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.

Editor's address:

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Dear ESID members,

Soon, we will see each other in Versailles! Undoubtedly, this Meeting will again be a fruitful one, scientifically and socially. We hope as many of you as possible will attend.

It has been some years now, probably, that you are a member of ESID. Have you ever thought about becoming part of the Board? This is your chance! Elections are coming up, and we ask you to think about candidates for Board positions: yourself, others … Please let us know if you are interested, or know someone who might be! (see page 8)

More and more members send me bits of information or their opinion on ESID-related subjects for the *News & Views* section. Please feel free to do so as well! Photographs of ESID-related activities are also very welcome.

In this issue, you will find an update on CVID in the *Invited Review* by Ulrich Salzer and Bodo Grimbacher.

In an interview with Andrew Cant as Established Member and Andy Gennery as Young Investigator you will be able to *Focus on a country*, by hearing some ins and outs of immunology in the United Kingdom this time!

Best wishes for the summer,

Esther DE VRIES, Editor

P.S. Do contact me at esther_de_vries_nl@yahoo.co.uk about anything you think is of interest for the ESID community that could be published in the ESID Newsletter.

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: Andrew Cant), Pathology (chair Fabio Facchetti), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Jean-Laurent Casanova), Genetics (chair: Anna Villa), and Education (chair: Anders Fasth). 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 2002 in Weimar, Germany; the next congress will be organized in Versailles, France in October 2004, and the one after that will be in Hungary, in 2006.

= ESID Information =

President's letter

Welcome to Versailles!

Dear friends and colleagues! The long-awaited moment is approaching! We are only three months from the ESID Meeting in Versailles. The program has been finalized, and the organization committee is doing its best to make this another successful meeting in the history of ESID.

The ESID Board met recently to discuss the program in detail. We all agreed that we would like to give as much time as possible to selected contributions. Therefore, you are all invited to send your best data!

Also, we very much look forward to the Educational Day, that – similar to Weimar – will take place the morning before the official opening of the Meeting itself.

Two years ago, we were pleased to see how much (even, too much, indeed!) the Educational Day was appreciated, and for this reason Alain Fischer and Anders Fasth have done their best to organize the symposium in order to make a large participation possible.

But, there is more than Science and Education to be discussed in Versailles! We will be called to vote several times. First of all, several positions in the ESID Board are now open for candidatures (for further details, see alongside and page 8). Among them, and importantly, we will also vote for the next President-Elect.

These are indeed "political" elections, in the sense that the Board has the great responsibility to plan for the future and drive the activity of our Society. As such, these elections are important to all of us. For this reason, it is crucial that candidatures are advanced now. Those of you who would like to propose their names as candidates for the various positions that are open, are kindly requested to send an e-mail to the ESID Secretary (Dr. Hermann Wolff).

The candidatures will be announced through the ESID website, so that the entire ESID community will have the chance to know about this before the ESID Meeting.

In Versailles, we will also have to make a final vote on the location of the ESID 2006 Meeting (for which an option was decided in Weimar for Hungary), and we will discuss about future venues as well.

In addition to Science, Education, and Politics, most of all the Meeting in Versailles will be an opportunity to meet old friends and make new ones. This is just another beauty of being part of our Society!

I very much look forward to meeting you in Versailles!

Luigi D. NOTARANGELO

= CALL FOR CANDIDATES FOR THE ESID BOARD =

We need candidates for several positions in the ESID Board; please feel free to tell us if you are interested!

Elections will take place during the General Assembly in Versailles in October. Candidates will be posted meanwhile on the ESID website.

Please let us know if you are interested by sending an email to our Secretary Herman Wolff at herman.wolf @ itk.at !!

= CALL FOR CANDIDATES FOR THE ESID BOARD =

Secretary's report

The ESID Board met recently (on May 17th, 2004) at Roissy – Charles DeGaulle Airport, Paris, France. The main topic on the agenda was the biennial ESID Meeting taking place in Versailles this autumn, October 21st to 24th, 2004. Alain Fischer, as the president of the organising committee, updated the ESID Board on the latest news. Due to the very professional organisation of the Meeting a relatively late abstract submission deadline (August 15th, 2004) is possible, in order to enable submission of the most recent scientific discoveries. The abstracts submitted will be reviewed by the Scientific Committee and the ESID Board within a very short time, to select the 22 papers that are to be presented as short oral communications. The reviewing process will be online, and the authors of the abstracts will be anonymous to the reviewers. Several thematic subcategories will be covered in the poster workshops, e.g. T- and B-cell immunodeficiency, defects in innate immunity, stem cell and gene therapy, immunoglobulin therapy, genetic counseling, and quality of life. The goal of the scientific program of the Versailles Meeting is to balance reports about basic scientific research with more clinically oriented studies. In addition to the lectures and workshops, an inviting social program is planned, e.g. attendees can use a break during the Meeting to visit the Versailles Castle, and a reunion party of ESID Summer and Spring School participants will take place (those interested in participating should contact Helen Chapel). Further information on the latest program details can be found on the ESID web site.

Once more, it is important to say that the next General Assembly will take place on Friday 22nd October, 2004, in Versailles at the occasion of the biennial ESID Meeting. All ESID members are cordially invited to attend the General Assembly, thereby helping to provide as much input and support for Board decisions and projects as possible. Important decisions are planned for this occasion, e.g. the election of new members to the ESID Board, the creation of new Working Parties, or the conclusion of existing ones. Candidates for the ESID Board should be nominated to the ESID secretary. Among other things, at the next General Assembly a change of the status "emeritus membership" to "honorary membership" will be voted on, and the discussion on the pro´s and con´s regarding the creation of a new Working Party called the ESID*juniors*, which should especially take care of the demands of younger ESID members, will be carried on.

A further topic on the agenda was the report by Bodo Grimbacher about the current status of the new online-version of the ESID patient registry. The parameter fields of the ESID main patient database and the first subregistry undergoing realization (the CVID subregistry) were discussed in depth, and a first version of the database will go online this summer. Teaching courses are planned to answer all questions regarding submission of patient information and how to use the database for queries. A number of additional subregistries are under debate, but their realisation will have to be postponed to the near future. For each subregistry, a Steering Committee has to be formed that decides on the contents of the respective subregistry´s database and which study goals should be pursued by queries of this database. Existing European patient databases should be integrated in these future subregistries wherever possible. The work done by the Freiburg group up to now was ratified by the ESID Board.

Anders Fasth suggested that the Educational Working Party should sponsor travel grants for members from LAGID, the South-American immunodeficiency group, to come to the ESID Meeting, as well as for one ESID member to go the their annual meeting, which was readily approved by the Board; additional travel grants should be made available for selected residents of countries

outside Europe to facilitate communication of ESID with the rest of the world. The ESID Newsletter will continue to be distributed quarterly, and Esther de Vries was praised by the other members of the Board for her successful work as editor of the Newsletter. Andrew Cant reported on the discussion about the accreditation of an EU-wide training program for pediatric immunology, and the input of the ESID Board members was welcomed. Luigi Notarangelo finally told the Board about his visit together with other ESID representatives to the EU parliament, aiming at the future possibility that PID will be more represented among the topics of coming EU framework programs. The ESID Board will further submit a proposition to the WHO to reintroduce immunoglobulins to the list of live-saving drugs.

Hermann WOLF

Treasurer's report

Unfortunately, mistakes were made in cashing the ESID membership fee from some American Express credit card holders, leading to *crediting* instead of *debiting* of their accounts. Although this has been corrected, this has led to a lot of confusion. Apologies, and let's hope it will not happen again!

For a lot of members it is not quite clear how the treasury works. Therefore, we will discuss a few things here that often cause misunderstandings.

First of all, the treasurer takes care (financially) of all regular ESID affairs, but has *nothing* to do (financially) with the biennial congress. For all congress matters, please always contact the congress secretariat!

Also, it happens that credit card companies refuse payment for no reason whatsoever. This cannot be helped. If it happens, the treasurer will have to ask you to again send your details for payment. Quite often, things work out OK then.

To keep costs at a minimum, there is no structural secretarial help for the treasurer! This means that your treasurer normally collects a lot of membership fee reply forms before temporary secretarial help is hired (students mostly) to cash the fees from the credit cards. It is not possible to send faxes, emails, etc. to all of you as soon as your ESID membership fee form is received because of this. We could change this, of course, but this would clearly lead to an increase of the membership fee. But, don't worry, if you sent your membership fee form in time, you can profit from the reduced congress rate in Versailles, no matter at what moment the ESID membership fee was actually cashed from your credit card!

We need your help on the following problem: several members cannot be traced anymore, mail and email are returned to the treasurer as 'unknown', 'moved', etc.

If you know the present address and/or email address of any of the following ESID members, please let us know at esther_de_vries_nl@ yahoo.co.uk:

Joe Unsworth, Sigune Schmidt
Maria dos Santos Guedes
Tuba Turul, Anna Berglof
Mona I Kidon, Antonio Nieto Diaz
Hirokazu Kanegane, Ron S Weening
Mary Ellen Conley, Andresen
Panisi Cristina, Magda Carneiro-Sampaio
RA Good, Kurenko-Deptuch Magdalena
Catharina Schuetz (Will)

It is of course possible that these people have not changed their address, but that a mistake has somehow slipped into the ESID membership database. In any case, please let us know where you / they are!

In this respect, **I ask all ESID members to check their details on the ESID website, including their email address.** If you find something is not correct, **please let us know** at esther_de_vries_nl @ yahoo.co.uk !!

Esther DE VRIES

= CALL FOR CANDIDATES FOR THE ESID BOARD =

Dear ESID members,

You are all cordially invited to apply for a position in the ESID Board! Your candidature will be posted on the ESID website, and elections will take place at the General Assembly in Versailles in October.

These are the positions in the ESID Board and their current status:

Position	*Currently*	*Situation at General Assembly*
President	Luigi Notarangelo	Renewable
President-elect	-	Candidate needed
Past-president	Edvard Smith	Term ended, no candidate needed
Secretary	Herman Wolf	Renewable
Treasurer	Esther de Vries	Term ended, but Board suggests possibility of 4 2-year terms for treasurer to General Assembly, in that case renewable
Congress 2002	Wilhelm Friedrich	Term ended
Congress 2004	Alain Fischer	Term not ended
Congress 2006	-	Laszlo Marodi in principal accepted in Weimar, final election in Versailles is needed
WP juniors	-	Candidate needed if starting this WP (as the Board suggests to do) is agreed upon at General Assembly
WP pathology	Fabio Facchetti	Term ended, Board suggests incorporation in Clinical WP, in that case no new candidate needed
WP BMT	Andrew Cant	Term ended, new candidate needed
WP registries	Bodo Grimbacher	Renewable
WP genetics	Anna Villa	Renewable
WP education	Anders Fasth	Renewable
WP clinical	Jean-Laurent Casanova	Term ended, new candidate needed

= CALL FOR CANDIDATES FOR THE ESID BOARD =

News & Views

The 1st J-Project event organized in Targu Mures, Romania

The first PID awareness event of the J-Project, initiated by the ECE IPI CTR, was organized in Targu Mures, Romania, together with the Romanian Immunodeficiency Working Group. Dr. Csilla Todea of Targu Mures took care of the local organization. She did a wonderful job in putting together the program, inviting doctors from all over Romania and from abroad, and in selecting a great venue for the meeting in the Bod Peter Deaconesses house. The meeting was attended by more than 60 pediatricians interested and/or involved in PID patient care. Doctors from other East-European countries including Ukraine (Dr. Alla Volokha, Kiev), Macedonia (Drs. Sonja Peova and Katarina Stavrik, both from Skopje), Yugoslavia-Monte Negro (Dr. Srdjan Pasic, Belgrade) were also attending. ECE IPI CTR was represented by Prof. Laszlo Marodi and Dr. Melinda Erdos both from Debrecen.

Reports on recent developments and current problems in PID patient care in Romania were presented. There were several, very nicely presented case reports (Drs. J. Z. Ellenes, M. Erdos, G. Miculschi) as well. The Romanian Primary Immunodeficiency Working Group has been established on April 2, 2003, in Oradea. At that time, the number of PID patients registered in the country was very limited. In Targu Mures, less than a year later, Dr. Maria Cucuruz and her colleagues presented 173 patients in the national PID registry! This number showed what an active search for immunodeficient patients has been going on during the past year in Romania. Importantly, most of the patients registered are from Transylvania indicating that professional activity in the field is not balanced yet in the country. From this perspective, it must be emphasized how important it was to have senior pediatricians from the Bucharest area (Prof. Ioan Ghergina) and from Iasi (Prof. Aurica Rugina).

The first steps were taken to organize the Romanian parents group as well. A couple from Targu Mures, parents of a patient with XLA, joined the meeting and appeared to be ready to organize the group. Drs. Todea and Ellenes promised to help with the work. It was proposed to apply for a WIN grant offered specifically for parents groups by the Jeffrey Modell Foundation.

The audience in Targu Mures, Romania

Diagnosis and treatment of PID patients in Romania is inappropriate. There are areas in which diagnostic reagents are available only for 5-6 months of the year, even for screening assays. Only a few patients are on regular IVIG, and bone marrow transplantation as a treatment facility has just become available for pediatric oncology patients only. Therefore, it was offered that:

1) Serum samples for immunochemical analysis (measurement of concentrations of IgG, IgA, IgM, IgE, C3, C4, anti-tetanus antibody, anti-pneumococcus antibody and activity of CH50) should be sent to Debrecen to ECE IPI CTR which will cover the expenses until the limitation of its budget.
2) Six young doctors from different areas of the country should become member of ESID. The membership fees for two years will be covered by ECE IPI CTR.
3) ECE IPI CTR will organize laboratory training for a small group of Romanian colleagues in Debrecen.
4) It was proposed to target health authorities in Romania in order to improve the availability of treatment.

5) It was suggested to send an abstract describing Romanian PID registry to the coming ESID meeting in Versailles and to apply for travel grants from the organizers.
6) Finally, everyone was encouraged to attend to the next J project events in Prague (May) and in Belgrade (June).

The Meeting was supported by Biotest and Baxter companies, and an EU grant (EURO PID NAS).

László MARÓDI

The J-Project: 4th meeting of awareness in PID, Mother and Child Health Institute, Belgrade, Serbia and Montenegro

The 4th meeting of the Central East European initiative of awareness in PID, the„ J-Project, took place at the Mother and Child Health Institute, Belgrade, Serbia and Montenegro on the 12th of June, 2004. An introductory lecture about Central East European perspectives in PID was given by professor Laszlo Marodi, Debrecen, Hungary. Antibody deficiency syndromes in Serbia and Montenegro were presented by dr Srdjan Pasic and dr Predrag Minic, Mother and Child Health Institute, Belgrade, while dr Dragana Janic, University Children Clinic, Belgrade, presented a group of patients with presumed or proven PID. Our invited guests were dr Malgorzata Pac, Warsaw, Poland, who gave a lecture about the Polish registry of DNA breakage syndromes, and prof Alla Volokha from Kiev, Ukraine, who presented an increasing number of patients with recognized PID in Ukraine. The other participants from regional centers in Hungary, Serbia and Macedonia were dr Melinda Erdos, dr Jelena Tomic, dr Milos Kuzmanovic and prof Sonja Peova, who presented case reports of patients affected with PID.

This one-day meeting was important for making contact among physicians who are engaged in diagnostics and care of PID patients. The participants also agreed that existing hospital registries of PID patients will be updated and the data should be joined together into a national registry.

Srdjan PASIC

The 3rd ESID Prague Spring Meeting, May 10-11, 2004, Institute of Immunology, 2nd Medical School, Charles University, Prague

On May 10 and 11, 2004, the third ESID Prague Spring Meeting was held in the University Hospital Motol, Prague. This year, 35 participants from 10 countries, namely Czech Republic, Germany, Hungary, Italy, Lithuania, Slovakia, Slovenia, Romania, Russia and USA, attended and actively participated in the event. The mean age of the participants was 36 years (with a range from 26 to 68), thus demonstrating the continuous exchange of knowledge between the generations among immunologists in Eastern European countries.

The third ESID Prague Spring Meeting was part of the J-project, a coordinated activity of Eastern European countries, represented by a chain of successive meetings in these countries, with the aim to increase the information about PID in Eastern Europe.

The main task of the Prague ESID Meeting has traditionally been the attempt to facilitate the exchange of information on PID between Western and Eastern Europe. This task was accomplished this year by an excellent attendance from these formerly separated, now mostly unified regions. Invited participating speakers for 2004 were Helen Chapel, Hans Ochs, Anna Villa and Bodo Grimbacher.

Topics for the first day were targeted mainly at the registries of PID in the countries of the participants. The topic was opened by the presentation of the European PID registry by Bodo Grimbacher. The program continued with the introduction of a new cluster of diseases on the border

between primary immunodeficiencies and autoimmune disorders, namely the group IPEX-APECED-ALPS, presented by Hans Ochs. News on SCID and the disorders of innate immunity were on the program on the second day of the meeting. A large part of the program was devoted to case reports. Unusual and interesting cases were valued most among all participants. This year's meeting introduced a new section concerning the involvement of patients in the PID area.

The meeting offered complementary activities, composed of information about the hosting facility, the 2nd Medical School and Charles University and University Hospital Motol in Prague, and an excellent cultural and social program. The meeting was followed by a bike trip that further enriched the basic motto of Prague Spring Meetings – to facilitate the spread of information of PID among immunologists. Eight participants took part in the bike trip that started in Prague and finished in Brno, in the laboratory specializing in the molecular diagnosis of PID. The meeting was supported by EURO-PID-NAS QLRT-2001-02742 FP5 EU project. Ten travel grants were provided for East European participants. The event was further supported by Immunotech, Baxter and the University Hospital in Motol.

This year's meeting confirmed the still growing scientific quality of the conference and the usefulness of these educational activities. The plans for the next year have already been initiated.

The programme with PowerPoint presentations (with the consent of the authors) and photo documentation is available at http: //imunologie.lf2.cuni.cz/ !

Anna SEDIVA

Internet-accessible interactive workshop on Wiskott-Aldrich Syndrome

At a recent EURO-PID-NAS meeting, it was decided that Adrian Thrasher and Mauno Vihinen will organize an internet-accessible interactive workshop on WAS on September 16. Further information will follow.

Report from the Annual Meeting of the API – Working Group on Pediatric Immunology

From May 14th to 16th this year the annual meeting of the API – Working Group on Pediatric Immunology was held in Anif near Salzburg in Austria. The main topics of the meeting this year were IgG Fc-receptors, new insights into primary antibody deficiency syndromes with defective isotype switching, and primary complement deficiency. Among the distinguished invited speakers was Neil Simister from Brandeis University, Waltham, MA, who told the audience about the control of IgG transport and homeostasis by the neonatal FcR (FcRn). In addition, he reported about new insights from his laboratory into the regulation of FcRn function, in particular about mutagenesis studies of candidate FcRn endocytosis signals. Reinhold Schmidt from Hannover University, Germany, pointed out in his overview of human IgG Fc-receptors that there are regulatory FcRs without cell-activating function such as FcγRIIB, The balance of the proinflammatory action of FcγRIII and the regulatory action of FcγRIIB is further regulated by C5a. Alessandro Plebani from Brescia and Anne Durandy from Paris gave an excellent overview about the different forms of HIGM syndromes caused by either defects at the level of the T-B-interaction such as CD40/ CD40L-deficiency or by defects intrinsic to B-cells such as AID- or UNG-deficiency. In their lectures, it was remarkable to see the differences in the clinical picture and the underlying immunological mechanisms for these different groups of HIGM syndromes. One afternoon was devoted to primary complement deficiency syndromes, where Michael Fischer from Vienna told us about the role of complement in adaptive immunity as studied in mouse models of complement component and complement receptor deficiency. Lennart Truedsson from Lund and

Reinhard Würzner from Innsbruck updated the audience about C2-deficiency and terminal complement component deficiencies, respectively. There, it was important to learn e.g. that susceptibility to infections, in particular to invasive infection with encapsulated bacteria, is an important but underestimated clinical problem in C2 deficiency. Peter Späth gave a brilliant lecture about C1-Inhibitor deficiency, in particular about the diagnostic pitfalls and the different treatment options. On the last day of the meeting Meinrad Busslinger from Vienna´s IMP reviewed the role transcription factors such as Pax5 have for B-cell development, including maintenance of B-cell lineage commitment in early B-cell development and control of Ig heavy chain rearrangement.

Hermann WOLF

Grandes Eaux du Bassin d'Apollon, Versailles

ESID Meeting in Versailles: October 21st to 24th, 2004

Preparations for the meeting in Versailles are ongoing!

- Don't forget to send your abstract with your last exciting results before August 15! Posters will be presented all along the Meeting, and there will be 5 sessions with oral presentations of selected abstracts.

- Arrangements have been made to welcome MDs, scientists, nurses and patients in the same place. So don't forget to suggest to your nursing staff and patients' organization to join together in Versailles. There will be specific sessions for them as well as plenty of opportunities to meet with doctors and scientists working on primary immunodeficiencies.

- Please check the program of the Educational Symposium on Innate Immunity to be held on most of the day on Thursday, 20th of September. If you are interested, be careful to arrange your stay accordingly (link www.esid2004.org).

- In your Meeting bag, you will find a ticket to visit the Versailles Castle, just across the street from the Conference Center. Some time has been allotted to a visit on Friday afternoon. Prepare yourself to that experience by readings on the French kings Louis XIV to…… the beheaded Louis XVI!

If you have any questions regarding the meeting please go the website at www.esid2004.org …

I am looking forward meeting you all in Versailles!

Alain FISCHER

Working Party reports

Clinical Working Party

Report on the ADA Questionnaire: An international study examining therapeutic options used in the treatment of Adenosine Deaminase Deficiency (ADA) Severe Combined Immunodeficiency (SCID).

ADA accounts for 10-20% of all forms of SCID, and in its classical form presents with profound lymphopaenia leading to severe recurrent infections. For most forms of SCID, the only curative option is allogeneic haematopoietic stem cell transplantation (HSCT). However, for ADA SCID, other options for treatment including enzyme replacement therapy with PEG-ADA and somatic gene therapy are currently available. As a first step towards the development of therapeutic guidelines, an international questionnaire-based study to evaluate current treatment strategies was undertaken. A total of 22 centres from 13 countries participated. Of these, 18 were from ESID affiliated countries and the rest from non-ESID countries. Eight of these centres had managed over 5 patients with ADA SCID, 12 had managed under 5 patients and 2 centres who responded had not managed any patients.

If faced with a matched sibling donor, all 22 centres opted for a sibling donor HSCT. If only a matched family donor was available, 19 (86%) stated that they would opt for transplant while the others preferred to start PEG-ADA and/or would look for another donor. Nearly all (90%) centres stated that they would start a child on PEG-ADA prior to transplant to improve poor clinical condition but two centres (10%) would not use PEG-ADA in this setting, the reasons being cost and the possible adverse effect of PEG-ADA on future transplant success. Most centres (86%) would initiate an unrelated donor search with 17 (77%) electing to start on PEG-ADA while waiting to find a suitable match. The number of centres willing to use matched unrelated or mismatched donors varied considerably. While 19 (86%) would use a fully matched unrelated cord or volunteer donor, only 2 (9%) and 4 (18%) of centres would consider mismatched unrelated volunteer or mismatched cord blood donor transplants, respectively. Six centres (27%) said that they would perform a haploidentical transplant. In general, 13-15 (60-68%) would start or continue on PEG-ADA while 10-12 (45-54%) were willing to consider gene therapy as an option in the absence of a fully matched donor.

These responses show both considerable consensus and variablility depending on the treatment options available. If a fully matched sibling, related or unrelated donor is available, the vast majority of centres would proceed to HSCT. However, in the absence of a well matched donor, only the minority would proceed to HSCT and in these cases, centres are willing to consider both PEG-ADA and gene therapy as possible alternatives.

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Bobby GASPAR

Registries Working Party

The ESID Main Patient and Research Registry is online!

Beginning in July 2004, the new ESID online registry with its full name "Clinical and Laboratory Online Patient- and Research Database for Primary Immunodeficiencies" entered the productive stage and password allocation has started. Sixteen centres from all over Europe have already registered. If you have not yet been contacted by us we either do not have your actual email address or you live in a country which is running or planning to run a national registry (Spain, Czech Republic, Sweden, Poland, etc.) Please contact the respective heads of your national registries for password allocation in that case (Belgium: CM Farber <cfarber

@ulb.ac.be>, Czech Republic: Vojtech Thon <vojtech.thon@fnusa.cz>, Poland: Beata Wolska <Immuno@czd.waw.pl>, Portugal: JCE Melo <joaocastroemelo@mail.telepac.pt>, Russia: Olga Paschenko <olgapasch @rambler.ru>, Spain: Nuría Matamoros <nmatamoros@hsd.es>, Sweden: Anders Fasth <anders.fasth@pediat.gu.se>).

If you do not live in one of the above mentioned countries and you have not been contacted by us, please send a short email to Barbara Frisch at <frisch@medizin.ukl.uni-freiburg.de>. You will then immediately be provided with (1) the "Agreement between the European Society for Immuno deficiencies (ESID) and a Documenting Centre regarding the ESID Online Registry", and (2) the "Application form to obtain a user name and a password for the ESID Online Database".

As soon as we have received the signed agreement and application form by Fax, we will automatically create the required passwords and user-roles. We will send them to you by mail. After receiving your password you may access the ESID online registry under the following URL http://www.esid-registry.org. With your user name and password you will be able to register patients. However, please regard that in this internet-based database only coded data can be stored. Thus, the patient identification number for each new patient is selected by the database. Please record this ID in a centre-specific list indicating which ID number matches which patient name. It is the responsibility of the centre to maintain this assignment list and to keep it securely locked. Lost assignment tables cannot be recovered by the ESID database! In addition, we would also like to remind that patients can only be registered into the ESID online registry after having signed an informed consent which may need to be approved by your local ethics committee or data-protection-manager, respectively. Therefore, you will be provided with the English version of the patient's consent form. Translations of this form into French, Italian, Spanish, Portuguese, German, Greek, Turkish, Czech, Croatian, Slovakian and Romanian are available already and will be published soon on the ESID registry website. For the time being, please ask for translations by sending an email to <frisch@medizin.ukl.uni-freiburg.de>. If the native language of your patient is not among the above mentioned languages, we may ask you to translate the English patient's consent form for us. We'd appreciate if you would then provide us with this new translation.

We also would like to point out the option to implement the ESID registry database system as a personalised version in your documenting centre to make use of all the other features of the database like the 'patient report generation' or the electronic import of laboratory data. Please contact us at <frisch@medizin.ukl.uni-freiburg.de> for the organisational and technical requirements.

If all of this takes too much time and you are interested in getting to know the system immediately, you may log onto our ESID-test-registry. This test-registry, which may be edited ad libitum, can be reached 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 onto the test-database!

The contract between ESID and the sponsoring party, the Plasma Protein Therapeutics Association (PPTA), has been finally signed on May 17 in Brussels.

Before going online, we had arranged a test phase, which was accomplished successfully between April 8 and May 31. During this test phase, carried out by honourable ESID members, we were provided with valuable suggestions e.g. concerning the validation of the PID-classification-tree which underlies the registry. Starting from the known 5 categories (T cells, B cells, etc.)

at the entry page of the registry, the "PID-tree" goes to the second level of about 50 PID groups and finally, at the third level, branches out into about 130 disease specific subregistries.

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. The datamodels of the single disease specific subregistries will be shaped one after the other by the respective steering committees. In August the first disease specific subregistry (CVID) will go online, followed by DGS. If you want to participate in the design of a certain subregistry, please feel free to contact the nominated heads of the respective steering committees (see Table, page 15), or contact Barbara Frisch at <frisch@medizin.ukl.uni-freiburg.de>.

On Thursday, July 22, the first ESID online registry training classes will be held in Freiburg, Germany, giving a general introduction on how to use the database and how the database may help in day-to-day work. This course will also cover all information which is needed to set up the documentation in the single documenting-centres. Twenty participants from sixteen countries have registered. We are looking forward to a great new ESID-online project! However, we do need your help to make this story another success for ESID…

Bodo GRIMBACHER and Barbara FRISCH

Petit Trianon, Versailles

Reception room, Versailles

Le Chateau, Versailles

List of heads of steering committees for disease specific subregistries, 15-Jun-04

1	Adrian Thrasher, a.thrasher@ich.ucl.ac.uk	WAS
2	Alain Fischer, fischer@necker.fr	X-linked (gc) (CD132), T-B+ SCID
3	Alberto Tommasini, tommasin@burlo.trieste.it	Co-head IPEX, FOXP3
4	Alessandro Plebani, plebani@med.unibs.it	CD40-deficiency
5	Anders Fasth, anders.fasth@pediat.gu.se	(QoL, DGS, Osteopretrosis, no head)
6	Anna Sediva, anna.sediva@lfmotol.cuni.cz	DGS
7	Anna Villa, anna.villa@itb.cnr.it	RAG 1/2 – deficiency, Osteopetrosis
8	Anne Durandy, durandy@necker.fr	AID-deficiency (AICDA), UNGdeficiency Unknown HIGM
9	Bernd Belohradsky, Bernd.Belohradsky@med.uni-muenchen.de	(HIDS)
10	Bobby Gaspar, h.gaspar@ich.ucl.ac.uk	ADA-deficiency, XLP
11	Claudio Pignata, pignata@unina.it	Nude/SCID (FOXN1)
12	Corry Weemaes, C.Weemaes@cukz.umcn.nl	ICF syndrome
13	Edvard Smith, edvard.smith@crc.ki.se	Agammaglobulinemias
14	Eleonora Gambinieri, elegambis@yahoo.it	IPEX, FOXP3
15	Ewa Bernatowska, bernatowskae@yahoo.com, immuno@czd.waw.pl	NBS
16	Raffaele Badolato, badolato@med.unibs.it	WHIM syndrome (CXCR4
17	Jean-Laurent Casanova, casanova@necker.fr	Defects with susceptibility to mycobacterial infections
18	Jean-Pierre de Villartay, devillar@necker.fr	Artemis deficiency
19	Jos van der Meer, j.vandermeer@aig.umcn.nl	CMC, (HIDS)
20	Jose R. Regueiro, regueiro@med.ucm.es	CD3-deficiency
21	Lennart Hammarstrom, lennart.hammarstrom@biosci.ki.se	DNA-breakage disorder
22	Luigi Notarangelo, notarang@med.unibs.it	Jak 3 - deficiency (JAK 3) CD40L-deficiency (CD154)
23	Naomi Taylor, taylor@igm.cnrs-mop.fr	ZAP 70
24	Silvia Giliani, giliani@master.cci.unibs.it	IL7R-deficiency (IL-7Ra)
25	Wilhelm Friedrich, wilhelm.friedrich@medizin.uni-ulm.de	ALPS, Other unclassified T-cell disorders
26	Mario Abinun, Mario.Abinun@ncl.ac.uk	- NEMO / IKKg-deficiency (XED) (conditional)
27	Ann Gardulf, ann.gardulf@labmed.ki.se, Anders Fasth, Fabian Schumacher	Quality of Life in PID (Head to be elected)

Invited review

UPDATE ON COMMON VARIABLE IMMUNODEFICIENCY (CVID)

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Common Variable Immunodeficiency (CVID) summarizes a heterogeneous group of diseases characterized by significant hypogammaglobulinemia of unknown cause, failure to produce specific antibodies after immunization, and typically recurrent upper respiratory tract infections (IUIS, 1999; Chapel et al., 2003).

The prevalence of CVID ranges from 1:25.000 among Caucasians to 1:100.000 in the Japanese population, and affects men and women equally (Cunningham-Rundles, 2001). While some patients are already diagnosed with CVID in early childhood, the major peak of onset lies between the second and third decade of life, frequently with some years delay between onset of symptoms and the definitive diagnosis (Cunningham-Rundles, 2001).

In some cases, family members of CVID patients may present with selective IgA deficiency (sIgAD), and cases of sIgAD have been described which gradually progress to CVID (Johnson et al. 1997).

CVID is a diagnosis of exclusion. Thus, any other cause for hypogammaglobulinemia needs to be ruled out. Among those, the most important conditions are listed in Table 1.

A patient with CVID may initially present with a history of recurrent upper and/or lower respiratory tract infections, gastrointestinal complaints like chronic diarrhoea or malabsorption, or with other manifestations of CVID like autoimmune phenomena such as ITP or AIHA (Table 2). The diagnostic and laboratory evaluation is shown in Table 3. The careful evaluation of the 'immunophenotype' may allow the classification of CVID (e.g. by Warnatz et al., 2002) and provides the basis for further genetic and clinical studies.

In about 20 % of CVID patients, a positive family history of either CVID or sIgAD deficiency can be observed. First degree relatives of CVID patients are at high risk to develop CVID/ sIgAD (Vořechovský et al., 1995). Most of the CVID families show an autosomal dominant trait, while only about 20% of these familial cases are autosomal recessive.

In 2002, we identified ICOS-deficiency (OMIM: 607594) as a monogenetic cause for CVID in two families with an autosomal recessive trait (Grimbacher et al., 2003). Due to a large homozygous genomic deletion the "inducible costimulator" (ICOS) is absent on the surface of the patients´ activated T cells. Despite of this lack of ICOS expression, the patients' T cells do not show any gross defects in function or phenotype. However, as a consequence of ICOS-deficiency on the T cells, cognate T - B cell interaction in germinal centers fails to generate substantial numbers of memory B cells. Moreover, terminal differentiation of B cells into plasma cells is severely affected, resulting in a markedly compromised humoral immunity. The clinical phenotype of ICOS-deficient patients is indistinguishable from that of other non-ICOS CVID patients. Therefore, we performed a genetic screening for the integrity of the ICOS gene in sporadic CVID patients and AR-CVID families (Salzer et al., 2003). While we could not detect any genetic abnormalities of ICOS in the sporadic CVID cohort, two out of nine AR-

Table 1. Causes of hypogammaglobulinemia.

Drug-induced	Cytotoxic drugs [1] Anti-B cell antibodies (anti-CD20) [1] Gold [1] High dose corticosteroids [1] Sulfasalazine [1] Chloroquine [1] Penicillamine [1]	Hydantoin [1] Carbamazepine [1] Zonisamide [2] Valproate [3] Captopril [3] Fenclofenac [3]
Monogenetic disorders	X-linked agammaglobulinemia:	XLA, Btk-deficiency
	Severe combined immunodeficiencies (SCID):	RAG1,2; γc-chain of IL2, IL4, IL7, IL9, and IL15 receptor; Jak3; ADA, PNP; CIITA, RFX5; CD3γ, CD3ε; ZAP70; TAP2
	Ataxia Teleangiectasia:	ATM
	X-linked lymphoproliferative syndrome:	XLP, SH2D1A
	Defects in class-switch recombination, 'hyper-IgM syndromes':	CD40-ligand deficiency (CD154), CD40, AID, UNG, IKKγ
	Dystrophic myotonia:	DM type 1, DM type 2 (PROMM; Kurschman-Steinert disease; ZNF9)
	ICOS deficiency Caspase 8 deficiency	
Chromosomal anomalies	Chromosome 18q syndrome Monosomy 22	Trisomy 8 Trisomy 21
Infectious	Human immunodeficiency virus (HIV) (primarily in children) Congenital infection with rubella Congenital infection with cytomegalovirus (CMV) Congenital infection with Toxoplasma gondii Epstein-Barr Virus (EBV) (± underlying genetic susceptibility)	
Hematologic malignancies	Chronic-Lymphatic Leukemia (CLL) Non Hodgkin Lymphoma (NHL) Other B-cell lymphomas	Immundeficiency with thymoma (Good syndrome)
Losses	Gastrointestinal	Severe diarrhea, Malabsorption, Protein losing enteropathy, Lymphangiectasis
	Renal	Nephrotic syndrome
	Skin	Severe burns

[1] may affect IgG and IgA
[2] may affect IgG2 and IgA
[3] may affect IgA

Table 2. Clinical manifestations of CVID.

		present in: [1]
Infections	Recurrent bronchitis, sinusitis, otitis	98%
	Pneumonia	76,6%
	Viral hepatitis	6,5%
	Severe herpes zoster	3,6%
	Giardiasis	3,2%
	Pneumocystis carinii	2,8%
	Mycoplasma pneumoniae	2,4%
	Chronic mucocutaneous candidiasis	1,2%
	Salmonella	1,2%
	Sepsis (with Pseudomonas, Pneumococci, H. influenzae, Listeria)	1,2%
	Campylobacter	1,2%
Autoimmunity		up to 25%
Splenomegaly		up to 30%
Granulomatous-like disease		up to 10%
Malignancies (especially lymphoma, increased risk according to some reports)		up to 40x
Nodular lymphatic hyperplasia of the mucosa		

[1] *Prevalence of infections in 248 CVID patients according to Cunningham-Rundles und Bodian, 1999.*

Table 3. Diagnostic and laboratory evaluation in case of suspected CVID.

Medical history	Family history Medication history Infection history Autoimmune complications
Laboratory testing	Quantitative immunoglobulins, Immunopheresis, Specific antibody production (e.g. Tetanus for protein responses, and pneumococci for polysaccharide responses), IgG subclasses if total IgG is in the lower norm or slightly decreased, to exclude selective IgG2 and IgG4 deficiency, Isohemagglutinins Autoantibodies (e.g. ANA, antibodies against parietal cells etc.) Differential blood count (e.g. autoimmune cytopenias or ITP) Urine analysis (to exclude renal protein loss) Liver function test (CHE, Alb, GOT, GPT) HIV-RNA and HCV-RNA testing, EBV testing
Additional	Chest X-Ray or CT scan, Ultrasound examination of the abdomen ENT evaluation, Gastroscopy Bone marrow biopsy – in order to exclude a malignancy Lymphocyte function analysis in vitro and in vivo: Specific antibody responses after vaccination Immunophenotyping of T and B cells and their subsets Functional analysis of B cells in vitro T cell proliferation in vitro T cell function testing in vivo (skin testing)

CVID families presented with five affected individuals carrying the same genomic deletion as the initially described patients. Although the genetic defect is identical in all the nine patients, the clinical phenotype is variable, fulfilling the whole spectrum of manifestations seen in CVID (Warnatz et al, manuscript in preparation). Thus, a simple algorithm to identify patients with possible ICOS-deficiency cannot be given. We suggest to do genetic testing or FACS analysis for ICOS defects in CVID-families with a recessive pattern of inheritance. ICOS-deficiency has been discovered in a candidate gene approach and now genes involved in the ICOS/ICOSL pathway are promising candidates to be investigated in CVID patients.

No genetic defect has yet been identified causing autosomal dominant CVID. Previous search for susceptibility loci for sIgAD and CVID to specific chromosomal locations focussed on the HLA region on Chromosome 6p. Most of these studies examined HLA haplotypes in a case-control study design (Volanakis et al. 1992). Based on the positive results of Vořechovský et al. (1999), the HLA region was designated as the susceptibility locus IGAD1, currently the only genomic susceptibility region associated with CVID or IgAD (Vořechovský et al. 2000). There is substantial disagreement in the cited studies regarding where in the HLA region a putative disease causing gene is located, if there is one, and whether it is a susceptibility locus for CVID or IgAD or both (Vořechovský et al. 2001). In a recent study, the same group could refine these findings in a genome-wide linkage analysis, and defined the HLA DQ/DR region as susceptibility locus for CVID and sIgAD (Kralovicova et al, 2003).

We recently reported on an autosomal genome-wide linkage scan of three families with multiple cases of CVID, IgAD, and dysgammaglobulinemia, exhibiting autosomal dominant inheritance (Braig et al., 2002). In larger families with many immunodeficient individuals, one may reasonably assume that multiple cases are due to the same gene(s) even if some individuals have CVID and others have IgAD or dysgammaglobulinemia.

The therapeutic basis in CVID is immunoglobulin replacement therapy. Intravenous (IVIG) and subcutaneous (SCIG) treatment is available. Doses of 400-600 mg/kg body weight are recommended and, an IgG through level of > 5g/L, or at least an increase of 3 g/L, should be reached. Prophylactic antibiotics can be helpful in some patients with persistent infections, as well as sinus surgery in case of chronic sinusitis.

Patients with CVID should be referred to a center specialized for the diagnosis and treatment of primary immunodeficiencies at least once a year. During those visits, a differential blood count, neurology screening (aseptic meningitis), screening for venous and arterial thrombosis, liver function tests (Alb, GPT) and renal function testing (Creatinine) should be performed. In patients on IVIG, the IgG through levels should be determined monthly, in patients on SCIG quarterly determination may be sufficient. In order to document the disease activity, chest X ray and lung function testing should be carried out in yearly increments. Ultrasound examination of the abdomen to capture enlarged abdominal lymph nodes, spleen pathology or granulomas of e.g. the liver should also be performed every year. Gastroscopy with evaluation of possible Helicobacter pylori and Giardia infections, and for the exclusion of any malignancy of the upper gastrointestinal tract (which are reported to be significantly increased in CVID), may be scheduled for every two years. In cases with bronchiectasis, persistent thoracic or abdominal lymph node enlargement, high resolution CT scans in yearly intervals are advisable. More in depth guidelines for the managementof CVID patients have been recently published by C. Cunningham-Rundles (1999, 2001) , L. Hammarstrom (2000), W. Strober (2000), WA Spickett (2001), MC Sneller (2001), GP Sewell (2003), HW. Schroeder (2004), and B. Grimbacher (2004, www.cvid.info).

References

Braig DU, Schäffer AA, Glocker E, Salzer U, Warnatz K, Peter HH, Grimbacher B. Linkage of autosomal dominant common variable immunodeficiency to chromosome 5p and evidence for locus heterogeneity. Hum Genet 2003, 112:369-378.

Chapel H, Geha R, Rosen F; IUIS PID (Primary Immunodeficiencies) Classification committee Primary immunodeficiency diseases: an update. Clin Exp Immunol. 2003 Apr;132(1):9-15.

Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999, 92:34-48.

Cunningham-Rundles C: Common variable immunodeficiency. Current Allergy and Asthma Reports 2001, 1:421-429.

Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Dräger R, Eibel H, Fischer B, Schäffer AA, Mages HW, Kroczek RA, Peter HH: Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nature Immunol 2003, 4: 261-268.

Grimbacher B, Warnatz K, Peter HH. The genetics of hypogammaglobulinemia. Current Allergy and Asthma Reports 2004 (Sept), in press.

Hammarstrom L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol. 2000, 120:225-31. Review.

International Union of Immunological Societies (IUIS): Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. Clin Exp Immunol 1999, 118 (Suppl.1): 1-28.

Johnson ML, Keeton LG, Zhu ZB, Volanakis JE, Cooper MD, and Schroeder HW, Jr.: Age-related changes in serum immunoglobulins in patients with familial IgA deficiency and common variable immunodeficiency (CVID). Clin Exp Immunol 1997, 108: 477-483.

Kralovicova J, Hammarström L, Plebani A, Webster ADB, Vorechovsky I: Fine-scale mapping at IGAD1 and genome-wide genetic linkage analysis implicate HLA-DQ/DR as a major susceptibility locus in selective IgA deficiency and common variable immunodeficiency. J Immunol 2003, 170:2765-2775.

Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Jiri Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W and Grimbacher B. ICOS-Deficiency in Patients with Common Variable Immunodeficiency. Clin Immunol, in press.

Schroeder HW Jr, Schroeder HW 3rd, Sheikh SM. The complex genetics of common variable immunodeficiency. J Investig Med. 2004 52:90-103. Review.

Sewell WA, Buckland M, Jolles SR. Therapeutic strategies in common variable immunodeficiency. Drugs. 2003, 63:1359-71. Review.

Sneller MC. Common variable immunodeficiency. Am J Med Sci. 2001, 321:42-8. Review.

Spickett GP. Current perspectives on common variable immunodeficiency (CVID). Clin Exp Allergy. 2001, 31:536-42. Review.

Strober W, Chua K. Common variable immunodeficiency. Clin Rev Allergy Immunol. 2000, 19:157-81. Review.

Volanakis JE, Zhu ZB, Schaffer FM, Macon KJ, Palermos J, Barger BO, Go R, Campbell RD, Schroeder HW Jr, Cooper MD. Major histocompatibility complex class III genes and susceptibility to immunoglobulin A deficiency and common variable immunodeficiency. J Clin Invest 1992 89:1914-1922.

Vořechovský I, Zetterquist H, Paganelli R, Koskinen S, Webster ADB, Björkander J, Smith CIE, Hammarström L: Family and linkage study of selective IgA deficiency and common variable immunodeficiency. Clin Immunol Immunopathol 1995, 77:185-192.

Vořechovský I, Webster ADB, Plebani A, Hammarström L : Genetic linkage of IgA deficiency to the major histocompatibility complex: Evidence for allele segregation distortion, parent-of-origin penetrance differences, and the role of anti-IgA antibodies in disease predisposition. Am J Hum Genet 1999, 64: 1096-1109.

Vořechovský I, Cullen M, Carrington M, Hammarström L, Webster ADB: Fine mapping of IGAD1 in IgA deficiency and common variable immunodeficiency: Identification and characterization of haplotypes shared by affected members of 101 multiple-case families. J Immunol 2000, 164:4408-4416.

Vořechovský I, Webster ADB, and Hammarström L: Mapping genes underlying complex disorders: progress on IgA deficiency and common variable immunodeficiency. Adv Exp Med Biol 2001, 495: 183-190.

Warnatz K, Denz A, Dräger R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH: Severe deficiency of switched memory B cells (CD27+IgM-IgD-) in subgroups of patients with common variable immunodeficiency: A new approach to classify a heterogeneous disease. Blood 2002, 99: 1544-1551.

Warnatz K, Bossaller L, Salzer U, Skrabl-Baumgartner A, Schwinger W, van der Burg M, Dongen JM, Orlowska-Volk M, Knoth R, Durandy A, Draeger R, Schlesier M, Peter HH and Grimbacher B. Human ICOS-deficiency abrogates the germinal center reaction and provides a monogenic model for common variable immunodeficiency, manuscript in prepararation.

Focus on a country:

Established member Q&A
Andrew Cant
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Can you give me some information about your background and can you tell me something about your career history?

I come from a Scots family who lived in the USA for a time, but I was born and brought up in Southern England. I was always fascinated by biology, and wanted to be a doctor from a very early age. Before leaving school, my headmaster told me that doing medicine was a good idea, although had I been cleverer I could have been a scientist like my father! I went to medical school in London and despite my headmaster's views, I was given the opportunity to do some extra studies and so obtained a science degree as well as a medical degree. One of the science courses on offer was a "new" subject called "Immunology". It was only the second year the course had run; it was taught by a parasitologist who had become fascinated with immunology. His enthusiasm was "infectious", and immunology has fascinated me too ever since!

After qualifying, I worked in general medicine, paediatrics and infectious diseases; I very much enjoyed all of these, but decided I preferred to work with children as this seemed more like helping patients on the upward slope of life rather than trying to prevent a sometimes inevitable downward slide! Much as I liked, and still like, the puzzle of an interesting infectious diseases case, I was intrigued by the "other side of the coin" . . . . . how the immune system responded to infection and what happened when it went wrong . . . . . Indeed, the interaction of infection and immunity remains a theme that absorbs my interest; microbes evolving to outwit the immune system, immunity evolving to outmanoeuvre microbes. In 1980, someone gave me some very interesting career advice, "Infection and Immunity! No career opportunities there. Why - antibiotics and vaccination have sorted out all that!!" How wrong they were and what a good thing that I ignored what they said!

After passing my specialist exams, I spent a period in research working on the immunology of infant feeding. This gave me a grounding in laboratory work, clinical trials and writing, and although I learnt much about allergic disease, I found the sketchy scientific basis to allergy somewhat frustrating.

How did you became interested in immunodeficiencies?

I saw two brothers with XLA soon after I first qualified, but I did not see any more patients with primary immunodeficiency until after my research fellowship when I returned to clinical paediatrics. I was intrigued by the way it was becoming possible to correlate a clinical condition with an identifiable defect in the immune system, especially as this seemed to open up possibilities for effective rational treatment. I therefore applied for a post at Great Ormond Street Hospital in London as, at that time, it was the only centre in the UK where you could get training in the field. I really enjoyed my time at "GOS". Lots of patients to see, a bone marrow transplantation programme just getting going, so many new things to learn, so much

to discuss, so many possibilities for research. Towards the end of my time at GOS, I had to think about applying for a consultant post. There were very few posts in paediatric infectious diseases and none in paediatric immunology. It looked as if I would have to take a post in general paediatrics. However, a plan was evolving to obtain UK government funding to set up a national programme for the assessment and treatment of children with severe primary immunodeficiency which would be centred in London and Newcastle. Then a tragedy occurred - Graham Watson, the doctor who was going to set up the unit in Newcastle, died in a climbing accident in Scotland at the age of 44. Unexpectedly, there was an exciting job to which I was appointed.

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

Finding myself suddenly appointed to set up one of two national units for the assessment and treatment of children with primary immunodeficiency was very daunting. Roland Levinsky, my boss at Great Ormond Street, advised me to delay starting in Newcastle so I should get some extra training and experience. Alain Fischer kindly invited me to spend some time in Paris, and in 1990 I learnt a great deal in London and Paris, and so enjoyed my time in Paris, seeing how excellent patient care and scientific investigation proceeded side by side. The lively team discussions were also very valuable, even if my French wasn't good enough to understand all that was being said. Before I left Paris, Alain gave me some extremely useful advice, namely to build a very good clinical service and then develop a research programme. For my first two years, I was single-handed and also covered general paediatrics, neonatal intensive care, infectious diseases and allergy! I had one immunodeficiency clinic a month and we carried out two bone marrow transplants in the first year! Things began to develop, and after two years, I was so grateful that Mario Abinun came and joined me. Gradually, we were referred more and more patients, so that fourteen years later we receive some four hundred new referrals and carry out over thirty bone marrow transplants a year. We have a team of six consultants, two Associate Specialists, as well as fellows and interns. In 1994, we moved into a purpose-built eight bedded transplant Unit, and over the last few years we have developed a network of clinics across the Northern UK and Ireland including Manchester, Dublin, Sheffield and Edinburgh and patients are referred from across this area.

Most of our research has focused on the clinical problems that we have encountered. In the early years, haploidentical transplants for SCIDS were only 50% successful. In collaboration with the experimental haematology department in Newcastle, we improved our techniques of graft manipulation and patient care; nowadays 90% of the patients survive. We were also very frustrated by the number of our SCID patients who developed pneumonitis, often provoked by pre-existing viral infections. This lead to research into ways of modulating the immune response to lung inflammation in this situation. We then became interested in the acquired antibody deficiencies seen in some very immunosuppressed patients which lead to Andy Gennery's research programme, looking at polysaccharide antibody responses in various conditions including Di George syndrome and patients who had undergone solid organ and bone marrow transplantation. The difficulties we encountered in treating patients with Omenn's syndrome lead to some research in this area too. More recently, we have become very interested in cord blood stem cell transplantation, and in developing stem cell transplantation as a curative therapy for conditioning such as CD40 Ligand deficiency, CGD and auto-immune disease.

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

The last ten to fifteen years have been a fantastic time to be in the field of primary immunodeficiency. New understandings of molecular mechanisms along with clinical studies of patient groups, give us a much clearer picture of the natural history of the diseases that interest us. At the same time, our treatments have become much more effective, so that bone marrow transplant results have improved dramatically and patients on immunoglobulin substitution therapy are also doing so much better. Over the next few years, I would hope that we would see far more patients benefiting from curative therapy. This is just starting with bone marrow transplantation programmes for CD40 Ligand deficiency, Wiskott Aldrich syndrome and CGD, and gene therapy has been successful for a few patients, even though at present there are some difficulties to be overcome. I would hope that bone marrow transplantation results will continue to improve, both with better supportive care, less toxic conditioning regimens and the use of stem cells from sources such as umbilical cord blood. If we can succeed in manipulating haemopoietic stem cells to proliferate in vivo, and if we can isolate T cells that are specifically reactive to viruses but not to host tissues, then stem cell transplantation could become even more successful. Gene therapy also looks promising, and I would imagine that with better vectors and more refined techniques, this too will mean that it maybe possible to treat patients with genetically defined forms of primary immunodeficiency. By the low toxicities, the low risks will mean that it is feasible to treat patients with primary immunodeficiency that are life limiting and not just those that are life threatening.

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

If you are really interested in primary immunodeficiencies, then pursue your interest with all your energy, even if the job prospects don't look good. If you have enough enthusiasm, dedication and commitment, this should work out in the end! I would recommend working in a busy clinical unit where you get lots of experience and see lots of cases. There is nothing like seeing patient problems to stimulate the questions about what goes on in primary immunodeficiencies. Then find a laboratory where there are good immunological scientists. It is so important to have some understanding to get to grips with the laboratory techniques needed to study primary immunodeficiency.

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

I attended my first ESID meeting in Oxford in 1990. The impression I got then is still true today! ESID for me provides a warm, friendly and encouraging atmosphere, a stimulating environment to learn, and to share ideas and experiences other ESID members have given me. A place where I have gained great encouragement to try and find better ways to treat patients, and where I have so often gained tremendous new insights from the work of others. It has provided a fantastic opportunity to collaborate with colleagues in other European centres. Just look at the pan European collaborative publications on the treatment of SCID, CD40 Ligand or CGD as examples! This is so important as a number of patients we see in each centre is often too small for really good scientific work to be performed. It has also been an enormous pleasure to participate in the ESID Summer School; so good to get to know the bright, keen, enthusiastic doctors who will be the next generation of Clinical Immunologists. I

greatly value getting to know people who share the same joy, sorrows and frustrations in both patient care and research; I have so much appreciated the contact I have had by e-mail and telephone with people who are very busy, but always seem to find time to answer my many questions! Long may this continue!

Andrew Cant

Young Investigator Q&A
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Can you give me some information about yourself and your background?

I am 39 years old and I was born and grew up in the United Kingdom. I am married with 4 children. I now live in the North East of England.

Can you tell me something about your career history?

I studied medicine at the University of Sheffield. Immunology was covered in 3 lectures and I didn't understand a word of it! After completing my pre-registration year, I moved to the North East to train as a paediatrician. I was seconded to the Bone Marrow Transplant Unit for Severe Combined Immune Deficiency in Newcastle for 3 months, which was my first introduction to primary immunodeficiency. I spent a year working in paediatrics in Queensland Australia and became interested in the increased rate of infections of the indigenous aboriginal population. On my return to the UK, I studied the polysaccharide antibody responses of children who had received a heart transplant in early infancy for my MD thesis. Following this, I completed my training in paediatric immunology on the Bone Marrow Transplant Unit in Newcastle, and spent 12 months working with Anne Durandy and Alain Fisher

at the Necker Hospital in Paris. I have recently been appointed as Senior Lecturer in Paediatric Immunology at Newcastle and I am currently setting up a research group, as well as continuing with my clinical work looking after children with primary immunodeficiency.

How did you become interested in immunodeficiencies?

My interest was kindled during my 3 month secondment to the Bone Marrow Transplant Unit in Newcastle early in my paediatric career. I found the subject fascinating but thought that you had to be very clever to be a paediatric immunologist! My interest was rekindled during my MD studies when I became interested in polysaccharide antibody responses. I was privileged to spend a year working with Anne Durandy and Alain Fisher in Paris investigating patients suffering from autosomal recessive hyper IgM syndrome and was fortunate to be there when it was discovered that the AID gene was responsible for the clinical phenotype in some of these patients. The integration of basic research and clinical paediatric immunology was a model that was already being followed in Newcastle but I was very impressed by the way that this model was practised in Paris. To see the unsolved problems of clinical immunology taken into the basic immunology laboratory, unravelled and reintegrated into patient care in the clinic was exciting and is a model I hope we can emulate in Newcastle.

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

I demonstrated the marked effect of prolonged post-transplant immunosuppression on the developing immune system, depending on the age at which it is started. Adapting these basic observations has enabled pioneered infant cardiac transplantation across ABO blood groups. I was part of a team working on mechanisms of antibody production and their molecular basis. This lead to the discovery of the genetic basis of the autosomal recessive hyper-IgM syndrome, which has given fundamental insights into B cell maturation, antibody isotype switching and somatic hypermutation. I helped with the discovery of a novel immunodeficiency due to mutations in the DNA repair enzyme Ligase IV, work which links combined immunodeficiency with developmental delay. I have published important clinical observations regarding humoral immunodeficiency and autoimmune disease in patients with Di George Syndrome.

What do you hope to achieve in the future?

I have started to set up a laboratory based research group in Newcastle. We are beginning to look at polysaccharide antibody responses. We also have a project looking for a new gene defect that causes T-B-SCID. I would like to establish Newcastle as a productive centre of laboratory based primary immunodeficiency research, building on the very good clinical reputation that I believe we already have. I would like to see further improvements in stem cell transplantation in Newcastle including gene therapy. I would also like to see our umbilical cord stem cell transplantation programme expand for a greater range of conditions to older and bigger patients.

How are you planning to reach this goal?

I had hoped to give you a slightly different answer than others have previously given to the same question but I cannot! I can only emphasise the importance of collaboration. The field of primary immunodeficiency is too big for groups to work alone and it is only by collaborating with

other groups with experience and sharing our knowledge and other people's knowledge that we can hope to be successful.

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

Following on from the previous answer, one of the exciting things about ESID is the opportunity to meet people from different centres and different countries who share and understand the same problems that I do. It is a very exciting forum to learn new things and I have always found the formal sessions very stimulating. However, a very important part of ESID is the opportunity to meet informally with older and wiser colleagues as well as younger people who are at the same stage in their career as I am and to exchange ideas and build on collaborations for the future.

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

I would like to foster international travel, particularly for students and young researchers between groups. The ESID Summer School is a fantastic opportunity for young people from different countries to meet, but it would be great if there were funds available to make it much more easy for young scientists to travel to other laboratories within Europe for a few months to learn new techniques. I also think we should be encouraging people working in European countries whose PID services are developing so that they can take an active and more prominent role in ESID.

Andy Gennery