PhD project No. 15, Prof. Groß

Scientific Area	Innate and adaptive immunity
Two project titles	A) Molecular signals triggering inflammasome activation B) Macrophage-specific pro-inflammatory cell death mechanisms
Host country	Germany
Supervisor, institution	Prof. Dr. Olaf Groß, Medical Center - University of Freiburg, Germany
Co-Supervisor, institution	A) and B) Prof. Dr. Romeo Ricci, University of Strasbourg, France
Mentor, institution	A) Dr. Andrea D'Osualdo, Idorsia Pharmaceuticals, Basel, Switzerland B) Dr. Michael Bscheider, Roche, Basel, Switzerland
Secondment institution	A) and B) University of Strasbourg, France and Mentor labs

Short description of the supervisor's lab with introduction to the topic

We study the fundamental molecular mechanisms of innate immunity and inflammation, their integration with metabolism and cell biology, and their role in health and disease. Our focus is on a cytoplasmic signalling complex in macrophages known as the inflammasome that controls the activity of the potent proinflammatory cytokine IL-1beta and a form of lytic cell death known as pyroptosis. We study inflammasomes at the molecular, cellular, and organismal levels using a broad range of cutting-edge technologies, and have made important contributions to the understanding of inflammasome biology and related signalling mechanisms. In a recent collaboration with Novartis, Basel, Switzerland, we successfully screened for new small molecule modulators of macrophage cell death, metabolism, and inflammasome activation.

Topic description, including techniques to be used

Project A)

The precise molecular mechanisms of inflammasome activation are poorly understood. Our new small molecule activators of different types of inflammasomes will be used to study these. Complementary approaches involving medicinal chemistry, chemical proteomics and genetic screening will be applied to this challenge. A focus will be to map the general effects the new activators have on macrophages and to examine whether these are required or even sufficient for inflammasome activation. This will allow a better understanding of the physiological signals the inflammasomes were designed by nature to detect.

Techniques: Culture of primary murine macrophages and human monocyte cell lines, assays for inflammasome activation, signalling studies using small molecule activators and inhibitors, CRISPR-Cas9-based phenotypic screening.

Project B)

Lytic cell death is proinflammatory by releasing cellular content including danger-associated molecular patterns (DAMPs) or alarmins that are perceived by immune cells. Macrophage lysis, potentially as a consequence of the inability of these specialised immune cells to perform their normal function in tissue homeostasis and the defences against pathogens, is especially potent in this respect. Increasing evidence suggests the existence of specific macrophage cell death modalities. Our new small molecule activators of macrophage lysis will be used to study these. A focus will be to map cell type-specificity and study its mechanistic basis in cell biology and signalling.

Techniques: Culture of primary murine macrophages, various cell lines, and intestinal organoids, assays for cell death, signalling studies using small molecule activators and inhibitors, CRISPR-Cas9-based phenotypic screening.

Recommended applicant's training (technical expertise and knowledge)

Techniques: Cell culture, flow cytometry, Western blotting, ELISA, fluorescence microscopy
Knowledge: cell biology, signalling, innate immunity

The EURIdoc programme has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement number 101034170.

Maximum two relevant publications
Schneider K et al., 2017, Cell Reports: The inflammasome drives GSDMD-independent secondary pyroptosis and IL-1 release in the absence of caspase-1 protease activity. Gross CJ et al., 2016 Immunity: A mitochondrial target of imiquimod is involved in Nlrp3 inflammasome activation and cancer cell growth arrest.

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Ethics description

1. Humans	
This research involves human participants.	YES ☐ / NO ☒
This research involves physical interventions on the study participants.	YES ☐ / NO ☒
2. Human Cells /Tissues	
This research involves human cells or tissues, such as blood.	YES ☒ / NO ☐
3. Personal Data	
This research involves personal data collection and/or processing.	YES ☐ / NO ☒
This research involves further processing of previously collected personal data (secondary use).	YES ☐ / NO ☒
4. Animals	
This research involves animals, such as mice.	YES ☒ / NO ☐

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