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LETTER TO EDITOR

Fifteen Years of the J Project

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Over the past 15 years, remarkable progress has been made of clinical care, laboratory diagnosis, and in particular, genetics in the field of primary immunodeficiency diseases (PIDs) [1]. This progress resulted mostly from a better understanding of the relationship between genotype and phenotype variability in patients with "normal" immunity and in those with increased susceptibility to infection, inflammatory and autoimmune disorders, allergy, and cancer [2]. The wondrous unraveling of the human genome sequence by virtue of the human genome project from 1991 to 2004, and later on by other international collaborative projects like HapMap, 1000 genome project, and ENCODE, has opened the way to the rapid development of the field [3]. Introduction of new generation sequencing (NGS), whole genome sequencing (WGS), and whole exome sequencing (WES) in 2010 revolutionized the diagnosis and research of PIDs leading to the discovery of hundreds of novel inborn errors of immunity [4]. Progress in basic sciences usually precipitates an increased activity of professional education and emerging of new programs like the J Project ambitious physician education and clinical research collaboration platform focusing primarily on Eastern and Central Europe (ECE) [5].

The Concept of the J Project

The start of the J Project in 2004 curiously coincided with the completion of the human genome project and it was triggered by the genetic characterization of more and more PIDs and PID-causing genes. At that time, not only genetic diagnostics of PID was almost completely lacking in ECE but the number of clinically identified PID patients was also negligible creating a large gap between Western and Eastern Europe in terms of immunodeficiency diagnostics and patient care [6]. It was conceptualized at the beginning that one major focus of the J Project would be the genetics of PID in addition to clinical training and education. The reason for this resided in the recognition that the workflow from understanding the genetic basis of the disease towards making a clinical decision is less troubled whereas clinical knowledge alone may not be sufficient to understand the molecular mechanisms of these complex disorders. Medical education is unexciting and unstimulating when it is focused only on phenomenology and symptomatology. However, it becomes a challenging intellectual activity if it undertakes the transfer of advanced knowledge and mechanisms of diseases. The latter which we may refer to as future-oriented medical education should be based on recent research data relevant to understanding the genetic dimensions of PID in addition to clinical, cellular, and biochemical aspects.

At the turn of the millennium, most ECE countries were just waking from the depression of the communistic era and were looking for the best way to survive economically, politically, and culturally. Due to geographic and economic linkages, some countries remained in reasonable connection with Russia, whereas others, like the Baltic countries and Central and Southern European countries, were turning away from their past. Looking back to the past 15 years, we realize that despite unfavorable circumstances, we did find the way to form a strong professional community with remarkable achievements in the field. It is tempting to believe that we found at the beginning the best connection that brought us together and has kept us in a professional community since

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Dedicated to the memory of Jeffrey Modell who suffered from primary immunodeficiency disease and died at age 15. By his disease history and unique vision, Jeffrey inspired and motivated the immunology community to fight against immunodeficiency diseases and their formidable infectious complications and to make a better life on earth for children with primary immunodeficiency.

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then: the recognition that in the PID field we were very much behind. As responsible physicians, we were determined to try to close the gap in PID patient management that was obviously increasing between the two parts of Europe.

At an important international PID meeting held in Debrecen in 2002, opinion leaders from ECE and outstanding clinician scientists from Western Europe, the USA and Israel, and the Jeffrey Modell Foundation (JMF) were recruited for a brainstorming discussion on the current state and future challenges of PID care in ECE. At this meeting, we came to the conclusion that physician education in ECE countries should be carried out by organizing on-site meetings in different countries and regions rather than establishing schools at stationary venues. After 2 years of preparation and planning, we set out for the J Project tour and with a start in Targu Mures, Romania, we organized 8 successful meetings in line over a period of 1 year [7]. It was also defined at the beginning that we would not make any effort to forcefully export our program and concept. Actually, it was not necessary as the J Project started to spread spontaneously as a result of the devotion of local opinion leaders and ambitious colleagues.

J Project Laboratories

In order to teach genetics of PID in an authentic manner, we had to do molecular evaluation ourselves. It was not realistic to develop several genetic laboratories at the same time but at least one J Project Lab had to be established at the beginning. One of the most important contributions of the Debrecen PID group to the successful start and running of the J Project was the introduction of Sanger sequencing for analysis of PID genes and offering this service to PID centers in emerging J Project countries in 2004. We may proudly say that we had never refused any sample sent to us until 2015 when the Lab was closed. We established the analysis of more than 60 PID genes and performed more than 1200 targeted gene sequencing. The order of established gene sequencing protocols followed the order of patients' samples sent to our Lab. Identifying disease-causing sequence variants, confirmation of the pathologic role of the mutation by functional studies, family screening, and phenotype-genotype analysis provided excellent topics for discussions at subsequent JP meetings.

We also established protein chemistry and flow cytometry labs which were crucial to make the diagnosis of PIDs by detecting cell surface receptors or intracellular proteins and studying the functional effect of mutations like phosphorylation and hyper-phosphorylation [8, 9]. Analysis of a large number of genetically identified PID patients resulted in publications of several joint research papers in reasonable international journals.

To promote the development of genetic labs in ECE PID centers, we started training programs in 2013 which we called the J2 Project focusing on Sanger sequencing. We hosted young colleagues from Croatia, Romania, Russia, and elsewhere who brought samples from their centers and analyzed them in the Debrecen Lab under our supervision from DNA isolation to the evaluation of sequences in the dry lab. In 2015, we were ready to start the J3 Project aimed at establishing WES to further develop PID diagnostics and research in Debrecen when our Lab and the PID center were closed.

With the generous help of JL Casanova who offered the facility of his lab at the Rockefeller University, we could start WES analysis of more than 100 DNA samples that were submitted from ECE countries to us between 2015 and 2017. In the meantime, more and more ECE PID centers started to establish themselves for Sanger sequencing and WES and some of them, like the Lab in Minsk, offered sequencing help to patients in other countries. These developments were crucial to keep the J Project community together and to run the Project further with the help of the Semmelweis University in Budapest.

The J Project Education Campaign

The number of countries entering the J Project has steadily been increased and the Project now covers the whole area of ECE. During the first 5 years, 5 or 6 meetings were organized yearly, reflecting the limited territory covered (Fig. 1). In 2009, a rapid increase of the number of the J Project meetings resulted from the remarkable increase of the J Project area by association of projects like the J Daughters Siberia project in the Urals. The number of meetings remained constantly above 13 per year from 2011 (Fig. 1). The "J Project fever" resulted in a record number of meetings in 2012 and another record was achieved in 2018 (Fig. 1). The collaborative research, joint publications, and the JP congresses organized in Antalya in 2014 (42 participant countries) and 2016 (29 participant countries) all contributed to the year by year increase of the meetings.

Various patterns of meeting schedules were recognized in different countries. In Poland, 5 of the 11 meetings were organized in Warsaw and another 5 in the Cracow area (Fig. 2a). This schedule might suggest a polarized PID patient care in the country. However, the traditionally strong PID group in Warsaw assures a countrywide availability of diagnosis and treatment of PID patients. In Ukraine, the 14 J Project meetings were conceptually organized by L Chernishova and L Kostyuchenko in centers of various regions (oblasts) which hopefully will cover the whole country (Fig. 2b). Over the years, Ukraine has been one of the most consistent and

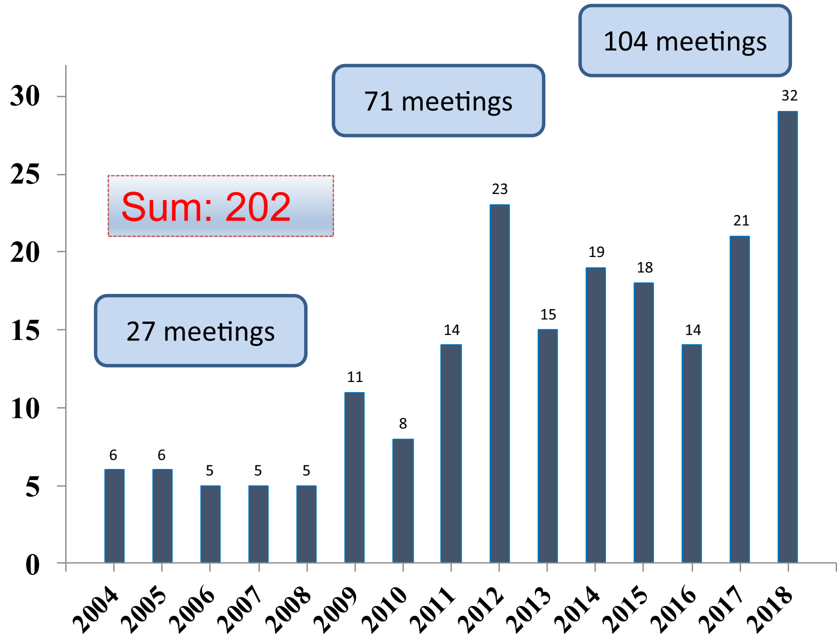

Fig. 1 The yearly number of J Project meetings until the end or 2018. Increases in the number of J meetings during 5-year periods are indicated above the respective columns

collaborative countries in the J Project and the meetings organized by the Kiev group attracted hundreds of clinicians. In Russia, 19 of the 26 J Project meetings were organized by the Urals group (12 meetings), and the St. Petersburg group (7 meetings). Considering the large area and population of Russia, the development of J Project centers in the rest of the country is demanding (Fig. 2c). This requires the joint effort of currently existing centers, especially those located in Moscow whether or not they identify themselves as J Project centers. It is critically important to define how many patients in the country may be reached better. A novel and successful approach seems to be the video conference initiated by colleagues in Moscow and Vladivostok to increase awareness on PID in Far-East Russia. A further, unique schedule of PID meeting organization was introduced as the East Anatolia J Daughter Project (Fig. 2d). Eastern Turkey is less developed in terms of health care level compared with the Western part of the country. Thus, an ambitious project was initiated in 2012 to close the gap and establish immunology centers similar to those in Western Turkey (Fig. 2d). To this end, a systematic approach similar to that in Ukraine was used to target more and more area of Anatolia. Konya, one of the leading PID centers in Turkey, and the neighboring Antalya where two J Project Congresses were also organized, hosted 9 of the 21 J Project meetings. Importantly, J Project meetings were also organized in the Western part of the country. Figure 2 d shows pediatric and adult immunology centers pointing to the striking difference between the two-half of the country in terms of immunology patient care. It can be expected that J Project meetings in Anatolia will improve PID care and treatment by establishing new PID centers for both children and adults.

Partnership with Sister Organizations

Close professional partnership with the European Society for Immunodeficiencies (ESID) was established from the beginning. Importantly, in 2006, the ESID Meeting was first organized in an ECE country (Budapest, Hungary) and we made it possible for more than 60 colleagues from ECE to attend the meeting by offering travel grants. A J Project session was included in the program allowing an introduction to the community of preliminary results of the J Project. Later on, in 2012, another ESID congress was organized in Prague, Czech Republic. The ESID PID in Development Working Party (WP) established in 2006 in Budapest was aimed at improving patient care in areas and regions with a low number of registered PID patients in Western European Countries. This WP was chaired by L Maródi (2006–2010) followed by A Sediva (2010–2014) and P Jandus (2014–2018). Young colleagues from ECE countries have been regular participants at ESID summer schools in addition to the traditional ECE Spring Prague meetings in Prague, and the ECE Winter School in Warsaw.

Partnership with the North American Clinical Immunology Society (CIS) is also relevant to the J Project. An important linkage with CIS has been the "Membership Committee" membership by L Maródi from 2014 to 2018 followed by I Reisli from 2018. To discuss various possibilities of collaboration, a separate J Project—CIS panel discussion was organized during the 2016 J Project Congress in Antalya attended by S Rosenzweig from CIS.

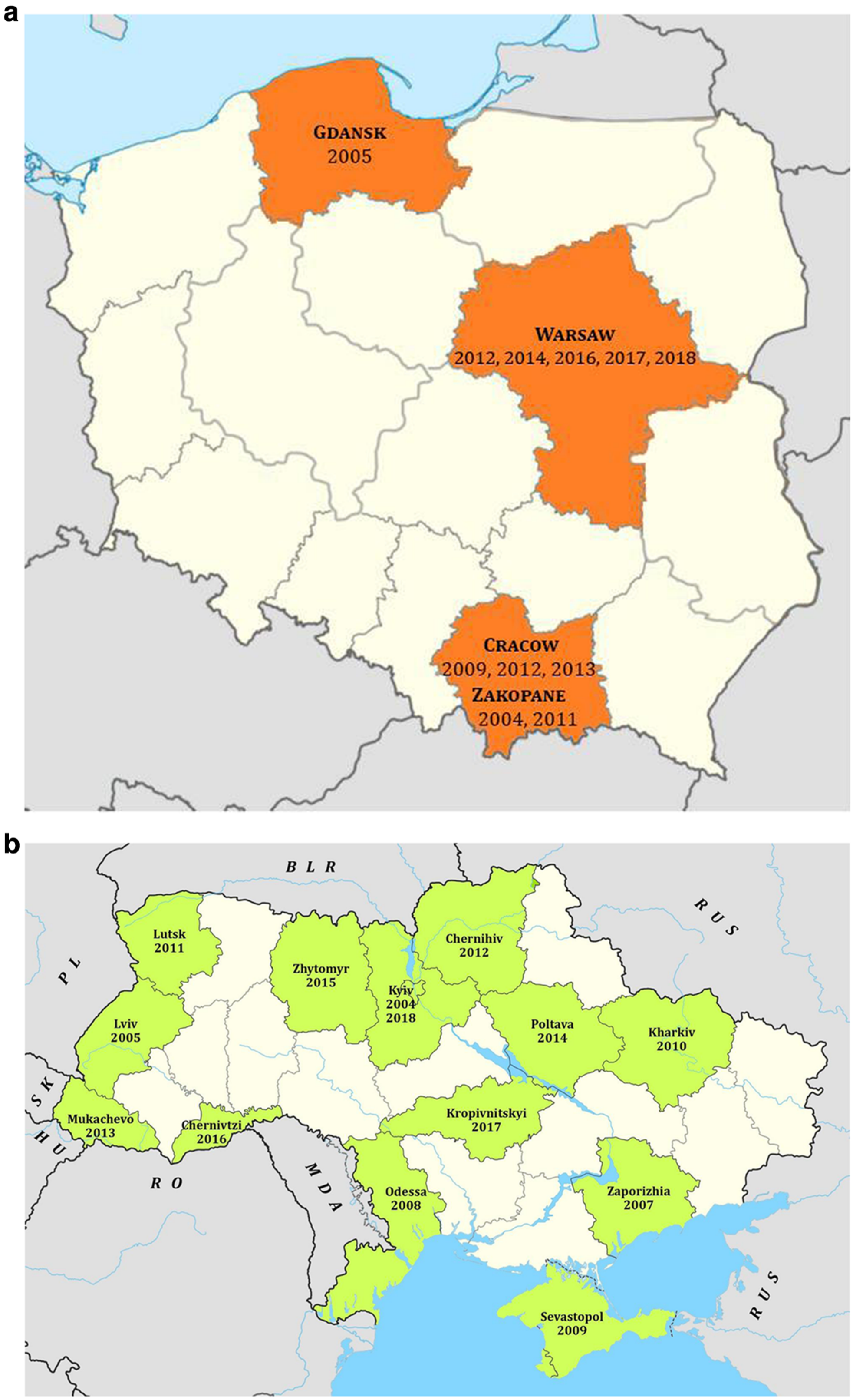

Fig. 2 Various meeting schedules are shown in Poland (**a**) and Ukraine (**b**). The 11 J Project meetings in Poland were organized mostly in the Warsaw and Cracow area whereas the 14 meetings in Ukraine were and continue to be organized in various regions (oblasts). J Project meetings organized by the Yekaterinburg group in Urals, Russia, and part of Central Asia are shown (**c**). JP meetings organized in Eastern Anatolia (EA) and other regions of Turkey are indicated with the J Project Logo (**d**). The numbers of pediatric and adult immunology centers in the country are shown in red and blue, respectively

Fig. 2 (continued)

The contribution of the JMF to PID care can hardly be overestimated. The global approach of this foundation running various programs like the World Immunodeficiency Network, World PID week (WPIW), research projects, promotion of JMF centers, and organization of research meetings are just a few to mention. The JMF support to the Debrecen PID center was indispensable to establish molecular testing and running the J Project. The recently implemented JMF-Octapharma center project in Central Europe provided remarkable support to advanced and developing PID centers. The new project started in 2011 in Central Europe is coordinated by the Advisory Board which has been chaired by L. Maródi (2011–2014), T Avcin (2014–2017), and by A Sediva (2017-).

The Foundation for Children with Immunodeficiency (FCI) established in 1991 in Debrecen provided enormous support to the J Project since the beginning. In 2016, the JP Steering Committee approved that FCI should be the primary coordinator of the J Project. This Foundation provided outstanding support and helped to perform WES analysis of patients' samples from ECE at the St. Giles Laboratory of Human Genetics of Infectious Diseases of the Rockefeller University and the Necker Hospital, Paris.

In 2012, the JP has become one of the societies that partnered with the Central European Journal of Immunology and delegated T Avcin, E Bernatowska, P Ciznar, J Litzman, and L Maródi as editorial board members. In 2013, the JP was affiliated by The Journal of

Clinical Immunology (JoCI), and L Maródi served from 2013 to 2017 as associated editor of the journal. Importantly, JoCI has become over the past years the leading PID journal providing the most up to date clinical and research information in this rapidly evolving field of medicine.

The partnership with national professional societies has also been established in many JP countries. Most of the active JP members are those who are also members of PID working groups of such societies and organize JP meetings as part of the annual events of the national societies.

Future Perspectives

It is critically important that the existing diagnostic and treatment problems are managed, at least in part, as a result of the J Project and in particular, the JP meetings in the given region or country. The number of diagnosed and treated PID patients should reflect the impact of the JP meetings.

A stronger collaboration between JP countries in the field of molecular testing is highly needed. The majority of JP countries are still hanging on centers in Western Europe and the USA for WES or WGS analysis or even Sanger sequencing. This should be changed by investment in developing new molecular genetic labs and active grant application for running the existing laboratories. PID centers may be able to purchase instruments and equip their labs but may encounter difficulties in running them or hiring adequately trained experts in bioinformatics and establish wet lab background to validate NGS data.

It was clear from the beginning that the development of PID patient care would be unequal in various JP Countries because of differences in socio-economic conditions and financial resources of health care. In the JP member countries, the prevalence of PID in the general population varies remarkably. This implies that the target of the J Project programs in different countries should also be different. The challenges are still enormous despite our efforts over the past decade. Cessation of intravenous immunoglobulin (IVIG) treatment between 2016 and 2018 in Romania, an EU member country, intramuscular immunoglobulin replacement as a general practice in adult X-linked agammaglobulinemia patients in Moldova because they registered IVIG and subcutaneous immunoglobulin preparations only in 2018, no diagnosed PID patients in Uzbekistan with a population of more than 32 million, as well as in some other Central Asian countries, or the demolition of the PID center and Genetics Laboratory in Debrecen are just a few negative examples. The increasing difficulties our colleagues are facing in diagnosis and treatment of PID patients in Bosnia and Herzegovina, North Macedonia, Rep. of Moldova, Kosovo, and elsewhere add to the ongoing responsibility of the J Project to help to manage or at least ameliorate these problems. New and targeted programs and approaches by the J Project are needed in these countries to increase awareness and establish PID diagnostic centers and treatment. In parallel, advanced programs should be implemented to promote PID care in more developed countries in Central Europe like Slovenia, Czech Republic, Slovenia, and Poland. Ongoing research projects should be carried on and novel research projects should be started.

A new European Reference Network (ERN) program on Rare Immunodeficiency, Autoinflammatory, and Autoimmune diseases (RITA) was launched recently by the European Union (EU) to improve collaboration between disease centers and exchange knowledge in the field of inflammatory and autoimmune/rheumatic diseases and immunodeficiencies. In general, the ERN-RITA project is promising and suggests the commitment of the EU to ensure uniform access to diagnosis and treatment of patients with PIDs in Eastern and Western Europe. Importantly, this concept is in full agreement with the Antalya Declaration approved at our J Project Congress in 2014 (www.jprojectnetwork.com).

Conclusion

The J Project is based on the vision that Eastern and Western Europe should be an undivided continent in terms of PID patient care. The project has achieved remarkable successes over the past 15 years. However, important obstacles, e.g., inattention to PID patients in a number of J Project countries and J Daughter Countries, late diagnosis and lack of adequate treatment like immunoglobulin replacement therapy, PID newborn screening, and hematopoietic stem cell transplantation are still existing and the final solution to these problems remains to be demonstrated. It seems thus that the J Project should further search for complex programs until “all PID patients receive personalized immunoglobulin replacement and hematopoietic stem cell transplantation and it should not be restricted by funding or infrastructure constraints” as it stands in the 2014 Antalya Declaration. Such programs should incorporate awareness, physician education, and improved genetic diagnostics of inborn errors of immunity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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