A First-in-Class CD64-Targeting ADC for the Selective Depletion of Pathogenic Monocytic Cells in Hematologic and Solid Tumors

Lia Buffa, Cintia Garro, Constanza Marin, Alejandra García, Diego Andino, Melisa Capitanelli, Laura Bertoldi, Florencia Villafañez, Tarek Zaki, Gerardo Gatti, Candelaria Llorens de los Ríos and **Gastón Soria**

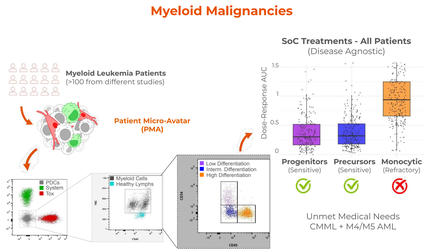
OncoPrecision, New York, NY

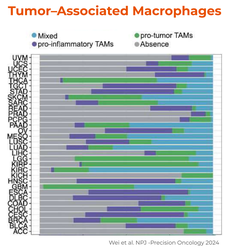
CD64-targeting by ADCs emerges as a therapeutic strategy to deplete leukemic monocytes and TAMs

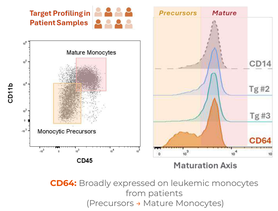
Cells of monocytic origin are widely refractory to standard of care treatments, potentially due to their highly differentiated phenotypes and low proliferative capacity. In monocytic leukemia, this is not only reported for small molecules, but also for naked antibody approaches, which historically displayed poor performance against leukemic monocytes. In this work, we sought to develop an ADC approach to overcome monocyte-driven resistance by guiding the target, payload-linker and lead antibody selection with our ex vivo Patient-Micro Avatar (PMAs) technology. This discovery campaign led to identification of CD64 and PNU-159682 as the optimal target and payload, respectively, to develop ONC001, a first-in-class ADC to deplete pathogenic monocytes/macrophages in myeloid leukemia and solid tumors.

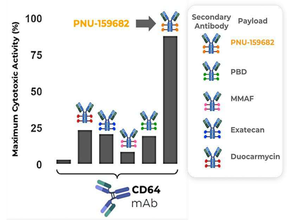
ADC Development

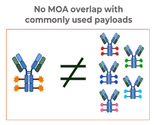
Unmet Medical Need Validation → Target ID → Payload Selection → Development Candidate











ONC001
(First-in-Class CD64-targeting ADC)

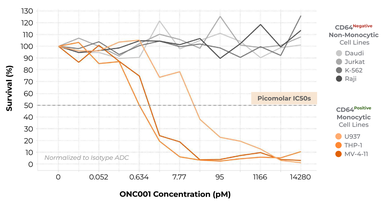
- Selected from >500 proprietary IgG1 mAbs
- Coupled to PNU through a non-cleavable linker
- Maleimide-based conjugation: DAR ~4
- Humanized IgG1κ manufacturability by Lonza

ONC001 Efficacy

Myeloid Malignancies

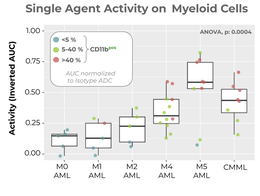
In Vitro (Cell Lines)

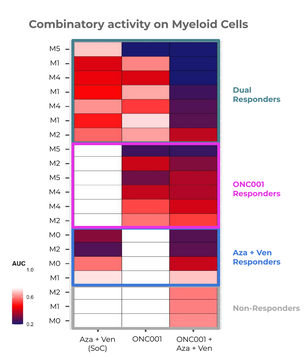
ONC001 **potency and selectivity** were evaluated across a broad panel of monocytic and non-monocytic cell lines in a wide dose-range to explore target specificity and potential off-target activity.



Ex Vivo (PMAs)

ONC001 **single agent activity and combinatory potential** with SoC schemes was evaluated ex vivo in a large cohort of myeloid leukemia patients, including monocytic and primitive types of AML, as well as CMML.

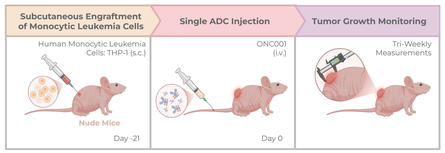


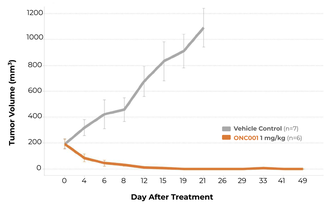


In Vivo (Mouse Models)

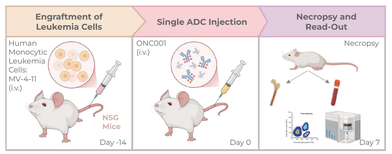
Th single-dose efficacy of ONC001 was evaluated in **two monocytic leukemia CDX models.** The heterotopic model assessed durability of response, monitoring tumor growth until post-remission regrowth or control endpoints. The disseminated model evaluated leukemic burden in peripheral blood and bone marrow at a one-week endpoint.

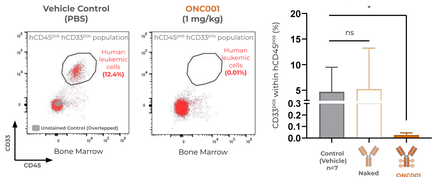
Heterotopic Kinetic Model





Orthotopic Disseminated Model

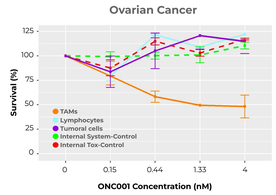


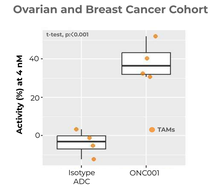


Solid Tumors

Ex Vivo (PMAs)

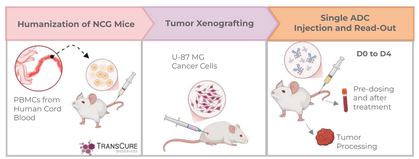
To confirm selectivity toward **autologous CD64-expressing TAMs** in patient samples, a dose-response of ONC001 was assessed in an ovarian cancer PMA. Investigation of ex vivo activity against TAMs was further expanded to three ovarian cancer samples and one triple-negative breast cancer (TNBC) at the highest validated dose.

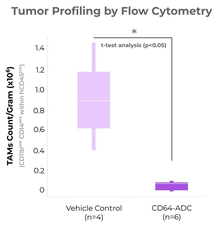


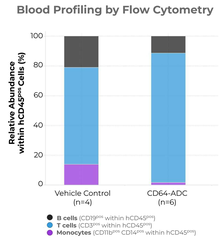


In Vivo (Humanized Mouse Model)

A humanized NCG model with enhanced myeloid/DC differentiation was utilized to assess the **depletion of circulating human monocytes and TAMs**. U-87 MG glioblastoma CDX mice, representative of high-infiltration solid tumors, received a single 0.75 mg/kg dose of a tool CD64-ADC.



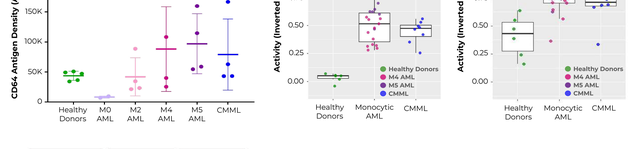


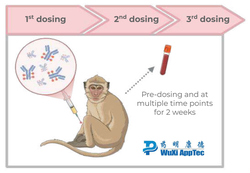


ONC001 Safety & Tolerability

Ex Vivo (PMAs)

CD64 Antigen Density quantification and high resolution tracking of ONC001 activity on subpopulations of PBMCs from Healthy Donors compared with Myeloid Leukemia Patients to explore its **therapeutic index**.



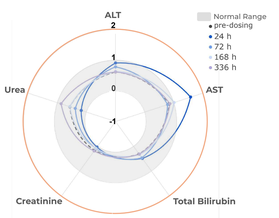


In Vivo (Non-Human Primates)

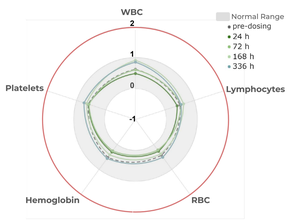
A **repeat-dose toxicology study** was conducted in naïve cynomolgus monkeys (n=8) administering ONC001 in three cycles at 15-day intervals (0.03 and 0.1 mg/kg).

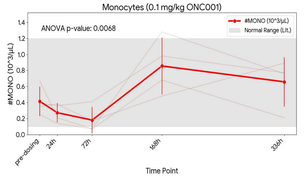
The results presented highlight data from the high-dose cohort (0.1 mg/kg; n=4) following the second administration as a representative cycle.

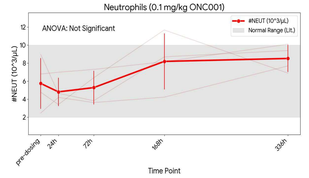
Clinical Chemistry



Hematology







Contact Information: gaston@oncoprecision.bio

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