Department of Allergy and Clinical Immunology
Lyon University Hospital Center

2018 Activity Report

Contents

Highlights 2017-2018

- Creation of a post-graduate degree (DES) in allergology; the department welcomes its first residents in November.
- European certification as an "allergology training center" by the European Union of Medical Specialists (UEMS).
- ADCare (under the aegis of the European Academy of Allergy and Clinical Immunology (EAACI)) certification as a center of reference and excellence.

1. Department presentation

We are happy to share with you our 2018 Annual Report for the Department of Allergy and Clinical Immunology of the Lyon University Hospital Center (CHU de Lyon or HCL). The creation of this report afforded us an opportunity to take a moment and reflect on our projects and missions, **including our principal mission of improving healthcare** to adult patients with allergies or chronic inflammatory diseases.

a) Department history

The history of the department comprises five main events:

- The creation of the "**Drug Allergy Care Unit**" in **1999** within Lyon-Sud's Pulmonology Department to provide consultations and programmed day- and week-stay (programed admission during the Monday-to-Friday work-week) hospitalization services. In only a few years, this "functional unit" (UF; the smallest defined service unit in French hospitals) became a regional and national center of reference and expertise for drug allergies.

- The creation of a **complementary specialty training degree** (DESC) in **2000** in **allergy and clinical immunology**.

- The creation of the **CHU de Lyon's Allergology Coordination Unit** in **2004** to harmonize practices among private-practice and hospital care physicians and deploy a good practices validation process.

- The creation of the **Allergy and Clinical Immunology Department (CR 36 093)** in **2009.** The department works closely with two structures, with which most of its members are affiliated: the Lyon-Sud Immunology Clinical Research Unit (URCI-LS) for clinical research and Inserm U1111 International Center for Infectiology Research (CIRI) for basic and pathophysiological research. Thanks to these collaborations, the department's patients may be candidates for inclusion in clinical research protocols, and inversely, any research-enrolled patients experiencing clinical incidents can be admitted to the department for care.

- Creation of a **post-graduate degree (DES) in allergology** in **2017**. Allergology is becoming a medical specialty and a university/teaching hospital curriculum for it is being developed.

b) Department components

There are several structures within the department:

- The Allergy and Clinical Immunology clinical service (department chief: Frédéric Bérard) is located in Pavilion 1K of the Lyon-Sud Hospital Center.

- The Inserm research team (team 17, U1111-CIRI, principal investigators: Jean-François Nicolas and Marc Vocanson) works in the Gerland neighborhood of Lyon. Their focus is skin allergy immunology and vaccination (see § 5).

- The clinical research unit (a part of LyREC; director: Sophie Gilibert), located within the department, oversees clinical trials in inflammatory diseases and vaccinology (see § 6).

- The Allergobiotec biobank collects and stocks patient samples for future use in academic and industrial research (see § 7).

- The Eczema Expert Center (CEE; director: Audrey Nosbaum) coordinates patient management across the Auvergne-Rhône-Alpes administrative region (see § 8).

c) Department missions

Working in close partnership with all the actors in healthcare within Lyon's network of hospitals, our priorities for the department are to:

- offer high-quality, individualized care (personalized medicine);
- carry out clinical and pathophysiological research with the goal of improving patient care;
- furnish advanced learning and training;
- increase the medical community's knowledge of the cutaneous immune system in our three main fields of research: drug allergies, food allergies and skin allergies.

- Medical care. The Allergy and Clinical Immunology Department is a center of reference and excellence providing management for complex problems in drug allergies, food allergies and chronic inflammatory skin diseases. The application and optimization of protocols for desensitization/tolerance induction in drug or food allergies are important aspects of our care activities.

- Therapeutic education (ETP). TPA CAP ("Therapeutic and Accompaniment Program for Chronic and Allergic Skin Disorders") is a Regional Health Agency (ARS)-certified (2010 and 2015) education program led by Virginie Verdu. It was launched in 2009 to provide patients with the tools they need for the day-to-day self-management of their disease (see § 11.5).

- Interaction with patient associations. The department organizes yearly Eczema and Psoriasis Days and develops tools for patients.

- Research. The department's research is focused primarily on the pathophysiology of inflammatory skin diseases (eczema particularly) and on drug allergies. The research teams seek a better understanding of the causal mechanisms of these pathologies to improve diagnosis, prevention and treatment.

- Training. The department's immunology and allergology training is intended for medical students (allergology certificate, masters in medical immunology), residents (DESC in allergy and clinical immunology and DES in allergology) and PhDs (Francophone allergology degree, continuing professional development). Of particular importance to us is the transmission of the fundamentals of immunology, the base upon which a veritable understanding of allergic diseases is built.

- Valorization. Another ambition of the department is to promote progress in medical knowledge in the form of scientific publications, learning tools for healthcare providers and patients (see § XI), and the organization of conferences in our fields of expertise.

d) Department organization - Governance

The department is headed by Frédéric Bérard and Jean-François Nicolas with support from an organization and strategy committee (COORG) composed of the following managerial/supervisory staff.

- Clinical department: department administrator, senior physicians, teaching physician, nurse supervisor, nurse coordinator, secretary;
- LyREC: director;
- Inserm U1111-CIRI: director;
- CEE: director.

The COORG meets monthly to address current issues, propose projects and make operational decisions concerning the:

- structuration of clinical objectives;
- organization of inter-structure collaborations;
- development of research activities;
- organization of conferences, seminars and training days;
- training activities.

2. Department members - functional structure

The healthcare, therapeutic education and clinical research teams.

The Inserm U1111 research team,
International Center for Infectiology Research (CIRI)

Department of Allergy and Clinical Immunology CR 36093 – Lyon-south hospital group (GHS), medical activities group (PAM)

Prof. F. Berard - Prof. J.-F. Nicolas

Allergy and Clinical Immunology

Deputy department administrators
Dr. A. Nosbaum - Dr. F. Hacard

Sectors

Week-stay hospitalization UF 36 501
Day-stay hospitalization UF 36 408
Allergy functional analyses (EFA) UF 36 431
Consultations UF 36 730

Medical team

Prof. F. Berard, Dr. A. Bernede,
Dr. J.-S. Bernier, Dr. M. Braire,
Dr. M. Bourrel-Boutaz,
Dr. A. Catelain-Lamy,
Dr. F. Delcroix, Dr. A. Frappaz,
Dr. F. Godesky, Dr. C. Goujon,
Dr. S. Grande, Dr. F. Hacard,
Prof. J.-F. Nicolas, Dr. A. Nosbaum,
RESIDENTS

Paramedical team

Health manager M. Barbet
RNs
M.-N. Bouverot RN coordination + CEE
A. Montagnon RN coordination + ETP
V. Verdu RN coordination ETP
C. Calvano, M.-C. Bernay, A. Pequignot
P. Dubois, D. Demeure, C. Gasparoux
(V. Santus, January 2019)
CNAs
C. Soton, I. Moisan, N. Bonnet,
M. Ferroy, F. Picard-Agenelle
Hospital logistics pool, PAM
D. Patural, C. Soleilland, N. Raimond
M. Nicolas, M. Ghorab, M. Alexis, G.
Jullien, A. Kouider
Secretaries
L. Fabre Coordinator
K. Badaut
H. Pascual

Clinical research unit LyREC

Scientific director
Prof. J.-F. Nicolas

Scientific co-director
Prof. F. Berard

Coordinator
D. Bottigioli

General secretary
M. Faton

Project managers
S. Gilibert
Dr. K. Dahel

Clinical research associate
J. Penot

dermo-cosmetics and cutaneous biometrology
A. Lavoix (general manager)
S. Escobessa (administrative manager)
K. Sagorny (project manager)
E. Corgie (project manager)
S. Ponsero (CRT)
M.-J. Leculier (CRT)

Clinical research unit Inserm U1111, team 17, International Center for Infectiology Research

direction
M. Vocanson, J.-F. Nicolas

Researchers
P. Gamradt O. Hequet
A. Nosbaum E. Ono
O. Kanagawa

Technical team
A. Guironnet-Paquet
V. Lenief
A. Mosnier

Students
L. Laoubi C. Braun
A. Villani E. Botokeki

Physicians
F. Berard D. Jullien
F. Hacard B. Ben-Said
F. Delcroix

Higher education

Medical Sciences Extended Training (DFASM) 1, 2, 3
Prof. F. Berard
Dr. A. Nosbaum
Dr. F. Delcroix

Optional allergology module
Prof. J.-F. Nicolas

Master 1: Immunology And Pathophysiological Mechanisms
Prof. F. Berard

Master 2: Cutaneous Biology
Prof. J.-F. Nicolas
Dr. A. Nosbaum

DESC: Allergy and Clinical Immunology
Prof. J.-F. Nicolas

DES: Allergology
Prof. J.-F. Nicolas

Specialized transversal training (FST): Allergology
Dr. A. Nosbaum

Inter-university degree (DIU): Immunology and Biotherapies
Dr. A. Nosbaum

DUFRAL (Francophone allergology

Therapeutic education

ETP Center UF 36 851

Attending physicians
Prof. F. Berard
Dr. M. Bourrel-Boutaz,
Dr. F. Hacard
Dr. A. Nosbaum

Coordinating RN
V. Verdu

Occupational diseases

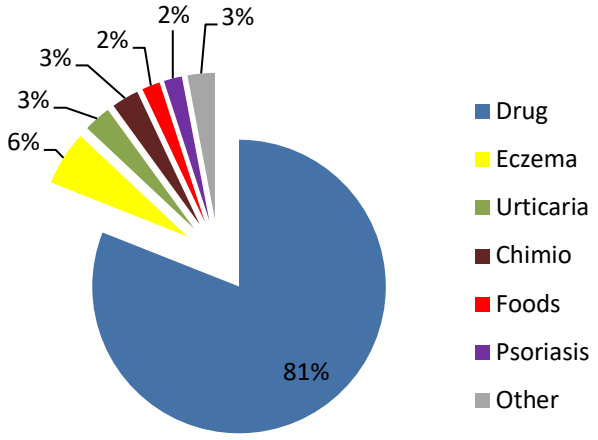
UF 36 306
Consultations
Dr. A. Catelain-Lamy,
Dr. E. Botokeky

3. Medical care

The Department of Allergy and Clinical Immunology has services for consultations, functional testing, and day-stay and week-stay hospitalization. Here, we present activity data from 2017.

a) Week-stay hospitalization

The 10-bed week-stay unit (UF 36501) receives patients from Monday to Friday for traditional allergy testing and immune tolerance induction. The unit is headed by the teaching physician who oversees two residents, one enrolled in the allergology DES, and another in a general medicine DES and the allergy and clinical immunology DESC. They primarily perform immuno-allergic tests and procedures in patients under programmed hospitalization. The activities include immediate and delayed reaction tests, standard hospital laboratory tests, specialized lab tests (Allergobiotec and Inserm U1111-CIRI), reintroduction and challenge tests, and finally tolerance induction protocols for foods or necessary drugs such as chemotherapies.
In 2017, we admitted 971 patients to the week-stay unit.
ALOS increased slightly (1.56 days in 2016 vs 1.68 in 2017) and the occupancy rate remained stable.



Distribution of pathologies addressed in the week-stay unit in 2017

Week-stay Allergy and Clinical Immunology in 2017

2017	Objective	Result
January	71	87
February	63	71
March	89	108
April	64	71
May	66	96
June	65	87
July	61	80
August	27	30
September	73	94
October	65	105
November	70	77
December	50	65
Total	764	971

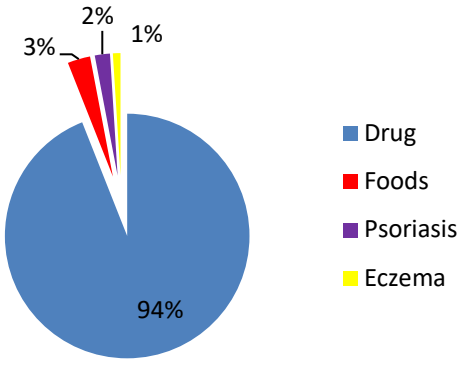
Summary:

- Drug allergy workups represented the primary occupation at the week-stay unit.
- In that setting, we performed **24** immune tolerance induction procedures in allergic patients.

b) Day-stay hospitalization

The day-stay unit (UF 36408) comprises four rooms and can receive up to seven patients per day. The unit is headed by the teaching physician who oversees one resident. In addition to performing workups for patients with severe drug or food allergies, the day-stay physicians also administer intravenous immunobiologicals to treat patients with severe inflammatory skin diseases. The

figure below shows the distribution of pathologies addressed at the day-stay unit in 2017.



Distribution of pathologies addressed in the day-stay unit in 2017

Day-stay Allergy and Clinical Immunology 2017

2017	Objective	Result
January	91	117
February	76	73
March	106	128
April	89	89
May	77	105
June	77	131
July	93	115
August	43	49
September	93	118
October	88	129
November	84	105
December	73	91
Total	780	974

Summary:

- Drug allergy workups represented the primary occupation at the day-stay unit. Food allergies were the second most frequent subject of workups, and furthermore the number of patients admitted in that setting has been growing consistently for several years. Thus, we submitted a new activity dossier (DAN) in 2018 with the goal of increasing the number of day-stay admissions to respond to this demand.
- In the day-stay unit, we exceeded our 2017 objectives by close to 25%.

c) Consultations et technical facilities

In 2017, we received 4654 people for outpatient consultations (UF 36730) and provided ambulatory services (including series of cutaneous tests) to 50 patients at our EFA facility (UF 36431).

In summary:

- **Drug allergies** were the primary subject of consultations.
- **Food allergies** led to numerous day-stay hospitalizations. The delay for consultations in the setting of allergies was more than six months.
- **The remainder of consultations were for inflammatory and allergic skin diseases** (eczemas, urticaria and psoriasis).

4. Experimental and translational research

The department's research is carried out at the International Center for Infectiology Research (Inserm U1111-CIRI), a part of the Lyon-Sud/Gerland Biosciences campus located in the Lyon neighborhood of Gerland.

a) Fields of research

Our research is focused on the pathophysiology of inflammatory cutaneous diseases, particularly eczemas (contact and atopic dermatitises), and on drug allergies. These pathologies are the result of a breakdown of immune tolerance for molecules found in the daily environment; those molecules become allergens for the patients who have become sensitized to them. Our allergens of interest are:

- organic chemicals provoking eczema with skin contact;
- airborne allergens (e.g., home dust mites) provoking atopic eczema;
- medicines provoking allergies and drug eruptions.

b) Objectives:

We seek to better understand how these allergens circumvent immunological tolerance and thus cause allergies. Toward that goal, we employ preclinical models and samples taken from our patients.

Our ultimate objective is to develop new strategies for the reestablishment of tolerance for cutaneous allergens.

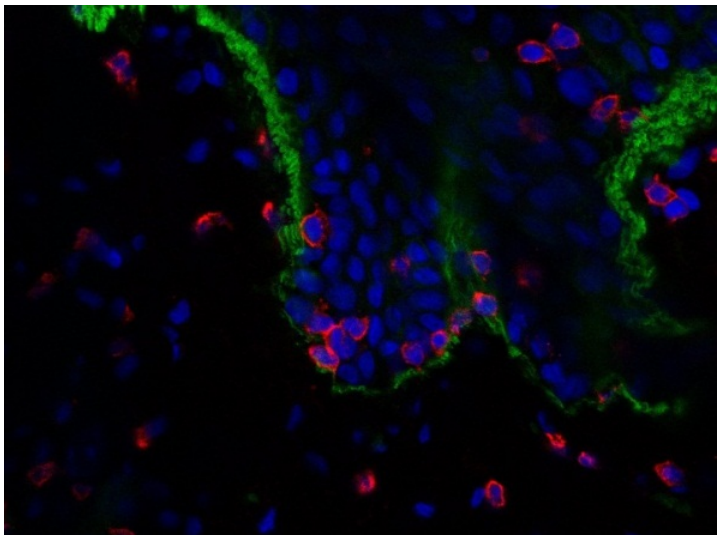
The research team

CO-DIRECTORS	Jean-François Nicolas Mark Vocanson
RESEARCHERS	Audrey Nosbaum Olivier Hequet Pia Gamradt Emi Ono
CLINICAL RESEARCH	Frédéric Bérard Benoit Ben-Said Florence Hacard Fanny Delcroix Denis Jullien
TECHNICAL TEAM	Vanina Lenief Aurélie Guironnet-Paquet Amandine Mosnier
STUDENTS	Axel Villani Léo Laoubi Camille Braun Elsa Botokeki

c) Results

Our most notable results over the past few years are outlined below:

- **Cytotoxic (CD8+) T lymphocytes (CTLs) are the primary effectors of eczema and drug eruptions**. They are necessary for the initiation of the allergen-specific immune response. We are currently trying to establish a better understanding of CTL activation mechanisms, which may provide clues on how a same type of cell can be responsible for diseases that differ greatly in terms of clinical presentation, severity and course.
- **T helper (CD4+) cells (T_h) control CTLs**. They provide the immunological tolerance of allergens in people who are not allergic and limit the intensity of reactions in people who are. A strongly suppressive T_h subgroup actively controls the expansion and activation of CTLs in these diseases. Projects are underway to develop techniques to activate T helpers *in vivo* and thus reintroduce tolerance to antigens in the skin.
- Also we have developed ***in vivo* or *in vitro* methods for the diagnosis of drug allergies** and the **prediction of the sensitizing properties of chemical compounds.**



CD8+ T-cells immunolabeled with anti-CD8α antibodies (red) in the dermis and epidermis of normal human skin. The epidermis (above) and the dermis (below) are separated by the epidermal basement membrane, immunolabeled with anti-CD49f antibodies (green). Skin cell nuclei appear in blue (DAPI staining) (photo P. Gamradt).

For more information on the methods employed by our research teams or our current research orientations: http://ciri.inserm.fr/en/team/all-teams/immunology-of-skin-allergy-and-vaccination/research-themes/

5. Clinical research

Our clinical research unit (UF 36768) was developed by Catherine Goujon and Jean-François Nicolas in 2001 within the Department of Allergy and Clinical Immunology. ARS authorization as a clinical research facility was obtained that same year and renewed in January 2014. That authorization covers clinical trials for medicines (phases I-IV), medical devices, cosmetics and dietary supplements, pathophysiological research, and trials on healthy or sick patients.

The not-for-profit organization **LyREC (Lyon Clinical Research)** is in charge of the structure and financially autonomous.

LyREC is able to **design and/or conduct research projects** (inclusion and management of patients or healthy volunteers). Also, the valorization of results is given great importance.

a) Historic fields of research

Historically, the primary fields of research at the clinical research unit have been the physiology of skin and the understanding of inflammatory and allergic mechanisms, the treatment of chronic inflammatory dermatoses (atopic dermatitis, psoriasis, urticaria) and cutaneous vaccination (intradermic, epicutaneous, transcutaneous). Particularly, the unit coordinated the entirety of the

clinical trials for three programs accredited by Lyon Biopôle and financed by the Single Interministerial Fund (development of an intradermal vaccination device).

b) Expansion of research fields

Although its historic fields of research maintain their importance, the clinical research unit has been evolving on several fronts over the past few years, driven by its strong desire for openness and diversification.

- The clinical research association welcomed new members in 2015. Particularly, researchers from the Lyon-Sud's Department of Rheumatology have considerably developed their clinical research activities, with notably the inclusion of close to 30 patients in four industry-sponsored clinical trials since the last quarter of 2017. LyREC is also bringing its support to the drafting and/or submission of protocols for translational research and for works within France's hospital clinical research program (PHRC).

- The development of clinical research projects in dermo-cosmetics and skin biometrology, started in 2016, led two years later to the launch of a center for skin biometrology, located in the Lyon suburb of Tassin. That center has grown around three differentiating axes:

    - innovative methods to quantify the efficacy of medical devices, cosmetics and medicines
    - international exportation of technical competencies
    - novel applications for lasers in dermatology

c) Projects for 2018

- Development of a quality system and renewal of research facility authorization (end of current authorization in early 2019)

- Pursuit of LyREC's expansion of services to all other hospital departments

- Recruitment of a coordinator for the collaborative immunodermatology program OPTI-DERM. This latter was launched in 2015 to optimize the management of chronic inflammatory skin diseases via different actions implemented in collaboration with the Allergy and Clinical Immunology Department at the Lyon-Sud Center:
    - Deployment of a private-practice/hospital practice work group to improve health coordination and patient itineraries;
    - Training / information initiatives for private-practice healthcare professionals (pharmacists, general practitioners, specialists);
    - Continuation of a psoriasis therapeutic education program (ARS-accredited) as a complement to already-active programs in atopic dermatitis and urticaria (TPA CAP);
    - Planning and facilitation of yearly learning days for patients (eczema - psoriasis);

- Enlargement and usage of a patient database with the double objective of increasing recruitment potential for clinical trials and profiting from a tool for the longitudinal follow-up of patients (epidemiological and pharmacoepidemiological studies meant for publication).

d) The team

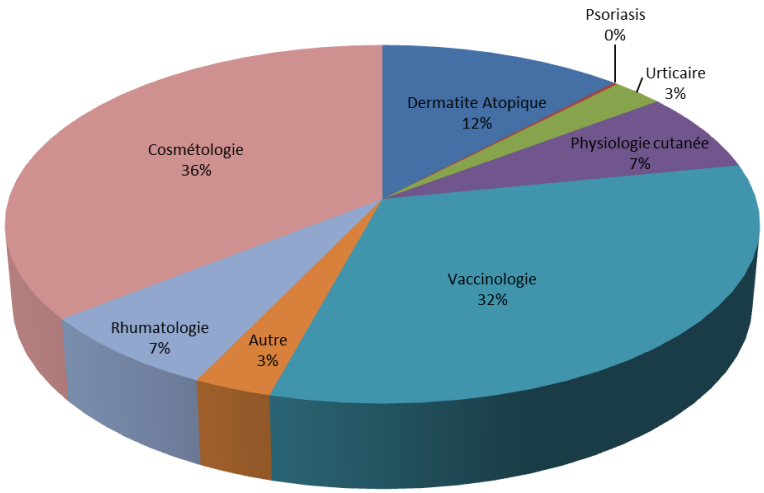
The team is composed of permanent staff and regular collaborators dedicated to clinical research:

- Collaborating clinician-researchers (dermatologists and general practitioners)
- 1 coordinator
- 1 manager for the cosmetology and skin biometrology activities
- 4 project managers
- 3 clinical research associates / technicians
- 1 administrative manager
- 1 administrative assistant

All staffing is financed by LyREC.

e) Results for the 2016–2017 period

Since its creation, the clinical research unit has participated in more than 200 clinical research projects involving more than 3500 patients or healthy volunteers.
From 2016 to 2017, more than 450 patients or healthy volunteers were included in clinical studies conducted by LyREC.



Distribution of topics of study for the LyREC clinical research unit.

6. Allergobiotec

a) Presentation

The purpose of the HCL's Allergobiotec biobank (UF 36853) is to stock tissue and blood samples from healthy subjects participating in preventive vaccination clinical studies, and from patients with cutaneous inflammatory diseases (eczema, atopic dermatitis, psoriasis) or drug allergies. These samples are used for research projects, in accordance with the French Laws n°s 94-653 and 94-654 dated 29 July 1994, respectively on the respect of the human body and on donations and use of elements and products of the human body.
Allergobiotec works actively with the Department of Allergy and Clinical Immunology, other services within the drug allergy reference center network, the LyREC clinical research unit and the Inserm U1111-CIRI team. Located at the Lyon-Sud Faculty of Medicine, Allergobiotec:

- receives and records samples using the biological sample management software TumoroteK;
- conditions samples;
- stocks samples at -80°C or in liquid nitrogen.

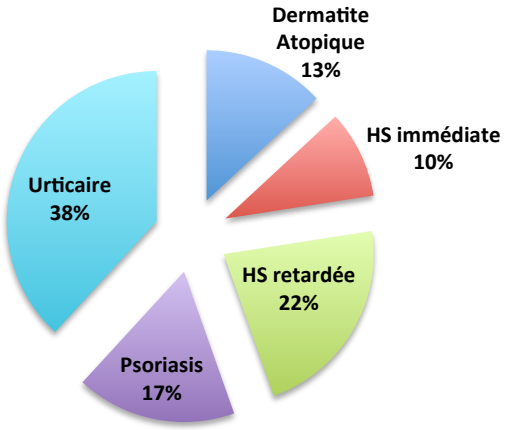
b) Results as of 31 December 2017

In the ten years of its existence, Allergobiotec has collected samples from 1761 subjects.

- Distribution of samples by pathology

Allergobiotec has four collections:

- Atopic dermatitis
- Immediate hypersensitivity (samples from patients having developed a reaction immediately after the administration of a drug)
- Delayed hypersensitivity (samples from patients having developed a reaction belatedly after the administration of a drug)
- Psoriasis
- Urticaria



Distribution of Allergobiotec samples by pathology (HS: hypersensitivity)

- Sample inclusion as of year-end 2017

  On 31 December 2017, Allergobiotec counted 6389 samples distributed as follows: 3055 blood samples (frozen PBMCs, 10% DMSO), 2943 serum samples and 333 biopsy or skin samples.

Collection	Number of subjects	Total number of samples	Number of PBMC samples	Number of serum samples	Number of cutaneous samples
Atopic dermatitis	231	1533	935	498	94
Immediate HS	166	587	205	381	0
Delayed HS	388	2226	921	1026	239
Psoriasis	304	1169	929	229	0
Urticaria	672	874	65	809	0
Total	1761	6389	3055	2943	333

7. Auvergne-Rhône-Alpes Eczema Expert Center

The Auvergne-Rhône-Alpes Eczema Expert Center (CEE) was launched in 2015 under the direction of Dr. Audrey Nosbaum to improve the management of eczemas (contact dermatitis, atopic dermatitis, hand eczema) over the Auvergne-Rhône-Alpes region.

The CEE may be described via its three constitutive aspects:

- The CEE is a collaborative, multidisciplinary network of specialized physicians and paramedicals working in eczema management within the region, specifically at the university hospital centers of Lyon, Saint-Étienne, Clermont-Ferrand and Grenoble, and the hospital centers of Annecy and Valence. The members of the network meet twice monthly at Lyon-Sud. Their mission is to:
  - homogenize diagnostic and exploratory tools (batteries of patch tests);
  - favor clinical research, e.g., the CEE enabled the inclusion of 40 patients with contact dermatitis for the TISA study (New Tools for the In Vitro Diagnosis of Skin Allergy) in 2017;
  - discuss difficult eczema cases.

- As of 2017, the CEE benefits from an exploratory platform for contact dermatitis within Lyon-Sud's Allergy and Clinical Immunology Department. The platform provides a combination of specialized consultation and patch testing and interpretation. In 2017, the platform provided services to 184 patients.

- As of 2018, the dermatology-allergology service of the CHU de Lyon was grouped within our department. This was a consequence of the retirement of Dr. Dominique Vital-Durand, contract physician for the dermatology department of the Lyon-center hospital group.

8. Teaching

The department's researchers, teaching researchers, physicians and nurses are all heavily invested not only in university and post-university education (medical and science students, interns and

residents, physicians, pharmacists, veterinarians and other healthcare professionals) but also in patient and public education. Collectively, they provide more than 400 hours of education per year.

We present below only the courses or programs headed, organized or coordinated by a department member.

For more details: *http://allergo.lyon.inserm.fr/enseignement.htm*

a) UEMS certification

In December 2018 the department was certified as an allergology training center by the European Union of Medical Specialists (UEMS), under the aegis of the European Academy of Allergy and Clinical Immunology.

b) Medical school curriculum

Courses / degrees (Claude Bernard University Lyon 1**)**

- Immunology, fourth year of medicine, DFASM 1 (F. Bérard, A. Nosbaum)
- Immune Mechanisms in Pathology, fifth year of medicine, DFASM 2 (A. Nosbaum)
- Optional module Allergology (J.-F. Nicolas)
- DESC Allergy and Clinical Immunology (J.-F. Nicolas)
- DES Allergology (J.-F. Nicolas)
- FST Allergology (A. Nosbaum)
- Master 1 Immunology and Immunopathological Mechanisms (F. Bérard)
- Master 2 Biology of the Skin (J.-F. Nicolas, A. Nosbaum)

c) Post-university education

- DUFRAL is a Francophone university diploma in allergology. It is intended for French-speaking physicians in Indian Ocean, sub-Saharan and Maghreb countries who seek to acquire competencies in allergy and allergy-related diseases. The diploma is co-organized by the Lyon 1 and Paul Sabatier (Toulouse) Universities.
  - The Indian Ocean DUFRAL exists since 2013: *http://allergo.lyon.inserm.fr/DIUFRAL.htm (website in French)*
  - The Maghreb DUFRAL was launched in 2017: *http://allergo.lyon.inserm.fr/DUFRAL_Maghreb.htm (website in French)*

- The department's staff members also participate in numerous post-university training programs organized by the HCL, other French universities, Inserm or academic associations (French Societies of Immunology, Dermatology and Allergology; SFI, SFD, SFA respectively).

9. Training – Conferences

Every year, the Department of Allergy and Clinical Immunology organizes numerous training opportunities in the form of conferences, seminars, or learning days. Beyond the obvious audience of physicians and other public or private healthcare personnel, these events are also intended for researchers, patient associations and even the general public.

- **The AllergoLyon Seminars** are two to three-day events held every two years. They are organized into thematic days: immunodermatology, drug allergies, urticaria and eczema. Half of the conferences are provided in English by foreign guest speakers.
- **The Auvergne-Rhône-Alpes Eczema day** is for patients, their loved-ones and their caregivers. This yearly event is organized with the help of the CEE and the French Association for Eczema.
- **For World Pathology Days,** the department participates every year in day events organized by patient associations for psoriasis, atopic dermatitis, chronic urticaria or allergies.
- **Guest Conferences** are held regularly to bring researchers and clinicians to our facilities and give them an opportunity to expose their work, and potentially establish collaborations with our teams.
- **The Vallières** are yearly internal training days that bring together the department's personnel (physicians, paramedicals, researchers, research technicians, pharmacists) to review its activities.
- **The Clinical Service Colloquiums** are monthly events focused on the department's areas of expertise.
- **Inserm team lab meetings** are held weekly and often give the lab's students and researchers a chance to present the advancement of their projects.
- **Bibliography meetings for residents and staff physicians** were launched in November 2015 and are held every Thursday from 4 to 6 p.m.
- **The AllergoLyon website,** developed by the department and hosted by Inserm, provides numerous informative documents for healthcare professionals and patients: *http://allergo.lyon.inserm.fr* (website in French).

10. Fields of research: IMMUNOLOGY-ALLERGOLOGY-DERMATOLOGY

a) Eczema

Audrey Nosbaum
M.D., Ph.D

Marc Vocanson
Ph.D

Eczema is a clinical symptom shared by several inflammatory dermatoses, such as atopic dermatitis (AD) or irritant or allergic contact dermatitis. Eczema is the leading reason for dermatological consultation in France, ahead of acne. Every day, the Department of Allergy and Clinical Immunology receives patients referred by their general practitioners, dermatologists, allergologists, pediatricians or other healthcare professionals for this symptom.

- Statistics

The number of patients received or admitted for eczema treatment increased in 2017.

- *Consultation*: 700 in 2016, 1122 in 2017.
- *Week-stay hospitalization*: 48 in 2016, 60 in 2017.
- *Therapeutic education*: 117 in 2016, 122 in 2017 (children and adults).

- Itinerary of eczema patients in the department

The patient care pathway is guided by the department's unit structure:

- consultations, including those specific to atopic dermatitis or contact dermatitis (CEE consultations), and therapeutic education;
- functional allergology exploration (EFA) for complementary examinations and allergy tests when necessary;
- week-stay hospitalization, with "AD weeks" for patients with moderate to severe atopic dermatitis who benefit from dermatological, allergological pulmonological and ophthalmological management as well as therapeutic education;
- therapeutic education program (see below).

- Partners – support structures

This always-evolving clinical activity is tightly tied to the:

- *Auvergne-Rhône-Alpes Eczema Expert Center (CEE),* headed by Dr. Audrey Nosbaum *(*see § 8).
- *INSERM U1111-CIRI basic research group*, which, under the direction of Dr. Marc Vocanson, seeks to better understand the pathophysiology of eczema and identify novel diagnostic, therapeutic and prognostic biomarkers. The team uses murine eczema models and translational approaches to move results from the lab's bench to the patient's bedside.

- *LyREC clinical research unit*, coordinated by Sophie Gilibert, which enables pathophysiological and therapeutic clinical studies.
- *Allergobiotec* and its collections of biological samples from patients with eczema.
- *biotherapies multidisciplinary team meetings*, which unite healthcare professionals from a number of disciplines (dermatology, allergology, rheumatology, gastroenterology, internal medicine) for collegial discussion of patient cases. All contribute vital competencies to ensure therapeutic decisions in coherency with the state of the patient and current medical knowledge. Decisions made there are documented and submitted/explained to the patient.
- *eczema workgroups*, in which the department's physicians participate: the Dermatology-Allergology Group and the Therapeutic Education Group of the French Society of Dermatology, the Atopic Eczema Research Group (GREAT), the Dermatology-Allergology Study and Research Group (GERDA-REVIDAL), the Dermatology Research Society (SRD), the European Academy of Dermatology and Venereology, the International Eczema Council (IEC).
- *Auvergne-Rhône-Alpes Eczema Day*, an annual event for patients, their loved-ones and their caregivers, organized by the department in partnership with the CEE and the French Association for Eczema.
- *training, communication actions* for health providers and the public (films on YouTube, https://www.youtube.com/watch?v=k24BlLHW3HM&t=134s, facebook.com/immunoallergolyon, articles in the local newspaper Le Progrès), *valorization* of activities via the publication of scientific articles.
- *French Association for Eczema* and the *Atopic Dermatitis Foundation*.

For more information on our current projects, see Annex 2 and

- http://allergo.lyon.inserm.fr/eczema_contact.htm (website in French)
- http://allergo.lyon.inserm.fr/dermatite_atopique.htm (website in French)

b) Drug allergy

Frédéric Bérard
M.D., Ph.D

Florence Hacard
M.D.

Marc Vocanson
Ph.D

The investigation of immediate or delayed hypersensitivity to medicines has been the department's leading activity over the past 20 years. Drug reactions are indeed numerous but only infrequently allergic. Skin and provocation tests enable diagnosis, which in turn eliminates unnecessary treatment interdictions and authorizes therapeutic administrations adapted to the patient case.

Should drug allergy be confirmed, we propose immune tolerance induction protocols with the goal of making administration possible while minimizing the risk of severe reactions. Of particular interest in this setting are chemotherapies, biotherapies and certain antibiotics.

When providing diagnostic assistance in complex cases, skin and/or blood samples may be taken and thereafter subjected to immunobiological tests (lymphocyte transformation tests, RT-qPCR) performed by the Inserm U1111-CIRI team to detect the presence of specific allergy biomarkers.

We also work closely with that team and Lyon-Sud's Biological Immunology Laboratory to conceive diagnostic biological markers.

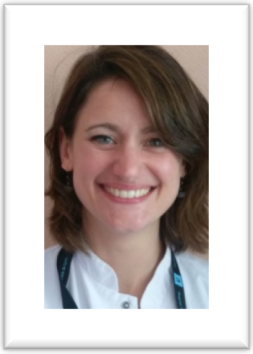
And finally, we collaborate actively with the Toxic Epidermal Necrolysis and Serious Drug Eruption Reference Center headed by Dr. Benoît Ben-Saïd. That center is now located at the Edouard Herriot Hospital, but was formerly a part of our department (2009-2017).

Our work is clinical, epidemiological, immunological and translational. Our objectives are to study the pathophysiology of severe allergic diseases such as toxic epidermal necrolysis or DRESS syndromes.

c) Urticaria

Frédéric Augey
M.D.

Frédéric Bérard
M.D., Ph.D



Florence Hacard
M.D.

Urticaria is one of the most frequent reasons for consultation in our department, because it is—wrongly—considered to be an allergic disease. Urticaria is in reality a chronic inflammatory disease, poorly understood by patients and physicians alike, and for which our service has become a national expert.
Through our specialization, we are able to explain the disease to patients in an easy-to-understand manner during their initial visits and provide them with written supports, furthermore downloadable from the department's website by their primary care physicians (*http://allergo.lyon.inserm.fr/fiches_patientes/URTICAIRE_2010.pdf)* (Website in French). A minority of the patients we see will need a more complete workup, often involving a search for stigmata of autoimmunity and skin tests.

- Therapeutic education

We have developed an urticaria therapeutic education program (see next section) that is open to all patients, ours or not, but particularly intended for those whose quality of life has been greatly

altered by the disease.

- New treatments

  For patients who fail to respond adequately to conventional treatments (antihistamines) and suffer from a reduced quality of life, we may propose exceptional and/or innovative treatments (e.g., omalizumab, an anti-IgE monoclonal antibody) if they agree to increased surveillance and discontinuation of corticosteroid therapy (self-medication frequently responsible for corticosteroid dependence).

- Networking for progress

  In 2010, the service contributed to the creation of, and, to this day, continues to participate actively in the Urticaria Group of the French Society of Dermatology. Therein, the service contributed to the creation of an informative consensus document on chronic urticaria, participates in prospective, multicenter clinical studies, and coordinates a national PHRC project evaluating the possible benefits of a dosage increase for second-generation antihistamines.

- Training

  We participate regularly in continuing medical education, provided as part of the Paris Dermatology Days (annual conference of the French Society of Dermatology) and the Francophone Allergology Conference (held by the French Society of Allergology).

d) Therapeutic education

Virginie Verdu
Coordinating RN

Therapeutic education team

Laure Fabre
Coordinating MA

Our program, entitled "Therapeutic and Accompaniment Program for Chronic and Allergic Skin Disorders (TPA CAP), is intended for patients with chronic inflammatory skin diseases, specifically atopic dermatitis (AD), chronic urticaria and psoriasis. Accreditation for the program was obtained in 2010 and renewed in 2015.

- Objective

  Our objective is to accompany patients on their path toward greater autonomy and efficiency for the day-to-day self-management of their disease and its treatment. The program builds upon the commitment of a multidisciplinary team comprising dermatologists, allergologists, psychologists secretaries, nurses, nurse assistants, dietitians and other specialized caregivers, all trained in therapeutic education.

- Patient itinerary

  Private-practice or hospital physicians furnish a written request to the coordinating RN for a patient's enrollment in the program. The referring physician maintains contact with the team to keep abreast of the patient's advancement in the program. With the patient's input as a

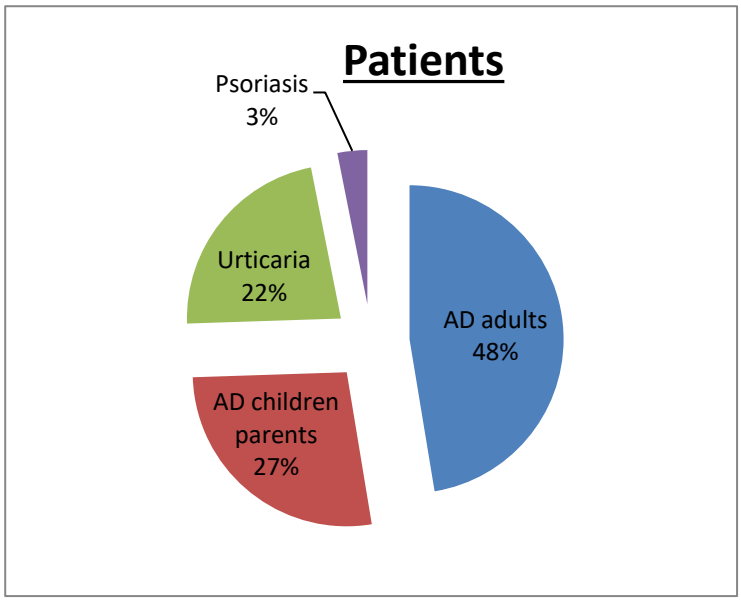
cornerstone, we construct a personalized disease management education program comprising individual and/or collective sessions, all leading to a final evaluation.

- Valorization – Conferences – Presentations

  Recognized for their expertise, the members of the therapeutic education service have been active in invited lectures and conferences since 2011. For example, in 2017, the team participated in the "Patient-Caregiver Partner" conference, jointly organized by the HCL and the University of Montreal Health Center, to present the emblematic work performed at the HCL to integrate "resource patients" in the institution's future projects.

- Recognition and projects

  The TPA CAP team also participates in other programs with the Foundation for Atopic Dermatitis (FAD), where it is recognized as a national-level "Atopy School". With that foundation, the TPA CAP team, in partnership with five other CHUs, is developing an E-learning training program to provide pharmacists with the educational attitude necessary for the help they provide to patients with atopic dermatitis.



Distribution of pathologies within the program TPA CAP

In 2017, TPA CAP helped 202 patients and provided 309 individual meetings for therapeutic education

- Projects accomplished in 2017
  - Creation and deployment of a therapeutic education workshop, common to the Lyon-Sud PAM, on psychosocial competencies. This workshop is transversal and focused on several chronic pathologies in the settings of immunology-allergology, pulmonology (asthma and COPD) and rheumatology (chronic inflammatory rheumatisms).
  - Creation of a Facebook page, "My Eczema, My Daily Life", which currently counts 91 followers who benefit from posts made by all the members of the team.
  - Creation of a YouTube video on gauze dressing in cases of moderate or severe atopic dermatitis. The video helps patients and their loved ones take charge of this treatment and better understand the disease.
  - Creation of a YouTube video series called "Lola's Eczema", an initiative of the department developed in partnership with the FAD. Lola's Eczema won the silver prize in the Medical Communications Category at the Health Communication Festival. The series was able to raise awareness among healthcare professionals and the public.

- Organization of the third Auvergne-Rhône-Alpes Eczema Days, an event intended for patient associations, held under the aegis of the HCL's Allergology Coordination Committee, and carried out in partnership with the Auvergne-Rhône-Alpes Eczema Expert Center and the French Association for Eczema.

11. Partnerships / Collaborations

- HCL/INSERM/University/CNRS/ENS

- Our activities are carried out within Lyon's university hospital system, Claude Bernard University Lyon 1, and the CIRI laboratory (INSERM/University/CNRS/ENS).

- Scientific partnerships
  Gérard Lina, CIRI, Lyon, Bertrand Dubois, Cancer Research Center of Lyon; Stefan Martin, Allergy Research Group, Department of Dermatology and Venereology, University Medical Center, Freiburg; Dean Naisbitt, Institute of translational medicine, University of Liverpool; Enrico Maggi, Immuno-allergology Unit, Careggi University Hospital, Florence; Andrea Cavani, Laboratory of Molecular and Cell Biology, IDI Hospital and Research Institute, Rome; Marc Pallardy, UMR-996 INSERM, Paris-Sud University, Châtenay-Malabry; Marie Baeck, Dermatology Department, Saint-Luc University Clinic, Brussels; Elena Rizova, Sanofi, Boston; Lucie Mondoulet / Vincent Diozhegy, DBV Technologies, Montrouge; Anne-Marie Schmitt, Pierre Fabre Pharmaceuticals, Toulouse; Hélène Pigeon-Hernandez and Sandrine Bessou-Touya, Pierre Fabre Dermo-cosmetics, Toulouse; Matthias Vey / Charles Laroche, IFRA, Brussels; Ichiro Katayama and Hiroyuki Murota, Dermatology department, University, Osaka; Roland Liblau, INSERM-UMR1043, Paul Sabatier University, Toulouse; Janet Maryanski, Gene and Cell Therapy Unit, URE 004, Nice; When-Hung Chung & Shuen-Iu Chung, Taipei; Micheal Rosenblum, Dermatology Department, University of California – San Francisco; Iris Gratz, Division of Allergy and Immunology, University of Salzburg; Daniel Yerly, Department of clinical research, University, Bern.

- Competitiveness cluster: Lyonbiopôle

- Industrial collaborations: Pierre Fabre/CERPER, Sanofi, DBV Technologies, Sigvaris and more

- Academic associations: SFI, SFA, SRD, SFD, EADV, IEC

- European consortiums: Cosmetics Europe, IFRA, SIAF Davos Institute

- Corporate foundations: Atopic Dermatitis Foundation /Pierre Fabre, Bioderma Foundation

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Annex 1: Experimental research: current research projects (financing, involved personnel)

AXE 1: ECZEMA INDUCTION

- *Project 1* – Activation of innate immunity by allergens: haptens detoxification mechanisms (ANR project Allergochem, VL/MV). We are investigating the role of a transcription factor (Nrf2) that plays a key role in the cell detoxification process against chemicals and inhibits or limits sensitization to the haptens present in our environment.
- PROJECT 2 – Contribution of tissue-resident memory T cells to eczema recurrence, severity and chronicity (academic/industrial collaboration, PG/EO/MV). We are looking into why eczema tends to recur in previously-affected zones, and particularly trying to shed light on the phenotype, specificity and functions of tissue-resident memory T cells that persist in the skin for weeks and even months.

AXE 2: ECZEMA AND DELAYED DRUG ALLERGY EXPRESSION

- Project 3 – Catalogue of cytotoxic lymphocytes responsible for eczema and drug allergy skin lesions (ANR project SCARs, national reference center, AV/AM/MV). We are seeking to identify the factors responsible for the severity of various forms of drug allergy. This aspect is at the heart of our translational research in patients with drug allergies.

AXE 3: REGULATION OF SKIN INFLAMMATION AND INDUCTION OF TOLERANCE

- Project 4 – regulatory T cells involved in eczema control (CB/AN). We intend to identify the main signaling pathways involved in the activation of CD4+Foxp3+ regulatory T cells in eczema (preclinical models, patients).
- Project 5 – Extracorporeal photopheresis, (French Blood Agency, AGP/OH). Extracorporeal photopheresis (ECP) is a procedure used to (re)induce immune tolerance in many transplant recipients with graft versus host disease, or in patients with certain autoimmune diseases. Our goal is to understand the immune mechanisms underlying that tolerance reinduction.
- Project 6 – Epicutaneous administration of specific immunotherapy (industrial collaboration, LL/MV). Using a murine model, we are hoping to identify mechanisms that will enable allergy desensitization by way of a device that continuously administers low-dose antigens to prevent future allergic reactions.

AXE 4: THE MICROBIOTA AND SKIN INFLAMMATION

- Project 7 – The contribution of saprophytic or pathogenic microorganisms to the development of skin allergies (CIRI/industrial collaboration, AM/MV). We are exploring the role of the skin flora in the development of lesions in atopic dermatitis to hopefully identify novel candidate therapies capable of countering the virulence of certain bacterial strains and thus interfering with the development of the disease.

AXE 5: DIAGNOSTIC AND THERAPEUTIC APPLICATIONS – (clinical and industrial collaborations)

- Project 8 – *in vitro* diagnosis of allergic contact dermatitis (MODAL project, industrial consortium, EB/AN/MV). We wish to develop two new *in vitro* diagnostic tests for skin allergies, i.e., a medical device for bedside diagnosis and an immunobiological test.
- Project 9 – Prediction of the allergenicity of chemical compounds. In collaboration with the European Union of Cosmetics Manufacturers, we are pursuing the development of an *in vitro* test, called the "human T cell priming assay" (hTCPA), for the prediction of the allergic potential of chemicals.

Annex 2: Eczema Research Topic: current goals

- Continue our basic and translational research on eczema
- Improve our regional, national and international visibility and valorize our work (publications, conferences)
- Develop telemedicine for eczema
- Optimize the adolescent-adult transition with pediatricians
- Deploy a dressing service in the EFA facility for patients with AD flare-ups
- Favor private practice-hospital care interactions for systemic AD treatment initiation and follow-up
- Ease access to the EFA facility and allergology tests for the private-practice physicians within the CEE
- Improve the traceability of our cohort

Annex 3: French abbreviations retained in the text

ARS	*Agence Régionale de Santé*
CEE	*Centre Expert Eczémas*
CHU	*Centre Hospitalier Universitaire*
CIRI	*Centre International de Recherche en Infectiologie*
CNRS	*Centre National de la Recherche Scientifique*
COORG	*Comité d' Organisation*
DAN	*dossier d'activité nouvelle*
DES	*Diplôme d'Études Spécialisées*
DESC	*Diplôme d'Études Spécialisées Complémentaires*
DFASM	*Diplôme de Formation Approfondie en Sciences Médicales*
DIU	*Diplôme Interuniversitaire*
DUFRAL	*Diplôme Universitaire Francophone d'Allergologie*
EFA	*Exploration Fonctionnelle Allergologique*
ENS	*École Normale Supérieure*
ETP	*Éducation thérapeutique*
FDA	*Fondation pour la Dermatite Atopique*
FST	*Formation Spécialisée Transversale*
GERDA-REVIDAL	*Groupe d'Étude et de Recherche en dermato-Allergologie- Réseau de vigilance en Dermato-Allergologie*
GREAT	*Groupe de Recherche sur l'Eczéma Atopique*
HCL	*Hospices Civils de Lyon*
IFRA	*Institut de Formation Rhône-Alpes*
Inserm	*Institut National de la Santé et de la Recherche Médicale*
LyREC	*Lyon Recherche Clinique*
PAM	*Pôle Activité Médecine*
PHRC	*Programme Hospitalier De Recherche Clinique*
SFA	*Société Française d'Allergologie*
SFD	*Société Française de Dermatologie*
SFI	*Société Française d'Immunologie*
SIAF	*Service interministériel des Archives de France*
SRD	*Société de Recherche en Dermatologie*
TPA CAP	*Programme Thérapeutique d'Accompagnement dans les affections chroniques et allergiques de la peau*
UF	*Unité Fonctionnelle*
URCI-LS	*Unité de Recherche Clinique en Immunologie Lyon Sud*