# PhD offer

## Investigation of nucleation and crystallization under confinement by microfluidics coupled with hyperpolarized NMR

A 3-year PhD contract is available at the University of Aix Marseille (Marseille, France) to work on the study of crystallization processes occurring under nano-confinement. The thesis will be funded by the "Inter-ED" program, and will involve the Doctoral Schools "ED 250" (Chemistry) and "ED 352" (Physics).

### Context and objectives

The formation of crystalline matter, or crystallization, is a ubiquitous phenomenon and one of the most important physico-chemical processes. Notwithstanding its relevance, this phenomenon remains poorly understood today due to the lack of analytical techniques capable of reaching sufficient levels of spatial and temporal resolution to reliably describe the different species forming along this process. In particular, the species formed during the early stages of crystallization, such as nucleation and pre-nucleation, become crucial in the case of *polymorphic* materials (*i.e.* that are able to crystallize in distinct crystalline forms). Published results strongly suggest these species play a key role in deciding which crystal structure is eventually produced, which in turn determines the final properties of the material. However, these species are often present in low concentrations and are characterized by a short lifetime, which makes their identification – and even more so their structural characterization – a real experimental challenge.

Recently, in Marseille, the group of Dr. Giulia Mollica at the Institute of Radical Chemistry (ICR UMR 7273) developed new strategies based on hyperpolarized NMR (*via* Dynamic Nuclear Polarization, or DNP) for the atomic/molecular level analysis of crystallizing solutions [1]. However, the temporal resolution of such approaches remains insufficient for some challenging applications. In parallel, the team of Dr Stéphane Veesler at the Interdisciplinary Center of Nanosciences of Marseille (CINaM UMR 7325) has developed original approaches based on microfluidics of droplets, which allow the required temporal resolution to be achieved [2]. However, these approaches lack spatial (*i.e.* atomic-level) resolution.

**The overarching aim of this thesis is to obtain details at the atomic scale of transient species forming during the first stages of crystallization that are characterized by lifetimes of the order of milliseconds, which is not possible by any other experimental means today.** To achieve this objective, the selected candidate will combine droplet microfluidics and DNP NMR spectroscopy, two traditionally distant fields, in order to develop an original experimental methodology to reach an atomic-level description (*via* DNP NMR) of species produced in the course of crystallization processes occurring in confined volumes (droplets), with particular emphasis on the early stages of crystallization, *i.e.* nucleation and pre-nucleation.

The specific objectives of this thesis will be:

1) to develop original experimental methods for:

-the preparation and manipulation of picoliter droplets of solutions by microfluidics to stop the crystallization at the desired time with a temporal resolution of the order of ms;

2) to characterize the first stages of crystallization (pre-nucleation, nucleation) of molecular solids in a confined environment (droplets to understand the mechanisms underlying nucleation and the selection of solid phases (polymorphism), at:

-i) atomic/molecular level, via solid-state NMR coupled to DNP;

-ii) nano/microscopic level, *e.g.* via microscopy.

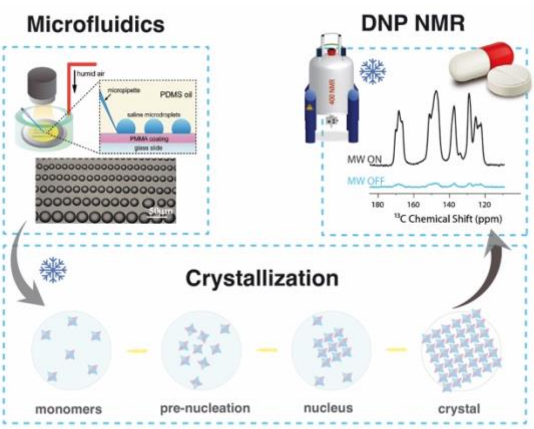


**Figure 1**. Main research axes developed in this PhD thesis

The first developments and tests will be realized on model systems with well-known crystallization behavior, such as glycine. Applications on real systems will include minerals or active pharmaceutical ingredients in collaboration with industrial partners.

### Thesis work implementation and environment

This thesis will involve two Doctoral Schools ("*Ecole Doctorale*", ED) of Aix-Marseille University, ED 250 (*Chemistry*, main ED) and ED 352 (*Physics*, secondary ED). The thesis will be carried out at the University of Aix-Marseille, co-supervised by Dr. Giulia Mollica (DR CNRS), who leads the research group "*NMR for polymorphism*" at the Institute of Radical Chemistry (ICR UMR 7273 - attached to ED 250, Campus St. Jérôme), and Dr. Stéphane Veesler (DR CNRS), who leads the research group "*Sources et Sondes Ponctuelles*" at the Interdisciplinary Center of Nanosciences of Marseille (CINaM UMR 7325 - attached to ED 352, Campus Luminy).

To carry out this thesis work, the candidate will have local access to a large number of facilities and research infrastructures located on the St. Jérôme and Luminy campuses of Aix-Marseille University. This will enable the preparation of crystallizing solutions *via* microfluidics combined with cryogenics, as well as their characterization *via* NMR DNP, microscopy (optical and electron), but also *via* other complementary techniques (*e.g.* DRX, IR, Raman).

The project will start between October and November 2023 for a period of 3 years. During this PhD thesis, the candidate will develop multidisciplinary skills in NMR spectroscopy, microfluidics, microscopy and instrumentation. He/she will have the unique opportunity to access, on site, a recently installed, cutting-edge Bruker 400 MHz DNP NMR spectrometer. He/she will have the opportunity to interact not only with the research teams directly associated to the project, but also with other researchers at the local, national and international level, as well as through the participation to international conferences and schools.

### Additional information and application procedure

This offer is open to candidates who have completed training in physical chemistry or physics, ideally with previous knowledge of NMR and/or microfluidic spectroscopy. He/she must demonstrate a real interest in the development of new experimental approaches in NMR and/or microfluidics for the study of crystallization. In addition, he/she will have to demonstrate his ability to carry out a project with a strong interdisciplinary character and to integrate research groups associating students and researchers from different fields, with a strong international character. Very good communication skills (oral and written) are required, especially in English (French is not required).

The project will be funded by an "*Inter-ED 2023*" thesis grant from the University of Aix-Marseille (https://college-doctoral.univ-amu.fr/fr/appel-a-projet-inter-ed ).

An **interview of the retained candidate is scheduled on June 12-13, 2023**.

The application file must include the following elements, combined in a single PDF file (vol < 50 Mb):

- **CV,**
- **letter of motivation mentioning the professional project after the thesis,**
- **2 letters of recommendation,**
- **Bachelor's and Master's transcripts**
- **copy of diploma(s)**

**Applications must be sent before Thursday 25 May by email to Giulia Mollica and Stéphane Veesler:** **giulia.mollica@univ-amu.fr**, **stephane.veesler@cnrs.fr**

### References:

[1] P. Cerreia-Vioglio, P. Thureau, M. Juramy, C. Hughes, A. Williams, F. Ziarelli, S. Viel, K. D. M. Harris, G. Mollica *J. Phys. Chem. Lett.* **2019**, *10*, 1505; M. Juramy, R. Chèvre, P. Cerreia Vioglio, F. Ziarelli, E. Besson, S. Gastaldi, S. Viel, P. Thureau, K. D. M. Harris, and G. Mollica *J. Am. Chem. Soc.* **2021,** 143, 6095.

[2] R. Cedeno, R. Grossier, M. Lagaize, D. Nerini, N. Candoni, A.E. Flood, S. Veesler, Nucleation in Sessile Saline Microdroplets: Induction Time Measurement via Deliquescence-Recrystallization Cycling *Faraday Discuss.* **2022,** *235*, 183.