IMGT®, the international ImMunoGeneTics information system®
Laboratoire d'ImmunoGénétique Moléculaire
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1. Research themes

Our researches concern immunoinformatics and rare human genetic diseases.

1) **IMGT®, the international ImMunoGeneTics information system®** http://imgt.cines.fr that we created in 1989 (University Montpellier 2 and CNRS). IMGT®:
- is the international reference in immunogenetics and immunoinformatics.
- is a CNRS registered trademark (France, EC, Canada, USA).
- is a high-quality integrated knowledge resource, specialized in the immunoglobulins (IG), T cell receptors (TR) and major histocompatibility complex (MHC) of human and other vertebrate species, immunoglobulin superfamily (IgSF) and MHC superfamily (MhcSF) proteins, and in related proteins of the immune system.
- provides a common access to expertly annotated nucleotide and protein sequences, genetic, genomic and structural information.
- includes six databases (IMGT/LIGM-DB, IMGT/GENE-DB, IMGT/3Dstructure-DB, etc.), Web resources which consist of 10,000 HTML pages, and fifteen interactive on-line tools (IMGT/V-QUEST, IMGT/JunctionAnalysis, etc.).
- is used by academic and industrial scientists in fundamental research, medical research (autoimmune and infectious diseases, AIDS, leukaemias, lymphomas, myelomas), veterinary research, genomics (genome diversity and evolution of the adaptive immune system), biotechnology related to antibody engineering, diagnostics (detection of minimal residual diseases) and therapeutical approaches (grafts, immunotherapy, vaccinology).
- is accessed by more than 80,000 sites a year with an exceptional response of more than 150,000 requests per month, the users being divided equally between Europe, the United States and the rest of the world.
- has contracts with CENTOCOR Johnson and Johnson (USA), MERCK (USA), AMGEN (USA), SANOFI-AVENTIS (Germany).

2) **rare human genetic diseases** in consanguineous Lebanese families, in collaboration with the Unit of Medical Genetics (Pr André Mégarbané), St-Joseph University, Beirut (Lebanon). Very rare autosomal recessive diseases, almost unknown in panmictic populations, are found in consanguineous families. In addition to a problem of public health, they are invaluable starting points for the fundamental research allowing to identify still unknown genes, their products and functions as well as unsuspected links to cell physiology. We are studying:
- Immunodeficiency, Centromeric region instability and Facial anomalies (ICF) syndrome that results from mutations of the DNA methyltransferase 3B (DNMT3B) for most cases (type 1) or of another unidentified methyltransferase (type 2).
- **Hyper-IgE syndromes (HIES)**, immunodeficiencies with recurrent staphylococcal abscesses and elevated IgE levels. Autosomal recessive HIES is due to mutations of the tyrosine kinase 2 (TYK2). Sporadic and autosomal dominant HIES encompass also connective tissue, skeleton and dental development. Mutations in the DNA

binding domain or in the SH2 domain of STAT3 are responsible for these clinical features in our patients.
- **Adaptive and innate immunodeficiencies** for which genes are not yet identified.
- Recessive infantile Osteopetrosis, a bone disease, with neural involvement for the most severe form, due to mutations of either of the TCIRG1 (Atp6a3), CLCN7 or OSTM1 (grey lethal) genes.
- Hepatic veno-occlusive disease with immunodeficiency (VODI) syndrome. Due to a premature stop codon, the Sp110 Speckled protein (a 110 kDa protein normally associated with the PML nuclear bodies and expressed in the immune system and liver cells) is truncated and lacks the C-terminal region including the LXXLL nuclear hormone receptor binding motif.

Moreover, the genome evolution (Alu sequences, mtDNA, Y chromosome) on the pathways of human expansion out of Africa is also analysed in the Tunisian and Lebanese populations. Markers of positive selection or, in contrast, of susceptibility towards infectious diseases (malaria…) are searched for in consanguineous families.

2. Publications

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- Giudicelli V., Chaume D. and Lefranc M.-P. IMGT/GENE-DB: a comprehensive database for human and mouse immunoglobulin and T cell receptor genes. **Nucl. Acids Res.** 33, D256-D261 (2005).
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antibodies approved for cancer treatment. **Critical reviews in Oncology and Hematology**, 64, 210-225 (2007).
- 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**. 31, 1050-1072 (2007).
- Lefranc M.-P. WHO-IUIS Nomenclature Subcommittee for Immunoglobulins and T cell receptors report. **Immunogenetics** 59, 899-902 (2007).
- Kaas Q., Ehrenmann F. and Lefranc M.-P. IG, TR and IgSf, MHC and MhcSF: what do we learn from the IMGT Colliers de Perles? **Briefings in Functional Genomics and Proteomics** (in press, 2008)
- Benayoun B., Baghdiguian S., Lajmanovich A., Bartoli M., Daniele N., Gicquel E., Bourg N., Raynaud F., Pasquier M.-A., Suel L., Lochmuller H., Lefranc G. and Richard I. NF-kB dependent expression of the antiapoptotic factor c-FLIP is regulated by calpain 3, the protein involved in limb-girdle muscular dystrophy type 2A. **FASEB J.** 2007 Dec11. Epub ahead of print (2008).

3. Keywords

IMGT, immunogenetics, immunoinformatics, bioinformatics, human genetics, rare genetic diseases, consanguinity, antibody engineering, T cell receptor, MHC

4. Main scientific collaborations

4.1 Collaborations with academic institutions

- National

Centre de Biochimie Structurale, UMR 5048, Montpellier (three-dimensional structures).
Laboratoire d'Informatique, de Robotique et de Microélectronique LIRMM, UMR 5506, Montpellier (IMGT-Choreography, IMGT/JunctionAnalysis).
Département de Mathématiques, Université de Montpellier 2 (statistical analysis of antigen receptors).
Centre de Reherche du Service de Santé des Armées (anti-*Bacillus anthracis* antibodies).
Techniques de l'Imagerie, de la Modélisation et de la Cognition, UMR 5525, Grenoble (IMGT/GeneInfo).
Unité de Virologie et Immunologie Moléculaire - Institut National de la recherche, Jouy-en-Josas (IgSF, MHC).
Immuno-Pharmaco-Génétique des anticorps thérapeutiques, Université François Rabelais, CHRU de Tours, Tours (therapeutical antibodies).

- International

European Bioinformatics Institute (EBI).
National Center for Biotechnology Information (NCBI).
Unit of Medical Genetics, University Saint-Joseph, Beirut, Lebanon.

Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, MA,USA.
Faculty of Medicine, Sousse, and Faculty of Pharmacy, Monastir, Tunisia.
University of Victoria, Centre for Biomedical Research, Victoria, BC, Canada.
Department of Microbiology and Immunology, Chicago, Illinois, USA.

4.2 Collaborations with pharmaceutical companies

- National companies
  - Institut de Recherche Pierre Fabre, Centre d'Immunologie Pierre Fabre CIPF, Saint-Julien en Genevois (Therapeutical antibodies, antibody humanization) (contract).
  - Laboratoire Français du fractionnement et des biotechnologies LFB, Les Ulis (antibody humanization) (contract).
  - OPI S.A., division d'EUSA Pharma, Dardilly, Lyon (contract).

- Internationales companies
  - AMGEN Seattle, WA, USA (Antibody engineering - antibody humanization) (contract).
  - CENTOCOR Johnson and Johnson, Malvern, Philadelphia, USA (Antibody engineering - antibody humanization) (licence and contract).
  - MERCK, WhiteHouse Station, New Jersey, USA (Antibody engineering - antibody humanization) (licence and contract).
  - SANOFI-AVENTIS, Germany (Antibody sequences and IMGT/LIGM-DB) (contract).

5. Affiliations

5.1 UPR CNRS 1142, Institut de Génétique Humaine (IGH)
IFR3 "Communications cellulaires normales et pathologiques".

5.2 Programmes Internationaux de Coopération Scientifique (PICS) between the French and Lebanese CNRS:
- 2001-2003 : « Déficits immunitaires génétiques au Liban ».
- 2005-2007 : « Syndromes ICF et Hyper IgE et déficits immunitaires génétiques au Liban ».

5.3 International IMGT® projects and labels

- International reference in immunogenetics and immunoinformatics.
- Antibody Society reference for the molecular standards.
- World Health Organization-International Union of the Immunological Societies (WHO-IUIS) Nomenclature Subcommittee for the immunoglobulins and T cell receptors.

- Partner via ReNaBi to the European Life sciences Infrastructure for Biological Information (ELIXIR) project.
- Institutional member of the International Medical Informatics Association (IMIA) since 2006.
- CNRS registered mark (France, European Community, Canada, USA).
- Referenced by the National Center for Biotechnology Information (NCBI) USA, in Entrez Gene.
- Partner of the ImmunoGrid (FP6-2004-IST-4) STREPS "The European Virtual Human Immune System Project" (6th EC Framework Programme).

5.4 National IMGT® projects and labels

- Bioinformatics national research platform (RIO platform) (INSERM, CNRS, CEA and INRA), since RIO creation in 2001.
- Member of the National network of Bioinformatics Platforms (ReNaBi).
- Member of the GIS "Infrastructures en Biologie Santé et Agronomie (IBiSA), Coordination des plates-formes de recherches en sciences du vivant", since the GIS creation in 2007.
- Member of the GDR Molecular Bioinformatics (BiM).

5.5 Regional IMGT® projects and labels

- "Grand Plateau Technique pour la Recherche Région (GPTR) Languedoc-Roussillon", since 2005.
- "Plan Pluri-formation" University Montpellier 2 since 1999.
- Member of the GIS Genopole Montpellier Languedoc-Roussillon.
- Bioinformatics Platform of the IFR3 "Communications cellulaires normales et pathologiques".
- Bioinformatics Platform of the "Cancéropôle Grand Sud-Ouest" (GSO).