ESID Newsletter

Contents

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

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

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

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

Front page:
Horseshow during ESID meeting in Budapest.

Dear ESID members,

Due to the very end-of-the-year busy days I had, it is only just in 2006 that I can send the ESID Newsletter 2006-4 to the printers. And you will probably receive it somewhere in January 2007.

We can look back on another very active and successful ESID year, with lots of new activities, and ongoing action on the old ones.

I am very happy to have several ESID junior members helping me in the Editorial Board from now on, and you can already see some effect of this in this issue of the ESID Newsletter. I hope it will become more obvious with every coming issue!

I once again invite everyone who is interested in working on the Editorial Board - be it junior or not ! - to join us in the effort to make an even better ESID Newsletter with every new issue.

Please read about the things we discussed during the General Assembly, the plans and achievements of the Working Parties, and about the efforts of Waleed Al-Herz to develop PID-care in Kuwait.

Do notice the dates that have been set for the ESID Summer School 2007, and let anyone who could be interested know about them! Further details will be published in the next issue of the ESID Newsletter, and on the ESID website, when available.

I wish you all the best for the year 2007 !

Esther DE VRIES

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

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

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

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

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

= ESID Information =

President's letter

Dear ESID members,

The ESID meeting in Budapest turned out to be a great success, with about 1,000 attendees from all over the world and an amazing series of outstanding oral and poster presentations.

The field of primary immuno deficiencies is growing at an ever-increasing rate! More clinical diseases, more disease-causing genes, more physicians and researchers involved, more patients, and a global trend of increased awareness and better care of primary immunodeficiency diseases. ESID plays a crucial role in this process and we can be proud of it.

We should go on promoting the core values that made ESID successful over the years: collaboration between centers, patient-based and patient-directed research, and a European society that is open to the world, for the ultimate benefit of patients world-wide. I can assure you that I will promote these values as the new President of ESID, following the line of thought and action of Luigi Notarangelo and former ESID Presidents. I can also assure you that I am immensely grateful to you. It is an honor to chair ESID and I will do my very best to deserve your trust.

Jean-Laurent CASANOVA

Secretarial report

Notes from the ESID general assembly held on October 5th (first part) and 6th (second part), 2006, in Budapest during the 12th ESID meeting

AGENDA for the ESID General Assembly
(topics have been published in advance on the internet, order of presentation has been regrouped into topics for Oct. 5 and Oct. 6)

October 5th, 14:00-15:00
- Welcome and presidential report (L. Notarangelo)
- Secretary´s report (H. Wolf)
- Treasurer´s report including the biennial ESID membership fee (E. deVries)
- Introduction to a proposal for statutes of ESID (a legal act) and decision whether corresponding changes to the current ESID constitution should be made (E. deVries)
- Election of ESID Board members – introduction to the voting procedure (voting pass)

October 6th, 14:00-16:00
- Reports of the chairpersons of the ESID Working Parties
- Report of the 2008 biennial ESID meeting president and approval of the meeting site by the assembly (E. deVries)
- Election of the meeting president for the ESID meeting 2010
- Proposal of the new ESID legal act and corresponding changes to the current ESID constitution – voting results
- Election of ESID Board members – election poll; transfer of duties from old to new Board members
- Proposal of changes to the current ESID Constitution with electronic voting later in 2006 (J.-L. Casanova)
- Clinical PID issues, e.g. raising PID awareness: PID warning signs for adults
- Varia

MINUTES OF THE GENERAL ASSEMBLY OF ESID

The 2006 ESID General Assembly was held in Budapest at the occasion of the 12th ESID meeting. The General Assembly was divided into two parts held on two consecutive days, with the voting procedure taking place in between.

The president of ESID Luigi Notarangelo opened the first part of the General Assembly. In his presidential report he introduced the audience to the most important topics on the agenda of this biennial General Assembly, such as the creation of a new Legal Act and the subsequent changes to the existing ESID Constitution. He also announced the recipient of the 2006 ESID fellowship grant and asked the General Assembly for consent to the creation of a new Working Party for PID care in development proposed by the ESID board. The ESID members voted in favor of this new Working Party, and elected Laszlo Marodi as its chairman without a contra votum.

In his report, the ESID secretary informed the General Assembly about the topics of the three ESID Board meetings that took place since the ESID 2004 meeting in Versailles. Most of the time delt with organisatorial aspects of the Budapest meeting such as the selection of the congress venue, the registration fee and the scientific program. Updates on the ESID finances were given regularly by the ESID treasurer who also reported on the upcoming ESID Newsletters. During these two years, a new ESID fellowship was created to support the work of young scientist in the field of PID, and a change in the organisation of the ESID homepage was realized. Other issues remained unsolved and should be further discussed in the future, such as how to deal with financial obligations and/or profits of ESID meetings.

The next topic in the agenda was the treasurer´s report. Esther de Vries updated the General Assembly on the ESID Summer School account, the ESID Registry account and the regular ESID account. The ESID membership fee will not be increased. There will be one last reminder to members that have not paid their membership fee for some time before there membership will be terminated. Martin Hadam from the audience asked whether automated bank transfer could be accepted in addition to online payment which is currently the only way to pay the membership fee, but according to the treasurer this would create administrative difficulties; for the realisation of this or other additional administrative actions at least one part-time administrative employee would be needed. A decision on this topic was postponed for future discussions. The balance of the three ESID accounts was accepted by the General Assembly.

Esther de Vries then presented the proposal for a new Legal Act. She explained the reasons why this Legal Act is necessary, most of all because it solves the question of liability not only for the members of the ESID Board but also for every ESID member. Her presentation was followed by a lengthy discussion about the pro and contra of the contents of the proposed Legal Act, with lively input from ESID members present in the audience. This was then followed by a vote of the General Assembly by hand raising on the following two questioins: 1.) does the General Assembly accept the need to have a Legal Act – 74 in favor, 1 against, 2 refraining from the vote; 2.) does the General Assembly accept that no discussion should be carried out about contents of the Legal Act that remain unchanged as compared to the current situation in the Constitution – 76 in favor, 0 against, 3 refrain from voting. The ESID members were then asked to vote on the new ESID Board members and the new ESID Legal Act by anonymous written ballot (voting pass).

On October 6th, 14:00 the second part of the General Assembly took place chaired by Jean-Laurent Casanova, the ESID president-elect ready to take over his duties.

Mario Abinun, chairman of the BMT &

SCT Working Party reported from the joined meeting with EBMT and the resulting updated treatment guidelines that will be published on the internet soon.

Bodo Grimbacher reported from the Registry Working Party and informed about a survey on specialist physician perspectives on PID in Europe – what is the current status of PID care in Europe, a survey that should be completed soon. He further proposed two draft versions of warning signs for PID in adults and asked for approval by the ESID General Assembly. A voting by hand raising was carried out on the questioin whether the General Assembly thinks it is ready to accept one of the two versions – 25 were in favor of voting now on the topic of warning signs for PID in adults, but the majority felt that this topic should be published on the ESID website and further discussion should be carried out before a final version could be accepted by electronic voting. An award will go to the center that reported the most patients to the Registry in 2006. Bodo Grimbacher finally informed us that personalized input of patient data into the ESID Registry is available on request, and that the number of disease-specific databases within the Registry is increasing.

Bobby Gaspar from the Clinical Working Party reported on the work on diagnostic guidelines for severe congenital neutropenia; in addition, information coming from the ADA survey on management and outcome of this disease has been evaluated, a form to include future patients should be available through the ESID website. More activities are in progress, news will be circulated through the ESID Newsletter.

Two recent studies have been conducted by the Genetics Working Party headed by Anna Villa: 1.) a retrospective study on transplant outcome in osteopetrosis, and 2.) a study on the biological effect of spontaneous reversion in PID. The results from the first study will be presented at the Inborn Error Working Party meeting in Prague in October 2006, the questionaire can be found on the ESID website. The first disease to be adressed in the second study in cooperation with Fabio Condotti and David Nelson will be WAS, the respective questionaire can be found on the ESID website.

Anders Fasth from the Educatinal Working Party reported on the ESID Summer School that is organized every other year, with an Educational Day at the beginning of the ESID meetings in the other years. The 5th ESID Summer School took place in Palma di Mallorca in 2005 with 40 students attending. Future Summer Schools may move more to the region of the East European countries. The Young Investigators Award is another important activity of the Educational WP, the recipient for 2005 spent a year in van Dongens Lab. Travel grants for visitors to the ESID meeting from outside Europe have been donated.

Eleonora Gambineri reported on behalf of Pim van der Vossen and Chris Königs from the ESID*juniors* Working Party. The idea for this group came out from the 2003 ESID Summer School and was formally established in 2004; one of the aims was to create a section for ESID*juniors* on the ESID website, and the creation of an ESID internet forum was particularly important for the activities of this Working Party. The Working Party chairperson changed twice during the previous two years, due to personal reasons. More will be discussed during a Working Party meeting taking place later on October 6th.

In her report on the ESID 2008 meeting Esther de Vries as the meeting president informed about the congress venue (an internet video of the Theater aan de Parade in s´Hertogenbosh and views of the city are shown), the scientific committee and the first announcement that has already been distributed. The organization of the meeting is very well advanced: the main hall of the congress venue has 900 theatre-like seats, various smaller rooms for workshops are available in the same building. Pre-reservations for hotel rooms have been made, the travel from Amsterdam´s Schiphol airport to the

congress will take about an hour by train (the direct train leaves the airport several times a day). As a novelty a special ESID members welcome club will be organized for this meeting as an opportunity for the ESID members to socialize. Reinhold Schmidt asked whether rooms for satellite symposia are available, parallel symposia with up to 400 attendants can indeed be held in a building close by. More time will be reserved for poster presentations, as requested by Klaus Warnatz. The General Assembly formally approved the ESID 2008 meeting venue by handraising vote (101 votes in favor, no contra votum).

Anna Sediva was then asked to give a presentation introducing Prague as a possible site for the ESID 2010 meeting, with Istanbul presented as an alternative by Necil Kutukculer. The congress venue in Istanbul (Rumeli Fair and Exhibition Hall) has large rooms of 1250 and 500 seats, in 15 minutes walking distance from the congress center are several international hotels. The General Assembly then decided by vote (handraising) in favor of Istanbul as the 2010 ESID meeting venue (52 votes for Istanbul, 30 votes for Prague).

Next in the agenda were the voting results for the new ESID Board presented by Esther de Vries: 91 voting passes had been returned, results for the Board positions whith more than one candidate were the following: for the position Genetics Working Party chairperson: Naomi Taylor 57 votes, Esther van der Vosse 15 votes, abstained 19; for the position of the Juniors Working Party chairperson: Eleonora Gambineri 46 votes, Ales Janda 31 votes, Abstained 14; in addition, 3 votes named Anders Fasth as secretary (he refused to overtake this position) and one vote proposed that he should remain chairman of the Educational WP (which was not possible according to the ESID Constitution). One member suggested Romain Micol for Registry WP, and two nominees were mentioned without designated position. For all other Board positions only one candidate had applied (Andrew Cant as new Educational WP chairman, Bodo Grimbacher as secretary, Mario Abinun reelected as BMT&SCT WP chairperson, Esther de Vries reelected as treasurer, Bobby Gaspar reelected as Chairman Clinical WP, Gerhard Kindle as new Registry WP chairman, Laszlo Marodi was elected as chairman of the new WP PID care in development, Luigi Notarangelo as past president). The General Assembly approved the new ESID Board.

In addition, the majority voted in favor of the Legal Act draft version containing the terms "member" and "restricted member". The General Assembly thus finally approved the final text of the Legal Act proposed during the second part of the General Assembly (i.e. two categories: members and restricted members decided by vote, other changes accepted as outlined by Esther de Vries, with all other text accepted as published as a draft in the recent ESID Newsletter), and no further questions were asked.

Jean-Laurent Casanova then explained a new proposal for changes in the ESID Constitution that were brought up in association with the new Legal Act and mainly deal with the criteria needed to qualify as an ESID member and/or a member of the ESID Board. In the past year the ESID Board carried out extensive discussions about this topic without coming to an agreement and finally felt that it would be best to leave it to the ESID members to decide between the different possibilities. Jean-Laurent outlined that ESID is a European Society and at the same time a Society with implications beyond Europe, with his own work but also that of many other ESID members showing broad international cooperations. The options to be further discussed in the months to come as criteria for ESID membership will be at least the following: 1.) geography and/or citizenship, 2.) professional background, 3.) industry relationship. The decision about the different possibilities should be by internet voting with one month time given. For 1.) there are in principal three levels of restrictions: a) no restrictions, b) no restrictions for members

but restrictions for the Board (e.g. residency and/or citizenship), c) restrictions for both members and Board. Suggestions from ESID members for other options are invited. Restricted membership would then be offered to ESID members not fulfilling these requirements. Several key questions arise, e.g. how to define Europe (e.g. no definition, EU-definition, EU plus other defined countries etc.), with several options to choose that will be presented for vote on the ESID homepage, and the possibility for ESID members to bring up additional options and/or criteria.

When Jean-Laurent´s presentation was open for discussion, several statements were made from behalf of members in the audience: Naomi Taylor questioned why would ESID need other options than "no definition"; Dirk Roos pointed out why not to make an international society (World Society for Immuno Deficiencies), which was postponed for further discussion as soon as the results of the internet voting will become available. Hans Ochs strongly argued for liberal criteria for ESID membership; Alain Fischer was strongly in favor of not excluding anyone, neither from a position in the Board nor from membership, although he admitted that the basis of ESID should remain located in Europe. Andrew Cant appealed to be as inclusive as possible. One additional option was raised from the audience for criterium 1.) for ESID membership: ESID members could be citizens of any country in the world but work and live in Europe while being full ESID members. Martha Eibl was in favor on inclusiveness with regard to members and cooperation, with the Board members residing in Europe. Amos Etzioni further extended the options: the ESID president should be European, all other Board members could have no restriction re criterium 1. Reinhold Schmidt argued that the General Assembly votes for the Board members anyhow, so why should the criteria for becoming a Board member be overregulated in the Constitution. he would prefer as an option that members and Board members could be citizens and live in any country world-wide. Jean-Laurent likes the option of splitting the Board into European and non-European members, with no geographical restriction for becoming full ESID member, and a European restriction for the ESID president and the secretary. Further option for restrictions on the members profiles were brought up, such as ESID members being of medical profession, i.e. doctors, only, or nurses and/or social workers and/or patients in addition. Martha Eibl wondered whether we really need a definition in addition to the respective text in the Legal Act, and also Alain Fischer felt that the definition of the Legal Act is enough. There seemed to be consensus among the members that no restriction above the text of the Legal Act is needed regarding the profession of the ESID members and /or their involvement in the PID field. The last point that was raised by Jean-Laurent Casanova regarding criteria for ESID membership was whether a potential conflict of interest exists e.g. for members of pharmaceutical companies or regulatory agencies. Andrew Cant mentioned that the two options should be separated, as he would see no problem with members from regulatory agencies. According to Anders Fasth this is more an issue for the regulation of ethical conduct of the ESID Board members, and there a potential conflict of interest should be answered by consultancy disclosure and/or restrictions. Dirk Roos would rather add as an additional option that consultants should be excluded from the Board, it could also be discussed whether the ESID Board could decide if a consultant should be excluded from a Board position. Hermann Wolf raised as another possibile option that the current selection criteria for Board members, namely voting by the General Assembly, might not necessitate the introduction of additional restrictions.

Under varia Esther de Vries pointed out that rules for the planned electronic voting will become necessary; in particular it is necessary to define a quorum for internet voting, e.g. the

simple majority of ESID members participates. According to Dirk Roos, 25% of ESID members as a quorum might be more realistic. Esther de Vries informed us that ESID currently has 523 members, 150 of those have not paid their membership fee, which makes about 350 members that would be allowed to vote. The majority of the General Assembly accepts a 25% quorum, and no one disagrees. The majority also agrees on 50% plus one vote (i.e. simple majority) for the decision process, with one vote against. Jean-Laurent Casanova finally suggests that ESID should decide whether taking photos during the talks of the ESID meeting is allowed, and that a rule regarding fellowship award recipients going to laboratories of ESID Board members might be required. It is decided that this should be on the agenda of the next General Assembly for voting. At the end of this biennial General Assembly Bodo Grimbacher apologized if the wording of a presentation from his group gave the impression of political incorrectness, as it was not intended to be offensive to anybody in the audience.
16:16 end of the general assembly.

Notes from the ESID General Assembly 2006 finalized on November 21st, 2006 by Hermann WOLF.

TEXT OF THE ESID LEGAL ACT AS APPROVED BY THE GENERAL ASSEMBLY OF ESID:

Notarial deed (draft)
Today, ¨two thousand and six, the following persons appeared before me, ¨, notary, practising in Boxtel:
¨, living at the address ¨, born in ¨ on ¨, identifying ¨him/herself with ¨his/her, number ¨, issued in ¨ on ¨, ¨;
…
The persons appearing declared that by virtue of this instrument they hereby incorporate a Society and establish the following articles of association:

Statutes of ESID
NAME AND REGISTERED OFFICE
Article 1
1. The Society shall bear the name: European Society for Immunodeficiencies, referred to hereinafter as 'ESID'.
2. ESID shall have its registered office in the municipality of `s-Hertogenbosch, the Nether lands. The actual domicile shall be the address of the Treasurer of ESID.
OBJECT
Article 2
1. ESID shall have as its object:
a. To facilitate the exchange of ideas and information among physicians, scientists and other investigators who are concerned with primary immunodeficiency diseases;
b.To promote research on the causes and mechanisms of these disorders;
c. To encourage clinicians and investigators in research institutions or private industry to share their knowledge of diagnostic and management procedures, and of immunologically active drugs;
d. To promote the application and the dissemination of recent advances in biomedical science for the prevention, diagnosis and treatment of immunodeficiency diseases;
e. To foster excellence in research and medical practice;
f. To promote interaction with nurses and patient associations, so as to increase exchange of information among patients, parents of patients, nurses, doctors and researchers.
2. ESID shall seek to realise this object among other things by:
a. setting up Working Parties for special purposes;
b. organising international gatherings and conferences;
c. cooperating with other scientific organisations;
d. doing all that which may promote the realisation of the object of ESID, in the widest sense.
MEMBERSHIP
Article 3
1. a. Members are people with an interest in primary immunodeficiencies. ESID shall contain

full members and restricted members.
b. Full Members are members who are involved in the treatment of, or research related to, primary immunodeficiencies. Their rights and obligations are further defined in the Constitution.
c. Restricted members are people with an interest in primary immunodeficiencies. Restricted members have no voting rights and are not eligible for positions as officer of ESID. The annual fee for restricted members is 100 percent of the full membership fee. However, restricted members can function as full members in all other aspects.
2. The Treasurer of ESID shall maintain an accurate register of members.
3. Membership shall not be transferable.

ENDING OF MEMBERSHIP

Article 4

1. Membership shall end:
a. by written notification by the member;
b. by termination on behalf of ESID after a majority Board decision.
2. a. Termination of membership by the member does not give right to a refund of membership fees paid in advance;
b. A member may terminate his/her membership with immediate effect within one month of its being notified of a decision to convert ESID into a different legal form.
3. Termination of membership by ESID may be effected by the giving of at least one month notice, if the member has failed to pay the ESID membership fee for two whole years after the initial notification, after having been at least twice reminded thereof in writing. The Board may decide not to effectuate the termination of membership in case of special circumstances.

FUNDS

Article 5

1. ESID is a non-profit organisation.
2. The funds of ESID may be formed among other things from:
- member's contributions;
- allocations;
- donations;
- subsidies;
- sponsorship monies;
- income from ESID's activities;
- bequests and gifts.
3. The General Assembly shall be empowered to introduce contribution categories.

THE BOARD

Article 6

1. The Board shall be charged with the administration of ESID, with due observance of the provisions of Article 7.
2. The Board consists of at least three administrators. The number of administrators and their respective functions are laid down in the Constitution.
3. The Board members shall be elected by the General Assembly. The procedure for the election is described in the Constitution.

REPRESENTATION

Article 7

1. The Board and/or the President together with at least one other member of the Board shall be empowered to represent ESID judicially and extra-judicially. They may also have themselves represented in this respect by a party specially authorised thereto in writing.
2. The Treasurer may be accorded limited or full representative authority by the Board in so far as the exercise of his/her task is involved.

FINANCES

Article 8

1. The Treasurer will report biennially to the General Assembly.
2. The Treasurer must keep records concerning the capital position such that the rights and obligations can at all times be determined therefrom.
3. The Treasurer must retain the documents referred to in section 2 for a period of ten years.
4. Each year, the Treasurer shall give a financial report to the Board during a Board meeting.

GENERAL ASSEMBLY

Article 9

1. The General Assembly of ESID shall consist of all members of ESID with voting rights who are present at the time of the meeting, which is announced at least one month in advance to

all ESID members.
2. All members with voting rights present at the General Assembly shall each have one vote. Delegates may not vote by proxy.
3. Voting on matters shall take place orally, voting on persons shall take place by written ballot. All proposals shall be decided by absolute majority of votes in so far as the Articles do not stipulate otherwise. In the event of a tie of votes, the proposal shall be rejected.
4. The General Assembly may decide to allow voting through the ESID website. In that case, at least one fourth of the total number of members with voting rights should cast their vote, and decision shall be by absolute majority of votes in so far as the Articles do not stipulate otherwise. In the event of a lack of quorum, or a tie of votes, the proposal shall be rejected.
4. The President of the Board shall lead the meeting. In his/her absence or hindrance the Secretary or one of the other Board members shall act as Chairman of the meeting.
5. The Secretary, or a member of ESID designated thereto by the Chairman, shall record the minutes of that which is discussed at the General Assembly, and these minutes shall form an item on the agenda of the following General Assembly.
AMENDMENT OF THE ARTICLES
Article 10
1. Amendment of the Articles may only take place following a decision of the General Assembly which was convened with the announcement that amendment of the Articles would be proposed at that meeting. Such a meeting must be convened at least four weeks in advance.
2. Decisions to amend the Articles may only be taken by a General Assembly in which at least one third of the total number of members with voting rights is present, with a majority of at least two thirds of the number of votes.
4. In the event that there is a lack of a quorum a decision to amend the Articles may be taken by a written ballot or through the ESID website.
Article 11
1. The amendment of the Articles shall not come into effect until a notarial deed containing the amendment has been drawn up.
2. The administrators must deposit an authentic copy of the amendment and a running text of the amended Articles at the offices of the Chamber of Commerce where ESID has its registered offices.
STANDING RULES
Article 12
The General Assembly may institute standing rules in the Constitution.
FINAL PROVISION
Article 13
In all cases for which neither the law nor the Articles nor the Constitution provide, the Board shall decide by majority vote.
FINAL DECLARATION
Finally, the parties declare:
As a member of the Society join all founders.
They appoint as members of the Board for the first time:
President: ¨;
Secretary: ¨;
Treasurer: ¨.
WHEREUPON THIS INSTRUMENT was executed in Boxtel on the date referred to at the head of this instrument.
The parties are known to me, the notary. The essential contents of this instrument were communicated and explained to them. The parties have declared that they have agreed that only limited parts of the instrument need be read out and that they have taken timely notice before the execution of the contents of the instrument.
After certain parts of this instrument had been read out, it was immediately signed, first by the parties and then by me, the notary.

THE TEXT FOR THE NEW CONSTITUTION

As decided by the General Assembly, the text for the new Constitution will be made up at a later stage, after voting through the website on the topics mentioned in the minutes has taken place.

Treasurer's report

Sascha Jansz did a lot of hard work at the ESID helpdesk during the Budapest meeting, which resulted in a lot of members paying their ESID membership fee that was still due, and in correcting their details (address, email, etc) online.

The ESID helpdesk at the Budapest meeting

As of now (end of December 2006), ESID has 410 members who have paid their ESID membership fee 2006-2007. We have never had that many paying members before!

If you have any problems entering the restricted part of the ESID website, please act as follows:

- Check whether you have paid your ESID membership fee 2006-2007, if not, pay it. (Did you receive a confirmatory email from Saferpay? Was the amount deducted from your credit card account?)

- Check whether you are using the correct email address (the one that you once entered!), and whether you are using the right password. If not, do so.

- If you still can't enter the restricted part of the ESID website, or you have forgotten which email address you once entered, and/or what your password is, please contact the ESID webmaster, *not* the ESID Treasurer!

Esther DE VRIES

Budapest by night

News & Views

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

A very successful EU-PID Consensus Conference has taken place, with lots of fruitful discussions. The Consensus statement that has been produced was launched during the opening session of the Budapest meeting.

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

On the inside of the front cover of this issue of the ESID Newsletter, you can find the new version of the '10 warning signs' poster that has been developed in the new IPOPI colours, incorporating the news about the EU-PID conference. At www.ipopi.org you can download this poster as a pdf-file. You can also download a template there, that you can use to translate the poster in your own language. You are free to spread the translated poster as a new pdf-file, but please also send it to IPOPI!

Journal of Experimental Medicine

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

Jean-Laurent CASANOVA

Electronic voting on the ESID website

Electronic voting is now available on the ESID website. When a vote is to be taken among ESID members, a poll will appear on the homepage when a member has logged in. So members please log on to the restricted part of the website regularly to check this. A notice will appear on the public homepage to remind you of this. We will also send an email to every ESID member (whose email address is listed online!) to alert her/him of the poll to be taken.

As for now, we have set up a poll on whether to use the 6 or the 12 warning signs for adult PID. The way the voting works is that we ask a question and offer several possible answers. All you have to do is tick the answer you like best. Your vote is saved and the result of the poll is automatically published on the homepage after voting has closed. In the case of the current poll on 6 or 12 signs of immunodeficiency, that was closed on November 30, 2006 (see next page).

Bodo GRIMBACHER

The 6 warning signs for adult PID

The Jeffrey Modell Foundation has developed 10 warning signs for Primary immunodeficiency diseases (PID). However, these were tailored to identify paediatric PID patients. Thus, during the last years there was the need to also identify warning signs for adult PID care.

During the EU-PID Consensus Conference in Langen in June 2006 this has been specifically addressed.

Two proposals were circulated, one developed in Sweden and validated in France with 6 warning signs, and one developed in Germany and approved by the AKI with 12 warning signs, basically tailored to capture all patients with severe diseases.

Both versions have been presented to the ESID general assembly (GA) in Budapest in October 2006, however, the GA felt that the members needed some more time to think about the two options. So we designed an internet based voting to finally come up with the decision, since the ongoing awareness campaigns rely on the ESID approval of a set of warning signs for adults.

Thus, during the last weeks, there was now a vote amongst the ESID members which set of warning signs they would prefer… and the winner is (39 pro 6 signs, 13 pro 12 signs, 3 no opinion):

The 6 ESID warning signs for ADULT primary immunodeficiency diseases:

1. Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)
2. Recurring infections or infection requiring prolonged antibiotic therapy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
4. Two or more radiologically proven pneumonia within 3 years
5. Infection with unusual localization or unusual pathogen
6. PID in the family

ESID would appreciate if this could be taken further and prospective studies on the value (sensitivity and specificity) of these warning signs would be designed.

Eric OKSENHENDLER
Lennart HAMMARSTRÖM
Helen CHAPEL
Bodo GRIMBACHER

An educational programme oriented to the self-care of patients with primary antibody deficiencies.

We briefly report on the experience with a one-year educational programme for patients with primary antibody deficiencies developed as a pilot experience in the Community of Madrid, Spain. The aim of the programme was to provide basic knowledges regarding the immune system and the management of primary antibody deficiencies with emphasis on aspects of self-care. In the first step of the programme (January 2005) a 1-hour educational session was presented to 50 patients and their relatives with an overview of the primary immunodeficiencies and their management. At the end of the educational session, patients and relatives were asked w if they were interested in the development of a one-year pilot educational programme oriented to the self-care. A total of 15 patients and relatives participated in 10 monthly sessions of the educational programme (Second step: September 2005-June 2006).

The contents of the educational programme included: The immune system; the primary immunodeficiencies with emphasis on primary antibody deficiencies; all aspects of the treatment of primary antibody deficiencies (indication, substitution therapy with immunoglobulins, antibiotics, nutrition, hygiene, dental care, common complications and their management, transplantation, sexualty, genetic council, psychological support, social, legal, work

and economic issues); importance of the self-care for the management of patients and barriers to its development; among other contents.

The methodology: Monthly two-hour sessions. First hour: The same doctor developed the educational contents in a very informal way, with constant interaction with patients. Second hour: the doctor, a psychologist and a social worker provided personal or group information regarding different aspects of the care of primary antibody deficiencies.

At the end of the programme a questionnaire was developed by patients and relatives to evaluate the development of the programme and if they had adquired any new information useful for the day-to-day care of their immunodeficiencies. All patients and relatives agreed to indicate as important issues: the possibility of sharing personal experiences and the opportunity to reach knowledge difficult to acquire in the hospital. A decision was reached to start a second-year "advanced" training programme including basic knowledge for the selfadministration of IVIG (not yet developed in Spain). We plan to start with another group with the basic contents of the first-year programme. The experience indicated that no more than 10-15 patients and relatives should be included in the sessions to facilitate a more fluid and continued interaction between patients and faculties.

Javier CARBONE

Nieves Moreno, Madrid, Spain.
carbone@teleline.es

ESID Meeting 2006, Budapest

The ESID-IPOPI-INGID Meeting in October was one of the most challenging and exciting events in my professional carrier. It was also an honor and I am grateful. We made every effort with colleagues at my Department and at Convention to ensure that the Meeting would be of the highest quality from both scientific and organization points of view. The ESID Board and the Scientific Committee provided great help throughout the organization process. The regular sponsors (Baxter, Octapharma, ZLB, Biotest, just to mention a few) continued to be as generous as they were at our previous meetings and helped to reach a balanced budget and to be able to invite the most outstanding speakers in the field.

When I first proposed in Weimar 4 years ago that Budapest might be a nice venue for a future ESID meeting, I was considering a meeting with about 500 participants. I must tell you I was wrong. With the background described above, we were able to attract a record number of 982 participants from 54 countries. We had 94 East-European participants and this may have been related to The J Project activity in the region over the past two years.

There were several reasons that might explain the high level of interest in this Meeting. First, we had a great program and I want to appreciate the help of the ESID Board in the formulation of the scientific program. The program was actually quite busy (maybe to busy). The table on the next page shows statistics of different presentations.

Presentations at the 2006 ESID Meeting:

Presentation category	No
Keynote lecture	2
Introductory lecture	14
Educationl Day presentation	8
Plenary oral presentation	29
Workshop presentation	12
Poster	358
Lunch Symposium presentation	10
TOTAL	423

It was clear in Budapest that the PID community in Europe is not only dynamic but is

getting more and more heterogeneous. ESID, IPOPI, INGID, the Jeffrey Modell Foundation, Prague Spring Meetings, Winter Meetings in Poland, The J Project, and recently the EU-PID initiative are active components of the professional, scientific, and social work for the benefit of immunodeficient children. Although it is not just ESID any more, I think it is important that ESID remains the driving force and the core organization of all these activities.

Our understanding of PIDs today is different from what we thought about it 8-10 years ago. The scientific level of the Meeting was indicated by the presentation of more than 10 new primary immunodeficiency diseases. Clearly, PIDs are not rare diseases anymore but instead, they create a public health issue.

I very much hope that all of you enjoyed your stay in Budapest!

László MARÓDI

Budapest by day

Nalinaj Fernando Memorial Award for paper from the Clinical Working Party of ESID

The Nalinaj Fernando Memorial Award is awarded annually by the Editors of Clinical & Experimental Immunology for the best research article into primary immuno deficiencies published during a particular year. The award (to the value of £350) has been generously donated by the Fernando family in memory of Nalinaj Fernando, who was born with the extremely rare primary immunodeficiency, Bare Lymphocyte Syndrome, and died age 32.

This year, the paper 'Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists', written by 20 ESID authors on behalf of the Clinical Working Party (Clin Exp Immunol 2006;145:204-214. Editorial Clin Exp Immunol 2006;145:201-203), was awarded the Nalinaj Fernando Memorial Award.

We are very happy with this. The award is an honour for ESID and what ESID stands for: achieving better care for PID patients through international cooperation.

We have decided to donate the money to the Peribosch Fund, which is dedicated to fund clinical research in children, and have labelled the money to be used for research concerning PIDs.

Esther DE VRIES and 19 co-authors

Anyone who wants to receive a pdf-file of the paper can ask me to send this by e-mail (esid@estherdevries.nl)

Working Party reports

Educational WP

Anders Fasth and Luigi Notarangelo led an excellent Educational Symposium at the recent ESID meeting in Budapest which was very well attended indeed, a tribute to the fascinating and innovative programme as well as the interesting speakers! B lymphocyte biology and disorders were covered in great depth with key new insights presented in a clear and useful way. This was followed by a comprehensive overview of treatments from subcutaneous immunoglobulin therapy through to stem cell transplantation and gene therapy.

At the ESID meeting the Working Party membership changed slightly as Anders Fasth had completed two excellent terms as Working Party Chairman, and under the Constitution had to stand down. With some hesitation I agreed to be nominated to succeed Anders and was encouraged that people seemed to want me to take on this role. Anders will be a hard act to follow because he has done a superb job in his quiet, unassuming yet imaginative and very effective manner. Fortunately for ESID he has agreed to stay in the Working Party, and together with Teresa Espanol, Esther de Vries and our new junior representative Eleonora Gambineri, I am sure we should have good continuity to carry on the excellent work which Anders has led up to now.

The next ESID Summer School will be held from 26 to 30 September 2007; a Faculty has been drawn together and we are evaluating some venues. We look forward to another exciting and instructive time!

Andrew CANT

DON'T FORGET TO RESERVE THE DATE IN YOUR AGENDA: ESID SUMMER SCHOOL 2007, 26-30 SEPTEMBER !!

Genetics WP

Genetic diagnosis of PID – division of tasks in the Netherlands

The ESID meeting is visited by people involved in care, treatment and diagnosis of primary immunodeficiencies (PIDs) from around the globe and these people appear to view the ESID meeting as the most relevant meeting in their field to disseminate new findings before they are published and to start up new collaborations. One of the observations made at the ESID meetings is that collaboration between participants who are involved in PID treatment or research from the same country is not always optimal.

The Netherlands is only a small country (16 million inhabitants) and -especially for rare PIDs- this can result in just a handful of patients detected each year per PID. This makes it too costly and time-consuming for each center involved in the diagnosis of PIDs to provide diagnosis for all PIDs. We have successfully divided the tasks at hand and we feel this approach may also be useful for other, larger countries.

The working group for immuno deficiencies (WID) in the Netherlands consists of physicians (and scientists) from about 15 university-, general- and pediatric hospitals involved in the care, diagnosis and treatment of patients with primary immunodeficiencies. This WID has (informal) meetings every 3 months to discuss new developments in the research and treatment of PIDs. In addition, individual patients of whom the diagnosis or treatment is difficult are discussed in depth in order to solve the problems.

One of the issues for which clear agreements have arisen is the issue of genetic diagnosis. In the Netherlands genetic diagnoses of common genetic diseases are provided by certified Clinical Genetics Departments. Due to the low number of patients for each individual PID and the number of functional tests that

are usually required before a genetic defect can be identified, genetic diagnoses of PIDs are not performed by the Clinical Genetics Departments. Instead, genetic diagnosis of PIDs is divided over a limited number of institutes.

Five groups in the Netherlands are together responsible for the identification of defects in about 80 genes. The division of work has arisen on historical grounds and is mainly based on prior research interests. The PIDs that the five groups cover can be roughly described by; SCID and antibody deficiencies (group of Prof van Dongen, at the Erasmus MC in Rotterdam), defects in signal transduction and immune regulation (group of Prof Sanders at the Children's hospital of the University of Utrecht), phagocyte defects (group of Prof Roos at Sanquin Research in Amsterdam), MHCI and MHCII defects (group of Prof van den Elsen, Leiden University MC) and unusual susceptibility to mycobacterial and salmonella infections (group of Prof van Dissel, Leiden University MC). The five groups together discuss the division of tasks, protocol details, required quality controls, and the logistic and financial aspects of these tasks. Most of the five groups have a close collaboration with the Clinical Genetics Departments of their respective Medical Centers and subsequent prenatal diagnoses in families in which the genetic defect has been identified are performed by the Clinical Genetics Departments. This division of tasks has proven to ensure a good collaboration between groups, is cost effective and allows the labs to specialize, which improves the speed and quality of diagnostics.

Esther VAN DE VOSSE
Mirjam VAN DER BURG

on behalf of the Genetics WP

Clinical WP

Over the past two years, a number of activities have been ongoing in the Clinical WP. Under Amos Etzioni's chairmanship, diagnostic guidelines for various PIDs were formalised and these have been of enormous help to physicians and researchers in the field. This has continued and recent guidelines for diagnosis of severe congenital neutropaenia have been agreed and were published in the last edition of the ESID Newsletter.

Our more recent activities have focussed on the management of patients with ADA-SCID and especially their responses to enzyme replacement (PEG-ADA), stem cell transplantation (HSCT) and gene therapy. A questionnaire was sent out last year and we have had an excellent response. Datasets from 46 patients who had been treated with PEG-ADA were received and responses from 77 patients who had undergone HSCT. A preliminary analysis of the data was presented at the ESID/EBMT inborn errors meeting in Prague in October and highlights how difficult this condition can be to treat. We are now in the process of performing more detailed analysis and are also, as a result of our former Presidents' defection (just kidding!) across the pond, recruiting patients from centers in the US and Canada. Hopefully we should then have over 100 patient datasets which will allow a fairly definitive analysis of the various treatment options. The questionnaire is also the basis for data entry for ADA deficiency into the ESID Registry database and this is presently being prepared.

There is also a new intiative that I would like to propose. One particular disease that we have very little data on with regard to clinical manifestations, phenotypic variability, management and outcome is X-linked lymphoproliferative syndrome. Since the SAP/SH2D1A gene defect was identified in 1998, it has been possible to make a definitive diagnosis. As a result, we have been able to recognise that a defect in SAP is the

underlying genetic abnormality in patients with CVID, aplastic anaemia, as well as in classical presentations such as FIM, HLH and B cell lymphoma. Many of us still refer to the Seemayer paper of 1985 for the frequency and outcome for these different manifestations but in an era where a definitive molecular diagnosis is possible, this should be updated. I think therefore, it would be timely and useful to prepare a study looking at presentation, clinical course and outcome. This can again like the ADA study form the basis for data entry onto the Registry. I think it is also timely in view of the fact that a second gene for XLP has recently been identified by excellent work in Sylvain Latour's group in Necker (XIAP in humans causes an X-linked lymphoproliferative symdrome: Rigaud et al., Nature (2006) 444, 110-114). It would be useful to compare through such a study whether there are any clinical differences between the two molecular defects. If anyone has any ideas or suggestions with regards to such a study I would be delighted to hear from them. I will prepare a questionnaire in the coming weeks.

Bobby GASPAR

HSCT & GT WP

Report on the 'HSCT/gene therapy' Working Party – November 2006, Chairman: M Abinun, and Workshop on 'Long term follow up of HSCT in PID' at ESID, Budapest, October 2006 (Organised/ chaired by Wilhelm Friedrich/Mario Abinun).

Susanna Muller (Ulm), Alain Fischer (Paris), Robbert Bredius (Leiden) and Bobby Gaspar (London) reviewed the 'state of the art' knowledge and the recent developments.

Our current understanding based on the evidence/data from Europe and USA has been recently reviewed by Fischer et al. (Immunol Reviews 2005;203:98-109).

There are new, interesting and exciting data on thymic function (Halnon et al. Ped Res 2005;57:42; Torfadottir et al. Clin Exp Immunol 2006;145:407; Terszowski et al. Science 2006;312:284) and development (Rossi et al. Nature 2006;441:988; Bleul et al. Nature 2006;441:992) that may (or may not!) be of relevance for this subject.

Alain (and the next day Benedicte Neven in the Oral Presentation section) presented data from Paris group on importance of early presence of TRECs, in particular for X-L SCID patients, and their association with donor myeloid engraftment, for the long term quality of engraftment (reported as an abstract at this year's EBMT, Hacein-Bey-Albina et al. Bone Marrow Transplant 2006;37(suppl 1):S200). The importance of the quality of early engraftment (and the early presence of TRECs) has as well been stressed by Robbert (Borghans et al. Blood 2006;108:763).

'Intermingled' with the topic of thymic function importance, the role of conditioning was only 'gently tackled', but it seems that all the data are pointing towards the fact that myeloablative doses of busulfan (16 mg/kg) are associated with good donor chimaerism and TRECs numbers, i.e. good engraftment (in comparison to 'low-dose busulfan of 8 mg/kg or no busulfan at all). Bobby outlined the efficacy of 'top-up' transplants without conditioning being limited to the period early post transplant (i.e. within 1 year) (Slatter et al. Bone Marrow Transplant 2005;35:683; Booth et al. Br J Haematol 2006;135:533).

Bobby (and P Titman in the Oral Presentation section) presented data on cognitive function (and hearing) impairment, known previously for the ADA SCID patients, but somewhat surprisingly other' SCID variants' have as well similar problems in the 'quality of life' section long term – an area we will need to put a lot more work in the years to come.

Joint EBMT/ESID WP Meeting, Prague, October 2006

Main topics discussed:

a/ immunodeficiencies
- DiGeorge syndrome/CHARGE
- ADA SCID (HSCT vs. PEG)
- CGD – new protocols
- SCETIDE registry data
- WAS – post-BMT autoimmunity
- HLH – ATG treatment
- Immune reconstitutuion – common lymphoid precursors

b/ inborn errors
- ADL
- Hurler's
- Osteopetrosis – genotype/phenotype correlation and new protocol

c/ HSCT in autoimmune disorders – JIA, SLE, periodic syndromes

d/ GENE therapy – CGD; ADA; X-l SCID; RAG1

Important messages:

Graham Davies (GOS, London) will be offering thymic transplant procedure in Europe, awaiting protocol approval by USA authorities (collaboration with Louise Markert, Durham, USA)

Reinhard Seger (Zurich) presented the proposal for a new, reduced conditioning regimen for 6-16 yr old of 'very risky patients', i.e. with infections/inflammation and organ damage (Flu 180 mg/me2; Bu 8 mg/kg/i.v.; ATG-rabbit 40mg/kg; CsA and MMF) for HLA-identical donors or 10/10 (mis)matched URD. Further discussions to take place, and Reinhard and Terry Flood (Newcastle) to provide the new protocol/ guidelines for the website.

Ansgar Schultaz (Ulm) and Colin Steward (Bristol) will be collating the new protocol proposal for HSCT in osteopetrosis, and the 'final version' will be available on the website.

Pheno-genotype correlation for osteopetrosis to continue.

SCETIDE registry data will be published during 2007.

WAS HSCT outcome/complications to be published in 2007.

Autoimmune disorders - Long term outcome (EBMT forms) to continue.

Gene therapy trials to continue with caution.

Marina and Mario (with a little help from our friends) will update the current 2004 guidelines on both EBMT and ESID websites.

Mario ABINUN

Registries WP

The ESID database team has experienced a number of changes during the last few months. We worked hard towards a successful and inspiring biennial meeting in Budapest and indeed it turned out to be an important conference.

After having headed the Registries Working Party for four years already, Bodo Grimbacher had to step down from this post. During the past four years he has been the moving spirit for the establishment of this online database and thanks to his commitment, the database now brings together people from 29 European countries and pools 2967 patients by end of November 2006. (For a more detailed overview of the current data please refer to the 'Database Statistics' section of the ESID website http://www.esid.org/statistics.php). Bodo has now handed over his place in the ESID Board to Gerhard Kindle, who was elected Head of the Registries WP by the General Assembly in Budapest. Since he is a physician and also an IT engineer, Gerhard combines expertise in both fields essential for the project. He has been working on the database for quite a while and we are all convinced that this combination will deliver both continuity and innovation to the project.

In Budapest, the database was presented in a lunch workshop with several innovative features.

Personalised Version

Firstly, all documenting centres and potentially interested centres were again informed of the option to choose a personalised version of the database and work with patient names instead of IDs, while keeping data security guaranteed by the multi-server concept that has been described in previous ESID Newsletters. However, it is worth emphasising that this data protection concept has now been approved by the state of Baden-Württemberg in Germany. This higher-ranking approval certainly is a good reference for centres all over Europe wishing to apply for approval in their institution. Please contact us for more details and if you wish to receive helpful documents for your documentation.

Mutation Browser

The database now features a mutation browser, which has been set up in cooperation with the Institute of Medical Technology (IMT) in Tampere, Finland, which maintains the IDbases, an electronic library for genetic mutations in PID. The Mutation browser has been implemented in the ESID database currently for 105 sub-registries. Users are now directed to the IDbases, where the entered mutation is stored, validated and sent back to ESID where it is displayed on the database surface as shown in Figure 1. However, all exchanged data is completely anonymous.

Predefined Queries

For all users with a password for the ESID database, a set of pre-defined queries is now always available within the database. It has been added at the bottom of the well-known search tree and is currently called "Main registry with predefined queries". When logged in there, you will see queries in real-time, ie current figures are displayed. Currently the following data is available: Number of patients in the database in my centre, PID diagnoses in the database by centre and by PID main category, PID diagnoses in my centre, age distribution and gender in the database. More queries are planned. The so-called main registry will enable users to move patients from one

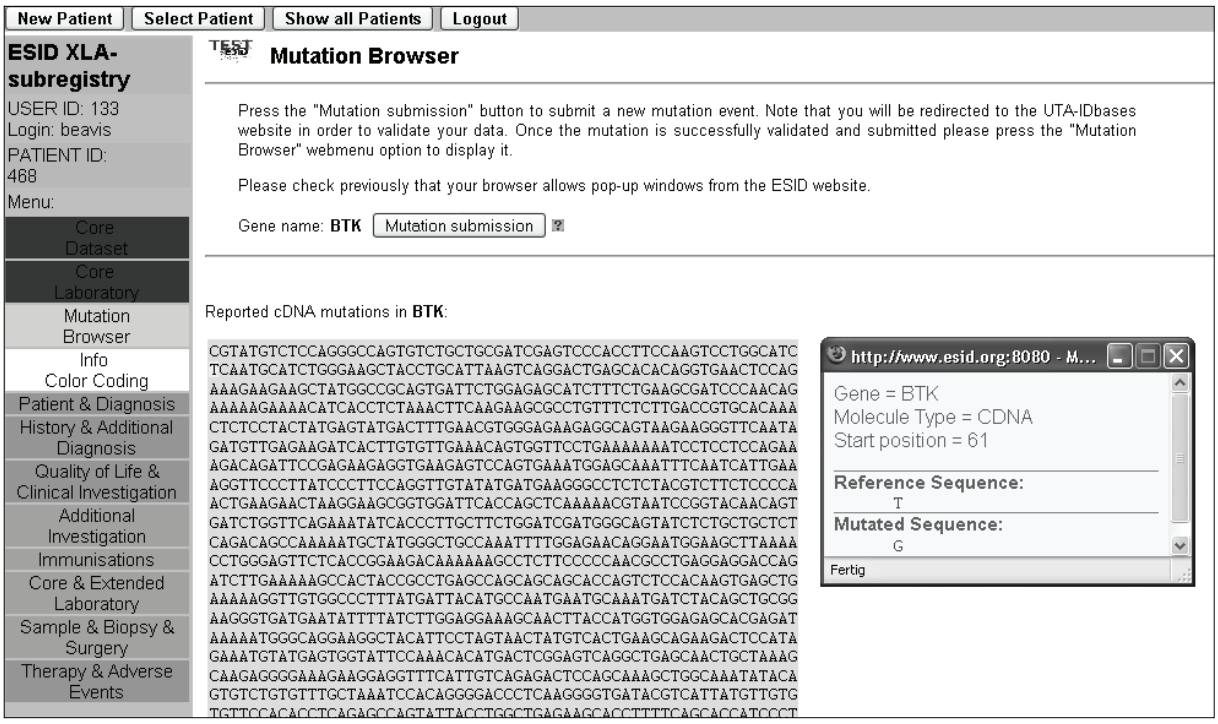

Figure 1: Mutation displayed in the ESID mutation browser

sub-registry to another, for example when the diagnosis has changed. This option will then be accessible on this branch of the search tree structure.

Percentile Curves

For pediatricians we have implemented a tool which automatically draws percentile curves from the database. The required data (weight, height, head circumference) is entered in the Quality of Life section of the core dataset and updated at every new visit date. The individual curves can then be generated by clicking on the green Percentile button in the left hand menu (see Figure 2).

SF36 Health survey

For the evaluation of the patient's Quality of Life, the Medical Outcome Short Form 36 (SF36) has been implemented in English so far. It has originally been designed for self-administration, but can easily be done in a face-to-face or telephone interview in 5 to 10 minutes.

Publication on ESID database

The first publication on the ESID database has come from the registry working group in Freiburg. Anne-Marie Eades-Perner is not only the webmaster of the ESID website, but also in charge of all questions concerning ethics and data protections. Her paper "The European internet-based patient and research database for primary immunodeficiencies: Results 2004-2006" has recently been accepted for publication in Clinical and Experimental Immunology. It deals with the overall structure of the database, its potential and first analysis of the data.

Patient consents

We would like to take the opportunity to remind database users that only data from patients who have signed an informed consent are allowed to go into the online database.

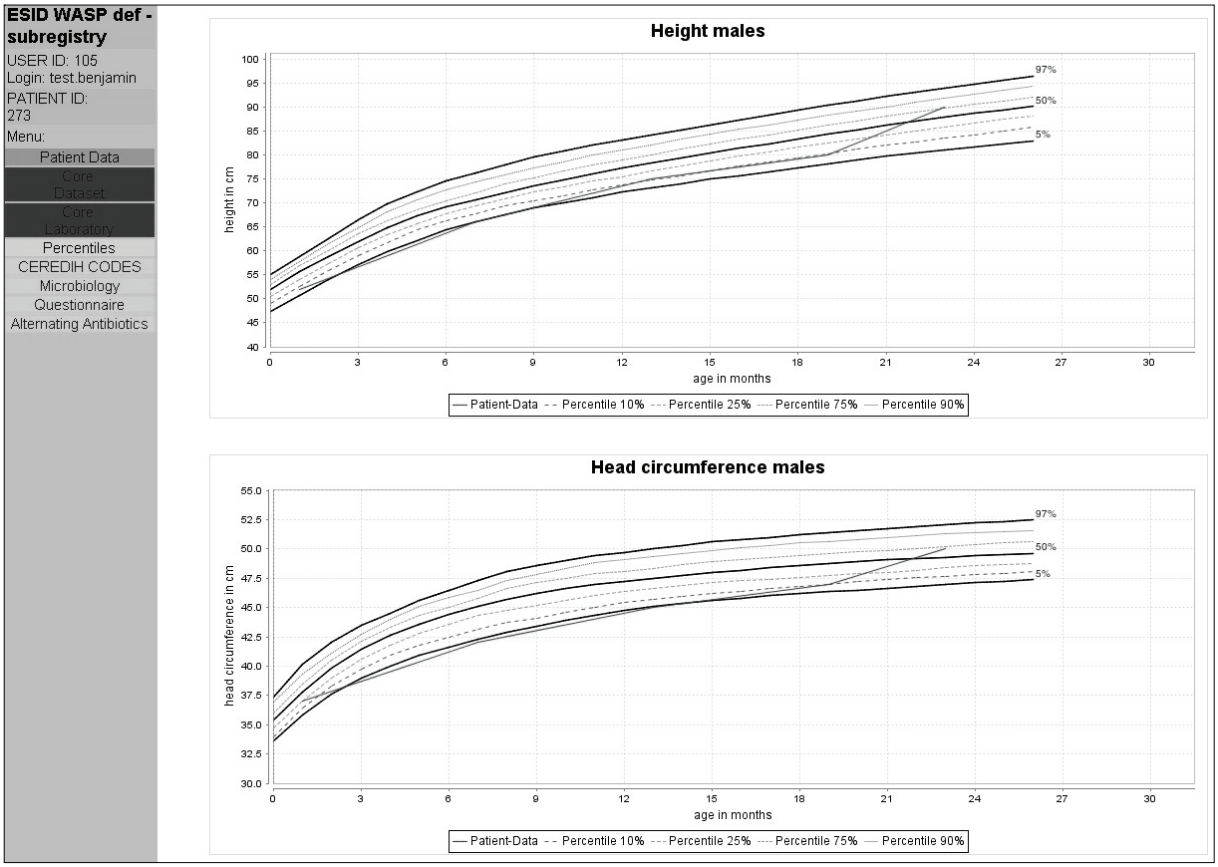

Figure 2: Percentile curves drawn from data in the database

Therefore we have removed the former option 'pending' and we will update the 'patient consent' dropdown menu with additional entries, reflecting the changes in the consent forms. If you do not have the patient's consent yet, please wait with the data entry. Translations of our draft consent form can be downloaded from the ESID website and adjusted to your centre's needs.

New addresses to note

One of our database coordinators, Viviane Knerr, has moved to the University College London, Royal Free Hospital and can now be reached at her address: Viviane Knerr, Dept of Immunology, Royal Free Hospital, University College London, Pond Street, London NW3-2QG, United Kingdom. Tel: +44 (0)207 794 0500 ext 35161, Fax: +44 (0)207 433 1943.
E-mail: v.knerr@medsch.ucl.ac.uk

All other contact details of the registry working party in Freiburg remain the same: Gerhard Kindle, Head of the Registries WP, Gerhard.kindle@uniklinik-freiburg.de, phone: +49 761 270 3784; Benjamin Gathmann (Database Coordinator), Benjamin.gathmann@uniklinik-freiburg.de, phone: +49 761 270 3445; Anne-Marie Eades-Perner (data protection, ethics, website), anne-marie.eades-perner@ uniklinik-freiburg.de, phone: +49 761 270 3445.

If you have any questions or suggestions, please do not hesitate to contact us personally or use the general ESID database E-mail address: registy@esid.org.

The Registries WP team

ESIDjuniors WP

First of all, I would like to thank all of you for giving me the opportunity to chair the ESID*juniors* Working Party for the next two years. I greatly appreciate the chance given to contribute to its future development.

For those who don't know, the ESID *juniors* WP was established after the ESID meeting held in Versailles in 2004. The idea to have a Junior group within ESID rose during the 2003 Summer School in Portugal, where I took part too. Together with Ellen, Chris, Pavel, Jana and many others, but most of all Pim, we wanted to bring outside the spirit of Summer School to continue the great experience during our daily work. The main aim of the WP was to create a platform for discussions to encourage young people to play an active role in the Society.

During the last ESID meeting in Budapest we had a great chance to "re-energize" the ESID*juniors* WP. We had a meeting among young members to discuss and set up a strategy to overcome the difficulties encountered in the past.

Briefly, these are some of the issues we mentioned during the discussion and we agreed to work on as a priority.

IMPROVE the network

We would like to encourage all Junior Members who wish to play an active role in the Working Party to show up! Please send me an e-mail (eleonora.gambineri@unifi.it) introducing yourself with a brief note about your background and with your suggestions to improve the activities of our WP!!!

Increase the use of the already existing ESID web-tools, especially the FORUM section to post discussion/problems, and create a dedicated "ESID Juniors section" through development of a 'bulletin board' where Juniors can communicate each other and the Board members posting their "every day troubles.

Together with Ales from Prague, Czech Republic, we will try to organize once a year an ESID Spring School open to all ESID juniors member as a platform to follow up the learning

progress.

BE MORE OPERATIVE within ESID activities

Any Junior who shows an interest in joining one of the others ESID Working Parties, is invited to step forward. The other WP heads are more than welcoming! Moreover, they have been encouraged to "call for Juniors" (i.e. " help needed for…") to involve an ESID junior member in his/her activities.

We are trying to organize an "interactive corner for Juniors" (i.e. dedicated poster section within the 2008 ESID meeting and/or new sections within the ESID Newsletter as "case reports", "young researchers' corner" etc.)

DEVELOP EXCHANGE PROGRAMS

Look for funding to promote short-time visits (one week up to one month) and collaborations of young trainees within European countries.

After the ESID meeting in Budapest we have been busy exchanging thoughts and suggestions through e-mails and I must say that, even if only 8 persons actively participated, it was very productive and we have been able to achieve already something concrete in such a short time! Besides several inputs in line with the issues above, new interesting topics rose to revitalize the WP. Some examples: Nima from Iran suggested to build a sort of "database from ESID Juniors background and activities", whereas Crina from Finland has encouraged all the juniors to use, beyond the ESID web-site, also other dedicated database services (i.e. http://bioinf.uta.fi/idr/, http://bioinf.uta.fi/IDdiagnostics/xindex.shtml, a sort of electronic encyclopedia for PIDs) to help in communication between laboratories and between doctors and scientists. Moreover, Esther de Vries was looking for Juniors who are interested to join the Editorial Board of the ESID Newsletter, and as you can see in this issue, new sections has been already developed from some ESID Junior members. Lucia from Italy is proposing a "Young Researcher's Corner" to actively exchange questions about laboratory protocols and methods in the field of PIDs and Ales is starting a new "Interesting Cases" corner to promote clinical discussions among young and experienced physicians. Finally, Crina will help with the selection of interesting papers.

So, if we were able to already accomplish something in only one month, I hope we can work even harder in the future. We are collecting great suggestions, but the most important point is to be able to execute these plans. And this point depends largely on the participation of the members. I hope we can recruit more active participants and stay motivated to create this organization that serves to facilitate education, communication and exchange of ideas.

I am looking forward to hearing back from more Juniors!!!

Eleonora GAMBINERI

Interesting Papers

Crina Samarghitean will from now on select some interesting papers for the readers of the ESID Newsletter. For a start, four papers were selected, as you can see below. In the future, Crina will also give a short overview about the papers, written by himself and others. If you have any interesting papers you would like to have incorporated in this section, please contact Crina at: Crina.Samarghitean@uta.fi .

1. Kim DD, Song WC, Membrane complement regulatory proteins, Clin Immunol. 2006 Feb-Mar;118(2-3):127-36. Epub 2005 Dec 9. Review.

2. Marodi L., Innate cellular immune responses in newborns, Clin Immunol. 2006 Feb-Mar;118 (2-3):137-44. Epub 2005 Dec 27. Review.

3.Broides A, Yang W, Conley ME.Genotype/ phenotype correlations in XLA, Clin Immunol. 2006 Feb-Mar;118(2-3):195-200. Epub 2005 Nov 16

4. de Vries E; Clinical Working Party of the European Society for Immunodeficiencies (ESID).Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol. 2006 Aug;145(2):204-14.

5. Broides A, Ault BH, Arthus MF, Bichet DG, Conley ME. Severe combined immunodeficiency associated with nephrogenic diabetes insipidus and a deletion in the Xq28 region, Clin Immunol, Volume 120, Issue 2 , August 2006, Pages 147-155.

Interesting Cases

During the meeting in Budapest this year a number of new ideas that could be implemented into the activities of the ESID*juniors* WP have been discussed. One of them was our contribution into the quarterly ESID Newsletter.

This brief new section is meant to be used for presentation of enigmatic cases we have come across in the clinics. The presumptive benefit of it could be elicitation of a distant „brainstorm" among the members of the Society that may help in the diagnosis and treatment of the patients; may contribute to cooperation between centres (one can offer diagnostic means unavailable in other places etc.); and the last but one positive effect could be the educational impact as through the discussion we (and I hope that „we" does not encompass only ESID*juniors*) can learn a lot.

This a very first case in the series. Let's say a trial one. So, please send me your opinion, advice or recommendation on how to run this section. My suggestion is that one or more cases are presented and then in the next issue of the ESID Newsletter a short summary of the advices that the author received through email from the other members of the Society together with details on further diagnostic and/or therapeutic progress could be published. I also suggest these cases to be put on ESID website into the Educational or Juniors' sections where other material e.g. images from X-ray, CT, MRI etc. could be placed.

CASE #1: 15 y-o boy with Evans syndrome and indefinite brain and pulmonary lesions.

The personal history of this boy was unremarkable until the age of 9 years, when the first symptoms of thrombocytopenia manifested. His mother suffers from diabetes mellitus and thyreopathy, he has 2 healthy sisters. He has polyvalent allergy. He received the usual vaccines, no adverse reactions after vaccination has ever been reported.

At the time of the first symptoms high titres of anti-thrombocyte IgG antibodies (Ab) were found, and because of inguinal lymphadenopathy, a biopsy of the lymph node was undertaken with finding of follicular hyperplasia, without signs of a granulomatous process or malignancy; he was treated symptomatically. One year later an episode of haemolytic anaemia occurred; due to the presence of anti-erythrocyte Ab, the diagnosis of Evans syndrome was made. He was put on steroids and a high dose of intravenous immunoglobulin (IVIg) was administered with a good clinical effect; after a few months the therapy was changed to steroid-sparing option, cyclosporin A (CyA). A few months later (11 y-o) several episodes of unconsciousness accompanied with spasticity and partial epileptic convulsions suddenly emerged. Multiple infra- and supratentorial lesions were found with MRI, the findings corresponded with acute disseminated encephalitis or lymphoma, however, the subsequent investigations and clinical course excluded both

of these diagnoses. The repeated MRIs showed clear dynamics and progression of the lesions, there was clear healing of the older lesions and occurrence of new ones. Due to the diagnostic dilemma and the progressive character of the affliction, a brain biopsy was done. Histological investigation revealed massive infiltration with frequent plasma cells (CD79a, CD138 positive), T cells and macrophages (some of them in a form of epitheloid cells similar to the situation in specific inflammation, however, no typical granulomas, no Langerhans cells were seen at this time), some plasma cells contained Russel's corpuscles, there was a low number of CD20+ B cells, within the T cell pool CD8+ predominance was apparent, there was remarkable low expression of granzyme B; microscopically acid resistant bacteria, mycophyta, amoebas were not found; extended PCR tests for a number of pathogens (including mycobacteria, JC virus) were negative. In the flow cytometric analysis the following picture was seen. Out of 20.000 cells there were 17% lymphoid cells CD45posCD14neg, out them 67% CD5posCD19neg, 70% CD2posCD19neg, 8% CD5negCD19pos, 28% CD3posCD4pos, 32% CD3posCD8pos. Through clonality of TCR lymphoma was excluded. It was concluded as multifocal necrotising encephalitis, the necrosis was considered to be secondary and viral aetiology seemed improbable. The clinical picture was not congruent with a diagnosis of viral encephalitis (also PML) as well.

Due to the probable infectious aetiology he was treated for 3 weeks with combination of co-trimoxazol, Meronem, Aphotericin B without any detectable effect on the brain lesions and its progression. The treatment with CsA continued, and steroids in boluses together with a single high dose of IVIg, there were clear positive effect on the symptoms of Evans syndrome, however, no effect on the brain lesions. The patient suffered from repeated attacks of intracranial hypertension. Administration of antiepileptic treatment (Topamax) started, later his neurological status stabilised. A few months later (12 y-o) regular infusions of IVIg were started and he stayed on this treatment for about 3 years. The IVIg therapy was applied mainly due to diagnosis of CVID, however, this diagnosis has been recently disapproved (the diagnostic criteria have not been fulfilled neither at the time of diagnosis or later). He has had mild neurological symptoms (partial paresis, tinnitus), he has been able to attend school and is doing relatively well.

He has never suffered from remarkable gastrointestinal problems. Since the diagnosis of Evans syndrome there has been persisting mild splenomegaly. Repeated investigation of cerebrospinal fluid (cytology, biochemistry, PCR) has always been with inconclusive findings. All standard tests provided in immunology lab did not reveal any pathology.

Autoimmune lymphoproliferative syndrome was excluded (double negative CD4negCD8neg T cells were within normal limits), perforin test was negative (perforin 73%), no lymphoproliferation was detected.

Recently (15 y-o, 6 years after the manifestation of thrombocytopenia), during a mild febrile respiratory infection, multiple patchy lesions in lungs were surprisingly found on chest X-ray (confirmed by HRCT); mycosis was suspected, however, the clinical course has not corresponded with this picture – despite of the pulmonary findings on X-ray, besides a brief febrile period he has been afebrile, clinically stable, with no elevation of CRP and without leukocytosis. The only detected pathogen (PCR) from bronchoalveolar lavage was HHV6. A lung biopsy of the lesions revealed granulomatous inflammation, with no signs of mycotic infection.

Could this disease be of infectious origin? Could it be caused by unknown, undetected organism? Is it due to unclear immunodeficiency? Does any autoimmune mechanism play a role in the brain and lung lesion? Could a part of the defects be iatrogenic? What other tests and investigations should be performed?

We would be very grateful for your suggestions and tips sent on my email address. If anybody is interested, we can provide more detailed information together with electronic version of MRI, CT and X-ray images.

Thank you for your cooperation!

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Young Researchers' Corner

Dear ESID *junior* members,

Don't you think it would be interesting to have a section where young researchers can make connections, discuss and exchange doubts and questions about laboratory protocols and methods in the field of Primary Immunodeficiencies? Now it is possible, and I'm very glad to introduce you to this novel ESID Newsletter section! I think it will be an interesting opportunity to improve our knowledge and a good possibility of staying in touch with other juniors, so I'm looking forward to your active participation to develop this section.

For this first time I would like to invite all of you to focus on the following flow cytometric method:

LYMPHOCYTE PROLIFERATION ASSAY

The estimation of lymphocyte proliferation is very important to understand the mechanism underlying immune response and to help in immunodeficiencies diagnosis. The flow cytometric analysis of lymphocyte division by the vital dye CFDASE (Carboxyfluorescein diacetate, succinimidyl ester) is currently the most informative and widely applied technique in immunological laboratories around the world. CFDASE consist of a membrane permeant and non-fluorescent molecule until it is deacetylated in the intracellular environment becoming CFSE, an highly fluorescent and non-permeant molecule. CFSE segregates equally between the two daughter cells upon cell division. The serial halving of the fluorescence intensity with each successive generation is visualized as distinct peaks of population of cells after flow cytometric analysis.

PROTOCOL

Preparation of PBMCs suspension from peripheral blood from the patient and an age matched healthy donor.
5x106 cell/ml suspension of PBMCs (or subpopulation of lymphocytes) in PBS + BSA 0.5% is incubated with CFDASE 2-10 µM (depending on the duration of the study; CFDASE stock solution: 5mM in DMSO) at room temperature (RT) for 8-10 min.
Add 2-3 volume of FCS cold for 3 min at 4°C to quench unbound CFDASE.
Spin down at 300xg at RT for 8 min.
Resuspend pellet in colture medium and incubate for 3-5 min at RT and then spin down at 300xg at RT for 8 min. (Repeat this "washing step" twice).
Finally resuspend cells according cell colture protocol.
Flow cytometric analysis after at least 72 hr of cell colture in the presence of mitogens.

DATA ANALYSIS

Although there are different analysis approaches that, using complex mathematical models, are able to measure several parameters such as cell cycle time, fraction of cells recruited into division, the average death rate and so on… how can we use this powerful experimental technique in a simple and practical manner to estimate the deficiency of lymphocyte proliferation from patients compared to normal controls? Where can we

set a "threshold" above which PBMCs proliferation from patients could be considered normal? How can we solve the problem of variability in PBMCs response to mitogens from normal subjects in different assays (i.e. using aCD3 versus PHA)?

I'M LOOKING FORWARD TO YOUR SUGGESTIONS!

...maybe we can interact also through the forum section on the ESID website!!!

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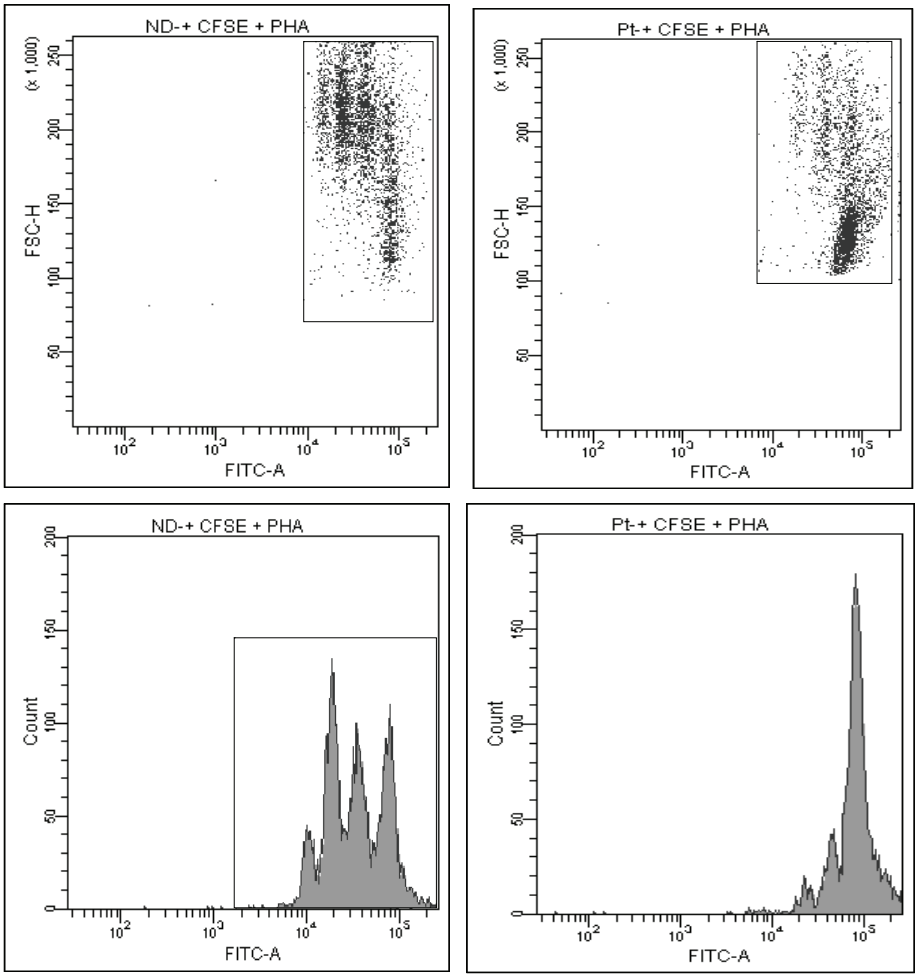


Dot plots (upper) and histograms (lower) of a flow cytometric analysis of a CFSE assay.

PID-care in development:

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

My name is Waleed Al-Herz and I am 36 years old. I graduated from the Faculty of Medicine at Kuwait University in 1996 then I finished training in pediatric at Miami children's Hospital, Miami, USA in 2000. After that, I joined the Fellowship program in allergy and clinical immunology at Thomas Jefferson University Hospital, Philadelphia, USA between 2000 and 2002. After returning back to Kuwait, I established a unit for allergy and clinical immunology disorders at the pediatric department in Al-Sabah Hospital, were all pediatric cases suspected to have immunodeficiency are referred.

Can you give me some information about health care in your country?

Kuwait is a small country (17,820 sq km) in the Arabian Peninsula with a population of 2,418,393. The health care in Kuwait is free of charge (supported by the government) and it is maintained by primary, secondary and more than 15 specialized centers. There are many private clinics and hospitals which are subjected to the regulations and rules of the Ministry of Health. The birth rate is 21.94/1,000, death rate is 2.41/1,000, infant mortality rate is 9.71/1,000 live births and the life expectancy at birth is 77.2 years.

Can you give me some information about PID care in your country?

The number of primary immuno deficiency patients in Kuwait is relatively high, probably because of high consanguinity rate. The care of these patients is shared with general pediatricians and the treatment of infections involves also pediatric infectious disease specialists. Since the establishment of the allergy and clinical immunology unit, the referral of patients suspected to have PID has increased steadily, and with the help of the laboratory at the Faculty of Medicine, we are able to perform the basic immunological work-up needed. However, molecular diagnosis for PID is not yet available. We are fortunate that intravenous immunoglobulins are available free of charge for all patients, but bone marrow transplantation service for pediatrics is not yet available in Kuwait. For this reason, patients in need for such service are referred to centers in Europe or North America for further management.

What has your role been in PID in your country until now? What do you hope to achieve in the future?

For the last few years, we have been trying to establish several links with centers both in Europe and North America for consultation regarding difficult cases and provision of unavailable molecular tests.

We hope to achieve the following for the future of PID in Kuwait:

- Improve the awareness of immunodeficiency among physicians so early intervention can be implemented.

- Develop a registry for PID to understand the pattern of these disorders in Kuwait.

- Start home care for intravenous immunoglobulin infusion.

- Develope adult clinic for PID.

- Initiate molecular diagnosis for some of the PID.

- Start a bone marrow transplant service for pediatrics.

- Establish a patient organization for PID and link it to IPOPI

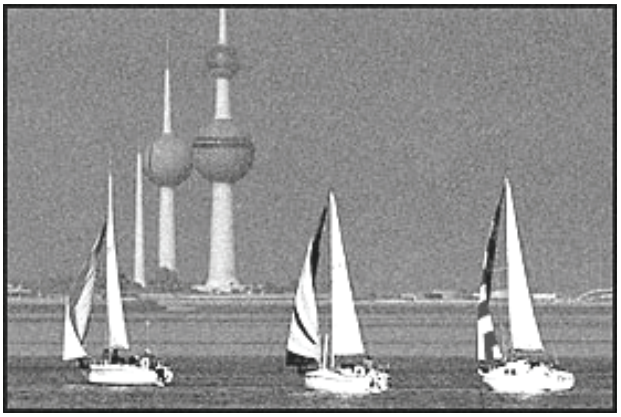
- Work with colleagues in the region (Arabian Peninsula and Iran) to understand the pattern of PID specific to this area.

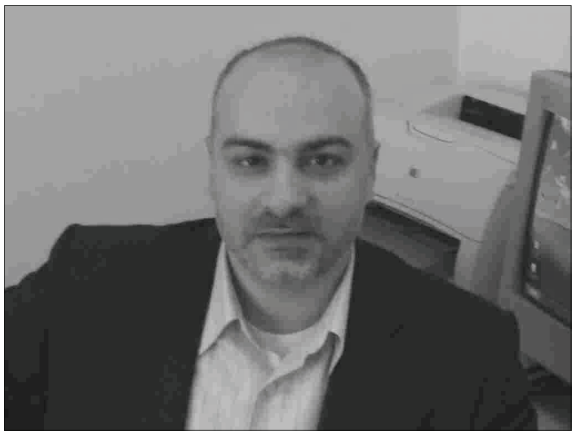
- Strengthen the existing relations with other centers both for clinical and research activities

How could ESID help to achieve this goal?

I believe ESID has been doing great in educating and linking physicians interested in PID through the biennial meetings, the ESID website, the Summer Schools and the ESID Newsletters. However, ESID needs to develop a network between different centers and countries for patient referral and consultation and provision of detailed immunological and molecular testing. Furthermore, ESID can play a role in involving centers outside Europe in the research activities done at well established and academic centers.

Waleed AL-HERZ





Kuwait

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