ESID Newsletter

Contents

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

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries.

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

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

Front page:
Marseille, seen from the Mediterranean.

Dear ESID members,

Before you is lying the latest edition of the ESID Newsletter, with several important issues.

First of all, I would like to draw your attention to the President's letter. Luigi Notarangelo raises the very important point of growth and its consequences on ESID finances, especially those concerning the ESID biennial meetings. Please read this carefully, form your own opinion, and come to the General Assembly in Budapest next year to help us decide on this important issue.

Lots of News & Views, this time, but no Focus on a Country or PID-care in development sections. Please give me your ideas about suitable countries / people to interview for these parts of the ESID Newsletter !!

We also have a new section to offer you: Interesting Papers by Claire Fieschi form Necker in Paris. In each issue, she will draw your attention to some important papers that have been published recently.

Do you have any ideas about subjects that can be covered in the ESID Newsletter? Please let me know at dr.estherdevries@tiscali.nl !

If you are under 35 (more or less), don't forget to fill in the form to become part of the new ESID *juniors* Working Party.

Best wishes to all of you,

Esther DE VRIES, Editor

ESID is the European Society for Immunodeficiencies. It was formed in 1994. The forerunner of ESID, the informal European Group for Immunodeficiencies (EGID) was established in 1983. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. You can find the necessary information to contact the treasurer Esther de Vries at www . esid . org.

Within ESID, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Bone marrow transplantation (chair: Mario Abinun), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Bobby Gaspar), Genetics (chair: Anna Villa), Education (chair: Anders Fasth), and ESID*juniors* (chair: Pim van der Vossen). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www . esid . org).

In 1994, a main registry of patients with various forms of immunodeficiency in Europe was established. Altogether, data from some 10,000 patients from 26 countries were received until now. In 1995, the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia – curators Mauno Vihinen and C.I. Edvard Smith). Since then, several additional locus-specific data bases have been established: ADAbase (adenosine deaminase deficiency – curators Mauno Vihinen and Michael Hershfield), BLMbase (Blooms syndrome – curator Mauno Vihinen), CYBAbase (autosomal recessive p22 phox deficiency – curators Dirk Roos and Mauno Vihinen), CYBBbase (X-linked chronic granulomatous disease (XCGD) – curators Dirk Roos and Mauno Vihinen), CD3Ebase (autosomal recessive CD3 epsilondeficiency – curators Mauno Vihinen and Jose R. Regueiro), CD3Gbase (autosomal recessive CD3 gamma deficiency – curators Mauno Vihinen and Jose R. Regueiro), CD40Lbase (X-linked hyper-IgM syndrome – curators Luigi D. Notarangelo and Mauno Vihinen), JAK3base (autosomal recessive severe combined JAK3 deficiency – curators Luigi D. Notarangelo and Mauno Vihinen), NCF1base (autosomal recessive p47 phox deficiency – curators Dirk Roos and Mauno Vihinen), NCF2base (autosomal recessive p67 phox deficiency – curators Dirk Roos and Mauno Vihinen), RAG1base (autosomal recessive severe combined RAG1 deficiency – curators Mauno Vihinen and Anna Villa), RAG2base (autosomal recessive severe combined RAG2 deficiency – curators Mauno Vihinen and Anna Villa), SH2D1Abase (X-linked lymphoproliferative syndrome (XLP) – curators Luigi D. Notarangelo and Mauno Vihinen), TCIRG1base (autosomal recessive osteopetrosis (arOP) – curators Mauno Vihinen and Anna Villa), ZAP70base (autosomal recessive severe combined ZAP70 deficiency – curator Mauno Vihinen), WASPbase (Wiskott-Aldrich syndrome – curators Mauno Vihinen and Luigi D. Notarangelo) (information is available at www . esid . org).

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

President's letter

A matter of growth

In one year from now, ESID will celebrate its XIIth Meeting. About twenty years after Lugano, ESID remains a gathering of friends interested in understanding the cellular and molecular bases of primary immune deficiencies, with the ultimate goal of offering better prevention and treatment to patients and families. In spite of this heritage from what used to be the "European Group for Immune Deficiencies" (EGID), much has changed, both in the format of the Meeting, as well as in the strategies and interests of the Society.

Originally, sharing of scientific advances and debate in a small community were the main themes of the Meeting. The "molecular revolution" was at the door. As many other biomedical Societies, ESID was ready and eager to learn what the gene defects would be, and thus what would really cause PID. Although that time is not over (rather, we are discovering how complex the molecular mechanisms of genetic diseases can be), ESID has identified new tasks. As an attempt to avoid shortage of physicians and physician-scientists interested in PID (a problem that other countries, such as the United States, are facing), ESID has identified the need for Educational Workshops. Back to patients or, even better, building up the basics that are essential for better recognition and treatment of PIDs, have become an essential momentum of ESID activities. Certainly, some of these needs have always been present in Europe, even before ESID was founded. Gathering of representatives from all bone marrow transplantation centers in Europe dealing with PIDs has been instrumental to share ideas, debate problems, and ultimately come up with common protocols. Undoubtedly, this has been the key to European supremacy in this field.

However, growth also carries along new, previously unfaced, issues. At the last meeting of the ESID Board, we were faced with a question that had never been raised before: whose is the responsibility to organize ESID Meetings, and who should pay or benefit in case of an uneven balance after the Meeting? As a matter of fact, historically ESID Meetings have been small meetings. Now, this is no longer the case, as demonstrated in the latest editions. The growing number of attendees (not only among physicians and scientists, but also patient representatives and nurses) requires an experienced agency to deal with all the logistics.

Growing numbers, growing costs.

Furthermore, life around ESID has changed, as the tragedy occurred in London recently has shown once again. Safety has to be carefully considered in the organization of any meeting, including ESID's. Even if the last Board Meeting decided that for the moment being, the Society itself should be left apart from the risks and the costs associated with the organization of the meeting, I believe this issue needs to be discussed in detail, and the only place to do it seriously is the General Assembly. It is a duty from all of us to give our opinion. If we fail to do so, we might even expect that not too many will be happy to organize Meetings in the future. Organizing an ESID Meeting has always been a matter of privilege. We should do our best to support this attitude, and not leave organizers alone with their growing problems. And what about the plus or the minus that comes out of the balance, once the Meeting is over? Up to now, the issue has never been discussed. With rather small meetings behind, and little problems associated with their organizations, there was also no doubt that the meetings would generate a financial surplus. Previous organizers have been very happy to return this surplus to ESID itself, happy as they were with having organized an ESID Meeting. However, since a few years, costs and problems have increased, and the balance (positive or negative) has become a challenge.

More and more, it is becoming an unpredictable one. Personally, I believe that as a Society we can no longer leave the risks and the burden with the organizer, and take the profit, if available. Does this mean that we need to build up a more solid structure to deal with financial aspects related to the Society? Whatever the final answer will be, this also is a matter of growth, and one more important issue to be debated in the General Assembly. **Do not miss the General Assembly in Budapest, or you may miss an important turnpoint in the life of ESID!**

Luigi NOTARANGELO

Treasurer's report

Many members have reacted to my calls for missing membership fees and /or addresses. Unfortunately, many members have **still** not paid their ESID membership fee. Do you know of anyone who is not getting the ESID Newsletters any more and wonders why? Alert him or her to a probable lack of payment.

With the next ESID Newsletter, you will find all the information about how to pay your membership fee for 2006/2007. This will be our first round of payments by the internet, and I hope this will make things a lot easier, and less prone to mistakes.

Esther DE VRIES

Secretary's report

The last ESID Board meeting was held on June 15, 2005.

The most important topic on the agenda was the ongoing organization of the next biennial ESID meeting to be held in October 2006 in Budapest. Like the previous ESID meetings, the 2006 congress will be held together with INGID and IPOPI. Laszlo Marodi from Debrecen University updated the other members of the ESID Board on the progress of the organization. Submission of abstracts for the conference will be possible via the internet, by fax or regular mail; registration will be possible online. Payment of the registration fee will be possible by credit card or money transfer, and reduced registration fees will be available for ESID members. Rooms in several hotels of different price categories will be offered, all in comfortable travelling distance from the congress site, the Budapest Congress Center (the congress site has been introduced by Laszlo Marodi at the last general assembly). Among the categories for submission of abstracts to a poster workshop are T cell immunodeficiencies; antibody deficiencies; complement deficiencies; neutrophil disorders; complex immunodeficiency syndromes; genetic predisposition to infection, autoimmunity and/or allergy; miscellaneous and novel immunodeficiency disorders; animal models and basic immunology; Immunoglobulin substitution therapy and cytokine therapy; stem cell transplantation and gene therapy; psychological issues and quality of life in PID; nursing in PID patients and PID registries.

The next General Assembly will take place at the occasion of the ESID 2006 meeting in Budapest. Among the more principal topics that should be decided by the Assembly are whether in the future there should be a selection criterium for ESID membership and how to handle a financial surplus resulting from a biennial ESID meeting, as well as how to organize the responsibility for potential financial losses from such a meeting.

Following the discussion about the ESID 2006 meeting was the treasurer´s report held by Esther de Vries: she underlined the require-

ment for online payment of ESID membership fees, and the ESID Board confirmed that this should be realized in the very near future. Esther de Vries also encourages all ESID members to send contributions to the ESID Newsletter, such as meeting reports, reports on interesting patients, interesting meetings that are coming up.

Anders Fasth reported on the new ESID fellowship: the visit of Tuba Turul, a colleague from Turkey (a pediatric immunologist/hematologist) to a European PID research lab will be supported.

Finally, Bodo Grimbacher updated the board on the ESID Registry and on his plans to redesign the ESID website.

Hermann WOLFF

Budapest, Hungary

News & Views

Brief report to ESID on the FOCIS International group meeting in Boston on May 13th 2005
Chairman: Stefan Meuer - Germany

Representatives of the twelve or so international Centres of Excellence in Clinical Immunology, recognised by FOCIS in 2003, met in Boston in May 2005 to discuss how the FOCIS format, proven to be so successful in the US, might be adapted to Europe. These centres are listed on the FOCIS website: www.focisnet.org .

The aims of FOCIS are to:
- Increase the visibility of clinical activities in Immunology, and
- Improve awareness of existing opportunities for education and research fellowships
- Provide new monies to enable an increase of opportunities.

There have been three main areas of immunological practice involved: Primary Immune Deficiencies, Rheumatology and Neuro-Immunology, though other specialties include Ophthamology, Nephrology and Infectious diseases.

There are several ways in which the success of FOCIS has been measured so far:
- A forum for uniting those interested in all aspects of immunological diseases to share experiences in promotion & evidence of translational research and provide leadership and support across specialties
- Provision of a framework for research across countries [Canada and Central America] as well as US states
- Shared ideas and platforms for education & recruitment of immunologists (medical and scientific)
- Provision of mentor-based fellowships
- Community benefit for awareness of immunological diseases
- Corporate business sponsorship for raising money from industry, private foundations & governmental agencies.

There has been no money to finance such activities in Europe as the substantial monies

raised so far have been dependent on being used in the US. So, there is a move to set up fund-raising in Europe and South-America along similar lines. There was agreement that, although successful for US centres, the international centres would not benefit from the existing network, as monies raised so far have to be spent in North-America.

The consensus agreement from this meeting was that more international FOCIS centres are needed to provide a quorum for setting up a network to raise funds and implement whichever of these aims are appropriate for Europe. Invitations to apply for such status will be posted on the website and circulated via EFIS, European national and specialist societies. If there is a good response, Stephan Meuer will call a meeting in Europe to discuss the appropriateness and feasibility of organising a similar or different organisation in Europe.

We were very aware that the Clinical Immunology Group (CIG) of EFIS has done an excellent job to promote Clinical Immunology in Europe. The clinical case discussion group and different themed meetings tracing topics from "bench to clinic" have done a really good job. The participants are keen to work with CIG to promote these activities further and we have a chance to get some finances to do now.

The FOCIS group would be grateful if this initiative could be discussed by both the ESID & the EFIS-CIG Board and the information put on the websites.

Helen CHAPEL

Boston, May 12.

Commentary for the Primary Immunodeficiency Diseases Consortium Conference for Summer School alumnae in Boston May 12, 2005

A unique forum for the discussion of all aspects of primary immunodeficiencies was held May 12 in Boston as a satellite meeting to the FOCIS meeting. Talecris Biotherapeutics, The American Red Cross, ZLB, and NIH generously sponsored this meeting. Abstracts were presented on common management issues, new diagnostic strategies, and expanded clinical information on particular immunodeficiencies. The audience comprised Immunologists from a variety of North American, South American, and European countries. All levels of training were represented, including excellent numbers of alumnae of both the CIS and ESID primary immunodeficiency summer schools.

Several themes emerged from the discussion. It is worth mentioning some of the recurring themes and highlights from this consortium meeting. Autoimmune disease is becoming increasingly important in the management of patients with primary immunodeficiencies. Joao Oliveira Filho presented a series of patients with autoimmune lymphoproliferative syndrome (ALPS) and a possible new genetic variation while Pasqualina Ferri described finding evidence of ALPS in patients with diverse autoimmune diseases. Clearly this disorder is more pleomorphic in terms of presentation and genetic heterogeneity than was previously thought. A very vigorous discussion of Immune deficiency, polyendocrinopathy, X-linked syndrome (IPEX) occurred after presentations by Troy Torgerson, Lisa Kobrynski and Meredith Heltzer. These discussions reminded the participants that IPEX might present atypically. Some features that were not previously published were highlighted, such as recurrent staphylococcal infections, developmental delay, recurrent thromboses, and nephropathy. Flow cytometric and immunohistochemical screening tests were described. Importantly in the discussion, Troy Torgerson pointed out that simply measuring CD4/CD25 T cells is not sufficient.

Several other discussions of autoimmune disease arose as the day progressed. Frank

Pessler and Ed Behrens were joined by Dan Kastner, who discussed haemophagocytic lymphohistiocytosis (HLH) secondary to other diseases including autoimmune disease. The distinction of the secondary form from the primary is not always easy and the fevers characteristic of HLH may suggest autoimmune disease or a periodic fever syndrome.

One of the more unusual autoimmune diseases occurs in approximately 10% of patients with common variable immunodeficiency disorders. A granulomatous infiltration of end organs occurs and may lead to significant end organ compromise. Yoshikazo Morimoto presented an elegant study of HHV8 associated with this feared complication. Further discussion from the audience led to the tentative conclusion that HHV8 is an important etiologic discovery and patients who are HHV8 negative may represent a distinct subset. Other topics related to autoimmune disease were the important caution raised by Adina Kay Knight that IgA deficient patients frequently have heterophile antibodies that can interfere with diagnostic assays that rely on antibody detection strategies. Specifically, IgA deficient individuals have a high rate of false positive b-HCG pregnancy tests. The last topic was inflammatory bowel disease in immunodeficiencies. Kimberly Risma presented a patient with NEMO who presented with inflammatory bowel disease and lymphoedema. Ashlesh Murthy presented a murine model of inflammatory bowel disease in which IgA deficiency increased the severity. The clinical association of IgA deficiency and inflammatory bowel disease has long been recognized. This model may allow a greater understanding.

The discussion of a NEMO patient and a patient with IRAK4 deficiency described by Stuart Turvey led to a broader discussion of diagnostic strategies. Stuart Turvey, Kimberly Risma and Jordan Orange discussed the testing of TLR function as a diagnostic strategy. These assays are not standardized between labs but an important point was raised that the assays typically give the same results. It was also pointed out that there does not have to be a complete absence of response to TLR ligands for a patient to be suspected of NEMO or IRAK4 deficiency. Other new diagnostic strategies that were raised included the new screening tests for IPEX mentioned above, utilization of spectratyping in DiGeorge syndrome (Blythe Devlin), and new flow cytometric strategies to detect SCID, WAS, XLP, and HLH (Kimberly Gilmour). The importance of confirmation by mutation analysis was clearly shown by an unusual case of IL-7Ra SCID presented by Punita Ponda. A fascinating new technique to identify SCID patients at the time of the neonatal screen was described by Manish Butte, who has designed and built a microfluidic chamber to detect T cells in a cost effective manner which seems extremely promising as a tool to identify SCID patients prior to infection.

Diagnostic assays for antibody defects and the definition of new genetic types of common variable immunodeficiency disorders represented another topic that engendered much discussion. Emanuela Castigli described patients with IgA deficiency and common variable immunodeficiency disorders found to have mutations in a gene called TACI. A characteristic feature, that was consistent with the TACI knockout model in mice, is a failure to switch to IgA after April stimulation. Bodo Grimbacher summarized his genetic studies of common variable patients. Of familial cases of common variable, 9 patients have been found to have ICOS deficiency, 4 patients have CD19 deficiency, 3 patients have BAFFR deficiency, and 24 patients have TACI deficiency. He thinks it is likely that TACI will ultimately be found to be one of the more common single gene defects associated with common variable immunodeficiency disorders. Klaus Warnatz described a flow strategy to define naïve, marginal zone, memory, transitional, and plasmablast B cells. While the strategy is more complex than most clinical laboratories would have available, it is certainly within reach to perform these studies at most institutions. Using this flow strategy, the genetic types identified by Bodo Grim-

bacher above, could all be confidently identified by flow cytometry with the exception of the patients with TACI deficiency who were heterogeneous in their flow findings. Expanded B cell flow cytometry may not completely predict genetic subsets but may lead to improved clinical subdivision.

The final theme to emerge was management. With uncommon immunodeficiencies, this forum represented an opportunity to academically discuss management options. Gene therapy for hyper IgM, by following the identification of the core translational promoter, was discussed by Philip Zoltick. Vector choice and incorporation of all necessary transcriptional control sequences were highlighted, to obtain activation-dependant CD154 expression in human CD4 cells in vitro. Gary Kleiner, David Amrol, Frank Pessler and Ed Behrens presented several cases of haemophagocytic lymphohistiocytosis. These patients are extremely difficult to manage. Etiologies other than autoimmune disease were discussed. Lysinuric protein intolerance, XLP, NK cell leukemia, Chediak Higashi syndrome and Griscelli syndrome have a high frequency of HLH. Hans Ochs reminded us the SAP/SH2D1A mutations are found in only 60% of patients that clinically have X-linked lymphoproliferative syndrome and thus, failure to find a mutation should not limit diagnosis. Lisa Kobrynski discussed her experience using Rituximab as a treatment for EBV positive haemophagocytic lymphohistiocytosis and Kimberly Risma reminded everyone that perforin mutations could also be seen in lymphomas. Rosalia Ayuso presented a case of an EBV positive NKT cell lymphoma, which presented with progressive hypogammaglobulinaemia. The fevers and immunohistochemistry of a lesion helped to identify the cause.

Management of two other unusual disorders was described. Comel-Netherton syndrome, often thought of as a dermatologic disorder, appears to have a substantial component of immunodeficiency as described by Ellen Renner. IVIG may be appropriate for some patients. Larry Jung presented his experience with multiple intestinal atresia, which is surely the largest series reported. Surprisingly, there was a range of immunologic dysfunction and it appears to be progressive over time.

This consortium presented an enormous range of issues both practical and academic. Beatriz Tavares Costa Carvalho presented data on an awareness survey of pediatricians in Brazil. After identifying a lack of familiarity with primary immunodeficiencies, she is now working on an outreach program to improve knowledge. While some of her findings may be unique to Brazil, her educational program is a model for all of us who do outreach. In a similar vein, the Jeffrey Modell Foundation is inaugurating a new website to act as a discussion forum and an opportunity to publish treatment protocols on patients with primary immunodeficiencies. A similar discussion forum already exists under the auspices of PAGID.

This meeting was highly valued by the participants. Opportunities for interactions centered on primary immunodeficiencies are critical for sharing new information relating to diagnosis and management of these underdiagnosed conditions. This informal setting prompted good discussions, as well as giving young investigators a chance to present cases and data in a friendly environment. A similar event is planned for San Francisco in the summer of 2006 – watch for the announcements on the ESID & CIS websites.

Report on the International Union of Immunological Societies (IUIS) meeting in Budapest 2005

The IUIS expert committee on Primary Immunodeficiency Diseases met in Budapest for 3 days in June this year, to discuss the new findings in Primary Immunodeficiency Diseases. Prior to the committee meeting, scientists and physicians met to present the evidence relating to these findings so that there could be (and there was) far reaching discussion. There were 105 physicians and scientists from 21 countries including those in North America, Europe, Japan, Iran, Australia and Brazil, in addition to the eleven IUIS committee members from round the world.

The range of primary immune deficiencies discussed was very wide, from gene defects such as those resulting in autoimmune problems to molecular studies in diseases as diverse as IgA deficiency and SCIDs. The science included new genes discovered in common and rare forms of PID disease in humans as well as the diseases in mouse models in which specific genes had been "knocked out". Studies on immunity in the lamprey, a new animal to be studied from early in evolution, were of great interest and will help to understand how the immune system developed and identify new basic mechanisms that can go wrong.

The scientific sessions were divided according to the human disease group to which each talk was relevant. The meeting started with innate immunity. There is great excitement in the new area of interest, Toll-like receptors and the associated signalling pathways, involving a central molecule NFκB. These responses relate to the most immediate response to infection and are proving to be very interesting and fruitful areas for new human diseases. It is already clear that defects in these pathways result in a wide range of immune problems. There was also news on potential gene therapy for chronic granulomatous disease, though as in gene therapy for SCID, these are early days. Two adults had their blood-forming stem cells harvested, and a correct copy of the gene was provided by a retrovirus. The corrected cells were re-infused after treatment; in the following year both men had unprecedented increases in neutrophil numbers and were able to clear long-standing, serious infections. In view of the recent reports of serious adverse events in gene therapy for X-linked SCID, careful monitoring of patients treated by gene therapy for CGD is mandatory; more work must be done to achieve safe as well as effective gene therapy treatments.

There was new information on regulation of immune cells. Whilst immune systems must be "activated " in order to work, they must also be controlled to prevent inappropriate responses, such as autoimmunity or excessive proliferation. If there are defects in regulation, immune deficiencies may and do result.

Another new area was that on cell trafficking. In order to move to sites where they can be effective, all types of immune cells must not only be flexible but must respond to specific signals. Trafficking of cells depends on molecular structures (and therefore genes) for receiving signals, structural changes to squeeze through blood vessels and shape to accommodate & assist other cells in the "immune team". Defects in the genes for any of the structures or messengers involved cause a defective immune system.

The final session was devoted to antibody production and started with new exciting findings in B cell development. There is much interest in trying to sort out the myriad of primary immune deficiencies involving antibodies, not least to improve treatment & management of patients with these conditions. In order to switch on plasma cells to produce large amounts of antibodies relevant to a pathogen, factors with names like BLIMP-1 and Bach1 and Bach2 have been found to be needed in mice and these may be missing in some patients with antibody defects.

Complex issues involving enzymes, genetic transcription factors & signalling pathways are involved in the recognition of germs by B cells.

Extrapolations from findings in mice have yielded exciting results in patients who fail to make antibodies. Laboratories in various parts of the world have independently found defects in several different genes responsible for B cell maturation in a small proportion of patients with the commonest forms of primary antibody deficiency (common variable immunodeficiency disorders). Patients have been found who are missing functional genes for B cell development; these include genes such as TACI and BAFF R and others are missing surface proteins such as CD19. The resulting defects cause a range of clinical diseases of varying age of onset and severity, indicating that these findings are not the whole story and that other genes will be found that modify these diseases. Furthermore, even the most optimistic only expect these defects to account for a very small proportion of the multiple genes involved in the various primary immune deficiencies involving antibodies. There may prove to be as many categories of antibody defects as there are SCIDs!

The need to continue to use animal models to indicate where to look in human immune systems, both adaptive (antigen specific) and innate (non-antigen specific), for potential gene defects was underlined by these presentations. The challenge of applying such findings from in-bred animals to out-bred humans, further compounded by the effects of the serious infections with which patients originally come to medical attention, will continue to encourage immunological scientists and clinicians for many years to come.

As ever, despite the fantastic surroundings, the delegates found the scientific sessions far too interesting to enjoy the delights of this beautiful city! A quick clamber up the hill on the gardens on the Buda side or a visit to the castle gave only a taste of the wonderful surroundings, but lively and friendly discussions more than compensated. We look forward to the ESID:INGID:IPOPI meeting in Budapest next year!

This meeting was organised by Luigi Notarangelo and Raif Geha with the Jeffrey Modell Foundation. We thank the following for their generous sponsorship: Baxter Healthcare, Octapharma, Talecris, Biotherapeutics, ZLB Behring and help from Correlagen, the US National Institute of Allergy & Infectious Diseases, National Institute of Child Health & Human Development and NIH Office of Rare Diseases.

Helen CHAPEL & Jennifer PUCK

(from Orphannet's home page)

PROPOSAL :

Collaborative study on the syndrome associating multiple intestinal atresia and immunodeficiency

We are interested in trying to identify the gene associated with multiple intestinal atresias associated with immunodeficiency (MIAI). This is a rare condition with autosomal recessive inheritance.

A small number of cases have been reported. The syndrome associates multiple intestinal atresias located on both the small intestine and the colon and a profound T+ B cell immunodeficiency. No molecular mechanism has yet been found. We are in the process of collecting DNAs from informative families in order to perform as a first step a genetic linkage analysis (genome scan).

References:

L.A. Moreno et al. American Journal of Medical Genetics. 1990; 37:143-46.

M. W. Walker et al. The Journal of Pediatrics. 1993;123:93-5.

M.E. Rothenberg et al. Immunodeficiency. 1995;5:171-8.

S.W. Moore et al. J .Pediatr Surg. 1996;31: 1733-5.

W. Lambrecht et al. J. Pediatr Surg 1998; 33:794-7.
J. Bass. J. Pediatr Surg. 2002; 37:941-2.
R.K. Gilroy et al. Blood. 2004; 103:1171-4.
G. Lopez-Herrera et al. Arch Med Res. 2004;35:348-58.

If you know such cases or have access to, please contact us at : Geneviève de Saint Basile, MD, PhD or Alain Fischer, MD, PhD; Inserm Unit 429, Necker-Enfants Malades Hospital. Tel : +33 1 44 49 50 80 , +33 1 44 49 50 71, +33 1 44 49 48 22, Fax : +33 1 42 73 06 40, +33 1 42 73 06 40. email : sbasile @necker.fr, fischer@necker.fr

Geneviève DE SAINT BASILE
Alain FISCHER

Meetings announced by

Proteomics: Challenges and Emerging Technologies. Friday, November 11, 2005. Birkbeck College, London.

The highlights include: The role of the alpha-v/beta-6 integrin in invasion. Connective tissue growth factor: A matricellular protein with key functions in tissue repair, scarring and fibrosis. Involvement of the Extracellular Matrix and RGD-Peptides in Apoptosis Induction. Novel functions for integrins in epithelial morphogenesis in Drosophila. MT1-MMP: a key metalloproteinase in cell migration in tissue. MT1-MMP activation by the adhesion receptor CD44 promotes extracellular matrix degradation. Transmembrane proteoglycan syndecan family: regulatory molecules for cell adhesion and migration.

The Deadline for early registration is October 10th. The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students)

SNP mapping. Friday 21 st October, 2005. Birkbeck College, London. The Deadline for early registration is September 10th The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students).

Assaying Chemokines and Chemotaxis. Friday October 28th, 2005. Birkbeck College, London. The Deadline for early registration is September 10th. The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students).

Assaying Vaccine Efficacy in Companion Animals. Wednesday, November 02, 2005. Birkbeck College, London. The Deadline for early registration is October 10th. The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students).

Regenerative Medicine. Friday, November 04, 2005. Birkbeck College, London. The Deadline for early registration is October 10th. The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students).

High Throughput Technologies and Data Analysis. Wednesday, November 09, 2005. Birkbeck College, London. The Deadline for early registration is October 10th. The early registration fee is £80 (£70 for IBMS members; £40 for students). After the early registration deadline the fee is £160 (£80 for students).

For General enquiries :enquiries @ euroscicon.com. To Register go to http:// www.euroscicon.com. CPD accreditation has been sought for this meeting.

Inga BIMBIRYTE, EuroSciCon

Interesting papers

Some papers of interest to the ESID community, selected by Claire FIESCHI from Necker Hospital, Paris, France:

- Three papers concerning the absence of NKT cells in patients with SAP deficiency:

1. Nichols KE, Hom J, Gong SY, Ganguly A, Ma CS, Cannons JL, Tangye SG, Schwartzberg PL, Koretzky GA, Stein PL. Regulation of NKT cell development by SAP, the protein defective in XLP. Nat Med. 2005 Mar;11 (3):340-5.

2. Pasquier B, Yin L, Fondaneche MC, Relouzat F, Bloch-Queyrat C, Lambert N, Fischer A, de Saint-Basile G, Latour S. Defective NKT cell development in mice and humans lacking the adapter SAP, the X-linked lymphoproliferative syndrome gene product. J Exp Med. 2005 Mar 7;201(5):695-701.

3. Chung B, Aoukaty A, Dutz J, Terhorst C, Tan R. Signaling lymphocytic activation molecule-associated protein controls NKT cell functions. J Immunol. 2005 Mar 15;174 (6):3153-7.

- The two papers of mutations in TACI in patients with CVID:

1. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005 Jul 10.

2. Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, Hammarstrom L, Grimbacher B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet. 2005 Jul 10.

- And last, a new cause of SCID:

1. de Saint Basile G, Geissmann F, Flori E, Uring-Lambert B, Soudais C, Cavazzana-Calvo M, Durandy A, Jabado N, Fischer A, Le Deist F. Severe combined immunodeficiency caused by deficiency in either the delta or the epsilon subunit of CD3. J Clin Invest. 2004 Nov;114(10):1512-7.

Some impressions of Budapest, where the bienial ESID meeting 2006 will take place:

Working Party reports

ESIDjuniors Working Party

Dear all, let's move on! The new ESID website will be operable soon!

With the form on page ... we want to invite you to become an active member of the ESID*Juniors* Working Party and express your ideas for the ESID*Juniors* Working Party and the ESID*Juniors* Webpage.

We would like to ask you to fill in the form enclosed with this issue of the ESID Newsletter, either by sending us an email to request this form as a data file or by faxing this form to Ellen or Pim (see contact addresses below).

Please, provide this form to all your colleagues and friends who might be interested!

Who can join? Every ESID member below or around 35 years of age or still feeling to be an ESID junior!

What are our main plans and goals? Exchange of helpful information on education topics like trainings, meetings, scholarships, a chat room, mailing list, case report/answer page, and links of useful websites. We will have a biennial meeting held at the same time as the ESID congress, which will be in Budapest, October 2006.

The new ESID Summer School is coming up at Mallorca in October and we wish them to have as much fun as we had in 2003!

Eleonora, Chris, Jana, Pavel, Ellen, and Pim

Contact information for the application form or any additional ideas or questions:

Pim van der Vossen
Nijmegen University & Children's Hospital St Radboud, Nijmegen (the Netherlands)
Fax: **31-24-3616428
Email: p.vandervossen@cukz.umcn.nl

Ellen Renner
University of Washington & Children's Hospital Medical Center, Seattle (USA)
Fax: **1- 206-987-7310
Email: erenner@u.washington.edu

Educational Working Party

Within the Educational WP, we have been busy selecting the candidates for the upcoming ESID Summer School at Palma de Mallorca, October 19 - 23. Twenty-six young doctors and scientists from different parts of the world were selected. Most of them from Europe of course, but as previously we also have persons coming from Australia, New Zealand and Latin America.

The agenda of the Summer School will as previously concentrate on three topics: SCID as the disease is such an important model for T cell development, receptor diversity plus that the disorder exemplifies important clinical and diagnostic issues. Also, SCID allows for discussions on treatment with stem cell transplantation and gene therapy. Hypogammas of different etiologies will of course be covered and this topic will allow for a thorough discussion of immunoglobulin substitution. Finally, we will this year cover innate immunology and its defects.

The Summer School is as previous years free to the students including accommodation. This is possible thanks to generous support from Baxter, Bayer, Grifolds, Octapharma and ZLB Behringer.

As reported elsewhere, the preparations for next year's ESID biennial meeting are going on. We plan for an Educational Day this time asa well, as at the previous meetings at Weimar and Versailles. The Educational Day will start at 9 a.m. so you should plan to come the day before, if you want to participate. The topic will be B cell differentiation and its defects.

Anders FASTH

Genetics Working Party

Dear Collegues,

As you know, I have the privilege to chair the Genetics Working Party. I am honored to cover this position, but at the same time it is very difficult to start any new project.

During the General Assembly in Versailles, I showed my idea to design a new study on transplantation in patients affected by malignant severe Osteopetrosis due to different genes, as we have observed a different outcome according to the affected gene. I asked many times your opinion also in my report in the Newsletter, but so far there are no reactions and it seems to be very difficult to convince people to join this study.

So we have decided to elaborate our clinical data form. We sent this form to clinicians interested in the study.

However, **I am still eager to receive your comments and opinion,** and whether you think that a similar analysis could be extended to other diseases.

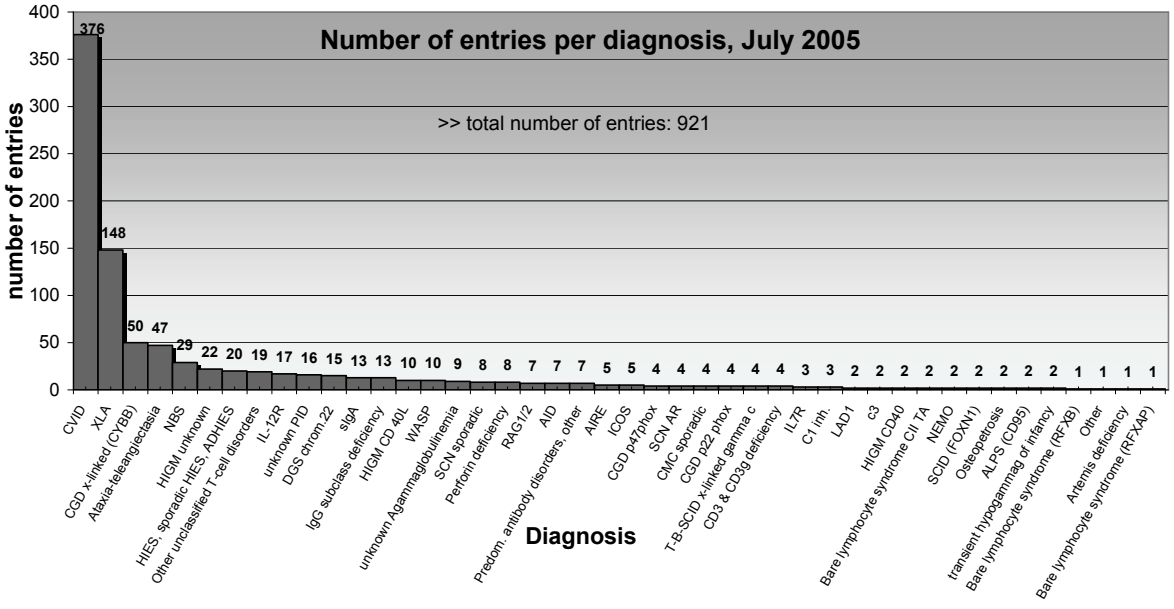
Finally a personal thank you to Fred S. Rosen who recently died (21 May). He has changed the story of Immunodeficiency, shedding a new light on the workings of the normal immune system. A brief comment on his life is published in Nature vol 435,2005.

Anna VILLA

Registries Working Party

In the last ESID Newsletter, we reported on our survey to find out what problems were keeping some documenting centers from entering their patients into the ESID online database. We found the main obstacles being a lack of time for documentation, difficulties to obtain an ethics/ data protection approval or technical problems.

This time, we are glad to say that the number of entries is constantly increasing and that now the total number of patients in the registry has reached 921 (from 231, end of March)!



This achievement however is mainly due to the fact that 336 patients have been imported on an electronic basis from the Italian AIEOP online PID registry. The AIEOP registry is the only national PID registry where the export of pre-existing data is useful and feasable. Please have a look at the chart on the previous page for a concise overview of the progress that has been made in the ESID database.

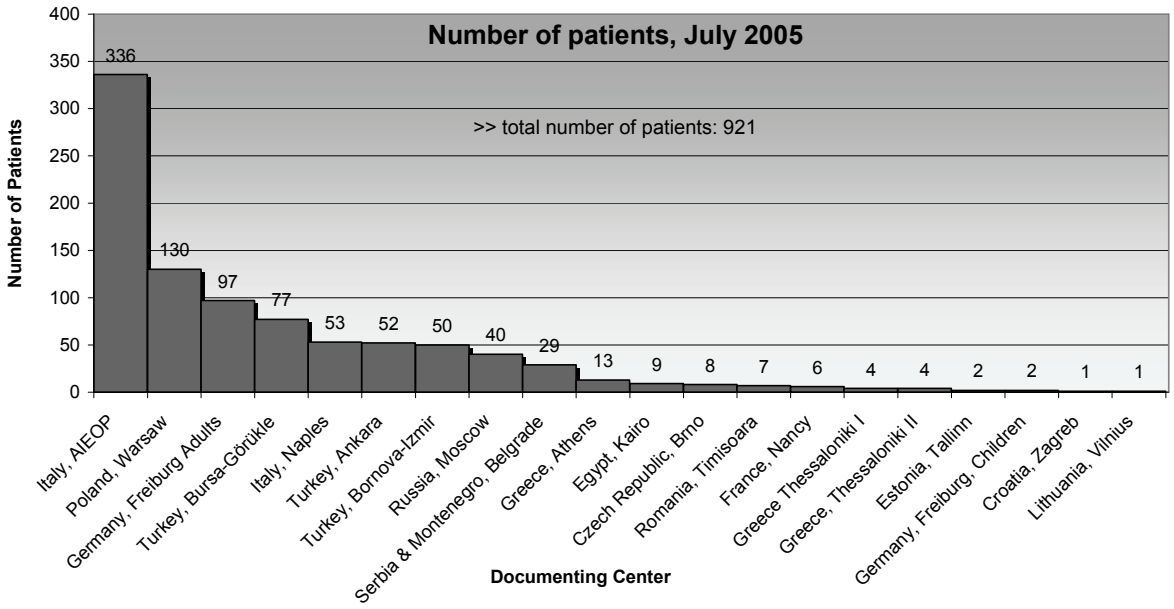
And the winner is…

As you all know, the sponsors of the database support the work of the documentalists by rewarding 10 Euro for each complete patient core dataset. But this is not the only documentation incentive: ESID awards travel grants to those centers that have entered the largest number of patient data. We are very happy to announce that the first prize of 3 travel grants of 500 Euro goes to Warsaw with 130 patients. Bursa-Görükle will receive 2 x 500 Euro for 77 documented patients. Furthermore, we decided to award not one but four single travel grants of 500 Euro each. These go to Naples (53 patients), Ankara (52 patients), Bornova-Izmir (50 patients) and finally to Moscow (38 patients in extremely short time). Congratulations!

An extra bonus of 2000 Euro goes to those centers who will have reached the mark of 50 patients by August 1st. In this context we have verified the data quality of all centers, especially that of the top centers, in order to make sure that all relevant fields of the red core dataset have been filled in correctly. As far as we can see today (at the editorial deadline in mid-July), the sum of 2000 Euro will be awarded to AIEOP, Warsaw, Freiburg, Bursa-Görükle, Naples, Ankara and Bornova-Izmir. Congratulations to these centers and thank you for your intensive work during the last months.

We are happy to welcome two new documenting centers, the Medizinische Hochschule Hannover, Germany, and the Polish-American Institute of Paediatrics in Krakow, Poland. We wish these two centers a good start in the documentation of their patients.

Some centers are still working on the application for an ethics approval, others have already obtained the approval by their local committees. We would now like to ask all of you to send us a copy of your ethics approval for our documents (by fax: +49-761-270-3531 or post). If you have difficulties in obtaining the ethics approval, please let us know. We will also try to find a way to make things easier for you,



e.g. by filling in your local application forms for you, providing written documentation on the database etc.

Since our programmers are permanently working on new disease-specific subregistries, they need the input of the steering committees who are still working on the evaluation of such data models. In this regard, we would like to ask the steering committees to finish and hand in their proposals soon, so that as many subregistries as possible can be programmed in the near future.

The following subregistries are already online: CVID, Secondary Hypogamma globulinemia, ICOS deficiency, IPEX-Syndrome, DiGeorge syndrome, Hyper-IgE syndrome, Nijmegen Breakage Syndrome (NBS1), ICF Syndrome (DNMT 3B). The subregistries for SCID, HIGM, IgAD, osteopetrosis, AT and TACI are currently in preparation, and will be available during 2005.

On September 30th and October 14th we will be organizing two identical workshops for ESID members in Freiburg in order to increase the familiarity with the functions and the handling of the database. Unfortunately, we were not able to accommodate everyone who was interested in the workshop because slots and funding are limited. However, smaller groups will keep the training highly effective for everyone and those disappointed this time will have another opportunity next year.

Bodo GRIMBACHER

See additional chart and form regarding the Registries WP on pages 18-20.

BMT Working Party

Two issues from the BMT Working Party:

1. the current guidelines/'protocols' - joint ebmt/esid wp - are now on the ESID website as well (as on the EBMT website); however, these are now already one year old and will need 'revamping' on the next Working Party meeting this autumn in Utrecht.

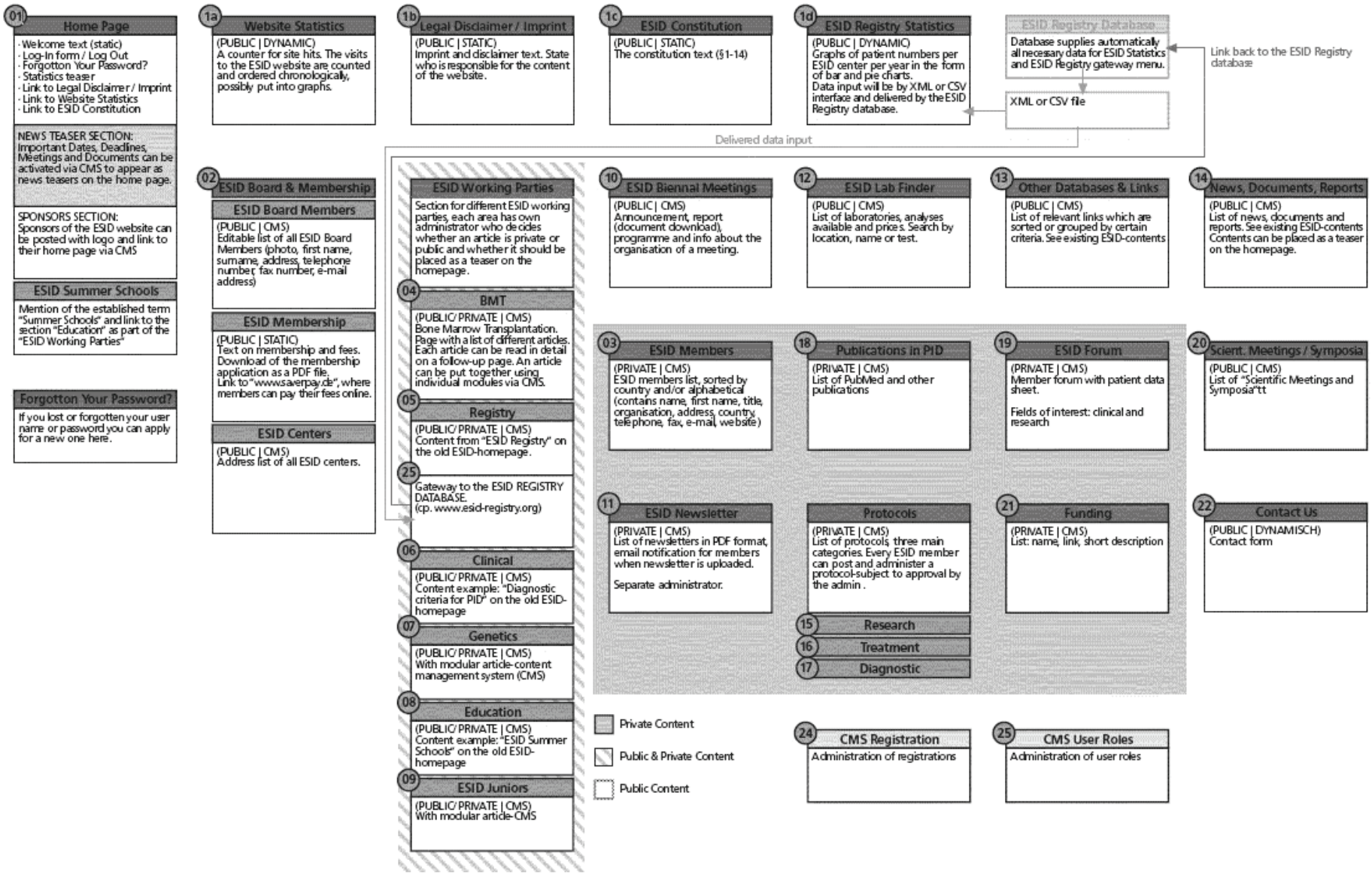
2. after 'informal' discussion with several colleagues earlier on this year about the indication for stem cell transplantation in a patient with cartilage hair hypoplasia (CHH), I would like to propose a multicentre study on the following (jointly with the Clinical Working Party - Bobby Gaspar). Therefore, **please answer the following questions for us:**

a/ do you routinely perform immunological tests on your CHH patients?
b/ how many patients with CHH and an associated immunodeficiency (including, but please report as separate figures, the 'scid' phenotype) have you seen?
c/ how many patients with CHH with a 'severe' viral infection (cmv, ebv, adenovirus) have you seen?
d/ what have you decided to do with these patients and what was the outcome?
e/ how many patients with CHH have you transplanted (including, but please report as separate figures, the 'scid' phenotype)?

And send the answers to:
h.gaspar@ich.ucl.ac.uk and/or
mario.abinun@ncl.ac.uk

Thanks a lot for your cooperation,

Mario ABINUN


01
Home Page
· Welcome text (static)
· Log-In form / Log Out
· Forgotton Your Password?
· Statistics teaser
· Link to Legal Disclaimer / Imprint
· Link to Website Statistics
· Link to ESID Constitution
NEWS TEASER SECTION:
Important Dates, Deadlines, Meetings and Documents can be activated via CMS to appear as news teasers on the home page.
SPONSORS SECTION:
Sponsors of the ESID website can be posted with logo and link to their home page via CMS
ESID Summer Schools
Mention of the established term "Summer Schools" and link to the section "Education" as part of the "ESID Working Parties"
Forgotton Your Password?
If you lost or forgotten your user name or password you can apply for a new one here.
1a
Website Statistics
(PUBLIC | DYNAMIC)
A counter for site hits. The visits to the ESID website are counted and ordered chronologically, possibly put into graphs.
1b
Legal Disclaimer / Imprint
(PUBLIC | STATIC)
Imprint and disclaimer text. State who is responsible for the content of the website.
1c
ESID Constitution
(PUBLIC | STATIC)
The constitution text (§1-14)
1d
ESID Registry Statistics
(PUBLIC | DYNAMIC)
Graphs of patient numbers per ESID center per year in the form of bar and pie charts.
Data input will be by XML or CSV interface and delivered by the ESID Registry database.
ESID Registry Database
Database supplies automatically all necessary data for ESID Statistics and ESID Registry gateway menu.
XML or CSV file
Link back to the ESID Registry database
Delivered data input
02
ESID Board & Membership
ESID Board Members
(PUBLIC | CMS)
Editable list of all ESID Board Members (photo, first name, surname, address, telephone number, fax number, e-mail address)
ESID Membership
(PUBLIC | STATIC)
Text on membership and fees. Download of the membership application as a PDF file.
Link to "www.saerpay.de", where members can pay their fees online.
ESID Centers
(PUBLIC | CMS)
Address list of all ESID centers.
ESID Working Parties
Section for different ESID working parties, each area has own administrator who decides whether an article is private or public and whether it should be placed as a teaser on the homepage.
04
BMT
(PUBLIC/ PRIVATE | CMS)
Bone Marrow Transplantation. Page with a list of different articles. Each article can be read in detail on a follow-up page. An article can be put together using individual modules via CMS.
05
Registry
(PUBLIC/ PRIVATE | CMS)
Content from "ESID Registry" on the old ESID-homepage.
25
Gateway to the ESID REGISTRY DATABASE.
(cp. www.esid-registry.org)
06
Clinical
(PUBLIC/ PRIVATE | CMS)
Content example: "Diagnostic criteria for PID" on the old ESID-homepage
07
Genetics
(PUBLIC/ PRIVATE | CMS)
With modular article-content management system (CMS)
08
Education
(PUBLIC/ PRIVATE | CMS)
Content example: "ESID Summer Schools" on the old ESID-homepage
09
ESID Juniors
(PUBLIC/ PRIVATE | CMS)
With modular article-CMS
10
ESID Biennal Meetings
(PUBLIC | CMS)
Announcement, report (document download), programme and info about the organisation of a meeting.
12
ESID Lab Finder
(PUBLIC | CMS)
List of laboratories, analyses available and prices. Search by location, name or test.
13
Other Databases & Links
(PUBLIC | CMS)
List of relevant links which are sorted or grouped by certain criteria. See existing ESID-contents
14
News, Documents, Reports
(PUBLIC | CMS)
List of news, documents and reports. See existing ESID-contents
Contents can be placed as a teaser on the homepage.
03
ESID Members
(PRIVATE | CMS)
ESID members list, sorted by country and/or alphabetical (contains name, first name, title, organisation, address, country, telephone, fax, e-mail, website)
18
Publications in PID
(PRIVATE | CMS)
List of PubMed and other publications
19
ESID Forum
(PRIVATE | CMS)
Member forum with patient data sheet.
Fields of interest: clinical and research
20
Scient. Meetings / Symposia
(PUBLIC | CMS)
List of "Scientific Meetings and Symposia"tt
11
ESID Newsletter
(PRIVATE | CMS)
List of newsletters in PDF format, email notification for members when newsletter is uploaded.
Separate administrator.
Protocols
(PRIVATE | CMS)
List of protocols, three main categories. Every ESID member can post and administer a protocol-subject to approval by the admin .
15
Research
16
Treatment
17
Diagnostic
21
Funding
(PRIVATE | CMS)
List: name, link, short description
22
Contact Us
(PUBLIC | DYNAMISCH)
Contact form
Private Content
Public & Private Content
Public Content
24
CMS Registration
Administration of registrations
25
CMS User Roles
Administration of user roles

OSTEOPETROSIS GENE DEFECTS DATABASE

I.T.B. - CNR

Patient's name:
Date of birth: (DD/MM/YY)

Referring physician: Name:
Institution:
Address:
Tel:
FAX:
e-mail:

1. Treatment (check all those that apply)

1a BMT: Age at BMT:
 Date of BMT:
 Type of donor:
□ genotypic / phenotypic HLA-identical family donor
□ HLA-mismatched family donor (HLA-type don/rec)
□ HLA-matched unrelated donor (HLA-type don/rec)
□ HLA-mismatched unrelated donor (HLA-type don/rec)
 Stem cell source:
□ PBSC (CD34/CD3 dose/kg, T-cell-depletion / method):
□ BM (NC / kg, preparation method):
…….
 Conditioning regimen:
 GVHD-prophylaxis:

1b BMT course / complications:

 Engraftment at day: ……
WBC >
Granulo.>
Reticul. >
 G-CSF until day

 Last blood trasfusion:

 Rejection (if yes, treatment):

 Acute GvHD (organ/grade):

 Chronic GvHD (organ/grade): ……...

 VOD (if yes, describe):

 Pulmonary complications (if yes, descibe):

 Other complications (if yes, descibe):

2b Outcome of BMT (clinical)

□ Dead at age
cause (specify) ……..

□ Alive and well, with engraftment
chimerism analysis (date/cells/method):
……

□ Alive, without engraftment

3.Present clinical status at day: …… / age : ……..

Last follw-up date:

□ Bone biopsy □ no
□ yes:
□ if yes: description

□ Vision impairment
□ Deafness
□ Acoustic evoked potential
age
□ VEP
age
□ NMR
age

□ Neural defects □ if yes: description

□ Growth defect □ if yes: description

□ Hematological defects
□ Anemia
□ Pancytopenia
□ Hepatoslenomegaly