVOLVED IN GENETIC DISEASES

STUDI STRUTTURALI E FUNZIONALI DEI COMPLESSI PROTEICI CLC COINVOLTI IN MALATTIE GENETICHE

PI **Alessandra Picollo**

DTI *Years:* **5** *Starting:* **2015**

235 – GGP15083

POTENTIAL THERAPEUTIC EFFECT OF BETA3-ADRENERGIC RECEPTOR AGONISTS ON X-LINKED NEPHROGENIC DIABETES INSIPIDUS

POSSIBILE EFFETTO TERAPEUTICO DEGLI AGONISTI DEI RECETTORI BETA3 ADRENERGICI SUL DIABETE INSIPIDO NEFROGENICO

PI **Maria Svelto**

Centres: **1** *Years:* **3** *Starting:* **2015**

236 – GGP14263

MOLECULAR MECHANISMS OF PATHOGENESIS AND PRECLINICAL TREATMENT IN RENAL DISORDERS ASSOCIATED WITH UROMODULIN MUTATIONS

MECCANISMI MOLECOLARI DI PATOGENESI E TERAPIA IN UN MODELLO PRECLINICO DI MALATTIE RENALI ASSOCIATE A MUTAZIONI DI UROMODULINA

PI **Luca Rampoldi**

Centres: **1** *Years:* **3** *Starting:* **2014**

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SYSTEMS BIOLOGY OF MEMBRANE TRAFFICKING

SYSTEMS BIOLOGY E TRAFFICO DI MEMBRANE

PI **Maria Antonietta De Matteis**

TIGEM **2016 - 2021**

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AUTOPHAGY AND CILIA COME TOGETHER: IMPLICATION FOR CILIOPATHIES

AUTOFAGIA E CIGLIA S'INCONTRANO: IMPLICAZIONI PER LE CILIOPATIE

PI **Brunella Franco**

TIGEM **2016 - 2021**

239 – GGP12183

TOWARDS THE COMPREHENSION OF POLYCYSTIN-1 FUNCTION AND IDENTIFICATION OF SPECIFIC TARGETS FOR THERAPY IN ADPKD

VERSO LA COMPRENSIONE DELLA FUNZIONE DI POLICISTINA-1 E L'IDENTIFICAZIONE DI TARGET TERAPEUTICI SPECIFICI PER ADPKD

PI **Alessandra Boletta**

Centres: **1** *Years:* **3** *Starting:* **2012**

240 – GGP11119

GENETICS AND PHARMACOGENETICS OF PAGET'S DISEASE OF BONE

GENETICA E FARMACOGENETICA DELLA MALATTIA OSSEA DI PAGET

Coordinator **Luigi Gennari**
Partner Fernando Gianfrancesco

Centres: **2** *Years:* **2** *Starting:* **2011**

241 – GEP15019

DEFINING THE MOLECULAR PATHOGENESIS OF THE RIBOSOMOPATHY CARTILAGE HAIR HYPOPLASIA

DEFINIZIONE DELLA PATOGENESI MOLECOLARE DELLA RIBOSOMOPATIA IPOPLASIA TRICO-CARTILAGINEA

PI **Lorenzo Montanaro**

Centres: **1** *Years:* **1** *Starting:* **2016**

242 – GEP15062

CHONDRODYSPLASIA WITH JOINT DISLOCATIONS GPAPP TYPE: INSIGHT ON THE MOLECULAR BASIS OF THE DISORDER AND THE ROLE OF IMPAD1 IN POST-NATAL SKELETAL DEVELOPMENT

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PI **Antonio Rossi**

Centres: **1** *Years:* **1** *Starting:* **2016**

243 – GGP11079

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PI **Antonio Rossi**

Centres: **1** *Years:* **3** *Starting:* **2011**

244 – GGP11097

TRANSLATING CURRENT AND NEW KNOWLEDGE ON THE DEVELOPMENTAL FUNCTIONS OF P63 INTO RESTORING NORMAL DEVELOPMENT IN MODELS OF ORGAN CULTURE AND IN VIVO

TRASFERIRE LE CONOSCENZE SUL RUOLO DEL GENE MALATTIA P63 DURANTE LO SVILUPPO EMBRIONALE ALLA POSSIBILITÀ DI RIPRISTINARE LO SVILUPPO NORMALE IN MODELLI DI COLTURE DI TESSUTO E IN VIVO

Coordinator **Giorgio Roberto Merlo**
Partner Luisa Francesca Guerrini, Antonio Costanzo

Centres: **1** *Years:* **3** *Starting:* **2011**

245 – GGP15196

NEW TREATMENT STRATEGIES FOR FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

NUOVE STRATEGIE PER IL TRATTAMENTO DELLA FIBRODISPLASIA OSSIFICANTE PROGRESSIVA

Coordinator **Roberto Ravazzolo**
Partner Tiziano Bandiera

Centres: **2** *Years:* **3** *Starting:* **2015**

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DEFINING A ROLE FOR GDD1/TMEM16E IN THE SKELETAL BONE SYNDROME GNATHODIAPHYSEAL DYSPLASIA

STUDIO DEL RUOLO DELLA PROTEINA GDD1 / TMEM16E NELLA DISPLASIA SCHELETRICA GNATODIAFISARIA (GDD)

PI **Anna Elisabetta Boccaccio**

Centres: **1** *Years:* **1** *Starting:* **2016**

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IDENTIFICATION OF MOLECULAR TARGETS FOR THE TREATMENT OF THE SKELETAL PHENOTYPE IN LYSOSOMAL STORAGE DISORDERS

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PI **Carmine Settembre**

DTI *Years:* **5** *Starting:* **2012**

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PI **Mara Riminucci**

Centres: **1** *Years:* **3** *Starting:* **2015**

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TARGETING ER STRESS TO TREAT OSTEOGENESIS IMPERFECTA

NUOVE STRATEGIE PER IL TRATTAMENTO DELL'OSTEOGENESI IMPERFETTA

Coordinator **Antonella Forlino**
Partner Laura Bianchi

Centres: **2** *Years:* **3** *Starting:* **2013**

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PI **Antonella Forlino**

Centres: **1** *Years:* **1** *Starting:* **2016**

251 – GGP14014

IN-DEPTH PHENOTYPING AND EXPERIMENTAL THERAPY OF AUTOSOMAL DOMINANT OSTEOPETROSIS

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PI **Anna Maria Teti**

Centres: **1** *Years:* **3** *Starting:* **2014**

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PI **Anna Villa**

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PI **Cristina Sobacchi**

Centres: **1** *Years:* **2** *Starting:* **2012**

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RUOLO DELLA PROTEINA AKTIP NELLE SINDROMI PROGEROIDI.

PI **Isabella Saggio**

Centres: **1** *Years:* **1** *Starting:* **2016**

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PI **Pietro Pichierri**

Centres: **1** *Years:* **1** *Starting:* **2016**

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MECHANISMS OF TRAFFICKING OF FIBRILLAR PROCOLLAGENS

MECCANISMI DI TRAFFICO DI PROCOLLAGENO FIBRILLARE

PI **Carmine Settembre**
PI Maria Antonietta De Matteis

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UNDERSTANDING THE GENETIC BASIS OF ACROFRONTOFACIONASAL DYSOSTOSIS 1

STUDIO DELLE BASI GENETICHE DELLA DISOSTOSI ACRO-FRONTO-FACIO-NASALE DI TIPO 1

PI **Cristina Sobacchi**

Centres: **1** *Years:* **1** *Starting:* **2014**

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MOLECULAR BASES OF THE BECKWITH-WIEDEMANN SYNDROME AND SILVER-RUSSELL SYNDROME

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PI **Andrea Riccio**

Centres: **1** *Years:* **3** *Starting:* **2015**

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MOLECULAR BASES OF NOONAN SYNDROME AND RELATED DISORDERS

BASI MOLECOLARI DELLA SINDROME DI NOONAN E DI MALATTIE GENETICHE CORRELATE

PI **Marco Tartaglia**

Centres: **1** *Years:* **2** *Starting:* **2013**

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CHROMATIN DETERMINANTS OF THE INNER-CENTROMERE RELY ON REPLICATION FACTORS WITH FUNCTIONS THAT IMPART COHESION

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PI **Dana Branzei**

Centres: **1** *Years:* **3** *Starting:* **2012**

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DISSECTING THE MOLECULAR AND CELLULAR MECHANISMS OF THE MACS/RIN2 SYNDROME

CARATTERIZZAZIONE DEI MECCANISMI MOLECOLARI E CELLULARI DELLA SINDROME MACS/RIN2

PI **Guido Serini**

Centres: **1** *Years:* **3** *Starting:* **2015**

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ELUCIDATING THE GENETIC HETEROGENEITY OF ZIMMERMANN-LABAND SYNDROME

CARATTERIZZAZIONE DELL'ETEROGENEITÀ GENETICA DELLA SINDROME ZIMMERMANN-LABAND

PI **Viviana Caputo**

Centres: **1** *Years:* **1** *Starting:* **2016**

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Coordinator **Claudio Talora**
Partner Gianfranco Biolcati, Claudio Palleschi

Centres: **3** *Years:* **3** *Starting:* **2012**

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GENERATION OF ANIMAL MODELS TO DEFINE MOLECULAR MECHANISMS AND NOVEL THERAPEUTIC STRATEGIES FOR FAMILIAL PRIMARY LOCALIZED CUTANEOUS AMYLOIDOSIS

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PI **Paul Heppenstall**

Centres: **1** *Years:* **3** *Starting:* **2014**

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PROTEOSTASIS IN THE EARLY SECRETORY COMPARTMENT AS A PATHOGENETIC MECHANISM AND THERAPEUTIC TARGET

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PI **Roberto Sitia**

Centres: **1** *Years:* **3** *Starting:* **2015**

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PI **Caterina Missero**

Centres: **1** *Years:* **3** *Starting:* **2016**

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PI **Carla Portulano**

Centres: **1** *Years:* **1** *Starting:* **2016**

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PI **Caterina Missero**

Centres: **1** *Years:* **1** *Starting:* **2016**

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Coordinator **Marco Barchi**
Partner Claudio Sette

Centres: **2** *Years:* **3** *Starting:* **2012**

270 – GGP13225

CONTROL OF KINETOCHORE FORMATION AND GOLGI INTEGRITY BY THE SNARE PROTEIN SNAP29

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PI **Thomas Vaccari**

Centres: **1** *Years:* **3** *Starting:* **2013**

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PI **Anna Maria Cariboni**

Centres: **1** *Years:* **3** *Starting:* **2013**

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PI **Pietro Pichierri**

Centres: **1** *Years:* **3** *Starting:* **2012**

INDEX BY AUTHOR (PIs, Coordinators, Partners) – INDICE PER AUTORI (Responsabili dei progetti)

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INDICE PER PATOLOGIA

POSTER

POSTER

Rome headquarter
Via Varese, 16/B
00185 Rome, Italy
Tel. +39 06 440151
Fax +39 06 44015521

Milan headquarter
Via Carlo Poerio, 14
20129 Milan, Italy
Tel. +39 02 2022171
Fax +39 06 44015600

www.telethon.it mail: telethon@telethon.it

FONDAZIONE Telethon