

EURASNET Interdisciplinary Focus Meetings

EURASNET SYMPOSIUM ON MIS-SPLICING AND DISEASE

Saturday May 31-Sunday June 1 2008
Villa Mondragone, Rome, Italy

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REPORT

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Context

The meeting was organized as an Interdisciplinary Focus Meeting by EURASNET members Francisco Baralle and Juan Valcárcel as a continuation of a similar meeting held in Cortina d'Ampezzo in January 2007. As was the case for this previous meeting, the main aim of the IFM was to highlight the importance of scientific exchange between alternative splicing researchers and clinicians and extend the efforts initiated by the consortium in this direction. The meeting was arranged to precede the EMBO Workshop on "RNA and Disease: RNA Metabolism and Associated Pathologies", which covered the general topic of RNA-based pathologies from a broader perspective, and which was organized by Claudia Bagni, Joel Richter, Francisco Baralle and Juan Valcárcel. This arrangement provided numerous opportunities for exchanges between participants in either of the meetings, which was particularly appreciated by attendees from the medical community.

Goals

The goals of the meeting were:

- 1) To underscore the importance of the scientific exchange between alternative splicing researchers and clinicians
- 2) Obtain up-to-date information about state-of-the-art technologies or developments of potential use within the consortium.
- 3) Establish interdisciplinary collaborations and make new technologies and approaches available to other NoE members and other European scientists as well as members of the biomedical community.
- 4) Evaluate progress made from the last meeting.

Organization

The EURASNET IFM meeting was organized around the following scheme:

- 1) A keynote lecture by Prof. Joan Steitz, Yale University School of Medicine, which opened the meeting.

- 2) One session on mechanisms behind splicing and disease, with contributions from three scientists who have made outstanding contributions to decipher splicing-based mechanisms of disease: Prof. Gideon Dreyfuss (Univ. of Pennsylvania School of Medicine), Prof. Thomas Cooper (Baylor College of Medicine) and Prof. Adrian Krainer (Cold Spring Harbor Laboratory, who is also a member of the EURASNET Scientific Advisory Board).
- 3) One session on “Splicing in the clinical practice,” with four excellent contributions from clinicians doing pioneering work in the practical aspects of splicing-based diagnostics and therapies: Dr. Diana Baralle (Univ. of Southampton, EURASNET Young Investigator), Dr. Guglielmina Pepe (University of Florence), Prof. Matthew Wood (Oxford University, and Associate Member of EURASNET) and Dr. Annalisa Botta (Tor Vergata University of Rome).
- 4) A round table discussion involving all participants of the meeting, on the potential for application of basic science discoveries to splicing-based clinical research and on the practical needs from medical practitioners to generate clinically acceptable diagnostics and therapies based on this knowledge.
- 5) Two discussion groups on “Splicing in diagnostics” and “Splicing-based therapies”.

Scientific and clinical sessions

The meeting opened with a keynote lecture by Joan Steiz (USA), who discussed how a small RNA encoded by the Kaposi's sarcoma virus influences the retention of cellular RNAs in the nucleus and miRNA biogenesis. The first formal session, on splicing and disease, featured talks by Gideon Dreyfuss (USA) on how spinal muscular atrophy is a disease of dysfunctional splicing, Tom Cooper (USA) on myotonic dystrophy and casual effects at the level of RNA splicing, Adrian Krainer (USA), who discussed an antisense strategy to treat spinal muscular atrophy. The second session covered clinical aspects, with Diana Baralle (UK) on the evaluation of splicing errors in several human syndromes, Guglielmina Pepe (Italy), who discussed Marfan's and other syndromes as a consequence of RNA deregulation, Matthew Wood (UK) who discussed therapeutic approaches for Duchenne Muscular Dystrophy, and Annalisa Botta (Italy) who discussed the link between splicing and myotonic dystrophy.

A highlight of the talks in the first part of the session was how high-throughput technologies are helping to work out in great detail molecular mechanisms of disease, and how this knowledge can have direct implications for understanding the underlying pathologies and, furthermore, to design improved diagnostics and therapeutic approaches. The latter was persuasively illustrated by the talk from Prof. Krainer, where extensive studies of regulatory elements in the SMN genes provided clues to design antisense strategies to promote the inclusion of exon 7 in SMN2, an approach that holds the promise of becoming a feasible therapy, as already documented in animal models. Interestingly, the

development and systematic improvement of tools with potential applications has generated additional basic knowledge, which is, again, feeding back on possible therapeutic strategies, clearly highlighting the power of combining both knowledge basis.

Great interest was also raised by the talks on splicing in the clinical practice. Not only the case for the impact of splicing in human disease was eloquently made, but the difficulties for applying basic knowledge to the medical practice were highlighted. These difficulties, ranging from logistic issues in diagnosis to the complexities of disease variation to the need for wider awareness of RNA processing not only among patients but even among the medical community, were not obvious to at least part of the audience of the meeting and raised numerous discussions in the session and afterwards. Most importantly, the initial results on splice correction therapies for Duchene muscular dystrophy left the feeling among the participants that we are indeed in the dawn of medical applications emerging from knowledge about the splicing process. This feeling permeated the whole meeting.

Round Table Discussion

Francisco Baralle chaired a lively Round Table discussion, which focused on the procedures for transferring basic knowledge into the clinic, their regulations and evaluation. How deep should a diagnostic procedure interrogate splicing mechanisms to provide useful information for the clinician and at the same time make the procedure feasible in a clinical lab and affordable for a national health system? When the use of various potential therapeutic reagents greatly enhances the effects on the correction of aberrant splicing, is it justified to request joint clinical trials for the set of reagents rather than for each individual molecule? Questions of this nature generated heated debate and manifested the need for continuous exchange of information, of “language” and even culture.

Discussion groups

Discussion groups on the topics “Splicing and diagnostics” and “Splicing-based therapies” gathered informally over lunch around discussion leaders Francisco Baralle and Diana Baralle. The discussions further elaborated on topics touched upon during the Round Table Discussion but tended to focus on issues of particular interest to the projects and clinical practice of the participants. These discussions led to the realization of the need to explore the possibility of establishing several collaborations, some of which involved basic and clinical groups.

Evaluation and conclusions

Judging from the feedback of the participants, the meeting achieved several important goals. First, it led to intense exchange of information and opinions, which we believe will have long-lasting effects in the form of contacts, collaborations and exchange of procedures and reagents. Second, it served to illustrate outstanding progress not only on our understanding of RNA-based

human pathologies, but also the existence of tangible, realistic opportunities for this research to have an impact on diagnostics and therapies. The need for continued expansion of EURASNET activities in this area and for enhanced exchange between scientists and clinicians clearly remains the most conspicuous conclusion of the meeting.

[Programme](#)
[Registration](#)
[Scientific Organisers](#)
[Conference Organiser](#)
[Hotel and Conference Site](#)
[Contact](#)

This meeting is supported by the European Commission



Programme

Saturday, 31 May 2008

- 15:00 - 19:00 Registration
19:00 - 21:00 Welcome Cocktail
21:00 - 21:15 Opening Remarks
21:15 - 22:15 Joan Steitz (Keynote)
Opening PANDora's Box: Nuclear RNA Decay and MicroRNA Biogenesis

Sunday, 1 June 2008

Session I: Splicing and Disease: Mechanisms and Mechanisms-Based Therapies

Chair: Irene Bozzoni

- 9:00 - 9:30 Gideon Dreyfuss
SMN deficiency causes tissue-specific perturbations in the repertoire of snRNAs and widespread defects in splicing
- 9:30 - 10:00 Tom Cooper
Alternative splicing in development and disease
- 10:00 - 10:30 Adrian Krainer
Antisense Strategy for Splicing Correction in Spinal Muscular Atrophy
- 10:30 - 11:00 Luis García
Re-establishment of dystrophin expression by exon skipping and/or trans-splicing approaches
- 11:00 - 11:30 **Coffee Break**

Session II: Splicing and disease: Splicing in the Clinical Practice

Chair: Matthias Hentze

- 11:30 - 12:00 Diana Baralle
Identification and analysis of mutations causing splicing disease
- 12:00 - 12:30 Guglielmina Pepe
RNA mutations in heritable connective tissue disorders
- 12:30 - 13:00 Michael Wood
Splice correction therapy for Duchenne muscular dystrophy
- 13:00 - 13:15 Annalisa Botta
Is the spliceopathy a link between genotype and phenotype of myotonic dystrophy type 1 patients?

Round Table Discussion: All invited speakers of the session

Chair: Francisco Baralle

All invited speakers of the session

- 14:00 - 15:00 Lunch and discussion groups "Splicing in diagnostics" and "Splicing-based therapies"
- 17:00 - 21:00 Start of the [EMBO Meeting on RNA and Associated Pathologies](#)

Registration

Please [register online](#). Only online registrations will be accepted.

If you are already registered for the EMBO conference on RNA and Disease, 31 May - 5 June 2008, Villa Mondragone, Rome, Italy, and selected the option to take part also in the EURASNET satellite symposium, then you **do not need to register again. Registration is only**

needed if you would like to take part in the satellite EURASNET symposium only.

Scientific Organisers

- **Francisco E. Baralle**, [International Centre for Genetic Engineering and Biotechnology](#), Italy
- **Juan Valcarcel Juarez**, [Center for Genomic Regulation](#), Spain

Conference Organiser

- **Bettina Schäfer**, [EMBL Heidelberg](#), Germany

Hotel and Conference Site

Rooms have been reserved at the [Villa Vecchia Hotel](#). This hotel is about 100 meters from the [Villa Mondragone](#), where the symposium takes place. Please enter your arrival and departure times upon registration, so a reservation can be made for you.

Villa Mondragone is located in the Alban Hills near the ancient town of Tusculum. This area, called the Castelli Romani (Alban Hills), is about 20 km southeast of Rome. The beautiful 16th century Villa is owned and operated by the University of Rome, and has hosted a number of scientific conferences. The Villa is easily accessible from central Rome.

Contact

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SPEAKERS LIST

1. Dr Diana Baralle

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6. Dr Tom Cooper

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8. Dr Luis Garcia (*participation cancelled at the last minute*)

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9. Prof. Matthias W. Hentze

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12. Dr Joan Steitz

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	FIRSTNAME	FAMILYNAME	COMPANY	COUNTRY	CATEGORY
1	Juan	Valcarcel	Centre de Regulacio Genomica	Spain	Scientific Organizer EMBO/EURASNET
2	Francisco	Baralle	ICGEB	Italy	Scientific Organizer EMBO/EURASNET
3	Claudia	Bagni	Catholic University of Leuven	Italy	Scientific Organizer EMBO
4	Joel	Richter	University of Massachusetts Medical School	United States of America	Scientific Organizer EMBO
5	Judith	Melki	Hadassah University Hospital	Israel	Roundtable EURASNET
6	Maria	Carmo-Fonseca/Salzar	Instituto de Medicina Molecular	Portugal	Roundtable EURASNET
7	Ian	Mohr	New York University School of Medicine	United States of America	Roundtable EURASNET
8	Oswald	Steward	University of California	United States of America	Roundtable EURASNET
9	Dazia	Limatola	Tebu Bio	Italy	Participant/Sponsor EMBO
10	Stavros	Milatos	BSRC Alexander Fleming	Greece	Participant
11	Olympia	Papadaki	BSRC Alexander Fleming	Greece	Participant
12	Helene	Gaillard	CABIMER, University of Seville	Spain	Participant
13	Tilmann	Achsel	Catholic University of Leuven	Belgium	Participant
14	Lara	Szewczak	Cell Press	United States of America	Participant
15	Nicolas	Barbezier	CNRS	France	Participant
16	Anthony	Henras	CNRS	France	Participant
17	Mohamad-Ali	Fawal	CNRS/UPS	France	Participant
18	Mai	Nguyen Chi	CNRS/UPS	France	Participant
19	Filippo M.	Cernilogar	Dulbecco Telethon Institute IGB CNR	Italy	Participant
20	Karin	Dumstrei	EMBO	Germany	Participant
21	Pamela	Bielli	Fondazione Santa Lucia	Italy	Participant
22	Roberta	Busà	Fondazione Santa Lucia	Italy	Participant
23	Maria Paola	Paronetto	Fondazione Santa Lucia	Italy	Participant
24	Lili	Wan	HHMI, University of Pennsylvania, School of Medicine	United States of America	Participant
25	Marco	Baralle	ICGEB	Italy	Participant
26	Madhuri	Bhuvanagiri	ICGEB	Italy	Participant
27	Andrea	D'Ambrogio	ICGEB	Italy	Participant

28	Lorena	Zubovic	ICGEB	Italy	Participant
29	Fabio	Martelli	IDI-IRCCS	Italy	Participant
30	Nicolas	Charlet Berguerand	IGBMC	France	Participant
31	Ludovic	Guigou	IGBMC	France	Participant
32	Caroline	Hammer	IGBMC	France	Participant
33	Chantal	Sellier	IGBMC	France	Participant
34	Stefania	Millevoi	INSERM	France	Participant
35	Kathrin	Meyer	Institute of Cell Biology	Switzerland	Participant
36	Ana Rita	Grosso	Institute of Molecular Medicine	Portugal	Participant
37	Luisa	Romao	Instituto Nacional de Saude Dr. Ricardo Jorge	Portugal	Participant
38	Ana Luísa	Silva	Instituto Nacional de Saude Dr. Ricardo Jorge	Portugal	Participant
39	Carla	Oliveira	IPATIMUP	Portugal	Participant
40	Paula	Soares	IPATIMUP	Portugal	Participant
41	Federica	Galeano	IRCCS Ospedale Pediatrico Bambino Gesù	Vatican City State	Participant
42	Angela	Gallo	IRCCS Ospedale Pediatrico Bambino Gesù	Italy	Participant
43	Silvia	De Rubeis	Catholic University of Leuven	Belgium	Participant
44	Chad	Swanson	King's College London	United Kingdom	Participant
45	Eva Maria	Riedmann	Landes Bioscience	Austria	Participant
46	Agnieszka	Piekielko-Witkowska	Medical Center of Postgraduate Education	Poland	Participant
47	Tilman	Heise	Medical University of South Carolina	United States of America	Participant
48	YLENIA	Bosio	Molecular Biotechnology Center	Italy	Participant
49	Ljiljana	Sjekloca	National Institute for Medical Research	United Kingdom	Participant
50	Paulina	Jackowiak	Polish Academy of Sciences	Poland	Participant
51	Miroslav	Dundr	Rosalind Franklin University of Medicine & Science	United States of America	Participant
52	Judith	Potashkin	Rosalind Franklin University of Medicine & Science	United States of America	Participant
53	Isabelle	Barlat	SANOFI-AVENTIS R&D	France	Participant
54	Eliane	Mandine	SANOFI-AVENTIS R&D	France	Participant
55	Berivan	Baskin	The Hospital for Sick Children	Canada	Participant

56	Flora	Tassone	University of California - Davis	United States of America	Participant
57	Pierre-Emmanuel	Gleizes	University Paul Sabatier	France	Participant
58	Oliver	Gruss	University of Heidelberg	Germany	Participant
59	Damien	Bregeon	University of Paris-Sud	France	Participant
60	Jenny	Blechingberg	University of Aarhus	Denmark	Participant
61	Leslie	Krushel	University of Colorado Denver School of Medicine	United States of America	Participant
62	Aldo	Pagano	University of Genoa	Italy	Participant
63	Dietmar	Richter	University of Hamburg -UKE	Germany	Participant
64	Silvia Carolina	Lenzken	University of Milan - Bicocca	Italy	Participant
65	Valentina	Sancisi	University of Modena & Reggio Emilia	Italy	Participant
66	Francesca	Boaretto	University of Padua	Italy	Participant
67	Laura	Biondini	University of Rome Tor Vergata	Italy	Participant
68	Valentina	Iadevaia	University of Rome Tor Vergata	Italy	Participant
69	Caroline	Lacoux	University of Rome Tor Vergata	Italy	Participant
70	Fabrizio	Loreni	University of Rome Tor Vergata	Italy	Participant
71	Claudio	Sette	University of Rome Tor Vergata	Italy	Participant
72	Alexandra	Alves Sampaio	University of Seville	Spain	Participant
73	Tarmo	Annilo	University of Tartu	Estonia	Participant
74	Yoshikazu	Nakamura	University of Tokyo	Japan	Participant
75	Howard	Lipshitz	University of Toronto	Canada	Participant
76	Michela	Denti	University of Trento	Italy	Participant
77	Erik Christian	Böttger	University of Zürich	Switzerland	Participant
78	Dimitri	Scherbakov	University of Zürich	Switzerland	Participant
79	Gadi	Zipor	Weizmann Institute	Israel	Participant
80	Tom	Cooper	Baylor College of Medicine	United States of America	Invited Speaker EURASNET
81	Christiane	Branlant	CNRS/University of Nancy	France	Invited Speaker EURASNET
82	Adrian	Krainer	Cold Spring Harbor Laboratory	United States of America	Invited Speaker EURASNET
83	Matthias	Hentze	EMBL	Germany	Invited Speaker EURASNET

84	Gideon	Dreyfuss	HHMI, University of Pennsylvania School of Medicine	United States of America	Invited Speaker EURASNET
85	Joan	Steitz	HHMI, Yale University	United States of America	Invited Speaker EURASNET
86	Guglielmina	Pepe	University of Florence	Italy	Invited Speaker EURASNET
87	Irene	Bozzoni	University of Rome La Sapienza	Italy	Invited Speaker EURASNET
88	Diana	Baralle	University of Southampton	United Kingdom	Invited Speaker EURASNET
89	Matthew	Wood	University of Southampton	USA	Invited Speaker EURASNET
90	Bart	De Strooper	Catholic University of Leuven	Belgium	Invited Speaker EMBO/Roundtable EURASNET
91	Jerome	Cavaille	CNRS	France	Invited Speaker EMBO/Roundtable EURASNET
92	Tamas	Kiss	CNRS	France	Invited Speaker EMBO/Roundtable EURASNET
93	Harald	König	Forschungszentrum Karlsruhe GmbH	Germany	Invited Speaker EMBO/Roundtable EURASNET
94	Anton	Wutz	IMP	Austria	Invited Speaker EMBO/Roundtable EURASNET
95	Elisa	Izaurralde	Max Planck Institute for Developmental Biology	Germany	Invited Speaker EMBO/Roundtable EURASNET
96	Robert	Schneider	New York University School of Medicine	United States of America	Invited Speaker EMBO/Roundtable EURASNET
97	Annalisa	Pastore	NIMR	United Kingdom	Invited Speaker EMBO/Roundtable EURASNET
98	Stuart	Peltz	PTC THERAPEUTICS INC.	United States of America	Invited Speaker EMBO/Roundtable EURASNET
99	Peter	Sarnow	Stanford University	United States of America	Invited Speaker EMBO/Roundtable EURASNET
100	Kazuko	Nishikura	The Wistar Institute	United States of America	Invited Speaker EMBO/Roundtable EURASNET
101	Utz	Fischer	Theodor-Boveri-Institute	Germany	Invited Speaker EMBO/Roundtable EURASNET
102	Maurice	Swanson	University of Florida	United States of America	Invited Speaker EMBO/Roundtable EURASNET
103	Rossella	Tupler	University of Modena & Reggio Emilia	Italy	Invited Speaker EMBO/Roundtable EURASNET
104	Scott	Hammond	University of North Carolina	United States of America	Invited Speaker EMBO/Roundtable EURASNET
105	Nicholas	Proudfoot	University of Oxford	United Kingdom	Invited Speaker EMBO/Roundtable EURASNET
106	Nancy	Bonini	University of Pennsylvania/Howard Hughes Medical Institute	United States of America	Invited Speaker EMBO/Roundtable EURASNET
107	Valentina	Mercaldo	Dept. of Molecular and Developmental Genetics, KU Leuven	Belgium	Helpers
108	Pietro	Pilo Boyl	University of Rome Tor Vergata	Italy	Helpers

Blue = NoE Member

Red = Clinicians