Elucidating the Spatial and Temporal Dynamics of Acute Myeloid Leukemia Progression Using Functional Omics and High-Throughput In Vivo Screening

Fact Sheet

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<tr>
<th>Project Information</th>
<th>Funded under</th>
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<tr>
<td>DynAML</td>
<td>European Research Council (ERC)</td>
</tr>
<tr>
<td>Grant agreement ID: 101088563</td>
<td></td>
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<tr>
<td>DOI</td>
<td></td>
</tr>
<tr>
<td>10.3030/101088563</td>
<td></td>
</tr>
<tr>
<td>Start date 1 March 2024</td>
<td>Total cost</td>
</tr>
<tr>
<td>End date 28 February 2029</td>
<td>€ 1 994 500,00</td>
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<tr>
<td></td>
<td>EU contribution</td>
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<td></td>
<td>€ 1 994 500,00</td>
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<td>Coordinated by</td>
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<td>INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE</td>
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**Objective**

Advances in sequencing-based phylogenetic studies applied to cancer evolution have led to the observation that the linear accumulation of oncogenic alterations over individuals’ lifespan does not match the late life pattern of cancer incidence. It has thus become clear that beyond the sequential accumulation of oncogenic driver mutations, additional factors also support cancer outgrowth. The temporal and spatial dynamics of tumor evolution represent two of the most critical mutation-independent variables to consider. Hence, we hypothesized that the dual features of
Aging and spatial dissemination promote critical fitness gains that are at least as significant as driver mutations in cancer. The goal of this proposal is to investigate the spatial and temporal determinants of tumor progression and to dissect the contributions of these processes to cancer pathogenicity.

Due to its quite unique occurrence pattern and propagation characteristics, Acute Myeloid Leukemia (AML) is the prototypical disease model that we have elected to template such spatiotemporal-dependent features of disease development. To study these features, we engineered two mouse models of leukemia dissemination and aging using serially-transplantable MLL-AF9-driven leukemic blasts. Using these two models, we propose to i) combine metabolomic- and epigenomic-based profiling to portray the spatiotemporal dynamics of leukemia growth; ii) deploy single-cell transcriptomics coupled with lineage tracing experiments to reveal the pre-deterministic attributes of such dynamics; and iii) leverage innovative multimodal in vivo shRNA and CRISPRa screening approaches to pinpoint and functionally characterize the critical age- and dissemination-related effector genes involved in leukemic progression. The comprehensive analysis of their unknown function will potentially define new therapeutic routes in AML, and, given the holistic nature of the spatiotemporal characteristics studied, in other cancers as well.

**Fields of science**

- natural sciences ➔ biological sciences ➔ genetics ➔ mutation
- medical and health sciences ➔ clinical medicine ➔ oncology ➔ leukemia

**Keywords**

- Preclinical Mouse Models of Acute Myeloid Leukemia
- Multi-Omics Analyses and In Vivo Loss-of-Function Screening Approaches
- Relationship Between Host Tissue and Leukemia Progression
- Influence of Aging on Leukemia Malignity

**Programme(s)**

- HORIZON.1.1 - European Research Council (ERC)
Topic(s)

ERC-2022-COG - ERC CONSOLIDATOR GRANTS

Call for proposal

ERC-2022-COG

See other projects for this call

Funding Scheme

HORIZON-ERC - HORIZON ERC Grants

Coordinator

INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE

Net EU contribution

€ 1 994 500,00

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Links

Contact the organisationWebsiteParticipation in EU R&I programmesHORIZON collaboration network

Other funding

€ 0,00

EC signature date 13 June 2023

Last update: 28 June 2023