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Harnessing the power of macrophage drug discovery

Macomics has developed a precision technology to develop cancer immunotherapy.

Building on grounding-breaking research into the immuno-suppressive role of tumor-associated macrophages (TAMs), Macomics has developed a unique platform, ENIGMAC combining a human bioinformatic pipeline, with novel cell models and human macrophage gene editing technology to help treat cancer. "The platform has enabled us to develop a pipeline of novel therapeutic programs, targeting tumor-associated macrophages, based on either first-in-class targets or first-in-mechanism approaches, and to also prosecute those programs in a completely new way," said Stephen Myatt, Macomics CEO. "Understanding drug action, accessing targets only found in patients, and biomarker discovery are all areas where we have seen a major impact, using our platform."

Macomics has built a seasoned drug discovery team, with 17 staff working across two sites—Edinburgh and Cambridge—with Krzysztof Wicher joining as VP Drug Discovery from Kymab, and former Roche macrophage drug discovery pioneer Carola Ries as CSO. The company plans to take its first therapy into the clinic in 2024.

Macomics was co-founded in 2020 by top macrophage experts from the University of Edinburgh, Jeffrey Pollard, who passed away in 2023, and Luca Cassetta, now Macomics VP for immunology. The duo were the first researchers to identify the disease-specific reprogramming of macrophages in cancer. TAMs are the most abundant immune cell in many types of cancer and modulating their behavior can enhance the body's ability to fight cancer.

Macrophage drug discovery has been limited by difficulties in identifying the changes that occur in different cancer types and identifying suitable drugs. "Many targets that are potentially therapeutically interesting in patient datasets, are just not found expressed on macrophages under normal conditions in a dish," explained CSO, Carola Ries.

A novel approach

The ENIGMAC discovery platform uses human gene expression data from both normal and diseased tissue to create a Macrophage Atlas—a large informatics pipeline based on RNA sequencing data that establishes which genes are up- or down-regulated in a variety of tumor types.

The platform allows gene editing at scale to establish the functional consequences of changes. "Gene editing of macrophages is inherently difficult, because macrophages are designed to degrade DNA and RNA," said Ries. Gene editing methods facilitate the expression of a gene or genes of interest in induced pluripotent stem cell (iPSC)-derived macrophages. "Our proprietary gene editing technology is new to the macrophage space and is enabling us to knockdown or express a target in human macrophages and show its function, and to do this efficiently thousands of genes at a time," added Ries.

Macomics is unlocking the many faces of macrophage disease reprogramming.
Image designed by co-founder Luca Cassetta and Daniel Soong.

The use of iPSC-derived macrophages is also more relevant to human macrophages found in a patient than traditional immortalised cancer cell lines models. "Crucially, these gene edited iPSC-derived macrophages are fully plastic, can be programmed into immunosuppressive states, and depend on the same survival factors as macrophages found in a patient," said Myatt. "It is impossible to currently fully recapitulate the complexity of a tumor environment in vitro, but we push the system hard, using highly immune-supressed conditions that are a better model for what we find in patients," said Ries. Macomics uses its platform to probe the activity of a potential therapeutic, support biomarker discovery and gain a better understanding of the mechanisms of action.

Macomics has a pipeline of novel therapeutic programs in immuno-oncology. The most advanced program targets the LILRB1/2 receptor protein, which is up-regulated on TAMs in a number of cancers and inhibits the stimulation of an immune response. The lead antibody-drug candidate aims to reactivate the macrophages to induce a pro-inflammatory cytokine release that activates other immune cells. It has been shown to have a novel mechanism of action that translates to increased activity.

Future directions

In March 2023, the company announced a worldwide drug discovery collaboration agreement with Japanese oncology veterans, Ono Pharmaceutical Co. The partnership will develop immuno-oncology drugs against a novel macrophage cancer target using the ENIGMAC platform to identify and characterise antibody candidates.

Macomics wants to explore future partnership possibilities. "We've now completed the technical validation of our platform and are excited about the potential, for the first time, to be able truly interrogate macrophage disease biology at scale," said Ries. "We are really at the tip of the iceberg in terms of macrophage therapeutic discovery across multiple disease settings. There is huge untapped potential, and we are open to working with partners that can bring value to new programs or biology, and who share our vision for delivering transformational macrophage therapies to patients," said Myatt.

The company is preparing for a series A funding round in 2024 and sees a bright future as the leading specialist in macrophage drug discovery and the partner of choice for companies seeking to exploit macrophage-based approaches to developing novel precision medicines. "We've built a unique toolbox that allows us to do macrophage drug discovery in a way that others just can't. Our ambition is to become a global leader in this space, and ultimately take multiple macrophage therapies into the clinic," said Myatt.

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>
> Carola Ries, CSO, Macomics Limited

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