CTMA

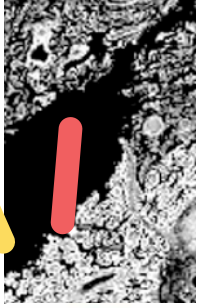
"The Centre de Technologies Moléculaires Appliquées (CTMA - Centre for Applied Molecular Technologies)" is a mixed academic-clinical-military biotechnological platform mutualizing the resources of three partners:

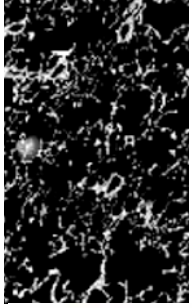
UCL/IREC (Université catholique de Louvain/Institut de recherche expérimentale et clinique). CTMA is the IREC-reference biotechnological platform (genetics and molecular genetics); it therefore directly supports IREC-related research activities while also developing proprietary research.

CTMA carries out clinical routine analysis and clinical research in the field of genetics and molecular genetics to support the medical activity of the academic hospital "Cliniques universitaires Saint-Luc" (CUSL).

MOD (Ministry of Belgian Defence). CTMA hosts several research projects and activities for the MOD to improve the detection and identification of biological threats in the CBRN domain (Chemical, Bacteriological, Radiological & Nuclear threats) spectrum. As such, CTMA is the "Biothreat control unit of the Defence Laboratory Department (DLD)" and is therefore specifically named DLD-Bio; from there its full acronym CTMA/DLD-Bio.

CTMA/DLD-Bio is also actively developing service activity for industry by producing fungal biomass for the preparation of vaccines in its CTMA-MYCO premises at Louvain-La-Neuve.





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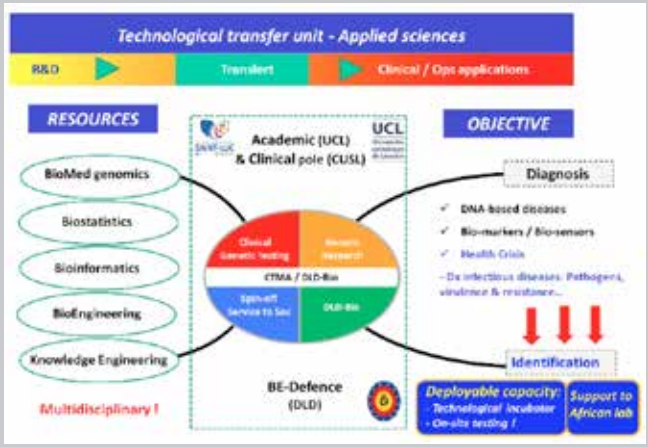
The cooperation between UCL/CTMA and the Belgian Defense has been formalized in a convention framework signed on 30 August 2016.
https://uclouvain.be/fr/sciencetoday/actualites/une-convention-de-recherche-inedite-entre-la-defense-et-l-rsquo-ucl.html

Research Thematics and 2017 Results

CTMA/DLD-Bio is active in microbial research (bacteria, viruses, helminths...) particularly in the diagnostic field, the characterization of virulence and resistance genomic determinants and the relationship with environment.

Through its involvement in several previous EC FP7 and current HORIZON 2020, the unit has developed a rapidly deployable bio-laboratory capacity thanks to the ESA funded B-LiFE project and used it as an operational capacity in case of health crisis or as testbed (technological incubator) for developing and/or testing emerging technologies for use under field conditions. The design and validation of new emerging technologies, including nanotechnologies, encompass multiplex immuno-chromatographic lateral flow assay and 3d generation sequencing for a better detection and protection against known and unknown biological agents, DNA- and RNA-based profiling of biomarkers in malignant and inflammatory diseases, genome characterization by re-sequencing and related signal processing, machine learning and bio-statistical analysis. CTMA/DLD-Bio is also developing decontamination methods.
As pictured here below the R&D activities imply multidisciplinary resources (Bio-medical genomics, -statistics, -informatics and engineering).



The R&D activities are interconnected and benefits from funding by the Belgian Defense, the Brussels (Innoviris, WBI) and Walloon (BioWin and WALinnov) regions, Federal (Defence, BELSPO, Food Chain Safety) and international institutions (EC, EDA and ESA).

CTMA/DLD-Bio is developing and continuously improving its rapidly deployable bio-laboratory for many years. This mobile lab can be scalable from a light version packed in a few flight cases to a fully autonomous and self-sufficient assembly with 2 fully equipped operational tent labs working simultaneously.

B-LiFE:
Biological Light Fieldable Laboratory for Emergencies
Phase II /Demonstration

Funding: ESA IAP Artes 20 (2014-2017)
Mostafa BENTAHIR, Nicolas DUBOIS, Jean-Luc GALA, Jean-Paul MARCEL, Leonid IRENGE, Alexander VYBORNOV, Olga VYBORNOVA

The successful management of sanitary crises relies on the ability to perform rapid detection and identification of pathogens. National and international agencies dealing with the response to bio-security crises need rapidly deployable capacities carrying out analyses close to the crisis area, and equipped with autonomous transmission and geo-location capabilities. The B-LiFE system contributes to fill this gap.

The B-LiFE system integrates space technologies, i.e. satellite telecommunications to communicate with the distant reach back home base laboratory, stakeholders and end users, GNSS (Global Navigation Satellite System) for geo-location and Earth Observation for site selection and monitoring. B-LiFE is also equipped with management tools (LIMS, decision support software...). B-LiFE has been involved in many exercises (Clueless Snowman in Munich with the Germane Defence Bundeswehr in February 2016 and EC MODEX in Revinge, Sweden in April 2017). The last operational deployment was the support of an Ebola Treatment Unit in Guinea (N'ZEREKORE) during the last Ebola outbreak in West-Africa (2014-2015).

Pictures of B-LiFE deployed within an Ebola Treatment Center – N'Zerekore (Guinea) (left above), Satellite Antenna (right above) and inside the Bio laboratory (left and right below)

In 2017 B-LiFE has successfully passed the EU certification as autonomous module belonging to the European Emergency response Capacity (EERC) and part of the European Medical Corps (EMC) (also known as voluntary pool), established under the EU Civil Protection Mechanism (EUCPM). Through EERC/EMC, teams and equipment from the EU Member States can be rapidly deployed to provide worldwide medical assistance and public health expertise in response to national and international emergencies.

Between two deployments, CTMA/DLD-Bio is continuously developing new diagnostic tools for sample analysis usable under field conditions in the B-LiFE laboratory.

HFM14/8: Novel multiplex method for identification of genetically modified or acquired bacterial resistance mechanisms

Funding: Belgian Defense Research Program (2014-2018)
Yann DECACCHE

Several assays previously developed and validated in the framework of research studies are now integrated in a multiplex, single, simple, rapid and sensitive method for assessing the antimicrobial resistance of clinical pathogens involved in nosocomial infections. The study enters its final stage in late 2017 – early 2018 by issuing a new method which targets a fast and reliable identification of resistance markers in bioterrorism-related class III infectious agents (i.e., B. anthracis, Y. pestis, F. tularensis, B. melitensis and B. Mallei): the complete process between sample receipt and genetic characterization of resistance markers lasts about 3 hours. The DNA purification of the bacteria present in the sample is followed by PCR-specific amplification of the targeted resistance markers and then a search by pyrosequencing for mutations causing resistance.

HFM 17-4: Development of on-site Next Generation Sequencing (NGS) and shotgun metagenomic analysis for unambiguous characterization of unknown and emerging agents in environmental and biological samples

Funding: Belgian Defense Research Program (2017-2021)
Catherine DUMONT, Oumaima LAKCHER

Started in midd-2017, this study aims to circumvent the limitations of current identification assays, i.e. the need for multiple targeted diagnostic tests to cover clinical syndromes and all related differential diagnoses and the limiting use of tiny parts of target genomes. To do so, a shotgun metagenomic sequencing approach is used for the identification of "unknown viral and bacterial agents" using the bench-top MiSeq-Illumina Next Generation Sequencing (NGS) platform and a pre-analytical enrichment step. We aim to optimize the identification workflow and to adapt it to the pocket sized MinION® (Oxford Nanopore) NGS in order to enable us to carry out NGS analysis in the B-LiFE fieldable bio-laboratory in case of public health issues requiring the B-LiFE laboratory deployment.

HFM 17-3: Development of innovative methods for ultra-fast amplification and specific detection of high pathogenic bio-agents (CBRN) on Operation Theater

Funding: Belgian Defense Research Program (2017-2022)
Mostafa BENTAHIR

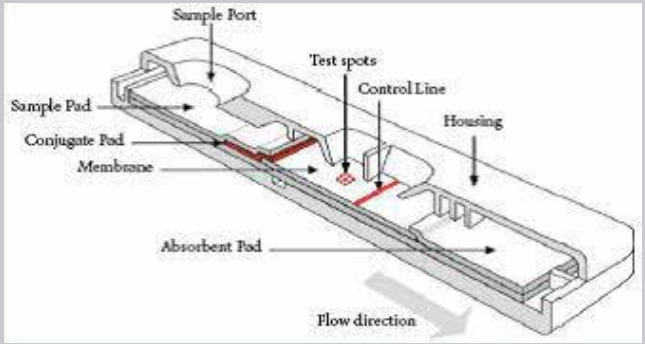
The study started in late 2017. A panel of assays based on high-speed isothermal genomic amplification will be used to rapidly identify highly pathogenic biological agents in a field setting. Lyophilized reagents will be tested and validated for use under field conditions in the B-LiFE laboratory.

ALLERT: Handheld Allergens Detector

Funding: RW BioWin (2014 – 2018)

Jamal BADIR, Benjamin SMITS, Bertrand BEARZATTO, Jérôme AMBROISE, Olga MINEEVA-SWANGO, Auxane LADANG, Nicolas DUBOIS

The study developed a portable, multiplex, qualitative food allergen detection system ("yes/ no" response) usable in field conditions booth by food industry and patients. This low-cost assay enables unexperienced users to quicly (results within 15 min) and simultaneously assess the presence of several key allergens.
The Chromatographic Lateral Flow ImmunoAssay (LFIA) is embedded into a casing and analysed by an electronic reader fitted with a high resolution camera, an algorithm for analysis and image processing and an automatic transfer of results.
The LFIA consists of several elements assembled using an adhesive backing card. Target antigens are captured by



the specific antibodies present in the conjugate pad and flow by capillarity through the membrane. This complex antibody-antigen is detected at the level of the test spots. In 2017 the LFIA passed the proof-of-concept of multiplexing 6 antigens.

TOXINE-ID: Specific multiplex and immuno-lateral flow detection of a well-defined panel of toxins inside a representative food sample

Funding: WALInnov (2017-2021)
Jamal BADIR, Mostafa BENTAHIR, Auxane LADANG, Benjamin SMITS, Florencia LINERO, Olga MINNEVA-SWANGO

Accidental or intentional food poisonings are a source of growing concern for public health authorities and stakeholders in the food chain (producers, consumers). A portable detection system, multiplex immunochromogenic device also called lateral-flow based assays (LFA), is developed to provide a rapid, reliable and qualitative multiplex detection and identification (answer yes/no) of food toxins (i.e, toxin A, B, and E from clostridium botulinum; saphylococcus aureus enterotoxins A and B; shellfish toxins (saxitoxin, okadaic acid, and domoic acid); myco-toxins (aflatoxin, ochratoxin).

CTMA/DLD-Bio is continuously developing new methods for monitoring the quality of inactivation and decontamination procedures such as those used under operational field conditions when deploying the B-LiFE laboratory.

MSP 16-4: Development of procedures for biological agent inactivation to enhance biosafety conditions during the procedure of identification under field conditions

Funding: Belgian Defense Research Program (2016-2019)
Cathy DELCORPS, Stéphane VAN CAUWENBERGHE

Different methods of inactivation, (chemical methods with or without additional exposure to UV) tested on different models of biological agents will be used to assess agents viability and to reach the best compromise in terms of specificity and sensitivity of their real-time identification.

Risk Assessment for chemical and biological exposure after decontamination (RACED) - European Defense Agency (EDA), 2d Joint Investment Programme on CBRN Issues (JIP-CBRN2).

Funding: EDA (2015-2018)
Mostafa BENTAHIR, Florencia LINERO

In military protection against chemical and biological (CB) warfare agents, decontamination is a crucial step. For ensuring a successful response to an attack involving CB agents, it is essential to clean contaminated surfaces well enough to avoid users' contamination.
RACED toke the following staged approach: (1.) Decontaminate a representative number of CB agents / surfaces by standard means and procedures. (2.) Apply state-of-the art analytical and micro/molecular biological assays to identify and quantify residual agent. (3.) Simulate and understand transport from decontaminated surface to exposure of human airways and skin. (4.) Relate exposure to toxicity and infectiousness, respectively.
In late 2017 – early 2018 the study outcome, a risk management tool, has been written which will enable operational decision makers either to rationally and confidently declare an asset clean, or to re-launch a decontamination step, or to clear away asset that remain dangerous for use.

The EU faces growing security and health threats, e.g. an intentional use of CBRN agents, large external crises, and pandemics due to the convergence of risk factors driving disease emergence, amplification and dissemination of pathogens with pandemic potential. Protecting the health and security of EU citizens against these threats requires a coherent response by all stakeholders.
For several years, CTMA/DLD-Bio has actively contributed by addressing those challenges as coordinator, end user or as operator of the B-LiFE laboratory on EC projects.

PANDEM - Pandemic Risk and Emergency Management – Phase 1

Funding : EU 7FP (2015-2017)
Anne-Sophie PIETTE

PANDEM Phase 1 assessed current pandemic preparedness and response tools, systems and practice at national, EU and global level in priority areas including risk assessment and surveillance, communication and public information, governance and legal frameworks.
End of 2017 PANDEM identified gaps and improvement needs leading to the development of viable innovative concepts focused on the needs and requirements of users and first responders across the spectrum of pandemic risk management.

Horizon2020 eNOTICE: European Network Of CBRN TraIning Centers

Funding: EU H2020 (2017-2022)
Olga VYBORNOVA, Aleksandr VYBORNOV
Project coordinator

The eNOTICE project seeks to better European preparedness, resilience and incident response to CBRN attacks and emerging threats through close multi-(stakeholders) and single-discipline (practitioners) interactions. Whilst using efficiently investments made across Europe in demonstration, testing, and training facilities for practitioners, this novel concept will issue meaningful users-guided recommendations to the EU R&D program, enhance CBRN product performance and competitiveness in order to reach long term sustainability.
eNOTICE is building a dynamic, functional and sustainable pan-European network of CBRN training centres (CBRN TC), testing and demonstration sites strengthening capacity building in training and users-driven innovation and research, based on well-identified needs.
The CBRN TC network organizes joint activities, training and debriefing, using real-life or simulated situations (e.g. field exercises, table top, serious gaming and simulations), with external partners, in order to foster the identification of 'genuine users' needs with users-driven technological solutions. Since late 2017 CTMA is preparing an exercise to be held in June 2018 involving the Belgian Crisis Centre, Civil Protection and the Scientific Police, an Hungarian Bio lab and CTMA B-LiFE bio Laboratory.

Horizon2020 ENCIRCLE: EuropeaN CBRN Innovation for the maRket CLustEr

Funding: EU H2020 (2017-2021)
Olga Vybornova, Anne-Sophie PIETTE, Nicolas DUBOIS
Project coordinator

To improve its resilience to new CBRN attacks and threats, the EU needs a specialized, efficient and sustainable industry. Competitiveness requests a less fragmented EU market.
ENCIRCLE uses an innovative approach to reach address

these issues in a short to long term perspective so that SMEs and large industries can propose and invest in the best end users-guided innovations.
The main expected impact is to enhance the EU CBRN industry competitiveness and enlarge its market while improving the impact and efficiency of EU research and innovation on CBRN preparedness, response, resilience and recovery.

Related Publications 2016-2017

Publications 2017

Irenge L, Dindart JM, Gala, JL.
Biochemical testing in a laboratory tent and semi-intensive care of Ebola patients on-site in a remote part of Guinea: a paradigm shift based on a bleach-sensitive point-of-care device. ***Clinical Chemistry Laboratory Medicine***, (2017); DOI 10.1515/cclm-(2016)-0456.

Mahy P, Collard JM, Gala JL, Herman P., De Groofs D, Quoilin S, and Sneyers M.
Health crisis due to infectious and communicable diseases: European preparedness and response tools in an international context. ***Journal of Business Continuity and Emergency Planning***, (2017); 10, 353-366.

Palich R, Irenge L, Barte de Sainte Fare E, Augier A, Malvy D, Gala JL.
Ebola virus RNA detection on fomites in close proximity to confirmed Ebola patients; N'Zerekore, Guinea, (2015).
PLoS One; May 11, (2017)
https://doi.org/10.1371/journal.pone.0177350

Nguyen THT, Guedj J, Anglaret X, Laouénan C, Madelain V, Taburet AM, Baize S, Sissoko D, Pastorino B, Rodallec A, Piorkowski G, Carazo S, Conde MN, Gala JL, Akoi Bore J, Carbonnelle C, Jacquot F, Raoul H, Malvy D, de Lamballerie X, Mentre F, and JIKI study group. Favipiravir pharmacokinetics in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted.
PLoS Neglected Tropical Diseases
11(2):e0005389.
doi:10.1371/journal.pntd.0005389

Selection of Publications 2016 with CTMA/DLD-Bio as first and/or last authorship

Vybornova O., Gala JL. Decision Support in a Fieldable Laboratory Management during an Epidemic Outbreak of Disease.
Journal of Humanitarian Logistics and Supply Chain Management, 2016; 6, 264-295.

Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, Camara AM, Maes P, Shepherd S, Danel S, Carazo S, Conde MN, Gala JL, et al. Experimental treatment of with favipiravir for Ebola virus disease (the JIKI Trial): A historically-controlled, single arm proof-of-concept trial in Guinea.
PLoS Med 13(3):e1001967.doi:10.1371/journal.pmed.1001967.

Vybornova O, Dubois N, Gueubel R, Gala JL. Information Management Supporting Deployment of a Light Fieldable Laboratory: a Case for Ebola Crisis.
Universal Journal of Management,
4(1): 16-28, (2016).

IREC technological Platforms

Caroline BOUZIN
IREC Imaging Platform 2IP

Davide BRUSA
Cytometry

Jean-Luc GALA
CTMA

Jérôme AMBROISE
CTMA

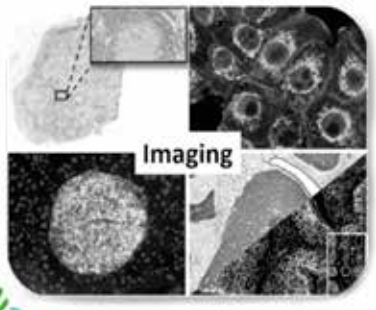
Bertrand BEARZATTO
CTMA

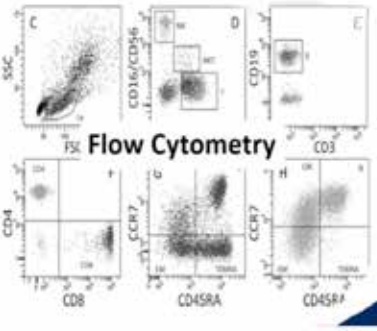
Solveig MOUTERDE
IREC Animal facility

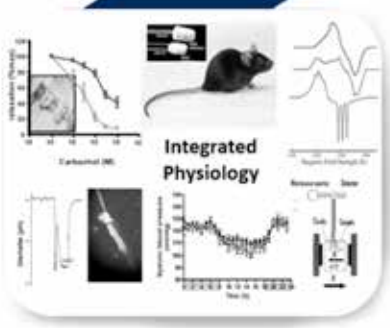
The objectives targeted by the technological platforms are:

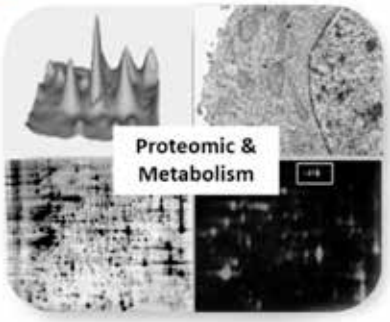
- the optimal use and maintenance of centralized high-end equipment;
- costs optimization ;
- the acquisition of new equipments according to common needs and technical advances;
- knowledge transfer to students and researchers;
- continuous training of the logisticians and dissemination of methodological innovation;
- collaboration creation or reinforcement ;
- improvement of our competitiveness.

In 2017, a floor (55+2) dedicated to the IREC platforms (except for CTMA) has been renovated and devices have been centralized together with their respective logisticians and technicians.









CTMA

9 ..... Research groups
391 ..... NGS Libraries Preparation/analysis
ILLUMINA: MiSeq/HiSeq/NovaSeq
41 .....- TRANSCRIPTOMIC (RNA-SEQ)
200 .....- GENOMIC (De NOVO / Resequencing)
150 - METAGENOMIC (Targeted / Shotgun)
Oxford Nanopore: MinION
11.....- GENOMIC (De NOVO / Resequencing)
1100 ... GB of NGS DATA sequenced/analyzed

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Bertrand Bearzatto
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Proposed services

As technological platform of the IREC institute, CTMA offers technological support and expertise to IREC-researchers members. CTMA is composed of a multidisciplinary team including doctors, PhD in biology, biostatistics and engineers. Two researchers (J. Ambroise and B Bearzatto) are dedicated to the services to IREC community.

CTMA provides to the IREC researchers an access and a support to use numerous molecular technologies including quantitative PCR, Sanger Sequencing, Pyrosequencing, Next-Generation-Sequencing (NGS) (Illumina-Miseq, Oxford Nanopore-MinION), and microarrays facilities (Affymetrix, Agilent, custom glass slide arrays...).

This support integrates the experimental design (technological choice, experimental workflow, sample size), the pre-analytical (DNA and RNA quantification and Quality control) and analytical steps, as well as the bioinformatic and biostatistic analysis of the data.

Since 2014, CTMA has particularly developed its Illumina platform and associated expertise through different NGS applications:

- Whole-genome sequencing
- Amplicon panel sequencing
- Metagenomics (Shotgun / Targetted)
- mRNA sequencing
- Targeted RNA sequencing
-

Since 2016, CTMA participated to the MinION Access Program from Oxford Nanopore. Ever since, CTMA has acquired a steadily larger expertise in the preparation, use, and analysis of the MinION long reads sequencer

- Resequencing of Bacterial, viral and protist whole genome.

In late 2017 CTMA also acquired on his own budget a new 8 capillaries Sanger sequencing machine (Beckman Coulter : GenomeLab GeXP).

PUBLICATIONS 2017

CTMA has been involved in a series of projects leading to specific publications

1. TP53 mutations in p53-negative dysplastic urothelial cells from Belgian AAN patients:
New evidence for aristolochic acid-induced molecular pathogenesis and carcinogenesis
S Aydin, J Ambroise, JP Cosyns, JL Gala
Mutation Research/Genetic Toxicology and Environmental Mutagenesis 818, 17-26

2. Salvage surgery in recurrent head and neck squamous cell carcinoma: Oncologic outcome and predictors of disease free survival
M Hamoir, E Holvoet, J Ambroise, B Lengelé, S Schmitz
Oral oncology 67, 1-9

3. The histological quantification of alpha‐smooth muscle actin predicts future graft fibrosis in pediatric liver transplant recipients
S Varma, X Stéphenne, M Komuta, C Bouzin, J Ambroise, F Smets, R Redings, E Sokal
Pediatric transplantation 21 (1)

4. Blood-testis barrier organization in a prepubertal and peripubertal boys' cohort: correlation with Sertoli cell maturation, clinical puberty and testicular anatomopathol...
F De Michele, MG Giudice, J Poels, F De Smedt, J Ambroise, C Wyns
Human Reproduction 32, i7