ESID Newsletter

Contents

Roland Levinsky, 1943-2007

Roland was a pioneer and inspirational leader in the field of primary immunodeficiency.

Although originally from South Africa, Roland spent his adult life in the UK, 26 years of it at the Institute of Child Health (ICH) and Great Ormond Street Hospital (GOS) in London. Roland attended medical school in London (University College London) and then trained in paediatrics in Birmingham and London before moving to Great Ormond Street Hospital in London in 1973. He subsequently became Senior Lecturer and Honorary Consultant Immunologist at GOS and Hugh Greenwood Professor of Immunology in 1985, a Chair he held at the Institute of Child Health, until he left London in 2002 to be Vice-Chancellor of Plymouth University.

Initially planning to become a Nephrologist, Roland became interested in the immunology of renal disease at GOS. This led on to immunology and in particular, the primary immunodeficiency disorders (PIDs), for which he pioneered the application of bone marrow transplantation (BMT) in the UK. This was also at a time when many similarly minded clinician scientists were interested in utilising the new techniques that were being developed in molecular biology and genetics to understand the molecular basis of disease. Roland was among a select group who understood the power of these new techniques and how they could eventually be used to "cure" these life-threatening diseases. Together with other like-minded individuals an informal grouping was established in 1983, the European Group for Immunodeficiency Disease (EGID), which was the forerunner of what is known as ESID today.

Using the large cohorts of patients, it was possible to use the new genetic techniques to identify the molecular basis of primary diseases and Roland was among the first to see this. This resulted in successful collaborations to identify the genes for X-linked agammaglobulinemia and X-linked hyper IgM syndrome. Roland also saw the potential for using this genetic knowledge to develop the techniques to treat PID using gene therapy. Roland was an enthusiastic advocate of gene therapy, being involved in the early European trials of gene therapy for adenosine deaminase deficiency. He was involved in the first research projects to obtain funding in the UK to develop gene therapy techniques for PID. His enthusiasm and vision lead directly to the successful gene therapy programme at GOS today.

Roland was a highly efficient administrator. He became Dean of the ICH in 1990 when it became apparent to him that he was the only person who had the vision and strength of will to lead it forward. Roland set about a complete reorganisation of the Institute's academic structure and abolished nearly all committees. He recruited many young clinical and non-clinical scientists, whose research interests ranged across diverse fields, from genetics to public health, but who all shared one thing: a desire to apply top quality science to diagnosis and treatment of children's disease. This resulted in one of Roland's greatest achievements; turning the ICH into a word-class children's research organisation, and a legacy of highly trained and motivated medical research scientists all over the world, many of whom hold University Chairs in their own right.

This success led to his appointment in 1999 as the Vice Provost for Biomedicine and Head of the Graduate School at University College London, and then Vice Chancellor of Plymouth University. Under his vision and leadership the university flourished and leapt up the rankings of the UK's universities.

Roland will be widely missed by everyone who knew him. He was a giant in every sense, a tremendous family man, whose wisdom and kindness touched the lives of many. He was a mentor to many of us, and will be sorely missed for his friendship, wisdom, and humour.

Christine Kinnon, Adrian Thrasher and Bobby Gaspar

The ESID Newsletter is made for the members of ESID – the European Society for Immuno Deficiencies.

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries (editor in chief), Lucia Bianchi, Ales Janda, Gustavo Lazo, Nima Rezaei, and Crina Samarghitean.

Any ESID member who is interested in publishing his or her views, research, new ideas or other material in the ESID Newsletter is cordially invited to submit copy to the Editor. Suitability for publication is assessed by the Editor in consultation with the other members of the ESID Board.

Editorial address:
Dr. Esther de Vries, pediatric immunologist, Jeroen Bosch Hospital loc GZG, P.O. Box 90153, 5200 ME 's-Hertogen bosch, the Netherlands, tel. +31-73-6992965, fax +31-73-6992948.

Please only use my *new email address*: esid@ estherdevries.nl

Front page:
Dutch tulips.

Dear ESID members,

We are very happy to present you a new issue of the ESID Newsletter. We hope you will find many things that interest you.

We are very sorry to have lost such an inspirational colleague as Roland Levinsky due to an unfortunate accident, and will all remember him.

The ESIDjuniors have done their part - and more! - to give you material to read and think about. Please give them your reactions, whether you are junior or senior yourself.

There are lots of interesting meetings to read about, and all kinds of information from the Working Parties.

Feel free to send us your ideas and comments, and contributions to the ESID Newsletter!

Don't miss the ESID Summer School advertisement on the back of this issue !! Please alert all young people in the field you know of to this event. Applications should be made online, all information about that can be found on the ESID website www.esid.org.

I wish you all a beautiful springtime,

Esther DE VRIES

ESID is the European Society for Immunodeficiencies. It was formed in 1994. The forerunner of ESID, the informal European Group for Immunodeficiencies (EGID) was established in 1983. The aims of this society are, among others, to facilitate the exchange of ideas and information among physicians, scientists and other investigators who are concerned with immunodeficiencies and to promote the research on these diseases. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. Registration is possible online at www.esid.org/members.php.

Within ESID, seven Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Stem cell transplantation and gene therapy (chair: Mario Abinun), Registries (chair: Gerhard Kindle), Clinical (chair: Bobby Gaspar), Genetics (chair: Naomi Taylor), Education (chair: Andrew Cant), PID-care in development (chair: Laszlo Marodi), and ESID *juniors* (chair: Eleonora Gambineri). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www.esid.org /board.php).

In 1994, a main registry of patients with various forms of immunodeficiency in Europe was established. Altogether, data from some 10,000 patients from 26 countries was compiled until 2002. However, given various shortcomings of this registry, ESID decided to develop a new state-of-the-art database for primary immunodeficiencies. This online registry was launched in 2004 and contains subregistries for more than 150 primary immunodeficiencies. It combines both clinical and laboratory data of PID patients and offers the possibility to document genetic data as well. Up to date, more than 2,000 patients have been registered in that database. Information, database statistics and a demo version of the registry can be found at www.esid.org/registry.php, or send an email to registry@esid.org.

The new ESID Online Registry is connected to the mutation databases (IDbases) in Tampere, Finland. These were created since 1995, when the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia). Since then, more than 100 additional locus-specific databases have been established. Information is available at http://bioinf.uta.fi.

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2006 in Budapest, Hungary , and the next one will be October 16-19 in `s-Hertogenbosch, The Netherlands, in 2008. Information is available at www.esid2008.org.

= ESID Information =

President's letter

Dear ESID members,

As you may recall, we decided during the last General Assembly in Budapest, that the ESID should amend its Constitution. We thought the new Constitution should meet the new challenges facing a rapidly growing Society. We decided to vote on several key questions by electronic voting, taking advantage of the availability of the ESID website. The voting period opened on February 1, 2007 and lasted until March 15th. ESID counts 413 members, implying that 103 votes were necessary to reach the requested quorum of 25%. We did reach the quorum, as there were at least 107 and up to 112 votes per question. I would like to express my gratitude to the voters. The ESID society is thriving, as attested by this vote. I also would like to encourage those who did not vote to take a second chance. Indeed, there will be a second round for 7 of the 12 questions, as an absolute majority is requested (>50%). Only five questions were settled in the first round. The results of the vote will be found elsewhere in the newsletter. Needless to say, I do also encourage those who voted for the first round to vote again. We do need as many votes as possible to make the decision as representative of our community as can be. I will not comment on the results of the first round yet. This would be premature. The time will come for a discussion. We are still in the middle of the results section.

All best wishes,

Jean-Laurent CASANOVA

Secretarial report

ESID Poll on changes to the constitution.

In Budapest October 2006, during the GA, it was decided that ESID needs to amend its Constitution in order to reflect new challenges for the rapidly growing Society. Thus, after many discussions, the ESID Board asked all ESID members to vote on the questions listed below and endorse the Board to adapt the Constitution accordingly. There were 12 questions in total but not all were answered by all voters. The poll was started on February 1, 2007 and initially it was planned to end it on February 28th but when it became obvious that we were not going to reach the quorum of 25% by that date, we extended the deadline to March 15th. ESID currently has 413 members, therefore 103 votes are necessary to reach the quorum of 25%. We reached the quorum of 25% and have between 107 and 112 votes. Thank you to those who have voted.

Here is the result of the vote: The percentage per answer is given with the actual number of votes in brackets.

1. ESID President citizenship/residence. Should the ESID President be: 1: a European citizen, working in Europe? - 33.90% (n=40) 2: a European citizen, working anywhere world-wide? - 8.47% (n=10) 3: a citizen from any country, working in Europe? - 39.83% (n=47) 4: a citizen from any country, working anywhere world-wide? - 17.80% (n=21) Total: 118 participants
2. ESID Secretary. Should the ESID Secretary be: 1: a European citizen, working in Europe? - 32.17% (n=37) 2: a European citizen, working anywhere world-wide? - 3.48% (n=4) 3: a citizen from any country, working in Europe? - 40.00% (n=46) 4: a citizen from any country, working anywhere world-wide? - 24.35% (n=28) Total: 115 participants
3. ESID Treasurer. Should the ESID Treasurer be: 1: a European citizen, working in Europe? - 42.61% (n=49) 2: a European citizen,

working anywhere world-wide? - 2.61% (n=3) 3: a citizen from any country, working in Europe? - 37.39% (n=43) 4: a citizen from any country, working anywhere world-wide? - 17.39% (n=20) Total: 115 participants

4. Heads of ESID working-parties. Should the head of an ESID working-party be: 1: a European citizen, working in Europe? - 17.24% (n=20) 2: a European citizen, working anywhere world-wide? - 8.62% (n=10) 3: a citizen from any country, working in Europe? - 34.48% (n=40) 4: a citizen from any country, working anywhere world-wide? - 39.66% (n=46) Total: 116 participants

5. ESID full members. Here we ask whether or not it is important that a full ESID member is European and/ or where he is working. Please check the present ESID constitution, §4 for the definition of an ESID full member.

Should an ESID full members be: 1: a European citizen, working in Europe? - 6.90% (n=8) 2: a European citizen, working anywhere world-wide? - 9.48% (n=11) 3: a citizen from any country, working in Europe? - 15.52% (n=18) 4: a citizen from any country, working anywhere world-wide? - 68.10% (n=79) Total: 116 participants

6. ESID members. ESID members shall be: 1: MDs, PhDs (biology), Veterinarians, Pharmacists, Dentists, or graduate students in any of these fields - 22.41% (n=26) 2: option 1 + PhDs (other fields) and corresponding graduate students - 25.00% (n=29) 3: option 2 + nurses and social workers - 18.10% (n=21) 4: option 3 + patients - 9.48% (n=11) 5: no restriction for membership. - 25.00% (n=29) Total: 116 participants

7. ESID board members. ESID board members shall be: 1: MDs, PhDs (biology), Veterinarians, Pharmacists, Dentists, or graduate students in any of these fields - 45.61% (n=52) 2: option 1 + PhDs (other fields) and corresponding graduate students - 25.44% (n=29) 3: option 2 + nurses and social workers - 15.79% (n=18) 4: option 3 + patients - 3.51% (n=4) 5: no restriction for board membership. - 9.65% (n=11) Total: 114 participants

8. Conflicts of interest: President etc. Do you agree that ESID president, secretary and treasurer should declare any financial or other possible conflict of interest 1: Yes - 92.17% (n=106) 2: No - 7.83% (n=9) Total: 115 participants

9. Conflicts of interest: all ESID board Do you agree that any ESID Board member should declare any financial or other possible conflict of interest 1: Yes - 88.79% (n=103) 2: No - 11.21% (n=13) Total: 116 participants

10. Declaration of conflicts of interest. If necessary, these conflicts of interest shall be declared 1: to the ESID board in writing - 57.02% (n=65) 2: to all ESID members on the protected part of the ESID website - 42.98% (n=49) Total: 114 participants

11. The right to expel any ESID member Do you agree that the ESID Board has the right to expel any ESID member as detailed above? 1: I agree - 75.44% (n=86) 2: I do not agree - 24.56% (n=28) Total: 114 participants

12. Definition of Europe for ESID Please select the definition of Europe that you think ESID should follow. Europe shall be defined as follows: 1: no definition of Europe - 25.00% (n=30) 2: EU (27 countries) - 2.50% (n=3) 3: option 2 + Iceland, Norway, Switzerland, Serbia, Bosnia, Montenegro, Croatia, Albania, Macedonia and small states

(Andorra, Monaco, Lichtenstein, San Marino, Vatican) - 13.33% (n=16) 4: option 3 + Ukraine, Belarus, Russia, Moldavia, Turkey, Israel - 44.17% (n=53) 5: a broader Europe (not satisfied with options 1-4) - 15.00% (n=18) Total: 120 participants

Conclusions

Their will be a new round of voting through the ESID website for those questions that were not yet decided by a majority of the votes (50% + 1). You have already had an email about this (if not, check your email address on the restricted part of the ESID website!! Please all cast your votes again!

Bodo GRIMBACHER

Treasurer's report

We now have 552 ESID members registered on the ESID website, which is more than we have ever had. Even better, 418 of them have paid their ESID membership fee 2006-2007 !! And this as well is much much better than we ever had. We are very happy about this, it shows that ESID is a thriving Society, of which people are eager to be a member.

Unfortunately, 134 ESID members have not paid their membesrhip fee 2006-2007, and they don't receive the ESID Newsletter anymore, they will have to be expelled from ESID if they don't pay. They will get one last reminder.

Esther DE VRIES

News & Views

Journal of Experimental Medicine

Dear All, I have been appointed Editor of the Journal of Experimental Medicine. As discussed by Ralph Steinman in previous editorials (Research on human subjects in the JEM, J Exp Med. 2005 May 2;201(9):1349-50), the JEM aims at publishing more high-quality human research. I would like to inform you that the JEM is now actively seeking for the best manuscripts in the field of primary immunodeficiencies, whether reports of novel disease-causing genotypes, reports of novel immunological and clinical phenotypes, or reports of immunological or microbiological studies taking advantage of patients with known genetic defects. I therefore encourage you to submit your best papers to the JEM!

Jean-Laurent CASANOVA

INSTITUT PASTEUR

"Genetics and Mechanisms of Susceptibility to Infectious Diseases"
Pasteur Institute, Paris 21-24 November 2007

Together with EMBO (European Molecular Biology Organisation), we are taking the initiative to launch a series of conferences that will take place every second year in the Pasteur Institute in Paris and will be dedicated to the Host Genetics Control of Infectious Diseases. We wish to cover a broad range of infectious agents and hosts and attract a large number of participants from around the world.

The subjects that we intend to cover in the first meeting include:

- Primary immunodeficiencies,
- Genetics of common infectious

diseases,

- Genetics and functional studies of resistance to viruses,
- Non mammalian models to study host genetics of infections,
- Mouse models to study host genetics of infections,
- Infections, chronic inflammation and autoimmune diseases,
- The impact of pathogens on human evolution and their diseases

A number of speakers listed below accepted to attend the meeting. The rest of the oral talks and poster communications will be selected among the abstracts submitted by the participants. L.Abel (Paris), A.Alcaïs (Paris), R.Balling (Braunschweig), M. Bamshad (Seattle), B. Beutler (La Jolla), S. Bolland (Bethesda), M. Carrington (Bethesda), JL. Casanova (Paris), S. Cherry (Philadelphia), ME. Conley (Memphis), A.Dessein (Marseille), A.Fischer (Paris), S. Foote (Hobart), C. Goodnow (Canberra), P. Goulder(Oxford), P. Gros (Montreal), O. Haller (Freiburg), J. Hodgkin (Oxford), J. Hoffmann (Strasbourg), C. Julier (Paris), D. Kwiatkowski(Oxford), M.Malim (London), G.Orth (Paris), L.Quintana-Murci (Paris), AW. Segal (London), L. Svensson (Linkoping) and S. Vidal (Montreal).

Further information can be obtained at http://www.pasteur.fr/infosci/ (conferences) or by mail from Moshe Yaniv " yaniv@pasteur.fr ".

Scientific Committee: Laurent Abel (Paris), Rudi Balling (Braunschweig), Jean Laurent Casanova (Paris), Chris Goodnow (Canberra), Cecile Julier (Paris), Michael Malim (London), Lluis Quintana-Murci (Paris) and Moshe Yaniv (Paris)

Local Organizing Committee: Laurent Abel, Sandra Bobichon, Jean Laurent Casanova, Philippe Despres, Jean Louis Guenet, Cecile Julier, Gerard Orth, Luis Quintana –Murcia and Moshe Yaniv.

The 6th Prague Spring ESID Meeting ,
Prague, May 14 and 15, 2007.

The meeting takes place at the Institute of Immunology of the 2nd Medical School, Charles University. This year we would like to provide more space for presentations of members of ESIDJuniors working party, however, we welcome applications from all ESID members. We expect everyone to show his/her results or expertise in any part of PID field. We expect broad discussion of the attending Juniors on the future activities of this working party as well. The names of the invited faculty will be announced as early as they confirm their attendance.

The meeting is organized in a same way as in the previous years. EACH participant is expected to present a short talk on a project he/she is currently involved in, results of previous research or an interesting case report (10-20 min talk). We can accept non-presenting participants only as an exception! There will be enough space to discuss any topic related to PID and we hope that it will be in quite an informal way as we experienced during the previous workshops.

If you are interested, please, fill in the enclosed registration form and return it to us. Since there could be only about 30-35 participants, the applications will be accepted on first-come-first-served basis. So, do not hesitate and respond as soon as possible. Please, specify a topic that you would like to share with the audience as the detailed programme will be composed according to the submitted papers.
Please, send the form back before March 30, 2007.

If you want to learn more about the

last years' programmes, visit our new website http://imunologie.lf2.cuni.cz/ and look at the section "ESID workshop". The programme and all the available presentations and material of this year's meeting will be placed here as well.

The essential conference information: Conference dates: May 14 and 15, 2007. Conference venue: University Hospital Motol, V Uvalu 84 150 06 Prague 5 – Motol, Czech Republic. Conference fee: FREE OF CHARGE. Accommodation: FREE OF CHARGE (depending on number of participants and available funds). Refreshments: lunch and snacks during both days will be provided FREE OF CHARGE. Social programme: to be specified later. Official language: English.

Contact: ales.janda@lfmotol.cuni.cz , anna.sediva@lfmotol.cuni.cz . Please, feel free to contact us in case of any questions (tel: +420-224-435-978, fax: +420-224-435-962).

We are looking forward to meeting you in Prague in May.

Ales JANDA
Anna SEDIVA

Suggestions to the ESID community for the Journal of Primary Immunodeficiency?

As you know, primary immunodeficiency diseases (PID) are a group of inherited disorders consist of more than 100 different disorders (IUIS, Budapest meeting 2005: J Allergy Clin Immunol 2006 Apr;117(4):883-96).

More than 100.000 articles have been published regarding immunodeficiency disorders in the last decade in different journals and there is a significant trend in publication of these articles in the recent years; i.e. regarding CVID disorder, one of these 100 different PID disorders, there are 1407 articles in which 220 of them (15.6%) have been published after 2005 (ISI Web of Knowledge). After searching 7 common disorders out of 100 PID in ISI Web of Knowledge [TS=(Common variable immunodeficiency) OR TS=(Complement deficiency) OR TS=(chronic granulomatous disease) OR TS=(Ataxia telangiectasia) OR TS=(Wiskott-Aldrich syndrome) OR TS=(IgA deficiency) OR TS=(severe combined immunodeficiency) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1990-2006], 17,878 results were found. It shows the high number of papers in this field.

Although there are several excellent journals in the field of Allergy and Asthma, there is not any specific journal about immunodeficiency disorders, while it consist an important part of immunology, and medicine in general. We currently have to publish the results of our work in different journals; i.e. immunology, genetics, infection, hematology, oncology, pediatrics, rheumatology, etc. Searched the ISI Web of Knowledge with the keyword of (TS=immunodeficiency) NOT (TS=AIDS) NOT (TS=HIV); DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1990-2006, shows 30,434 results. Forty top sources of titles contain 33% of all articles and they published more than 100 articles on PID after 1990: Although a number of important papers of PID are published in famous journals, i.e. NEJM, Blood, J Exp Med, J Clin Invest, JAMA, etc, 22 of 40 journals have IF<4 and 3730 of 10034 articles (37%) were from the journals by IF<4.

I believe that there is a need to have "Journal of Primary Immunodeficiency" and it is the time that a publisher starts publishing such journal. After discussion with the ESID Board and some experts in this field in 2006, several valuable comments are collected. Although I received several positive responses on this proposal, there were also several concerns as follow:

ESID Prague Spring Meeting, May 14 and 15, 2007

First Name:
Family Name:
Titles:
Date of Birth:

Department:
Address:

Telephone:
Fax:
E-mail:

Can we place your contact details in the list for a distribution among the participants?: Yes/No

Can we display the powerpoint presentation of your paper on our web site after the meeting?: Yes/No

Title of the presentation and approx. length of the talk (in min):

Please return to Ales Janda by email: ales.janda@lfmotol.cuni.cz or by fax: ++420-224-435-962.

1. This issue has been debated several times during last 2 decades, however even when the majority of clinical scientists involved were in favor of such an idea, we failed to find a publisher who was really interested.
2. The previous journal in this field "Immunodeficiency Review" did not continue!
3. A need for having a new journal should be discussed.
4. The good papers on PID find their way to good journals because of their high IF.
5. Any new journal would have to compete with current journals, and it will need a strong and very dedicated editor to succeed.
6. Most established large publishers will probably consider the field too narrow to sustain a journal, and will worry about a new journal.
7. If we cannot get support from ESID, then we will probably fail.
8. The journal would be restricted to primary immunodeficiency and not cover HIV/AIDS.
9. Given the attendance of over 1000 at recent ESID meeting, there seems to be great interest in this field and proposing that the Society start a journal should be welcomed by the membership.

Additionally I contacted several publishers to know their reaction to have a new title. I have received positive responses from a number of publishers, the best one was from Springer. The journal proposal is interesting for Springer; although they have also some concerns, they were finally happy with this new title in general. The only issue which they have still concerns is the subscription of this journal as a start-up publication. It would certainly be the best way if ESID would be willing to start this journal as an official publication of the ESID Society. Springer also needs the decision of ESID regarding this issue.
Finally, I should thank from all PID experts who send me their valuable comments. I just collected some documents and comments on such idea. Now, I would like to ask the ESID community to continue discussion on this proposal. If ESID member would agree with such proposal, they will support it and submit their manuscript to the new journal.

Thanks for your attention,

Nima REZAEI

(The ESID Board has discussed this proposal during the Board meeting on April 2nd, and is doubtful about the viability of such a Journal. We are however interested in your reactions!)

Scheduled J Project Meetings (No. 19 to 21) 2007

19. Ukraine (Zaporozhye), Liudmyla Chernyshova, Apr 19-20, chernyshova@ukr.net
20. Russia (St. Petersburg), Marina Guseva, May 29-30, gusevamarina@mail.ru
21. Hungary (Pécs), Bernadett Mosdósi, June 22-23, bernadett.mosdosi@aok.pte.hu

Report on the 1st J Project Meeting in Bucharest

The Institute for Mother and Child Care organized the first J Meeting in Bucharest, on 9th-10th June 2006, with the help of the Debrecen Jeffrey Modell PID Reference enter. The goal of this meeting was the improvement of recognition and treatment of patients with PID in South Romania. In order to meet this task, our Institute invited the regional representatives of all the 18 counties of South Romania and Bucharest, and also the heads of the Pediatric Clinics in this area (Craiova, Constanta, Galati, Bucharest). The programme included 16 PID-related presentations by

remarkable doctors and scientists from Romania and Hungary (see attached programme). The main areas of discussion were as follows:

- Current practices and management of IVIG substitutions in Romania
- Diagnosis and treatment of patients with IgG subclass deficiencies
- Testing of PID genes and collaboration at this point with the Debrecen JMC
- Availability of flow cytometry for analysis of patients with cellular ID

It was concluded that the Institute for Mother and Child Care should remain and further develop its activity as the center of physician education and PID screening in Southern Romania and should further develop collaboration with other centers in Romania as well as with the Debrecen JM reference center.

Nicolae IAGARU

J Project meeting in Zaporozhye, East-Ukraine, 19-20 April 2007

Travel information. Dnepropetrovsk Airport receives International flights and, in particular, Boeing-737. For example, there is a flight Vienna-Dnepropetrovsk on 18.04.2007 departing at 10:50 a.m. and arriving at 14:10 p.m. We shall meet all who will attend at Dnepropetrovsk and shall go together to Zaporozhye by car (maximum 1.5 hrs). If all the foreigners-participants want to come on the 18-th of April, we shall organize a social program. Up to now we have made hotel reservations for the 19th and 20th of April.

Liudmyla CHERNISHOVA

Laboratory of Human Genetics of Infectious Diseases, Laurent Abel, Jean-Laurent Casanova

Dear Colleagues,

I am writing to you to solicit your help in seeking three post-doctoral fellows (PhD and/or MD) who would wish to join our laboratory. A post-doctoral salary will be guaranteed for at least three years.

The fellows would explore the molecular genetic basis of human infectious diseases, following candidate-gene and/or genome-wide approaches. Depending on the applicant's scientific interest, his/her project may aim to decipher a novel primary immunodeficiency or to exploit known genetic defects for immunological purposes. Monogenic and/or complex traits may be studied. Infectious diseases investigated in the laboratory include mycobacterial, pneumococcal, and herpetic diseases. More information on the laboratory's theme of research can be found in a recent review (Casanova JL and Abel L, EMBO Journal, 2007).

No specific medical and/or scientific qualification is requested, besides either doctoral degree. A strong motivation is requested. Independent and interactive candidates are preferred.

The candidates are invited to contact me by email (casanova@necker.fr).

Thank you for your help. Best regards,

Jean-Laurent CASANOVA

Working Party reports

Educational WP

The ESID Educational Working Party is delighted to announce that the next 'ESID Summer School for Primary Immunodeficiencies' will take place from 26 to 30 September 2007. Anders Fasth and Teresa Espanol Boren have done a marvellous job visiting a number of venues before deciding on a great location in Malaga, Southern Spain. The hotel is in a quiet, idyllic setting but easily accessible from Malaga Airport. We are also very fortunate to have received support from pharmaceutical companies.

The Summer School is geared towards young doctors in training with a primary goal of education on the diagnosis, pathogenesis and treatment of primary immunodeficiencies. Feedback received from previous Summer Schools has been extremely positive; and individuals have found the course to be invaluable.

We are very pleased that Helen Chapel (one of the instigators of the ESID Summer School programme) has also agreed to join the Faculty this year, as well as Steve Holland from NIH in the US who has given such stimulating presentations at recent ESID meetings! Other Members include: Andrew Cant, Anders Fasth, Esther de Vries, Teresa Espanol Boren, George Holländer, Jacques van Dongen and Eleonora Gambineri, so between us there should be an exciting programme designed to cover a wide range of leading edge educational topics such as: innate immunity, T cell disorders, CVID, immunoglobulin therapy and much more!

The Summer School will be intense but we will also look forward to enjoying the beautiful sunshine in Malaga and going for a dip in the hotel swimming pool ...

For further details on how to apply and to obtain an application form, please e-mail Andrew Cant at:

Gale.Roberts@nuth.nhs.uk

Information will also be available on the ESID website: www.esid.org. Closing date for applications: 30 May 2007.

Please help spread the word amongst your young colleagues, especially in the eastern European countries, and also advertise in your country's immunology societies. Thanks.

Hope to hear from you soon!

Andrew CANT

Genetics WP

Under the direction of Anna Villa, the Genetics Working Party took on many important initiatives, two of which are still ongoing. I would like to bring your attention to the study of spontaneous reversion in Wiskott-Aldrich syndrome and if you have patients with reversions, it would be very helpful if you could fill out the questionnaire on the website (organized by Anna Villa, Fabio Candotti and David Nelson). The second ongoing action aims to determine whether there is a correlation between the muation in infantile osteopetrosis and the clinical course of the disease ; this information may help to improve treatment decisions for these patients (this action is led by Anna Villa, Wilhelm Friedrich, and Ansgar Schulz).

Another axe which we would now like to develop within the Genetics Working Party regards immunodeficient patients wherein the genetic diagnosis is not known. Two groups of patients for whom diagnoses have often been lacking are those with isolated CD4 or CD8 deficiencies, respectively. In the near future, we will begin a questionnaire concerning these two groups of patients.

Finally, I would like to bring your attention a new European initiative on collaborative funding across national borders. ERA-Net, an organization whose goal is to

coordinate research efforts on rare diseases within Europe <www.e-rare.eu>, has just announced a trans-national call for grant proposals in this field. Scientists from France, Germany, Israel, Italy, Spain, and Turkey (scientists from other countries may join the consortiums but cannot specifically request funding) are being invited to build collaborative efforts using series of patients that would not be available on the national level. Basic research aimed at establishing genotype/phenotype correlations, genetic and pathophysiological studies as well as research in diagnosis and therapies for rare diseases are included in this call. Funding can be requested for a maximum of 3 years and the deadline for proposals in May 11th. More information can be obtained from the program Secretariat at +33 1 58 14 22 85 or secretariat@e-rare.eu). These types of grant calls should help to foster our collaborative efforts within the Genetics Working Party so I hope that some of you will be able to take advantage of this offer.

Please don't hesitate to call or email me if you would like to take on an intiative within the Genetics Working Party or if you have any suggestions or questions.

Naomi TAYLOR

Registries WP

Numbers on a steady increase

During the past year, numbers in the ESID Online Database have increased remarkably. Within the last 14 months there has been a three-fold increase in the total number of patient datasets resulting in a current total of 3543 patients! Fig. 1 shows the distribution of this increase within individual countries. Most remarkable is France, where the establishment of the national centre CEREDIH (www.ceredih.fr) has led to the registration of more than 1000 patients in just one year. Although there is no national centre in the United Kingdom (yet), a similar trend is occurring there too, with more and more centres contributing their patient data. Other countries which have been very active for several years, like Turkey, Italy, Poland and Germany and - on a smaller scale - Serbia, Greece and Egypt, are continuing to input more and more patients into the database.

In view of these developments, we are very optimistic about the further development of the project.

Opportunity for studies

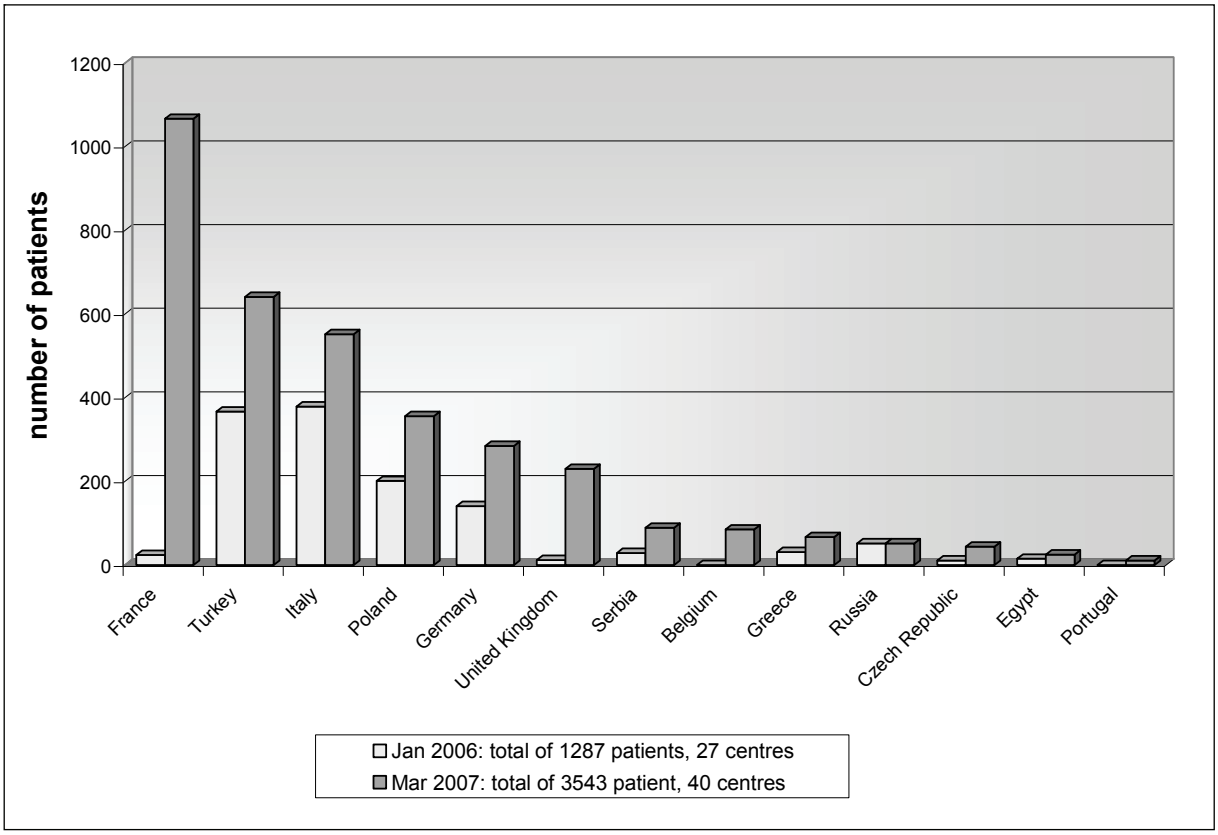
The size of the cohorts in the database now offers great opportunities for research on the different kinds of primary immunodeficiencies. Table 2 gives an overview on the biggest cohorts in the database.
Researchers who are working at one of the documenting centres and are interested in conducting a study on a certain PID in the database should contact the Registry WP at registry@esid.org.
The list of documenting centres is given at www.esid.org/centers.php. If a researcher is not working at one of these centres, his request will be forwarded to the ESID Board which has to decide whether he will be granted access to the database. Several studies are already under way. Information and contact details on these studies are given in the Registry section of the ESID website.

Improvement of data quality

The Registry WP has come to the conclusion that it needs to place more emphasis on data quality as there are still gaps in some sections of the database which cause problems during the analysis of data. For this reason, we have started to evaluate the data in respect to completeness and quality. In January, we have informed centres which have not completed the core dataset for all their patients, so they have enough time to complete the datasets by the next bonus payment deadline.

Disease	Entries
Common variable immunodeficiency (CVID)	913
Agammaglobulinemia X-linked (BTK)	291
Isolated IgG subclass deficiency	288
Immunoglobulin A deficiency 1 IGAD	255
Ataxia telangiectasia (ATM)	218
Transient hypogammaglobulinemia of infancy	175
Wiskott-Aldrich syndrome with mutations in WASP	115
DiGeorge Syndrome	113
Chronic granulomatous disease X-linked (CYBB)	86
Other Hypogammaglobulinemias	72
Unclassified immunodeficiencies	66
Hyper-IgE syndrome	65
CSR defects and HIGM syndromes with unknown genetic cause	63
CGD with unknown genetic cause	59
Nijmegen breakage syndrome (NBS1)	58
CD40 antigen ligand deficiency (CD154)	53
Wiskott-Aldrich syndrome with unknown genetic cause	48
Other unclassified T-cell disorders	42
Severe combined immunodeficiency X-linked (SCIDX1)	39
T-B+ SCID with unknown genetic cause	37
Agammaglobulinemias with unknown genetic cause	32
Severe congenital neutropenia with unknown genetic cause	26
T-B- SCID with unknown genetic cause	25
Recombination-activating gene 1 deficiency (RAG1)	23

Table 1: Cohorts (sub-registries) with more than 20 patients registered.



However we would like to remind users that it is the responsibility of each centre to ensure that data is complete and accurate. We cannot detect all mistakes, thus each centre should have a monitor to check up on their data. Only accurate and carefully documented data will yield useful information.

In addition, we have made many improvements to the data entry pages in the database. For example, all drop down menus are now in alphabetical order and have been cleared of double entries and spelling mistakes. If you notice any (new) mistakes in there please inform us at registry@esid.org.

Patient consent

We have adjusted the 'patient consent' field to correspond to the new version of the patient consent. A click on the '?' next to the consent now gives you an exact explanation of what to enter.

In this regard, we kindly ask all documenting centres to make sure they are using the latest version of the patient consent. The new patient consent which has been approved of by our data protection authorities offers three separate choices to the patient. If the patient consent you are using does not offer three "choice boxes", you are using an old version. In this case, please look at the patient consents on the ESID website (choose "Registry" on the left and then "Patient consent forms").
The new version is only available in ENGLISH and GERMAN. For the other languages, we would appreciate it if someone from each country could make the necessary changes in the translation and then send this new translation to us by email to registry@esid.org so we can put it on the website.

Website presentation

The Registry section on the ESID website has become quite full recently, with more and more documents and downloads available. Therefore, we have restructured this section to make it easier for people to find what they are looking for. Please have a look and let us know whether we have been successful.

Publications

We have now published a description of the database (Guzman et al) and a first analysis of the data in the database (Eades-Perner et al):

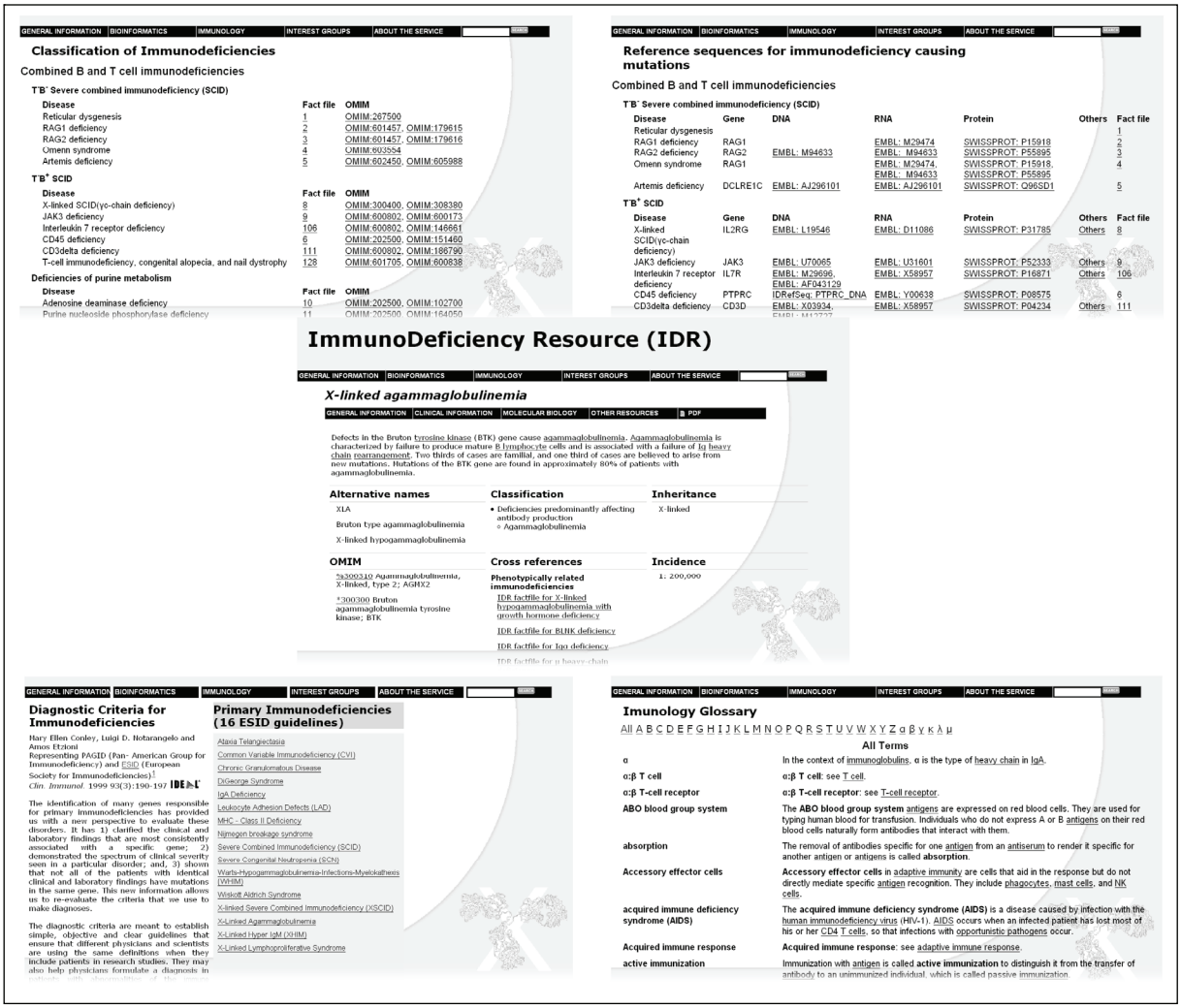
- D Guzman; D Veit; V Knerr; G Kindle; B Gathmann; AM Eades-Perner; B Grimbacher; for the ESID Registry working party, Bioinformatics 2007; doi: 10.1093/bioinformatics/btl675
- A.-M. Eades-Perner, B. Gathmann, V. Knerr, D. Guzman, D. Veit, G. Kindle, B. Grimbacher, for the ESID Registry Working Party. The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. Clin. Exp. Immunol. 147: 306-312, 2007.

Happy documenting! Remember the deadline of June 30th for the 2007 incentive bonus!

Gerhard KINDLE

INFORMATION SERVICES FOR PIDS

Information services related to PIDs have been maintained already about 10 years at the Bioinformatics group, Institute of Medical Technology, University of Tampere. We presented in Budapest ESID meeting last year these services and some innovative features. We maintain and distribute several services in Internet for this purpose. IDR, ImmunoDeficiency Resource is a comprehensive knowledge base, which contains all the essential data about PIDs. IDdiagnostics is two directories, one for laboratories performing PID related genetic and the other for clinical diagnostics. IDbases are disease specific



mutation databases. PIDexpert will be the newest resource dedicated to serve physicians in making diagnosis for suspected PID cases.

We frequently obtain requests about PIDs as well as laboratories and persons who would help with diagnosis. To make our services useful for the medical community we ask help from you. If you would want to be listed on the services please fill in the form. It takes just a couple of minutes.

ImmunoDeficiency Resource (IDR)

IDR is a knowledge base which integrates clinical, biochemical, genetic, proteomic, structural and computational data. The need of IDR arises from the lack of structured and systemized information about PIDs. IDR serves as a common platform for different kind of users (doctors, medical students, nurses, patients and their families, decision makers) interested in PIDs.

The knowledge base, first released in 1999, has grown substantially. It contains information for 158 diseases both from clinical as well as molecular point of view. The database has been reformatted and has a richer and more complete breath, depth and scope. IDR contains information ranging from diagnosis to affected genes, patient associations to gene expression, protein sequences to structures, and much more. The new user interface (Fig. 1) provides a better systematization of the information and is more user friendly and easy to handle. We are now moving to the next phase in the development of IDR. The service contains just reliable data sources. To further improve the knowledge base we are looking for curators for each disease. The task of these persons is to check the

database content, approve used links and inform the database staff of new developments to be included into the database. If you want to act as a co-curator for one or more diseases please fill the form from the IDR home page. We really appreciate the work of curators. The names of the persons will be provided on the IDR web pages.

IDdiagostics

The aim of IDdiagnostic registry is to collect, identify, describe and disseminate information of diagnostic services for immunodeficiencies. IDdiagnostics is formed of two independent registries for laboratories performing genetic and clinical tests for PIDs. The service is intended for physicians, researchers and other medical genetics health professionals. Laboratories are included in IDdiagnostics on voluntary basis. The registry is not complete, which means that it does not include all possible laboratories or services. Only those willing to have their information posted in Internet are included. Inclusion is at no charge. To be included, a completed registration form (available on the registry home page) should be submitted. The forms are easy to use and require usually just clicking the correct options from forms.
According to the guidelines of the services, laboratories are regularly contacted to verify the accuracy of their information. The curators keep the rights to remove information for a laboratory if there are problems e.g. with time schedule or quality of information. Currently the IDdiagnostics has gene test data for 43 diseases from 23 centers in 10 countries. In clinical test database there are 31 entries from 22 centres in 12 countries.

IDbases

We have generated mutation databases (IDbases) for practically all PID related genes unless there is a database somewhere else. We have currently 115 databases, which altogether contains 4616 mutations. Mutation databases can be used in many ways. Information from IDbases has been used for e.g. statistical analysis of mutations events, amino acids mutation types, retrospective analyses of diseases and symptoms. Recently IDbases have facilitated also phenotype-genotype correlations.
We request the PID community to submit information about the disease causing mutations. Web page for each database contains a link to submission page, which makes it easy to send the data to us electronically. For those submitting data to the ESID patient registry we want to remind that please provide also the mutation data. The ESID registry and our IDbases are interconnected so it is enough to send the data only once.

Human Mutation Special Issue

Human Mutation published a dedicated special immunogenetics issue on December 2006. Wiley, the publisher, has kindly made the whole issue publicly available so anybody can download the articles. There are 9 articles in the issue ranging from molecular diagnosis via mutation and immunological databases to effects of PID causing mutations. Please visit the journal web page.

Website names and addresses

ImmunoDeficiency Resource (IDR) http://bioinf.uta.fi/idr/. IDdiagnostic http://bioinf.uta.fi/IDdiagnostics/. IDbases http://bioinf.uta.fi/base_root/. Human Mutation Special Issue http://www3.interscience.wiley.com/cgi-bin/jissue/113399451.

If you have any questions or suggestions, please do not hesitate to contact us.

Crina SAMARGHITEAN
Hilka PIIRILÄ
Jouni VÄLIAHO
Mauno VIHINEN

ESIDjuniors WP

Dear all,

I must say that so far I haven't got many comments and/or suggestions from most of you concerning the activities of the ESID juniors WP. In this regard, the 6th Prague Spring ESID Meeting that will be held in Prague on May 14-15, 2007, will give us the opportunity to recover. The meeting is organized by Ales Janda and Anna Sediva. This year more space for presentations from ESIDJunior members will be provided. I hope that the upcoming Spring School will give us a good chance to meet and coordinate in order to improve the organization and the future activities of the WP. For those of you who are willing to help, please step up!

Looking forward to... seeing you in Prague in May!

Ciao

Eleonora GAMBINERI

PID care in development WP

The PID Care in Development Working Party (PIDCD WP) was established at the 2006
ESID Meeting in Budapest. Based on the success of the J Project in East-Europe over the past years, it was proposed that an ESID-associated working party with global European responsibility should be organized. The major aim of the PIDCD WP is to improve PID patient care, professional collaboration, and patient group activity in European countries/regions with low number of registered PID patients, and possibly inappropriate diagnostic facilities and treatment measures. To this end the WP should establish professional contacts in these regions, promote organization of educational meetings on PID which would allow on site discussion of PID care, diagnostic and therapeutic practices and problems, definition of specific areas to be improved and to be supported by ESID and other European professional and heath care groups, institutions, companies, and foundations. Updating regional PID registries, establishing local PID working groups, establishing PID patients' groups and nurses' group are also important goals and aims.

Please join and become an active member of this new Working Party!

László MARÓDI

Interesting Papers

In this issue of the ESID Newsletter, we want to draw your attention to the following articles which present new genes, new mechanisms of disease, functional interaction never suspected before, and updates of useful databases for the PIDs community. The selection of the interesting papers for this issue was made by Claire Fieschi and Crina Samarghitean.

Recently, Rigaud S et al identified new mutations in the gene that encodes the X-linked inhibitor-of-apoptosis XIAP in patients with X-linked lymphoproliferative syndrome (XLP) from three families without mutations in SAP. These mutations lead to defective expression of XIAP. The authors showed that apoptosis of lymphocytes from XIAP-deficient patients is enhanced in response to various stimuli including the T-cell antigen receptor (TCR)-CD3 complex, the death receptor CD95 and the TNF-associated apoptosis-inducing ligand receptor (TRAIL-R). They also found that XIAP-deficient patients, like SAP-deficient pa-

tients, have low numbers of natural killer T-lymphocytes (NKT cells), indicating that XIAP is required for the survival and/or differentiation of NKT cells. The observation that XIAP-deficiency and SAP-deficiency are both associated with a defect in NKT cells strengthens the hypothesis that NKT cells have a key role in the immune response to EBV. Furthermore, by identifying an XLP immunodeficiency that is caused by mutations in XIAP, they showed that XIAP is a potent regulator of lymphocyte homeostasis in vivo. You can read more in Rigaud S, Fondaneche MC, Lambert N, Pasquier B, MateoV, Soulas P, Galicier L, Le Deist F, Rieux-Laucat, F.Revy, P.Fischer, A.de Saint Basile, G.Latour, S. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature. 2006 Nov 2; 444 (7115):110-4.

A novel mechanism for complement activation at the surface of B cells following antigen binding is presented by Manderson AP. et al . Using BCR transgenic mice, the authors demonstrated that C3 was deposited on the surface of B cells following both high- and moderate-affinity Ag binding. This was dependent on the specific binding of IgM to the BCR-bound Ag and can occur independently of soluble immune complex formation. Based on these data, the authors propose a novel model in which immune complexes can form directly on the surface of the B cell following Ag binding. This model has implications for our understanding of B lymphocyte activation. More information in : Manderson AP, Quah B, Botto M, Goodnow C, Walport MJ, Parish CR. A novel mechanism for complement activation at the surface of B cells following antigen binding. J Immunol, 2006, 177: 5155-5162.

Adriani M. et al paper is the first report of a new and never suspected before functional interaction between the growth hormone receptor (GHR) and common gamma chain signal complexes. This study supports what the group of Prof. Claudio Pignata has previously reported before on growth hormone hypo-responsiveness as part of the SCID-X1 phenotype and directly related to the genetic alteration of the IL2RG. This study highlights the involvement of gamma in receptor complexes that are not directly implicated in hematopoiesis. Thus, it may help discover additional clinical features not hematological features of the SCID phenotype. More information in Adriani M, Garbi C, Amodio G, Russo I,Giovannini M, Amorosi S, Matrecano E, Cosentini E, Candotti F, Pignata C. J Immunol. 2006 Nov 15;177(10):6889-95.

X linked agammaglobulinemia: BTKbase, the data base concerning molecular biology of X linked agammaglobulinemia, located in Finland has been updated. The paper gives new insights in this immunodeficiency, which is mainly diagnosed in agammaglobulinemic boys with no circulating B cells, but also sometimes in patients with a leaky immunological phenotype, including few circulating B cells and residual production of immunoglobulins. The authors now report on 1111 patients from 973 kindreds with 602 different molecular events. The address of the database is http://bioinf.uta.fi/BTKbase. Structure-function analysis should allow a better understanding of leaky clinical and immunological phenotypes.
Valiaho J, Smith CI, Vihinen M. BTKbase: the mutation database for X-linked agammaglobulinemia.Hum Mutat. 2006 Dec;27(12):1209-17.

APC cells from patients with XLA produce no TNFa and no IL-6 upon TLR8 activation by ssRNA, whereas the production of these 2 cytokines are similar upon TLR1-6 activation through specific activators: a possible explanation for susceptibility to enteroviral disease in these patients?
Sochorova K, Horvath R, Rozkova D, Litzman J, Bartunkova J, Sediva A, Spisek R. Impaired Toll-like receptor 8-mediated IL-6 and TNF-a production in antigen-presenting cells from patients with X-linked agammaglobulinemia. Blood. 2007 Mar 15;109(6):2553-6.

SCID due to ADA deficiency: report of

an EBMT satellite symposium in November 2006. The 3 therapeutic options (BMT, gene therapy, enzyme replacement therapy) are discussed in this paper. Enzyme replacement therapy gives good results but patient still need Ig infusion in 50% of cases. BMT is probably the best alternative if a familial donor is available, but MUD transplant and haploidentical familial transplant showed poor results with deaths attributable to infection. Gene therapy also gives good results but long term effects are not available for evaluation.
Booth C, Hershfield M, Notarangelo L, Buckley R, Hoenig M, Mahlaoui N, Cavazzana-Calvo M, Aiuti A, Gaspar HB. Management options for adenosine deaminase deficiency; proceedings of the EBMT satellite workshop (Hamburg, March 2006). Clin Immunol. 2007 Feb 12 (AOP)

12 long term surviving ADA deficient patients that received BMT in a single center are analysed. If the immune reconstitution is good in all patients, 6/12 have severe neurological impairement with mental retardation, motor deficit and hearing dysfunction. No infectious event nor BMT procedure can be established to explain the CNS abnormalities in such patients. Authors suggest that if BMT allows an immune reconstitution in ADA deficient patients, it can not prevent CNS involvement in some ADA deficient patients.
Honig M, Albert MH, Schulz A, Sparber-Sauer M, Schutz C, Belohradsky B, Gungor T, Rojewski MT, Bode H, Pannicke U, Lippold D, Schwarz K, Debatin KM, Hershfield MS, Friedrich W. Patients with Adenosine Deaminase Deficiency surviving after hematopoietic stem cell transplantation are at high risk of CNS complications. Blood. 2006 Dec 21; (AOP)

A novel X-linked recessive form of Mendelian susceptibility to mycobacterial disease in a large french kindred. After description of NEMO mutations predisposing to mycobacterial disease, the authors report on 2 candidate regions on X chromosome with a maximum lod score of 2.
Bustamante J, Picard C, Fieschi C, Filipe-Santos O, Feinberg J, Perronne C, Chapgier A, de Beaucoudrey L, Vogt G, Sanlaville D, Lemainque A, Emile JF, Abel L, Casanova JL. A novel X-linked recessive form of Mendelian susceptibility to mycobaterial disease. J Med Genet. 2007 Feb;44(2):e65.

If you have interesting papers you would like to have incorporated in this section, please send and email to Crina.Samarghitean@uta.fi or claire.fieschi@sls.ap-hop-paris.fr

Crina SAMARGHITEAN

Interesting Cases

CASE #2

42 y-o man suffering from recurrent fevers and hives

The patient was referred to our clinic in 2006 complaining of recurrent high fevers with shivering fits and hives all over his body.

The symptoms had relatively clear beginning in 2002. A few weeks before the first episode of severe fevers and exanthema the patient was heavily bitten by insect while visiting Spain. The first attack was accompanied with urinary tract infection (UTI) and prostatitis followed by gastrointestinal disturbance. Since then the frequency of attacks has increased, there have been only short asymptomatic intervals. Apart from intermittent febrile attacks and hives he complained of arthralgia without swelling of the surrounding tissue. Since beginning of the disease he has lost about 12 kg.

Surveying his medical history we

found that he suffered from chronic fatigue (1996-98), transient ischemia attacks (TIA, in 1999) - multiple sclerosis was suspected at that time, however, it was not confirmed and he is now without any neurological symptoms. In 2002 hypothyreosis was detected, requiring only transient hormonal substitution. Since his childhood he has been treated for bronchial asthma, allergy (dust, pollen, mites). He has cholelithiasis (polypus in gall bladder found), mild hyperliproteinaemia, he has been treated for internal haemorrhoides.

He was born in the Czech Republic, his family comes from a region stretching from Romania to Montenegro and European part of Turkey. No similar condition has been noted in the family. He works as a technician, he was active sportsman (diving).

Since the initial symptoms, the patient was repeatedly thoroughly investigated. The inflammation markers (erythrocytes sedimentation rate - ESR, C-reactive protein - CRP, number of leukocytes) has been permanently increased. There has been neutrophilia and lymphopenia, no eosinophilia. Level of IgG slightly above norm (16.20...11.20 g/l), IgM significantly high with tendency to increase (4.25...7.09 g/l), monoclonal gammapathy IgM kappa was found. Other immunoglobulins have been within normal range. Circulating immunocomplexes have been increased. ANA autoantibody showed mild positivity in 1:80 titre, other auto-antibodies were negative. Antibodies against vaccination antigens were created, extended serology was insignificant, apart from high titre of IgG VCA EBV and CMV anamnestic antibodies. Investigation of cellular immunity did not show any abnormalities. Proliferation assay and chemiluminescence were normal. Serum chemistry was within normal limits, level of angiotensin-converting enzyme (ACE) was low. He has had repeated biopsy of bone marrow, there were no signs of malignancy. Positron emission tomography (PET), computer tomography (CT), gastroscopic and colonoscopic investigations were without pathological findings as well.

He was treated with several antibiotics without any substantive effect. Use of steroids brought him relieve only for a few hours than the fevers relapsed. Non-steroidal anti-inflammatory drugs (NSAID) showed minimal effect as well as a trial with colchicin.

Based on the clinical course of the disease we diagnosed him with one of the periodic fever syndromes - Schnitzler syndrome. In October 2006 we started daily anti-IL-1 therapy with Anakinra (Kineret). We saw an immediate effect of the therapy. However, due to the complicated funding of this extremely expensive drug, the patient has been transiently without the medication. Each time when the treatment was discontinued the symptoms occurred with increased severity. The only adverse reaction of Anakinra administration seen was mild erythema in the place of injection. Apart from the clinical improvement, the laboratory markers of inflammation substantially decreased, however we have detected progressive slow increase of IgM levels (currently approx. 7 g/l).

The remaining questions are: What is the long-term prognosis of these patients treated with Anakinra? How to finance this extremely expensive therapy? What is the danger of occurrence of lymphoproliferative disorder or Waldenström macroglobulinaemia in this patient? Is it reasonable to use anti-CD20 therapy?

Partial answers to some of the questions could be found in the literature, however, we are seeking for colleagues having their own experience with this condition as well. The summary of facts from the literature together with your contributions will be published in some of the following issues of the Newsletter and on our departmental web page.

More information on Schnitzler syndrome (Orphanet ID: ORPHA37748) could be found on

these webpages:
www.emedicine.com/derm/topic489.htm
http://www.schnitzlersyndrome.com/

The selected recent papers on this syndrome:

1. Lipsker, D., et al., Hot and hobbling with hives: Schnitzler syndrome. Clin Immunol, 2006. 119(2): p. 131-4.
2. Ramadan, K.M., H.A. Eswedi, and M.R. El-Agnaf, Schnitzler syndrome: a case report of successful treatment using the anti-CD20 monoclonal antibody rituximab. Br J Dermatol, 2007.
3. Dalle, S., et al., Schnitzler syndrome associated with systemic marginal zone B-cell lymphoma. Br J Dermatol, 2006. 155(4): p. 827-9.

The case report together with photos showing changes of the patient's skin condition before and during the treatment with Anakinra could be seen at the website of our department (teaching/case reports/ schnitzler syndrome):
http://imunologie.lf2.cuni.cz/en/vyuka.php?str=kazuistiky

We are looking forward to your comments!

Aleš JANDA

Young Researchers' Corner

Dear ESID Junior member's,

Here we are at the second appointment with Young Researcher's Corner, what do you think about it? I would really appreciate it if this novel ESID Newsletter section will be improved and developed with an active participation of all of you!
If someone would like to suggest an interesting lab protocol to be posted here and/or discuss about the previous or current theme, PLEASE don't hesitate to take advantage of the great opportunity to make connections and exchange our opinions in the FORUM section within ESID website!!!

This time, waiting for the upcoming 6th Prague Spring ESID Meeting in May where we can finally meet and interact, I would like to invite you to focus on an important topic in the field of Primary Immunodeficiencies.

TRECs

During their development process through the thymus, T-cell precursors encounter T-cell receptor (TCR) genes rearrangement to create a diverse TCR Repertoire. This step requires two excisions of subsequent segments of gDNA, the ends of which are then ligated to form small circles of episomal DNA (signal and coding joint), named T-cell Receptor Excision Circles (TRECs). This products are stable, unique to T cells, and are not replicated during mitosis but diluted among daughter cells in the peripheral T-cell pool during the switch from naïve to memory phenotype. Therefore, by measuring the proportion of peripheral T-cells containing TRECs, an estimate of recent thymic function can be obtained. For this reason TRECs may be a promising marker for a newborn screening program for SCID. Moreover, monitoring TRECs number during haematopoietic stem cell transplantation (HSCT) follow up may be very useful to predict patient T-cell reconstitution.

TRECs analysis.

Today real-time quantitative PCR is the most advantageous method to accurately determine TRECs amount. Indeed, it is a simple, reproducible and fast protocol that requires small amount of DNA. In literature are described different approaches, even though an housekeeping gene to normalize the results and standard curves, generated from serial diluted plas-

mids to calculate relative copy numbers of TRECs and housekeeping gene, is mostly used. Significant differences consist in type of sample analyzed and extent of TCR rearrangements detected.

Is it better to detect TRECs amount in total PBMCs or in specific T cell subsets magnetically purified or sorted by FACS?

Is it adequate to detect only δRec-φJα TREC, produced late in maturation by 70% of developing T cells expressing αβ TCRs, or the overall extent of TCR rearrangements?

Which method is more accurate to express TRECs amount? Can it be calculated as a ratio of TRECs number and percentage of T cell subsets (i.e. %CD4+)?

I'm looking forward your suggestions (e-mail: l.bianchi@meyer.it), questions and any kind of comments in the ESID FORUM on the ESID website or in PRAGUE!

REFERENCES:

1. Ponchel F et al. Real-time PCR based on SYBR-Green I fluorescence: An alternative to the TaqMan assay for a relative quantification of gene rearrangements, gene amplifications and micro gene deletions. BMC Biotechnology 2003;3:18.
2. Chan K, and Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol 2005;115:391-8.
3. Chain JL et al. Real-time PCR method for the quantitative analysis of human T-cell receptor γ and β gene rearrangements. J Immunol Methods 2005;300:12–23.
4. Borghans JA et al. Early determinants of long-term T-cell reconstitution after hematopoietic stem cell transplantation for severe combined immunodeficiency. Blood 2006;108:763-769.
5. Cavazzana-Calvo M et al. Long-term T cell reconstitution after haematopoietic stem cell transplantation in primary T cell immunodeficient patients is associated with myeloid chimerism and possibly the primary disease phenotype. Blood 2007; prepublished online Feb 1.

Lucia BIANCHI

Figure: TRECS GENERATION