Bologna 15 Dicembre 2014

ERA-Net COFUND Research Programmes on Rare Diseases (E-RARE)

The Role of RER-ASSR

Antonio Addis
Research Governance Area
Agenzia Sanitaria e Sociale Regionale


How do Regions might have a role in the ERA-Net COFUND Research Programmes on Rare Diseases (E-RARE) ?

ERA-NET Cofund: Eligibility conditions

Who can participate?

- ü national and regional programmes (Joint call)
- ü research funders owning or managing public research and innovation programmes.
- ü Programme Owners
- ü Programme Managers

Minimum conditions for participation:

three independent legal entities from three different Member States or associated countries.

Emilia Romagna Research Facilities and Activities for Rare Diseases (RD)

- Network of Reference Centres for Rare Diseases (Reg.Act n. 160/2004): local health centres/specialized units (medical services, genetic and clinic laboratories):

  Certification and treatment of individual RD (Hub and Spoke model).

  Theoretical Research and application in clinical practice

  Training of professionals

  Epidemiological activities

  Regional Coordination Board

  Regional Technical Group

  Regional Registry: diagnoses and data of RD patients (June 2007)

Emilia Romagna Region Capacity to Fund and Manage Research Programmes

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Programma di ricerca Regione-Università

Regional Law 29, 2004

R&D as the core duty of the Regional Health Service

Close collaboration with the Regional University system
key to make R&D effort successful and to improve its quality and sustainability

3 editions

2007 - 2009: 30 mil € = 71 projects
2010 - 2012: 30 mil € = 51 projects
2013: 5 mil € = 22 projects

144 projects

Programme peculiarities

- 3 Areas: Innovative research; Clinical governance; Training
- Two-step assessment process: Maieutic Approach
- Research Prioritarization: selecting research themes and research questions
- Programme for Young Investigators

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Programma di ricerca Regione-Università

Aims:

- ü To enhance the research role of University hospitals within the regional healthcare service;
- ü To develop excellence in centers;
- ü To recognize the existence of professional networks;
- ü To promote scientific innovation;
- ü To foster new management methods and organizational changes;
- ü To increase training opportunities

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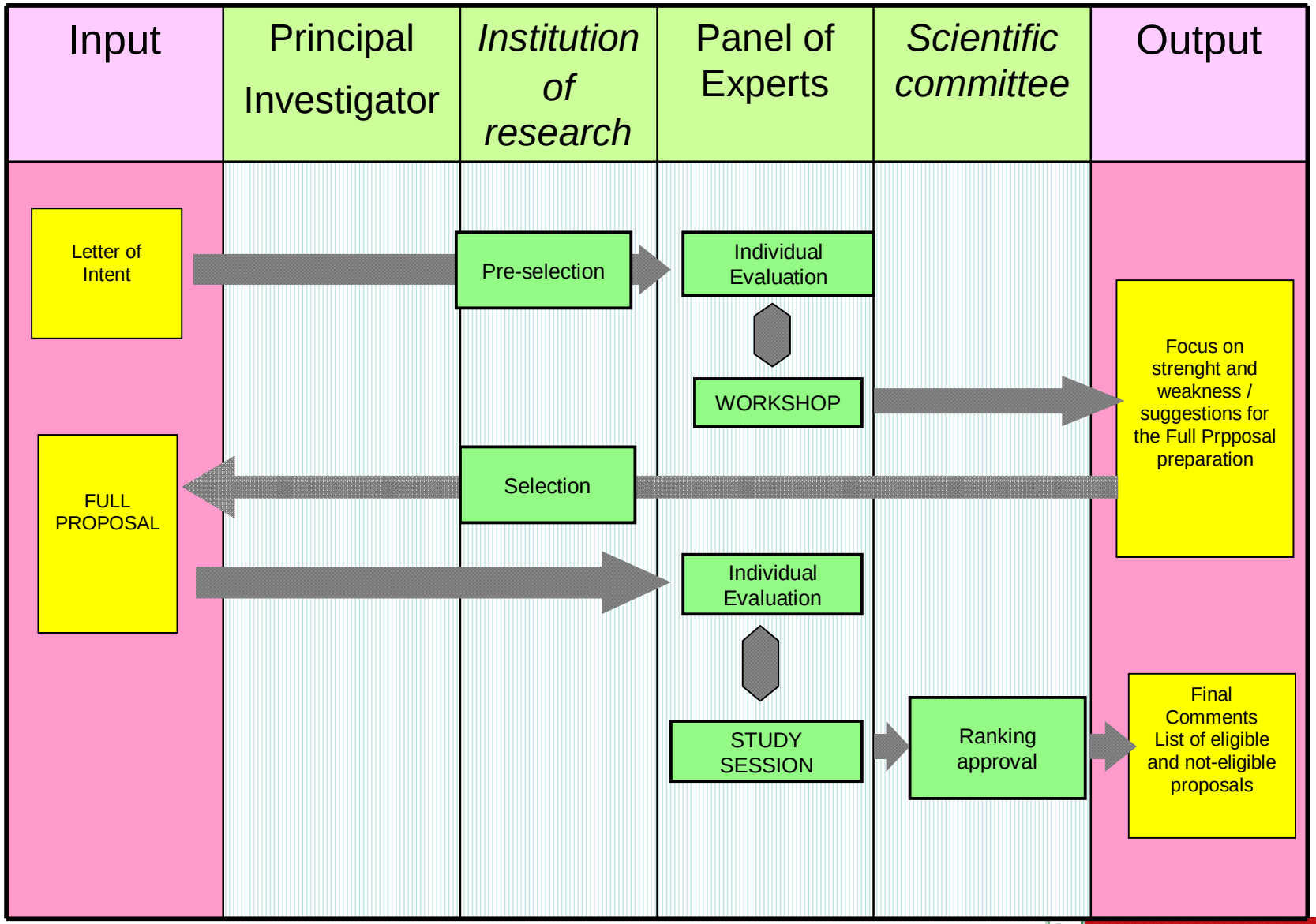
The Assessment process



Regione Emilia-Romagna

Emilia Romagna Funding Programme on RD

Next-Generation Sequencing and Gene Therapy to Diagnose and Cure Rare Diseases (Strategic Programme)
Azienda ospedaliero-Universitaria Policlinico di Modena
1.985.000 EURO

Specific objectives

1. To improve diagnosis and management of patients with RD by generating 8 clinical databases for specific IMD populated with homogeneous and comprehensive genetic and clinical data.

2. To improve diagnostic accuracy measures of genetic test and provide patients referred for IMD with an accurate comprehensive and cost-effective genetic diagnosis by developing and implementing 3 disease-customized gene arrays.

3. To offer patients with IRD a cure in Italy by developing a protocol and implementing a gene therapy trial for a RD.

4. To identify new pathogenic genes for selected RDs where the pathogenic gene is unknown.

Emilia Romagna Funding Programme on RD

Recognition, Diagnosis and Therapy of Mitochondrial Disorders in Neurological Services of the Emilia-Romagna Region (Strategic Project) *Dr. Valerio Carelli, MD, PhD*

IRCCS Istituto delle Scienze Neurologiche di Bologna
1.323.300 EURO

Specific objectives

Primary:

1. To recognize the minimal prevalence and/or incidence of four frequent clinical phenotypes of MitD;
2. To create and harmonize a regional network of specialists using defined diagnostic pathways, shared among neurological/neuropsychiatric and pediatric services,
3. To recognize the four MitD phenotypes;
4. To provide the regional services with guidelines for clinical follow up of MitD patients and some feasible therapeutic options.

Secondary: to discover new molecular defects causing MitD; to search for pathology biomarkers.

Emilia Romagna Funding Project on RD

Bando Giovani ricercatori "Alessandro Liberati" 2013

Diagnostic accuracy and cost-effectiveness of Next Generation Sequencing (NGS) strategies in the genetic testing of Rare Orthopaedic Diseases

IRCCS ISTITUTO ORTOPEDICO RIZZOLI

BUDGET: € 246.950

The NEW ENGLAND JOURNAL of MEDICINE

Limbal Stem
Co

Paolo Rama, M.D.,
Alessandra Spinelli, M.D

BACKGROUND

Corneal renewal and repa
zone between the cornea
limbus, causing limbal st
results of cell therapy in
with limbal stem-cell defi

METHODS

We used autologous limb
corneal damage, most of
Clinical results were asse
variate and multivariate
outcome according to the
cells that stain intensely

RESULTS

Permanent restoration of
in 76.6% of eyes. The fail
stable over time, with up
In post hoc analyses, succ
nor stroma — was associ
stem cells in culture. Cul
of the total number of clo
tion in 78% of patients. In
of the total number of cel
11% of patients. Graft fa
damage and postoperativ

CONCLUSIONS

Cultures of limbal stem c
treatment of destruction

N Engl

Opinion

Trends

Vision from

Graziella Pellegrini[1], Paolo

[1] Centre for Regenerative Medicine "Stefa
[2] San Raffaele Scientific Institute, Ophthal

Cultures of limbal cells are a safe and
for the destruction of the human corn
ical burns. The essential feature of th
ence of an adequate number of stem
determined by the expression of the
factor. Here, we will discuss the gene
ing the rigorous criteria for graftable
light of their clinical performances.
prove relevant to the future therap
cultured cell type.

Stem cells and epithelial grafts

Cultures of autologous keratinocytes h
to prepare grafts that can permane
epithelial defects, such as massive ski
[1]. There have also been failures of thi
can be attributed to the lack of crite
control of cultures, inappropriate med
and/or substrates used for the cultur
of the preparation of the wound bed
cedures [1]. In studying the low succes
the literature, we found it impossible
contributions of these variables to
mances of the cultures. Rather, the r
renewing tissues requires specific ster
fore, an essential feature of any epit
quate numbers of stem cells, which a
the renewal and restoration of squa
Only when this criterion is met is it po
assess the clinical/surgical factors. He
teria for estimating the numbers of ste
grafts generated by corneal stem cells,
a paradigm for other types of squam
analyze these criteria from a patient
based on clinical outcomes) to see whe
shed light on the nature of epithelial
define requirements for epithelial cu
clinical application.

The corneal epithelium and its limba

The human ocular surface is covered
and conjunctival squamous epithelia
corneal epithelium is flattened, trans
fied; it contains a basal layer of cuboid
Bowman's membrane (see Glossary)
neal stroma. Corneal renewal and rep
stem cells located in the limbus, the na
the cornea and the bulbar conjunctiv
Relatively undifferentiated slow-cycli

Corresponding author: De Luca, M. (michele.delu

1471-4914/$ – see front matter © 2010 Published by Elsevier Ltd. doi:10.1016/j.molmed.2010.10.003 Trends in Molecular Medicine, January 2011, Vol. 17, No. 1

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Review article

The sixth sense: hematopoietic stem cells detect danger through purinergic signaling

Lara Rossi,[1] Valentina Salvestrini,[1] Davide Ferrari,[2] Francesco Di Virgilio,[2] and Roberto M. Lemoli[1]

[1]Department of Hematology and Oncological Sciences, L. and A. Seràgnoli, Institute of Hematology, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy; and [2]Department of Experimental and Diagnostic Medicine, Section of General Pathology and Interdisciplinary Center for the Study of Inflammation, University of Ferrara, Ferrara, Italy

Over the past decade, extracellular nucleotides (such as ATP and UTP) have emerged as key immunomodulators. This family of molecules, already known for its key metabolic functions, has been the focus of intense investigation that has unambiguously shown its crucial role as mediators of cell-to-cell communication. More recently, in addition to its involvement in inflammation and immunity, purinergic signaling has also been shown to modulate BM-derived stem cells. Extracellular nucleotides promote proliferation, CXCL12-driven migration, and BM engraftment of hematopoietic progenitor and stem cells. In addition, purinergic signaling acts indirectly on hematopoietic progenitor and stem cells by regulating differentiation and release of proinflammatory cytokines in BM-derived human mesenchymal stromal cells, which are part of the hematopoietic stem cell (HSC) niche. HSC research has recently blended into the field of immunology, as new findings highlighted the role played by immunologic signals (such as IFN-α, IFN-γ, or TNF-α) in the regulation of the HSC compartment. In this review, we summarize recent reports unveiling a previously unsuspected ability of HSCs to integrate inflammatory signals released by immune and stromal cells, with particular emphasis on the dual role of extracellular nucleotides as mediators of both immunologic responses and BM stem cell functions. (Blood. 2012;120(12):2365-2375)

Introduction

Living organisms are constantly exposed to foreign, and sometimes harmful, agents. To protect tissues from damage and preserve homeostasis, multicellular organisms have developed an array of defense responses of which inflammation is a major manifestation. As part of this defense mechanism, inflammation is instrumental for mounting an effective innate and adaptive immune response. Terminally differentiated cells (granulocytes, monocytes/macrophages, dendritic cells, B- and T-lymphocytes) have classically been considered the principal players in inflammation and immunity. Conversely, hematopoietic stem cells (HSCs), from which all immune and inflammatory cells derive, are usually thought not to be part of the immune system. Localized in the nurturing environment of the BM niche, HSCs were thought to reside within an "immunologic sanctuary," protected from the insults affecting peripheral tissues. However, recent findings suggest that HSCs are not confined in a "splendid isolation": BM-HSCs and circulating HSCs can sense the presence of danger or stress signals in the surrounding microenvironment and switch to an activated state or reach injured tissues in need of repair.[1,2] Therefore, HSCs respond to early mediators of inflammation and distress that were so far thought to be active on immune cells only, such as TNF-α, IFNs, Toll-like receptor (TLR) ligands and, most interestingly, extracellular nucleotides (eNTPs).

From the evolutionary standpoint, nucleotides are among the most ancient biologic molecules; thus, it is not surprising that they have been used by living organisms for multiple purposes: storage and transmission of genetic information, energy metabolism, and extracellular communication.[3] eNTPs compose both extracellular purines (ATP and its derivatives, ADP and adenosine) and extracellular pyrimidines (uridine-5′-phosphate [UTP] and [UDP]), which intervene in a variety of biologic processes by binding NTP-specific cell-membrane receptors, collectively named purinergic receptors. The presence of purinergic signaling in taxa as diverse as mammals, plants, yeasts and bacteria suggests that nucleotides are indeed an archaic, ubiquitous, communication system.[4,5] However, their messenger role has been realized comparatively late, and only thanks to the pioneering studies of Geoffrey Burnstock in the central and peripheral nervous system.[6] It is now well established that nucleotides mediate intercellular communication in virtually all tissues and typify one of the most important indicators of cell stress in the pericellular environment.[7] In the hematopoietic and immune systems, eNTPs act as potent immunomodulators of neutrophil, monocyte, macrophage, dendritic cell, and T-lymphocyte responses.[8] In addition, eNTPs drive blood cell proliferation and differentiation at different levels, including the compartment of hematopoietic progenitors and stem cells (HPSCs). Here we discuss how HSCs react to signals of cell injury and inflammation to mount an integrated response to pathogens and tissue damage. In our view, purinergic signaling activated by eNTPs emerges as a key element bridging inflammation to HSC activation.

How immunology blends into stem cell biology: the effect of immunomodulators on HSCs

Lying at the roots of the hematopoietic system, HSCs are a reservoir of rare, multipotent stem cells that provide a continuous supply of cells circulating in the peripheral blood (PB), such as erythrocytes, platelets, lymphoid cells, and myeloid cells. Under

Submitted April 5, 2012; accepted July 2, 2012. Prepublished online as Blood First Edition paper, July 11, 2012; DOI 10.1182/blood-2012-04-422378.

Blood. 2012 Sep 20;120(12):2365-75. Epub 2012 Jul 11

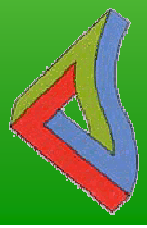
E-RARE

Main Objectives

•Harmonize and develop synergies among national research programmes on rare diseases
•Set up cooperation between E-Rare partners
•Develop a common research policy
•Coordinate national actions to overcome the fragmentation of research and promote interdisciplinary approaches while intaining competitiveness

Specific Goals and Activities

•Create a knowledge base for the development of joint and transnational activities
•Define strategic priorities, to develop and influence research policy on rare diseases and to shape national, transnational and European programmes
•Implement transnational cooperation (transnational calls)



E.RARE-3: The Role of RER-ASSR

The Consortium:

23 partners from 17 EU, Associated and non-European Countries

Opportunities:

- Internationalization of Research (EU/non EU)
- Shared Funding for International Research Projects
- Contribute to define Policies and Strategies (National, EU) for research on Rare Diseases

E.RARE-3: The Role of RER-ASSR

General

- Identification of research priorities, preparation, launch and evaluation of transnational research calls (co-funded and non co-funded)

- Monitoring and evaluation of financed projects

- Communication, exploitation and dissemination of results of transnational funded projects

Regional

- Information, Communication, Secretariat

- Technical support to Regional/Local entities and Institutions on the transnational research calls (co-funded and non co-funded)

E.RARE-3: The Role of RER-ASSR (1)

Specific Technical Support

WP8- Strategic Research Funding Policy: implementing IRDiRC Objectives and collaborating with other initiatives on Rare Diseases

8.1 Development of the Strategic Research Agenda

8.1.1 Gathering research needs from National Agencies, International Networks and EU projects

8.1.2 Organize strategic workshops for the identification of research topics (non co-funded calls)

8.2 Collaboration with EU Research Infrastructures (EATRIS, BBMRI, ECRIN) and other EU initiatives (EU-OPENSCREEN, INTRAFRONTIER) RER ASSR Task Leader

8.3 Involvement of Patient's Association in research funding

E.RARE-3: The Role of RER-ASSR (2)

Specific Technical Support

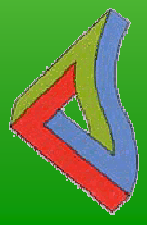
WP9- Strengthening Research Collaboration and enhancing knowledge translation

9.1 Development of the collaboration Platform for rare diseases researchers (RER-ASSR co-Leader)

9.2 Connection with other Rare Diseases research initiatives and instruments (EU research infrastructures, regulatory bodies, expert groups, others) RER-ASSR task Leader

9.3 Dissemination of E.Rare Results and achievements (IT: ISS-MOH)

9.3.2 Final strategic meeting (IT: ISS-MOH)



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Regions might have a role in the ERA-Net COFUND Research Programmes on Rare Diseases (E-RARE)