Discovery in I&I

Autograph: ex vivo precision immunology for ML-driven discovery of clinically relevant targets in rheumatoid arthritis

Programm / Ausschreibung	Life Sciences 24/26, Life Sciences 24/26, LIFE: Life Science Ausschreibung 2025	**Status**	laufend
Projektstart	03.03.2025	**Projektende**	02.06.2026
Zeitraum	2025 - 2026	**Projektlaufzeit**	16 Monate
Projektförderung	€ 803.908		
Keywords	precision immunology; target discovery; ex vivo perturbation screening; lab in the loop; multi-modal machine learning		

Projektbeschreibung

Graph Therapeutics möchte die Medikamentenentwicklung für immunvermittelte Erkrankungen durch die Entwicklung einer KI-gestützten Präzisionsimmunologie-Plattform mit iterativer Laborvalidierung grundlegend verbessern. Diese Plattform soll neue Erkenntnisse über Krankheitsmechanismen aufdecken und dabei skalierbare ex-vivo-Perturbationsmodelle von primären Patientenproben mit fortschrittlichen KI-Methoden zum aktiven kausalen Lernen kombinieren. Das vorliegende Projekt konzentriert sich auf biologische und technische Entwicklungen zur Identifizierung neuer Zielmoleküle bei rheumatoider Arthritis, mit dem Ziel, Partnerschaften und Entwicklungsprogramme zu etablieren.

Zentrale technische Ziele:

1. Etablierung und Validierung eines skalierbaren ex-vivo-Perturbationsmodells für rheumatoide Arthritis.

2. Integration multimodaler Analysen durch Kombination hochauflösender Mikroskopie-Daten mit Einzelzell-RNA-Sequenzierung (scRNAseq) unter Perturbationsbedingungen.

3. Entwicklung KI-gestützter Methoden zur Identifizierung von Zielmolekülen durch maschinelle Lernmodelle, die sowohl die Wirksamkeit von Medikamenten vorhersagen als auch neue therapeutische Angriffspunkte aufzeigen.

Das Projekt wird letztlich die robuste Erfassung wesentlicher Aspekte der rheumatoiden Arthritis in einem klinisch relevanten Modellsystem ermöglichen, neue therapeutische Zielmoleküle identifizieren und validieren sowie umfassende Datenpakete für klinische und pharmazeutische Partnerschaften generieren.

Endberichtkurzfassung

Graph Therapeutics successfully established and validated an ex vivo perturbation platform for rheumatoid arthritis (RA) and

a scientifically motivated expansion to systemic lupus erythematosus (SLE). The project delivered end-to-end results across platform development, large-scale patient profiling, and AI-driven target discovery.

In WP2, the core RA disease model was established and validated using matched peripheral blood mononuclear cells (PBMCs) and synovial fluid (SF) from RA patients, with optimised co-culture conditions and a validated extended marker panel for high-content microscopy (HCM). Orthogonal assays were deployed to validate the experimental approach, such as Olink to confirm the differential soluble factor profile across SF, or Transwell® migration assays to confirm the link between a T cell activation morphology and migration.

In WP3, large-scale functional screening was completed across more than 20 RA patient samples (matched PBMC/SF), with a broad perturbation panel covering standard-of-care drugs and targeted immunomodulatory compounds. Distinct disease-specific functional response profiles were identified across patient backgrounds and confirmed to recapitulate known biology, including expected responses to biologic agents and other preclinical inhibitors. Matched single-cell RNA sequencing (scRNAseq) was generated for a subset of samples and perturbation conditions, providing molecular resolution on cellular response mechanisms..

In WP4, our multimodal target prediction framework integrating functional and molecular profiling embedded with priors (protein protein interaction networks, clinical landscape) generated disease contextualised target hypotheses. A focused validation screen was executed to test top predictions functionally and molecularly, including identification of disease fingerprint-reverting compounds not represented in the current standard of care. A set of receptor antagonists were identified as a disease fingerprint-reverting compound with a partially explored target space and was selected for deeper investigation. Results from the target discovery workflow were presented at the AAI 2025 symposium (Boudesco et al., 2026) and form the basis for continued target and I&I drug discovery.

Collectively, the project delivered a validated, multi-modal, lab-in-the-loop discovery platform for immune-mediated inflammatory diseases, with first novel target candidates identified and biologically contextualised in clinically realistic patient models. Building on these results, Graph Therapeutics is actively pursuing follow-on funding to advance the platform from TRL4 to TRL5 and beyond, transitioning from industrial research into experimental development with deeper target validation and expanded indication coverage. In parallel, the validated target data package and mechanistic characterisation of lead candidates provide a foundation for early engagement with pharmaceutical partners, with the goal of establishing collaborative discovery or licensing arrangements in RA and associated indications.

Projektpartner

- Graph Therapeutics FlexCo