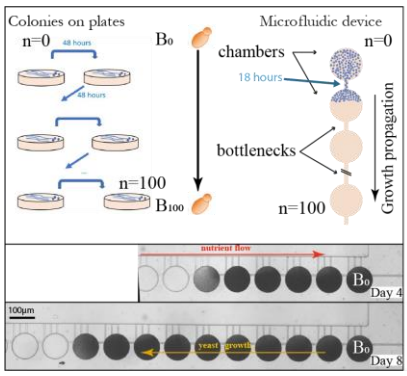
**Development of a microfluidic device for the analysis of massive mutation accumulation**

## Context

Mutations in DNA have large-ranging consequences, from evolution to aging and diseases. Dysfunctions in DNA repair and transcription, as well as mutagen exposures can increase the rate of mutations. It remains poorly understood how the complex relationship between transcription and DNA repair influences mutational processes. Model organisms and mutation accumulation (MA) experiments are the key standards for studying mutagenesis. The yeast *S. cerevisiae* is an excellent eukaryotic model for these experiments thanks to its powerful genetics and genomic tools, as well as a short generation time (90 min in rich medium) compared to human cells. Unfortunately, MA experiments are very long (6-12 months) and tedious (human intervention every 48 hours) reducing the number of cell lines and parameters studied.




To avoid a cumbersome and lengthy colony formation stage with a large number of agar dishes and to set up automated and high throughput MA experiments, we developed a PDMS-based microfluidic device containing MA lines operating in parallel (see Figure). With this approach, we speed up the time (1-3 months) necessary for genome-wide measurements of mutational profiles in terms of duration and hands-on in cell cultures. At the end of the device, yeast cells are collected for genome sequencing. We recently published the proof of concept (Lab Chip 2021). Among the most important and less understood mechanisms that contribute to mutagenesis is a complex interplay between transcription and DNA repair. DNA repair mechanisms play an important role in preventing mutations responsible for aging and diseases. Nucleotide excision repair (NER) is a major repair pathway that removes DNA lesions arising upon UV irradiation on the transcribed regions (transcription-coupled repair, TCR) or in the entire genome (global genome repair, GGR). Understanding the complex relationships between transcription and DNA repair in vivo is thus a key biological question directly relevant for human diseases.

## Mission

The candidate will have to fabricate a new design, which include at least 40 lines in parallel in order to make massive parallelization including wild-type and well-characterized mutants in DNA repair and transcription. Based on the existing microfluidic platform, the design will be optimized, especially the growing environment, and fluid management will have to be mastered. The microfabrication of the mold, which involves several alignment steps, will be challenging. In addition to endogenous processes, exogenous mutagen exposure represents an important factor increasing the rate of mutations. To extend our work to DNA-damage induced mutagenesis, the candidate will adapt the microfluidic device to UV treatment or the presence of mutagenic chemicals. The candidate will also be responsible for making the first mutation accumulation measurements in close collaboration with the biologists and bio-informaticians involved in the project.
The candidate will mainly works in the LIONS for the microsystem development but he/she will be in close collaboration with the biologists of the SBIGeM.

## Profile

With an engineering background (or equivalent) and/or a PhD in Microfluidics/Engineering/BioPhysics, the candidate must be able to make proposals, be independent and be motivated by challenges in a multidisciplinary team.
Applicants will have an experimentalist profile.
Applicants shall speak English or French, and have good communication skills.
**Duration:** 12 months
**Starting date:** To be filled February-March 2023
**Localization:** LIONS and SBIGeM at CEA/Saclay, Gif sur Yvette France

**Contacts** CV, motivation letter and recommendation letter should be sent to both contacts.
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