MACRO-SCREEN

CRISPR Screening in primären humanen Macrophagen

Programm / Ausschreibung	Life Sciences 24/26, Life Sciences 24/26, LIFE: Life Science Ausschreibung 2025	**Status**	laufend
Projektstart	01.03.2025	**Projektende**	28.02.2026
Zeitraum	2025 - 2026	**Projektlaufzeit**	12 Monate
Keywords	human primary cells, macrophages, CRISPR screen		

Projektbeschreibung

Im Rahmen dieses Projekts wird eine Technologieplatform für fortschrittliche CRISPR-Screens in Makrophagen und anderen primären Zellen entwickelt, um die zugrunde liegenden molekularen Mechanismen, die die Funktion dieser Zellen steuern, systematisch zu entschlüsseln. CRISPR-Screens bieten eine leistungsstarke Methode zur Identifizierung von sowohl bekannten als auch neuartigen Regulatoren, die entscheidend für die Steuerung von Makrophagen sind. Durch die Kombination von CRISPR-vermittelten Geneditierungstechniken und Einzelzell-RNA-Sequenzierung (scRNA-seq) können wir spezifische Gene und regulatorische Programme ableiten, die für die Kontrolle unterschiedlicher Funktionen, wie Antigenpräsentation, Zellrekrutierung und Zytokinproduktion, verantwortlich sind.

Endberichtkurzfassung

The focus of the project was to establish CRISPR screening workflows in primary human macrophages and to develop an AI model capable of predicting transcriptomic responses to genetic perturbations. We successfully overcame long-standing challenges associated with performing pooled CRISPR screens in macrophages by building a versatile platform that supports both CRISPR knockout and CRISPR interference. We conducted two complementary screening campaigns: a CRISPR screen combined with single-cell transcriptomics focused on a targeted gene set associated with macrophage activation, and a large pooled FACS-based screen targeting druggable genes. Together, these efforts generated rich datasets that revealed key regulators of macrophage activation and polarization, validated known pathways, and uncovered novel macrophage biology. Importantly, the work demonstrated that pooled CRISPR screening is feasible in primary human macrophages at scale, marking a major milestone for the field.

In parallel, we performed a large-scale single-cell CRISPR screen in THP-1 cells, a routinely used macrophage model system, to support AI model training. The resulting perturbation dataset was integrated into a broad training corpus combining public resources with internally generated data. Building on this foundation, we developed and benchmarked our model and introduced new evaluation frameworks to rigorously assess predictive performance.

Together, these experimental and computational advances place Myllia at the forefront of AI-enabled target discovery. The

integration of large-scale CRISPR screening with predictive modelling establishes a closed-loop discovery engine in which experimental data continuously improves model accuracy, while model predictions guide the selection of new perturbations for screening. Collectively, these achievements establish a unified experimental–computational framework for next-generation drug target discovery.

Projektpartner

- Myllia Biotechnology GmbH