ImmunoRio2007

Profile

Marie-Paule Lefranc

Place of birth: Oignies, France
Scientific training (places): MS Natural Sciences: Lille University; Doct. Pharmaceutical Sciences: Paris11 University; PhD: Montpellier 2 University, France; Part of PhD and Post-Doc at the MRC, Center of Cambridge, UK.
Former supervisors: Gérard LEFRANC; Terry RABBITTS
Current areas of research: Immunogenetics and Immunoinformatics
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Laboratory: how many students and post-docs: 4 students (2 graduate and 2 PhD); 1 post-doc; 10 permanent researchers.
Laboratory: available techniques: immunoinformatics: IMGT databases and tools for immunoglobulin, T cell receptor, MHC, IgSF and MhcSF sequences, gene and 3D structure analysis, design of humanized antibodies .
Talk at ImmunoRio2007: (Title of talk) MHC, what do we learn from IMGT Colliers de Perles?
When and how can you be reached at the meeting: August 21-22

A Word with the Speaker: Marie-Paule Lefranc

- ImmunoRio2007: What were your greatest motivations to enter your current area of research?
- Speaker: My great motivations for Immunogenetics start with the following story: In the human immunoglobulin (IG) system, there are five classes (IgA, IgD, IgE, IgG and IgM) and four IgG and two IgA subclasses, responsible for the humoral immunity. They are present in all people and, therefore, are regarded as essential for the health. In 1982, surprisingly, we unambiguously demonstrated the simultaneous absence of the IgG1, IgG2, IgG4 and IgA1 subclasses in a healthy woman, 75-year-old. Only IgM, IgD, IgG3, IgA2 and IgE were present. The lack of the IgG1 and IgG2 subclasses, quantitatively the most important, without excessive susceptibility to infections, was totally unexpected. Two major problems were raised from these results: first, the humoral defense without IgG1, IgG2, IgG4 and IgA1 immunoglobulins; second, the genetic event responsible for the simultaneous absence of these four subclasses. The fact that this woman did not exhibit any pathological symptoms, suggested that the lack of the IgG1, IgG2 and IgG4, on the one hand, and that of IgA1, on the other hand, were counterbalanced by the IgG3 (biologically similar to the IgG1 and significantly increased in this woman) and IgA2 subclasses, respectively. Molecular analysis revealed that she was homozygous for an extensive DNA deletion including the G1, G2, G4 and A1 functional genes, coding the constant region of the corresponding IG heavy chains (Nature 1982). This exceptional autozygous genotype was due to the consanguinity, frequent marriages occurring between cousins, just as this was the case with the parents of this woman and some of her children who married their cousins: thus, two healthy grandsons of the 75-year-old woman were also autozygous for the same deletion. An identical deletion, also at the homozygous state, was found in three healthy individuals belonging to a second consanguineous family. These results were the first demonstration of different multigene deletions in the human IG system (Mol. Biol. Med. 1983).

The deletion also has given information on the ordering of the IGHC genes. When the deletion of the G1, G2, G4 and A1 functional genes was described, two groups of cosmid clones had just been identified in Terry Rabbitts' lab, the first one encompassing the G3-G1-EP1-A1 genes, the second one the G2-G4-E-A2 genes.

The pattern of the deletion enabled us to predict the order of the genes with G3-G1-EP1-A1 in 5' of G2-G4-E-A2 (Nature 1982). Moreover, the absence of IgA and IgG subclass(es) allowed us to study the generation of the antibody repertoire as well as the **s** ubclass distribution and restriction pattern of antigen-specific antibodies in normal donors and in individuals lacking either of the IgA and IgG subclass(es). The absence of IgE was also demonstrated in a consanguineous healthy man, homozygous for another deletion (Hum. Genet. 1994).
This research has been the incentive of all my work on the molecular genetics of the IG since 1981, on the molecular genetics of the T cell receptor (TR) since 1984, on antibody engineering since 1985, and on bioinformatics since 1989. The milestones were the complete characterization of the human TR gamma (TRG) locus (Nature 1985, 1986, Cell 1986) and the mapping of the human IG lambda (IGL) locus (Hum. Mol. Genet. 1995). Then, my activity has been primarily devoted to the development of **IMGT®, the international ImMunoGeneTics information system®** (http://imgt.cines.fr), the global reference in Immunogenetics and Immunoinformatics, that I created at Montpellier in 1989 (Montpellier 2 University and CNRS).

- ImmunoRio2007: In your opinion, which were the breakthroughs in this area of research in the last years?
- Speaker: The extremely diverse repertoires of antigen receptors in the vertebrate adaptive responses (10^{12} IG or antibodies, and 10^{12} different TR per individual, in humans) result from complex rearrangements at the DNA level followed by somatic hypermutations of IG. A considerable polymorphism exists also for the MHC which presents antigens to T lymphocytes. IMGT®, the international ImMunoGeneTics information system® (http://imgt.cines.fr), is the first and the only integrated information system specialized in the sequences, structures and genetic data of IG, TR and MHC. IMGT® is also specialized in the proteins of the IgSF and MhcSF superfamilies, and in the related proteins of the immune system (RPI). The accuracy and the consistency of the IMGT® data, as well as the coherence between the different IMGT® components (databases, tools and Web resources), are based on IMGT-ONTOLOGY, the first ontology for immunogenetics and immunoinformatics.

- ImmunoRio2007: What do you consider to be a particularly relevant or challenging question to be answered in this area of research?
- Speaker: To develop a systemic approach that could help to detect, to monitor and to prevent or to treat infections (AIDS, tuberculosis, etc.) and diseases (asthme, allergy, leukemias, cancer, etc).

- ImmunoRio2007: What do you regard to be a particularly challenging question to be answered in Immunology?

- Speaker: To understand the complexity, the dynamic organization and the quality-control of the adaptive and innate immune responses, finely-tuned between autoimmune diseases and efficiency to fight infections and tumours.

- ImmunoRio2007: In your opinion, what is an important scientific contribution that you and your group have made? And why?

- Speaker: To have created IMGT®, the international ImMunoGeneTics information system® (http://imgt.cines.fr) and have made it the global reference in immunogenetics and immunoinformatics (NAR 2005). An important step was the first demonstration on-line of the nucleotide database IMGT/LIGM-DB at the 9th ICI in 1995, in San Francico. The second major step was the approval, in 1999, of the IMGT human IG and TR genes by the Human Genome Organisation (HUGO) Nomenclature Committe (HGNC) and their entry in LocusLink and Entrez Gene at the National Center for Biotechnology Information (NCBI) and in IMGT/GENE-DB. Two FactBooks on the human IG and TR genes and alleles were published in 2001. Another major contribution has been the setting up of a IMGT unique numbering for the V-DOMAIN and the C-DOMAIN of the IG and TR, and for the G-DOMAIN of the MHC. The corresponding graphical representations or IMGT Colliers de Perles bridge the gaps between sequences and 3D structures. They have been extended to the V-like, C-like and G-like domains of the IgSF and MhcSF.

- ImmunoRio2007: Do you think your results have the potential to be translated into some clinical application? Tell us how and if you think this could be achieved in the near future.

- Speaker: IMGT® is already widely used by clinicians and biological scientists from both academic and industrial laboratories, in diverse research domains: (i) fundamental and medical research (repertoire analysis of the IG antibody sites and of the TR recognition sites in normal and pathological situations such as autoimmune diseases, infectious diseases, AIDS, leukemias, lymphomas, myelomas), (ii) veterinary research (IG and TR repertoires in farm and wild life species), (iii) genome diversity and genome evolution studies of the adaptive responses, (iv) structural evolution of the IgSF and MhcSF proteins, (v) biotechnology related to antibody engineering (single chain Fragment variable (scFv), phage displays, combinatorial libraries, chimeric, humanized and human antibodies), (vi) diagnostics (clonalities, detection and follow up of residual diseases) and (vii) therapeutical approaches (grafts, immunotherapy, vaccinology).

- ImmunoRio2007: Can you share with us the memory of a special moment of scientific discovery in your life?

Speaker: IMGT Collier de Perles confirmed by 3D structures.

PING-PONG

- Two of your most important papers:
1) Lefranc, M.-P., Forster, A., Baer, R., Stinson, M.A. and Rabbitts, T.H. Diversity and rearrangement of the human T cell rearranging gamma genes : Nine germ-line variable genes belonging to two subgroups. Cell, 45, 237-246 (1986). PMID: 2938743

2) Lefranc, M.-P., Giudicelli, V., Kaas, Q., Duprat, E., Jabado-Michaloud, J., Scaviner, D., Ginestoux, C., Clément, O., Chaume, D., Lefranc, G. IMGT, the international ImMunoGeneTics information system®. Nucl. Acids Res., 33, D593-D597 (2005). PMID: 15608269

- **Most relevant messages from these papers:**
The Cell 1986 paper provides the first complete description of the functional T cell receptor gamma V genes in human.
The NAR 2005 paper provides a description of the IMGT®, the international ImMunoGeneTics information system® (http://imgt.cines.fr), databases, tools and Web resources. The IMGT Web server at Montpellier receives more than 150,000 requests per month, from Europe, the USA and the rest of the world.

- What would you like to accomplish along your line of research?
To further develop intereactions between the IMGT databases, tools and Web resources, based on the IMGT-ONTOLOGY, and keep IMGT at the forefront of the immunogenetics and immunoinformatics research.

- **A message or advice to students and young scientists coming to the meeting:**
Ask the right biological question, be curious and motivated.

Brief CV - Marie-Paule Lefranc

Marie-Paule Lefranc was born in North of France on March 6, 1943. She married Gérard Lefranc in 1968 and they have five children. She received a Doctorate in Pharmaceutical Sciences at the Paris University, and a PhD in Biochemistry, Molecular Biology and Genetics at the Montpellier University. She taught from 1968 to 1976 at Beirut, Lebanon, and from 1976 to 1982 at the Monastir University, Tunisia where she contributed to the creation of the Biochemistry Department. She spent one year as EMBO fellow at the Medical Research Council in Dr. Terry Rabbitts's laboratory. She is Professor at the Montpellier 2 University, Member of the Institut Universitaire de France, and Head of the Laboratoire d'ImmunoGénétique Moléculaire (LIGM) that she created with Gérard Lefranc, in 1982 at Montpellier, lab. now located within the

Institute of Human Genetics, UPR CNRS 1142. She has authored over 250 scientific publications in international journals on the molecular immunogenetics of immunoglobulins (IG), T cell receptors, antibody engineering, and in human genetics and immunoinformatics. Two of her major contributions are, firstly, the finding of large chromosomal deletions including several IG genes accounting for the simultaneous absence of certain isotypes in healthy individuals and allowing the overall ordering of the human IGHC genes and, secondly, the full characterization of the human T cell receptor gamma locus. She received the ROSEN prize of Cancerology in 1988. She is director of IMGT®, the international ImMunoGeneTics information system®, http://imgt.cines.fr, that she founded in 1989, at Montpellier, France and which is the global reference in immunogenetics and immunoinformatics.

Publications – Last 3 years- Marie-Paule Lefranc

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2. Pelat, T., Hust, M., Laffly, E., Condemine, F., Bottex, C., Vidal, D., Lefranc, M.-P., Dubel, S. and Thullier, P. "A high affinity, human-like antibody fragment (scFv) neutralising the lethal factor (LF) of Bacillus anthracis by inhibiting PA-LF complex formation" Antimicrob Agents Chemother., May 21 (2007)

3. Garapati, V.P., Lefranc, M.-P. "IMGT Colliers de Perles and IgSF domain standardization for T cell costimulatory activatory (CD28, ICOS) and inhibitory (CTLA4, PDCD1 and BTLA) receptors" Dev. Comp. Immunol., Mar 5 (2007)

4. Kaas, Q. and Lefranc, M.-P. "IMGT Colliers de Perles: standardized sequence-structure representations of the IgSF and MhcSF superfamily domains" Current Bioinformatics, 2, 21-30 (2007).

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T cell receptor gamma TRG loci and localization of the TRGC5 cassette" Vet. Immunol. Immunopathol. 2006, Oct 26;

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