Socio-economic and scientific context (approximately 10 lines):
Sepsis causes more than 5 million deaths worldwide with an estimated cost of $17 billion annually in the USA. It is now assumed that most of the death is due to sepsis-induced immune suppression (SIIS) for which there is no FDA-approved specific therapeutic option. This SIIS renders septic patients prone to new secondary infections and alters their long-term functional status. The patients who die during the late phase of sepsis have usually an immune system that does not recover. However, the mechanisms of the SIIS are still poorly known.

Working hypothesis and aims (approximately 8 lines):
Severe alteration of the lymphocyte compartment is a hallmark signature of SIIS. A dramatic decrease of circulating CD4+ T cells and the persistence of an increased percentage of CD4+FoxP3+ regulatory T cells (Treg) cells were predictive of secondary nosocomial infections and poor outcomes in septic patients. There are good experimental evidences that Treg, which play a major role in immune suppression, impair the CD4+ T cell compartment during sepsis. We propose that one of the major mechanisms of SIIS is that TNF, released in high amount during sepsis, boosts expansion and suppressive activity of Tregs through the TNF receptor 2 (TNFR2) which is the working hypothesis of our research project.

Main milestones of the thesis (approximately 12 lines):
To get further insight into the role of TNFR2+ and Treg in SIIS, our proposal will address the following specific aims: 1. To perform deep and unbiased profiling of TNFR2+/− Treg in patients during severe sepsis (D1 and D4) at the single cell level using Cellular Indexing of Transcriptome and Epitopes by Sequencing (CITE-seq) of blood CD4+ T cells. 2. To study the role of TNFR2 and its downstream NF-κB signaling pathway expressed by Treg in SIIS by using conditional knockout mice that we have recently developed, which are animal models not available by other groups. 3. To study the sensitivity to TNF of Treg from septic patients and the therapeutic effect of human TNFR2 antagonist on SIIS in humanized knock-out mice expressing the extracellular portion of human TNFR2 fused to the mouse intracellular TNFR2 tail.

The fellow will work on the aim 1 of this project and will develop the CITE-seq experimental approach (CITE-Seq) and bioinformatics to characterize in details Treg molecular remodeling and to identify gene programs associated with TNFR2+ in Treg during the course of sepsis in patients.

Scientific and technical skills required by the candidate (2 lines):
Highly motivated candidates holding a master’s degree with strong interests in the field of human immunology, single cell genomics and bioinformatics are welcome to apply. The candidate is expected to be able to work independently, while actively cooperating with other members of the group.

3 publications from the team related to the topic (last 5 years):

National and international collaborations:
This position is available for 3 year and is funded by ANR in the context of a collaborative project between Pr K Asehnoune and.
(Coordinator, EA 3826 Nantes) Dr B Salomon (Partner, CIMI UMR1135, Paris) and Pr R Josien (Partner, CRTI UMR1064, Nantes). The candidate will work under the supervision of Pr R Josien and Dr. J Martin.