Research Collaboration Agreement

This agreement (the "**Agreement**") is made this 5th of February 2024 (the "Effective Date") by and between

The Dipartimento di Patologia Umana dell'Adulto e dell'Età Evolutiva of the Università degli Studi di Messina, ("**UNIME**"), having its offices at Pad. F, AOU G. Martino, Via Consolare Valeria 1, 98125, Messina

and

Humanitas Mirasole S.p.A. ("**INSTITUTE**"), having its offices at Via Manzoni 56, 20089 Rozzano (Milan), Italy.

UNIME and INSTITUTE are hereinafter referred to individually as a "**Party**" and collectively as the "**Parties**".

WHEREAS

Humanitas is a renowned centre of excellence for research and treatment of immune system-related disease, from cancer to cardiovascular diseases, inflammatory and autoimmune diseases, acknowledged by the Italian Ministry of Health as a Clinical Research Institute (IRCCS);

UNIME is a public entity involved in medical research, teaching and patient's treatment;

Humanitas has developed an expertise in innate immunity responses. Specifically related to the present collaborative research agreement, Humanitas has a strong expertise in the field of transcriptional responses of immune cells, as detected by RNA sequencing.

Humanitas and UNIME are willing to collaborate to perform certain research as more fully described in the research project jointly defined by the Parties and attached hereto in Annex 1. In brief, Parties wish to collaborate for the purpose of analysing RNA samples for their sequence, as listed in Annex 2. Each Party is willing to perform the work assigned to it in the research project, in each case subject to the terms set forth below.

NOW THEREFORE, in consideration of the foregoing premises (that, together with Annex 1 and 2, constitute part of the Agreement) and the mutual covenants set forth below, the Parties agree as follows:

Article 1. RESEARCH

1.1 Research.

UNIME and INSTITUTE shall perform collaborative research conducting the work assigned to them as described in Annex 1 (hereinafter "**Project**"), in a professional manner and in compliance with all applicable laws and regulations. Both Parties shall use reasonable efforts to achieve the assumed outcomes of the Project, provide the other Party, according to the provisions of this Agreement, with all data, materials and know-how in its possession that are necessary for the other Party to carry out their work under the Project, to ensure the performance of the research activities in compliance with the timeline set forth in the Project. In no case, other than in case of a Party's wilful misconduct or gross negligence, a delay in the performance of the research activities to be conducted under the Project shall be considered a breach of a Party's obligations hereunder. Each Party may propose in writing modifications to the Project provided that any amendment to the Project shall be in any case subject to approval in writing by both Parties.

1.2 Expenses.

Each Party shall bear its own expenses and costs in connection with the work under the Project.

1.3 Collaborators.

Each Party shall not subcontract any parts of its activities under the Project to a third party ("**Collaborator**") without the prior written consent of the other Party. It being understood that that the subcontracting Party shall remain responsible for the performance of any subcontracted activity.

1.4 Reports

At the expiration of each six (6) month period starting from the Effective Date, each Party shall provide the other Party a written report (including in slides, PPT format) describing the progress of the research activities under the Project (each a "**Report**"); additionally, each Party shall provide the other Party with a final Report containing a detailed description of all works done, materials and methods used in carrying out the applicable Activities, the Results (including the raw data when possible) obtained, within thirty (30) days from the end (or early termination of the Agreement) of the Project (the "**Final Report**").

Article 2. PUBLICATIONS AND CONFIDENTIALITY

2.1 Definition.

For the purposes of this Agreement, the term "**Confidential Information**" means any and all information and data owned or controlled by, or in any case related to, a Party or its directors, officers, employees, contract researchers, consultants ("**Representatives**"), and disclosed by either Party or in its behalf to the other Party or its Representatives in furtherance of this Agreement, whether such information is stored on electronic media as well as written and oral information and data, whether such information is labelled as "confidential" or not. For avoidance of doubt, Sole Results shall be deemed as Confidential Information of the Party that owned such Results, Joint Results shall be deemed as Confidential Information of both parties.

2.2 Publication Policy.

Parties recognise that under their academic policies, the Results obtained by either Party must be publishable or publicly presentable and each Party (or its principal investigator for the Project), shall be permitted to present and to publish the methods and results of the Project at symposia and professional meetings, in journals, theses or dissertations, or otherwise of their own choosing in any medium, including without limitation any article, manuscript, data, text, abstract, diagram, poster, chart, slide or picture ("**Publication**"), subject to the provisions of Article 2.3.

With respect to said Publications, Parties shall agree upon appropriate co-authorship in accordance with academic customs.

2.3 Submission.

Each Party shall submit to the other Party all intentions to publish or to otherwise disclose the methods and Results of the Project, sending copy of such proposed Publication at least thirty (30) calendar days prior to its intended submission for publication or disclosure. The receiving Party shall report in writing within thirty (30) days its comment and review. If such non-publishing Party is of the opinion that its confidential information or its intellectual property is likely to be prejudiced by the aforementioned Publication such Party may request to delay the Publication and may request to modify the Publications, or omit Confidential Information of such Party and/or to delay the Publication. Such delay shall sufficiently be motivated in writing and shall not exceed forty-five (45) days or, if longer, the period to afford the non-publishing Party the opportunity to file a patent application with respect to the subject matter of the proposed Publication, except if otherwise agreed in writing between the Parties. Either Party shall not use the name of the other Party in any publicity, Publication, advertising, or news release without the prior written consent of an authorized representative of the other Party.

2.4 Treatment of Confidential Information.

The receiving Party shall (i) maintain the Confidential Information in confidence, and shall not, without written permission from the disclosing Party, disclose, divulge or otherwise communicate such Confidential Information to others, except to its Representatives and Collaborators who need to know such information for the purpose of the Project and that are bound by like terms of confidentiality at least as protective as the provisions hereof prior to any disclosure of Confidential Information to them (it being understood that the receiving Party remains responsible for any use of Confidential Information by its Representatives and Collaborators in breach of this Agreement); (ii) use Confidential Information only for the purpose of perform the Project under this Agreement and never for any other purpose; (iii) not attempt to modify, alter, copy, reproduce, reverse-engineer, decompile or disassemble any Confidential Information. Upon the expiry or termination of the Agreement, each Party shall promptly return any Confidential Information belonging to the other Party or destroy it if so required in writing by such other Party, providing a signed statement from its duly authorised representatives of such destruction.

2.5 Release from Restrictions.

The provisions of section 2.4 shall not apply to any Confidential Information if and in so far as the receiving Party can prove that such Confidential Information:

- at the time the receiving Party discloses it to a third party, is generally known to the public through no fault of such Party or its representatives; and/or
- at the time the receiving Party discloses it to a third party, has been made available to such Party by a third party having the lawful rights to do so without breaching any contractual or legal obligation of non-use or confidentiality; or
- is proven to have been independently developed by the receiving Party without the use of Confidential Information; or
- the receiving Party is required to disclose pursuant to law, an order/request of a judicial or administrative authority, for regulatory purposes or defence purposes in a proceeding related to this Agreement, provided the receiving Party, to the extent permitted by the applicable law made reasonable efforts to obtain confidential treatment of such disclosure and to minimize the degree of such disclosure to the extent it is strictly necessary and promptly notifies in writing the disclosing Party of such disclosure to provide the disclosing Party sufficient time to contest such order The recipient Party will continue to treat such disclosed information as Confidential Information in accordance with the terms of this Agreement.

Article 3. TRANSFER OF MATERIAL

3.1 Definition.

For the purpose of this Agreement, "**Material**" shall mean the material owned or controlled by a Party, to be transferred by such Party to the other Party under this Agreement, together with any parts or sub-units, descendants, progeny, mutants, mutations or other derivatives thereof.

3.2 General.

In the framework of this Agreement, each Party shall provide the other Party, the Materials listed in Annex 2 to this Agreement according to the Project and in a timely manner and will do its best efforts to avoid delaying the activities under the Project. Ownership.

The supplying Party shall remain the sole owner of the Material, unless differently expressed in this Agreement.

3.3 Restricted Use.

The receiving Party shall utilise the Material solely for the purpose of carrying out the researches activities of the Project and shall in no case seek or have any person or corporate body seeking any commercial use of the Material or any other material that could not have been made but for the Material, unless explicitly agreed upon in this Agreement.

Any Material remaining upon completion of the Project shall be, as for the request of the supplying Party or (in any case) at the expiration or early termination of this Agreement, returned to the supplying Party or destroyed immediately.

3.4 No Transfer to Third Parties.

The receiving Party shall not transmit by any means whatsoever all or part of the Material to any third party without the prior and written consent of the supplying Party.

3.5 Warranties and Indemnification.

The supplying Party does not warrant that the use of the Materials does not or will not infringe any patent. The supplying Party is under no obligation to obtain or provide licenses that may be required for the use of the Materials by the receiving Party. **The Material is experimental in nature and is provided by the supplying Party with no warranties, express or implied, including any warranty of merchantability, title, or fitness for a particular use.**

The receiving Party will indemnify the supplying Party and hold supplying Party harmless from any claims or liabilities that might arise as a result of the receiving Party's use of the Material in breach of this Agreement, to the extent that such claims and liabilities are not caused by the wilful misconduct or gross negligence of the supplying Party.

3.6 Regulations.

The receiving Party will use the Material in compliance with all applicable laws and regulations both nationally and internationally, including regulations for work with recombinant material.

Article 4. BACKGROUND, RESULTS AND INTELLECTUAL PROPERTY RIGHTS

4.1 Background

For the purpose of this Agreement, "**Background**" means any and all data, information, knowledge, discoveries, know-how, material (including Materials), process, invention, in any form whatsoever, whether patentable or not, whether actually patented or not, and any and all related intellectual property rights, which is owned or controlled by a Party prior to the Effective Date (or developed, conceived, licenced to or acquired by a Party during the term of this Agreement, outside and independently from the works within the Project). All rights, title and interests on Background shall remain of the owner or controlling Party of such Background and such right, title and interest shall not be affected by this Agreement or a Party's performance of its obligation hereunder.

Each Party hereby grants to the other Party a non-exclusive, non-transferable, royalty-free right and license to use the Background owned or controlled by such Party which is necessary solely to conduct the research activities assigned to such other Party under the Project and for no other purpose. Such license shall expire upon the expiration or termination of this Agreement. Except as specifically provided in this Agreement, under no circumstances shall a Party obtain any ownership interest or other right in any invention, discovery, composition or other technology, or in any patent right or other intellectual property right, of the other Party.

Any improvements to a Party's Background generated in the conduct of the Project and all title and interest therein shall be owned exclusively by the Party owning or controlling such Background, and such Party shall be free to use and exploit the same at its discretion.

4.2 Project Results and Inventions.

Any and all rights, title and interest in all tangible or intangible results/output/deliverables in any form whatever – including but not limited to all data, records, material, process, method, technique, product, information and know-how, inventions, whether patentable or not ("**Inventions**") - generated, conceived or first actually reduced to practice in performance of the Project, as well as any rights attached to it, including intellectual property rights (**"Results**") will be regulated as follows in sections 4.2.1 – 4.2.5.

4.2.1 Sole Results - All Results generated, conceived or first actually reduced to practice solely by UNIME (and its Representatives and/or Collaborators) shall be owned solely by UNIME and shall be disposed of in accordance with UNIME Policy; and all Results conceived and first actually reduced to practice solely by INSTITUTE (and its Representatives and/or Collaborators) shall be owned solely by INSTITUTE and shall be disposed of by INSTITUTE (respectively "**Sole Results** "). The Party who is the sole owner of such Sole Result shall, at its option, use and dispose in any way of them, prepare, file, prosecute, and maintain applications throughout the world in countries of its choice.

4.2.2 Joint Result – All Results generated, conceived and first actually reduced to practice jointly by UNIME and INSTITUTE (and, respectively, their Representatives and/or Collaborators) (hereinafter "**Joint Results**") shall be the mutual property of both Parties and both Parties shall, to the extent permitted by law, jointly hold all rights, title, and interest in such Joint Results. The share of each joint owner party to the Joint Results shall be defined according to the contribution provided by such joint owner Party, in terms of its inventive contribution as well as the Background made available for the achievement of the applicable Joint Results. If not possible to define the contribution of each joint owner, the Results shall be equally jointly owned (at 50%) between them. The Parties agree to negotiate in good faith, for the purpose of managing the protection and the exploitation of Joint Results through an inter-institutional agreement ("**Joint Ownership Agreement**") as soon as necessary to allow any industrial and/or commercial exploitation of the Joint Results.

4.2.3 Disclosure. Each Party shall promptly disclose to the other Party in writing and on a confidential basis any Sole Results or Joint Results.

4.2.4 Patent Activity and Exploitation of Joint Result.

In relation to Joint Results, unless otherwise agreed in, or in absence of a Joint Ownership Agreement, the following provisions shall apply.

4.2.4 (a) Patent Activity

The Parties shall cooperate in the preparation, filing, prosecution, maintenance of any patent application and/or patent thereof related to the Joint Invention, bearing the related costs in accordance with percentage of respectively quote of ownership (the "**Patent Activity**"). The Patent Activity shall be carried out using counsels and patent attorneys selected by the Parties.

If one Party does not wish to conduct any Patent Activity of any patent and/or patent application related to one Joint Invention in any country of the world, such Party will promptly notify the other Party in writing and the other Party will be entitled to effect the Patent Activity in its own name and at its own expense, with respect to said countries/territories by notifying the abandoning Party in writing within 15 days of the notice of abandonment.

4.2.4 (b) Exploitation

Each of the joint owner Party shall be entitled:

- without requiring the prior consent of the other joint owner, subject to appropriate undertakings of confidentiality (if applicable), to use the Joint Results for its non-commercial research activities and/or education purposes on a royalty-free basis, including in

collaboration with third parties (but without granting any right to such third parties, other than the right to use such Results for the purpose of performing the applicable research activities of such Party); and

- to exploit the Joint Results for commercial purposes and to grant non-exclusive licenses to third parties, subject to the following conditions (for clarity, exclusive licence shall not be granted without the written consent of the other Party):

  (a) at least 45 calendar days prior written notice must be given to the other joint owner; the other joint owner may object within 30 days of receiving such notice if it can show that the exploitation of Joint Results would adversely affect its rights; the exploitation may not take place until agreement has been reached between the Parties; if no objection is made within the time limit stated above, the exploitation is permitted;

  (b) in case of royalty bearing non-exclusive licence, the Party concluding such a non-exclusive license shall collect and distribute any and all revenues accrued from the exploitation of a Joint Result which distribution shall equal the ratio of ownership in such Joint Results

  (c) any license agreement granted in respect of the Joint Results shall contain, inter alia:

  - the terms securing the full indemnification and holding harmless the Parties, and those employed by them from and against any claim, damage, expense of any kind resulting from any use of the licensee or those authorized by him may make of such Results or other licensed information;
  - a disclaimer as to any representations or warranties in respect of such Result, its potential, use, exploitability and/or that it does not infringe third party's rights;
  - full reimbursement of patent costs by the licensee; and
  - specific undertakings of commercialisation.

4.2.5 Transfer of Results

Each Party is free to transfer the ownership of its Sole Results in whole or in part. Each Party may transfer its share of Joint Results to third parties with prior written consent of the other Party only (such consent shall not be unreasonable withheld). The transferring Party shall grant to the other Party the first right to acquire the transferring share of Joint Results (under the same conditions offered by or to third parties, if any). The co-owner shall express the interest to acquire such share within 30 days of receiving the transferring Party's offer. After the transfer of the ownership to a third party, the Party concerned shall notify the other Party of such transfer, identifying the new owner. The transferor Party shall ensure that all the obligations regarding the transferred Results will pass to the transferee.

Article 5. INDEMNIFICATION

5.1 Indemnification.

Each Party agrees to indemnify, defend and hold harmless the other Party and its Representatives against any and all losses, liabilities, damages, costs, damages and expenses ("**Losses**") suffered by such Party or which the latter may be required to pay to one or more third parties (including fees, expenses and costs of claims and suits for loss, damage, injury, or loss of life), if such Losses arise from (i) any breach of the identifying Party of its representations or warranties under this Agreement, (ii) any negligent or wilful misconduct of the identifying Party in connection with the performance of its obligations under this Agreement. A Party is released from this obligation as far as the aforementioned is caused by gross negligence, wilful misconduct or malicious intent of the other Party or any of its Representatives.

5.2 Indirect Damages.

Subject to section 5.1 Parties shall not be liable against one another for any indirect or consequential damages (including loss of profit) in connection with this Agreement unless these damages are caused by gross negligence or wilful misconduct of a Party, its Representatives or Collaborators.

Article 6. REPRESENTATION AND WARRENTIES - DISCLAIMER OF WARRENTIES

Each Party hereby represents and warrants to the other Party that: (i) as of the Effective Date it is not and will not be during the Term under any obligation to any person, contractual or otherwise, that is conflicting or inconsistent in any respect with the terms of this Agreement or that would impede the diligent and complete fulfilment of its obligations hereunder; and (ii) it shall comply, and the Project shall be conducted, in compliance with all applicable laws, rules and regulations, having all permissions and authorisations required for the performance of the relevant activity.

Neither Party makes any warranties, express or implied, as to any matter whatsoever, including, without limitation, warranties with respect to the conduct, completion, success or particular results of the Project, or the condition, ownership, merchantability, or fitness for a particular purpose of the Project or any materials, inventions, or results or that use of the Results will not infringe any patent, copyright, trademark or other Intellectual Property Right of a third party.

Article 7. TERM AND TERMINATION

7.1 Term

Either Party's obligations with respect to the Project shall become effective on the Effective Date and – unless earlier terminated in accordance with this Section 7 – expires upon the completion of the Activities in accordance with Annex A and the receipt of the Final Report (the "**Term**").

7.2 Termination

(i) Either Party may terminate this Agreement at its sole discretion upon ninety (90) days written notice to the other Party.

(ii) A Party may early terminate for cause this Agreement, if the other Party breaches this Agreement and the breach is not capable to be cured or, if it is capable to be cured, it is not cured by the defaulting Party within thirty (30) days after receipt of a written notice from the other Party specifying the breach.

7.3 Consequence of expiration/termination

The expiry or termination of this Agreement shall not affect the rights and obligations of the Parties that have accrued prior thereto. In particular, and without limiting the foregoing, any and all provisions contained in the Agreement which by their nature or effect are intended to be observed, kept or performed after termination or expiration of this Agreement, including but not limited to, as applicable, the provisions of articles 2, 3, 4, 5, 6, 7 and 8, shall survive the expiry or termination hereof. The provisions of confidentiality under Section 2 shall survive the expiry or termination of this Agreement until the applicable Confidential Information becomes part of the public domain through no breach of the receiving Party's and/or its representatives' confidentiality obligations.

Article 8. MISCELLANEOUS

8.1 No License.

Except as expressly provided in this Agreement, this Agreement does not confer by implication, estoppel, or otherwise any license or other rights under any patents, patent applications, trade secrets or other proprietary rights of either Party.

8.2 Invalidity

If any provision of this Agreement is held to be void or otherwise unenforceable by a court of competent jurisdiction from whose decision no appeal is made within the applicable time limit, then the provision shall be omitted and replaced with a new provision to the maximum extent permissible consistent with the Parties' original intent, and the remaining provisions of this Agreement shall continue in full force and effect.

8.3 Privacy

Any personal data provided by a Party to the other Party in relation to this Agreement will be processed to fulfil the obligations arising from the Agreement pursuant to the applicable laws, including Regulation (EU) no. 2016/679 (GDPR).

8.4 Notices

Any notice required or permitted to be given to the parties hereto is properly given if delivered, in writing by any lawful means (that provide a proof of the receipt, including email with acknowledgment of receipt, in person, by first-class certified mail or by overnight carrier) to the following addresses, or to such other addresses as may be designated in writing by the parties from time to time during the term of this Agreement (and shall be effective upon receipt by the addressee):

To UNIME:	To INSTITUTE:
Dipartimento Di Patologia Umana	Humanitas Mirasole S.p.A.
Dell' Adulto e dell'Età Evolutiva	via Manzoni 56,
AOU Policlinico G. Martino	
Pad. F Via Consolare Valeria 1	
98125 Messina, Italy	20089, Milan, Italy
Attention: Prof. Giuseppe Navarra	To the attention of: Paola Vella
dipartimento.patologiaumanadetev@unime.it;	paola.vella@humanitasresearch.it
cc: cbeninati@unime.it	cc: tto@humanitasresearch.it

8.5 Law and Disputes.

Parties shall use reasonable endeavours to solve any dispute that will arise in connection (for example, its negotiations, execution, validity, enforceability, termination, interpretation, including any non-contractual obligation) to this Agreement by mutual arrangement. If Parties will not come to any solution, the Court of Milan according to the laws of Italy will have exclusive jurisdiction on the dispute.

8.9 Signature.

This Agreement may be executed in any number of counterparts, each of which, when executed and delivered, shall constitute an original of this Agreement. Transmission of an executed counterpart of this Agreement (but for the avoidance of doubt not just a signature page) by email in PDF format shall take effect as delivery of an executed counterpart of this Agreement and it may be used in lieu of the original agreement for all purposes (including judicial purposes).

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives.

UNIME	INSTITUTE
_____	_____
signature	signature
by: Prof. Giuseppe Navarra	by: Giorgio Ferrari
title: Director of Department Pat.Um. ADEV	title: Director of Research
date:	date:
Read and acknowledged by:	Read and acknowledged by:
_____	_____
Signature	Signature
by: Prof. Concetta Beninati	by: Prof. Sebastien Jaillon
title: Prof. of Microbiology, UNIME	title: PI at Humanitas
date:	date:

Annex 1: Description of the research Project

Pharmacological blockade of caspase 8 has been demonstrated to alter the transcription of genes in neutrophils and modify the subsequent release of pro-inflammatory cytokines [1]. This suggests the involvement of caspase 8 in regulating a spontaneously activated pro-inflammatory pathway in neutrophils.

As part of the collaborative research between Humanitas and the University of Messina, it was decided to obtain a comprehensive overview of the genes whose transcription is under the control of caspase 8. For this purpose, mouse neutrophils (obtained from bone marrow) were stimulated with a caspase 8 inhibitor (n=4) or a vehicle (n=4). After two hours, RNA was extracted. Similarly treated mouse macrophages were used as control cells (n=4 with caspase 8 inhibitor and n=4 with vehicle).

A total of 16 samples were obtained, and the RNA from these cells was isolated by the University of Messina. Humanitas will analyse these RNAs for quality control and conduct RNA sequencing (Bulk RNAseq Analysis) if the quality permits. Results will be shared between the two institutes, including raw data.

References:

1 Lentini, G. *et al.* Caspase-8 inhibition improves the outcome of bacterial infections in mice by promoting neutrophil activation. *Cell Rep Med* **4**, 101098 (2023).

Annex 2 : Material

RNA (16 samples) isolated from mouse cells isolated at the University of Messina.