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 (editor in chief) and Gustavo Lazo.

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 !!!
Only use my *new email address*:
esid@ estherdevries.nl

Front page:
'Beautiful Budapest'

Dear ESID members,

Already, the second ESID Newsletter of this year is brought to you, containing lots of useful information.

Please pay special attention to the information from the ESID Board. We need your opinion on important matters, as Luigi Notarangelo points out to you in his president's letter. Many addresses and email addresses are missing or incorrect, please see if it concerns you or someone you know in my Treasurer's report.

For those of you who haven't yet paid their ESID membership fee: see my plea as your treasurer on page 5, and act accordingly. ESID needs all the fees, to be able to continue its activities.

An important event is soon going to take place at the Paul Ehrlich Institute in Frankfurt, Germany: the EU-PID Consensus Conference. Read all about this on page 6, and on the meeting website.

Read about the candidates and vacancies for the ESID Board, and why not offer your candidature to us ?

And—last but not least—find another update of the ever active Registries Working Party, and all the others.

Want to see your name in the next issue of the ESID Newsletter? Then send me your copy at esid @ estherdevries. nl !

Best wishes to all of you,

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. 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: Stem cell transplantation and gene therapy (chair: Mario Abinun), Registries (chair: Bodo Grimbacher), Clinical (chair: Bobby Gaspar), Genetics (chair: Anna Villa), Education (chair: Anders Fasth), and ESID*juniors* (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.

= ESID Information =

President's letter

Dear friends,

What should (or could) ESID be?

While my mandate as President of ESID is going to terminate, I will refrain from judging on the achievements reached during these years, because I think that it is up to the ESID Community to evaluate what good or bad has been done during these 4 years in which I have had the honor to chair our Society. In my one-but-last Presidential report for the ESID Newsletter, I want already to thank the entire ESID Community, and in particular the Board Members, who have been essential to help me during my mandate.

The present ESID Newsletter gives me the chance to share with you a broader vision of ESID, that I have tried to anticipate several times during my notes. The key question that is around us is: "What should ESID be?". It is not at all a theoretical question. Indeed, it has been very much debated within the Board, when we had to agree on a common text for the new Statute and Constitution to be presented to the ESID General Assembly for formal approval in October 2006. It is important to say that the text that will be presented to the General Assembly will be as unanimously agreed by the Board, yet I think it is also important that we start reasoning about the future of ESID.

There is no doubt that EGID/ESID have really set up the arena at an international level on Primary Immunodeficiencies for many years. Nothing similar has existed for decades elsewhere, apart from the WHO-IUIS Committee and Meetings, which however had (and still have) different purposes, as shown by the fact that attendance to these meetings is restricted by invitation only, and there is no room for free presentations. Also, it is important – I believe – to consider that the birth of EGID and ESID was not based on the pure will of a few people, but reflected what was already going on for years, i.e. a truly international collaboration across Europe and some other States in the field of PIDs. This has been essential to give Europe the international leadership in the field. This process is still going on, as clearly demonstrated by continuous improvements in the identification of the molecular and cellular bases of PIDs (Cernunnos being one last good example) and in the treatment of these disorders.

That the EGID/ESID initiative has been highly successful is also firmly established by the fact that, more recently, similar initiatives have been initiated in other areas of the world. I am thinking of LAGID, of PAGID, and of the USIDNET. Even the Summer School, one of the last major contributions that ESID has given to foster education in the field of PIDs, has now been replicated, with some differences, in the United States. There are – as just stated – some significant differences in the format, the content, and even the purposes of ESID vs. others' initiatives, yet the message is clear. We are no longer alone in this march, and I think we should be happy about this.

Then the issue becomes: should all these initiatives in the world continue to run in parallel or should we try to exchange experiences? More in general, can we start thinking of a global initiative in the field of PIDs and, if so, what should the role of ESID be? These are fundamental questions that the ESID Community can no longer ignore. I look forward to your ideas during the next General Assembly and, why not?, in reaction to this Newsletter and on the forum of the ESID website!

Luigi NOTARANGELO

Treasurer's report

Until now (May 5, 2006), I have received the ESID membership fee 2006/2007 from 178 members. Thank you so much for paying in time! This means however, that I have NOT received the ESID membership fee 2006/2007 from 292 (!!) ESID members. I strongly urge all of you **to check on the ESID website whether you have paid the ESID membership fee** according to my administration (give me a few days to put your payment in your webfile). It might be that a mistake has been made, and that you have paid after all. In that case, please send me a copy of the confirmatory email you have had from Saferpay, and I will immediately change your status to 'paid'. On the other hand, you may have forgotten to pay in time… If so, please do so very soon. You will not be able to profit from the reduced fee for members for the Budapest meeting if you haven't paid, and this is a waste of money for you, and loss of income for ESID …

I still have some addresses missing or incorrect: Cunha, Belevtsev, Micol, Nieto Diaz, Freihorst, El-Shanawany, Dupuis, Notheis, Cucuruz, Oksenhendler, Drewe, Carneiro-Sampaio, Datkova, Duthey, Panisi, Anjou Maine Pellier, Patel, Schütz, Strobel, Soler, Berg, Perez, Lucas. Please go to the ESID website and correct your personal details (go to 'ESID members & membership, click 'ESID members' tab, you can change your profile there after logging in under 'profile' in the upper right corner).

Also, many people don't have their correct email addresses in the ESID database. To enable entry onto the website, fake email addresses have been made for all people without email address, and a letter has been sent to them to urge them to put their own email address on the website. However, many haven't done so! **If you find yourself in the ESID database with a fake email address (all …@esid.org addresses), please change it into your own real email address.** Like this, we cannot reach you by email !! Since more and more correspondence will be by email, you will miss all the ESID information that is forwarded to the members! The fake email addresses are found under the names of:

Mariam Al Hilali, Abdulaziz Al-Ghonaium, Schahin Aliani, Christin Angouadakia, Ömür Ardeniz, Magnus Aurivillius, Torben Barington, Andrey Bologov, Robbert Bredius, B. Cantinieaux, Isabel Caragol-Urgelles, Magda Carneiro-Sampaio, Maria Christina Casas Vila, Julian Clemente Pollan, Roberto Jorge Craviotto, E. Cuadrado, Eva Datkova, Alexandra Dias, Deborah Dockey, Esin Figen Dogu, Jasper Drenth, Sophie Dupuis, Marzia Duse, Joanna Economidou, Fügen Ersoy, Emilia Maria Antunes Gomes de Faria, Gumersindo Fontan Casariego, Vanda Friman, Alenka Gagro, Maria Cruz, Garcia Rodriguez, Juana Gil Herrera, Maria Ana Gonzalez del Castillo, Jimmy C. Gooi, Dolores Gurbindo Gutierrez, Zeev T. Handzel, Anders Holmér, Cathryn Hope, Mona I. Kidon, David Komarek, Otakar Kopeck, Olga Krystufkova, Magdalena Kurenko-Deptuch, Manolis Liatsis, Michaela Lucas, Sarka Lukesova, Giuseppe Luzi, Juan Martin Garcia-Sancho, Mariam Marzouq Al-Hilali, SSA Evelina Mazzolari, Karin Mellgren, Luigi Mori, Vasantha Nagendran Bénédicte Neven, Antonio Nieto Diaz Jeroen G. Noordzij, Nelly Noraz Gundula Notheis, Ann Margreth Olinder-Nielsen, Vivi-Anne Oxelius, Malgorzata Pac, Cristina Panisi, Neven Pavlov, Isabelle C.A. Anjou Maine Pellier, Barbara Pietrucha, Guilhermina Reis Veloso, Jose Carlos Rodriguez Gallego, Paolo Rossi, Olli Ruuskanen Carmem Maria Sales Bonfim, Alexandra Salmon, Almudena Sampalo Lainz, Elizabeth Sarmiento, Anna Scherbina, Fiona Shackley, Henryka Siwinska-Gotebiowska, Arne Svejgaard, Naomi Taylor, Ilhan Tezcan, Laszlo Timar, Paola Toniati, Maria Trachana, Lourdes Tricas, J. Unsworth, Esther van de Vosse, Jutte van der Werff ten Bosch, Julia Maria Andrade Mendes de Vasconcelos, Montserrat Vendrell Relat, Doris Vokurkova, Effie Vrachnou, A.P. Williams, Ben JM. Zegers.

News & Views

The EU-PID Consensus Conference at the Paul Ehrlich Institute in Langen, Germany, 19-20 June, 2006.

Soon, the EU-PID Consensus Conference will take place, and we all hope that it will lead to fruitful discussions, and a Consensus statement that will be known and acknowledged by policy makers throughout Europe.

You can find more information in the previous issue of the ESID Newsletter, and please also visit the website of this conference at www.eupidconference.com !

Journal of Experimental Medicine

Dear All, I have been appointed Editor of The . 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

J Project Meeting in Debrecen, Hungary, 4-5 November, 2005: PID genetic diagnostics in East-Central Europe

The J Project meeting in Debrecen was jointly organized by the Department of Infectious and Pediatric Immunology of the University of Debrecen Medical and Health Science Center and the Hungarian Working Group for Pediatric Immunology (HWGPI) established in 1995. This Meeting provided the possibility to celebrate the 20th anniversary of the establishment of the HWGPI. In addition, the Meeting was part of a series of scientific symposia organized all over Hungary under the heading of Hungarian Science Day. The venue was the Civis Grand Hotel Aranybika, the most traditional hotel in Debrecen.

The Meeting was opened by Dr. László Szabó, secretary of the Hungarian Society of Pediatricians, who honored the HWGPI with a Certificate of Merit on behalf of the Society. Similarly, Dr. Imre Kacskovics presented a Certificate of Merit to the HWGPI on behalf the Board of the Hungarian Society for Immunology. Dr. Pál Gergely, science director of the University of Debrecen Medical and Health Science Center expressed his appreciation to the successful activity and achievements of the HWGPI over the past twenty years.

A special talk was delivered by Dr. György Kosztolányi, member of the Hungarian Academy of Sciences, on an European database for rare diseases. He invited experts from J Project countries to join this program also referred to as ORPHANET. Another network project developed for the benefit for patients with C1-esterase inhibitor deficiency was presented by Dr. Henrietta Farkas. Dr. Maria Bataneant and Dr. Alla Volokha from Romania and Ukraine, respectively, presented data on autoimmune lymphoproliferative diseases and pulmonary manifestations in patients with PIDs. Two presentations were focused on molecular genetic aspects of PID diagnostics, one by Dr. Karl Schwartz and another by Dr. Tamas Freiberger. Case reports were presented by Dr. Melinda Erdős, Vera Gulácsy, and Andrea

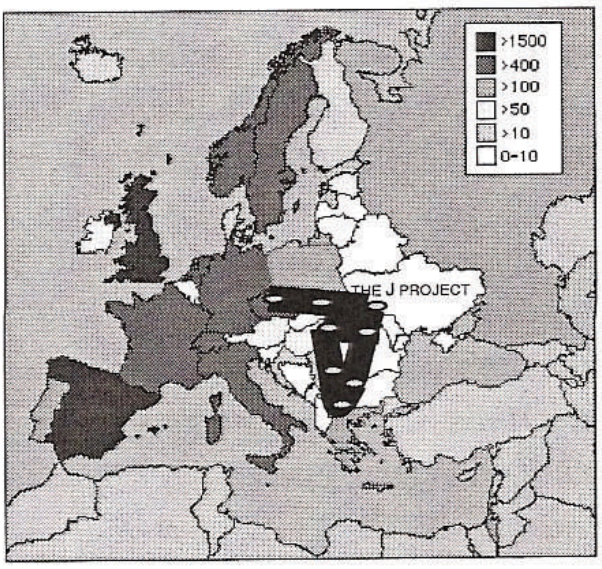
Two Hungarian societies gave Certificate of Merit to the Working Group for Pediatric Immunology

Lakatos, all from Debrecen, in which molecular genetic analysis of Shwachman-Diamond syndrome, Wiskott-Aldrich syndrome, and X.linked lymphoproliferative syndrome were shown. Dr. Olga Török gave a very nice talk on methods used in fetal sampling for prenatal diagnosis in PID. At the end of the first day of the program a panel discussion moderated by Dr. László Maródi was devoted to discuss technical details of how the Debrecen Jeffrey Modell diagnostic Center can be of help to provide molecular genetic diagnosis for patients in East-Central Europe.

The main subjects of the second day of the Meeting included a basic and clinical talks on apoptosis in PIDs, recent advances in understanding immunpathology of selective IgA deficiency, and updates of immunreconstitution and IVIG substitution. A clinical summary of LAD deficiency was given by Dr. Gergely Kriván. Dr. Zoltán Szekanecz, and adult rheumatologists gave a comprehensive talk on perspectives of biologic therapy in rheumatic disease.

The final session was devoted to case reports on macrophage activation syndrome, recurrent hepatic abscess as the sole manifestation of CGD, mycobacterial infections in HIGE, and X-linked SCID.

Melinda ERDÖS
László MARÓDI



Participants at the J Project Meeting in Oradea, Romania. From left to right: Zoltán Ellenes, László Ritli, Maria Cucuruz, László Maródi

ESID Board Elections!

Dear ESID members,

The following candidates would like to present themselves to you as candidates for the vacancies in the ESID Board as of October 2006. Elections will take place during the ESID General Assembly in Budapest. Luigi Notarangelo will step down as president, and president-elect Jean-Laurent Casanova will take over. Hermann Wolf will step down as secretary, Esther de Vries is available for re-election for one last term as Treasurer. For the Working Parties, Mario Abinun is available for re-election for Stem cell transplantation and gene therapy, and Bobby Gaspar is available for re-election for Clinical. Bodo Grimbacher will step down for Registries, Anna Villa for Genetics, Anders Fasth for Education, and Pim van der Vossen for ESID*juniors*.

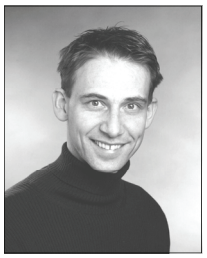
Secretary

With this proposal I would like to candidate for the ESID secretary post. During the last 4 years, I headed the ESID Registries Working Party. Needless to say that this was a lot of fun, success and very good progress for me and the Society. During my work, I started to be involved in the executive work of the ESID Board, since with the new ESID online registry, contracts between ESID and pharmaceutical companies needed to be concluded and in the near future also the collaboration between ESID and USIDnet needs to be defined on legal grounds. This work for ESID has fascinated me very much and I would love to continue to work in this field and serve ESID as secretary.

Especially the need to file a legal act for ESID in order to limit the liability of its members initiated discussions we need to solve within ESID: How about the liability of Board members? How about the liability of ESID members? Who will take the financial risk of larger projects such as the biennial ESID meetings and such projects as the ESID online database? Who will be eligible for ESID membership? Do we need letters of recommendation? So I would like to urge everybody to come to this General Assembly of ESID members to shape the Society's future.

I will need to learn how to type (not genotype;-) faster, but this shall not be a problem. I guess I will have enough support from my Departments either here in Freiburg, or in my new Department at the Royal Free Hospital in London, where I plan to move in October 2006.

Bodo GRIMBACHER



Registries Working Party Head

My name is Gerhard Kindle and I would like to candidate for the position of 'head of the registry' for the ESID online database. I am a physician (MD since 1995) and also a computer scientist (master in computer science since 2004). I have spent part of my training as a physician at the department of infectious diseases at the University Hospital of Freiburg. I am 41 years old and married.

In March 2005, I started to work in Bodo Grimbacher's team at the University Hospital of Freiburg and have been responsible for the development and support of the ESID database system.

I would be grateful to have the chance to carry on the work we have started with a lot of dedication during the last few years and I would love to participate in further advancements of the ESID database.

As you may have realised, the main focus during these last years was on setting up the system and implementing new disease-specific subregistries. Also a lot of effort was put into recruiting centres from all over Europe to contribute to this system and enter their patients' data into the database. We now have over 70 centres in 26 countries with signed agreements. Thus in the beginning of the project we have addressed basically the 'data input'.

Since we have now set up the system in all its essential components for data entry and 'data input' is now being taken care of, we have concluded that at this stage we ought to shift the focus and to concentrate more on the 'data output' of the database system.

Another important issue to address - since we have already the data of almost 2000 patients registered into the database - is the quality management of the data (monitoring).

To achieve this, we are planning to set up reporting services that will facilitate access to the data. These services will be capable of allowing researchers to access the data independently of a database specialist. It will also be possible to simply extract all data from one centre including statistical information similar to the information covered in the database statistics section of the ESID homepage.

In addition to these 'reporting and monitoring' issues, we are also planning to implement tools that will help the users to classify their data by visualising the output by means of graphical visualization tools (e.g. weight/height-percentile charts or in form of a pedigree drawing tool).

I hope I can count on your vote for the election in October and your support for the work that has to be carried out in the future so that this unique project can continue in the spirit started by Lennart Hammarström and Bodo Grimbacher.

Gerhard KINDLE

Education

Under the leadership of Helen Chapel and Anders Fasth, ESID has developed an innovative and exciting series of training initiatives which have received much positive feedback from trainees. In particular the biennial Summer Schools, together with the training sessions at the ESID meetings have been most successful. I would be honoured to be elected to the Chairmanship of the Educational Working Party and would do my utmost to further develop this important part of the life and work of ESID.

For those who don't know me, perhaps I should introduce myself? I became interested in immunology over 30 years ago when I spent a year studying this "new" subject as part of an optional year in the middle of my medical studies. After working in internal medicine and infectious diseases, I "crossed the floor" to paediatrics and held an MRC research fellowship studying the immunology of infant feeding. I then trained in immunodeficiency in London (and for a short time in Paris) before moving to Newcastle 16 years ago to set up one of the UK's 2 national centres that treat children with complex problems of immunology and infection. We now have a team of 7 specialists and 5 trainees, seeing 500 patients a year, carrying out 35 HSCTs a year, as well as having wide ranging research and teaching programmes. Usually 2 to 3 visiting fellows are

also attached to our unit.

I have been an active member of ESID since 1990 and served as Chairman of the BMT Working Party from 2000 to 2004. I was Chairman of the UK's Paediatric Immunology and Infectious Diseases Training Committee from 1999 to 2006, successfully devising and implementing a national training programme for training and accreditation in the subspecialty. Since 2000, I have represented ESPID and ESID at the Paediatric Section of the European Medical Union, and by 2004 successfully negotiated acceptance of a modular system for training for paediatric immunology. I am also active at training days and summer schools across Europe, the Far East and North America.

The current ESID Summer School core team (Anders Fasth, Teresa Espanol, Esther de Vries) work very well, and I am sure we should continue to support and encourage their excellent work. At the same time there should be opportunities for new initiatives linking up with work already in progress in Eastern Europe and Latin America. We could also explore ways of better encouraging and supporting trainees to spend periods in other units in Europe, for either research or clinical training fellowships. With the newly approved Europe-wide immunology module programme, we should now be able to do this much more effectively.

I very much look forward to further participating in this aspect of the life and work of our excellent Society and hope you will elect me in Budapest in October!

Andrew CANT

ESID*juniors*

I am Eleonora Gambineri from Florence, Italy. I want to candidate for the junior ESID Chair in Budapest this fall. I would like to take this opportunity to introduce myself for those who don't know me. I've received my medical training at the University of Florence, and my research fellowship at the University of Washington under Professor Hans Ochs. Currently, I'm a junior faculty member of the Department of Pediatrics at the University of Florence, "Anna Meyer" Children's Hospital. I have been part of the ESID*juniors* since the very beginning. During the wonderful experience of the Summer School in Faro, Portugal, together with Chris, Ellen, Pavel, Jana, Manfred, but most of all Pim, the idea of the Junior WP was born. We all learned a lot from the lectures, but more importantly through the stimulating discussions over many topics, exchanging ideas, doubts, and questions. We learned to face problems arising from clinical cases and to interact with each other to solve them. The main goal of the ESID*juniors* was to keep the spirit of the Summer School and to have the possibility of staying in touch with other juniors as well as seniors who are involved in the field of Primary Immunodeficiencies. Pim put a lot of effort in initiating to establish the WP, and we all thank him for the great job he's done to keep the network together. Now that more people are interested and the organization is growing, we need to work even harder together to continue to build on the foundation.

These are some of the ideas I would like to propose for the upcoming years:

Setting up a virtual bulletin board where we can post our questions/receive suggestions about clinical issues and/or scientific problems.

Explore the EU funding opportunities for European exchange/collaboration programs applicable to the ESID*juniors*.

Short-term exchange programs for visiting scholars from the member countries (e.g. to learn diagnostic and/or research techniques, or to attend particular clinical procedures).

Solidify our network and foster the exchange of ideas through an annual retreat (2-3 days) with faculty and Summer School attendees.

Last, but not least, to further define the organizational structure of the ESID *juniors*.

I hope these topics will stimulate interesting discussions at the upcoming ESID meeting in Budapest. I am looking forward to meeting you all there!

Eleonora GAMBINERI

Genetics

VACANCY !! So please, send in your candidature, if you are interested in becoming head of the Genetics Working Party of ESID. For more information, please contact the present Head of the Genetics Working Party Anna Villa from Milan at anna.villa @ itb.cnr.it . **VACANCY !!**

If you want to put yourself forward **as another possible candidate** for one of the posts mentioned above, feel free to do so, but let us know **before July 1 (!)** by sending an email with your proposal and a picture of yourself to Esther de Vries (esid@estherdevries.nl) so that your candidature can be published in the next issue of the ESID Newsletter, in due time for the elections during the General Assembly in Budapest in October.

Budapest

Interesting papers

Chronic granulomatous disease

The team of Steven Holland from the NIH has identified a novel gram-negative rod in relapsing lymphadenitis of a patient with gp91 phox deficiency. They demonstrated the pathogenicity of this new micro-organism by using a murine model of CGD. You can read about this in: Greenberg DE, Ding L, Zelazny AM, Stock F, Wong A, Anderson VL, Miller G, Kleiner DE, Tenorio AR, Brinster L, Dorward DW, Murray PR, Holland SM. A Novel Bacterium Associated with Lymphadenitis in a Patient with Chronic Granulomatous Disease. PLoS Pathog. 2006 Apr 14;2(4):e28.

Gene therapy of CGD

You can read about the first description of gene therapy of CGD by using retroviral mediated gene transfer, associated to a myeloablative conditioning regimen, in two adults with GP91phox mutations in: Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M. Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med. 2006 Apr;12(4):401-9.

SCT in hemophagocytic lymphohisticytosis

A report of hematopoietic stem cell transplantation in 48 patients from a single center with hemophagocytic lymphohisticytosis of various origin demonstrated that the survival was 58%, and that active disease and haploidentical transplantation are associated with poorer outcome due to graft loss. Neurological involvement, if present at the time of the procedure, rarely persist in the years following the transplantation. Ouachee-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, Neven B, Casanova JL, Tardieu M, Cavazzana-Calvo M, Blanche S, Fischer A. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics. 2006 Apr;117(4):e743-50.

CD19 deficiency

Homozygous mutations in CD19 lead to CD19 deficiency in 3 patients from 2 unrelated kindreds with CVID features and first infectious episodes during childhood : a new genetic explanation for the CVID syndrome. Read about this in: van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med. 2006 May 4;354(18):1901-12.

Locus identification for AD-CVID

A new locus identification for autosomic dominant CVID. Described by: Finck A, Van der Meer JW, Schaffer AA, Pfannstiel J, Fieschi C, Plebani A, Webster AD, Hammarstrom L, Grimbacher B. Linkage of autosomal-dominant common variable immunodeficiency to chromosome 4q. Eur J Hum Genet. 2006 Apr 26.

Mutations in the gene encoding CD3z

Germinal and somatic mutations in the gene encoding CD3z coexist in a child and lead to a T-B+ SCID phenotype. You can find this in: Rieux-Laucat F, Hivroz C, Lim A, Mateo V, Pellier I, Selz F, Fischer A, Le Deist F. Inherited and somatic CD3zeta mutations in a patient with T-cell deficiency. N Engl J Med. 2006 May 4;354(18):1913-21.

Claire FIESCHI

Budapest Meeting

Dear ESID member,

Please visit www.ESID2006.com !

On behalf of the ESID Board and the Scientific Committee, I invite you again to attend the XIIth Meeting of the European Society for Immunodeficiencies which will be held in the renovated Novotel Budapest Congress Centre, in the beautiful city of Budapest, Hungary, on 4-7 October, 2006. The preliminary scientific program has been set, and it includes keynote talks and invited presentations on, among others, the clinical and genetic aspects of innate immunodeficiencies, defects of T- and B-cell development, bone marrow failure syndromes, and gene therapy. Interactive workshop sessions will be organized to discuss infections in PID patients, immunoglobulin replacement therapy, and long-term outcome of stem cell transplantations. To facilitate active participation of the broad membership of ESID as well as non-ESID members from various fields of clinical immunology, poster sessions will be an integral part of the scientific program. According to our tradition, an Educational Day will precede the two and a half day Meeting. This time the subject of the Educational Day will be the development and defects of B-cells.

The deadline for submission of abstracts is June 1. All contributions will be evaluated by the Scientific Committee and recommended for either an oral or poster presentation during the main program. Because of the busy schedule, the Meeting will also include lunch symposia. During these symposia you will have the opportunity to exchange views on topics such as the current status of the ESID Registry and an update on the ESID Website.

I hope that the preliminary program of the Meeting that you can see on the web (www.ESID2006.com) is inspiring, and that you will join us to make another successful ESID Meeting together. Your participation is critical for the success of this Meeting, and therefore I encourage you to send your abstracts and case reports, and call the attention of your colleagues and collaborators to this important scientific and professional event.

I look forward to seeing you in Budapest!

Sincerely,

László MARÓDI, Congress President.

Working Party reports

Registries WP

Personal thanks and report from the Head of the Registry Working Party:

Dear all, in 2002 in Weimar, I was elected to host the ESID patient registry, following Lennart Hammarström who has set up the first European PID registry starting in 1992 and who collected more than 10,000 patients! At that time, my tasks were i) to include data from the new EU members of Eastern Europe, and ii) to obtain clinical update information on the existing patients.

So, my first decision was to change the paper-based one-time registration and to switch to an online-based registration with easy follow-up data collection. It took us less then 2 years to set up a productive online system and I am specially thankful to Dominic Veit, the computer wizard who basically did all the IT part of it. I am also grateful to Barbara Frisch, who during this time was a big help for me to get the project of the ground. Both are financed by a generous grant from PPTA to ESID. Barbara has been replaced by Viviane, and since the project has been also included into the 6th framework of the EU, thanks to Edvard Smith, we have an additional programmer, Dr. Gerhard Kindle (he is a physician and IT programmer), and an additional database manager, Benjamin Gathmann, working for ESID. Since I now served for 4 years, I cannot be re-elected, but Gerhard from the Freiburg IT group will run for the post to follow me as head of the registry. I strongly support his candidature, since this new online project needs continuity during its first years of its being implemented very much.

The latest development was that the USIDnet was also interested in obtaining an online patient registry, and they decided in 2005 that they would like to adopt the ESID system for their needs. However, since it turned out that USIDnet wanted to create their own dataset, we needed to hire an additional programmer, David Guzman from Chile, who also is our link to LAGID, since David agreed to also set up the online registry in Chile and in other Latin American countries if requested. During the last months, we received requests from Canada, Japan and other non-European countries to evaluate our online system, so that we (ESID) are looking forward to providing a world-wide platform for the registration of PID patients in the not to far future.

The whole issue of a close collaboration with ESID and other non-European organizations created the need for ESID to finally make up Articles that will be passed by a lawyer. Until now, we were a Society (since Sitges), but only had a Constitution. This all initiated the very important discussions we will have during the General Assembly in Budapest about the future of our Society.

In addition, I took the task to revitalize the ESID website which is now run by a modern content management system and provides lots of new useful information. In the next 4 years, I would especially like to see a lively ESID community, with lots of hits to our website, with an active online discussion forum which we now have, and with lots of research protocols being shared!

Yours, Bodo GRIMBACHER.

The ESID Mutation Browser

The ESID Mutation Browser is an additional multicomponent feature included in the ESID Online Registry for the deposition of mutation data in subregistries where the genetic cause of the disease is known. Since 1994, the IMT Bioinformatics at the University of Tampere, Finland, headed by prof. Mauno Vihinen, maintains databases for mutations which can cause immunodeficiencies. All

mutations which are responsible for a PID are stored, however, without the clinical data. The ESID Mutation Browser will store validated mutation data from the different subregistries which are linked with the entry forms of IMT Mutation databases in Tampere, Finland.

The Mutation Browser has three components: The first is the AddOn component which oies inside the ESID Registry in Freiburg, working as a submission module for entry of the data into the system and redirecting the user to the IDbases Database in the Institute of Medical Technology at the University of Tampere. On the Finnish side, which plays the second role in the tool, the mutation information is deposited and validated with bioinformatics tools and automatically submitted back to Freiburg to the ESID Mutation Web Service, the last component. This receives the validated data, matches it with the patient and deposits the data. Then, the AddOn component displays the validated data through the ESID Online Registry as usual. The start and end point of the Mutation Browser is the respective module in the subregistries where it is available.

The transmission of data between Freiburg and Finland is SSL encrypted (secure connection). No personal data is exchanged, i.e. the data received in Finland is anonymous. The Tool suport is planned to be extended to approximately 90 subregistries.

Contact: registry @ esid.org .

Personalised data

In addition to the coded system, the ESID Online Database now offers the possibility to work with personalised data. This has been requested by many users since it makes working with the database much more comfortable. It is now possible to see the patient's name, address, etc. while entering data and thus the ESID database comes close to an electronic patient chart for your centre.

The new system has been developed by our programmers in Freiburg, according to an accepted data protection concept for medical research networks, and is based on a multi-server-solution. This means that data is stored on several servers. One server keeps the identifying data, the other stores diagnostic data and lab values. Only by entering the correct password, the information from both servers will be combined through a third so-called Gateway-server and the physician can see the whole patient data on his screen (Figure on next page).

This concept guarantees data security on the one hand and complies with the requirements of a modern research platform. However, the coded version will still remain available for those who want to stick to the established system.

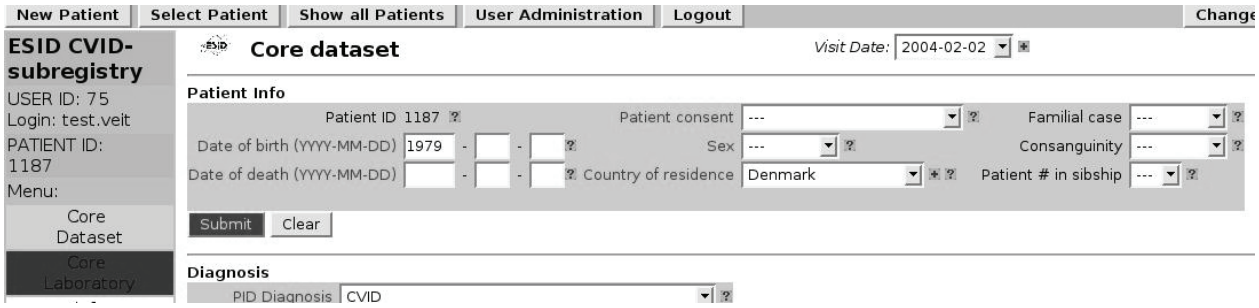
You can find an application form to switch to the personalised version of the ESID Online Registry for existing documenting centres in this issue of the ESID Newsletter. Please send the form to Freiburg if you want to start using the personalised version!

If your centre is not yet documenting patients in the ESID Online Registry, please feel free to contact us for information.

Don't forget about your data in the ESID database: go to the website and correct them if necessary.

See also page 5 !!

coded version



personalised version

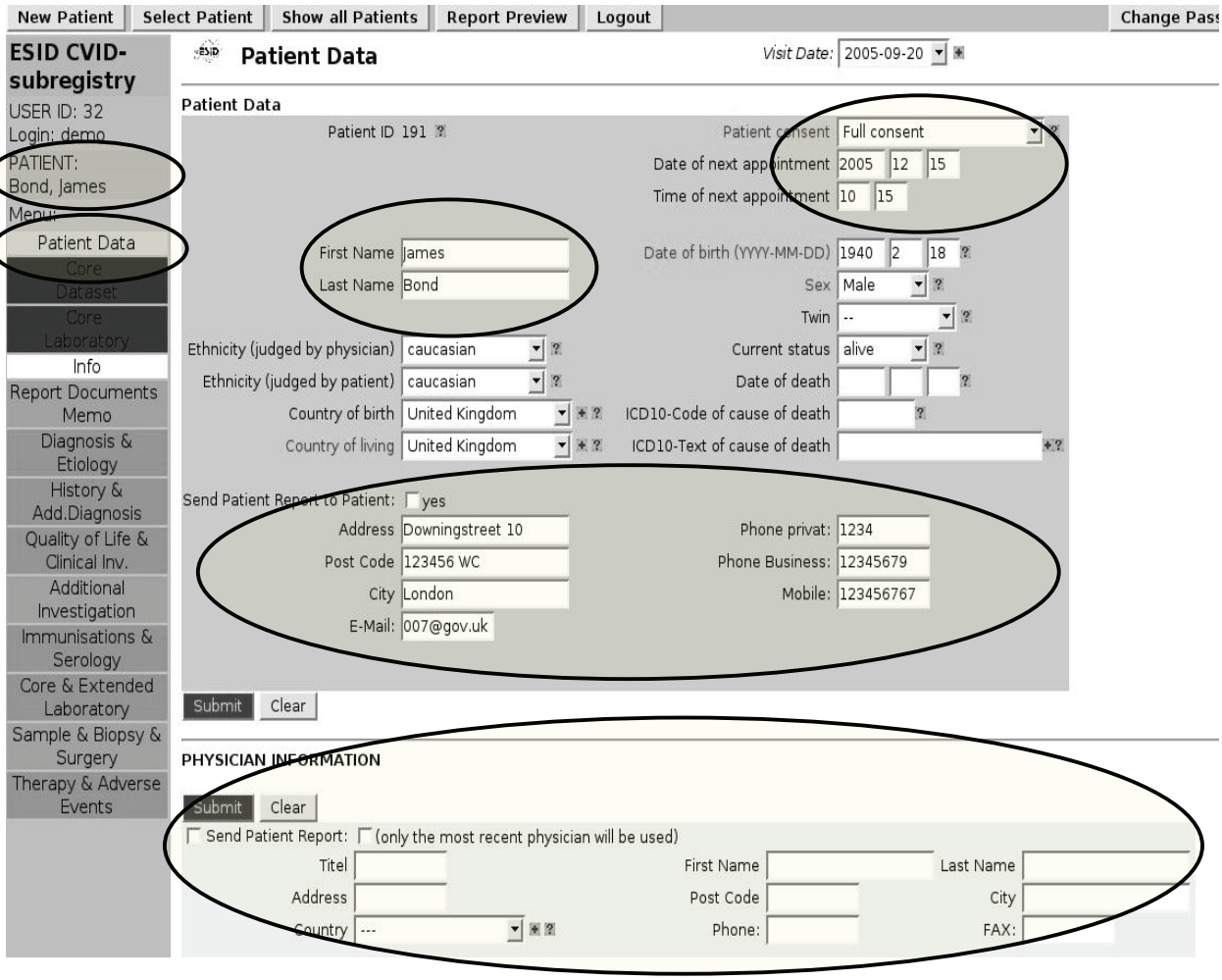


Figure: Personalized data are possible, but not obligatory.

Application for the switch to the personalised version of the ESID Online Registry for existing documenting centres

In addition to the already established coded version of the online database, ESID has set up a new version which allows the documentation of patients with personal data. This new version stores the personal data on a separate server and keeps the PID-related data on a second server. The information from both servers can only be combined via a third gateway-server, which requires a user name and password. Data protection is thus guaranteed. This solution has already been published by Reng CM et al [1] and been implemented in other patient registries (e.g. https://clearinghouse.uni-muenster.de/, http://www.akteonline.de/).

The coded version of the ESID Online Database will continue to be available.

If you wish to switch to the personalised version of the ESID Online Database, please send this form by fax to +49 (0)761 270 3531.

The activation takes place in Freiburg. The Documenting Centre will not have any disadvantages due to technical changes. We will inform you as soon as the personalised version is activated for your documenting centre. All users in your centre (and only those) will then be able to see additional personalised fields in all datasets. Personal information of patients can be added there.

The terms and conditions of the previously signed agreement with ESID remain valid. You should inform your data protection and ethics authorities about this change. See this document for details: [ref] Comp. Reng, CM et al: Akzeptiertes Datenschutzkonzept, Dtsch Arztebl 2003; 100: A 2134–2137 [Heft 33].

I hereby apply for the personalised version of the ESID Online Database. Please convert my system to the new version.

Name of the Documenting Centre : ……

Name of Director + Title : ……

E-Mail : ……

……

Place, Date Signature of the Director of the Documenting Centre

Please send the signed application form to:

Dr. Bodo Grimbacher
Department of Rheumatology and Clinical Immunology
Albert-Ludwigs-Universität Freiburg, Medical Centre
Hugstetter Straße 55, 79106 Freiburg, Germany
or by fax to +49 (0) 761 270 3531

Agreement between the European Society for Immunodeficiencies (ESID) and a Documenting Centere regarding the ESID Online Registry

Name of the Documenting Centre

Department

Address

Name of Director + Title

Phone number(s)

Fax number

E-Mail

ESID has set up an online database system for research purposes for the collection and exchange of data of patients with primary immune deficiency diseases ("PID"). The design, realisation and maintenance of the aforesaid online database ("ESID Online Database") will be financially supported by sponsors who will have a specifically defined access to a clearly defined subset of data within the ESID Online Database ("Red Fields") for defined purposes only. The Documenting Centre intends to participate in the ESID Online Database system by providing coded data of patients with PID and by receiving a right of access to the ESID Online Database.

By signing the present application form, I agree to the following terms and conditions

ESID will pay to the Documenting Centre a compensation of EUR 10 for the provision of each patient's data who in which at least completes a core dataset as predetermined by the "Red Fields" of the ESID Online Database has been completed (provided the Documenting Centre has complied with all applicable data protection regulations) by June 30th of each year. The accumulated compensation is due on September, 15th of each year.

The Documenting Centre shall be and remain the owner of any data it has provided to the ESID Online Database. ESID shall be entitled to make available the "Red Field"-data to the sponsors of the ESID Online Registry for the following purposes: to enable genetic and therapeutic research across different authorised users; for genetic and therapeutic trials; for the treatment and care of patients; for the development and improvement of medication; for evaluations of epidemiologists. The receiving parties of such data ensure to use the data for internal use only, unless they have obtained the prior written consent from ESID to publish them or to use them for publication.
The Documenting Centre retains the right to define the access of other ESID Centres, PID researchers or epidemiologists to its data. These other participating documenting centres or researchers shall only have access to the data provided by the Documenting Centre if the

enquiring documenting centre submits to ESID a respective application in writing, and if the Documenting Centre gives its written consent. Unless otherwise specified, the authorised documenting centre shall be entitled to use the data provided by the Documenting Centre to the same extent and for the same purposes as the sponsors of ESID.
ESID shall ensure that the sponsors obtain access to the ESID Online Database only for the purposes as stipulated hereunder and that the access granted to other documenting centres corresponds to the written consent given by the Documenting Centre. Moreover, ESID shall obligate all authorised users of the ESID Online Registry not to disclose the data of such database to any unauthorised third party.

The Documenting Centre ensures to observe the European data protection regulations as well as the data protection regulations applicable at its location.
In particular, the Documenting Centre shall procure the necessary informed consent of the patients regarding the use of the data as stipulated hereunder. The Documenting Centre acknowledges that it is responsible to ensure the observance of local data protection regulations on an organisational as well as on a technical level, particularly with regard to confidentiality, integrity, availability, authenticity and reliability of the collected data.

ESID is responsible for implementing the technical and organisational measures required to ensure the highest level of security for the storage and processing of the data. The relevant technical information and the standard operating procedures (SOP) are available in the brochure "The ESID Online-Database.

The use by the Documenting Centre of data provided by other documenting centres is restricted to the purpose as agreed with the respective other documenting centre. Publications regarding the ESID Online Database require the prior written consent of ESID. ESID shall not unreasonably withhoeld this consent. Any publications approved by ESID have to be in accordance with the ICMJE guidelines (International Committee of Medical Journal Editors; www.icmje.org/index.html).

The Documenting Centre may register different persons of its organisation as users of the ESID Online Database by submitting a written application to ESID (see application form). Each of these users shall receive from ESID a user name and a password. The password shall enable the registration of data within the ESID Online Database, access to the provided data, and extended access to data of other documenting centres, if this has been agreed between the Documenting Centre and the documenting centres that ownsown the data.

The Documenting Centre shall guarantee that the user names and passwords are treated absolutely confidentially and are not used for any other purposes than those defined herein. The Documenting Centre shall immediately inform ESID about any unauthorised disclosure of the user names and / or passwords of the users of its organisation as well as about the expiry of the right of single users within its organisation to use the ESID Online Database. The Documenting Centre shall be responsible for the observance of all terms and conditions hereunder by all users of the ESID Online Database within the Documenting Centre's organisation.

With the ESID Online Database ESID only offers a forum for data collection and/or data exchange and does not assume any liability for the following: the efficient functionality and usability of the ESID Online Database, the integrity and/or usability of the data therein or

the grant of access rights to third parties.

The Documenting Centre shall choose between two database versions:

a. **Coded Patient database:** Each new patient entry automatically receives an identification number (ID) from the system which has to be recorded in a separate list by the documenting centre. This patient ID key has to be kept secure and is the responsibility of the documenting centre.

b. **Personalised Patient database:** Here personal patient data can be used. Personal data and disease-specific data are stored on two separate servers. The information from both servers is combined via a gateway server for users of the documenting centre when they log in with their username and password. If another centre has been granted access to a subset of data from that centre (see point 2), this data will only be available in coded form as in point 8a. Data security is guaranteed.

Both parties may terminate this agreement by giving one month's prior written notice to the other party. The Documenting Centre acknowledges that after the termination of this agreement ESID shall on the conditions as stipulated hereunder be entitled to continue to use the data which have been provided to the ESID Online Database until before the date of termination.

This agreement shall be governed by German law. Landgericht (District Court) Freiburg, Germany, shall be the exclusive place of venue for all disputes arising out of or in connection with the present agreement.

□ This documenting centre requests the coded version of the ESID Online Database, as described in point 9a.

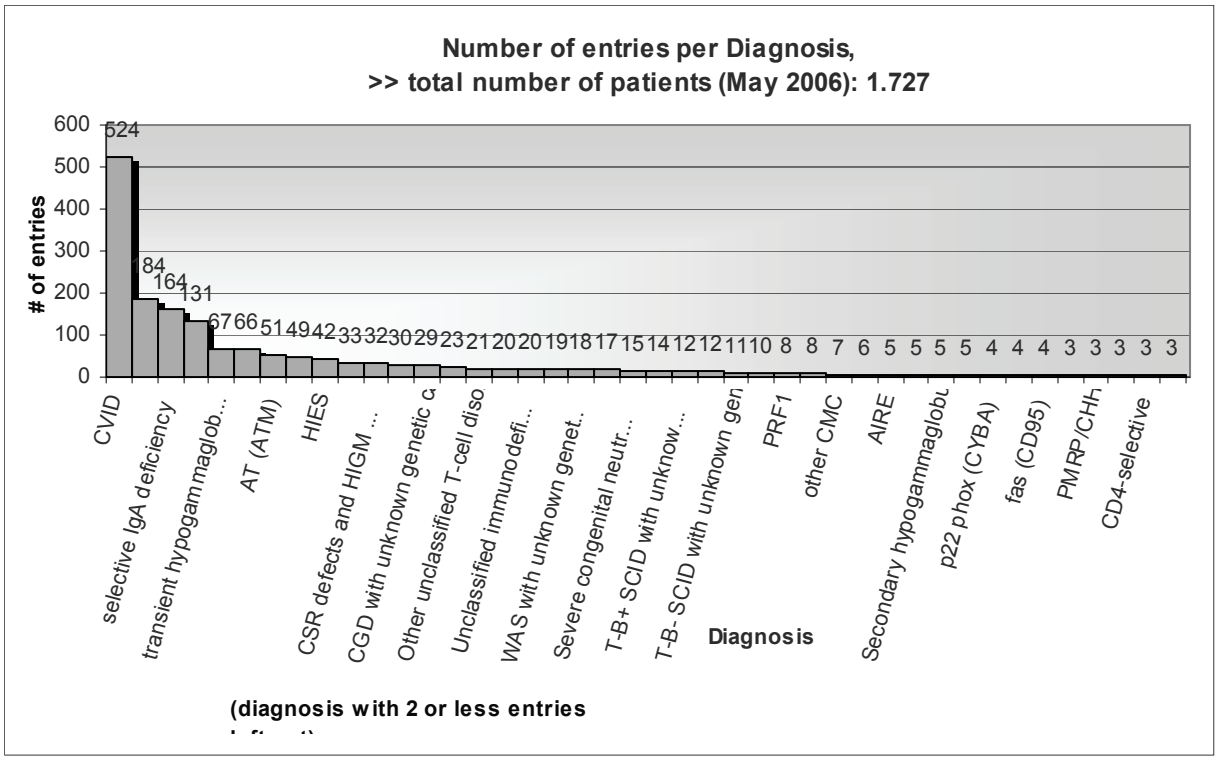
□ This documenting centre requests the personalised version of the ESID Online Database, as described in point 9b.

(Please tick one option)

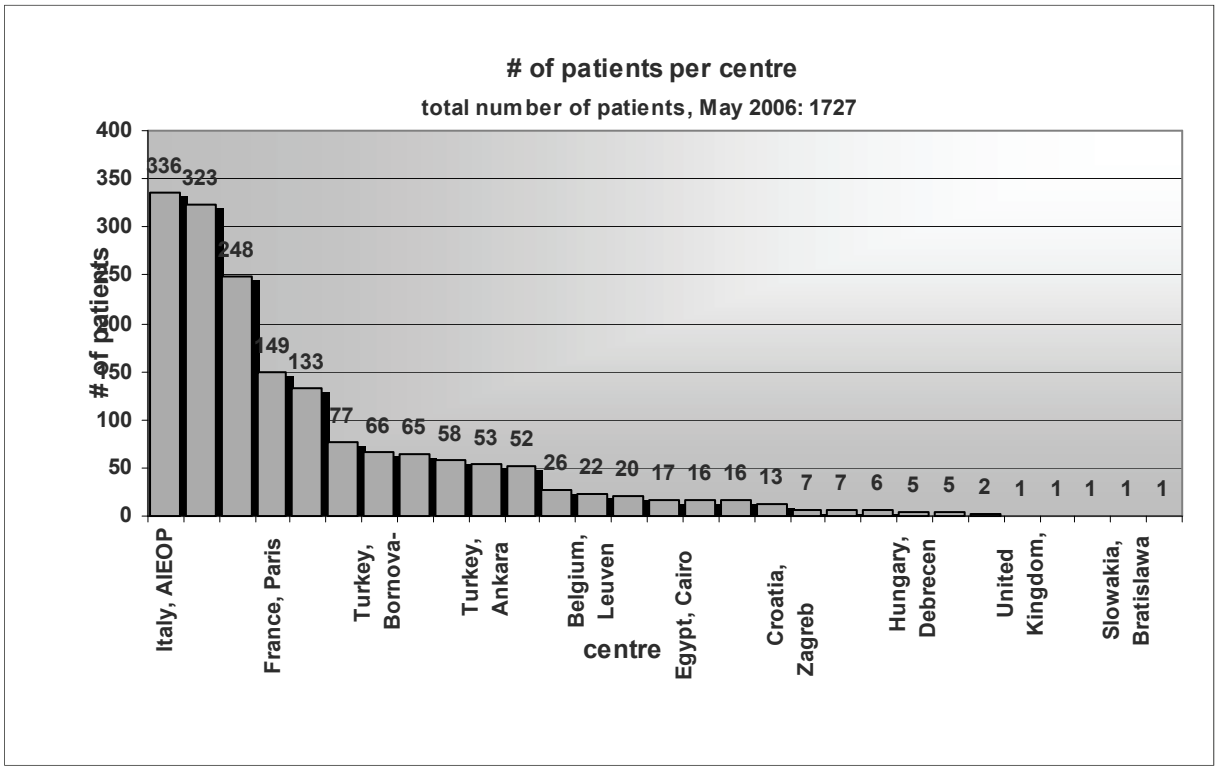
Place, Date …… ……..
Signature of the Director of the Documenting Centre

Place, Date …… ……..
Bodo Grimbacher, Head of ESID registry

Please send the signed application form to:
Head: Dr. Bodo Grimbacher
Department of Rheumatology and Clinical Immunology
Albert-Ludwigs-Universität Freiburg, Medical Centre
Hugstetter Straße 55, 79106 Freiburg, Germany



ESID Online Registry



Genetics WP

Dear Friends and Colleagues,

During the next ESID meeting, we will see the renewal of heads of several Working Parties. So far, I have not received any application for the ESID Genetics Working Party position, which I am going to leave. I kindly ask if anyone is interested in this position to contact one of the Board members !

Before leaving, I would like to inform you about the new retrospective study on Bone marrow transplant Outcome in Osteopetrotic patients. This study will be performed on behalf of the Inborn Error Group of EBMT, and Genetic Working Party of ESID, and it was announced during the last EBMT meeting held in Hamburg last March.

The Members who will be in charge of the study coordination based on the decisions taken during the Hamburg Meeting are the following:

- for the clinical analysis : A. Schultz (Ulm) and Chiara Messina (Italy),
- for the cord blood data : M. Bierings (Utrecht),
- and for the genetic analysis : A. Villa (Milan).

We have prepared a questionnaire, which was already published in the ESID Newsletter. In case some of you are interested in joining our study, please contact us.

Finally, I would like to inform people who are interested in revertant mutations in primary immunodeficiency, such as Wiskott Aldrich, ADA and Omenn syndrome, that David Nelson and Fabio Candotti are preparing a workshop dedicated to this issue. Revertant mosaicism acquires a particular clinical relevance as this mechanism may lead to selective growth advantage of the corrected cells and improvments of the disease symptoms.

The aim of the workshop is to gather groups who have observed these cases, in order to understand 1) What is the incidence of these reversions 2) What sort of mutations are being reverted and by which process/ mechanism 3) What are the cell lineages reverted and 4) What are the clinical characteristics of patients who revert.

If anyone is interested, please submit a small abstract or contact us at the following email addresses: anna.villa@itb.cnr.it , or fabio@mail.nih.gov .

Anna VILLA

Clinical WP

Diagnostic criteria for IPEX

IPEX Syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy X-linked Syndrome): Clinical and molecular diagnostic criteria.

Definitive

Male patient < 1 year of age or older at the time symptoms developed, affected by at least one of the following clinical features:

Enteropathy (non-infectious severe watery diarrhea)

Type I Diabetes and/or thyroiditis

Eczema-like skin disease or erythema or psoriasiform lesions

Cytopenias (autoimmune hemolytic anemia or thrombocytopenia or neutropenia

These symptoms are associated with at least one of the following:

Mutation in the FOXP3 gene

Absent FOXP3 mRNA expression by real-time quantitative PCR analysis of lymphocytes and absence of FOXP3 protein in lymphocytes (e.g. lack of CD4+CD25+FOXP3+ regulatory T cells

Maternal uncles or cousins affected by similar clinical phenotype

Probable

Male patient with symptoms appearing at < 1 year of age or later, affected by at least two of the following clinical features:

Enteropathy (non-infectious severe watery diarrhea)

Type I Diabetes and or thyroiditis

Eczema-like skin disease or erythema or psoriasiform lesions

These symptoms are associated with at least one of the following:

Low FOXP3 mRNA expression by real-time quantitative PCR analysis of lymphocytes

Low FOXP3 protein levels in lymphocytes (e.g. lack or very low numbers of CD4+CD25+FOXP3+ regulatory T cells).

Possible

Male patient with symptoms appearing < 1 year of age or later, affected by severe enterophathy often associated with one of the following:

Dermatitis (most commonly eczema, but also erythroderma, psoriasiform lesions, and alopecia)

Endocrinopathy (type I diabetes and/ or thyroiditis)

Autoimmune diseases (especially haematological, renal, hepatic)

Spectrum of disease

The clinical triad of enteropathy, endocrine abnormalities and dermatitis, is the typical diagnostic hallmark of IPEX. Patients commonly present with watery or bloody diarrhea (most frequently associated with villous atrophy on biopsy), insulin dependent diabetes mellitus, and eczema. Other autoimmune manifestations such as thyroditis, hemolytic anemia, thrombocytopenia, neutropenia, nephropathy and hepatitis are described less consistently and can occur over time. In the majority of the cases, affected males develop symptoms early in infancy. Patients with later onset or milder phenotype, not readily recognized as IPEX, have also been described. Most affected males die prematurely of either metabolic alterations due to intractable diarrhea, or severe infections, which occurs prior to the initiation of immune suppressive treatment. Laboratory findings are not well correlated with the syndrome. Elevated IgE levels appear to be an important feature reported in the majority of patients; persistent or periodic eosinophilia is also a common finding. Patients presenting with a clinical phenotype suggestive of IPEX but without an identifiable mutation within the FOXP3 gene are considered "IPEX-like" and may have a different molecular defect.

Please give us your comments on these criteria for IPEX at h.gaspar@ich.ucl.ac.uk !

Education WP

Talecris travel grants

With the help of Helen Chapel, we have received money to issue travel grants to young PID investigators to go to important meetings. For the the CIS PID Consortium at the 6th FOCIS Annual Meeting on Thursday, June 1, 2006 in San Francisco, we have given grants to Eleonora Gambineri from the University of Florence in Italy, to Jennifer Birmelin from the University Hospital Freiburg in Germany, and to Sigune Goldacker, from the Medizinische Klinik in Freiburg, Germany. There is some money left still to issue a travel grant to young PID investigators for future meetings.

Repeated message - travel grants

Travel grants for Budapest

The Educational WP offers two travel grants for two doctors/scientists (not students) from outside Europe to attend the ESID biennial meeting in Budapest, October 2006. The grants include travel in economy, meeting fee and hotel. The application should be a personal letter that outlines the applicant's interest and work with PID, and any other available funds for participation in the ESID meeting. Please, include CV, publication list and letter of support from superior or tutor with the application. The application deadline is July 1st 2006. Please send the application, preferably by email with scanned documents, to Anders Fasth at anders.fasth@pediat.gu.se.

Young Investigators Award

At the recent Board meeting the ESID Board decided to announce, also this year, a Young Investigators Award. 10,000 euro will be awarded to a young doctor or scientist that would like to pursue research training during at least 6 months at an institution within Europe. The application should include a personal letter (preferably by email) sent to Anders Fasth depicting her/his background training, interest in PID, the goal with the training and future career goals. To the application should be added CV, publication list, and project plan for the intended research to be done, letter of support from sending institution and letter of support from receiving institution.

Deadline is July 1, 2006.

The application will be reviewed by members of the ESID Board and the recipient of the award will be announced at the ESID biennial meeting in Budapest.

Please, send the application to Anders Fasth, if possible as an e-mail with attachments at anders.fasth@pediat.gu.se.

Repeated message - Young Investigators Award