Poster 2751

macomics

ENIGMAC™ discovery platform enables gene to function target validation for macrophage therapy

Martha Lopez-Yrigoyen[1], Thomas W. Crozier[1], Helena Engman[1], Yuxin Cui[1], Moritz Haneklaus[1], Krzysztof B. Wicher[1], Steven Myatt[1], Jeffrey W Pollard[1,2] , Luca Cassetta[1] and Carola Ries[1].

[1]Macomics Ltd, 137a George St, Edinburgh EH2 4JY

[2] MRC-Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh EH16 4TJ

ABSTRACT

The main goal of the ENIGMAC™ discovery platform is to support gene-to-function studies and to deliver new validated macrophage targets. The platform is designed to develop novel assay systems, unique genome editing methods, and supported by the multi-omics bioinformatics analyses. We use a human Induced Pluripotent Stem Cell (iPSC) line that yields macrophages phenotypically and functionally very similar to MDM. By employing this iPSC system, we can produce millions of macrophages per week, which allows multiple high throughput assays to support target validation and drug discovery. Furthermore, we developed several technologies to allow fast and reliable gene editing of macrophages.

Our proprietary toolbox allows us to perform gene Knock In (KI), Knock Out (KO) and Knock Down (KD) with high efficiency both at iPSC and macrophage level while maintaining expression/silencing during macrophage differentiation. KD can be performed using a pooled approach that enables screening by flow cytometry-based phenotypes at large scale. In conclusion, the ENIGMAC™ platform represents a unique tool for gene-to-function studies using human macrophages. Notably, it is disease agnostic and can be integrated with a variety of disease-specific conditions and phenotypic readouts.

CONTACT

Luca Cassetta, Co-Founder, VP Immunology, Macomics LTD
Email: cassetta@macomics.com
Website: www.macomics.com

INTRODUCTION

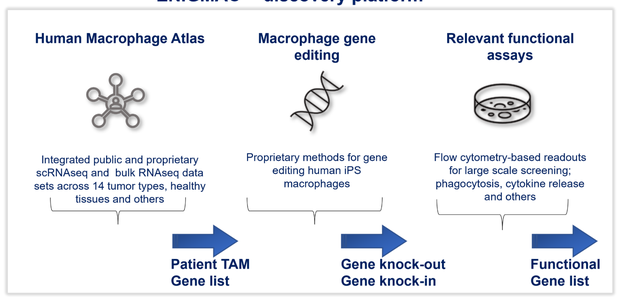
Macrophages are key players of the tumor microenvironment. Most tumors are populated by macrophages and a rich infiltration of this myeloid cell is generally correlated with poor prognosis at the clinical level (1). TAMs influence all the other cell types in the tumor by creating a pro-tumoral niche which favours cancer cells to proliferate and invade other organs (2)

Different strategies have been used to modulate TAMs in cancer in the clinical setting (3). We believe that TAMs reprogramming is a very effective strategy. By changing the phenotype of a high number of intratumoral TAM, we achieve not only the abrogation of their tumor-supporting functions but importantly also the increase of their tumor-killing properties. In this way, at Macomics, we plan to tip the balance and create a reprogramming domino effect which will influence other immune cells to mount an effective anti-tumor immune response.

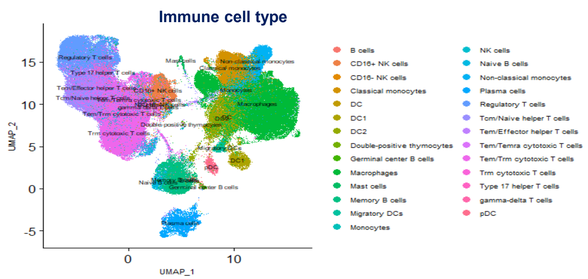
Using 'Omics' techniques is fundamental to fully understand the extreme complexity of the TME and identify new targets. However, in the last few years we have experienced what we define as "dataset infodemic"; a lot of datasets have been produced, but they lack proper validation at the functional level.

Hence, we have developed the ENIGMAC™ discovery platform, which allows stringent bioinformatic analysis coupled with macrophage gene editing and subsequent functional analysis. Our platform enables the identification of genetically validated macrophage therapeutic targets and informs the drug screening assay strategy.

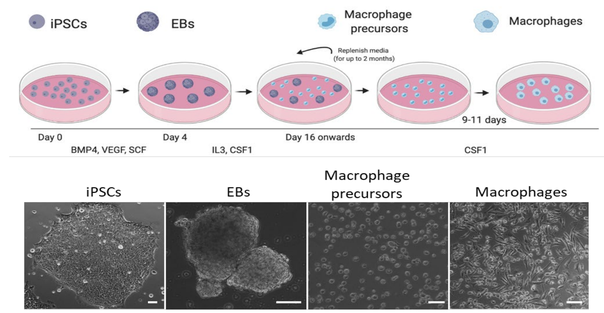
ENIGMAC™ discovery platform



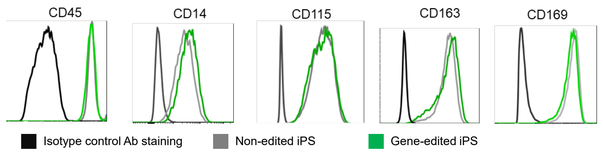
Immune cell atlas

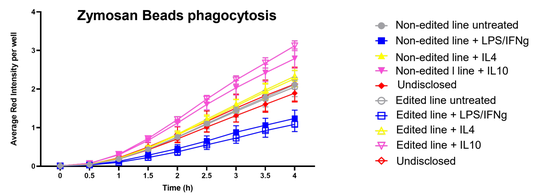


iPS technology allows at-scale macrophage production

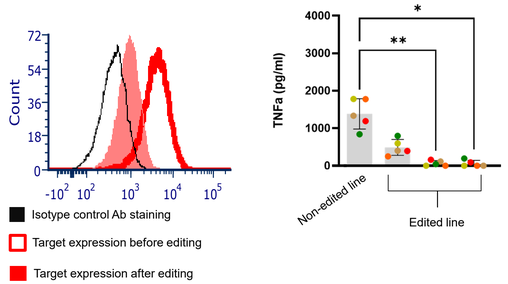


iPS editing does not impair macrophage phenotype and functionality

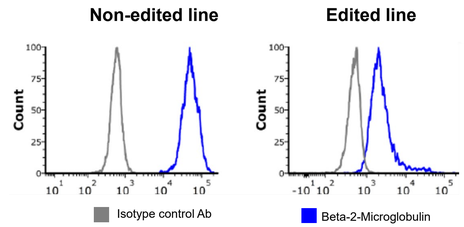




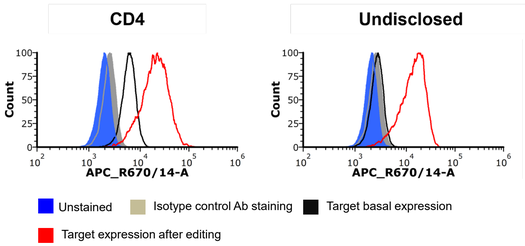
Gene editing at iPS level allows expression of functional targets on macrophages



Gene editing at macrophage stage: target downmodulation



Gene editing at macrophage stage: target upregulation



ENIGMAC™ platform summary:

- Fully integrated platform for novel target identification & validation, and drug screening
- Combining:
  - Disease relevant assays
  - Extensive bioinformatics macrophage (and other immune cells) atlas
  - Genomic engineering of human macrophages
- Disease agnostic
- High throughput screen ready

REFERENCES

1- Zhang, Q. W. et al. Prognostic significance of tumor-associated macrophages in solid umor: a meta-analysis of the literature. *PLoS ONE* 7, e50946 (2012).
2- Cassetta, L. & Pollard, J. W. Targeting macrophages: therapeutic approaches in cancer. *Nat. Rev. Drug. Discov.* 17, 887–904 (2018).
3- Cassetta, L. & Pollard, J. W. A timeline of tumor-associated macrophages. *Nat. Rev Cancer,* doi: 10.1038/s41568-022-00547-1 (2023)
4- Lopez-Yrigoyen et al. Production and characterization of human macrophages from pluripotent stem cells. *J Vis Exp,* 16158) (2020)