ESID Newsletter

Contents

Introduction	2
ESID information	3
President's letter	4
Secretary's report	5
Treasurer's report	5
News & Views	6
The Jeffrey Modell Foundation (JMF) establishes new Diagnostic Centers for Primary Immunodeficiencies in Berlin, Munich and Vienna	6
The 1st Basic and Clinical Immunogenomics Meeting, Budapest, 3-7 October, 2004	6
The 2nd Autumn - Winter School of Clinical Immunology : Progress in Education in Clinical Immunology, in Zakopane, Poland, December 16-18, 2004	6
Call for collaboration	7
ESID Prague Spring Meeting, May 10-11, 2004	7
The J-Project: another ESID initiative!	8
XIth Meeting of ESID, October 21-24, Versailles, France	8
Working Party reports	9
Clinical Working Party	9
Registries Working Party	9
Invited Review	15
Transplacentally acquired maternal T-cells in SCID. Susanna M. Müller and Wilhelm Friedrich. University of Ulm, Germany.	
Focus on a country: Israel	20

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

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

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

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Front page:
Winter sun, the Aletsch glacier, Switzerland.

Dear ESID members,

Let me start with wishing you all the best for the year 2004!

In this issue you will again find a lot of information about the ESID online registries, an ongoing effort that we hope will really get started soon. It should become a great impulse to research and patient care in PID in Europe.

Also, you find a request from the Clinical Working Party regarding the ADA questionnaire. Please send it back with all your answers!

More and more members are finding their way to the editor, and send me items for the News& Views section. Please don't hesitate to do so as well.

In the invited review you find an overview of the knowledge on maternal T-cells in infants with SCID. And in the 'Focus on a country' section you find contributions from Israel with Amos Etzioni as Established Member, and Ilan Dalal as Young Investigator (you really stay young in Israel for a long time!!).

Please don't hesitate to suggest countries or people for the 'Focus on a country' section, the 'PID-care in development' section or the 'Invited Review'!! The ESID Newsletter exists for all of you…

So: do contact me at esther_de_vries_nl @ yahoo.co.uk.

Esther DE VRIES, Editor

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

Within ESID, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Bone marrow transplantation (chair: Andrew Cant), Pathology (chair Fabio Facchetti), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Jean-Laurent Casanova), Genetics (chair: Anna Villa), and Education (chair: Anders Fasth). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www . esid . org).

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

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2002 in Weimar, Germany; the next congress will be organized in Versailles, France in October 2004, and the one after that will be in Hungary, in 2006.

President's letter

When names can go wrong…

Clinical Immunology has passed through extraordinary changes during the last decades. In the field of Primary Immune Deficiencies (PID), we have moved from a clinical era (from 1950 to the mid-sixties, when several forms of PID's were described based simply on clinical grounds) to the immunological era (up to the late eighties, when distinct immunological abnormalities were defined to further dissect PID's), and eventually – more recently – to the molecular era, when specific gene and functional defects were disclosed.

Such a revolution has been accompanied by the inclusion of a growing number of diseases among PID's. Very often, rather broad designations were used, that were based either on common clinical features or on selected immunological abnormalities. This is the case for severe combined immunodeficiency diseases (SCID's), but also for immunodeficiency with hyper-IgM and for common variable immune deficiency (CVID). From a patient's perspective, receiving a diagnosis is very important. It gives him or her the right to say: "Here I am. From here I will move with treatment". From a physician's perspective, a diagnosis of a rare disease is also important, but may have a different impact depending on the knowledge that that particular physician has. SCID's are not all alike; even more so, hyper-IgM syndrome (also referred to as HIGM) and CVID are obviously heterogeneous. The more rare a disease (or the more heterogeneous its phenotype), the more difficult it is to give appropriate advice to each single patient.

Advances in molecular genetics are challenging our classification of PID's, that is still based on clinical and immunological grounds. Just to give an example, a large variety of gene defects have been shown to cause SCID in humans. Also, a few gene defects have been identified in HIGM. However, even if gene identification and mutation analysis have added further "entropy" to the system, they also represent a unique opportunity to analyze in detail what are the clinical features, and eventually the perspective of life (in terms of duration and quality), and the opportunities for treatment in each rare form of PID. More than this, such an effort may in fact disclose how confusing, misleading, and dangerous a classification based on immunological grounds can be.

In a recent e-mail that Anne Durandy has sent to me, she was complaining of the large use that is made in the scientific community of the term HIGM, followed by various numbers (1 to 4, or even to 5), to define the various forms of hyper-IgM syndrome. Importantly, she was not complaining about the system itself, but about the impact that such a classification may have on patients and their physicians, who may think that in fact we are simply dealing with varieties of the same disorder. I think that Anne is right, and that as a Scientific Society we should make an effort to be clear to ourselves, our less experienced colleagues, and most importantly to our patients. In the Internet era, it is clear that patients and families who are given a diagnosis of a rare disease (something they never heard about) seek information wherever available. We know that hyper-IgM syndrome may be very different in terms of prognosis and treatment. Finding data that pertain to a form of hyper-IgM syndrome that is unrelated to their clinical problem, may lead patients and parents to severe mistakes, and be distressful.

Anne – and myself – would therefore like to propose to the ESID community to abandon the term HIGM, and to start defining these heterogeneous disorders in a more specific way. In particular, Anne has proposed to use the following nomenclature.

Defective Ig Class Switch Recombination (DICSR):

1) T and B cell defects
XL-CD40L-deficiency
AR-CD40-deficiency

2) B cell defects
AR-AID-deficiency
AR-UNG-deficiency
Other DICSR

"Nomina sunt consequentia rerum" (names are the consequence of things). Accordingly, I share her proposal.

Should ESID embark onto this debate? I think it should, because our goal is eventually to understand more in order, eventually, to help better. I am strengthened in this opinion by the fact that the ESID Registry, that Bodo Grimbacher will take care of, has eventually been organized based on the specific gene defects, rather than on similarities in the clinical and immunological phenotype. At last, it is perhaps time to call things (and diseases) for what they are.

On this, and other similar topics, it would be important that the ESID community gives their thoughts.

Au revoir à Versailles!

Luigi D. NOTARANGELO

Secretary's report

Suggestions for improvements/new features for the ESID web site are wanted !

During the last ESID Board meeting it was discussed whether the ESID web site should undergo renovation and/or present new features. I would like to encourage all ESID members to make suggestions what they expect from "their" website, i.e. what they want to remain unaltered or what features they are currently missing and want to have included in a new version. **Please contact the ESID secretary by email at hermann.wolf@itk.at**

Hermann M. WOLF

Treasurer's report

Everybody has received the ESID membership renewal form 2004/2005 with the last issue of the ESID Newsletter (2003-3). Many have already returned it, and renewed their membership. Don't forget to do so in time, in case you weren't one of them! If I do not receive the money in time, you cannot register as a member for the biennial congress in Versailles, which means that you will have to pay more to go there.

Esther DE VRIES

Nomina Sunt Consequentia Rerum

I felt within my heart awake and glow
A spirit of Love's excellence that slept,
Then I beheld Love as from afar he stept
So joyful that his face I scarce could know.
He said: Now think all honour me to show
And through each word of his Love's laughter crept;
Then as my lord awhile his splendour kept,
Gazing there whence he came, where he would go,

Nuala and Columba did I see
Come towards the place where I was lingering,
One marvel first, the other following,
And, even as retelleth memory,
Love said: That one who follows this our Spring
Hath Love for name, so like is she to me.

(From the Vita Nuova of Dante, translated)

Written by Joseph Mary Plunkett, nearly a century ago

(added by your editor)

News & Views

The Jeffrey Modell Foundation (JMF) establishes new Diagnostic Centers for Primary Immunodeficiencies in Berlin, Munich and Vienna

The new Jeffrey Modell Foundation (JMF) Diagnostic Centers for Primary Immunodeficiencies have been established to increase public awareness of primary immunodeficiencies in the region. Additional aims are to initiate physician education programs and to support local patient groups. While two of the new JMF Diagnostic centers are situated in different parts of Germany, the aim of the JMF Diagnostic Center in Vienna is to improve diagnostic coverage of primary immunodeficiencies in Austria and Central Europe. Help will be offered to make appropriate therapy available for newly diagnosed patients with PID. In addition, the importance of early diagnosis and initiation of therapy for patients with primary immunodeficiencies still needs to be communicated to non-specialized physicians and the public in this region. It should be emphasized more strongly that not only children, but also adults can suffer from newly diagnosed primary immunodeficiency, as various genetic defects of the immune system can lead to a first onset of clinical symptomatology relatively late in life (for further information see www.jmf-centraleurope.com).

Hermann M. WOLF

The 1st Basic and Clinical Immunogenomics Meeting, Budapest, 3-7 October, 2004

All ESID members are cordially invited to attend this meeting. You can find more information at http: //www.diamond-congress.hu/bci2004, or ask information from László Maródi at fax: 00-36-52-430 323, tel: 00-36-52-416 841, and e-mail: lmarodi @jaguar.dote.hu.

There will be a Hereditary Immunodeficiency Symposium included in the program.

László MARÓDI

The 2nd Autumn - Winter School of Clinical Immunology : Progress in Education in Clinical Immunology, in Zakopane, Poland, December 16-18, 2004

The 2nd Autumn – Winter School of Clinical Immunology will be organized in Zakopane in the Tatra Mountains (see also 'The J-Project' on page 8). We expect some 50 participants more than were present in Kazimierz Dolny (see information in ESID Newsletter 2003–3). The next group of young immunologists from both Central-Eastern and from Western European countries will attend this meeting including young Polish physicians specializing in clinical immunology - a group now composed of 15 clinicians. We expect lectures by scientists from many European countries, and also from some young immunologists. Most of the lectures will be on PID – related topics. The topics presented will range from the current status of primary immunodeficiency diseases in Europe, and registries in individual countries, to the diagnosis, safety and types of therapy including stem cell transplantation and immunoglobulin treatment. Time is also reserved for presentations of patients with unusual features of primary immunodeficiencies including patients with AT–related DNA repair disorders .

The 2nd Autumn-Winter School of Clinical Immunology, Progress in Education in Clinical Immunology in Zakopane, Poland, December 16 - 18, 2004 is sponsored by

EURO-PID-NAS QLGI-CT-2001-01395, PERPECT QLG1-CT-2002-90358 and by pharmaceutal companies.

For further information please contact me at bernatowskae@yahoo.com!

Ewa BERNATOWSKA

Call for collaboration

Human Herpes Virus-8 is the infectious agent of Kaposi Sarcoma (KS), which is relatively common in adults but exceedingly rare in children. Although immunosuppression and HIV-infection may be involved in some cases, a substantial fraction of KS in childhood remain completely unexplained. We hypothesize that such "idiopathic" KS are favoured by a novel type of primary immunodeficiencies. We would like to ask the collaboration of all ESID members to recruit these rare children, particularly in the Mediterranean basin where HHV-8 is endemic. Please contact Jean-Laurent Casanova at casanova@necker.fr.

Jean-Laurent CASANOVA

ESID Prague Spring Meeting, May 10-11, 2004

Dear ESID members, we wish you a lot of happiness and success in the coming year 2004 and we would like to inform you about the ESID Prague Spring Meeting.

Every May since 2002, the ESID Prague Spring Meeting has been organized in Prague, Czech Republic. The advantageous location of Prague between the Eastern and Western parts of Europe is used for joint meetings of the specialists in primary immunodeficiencies from Eastern postcommunistic countries and the scientists from the established centers in the West.

Both meetings organized so far were very successful, and already proved to provide the substantial help for both specialists and patients from the Eastern part of Europe.

The plans for 2004 are already in preparation. The meeting will take place in Prague, May 10-11, at the Institute of Immunology, 2nd Medical School, Charles University. The major topics will be the early diagnosis and treatment of primary immunodeficiencies, the improvement of public awareness, the national registries in the countries of the participants and the latest developments in the field. All these topics, and the possibility of detailed discussion of difficult and unusual cases are of great importance to the improvement of the care for primary immunodeficiencies, particularly in Eastern Europe. Each participant will present his/her current project in the form of a short lecture.

The meeting will be followed by a bicycle trip from Prague to Vienna under the leadership of Hans Ochs. We plan to spend 5 days "on the road" (May 12-16). We will bike through the beautiful parts of Southern Bohemia and Moravia with its lakes, deep forests and fruitful vineyards. A visit of a wine cellar will be an inherent part of the trip. The final destination is the immunology department and lab in Vienna. Those participants who wish to visit the department and prof. Martha Eibl can stay until Monday, May 17 in Vienna.

The length of the trip will be about 300 km; intermittent use of the car that will accompany the group is possible. Preliminary cost estimation is about 300 Euro per person (included are: accommodation, entrance fees to castles, bike rental and transport), however, we hope for some sponsors that will allow us to reduce the price. The final price also depends on the number of participants. The trip will be a unique opportunity to enjoy sport, nature and also to discuss with colleagues from all around Europe in a very informal way.

There will be scholarships available for

the meeting (to cover travel costs and accommodation). They will be distributed on the first come - first served basis.

If you are interested and want to take part in this Spring School, please, contact us by email at annasediva@hotmail.com or alesjanda@hotmail.com. Indicate, please, if you would like to join us on the bicycle tour, too.

Looking forward to seeing you in Prague next spring!!

Anna SEDIVA

The J-Project: another ESID initiative!

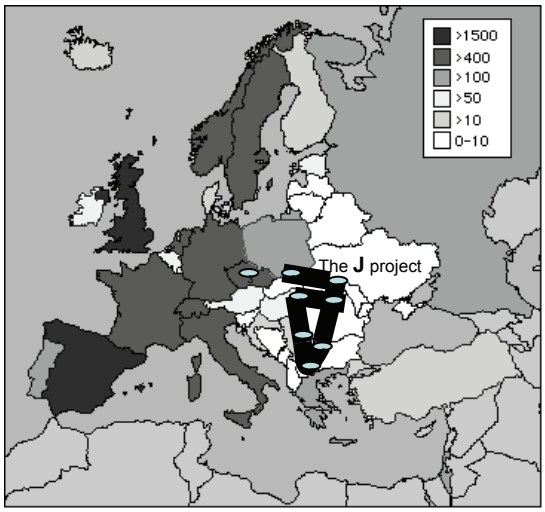
In East-Central Europe 8 centers have joined forces to increase the awareness of PID. As you can see on the map (top right of this page), these centers form a "J" together, which is why we have called this the J-Project. A preliminary program of meetings has been made. Formally, we shall organize one-day awareness meetings at these venues with the help of local organizers.

Each meeting will aim at the following goals:

- recruiting doctors and parents/patients from the particular country
- discussing PID patient care
- updating the national PID registry
- establishing a professional PID Working Group
- establishing a PID patients group

The structure of each meeting will be as follows:

- informal discussions the night before the meeting
- introductory lectures mostly by invited speakers
- case reports mostly by local speakers
- reports on PID patients, the Working Group and the patients group
- National Registry Update



The following meetings are scheduled for 2004:

- Turgu Mures , Romania, March 11-12, 2004. Local organizer: Csilla Todea
- Sofia, Bulgaria, April . Local organizer: pending.
- Prague, Czech Republic, May, 2004. Local organizer: Anna Sediva
- Belgrad, Yugoslavia, June 11-12. Local organizer: Srdjan Pasic.
- Debrecen, Hungary, August 13-14, 2004. Local organizer: László Maródi
- Skopje, Macedonia, September 17-18. Local organizer: Katarina Stavrik.
- Cernivci, Ukraine, November. Local organizer: pending.
- Zakopane, Poland, December 16-17, 2004. Local organizer: Ewa Bernatowska.

László Maródi

XIth Meeting of ESID, October 21-24, Versailles, France

Together with this ESID Newsletter you received the 2nd announcement of our biennial congress in Versailles. We hope to meet all of you there! Soon you will be able to get more information on the special website at www.esid2004.org.

Alain FISCHER

Working Party reports

Clinical Working Party

A questionnaire about the treatment guidelines for ADA-SCID was printed in the ESID Newsletter 2003-2. The aim of this was to ascertain how different centres treated ADA-SCID given the different number of treatment options now available (e.g. HSCT from different donors, PEG-ADA, gene therapy). We have now received a number of responses to this questionnaire. The total number of responses is 20, and these range from centres in Europe and North America to Saudi Arabia. There is considerable variation in the size of centres from those that have seen just the one patient to large SCID BMT centres. In a couple of cases, the response to the questionnaire was not accompanied by a name or signature, so it was difficult to know which centre had responded!

We obviously need more responses in order to get a better feel of how people would treat this condition, **so could any centre who has not yet replied please try to do so as soon as possible?** A copy of the questionnaire is printed again on pages 10 and 11 for your use. Our apologies and thanks to those who have already done so! We look forward to hearing from you.

Jean-Laurent CASANOVA
Bobby GASPAR

Registries Working Party

Dear ESID members, In the last three months there has been some progress in drafting a contract with PPTA for the financing of the new ESID-online databases. We involved lawyers, and once you involve lawyers... you all know). However, we are hoping to sign the contract in the beginning of February.

Despite these delays, my group here in Freiburg is already actively working on the project since September 1st. Therefore, the new ESID-online main registry may be operational as early as March or April 2004!

The datafields to be documented in the 'ESID main registry' are subject to financial compensation by ESID, meaning that for each patient for whom this core dataset (red fields) has been documented per June 30 of each year, ESID will be able to pay EURO 10,- as compensation for the work to enter these data.

This core dataset consists of the following datafields:

PATIENT: Sex, date of birth, region of residence (clustered in regions with >30 million inhabitants)
DIAGNOSIS: Date of diagnosis, onset of symptoms, disease/diagnosis
THERAPY: Date, drug, dose per weight, dose interval, route (oral/SC/IV), from, until, side-effects, reason stopped, compliance
PHARMACO-ECON: Days in hospital, days missed at school, days missed at work
IMMUNISATIONS: Date, vaccine, post vaccination titres
LABORATORY: Date, time, label, value (for: IgG, IgA, IgM, CD3, CD4, CD8, CD19 or CD20, CD56, Leukocytes, Thrombocytes, Erythrocytes, Lymphocytes, Granulocytes, Hb, Eosinophils, Basophils, Macrophages) in percent or/and in absolute values.

In addition, we drafted the first PID-subregistry datamodel which is designed to cover most patients with hypogamma globulinemias. You will find the so called "CVID-datamodel" on page 13. The CVID-registry will be the first disease specific registry to go online in March/April 2004 if things are progressing smoothly.

In order to enter patients into the new ESID-online registry you will need to:

- get a login and password from ESID (address see below)
- get a positive statement from your local ethics committee and/or data-protection manager (we will provide

Continued on page 12

Questionnaire re: guidelines for ADA-SCID

These questions concern the treatment of a child with clinical and immunological features of typical ADA-SCID (85-90% of all cases), as defined by peripheral blood autologous lymphocytes below 100/mm3 and lack of response to mitogens. We are assuming that all children will be placed on immunoglobulin, and anti microbial prophylaxis as for all SCIDs. With regard to transplant, the questions relate to whether you would perform a transplant or not; please do not address what sort of transplant would be performed (i.e. conditioning/T cell depletion, as those questions/guidelines will be dealt with by the BMT Working Party)

To start with, please answer the following questions:

How many ADA patients have been followed at your PID clinic since it was established ?

How many ADA patients are currently being followed at your center ?

ADA-SCID guidelines questionnaire
(please choose "Y or N" within each question if you feel this is appropriate)

1. If a match sibling donor (MSD) was available, would you:
A. proceed to haematopoietic stem cell transplant (HSCT) Y/N
B. treat with PEG-ADA Y/N

2. If no MSD but a phenotypic matched family donor (MFD) was available, would you:
A. proceed to haematopoietic stem cell transplant (HSCT) Y/N
B. treat with PEG-ADA Y/N
C. look for an unrelated/cord blood donor Y/N

3. For questions 1 and 2, if the child was in a poor clinical state (defined by serious infection *or* failure to thrive *or* organ damage), would you initiate PEG-ADA prior to transplant ?
Y/N

4. If the answer is no, what is the reason:
A. concerns regarding effectiveness of PEG-ADA Y/N
B. concerns regarding side effects Y/N
C. concerns regarding expense Y/N
D. concerns regarding impact on success of HSCT Y/N
E. other reason:

5. What criteria would you use to define a successful response to PEG-ADA:
A. good clinical response with weight gain, clearance of infection Y/N
B. increase in absolute lymphocyte count > 1000 cells/mm^3 Y/N
C. CD3 count >500 cells/mm^3 Y/N
D. CD4 count >300 cells/mm^3 Y/N
E. proliferation to mitogens Y/N
F. production of IgG/A/M Y/N
G. production of T cell antigen specific responses Y/N
H. production of B cell antigen specific responses Y/N

6. If no MSD or MFD is available, would you initiate an unrelated or cord blood donor search? Y/N

7. While waiting for an unrelated, cord blood or a parental donor transplant would you start the child on PEG-ADA? Y/N

8. If the answer is no, what is the reason?
A. concerns regarding effectiveness of PEG-ADA Y/N
B. concerns regarding side effects Y/N
C. concerns regarding expense Y/N
D. concerns regarding impact on success of HSCT Y/N
E. other reason

9. If a fully matched unrelated donor (MUD) (inc. unrelated cord) was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. wait for a better donor (eg MSD/MFD/MUD) Y/N
D. enroll into gene therapy trial Y/N

10. If only a mismatched unrelated donor (mMUD) was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. enroll into gene therapy trial Y/N
D. wait for a better donor (eg MSD/MFD/MUD) or proceed to a haploidentical parental donor transplant Y/N

11. If only an unrelated mismatched cord blood was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. enrol into gene therapy trial Y/N
D. wait for a better donor (eg MSD/MFD/MUD) or proceed to a haploidentical parental donor transplant Y/N

12. If only a parental donor was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. wait for a better donor (eg MSD/MFD/MUD/mMUD/cord blood) Y/N
D. enroll into gene therapy trial Y/N

Thank you for completing the questionnaire!

Please send your responses to Bobby GASPAR
by Fax (44 207 831 4366) or e-mail (h.gaspar @ ich.ucl.ac.uk)

your center with the necessary paperwork once you have applied for a password)

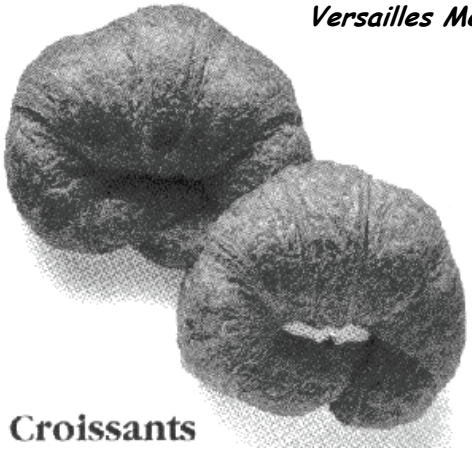
- get a signed consent form from the patients or their legal representatives (we will provide your center with consent forms in six different European languages (English, French, Italian, German, Spanish, Portuguese), so depending on the patient's mother tongue, you may need to translate this form. You will find the English version of the patient-consent form on page 14.

Additional subregistries will be designed by so called Steering Committees. There are a total of at least 130 possible subregistries grouped into approximately 50 "groups" and five categories (T cells, B cells, phagocytic disorders, complement and other well defined PID's) which you already know from the current ESID-registry designed by Lennart Hammarström). The ESID Board has started to form these Steering Committees. In some cases the ESID Board has nominated a head for the respective Steering Committee, in others, the head will be elected among the members of the Steering Committees themselves. A provisional list of disease specific Steering Committees is printed on pages 18&19.

Please contact the respective people if you are interested in the design of a certain disease specific database, **or contact me** if you are interested in taking the task to organize a Steering Committee of a yet "orphan" PID (Clinical Immunology and Rheumatology, Medical Center University of Freiburg, Hugstetterstr. 55, 79106 Freiburg, Germany. Tel.: +49-761-270-3696, Fax: +49-761-270-3531. E-mail: grimbacher @ medizin.ukl.uni-freiburg.de).

Bodo GRIMBACHER

Getting in the mood for the Versailles Meeting …?



Data-model: CVID-Database-system

USER: ID, center, password, role (data for administrative use only)

PATIENT: ID, patient consent, sex, twin, date of birth, country of birth, ethnicity, who-region, current place of living, current status, date of death, cause of death (ICD 10)

DIAGNOSIS: ESID criteria, date of diagnosis, onset of symptoms, kinds of symptoms, date of first evaluation by a physician, date to an immunologist, classification type, classification value, status (definite / probable / possible), speciality of referring physician, number of physicians seen before, other physicians following patient

ADDITIONAL DIAGNOSES: Date, date of resolution, ICD 10 Code, date of diagnosis, value, value-date, value-label

PATIENT HISTORY/ANAMNESIS: diagnosis/complication, value, smoking history, start, end

FAMILY HISTORY: Unknown/known, Relative, date of birth, diagnosis (PID, other), date of diagnosis (PID), status (alive), date of death, pedigree, memo-field: more about family history...

INFECTION HISTORY: Diagnosis/complication, date, organ, type (refers to different types of infection)

IMMUNIZATIONS: Date, type, vaccine, interval, postvaccinal titres, side effects

AUTOIMMUNE OR RHEUMATIC DISEASES: date, ICD 10 Code, date of diagnosis, label, value with date

AUTOANTIBODIES (TITRE): Time, label, value

ALLERGIES: (food, drugs, animals, pollen, acarians, contact materials or working materials), allergen, test, date of testing, manifestation, eczema

NEOPLASMS: date, (references to add. diagnosis), date of diagnosis, diagnosed by... , organ, diagnosis

SEROLOGY: Date, test, result, titer

LABORATORY: Date, time, label, value (IgG, IgA, IgM, IgE, IgD, IgG1-4, kappa-light-chains, lambda-light-chains, overall-proteins, CD3, CD4, CD8, CD10, CD16, CD19, or CD20, CD21, CD23, CD56, CD5-CD19, CD3s-CD25, CD4-45RA, CD8-45RA, CD4-45RO, CD3s-DR, CD8-CD57, CD15-CD56, CD3-CD16, leukocytes, thrombocytes, erythrocytes, (overall)-lymphocytes, monocytes, granulocytes (ALC, ANC, AEC), Hb, TRC, WCC, PMN, MNC, neutrophils, eosinophils, basophils, macrophages in percent or/and in absolute values, anemia

GENETIC TESTING: Date, result, laboratory, gene, allele, exon, NT mutation, predicted AA alteration, HLA type

ETIOLOGY: Date, type (refers to different types of etiology), value

LUNG FUNCTION: Date, time, type, value

IMAGING: Date, time, region, type, result, value

PREVENTIVE: Date, type, result, interval

CLINICAL INVESTIGATION: Date, label (refers to any possible entry concerning clinical investigation), value, findings

PHARMACOECONOMICS: Days missed at school, days missed at work, days in hospital, number of episodes, patient disabled

QUALITY OF LIFE: Date, label (e.g. SF-36 health survey, MOS health survey), value, physician's approval

BIOPSY/BONE MARROW: Date, organ, storage, left over tissue, result

SURGERY: Date, organ, type of surgery, result (diagnosis: ICD10)

THERAPY: Date, type of therapy, drug group (e.g. antibiotic/immunoglobulin/immunosupressant/...), drug (brandname included), dose per weight, dose interval (per day / per wk / per mos), route of administration (oral / SC / IV / IM), from, until, side effects, reason stopped, compliance, optional medication, home/hospital, organ transplant (date, organ),

ADVERSE EVENTS: Date of onset, date of resolution, organ system, type of reaction, severity, action taken

Statement of consent for the maintenance of patient data on an internet database for research (Informed Consent)

The Department of _____
participates in the research project "ESID Online Patient- and Research-Registry". This is a pseudo-anonymous internet database with password-protected access. Pseudo-anonymity means that the data obtained from the database are anonymous for the receiver i.e. the confidentiality of records identifying the subject will be maintained. In a medical emergency the treating doctors could retrieve a specific patient's data using a highly protected encryption code. Patient data relating to a medical condition are saved and stored automatically without the patients personal data.

The aim of this project is to compile clinical and laboratory data in order to provide improved diagnosis, classification, prognosis and therapy for the patient.

The aim of the database is a continuous long-term compilation of data on PID (Primary Immunodeficiency disease) patients.

Therefore, the patient data obtained in the course of their treatment is not deleted but instead stored in a pseudo-anonymous and coded form in a password-protected internet database. These pseudo-anonymous data can be made available to centers that specialize in treating PID (Primary Immunodeficiency disease) patients, to laboratories that are researching the cause of PID (Primary Immunodeficiency diseases), to pharmaceutical companies developing or improving medication, or to epidemiologists for evaluation.

Participation in this research project is voluntary. Refusal to participate will involve no penalty or loss of benefits to the subject, and the subject may discontinue participation at any time without penalty or loss of benefits.

I give my consent that confidential data relating to my PID (Primary Immunodeficiency disease), obtained in the course of the research project "ESID Online Patient- and Research-Registry", can be compiled and evaluated as described above.

Date:

Name of doctor involved: *Patient's name and DOB:*

_____ _____

Doctor's Signature: Patient's Signature:

_____ _____

Invited review

TRANSPLACENTALLY ACQUIRED MATERNAL T-CELLS IN SCID

Susanna M. Müller and Wilhelm Friedrich

Dept. of Pediatrics and Dept. of Immunology, University of Ulm, Ulm, Germany

Passage of maternal and fetal blood cells across the placenta during pregnancy is a well known phenomenon.[1] Since the early 1960´s it is known, that maternal cells may be detectable in the blood of healthy newborns.[2] In more recent studies these were found in 40% to 100% of analysed cord blood samples, depending on the sensitivity of the method used.[3,4,5] Maternal cells could be found in fetal blood already during pregnancy (in 8 of 9 fetal blood samples analysed)[6] and may be observed as early as the 13th gestational week (1 of 5 fetal blood samples studied).[7] Maternal cells have also been detected in organs such as liver, thymus, thyroid and skin.[8] In an immunocompetent fetus, engraftment of maternal cells most likely is controlled by the fetal T-cell system, which recognizes and rejects these allogeneic cells, although permanent maternal microchimerism in immunocompetent individuals has been described.[1]

According to these data, one would expect that persistent engraftment of maternal cells is a common phenomenon in patients with SCID, who are unable to mount an effective alloresponse. Indeed this phenomenon was first described in 1965[2] and subsequently in 1982 in several SCID-patients.[9]

In an analysis of 145 SCID patients, referred since 1982 to our center (published in 2001),[10] we studied the prevalence of maternal T-cell engraftment in this large cohort of patients as well as clinical and immunological findings associated with it. For detection of maternal cells, peripheral blood mononuclear cells were isolated and T-cell enriched fractions were HLA-typed by standard, complement-mediated cytotoxicity assay or, since 1994, by direct immunofluorescence using anti-HLA-antibodies, lowering the detection level to about 1% of lymphocyte populations.

In the whole cohort of 145 patients, 56 children (39%) were found to have circulating maternal lymphocytes. Within the mononuclear cell fraction, maternal cells were restricted to the T-cell compartment with one exceptional case, in whom in addition NK-cells of maternal origin were found.

As shown in Table 1, maternal T-cells were always noted in patients with reticular dysgenesis, whereas in SCID-variants characterized by the presence of autologous, non-functional T-cells, maternal T-cells were never found. In T-negative SCID-variants, maternal T-cells were detected in 50 % of the patients (59% in B^- SCID and 45% in B^+ SCID).

Clinical manifestations in engrafted patients were quite variable, and, if present, resembled graft-versus-host disease (GvHD). Remarkably, about 50% of patients showed no clinical evidence of GvHD (group1). A second group had mild abnormalities, consisting mainly of chronic eczematous rashes (group 2). A third group showed severe manifestations with generalized exfoliative dermatitis (group 3). Patients with this latter form usually also developed enlarged lymph nodes, hepatosplenomegaly and alopecia, clinically not distinguishable from manifestations in patients with Omenn Syndrome. Furthermore, eosinophilia,

Table 1:Prevalence of engraftment of maternal T-cells in SCID

	total number of patiients studied	patients with maternal T-cells
all patients	145	56 (39%)
Reticular Dysgenesis	7	7 (100%)
B^- SCID	32	19 (59%)
B^+ SCID	64	29 (45%)
ADA/PNP deficiency	16	0
MHC class II deficiency	8	0
Omenn Syndrome	11	0
ZAP 70 deficiency	4	0
other T+ SCID variants	3	0

Table 2: Clinical presentation in T^- SCID patients with maternal T-cells

		GvHD symptomatology		
	Patients (no)	None (group 1)	Mild (group 2)	Severe (group 3)
B^- SCID	19	8	1	10
RAG 1/2 deficiency	6	3	0	3
Artemis deficiency	5	2	1	2
Unknown	8	3	0	5
B^+ SCID	29	18	9	2
gc deficiency	10	5	4	1
JAK3 deficiency	3	1	2	0
Unknown	16	12	3	1

agranulocytosis and exceptionally nephritis were observed.

As shown in table 2, severe manifestations were almost exclusively found in patients with a B^- SCID phenotype, whereas patients with B^+ SCID usually showed no or only mild abnormalities (group 1 or group 2).

The absolute number of circulating maternal T-cells was highly variable. In asymptomatic patients (group 1), almost 50% had T-cells below 100/µl (< 5% of blood MNC); in the other patients without GvHD, T-cell counts were in a similar range as in patients with mild GvHD (range 180/µl to 800/µl, median 418/µl) or severe GvHD (range 670/µl to 4300/µl, median 1738/µl). Patients with severe manifestations presented with the highest T-cell numbers, predominantly $CD4^+$ cells. Altogether, higher numbers and significant mitogen-induced proliferation of maternal T-cells were associated with more severe GvHD-like symptomatology and the inverse correlation held with low T-cell numbers and less severe or absence of clinical manifestations. A highly restricted T-cell receptor repertoire and lack of antigen-specific proliferation were always noted, consistent with the lack of clinical evidence, that maternal T-

cells provide protective effects in the patients.[10,11]

In patients with symptomatology from maternal T-cell engraftment, immunosuppressive treatment like cyclosporine with or without prednisolone was usually effective to control clinical manifestations of GvHD. In most patients, in particular in those with severe symptomatology (group 3), this treatment had to be continued until stem cell transplantation was performed in order to prevent recurrence of GvHD.

Regarding the relevance of maternal T-cell engraftment for stem cell transplantation to treat SCID, several issues need to be considered. One is the selection of the donor: do engrafted maternal cells increase the risk of graft failure and is therefore the mother rather than the father the preferred donor if no matched donor is available? Are these considerations also valid if pretransplant conditioning is applied in order to improve the chance of complete immunological reconstitution? Do engrafted maternal T-cells play a role for the development of GvHD after BMT? Most of these issues are at present incompletely resolved and require further studies.

In patients undergoing matched sibling donor transplantation, using unmodified, T-cell containing grafts and no conditioning, grafted mature donor T-cells expand rapidly in the host and appear effective to eliminate the HLA-haploidentical maternal T-cells. During this initial phase of donor-derived T-cell expansion, skin inflammation or liver disease may develop or aggravate but usually resolve without further intervention and maternal T-cells disappear.

The majority of SCID patients lack an HLA-matched donor and therefore are transplanted from an HLA-haploidentical parent. HLA-nonidentical grafts have to be depleted of mature T-cells in order to prevent GvHD. T-cell reconstitution in this setting is delayed for several months, recapitulating thymic ontogeny and newly generated donor-derived T-cells are tolerant to the host. As a consequence, rejection mechanisms probably do not play such an important role to eliminate maternal T-cells as after matched, unmanipulated transplantations.

We recently performed an analysis in our cohort of SCID patients, undergoing haploidentical transplantation with conditioning during a more recent period (since 1995). In the group of patients with maternal T-cells, in whom mostly the mothers were used as donors, we observed a strikingly higher rate of GvHD after transplantation compared to patients without engrafted maternal cells (table 3). In several of these patients, prolonged immunosuppressive treatment was required to control and overcome this complication.

Summary

The presence of maternal T-cells in SCID is restricted to patients with complete lack of autologous T-cells and occurs with a prevalence of 50%. Clinical symptomatology may be absent but includes also cases with severe manifestations of GvHD, resembling Omenn Syndrome. Surprisingly, this severe form is predominantly observed in B^- SCID variants. These variants are characterized by a functioning NK-cell system, a constellation in which one could expect rejection of maternal cells by host NK-cells. The basis for this phenomenon is currently open. The use of immunosuppressive treatment is essential for management of SCID patients with symptomatic maternal T-cell engraftment. Stem cell transplantation, especially from HLA-nonidentical donors, bears an increased risk for developing GVHD, possibly from reactivated maternal cells, requiring careful monitoring and continued immunosuppressive prophylaxis or treatment.

References: *1.* Lo et al., Blood 88, 2105ff, 1996. *2.* Kadowaki et al., Lancet, 1152ff, 1965. *3.* Petit et al., Exp Hematol 23, 1601ff, 1995. *4.* Scaradavou et al., Blood 88, 1494ff, 1996. *5.* Lo et al., Clin Chem 46, 4390ff, 2000. *6.* Petit et al., Br J Haematol 98, 767ff, 1997. *7.* Lo et al., Br J Haematol 100, 605ff, 1998. *8.* Srivatsa et al., J Pediatr 142, 31ff, 2003. *9.* Pollack et al., N Engl J Med 11, 662ff, 1982. *10.* Müller et al., Blood 98(6), 1847ff, 2001. *11.* Knobloch et al., J Immunol 146, 4157ff, 1991.

ESID Online Registry

provisional list of disease specific steering committees:

Predominantly antibody disorders

Agammaglobulinemias XLA (Btk.), BLNK / SLP65, μ-chain (IGHM), Igα CD79 A, Igß CD79 B, λ5/14.1 (CD179B/IGLL1), Vpre ß, syk, CD19 deficiency (CD19), unknown. Head: Edvard Smith (agreed). Alessandro Plebani, Graham Davies, Laszlo Marodi, Carl Granert (all agreed).
Hypogammaglobulinemias CVID, sIgM-deficiency, sIgA-deficiency, Ig-gene deletions, IgG subclass deficiency, Ig light chain deficiency, deficiency of specific IgG, transient hypogamma of infancy, Good-syndrome (associated with thymoma), ICOS-deficiency (ICOS), caspase 8 deficiency, transcobalamine deficiency. Head: Bodo Grimbacher (agreed).
Carrock Sewell , Lazlo Marodi, Michael Borte, Lennart Hammarström, Peter Arkwright, Sean Riminton, Jindrich Lokaj, Vojtech Thon, Jiri Litzman, Andy Gennery (all agreed).
Hyper-IgM – Syndromes (HIGM) CD40-deficiency, Head: Luigi Notarangelo (agreed). CD40L-deficiency (CD154), Head: Luigi Notarangelo (agreed). AID-deficiency (AICDA), Head: Anne Durandy (agreed). UNG-deficiency, Head: Anne Durandy (agreed). NEMO / IKKg-deficiency (XED), Head: Mario Abinun (proposed). Unknown HIGM, Head: Anne Durandy (agreed).
Hyper-IgE – Syndromes (HIES) AD-HIES, AR-HIES, sporadic HIES, HIES-variants. Head: Bodo Grimbacher (agreed). Bernd Belohradsky (agreed).
Hyper-IgD – Syndrome (HIDS) MVK. Jos van der Meer (agreed). Bernd Belohradsky (agreed).

Predominantly T cell deficiencies

T^-B^- SCID Head: Alain Fischer (agreed). ADA-deficiency. Head: Bobby Gaspar (agreed). RAG 1/2 – deficiency. Head: Anna Villa (agreed). Klaus Schwarz (agreed), Andy Gennery (agreed). Artemis deficiency. Head: Jean-Pierre de Villartay (agreed). Klaus Schwarz (agreed), Andy Gennery (agreed). Reticular dysgenesis.
T^-B^+ SCID Head: Alain Fischer (agreed). X-linked (gc) (CD132), Head: Alain Fischer (agreed). Jak 3 - deficiency (JAK 3), Head: Luigi Notarangelo (agreed). IL7R-deficiency (IL-7Ra), Head: Silvia Giliani (agreed). Amos Etzioni (agreed), Evelina Mazzolari (agreed). CD45-deficiency(CD45/PTPRC), IL-2Ra - deficiency (CD25).
CD8-deficiency (CD8a).
PNP-deficiency (PNP).
HLA class II deficiency CII TA, RFXB, RFX5, RFXAP.
TAP-deficiency TAP 1, TAP 2.
ZAP-70-deficiency ZAP 70.
CD3-deficiency CD3G, CD3D, CD3E. Head: Jose R. Regueiro (agreed).
WHN-deficiency Head: Claudio Pignata (agreed).
IPEX FOXP3. Head: Eleonora Gambineri (agreed). Co-Head: Alberto Tommasini (agreed).
ALPS fas (CD95), caspase 10, FAS-L (CD178). Head: Wilhelm Friedrich (agreed).
APECED AIRE.
DGS chrom. 22 deletion. Head: Anna Sediva (agreed). Anders Fasth, Ales Janda, Andy Gennery, Jan Vejvalka (all agreed).
CMC AD, AR, sporadic.
Other unclassified T-cell disorders Head: Wilhelm Friedrich (agreed).

Phagocytic disorders

Defects with susceptibility to mycobacterial infections IFN-gR1-deficiency (CD119/IFNGR1), IFN-gR2-deficiency (IFNGR2), IL-12 deficiency (IL12B), IL-12R b1 (IL12RB1), IL-18 deficiency (IL18), IL-23 deficiency (IL23A), STAT-1 deficiency (STAT1) , STAT-5 deficiency (STAT5). Head: Jean L. Casanova (agreed).
PID with partial albinism
Severe congenital neutropenia (Kostmann) X-linked, AD, AR, sporadic.
Schwachman-Diamond syndrome
CGD X-linked (CYBB), p22 phox (CYBA), p47 phox (NCF1), p67 phox (NCF2). Pending.
LAD LAD1 = CD11/CD18 (CD18/ITGB2), LAD2. Amos Etzioni (agreed).
Griscelli Syndrome MYO5a, RAB27A.
MPO-deficiency G6PD.
Neutrophil elastase deficiency = cyclic neutropenia ELA2.
Chediak-Hijashi Syndrome CHS1/Lyst.
MBL-defect MBL.
RAC2-GTPase defect RAC2.
Specific granule defect CCAAT-Bpe.
Perforin deficiency PRF1.
Localized juvenile periodontitis (formyl peptide receptor).
WHIM - Syndrome CXCR4. Fernando Arenzana (agreed).
Other

Complement deficiencies

C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, C9, Properdin (PFC), Factor B, Factor D (CFD), C1 , inhibitor (C1NH), C3b inact.

Other well defined PID's

XLP SH2D1A. Head: Bobby Gaspar (agreed). Luigi Notarangelo (proposed), Stephan Ehl (agreed).
DNA-breakage disorder AT (ATM), AT-like, NBS (NBS1), other. Head: Lennart Hammarström (agreed). Ewa Bernatowska (agreed), Beata Wolska (agreed).
WAS - WASP Head: Adrian Thrasher (agreed). Luigi Notarangelo (agreed).
Osteopetrosis TCIRG1. Head: Anna Villa (agreed). Anders Fasth (agreed), Annalisa Frattini (agreed), Wim van Hul (proposed), Anna Teti (proposed).
ICF syndrome DNMT 3B.
Cartilage hair hypoplasia PMRP/CHH.
Fc receptor deficiencies Fcg I (CD64/FCGR1), Fcg IIa (CD32/FCGR2A), Fcg IIb (CD32/ FCGR2B), Fcg IIIa (CD16/FCGR3A), Fcg IIIb (CD16/FCGR3B), FCRN (neonatal Fcg receptor).
Comèl Netherton Syndrome SPINK5.

Immuno-deficiencies of unknown cause

Head: Bodo Grimbacher (agreed).

QoL (Quality of Life) in PID

Ann Gardulf (agreed), Anders Fasth (agreed), Fabian Schumacher (agreed), Head to be elected.

Focus on a country:

Established member Q&A
Amos Etzioni
Dept Paediatrics
Rambam Medical Center
Haifa, Israel

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

I was born in Israel just before its independence, and both my parents emigrated from Poland before World War II. As every Israeli, I joined the army after high school and served for almost 30 years in the Israeli reserve army as a medical officer. In the late sixties, only one medical school existed in Israel, and therefore I began my medical education in Bologna, Italy. I was able to come back for the clinical years and to be one of the first graduates of the faculty of medicine at the Technion in Haifa. I did my internship and residency at the Rambam Medical Center in Haifa, which is a tertiary hospital for the Northern part of Israel. During my residency I did a 6 months rotation in basic science in the Department of Immunology. My research project was to detect anti-islet-cell antibodies, which were just then reported for the first time by Dr Bottazzo from London in patients with juvenile diabetes (now called IDDM). I then went for a fellowship in immunology at St. Christopher's Children Hospital in Philadelphia, under the supervision of Dr Harold Lischer. Harold was one of the first pediatric immunologists in the USA, and contributed mainly to define together with Dr Angelo Di George, the famous Di George syndrome.

In the mid-eighties, I came back to Israel and worked as a senior physician in the Department of Pediatrics. I then started the first Pediatric Immunology Service in the Northern part of the country. Later on, I became the head of the department and currently I am the director of our new Meyer's Children's Hospital. I am a full professor in our faculty, and also serve as the vice dean.

I'm happily married for more than 30 years and one of my daughters (out of two), Tamar, is a fourth year student at our medicine faculty.

How did you became interested in immunodeficiencies?

As our older colleagues may remember, at our time immunology was not a topic by itself and we learned about lymphocytes during our course in microbiology. During my 6 months in basic science, I started to learn about the immune system and became fascinated by it. This was even before monoclonal antibodies were discovered, and the knowledge about the various components of the immune system was just beginning to emerge.

As consanguinity is very frequent in our area, I treated many patients with PID and thus thought that it would be a good idea to study PID (I never ever regret this idea)! It was clear to me that studying those "rare experiments of nature" will help us to better understand the immune system, and as one who was interested both in basic research as well as clinical research, I found in PID indeed this extremely interesting combination.

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

Upon my return from the States, I opened the PID Service and was able to describe a unique CID with veno-occlusive disease of the liver (J. Pediatr. 1986). During the years we started IVIG and treated many patients with hypogammaglobulinemia. In the beginning of the nineties, we discovered a

new Leukocyte Adhesion Defect, LAD II, (NEJM, 1992) which was due to a defect in the carbohydrate ligand of the selectins, which is so important for the first phase of the adhesion cascade. We collaborate with people from the USA, Holland, Italy and Germany, and were able to delineate the various immune defects in LAD II and to discover the primary defect, a mutation in the specific transporter of fucose into the Golgi apparatus. Recently, together with Dr. Aker and Alon we defined a third LAD syndrome (Blood 2003). In this case the patients are suffering from both recurrent infections, as well as severe bleeding tendency. While the integrin structure is normal, the primary defect in LAD III is a general defect in integrin activation, which is essential for leukocyte adhesion, and in platelet aggregation.

We operate a growing clinic for patients with PID and perform BMT when needed. Recently, with the help of the Modell foundation and other American friends we inaugurated a center for PID!

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

This is a very interesting question. If you will look at what was achieved in the last 10 years, how many genes were found, the new therapeutic modalities etc, you really can imagine almost anything. Still, I believe that in the near future we will understand much better the exact roles of each of the molecules that are defective in the various PID (take for example CD40L or ATM). Furthermore, many new PID syndromes will be recognized, especially ones with some saddle defects (the exciting work of Dr Casanova's group for example). In the field of therapy, more biological products will be introduced, BMT will become even more successful and hopefully, the side effects of gene therapy will be overcome and clinical trials will be able to start again in this fascinating field.

I remember that in a PID meeting in Orvieto (Italy) the late Dr Good summarized the symposium. Many new genes were discovered, and some people thought that it would bring the research on PID to an end . Dr Good said "I am sure that this is not the end, maybe just the end of the beginning". I believe that these words by the founder of our field still hold true for the future!

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

Go on !! This is an exciting area, much has still to be studied. It is an ideal field for someone who wants to combine clinical and basic science. While studying these rare diseases, you can help many families. Another advice: be curious! Do not believe in every word your boss tells you. Go into depths in order to understand the medical problems you face. Remember, there are still many secrets that nature is trying to hide and must be revealed in the future.

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

ESID is a very important Society for me. It is a forum that gathers all the people involved in PID. Through the meetings, I was able to communicate with many other researchers and to get their help in solving difficult clinical and basic problems. The database is the best source to get data on a huge number of patients. From the educational point of view the ESID meeting is by far the best place to be updated in our exciting field. The Summer School - which was initiated by Dr Chapel - is also a major achievement of ESID and should go on.

Young Investigator Q&A
Ilan Dalal
Pediatric Allergy & Immunology Unit
E. Wolfson Medical Center
Holon, Israel

Can you give me some information about yourself and your background?

I was born in Israel in Tiberias near the Sea of Galil, (where Jesus did some of his most famous miracles). I am married and have 3 sons.

Can you tell me something about your career history?

I graduated with honor in 1987 from the B. Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa. I did my residency in Pediatrics in Carmel Medical Center, Haifa, Israel between 1987-1993. During that period, I had the first opportunity to be exposed to cases of PID. Although rare, I found them fascinating. The intellectual challenge in making the diagnosis, and in a way that once you treat these potentially lethal disorders appropriately, you can offer them an almost normal life. I did my fellowship in Allergy/Immunology in the Hospital for Sick Children in Toronto, Canada in 1994-1997 under the supervision of Professor Chaim Roifman, the head of the division. Since then, I am a senior pediatrician in the Department of Pediatrics at E. Wolfson Medical Center as well as a senior staff member in the Pediatric Allergy/Immunology/ Infectious Unit. I am affiliated with the Sackler Faculty of Medicine in Tel Aviv University.

How did you become interested in immunodeficiencies?

The main interest of the division in the Hospital for Sick Children in Toronto is primary immunodeficiency and this is one of the reasons why I chose this place for my fellowship. I was lucky to have Professor Chaim Roifman, a top leader in the field of PID, as my mentor. I found this field fascinating both from the clinical point of view as well as the research aspects.

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

During my fellowship, and also here in Israel I have been taking care of many patients with primary immunodeficiency disorders. This includes diagnosis, treatment, follow-up visits and in appropriate cases also bone marrow transplantation (This is done in collaboration with the BMT Unit in Tel – Hashomer Medical Center).

What do you hope to achieve in the future?

As a clinician, my research projects include a combination of clinical and basic science papers: Hypogammaglobulinemia of infancy, the outcome of matched unrelated BMT for combined immunodeficiency disorders, knock-out of the PNP gene in a mouse model, novel mutations in PNP deficient patients, detection of mutations in RAG1/RAG2 genes in T-B- SCID or Omenn syndrome.

How are you planning to reach this goal?

My hope in the future is to continue my research projects and to establish the Israeli Internet – based network for PID including a "DNA Bank" of samples from patients and family relatives in order to help in diagnosis, treatment, and prenatal counseling. This project will be funded by the Canadian Friends of Tel Aviv University.

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

ESID for me means excellency in the field of PID. The two-year meetings are the top in the field both clinically and research wise. In this meeting, the participants have the chance to meet the real people behind the names and get to know them in a non-familiar way. ESID was the inspiration for our first Israeli Registry for PID. Based on the ESID form, we collected data of more than 300 PID patients from centers all over the country.

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

I would try to put more efforts in order to increase the international collaboration in order to strength the field of PID.