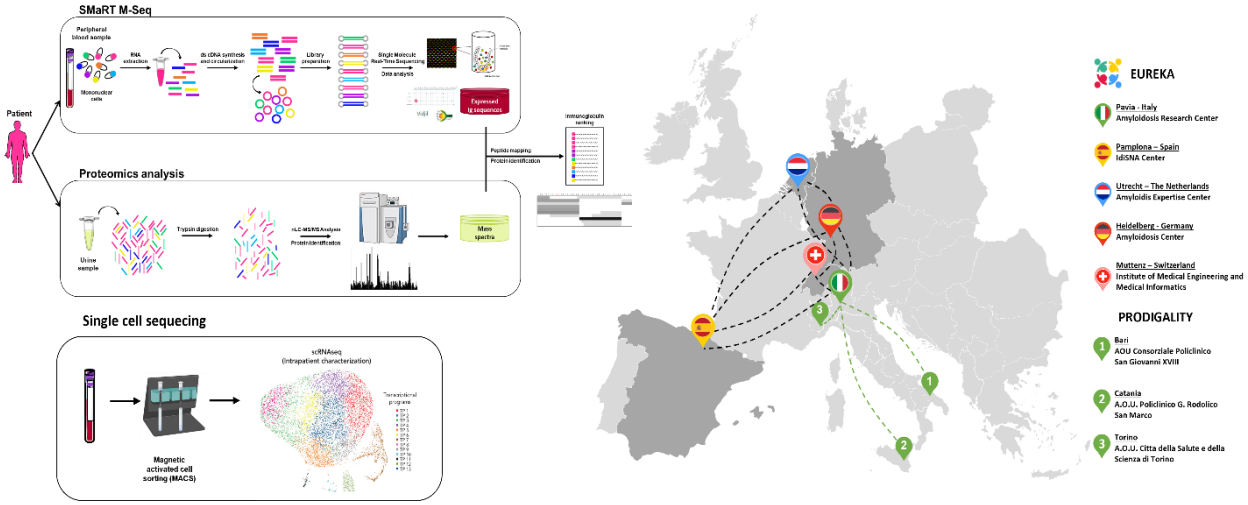
Project title: Patients-specific M protein sequences as a key to study and track B cell / plasma cell tumors.
PI: Mario Nuvolone
Hosting Lab: Biotechnology Laboratory, Amyloidosis Center, Foundation IRCCS Policlinico San Matteo

Background: Monoclonal gammopathies are caused by bone marrow-residing B cell or plasma cell clones secreting a tumor-specific monoclonal antibody (the M protein). Clinical manifestations can arise due to massive proliferation of tumor cells, the pathologic behaviour of the M protein, or a combination thereof. Besides mature B cells/plasma cells, the disease-causing clone also includes more undifferentiated elements in the bone marrow, as well as rare circulating elements. Yet, a detailed characterization of more undifferentiated precursors and circulating tumor cells (CTCs) in these diseases is presently lacking.
We have developed and validated a novel, sensitive and accurate high throughput methodology based on long-read DNA sequencing (SMaRT M-Seq) to sequence the antibody repertoire and unambiguously identify the full-length variable sequence of M protein genes in patients with monoclonal gammopathies. Leveraging on the presence of CTCs, we have successfully applied SMaRT M-seq based antibody repertoire sequencing with proteomics to identify patients-specific M proteins in peripheral blood without bone marrow analysis.

Scientific hypothesis and aims:
We hypothesize that sequencing patients' specific M proteins has the potential to:
1) identify and characterize more undifferentiated clonal cells through single cell RNA sequencing;
2) contribute to the development of personalized diagnostic tools for tumor tracking;
3) facilitate studies of the molecular determinants of M protein pathogenicity.

By exploiting a large and well-characterized cohort of samples/patients with monoclonal gammopathies, well-established analytical platforms based on cutting-edge technologies and a network of scientific collaborations with research groups with synergistic and complementary expertise through a European and an Italian study (EUREKA and PRODIGALITY), both coordinated by our group, we aim to characterize precursor cells and to develop innovative, personalized diagnostic assays for precise and highly sensitive tumor tracking. This study will also generate sequence information from large cohorts of patients with monoclonal gammopathies, thus contributing to investigate the molecular underpinnings of M protein pathogenicity.



Techniques:
SMaRT M-Seq, sc-RNA seq, MS/MS, flow cytometry, other molecular and biochemical analyses.

Bibliography:
Cascino et al. Am J Hematol 2022. https://doi.org/10.1002/ajh.26684
Nevone et al. Leukemia 2022. https://doi.org/10.1038/s41375-022-01599-w