GM102, a low fucosylated anti-Müllerian Hormone type II Receptor (AMHRII) antibody promotes *in vitro* anti-tumoral activities of innate (macrophages) and adaptative (CD4+ and CD8+ T cells) immune cells

B77

Mélissa Prat[1], Marie Salon[2], Jean-Marc Barret[3], Thibault Allain[2], Olivier Dubreuil[3], Nathalie Van Acker[4], Lydie Cassard[5], Bernard Pipy[2], Jean-François Prost[3] and Agnès Coste[1,2]

[1]UMR152 UPS-IRD, Toulouse, France; [2]InflamLab, Toulouse, France; [3]GamaMabs Pharma, Toulouse, France; [4] IUCT, Toulouse, France; [5]Institut Gustave Roussy, Villejuif, France

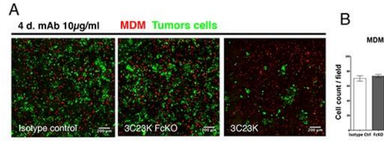
INTRODUCTION

AMHRII

- Anti-Müllerian Hormone and its membrane Receptor II (AMHRII), induce regression of Müllerian ducts in the male embryo
- In normal adults, AMHRII expression is restricted to Sertoli cells (testis) and Granulosa cells (ovary).
- AMHRII is re-expressed in approx. 70% of gynecological tumors and in more than 50% of several major cancers including NSCLC, CRC, HCC.

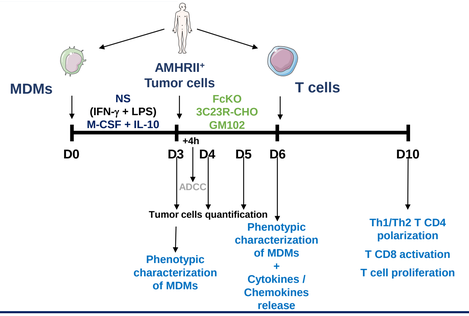
GM102

- Low-fucose IgG1 anti-AMHRII antibody
- Acts through macrophage engagement via CD16 high affinity binding
- Results in enhanced tumor phagocytosis (see Figure extracted from Bougherara et al., 2017)
- **Bougherara suggested an activation of T lymphocytes via Monocyte Derived Macrophages (MDM) that is being explored in this study.**

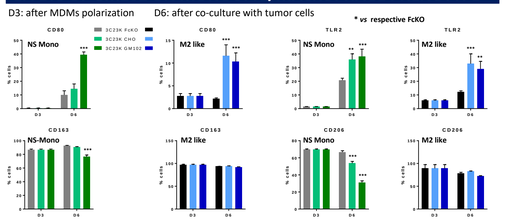


3C23K eliminates ovarian tumors cells by directing TAM to induce ADCC and ADCP *in vitro* and ex vivo.
A Representative IF microphotographs of MDM2/COV434-AMHRII co-culture after 4 days of treatment with either an irrelevant mAb, the anti-AMHRII FcKO or the anti-AMHRII GM102 (also named 3C23K).
B Quantification of MDM2 and COV434-AMMHRII tumor cells after 4 days (cell count per field of view +/- Standard Deviation).
C Representative IF microphotographs of MDM2/COV434-AMHRII co-culture after 2.5h of treatment with the anti-AMHRII mAb GM102. (Left panel) White arrows indicate phagocytosis events, (Middle panel) reconstituted 3D volume view, (Right panel) reconstituted 3D section view. GM102 targeted tumor cells are engulfed by MDM2 macrophages.

EXPERIMENTAL PROTOCOL

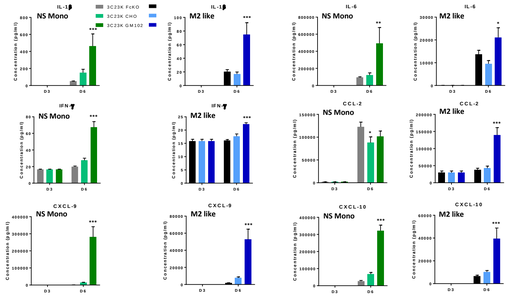


EFFETS OF GM102 ON MONOCYTE/MACROPHAGE PHENOTYPE



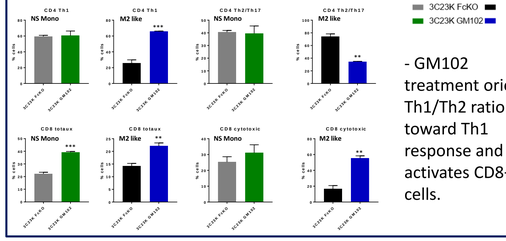
- GM102 orients unstimulated and M2-like macrophages toward M1-like macrophages, characterized by an increased expression of CD80 and TLR2 and a decrease of CD206 expression.

EFFETS OF GM102 ON MONOCYTE/MACROPHAGE RELEASE



- GM102 promotes the secretion of pro-inflammatory cytokines and chemokines involved in Th1 T cell recruitment and activation. Effects with this low fucose antibody are stronger than with the same antibody produced in CHO cells (normal fucosylation).

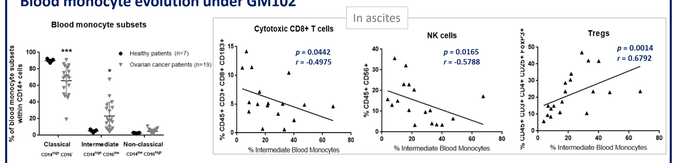
EFFECTS OF GM102 ON T CELLS THROUGH MACROPHAGES



- GM102 treatment orients Th1/Th2 ratio toward Th1 response and activates CD8+ T cells.

CLINICAL OBSERVATIONS

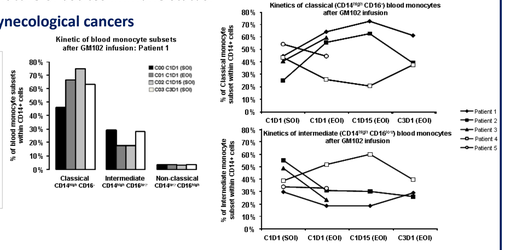
Blood monocyte evolution under GM102



- Circulating intermediate blood monocyte expansion in ovarian cancer patients is associated with decreased effector/Treg cell ratio in tumor ascites, highlighting intermediate subset as a potential predictive signature of ascites immune status.

C101 phase I study in gynecological cancers

GM102 was administered to the patients either every two weeks (Q2W): on days 1 (D1) and 15 (D15) in 4-week cycles (C), or every week (Q1W): on days 1, 8, 15 and 22 (D1, D8, D15, D22) in 4-week cycles (C). Circulating immune cells were analyzed at the first day of the first cycle (C1D1) before Start Of GM102 Infusion (SOI) and at the End Of Infusion (EOI), at day 15 of cycle 1 (C1D15) EOI and at day 1 of cycle 3 (C3D1) EOI.

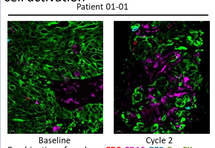


Patients	Surrogate tumor markers *Inhibin B [normal < 10-5 pg/mL]; CA125 [normal < 35 U/L]*					Tumor assessement based on CT-scans (RECIST 1.1 criteria)		
	Baseline	1 month under treatment	2 months under treatment	3 months under treatment	5 months under treatment	End of C2	End of C4	End of C6
Patient 1 (10mg/kg - Q1W)	Inhibin B = 229 pg/ml	Inhibin B = 206 pg/ml	Inhibin B = 283 pg/ml	Inhibin B = 290 pg/ml	Inhibin B = 325 pg/ml	Stable Disease	Stable Disease	Stable Disease
Patient 2 (15mg/kg - Q2W)	CA125 = 387 U/L	CA125 = 512 U/L	CA125 = 532 U/L	CA125 = 541 U/L		Stable Disease	Progressive Dis.	
Patient 3 (3 mg/kg - Q2W)	CA125 = 962 U/L	CA125 = 1100 U/L	CA125 = 1286 U/L	CA125 = 1402 U/L		Stable Disease	Stable Disease	
Patient 4 (10 mg/kg - Q2W)	CA125 = 544 U/L	CA125 = 762 U/L	CA125 = 1100 U/L	CA125 = 1089 U/L		Stable Disease	Stable Disease	
Patient 5 (20 mg/kg - Q2W)	CA125 = 3522 U/L	CA125 = 6760 U/L				Progressive Dis. (brain metastatic lesions)		

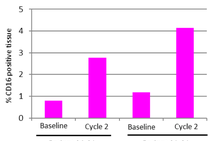
- Under GM102, the proportions of classical and intermediate blood monocyte subsets are restored toward normal.
- The improvement of the level of classical blood monocytes observed with GM102 is associated with a stabilization of the surrogate tumor markers and tumor burden evaluated by CT-scan according to RECIST1.1. criteria.

Tumor MicroEnvironnment (TME) evolution under GM102, paired biopsies, IF (n = 2 evaluable patients)

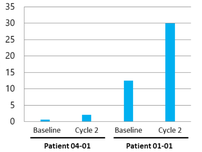
- CD16+ cells are abundantly present in the TME
- Under GM102: CD16 expression increase and Granzyme B expression increase in CD16+ cells, reflecting TME cell activation



Combination of markers: CD8-CD16-GZB-PanCK
CD16 (pink), CD8 (red) and Granzyme B (blue) expression at baseline and cycle 2 on tumor biopsies (patients 04-01 and 01-01).
Pan-cytokeratin (green) is used as a tumor cell marker.

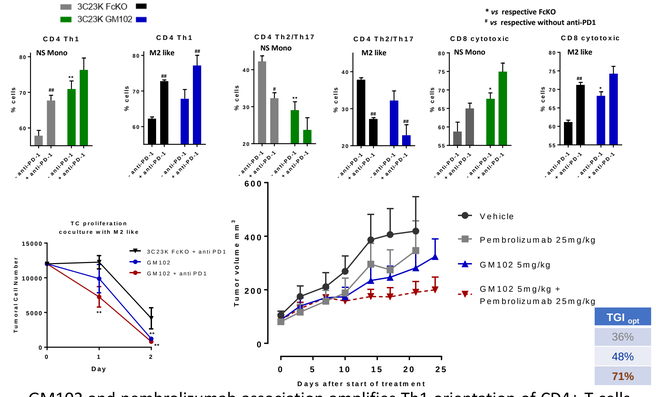


Percentage of CD16 + stained area evaluated using the HALO HighPlex Immunofluorescence module of Indica Labs, at baseline and cycle 2 on tumor biopsies (patients 04-01 and 01-01).



Cellular based cell count (number/mm2) of cells expressing Granzyme B and CD16 in tumor biopsies from patients 04-01 and 01-01 at baseline and cycle 2.

COMBINATION GM102 + PEMBROLIZUMAB



TGI opt
36%
48%
71%

- GM102 and pembrolizumab association amplifies Th1 orientation of CD4+ T cells and CD8 T cell activation.
- Combination of GM102 and pembrolizumab shows synergistic effect on lysis of SKOV3-AMHRII+ ovarian cancer cells when co-incubated with M2-like macrophages and T lymphocytes.
- GM102 and pembrolizumab combination shows synergistic antitumoral effect on COV434-AMHRII+ ovarian cancer cells engrafted in humanized GM-CSF/IL3/IL4 hu-NOG mice (Taconic). This synergy was observed as well on increase of hCD86 a decrease of hCD163 markers in blood mice.

CONCLUSIONS

- **GM102 induces a switch of M2-like toward M1-like macrophages, characterized by secretion of inflammatory cytokines and chemokines which results in both CD8+ T cell activation and CD4+ T cell Th1 orientation.**
- **Preliminary data on PD markers from circulating immune cells and TME assessed during the phase 1 clinical trial confirm activation of antitumoral immune system.**
- **Such properties lead to synergistic effects when GM102 is combined with pembrolizumab, characterized by an increased activation of T cells and hence stronger antitumoral activity.**
- **These results strongly suggest to test in the clinic the combination of GM102 with immune-checkpoint inhibitors.**