ESID Newsletter

Contents

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.

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.

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PLEASE NOTE !!! email has changed into: dr.estherdevries @tiscali.nl

Front page:
Objets d'art, Musée du Louvre, Paris, France.

Dear ESID members,

A bit later than planned, you find before you the last ESID Newsletter of 2004.

We can look back upon a successful Meeting in Versailles, full of scientific news, meeting with colleagues and friends, and the historical beauties of Versailles (and Paris for some who stayed a few days more).

The - partly renewed - Board is going to work for you, the ESID community, during the coming two years, after which we will all meet again in Budapest, Hungary, where Laszlo Marodi is already working hard on the new Meeting that will take place in 2006.

In this Newsletter, you will find the latest developments in the big project of the ESID Registry, on which Bodo Grimbacher is doing so much work.

Also, various people from different European countries have sent their news and views to me; you can find them in the section of the same name!

If you want to write something for the ESID Newsletter, please feel free to do so, and send me the copy at dr.estherdevries@tiscali.nl. The deadline for the next ESID Newsletter (2005-1) is February 15, 2005.

Best wishes for the new year to all of you !

Esther DE VRIES, Editor

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. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. You can find the necessary information to contact the treasurer Esther de Vries at www . esid . org.

Within ESID, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Bone marrow transplantation (chair: Mario Abinun), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Bobby Gaspar), Genetics (chair: Anna Villa), Education (chair: Anders Fasth), and ESID*juniors* (interim chair: Pim van der Vossen). 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).

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 were received until now. In 1995, the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia – curators Mauno Vihinen and C.I. Edvard Smith). Since then, several additional locus-specific data bases have been established: ADAbase (adenosine deaminase deficiency – curators Mauno Vihinen and Michael Hershfield), BLMbase (Blooms syndrome – curator Mauno Vihinen), CYBAbase (autosomal recessive p22 phox deficiency – curators Dirk Roos and Mauno Vihinen), CYBBbase (X-linked chronic granulomatous disease (XCGD) – curators Dirk Roos and Mauno Vihinen), CD3Ebase (autosomal recessive CD3 epsilondeficiency – curators Mauno Vihinen and Jose R. Regueiro), CD3Gbase (autosomal recessive CD3 gamma deficiency – curators Mauno Vihinen and Jose R. Regueiro), CD40Lbase (X-linked hyper-IgM syndrome – curators Luigi D. Notarangelo and Mauno Vihinen), JAK3base (autosomal recessive severe combined JAK3 deficiency – curators Luigi D. Notarangelo and Mauno Vihinen), NCF1base (autosomal recessive p47 phox deficiency – curators Dirk Roos and Mauno Vihinen), NCF2base (autosomal recessive p67 phox deficiency – curators Dirk Roos and Mauno Vihinen), RAG1base (autosomal recessive severe combined RAG1 deficiency – curators Mauno Vihinen and Anna Villa), RAG2base (autosomal recessive severe combined RAG2 deficiency – curators Mauno Vihinen and Anna Villa), SH2D1Abase (X-linked lymphoproliferative syndrome (XLP) – curators Luigi D. Notarangelo and Mauno Vihinen), TCIRG1base (autosomal recessive osteopetrosis (arOP) – curators Mauno Vihinen and Anna Villa), ZAP70base (autosomal recessive severe combined ZAP70 deficiency – curator Mauno Vihinen), WASPbase (Wiskott-Aldrich syndrome – curators Mauno Vihinen and Luigi D. Notarangelo) (information is available at www . esid . org).

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2004 in Versailles, France; the next congress will be organized in Budapest, Hungary in October 2006, and the one after that will be in The Netherlands, in 2008.

President's letter

Dear colleagues,

I am sure you all share my view that we had a great Meeting in Versailles! My thanks go to Alain Fischer and all his group for a wonderful organization, in a nice setting, with a very sound and fruitful scientific programme. This Meeting showed once again that Europe is at the front line in scientific discoveries and exploitation of novel therapeutic approaches in the field of primary immune deficiencies. The illustration of TACI and BAFF-R mutations in patients with hypogammaglobulinemia, and the new finding of CD3e and CD3z defects in infants with SCID are good examples of the former, whereas gene therapy in CGD is just an example of new therapeutic developments. Workshops were also well attended, and many of them were particularly appreciated by the audience. Finally, the Educational Symposium raised a very strong interest, as demonstrated by the fact that the room was full. Indeed, from a small group of friends, we have turned into a big community. This is definitely rewarding, but at the same time it calls us to make sure that we do not lose the friendly and fruitful atmosphere that has always characterized our meetings.

The Meeting in Versailles was also the occasion on which changes have occurred in the composition of the ESID Board. I would like to thank all the colleagues who have finished their duty, and to greet the new ones who have entered the Board. A special welcome is for Jean-Laurent Casanova, who has been chosen as President-Elect, and will therefore likely take my place in 2006. Among changes, we have dismissed the Pathology Working Party, but have also decided to initiate the ESID Junior Working Party. I consider this a very important perspective. We very much depend on the young colleagues to continue and improve our work in the years to come. The enthusiasm that was generated by the proposal to start this new WP is the best guarantee that the future of ESID is in good hands! The Assembly has also been informed (and has approved) of other decisions by the Board. Among them, the opportunity to start the ESID Fellowships Program (to enjoy a trainee period abroad at one of the ESID Centers in Europe) is particularly valuable, as it serves to promote integration of scientific culture and human experiences across our Continent. You will hear more about this initiative through Anders Fasth, the Chairman of the Educational WP.

I would also like to take this opportunity to greet Bianca Pizzera (the new Chairman of IPOPI) and Ann Gardulf, who will co-chair INGID with Julia Griffin. Both the IPOPI and the INGID Meeting were also very well attended (more than ever!), showing once more how important is the opportunity to meet and exchange experiences among families and nurses from all over the world.

A Meeting is over, a new one is already approaching! We very much look forward to visiting Budapest in 2006. Laszlo Marodi is already working at the Program; the ESID Board and the entire ESID community will be pleased to work with him to make the 2006 Meeting another success.

Finally, let me finish by congratulating Esther de Vries, the real beating heart of the ESID Board. She is not only a Treasurer, but a friend who solicits all of us to think of ESID and to work for ESID. Giving her the opportunity to organize the 2008 Meeting is just one way to show how much the ESID community appreciates her work!

Luigi NOTARANGELO

Secretary's report

Report from the ESID General Assembly held in Versailles on October 23rd, 2004 at the occasion of the 2004 biennial ESID Meeting

The agenda as published on the ESID homepage was introduced by ESID president Luigi Notarangelo, who once again congratulated Alain Fischer for a very successful and interesting meeting. He also acknowledged the work of the ESID Board during the two years since the last General Assembly in Weimar. In particular, he mentioned the very successful ESID Newsletter, and, as a very recent new project, the creation of a new ESID fellowship intended to support one young scientist active in PID research per year (applicants are asked to contact Anders Fasth for more details). The ESID secretary´s report followed; the ESID Board met 4 times since the last General Assembly, and devoted most time during these meetings to the planning and discussion of the new internet-based ESID patient database (the ESID patient registry and its disease-specific subregistries). Further topics discussed during the Board meetings included the ESID business plan, the contents of the ESID Newsletter, possible improvements and new features for the ESID website, communication with regulatory institutions, other scientific societies and representatives of the pharmaceutical industry, as well as the activities of the different ESID Working Parties. The treasurer´s report included the balance of the regular ESID account, the ESID registry account and the ESID Summer School account, as well as income and expenses since the last General Assembly. Once again, as in previous reports, the problem of outstanding membership fees was adressed. To facilitate payment, it was decided to explore within the Board the future possibility of electronic payment via bank card/bank account. The members agreed to the treasurer´s report without objections.

Next followed the reports of the Working Party chair persons: Andrew Cant mentioned the close cooporation of the ESID and EBMT Working Parties, which led to well-noticed publications about the outcome of stem cell therapy all over Europe in patients with CGD, WAS and CD40L deficiency. The European BMT database needed continuous updating, and overall improvements in therapy are noticed as the result of a continuing cooperation. Bodo Grimbacher reported on the new online version of the main ESID patient registry. About 10,700 patients were reported to this registry as of today, of these only relatively few new patients (about 700) have been reported during the last two years since the database file was transferred to Freiburg. The technical features of the main registry and the CVID subregistry, the first registry that is already online, were described in brief, emphasizing that the local data protection officer and the patient have to agree before submission of data to the registry. 37 documenting centers from 21 countries are currently interested in registering new patients. Jean-Laurent Casanova reported about the questionnaire survey on treatment of WAS initiated by the Clinical Working Party. A publication of this survey appeared in 2003 in Clinical Immunology. Bobby Gaspar went on by telling about the current status of the survey on treatment of ADA deficiency initiated at the last ESID meeting in Weimar. 22 centers from 13 countries responded to the questionnaires, and a publication is in preparation. Anna Villa heading the Genetics Working Party, initiated a network collaboration on genetics of osteopetrosis. Anders Fasth mentioned recent achievements of the Educational Working Party such as the successful organisation of the 2003 ESID Summer School, the Educational Day at the Versailles meeting,

and the donation of three travel grants for colleagues from outside Europe, two for visits to the ESID meeting, one to visit the annual meeting of the EBMT/ESID BMT Working Party. Planning is proceeding for the next ESID Summer School held in 2005. A recent survey organised by Helen Chapel among the students of previous Summer Schools has shown the high praise and success of this ESID project. Former ESID Summer School students stay in the field of PID, thus showing that it is possible to create a network of ESID-trained PID specialists all over Europe. Anders Fasth also acknowledged the generous support of the pharmaceutical industry through which the success of this project was possible. The General Assembly then voted to close the Pathology Working Party due to problems to create a network during the previous years. As a major achievement of this Working Party headed by Fabio Fachetti, a PID pathology picture collection will be distributed on CD-ROM to the members. The General Assembly agreed on the generation of a new working party ,the ESIDjuniors. Pim van der Vossen, the nominated chairman, introduced the idea of having a Working Party specially devoted to ESID members below the age of 35. One of their first projects should be the establishment of an ESIDjuniors chatroom on the ESID web page. A report from the election of ESID Board members that took place by anonymous voting during the meeting followed: newly elected to the ESID Board were Bobby Gaspar for the Clinical Working Party chair (replacing Jean-Laurent Casanova), Mario Abinun for the BMT Working Party chair (replacing Andrew Cant), and Jean-Laurent Casanova as President-Elect (replacing Alain Fischer, the Past-President). All other Board members were reelected. The General Assembly then agreed to two changes in the ESID constitution proposed by the Board: the term "emeritus ESID member" should be changed to "honorary ESID member" elected by the ESID Board. Furthermore, the treasurer can now be reelected three times, thus serving a maximum of eight years. The last topic on the agenda was devoted to the next ESID meetings. Laszlo Marodi, the president of the ESID meeting 2006 in Hungary, reported about the meeting venue, the Novotel Budapest Congress Center, which is located close to the famous Hotel Gellert in Budapest. The date will be October 5th-8th, 2004, and many participants from Eastern and Central European countries are expected. Esther de Vries proposed to have the 2008 meeting in the south of Holland, at ´s-Hertogenbosch, which the General Assembly received with applause.

Treasurer's report

During the recent General Assembly in Versailles, the membership fee was not changed (€ 100 / 2 years, with a reduced fee of € 50 / 2 years for those < 35 years of age and those living in Eastern Europe).

The General Assembly agreed to start preparations for online payment of the membership fee. You will hear more about this when the membership fee 2006/2007 is due.

All of you who have not paid their membership fee 2004/2005 will find another membership fee renewal form enclosed with this issue of the ESID Newsletter. This is the last reminder. After this, you will not receive the ESID Newsletter anymore, until you have paid your fee. In case of any mistake, please contact me **at my new email address dr.estherdevries@tiscali.nl !**

News & Views

Meetings organised by

Establishing, Optimizing and Producing Microarrays Dr Colin Cooper. Friday 14th January 2005. Birkbeck College, London, UK.
Advances in the detection of Rodent Cytokines Dr Sonia Quaratino. Friday 28th January 2005. Birkbeck College, London, UK.
Improvements in Laser Capture Micro-dissection and Downstream Applications Dr Sharon Brookes. Friday 11th February 2005. Birkbeck College, London, UK.
Recent Advances in Apoptosis Analysis Dr Charlotte Lawson. Friday 11th March 2005. Birkbeck College, London, UK.
Targeted Technologies to Detect Signalling Pathways Dr Lynn Williams. Friday 4th March 2005. Birkbeck College, London, UK.
Advances in Endothelial Cell Isolation and Culture Dr Charlotte Lawson. Friday 11th March 2005. Birkbeck College, London, UK.
RNA Mediated Interference in Practice Dr Buzz Baum. Friday 8th April 2005. Birkbeck College, London, UK.
Improving Immunohistochemistry 'Sensitivity, specificity and reproducibility addressed by the latest advances in technology, together with clinical and research applications of immunohistochemistry covered in one showcase meeting.' Dr Tony Warford. Friday 15th April 2005. Birkbeck College, London, UK.
Identifying T cell subset phenotype and function Dr Catherine Derry. Friday 22nd April 2005. Birkbeck College, London, UK.
Growth, Expansion and Differentiation of Stem Cells The aim of this meeting is to address the following questions what is the best way to define a stem cell? How do you get stem cells to grow? What are the best reagents to use? How can stem cells be induced to differentiate? Dr Stephan Przyborski. Friday 13th May 2005. Birkbeck College, London, UK.
Identifying Gene Expression in Mammalian Development and Disease Dr David Tannahill. Friday 20th May 2005. Birkbeck College, London, UK.
Non-Mammalian Gene Analysis Dr Steven Russell. Friday 3rd June 2005. Birkbeck College, London, UK.
Viral Techniques for Gene transfer Dr Griesenbach. Friday 10th June 2005. Birkbeck College, London, UK.
Proteomics: An approach to biomarker discovery Dr Ayesha De Souza. Friday 17th June 2005. Birkbeck College, London, UK.
Cell isolation in Diagnosis Dr Brian Shenton. Friday 24th June 2005. Birkbeck College, London, UK.
Identifying Extracellular Matrix and Adhesion Molecules Dr Catherine Derry. Friday 8th July 2005. Birkbeck College, London, UK.

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The 4th J-Project event organised in Skopje, Macedonia

The 4th J-Project PID event was organized in Skopje, Macedonia, by Dr. Stavric, Dr. Mironska, Dr. Kareva and Dr. Peova, members of the Macedonian Immunodeficiency Working Group. The meeting venue was the University Children's Hospital in Skopje. In addition to the organizers and local doctors, 20 pediatricians and immunologists involved in PID patient care and PID laboratory diagnosis attended from Macedonia. Doctors Shumkov, and Mihailova from Sofia, Bulgaria, Prof. László Maródi and Dr. Melinda Erdős from Debrecen, Hungary, and Prof. Dr. Anna Sediva from Prague, Check Republic attended from abroad.

The University Children's Hospital has a primary role in the education of

paediatricians in Macedonia. The Department of Immunology of the University Children's hospital was established in 1976 to assure clinical and laboratory investigation of children with immunodeficiencies. It provides both ambulatory and inpatient consultation services for children with all forms of immune disorders. Over the years, our Department became a centre for PID patients in Macedonia. Children with PID are registered by our Department. We have registered 32 patients until now (selective IgA deficiencies are not taken into account). The number of PID patients is limited because we miss the adult patients with PID. It was therefore important at this meeting that we invited internists and specialist for infectious diseases to increase the awareness of PID in adults. It was decided that Dr Mironska will organise the Macedonian PID Registry and will report the patients to the European Registry. She will attend the conference in Versailles, thanks to the ECE IPI CTR in Debrecen covering her registration fee. Also, five doctors from Macedonia should become members of ESID. ECE IPI CTR will cover the membership fee in concert with the J-Project initiative.

We visited the Institute of Immunobiology and Human Genetics, Faculty of Medicine before the Meeting was started. The Institute was established in 1990 to improve genetic diagnosis of inherited diseases. Report on possibilities for immunodeficiency diagnosis at the Institute of Immunobiology and Human Genetics was discussed in detail. Current program for teaching pediatric immunology, PID patient care, review on Hyper IgM syndrome and case reports were presented and discussed.

Importantly, a mother of a patient with PID attended the meeting and she is preparing to organize the Macedonian PID Parent's Group with the help of Dr.Stavric. It was decided to apply for a WIN grant offered by Jeffrey Modell Foundation.

Finally, it was encouraged to attend the next meeting in Kiev in November where the activities from the meeting in Skopje will be reported. ECE IPI CTR will cover the travel costs for one or two Macedonian doctors.

The meeting was supported by ECE IPI CTR, EU grant (EURO PID NAS), and by pharmaceutical sponsors including GlaxoSmithKline, Krka-lek and Libra 1.

Katarina STAVRIC

The 5th J-Project Meeting organised on November 19th, 2004 in Kiev, Ukraine.

The 5th PID awareness meeting in East-Central Europe referred to as the J-Project was organized in Kiev, Ukraine, together with the Department of Pediatric Infectious Diseases and Immunology, Kiev Medical Academy of Postgraduate Education. The Meeting was attended by more then 100 pediatricians, most of them pediatric immunology specialists who are interested and involved in PID patient care in this large country of 48 million inhabitants.

The participants were from all 27 regions of Ukraine. Doctors from East-Central Europe attending the Meeting were: Malgorzata Pac, Warsaw (Poland), Katarina Stavric, Skopje (Macedonia), Irina Kondratenko, Andrey Prodeus, and Evgeniy Pashanov from Moscow (Russia), Henriette Farkas and Lilian Varga from Budapest (Hungary). ECE IPI CTR and the Debrecen Jeffrey Modell Center were represented by László Maródi and Melinda Erdős from Debrecen (Hungary). According to the traditions at J-Project meetings, most presentations were in the local language, but the speakers presented figures and tables with English text. English presentations by invited speakers were translated into Ukrainien to assure optimal targeting of the messages. This worked out very well here, as well as at previous meetings.

Currently, there are three acknowledged pediatric immunology centers in Ukraine. Ludmila Chernyshova presented data on recent developments and current

problems in PID patient care in Ukraine in general, and in Kiev in particular. There were also reports from the other two centers, Kharkiv and Lwiw, by Ludmila Pushkarenko and Larisa Kostyucsenko, respectively, on recent achievements in diagnosis and treatment of PID patients in Eastern and Western regions of the country. Katarina Stavric reported on impressive achievements and increase of the overall activity of the PID Working group after the recent J-Project Meeting in Macedonia, including the establishment of the Parent's group. The Macedonian Parent's group is applying for a WIN grant, and provides help to initiate parent's activity in two neighbouring countries, Bulgaria and Serbia-Montenegro.

Irina Kondratenko updated us on the immunologic and genetic spectrum of hyper-IgM syndrome, and presented data of patients in Russia. László Maródi gave a review on XLP, and presented a Hungarian family with two male patients who died of FIM. A case report on IRAK-4 deficiency was presented by Melinda Erdős. These presentations emphasized the importance of molecular genetics in carrier detection and prenatal diagnosis in X-linked PIDs. It was announced that genetic analysis of 10 PIDs is now available in Debrecen for the J-Project countries.

Malgorzata Pac from Warsaw gave an overview on twenty-five years of experience with IVIG substitution, and she discussed the perspective of SCIG substitution. Evgeniy Pashanov shared with us his experience on bone marrow transplantation in children with primary immunodeficiency in Russia. I gave a lecture on treatment and prophylaxis of infections in immunocompromised patients.

There were several presentations on complement deficiencies, including complement in health and disease by Andrey Prodeus. Henriette Farkas reviewed the diagnosis and treatment of hereditary angioedema (HAE) and Lilian Varga presented data on the importance of developing centers for diagnosis and management of this disease. They are able to help East-European doctors to make the diagnosis of HAE.

It is remarkable how active the audience was during the discussions following the presentations, and continuing during breaks and dinner. Participants of this meeting received useful information about new approaches to diagnosis and treatment of primary immunodeficiencies. I strongly believe that the J-Project Meeting in Kiev was a very successful event, not only because it provided a useful educational program, but also because we could summarize current problems and outline future responsibilities in PID patient care in Ukraine.

Alla VOLOKHA

Letter to all ESID members

On 17th March, a hearing on Primary Immune Deficiencies (PIDs) took place at the European Parliament in Brussels, followed by a reception hosted by IPOPI.

The meeting was organised by the Parliament's Scientific & Technical Options Assessment Unit (STOA), with the support of Baxter. [STOA is an internal committee to advise the EU parliament itself on technical and scientific priorities] Subsequently, the EUP directed that PIDs should be a priority for national governments in the next year, 2005.

We need to be sure that we engage directly with national health policy makers to secure this prioritization. A **power point presentation** has been put together by a group of ESID members, as a direct result of the European Initiative for Primary Immunodeficiency Diseases, QLQ1-CT-2001-01395, lead by Edvard Smith. It is intended to be used as a template when negotiating to increase governmental awareness of PIDs locally. **You can download it from the ESID website.** We hope it is helpful!

Helen CHAPEL
Luigi NOTARANGELO
Sophie LUDGATE

Poland's first nation-wide meeting of parents with children suffering from the AT-syndrome

Parents of children suffering from a serious disease feel very helpless, and if the disease is a rare one, like the syndrome of ataxia-telangiectasia, additionally often feel left alone with their problems. The Clinical Department of Immunology at the Children's Memorial Health Institute in Warsaw and the Association of Friends to Children with Immunological System Deficiencies decided to help such families to cope with their every day problems, and organised the first Polish nation-wide meeting for parents and their children affected by the AT-syndrome. The meeting was held on 22-23 May, 2004, in the Children's Memorial Health Institute in Warsaw.

Fourteen families from Poland and one from Germany had the unique opportunity to share their experiences on AT treatment as well as to ask for professional advice. The treatment of AT patients, due to its complex nature, requires co-operation of many clinical specialists such as paediatricians, neurologists, rehabilitation specialists, pulmunologists and others. Therefore, the organisers prepared a series of lectures on neurology, rehabilitation, nutrition, and lung diseases. There were activities organised for children as well: the children were taken to the Warsaw ZOO, and then to a concert given by a school band and one other group.

The meeting was organised thanks to sponsors and volunteers who shared their funds, time, commitment and enthusiasm to make it happen. Both the parents and the children were very grateful, and welcomed the idea of such support meetings with relief - they realised that they would not be left alone with their problems. They hope the meetings will continue. The organisers would like to plan further meetings, and hope that sponsors will be found to make it possible.

I appreciate very much the commitment of Ms Maria Bukaty, President of the Association of Friends to Children with Immunological System Deficiencies as well as the enthusiastic participation of two nurses, Ms Bożena Kuśmirek and Ms Maryla Podemska. I would like to give my special thanks to Professor Ewa Bernatowska, who kindly agreed to take part in the meeting. I am really grateful for her professional guidance. Also to the General Manager of the Children's Memorial Health Institute, the General Manager of the Warsaw ZOO, Mr. and Mrs Jakubowscy, Towarowa Gielda Energii, and the Pharmaceutical Companies Baxter, Grifols, Mead Johnson, Nutricia, Servier, and Polfarma.

Barbara PIETRUCHA

Pictures taken at the Meeting

The Italian Network of Primary Immunodeficiencies (PID).

The treatment of PIDs presents problems concerning assistance organization, which are typical of rare diseases. Usually, highly specialized centers are rare, and patients are often faced with two penalizing choices: be treated by a highly specialized center through continuous trips, which are often long and are accompanied by elevated financial, social and family costs, or be treated by a hospital close to home, which almost always lacks the necessary competences and experiences. The problem is particularly noticed in Italy where a majority of the centers highly specialized in diagnosis and treatments of PID are found in the north and center of the country, while the majority of children are born in the south and on the islands.

In an attempt to confront and to solve this problem, the AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) Immunodeficiency Strategic Scientific Group was created in Italy in 1999 with three main objectives:

- provide patients with the possibility of a definite and early diagnosis;
- offer patients the possibility of treatment, even through their local hospital, based on modern therapeutic protocols;
- define the natural history of the disease, and the long-term risks of complications after providing adequate measures of prevention.

For these aims, a web of 54 centers has been created, which are distributed equally throughout Italy. These centers are mainly represented by non-specialized hospital and university centers which already are in the process of treating patients with PID, and by Italian centers highly specialized in the diagnosis and treatment of PIDs. Representatives from these centers, along with the Italian Association of parents and patients affected by primary immuno deficiencies (AIP) have prepared and approved protocols for the diagnosis and treatment of XLA, CGD, CVID, Transient Infancy Hypogammaglobulinemia and WAS. These protocols, available on www.aieop.org, provide detailed diagnostic criteria and treatment regimens for these disorders, both in children and adults. Furthermore, 3 laboratories have been identified which are used as a reference for the immunological and molecular confirmation of the suspected diagnosis. Each center enters patients' data on-line using electronic case report forms concerning registration, diagnosis and treatment, side effects and annual follow-up. The information is centralized and stored in a web-based database at the Interuniversity Computing Center (CINECA).

The system allows for the management of the whole informative flow: from data entry, to monitoring and online interactive data analysis by means of a website that also allows online consultation of all protocols, and exchange of information across a forum dedicated to each individual protocol.

To date, 125 patients have been enrolled in the XLA protocol. BTK gene sequence analysis has been carried out in 114 (91%) patients, and resulted positive in 103 patients. In the remaining patients, a diagnosis of autosomal recessive form of agammaglobulinemia is in progress via molecular analysis. Only 1% of the patients are currently treated with immunoglobulin substitution therapy, (serum pre-infusion values < 500mg/dl), as compared to 15% at the time of enrollment. Among others, this finding demonstrates the efficacy of the protocol in improving treatment regardless of the specialization of the center. As for the CGD protocol, 60 patients have been enrolled so far. At the time of enrollment only 53% of the patients were receiving antibacterial and antifungal prophylaxis. Two years later, the percentage of the patients adequately treated had increased to 88%.

Two hundred and four patients with CVID from all Italian regions have been enrolled and followed-up in the ad hoc protocol.

After five years of work, the Italian Network for Primary Immunodeficiencies:

has proved effective for improving the treatment of patients with PID, irrespective of the degree of specialization of the following center; is providing badly needed data on the little known history and long-term response to treatment and prognosis of these diseases, possibly resulting in the development of safer and more efficacious therapeutic regimens; is also providing useful data for a more profound scientific knowledge of the molecular and cellular mechanisms of PIDs.

The pivotal experience of the Italian Network for Primary Immunodeficiencies represents a model which may be applied for the diagnosis and treatment of many rare diseases.

The Associazione Italiana Ematologia Oncologia Pediatrica (AEIOP) consists of:

A. Plebani (Coordinator XLA Protocol), D. De Mattia (Coordinator CGD Protocol), Isabella Quinti (Coordinator CVID Protocol), Pession, (Coordinator AIEOP Operation Office), A. G. Ugazio (Chairman AIEOP PID Network).

Alessandro PLEBANI

Working Party reports

Registries Working Party

Dear collegues, today I would like to inform you on two topics: the new developments in the ESID patient registry and, our most recent efforts to re-vitalise the ESID website!

As of Monday, 11 October, 2004, the CVID online subregistry is productive. If you do not have a valid password for the productive system, you may already give it a try at the ESID-TEST-registry. **Please log into the test-registry on www.esid-registry.org/TEST.jsp**. Please use one of the following logins (test1, test2, test3, test4, test5, test6, test7, test8, or test9) and START_PASSWORD as the password. Please do not change this password (if you change it, other test-users will no longer be able to log into the test-database). We would hereby like to re-emphasise that in the test system only "dummy data" is provided (for the members of the steering committees to test the newly developed subregistries). Subsequent subregistries to go online in the course of the next months will be DiGeorge, IPEX, Hyper-IgE, osteopetrosis, RAG (the first SCID subregistry!), Nijmegen breakage syndrome, and ICF-Syndrome.

The ESID main registry contains the so-called core data set, the "red fields" and the "red lab". These are the same for all subregistries. In contrast, the datamodels of the disease specific subregistries are developed by the various ESID steering committees. The list of the steering committees will be published in December 2004 on the ESID website.

If you want to participate in the design of a certain subregistry, please contact the nominated heads of the respective steering committees, **or contact frisch@medizin.ukl.uni-freiburg.de**.

We would like to point out again that, due to European data protection laws, a writ-

ten patient's informed consent is necessary to enter patient's data into ESID online registries, and an IRB approval (statement of the local ethical board) is required for each ESID registry documenting centre. In addition, in some centres a data protection approval by the responsible officials will be necessary. Translations of the patient's informed consent form into Croatian, Czech, Dutch, English, French, German, Greek, Italian, Portuguese, Romanian, Slovakian, Spanish, and Turkish are available already and will be published on the new ESID registry website.

In addition to the web-based registration, a paper-based registration shall be provided for centres which do not have a convenient online access. Newly edited PDF forms will be developed for the ESID core-dataset and will be available for a download on the ESID website. The "old" entry forms will no longer be used.

By November 15th 2004, the number of registered documenting centres for the online registry has increased to 41 centres in 21 countries. Password allocation is proceeding, and if you would like to apply for an online password, **please send a short email to frisch@medizin.ukl.uni-freiburg.de**. You will then immediately be provided with (1) the "Agreement between the ESID and a Documenting Centre", and (2) the "Application form to obtain a user name and a password".

As you know, each documenting centre may make use of the option to implement the ESID registry database system as a personalised version and thus to acquire the advantages of all the other features of the database like the 'patient report generation' or the electronic import of laboratory data. The Dr.-von-Haunersches-Kinderspital in Munich is the first documenting centre going to run a personalised version of the ESID registry database system outside Freiburg.

We would like to place emphasis on the importance of existing national PID registries, which are essential for the implementation of the documenting network in each country and will be supported by ESID, as well as the creation of new European national PID registries. National registries therefore will be enabled to use the database platform provided by ESID. In this regard, the Czech Republic will be the first country running a nation-wide online network with the ESID system.

Likewise important are the existing disease specific databases, which shall be linked to the ESID registry. Disease specific registries are very important since they represent the kind of data-collection teaching us lessons on a specific disease in addition to the incidence and epidemiology.

A workshop on "Clinical and research databases in primary immunodeficiencies" has been held at the biennial ESID meeting in Versailles on Saturday, October 23, giving a survey of thirteen important existing national and disease specific databases in PID. These presentations and the email addresses of the presenters will be published on the ESID website in December 2004.

Self-portrayals of existing national registries were contributed for:

- the Spanish Registry for Primary Immunodeficiency Diseases (REDIP), presented by Núria Matamoros from Palma de Mallorca,
- the Italian national registry & AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica), presented by Alessandro Plebani from Brescia,
- the Belgian national registry, presented by Claire-Michele Farber from Bruxelles,
- the Czech national registry, presented by Vojtech Thon from Brno,
- the Polish national registry, presented by Ewa Bernatowska from Warsaw,
- the Russian national registry, presented by Irina Kondratenko from Moscow,
- the Iranian Primary Immunodeficiency Registry (IPIDR), presented by Nima Rezaei from Teheran
- the national registry of Australia and New Zealand (ASCIA), presented by

Sean Riminton from Sydney, Australia
and the US-PID registry and USIDnet, presented by Hans Ochs, Seattle, USA.

The following three existing disease specific databases have been portrayed:

the European registry for Neutropenia, presented by Cornelia Zeidler from Hannover, Germany,
the European registry for CVID, presented by Lennart Hammarström from, Huddinge, Sweden,
the European registry for CGD, presented by Taco Kuijpers from Amsterdam, Netherlands.

Mauno Vihinen from Tampere, Finland, presented the 90+ Immunodeficiency mutation databases (IDbases), which will be linked to ESID online registry aiming at the amalgamation of clinical registries with the respective mutation to facilitate phenotype-genotype studies.

Collaboration with Australian/New-Zealand (ASCIA), North American (USIDnet) and South American (LAGID) registries and Asian registries is important and will be supported. A common online database system is envisioned.

As a result of the workshop diagnostic and treatment protocols shall be developed for each specific disease. The Italian AIEOP protocols shall serve as examples.

By the decision of the ESID Board on October 21, 2004, the ESID website will be transferred to the ESID server in Freiburg. We will to do this as soon as possible, most likely in December 2004.

Freiburg will increase the content and the actuality of the website, including new guidelines. The new ESID*junior* WP will also be responsible for the liveliness of this website.

In addition, there shall be:

information on how many logins to the ESID website there have been,
a link to facilitate an internet payment for the ESID membership fees,
it shall be attempted to facilitate an internet voting system for the ESID Board elections in 2006,
an email in-box for each ESID member to retrieve ESID specific messages will be implemented. Members may forward their mails to their local accounts,
a forum to discuss patients among the ESID community will be integrated as well into the ESID website. This project will be coordinated by Maria Kanariou.

If you have any suggestions to improve the ESID website, please e-mail us at frisch@medizin.ukl.uni-freiburg.de.

Bodo GRIMBACHER
Barbara FRISCH

Focus on a country:

Established member Q&A
Luigi Notarangelo
Clinica Pediatrica
Spedali Civili
Brescia, Italy

Can you give me some information about your background and can you tell me something about your career history?

I am a Pediatrician. After graduating at the Medical School in Pavia, Italy, in 1980, I finished my residency in Pediatrics in 1984, under the supervision of Prof. Burgio. The same year, I followed Prof. Ugazio and moved to Brescia, and started working on primary immune deficiencies. I was lucky enough to meet Giovanna Camerino, who trained me in molecular genetics, and when I moved to David Nelson's lab at the National Cancer Institute, Bethesda (USA) from 1986 to 1989, I could apply molecular genetic techniques to the study of primary immune deficiencies.

After my return to Brescia, I became Associate Professor of Pediatrics in 1994, and Full Professor in 1996. I have served as Secretary of ESID from 1994 to 1998. Since the year 2000, I am the Head of the Department of Pediatrics at the University of Brescia, and since 2002 I have the privilege to act as ESID President.

How did you become interested in immunodeficiencies?

While studying at the Medical School in Pavia, I had a strong interest in Immunology. One of my colleagues in my college was Antonio Lanzavecchia, who at that time was finishing his residency in Pediatrics. Antonio adviced me to contact Prof. Burgio (the Head of the Department of Pediatrics in Pavia), as a bright person and an excellent mentor with a strong interest in Immunology. Knowing him and Prof. Ugazio gave me the opportunity to practice Immunology. Originally, however, my main interest as a medical fellow was in immune-mediated kidney and rheumatological diseases. It was only when I moved to Brescia with Prof. Ugazio, that I had the opportunity to get involved with primary immune deficiencies, a field that I loved so much that it became the main goal in my scientific and medical career.

What have been your achievements in research and patient care in the field of immunodeficiencies?

From the scientific point of view, my main contributions have been in the molecular characterization of several primary immune deficiencies. These achievements, however important, could only be obtained through an extensive collaboration with several people both within and outside my group. I have also taken part in the first European experience of gene therapy in ADA deficiency, and in one of the first experiences of prenatal stem cell transplantation.
However, personally, I consider as my most important achievements the possibility to work with infants affected with severe forms of PID, and to have been able, together with my colleagues, to cure many of them by means of stem cell transplantation. More in general, when with Prof. Ugazio we decided to set up a center in Brescia that covered from molecular diagnosis to treatment (including BMT), we really worked at developing a comprehensive approach to the needs of the families with PID. This has been and will always be an unforgettable achievement in my career.

What kind of developments in immunodeficiency do you expect in the near future?

During the last 15 years, molecular genetics and immunology have allowed to define the basis of many forms of PID. There are relatively few significant typical forms of PID for which we still do not know the molecular basis. While this gap should be filled within a few years, yet I anticipate that many other forms of defects in the immune system will be recognized. I am particularly in admiration of the work of Jean Laurent Casanova and others, who are actually proving how specific defects in the immune system may lead to unique susceptibility to selected pathogens. I suppose we are still at the beginning of a fascinating adventure.

Also, gene therapy has just started to disclose its promises. More in general, I believe we will see important advances in gene and molecular therapy in the years to come.

Once again, however, I think our attention should be focused particularly on quality of life. We must work more closely with the nurses and with the patients (and their family members) if we want to really appreciate how well we are doing or we could do for our patients. Changing their quality of life is the most significant development that we may achieve as physicians.

What is your advice for young people who want to launch their career in immunodeficiency?

Learn from the work of others, read the "old" papers (that are full of experience and give an important historical perspective), always favor collaboration, get a chance to travel and exchange experience in other groups, never get frustrated if your experiments do not work as you would like, but try again and again… (and perhaps ask yourself why it isn't working…)

If you want to become a physician particularly interested in PID, read a lot, but also listen to your patients.
In any case, should you like to become a scientist or a physician, always be curious.

And – last but not least – what does ESID mean to you?

ESID is an extraordinary opportunity to realize what I said in my last answer. It is a special forum where physicians and scientists from different countries can meet, both at regular meetings, and through other occasions (such as the Summer School, or even by e-mail), and share their experience. We are very lucky in Europe, particularly in the field of PID, that we have always been able to couple a fair competition with an excellent collaboration. This has been the real secret of ESID. Attracting young people, who will be ESID's future, is now the goal to pursue.

Young Investigator Q&A

Silvia Giliani
Clinica Pediatrica
Spedali Civili
Brescia, Italy

Can you give me some information about yourself and your background?

I'm 38 years old. I was born in Brescia, a small town in Northern Italy, where I actually live. I'm married with two children (5 and 3).

Can you tell me something about your career history?

I studied Biology at the University of Pavia, where I took my degree in Genetics in 1988. Then I continued my internship at the Human Genetics Department of the National research council (CNR) with Dr. De Carli and Dr. Stefanini characterizing the complementation groups of xeroderma pigmentosum and trichothiodystrophy. There I got my first fellowship.

Then, in 1991 I moved back to my hometown Brescia, joining the starting group of a young promising researcher (Prof. Notarangelo). At that time, no genes responsible for immunodeficiencies were characterized, so my first work was to set up linkage analysis in families of patients with Wiskott-Aldrich syndrome, and to screen candidate genes for HyperIgM syndrome. Then, CD40L was discovered as the cause of X-linked hyperIgM and I started a project on its genomic organization and the characterization of the promoter.

In 1993, I stayed for 6 months in Mike Blaese's Lab where I generated, with the invaluable help of Fabio Candotti, a retroviral vector carrying the CD40L gene, and a transduced cell line carrying the vector.

Since 1999, I have a permanent position in research and molecular diagnosis of primary immunodeficiencies at the Nocivelli Institute of Molecular Medicine belonging to the Dept of Pediatrics of the Brescia University Hospital. I have a PhD in biotechnology applied to medical sciences and a specialization in biochemistry.

How did you become interested in immunodeficiencies?

Just by chance. I was told there was a fellowship available in my hometown and I went there for an interview. There, I met Prof. Notarangelo, and I was fascinated by the possibility to work in a lab inside a hospital, just near to the patients. This was absolutely unusual to me, coming from a research institute. This approach from the bed-side to the bench induced me to completely change fields, even if my preparation was totally avoid of immunology, so I was really frightened starting this new work.

What have been your achievements in patient care and/or immunodeficiency research up to now?

I was so lucky to collaborate with Gigi Notarangelo, Anna Villa and Paolo Vezzoni to the disclosure of the molecular bases of some immunodeficiencies (JAK3-SCID, Omenn syndrome, some cases of Osteopetrosis). I've learned new methods from Ornella Parolini to perform molecular diagnosis, and, in 1994, I started the molecular analysis of CD40L that was one of the first big ESID projects aiming to establish a database of molecular and clinical data of primary immunodeficiencies.

Recently, I characterized the first cases of hyper IgM syndrome due to CD40 defects with Simona Ferrari (a project headed by Alessandro Plebani), and described a new milder form of thrombocytopenia due to WASP defects in collaboration with Lucia Notarangelo, Cinzia Mazza and Hans Ochs.

Most of my time in the lab is now occupied by diagnostic work. I'm involved in molecular diagnosis of most SCID's, I have a project on autosomal recessive hyperIgM in which Gaetana Lanzi is the main person involved, aiming to characterize the pattern of CD40 expression in HIGM3 patients. Moreover, I have a project on functional analysis of different cell type characteristics in patients with different WASP defects. Recently, I set up a new protocol for the intracellular staining of WASP protein with the help of Daniele Moratto and Elisabetta Bandiera which allows us the diagnosis even of milder forms, and the monitoring of post-transplantation reconstitution in Wiskott-Aldrich patients. I'm involved with Gigi Notarangelo and Anna Villa in an international project aiming to characterize T-B-SCIDs. Part of this work is the molecular diagnosis of new cases, even of unknown origin. From this point of view we are describing, in collaboration with Francoise Le Deist and Carmem Bonfim the first case of Omenn syndrome due to IL7RA deficiency. Moreover, we have recently collected 18 new cases of SCID due to IL7RA defects, which is the most numerous group described so far.

What do you hope to achieve in the future?

I'd like to improve the comprehension of some disease mechanisms, such as the etiopathology of Wiskott Aldrich syndrome, but I'm perfectly conscious that this is at the moment unattainable for me! Something interesting could be to understand why different genetic defects could give rise to exactly the same clinical phenotype (as in the case of Omenn syndrome).

How are you planning to reach this goal?

Only a big effort of collaboration can give big results, and I mean collaboration with clinicians giving accurate clinical data, with pathologists and biologists using all the new powerful technical tools. I'd like to make better use of instruments such as microarrays and proteomics, and to improve the diagnostic tools we are now using that can cover only a little part of the mutations really affecting a gene. Moreover, I'd like to get the MD degree: if I will not be able to disclose some new disease mechanisms, I will at least participate in the so celebrate ESID Summer School!

And – last but not least – what does ESID mean to you?

I think is a big opportunity to meet people sharing the same interests, even if in the last years the topics covered are really rising and modifying, with the improving of our knowledge of the immune system. I think that Meetings like the last one in Versailles are a great chance for all the people working on primary immunodeficiencies, and the big movement of young people (and I mean really young!) that I've seen this year is something really important.

What would you want to change if you were president of ESID?

I would enforce and promote the collaboration among groups, encouraging the movements, especially of young people, between groups. Something is still ongoing, but I will also recommend to host for short periods even 'experienced' people. As I've seen in our Lab and Clinic, this is a really

formative experience for all the different participants.

PLEASE NOTE:

CHANGE OF EMAIL ADDRESS OF ESID TREASURER INTO:

dr.estherdevries@tiscali.nl

DO NOT USE THE OLD YAHOO ADDRESS ANYMORE !!

CHANGE OF EMAIL ADDRESS OF ESID TREASURER

PLEASE NOTE !!

CALL FOR HELP

Dear ESID members,

We need your help. Some addresses of ESID members are no longer correct.

These people can no longer be reached at the address we have in the database:

Anna BERGLÖF, Sweden
Mona I. KIDON, Israel
Antonio NIETO DIAZ, Spain
Hirokazu KANEGANE, Japan
Sigune SCHMIDT, Germany
Ron S. WEENING, the Netherlands
Cristina PANISI, Italy
Magda CARNEIRO-SAMPAIO, Brazil
Catharina SCHÜTZ, Germany
Magdalena KURENKO-DEPTUCH, Poland
Tuba TURUL, Turkey
Maria DOS SANTO GUEDES, Brazil
Stephan STROBEL, United Kingdom

Please help us to find them, and give their correct addresses to us, or focus their attention upon the problem!

THANKS FOR YOUR COOPERATION !!