# Newsletter

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European Society for Immunodeficiencies




ESID members are invited to publish in this newsletter

treasurer@esid.org

## Letter from the editor

Dear ESID members,

This is my first newsletter as Editor-in-Chief and I am very pleased and very honoured to contribute to the ESID community managing this great tool!

I believe that the Newsletter is a very useful way to keep ESID members in touch. Esther did a great job in running the newsletter and constantly looking for interesting topics to discuss. However, I trust that there is always room for improvement! If you have interesting stories/life experiences/clinical topics/ research activities or proposals to share with the community please step forward and contact me at treasurer@esid.org! The newsletter is a tool available to every member and any contribution you might have is very welcome!!

In this issue you will find reports from the latest ESID activities. In particular from Sherif Badawy, travel grant recipient for the ESID Junior Workshop in Florence, who will share with us his experience about the event. Speaking of juniors; new short-term fellowships are available for exchange programmes amongst European countries. Moreover, calls for new ESID board positions are still open until June. Finally, all is ready for the upcoming ESID meeting in Istanbul and you will find in this issue all the final details.

Enjoy reading! I wish you all a super spring time!

**Eleonora Gambineri**
New Editor-in-Chief

## In this issue



**NOT A MEMBER YET?**

**BECOME A MEMBER AND ENJOY THE FOLLOWING BENEFITS:**

- **Reduced fee to the Istanbul ESID congress**
- **Reduced fee to FOCIS meetings**
- **Access to a network of PID**
- **Eligibility to receive awards**
- **Eligibility to participate in ESID PID Schools**
- **ESID Newsletter (quarterly)**
- **Access to ESID website members only area**




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## A note from the President

Dear All,

The organisation of our upcoming ESID meeting in Istanbul is brilliantly led by our friend and colleague Necil Kutukculer, with the help of a dynamic organising committee and the strong support of the ESID board. The news is very good, with fantastic speakers and an increasing number of registrations. Once again, I would like to invite you all to spread the word, in any way you can think of, and to convince as many physicians, scientists, and physician-scientists as possible, both from the traditional world of PIDs and from beyond, and both from Europe and from overseas, to join us in Istanbul in October.

All best wishes,

**Jean-Laurent Casanova, MD, PhD**
ESID, President

## Secretary's report

The ESID 2010 biennial meeting that is taking place in Istanbul from 6-9 October is definitely the highlight of this year activities. Nevertheless, our Executive Board is working in parallel on many other initiatives all aimed to contribute to the mission of ESID and respond to the needs of its members.

### Istanbul biennial meeting

Further on in this newsletter Necil Kutukculer, 2010 biennial meeting President, will give you a more thorough update regarding the event. All the same we wish to congratulate both the organisation and the scientific committees for the wonderful programme they have put in place. A lot of work and dedication has been put together in order to combine an exciting scientific and educational programme with relevant social activities.

The biennial meeting is also a key opportunity for ESID to raise its profile as a society and for participants to network with other peers and get acquainted with the latest developments in the field of PID. For the first time ESID will be having a **booth** in the exhibition area to welcome all those interested in learning more about the society. We will also encourage all those wishing to join our society or propose new relevant activities.

ESID has also decided to award **10 travel grants** to Junior members wishing to attend the meeting. This decision falls within our society willingness to promote attendance of Junior members to key events on immunology related diseases. The Istanbul meeting represents one of the top events in the field and therefore an obligatory stopping point for all those wishing to improve their in-depth knowledge on PID.
Each travel grant will be of Eur 1'000,- and will help covering partially or totally travel and registration expenses of the awardee. Travel grants will only be open to members that have submitted an abstract to the congress. The definite Istanbul Travel Grant guidelines are currently being drafted and they will be published in the upcoming months in our website.

As it happens at the biennial event, ESID will hold its General Assembly (GE) meeting, open to all members, and its Executive Board meetings. The GE will take place Saturday 9 October from 4:00 pm to 5:30 pm. ESID Board meetings will take place Wednesday 6 October from 7:30 am to 9:00 am, and on Saturday from 5:30 pm to 7:30 pm.

## ESID 2014 call for bids

As you know bids for ESID Biennial Meetings take place four years in advance. In the light of this we would like to ask your **nominations regarding the 2014 Biennial meeting**! The President and the location for the 2014 Biennial Meeting will then be decided by electronic voting after a presentation of the bid at the ESID General Assembly in Istanbul.

The agreement between ESID and Kenes – our core PCO from 2012-, will make it easy for you to host ESID biennial meeting. The agreement will delegate much of the organisational burden and the labour of soliciting and receiving abstracts to Kenes. Kenes will also take over the scores of publishing programs and abstracts, and the major work of arranging hotels, meeting rooms, and so forth. The scientific program will be the joint responsibility of ESID and the local Organising Committee.

Call for bids 2014! Check the guidelines for destination congress submission!

Your active participation in the bidding process is important for us!

### The following information may serve as a guideline for the bidding process:

- **The *Host* must be a full member of ESID**
- **include details of the proposed city and venues - including description of facilities, travel connections and clear indications of restrictions for entering the country;**
- **include availability of hotel rooms in the proposed city;**
- **propose dates (preferably for October)**
- **include suggested programme outline**
- **include possible social events**
- **provide finances/provisional budget and information on local tax rules**

**Deadlines for bidding**: **1st of August 2010**
Send us your letter of intent and application to esid.admin@kenes.com

## Board Elections

Every two years we need to elect or renew the term of office of some of our Executive Board members. The next article of this newsletter will give you the full details about the terms of each position, the summary of applications received so far and the online voting dates.

Your participation is crucial to identify the members that will be integrating the next Executive Board until 2012. They will not only give voice to your needs, but will also continue develop new initiatives that are relevant to the diagnosis, management and treatment of PID related diseases.

**Bodo Grimbacher**

# 2010 Board Elections

As it happens every two years we need to elect or renew the term of some of the members of our Executive Board.
In light of that we would like to invite the most distinguished physicians, scientists, and physician-scientists in the field of PIDs in Europe to actively participate within the ESID board. We would like to achieve a more equal gender representation and maintain a good representation of the diverse European regions and countries, as has always been in the past. **Finally, we would like to encourage new applicants, so that ESID benefits from a new generation of board members.**

Each term of office is two years for the President, Secretary and chairpersons of all Working Parties, renewable at the next Biennial meeting, but limited to two terms (four years) only.

Our President-elect, Amos Etzioni has already been identified as the next ESID President during the last elections held prior to the s-Hertogenbosch AGM.

Our Treasurer, Eleonora Gambineri is entitled to be elected for four consecutive terms (eight years) and she is now completing her first mandate (two years).
Moreover, Klaus Warnatz our Clinical Working Party chairperson, Bobby Gaspar our SCT/GT Working Party chairperson and Crina Samarghitean our representative for the ESIDjunior Working Party have done a great job in the past two years and accepted to stand for re-election.

Want to Get Involved in ESID?
Call for nominations to serve on ESID Executive Board!

The term of office for some of our board members are also reaching the end and we have now received the following applications for these open positions:

- Secretary: Christoph Klein and Anna Villa
- Educational Working Party Chairperson: Esther de Vries and Laszlo Marodi
- Genetics Working Party Chairperson: Bodo Grimbacher and Capucine Piccard
- PID Care in Development Chairperson: Raffaele Badolato and Anna Sediva
- Registry Working Party Chairperson: Stephan Ehl

The online voting will go live on the ESID website www.esid.org on September 8th, one month prior to our biennial congress and will be close on October 8th 2010 at 12noon CET. Only members of ESID will have a password to the protected part of the ESID website and can vote.

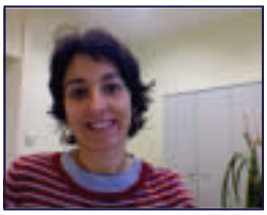
During that time you will be able elect the new board members for the opening positions and also to renew the mandate for those who have accepted to stand for re-election. Please note that you will have to be a full ESID member to be able to vote and this implies that you have already paid your dues for 2010 and 2011.

Please submit your applications to the ESID Secretary Professor Bodo Grimbacher at b.grimbacher@ucl.ac.uk by **15 June 2010**. This is the final deadline and applications received after June 15th 2010, noon CET, will not be considered.

All applications will be published in the ESID newsletter (July issue) and on the ESID website (immediately).

Best wishes,
Bodo Grimbacher and Jean-Laurent Casanova
*On behalf of the ESID board*

## Treasurer's report



Dear ESID members,

With the valuable contribution of Kenes, the membership campaign has commenced. If you haven't renewed your membership yet, you are still in time to take advantage of all the benefits, in particular the upcoming ESID biennial meeting in Istanbul - please check the programme and deadlines on the website www.esid2010.org

Moreover, we are looking for new sponsorships to support more initiatives within the society and to promote the ESID activities within affiliate societies. So a lot of effort to grow even more!

Finally, keep an eye on our educational programme and workshops. In particular, I would like to remind you about the Spring Meeting in Prague organised by Anna Sediva, where young people from Eastern and Western European countries have the opportunity to share their experience on PID!

So keep joining the community!

Best wishes

**Eleonora Gambineri**
ESID Treasurer

## News and views

### The ESID Meeting in İstanbul, Turkey, October 6-9, 2010

Dear ESID Members,

It is my great pleasure to invite you to the forthcoming meeting **ESID to be held in Istanbul, from October 6 to 9, 2010.**

The ESID Board has worked out an outstanding scientific programme covering the most recent developments in the field of Primary Immunodeficiency Diseases. The ESID program will consist of 17 conferences, 2 keynote lectures, 3 parallel workshops, 37 oral presentations, 7 ESID working party dinners, 1 late breaker session, 11 workshop education groups, 2 plenary education sessions, 9 sunrise education sessions and 6 satellite symposia. The Scientific and educational program is now finalised and you view all details on the official congress website at www.esid2010.org

Full programme available on www.esid2010.org

We invite you to use this opportunity to present your original work and exchange your experience in this field. The top ranking abstracts will be presented orally. You may find all relevant information and instructions for electronic abstract submission and registration directly in the congress website.

**Abstract submission deadline is June 1, 2010 and early registration fee deadline is June 15, 2010.**

Abstract submission deadline is June 1, 2010

Early registration deadline is June 15, 2010

A couple of social events will make your stay most enjoyable. A famous Turkish entertainment group by the name of "Fire of Anatolia" will perform before the opening cocktail. On the second night, during dinner cruise, we will sail up the Bosphorus, the waterway between Europe and Asia, as far as the Black Sea, passing under the suspension bridges and viewing Ottoman summer palaces, waterside mansions and modern villas which line the European and Asian coasts.

The exciting city of Istanbul is expecting you to show you not only its science, but also the treasures of its museums and monuments. **Istanbul is the European Capital of Culture at 2010** and it is a perfect place to experience four enriching and enjoyable days with this congress.

We look forward to welcoming you at the Istanbul Exhibition and Convention Centre.

With my best wishes,

Istanbul capital of culture 2010!

**Dr.Necil Kutukculer**
Congress President

## Congress registration fees for ESID Members:

| | Before 15 June, 2010 | After 15 June, 2010 | After 1 October, 2010 |
|---|---|---|---|
| **ESID MEMBERS** | **EUR 350,-** | **EUR 450,-** | **EUR 500,-** |
| **ESID MEMBERS withe less than 30 years old** | **EUR 250,-** | **EUR 350,-** | **EUR 400,-** |

## ESID juniors short term visit award/ Tampere Graduate School in Biomedicine (TGSBB) lab visit

**Report by:**
Crina Samarghitean,
MD, MSc

**Supervisor:**
**Prof. Mauno Vihinen**,
Bioinformatics group, Institute of Medical Technology, University of Tampere, Finland

**Host Laboratory:**
**Dr. Andrew Gennery**,
Paediatric Immunology/BMT, Newcastle University, Newcastle General Hospital, United Kingdom, 1-14 June 2009

**Host Laboratory:**
**Prof. Alessandro Plebani**,
Childrens Hospital, University of Brescia, Italy, 9-23 January 2010

## Paediatric Immunology/BMT, Newcastle University, Newcastle General Hospital, 1-14 June 2009

A short term-programme in one of the most important European hospitals has been a real help to develop a deeper understanding of PIDs and also facilitated new ideas for future applications and collaborations between the groups.
Thanks to a travel grant from Tampere Graduate School in Biomedicine and Biotechnology (TGSBB) and ESID juniors working party awarded by Dr. Eleonora Gambineri in 2008, I have been able to spend two weeks in the summer of 2009 at the Royal Victoria Infirmary Newcastle upon Tyne, United Kingdom under the supervision of Dr. Andrew Gennery and two weeks at Childrens Hospital, University of Brescia, Italy, under the supervision of Prof. Alessandro Plebani and Dr. Annarosa Soresina.

In Newcastle I had the chance to meet Dr. Gavin Spicket, who helped when we developed IDdiagnostics (Samarghitean, Väliaho et al. 2004), a genetic and clinical test database for immunodeficiencies. I attended the immunology/allergy clinic, SCID/BMT rounds together with other established senior doctors, such as Drs. Abinum, Marry Slatter, and other ESID juniors, such Drs. Sanjay Patel and Teresa Cole. The group from Newcastle, lead by Prof. Andrew Cant freely shared their experience and expertise and helped me to get a deeper understanding of the diagnostic process in PIDs. The knowledge accumulated here helped me to improve the user interface and the query base for PIDexpert, a decision support system for immunodeficiencies (Samarghitean and Vihinen 2008) under development. At the moment, we have described the most important parameters involved in the clinical and laboratory features of PIDs and we are working to stabilise the knowledge base and the inference mechanism for the system. Further real clinical cases are needed in order to test and release the system in clinical settings. We hope to get some anonymous patient datasets for testing PIDexpert from the Newcastle centre.

During my visit to Newcastle I had been fortunate to see some interesting PID patients with IPEX, Cernnunos deficiency, JAK3 defieciency, HLH, CD40L, WAS. Attending to weekly SCID/BMT rounds I could learn the latest therapeutic approaches and the best clinical practice (Gennery and Cant 2008; Gennery and Cant 2009).
Thanks to support from the Jeffrey Model Foundation, a couple of days were spent at the IUIS meeting, in Dublin, 3-6 June. Besides active participation to the ESID board meeting I could listen to the latest advances/discoveries in PID field and inspiring lectures (Glocker, Hennigs et al. 2009; Glocker, Kotlarz et al. 2009; Klein 2009). The knowledge acquired here will help me to develop new factfiles in IDR (http://bioinf.uta.fi/idr/index.shtml), a knowledge service for immunodeficiencies (Samarghitean, Valiaho et al. 2007) and improve the knowledge base for PIDexpert.

Some time was spent with Patricia Tierney, Paed. BMT Data Manager, and Dr. Marry Slatter observing the ‘in house’ PIDs patient registry, including the type of data collected, forms used and searches performed. The Newcastle group had interesting results on SCID and CGD cohorts (Gennery and Cant 2008; Jones, McGrogan et al. 2008; Straathof, Rao et al. 2009). Time was spent also observing and learning about SCETIDE, a database on bone marrow transplantation patients and the most recent results from the database (Soncini, Slatter et al. 2009). It was useful to see how the databases are connected with each other and how the transfer of the information is performed between the local database and the UKPIN national database and ESID registry. We exchanged experiences and may use the base for a possible future collaboration.

Useful ideas and suggestions were obtained from Prof. Andrew Cant and Dr. Gavin Spickett regarding the query base for PIDexpert and the diseases to be included. They both agreed to a possible collaboration regarding the developing of PIDexpert and the testing dataset.

After the Newcastle visit, I was able to finish the PIDs classification paper, accepted by one of the most prestigious Immunology journals (Samarghitean, Ortutay et al. 2009). Recently, this paper was included in Faculty of 1000 Medicine (www.f1000medicine.com), a revolutionary literature awareness service that identifies and evaluates the most important articles published in Medicine based on the recommendations of a Faculty of over 2000 peer-nominated leading researchers and clinicians. The article's identification and inclusion provides recognition from peers of its scientific merit and the positive contribution it makes to the medical literature (Bonilla 2010). Also, I finished another important invited review paper in Current Opinion in Allergy and Immunology (Samarghitean and Vihinen 2009). This paper presents the development over time of different PIDs bioinformatics tools and discusses some future applications and challenges in the field.

## Children's Hospital, University of Brescia, Brescia, Italy, 9-23 January 2010

The second part of the short term lab visit took place in January 2010. During the first two days I was fortunate to take part in ESID juniors workshop, in Florence, organised by Dr. Eleonora Gambineri with the help from Kenes. Here, ESID juniors not only interacted with each other and presented their work, but they also had the chance to listen to inspiring lectures taught by leaders in the field. Information learnt will be useful in the development of PIDexpert and I could also establish new collaborations with young doctors, such as Dr. Luis Gonzales from Spain willing to participate in developing and testing of PIDexpert.

For the rest of the week I visited the Children's Hospital, University of Brescia. Here, I learnt new lab techniques and diagnostic procedures for PIDs patients. Prof. Alessandro Plebani, the head of the Pediatric Clinic and his collaborators, Dr. Annarosa Soresina, Dr. Vassilios Lougaris, Prof. Raffaele Badolato and Dr. Silvia Giliani were wonderful hosts. I saw not only different phenotype of CGD patients but also different patients with ataxia-telangiectasia, characteristic facies of del22 (DGS syndrome), unique patients with STAT 1 and Cernunnos deficiency, different CVID and complement deficiencies patients. All the patients and different therapeutic strategies were discussed by the whole group during their weekly meeting.

During my stay in Brescia, I visited the Institute of Molecular Medicine A.Novicelli a referral centre for PID, currently headed by Prof. Alessandro Plebani. This institute, formerly headed by
Prof. Luigi Notarangelo has contributed to the identification of different genetic defects causing PIDs (Giliani, Bonfim et al. 2006; Borzutzky, Crompton et al. 2009). In addition, this institute has had fruitful collaboration with our group in the past, helping not only in developing of IDbases, a mutation database for PIDs (Vihinen, Cooper et al. 1995; Notarangelo, Peitsch et al. 1996) but also in developing of IDdiagnostics (Samarghitean, Väliaho et al. 2004). The genetic lab from this institute is a documenting centre for IDdiagnostics and each month runs more than 100 genetic tests from all over the world under the supervision of Dr.Silivia Gigliani, an expert in PIDs genetics (Giliani, Bonfim et al. 2006; Borzutzky, Crompton et al. 2009). I was very excited and happy to see in real life the place where some of the genetic defects causing PIDs were identified, and how skilful and knowledgeable the people in the lab are with the most recent PIDs technologies and also with bioinformatics tools for PIDs.

Another important time in Brescia was spent learning about IPINET, the Italian network for primary immunodeficiencies (Plebani, Soresina et al. 2004). Prof. A.Plebani, the current coordinator of the IPINET and Dr. Annarosa Soresina, the person supervising the IPINET registry, happily shared with me different steps in the development of IPINET and their achievements during a period of 10 years (Ferrari, Giliani et al. 2001; Plebani, Soresina et al. 2002). The results from the Italian registry on different PIDs cohorts have been published in numerous prestigious journals and presented all over the world (Plebani, Soresina et al. 2002; Martire, Rondelli et al. 2008; Moschese, Graziani et al. 2008; Quinti, Soresina et al. 2008; Soresina, Meini et al. 2008; Di Matteo, Giordani et al. 2009; Soresina, Nacinovich et al. 2009). I was very happy and grateful to have this unique chance to learn from their broad experience about how an exemplary PID patient registry should be developed and run.

We spent some time seeing how PIDexpert works at the moment, how IPINET could help PIDexpert and how PIDexpert could advance IPINET. The base for a future collaboration has been set up.

Another happy coincidence was the possibility to meet and listen to several seminal lectures taught by Prof. Luigi Notarangelo, previously Head of Pediatric Clinic in Brescia, former President of ESID, and presently Professor of Pediatrics and Pathology at Children's Hospital Boston, Harvard Medical School. For three days an enthusiastic audience had the privilege to listen to insightful advances on the role of immune system in the regulation of central and peripheral tolerance and different molecular and cellular mechanisms in lymphoid development. The seminar series ended with the description of the latest approaches in understanding, diagnosis and treatment of SCID and the most exciting biomedical discoveries in the last three years.

Finally, I would like to thank ESID, especially Dr. Eleonora Gambineri, who had an essential role in the set up of the short term visit award programme for ESID juniors, and to Prof. Andrew Cant, the Head of ESID Educational Working Party who supported many times the ESID juniors Working Party. I am very grateful to Dr. Andrew Gennery and to Prof. Alessandro Plebani, who accepted my visit and to all the wonderful doctors from Newcastle and Brescia who were such friendly and inspiring hosts to me. I am also very grateful to Tampere Graduate School Biomedicine (TGSBB) for supporting a part of the trip and to Prof. Mauno Vihinen for his excellent guidance and support.

I would like to **encourage all ESID juniors and TGSBB graduate students** to consider these kind of activities, as they are very useful not only for learning diagnostic and therapeutic procedures in the field of PIDs but also in setting up new fruitful collaborations between the centres.

**Crina Samarghitean**

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## Report - ESID Winter workshop, Florence 2010-04-13

The Junior ESID workshop in Florence was really for me amazing, gorgeous and out of the expectations regarding organization, programme, scientific contents and social activity. Everybody was helpful at different all the time not only in Florence but also while I was still here in Egypt I will never forget that Celine Deballon, from Kenes, called me on my mobile 2 days before I leave to help me to get the visa and she did send an e-mail to the embassy by fax to support me till last minute!! Amazing person!!

The faculty also were all very informing, targeted to the point and know how do it very well. This experience is considered to be for me the best I ever had because of both knowledge and exchanging experiences between all students from many different countries that give the meeting a wonderful taste and without the Junior ESID Workshop all these students and faculty would never be able to meet together in one place for couple of days.

Thanks to ESID and all its team especially Prof. Andrew Cant, Prof. Esther, Dr. Eleonora and Celine. Participating in well organized workshops like that did help me a lot to establish good basic and clinical background out of the lectures beside having perfect exposure to different European experiences in applying protocols dealing with PID in many hospitals inside and outside Europe together with having activities as spreading protocols and immunology related data, books, magazines and websites between all members...and these days I am trying to begin a national society for PID Egyptian Society of Primary Immunodefieciency (ESPID) caring for PID patients all over Egypt with immunologists from the biggest university hospitals caring for PID patients and having more research of PID here in Egypt with increasing awareness of all paediatricians and general physicians about PID in my country.

Best regards,

**Dr. Sherif Badawy**

# Working parties - Reports

## Report from ESID Juniors
### ESID juniors WP/1-2010

Dear ESID juniors,

We had a wonderful year in 2009, with many achievements and events and it seems that 2010 brings us even more important events and opportunities: ESID junior workshop in Florence, ESID Prague meeting, ESID biennale meeting in Istanbul to name just a few.

**ESID Junior Workshop**

As I mentioned in the previous ESID newsletter, between 11-12 January in Florence, Italy, thirty enthusiast ESID juniors had the chance to meet each other and present their work. We had lively discussions and inspiring lectures and could successfully reinforce our network.
The event was excellently organised by Dr. Eleonora Gambineri (ESID Treasurer) with the great help from Celine Deballon, from Kenes, and took place in the main lecture hall of Anna Meyer Children's Hospital.
The opening lecture by Prof. Romagnani, from University of Florence gave a broad overview of the immune system. Then, Dr. Esther de Vries challenged the audience with an interactive presentation on different PIDs clinical cases and diagnostics protocols. She included for illustration also some interesting and unusual clinical cases presented by ESID juniors: Kerstin Felgentreff, Gaspar Markelj, and Sybille Kenzel. Prof. Andrew Cant gave an interesting presentation on T cells and Prof. Maurizio Arico presented different diagnostic challenges for NK cells disorders. I ended the first day of the workshop with a presentation of ESID juniors activities and achievements in 2009.
The second day of the workshop debuted with Prof. Bobby Gaspar's presentation on Human Stem Cell Transplantation and other treatment options for severe congenital immunodeficiencies. Then, Prof. Alessandro Plebani from University of Brescia gave us some new insights on antibody deficiencies. The symposium successfully ended with an inspiring lecture on latest insights on PIDs presented by Prof. Bodo Grimbacher.
After ESID Junior workshop in Florence I continued the trip to Brescia to perform the last part of the lab visit award received in 2008. A detailed report of the whole programme is presented in this issue of the ESID newsletter. I hope other ESID juniors will be inspired by this story and will repeat these kind of activities.

Travel grants and short-term visit awards available to Junior members !

**ESID juniors travel awards**

- **Travel awards** are available for Junior members willing to participate **in ESID meetings during 2010 .** Details can be found directly in the ESID website at www.esid.org . Please send your questions and applications to Rita Louro by email at esid.admin@kenes.com
- **Two short term visit awards of 1,000 Euros** are available for ESID Junior members, who are physicians or scientists in training, interested in learning diagnostic/therapeutic procedures or lab techniques in the field of Primary Immunodeficiencies.

  **Aplications:**

  The application should include (a) a personal letter with a statement of career goals and plans and how to achieve these, (b) a short project plan, (c) CV with a list of publications, (d) a letter of invitation from the accepting institution, and (e) a letter of support from the applicant's head of department or supervisor.

After the completion of the trip the applicants are asked to prepare a short report of the lab visit performed.

**Deadlines:** Final deadline 15 July 2010

Please send your questions or application to Rita Louro by email at esid.admin@kenes.com

Cross-collaboration with APPID! One travel grant awarded to APPID Summer School 2010 in Australia!

We would like to thank again the **ESID board**, especially our Treasurer **Eleonora Gambineri** and Chair of the Educational Working Party, **Andrew Cant** and all the sponsors for supporting our activities. We hope more activities like these will be brought into reality.

## APPID 2010

The Australasian Society of Clinical Immunology and Allergy (ASCIA) offered a place to APPID Summer School 2010 to one trainee Clinical Immunologist, who is a member of the European Society for Immunodeficiencies (ESID). 2nd Asia Pacific Primary Immune Deficiency (APPID) Summer School was supported by an educational grant from CSL Biotherapies. The announcement was on the ESID website and spread to ESID juniors email list.

We are pleased to announce that Dr Reem Elfeky, Lecturer of Pediatrics, Ain Shams University, Cairo,Egypt, who is also an ESID junior member has been selected to attend APPID 2010. Congratulation to the winner!

We thank to the Australasian Society of Clinical Immunology and Allergy (ASCIA) and CSL Biotherapies for such a wonderful opportunity offered to ESID juniors and hope that more activities like these will be available in the future.

**Do you have new suggestions, ideas and activities for the ESID juniors working party? Don't hesitate to send them to us. Anyone interested in playing an active role in ESID Juniors working party is welcome!**

ESID Registry database hosting data on 11,017 patients at present!

Good luck in all your endeavours and I look forward to hearing from you!

**Crina SAMARGHITEAN**
Chairperson ESID juniors working party

# Report from the ESID Registry Working Party

## Current results and publications

As of March 16th, 2010, the **ESID Database held data on 11,017 patients** with a primary immunodeficiency disease. Of these, 9,951 were alive, while 842 had deceased. Of the remaining 224 patients, the status was unknown. Of the 9,951 still alive patients, the current treatment was documented in 8,718 patients (87.6%). Immunoglobulin replacement still represented by far the most frequent treatment in PID patients. It was applied in 3,669 (42.1%) of these patients. Haematopoietic stem cell transplants had been performed in 924 patients.
The distribution of patients on the main PID categories shows interesting results: Primarily antibody deficiencies account for 55% percent of all entries, which is less than what has been recorded in former registries (see Fig. 1). It must be noted, however, that the registered patients represent only a fraction of all PID patients in Europe. They may be prone to bias and do not necessarily represent the real PID distribution.

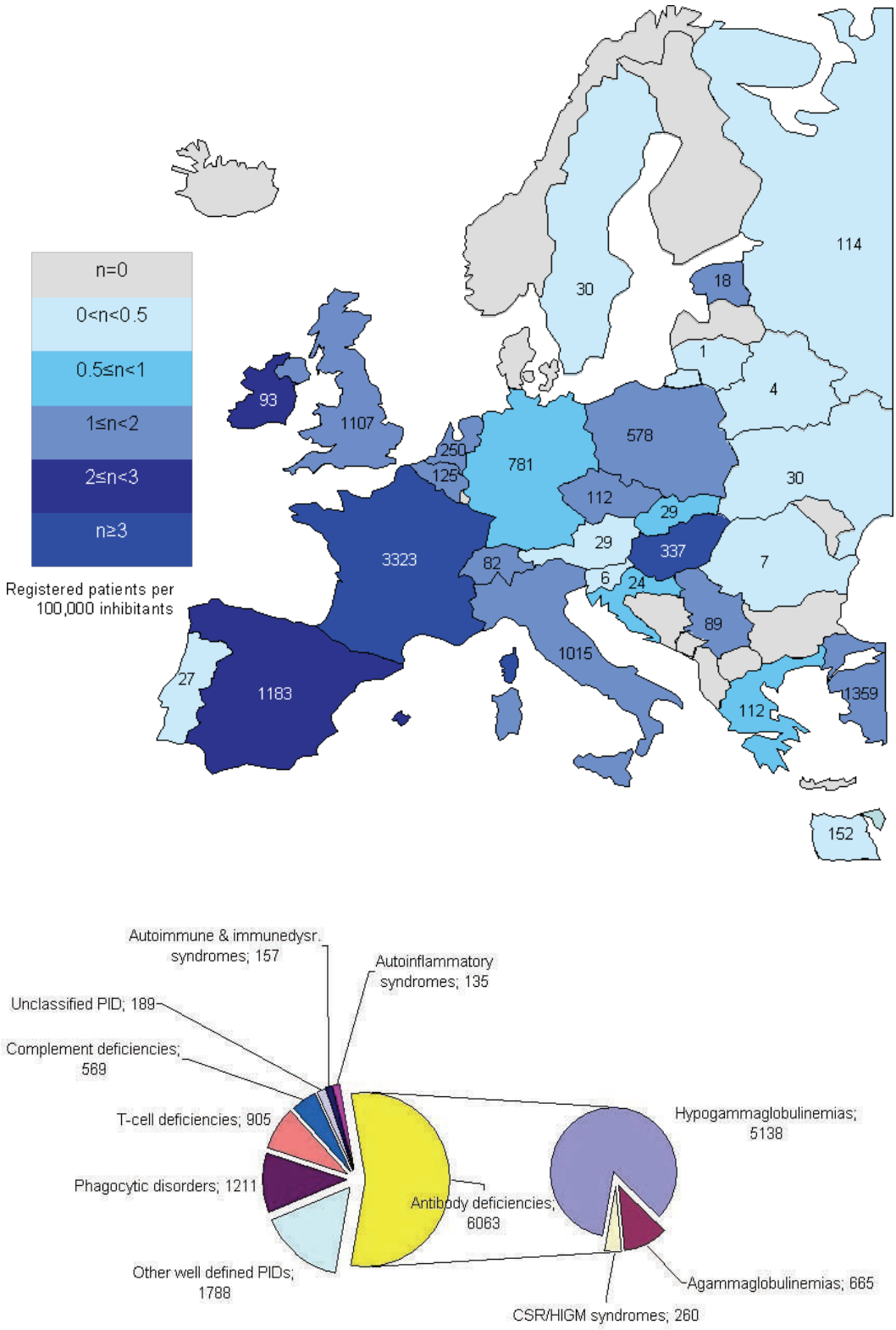


Fig.1: Number of patients registered in the ESID Database by main PID categories, with distribution of antibody deficient patients on the main subcategories.

## Registry-related publications

A **study on XLT by Michael Albert which used the ESID Database** to gather data has recently been published in Blood:Albert M et al.: X-linked thrombocytopenia (XLT) due to WAS mutations: Clinical characteristics, long-term outcome, and treatment options. Blood. 2010 Feb 19. [Epub ahead of print] (PMID: 20173115).

Furthermore, **CEREDIH** announced the first publication on the French data in Clinical Immunology which is due to be published in May 2010: "The French national registry of primary immunodeficiency diseases. CEREDIH: the French PID study group".

Our ESID colleague Crina Samargithean has recently published an interesting paper which suggests a systemic mathematical classification of primary immunodeficiencies:
Samarghitean C et al.:Systematic classification of primary immunodeficiencies based on clinical, pathological, and laboratory parameters. J Immunol. 2009 Dec 1;183 (11):7569-75. (PMID: 19917694)
The ideas presented in this paper represent a useful input for the further development of the classification used in the ESID Database.

**Gerhard Kindle** and **Benjamin Gathmann**

## Report from the ESID Clinical Working Party

Dinner workshop of the Clinical Working party on Thursday the 7th October, 2007

As we approach the 14th meeting of the ESID this year in Istanbul, I would encourage you to mark your calendars already and join us at the **Dinner workshop of the Clinical Working party on Thursday the 7th October.** By then we will have introduced the changes to our website as suggested in the last newsletter posting Minireviews on PIDD and ongoing clinical trials. IPIDnet, presenting immune phenotyping in primary immunodeficiency, will reach the 20 PIDD and protocols by the end of June 2010.

Regarding clinical trial activity Sergio D. Rosenzweig and N. Rezaei launched the trial "BCG infection in SCID patients" in 2008 and have already received thanks for your help from a substantial number of patients.

Post-vaccinal BCG infection in SCID patients International Survey

Please see their Update on the **"Post-vaccinal BCG infection in SCID patients International Survey ":**

So far we have collected information from 72 BCG vaccinated SCID patients from different countries in Latin America, the Middle East and Africa. Even a variety of genetic forms of SCID are represented (gammaC, ADA, Artemis, IL7Ra, MHCII, Zap70, and RAG), undefined forms of SCID are the most prevalently reported (64%). Our preliminary analysis shows that 45% percent of SCID patients developed BCG complications after vaccination, 18% localized and 27% disseminated. As an example of the relevance of this preventable complication, post-vaccinal BCG infection-associated manifestations accounted for 1/3 of the reported deaths (total deaths, 37), all of them in patients with disseminated forms of BCGosis. Moreover, 92% of SCID patients with disseminated BCGosis died due to its complications. At this point of the preliminary analysis, no significant differences on BCG complications were detected between B+/B- or NK+/NK- SCID patients, and we are still working on other aspects of the survey in order to analyse for the best diagnostic and therapeutic approaches, as well as for prognostic factors. We are actively encouraging our colleagues from around the world to participate in the "BCG infection in SCID patients' interest group" by submitting and sharing their experiences. Needless to say, we depend on these collaborations to get a large enough and comprehensive set of data that would help us to dissect and better understand this complication. Any actions that you can take in this direction will be highly appreciated. The current deadline for recruitment is the end of March 2011.

The clinical trial "Immunosuppressive therapy in patients with primary antibody deficiencies" has included 70 patients and a first analysis revealed that the main conditions treated with immunosuppressive drugs are autoimmune cytopenias followed by granulomatous disease. After steroid failures the treatment regimen decisions vary substantially between centres indicating the need for better evidence for optimal treatment strategies. We will present the first data at the 14th ESID meeting. When we will have evaluated our study protocol and adapted it to a multicentre setting we will open this trial also to other centres to collect more data on immunosuppressive treatment. This will be essential for sufficient data in order to provide better recommendations for immunosuppressive therapy in antibody deficiency.
We will all benefit from increased cooperative activity like surveys and trials. Therefore I ask you again to get involved in the Clinical Working Party, develop project ideas and support the activities of others in order to improve patient care. Please see the attached Form for announcing your clinical trials on the ESID website (for more detailed information on ongoing trials see the section "Protocols" for ESID members only). This form will be sent by email to all ESID members and will be made available on the website of the ESID clinical WP.

Call for update of specific PIDDs

Finally and most importantly, we discussed amongst the **ESID board the need for updating some of the current Diagnostic guidelines.** These diagnostic guidelines were developed over ten years ago by expert committees of the ESID and PAGID. Since then, our knowledge in certain PIDDs has substantially progressed. **Therefore I would like you to contact me if you see a special need for an update of specific PIDDs as we prepare for the update . I will inform you in more detail about the first** projects and procedures at the dinner workshop in Istanbul.

Hope to see many of you at the Clinical WP session in Istanbul.
**Klaus Warnatz**

## Interesting papers

### X-linked thrombocytopenia (XLT)

In a retrospective multicentre study the clinical phenotype of XLT was defined and the probability of severe disease related complications was determined. The study involved 173 patients (median age 11.5 years) from 12 countries spanning 2830 patient years. This analysis of the clinical outcome and molecular basis of XLT patients demonstrates excellent long term survival but also a high probability of severe disease related complications. These observations will allow better decision making when considering treatment options for individual XLT patients (**Albert MH et al, Blood 2010 Feb 19)**.

### Animal models

A knock-in mouse model with a homozygous Lig4 R278H mutation that corresponds to **the first LIG4 mutation reported in humans** was recently generated. DNA ligase IV (LIG4) is an essential component of the nonhomologous end-joining (NHEJ) repair pathway and plays a key role in V(D)J recombination. Hypomorphic LIG4 mutations in humans are associated with increased cellular radiosensitivity, microcephaly, facial dysmorphisms, growth retardation, developmental delay, and a variable degree of immunodeficiency. The phenotype of homozygous mice includes growth retardation, a decreased life span, a severe cellular sensitivity to ionizing radiation, mutant and a very severe, but incomplete block in T and B cell development. Peripheral T lymphocytes show an activated and anergic phenotype, reduced viability, and a restricted repertoire, reminiscent of human leaky SCID. Genomic instability is associated with a high rate of thymic tumor development. Lig4(R/R) mice spontaneously produce low-affinity antibodies that include autoreactive specificities, but are unable to mount high-affinity antibody responses.

These findings highlight the importance of LIG4 in lymphocyte development and function, and in genomic stability maintenance, and provide a model for the complex phenotype of LIG4 syndrome in humans (**Rucci F et al, Proc Natl Acad Sci U S A. 2010 Feb 16;107(7):3024-9)**.

## Diagnosis guidelines

The hyper-IgE syndrome (HIES) is a primary immunodeficiency characterized by infections of the lung and skin, elevated serum IgE, and involvement of the soft and bony tissues. Recently, in a multicentre study was determined whether there is a correlation between the genotype and the phenotype of patients with HIES and was established diagnostic criteria to distinguish between STAT3 mutated and STAT3 wild-type patients. The authors explored diagnostic criteria by using a machine-learning approach to identify which features best predict a STAT3 mutation. A combination of 5 clinical features predicted STAT3 mutations with 85% accuracy. The following **diagnostic guidelines for STAT3-deficient HIES** was proposed. **Possible**: IgE >1000IU/mL plus a weighted score of clinical features >30 based on recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic face, and high palate. **Probable**: These characteristics plus lack of T(H)17 cells or a family history for definitive HIES. **Definitive**: These characteristics plus a dominant-negative heterozygous mutation in STAT3 **(Woellner C et al, J Allergy Clin Immunol. 2010 Feb;125(2):424-432)**.

## New genes

The genetic etiologies of the hyper-IgE syndromes are diverse. Approximately 60% to 70% of patients with hyper-IgE syndrome have dominant mutations in STAT3, and a single patient was reported to have a homozygous TYK2 mutation. In the remaining patients with hyper-IgE syndrome, the genetic etiology has not yet been identified. A genome-wide single nucleotide polymorphism analysis for 9 patients with autosomal-recessive hyper-IgE syndrome was performed to locate copy number variations and homozygous haplotypes. Homozygosity mapping was performed with 12 patients from 7 additional families. Subtelomeric biallelic microdeletions were identified in 5 patients at the terminus of chromosome 9p. In all 5 patients, the deleted interval involved dedicator of cytokinesis 8 **(DOCK8**), encoding a protein implicated in the regulation of the actin cytoskeleton. DOCK8 mutation is associated with a phenotype of severe cellular immunodeficiency characterised by susceptibility to viral infections, atopic eczema, defective T-cell activation and T(h)17 cell differentiation, and impaired eosinophil homeostasis and dysregulation of IgE **(Engelhardt KR et al, J Allergy Clin Immunol. 2009 Dec;124(6):1289-302).**

## Gene therapies

Severe-combined immunodeficiency (**SCID-X1**) has been treated by therapeutic gene transfer using gammaretroviral vectors, but insertional activation of proto-oncogenes contributed to leukemia in some patients. A longitudinal study of gene-corrected progenitor cell populations from eight patients using 454 pyrosequencing to map vector integration sites, and extensive resampling to allow quantification of clonal abundance was recently reported. The number of transduced cells infused into patients initially predicted the subsequent diversity of circulating cells. The longitudinal analysis emphasises that key features of transduced cell populations-including diversity, integration site clustering, and expansion of some clones-were established early after transplantation. The approaches to sequencing and bioinformatics analysis reported here should be widely useful in assessing the outcome of gene therapy trials (**Wang GP et al Blood. 2010 Mar 1**).

Hope you enjoyed the papers selected for this issue. Wishing you a wonderful spring, good ideas and inspiration for many interesting and challenging papers! Do you have interesting articles you want to share with the whole ESID community? Don't forget to send them to us. Please, write your comments and suggestions to crina.Samarghitean@uta.fi

# Young researchers' corner

## Review on primary antibody immunodeficiencies

I would like to invite all ESID junior researchers and clinicians to make their contribution to the newsletter, by sending in suggestions, protocols or interesting papers focusing on Primary Immunodeficiencies.

And now here I am again, this time with a review of lab work on primary antibody immunodeficiencies.

B lymphocytes are specialized cells of the immune system whose major function is to produce antibodies (or immunoglobulins), which are a group of heterogeneous proteins able to recognise and bind a specific antigenic determinant of a proteic or polysaccharidic nature. For every foreign antigen there are antibodies specifically designed for that antigen. The physiologic role provided by antibodies includes helping rid the body of disease-causing bacteria, protection from viral infection and neutralising bacterial toxins.
Five distinct classes or isotypes of immunoglobulins have been identified in human serum on the basis of their structural, biological and antigenic differences:
IgG is the major class of immunoglobulins found in the blood, comprising 75% of total serum immunoglobulins, and is the only class of antibodies which goes through the placenta and passes immunity from the mother to the foetus. Human IgG has been subdivided into four subclasses on the basis of unique antigenic determinants IgG1, IgG2, IgG3, and IgG4).
IgA is the second most common immunoglobulin in human serum and is most active at mucosal surfaces. IgA includes two subclasses, IgA1 and IgA2.
IgM is a pentameric immunoglobulin that represents the third most common serum immunoglobulin (5 -10% of total levels) and is also a component of secretory immunoglobulins such as found in mucosal surfaces and breast milk. Monomeric IgM, together with IgD, is the major immunoglobulin that is expressed on the surface of B cells, where it serves as an antigen receptor. They predominate as an antigen receptor in early immune response to most antigens.
IgD is a monomer normally present in serum in trace amounts and it predominantly serves as a membrane-bound antigen receptor on the surface of B cells.
IgE is the less common serum immunoglobulin. It possesses a clinically significant biological function by binding the Fc receptor on basophils and mast cells responsible for Type 1 hypersensitivity reactions or immediate hypersensitivity reactions.
There are a variety of Primary B cell immunodeficiency disorders that can produce immunoglobulin patterns ranging from a complete absence of all isotypes of immunoglobulins (e.g. hypogammaglobulinemia) to a selective decrease in a single isotype (selective IgA deficiency). Sometimes a deficiency in one or several isotypes (e.g. IgG and IgA) can be associated with an elevated level of a third isotype (e.g. IgM). All antibody deficiencies are associated with an increased susceptibility to infection with encapsulated bacteria and giardia.
Therefore the level of serum immunoglobulins is commonly measured to identify an underlying defect in the humoral immune system. Currently three types of assay are used to quantify human IgG, IgA, IgM, IgD and IgE and the k and λ light chains.
Radial Immunodiffusion Assays employ polyclonal antisera or a mixture of monoclonal antibodies in a porous agarose gel into which a small quantity of serum is pipetted. In the presence of immune-complexed serum proteins, during migration through the gel, it is possible to observe a white precipiting ring with a diameter that is proportional to the concentration of the particular analyte specific for the antiserum in the gel. Gel-based immunodiffusion methods tend to be limited in analytical sensitivity and are not clinically useful in the measurement of immunoglobulins that are normally in low concentrations in serum (IgE).

In nephelometric and turbidimetric assays, the serum containing the analyte is added to the reaction chamber containing a constant amount of optically cleared IgG-, IgA- or IgM-specific antiserum. Immune-complex formation is obtained if the antiserum recognizes the specific analyses. The presence of immuno-complex is measured by the extent of light incident on the reaction chamber that is either scattered/reflected toward a detector that is not in the direct path of the transmitted light (nephelometry) or attenuated in intensity as measured by a detector in the direct path of the transmitted light as a result of scattering, reflectance and absorption (turbidimetry). The extent of absorption or scatter of a diluted reference serum containing known quantities of IgG, IgA or IgM makes it possible to calculate a sample analyte concentration by interpolation of the sample result with the reference standard. The method is quick and simple, but has the limitation of possible interference caused by high levels of lipoprotein or bilirubin in the serum and hemolyzed blood.

The immunoassay is the more sensitive assay, able to measure 1 ng/mL of human immunoglobulins in serum, urine and other body fluids. This is particularly used to evaluate the amount of specific immunoglobulin subclasses, such as IgG1, IgG2, IgG3, IgG4, and IgA1, IgA2 and IgE, by the capture method. This is based on the use of a plate binding a capture monoclonal antibody that recognises the specific immunoglobulin isotype of interest from serum and a second biotin-, enzyme-, fluorophor- or radio-labeled polyclonal or monoclonal antibody binding a different immunoglobulin epitope. The use of a reference curve obtained with serial dilution of a reference serum allows the amount of the analyte in the tested serum to be calculated.
There are also tests to evaluate specific antibody production. This measures how well the serum immunoglobulins function as antibodies aimed at specific antigens such as viruses and bacteria. In this approach the fact that the patient has been immunised with common vaccines, including protein antigens (e.g. tetanus toxoid, diphtheria toxoid) and carbohydrate antigens (e.g. Pneumovax, Hib vaccine) is used to see how well the patient is able to form specific antibodies.
The ability to evaluate the antibody response in patients receiving immunoglobulin replacement is more difficult because immunoglobulin is rich in most of the specific antibodies that are generated following immunisation. When immunised with common vaccines it is diffucult to tell the difference between the antibodies provided by immunoglobulin treatment and any that may have been generated by the patient. In this condition the solution is to immunise the patient with vaccines that are not normally encountered by the general population and therefore are unlikely to be present in immunoglobulin preparations. Uncommon vaccines, such as typhoid and rabies vaccines, can provide these new antigens.
Additonal studies to evaluate patients with antibody deficiency include measuring the different types of lymphocytes in the blood by flow cytometry. Staining with fluorescenced anti-CD19 and anti-CD20 monoclonal antibodies can identify the number of B cells present in circulation. In fact, some immunoglobulin disorders such as X-linked agammoglobulinemia are associated with the absence of $CD20^+$ B cells.

Flow cytometry can also be useful to classify CVID patients into subgroups according to B cell subsets. Patients in group 1 have a low percentage of class-switched memory B cell $CD19^+CD27^+IgM^-IgD^-$ while patients in group 2 have a normal percentage. The former can be subdivided into patients with an increased proportion of $CD19^+CD21^{low}CD38^{low}$ peripheral B cells (1a group) and those with a normal proportion (1b group). Many patients with splenomegaly and autoimmune cytopaenias have been found to segregate into 1a group. To perform this analysis, after gating on $CD19^+$ cells, the detection of IgM, IgD and CD27 expression is used to identified naïve ($CD19^+CD27^-IgM^+IgD^+$), marginal zone like ($CD19^+CD27^+IgM^{++}IgD^+$), class-switched ($CD19^+CD27^-IgM^-IgD^-$) and IgM only memory B cells ($CD19^+CD27^+IgM^{++}IgD^-$). The staining for CD19, CD21, CD38, IgM allows the additional distinction of transitional B cells ($CD19^+CD21^{int}CD38^{++}IgM^+$), plasmablasts ($CD19^+CD21^{int}CD38^{+++}IgM^{+/-}$), and $CD21^{low}$ B cells ($CD19^{++}CD21^{low}CD38^{low}IgM^+$), usually rare in normal subjects.

Moreover, analysis of specific DNA mutations can be performed to confirm a particular diagnosis (e.g mutations in the gene encoding Bruton Tyrosyne Kinase -BTK- are associated with X-linked agammoglobulinemia).

**Sara Ciullini Mannurita**

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## Take part in the Newsletter!

We are looking for volunteers to join the editorial board of ESID newsletter.
People interested, please contact Editor in Chief, Eleonora Gambineri at

treasurer@esid.org or Rita Louro at esid.admin@kenes.com

Wish you good ideas and inspiration for many interesting and challenging papers!
Do you have interesting articles you want to share with the whole ESID community?
Don't forget to send them to us!

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