# ESID Newsletter

## Contents

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

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries (editor in chief) and Gustavo Lazo.

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

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

***Front page:***
***'Croatian anemone'***

# *Dear ESID members,*

Soon, we will see each other in Budapest, at another ESID meeting that looks as promising as the ones that we have had in the past.

During that meeting, we will have to take some important decisions at the General Assembly. Candidate members for the Board have presented themselves to you in the last issue, and some more present themselves in this one. We will elect the new Board members in Budapest together; don't forget to cast your vote!

A very important issue during the General Assembly this time will be the proposed ESID legal act and revised Constitution. Please read our proposals carefully, form your opinion, and come to the discussion and voting at the General Assembly. Together, we will decide about the future of ESID.

Of course, the usual items can be found in this ESID Newsletter as well: Working Party reports, News & Views, and another country presenting itself in the PID-care in development section, Sudan.

Best wishes to all of you, and hoping to see you in Budapest,

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, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Stem cell transplantation and gene therapy (chair: Mario Abinun), Registries (chair: Bodo Grimbacher), Clinical (chair: Bobby Gaspar), Genetics (chair: Anna Villa), Education (chair: Anders Fasth), and ESID*juniors* (chair ad interim: 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 may 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 2004 in Versailles, France; the next congress will be organized in Budapest, Hungary in October 2006, and the one after that will be in The Netherlands, in 2008.

## = ESID Information =

# President's letter

Dear friends:

With only a few weeks to the next ESID Meeting in Budapest, it is time for me to wrap-up after four years of Presidency.

It has certainly been a privilege to serve as President for our Society. I wish to express my deepest gratitude to all of you, who as members of the ESID community, have made this possible.

Others will say what of good and bad has marked these four years of Presidency. I will bring with me unerasable memories of ambitious plans for the growth of our Society, of long and sometimes frank, but always fruitful, discussions with other members of the ESID Board. No doubt, I could have done more, yet I am proud and thankful to all of you, and to the members of the ESID Board in particular, for what has been achieved.

A special thanks goes to Hermann Wolff, a wise Secretary who has always helped me take timely decisions, while remaining behind the scene. A special thanks also to Esther de Vries, who has been able to manage the financial balance of ESID within proper limits, and has taken important initiatives (such as on-line payment, which has certainly simplified paying membership fees). Even more importantly, she has to be congratulated for bringing so much enthusiasm into a renewed Newsletter. I wish her attention and dedication could receive a warmer response from all of you (I continue to see little interest in the Newsletter, which I personally regret).

All members of the ESID Board, from President Elect Jean Laurent Casanova to the Past-President Edvard Smith to the President of the last ESID Congress Alain Fischer, to Laszlo Marodi, President of the next Congress, to the chairpersons of the Working Parties (Anna Villa, Mario Abinun, Bobby Gaspar, Anders Fasth, Bodo Grimbacher, Eleonora Gambineri) have given to me an incredible support during these years, and there would be no words to thank them properly.

Also, it has been a pleasure for me to continue and reinforce our collaboration with IPOPI, INGID, and the Jeffrey Modell Foundation, and initiate a more solid collaboration with EFIS. Notably, this network of people and Institutions with a specific interest in Primary Immune Deficiencies has received official recognition by the European Parliament and by the European Union, with two significant events during these four years.

ESID must go on. There is a need for further changes and further initiatives. It is appropriate that others now bring new ideas, will and strength. In stepping down from Presidency, I will remain an active member, and will continue to add my voice to yours.
Thank you so much for these wonderful four years.

Luigi NOTARANGELO


*A new ship for ESID as well … ?*

# Secretarial report

## Invitation and Agenda for the ESID General Assembly 2006

Dear ESID member,

May I cordially invite you to attend the General Assembly of ESID that will take place on Friday October 6th, 2006, 14:00 – 16:00, at the occasion of the XIIth ESID Meeting 2006 in Budapest, at the Novotel Budapest Congress Centre.

Several important decisions have to be taken and new ESID Board members have to be elected. **It is important that as many ESID members as possible attend the General Assembly, as this is the most important occasion to define the future of our society.**

**AGENDA**

1. Welcome and presidential report
2. Secretary´s report
3. Treasurer´s report including the biennial ESID membership fee
4. Reports of the chairpersons of the ESID Working Parties
5. Proposal for statutes of ESID (a legal act) and corresponding changes to the current ESID Constitution
6. Clinical PID issues, e.g. raising PID awareness: PID warning signs for adults
7. Report of the 2008 biennial ESID meeting president and approval of the meeting site by the assembly
8. Election of the meeting president for the ESID meeting 2010
9. Election of ESID Board members and transfer of duties from old to new Board members
10. Varia

Hermann WOLF,
ESID Secretary, on behalf of the ESID Board, August 27th, 2006

# Treasurer's report

Dear ESID members,

I am very happy that so many members have paid their ESID membership fee through the Saferpay link on the ESID website. At this moment, 301 members have paid the 2006-2007 ESID membership fee !

Unfortunately, 198 members have NOT done so. They will find a last reminder with this ESID Newsletter. Immediately after the ESID meeting in Budapest all members who have not paid their 2006-2007 membership fee will be deactivated. They will no longer receive the ESID Newsletter, and will no longer be able to enter the restricted part of the ESID website. I hope all of you will decide to pay after all, so I will not have to do this to you !

If you received a last reminder, but have paid recently, go to the ESID website and check your payment status in the restricted area. If you are listed as having paid, your payment and this last reminder have crossed, and everything is all right. If not, a mistake may have been made. In that case, please send me a proof of payment (copy of the email you received from Saferpay) at esid @ estherdevries.nl . I will then correct your payment status on the website, and of course not deactivate your membership.

Those who are not stated as having paid on the ESID website, will not be able to enter the meeting in Budapest paying only the reduced fee. The congress organisation has access to the payment status of all members, and will check this !

Another important issue: still many email addresses in the ESID online member list are missing or incorrect. Please check if your details are listed correctly, and if not change them. If you have any difficulty in doing so, please contact the webmaster.

Esther DE VRIES

# Important voting General Assembly

Dear ESID members,

Over the years, ESID has grown into a Society with many funds: membership fees, sponsoring for the ESID Newsletter, sponsoring for the online database, sponsoring for the ESID Summer School. Lots of money are flowing through the accounts of the Society. Until now, ESID is an unofficial society with only a Constitution containing rules we have set up ourselves, but for the law, we are just a set of individuals, and as such each of us liable for everything that happens within ESID, including the cash flows.

Lawyers have advised us strongly to turn ESID into an official Society made up by a notarial deed (legal act). It is easiest, since ESID is registered in the Dutch Chamber of Commerce, to do this together with a Dutch lawyer.

We now put before you the draft text of the legal act, and the adapted Constitution (some things that were originally regulated in the Constitution are now dealt with in the notarial deed).

During the General Assembly, we will ask your permission to pass the legal act before the notary, and to change the Constitution accordingly.

Lots of issues in such a notarial deed are mere formalities, but several issues have an important impact on our Society. During the General Assembly, we will ask your opinion on these issues separately. They concern the following items:

- Membership: full members and restricted members, *or* full members, associate members and restricted members. Points of discussion: do we want to make a difference between European and non-European members , and do we want to put a restriction on all members who are employed by the pharmaceutical industry or not? (see Article 3; several variants are suggested)
- Board: do we want to restrict Board membership to Europeans, to people working in Europe, or not, or only certain posts? (see Article 6; several variants are suggested)
- Voting / General Assembly: do we want to make a difference between European members or not? (see Article 9; several variants are suggested)

In the draft of the new Constitution, you again see two variants concerning restriction to European members or not (rights of members in § 3). We will ask your opinion on this as well.

It is very important to read the proposal for the legal act and revised Constitution very carefully, and to come to the General Assembly to give your opinion and votes. Once decisions have been taken, they cannot so easily be changed. After a legal act has been passed by a notary, it can only be changed by another notarial deed, after the General Assembly has agreed to that (see the proposed text of the legal act). The Constitution can only be changed after another voting takes place in the General Assembly.

Under Dutch law, Board members as well as members are no longer liable for the financial decisions of ESID, unless it is a matter of gross malfunctioning or fraud.

# Important voting General Assembly

## Notarial deed (draft)

Today, ¨two thousand and six, the following persons appeared before me, ¨, notary, practising in Boxtel:

1. ♦, 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. They obtain the right to elect officers in ESID and to stand for election.

♦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.

♦[or:]

♦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. People employed by a pharmaceutical company always fall in the category of restricted membership.

2. The Treasurer of ESID shall maintain an accurate register of members.

3. Membership shall not be transferable.

♦[or:]

♦Article 3

1. a. Members are people with an interest in primary immunodeficiencies. ESID shall contain full members, associated members and restricted members.

b. Full Members are European members who are involved in the treatment of, or research related to,

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primary immunodeficiencies. They obtain the right to elect officers in ESID and to stand for election.
c. Associate Members are non-European members fulfilling the criteria as stated in 1b. An Associate Member

is not eligible for President, Secretary, or Treasurer of ESID. However, associate members can function as full members in all other aspects. The annual fee for associate membership is 100 percent of the full membership fee.
♦d. 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. However, restricted members can function as full members in all other aspects. The annual fee for restricted members is 100 percent of the full membership fee.
♦[or:]
♦d. 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. However, restricted members can function as full members in all other aspects. The annual fee for restricted members is 100 percent of the full membership fee. People employed by a pharmaceutical company always fall in the category of restricted membership.
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. A Board member must be a full member of ESID.
4. The Board members shall be elected by the General Assembly. The procedure for the election is described in the Constitution.
♦[or:]
♦Article 6
1. The Board shall be charged with the administration of ESID, with due observance of the provisions of Article 7.

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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 President, Secretary and Treasurer must be full members of ESID.
4. The Board members shall be elected by the General Assembly. The procedure for the election is described in

the Constitution.
♦[or:]
♦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 President, Secretary and Treasurer must be full members of ESID, and working in Europe while serving on the board.
4. 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 full members of ESID who are present at the time of the meeting, which is announced at least one month in advance to all ESID members.
2. All full members 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 third of the total number of full members 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.
♦[or:]
♦Article 9
1. The General Assembly of ESID shall consist of all full and associate members of ESID who are present at the time of the meeting, which is announced at least one month in advance to all ESID members.
2. All full and associate members 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

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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 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 follow

ing 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 full members 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.

## *ESID Constitution (revised; draft)*

The forerunner of the European Society for Immunodeficiencies, (hereafter referred to as ESID), was established in September 1983 in Rome, Italy, as an informal group (EGID) interested in sharing experience and developing co-operative studies in the field of immunodeficiency diseases. In the 1990's the number of co-operative teams has risen substantially and this expansion has been commensurate with a growth in the complexity of the organisation, necessitating a clearer definition of its purpose and activities. At the Biennial Meeting in Sitges in 1994 the first constitution of ESID was approved. In 2000 the constitution was revised in Geneva in order to better reflect the evolution of this organisation. In 2006 the Constitution was adapted when official Articles were made up by drawing up a notarial deed.
§1 THE EXECUTIVE BOARD

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The Board consists of the President, the Secretary, the Treasurer, and the chairpersons of all Working Parties. Each term of office is for 2 years, renewable at the next Biennial meeting, but limited to 2 terms (4 years) only. The Treasurer can serve 4 terms (8 years). The President-Elect is elected at the General Assembly two years prior to office, the President of a Biennial Meeting is elected at the General Assembly during the Biennial Meeting four years before the Biennial Meeting he/she will organise. The Past-President is part of the Board for two years after his/her presidency, the President-Elect for two years before his/her presidency, the president of the Biennial Meeting from the two years before to the two years after the Biennial meeting that he/she is organising.
Decisions are taken by a majority vote. The President has the deciding vote, if the vote is otherwise tied. The Board should meet at least once a year.
§2 THE GENERAL ASSEMBLY
The General Assembly meeting is open to all members of ESID and to the president and the board of the International Patient Organization for Primary Immunodeficiencies (IPOPI) and the International Nursing Group for Immunodeficiencies (INGID). It normally takes place at the time of the Biennial ESID Meeting. It is chaired by the President and includes the Presidential report, the Secretary´s report, the Treasurer´s report and any other business. The agenda for the meeting is made available over the internet, mailed, or published in the ESID Newsletter at least one month in advance.
Elections for ESID officers occur during the General Assembly on a biennial basis. At least three months prior to this meeting, the Board will encourage ESID members to consider their candidature for available posts. This is primarily the responsibility of the Secretary. At least one month prior to the meeting, available candidates will present themselves to the ESID members in the ESID Newsletter and on the ESID website.
The General Assembly also has the following obligations: To elect the president and the location of the Biennial Meeting; To decide on the biennial fee for membership of ESID as proposed by the Board; To either agree or disagree with policy decisions as proposed by the Board; To make proposals as to starting/discontinuing activities of the Society; To decide about amendments to the Articles, the Constitution and dissolution of the Society (see also §13).
§3¨ESID MEMBERS
ESID full members are encouraged to participate in co-operative ESID and ESID related EU/Biomedicine studies; they can enter reports on immunodeficiency diseases and patients into the ESID registries; they are entitled to a password to enable them to enter the restricted part of the ESID website. All members are entitled to receive ESID Newsletters and regular information about meetings, co-operative studies and results of ESID research projects, ESID summer schools etc.;
♦[or:]
§3¨ESID MEMBERS
ESID full and associate members can participate in co-operative ESID and ESID related EU/Biomedicine studies; they can enter reports on immunodeficiency diseases and patients into the ESID registries; they are entitled to a password to enable them to enter the restricted part of the ESID website. All members are entitled to receive ESID Newsletters and regular information about meetings, co-operative studies and results of ESID research projects, ESID summer schools etc.;

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§4 WORKING PARTIES
The Board takes the initiative to establish and close Working Parties. Each Working Party is headed by a chairperson who becomes a member of the Board. Six Working Parties (Clinical, Genetics, Registries, Bone Marrow Transplantation&Gene Therapy, Juniors and Education) are presently operating within ESID, but more can be established if and when required. The Chairperson of each Working Party is elected by the General Assembly every two years and may stand for one re-election. The substructure of the Working Party is determined by the Chairperson. The Working Party Chairpersons give an annual report to the Board on Working Party activities and publications and a biennial report to the General Assembly.
§6 THE PRESIDENT
The President shall be a member of ESID of at least two years standing. He/she is elected by the General Assembly, and serves for two years. The President may stand for one re-election. He/she may thus serve for a maximum period of 4 years. The President serves as President-Elect for two years before becoming President. The President promotes the activities of ESID. These include fund raising, co-ordination of Working Party activities, giving guidelines to the organisers of the Biennial Meeting, and in negotiations with other organisations.
§7 THE SECRETARY
The secretary is elected for two years. He/she may stand for one re-election. He/she may thus serve for a maximum period of 4 years. The secretary writes the annual business plan with the executive officers, organises board meetings, agendas, keeps and circulates the minutes, chases up the reports for the General Assembly meetings, writes the agenda and minutes and circulates these to the members through the ESID Newsletter and ESID website.
§8 THE TREASURER
The Treasurer is elected for a period of two years which is renewable three times. He/she may thus serve for a maximum period of 8 years. He/she collects the two-yearly membership fee and accounts for the use of the funds for ESID purposes. He/she is also responsible for fundraising and maintaining the finances to support the infrastructure of ESID.
§9 INFORMAL NETWORKS
ESID encourages the formation of informal national networks among its members to locally promote the aims of ESID. The chairman/ co-ordinator of such a network (presumably elected for a limited time period) would have an advisory function to the Board. They will promote the interaction between ESID and National Immunology and Clinical Immunology Societies or Groups.
§10 MEMBERSHIP FEE
Each member pays a two-yearly membership fee to ESID which is fixed by the General Assembly after proposal by the Board. The fee can be reduced by the Board in particular circumstances on request. In addition, the Board has the discretionary power to identify exceptional circumstances and modify the fee for some countries. Members under 35years of age pay a reduced membership fee (50% of the full fee).
§11 BIENNIAL MEETING
Meetings of ESID take place once every two years. The President and the location of the Biennial Meeting is decided by the General Assembly upon proposal by the Board or members.

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The local host must be a full member of ESID. The ESID meeting is organised in close collaboration with the Board of ESID.

§12 USE OF ESID FUNDS

ESID funds consist of subscription fees and of funds raised from public organisations, charities and pharmaceutical companies.

ESID funds can be used for the following purposes:

Funding studies on co-operative European data of immunodeficiency diseases.
Funding activities of the Working Parties, e.g. reasonable travel expenses to Working Party meetings taking place outside the Biennial Meeting.
Funding the dissemination of information by the Secretary to members of the Group.
Funding of other administrative costs considered necessary by the Board.
Maintaining the ESID online Registry.
Maintaining the ESID website.
Organising the biennial ESID Summer Schools, and biennial ESID Educational Days.
Publication of the ESID Newsletter and Supplements.

§13 CHANGING THE CONSTITUTION

Amendments to and changes of the Constitution are made by the General Assembly with a two-thirds majority vote. Notice of the intention to change the Constitution shall be made available to all members at least 4 weeks before the relevant business meeting of the General Assembly.

# Come to the General Assembly

# and cast your vote,

# this will influence every single member !

# 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 will be launched during the opening session of the Budapest meeting. Be sure not to miss this important event!

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

*Journal of Experimental Medicine*

Dear All, I have been appointed Editor of the 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

*The 5th ESID Prague Spring Meeting*
*May 8-9, 2006, Prague*
*Institute of Immunology, 2nd Medical School, Charles University, Prague*

On May 8 and 9, 2006, the fifth ESID Prague Spring meeting was held at the University Hospital Motol, Prague, Czech Republic. Twenty seven participants from 10 countries, namely Czech Republic, Estonia, Germany, Hungary, Lithuania, Poland, Slovakia, Romania, Russia and the UK attended and actively participated in the event; this represents a further increase in participants from a continually widened area. In addition we welcomed again a member from IPOPI and representatives from the sponsoring companies.

Traditionally the main task of the Prague ESID meeting is devoted to the exchange of information on primary immunodeficiencies (PIDs) between Western and Central Europe. This task was accomplished this year through an excellent attendance from both parts of the European continent. The invited speakers were Christine Kinnon from Molecular Immunology Unit, UCL Institute of Child Health in London and Benjamin Gathmann from Department of Rheumatology and Clinical Immunology in Freiburg. As in previous years, Helen Chapel, from the University of Oxford has provided great support in participating in the meeting and helping to organise the educational dimension.

The introductory lecture of the meeting served as an overview of the current state of gene therapy. Christine Kinnon covered the history of this pioneering treatment option for severe forms of PIDs and outlined its potential prospects as well. One section of the programme of the first day focused on issues with pan-European impact, including the new ESID on-line registry of PIDs and disparities in the diagnosis, care and treatment of PIDs amongst European countries. All the participants, representing 8 EU member states, Romania and Russia, took an active part in the discussions. The outcomes from these fruitful discussions will serve as a base for discussions at the forthcoming EU Public Health Consensus

meeting in June 2006 in Germany.

The programme of the second day concentrated on humoral deficiencies, the crucial topic of this year's meeting. The latest advancements and discoveries in the research of molecular background of antibody deficiencies were discussed as well as laboratory tools used for the classification of these entities. Case reports formed a substantial part of the programme, including newly discovered immunodeficiencies, as for example, the recently described Cernunnos deficiency. The unusual and interesting cases were highly appreciated.

The social programme is an important part of the ESID Prague Spring meeting, as it enables further fostering of close cooperation between Central and Western European countries. The relaxing stroll through Prague Castle, the dinner in a restaurant in the historical quarter of Prague and a concert in a jazz club were all enjoyed by the participants.

The meeting was supported by the Charles University, 2nd Medical School, Prague and by the University Hospital in Motol, Prague and substantial contributions from pharmaceutical companies Baxter, Grifols, Exbio and Immunotech. The Meeting was organized as a part of the activities related to the Day of Immunology, declared by EFIS on 29th April, 2006.

This year's meeting has confirmed the still growing scientific quality of the conference and the usefulness of this educational activity.

The next ESID Prague Spring Meeting will be directed mainly at ESID Juniors from as many countries as possible and will be held in Prague on May 14 and 15, 2007.

Anna SEDIVA
Ales JANDA

*Budapest Meeting, 4-7 October, 2006*

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

I hope that the program of the Meeting that you can see on the web (www.ESID2006.com) is inspiring, and that you will join us to make another successful ESID Meeting together.

I look forward to seeing you in Budapest!

László MARÓDI, Congress President.

# ESID Board Elections!

Dear ESID members,

In addition to the candidates that have already presented themselves in the 2006-2 issue of the ESID Newsletter, the following candidates would like to present themselves to you as candidates for the vacancies in the ESID Board as of October 2006. Elections will take place during the ESID General Assembly in Budapest. Luigi Notarangelo will step down as president, and president-elect Jean-Laurent Casanova will take over. Hermann Wolf will step down as secretary, Esther de Vries is available for re-election for one last term as Treasurer. For the Working Parties, Mario Abinun is available for re-election for Stem cell transplantation and gene therapy, and Bobby Gaspar is available for re-election for Clinical. Bodo Grimbacher will step down for Registries, Anna Villa for Genetics, Anders Fasth for Education, and Pim van der Vossen for ESID *juniors*.

*Genetics Working Party*

My long-standing interest in pediatric immunodeficiencies began as a result of my PhD research, elucidating the mechanisms of activation of Epstein-Barr virus, and my clinical pediatrics training at Yale University. This interest was fostered during my subsequent training in the Division of Research Immunology and Bone Marrow Transplantation at Childrens Hospital of Los Angeles. During that time, I had the opportunity to study how the signaling and fate of lymphocytes are modulated in patients with mutations in the ZAP-70 protein tyrosine kinase as well as gc cytokine receptor. Moreover, we made some initial progress in achieving gene transfer in lymphocytes from these patients. Following this experience, I had the opportunity to move to Europe in 1996 and start my own research group at the Institut de Génétique Moléculaire de Montpellier, France. During the past 10 years, my research group has continued to focus on genetic immunodeficiencies and potential cell- and gene-therapy treatment strategies. We have had the opportunity to interact with clinicians from France, Morocco, Portugal, England, Israel, Turkey, Germany, Spain and the U.S., amongst others, in an attempt to further the diagnosis and treatment of immunodeficiency patients.

ESID is clearly the leader in assembling immunodeficiency research and fostering interactions between clinicians, basic scientists and patients world-wide. As a member of the scientific "Immunodeficiency" community, I have always been extremely impressed by the functions fulfilled by ESID. Furthermore, I have had the opportunity to benefit from the extensive networks of ESID. It is in this context that I would be enthusiastic to head the Genetics Working Party and be involved in the future of this important organization. It is crucial that ESID helps to organize a coordinated basic and clinical research effort for the diagnosis of patients with immunodeficiencies. I hope to work together with the present ESID Board to achieve that goal.

Naomi TAYLOR

*Genetics Working Party*

My name is Esther van de Vosse and I would like to introduce myself as candidate for the position of 'head of the Genetics Working Group' of ESID. I am a molecular biologist (I studied biomedical sciences at the medical faculty of Leiden University) and have a PhD in human genetics (1998). After obtaining my PhD I worked for 3.5 years as a post-doc studying the genetics of early development in Drosophila at the University of Colorado at Boulder (USA). This was a very interesting experience and I learned a lot, but since my primary interest has always been genetic defects in humans I decided to return to human genetics. In 2001, I accepted a job in the Department of Infectious Diseases of the Leiden University Medical Center (in Leiden, the Netherlands) studying the genetics of infections with intracellular bacteria. Part of my work is focused on the identification of genetic defects in patients with a.o. the immunedeficiency known as Mendelian susceptibility to Mycobacterial Disease (MSMD). Another part is focused on large scale population studies where we try to identify genetic factors that influence susceptibility to infection with mycobacteria (tuberculosis and leprosy) and salmonellae (typhoid fever).

I have been an ESID member since 2004 and have not had the opportunity to become an active member until now. Heading, or at least participating in, the Genetics Working Party of ESID may be the fastest way to start my active participation. The current board of ESID consists mainly (if not entirely?) of clinicians and my perspective as a molecular biologist/geneticist may be helpful. I hope to meet with other ESID members at the meeting in Budapest in October, exchange ideas and discuss plans for the Genetics Working Party.

If I am chosen to head the Genetics Working Party, I would like to propose to make a start to try and solve in a European collaborative effort some of the rare immune deficiencies that have a probable genetic cause but that are not well understood. Most departments have –in addition to the patients with known immune deficiencies- a small collection of patients that clearly have an immune deficiency but in which the cause has not been identified yet. It is very difficult to build a consistent clinical picture, let alone determine the cause of a deficiency, if only one or a few patients with a specific phenotype are available. A collaborative effort could make the difference. First, interested people would have to get together or assemble a list through email contact in order to discuss these patients, see if we can identify some common phenotypes. Then, if any patients can be grouped, a collaborative effort to systematically analyze and identify the defect can be started. I am hoping to obtain government/EU funding to organize occasional small meetings for the people interested in such an effort.

Of course, if other ESID members have suggestions for other genetic defects that should be studied in a collaborative effort, or other suggestions regarding the tasks of the Genetics Working Party, I am very eager to hear these so we can discuss the possibilities. I hope I will be elected in Budapest for this position as I am looking forward to heading the Genetics Working Party of ESID.

Esther VAN DE VOSSE

*ESIDjuniors Working Party*

My name is Ales Janda and I would like to candidate for the chair of ESID*juniors* that is to be elected in Budapest this October.

Let me shortly introduce myself. After graduation from medical school in 2000, I started paediatric residency at the Teaching Hospital Motol affiliated to the Charles University, Prague, Czech Republic. Meanwhile, I received Educational Commission for Foreign Medical Graduates (ECFMG) certificate enabling me to enter into clinical programmes in the U.S.A., however, I decided to stay in Europe and continue my training on the "old" continent. During the residency I chose immunology as the further field of interest and moved to the Department of Immunology within the same hospital. Shortly after this change I received a unique chance to attend a one-year master course on immunology at the University of Oxford lead by Dr Chapel and Prof Austyn (MSc in Integrated Immunology, graduated with distinction) that was followed by 3-month fellowship focused on research of common variable immunodeficiency. Since I became a member of ESID in 2004, I have been involved in the discussion over the ESID on-line registry and I have taken part in the creation of the DiGeorge syndrome sub-registry that is currently fully functional. I was in charge of organization of two (out of five) annual ESID Prague Spring Meetings as well. I am currently enrolled in the Czech immunology training programme. Apart from the clinical work, my main research interest are humoral immunodeficiencies. I am 32 year-old and I live in Prague with my wife and son.

What are the ideas I would like to promote within the ESID junior group? If I am to express it briefly, I would summarize it in a simple motto: "Enhancement of communication, exchange of experience and emphasis of education".

Thanks to the effort of the previous board members and their collaborators the new ESID web site started to serve as a perfect communication platform within ESID. To take maximal advantage of this electronic means of communication some useful tools could be added. One of them is a database of solved PID cases with a clear structure and multimedia content that could function as a teaching tool not only for ESIDjuniors. The contribution into this database could be awarded through travel grants, prizes and increased chance of publication in the high-quality journals (e.g. in JEM as mentioned by JL Casanova in the previous Newsletter). Another add-in could be a discussion board (or a chat room) for junior members where different topics can be debated. This would be the place where questions regarding difficult or peculiar patients could be brought up. Supervision of a senior advisor would be indispensable and I hope that together with the Educational WP we would create some form of „electronic tutoring". This could later lead to an establishment of an on-line course on PIDs based on principles of distant learning.

Electronic communication is useful, however, it cannot replace personal meetings and face-to-face discussions. The ESID Summer School has shown to be a very pleasant and beneficial activity. The main advantage of these workshops is the relatively low number of participants enabling easy and lively discussion among juniors and faculty. Since 2002, we organize a similar seminar in Prague called the ESID Prague Spring Meeting. It is an annual 2-day meeting and as you might know from the reports published in the Newsletter, it has focused mainly on the physicians from Central and Eastern Europe. There have always been about 30 participants (all of them have to present results of their research or case reports) and a few invited speakers from established PID centres. From the next year onwards, we would like to focus on all ESID junior members, making it a regular part of the ESID junior "schedule" and a place of annual meeting of its members.

As money is not a problem only if you have it, I would like to assist in searching other

funding opportunities to support attendance of young researchers and clinicians at conferences and scientific meetings and to undertake short-term research and clinical fellowships.

I would also promote closer cooperation with junior sections of other European organizations dealing with clinical immunology, e.g. European Academy of Allergology and Clinical Immunology (EAACI) and non-European societies, e.g. PAGID.

All of these points may look very nice on a paper, however, it will require a substantive amount of work to put it into practice and a good cooperation within the junior group is necessary. Discussion over the priorities and organizational structure of this Working Party should precede. I am looking forward to further suggestions and hopefully vibrant talks on the future of ESIDjuniors during the meeting in Budapest.

I would like to contribute with these topics to the discussion over the junior section activities either as a regular member or if I receive enough of your votes as its chairman!

Have a nice and pleasant summer and see you soon in Budapest.

Ales JANDA

***Summary of candidates for positions in the ESID Board:***

| | |
|---|---|
| President | Jean-Laurent Casanova |
| Past-president | Luigi Notarangelo |
| Secretary | Bodo Grimbacher |
| Treasurer | Esther de Vries |
| SCT&GT | Mario Abinun |
| Registries | Gerhard Kindle |
| Clinical | Bobby Gaspar |
| Genetics | Naomi Taylor<br>Esther van de Vosse |
| Education | Andrew Cant |
| Juniors | Eleonora Gambineri<br>Ales Janda |
| Meeting 2008 | Esther de Vries |
| Meeting 2010 | to be determined |

Please come to the General Assembly in Budapest in October, and give your vote!

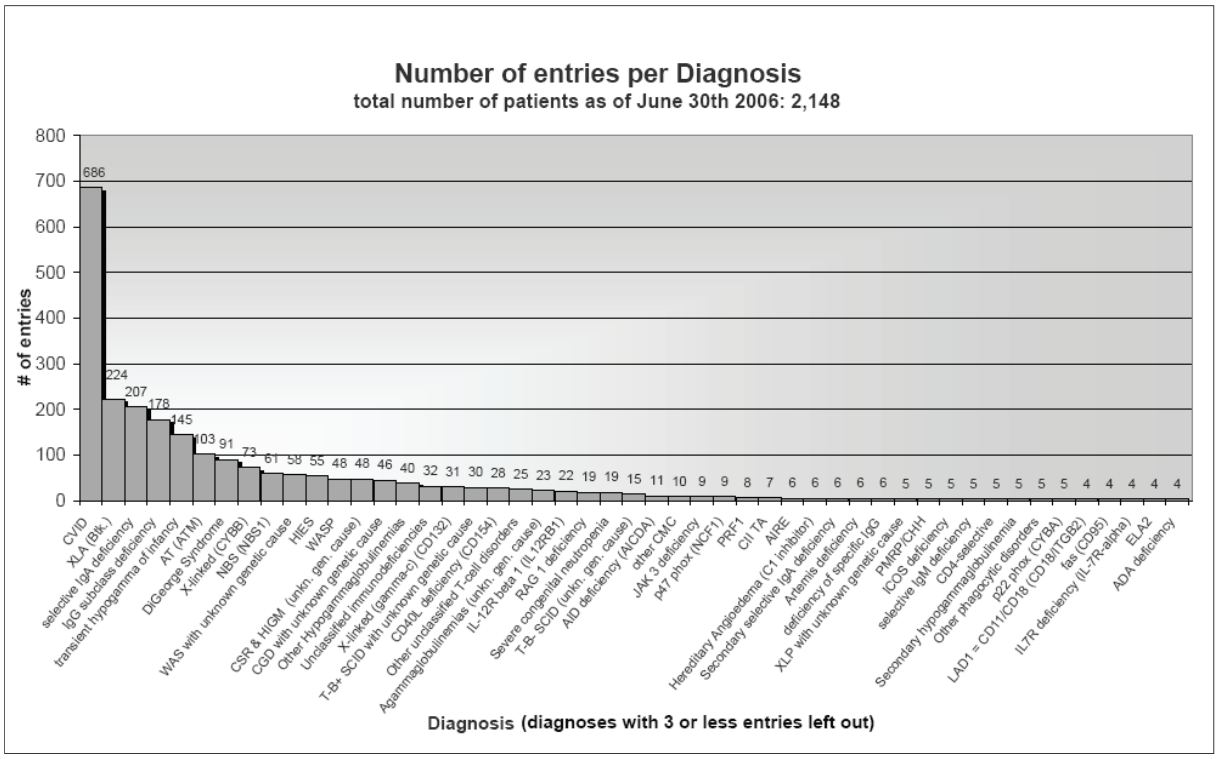
You can read more about the candidates in this issue and in the previous issue of the ESID Newsletter.

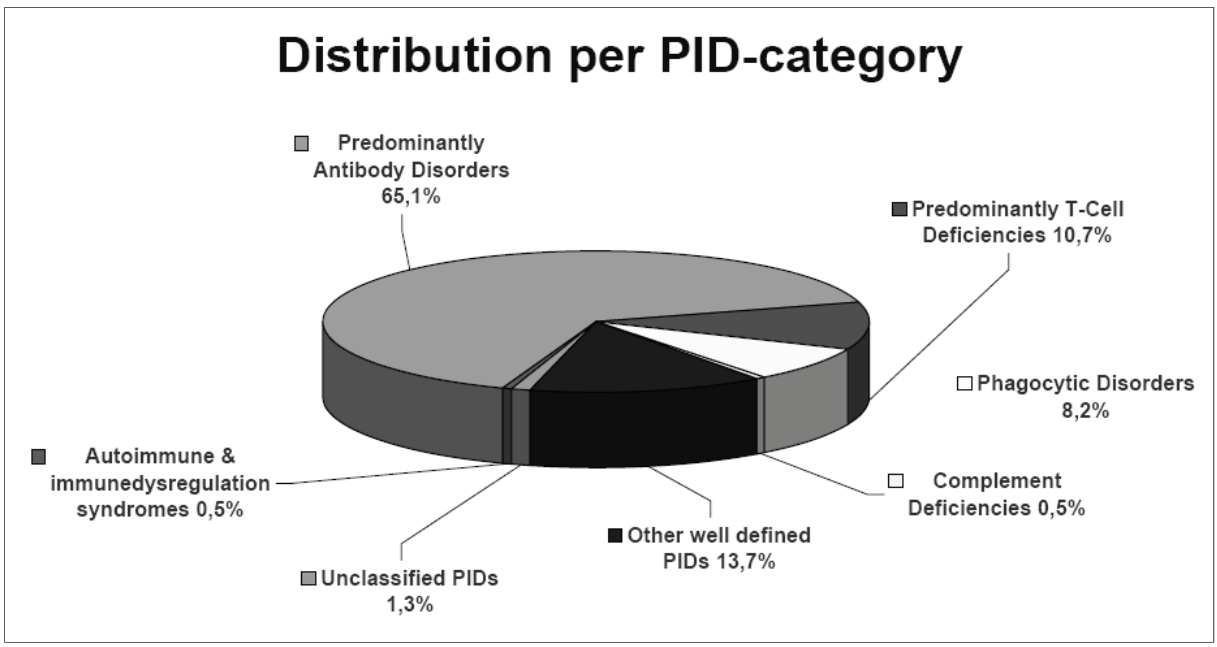
**ESID Board Elections!**

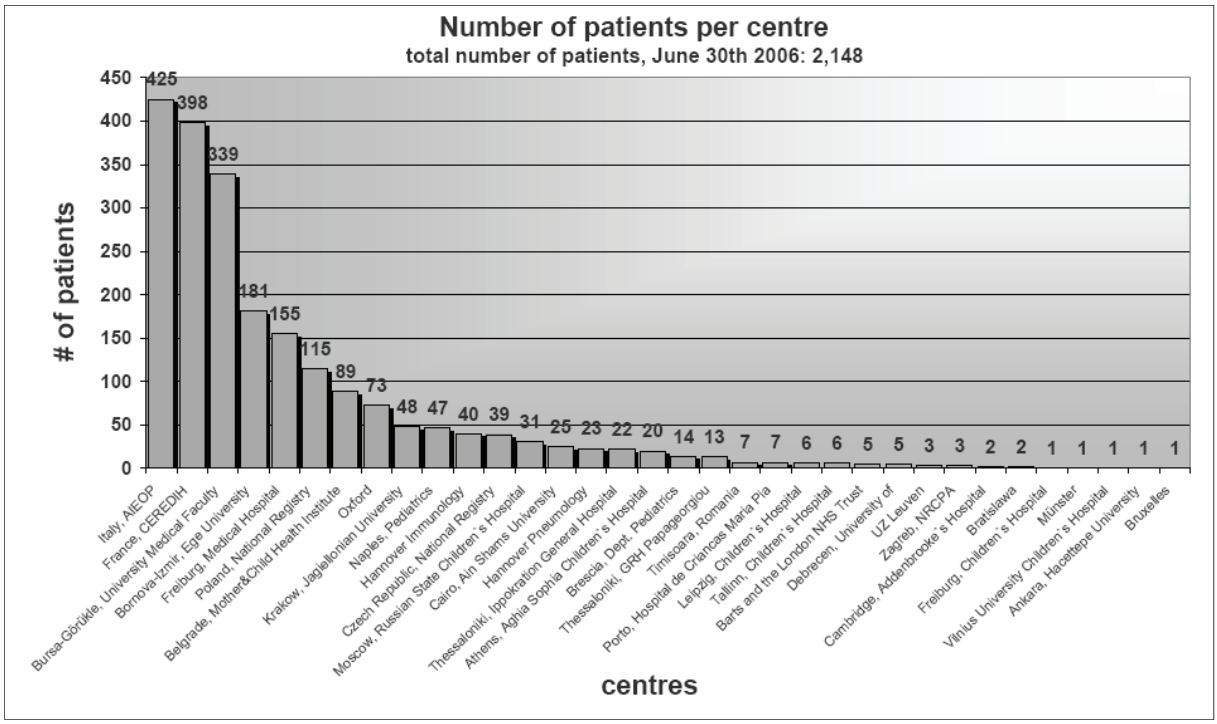
*Registries WP*

The ESID Online Database has recently seen another considerable increase in numbers of registered patients. The total number of patients has gone up from 1,727 in May 2006 to 2,148 on June 30th 2006. This was also the deadline for the annual bonus payment of 10 Euro for secretarial assistance. During the last year, 1,229 new patients were registered in the database. Furthermore, there was follow-up documentation for 536 of the 919 already registered patients. We are especially happy about this considerable amount of follow-up documentation, because this will provide us with valuable data for evaluation in the long run.

Further numbers from the database are shown in the figures below. All numbers, which are updated regularly, can be found at






www.esid.org/statistics.php.

There is also a number of centres which have recently joined the database, such as the Hospital de Criancas Maria Pia in Porto, Portugal, the West Ukrainian Centre of Children Immunology in Lviv, Ukraine and the University Children's Hospital in Ulm, Germany. All documenting centres with contact information are presented at www.esid.org/centers.php.

A rather big obstacle for many centres wishing to participate in the ESID Online Database is to receive approval from their local ethics and data protection authorities. Therefore, the Registry Working Party is proud to announce that it has received approval from the Ministry for the Interior of the German State of Baden-Württemberg for both the coded and the personalised version of the database which has been recently launched.

Although the university's ethics committee and data protection officer have already approved of the project two years ago, this new approval at the state level is very valuable. We hope that this approval will support other centres in Germany and abroad in their applications for ethics and data protection approval. It is available in English and German. **Please send an email to registry@esid.org to receive a copy!**

With the ESID Meeting in Budapest approaching, we once more call for researchers to use the registry for disease-specific studies, as the meeting in Budapest is a good opportunity to initiate studies. Studies for the following diseases are currently under way: Common Variable Immunodeficiency (CVID), Nijmegen Breakage Syndrome (NBS), DiGeorge Syndrome (DGS) and X-linked Agamma globulinemia (XLA).

The Registry Working Party will host a workshop at the ESID Meeting in Budapest. This will be on Friday, October 6, 2006, from 12:30 to 14:00 hrs. We invite everybody interested in the database or already using it to come to this workshop. We will give an update and show how the database works. After that, there will be plenty of time for questions and comments as well as criticism and praise from the audience.

We are looking forward to seeing you in Budapest!

Viviane, Benjamin, Gerhard, David, Anne-Marie,
Bodo GRIMBACHER

*Clinical WP: ESID/PAGID Diagnostic criteria for isolated Severe Congenital Neutropenia (SCN)*

**Definitive diagnosis**

Male or female with isolated severe chronic neutropenia*, defined as absolute neutrophil count (ANC) < 0.5 x $10^3$/mL on at least 3 determinations over a period of 6 months), without cycling of ANC, and associated with one of the following:

- mutation of the ELA2 gene,
- mutation of the Gfi1 gene,
- activating mutation of the WASP gene.

**Probable diagnosis**

Male or female with isolated severe chronic neutropenia*, defined as absolute neutrophil count (ANC) < 0.5 x $10^3$/mL on at least 3 determinations over a 6 months period), associated with a block at the promyelocyte stage upon examination of bone marrow aspirate.

Possible diagnosis

Male or female with isolated severe chronic neutropenia*, defined as absolute neutrophil count (ANC) < 0.5 x $10^3$/mL on at least 3 determinations over a 6 months period).

*severe chronic neutropenia associated with other features is not considered, but is briefly discussed under "Spectrum of the disease".

**Spectrum of the disease**

Isolated SCN can be inherited as an autosomal dominant or (less commonly) as an autosomal recessive or as an X-linked trait. However, many cases represent sporadic presentations due to de novo mutations. As many as 50% of all cases of isolated SCN remain genetically undefined at present. In particular, no mutations in any of the known SCN genes have been identified in the original Kostmann family.

The low ANC predisposes to recurrent and severe infections since infancy. Infections are mainly of bacterial or fungal origin. No other haematological abnormalities (anemia, thrombocytopenia) are present.

Most patients with isolated SCN respond to treatment with recombinant G-CSF; however 3-5% of patients fail to respond to such treatment, even if high doses of rhG-CSF are used.

Patients with isolated SCN are at high risk for myelodysplasia and acute myeloid leukaemia. Transformation is frequently associated with somatic mutations of the G-CSF receptor gene, and is more common in patients with selected gene defects, such as G185R mutation in the ELA2 gene.

A high incidence of sepsis and of myeloid transformation has been observed among patients on long-term treatment with high-dose rhG-CSF.

Activating mutations of the WASP gene have been also reported to cause a higher risk of myelodysplasia/myeloid transformation.

SCN may also associate with additional features, as in Shwachman-Bodian-Diamond syndrome (due to mutations of the SBDS gene), Hermansky-Pudlak type 2 syndrome (due to mutations of the AP3B1 gene), Barth syndrome (due to mutations of the TAZ gene), glycogenosis type 1b (due to mutations of the G6PT1 gene), and WHIM syndrome (due to mutations of the CXCR4 gene).

In addition, neutropenia may occur in the context of other forms of primary immunodeficiency, either as chronic neutropenia (as in reticular dysgenesis, SCID with maternal T-cell engraftment, CD40L deficiency, CD40 deficiency), or as transient neutropenia during infections (as in XLA). Finally, autoimmune neutropenia can be observed in patients with common variable immunodeficiency or with autoimmune lymphoproliferative syndrome.

*These guidelines have been prepared by a list of experts, as part of the activity of the European Union grant "Policy-oriented and harmonising research activities in the field of primary immunodeficiency diseases (PIDs)" (EURO-POLICY-PID), contract SP23-CT-2005-006411.*

## *Clinical WP: Questionnaire on WAS spontaneous reversions*

**Your Name / Laboratory:**

**Address:**

**Telephone:**

**FAX:**

**E-mail:**

**Please respond to as many questions as possible:**

**1. Number of Wiskott-Aldrich syndrome (WAS) patients you follow or have followed, if they have died: ___**

**2. Have you looked for revertant cells in the WAS patients you follow?**
**Yes – continue; No – please go to Question #8.**

**3. How many of your WAS patients have you studied for WASP expression by flow cytometry before hematopoietic stem cell transplantation? ___**

**4. How many of your WAS patients have you studied for WASP expression by other means before hematopoietic stem cell transplantation? ___**

**5. Number of patients that have shown presence of revertant cells (i.e. WASP-expressing cells) by flow cytometry: ___**

**6. Number of patients that have shown presence of revertant cells by means other than flow cytometry: ___**

**7. For each patient with presence of revertant cells, please fill out the following:**

**What cell lineages contained revertant cells?**

**T-cells: No ___; Yes ___ (___%)**
**B-cells: No ___; Yes ___ (___%) (please indicate CD used ___)**

**NK-cells: No ___; Yes ___ (___%) (please indicate CD used ___)**
**Monocytes: No ___; Yes ___ (___%)**
**Other cells (please specify _____): No ___; Yes ___ (___%)**
**Not determined ___**

**What is the original disease-causing mutation in this patient and what is/are the genetic change(s) in the revertant cell?**

_____
_____

**How many times was the patient studied? ___ At what age? _____ How many times were the revertant cells detected? ___**

**What was the clinical score of the patient before ___ and after ___ the appearance of revertant cells?**

**Do you have information about the clonality of the revertant cells?**

_____
_____
_____

**Please indicate the relevant reference, if this case was published:**

_____

**8. Have you observed the presence of revertant cell in other primary immunodeficiency patients?**

**No ___;**

**Yes ___ please specify disease entity _____**
**Yes ___ please specify disease entity _____**
**Yes ___ please specify disease entity _____**
**Yes ___ please specify disease entity _____**
**Yes ___ please specify disease entity _____**
**Yes ___ please specify disease entity _____**

**Please return this questionnaire to the ESID Clinical Working Party:**

**Dr. Bobby Gaspar, Molecular Immunology Unit, Institute of Child Health, Guilfordstreet 20, WC1N 1EH Londen, UNITED KINGDOM.**

**Or email to: h.gaspar@ich.ucl.ac.uk .**

*Genetics WP: First announcement of a new collaborative study on Spontaneous reversion events in Primary Immunodeficiency.*

Dear Friends,

Before leaving the genetic Working Party, I am glad to give rise to a new study that you can find on the ESID web site:

Dear Colleagues,

We are interested in characterizing the frequency and biological effects of spontaneous reversion events primarily in patients with Wiskott-Aldrich syndrome, but also in other forms of primary immunodeficiency. To this aim, we would like to ask you to respond to the following brief questionnaire, that you can find also in the ESID web site. We plan to collect the data and share them with all interested parties at the 12th Meeting of the European Society for Immunodeficiencies in Budapest, October 4-7, 2006, where there will be a Genetics Working Party workshop dedicated to this topic Friday, October 6th at noon.

We hope you will find the time to fill out and return the form to us (dln@helix.nih.gov or anna.villa@itb.cnr.it) before September 15 and that you will be able to join us in Budapest! Please let us know if you have any questions.

Finally, I would like to remind you another Genetic WP study we have already started in collaboration with Inborn Error Group of EBMT. We will meet in Prague (October 13-15, starting Friday at 2 PM) during the Inborn Error Working party to further discuss the data we have collected so far. You can find the questionnaire on the ESID web site.

Yours ,

Anna VILLA

*Educational WP*

Since the last ESID Newsletter, the Educational Working Party has been busy with the Educational Day at the upcoming Budapest meeting. The theme will be B cell development and defects. It promise to be an interesting prelude to the ESID meeting itself covering both an update on basic science data on B cell development and the clinical care of selected B cell defects.

The Working Party has also awarded travel grants to two colleagues coming from outside Europe. As in previous years, we had many young doctors from Latin America and especially Brazil applying for a travel grant. One of the grants this year was given to Dr Carolina Prando from Campinas outside Sao Paulo. The other grant was awarded to Dr Pramod Shankhpal from a small city outside Bombay, India. Dr Shankpal has promised to tell about his work and his impression from the ESID meeting in a coming issue of the Newsletter. The Working Party together with the ESID Board has made decisions on a research award to a young scientist or clinician that wants to work at a European institution for at least 6 months. The award is on 10 000 euros. This year there were 5 very talented applicants. One was chosen and the person selected will be presented at the Budapest meeting. You can read Tuba Turul's report (last year's grant) on the following pages.

The ESID working party is also represented at the first LAGID Summer School held in Sao Paulo August 27 – 31.

Finally, this will be my last report as according to the statutes, I will after 4 years step down as chairman for the Educational Working Party. It is with a bit of sorrow I leave as especially the ESID Summer School is just a joy and a most rewarding task. The Summer School has given me the opportunity to meet many wonderful and brilliant young persons and the experience tells me that the future looks most promising for continuing excellent research on PID and the care of our patients.

Anders FASTH

# ESID SCHOLARSHIP REPORT, June 2005 - May 2006

## LABORATORY TRAINING IN THE FIELD OF PRIMARY IMMUNODEFICIENCIES

**Tuba Turul, MD**

*Host Laboratory:* Mirjam van der Burg, PhD, and Prof. Jacques J.M van Dongen, MD, PhD, Department of Immunology, Erasmus MC, Rotterdam, The Netherlands.

**Training in laboratory diagnostics of primary immunodeficiency diseases.**

This part of the training consisted of both theoretical lectures and practical laboratory work.

1.1 *For the theoretical background formation* I joined the following courses and meetings organized at the Department of Immunology, Erasmus MC by the Molecular Medicine School;

- Course Molecular Medicine, Postgraduate School of Molecular medicine, Erasmus MC, June 27-July 1 2005, Rotterdam
- Course Boimedical research Tecniques IV, Postgraduate School of Molecular medicine, Erasmus MC, 26-30 September, 2005, Rotterdam
- Dutch Society for Immunology Annual Meeting, 8-9 December 2005, Leiden
- Frontiers of Mucosal Immunology, Postgraduate School of Molecular Medicine, Erasmus MC, 26-27 January 2006, Rotterdam
- Molecular Immunology: A short course for PhD students “Immunobiology-The immune system in health and disease”, Postgraduate School of Molecular Medicine, Erasmus MC, 2-10 March, 2006 Immunology Department, Erasmus MC, Rotterdam
- Weekly journal club on molecular immunology basic science topics organised by the department of Immunology in Erasmus University MC
- Weekly brainstorm research meetings in the field of molecular keystone mechanisms underlying primary immunodeficiencies and lymphoproliferative diseases for PhD students and post-docs of the Unit Molecular Immunology Department of Immunology
- Regular seminars (twice a month) on different molecular immunology topics

*For practical education purposes,* I had training on the following diagnostic laboratory procedures:

- Isolation and storage of DNA, RNA and mononuclear cells out of whole blood or bone marrow samples,
- Performing flow cytometry on either fresh or thawed cells for defining specific lymphoid cell populations,
- Analysis and interpretation of flow cytometry results of both peripheral blood and bone marrow samples for diagnosis of primary immunodeficiency diseases,
- Mutation analysis of the specific PID candidate genes by PCR amplification and fluorescent sequencing,
- Interpretation of sequencing results

**Participation in the diagnostic routine laboratory work.**

- Selection of candidate primary immunodeficient cases based on clinical characteristics for whom diagnostic laboratory support was asked from other centers and especially from Turkey
- Participation in the diagnostic work-up of clinical samples starting with the whole blood or bone marrow sample, followed by the mutational analysis in consecutive steps based on the laboratory training indicated above.

One week visit as an observer to Bone Marrow Transplantation Unit, LUMC, Leiden (Arjan Lancester, Robert Bredius).

**Participation in a collaborative research project on disturbed B cell development in SCID patients before and after bone marrow transplantation.**

See the attachment

**Additional topics**

Meanwhile as a collaborative work, we performed a study on three ZAP70 deficient patients who have been diagnosed recently. We are currently writing an article on these three cases.

## Project supported by ESID scholarship:

## Effect of pre-BMT conditioning on reconstitution of B-cell and T-cell function after bone marrow transplantation in B-negative SCID patients

*ESID Scholarship:*
T. Turul, MD, Dept. of Immunology, Hacettepe University, Yenisehir Ankara, Turkey

*Hosts and responsible scientists:*
M. van der Burg, PhD, and Prof. J.J.M. van Dongen, MD PhD, Dept. of Immunology, Erasmus MC, Rotterdam, The Netherlands

*Tutor:*
Prof. I. Tezcan, MD PhD, Dept. of Immunology, Hacettepe University, Yenisehir Ankara, Turkey

***SCIENTIFIC BACKGROUND***

***Severe combined immunodeficiency***

Patients with severe combined immunodeficiency (SCID) present in the first months of life with opportunistic infections, protracted diarrhea and failure to thrive due to a severe impairment of both cellular and humoral immunity that leads to death in the absence of treatment. Bone marrow (BM) transplantation (BMT) is the treatment of choice, if a donor is available.

Although, SCID is used to describe a well defined and common clinical picture of severe functional T cell deficiency associated mostly with functional impairment of B cells, it is known to be caused by a very diverse group of genetic defects. Up to now, mutations in 10 different genes have been shown to cause a well defined SCID phenotype[1]. These are namely, the *ADA*, *IL2RG, JAK3, CD45, RAG1, RAG2, Artemis, IL7RA, CD3D, CD3E genes.*

However, the clinical picture is not always typical ranging from severe cellular dysfunction to negligible dysfunction. Heterogeneity is especially seen in case of genetic defects that affect the signal transduction pathways that are essential for T-cell activation including, such as components of the CD3 complex (CD3g, CD3d, CD3e and CD3z), MHC class I deficiency, MHC class II deficiency , ZAP70 deficiency, and CD8a deficiency.

Immunophenotypically, two major categories of SCID have been defined. The first category concerns B-negative SCID (T-B-NK+), which is characterized by absence of B and T cells, mainly due to a defect in the V(D)J recombination process of immunoglobulin (Ig) and T-cell receptor (TCR) genes, for example caused by mutations in *RAG1, RAG2, Artemis,* or *LIG4* . Mutations in *Artemis* also give rise to increased sensitivity to ionizing radiation. Adenosine deaminase deficiency due to a defect in the *ADA* gene is associated with T-B-NK+ phenotype. The second category concerns B-positive SCID, associated with an X-linked or autosomal recessive mode of inheritance. The X-linked variant (T-B+NK-) is caused by a mutation in the common gamma chain, which is normally associated with multiple cytokine receptors. The autosomal recessive forms can be caused by a mutation in the *JAK3*

gene, which encodes a signalling molecule associated with the common gamma chain (T-B+NK-), or by mutations in the *IL7RA* gene, *XLF* or *CD3D* gene which only results in absence of T cells (T-B+NK+).
This classification is not only useful for selection of the candidate genes to be checked for mutational analysis, but also it helps to limit the number of genes that could be responsible for the phenotype. However, there are exceptions; for example the presence of maternal T lymphocytes, peripheral expansion of clonal T-cells of host origin or presence of some mature T or B-cells due to a leaky phenotype can lead to misinterpretation of the immunophenotype. Presence of T cells masks the clinical phenotype, making the diagnostic process more complicated. In addition, the broad range of genetic defects underlying T-B+NK+ phenotype further complicates laboratory diagnostics. Despite the efforts that have been put on the identification of genetic defects underlying SCID, still a 15-20 % of cases can not yet be solved.

***Differences in outcome of BMT in B-positive SCID and B-negative SCID***
In retrospective studies, it was demonstrated that the results of HLA non-identical T-cell depleted BMT were significantly better for B-positive SCID than for B-negative SCID patients. Reduced survival of patients with B-negative SCID appeared to be associated with a diminished rate of engraftment (particularly in absence of a conditioning regimen), a higher frequency of chronic graft versus host disease (GVHD), increased severity of GVHD, a slower recovery of T/B immune function, and a lower rate of full T/B cell function.[2,3]
Engraftment of T-cell depleted BM in patients with B-negative SCID required the use of a conditioning regimen, a setting known to increase the risk of GVHD and associated with delayed immune function development.[2]

***Precursor B-cell compartment in B-negative SCID***
Detailed flow cytometric immunophenotyping of the precursor B-cell compartment in bone marrow of SCID patients has shown that in B-negative SCID a (virtually) complete block in precursor B-cell differentiation occurs at the transition of the pre-B-I to pre-B-II cells with accumulation of pro-B-cells and pre-B-cells before this block.[4,5] In bone marrow of healthy children and bone marrow of B-positive SCID, the pro-B-cells and pre-B-I cells represent only 20 to 25% of the precursor B-cell compartment, but in B-negative SCID they cover 95 to 100%.[4-6] Since the total size of the precursor B-cell compartment in B-negative SCID is not smaller than in healthy children, it can be concluded that the early precursor B-cells completely occupy the precursor B-cell “space”.

***Influence of cytotoxic treatment on precursor B-cells***
Monitoring of BM samples from children with acute lymphoblastic leukemia (ALL) during and after cytotoxic treatment has shown that highly intensive treatment blocks virtually eradicated the precursor B-cell compartment.[7,8] The combined results suggest that relatively mild cytotoxic treatment (e.g. mild pre-BMT conditioning) will not affect the early precursor B-cells. Consequently, in B-negative SCID patients the precursor B-cell “space’ remains occupied with high frequencies of early precursor B-cells (pro-B and pre-B-I cells) that are stringently attached to their breeding sites. Therefore, there is potentially not sufficient physical space for development of a donor-derived precursor B-cell compartment (Burg *et al*. manuscript submitted).

## *HYPOTHESIS*

The better bone marrow engraftment in B-positive SCID versus B-negative SCID patients after bone marrow transplantation might be caused by lack of physical space in bone marrow of B-negative SCID patients due to the presence of a high frequency of early precursor B-cells (pro-B and pre-B-I), which strongly attach to their homing area and which are not eradicated with mild pre-BMT conditioning regimens. Better understanding of reconstitution of B-cell and T-cell function after transplantation using different conditioning strategies will give new insights and may result in adaptation of protocols for the treatment of the different forms of SCID.

## *KEY OBJECTIVES*

To determine retrospectively the exact influence of conditioning regimens on clinical outcome and bone marrow engraftment after transplantation in B-negative SCID compared to B-positive SCID patients. Preferably, the molecular diagnosis of both types of SCID patient should be available.

To study in detail the composition and chimerism status of the precursor B-cell compartment in bone marrow of B-negative SCID patients without peripheral B-cells post-BMT, who might benefit from a second BMT (from the same donor) after adapted pre-conditioning. After such second BMT, the composition and chimerism status of the precursor B-cell compartment will be analyzed again.

To investigate prospectively the composition of the precursor B-cell compartment pre- and post-BMT of B-negative SCID patients and B-positive SCID patients as well as the reconstitution of B-cell and T-cell function and chimerism status post-BMT in peripheral blood and bone marrow.

***OUTLINE OF INVESTIGATION***

***Part 1. Evaluation of effect of pre-BMT conditioning on clinical outcome and engraftment after transplantation in B-negative SCID compared to B-positive SCID patients***

To study the effect of pre-BMT conditioning on the clinical outcome and engraftment, the results of a series of B-negative SCID patients with known genetic defects will be compared to the results of B-positive SCID patients with known genetic defects. The aim of this part of the study is to get insight in the effect of the different types and different intensities of pre-BMT conditioning regimens.

***Part 1a. Molecular diagnostics of SCID patients:***

Mutational analysis of a series of patient was done based on the immunophenotypic group they belonged. We had three immunophenotypic groups of 44 SCID patients: T-B+NK- (n=12), T-B+NK+ (n+11) and T-B-NK+ (n=21). Meanwhile 4 additional patients (4 T-B-NK+, 1 T-B+NK-) were included in the mutation analysis study. Finally a total of 49 patients have been included in the study.

*In the T-B+NK- SCID group*, there were 12 patients when we started the project. Six of 12 patients had already been checked for genetic defects ending up with 4 *JAK3* and 2 *IL2RG* gene defects. In three patients, no analysis could be done previously who are defined as “unknown” patients and 3 patients did not have any sample to be analysed (Table 1). During the study one additonal patient was included. One step and 2 step mutation analysis were carried out for 3 and 1 patient, respectively. So far in 8 of 13 patients a mutation could be found: 3 IL2Rg, 5 JAK3 (Fig. 1). Four patients are currently being further analysed for the responsible genetic defect and we need skin biopsy sample from one patient (Table 2).

*In the T-B+NK+ SCID group*, 11 patients were included and no new patient was added. None of the patients were analysed for genetic defects before the start of the project. Four patients even did not have any sample for mutation analysis (Table 1). Meanwhile, one step mutation search was done for 3 patients, two step analysis was performed for 5 patients and finally only for one patient analysis consisted of 3 step search. So far in 3 out of 11 patients, the genetic defect could be defined: One patient with the *CD3D* gene defect, one patient with the *XLF* gene defect and one patient with the *IL2RG* gene defect (Fig. 2). Still the mutation analysis for 6 patients is pending and no sample is available for 2 patients who had died before a sample could be obtained (Table 2).

*Finally in T-B-NK+ group* where the majority of the patients have been clustered, there were 21 patients previously and 4 patients were added during the one-year interval. Only 15 patients did have a known mutation and 5 patients were not yet analysed for mutations despite they had samples. Only one patient had died before any sample could be obtained (Table 2). One step mutation analysis was performed for 6 patients whereas only 1 patient was analysed by one step analysis. Five patients’ mutation search is still pending. Distribution of 19 mutations identified till now are: 7 RAG1, 5 RAG2, 7 Artemis (Fig. 3).

***Part 1b. Evaluation of the effect of pre-BMT conditioning on the clinical outcome*:**

This part of the project can only be fullfilled as soon as the genetic defects in the whole group has been identified. Based on the overall data regarding the underlying mutations, it will be possible to compare the outcome of BMT in B+ and B- SCID pointing out the effect of conditioning regimen.

The majority of the unknown mutations were in the T-B+NK+ group (Fig 2). In this group of patients, we showed *IL2Rg* mutation in a patient confirming the conclusion that for patients with B+ SCID, both

the *IL2Rg*, *JAK3* and *IL7Ra* should be checked. Also in this very heterogenous group we identified a patient with CD3D mutation. A female patient with growth retardation, microcephaly and bird like facies having consanguineous parents was proven to have a mutation in the very recently defined gene *XLF*. Our search for the *CD3D* and *JAK3* gene in T-B+NK+ group is still pending.
When the overall distribution of mutations was compared before and after the ESID project, RAG1/2 and Artemis gene defects appeared to cover almost the same percentage and the majority of unsolved cases can be grouped under T-B+NK+ SCID (Fig. 4 and 5). We hope to clarify the genetic defect in more than 90% of SCID cases.

Table1. The status of mutational data of SCID patients before the start of project

| *Group* | *Mutation analysis known* | *Unknown* | *No sample available* | *Total #* |
|---|---|---|---|---|
| **T-B+NK-** | **6** | **3** | **3** | **12** |
| **T-B+NK+** | **0** | **7** | **4** | **11** |
| **T-B-NK+** | **15** | **5** | **1** | **21** |
| **Total** | **21** | **15** | **8** | **44** |

Table 2. The status of mutational data of SCID patients after one-year

| *Group* | *Mutation analysis known* | *Pending* | *No sample available* | *Total #* |
|---|---|---|---|---|
| **T-B+NK-** | **8** | **4** | **1** | **13** |
| **T-B+NK+** | **3** | **6** | **2** | **11** |
| **T-B-NK+** | **19** | **5** | **1** | **25** |
| **Total** | **40** | **15** | **4** | **49** |

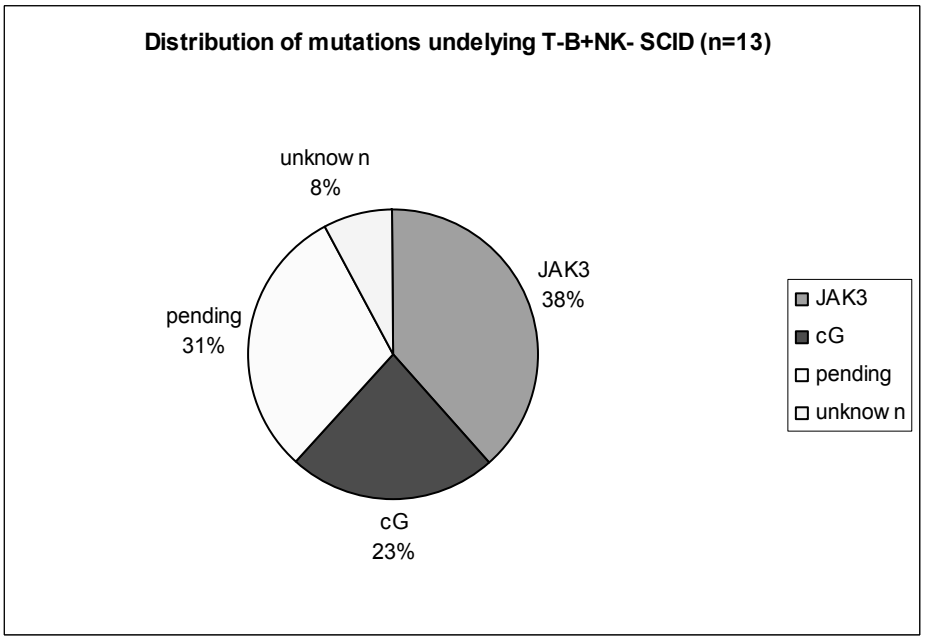



**Figure 1.**

Distribution of mutations underlying the T-B+NK- SCID group.

"Unknown" is used to define the patients without any sample for analysis.

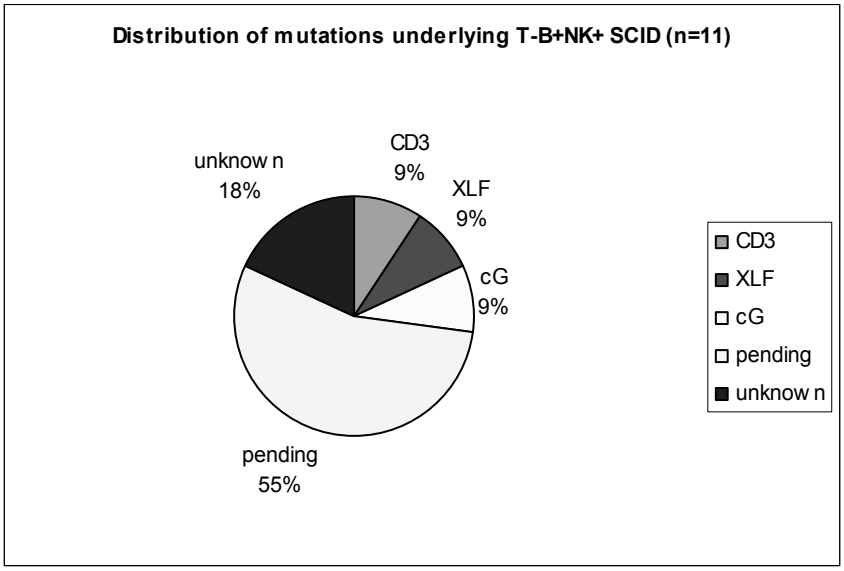



**Figure 2.**

Distribution of mutations underlying the T-B+NK+ SCID group

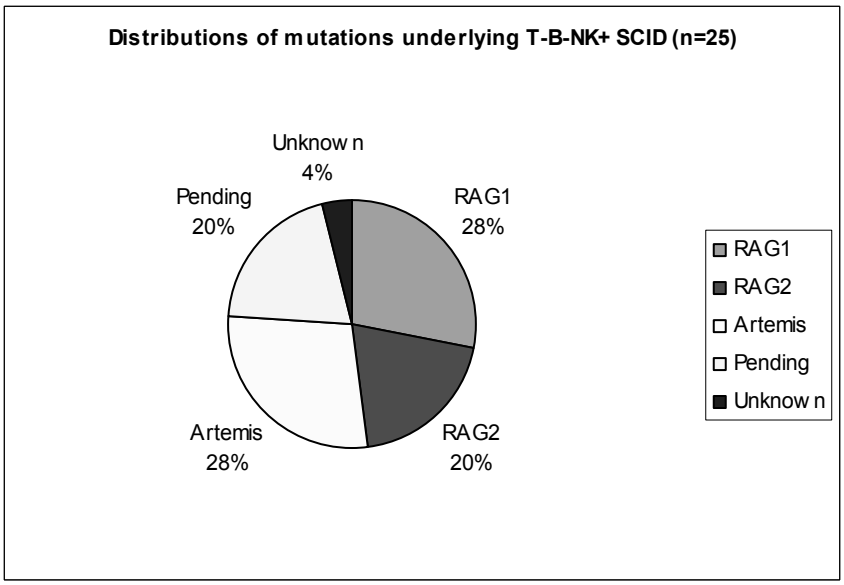



**Figure 3.**

Distribution of mutations underlying the T-B-NK+ SCID group

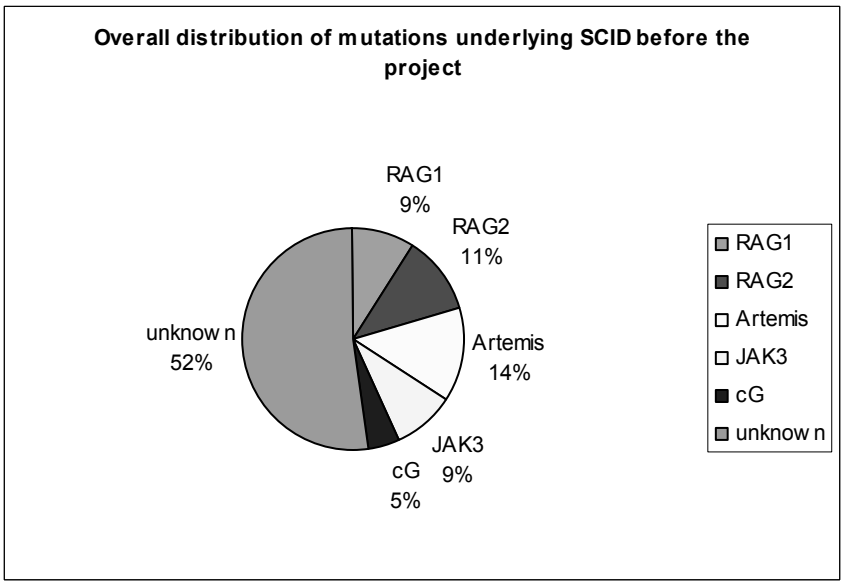



**Figure 4.**

Overall distribution of mutations underlying SCID before the project

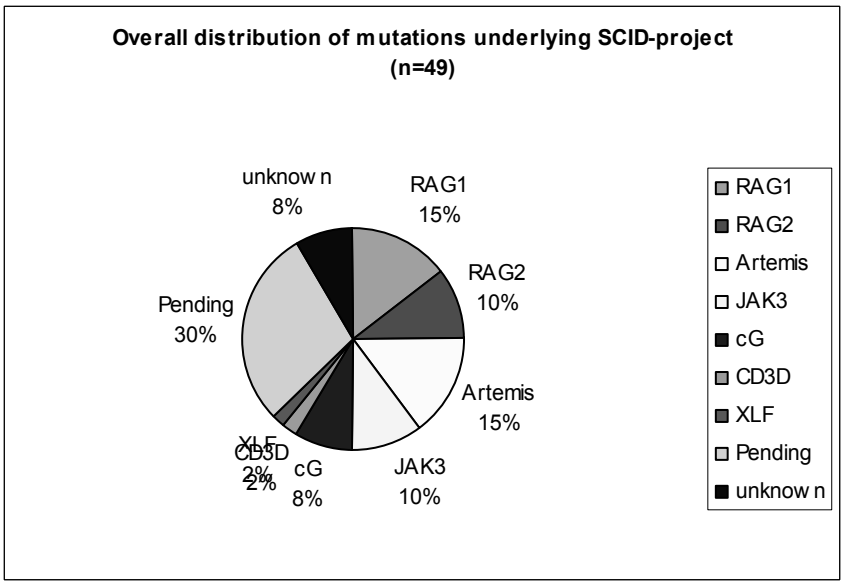



**Figure 5.**

Overall distribution of mutations underlying SCID in one year project study

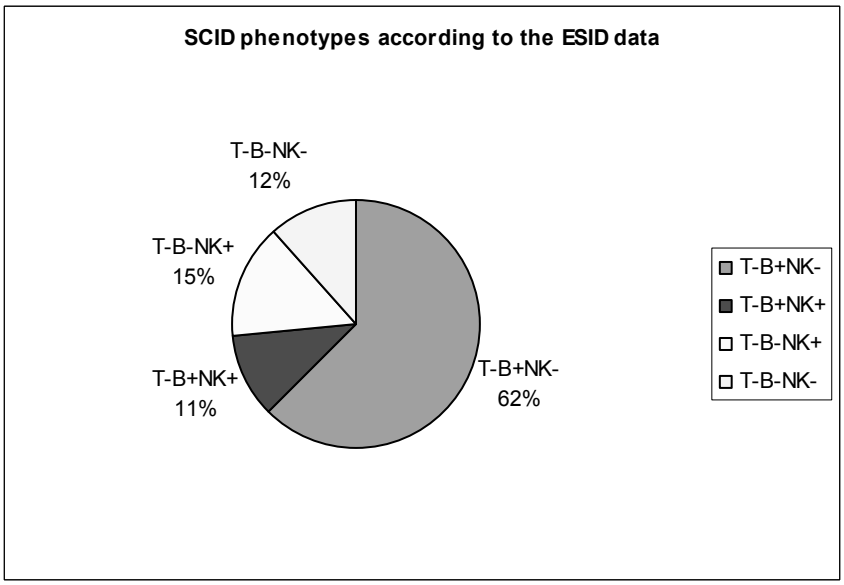



**Figure 6.**

SCID phenotypes according to the ESID data

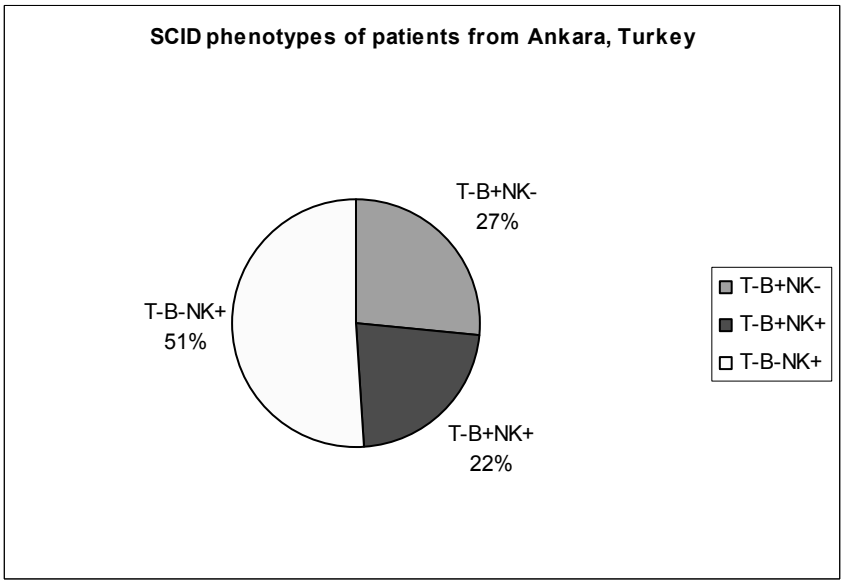



**Figure 7.**

SCID phenotypes of patients from Ankara, Turkey

***Part 2. Analysis of the composition and chimerism status of the precursor B-cell compartment in bone marrow of B-negative SCID patients without peripheral B-cells post-BMT***

Bone marrow samples of 5 B-negative SCID patients without peripheral B-cells post-BMT despite the production of serum immunogloblins were collected. The total composition of the BM sample was determined using flow cytometric immunophenotyping with a focus on the precursor B-cell compartment. They all showed absence of B cell engraftment based on the BM immunophenotyping showing a block in precursor B-cell development. Our aim was to find an explanation for the presence of immunoglobulins despite the absence of peripheral B-cells. We hypothesised that plasma cells of host origin could have been engrafted in these patients locating in the BM or peripheral lymphoid tissues. If we could show that the precursor B cell compartment other than plasma cells were of host origin, whereas the plasma cells were of donor origin then it would be possible to confirm the hypothesis.
Using CD22, CD19, CD38 and CD138 monoclonal antibodies we aimed to sort pro-B-cells (CD22+19-), pre-B-cells (CD22+19+) cells and plasma cells. We could succesfully sort and analyse pre and pro B-cells but plasma cells could not be sorted. We isolated DNA out of these cell groups. Although we could isolate $>10^4$ cells also for the plasma cell group and could isolate DNA out of these cells, chimerism analysis proved to be of host origin for pro and pre-B- cells whereas chimerism analysis yielded no signal for the plasma cell population. We repeated this experiment but could not solve the problem. Plasma cells, as a very minute component of the B cell compartment in the BM (usually <0.1%) lose the cell surface marker and are not viable any more after thawing procedure which is the case for our patients. Therefore, we planned to receive fresh sample from at least one of these patients after a control study.
Below you can see the BM precursor B-cell compartment graphs of the 5 patients included.

***Part 3. Prospective study on the composition of the precursor B-cell compartment pre- and post-BMT of B-negative SCID patients and B-positive SCID patients and monitoring of reconstitution of B-cell and T-cell function post-BMT***

For this purpose we sorted four CD19-positive precursor B-cell fractions: pre-B-I cells ($CD34^+CD10^+CD20^-$), pre-B-II large cells ($CD34^-CD10^+CD20^-$), pre-B-II small cells ($CD34^-CD10^+CD20^+$) and immature B-cells ($CD34^-CD10^+CD20^{++}$). DNA was isolated from these sorted populations for chimerism analysis (and for future Ig gene rearrangement studies). For assessment of the chimerism status, short tandem repeats (STR) are being analyzed using the PowerPlex16 system (Promega).
Analysis of the composition of the precursor B-cell compartment and analysis of the origin of this compartment (i.e. donor or patient origin) can be used as read out for the effectiveness of pre-BMT conditioning. If these analyses indicate that the pre-BMT conditioning was not sufficient to eradicate the autologous precursor B-cells of the B-negative SCID patient, a second BMT might be considered using an adapted conditioning regimen. After a second or in rare cases a third BMT, analysis of the composition and the chimerism status of the precursor B-cell compartment were repeated to evaluate the effect of the adapted conditioning.

*Peripheral blood and bone marrow pre-BMT (time point T0)*
The absolute number of B, T and NK cells were determined in the peripheral blood samples. The total composition of the bone marrow sample will be determined using flowcytometric immunophenotyping with special focus on the precursor B-cell compartment. DNA of the patient and the donor were isolated for chimerism testing post-BMT (Table 3).

*Peripheral blood and bone marrow post-BMT*
The absolute numbers of B, T and NK cells in peripheral blood was determined during the first half year post-BMT (Ta-n). Time points are showed in the table below. The B, T, and NK cells will also be sorted to determine the chimerism status (Table 3).

Below in Table 4, the prospective study data is summarized. Also the flow cytometric analysis of precursor B-cell compartment in these patients are shown in the charts below (Fig. 8, Fig. 9, Fig. 10). Up to now, 4 patients could be included in the study. As it is observed in Table 4, T2 time point BM precursor B-cells of patient ID240 and both T1 and T2 time point of ID277 could be sorted and DNA was isolated. For Patient ID277, as the BM compartment seemed almost normal at T2 and T3 time points, we concluded that the patient had apparent B-cell engraftment and we did not sort the cells.

Table 3. Schedule for bone marrow and peripheral blood sampling

| *Time point* | *Description* | *Bone marrow* | *Peripheral blood* |
|---|---|---|---|
| *T0* | *Pre-BMT* | *X* | *X* |
| *T1* | *1 month post-BMT* | *X* | *X* |
| *T2* | *3 months post-BMT* | *X* | *X* |
| *T3* | *6 months post-BMT* | *X* | *X* |
| *Ta-n* | *Regular time points for chimerism* | | *X* |

Table 4. List of the patients included in the prospective part. We are going to collect the samples in the coming year.

| Patients | T0 (pretx) | | T1 (1mo) | | T2 (3mo) | | T3 (6mo) | |
|---|---|---|---|---|---|---|---|---|
| | PB | BM | PB | BM | PB | BM | PB | BM |
| ID177 | + | + | - | - | + | + | + | + |
| sorted | N | N | - | - | N | N | N | N |
| ID240 | + | + | - | - | + | + | + | + |
| sorted | N | N | | | N | Y | N | Cells not enough |
| ID277 | - | - | + | + | + | + | + | + |
| sorted | N | N | N | Y | N | Y | N | N |
| ID347 | + | + | + | + | | | | |
| sorted | N | N | N | N | | | | |

Symbols: +; present, -; absent, Y; sorted, N; not sorted

Figures 8, 9 and 10: see next page.

**Conclusions and further planning:**

During the project study, a total of 23 patients have been analysed and out of 23 patients 9 mutations were found. In 14 patients still the process of mutation search is still ongoing. Currently, in 4 patients we did not have any sample and in one patient out of 4, it might be possible to do the analysis in case of receiving skin biopsy as the patient is still alive. Therefore, absolutely in 3 patients we will not be able to define the defect because they died without any sample could be obtained. We hope to solve more than 90% of the cases. Only after this is provided, we can compare the B- and B+ SCID group for differences in outcome of BMT.
Unfortunately, due to technical challenges we could not identify the plasma cells and their origin as well. Therefore we should develop new approaches to identify and sort plasma cells in the very specific group of B-SCID patients who received BMT and despite absence of B cells have some immunogloblin production.
In the prospective part of the study, only 4 patients could be included up to now. So for the coming one year, to increase the number of patients enough to conclude, we are planning to include new patients. Then the following 6 months will be the period to complete the prospective data of the whole patients who have been included in the study in the mentioned period.

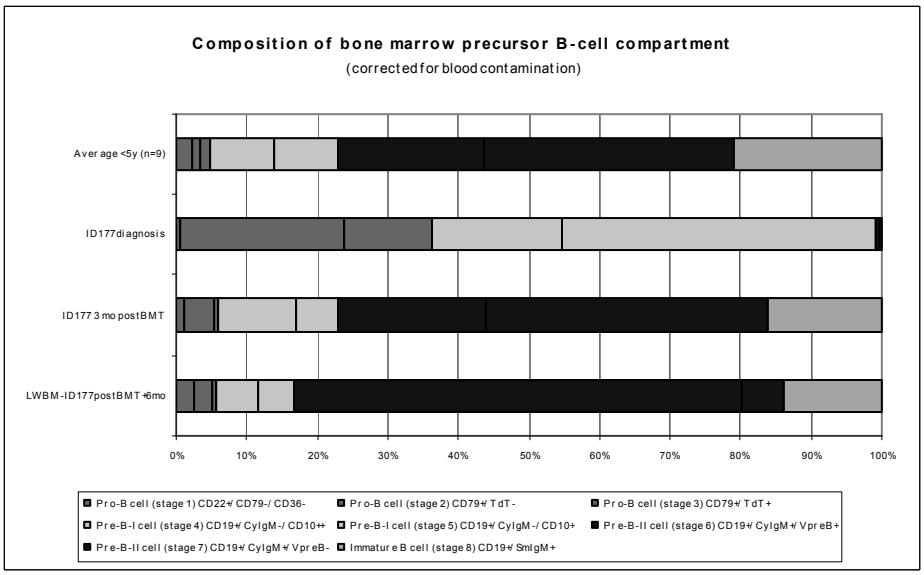



**Figure 8.**

Composition of precursor B-cell compartment in patient ID177

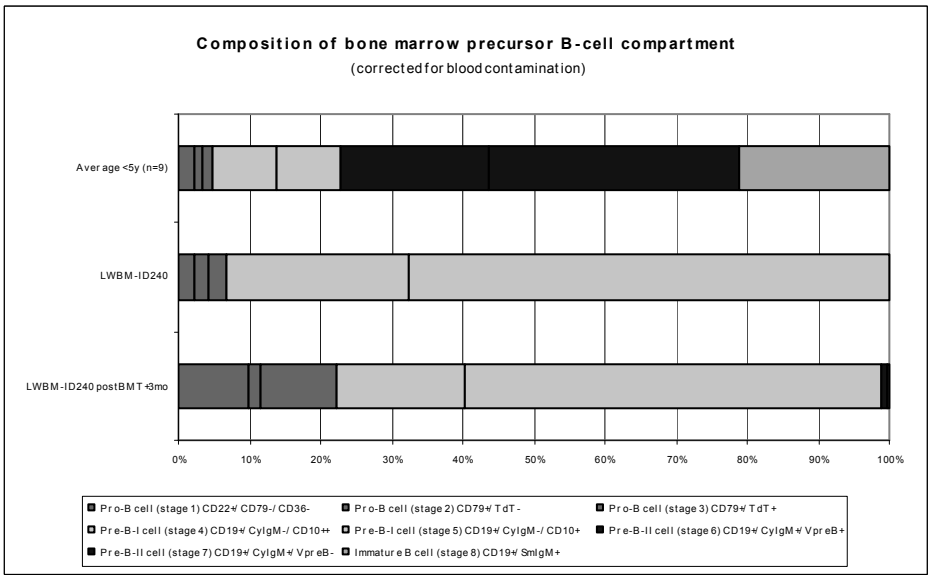



**Figure 9.**

Composition of precursor B-cell compartment in patient ID240

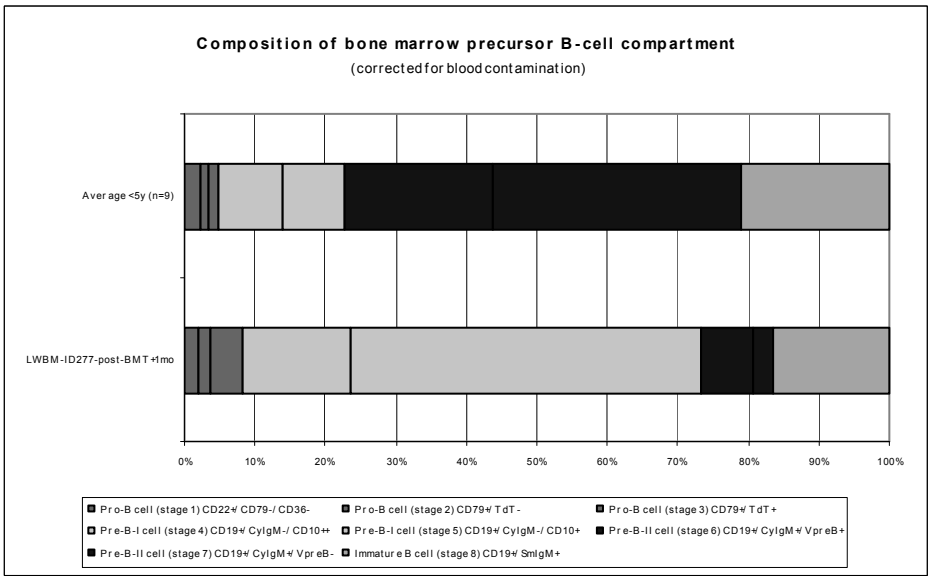



**Figure 10.**

Composition of precursor B-cell compartment in patient ID277

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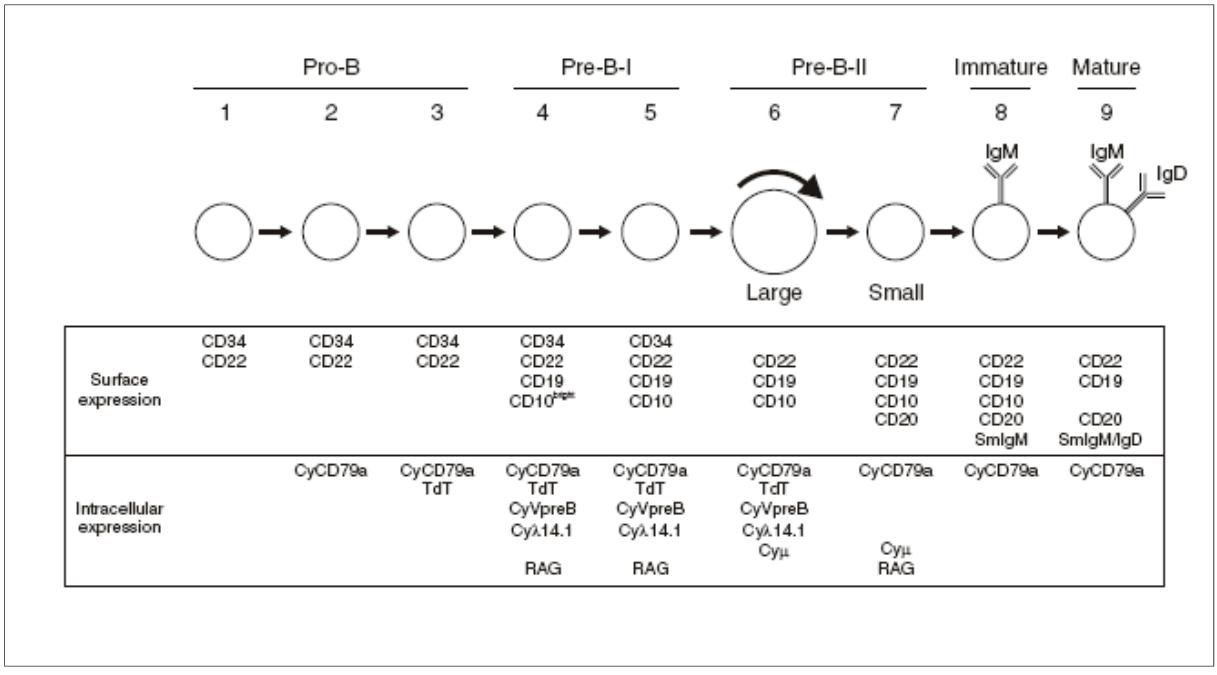


(Lay-out adapted for the ESID Newsletter; anyone who is interested can ask Tuba Turul for the original full-colour report by email at tubturul@yahoo.com.)

## PID-care in development:

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

I am Nahla Erwa, originally from Sudan where I graduated from the Faculty of Medicine, University of Khartoum, 1994. I finished my basic clinical training in Sudan and completed the first part of Clinical MD in Pathology in 1999 after being appointed as a teaching assistant in the Department of Microbiology, Faculty of Medicine, University of Khartoum. I moved to the UK in 1999 and started training in clinical immunology in 2002 at the Royal Victoria Infirmary, Newcastle upon Tyne. During the past few years, I learnt a lot about primary immunodeficiencies mainly in adults.

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

Sudan is a huge country with a total area of about 1 million square miles with a relatively small population of about 33 millions concentrated mainly in big cities especially the Capital Khartoum. Its economy and infrastructure have been severely damaged by various wars. Although Sudanese economy was meant to rely mainly on agriculture this hardly covers any expenditure. For both these reasons health came lower down the list in governmental budgets priorities. More recently however a peace treaty (2005) was signed between the northern and the southern parts of the country saving the country millions of pounds and thousands of lives. Oil is also being hugely invested on which is expected to bring the country a lot of wealth in return. Unfortunately, more problems have now arisen in the Western parts of the Country in the Darfur Region.

Health care in Sudan concentrates on the prevention and control of communicable endemic diseases with a lot of concentration being put towards fighting malaria and other tropical diseases. There is also an established programme to control AIDS. A reasonable amount of money is meant to be spent on primary health services mainly mother and child health. Health services are under the control of the Federal Ministry of Health while different regions have their own regional ministries. The Federal Ministry gets its money from the central government. This budget covers part of the expenses which means that patients have to pay for their own treatment expenses even in state hospitals. As this can be very expensive patients can get some help from the Taxes and Zakat Firm. There are also some national health insurance schemes that can cover some of the treatment costs for patients. There is also a large number of private hospitals.

Most of the big hospitals and centres are located in the Capital; Khartoum. At least one of them is under the control and belongs to the Faculty of Medicine, University of Khartoum and gets its funds directly from the University.

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

Clinical Immunology existed as a sub speciality under the Department of Microbiology, Faculty of Medicine, University of Khartoum since the 70's and until late 1980's. This was unfortunately deprived of man power by the extensive brain drain the country went through during those days. Although no primary immunodeficiency services existed as such, this department was functional and reasonably efficient, covering all aspects of immunology including solid organ transplantation. It is worth mentioning that the first renal transplantation work up in the Middle East was done in the laboratory of this department in the 70's. At the time being there is no established clinical immunology service in the country and awareness of the sub speciality is pretty slim, and there are no

statistics on the size of the problem. Currently, PID patients are not attended to in Sudan. Of the few survivors we know about one or two possible CGD patients looked after the by the Paediatricians. I am not aware of Ig substitution facility in the country and obviously no stem cell transplantations.

*How did you become interested in immunodeficiencies?*

I became interested in Immunology since I was an undergraduate and my passion about the subject grew through the years. The years I spent in Newcastle have certainly channelled this passion towards primary immunodeficiencies.

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

I have been away from the country for at least 6 years which means that I haven't been actively involved in any activities back home. The future vision for my return includes plans of going back to my academic career in the department of Microbiology, University of Khartoum, helping to train both undergraduates and post graduates. At the time being effort is made to revive, at least some of, the lost clinical immunology service and when I go back I hope to improve on that a lot and also to re-establish a basic diagnostic laboratory to complement this service. These efforts will hopefully aid the diagnosis and management of primary immunodeficiencies as well as increase the awareness, amongst both clinical colleagues and the public, on the importance of this subject. They will also help us establish the magnitude and qualities of PID problems.

I am not expecting these goals to be easily achievable. They need more refining and planning. I think a major part of the work will only be achieved if I manage to identify the appropriate sources of funding and also if I manage to increase the awareness on the subject among fellow clinicians which is going to increase our numbers and consequently our power.

*How could ESID help to achieve this goal?*

ESID could provide the support in improving the awareness amongst clinicians by contributing to local workshops and meetings. The society can also help by providing short training exchange programmes for clinical and technical staff. Collaboration at the level of individual patient care will assist in the diagnosis and in setting management plans compatible, whenever possible, with the limited resources. ESID may also be able to help with identifying additional sources of finance and funding for the service.

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## Sudan