

REPORT OF THE SCIENTIFIC SESSIONS OF THE XIVth MEETING OF THE EUROPEAN SOCIETY FOR PRIMARY IMMUNODEFICIENCIES



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Introduction

The XIth Meeting of the International Patient Organization for Primary Immunodeficiencies (IPOPI) was held in Istanbul, October 6-9, 2010.

As it has been established over the years, the meeting was held at the occasion of the XIVth Meeting of the European Society for Immunodeficiencies (ESID) and the IXth Meeting of the International Nursing Group for Immunodeficiencies (INGID).

Istanbul, “the city of the four elements”, greeted delegates with its interesting history dating far back into the past, the magnificent historical buildings, the very busy street life with formidable traffic jams, the oriental cuisine, however not with the weather conditions attendees would have liked - except for the first day - congress days were cold and rainy to a degree not encountered for some 20 years, according to the unanimous opinion of locals.

Delegates of IPOPI, ESID and INGID met the first time in a country which in the last decade has seen an admirable improvement in recognition of PIDs and has contributed interesting cases to the knowledge of diversity of genetic defects and the variability of the clinical manifestations of PID. IPOPI was represented by delegates from 34 nation member organizations.

The scientific presentations encompassed Educational Workshops and Sessions on the first day, Plenary Sessions, Satellite Symposia, Workshops and Poster Sessions, some of them held in parallel. The congress presentations confirmed that knowledge is progressing constantly although big breakthroughs had not been accomplished since the last meeting in The Netherlands two years ago. Beside the array of well known PID, less recognized deficiencies, like those of the complement system, were discussed as well.

Whilst IPOPI’s Medical Advisory Panel (MAP) provided an excellent session chaired by Teresa Espanol (Chair of IPOPI’s MAP) at the end of the meeting to summarize the scientific programme, below is an attempt to highlight some interesting aspects of evolving knowledge the participants were able to gather in some more detail.

Scientific Presentations Highlights

A series of plenary sessions gave an overview on various aspects of the immune system, the immune deficiencies and the treatment progresses. In his opening keynote lecture Max Cooper, Alabama, USA, lined out the evolutionary development of the adaptive immune system. The adaptive immune system is found in vertebrates only. The subphylum vertebrates have two super classes, the jawless (agnatha) and the jawed (gnathostomes). In both the principle of adaptive immunity evolved independently. The principle is the communication between two cell types having the ability to change and adapt their cell surface receptors. Deficiencies of the adaptive immune system are those of which the majority of people with PID suffer from and, for example, might need immunoglobulin replacement therapy.

The diversity of gene defects in all fields of PID research and the variability of manifestations constantly increases: more patients with a given rare disease, more mutations of phenotype genotype correlations, and more biology behind these diseases were reported – for example a growing family of genes associate with XLA disease. In CVID the ever increasing heterogeneity of genetic defects raised the question whether this has consequences for therapy (not yet), but understanding emerges of the possibility of somatic mutations leading to PID. Autoimmunity in association with PID is an emerging field. Autoimmune-like manifestations of complement deficiencies have been known for decades and the background to this is well established: impaired removal of altered/senescent ‘self’ leads to prolonged presentation of ‘self’-structures to the immune system leading to breakdown of tolerance. Association of antibody deficiency syndromes with cytopenias are known. The background to these autoimmune phenomena is likely to be associated with an intrinsic loss of B cell tolerance. The autoimmune-like symptoms can start after adolescence, and might allow for oversight the infectious manifestations, and patients might face the problem of not finding a clinical immunologist for adult patients as there are only a few around. Patients face the threat of delays in correct diagnosis of their disease. Although knowledge was around for a while, it is now realized by a broader community that some forms of innate immunity defects, particularly defects of interferon metabolism, might mean that patients feel as if they

are suffering from an infection although they have not been in touch with a micro organism. The derailed cytokine network produces pro-inflammatory cytokines in absence of natural triggers, the microorganisms.

The meeting also highlighted the importance of patient registers. Registers should not just register a disease but should also gather the data from the 'look at the patient'; a good mix of scientific and patient oriented questions are more and more recognized being the heart of a registry providing high value. Registries should have a strong impact in improving quality of life (QoL) of patients after having better defined the natural history of the patients/the diseases, to better understand compliance, the long-term evaluation of the disease (propagation rates) for better therapeutic and prophylactic interventions and to compare the outcomes of different treatments. As an example registries might become one of the four cornerstones of diagnostic approach for e.g. COVID (the others being: i) genetic fishing; ii) evaluating biologic processes in order to subdivide disease, iii) problems of the lung, i.e. bronchiectasis and fibrosis; enlarged spleen, enlarged lymph nodes, inflammation of the gut).

Reports on efforts of IPOPI and the attendees of the ESID meeting for better awareness in regions like Africa, Asia and Latin America were numerous. Sometimes the obstacles faced are enormous. The rarity of PIDs and the continuous (complicated) care they need make doctors very uncomfortable and they might not be keen at all having such patients. Furthermore, epidemics in these countries (HIV, tuberculosis) pose great problems for health care and simply allows for neglect of PIDs. Although diagnosis might be provided, care and therapy often will remain a problem. Making therapy for the treating physician and the patient 'as simple as possible' the replacement therapy for antibody deficiency syndromes via the subcutaneous route might be a valid option particularly when combined with home treatment. However, home treatment needs careful teaching on a 1st level of health care personal to be able to teach as 2nd level patients. The process can be shortened by getting the expertise from countries with long-standing experience in this field of treatment. Where information is missing it should be generated, e.g. by networking of societies/patient organizations of the region and by networking with well established patient organizations. Gathering information from (local) registries can be very helpful. Knowledge can be improved by teaching activities provided by a

tutorial country as was the case for Morocco by France. The activities of J project of ESID for several countries were appreciated as a full success. In conclusion data and knowledge are needed to allow local organizations for fighting for the benefit of patients. For IPOPI there is the challenge of 'more patients being out there' than is currently known.

Diagnosis of PIDs

Improving diagnosis in our time: for all immune deficiencies early diagnosis is a key for reducing complications and for allowing optimal outcome of therapeutic measures, e.g. BMT or SCT (see therapy section and abbreviations). In recent years the screening of SCID and severe T-cell defects from Guthrie cards has become possible and was introduced in two states of the USA and a third state will follow. On Guthrie cards drops of blood of newborns is collected and an aliquot can serve for population-based screening of metabolic diseases by cheap automated methods. A Guthrie specimen can further serve for extraction of DNA from which the T-cell receptor excision circles (TRECs)' can be amplified by molecular techniques. TRECs are specific functional markers of T-cells and the amount of TRECs indicates presence or absence of a T-cell defect. If the number is low, a confirmation sample is drawn. If the second analysis confirms the result of the first screening, a detailed analysis by FACS follows (see below). The obstacles this screening method encounters are as follows i) applicability is only for mature children (>37 weeks of gestation), and ii) the price per test; metabolic disease testing costs less than a dollar while SCID screening cost today about 6 dollars. In IPOPI discussions with key opinion leaders, it was stressed that this screening method did not miss a single case of SCID so far. IPOPI board members were encouraged to take action in favor of introduction of this screening test. Health authorities have to be informed about the relative low costs of the test and the health cost savings which can be achieved by (very) early diagnosis of SCID or severe T-cell defects. Lobbying for this screening opportunity is becoming even more important when considering the latest development: detection with help of Guthrie-cards of some B-cell defects, i.e. antibody deficiencies by assessing a specific functional marker of B-cells, the 'signal

joint kappa chain excision circles'. The principle technique is the same as for TRECs. There was agreement on routine newborn screening being a medical indication - however, the decision for performing the population-based testing is a political question.

Plasma cells are the cells producing antibodies. They differentiate from precursor B-cells. B-cells undergo several stages of development before they can differentiate into plasma cells. Genetic defects might stop B-cell development at a given stage. The knowledge regarding the stages of B-cell development is constantly increasing. B-cell development can be followed by cell surface molecules differently expressed at different development stages. The surface molecules can be 'marked' with specific antibodies which are able to emit fluorescent light when excited. A particular machine, called FACS, is able to analyze cell by cell the various differentiation markers expressed on the cell surface and can help in defining the stage at which development of patients' B-cells has arrested. As B-cell defects leading to antibody deficiencies, e.g. CVID, mainly occur in late B-cell maturation stages it is ensured that the number of cells available from patients is high enough for routine FACS analysis. With the development of more and more sophisticated methods, it has become possible to diagnose more and more forms of B-cell defects by FACS. By the way: the FACS technique also can be used for routine diagnosis of some T-cell defects.

The FACS technique is not able to provide information about the functional status of cells. For correct diagnosis often functional assays can provide the necessary information e.g. about the pathophysiology of extra-immune manifestations. In 2006 the epigenic reprogramming of somatic cells through the exogenous expression of transcription factors to become induced pluripotent stem cells (iPSC) was reported for the first time. Application of this technique is possibly a very important tool for functional investigation of human PIDs. As starting material the easily obtainable fibroblast were obtained from patients. Fibroblast are the predominant cells of connective tissue, i.e. the skin. Fibroblast were reprogrammed to PID-specific iPSCs clones (n = 30). It has become possible to induce *in vitro* differentiation of PID-specific iPSCs into embryoid bodies that had the potential to develop along specific lineages affected by the individual PIDs. Having access to previously inaccessible

diseased tissue enables disease investigation and in future might help development of novel treatment strategies.

Another approach to further differentiate the approx. 65 distinct forms of B cell defects, a 'high content analysis of the transcriptosome and cytochrome of B cells during activation' has been reported. Functional analysis of *in vitro* activated B cells might become a diagnostic tool in differential diagnosis of hypogammaglobulinemias.

PIDs are rare diseases, manifest at different ages with sometime astonishing variable, patient-specific clinical manifestations. To cope with the increasing complexity of PID diagnosis, there are efforts taken to establish expert network systems with the help of modern informatics like the semantic web. This shall allow world-wide access to often life-saving knowledge.

Pitfalls of diagnosis were also raised. As an example, at appropriate clinic lymphadenopathy together with autoimmune phenomena even in presence of normal IgG level should initiate a PID workup.

Screening for gene defects - the future: In the past research and industry with a lot of effort have paved the way towards full human genome analysis. Detection of a genetic defect by whole genome analysis was reported first time in March 2010. At the congress delegates got the impression the road is now being enlarged to a highway by making effort to remarkably lower costs so that in few years screening will become affordable - it is expected a whole genome analysis costing about \$1000 in the year 2014. However, the challenges are considerable. Straight forward, well rationalized and standardized methodology has to be implemented. As it looks these days, the primary methodology will be exon screening. Exons are those parts of the genome which are translated into proteins. The 20,000 to 25,000 protein coding genes are about 1-2% of the whole human genome which is about 3 billion base pairs. Proteins are encoded by several exons. Analyzing at first attempt exons will restrict work load and enable high throughput. It is foreseeable that not all deficiencies - e.g. defects of gene regulatory elements - will be detected by this method and that for a relatively small number of patients whole genome sequencing will have to be performed. For the medical community human exon/genome screening appears to bring a paradigm shift: instead of seeing the patient first, making a diagnosis and checking the correctness of the diagnosis, a suspicion for

PID will first require a blood sample for exon/genome wide screening (fishing for genomic disease markers) and only when the result data are available, the doctor will see the patient for diagnosis and initiation of appropriate therapy. Producing screening data is one thing; interpretation of the huge amount of data is another. The challenges are as follows: a large number of exons/genomes from 'normal' human beings are to be sequenced in order to evaluate the variability of the human genome which is not causing disease but results in various phenotypes, e.g. blue or black eyes. Although, the number of human genes encoding for proteins are far fewer than expected this does not mean that the effective number of proteins synthesized in humans, the human proteome, is equally low. Indeed, human cells extensively use genes 'multifold' resulting in a large human proteome. Again the 'multifold' use of genes has first to be mapped in depth before an appropriate diagnostic use can be drawn from human exon/genome analysis. Last but not least the huge data of variability what is 'normal' have to be compared to the individual patients data, needing a sophisticated IT and software technology. IPOPI is convinced next year several very interesting studies being published around whole genome analysis.

The 'multiple' use in humans of genes for the cellular protein synthesis will, in the longer term, also encourage for the development of screening methods analyzing the human proteome. Interesting developments are expected to be reported at the next ESID meeting scheduled for being held in Florence, Italy.

Gene therapy, bone marrow (BMT) and stem cell transplantation (STC) for PID

Gene therapy is considered being (in the future) the ultimate cure of genetic defects and therefore communications/publications regarding gene therapy always get a lot of attention. The aim of gene therapy is bringing the proper gene into the cell and have it incorporated at the right place in the genome of the recipient. The first part of the problem is more or less well achieved. However, incorporation at the right place in the genome has not yet been solved to a satisfactory level. Thus, gene therapy in our days remains practically the field for T-cell defects and further patients in whom BMT is not applicable might be eligible. Furthermore, SCT has meanwhile reached a high level of success making a therapeutic decision in favor of gene therapy quite difficult.

Indeed, new condition regimes have considerably improved survival of SCT receiving children. The most recent good news reported at the congress was that hematopoietic SCT after low dose Busulfan, full dose Fludarabine and *in vivo* T-cell depletion of high-risk pediatric and adult chronic granulomatous disease (CGD) patients resulted in a 100% success. The experience in children makes one believe the 'reduced intensity condition regimen' might indeed be a success. Despite the good results in adults reported at ESID 2010, it has to be kept in mind that the immune system in adults is 'experienced' to a higher level and might do less well, i.e. might bring along a higher risk for graft-versus-host disease because of the infections the individual has encountered before transplantation. Results await confirmation and hopefully the special condition regimen will establish as a story of great success in future patients.

Taking the reports on SCT together, the information drawn from the meeting might be: no magic breakthrough has been achieved but many unspectacular steps with a bit here, a bit there, unrelated donor transplantation virtually being as safe as matched sibling donor transplantation; a better matching of HLA of donors and recipients because the higher number of donors available for matching, a better conditioning with reduced adverse effects of conditioning, better anti-viral drugs over the years finally summed up to a fantastic success.

Exploring opportunities of transplantation further, IPOPI featured the role of umbilical cord blood for therapy options by inviting Prof. Anders Fasth, Göteborg, Sweden, to present on "*Cord blood newborn screening, blood banks, SCT. The future possibility for cure?*" Prof. Fasth eluded on the importance of teaching and 'how we can do it best'. With the possibility of very early diagnosis of SCID and further severe T (and B) cell defects in the frame of newborn screening (making use of the Guthrie-cards; see above), it is possible to get best profit for the benefit of the patient with transplantation being performed within the shortest possible time after birth. Available results clearly show superior survival for children with severe combined immunodeficiency transplanted within the first months of life compared to later in life. Newborn screening and cord blood banks might offer a great help in achieving speedy medical action. Cord blood banks can be organized so that an ethnic/minority balance is reached which is not given with the BMT registries because HLA-testing data necessary for bone marrow donations and the readiness

for such donations from given ethnics/minorities often are missing. Running cord blood banks should not be an activity of private (cord) blood banks, as autologous (the patient's own) marrow cannot offer cure of an inherited disease. The disease is also in the stem cells of the cord blood. In view of most patients lacking a suitable matched related donor, use of cord blood transplantation for PID is a viable option and may be advantageous in many situations. Cord blood transplantation is less dependent on stringent HLA matching between donor and recipient. It is believed that a particular feature of cord blood is associated with pregnancy. In pregnancy the fetus can be considered as a 'transplant in the mother' making necessary for survival of the fetus the down regulation of T cells. This down regulation might be advantageous for cord blood transplantation. The additional advantages of cord blood transplantation are the almost indefinite supply when well organized cord blood banks have been established, no risk to the mother or the child, lower risk for GvHD, lower risk for viral contamination and the relative high plasticity of the stem cells, availability on demand, easy shipping worldwide. Some disadvantages however exist when compared to BMT: above all the limited number of cells available for transplantation and thus longer time for the graft to take and establish hematological and immunological reconstitution of the recipient.

Replacement therapies with immunoglobulin concentrates for antibody deficiency syndromes

Preventing lung diseases (and intestinal complications) has become main targets of care in antibody deficiency syndromes. Patients with CVID are generally doing better than patients with XLA. Data from the ESID registry and a very recent report from the U.S.A. suggest that days missed work/school, days in hospital, number of all infections and number of serious infections drop with increasing IgG trough levels, at least for i.v. replacement therapy; data for patients under s.c. replacement therapy are less clear cut. Because the time which has elapsed is not long enough since replacement therapy at high doses is practiced the discussion remains open whether IgG trough serum levels in the normal range might prevent these complications or

whether replaced IgG is simply not able to reach and to mediate protection on the mucous surface.

A bunch of poster presentations dealt with the line extension of various companies' products or the s.c. use of a preparation originally dedicated for i.v. application. Probably worth mentioning is a liquid product intently developed for s.c. application. The liquid preparation has strength of 20%, the highest strength of an immunoglobulin concentrate ever on the market. The high strength of the solution allows for lowering the volume to be applied or apply daily small volumes ('push' option, of which the safety must first be demonstrated). The production of this immunoglobulin concentrate corresponds to its 10% i.v. counterpart. Plasma origin, production method, safety measures and stabilizer are the same in both products. It becomes possible to choose the route of application according to the actual needs of a patient by using an intently s.c. or an intently i.v. designed product without rising concerns about changing the 'brand'. An other interesting approach for s.c. products is to add recombinant hyaluronidase to the SCIG solution. Hyaluronidase enhances tissue permeability and supposedly enables infusion of larger volumes.

The struggle for market share and customers (it is supposed companies mean patients) is further slugged out on tolerability at high and even higher infusion rates. In some occasions, infusion rate is looked at as mL/min or drops/min infused. When changing a brand with strength of e.g. 5% to one with strength of e.g. 10% and keeping the infusion rate (as mentioned above) 'constant' IPOPI has heard that a considerably elevated frequency of adverse events result. This is no wonder because the double amount of IgG is administered in the same time period. Some other uncomfortable feelings came up on reading several posters about tolerability profiles and hearing about withdrawal of marketing authorization for the same product. Indeed, IPOPI arranged an ad hoc session for an update on the clinical safety problems of one company.

Since a possible transmission of vCJD either by large quantities of 'non- implicated' plasma or by 'implicated' coagulation factor VIII concentrate was reported, some UK patients receiving plasma products might have a feeling the Sword of Damocles is hanging over them. These patients should note that in a cohort of 44 UK PID patients receiving IVIG for which the plasma was collected between 1997 and 2000 from British donors, no evidence for infection has been found to date.

Four companies booked a satellite symposium over lunch times. Several of the presentations were of outstanding quality and some of the companies even had the strength to withhold allocating time for company presentation in favor of spreading clinical knowledge.

PID and vaccination

Professor Andrew Cant, Oxford, UK, was kind enough to accept IPOPI's invitation for a presentation on "What are the risks of vaccinations for PID patients? Will anti flu vaccinations be recommendable for primary immunodeficiencies?' Prof. Cant first gave a historical overview of development in the field of vaccination. He outlined the various strategies of vaccination. In PID vaccination cannot have a universal role because the difference in the various forms of PIDs – no ability to form specific antibodies or cytotoxic cells. There are only very few controlled studies reported with most data generated in children. The grade of treatment recommendation drawn from these studies remains C (possible effective; 2nd or 3rd line treatment) and in rare cases it might reach recommendation grade B (possibly effective, use as alternative to other therapy options). In general, it is recommended to refrain from the vaccination with (attenuated) live vaccines and this is strictly to be followed for T-cell PID, phagocyte defects, and defects of the innate immune system. Otherwise, if considered as safe, and after having consulted a PID specialist, vaccination may be performed. Thus, dead influenza vaccine is safe, can be applied but may not work well in patients with immunodeficiency.

When patients are receiving immunoglobulin therapy this might already provide protection against selected pathogens (haemophilus, pneumococcus, tetanus, hepatitis B, parvovirus B19 and influenza). Otherwise one has to keep in mind that vaccines are less likely to help because specific antibodies might neutralize the vaccine; however there are also ideas discussed that the immune complexes formed might help efficient immune response. When necessary/reasonable, vaccination should be performed just before IVIG application or at the end of the second, beginning the third week after IVIG. For SCIG there is no reason to schedule a

particular time point. Patients with complement deficiencies usually profit from vaccinations (see below). In any case, 'something' might be better than 'nothing'.

PID patients have always to bear in mind that vaccination might do good to them but they should not count on it. It is advisable to quantify effect of immune response whenever possible in order to have an idea about the level of protection achieved. This might particularly be of value for PID travellers. Prof. Cant recommended IPOPI to think about taking the driving seat in elaboration of a recommendation/guideline for vaccination in PID. Some best practice statement (UK) or patient organization statements (CAN) already exist.

Complement deficiencies – Diagnosis and therapy options

An Educational Workshop “*Complement Disorders: understanding old and new*” was held on the first day of the ESID Meeting 2010. The complement system is a complicated cascade of protein activation events in the blood, similar to the coagulation cascade. The complement system is a mediator of inflammation and also a mediator between the innate and adaptive immune system. Routine screening for complement deficiencies has become relatively easy by the introduction of well standardized ELISA methods available on the market. In general, deficiencies in complement proteins manifest by recurrent, sometimes pyogenic, invasive bacterial infections or single infections with the same germ in various members of the same family/kindred. Another series of complement protein deficiencies is particularly at risk for *Neisseria* infections. The infections resemble those in antibody deficiency syndromes. However, the particular difference to antibody deficiencies is the presence of normal immunoglobulin levels, normal cellular counts and cell functions when assessed with routine methods and, with few exceptions, adequate vaccination response. As far as vaccines are available for corresponding pathogens complement deficient patients should be vaccinated to achieve a certain level of protection. A series of complement protein deficiencies manifest as autoimmune-like diseases and an increased risk for recurrent bacterial infections.

Deficiencies in the following complement proteins were reported at ESID 2010: ficolin-3, properdin, factor D, factor I, factor H, C2 and C1-esterase inhibitor (C1-INH;

see below). On one hand C2 deficiency can manifest by recurrent infections and has been found in >10% of Danish children with recurrent pneumococcal diseases. On the other hand C2 deficiency can manifest as autoimmune-like disease; a case with immune-complex mediated leukocytoclastic vasculitis was efficiently treated by B cell/antibody depletion; on top of an immune deficiency an iatrogenic antibody deficiency was placed – surely a last resort intervention. Complete selective deficiency in ficolin-3 and factor B were reported the first time, in both cases the patient were suffering from severe bacterial infections.

Finally, some complement protein deficiencies might predominantly present with a noninfectious clinical phenotype that may be restricted to single organs, as in the case of a particular form of glomerulonephritis, atypical hemolytic uremic syndrome (atypical = no preceding diarrhea) or age-related macular degeneration. It might be worthwhile mentioning that many complement deficiencies may or may not become manifest and that complement deficiencies are not associated with an elevated risk for viral infections.

When PID is defined as a genetic defect with the presence of recurrent infections or single infections with unusual pathogens, the second most abundant complement deficiency, i.e. deficiency in C1-INH, does not fit into PID: there is no elevated risk for infections. In fact C1-INH deficiency is a defect of the regulation of an innate inflammatory system, the bradykinin generating pathway leading to hereditary angioedema (HAE). Patients with C1-INH deficiency suffer from recurrent, non-allergic, non-itching, non-pruritic, hard swellings of the extremities and severe recurrent colic-like gastrointestinal pain. The most feared manifestation is laryngeal edema leading to acute asphyxiation and eventual death when not treated. C1-INH is one of the very few complement deficiencies for which therapy options exist. One 'Sunrise Education Session' "*Novel insights into hereditary angioedema*" was held in the frame of ESID. In addition IPOPI invited Dr. Hilary Longhurst, London, UK, to update IPOPI members on HAE. In the recent years several randomized controlled trials with different drugs have been published. Plasma-derived C1-INH concentrate is available for replacement therapy. Therapy very much corresponds to application of immunoglobulin concentrates to patients with primary antibody deficiencies. Dr. Longhurst mentioned the registered dose to treat acute HAE attacks is 20 U/kg. However, she also mentioned the importance of early treatment which usually is

efficacious at lower doses. Thus, independent of the drug used, home treatment, because the possibility of treatment in the early phase of attack onset, becomes an interesting alternative for patients and health care finances. Dr. Longhurst also mentioned another way to get the bradykinin-mediated inflammatory process back into balance. In contrast to C1-INH concentrate, which is effective preventing at the initial steps of uncontrolled bradykinin formation, a bradykinin analogue is able to prevent edema formation by efficiently competing for the function of bradykinin. This bradykinin analogue is registered for subcutaneous application and has the potential for application at home. Corresponding studies are missing so far.

Abbreviations

BMT: bone marrow transplantation

C1-INH: C1-esterase inhibitor

ESID: European Society for Immunodeficiencies

FACS: fluorescence-activated cell sorting, a particular form of flow cytometry (for technical details see http://en.wikipedia.org/wiki/Fluorescence-activated_cell_sorting#Fluorescence-activated_cell_sorting)

HAE: hereditary angioedema

HSCT: hematopoietic stem cell transplantation

INGID: International Nursing Group for Immunodeficiencies

IPOPI: International Patient Organization for Primary Immunodeficiencies

iPSCs: induced pluripotent stem cells, as a result of reprogramming somatic cells

PID: primary immunodeficiency

PIDD: primary immunodeficiency disease

SCID: severe combined immunodeficiency

SCT: stem cell transplantation

SJKREC: signal joint kappa chain excision circles

TREC: T-cell receptor excision circles are specific markers of functional T cells