

















2ND ISSUE OF THE EURASNET NEWSLETTER – JUNE 2009



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EDITORIAL

Dear EURASNET members,

Let me first introduce myself: my name is Franziska Werba and I am taking over Claudia Panuschkas work as a public scientific officer. I have a master degree in biology with focus on ecology. In the last years I worked on my own at several scientific projects mostly on ecological / herpetological topics, such as "Amphibian Monitoring in the national park Gesäuse" or "Herpetological Monitoring in the Vienna zoo Tiergarten Schönbrunn" and so on.

Let's go back to the main topic the EURASNET! Half a year has past since the last newsletter was published and a lot of things have happened and will continue to happen.

One of the principal aims of EURASNET is to be a link between medical scientists and the molecular biologists – the networking between these disciplines. Alternative splicing is essential for human health and diseases. Therefore the transmission of research results to the medicine is very important and highly promoted by EURASNET. Besides, a couple of EURASNET members are strongly engaged in the field of disease diagnosis. Along these lines are the reports of Tito Baralle and Jamal Tazi, which are published in this issue.

Several EURASNET meetings and workshops, such as the fourteenth meeting of the RNA Society (Madison, May 2009), High-throughput technologies for the analysis of alternative splicing (Valencia, February 2009), the Inter Disciplinary Focus Meeting 'Mouse models for alternative splicing' (Assisi, April 2009) and the Fourth Annual EURASNET Meeting (Assisi, April 2009), took place and will be reported in this newsletter.

Networking within the EURASNET is also of particular importance. Thus, a couple of exchanges of PhD students and postdocs occurred during the last six months. Some of their experiences are reported in this issue as well.

Find out more about all those activities and news in this newsletter!

Enjoy yourself! Happy reading!



Franziska Werba



Franziska Werba
Public scientific officer

THE NETWORK

EURASNET, the European Alternative Splicing Network of Excellence aims to understand the link between alternative splicing and human health and disease. The EURASNET brought together 30 groups in the field of alternative splicing in the beginning of the year 2006 and additional ten young investigators joined the network in the following two years.

The main project objectives set out to be reached are:

- To carry out an ambitious research programme to increase the understanding and knowledge of alternative splicing at the molecular, cellular and organismal level.
- To ensure the exchange of information, procedures, reagents and personnel by creating a network structure, involving all EURASNET members.
- To support ten young investigators to join EURASNET and establish new research groups.
- To raise awareness of EURASNET and the importance of alternative splicing among the RNA community in Europe and to bring an understanding of alternative splicing to medical practitioners, policy makers and the general public.

At the time of writing, it is clear EURASNET functions exceptionally well as a network. Importantly, the network has catalysed multiple interactions among groups with different expertise and has considerable scientific success with many novel discoveries and high profile publications. This generates the fundamental knowledge of alternative splicing which forms the basis of application in medicine and the expanding contacts and interactions with clinicians and diagnosticians reflects the effort of the network in this area.

Major successes of the network are:

- Training of students and scientists in this area of research with many workshops, national and international meetings organised by EURASNET.
- Raising the awareness of the need for alternative splicing research and bringing scientists together with clinicians and diagnosticians.
- Information for the general public and schools on the importance of alternative splicing to human health and disease.
- Providing a website with educational material.
- Wide distribution of pamphlets, booklets and articles in popular science and the general press.

SPlicing CONNECTS

The term 'splice' refers to the connection of two or more pieces of any linear material. Its most common usage is in mariner's language for connecting the endings of a rope and is also used to describe the joining of audio tape or film.

In genetics the term splicing is used for the connection of two ends of parts of an RNA molecule that is derived from a gene, to give the final molecule of messenger RNA that is further translated into a protein.

Splicing – the sp(I)ice of life How do we get protein products from genes?

The genetic information of every known organism is stored in long chains of DNA (deoxyribonucleic-acid) molecules. The functional units of the genome are genes, which are arranged in succession on the DNA strands. Usually one gene codes for one protein so the sequence of the DNA (gene) determines the sequence of amino acids of that specific protein. However, the information stored in the DNA cannot be translated into proteins directly; instead, the DNA serves as a template which is copied into RNA (ribonucleic-acid) molecules. This process is called transcription. The product, the messenger-RNA (mRNA) is recognised by a big cellular machine – the ribosome – which is able to decipher the information encoded by the RNA and translate it into a sequence of amino acids that forms the protein molecule. This process is termed translation.

But now it gets a little more complicated...

Most genes are made up of pieces of DNA which code for proteins (exons) and pieces which don't (introns). After transcription the introns must be removed from the mRNA and the exons have to be joined together (this is where 'splicing' comes into it). After these steps, the mature mRNA is transported to the cytoplasm where protein production proceeds (translation).

Humans produce around 150,000 different proteins from their 25,000 – 30,000 genes. They do this by alternative splicing (AS). Alternative splicing means, that during the RNA splicing event different combinations of exons can be joined together to create a diverse array of mRNAs from a single gene such that one gene can actually make more than one protein and sometimes even hundreds of proteins.

More than 70% of the human intron containing genes are alternatively spliced. This explains the fact that the relatively small number of 25,000 genes can lead to production of over 100,000 of proteins. Alternative splicing is involved in all aspects of our growth and development and how our bodies work.

*For further information on this topic, please visit the EURASNET webpage:
www.eurasnet.info*



WP 17 – STAFF EXCHANGE AND TRAINING INFORMATION ON PROCEDURES AND REIMBURSEMENTS

Staff exchange

For students and post-docs, who visit a member lab for training or collaboration. Reimbursement of travel and accommodation expenses only, no daily allowances or bench fees.

Before the exchange

Send the following information to Angela Krämer (angela.kraemer@unige.ch):

- who is going (indicate PhD student or post-doc)
- the host lab
- intent of training, which method(s) will be learnt, purpose of collaboration, etc.
- intended duration of stay
- approximate costs

After the exchange

- Pay the bills through your grants/institution and send Reinhard Rauhut (reinhard.rauhut@mpibpc.mpg.de) a university invoice to be reimbursed to a university account (original documents are not required)
- OR: send all original documents (train/plane tickets, boarding passes, hotel bills etc.) to Reinhard for reimbursement.
- send a short (half page) summary about the exchange and the exact dates to Angela Krämer

*Travel bursaries
for EURASNET
group leaders are
NOT available.*

Attendance of meetings

Participation of students and post-docs (travel, registration fee and accommodation) at

- Intra-work package meetings (i.e. small meetings of work package members to discuss results, strategies etc.)
- EURASNET Workshops
- EURASNET Interdisciplinary Focus Meetings (IFMs)
- other splicing related conferences, such as RNA Society, EMBO, Cold Spring Harbor meetings (2 meetings per year per lab)
 - » Inform Angela Krämer (with copy to Reinhard Rauhut) about who is going (indicate PhD or post-doc) to which meeting
 - » Pay the bills through your grants/institution and send Reinhard Rauhut a university invoice to be reimbursed to a university account (original documents are not required)
OR: send all original documents (train/plane tickets, boarding passes, registration information, hotel bills etc.) to Reinhard Rauhut for reimbursement.



Angela Krämer

Reimbursement of invited speakers of EURASNET meetings

- Organizers should contact Reinhard (with copy to Angela Krämer)

Travel bursaries for participation of medical doctors at EURASNET IFMs focusing on alternative splicing and disease

- The availability of such fellowships should be announced on meeting web sites and/or posters. Selection should be based on CVs of interested people (to be done by organizers). Organizers should inform Reinhard Rauhut (with copy to Angela Krämer).

NEWS SECTION

- new paper from Prof. Lührmann
Exon, intron and splice site locations in the spliceosomal B complex.
Wolf E, Kastner B, Deckert J, Merz C, Stark H, Lührmann R.
EMBO J. 2009 Jun 18.
- new paper from Karla Neugebauer's lab
SR protein family members display diverse activities in the formation of nascent and mature mRNPs in vivo.
Sapra AK, Ankö ML, Grishina I, Lorenz M, Pabis M, Poser I, Rollins J, Weiland EM, Neugebauer KM. Mol Cell. 2009 Apr 24; 34 (2):179-90.
- cell paper from Alberto Kornblihtts group
DNA damage regulates alternative splicing through inhibition of RNA polymerase II elongation.
Muñoz, M. J., Pérez Santangelo, S., Paronetto, M. P., de la Mata, M., Pelisch, F., Boireau, S., Glover-Cutter K., Ben-Dov, C., Blaustein, M., Lozano, J. J., Bird, G., Bentley, D., Bertrand, E. & Kornblihtt, A. R. Cell 137, 708-720 (2009). Commented as Leading Edge in Cell 137, 600-602 (2009)..
- Happy birthday to Prof. Reinhard Lührmann!



*„Happy birthday
to Reinhard Lührmann“,
©[http://www.rezeptbuechlein.de/kuchen/
Linzer_Torte.html](http://www.rezeptbuechlein.de/kuchen/Linzer_Torte.html)*



*Jean Beggs presenting an
Album with nostalgic pictures
to Reinhard Lührmann
for his birthday.*

THEORETICAL COURSE – “RNA STRUCTURE AND FUNCTION”

At the beginning of April a theoretical course in Trieste took place. The target group of this course were people, who have a basic working knowledge of biochemistry, genetics and molecular biology and who are involved in research as well. Preferences have been given to students and junior scientists. The aim was to instruct these participants, so that they are able to use the teaching contents in their work.

The Topics:

- RNA structure, structure prediction
- Editing
- Ribozymes
- Transport
- RNA-protein recognition
- Translation
- Processing, splicing
- Evolution of RNA sequences

Students of EURASNET labs were participating in this course. As usual the response of the participants was very positive.

*Organiser:
Glauco
Tocchini-Valentini,
March 30th to April
2nd, 2009 Trieste*

Poster: The poster of the theoretical course – “RNA structure and function”.

ICGB
International Centre for Genetic Engineering and Biotechnology

2009 Meetings and Courses

**Theoretical Course
“RNA Structure and Function”
Trieste, Italy**

Organiser: Glauco Tocchini-Valentini (Director of Cell Biology/CNR, Rome, Italy)

Speakers will include: Francisco E. Baralle (IGSB, Paris, Italy); James E. Drenth (University of Wisconsin, Madison, USA); Lynne E. Margul (University of Arizona, AZ, USA); Oleg Miron (Department of Biology of the University of Strasbourg/UMR, Strasbourg, France); Henry Hoyle (GlaxoSmithKline, Harlow, Essex, UK); Doris O’Connell (JNRC, Mediterranean Biotech Strategy Unit, Rome, Italy); Oleg C. Ustavskan (Northwestern University, Evanston, IL, USA); Marko Wilkome (University of Wisconsin, Madison, USA)

Topics: RNA structure, structure prediction; Editing; Ribozymes; Transport; RNA-protein recognition; Translation; Processing, splicing; Evolution of RNA sequences

Participants: Participants must have a basic working knowledge of biochemistry, genetics and molecular biology and be involved in research where the potential application of the course material would be useful. Preference will be given to students and junior scientists. Registration is limited to 50 participants.

Funding: A limited number of grants, covering accommodation (own share) and local transport for the duration of the Course, are available to members of ICGB Member States*. Travel is NOT funded. Please state that there is no registration fee.

Closing date for applications: 6 November 2008

Contact: Submit your participation form, reimbursement form (if applicable) and a short CV of publications (if any) to: ICGB - Conferences and Meetings, P.le F.lli 1, 34122 Trieste, Italy. Tel: +39-040-3767333, Fax: +39-040-3269333, E-mail: meetings@icgb.org

*ICGB Member States: Argentina, Bangladesh, Belarus, Bolivia and Paraguay, Brazil, Bulgaria, Cameroon, China, Cuba, Colombia, Costa Rica, Cote d’Ivoire, Croatia, Czech Republic, Egypt, FR Yugoslavia, Hungary, India, Iran, Iraq, Italy, Jordan, Kuwait, Kyrgyzstan, Libya, Libyan Arab Jamahiriya, Maldives, Mauritius, Mexico, Morocco, Nigeria, Pakistan, Panama, Peru, Poland, Saudi Arabia, Serbia, Slovakia, South Africa, Taiwan, Turkey, Tunisia, Ukraine, United Arab Emirates, Uzbekistan, Viet Nam.

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EURASNET- REACH OUT TO THE CLINICS

The networking between molecular scientists and medicines – alternative splicing in the clinics

Whilst we feel that we are continually communicating and exchanging ideas with our medical colleagues, alternative splicing can still be an uncharted world for clinicians. However EURASNET has facilitated pathways to ensure that we intensify this activity and assist with the development of diagnostic technologies in the medical field.

The dissemination of information and education has been successful through the IFMs and workshops. In particular we have provided an efficient meeting specifically for the heads of molecular diagnostic laboratories in the UK and will be repeating this in France in 09. At the meeting each lab was able to recount their own experience of dealing with the unclassified sequence variants found during diagnostic sequencing. Most labs have attempted some RNA work but have found it difficult to develop and fit it into the necessary robust systems of diagnostic testing. Quality assurance in diagnostics requires tests to be sensitive, specific and unambiguous. Time and money constraints require them to be efficient and preferable high throughout. Indeed the consensus opinion was that these methods whilst desirable would probably be better accessed through a few expert centres in the country that would develop a best practice reproducible system of testing.

In the UK a National Genetics Reference Laboratory (NGRL) was established in 2002 by the Department of Health to support the UK genetic laboratory services by the development of research and technology in genetic testing. The laboratory works closely with the genetics communities and benefits from being based next to the Wessex Genetics Laboratory and associated with the University of Southampton. It is well placed to evaluate technologies and systems that are close to service. In collaboration with the NGRL, EURASNET has set up a flagship study to develop and test all unclassified sequence variants found in patients tested for Breast cancer/ BRCA screening and in the fibrillin gene causing Marfans syndrome, for splicing abnormalities in the Wessex Genetic Laboratory. This will test not only the feasibility of placing RNA and minigene assays into diagnostic testing but will also give us for the first time an idea of how many intronic and exonic mutations found really cause splicing aberration. This project will last one year and is being carried out by Dr Feng Lin.

The network has also successfully organised a practical workshop at Montpellier on this subject which has been positively received in the diagnostic community and will be repeated this year in July.

The IFM specialist interest groups have been particularly useful for inter-communication between scientists and clinicians. Through the presentation of our splicing work and listening to others from outside our network we have been successful in creating a number of exciting future collaborative projects.

*Authors:
Diana Baralle and
Francisco Baralle*



Diana Baralle



Francisco Baralle

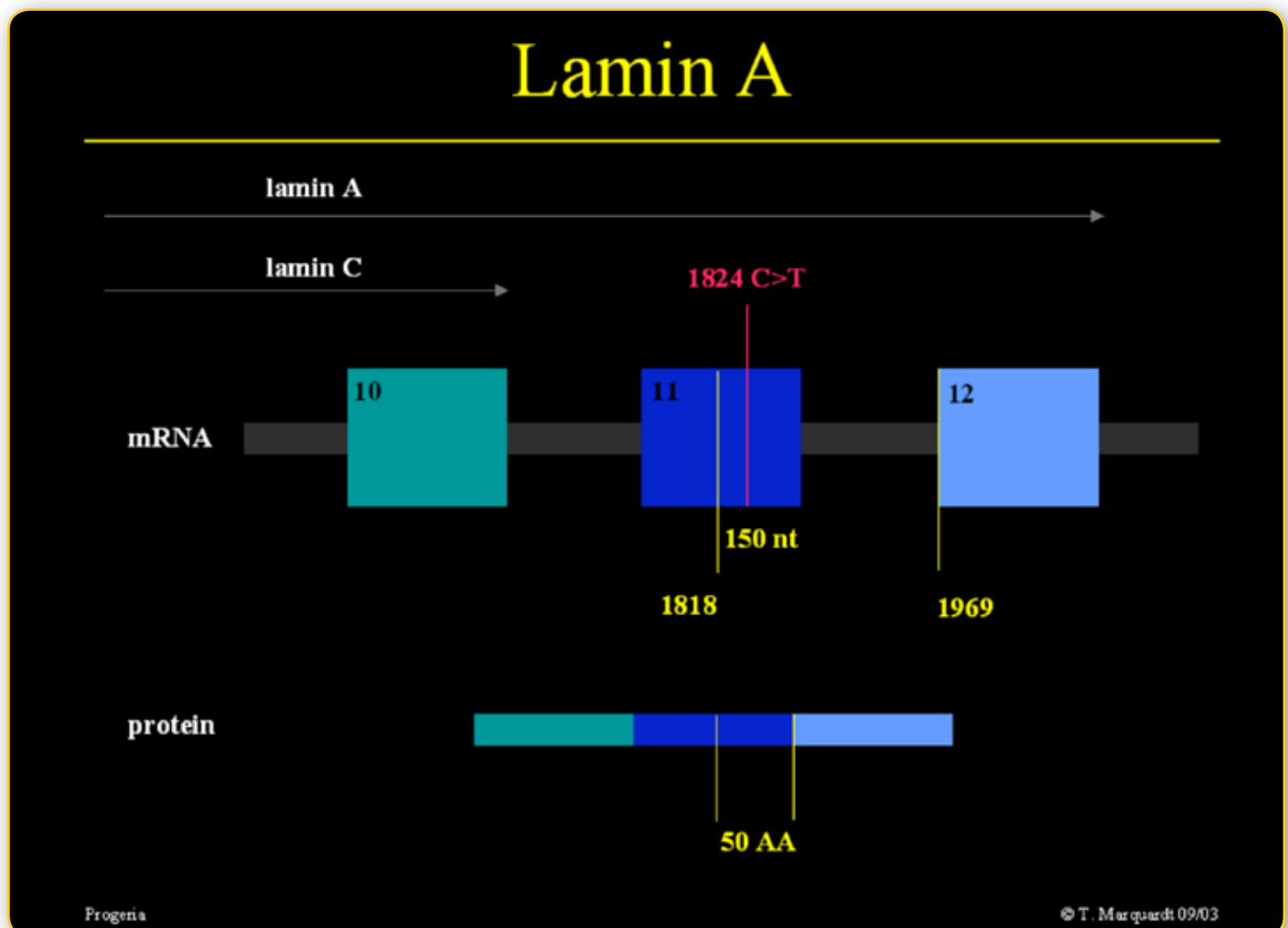
„TOO YOUNG TO BE OLD“

- HUTCHINSON-GILFORD PROGERIA SYNDROME (HGPS)

Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disorder phenotypically characterized by many features of premature aging. It is clinically characterized by postnatal growth retardation, midface hypoplasia, micrognathia, premature atherosclerosis, absence of subcutaneous fat, alopecia and generalized osteodysplasia (Khalifa, 1989). At birth, the appearance of patients is generally normal, but by 1 year of age patients show severe growth retardation, balding and sclerodermatous skin changes. They average ~1m in height and usually weigh less than 15 kg even as teenagers. The age at death ranges from 7 to 28 years, with a median of 13.4 years (Hutchinson 1986, Gilford 1904). Over 80% of deaths are due to heart attacks or congestive heart failure (Baker et al., 1981).

Author:
Jamal Tazi

Most of HGPS patients carry a heterozygous silent mutation that activates the use of a cryptic 5' splice site in exon 11 of LMNA pre-mRNA. This aberrant splicing event leads to the production of a truncated protein (progerin) with a dominant negative effect which is responsible for the observed phenotype (De Sandre-Giovannoli et al., 2003; Pendas et al., 2002a).



So far, therapeutic approaches have been mainly focused on progerin which is attached to a lipid anchor (a farnesyl lipid anchor) (Navarro et al., 2008, Fong et al., 2006). This lipid anchor is attached to progerin by a specific cellular enzyme, protein farnesyltransferase. Experiments in mouse models suggest that farnesyltransferase inhibitors (FTIs) may have beneficial effects in humans with progeria (Fong et al., 2006). More recently, Nicolas Levy's team has used a combination of a statin and an aminobisphosphonate to prevent the fixation of the fatty acid to the progerin, and thus reduce its toxicity (Varela et al., 2008).

In the frame of EURASNET network we have attempted to develop an entirely novel approach based on the inhibition of aberrant splicing leading to progerin production. Tazi's lab has obtained novel molecules that prevent usage of the cryptic 5' splice site in exon 11 of LMNA, allowing to overcome deleterious effect associated with progerin. Given that similar alteration of lamin A/C splicing was observed in aged individuals, finding novel molecules that interfere with aberrant splicing will be useful for the comprehension and hopefully the treatment of some of the features associated with pathological and physiological aging.

REPORTS ON EURASNET MEETINGS 2009

FOURTH ANNUAL EURASNET MEETING

The Fourth Annual Eurasnet Meeting, organised by Giuseppe Biamonti and Ian Eperon, was held at the Grand Hotel Assisi, in Italy. We were all pampered by heavenly food at the hotel and by beautiful landscape of Umbria. The meeting gathered researchers and students from around 40 laboratories.

At the reporting meeting, most of the time was spent on the reporting sessions for all work packages. However, the meeting gave the opportunity for all EURASNET members to discuss their future plans and collaborations between labs.

The meeting started on Thursday morning, with the welcome talk by Reinhard Lührmann, highlighting EURASNET achievements in the previous year. The reporting sessions from all work packages were also graced by some brilliant scientific talks.

For example Hennig Urlaub talked about the importance of reversible phosphorylation as a driving force for spliceosome remodeling and showed a new comprehensive MS-based method for analysis of phosphopeptides.

Reinhard Lührmann presented his recent results on the proteomic analysis of the yeast spliceosome. His study revealed that spliceosome from yeast contains a radically lower number of proteins, compared to the human one, with almost all of them being evolutionally conserved.

After busy, science-filled mornings many of us were tempted to spend the afternoons exploring the beautiful Umbrian landscape. It was a charming spring in Assisi with its medieval streets and beautiful churches, and the capital of Umbria – Perugia - a heaven for chocolate-lovers.

The meeting was closed on Friday evening with a guided tour for all participants to the magnificent 13th-century Basilica of San Francesco d'Assisi, which was followed by a fantastic dinner in the nearby Hotel Subasio. From the open-air restaurant terrace we could admire stunning views of the Basilica during a wonderful Mediterranean sunset.

In summary – I believe we all had a fantastic (and very productive for our research) time in Assisi and I am looking forward to meet all EURASNET members again during the annual meeting in Portugal next year.

*Organisers:
Giuseppe Biamonti
and Ian Eperon,
April 23rd to 24th,
2009 Assisi
Author: Dominika
Lewandowski*



Giuseppe Biamonti



*Christina
Kyriakopoulou,
EU-officer*



*Philip Avner,
EU-reviewer*



Francisco Baralle

INTER DISCIPLINARY FOCUS MEETING 'MOUSE MODELS FOR ALTERNATIVE SPLICING'

The IFM on "Mouse models of alternative splicing" provided an overview of current state-of-the-art technologies for gene manipulation in mice as well as the application of these technologies to understand the in vivo function of splicing factors, alternatively spliced isoforms and their alterations in disease. The selection of speakers was a lucky one, not only because of the outstanding quality of their science, but also because their excellent presentations were adapted to a mostly non-specialized audience of splicing aficionados to illustrate the principles and possibilities opened by new advances in gene manipulation of animal models. Efficient recombination technologies are making possible to tackle high-throughput projects for gene knockout in ES cells. EURASNET members were somewhat disappointed to hear that there are no plans in such EU-funded massive knockout projects to extend these analyses to alternatively spliced exons. This realization should encourage both communities to lobby for large-scale analysis of spliced isoforms as a necessary step to describe gene regulation in higher eukaryotes in vivo. It also emerged that issues relevant to the correct processing of pre-mRNAs should be taken into consideration in the design of knockout strategies. It is increasingly clear that tissue-specific knock-out and knock-in of splicing regulatory factors can not only provide essential tools to dissect splicing-related pathologies, but also that many completely unexpected insights on the physiological requirement and function of these factors and their regulation will be obtained. The long-term investment required to generate these reagents will be worthwhile, and a community effort to systematically generate animal models and analyze them at the molecular and phenotypic level would be a visionary step forward for our field.

Organisers:
Juan Valcárcel
April 22nd, 2009.
Assisi
Author:
Juan Valcárcel



Reinhard Rauhut



Dominika Lewandowski



Jamal Tazi

INTERNATIONAL WORKSHOP ON

HIGH-THROUGHPUT TECHNOLOGIES FOR THE ANALYSIS OF ALTERNATIVE SPLICING

I came to Valencia for the first time and was overwhelmed by the breathtaking beauty of this city and the hospitality of its inhabitants. It was a perfect venue for the multifaceted meeting, organized by SPLIRED (Spanish network of spliceomics and transcriptomics) and EURASNET.

The program of the workshop covered the latest technologies in characterization of alternative splicing events, including deep sequencing, splicing-sensitive microarrays, large-scale RT-PCR analysis and proteomics. An important question for many participants was: 'which of modern tools give the most accurate and comprehensive picture of alternative splicing events'. It was addressed by several speakers.

Chris Smith presented comparison of variety of approaches to identify PTB targets, including newly developed Affymetrix array with probe sets for both exons and exon junctions. Xiang-Dong Fu shared the results of identification of SR proteins targets using RNAseq, CLIPseq and splice junction arrays. Large-scale quantitative analysis of alternative splicing in variety of conditions, tissues and species using custom microarrays and deep sequencing was presented by Ben Blencowe. Results of profiling of cancer-associated genes using high-throughput RT-PCR platform were reported by Benoit Chabot. Juan Valcarcel was talking about identification of sex- and tissue-specific isoforms in flies using splicing-sensitive arrays. Talks by Jamal Tazi and Douglas Black addressed large-scale screening of chemical compounds which can modulate alternative splicing. Development and integration of different technologies to study alternative splicing was a subject of many exciting talks.

High throughput technologies generate a huge mass of data, and it is not trivial how to analyse it in respect of alternative splicing. It becomes clear that strong support of bioinformaticians is needed for these analyses. Development of computational strategies and data analysis procedures was addressed by several speakers.

Three days of the workshop were filled with interesting and fruitful discussions. The workshop was a great opportunity to learn about modern technologies, to share experiences in using them, and to discuss recent results. RNA 2009: The fourteenth meeting of the RNA Society

Organisers:
Juan Valcarcel,
Frederico Pallardù
and Chris Smith
February 5th to 7th,
2009. Valencia
Author:
Maria Kalyna



Impression of Valencia
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Language School

RNA 2009: THE FOURTEENTH MEETING OF THE RNA SOCIETY

After the successful RNA meeting last year in Berlin (Germany), which was organized by Reinhard Lührmann, this year's meeting was again held at the University of Wisconsin located at the beautiful lake Mendota. Andrew Feig and his team organized a meeting centered around the basics of RNA Molecular Biology, like structures of RNA and RNA-Protein complexes, catalytic RNAs and biogenesis and degradation of RNAs. However, it became clear that alternative splicing is playing a central role in RNA metabolism as many talks in non-splicing specific sessions dealt with alternative splicing related phenomena, in particular in the session RNA and disease.

The international RNA Society is a multidisciplinary society and promotes all aspects of RNA science to serve the RNA scientist and to disseminate important results to other scientists and to the public. EURASNET members take their share of responsibilities for the RNA society and frequently serve as officers. This year's president is EURASNET coordinator Reinhard Lührmann whereas Angela Krämer and Andrea Barta are Treasurer and Director, respectively.

In a touching award ceremony Reinhard Lührmann presented the 2009 RNA Society Life Time Achievement Award to Tom Cech who won the Noble prize for discovering catalytic RNAs and who is a devoted member of the RNA Society.

Organisers:

Andrew Feig, Narry Kim, Fatima Gebauer, Benoit Chabot 26th to 30th of May, 2009, University of Wisconsin - Madison

Author:

Andrea Barta



Tom Cech



EURASNET - South America connection:
Javier Caceres, Adrian Krainer, Alberto Kornblihtt



Reinhard Lührmann

STUDENT EXCHANGES WITHIN THE NETWORK FROM POLAND TO SWITZERLAND

Lukasz Sobkowiak (PhD students from Poland) went on a voyage - to discover Basel's labs in Biozentrum, Switzerland...

My name is Lukasz Sobkowiak, I'm PhD student in Prof. Zofia Szweykowska-Kulinska's and Prof. Artur Jarmolowski's lab in Poznan, Poland. We are interested in the influence of the plant CBC complex on alternative splicing as well as in *Arabidopsis thaliana* microRNA biogenesis. 5' and 3' RACE analysis, together with the sequences deposited in GeneBank and miRBase, allow us to determine the length and sequence of 22 pri-miRNAs and to establish the structure of respective MIRNA genes. We have shown the presence of U2-type introns in 13 out of 22 MIRNA genes analyzed. Three of intron containing MIRNA genes undergo alternative splicing events such as: exon skipping and 3' and 5' alternative splice sites usage.

Unexpected lengths of pri-miRNAs taking together with their complex splicing pattern seem to be very intriguing. One of the possible explanation is that pri-miRNAs contain additional, yet uncharacterized, small RNA molecules. In the last year I was in Mihaela Zavolan's lab in Biozentrum, Basel, Switzerland. Our lab (Department of Gene Expression, Adam Mickiewicz University, Poznan, Poland) was totally inexperienced in biocomputational analysis; Mihaela Zavolan helped us in the pri-miRNAs secondary structures predictions. I have never developed source code using 'Perl'. Furthermore it was difficult to understand the basics of programming language. I really like challenges... People in Biozentrum were very helpful. During my stay in Mihaela Zavolan's lab I understood that bioinformatics is very helpful for biologists. Actually I'm learning Perl and I'm in collaboration with scientist from Bioinformatics Laboratory, Adam Mickiewicz University, Poznan, Poland.



Lukasz Sobkowiak

A TRIP FROM TRIESTE TO GÖTTINGEN...

IN QUEST OF SPLICEOSOMES.

I am Ashish Dhir, a PhD fellow in the lab of Prof. Baralle at ICGEB, Italy. Our main research focuses on understanding the splicing mechanisms involved in diseases. My research interest center on understanding the splicing regulation of pathological pseudoexons. As we were interested in the pseudoexon splicing of the ATM gene, we sought to characterize the spliceosomal complexes assembled on this pseudoexon. Being a part of the EURASNET network, I got the opportunity to carry out the experiments in the lab of Prof. Reinhard Lührmann that has established a very efficient MS2- affinity based technique for the isolation and characterization of spliceosomes. I couldn't have asked for more...!

Getting to Gottingen was a beautiful and interesting journey, as I also managed to catch a view of Hannover on the way. My stay was arranged at the Institute guest house, a beautiful place very close to the lab. It was just perfect for me as it gave me the freedom to stay longer at the lab, something that you wish to have when you are for a limited stay.

On my first working day I got to know the lab members, the staff and the lab set-up as a whole. Initial days were spent in getting acquainted with the new techniques, protocols and setting up the experimental conditions. Since, I had been there to learn a new technique, I would like to especially thank Marieke who had been a great help and a wonderful colleague.

Days became quite busy, as I started with my actual experiments, not leaving me much time to explore the city. Nevertheless, I didn't fail to do so during the weekends. Language was never a problem as almost everyone in the town could speak English (though I managed to learn a few very basic phrases such as Guten Morgen, Guten Tag, Bitte and Danke). The various hurdles faced during the initial days of my experiment were overcome... thanks to the fruitful discussions with my colleagues (Marieke, Marc, Cindy, Sergey, Peter...). I would like to take this opportunity to thank especially Prof. Lührmann for taking out his precious time for me, despite his very busy schedule. The long discussions with him truly were an enriching experience.

Apart from the lab work, I also cherished playing tennis with Zbigniew and others, the get-together that we had at the wonderful Lebanese restaurant with all the lab members and Prof Reinhard Lührmann (sad, that I don't have a picture of everyone) and the pizza party... The description of my stay would not be complete without a few words about the beautiful city Göttingen... a well preserved old town with its cobblestone streets, the beautiful City Hall, the Rathaus and the famous Gänseliesel located in the center of the old town.

Altogether, it was a great learning experience which will help me to stretch my limits in life.



Ashish Dhir



Marieke



Marc



FORTHCOMING MEETINGS

Workshop on Alternative Splicing and Disease

Meeting Location:	Montpellier, France
Meeting Date:	July 20-25, 2009
Organisers:	Jamal Tazi and Stefan Stamm

'RNA-protein interactions in pre-mRNA splicing' EURASNET practical course

Meeting Location:	Barcelona, Spain
Meeting date:	July 20-24, 2009
Organizers:	Juan Valcarcel and Veronica Raker

French workshop on RNA splicing and genetic diseases

Meeting Location:	Institut Pasteur and Institut Curie, Paris, France
Meeting date:	October 1-2; 2009
Organizers:	Diana Baralle (University of Southampton, UK), Mario Tosi (University of Rouen, France)

Evaluation of bioinformatics predictions of splicing

Meeting Location:	Institut Curie, Paris, France
Meeting date:	2 October 2009, 9:30-13:00
Organizers:	Claude Houdayer (Institut Curie), Christophe Bérout (Montpellier), André Blavier (Interactive Biosoftware, Rouen)

EURASNET HEADS

In each issue of the EURASNET newsletter we will introduce eight of the network laboratory heads.

Francisco E. Baralle

Some pre-mRNA splicing defects are involved in the pathogenesis of human diseases. Recombinant DNA procedures might help to prevent these diseases or provide an attractive tool to treat certain defects. The systems under investigation include the aberrant splicing of disease related genes causing some forms of Cystic Fibrosis. Another of Francisco's research interests is the elucidation of the basic molecular mechanism of alternative splicing involved in the generation of fibronectin isoforms.



Ian Eperon

The spliceosome is a dynamic machine, which undergoes major conformational changes upon its self-activation. To study these changes Ian develops – in cooperation with a group in Leicester – methods for kinetic analysis of spliceosome dynamics. One very important time point knowing about the dynamics of the spliceosomal complex is during splice site selection. Activator and repressor proteins being involved in determination of splice site choice should therefore be further investigated.



Karla M. Neugebauer

The primary topic of interest of research in Karla's lab is the organisation of pre-mRNA splicing in the cell nucleus. Therefore a novel approach to localize the assembly and function of essential splicing factors was established. On the other hand she investigates the action of snRNPs in co-transcriptional spliceosome assembly and alternative splicing.



Jørgen Kjems

Studying the mechanisms of alternative splicing in mammalian systems is the main aim of Jørgen and his group. In detail they examine the regulation of mRNA splicing in HIV-1 and medium chain acyl-CoA dehydrogenases (MCAD). Their attention is turned to the question, how cellular splicing factors interact with the RNA and direct the spliceosome to the right splice sites. Additionally the role of the HIV-1 proteins Rev and Tat in HIV splicing should be clarified. The second project in Jørgen's group deals with clarification of the mechanism for exon skipping in mutated versions of the medium chain acyl-CoA dehydrogenase (MCAD) gene, which leads to deficiency of the MCAD enzyme.



Daniel Schümpert

Daniel and his lab crew have pioneered methods to manipulate specific alternative splicing events. One approach uses derivatives of U7 snRNA, a short non-coding RNA involved in histone RNA 3' processing. These RNAs can induce the skipping of internal exons from a targeted mRNA in the context of genetic (β -thalassemia, Duchenne muscular dystrophy) or acquired diseases (HIV/AIDS). The therapeutic U7 snRNA accumulates as a stable small ribonucleoprotein particle in the cell compartment where splicing occurs, the nucleus.



Chris Smith

Tropomyosin and actinin are alternatively spliced gene products. Their splicing is performed with smooth muscle specificity. Further investigations of this permit analysis of molecular mechanisms of regulated alternative splicing in model gene systems and the function of splicing regulators. Chris has developed a quantitative proteomic technique to define functional targets of splicing regulators. This approach might complement other global approaches (microarrays) in the attempt to define the "circuitry" of alternative splicing programmes.



Jamal Tazi

"Prp8 is a highly conserved U5 snRNP protein that functions at the catalytic centre of the spliceosome. It has been a focus of our research over many years. We recently showed that mutations in the C-terminus of Prp8 that cause Retinitis pigmentosa in humans, cause a defect in U5 snRNP maturation and splicing in yeast. This type of Retinitis pigmentosa may therefore be a consequence of a splicing defect. We are also investigating links between transcription and splicing."



Juan Valcárcel

The understanding of the molecular mechanisms of alternative splicing regulation is the main interest of Juan's research. He studied how the Sex-lethal protein in *Drosophila* enforces the development of a female specific splicing pattern on target genes. Additionally he investigates the functions of trans-acting factors in alternative splicing and the link to cell differentiation and cancer progression.





Henning Urlaub

Up to now unknown proteins which are in direct contact with RNA in ribonucleoprotein (RNP) particles can be identified after UV cross-linking of native RNP particles. Henning is especially interested in the investigation of protein-RNA interactions. For the detection he and his research group is establishing new, improved and increasingly sensitive mass-spectrometric methods (MALDI and ESI) combined with chromatographic enrichment strategies. The extremely low quantity of material needed for this technique renders analysis possible of RNP complexes which are low abundant.

Mihaela and Henning are two Young Investigators who joined the EURASNET network in 2007



Mihaela Zavolan

Studying different aspects of RNA biology can take advantage of the use of several computational methods. Mihaela developed a fully-automated software tool to generate a web-accessible database of all splice forms observed in the sequence data. It starts from large scale sequence data sets and performs all the steps that are necessary. This enables to analyze splice variation in a simplified way. An essential component of this tool is a novel algorithm that was developed for mapping cDNA and EST sequences to their corresponding genome. (The algorithm integrates information about gene structure, splice sites and sequencing errors in a Bayesian probabilistic framework to infer the most likely mapping of a cDNA sequence to the genome.)

Andrea Barta work package leader "Public Understanding in Science".

John Brown work package leader "Reachout to the Broader RNA Community".

Franziska Werba Public scientific officer.

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