UNIVERSITÉ LAVAL

Consiglio Nazionale delle Ricerche

AGREEMENT FOR THE RENEWAL OF THE
JOINT INTERNATIONAL RESEARCH UNIT (JIRU)

BETWEEN

Université Laval, hereinafter "Université Laval," a private corporation duly incorporated under the provisions of an act of the National Assembly, sanctioned on December 8, 1970, (S.Q. 1970, c. 78), having its head office at 2320, rue des Bibliothèques, Pavillon des Sciences de l'éducation Québec City, Province of Québec, Canada, G1V OA6, herein represented by its Rector, Mrs. Sophie D'Amours, who declares that she is duly authorized to act as representative of the University;

AND

Consiglio Nazionale delle Ricerche, hereinafter the "CNR" a public Italian scientific institution with a mission to develop, encourage, transfer, evaluate and value research in the main areas of knowledge aiming at the scientific, cultural, technological, economic and social development of the country, the head office of which is located at Rome, Piazzale Aldo Moro, 7, herein represented by its President, Professor Maria Chiara Carrozza, who declares that she is duly authorized to act as representative of the CNR;

Hereinafter the "Parties" or, individually, the "Party"

CONSIDERING that the Parties signed an Agreement in February 2016 to create the Joint International Research Unit for chemical and biomolecular research on the microbiome and its impact on metabolic health and nutrition (JIRU MicroMeNu);

CONSIDERING the achievements of the JIRU MicroMeNu over the past eight years;

CONSIDERING that Pr. Vincenzo Di Marzo, Full Professor at Université Laval and former Research Director of the Institute of Biomolecular Chemistry of the CNR, was originally granted a Canada Excellence Research Chair (hereinafter the "CERC") on the gut microbiome – endocannabinoidome axis in metabolic health at Université Laval, and whose activities since 2017 have created a fruitful substrate for further biomolecular studies on the microbiomes;

CONSIDERING that Pr. Di Marzo continues his research activities at his laboratory in the Institute, thereby allowing him to have access to subsidizing Italian and European organizations;

CONSIDERING Université Laval's intention to maintain a relationship of close cooperation with the CNR for various fundamental and clinical research projects related to Dr. Di Marzo's research activity at Université Laval, through its following faculties: Faculté des sciences de l'agriculture et de l'alimentation, Faculté de médecine, the Institut sur la nutrition et les aliments fonctionnels (INAF), and the Centre de recherche de l'Institut universitaire en cardiologie et pneumologie de Québec–Université Laval (IUCPQ–UL);

CONSIDERING the common intention of the Parties to encourage the exchange of knowledge and the mobility of research teams and students;

CONSIDERING the intention of the Parties to collaborate and to invest in the establishment of a framework to facilitate the transfer of knowledge and technologies as well as the pooling of scientific results for the purpose

of joint publications in this important field of research;

CONSIDERING the common intention of the Parties to make the efforts required to set up a Joint International Research Unit (JIRU) dealing with biomolecular chemistry, the microbiome, nutrition and cardiometabolic and mental health, which may benefit from the work performed in Dr. Di Marzo's CERC and from the work of the Institute of Biomolecular Chemistry of the CNR;

CONSIDERING the common intention of the Parties to establish a governance structure and operating rules for the JIRU;

CONSIDERING the necessity of specifying the terms and conditions regarding intellectual property resulting from the research and innovation work conducted within the projects associated with the JIRU;

CONSIDERING the common interest of the Parties to undertake such collaboration on a reciprocal basis;

THE PARTIES AGREE TO THE FOLLOWING:

The Parties shall renew the JIRU MicroMeNu." This cooperation structure, without a legal personality, is renewed by the Parties for a period of five (5) years from the signature of this **"Agreement."**

The purpose of this Agreement is not to establish, create, make effective or acknowledge a joint venture, mandate, agency, partnership, interest grouping or any other grouping or commercial entity or *de facto* partnership between the constituent Parties, and this Agreement shall not be interpreted so as to establish, create, make effective or acknowledge a joint venture, mandate, agency, partnership, interest grouping or any other grouping or commercial entity or *de facto* partnership between the Parties.

1. **Constituent Parties**

The JIRU is composed by the Parties which are a signatory to this Agreement, and specifically includes the following entities:

- The Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec -Université Laval (IUCPQ-UL);
- The Institut sur la nutrition et les aliments fonctionnels (INAF), which is part of Université Laval;
- The Institute of Biomolecular Chemistry which is part of the CNR;
- The Faculté de médecine from Université Laval
- The Faculté des sciences de l'agriculture et de l'alimentation from Université Laval
- Any other entity in connection with the proposed theme and which the Parties approve in writing.

2. **Objective**

2.1 The objective of the JIRU is to be a world reference in the field of biomolecular chemistry, the microbiome, nutrition and cardiometabolic health through the specialized training it offers, its joint inter-university development model and its capacity to transfer the knowledge and technologies resulting from its work.

2.2 The mission of the JIRU is to encourage networking, expansion and an international presence for the joint research and educational activities of its members.

3. **Governance of the JIRU**

3.1 The governance of the JIRU is ensured by a Steering Committee and a Scientific Committee. If necessary, the Steering Committee may establish any other committee or working group deemed relevant. Depending on the scope of the Projects associated with the JIRU, it may also be necessary to establish project groups specific to a Project

or to a group of Projects.

3.2 The Director of the JIRU shall be unanimously and jointly appointed by the Vice President, Research and Innovation of Université Laval and by the President of the CNR. The Parties agree to appoint Dr. Vincenzo Di Marzo as Director of the JIRU for the five (5) years. The Director of the JIRU shall coordinate the establishment of its organizational structure.

3.3 Steering Committee

3.3.1 Composition

Unless specified otherwise, the members of the Steering Committee are appointed for a term of office of five (5) years.

The following members sit on the Steering Committee of the JIRU:

- The Director of the JIRU;
- The President of the CNR or his/her representative;
- The Vice President, Research and Innovation of Université Laval or his/her representative;
- The Dean of the Faculté de médecine or his/her representative;
- The Dean of the Faculté des sciences de l'agriculture et de l'alimentation or his/her representative;
- The Director of the IUCPQ - UL Research Centre or his/her representative;
- The Director of the INAF or his/her representative;
- The Director of the Institute of Biomolecular Chemistry of the CNR or his/her representative.

The Steering Committee may invite any expert whose presence it considers to be necessary, to attend its meetings, provided said expert signs a confidentiality agreement.

The Steering Committee shall meet at least once a year and as often as necessary, at the Director's initiative. As required, and with the agreement of the committee members, said meetings may be held by teleconference. The Steering Committee makes its decisions on a majority basis. Each constituent Party shall be represented at these meetings. In case of absence, a representative may appoint a replacement.

Minutes shall be taken of each meeting of the Steering Committee. The minutes are forwarded to each member of the Steering Committee.

3.3.2 Responsibilities

The Steering Committee of the JIRU is namely responsible:

- To ensure that the JIRU progresses according to the orientations of the constituent Parties in compliance with the terms of this Agreement;
- To adopt guidelines regarding the management of the following:
    - opportunities, priorities, resources and the cost of Projects (research and innovation, education, transfer, communications, etc.);
    - progress in the implementation of the JIRU, namely concerning its Projects;
    - cooperation to be established with third parties regarding financing, research or innovation.
- To approve the annual activities programming;
- To approve the JIRU's budget;
- To approve the specific Agreements which are proposed by its Director;
- To approve the financial and scientific results submitted to it by the Scientific Committee;
- To rule on any difficulty in interpretation or decision to be made by the JIRU;
- To adopt the policy and conditions of visibility of the JIRU;
- To ensure that public relations, conferences and the dissemination of knowledge correspond to the mission and objectives of the JIRU;

- To establish with the Management Team, a short and simple list harmonized with the practices of the constituent Parties, containing process indicators and results to facilitate a follow up of activities, and specifically JIRU Projects.

3.4 Scientific Committee

3.4.1 Composition

The JIRU Scientific Committee is composed of the following members:

- The Director of the JIRU, who presides the Scientific Committee;
- A maximum of two (2) scientific representatives appointed by each of the constituent Parties, for a term of office of five (5) years, which may be renewed;
- Two (2) external scientific representatives invited by joint agreement of the constituent Parties for a term of five (5) years, provided said representatives sign a confidentiality agreement;
- A maximum of four (4) representatives from the user community or industrial sector, appointed by the constituent Parties for a term of office of five (5) years, which may be renewed, provided said representatives sign a confidentiality agreement.

The Scientific Committee may request that an expert who may have useful knowledge, attend its meetings, provided said expert signs a confidentiality agreement.

3.4.2 Responsibilities

The Scientific Committee shall support the JIRU Director in establishing and coordinating the research and innovation program. To do so, the members of the Scientific Committee shall:

- Support the Director in developing Projects which are to be part of the research and innovation program;
- Study national and international opportunities in connection with calls for tenders or projects in JIRU's field of research and encourage research teams to participate in these financing programs;
- Propose to the Steering Committee guidelines regarding financial, scientific or industrial partnerships;
- Participate in the organization of transfer activities sponsored by the JIRU;

The Scientific Committee shall meet at least once a year or as often as necessary at the Director's request. As required, and with the agreement of the committee members, said meetings may be held by teleconference. Minutes shall be taken of each meeting of the Scientific Committee and shall be forwarded to all committee members.

4. Means Available to the JIRU

4.1 Staff

4.1.1 The JIRU is made up of researchers who are part of the entities and laboratories specified in article 1.

4.1.2 Each of the constituent Parties continues to pay the compensation of its staff members who are made available, as well as all civil, social and tax obligations which must be paid by the employer under its national law. Each of the constituent Parties shall exercise all management prerogatives regarding its staff. Each of the constituent Parties shall ensure that its staff members are covered under industrial accident and professional sickness legislation, without prejudice to any eventual recourse against faulty third parties. As a respective employer, each of the constituent Parties shall exclusively exercise disciplinary measures regarding its own staff members.

4.2 Financial Provisions

4.2.1 Each constituent Parties is responsible for its own budgets devoted to the JIRU's activities. No Party may be required to cover costs which another Party may have incurred with the JIRU. Each of the constituent Parties attributes and manages the budgetary credits which correspond to its own financing and its participation in the JIRU.

4.2.2 The JIRU may respond to calls for projects for national and international financing requests.

4.3 Equipment

4.3.1 Each of the Parties shall designate the infrastructures and the equipment to be used by the JIRU.

4.3.2 Each of the Parties shall remain the owner of its equipment and shall be responsible for its maintenance.

4.3.3 Any equipment or material acquired by one of the Parties for a Project completed within the JIRU shall remain its exclusive property. This Agreement shall not have the effect of transferring the ownership of the equipment or material acquired.

4.3.4 Any equipment or material acquired for the JIRU shall be used on a priority basis for its activities.

5. JIRU Activities

5.1 Specific Agreements

The constituent Parties shall enter into specific agreements (hereinafter "Specific Agreements") for the implementation of this Agreement. These Specific Agreements shall provide the conditions for the performance, financing and schedule for the completion of the Projects in question.

5.2 Research and Innovation

The research and innovation program shall deal with the development, characterization and biological validation of new biomolecules from the microbiome and the most appropriate formulation to improve cardiometabolic health through nutritional approaches. A summary of the program is presented in Appendix 1.

5.3 Education and Residence of Professors and Researchers

5.3.1 The JIRU's research and innovation program shall allow participating professors, researchers and students to work in a unique context including the supervision of graduate students and cotutelles, as the case may be, giving educational sessions through research at all academic levels, travelling and receiving professors and researchers.

5.3.2 The JIRU shall also contribute an added value component to the training of highly qualified personnel in the specified fields of research and innovation. The proposed activities shall include participation in cutting edge seminars and specialized training in leading edge fields associated with the know-how of JIRU researchers and the needs of the labor market.

5.3.3 The JIRU may also contribute to the development of distance educational activities and/or continuous education, especially for the development of a fellowship program, thereby allowing student and doctoral student exchanges.

5.4 Transfer and Scientific Activities

5.4.1 The transfer of knowledge and technologies to the receiving communities shall be at the heart of all of the JIRU's endeavours and actions. Proposed activities shall allow for an increased representation of the JIRU within regional, national and international research networks as well as the dissemination of its researchers' accomplishments. The following is agreed for the purpose of attaining these objectives in connection with transfers:

- Organizing theme seminars by video-conferencing given by JIRU researchers or by distinguished guest lecturers;
- Organize when necessary, scientific "JIRU" meetings, alternatively in Italy and Quebec, to present and enhance researchers' accomplishments;

- Participate in broad-ranging scientific and commercial initiatives to promote the results of research as a result of the JIRU's work.

6. Confidentiality and Intellectual Property

6.1 Definitions

"Intellectual Property Rights" means all intellectual property rights, whether registered or not, including all rights regarding patents, copyright, industrial designs, printed circuits, inventions (patentable or not), discoveries, trade secrets, know-how, domain names, trade-marks, trade- names and other rights acknowledged under statutory or general law in the above, including any application for protection.

"Prior Intellectual Property Rights" means all the intellectual property rights defined above, which are devised, developed, acquired or otherwise obtained by any of the Parties prior to the coming into force of this Agreement. Intellectual property rights acquired by any Party during the performance of this Agreement but independently of this Agreement as a result of its own research shall also be considered as Prior Intellectual Property Rights.

"New Intellectual Property" means intellectual property which issues from a Result designed, obtained and/or developed by any of the Parties or by several constituent Parties in JIRU research work.

"Confidential Information" means any information disclosed in writing, graphically, verbally or physically, including without limitation, scientific knowledge, know-how, processes, inventions, technical information, formulas, products, plans, biological material and software belonging to or under the control of any Party. Confidential Information shall be identified as such when it is disclosed, and if disclosed orally, said information shall be protected in writing within thirty (30) days and marked as being confidential.

"Results" means ideas, scientific and technical knowledge, inventions or new processes, studies under way and the results of studies, reports, trials, know-how, biological material, software, information developed *"ex nihilo"* and which result from the JIRU, no matter of what nature or type of media, whether or not said results are an invention, and whether or not they are covered by intellectual property rights created by one or several of the Parties as a result of the JIRU.

"Own Results" are results which are developed by only one Party.

"Joint Results" are results which are developed by two or more Parties.

6.2 Confidentiality

6.2.1 A Party shall not disclose or disseminate Confidential Information to anyone, except to its own staff members who have a need to know for the purposes of this Agreement.

6.2.2 A Party shall take reasonable measures to ensure compliance with these confidentiality obligations by its staff by using efforts which are similar to those it uses to protect its own confidential information. A Party shall not use Confidential Information for purposes other than for which said Confidential Information was disclosed.

6.2.3 These confidentiality obligations shall not apply to information that:

a. Is already known to the receiving Party in the performance of this Agreement;
b. Is obtained by the Party from another source without a confidentiality obligation, as shown by valid physical evidence thereof;
c. Is part of the public domain at the time of its disclosure or which is rendered public otherwise than by the actions or faults of the receiving Party;

d. Is developed independently by the receiving Party as shown by valid physical evidence thereof;
e. Is disclosed by a Party which is required to do so under regulations or a decision of a judicial or administrative authority.

6.2.4 Nothing mentioned above shall prevent:
a. The submission of a thesis or a student's brief to examiners, pursuant to the usual rules and practices of the Parties, provided that as the case may be, these examiners are bound by confidentiality provisions which are no less stringent than those provided above;
b. The requirement a Party may have to issue a scientific activities report to its own government authorities or its tutorship organization. Such a report shall not be considered as a public disclosure, but shall be an internai document for that Party.

6.2.5 The termination or the expiry of this Agreement shall not release the Parties from the rights and obligations which result from this article until the information in question is in the public domain.

6.3 **Management of Intellectual Property Rights**

6.3.1 Each of the Parties shall remain the exclusive owner of the Prior Intellectual Property Rights which are its own.

6.3.2 Any New Intellectual Propeıy developed individually by a Party on the basis of its Own Results in a Project belongs exclusively to that Party.

6.3.3 Any New Intellectual Property developed jointly by the two Parties on the basis of Joint Results shall be the joint property of the two Parties according to a share that shall be established at a later date on the basis of the intellectual, financial, material and human contributions by the Parties.

6.3.4 Notwithstanding the above, a student shall remain the owner of the copyright to his/her essay, master's thesis or doctorate's thesis.

6.3.5 In any case in which the Joint Results could possibly be filed for a patent application, a co-ownership agreement shall be established by the Parties concerned as soon as possible and in any case before any industrial or commercial use, so as to determine the shares as well as the conditions for the management of their rights and obligations on the basis of the intellectual, financial, material and human contributions of each Party which contributed to obtaining said Joint Result.

6.3.6 Use of Results for Research Purposes

The Parties may use the Results of the JIRU free of charge, whether they are their Own Results or Joint Results, for their research purposes, to the exclusion of any direct or indirect use for commercial or industrial purposes under the following conditions:
a. The Results in the public domain shall be freely usable;
b. Results which are not in the public domain
   - shall be freely usable for internal research purposes by the Parties;
   - Own Results shall be freely usable for collaborative research by the Party to whom they exclusively belong;
   - Joint Results may be used by a Pruiy for collaborative research purposes following an agreement with the other Party. Said agreement cannot be refused except for duly warranted reasons.

6.3.7 Use of the Results for Industrial or Commercial Purposes

In case the work should entail Results which are likely to be used for industrial and/or commercial purposes (whether obtained by one Party or jointly), the Parties shall work together within the Scientific Committee to examine the conditions according to which the Results may be used.

7. Publications of results

7.1 The Parties shall share all information required to complete the JIRU joint research and innovation program. Publication of Results shall take place according to the rules applicable within the scientific community.

7.2 Publications resulting from the work conducted jointly in the JIRU shall mention the connection with the Parties. Said Publications shall mention the following: "Research conducted by the "Joint International Research Unit on Chemical and Biomolecular Research of the Microbiome: Nutritional Applications and Impact on Metabolic Health".

7.3 Throughout the duration of this Agreement and in the two (2) years which follow its termination or expiry, each Party shall request the consent of the Director of the JIRU when it considers any publications regarding JIRU Projects. Such consent may only be refused on serious and legitimate grounds (protection under an intellectual property right, commercial use). The lack of an answer by the Director within one (1) month shall be considered to be an authorization.

7.4 No publication or communication may be postponed for more than three (3) months because of a disagreement between the Parties, unless such publication or communication contains important information of an industrial, commercial or strategic nature regarding the activities of one Party or the other. In such a case, the Steering Committee shall decide on the nature and duration of the confidentiality.

Nevertheless, in the latter case, the staff members who participate in the activities of the JIRU may communicate their results in a confidential report to their hierarchical authorities.

7.5 When a student participates in obtaining Results which are specified in article 6.3.7, any delay in the public dissemination of these Results cannot exceed a period of one (1) year. The possible delay required before public disclosure of a student thesis, brief or other of these publications shall not hinder the award of the diploma to the student.

8. Visibility

It is agreed to develop a brand image for the JIRU. This should be done by showcasing the contributions of the founding organizations.

9. Liability

9.1 Each of the Parties is Hable according to the provisions of the general law, for the damage its staff members may cause to third parties and to the staff of the other Party during the performance of this Agreement, including damage caused by the use of material and equipment belonging to the other Party and made available to those staff members.

9.2 Each of the Parties shall support the damage caused to its property during the performance of this Agreement, without any recourse against the other Party, except in case of gross negligence or intentional fault.

10. Notices

Any notice or communication hereunder shall be in writing and sent to the recipient by email using the contact information below:

UNIVERSITÉ LAVAL

Consiglio Nazionale delle Ricerche

For Université Laval: Kaouther Bessrour
Director
Bureau des chaires et des entités structurantes
Vice-rectorate for Research and Innovation
Université Laval
Pavillon Jeanne-Lapointe, Room 1458
2320 des Bibliothèques
Quebec City, Quebec G1V OA6
Email: kaouther.bessrour@vrr.ulaval.ca

For the CNR: Unità Relazioni Internazionali
Piazzale Aldo Moro, 7
00185 Roma, Italy
Email: segreteria.relint@cnr.it

11. Scope and Duration of the Agreement

11.1 This Agreement shall be in force for five (5) years following its signature. It may be renewed by the mutual written consent of the constituent Parties.

11.2 This Agreement comes into force when it is signed by all of the constituent Parties.

12. Termination

12.1 In case of a default in performing one of the obligations assumed under this Agreement, a Party may terminate said Agreement by giving the defaulting Party a prior written notice of thirty (30) days. If the defaulting Party refuses or neglects to remedy said default within this time limit, termination shall be effective without any other notice or time limit.

12.2 Each Party may terminate this Agreement by giving a prior written notice of six (6) months to the other Party.

12.3 In case of termination or at the expiry of this Agreement, each Party shall pay all expenses in connection with the work performed by its members to complete Projects under way, as well as to respect reasonable joint commitments made before the termination or expiry date. The Parties shall take measures not to cause any prejudice to the students associated with the Projects under way. Notwithstanding the termination or expiry of this Agreement, the provisions of articles 6 and 7 shall remain in force.

13 Membership

The JIRU Steering Committee shall examine any application for membership by third parties. To be accepted, all of the Parties shall unanimously consent in writing to such an application. Such consent shall be included in this Agreement by means of an amendment to the present Agreement.

14. Applicable Legislation and Settlement of Disputes

14.1 The performance of this Agreement shall be governed by Quebec law for activities conducted in Quebec and by Italian law for activities conducted in Italy.

14.2 The Parties shall strive to settle their disputes by negotiation. In case no settlement may be reached, all disputes shall be governed under the conciliation and arbitration rules of the International Chamber of Commerce by

one or more arbitrators appointed pursuant to said rules.

15. Language

The Parties have expressly agreed that this Agreement be drawn up in English. Les Parties aux présentes ont expressément requis que la présente entente soit rédigée en anglais. Le Parti hanno espressamente richiesto che la presente intesa sia redatta in inglese.

16. Intervention

The following parties intervene in this Agreement: the Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, the Institut sur la nutrition et les aliments fonctionnels, the Faculté des sciences de l'agriculture et de l'alimentation and the Faculté de médecine from Université Laval, which agree to all of the terms and conditions of this Agreement, and acknowledge being bound by it to the extent they are concerned by it and agree to ensure that all of the members of their teams involved in JIRU work are informed of their obligations under this Agreement.

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IN WITNESS WHEREOF, the Parties signed this Agreement in two (2) originals.

Signatories:

Consiglio Nazionale delle Ricerche

Maria Chiara Carrozza
President

Date

Université Laval

Sophie D'Amours
Rector

31 mars 2025

Date

Intervening Parties :

Director of the JIRU MicroMeNu

Date

CNR Institute of Biomolecular Chemistry

27/02/2025

Date

Faculty of Medicine, Université Laval

28/03/2025

Date

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Consiglio Nazionale delle Ricerche

IN WITNESS WHEREOF, the Parties signed this Agreement in two (2) originals.

Signatories:

Consiglio Nazionale delle Ricerche

Maria Chiara Carrozza
President

Date

Université Laval

Sophie D'Amours
Rector

Date

Intervening Parties :

Director of the JIRU MicroMeNu

20-03-2025

Date

CNR Institute of Biomolecular Chemistry

27/02/2025

Date

Faculty of Medicine, Université Laval

Date

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Consiglio Nazionale delle Ricerche

Faculté des sciences de l'agriculture et de l'alimentation, Université Laval

20 mars 2025

Date

Institut sur la nutrition et les aliments fonctionnels, Université Laval

Date

Centre de recherche de l'Institut universitaire en cardiologie et pneumologie de Québec – Université Laval

Date

UNIVERSITÉ LAVAL

Consiglio Nazionale delle Ricerche

Faculté des sciences de l'agriculture et de l'alimentation, Université Laval

_____ _____

Date

Institut sur la nutrition et les aliments fonctionnels, Université Laval

Renée Michaud 20-03-2025

_____ _____

Date

Centre de recherche de l'Institut universitaire en cardiologie et pneumologie de Québec – Université Laval

_____ 20-03-2025

_____

Date

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Appendix 1

Mission, objectives and scientific program of the Joint International Research Unit between the Italian National Research Council (CNR) and Université Laval (UL) on Chemical and Biomolecular Studies on the Microbiome and its Impact on Metabolic Health and Nutrition (JIRU-MicroMeNu, Director: Vincenzo Di Marzo)

Mission

The Joint International Research Unit (JIRU) is a bilateral research unit between the Italian National Research Council (CNR) and Université Laval (UL) of Quebec. It was founded in 2016 following the signature of an agreement of mutual collaboration between the legal representatives of the two institutions. The JIRU aims at strengthening the scientific and technological cooperation between Université Laval and the CNR through exchanges of students and professors in the framework of pioneering bilateral research projects.

Indeed, the JIRU collects experts in the field, coming for example from the Research Centre of the Heart and Lung Institute of UL (IUCPQ – UL), the Institute of Nutrition and Functional Foods (INAF) and the Centre de Nutrition, Santé et Society (NITRISS), from the Faculties of Medicine (FMED) and the of Agricultural and Food Sciences (FSAA) of UL; the Institute of Biomolecular Chemistry (ICB-CNR) and the Departments of Chemical Sciences and Materials Technology, of Biomedical Sciences and of Agricultural and Food Sciences of the CNR. Over the years, however, the JIRU has seen the inclusion in this cooperation also of other European institutions, such as the Université Catholique de Louvain in Bruxelles (Belgium) and the University of Cagliari (Italy), and of several Italian and Canadian private companies in the pharmaceutical, nutraceutical and food science sectors, who also have representatives in the Scientific Committee of the JIRU.

Under the leadership of its director, Prof. Vincenzo Di Marzo (also holder of the Canada Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health, CERC-MEND, https://cerc-mend.chaire.ulaval.ca/en/the-chair/), the JIRU has among its ambitious goals the development of research projects, and the innovation, education and knowledge transfer in the emerging field of the biomolecular study of the microbiomes.
To achieve this general aim, the JIRU intends to continue - thanks to fund raising from national and international financial organizations – its networking, international, scientific and educational activities and joint and interdisciplinary research and training, aiming at promoting the full participation of professors, researchers and students from around the world.
The JIRU will also continue to provide a teaching environment, where seminars, specialized courses and periodic conferences and continuing education will respond to the concrete needs of future health professionals and individuals afflicted by chronic societal disorders, such as metabolic and cardiovascular diseases and related psychiatric disturbances affecting mood (anxiety, depression) and eating behaviours, inflammatory/autoimmune disorders, and cancer, in which the gut microbiome has emerged as being deeply involved.

By giving value to equity, diversity and inclusion, the JIRU is committed to fostering excellence in research and research training and to ensuring equal opportunities for all qualified candidates. The JIRU supports the principle that excellence and equity are compatible and complementary and recognizes that good equity practices ensure access to the largest possible pool of qualified people. This includes prioritizing the inclusion of women, members of visible and ethnic minorities, indigenous peoples (in Canada) and persons with disabilities, where these groups are under-represented.

Objectives and program

Objective 1. Identification of new microbiome-based therapeutic (pharmacological, nutraceutical, nutritional) strategies to prevent and treat metabolic and cardiovascular disorders and their co-morbidities, such as affective and eating disorders, cancer and inflammatory/autoimmune diseases of central and peripheral organs. Exploration of the use of such strategies, also through the elaboration of appropriate formulations, in humans as well as their co-existing external ecosystems, in the framework of the *One Health* policy of the World Health Organization. This objective will be pursued through the application of the following experimental approaches to samples from conditions of both medical and veterinary interest:

1.1 Cross-sectional and longitudinal characterization of the metagenomics, transcriptomics, metabolomics and lipidomics profiles of the gut and, when possible/appropriate, oral and milk, microbiomes of healthy individuals as compared to those of individuals with disorders of interest (see above). Corresponding mouse models of these disorders will also be used and will allow both the characterization of tissue-resident microbiomes and the study of therapeutic interventions with microbiome-modifying treatments.

1.2 Identification and chemical characterization of microbiome-derived bioactive small metabolites ("post-biotics") associated with the presence or lack of symptoms of the disorders of interest. *In silico* analyses of these metabolites in order to predict their potential interactions with molecular targets of medical and veterinary relevance. Organic synthesis of these metabolites to ensure their production on a medium-scale, and subsequent investigation of their biological activities in *in vitro* (target overexpression cellular systems, cell cultures, intestinal organoids, etc.) and *in vivo* models of the disorders of interest. Non-mammalian animal models will also be used, especially for high throughput screening of new metabolites. Development of analytical techniques (e.g. LC/MS-MS or GC/MS-MS) for the quantification of these metabolites in human and animal samples obtained from other clinical and preclinical studies. Formulation of the synthetic bioactive metabolites by using nanotechnologies suitable for nutritional approaches, in order to increase their stability and bioavailability *in vivo*, and ensure their delivery to target, in animal and human subjects.

1.3 Identification of the microbiota species and strains, or of more complex gut microbial ecosystems, that either produce the metabolites of 1.3 or are associated with presence or lack of symptoms of the disorders of interest, or both. Their study in vitro in single strain cultures, culturomics and colon-simulating bioreactors, to understand what nutritional factors (in terms of both macro- and micro-nutrients) and pre-biotics enhance their abundance, to throw the bases for their enrichment *in vivo* through new nutritional approaches.

1.4 Identification, from the several clinical and pre-clinical intervention and/or longitudinal studies carried out by the JIRU in its first 8 years of activity (see Notes 1), of gut microbiome (metagenomics, proteomics, metabolomics) and host (proteomics, transcriptomics, metabolomics, lipidomics) profiles associated with previously assessed reduced cardiometabolic, inflammatory and affective disorder parameters. Application of machine learning and other AI approaches to these profiles, in association when applicable, with the nutritional interventions that have engendered them, to design, and eventually test, new diets for the prevention of the disorders of interest.

Objective 2. Dissemination and possible industrial exploitation of the results obtained through Objective 1, also with the aim of gathering resources and funds necessary to carry out the activities of the JIRU.

2.1 Industrial partners will be sought (first among the actual JIRU participants, and subsequently within other collaborating entities) as either: *i)* sources of valuable samples from clinical or veterinary studies performed under their R&D pipelines, to be studied with the approaches outlined in Objective 1, or *ii)* potential investors for the further biotechnological development of the discoveries of the UMI. Patents will be submitted to protect discoveries of potential industrial interest, or else data will be published and disseminated at conferences.

2.2 Dissemination of the JIRU discoveries to the scientific communities, after their putative protection in patents, and beyond their publication in high impact papers, will be ensured through the participation of the JIRU members to conferences, including the JIRU conference, which the JIRU director will strive to organize every other year, in locations alternating between Italy and Quebec, as it has been done so far (7 conferences having been organized since 2017, 4 in Italy and 3 in Quebec), using support from private sponsors and registration fees.

2.3 Establishment of direct and tight contacts with national stakeholders to further enhance the impact, and possibly future funding, of the activities of the JIRU. Dedicated offices at UL and CNR (who has an office also in Brussels, within the EU) will be updated periodically on the major discoveries of the JIRU, in order to help improving their dissemination also to the public, and in contexts beyond the scientific communities. The recently acquired possibility for Canadian institutions to directly participate in the Horizon Funding Programme of the EU will offer new opportunities to gain to the JIRU sufficient funds for its research, dissemination and educational activities. Additionally, as witnessed by the many grants obtained by CNR researchers thanks to the activity of the JIRU between 2018 and 2024, applications will be submitted to other national and international funding organizations (e.g., charities, US DoD, foundations, etc.).

2.4 Enrichment of the format and contents of the JIRU website (www.umilaval.cnr.it) through the dedicated activity of a webmaster.

Objective 3. Education and technical formation of new scholars in the field of the chemical and biomolecular study of the microbiomes. The JIRU represents a unique and integrated research and training environment through which companies, research institutes and universities can synergistically plan their activities and enact them. To cope with the ever changing evolution of microbiome-impacting environmental urgencies and the emergence of novel (e.g. covid-19) microbiome-related health problems, the JIRU realises scientific and educational research. In this effort, it fosters the high qualification of, and strong relationships between, different scholars, through a stable network capable to optimise the synergy among diverse social actors (academic, industrial, governmental, according to the Triple Helix concept, https://www.helixsociety.org/), thus enhancing their value also by coordinating and promoting their common actions and facilitating their contacts and exchange of experiences and pools of use.

3.1. The JIRU is deeply involved in active research activities in the fields of organic, analytical and materials chemistry; biochemistry; bioinformatics; pharmacology; neurobiology and, of course, microbiology. Its research projects have always been performed through the collaboration between expert researches and post-graduate and post-doctoral students, as well as research professionals, and they will continue this way.

3.2. The JIRU will continue to promote seminars, courses and schools, to be held at both UL and the >100 institutes of the CNR, with continued training programs aimed at responding to the practical needs of future health professionals within populations afflicted by the chronic societal disorders of interest.

3.3. The JIRU will continue to realise the international networking of scientific and educational activities in order to ensure joint and interdisciplinary research and training, thereby favouring the full participation of professors, researchers and students from the countries and all over the world, as witnessed by the >15 Italian post-graduate and post-doctoral students that, in the first 8 years of the JIRU, have visited UL.

Notes

1. Over the first 8 years of its activity, the JIRU funding from the Sentinelle Nord programme, has allowed for several bilateral projects between UL and the CNR for the years 2018-2020:

1) Arctic biofilms: sentinels of environmental change and microbial reservoirs of novel biomolecules;
2) Bio-agri-food sciences "Functional Lab" CNR-ISPA Bari - UL
3) A platform for understanding and exploiting polyphenols microbial metabolites based on a combined experimental-chemoinformatic approach;
4) Targeting the gut microbiota with new extracts enriched with omega-3 PUFAs and polyphenols from nordic biosources to alleviate cardiometabolic diseases;
5) Defining the endocannabinoidome and the microbiota in asthma and its severity also through the chemical synthesis of microbiota-derived endocannabinoid-like anti-inflammatory metabolites;
6) Nordic berries as sources of polyphenols and indigenous lactic acid bacteria for the development of unique synbiotic and postbiotic products;
7) Investigation into the effects of vitamin D on antipsychotic drug metabolic side effects: focus on the gut microbiome;
8) Novel biomarkers for early diagnosis of Parkinson Diseases;
9) Pinealocyte-derived melatonin modulates metabolic health through photoperiod-mediated effects on the gut microbiome and endocannabinoidome;
10) Role of the gut microbiome-endocannabinoidome axis in mood disorders related to obesity (ongoing);
11) Machine learning-guided design of new diets against metabolic and related affective disorders (ongoing);

Additionally, funding secured by the CNR colleagues, has allowed to perform the following projects:
1) Role of the gut microbiome-endocannabinoidome axis in the etiopathology of Duchenne's muscular Dystrophy (ongoing);
2) Role of the gut microbiome in oleic acid-derived endocannabinoid-like molecules as anti-food addiction treatments;
3) Role of the gut microbiome in diet-induced-obesity associated prostate cancer resistance to treatment and possible therapeutic use in this context of non-psychotropic cannabinoids;
4) Role of the gut microbiome-endocannabinoidome axis in the consequences on cognition and neuroinflammation of mild brain trauma (ongoing);
5) Role of the gut microbiome-endocannabinoidome axis in obesity-induced neuroinflammation, microglia dysfunction and cognitive disorders (ongoing);
6) New molecules targeting TRPM8 channels and the gut microbiome against colorectal cancer.

Finally, the collaboration with two JIRU industrial partners, i.e. Epitech Italy and BioK+, Quebéc, provided part of the funds and resources for the two following projects:
1) Role of the gut microbiome-endocannabinoidome axis in the effect of BioK+ probiotics on glycated hemoglobin in type 2 diabetes patients;
2) Effect of new ALIAMIDES on enhanced intestinal permeability and dysbiosis caused in animal models by either colitis, diet-induced obesity or vitamin D deficiency: role of the gut microbiome-endocannabinoidome axis (ongoing).

Many of these projects, in addition to those carried out through the close collaboration between the JIRU and CERC-MEND (https://cerc-mend.chaire.ulaval.ca/en/projects/), have provided interesting results and samples that could be used for the achievement of Objective 1. They have also expanded the original

scientific objectives and programme of the JIRU, resulting in this new outline for the future 5 years.