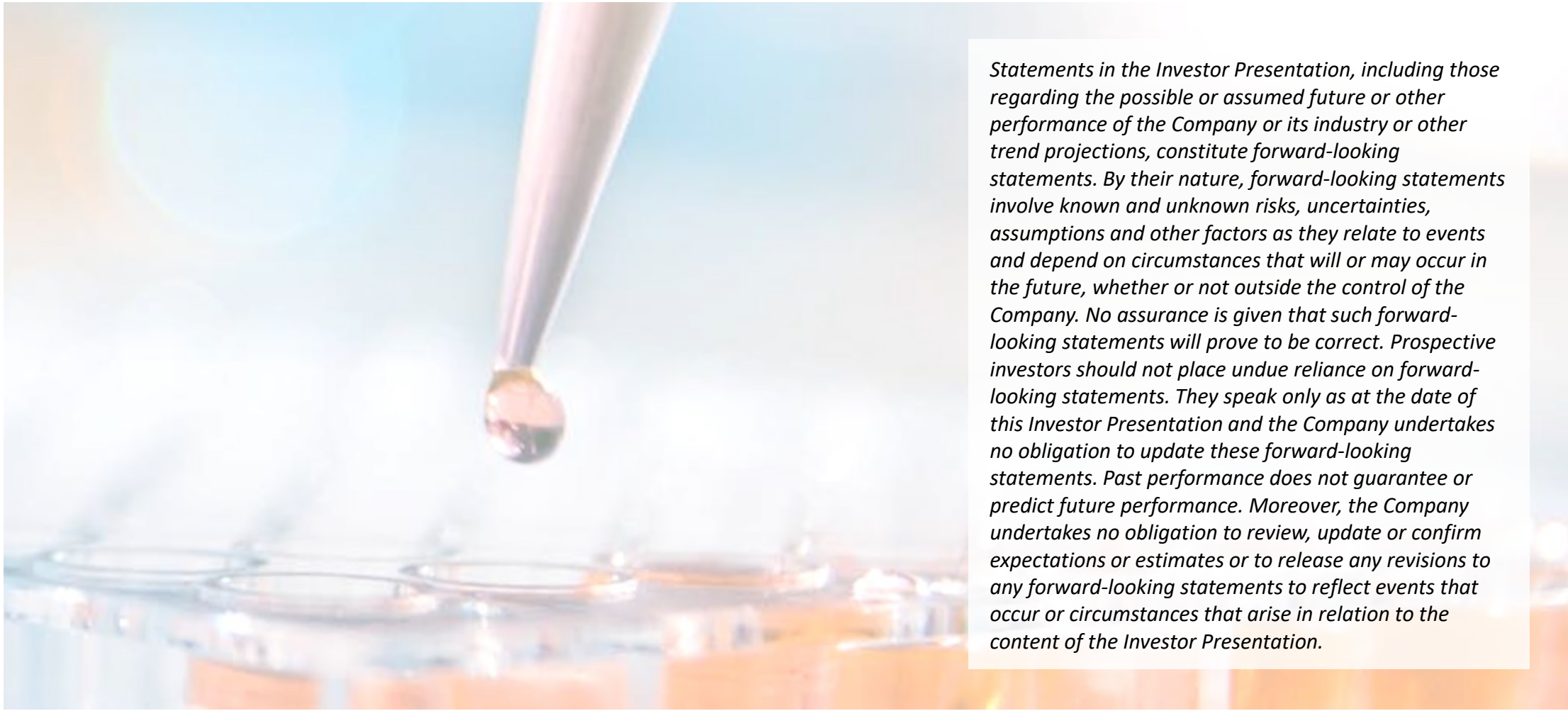
IL1RAP as a target for antibody therapy in oncology and inflammation

Göran Forsberg, CEO

Aug 2021

Safe Harbour Statement



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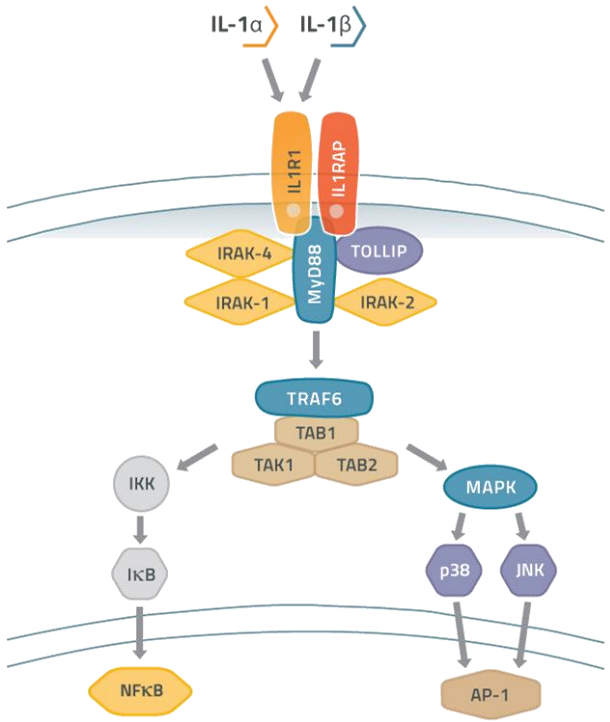
I. INTRODUCTION

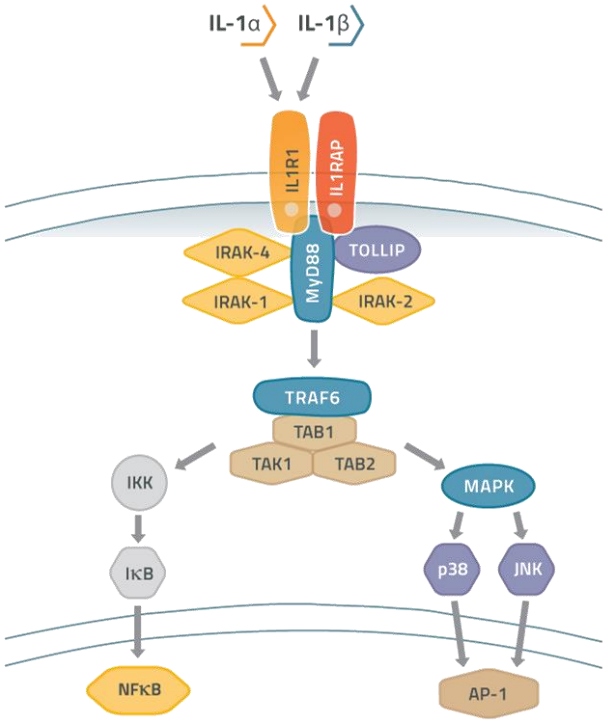
Targeting IL1RAP and relevance in cancer



- IL1RAP is an essential part of the IL-1 receptor complex
- IL1RAP is an inflammatory protein expressed by tumor cells and by tumor-supporting cells in the tumor vicinity
- IL1RAP is involved in chronic tumor inflammation and promotes tumor growth and immune suppression – both on tumor cells and on tumor-supporting cells
- IL1RAP is involved in tumor cell survival and resistance to therapeutic interventions

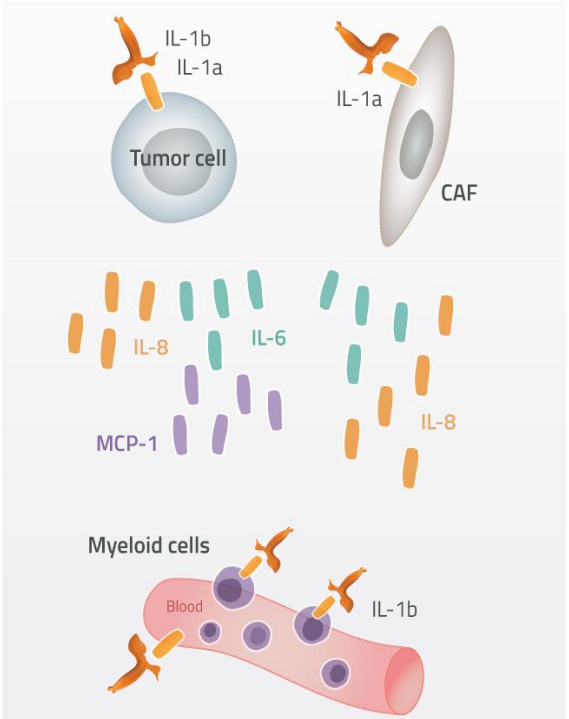
IL1RAP IS A NOVEL TARGET FOR THERAPY

Nadunolimab (CAN04) – Mechanism of action

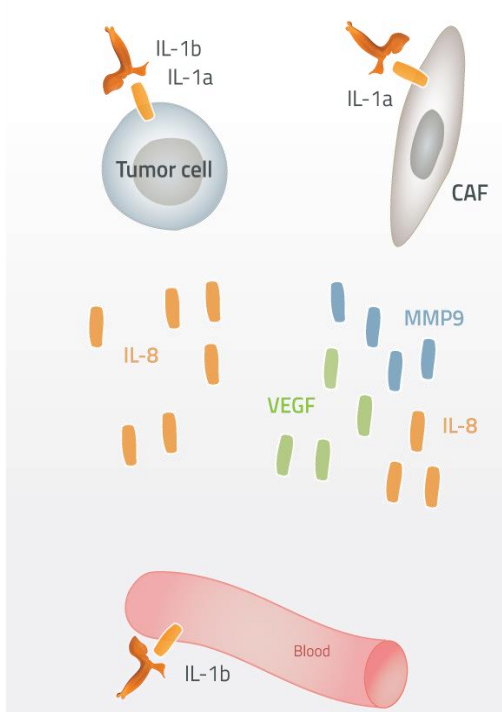


ADCC – Tumor cell death

Reduced activation and infiltration of immunosuppressive cells



Reduced angiogenesis

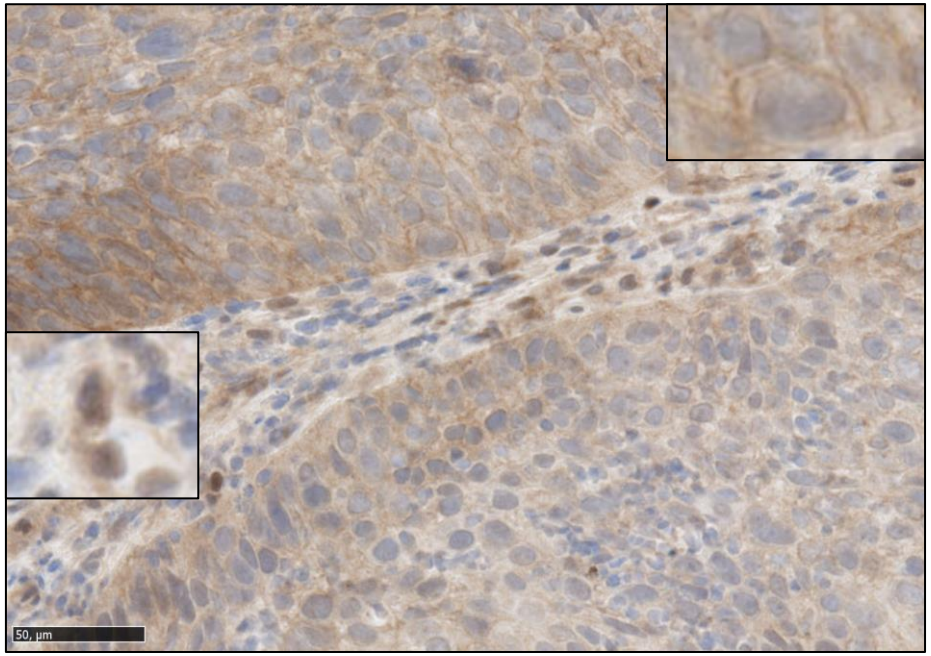


CAN04 BLOCKS BOTH FORMS OF IL-1 AND CAN ERADICATE CELLS MEDIATING THE EFFECTS OF IL-1

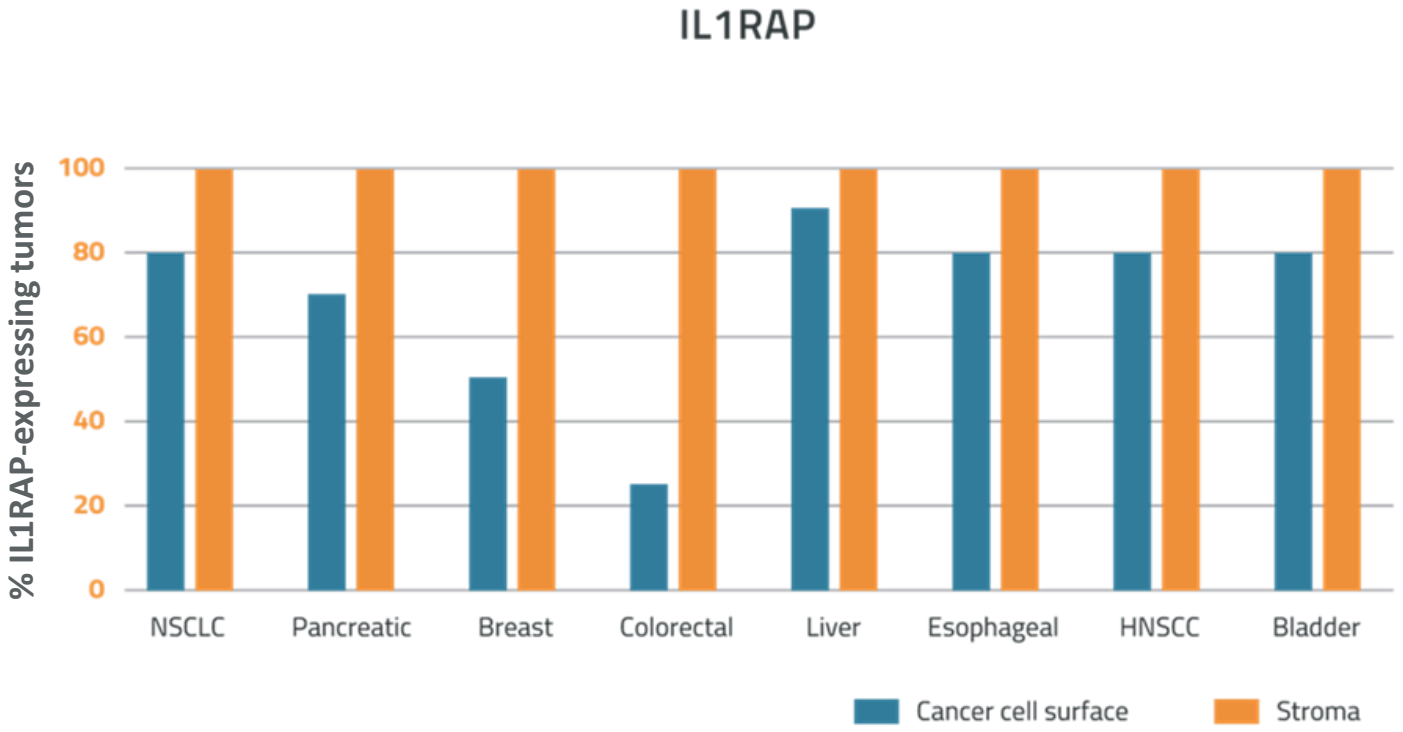
Note: ADCC = Antibody-Dependent Cellular Cytotoxicity. CAF = Cancer-Associated Fibroblast. NK = Natural Killer. MCP = Monocyte Chemoattractant Protein. MMP = Matrix Metallopeptidase. IL = Interleukin. VEGF = Vascular Endothelial Growth Factor

Cantargia

IL1RAP expression in solid tumors



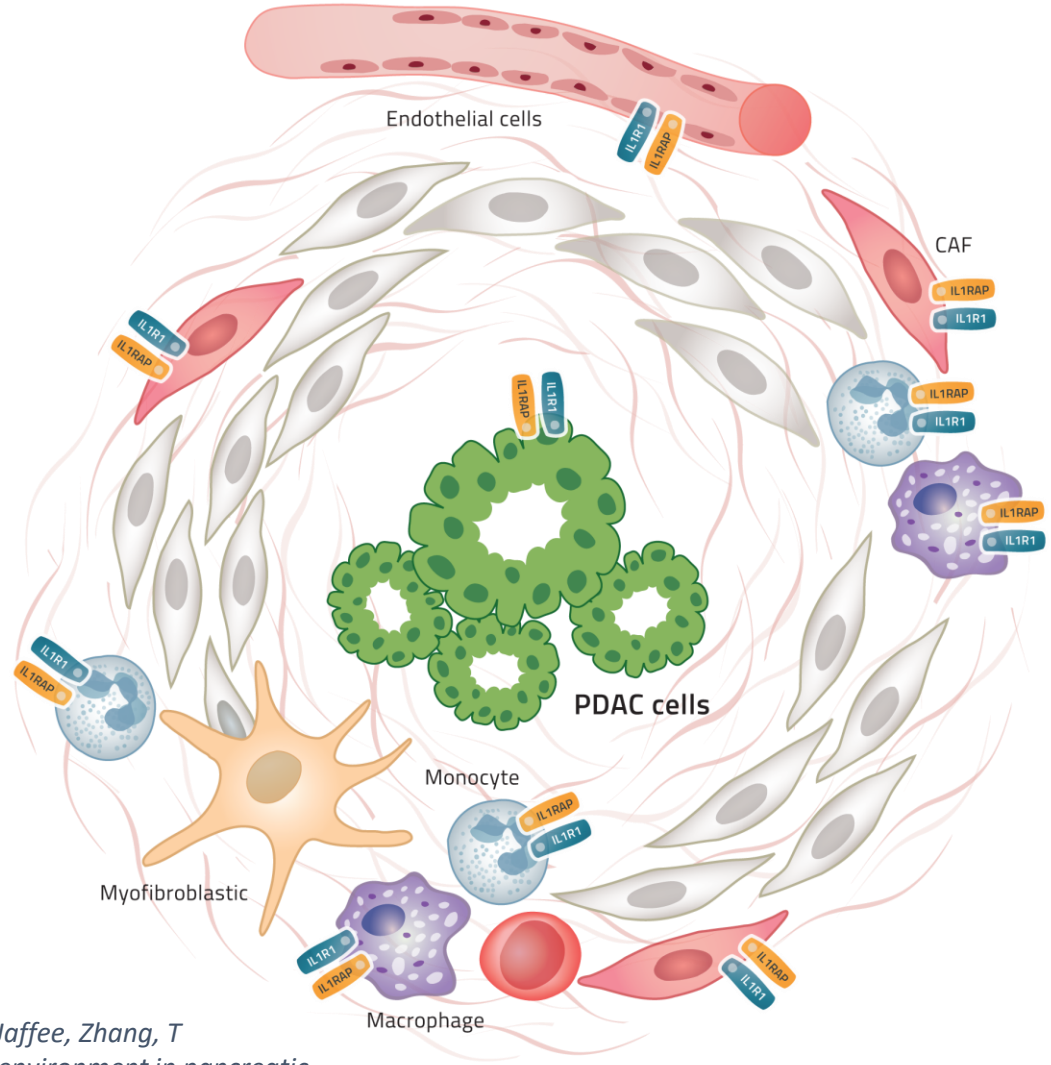
NSCLC biopsy CANFOUR, IL1RAP staining



IL1RAP IS EXPRESSED BROADLY IN SOLID TUMORS

NSCLC – non-small cell lung cancer
HNSCC – head and neck squamous carcinoma

IL1RAP expression in solid tumors



IL1RAP is expressed by:

- tumor cells
- cells in the tumor microenvironment:
  - cancer-associated fibroblasts (CAF)
  - tumor-associated macrophages (TAM)
  - monocytes
  - neutrophils
  - endothelial cells

IL1RAP-expressing cells react to IL1α or IL1β in the tumor microenvironment

Adapted from Ho, Jaffee, Zhang, T The tumour micro-environment in pancreatic cancer — clinical challenges and opportunities, Nature Reviews Clinical Oncology 2020

PDAC – pancreatic ductal adenocarcinoma

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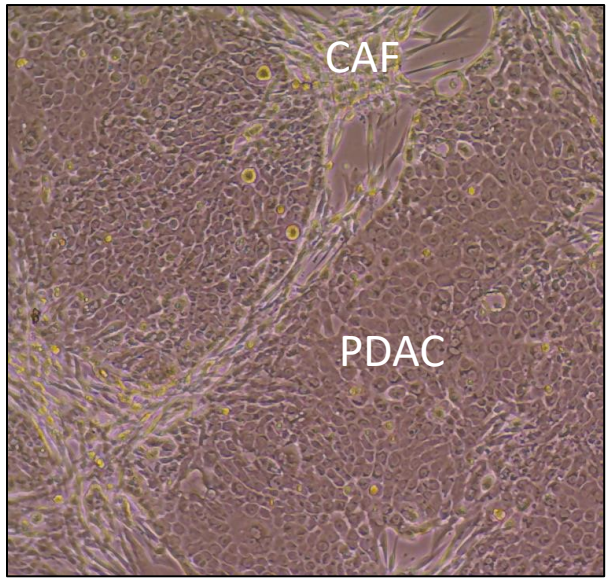
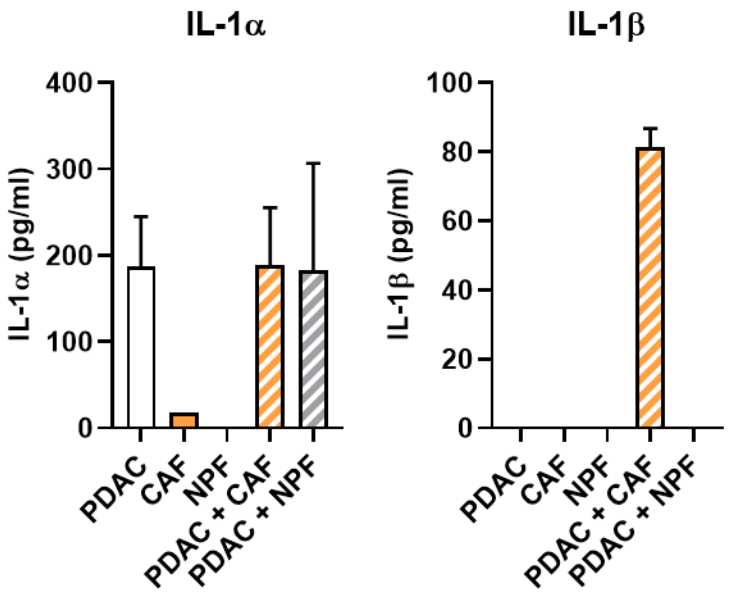
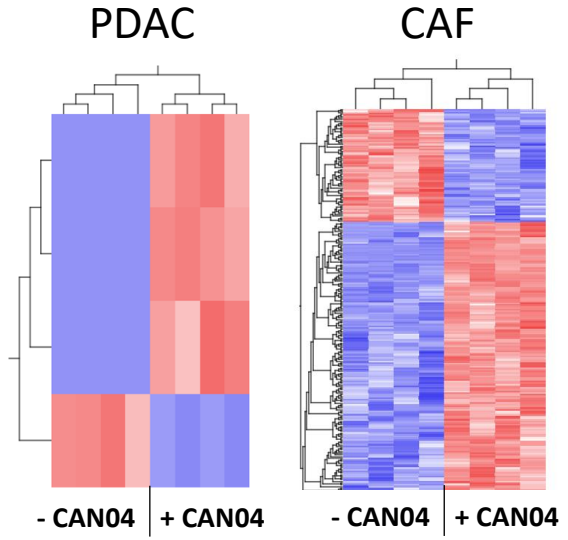
The pancreatic tumor microenvironment in vitro

Human pancreatic cancer cells cultured with human cancer associated fibroblasts





CAF = Cancer-associated fibroblast
NPF = Normal pancreatic fibroblast



4 genes changed by CAN04

230 genes changed by CAN04

RNAseq

CROSS-TALK BETWEEN CANCER CELLS AND STROMAL CELLS INVOLVE BOTH FORMS OF IL-1
CAN04 TREATMENT HAS MAJOR IMPACT ON TUMOR CELL-INDUCED REPROGRAMMING OF CAF-S

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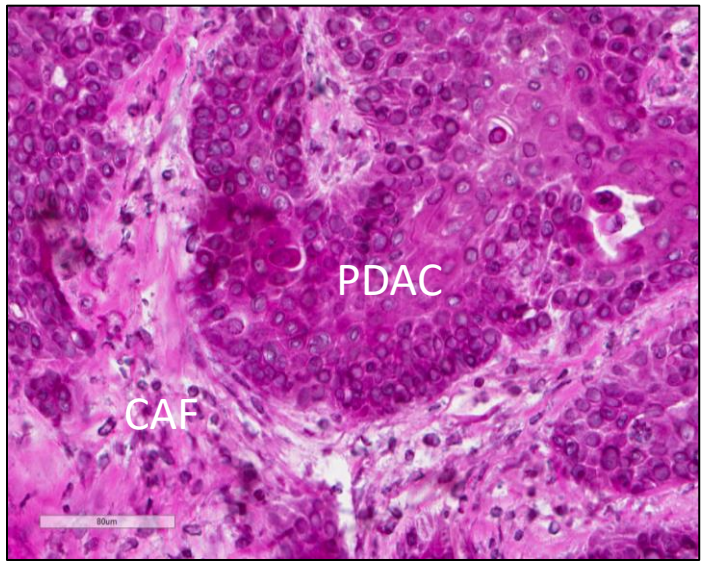
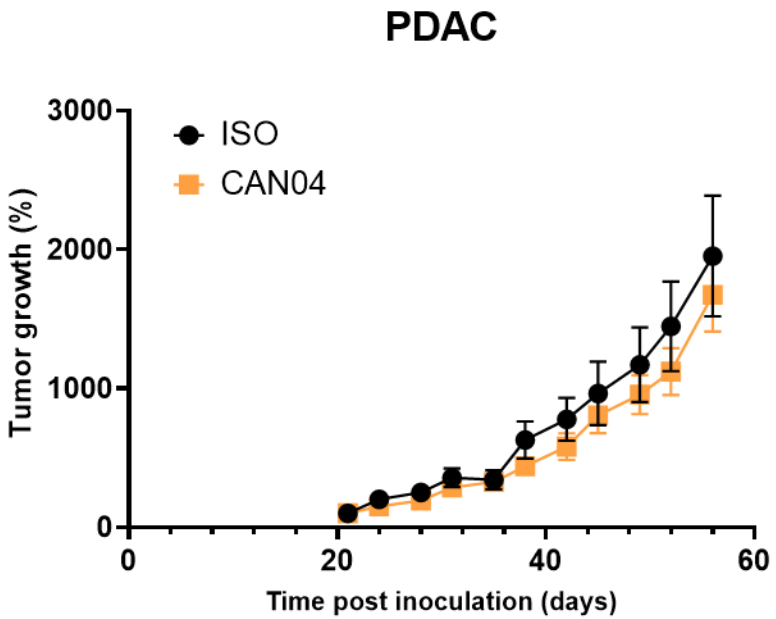
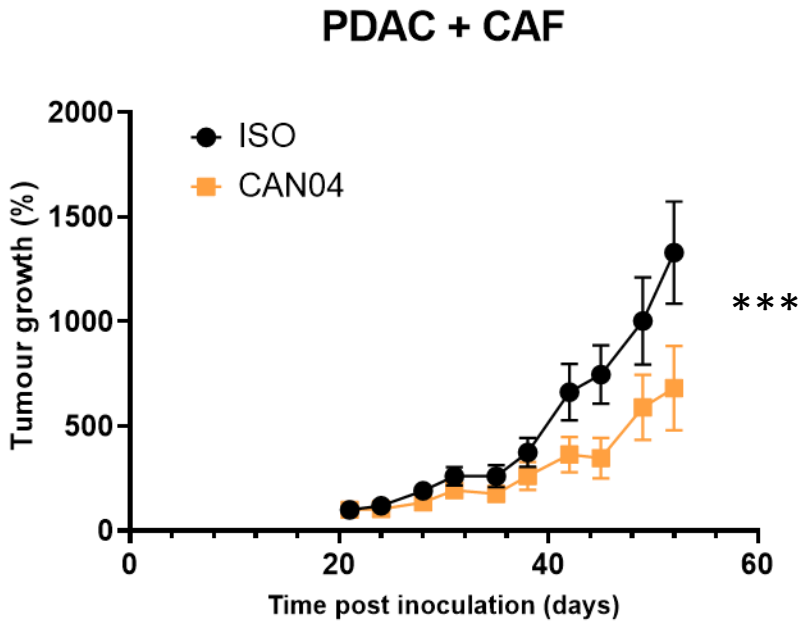
Inhibition of pancreatic tumor growth by CAN04

Tumor growth in a CAF-PDAC xenograft model of human pancreatic cancer



PDAC – cancer cells
CAF – tumor stroma





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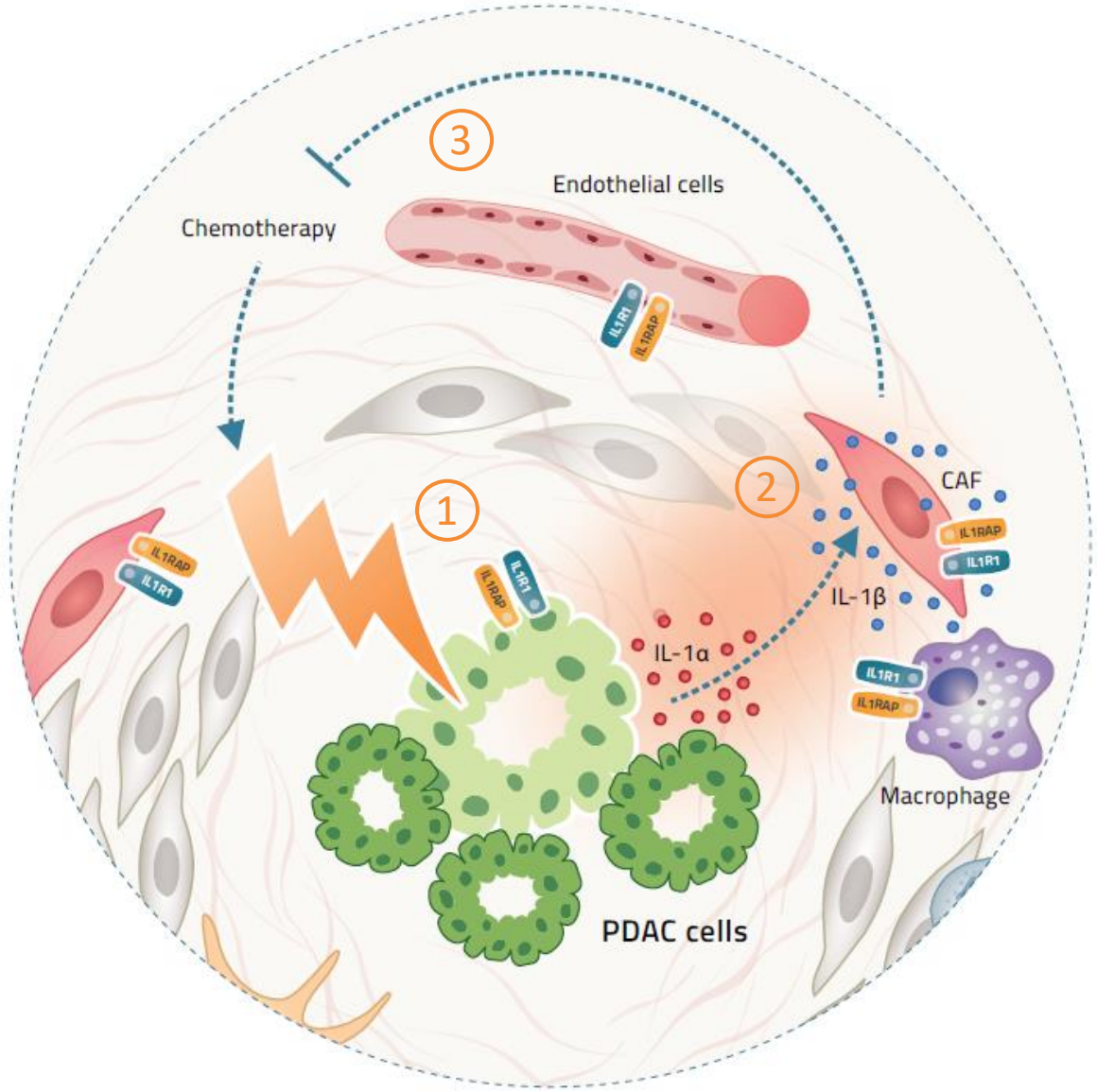
INHIBITION OF TUMOR CELL GROWTH BY CAN04 MEDIATED BY CAF-S

The IL-1 system is induced by chemotherapy



1. Chemotherapy induces cell killing and IL1α upregulation in tumor cells
2. IL1β is induced in the tumor stroma
3. IL1α and IL1β mediates chemoresistance

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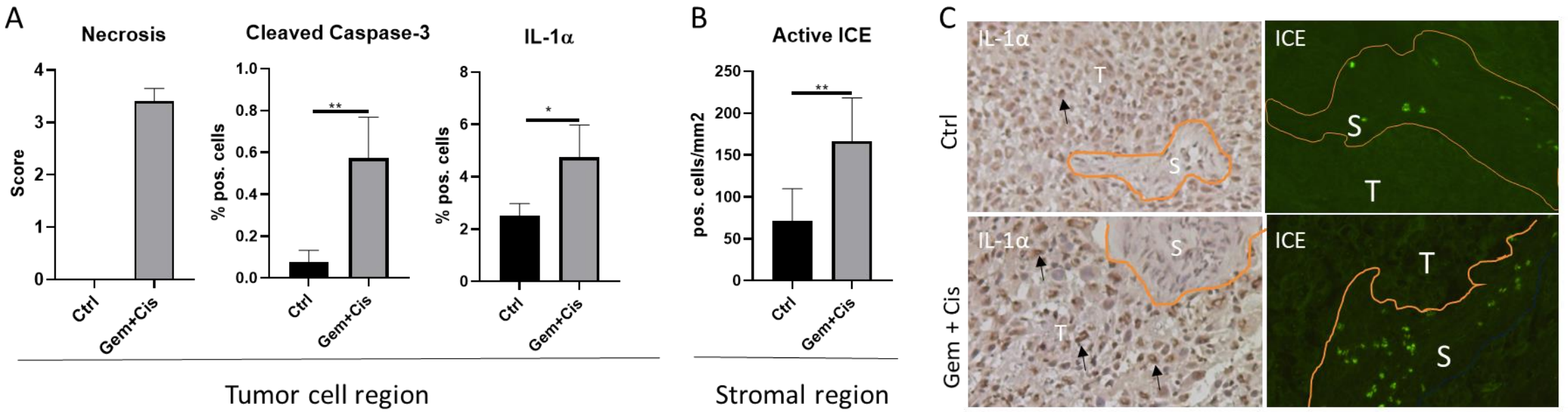
The IL-1 system is induced by chemotherapy

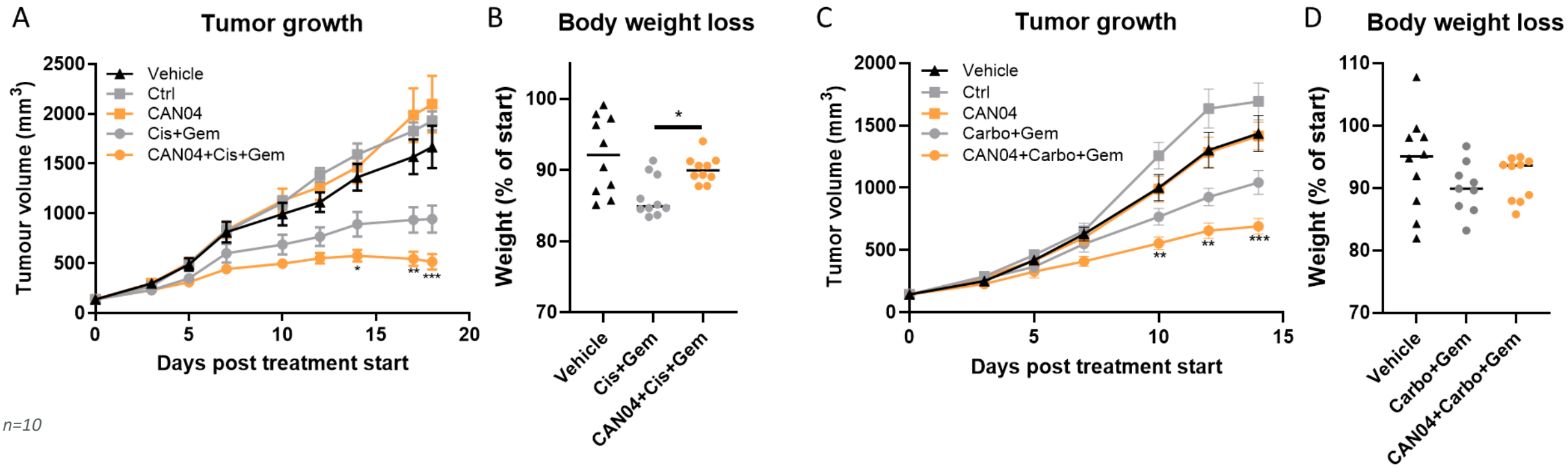
Immunohistochemistry of tumor tissue in a NSCLC patient-derived xenograft model



IL-1α is upregulated in tumor cells after chemotherapy and Interleukin 1β-converting enzyme (ICE/Caspase-1) in the tumor stroma

CAN04 increases the efficacy of chemotherapy

Tumor growth in a NSCLC patient-derived xenograft model



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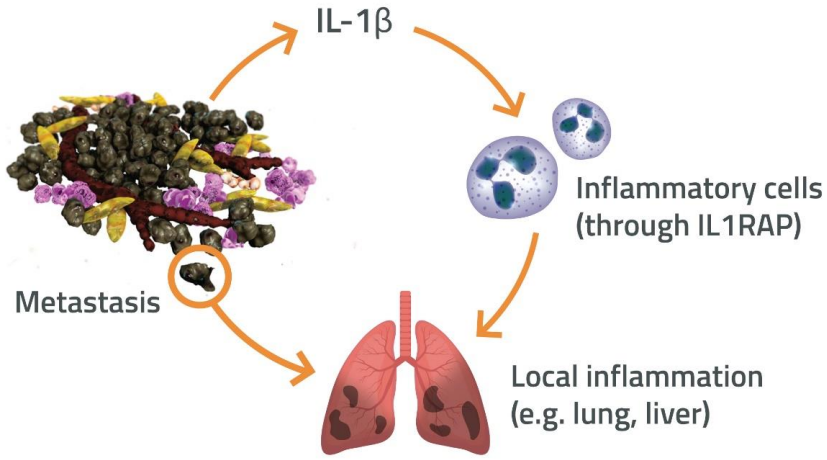
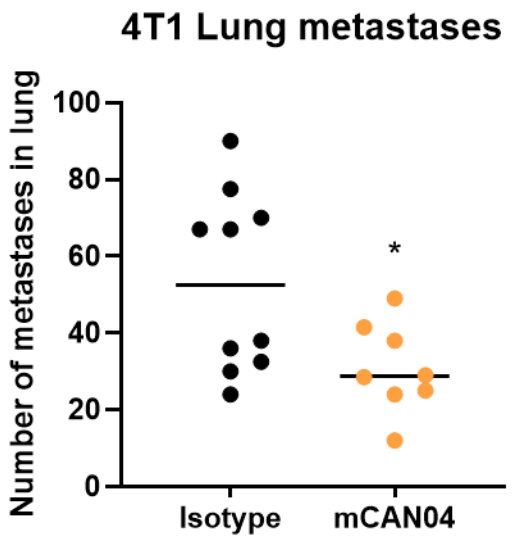
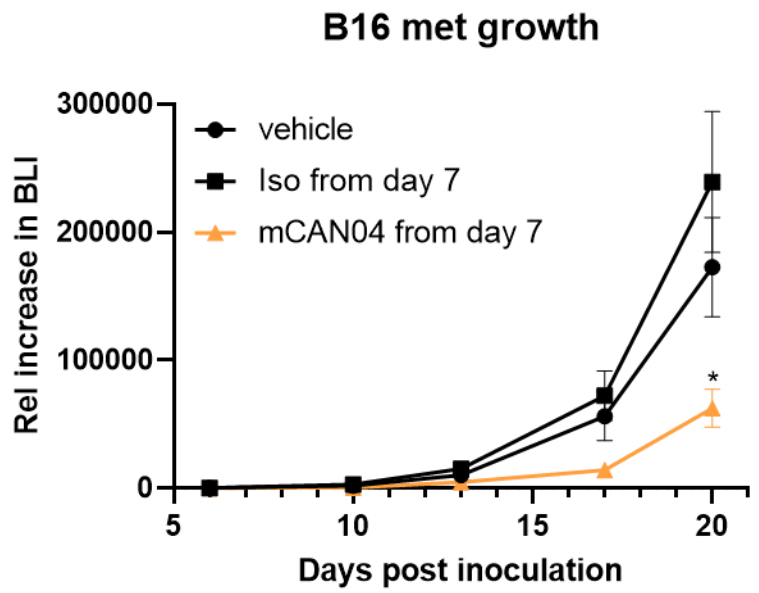
CAN04 increases efficacy of chemotherapy regimens and counteracts weight loss

mCAN04 targets metastatic niches and counteracts lung metastases in the IL1RAP low/neg 4T1 and B16 syngeneic models





Orthotopic implantation of 4T1 TNBC cells mCAN04 is an anti-murine IL1RAP CAN04 surrogate antibody



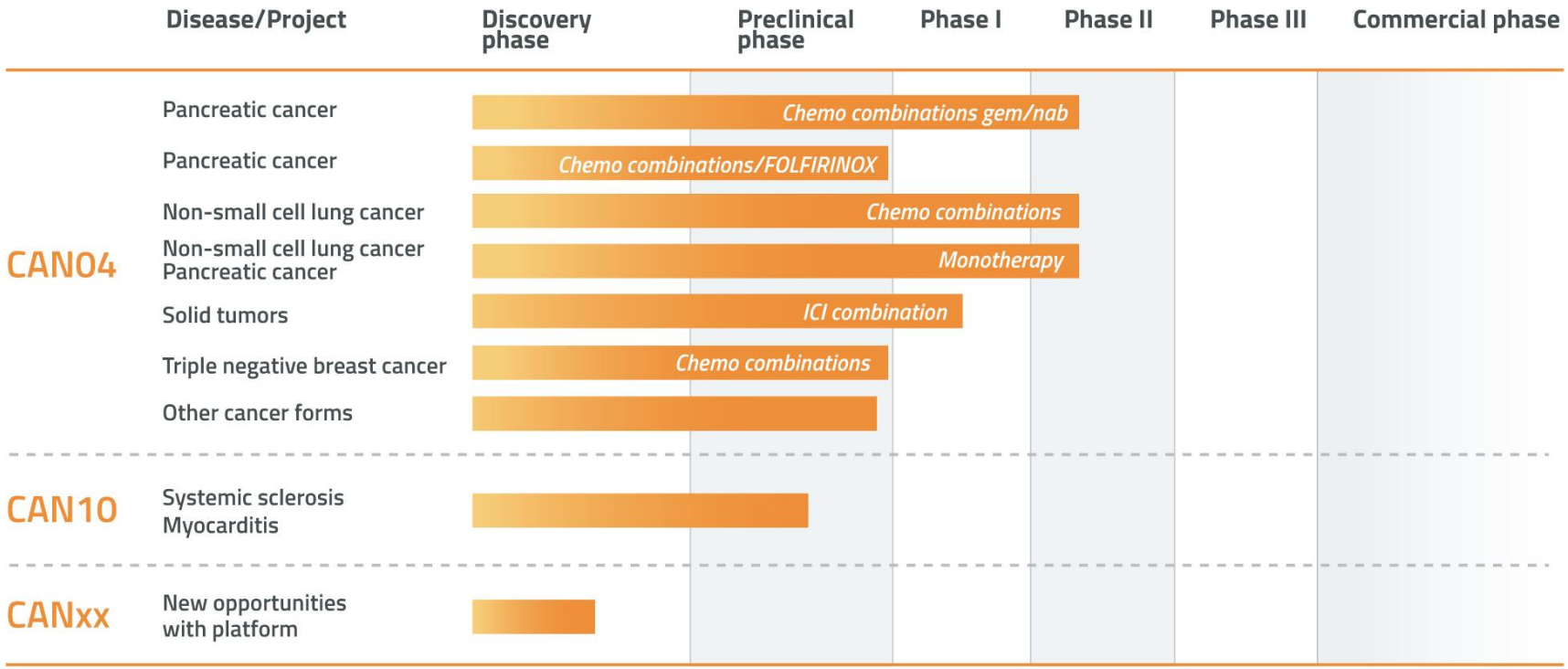
Intravenous injection of B16 melanoma cells, n=10 mice

Summary

- CAN04 (nadunolimab) blocks IL1α/IL1β signaling and induces antibody-mediated cell killing of IL1RAP-expressing cells
- IL1RAP is broadly expressed in solid tumors, both on tumor cells and in tumor stroma
- CAN04 targets both tumor cells and components of the tumor stroma
- Chemotherapy activates the IL1α/β-system in the tumor microenvironment
- CAN04 and chemotherapy act in synergy to inhibit tumor growth
- CAN04 can target metastatic niches and counteract metastases

II. CLINICAL TRIALS AND RESULTS

Cantargia – Opportunity to save lives and create value

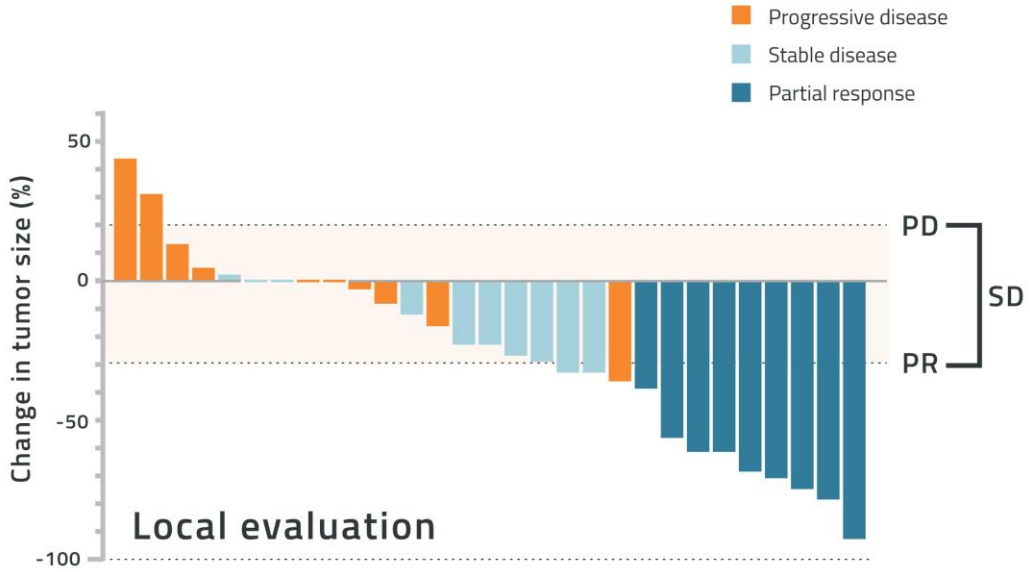


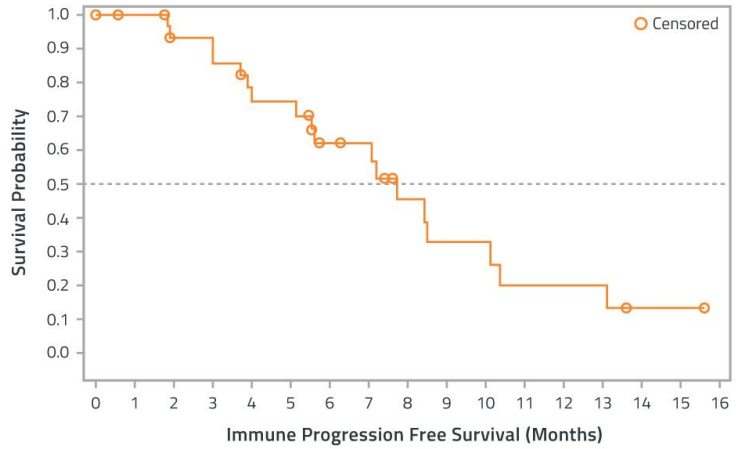
- Potentially more effective treatment against novel target in clinically validated pathway
- First in class platform technology against novel target
- Well financed to build a broad, diversified pipeline
- Right team and clear plan to position our projects and maximize value

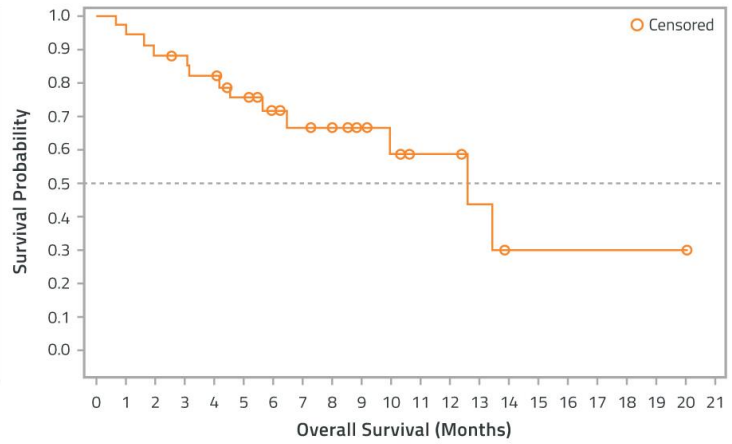
Positive data in pancreatic cancer

CAN04 in combination with 1st line gem/abraxane:

- Durable responses observed (median DOR 6.8 mo, 27% response rate)
- Important finding of pseudoprogression-like response in 5 (15%) patients predicting long PFS.
- Promising PFS (7.8 mo) and OS (12.6 mo, 42 % events), seven patients still on treatment





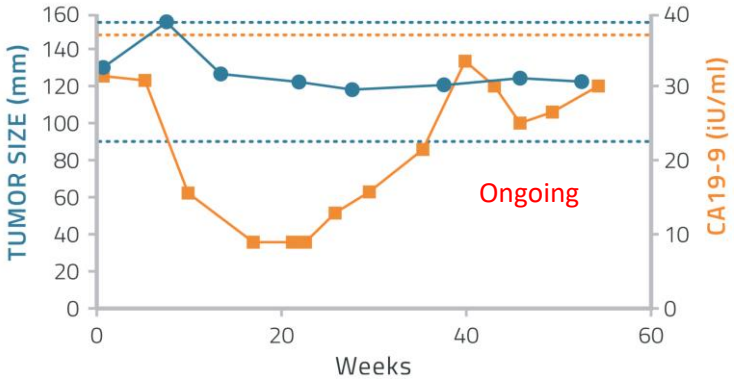


EXTENSION PHASE TO OBTAIN MORE INFORMATION ON VARIOUS DOSE LEVELS ONGOING
DURABLE RESPONSES AND PSEUDPROGRESSION LEADS TO LONG PFS

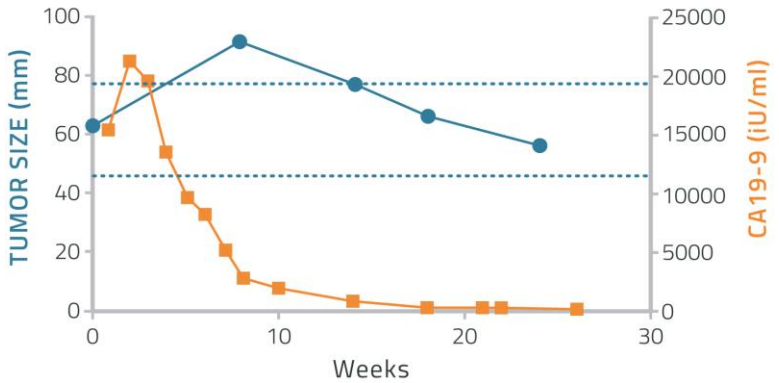
Patients with Pseudoprogression-like response

- All presented PD at 1st CT scan evaluation (8 weeks)
- All showed concomitant reduction of CA19-9

Subject 1



Subject 2



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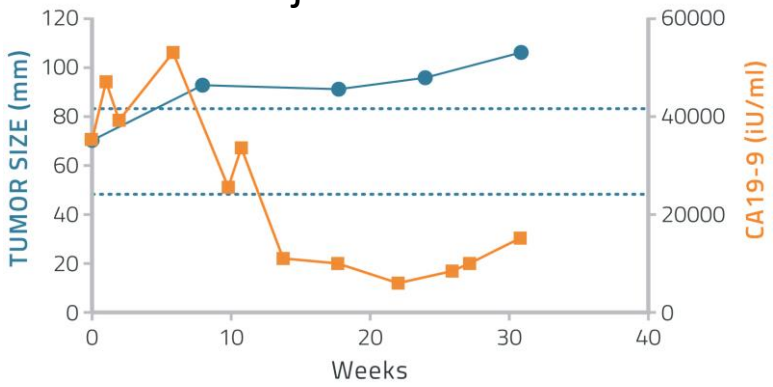

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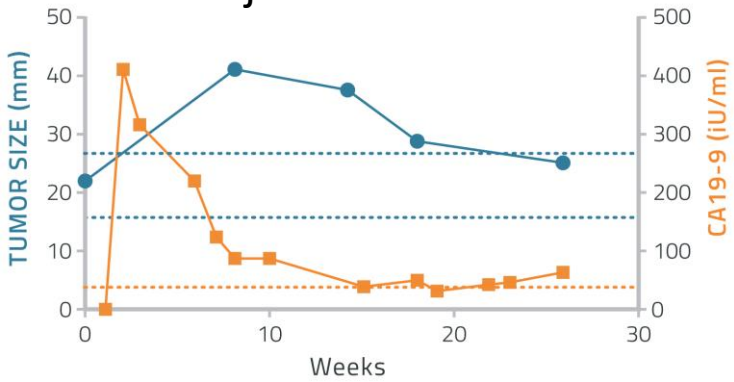

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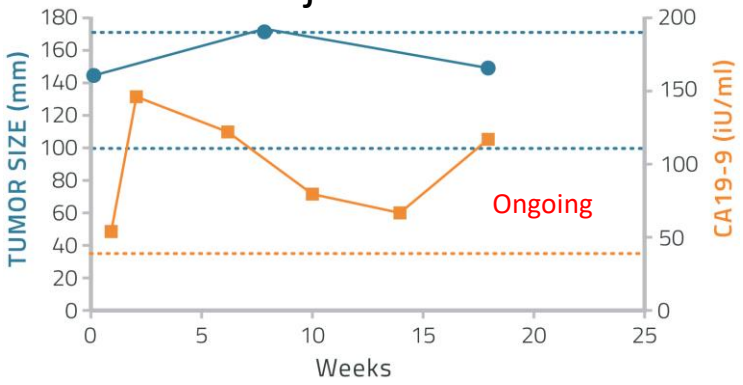


PSEUDOPROGRESSION VERY UNCOMMON IN PANCREATIC CANCER
INDICATE IMMUNE RELATED MECHANISM OF CAN04 LEADING TO LONG TERM BENEFIT

CAN04/GN in PDAC safety summary and benchmark

Grade 3 or higher AEs	Gem/Abraxane (von Hoff, 2013) N=421	CANFOUR CAN04/GN N=36	FOLFIRINOX (Conroy 2011) N=171
Neutropenia	38%	67%	46%
Febrile neutropenia	3%	17%	5%
Thrombocytopenia	13%	19%	9%
Anemia	13%	14%	8%
Fatigue	17%	6%	24%
Peripheral neuropathy	17%	0%	9%
Diarrhea	6%	3%	13%
Elevated ALT	ND	3%	7%
IRR	ND	3%	ND

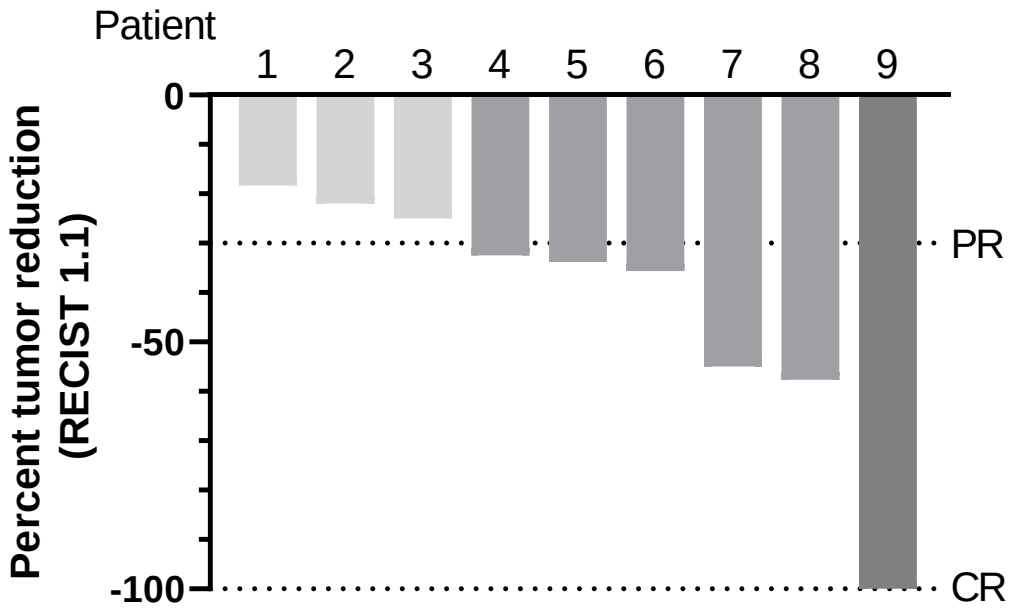
The beneficial effect in fatigue and chemotherapy-induced neuropathy[2] (nab-paclitaxel or oxaliplatin) can be mediated by IL-1 blockade.

- G-CSF not used proactively/prophylactically in this trial. In later trials, G-CSF counteracts neutropenia.
- Median duration of treatment 4.8 months (reference 3.9 months)
- Most common reasons for termination: gastrointestinal events or general health deterioration

WITHOUT PROACTIVE USE OF G-CESF, NEUTROPENIA AND FEBRILE NEUTROPENIA HIGHER THAN CHEMOTHERAPY ALONE
NEUROPATHY AND FATIGUE LOWER THAN EXPECTED FROM CHEMOTHERAPY

cantargia

Tumor shrinkage – NSCLC combination



- CAN04 in combination with gem/cis in 1st line chemotherapy
- 6 of 9 evaluable patients with metastatic non-small cell lung cancer (NSCLC) showed objective response including 1 complete response (67% vs historical control data 22–28%)
- The complete response has lasted more than 1 year
- 5 patients were second line to pembrolizumab monotherapy, 4 patients first line
- No major side effects observed except those from chemotherapy or CAN04 alone. *Neutropenia frequency higher than expected from chemo (treated with dose reductions/GCSF)*

POSITIVE INTERIM DATA, RECRUITMENT CONTINUE FOR PRIMARY ANALYSIS, INTERIM DATA PLANNED FOR Q3 2021
BROADENING OF NSCLC DEVELOPMENT INTO ADDITIONAL MARKET SEGMENTS

Note: CR Complete response, PR Partial response, SD Stable disease, PD progressive disease

Nadunolimab clinical development status

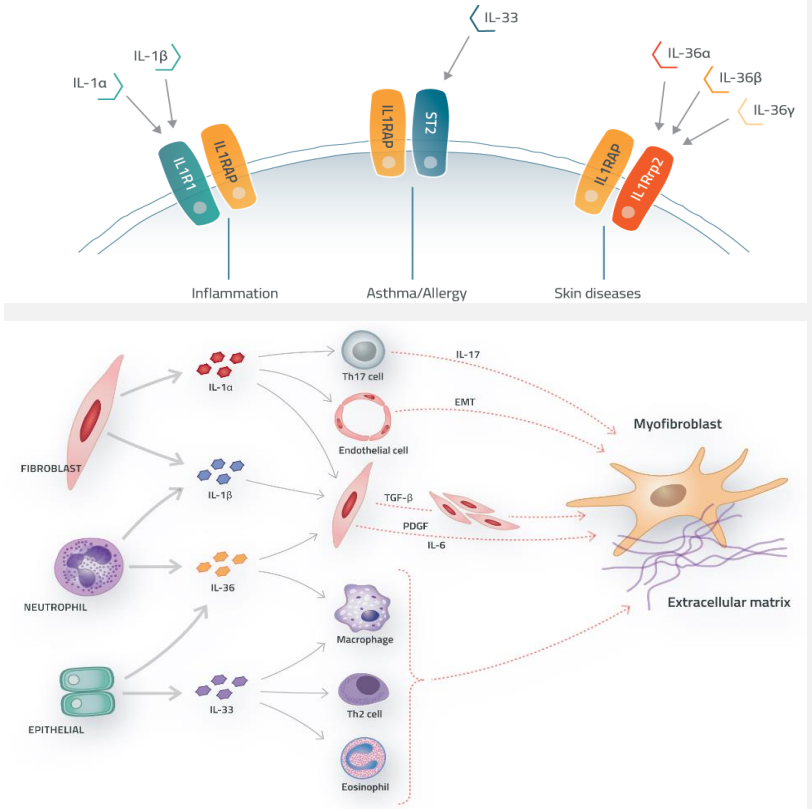
Study	Indication	CAN04 combination	Status	Planned milestone(s)
CANFOUR	NSCLC	Gemcitabine/cisplatin	Recruitment ongoing,	Results planned for Q3 2021
	PDAC	Gemcitabine/nab-paclitaxel	Extension phase ongoing. (Dosing schedule, lower doses, G-CSF)	Main study interim results presented 20 May LPI extension phase expected Q3 2021 Results update H2 2021
CIRIFOUR	NSCLC, HNSCC, melanoma, bladder cancer	Pembrolizumab	Recruitment ongoing	LPI Q3 2021 Results H2 2021
CAPAFOUR	PDAC	mFOLFIRINOX	Recruiting	FPI Aug 2021 (estimated)
TRIFOUR	TNBC	Gemcitabine/carboplatin	Submitted	FPI Nov 2021 (estimated)
CESTAFOUR	Colorectal cancer	mFOLFOX	Submitted	FPI Sep 2021 (estimated)
	Biliary tract cancer	Gemcitabin/Cisplatin	Submitted	FPI Sep 2021 (estimated)
	NSCLC	Docetaxel	Submitted	FPI Sep 2021 (estimated)

DEVELOPMENT ADVANCING TOWARDS LATE STAGE IN PDAC AND NSCLC
PARALLEL BROADENING TO NEW SEGMENTS AND DISEASES

III. TARGETING IL1RAP IN AUTOIMMUNE DISEASES

CAN10 – New development project

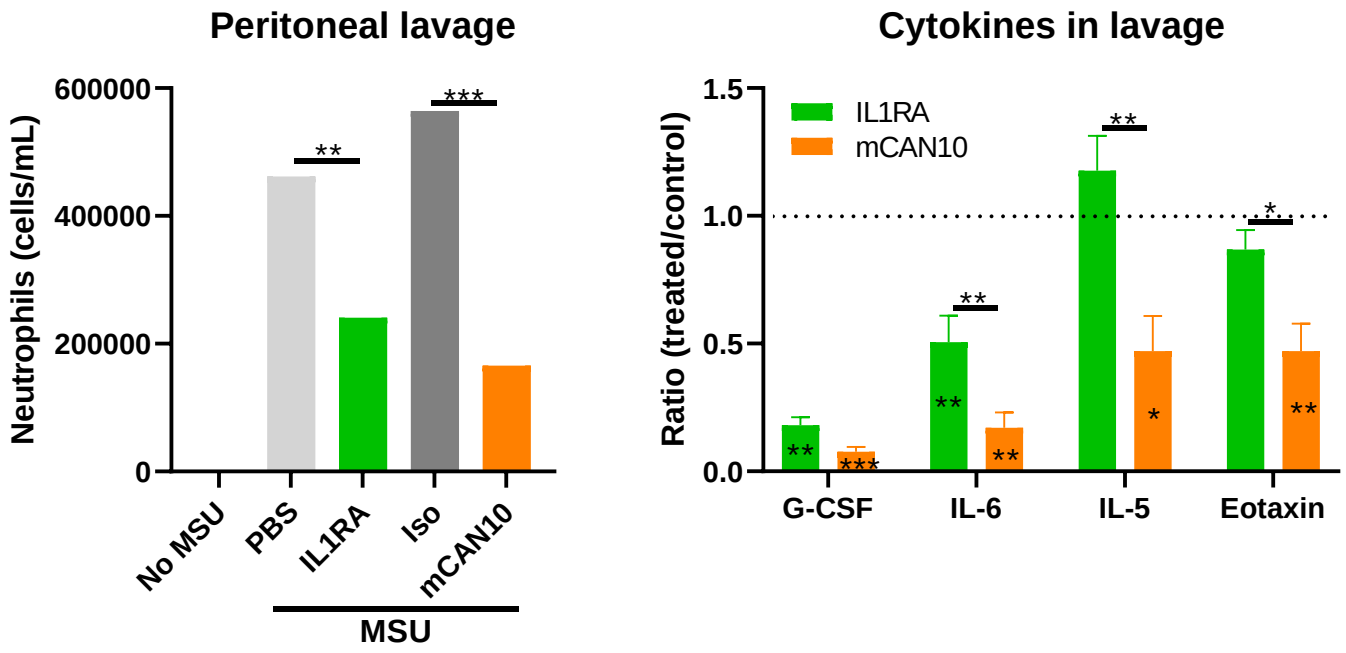
- IL1RAP binding antibody potently blocking IL-1, IL-33 and IL-36
- Unique anti-inflammatory activity observed in different mouse models (myocarditis, psoriasis, inflammation)
- Development focusing on unmet medical need in systemic sclerosis and myocarditis. Disease selection in collaboration with experts based on scientific rational, medical need, development opportunity and competition
- Clinical trials start early 2022



UNIQUE OPPORTUNITY FOR CAN10 IDENTIFIED IN LIFE-THREATENING DISEASES

IL1RAP inhibition is a potent strategy to block inflammation

MSU-induced peritonitis (i.p. injection with MSU-crystals, measure cells and cytokines after 6h)

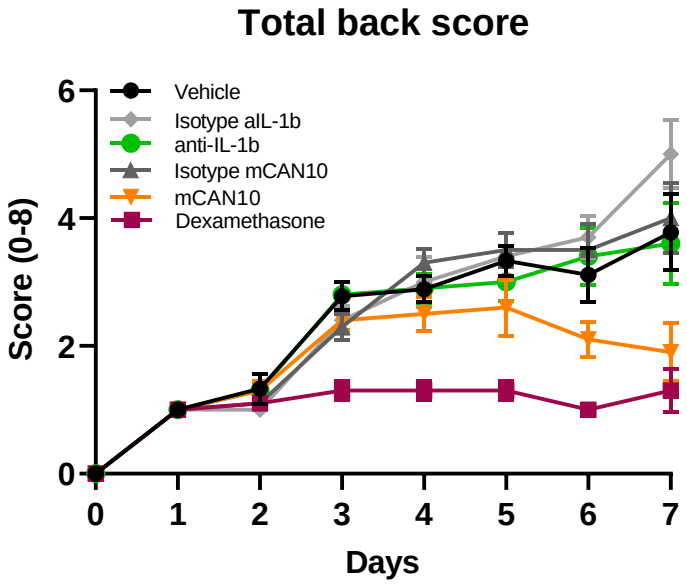


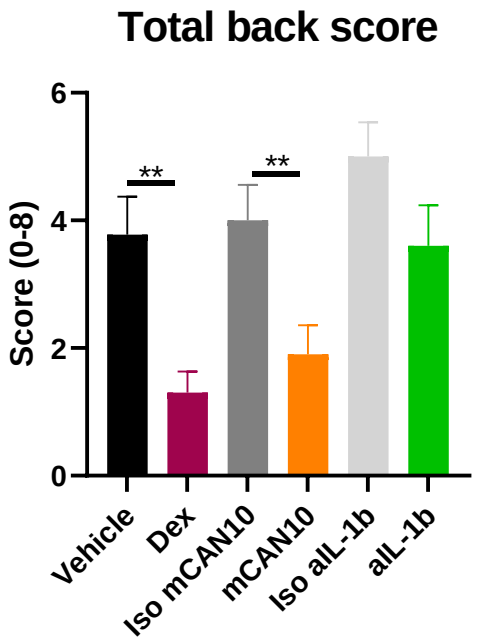
…in a way that is not recapitulated by IL1α/β-blockade alone

MSU, monosodium urate
IL1RA/anakinra, blocks IL1α/β signaling

IL1RAP inhibition modulates local and systemic inflammation

IMQ-induced Psoriasis (topical daily administration of IMQ, biweekly i.p treatment with ab or daily topical with dex)

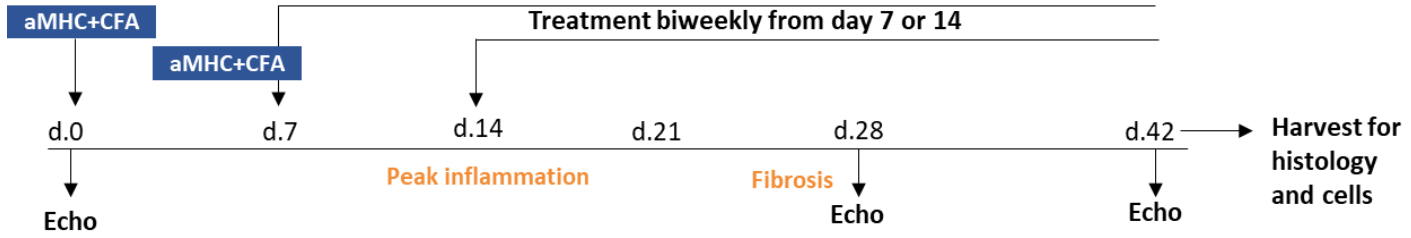


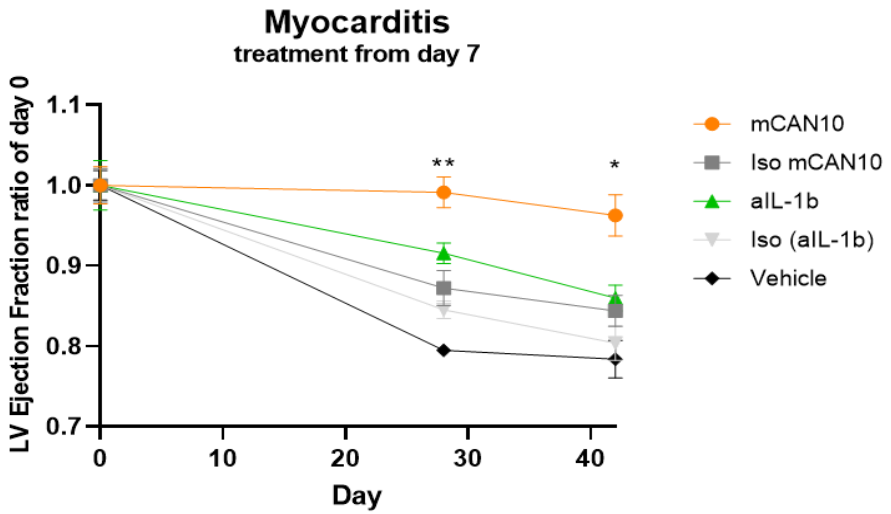


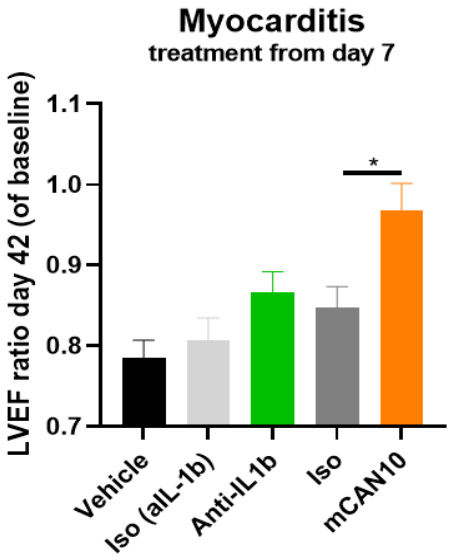
- Skin inflammation involves IL1, IL33 and IL36
- Experiments performed to study inhibition of local and systemic inflammation by systemic antibody
- CAN10 is a feasible treatment for skin inflammation

IMQ, imiquimod

mCAN10 improves heart function in experimental autoimmune myocarditis







IV. SUMMARY

Targeting IL1RAP is a novel strategy in treatment of cancer and autoimmune/inflammatory disease

CAN04 (Nadunolimab)

- In phase II clinical development with lead indications NSCLC and PDAC
- Early clinical results in combination with chemotherapy are encouraging
- Several clinical trials ongoing or starting broadening the development
- Can function through
  - ADCC and IL-1 blockade
  - Counteracting immune suppression in tumor microenvironment
  - Synergy with chemotherapy
  - Counteracts metastases

CAN10

- Developed for autoimmune/inflammatory disease
- Myocarditis and systemic sclerosis lead indications
- Blocks IL-1, IL-33 and Il-36 signaling through IL1RAP
- Plan initiation of clinical trial early 2022