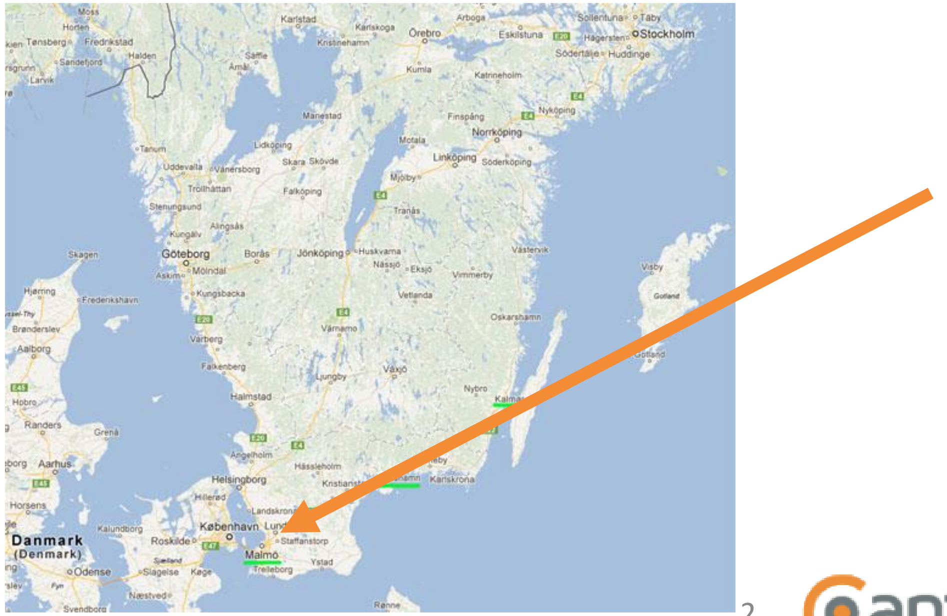
IL1RAP as a therapeutic target

Göran Forsberg, CEO

Cantargia

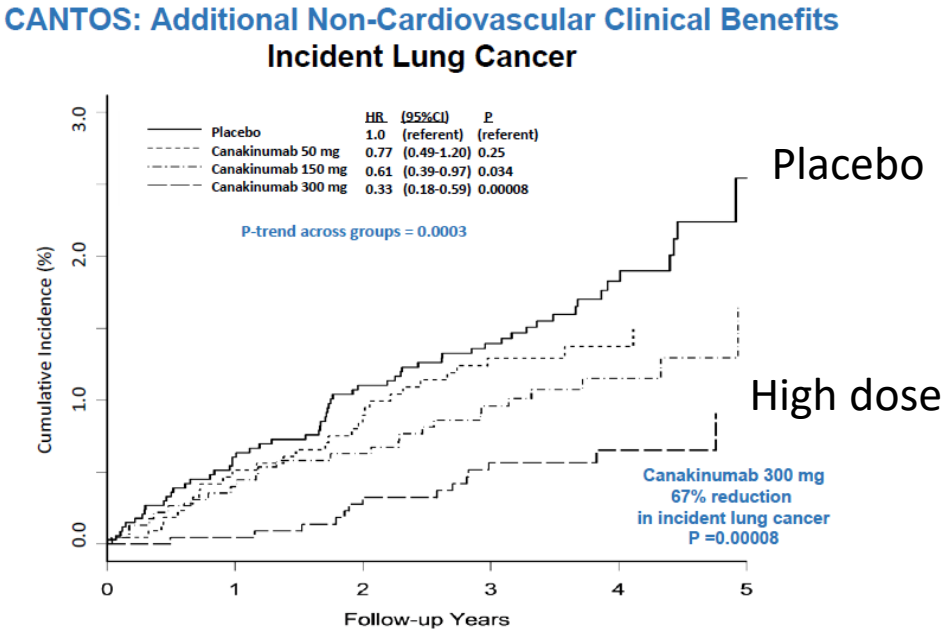
- Specialized in antibody therapy/immunology, with initial focus on oncology
- Lead antibody CAN04 (nidanilimab) in clinical development
- Listed on Nasdaq Stockholm, approximately 5000 shareholders
- Based in Lund, Sweden at Medicon Village Science park
- Virtual company, with strong academic and corporate collaborations



IL-1 blockade - recent intriguing clinical data

CANTOS trial (>10000 pat)

- Canakinumab (anti-IL-1β)
- Reduced lung cancer incidence by 67 % and death by 77 %.



Canakinumab NSCLC phase 3 trials

Adjuvant NSCLC
After surgery, no mets, placebo control
1500 patients, recruitment ongoing
Completion 2021/22

First line (CANOPY-1)
Untreated locally advanced/metastatic
Combination Pembro/Platinum doublet
627 patients, start Dec 2018
Completion 2021/22

Second line metastatic (CANOPY-2)
Previously treated loc adv/metastatic
Combination Docetaxel
240 patients, start Dec 2018
Completion 2021

Source clinicaltrials.gov

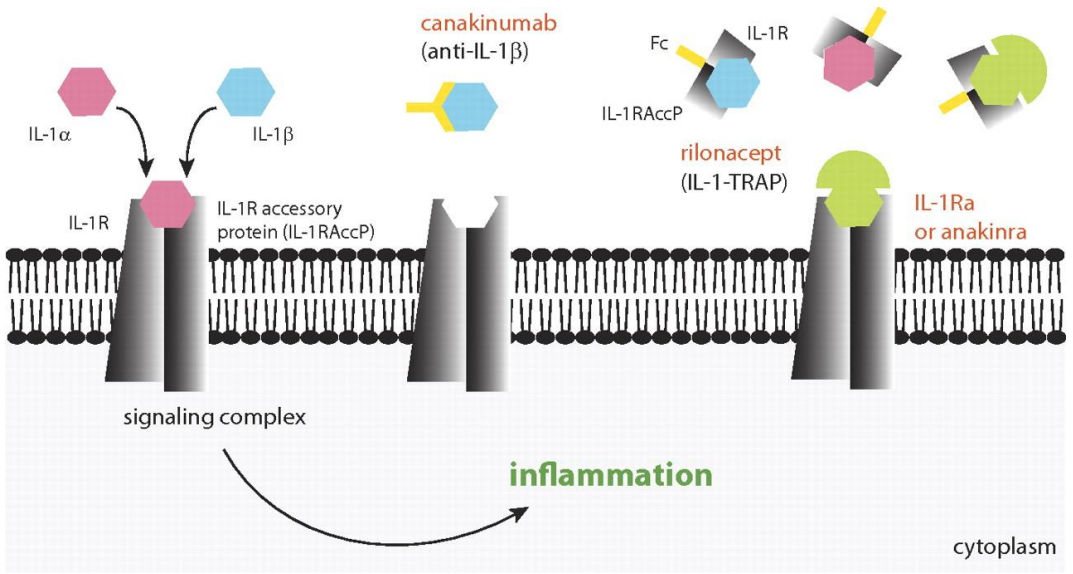
CANTOS additional findings (from Canakinumab)

CANCER decreased risk of death with treatment (high dose)			
Lung cancer	77 %	P=0.0002	
Non-lung cancer	37 %	P=0.06	
Decreased incidence of inflammatory disease (all doses)			
Arthritis	32%	p<0.0001	
Ostheoartritis	28%	P=0.0005	
Gout	53%	p<0.0001	
Cardiovascular	12%	P=0.02	
Biomarker levels (reduction)			
CRP	26-41%	P<0.0001	
IL-6	25-43%	P<0.001	

IL-1 is a “broad-spectrum” cytokine implicated in a number of inflammatory diseases

- IL-1 is released by tissues or the innate immune system to induce inflammation, IL-1 has highly pro-inflammatory properties and affect a large number of cells
- IL-1 is involved in several autoimmune diseases and is the dominant cytokine in autoinflammatory diseases
- Blocking drugs are on the market (anakinra, rilonacept, canakinumab)

Approved IL-1 inhibiting drugs, IL1RaccP = IL1RAP



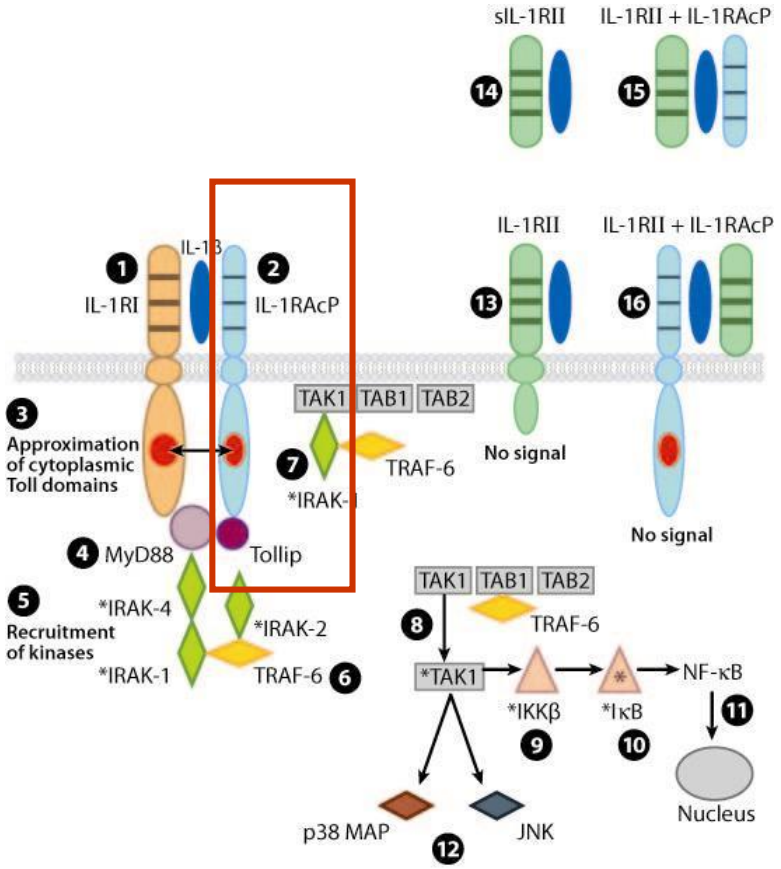
Doherty et al., J Leukoc Biol 90(1):37-47 2011

Next step in IL-1 blockade?

- IL-1 blockade can be used to treat disease
- Approved for autoimmune/inflammatory disease
- Promising clinical data for cancer treatment/prevention

- Is IL-1β the optimal target?
- Advantages of receptor targeting?
- Antibodies against IL1RAP.

IL1RAP – IL-1 Receptor Accessory Protein



Dinarello CA. 2009.
Annu. Rev. Immunol. 27:519–50

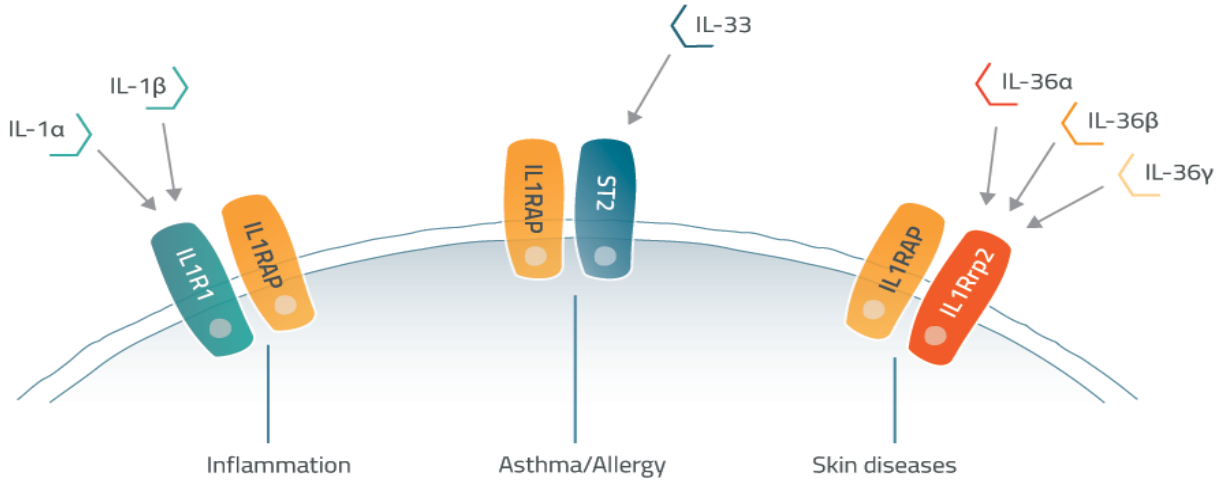
Low expression of IL1RAP on normal cells

- Low reactivity on monocytes and lymphocytes
- No significant tissue reactivity seen on normal tissue (frozen tissues FDA/EMA panel)
- Low-to-moderate expression on monocytes

- The highest expression is found on cancer cells

IL1RAP

- Three different systems signal through IL1RAP
- These systems contribute to various inflammatory diseases
- Can be blocked by antibodies against IL1RAP



The IL-33 and IL-36 signaling pathways - novel targets for several diseases

- IL-33 and IL-36 are barrier-associated cytokines highly expressed in skin and mucosal tissues.
- IL-33 is involved in allergic inflammation and Th2-responses
- IL-36 is heavily upregulated in inflamed skin and mediates *e.g.* certain psoriatic conditions
- No approved product on the market but several projects in preclinical or clinical phase
  - Allergy
  - Asthma
  - Atopic Dermatitis
  - Rhinosinusitis
  - Pustular psoriasis
  - Palmo-Plantar Pustulosis
  - Ulcerative Colitis
  - Crohn's Disease

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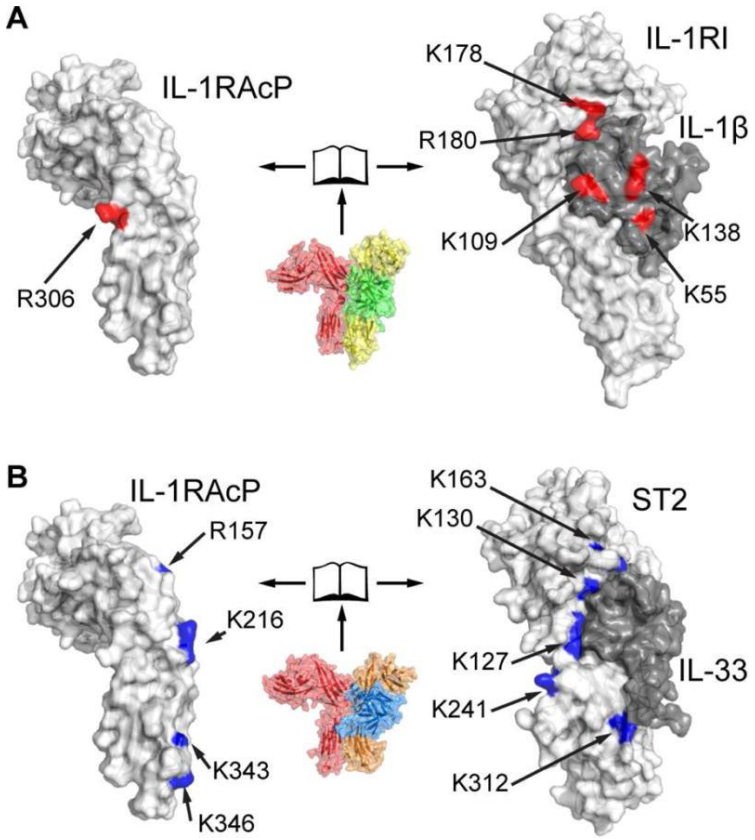
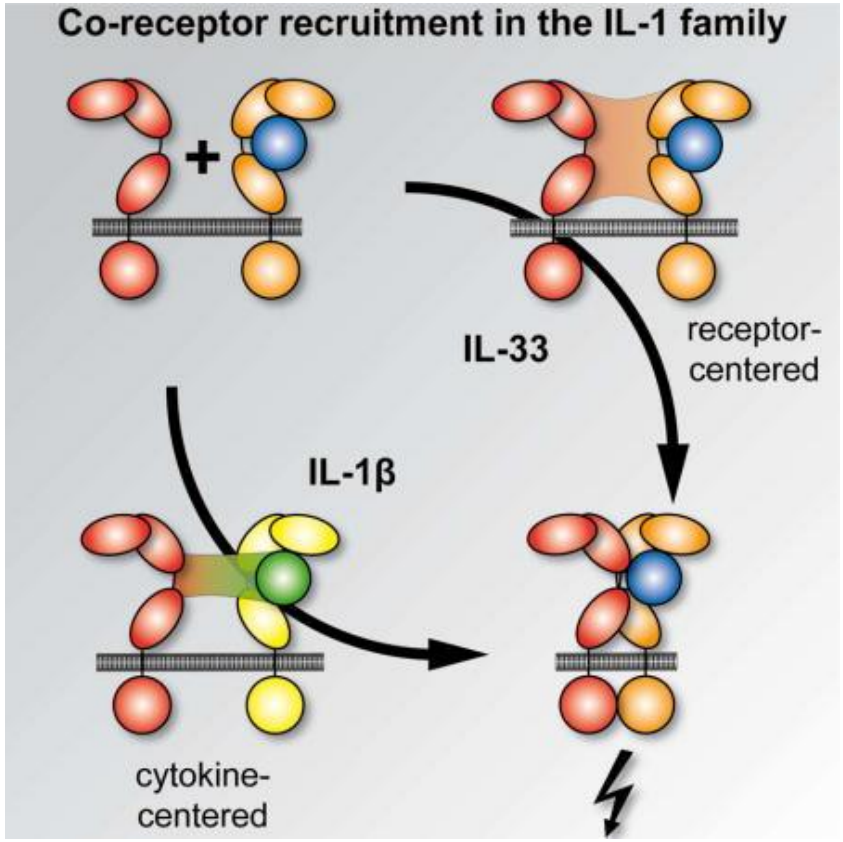
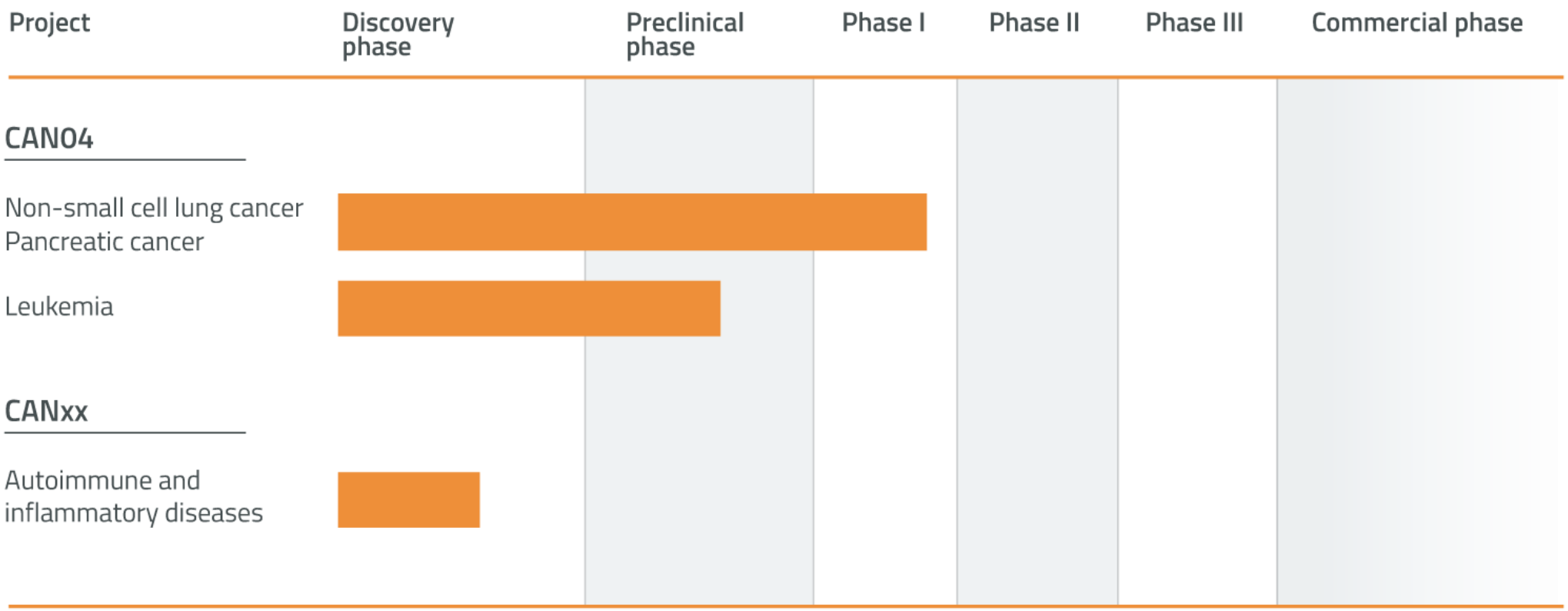
Unique binding properties of IL-1 and IL-33



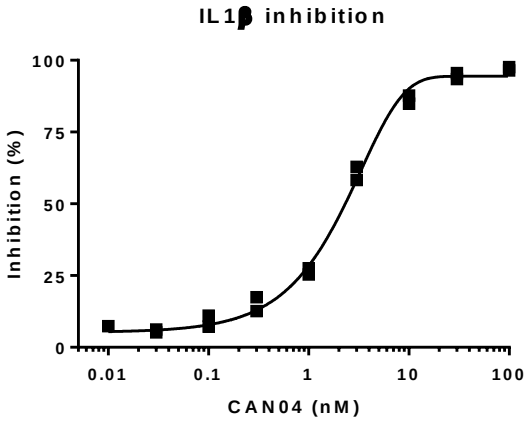


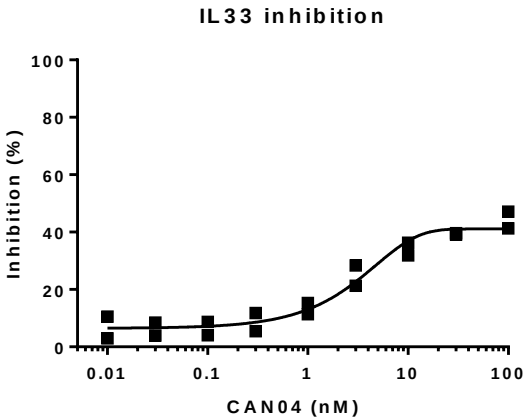
Günther et al, Immunity 2017, 47, 510-523

Cantargia pipeline



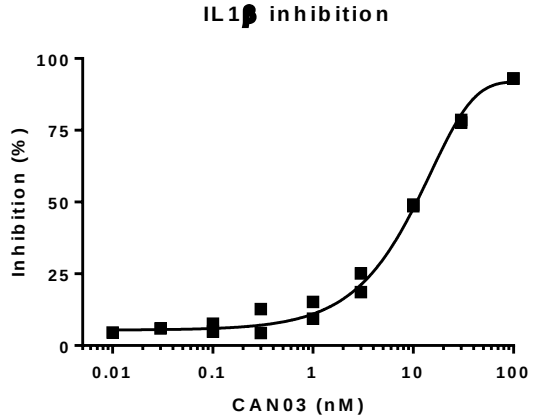
CAN04 and CAN03 both inhibit IL-1β and IL-33 signaling but with different properties

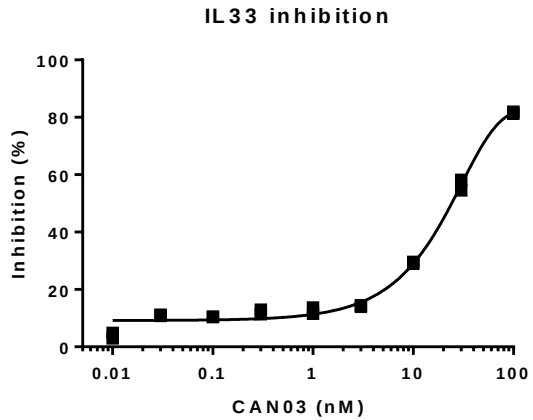




CAN04

Potent IL1β and IL33 inhibitor, but only blocks IL33 signaling partially





CAN03

Less potent, but the binding mode allows full inhibition of IL1β and IL33 signaling

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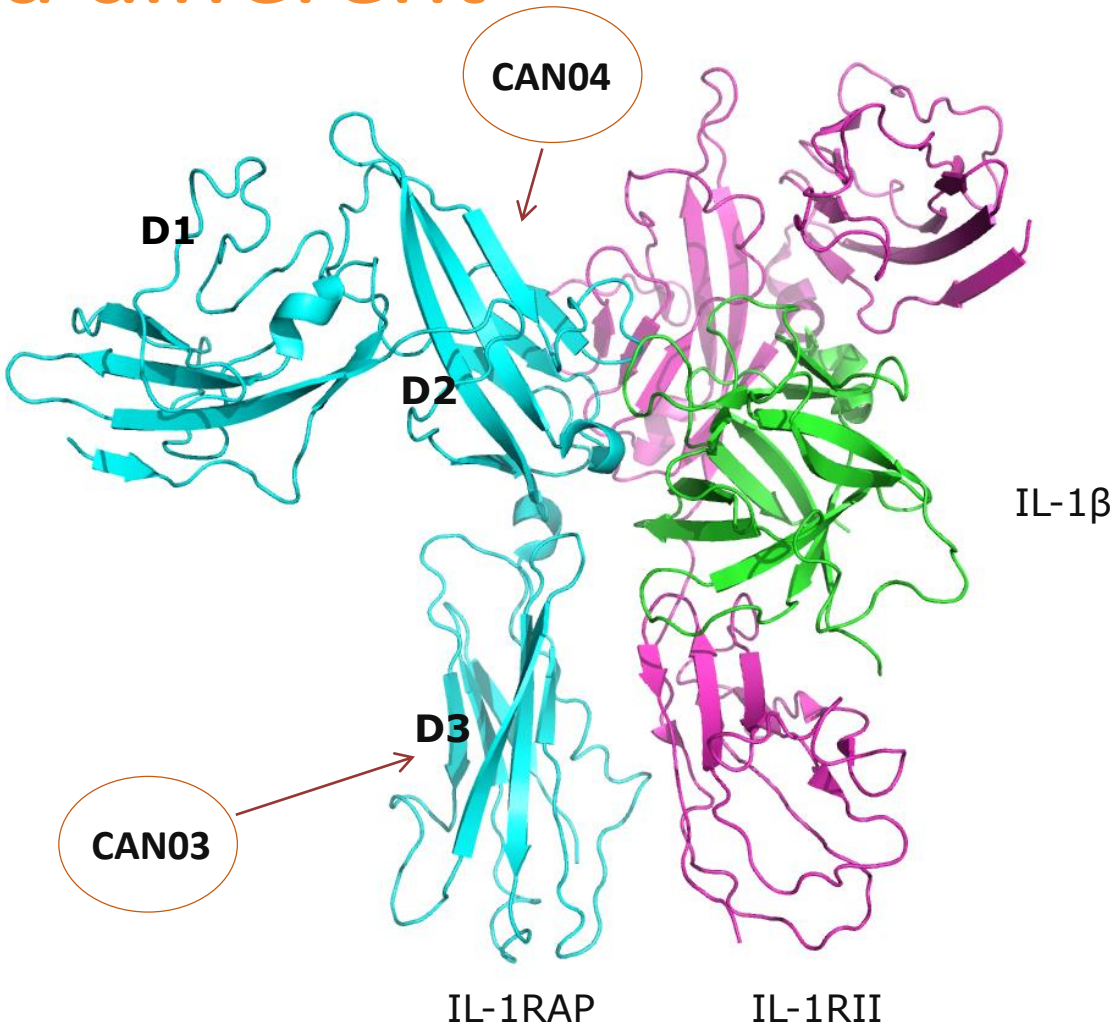
CAN04 and CAN03 bind different domains of IL1RAP

Measurement of binding affinities to IL1RAP by SPR

Antibody	ka (1/M•s)	kd (1/s)	KD (M)
CAN03	2.26E+05	7.25E-05	3.21E-10
CAN04	4.27E+05	4.72E-05	1.10E-10



Wang et al., 2010, Nature Immunology, 11, 905-912.

Epitope mapping in collaboration with
Eric Sundberg, University Maryland

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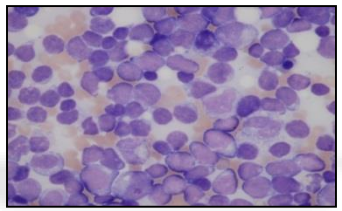
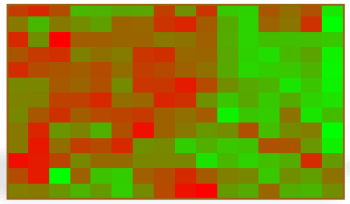
IL1RAP as a target in cancer

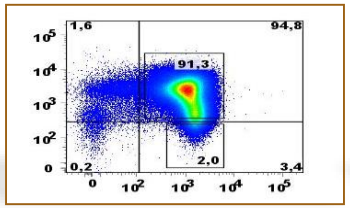
The original finding:
IL1RAP - a novel target on cancer cells



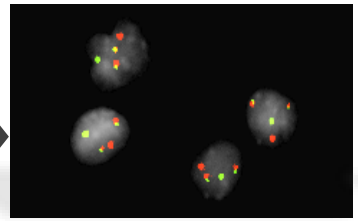
Leukemic cells from patients



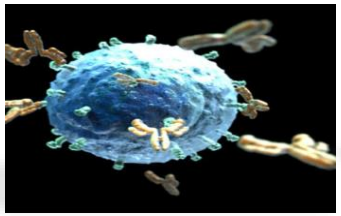
Genomics & Bioinformatics



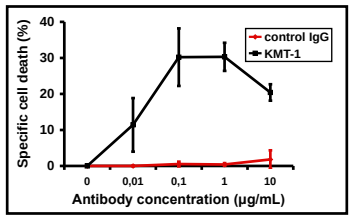
IL1RAP identified as upregulated on CML leukemia stem cells



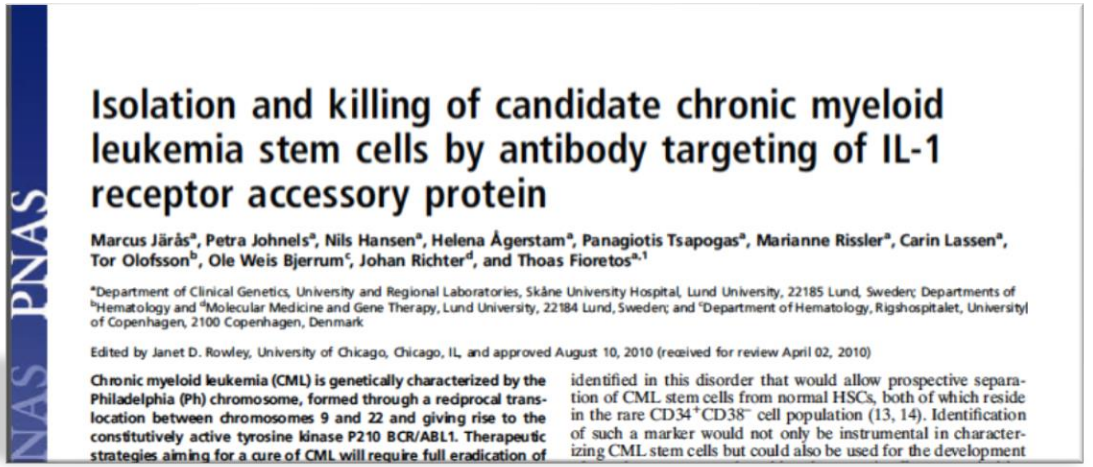
Isolation of CML leukemia stem Cells based on IL1RAP expression



Production of a polyclonal anti-IL1RAP antibody (KMT1)



Selective killing of leukemia stem cells using antibodies



PNAS

Isolation and killing of candidate chronic myeloid leukemia stem cells by antibody targeting of IL-1 receptor accessory protein

Marcus Järås[a], Petra Johnels[a], Nils Hansen[a], Helena Ågerstam[a], Panagiotis Tsapogas[a], Marianne Rissler[a], Carin Lassen[a], Tor Olofsson[b], Ole Weis Bjerrum[c], Johan Richter[d], and Thoas Fioretos[a,1]

[a]Department of Clinical Genetics, University and Regional Laboratories, Skåne University Hospital, Lund University, 22185 Lund, Sweden; Departments of [b]Hematology and [d]Molecular Medicine and Gene Therapy, Lund University, 22184 Lund, Sweden; and [c]Department of Hematology, Rigshospitalet, University of Copenhagen, 2100 Copenhagen, Denmark

Edited by Janet D. Rowley, University of Chicago, Chicago, IL, and approved August 10, 2010 (received for review April 02, 2010)

Chronic myeloid leukemia (CML) is genetically characterized by the Philadelphia (Ph) chromosome, formed through a reciprocal translocation between chromosomes 9 and 22 and giving rise to the constitutively active tyrosine kinase P210 BCR/ABL1. Therapeutic strategies aiming for a cure of CML will require full eradication of identified in this disorder that would allow prospective separation of CML stem cells from normal HSCs, both of which reside in the rare $CD34^+CD38^-$ cell population (13, 14). Identification of such a marker would not only be instrumental in characterizing CML stem cells but could also be used for the development

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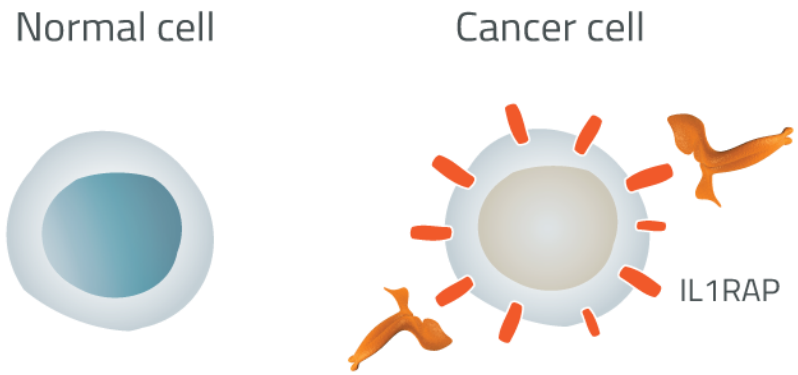
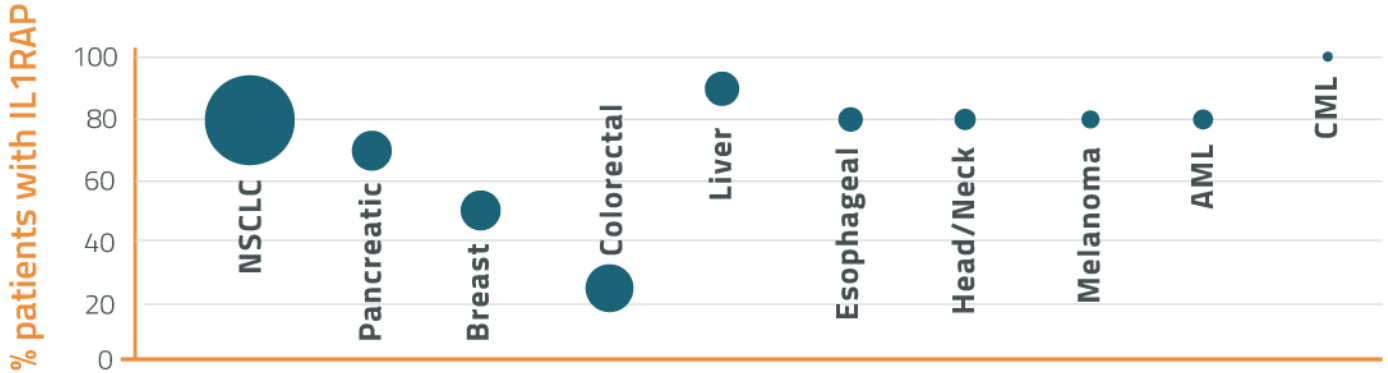
IL1RAP expressed in several tumor forms





Size of each indication corresponds to annual deaths in USA

Tumor inflammation – key to cancer progression

Enablers

Genomic instability and mutation (2000)

Tumor-promoting inflammation (2011)

- Deregulating cellular energetics
- Sustaining proliferative signaling
- Evading growth suppressors
- Resisting cell death
- Enabling replicative immortality
- Inducing angiogenesis
- Activating invasion and metastasis
- Avoiding immune destruction

Cancer hallmarks

The inflammatory cytokine IL-1 – Well established role in cancer progression:

Tumor cells

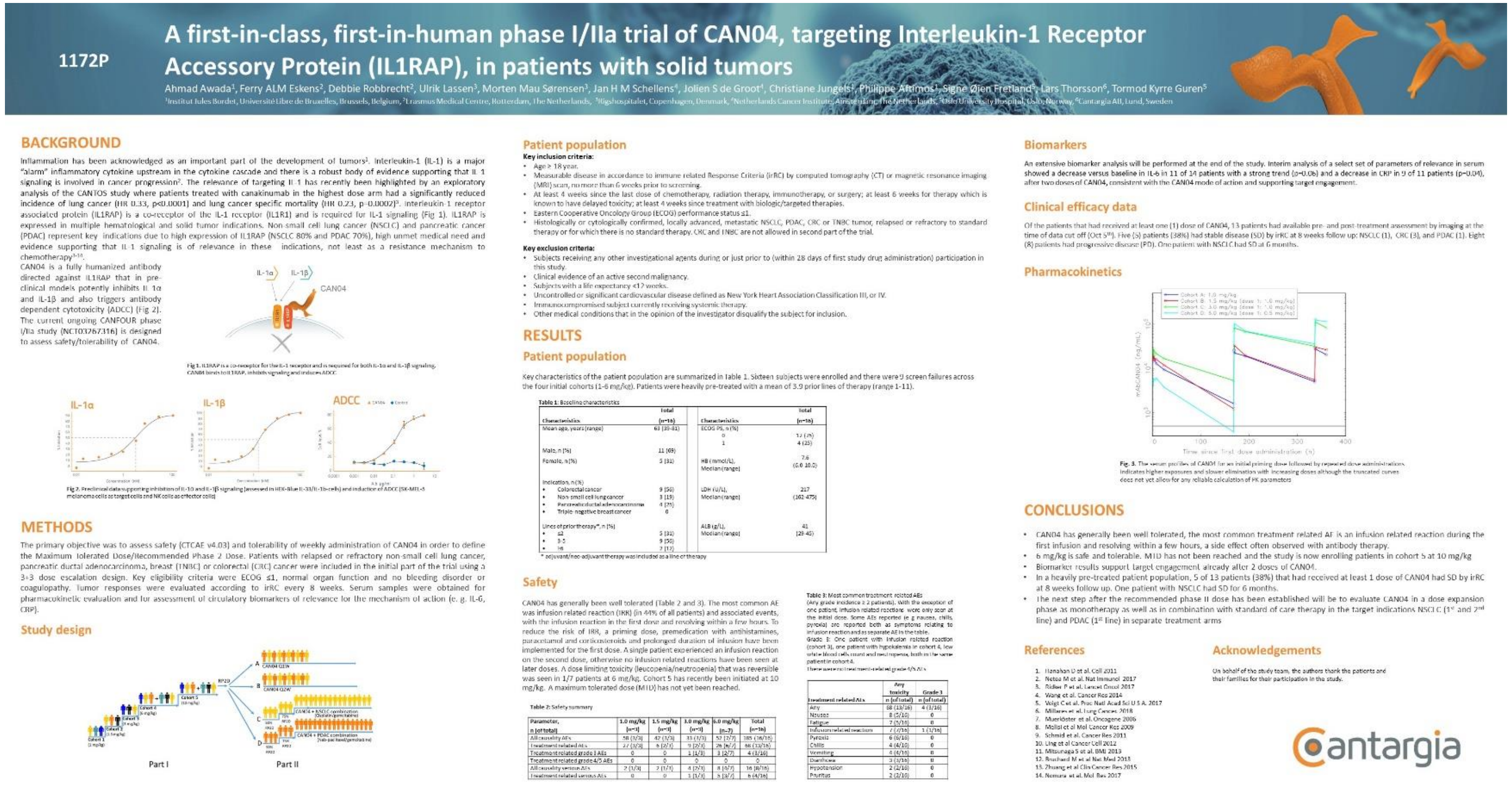
- *Signaling/proliferation of cancer cells*
- *Chemoresistance*

Tumor microenvironment

- *Metastasis*
- *Crosstalk between tumor cells and stroma*
- *Inflammation and local suppression of the immune system*

Hanahan D & Weinberg RA, The Hallmarks of Cancer, Cell 2000; Hanahan D & Weinberg RA, Hallmarks of Cancer: The Next Generation, Cell 2011

CAN04 phase I clinical data at ESMO (Oct 2018)



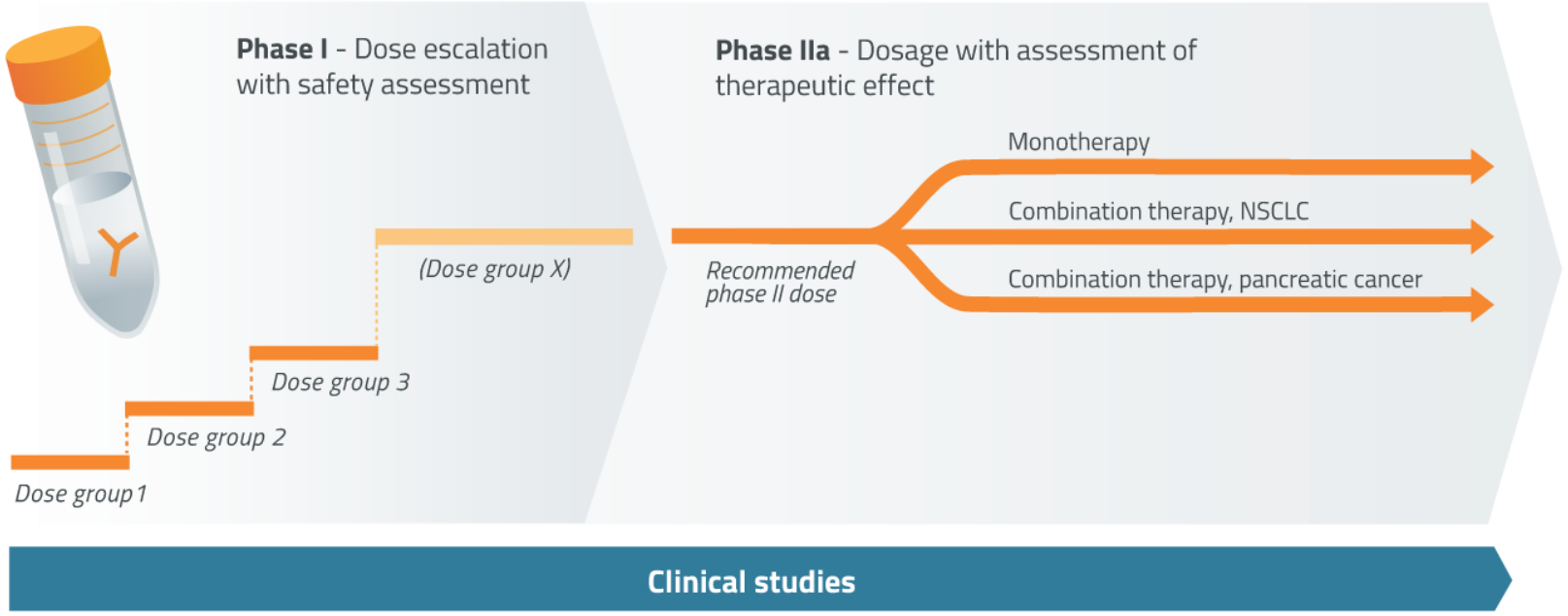
- CAN04 has generally been well tolerated
- 6 mg/kg is safe.
- Biomarker results (IL-6 and CRP) support target engagement already after two doses of CAN04.
- In a heavily pre-treated patient population, 5 of 13 patients (38%) had SD. One patient with NSCLC had SD for 6 months.

- Recently 10 mg/kg was shown to be safe (Dec 2018)

CAN04 – CANFOUR clinical trial

Phase I/IIa trial - NSCLC and pancreatic cancer

- Norway, Denmark, Netherlands and Belgium
- 22 patients treated, good safety
  - NSCLC, pancreatic cancer, colon cancer, triple negative breast cancer
- Phase IIa: focused on NSCLC and pancreatic cancer (appr 20 centres)
  - Monotherapy
  - Combination with standard therapy
    - NSCLC Cisplatin/Gemcitabine
    - Pancreatic cancer Gemcitabine/nab-paclitaxel

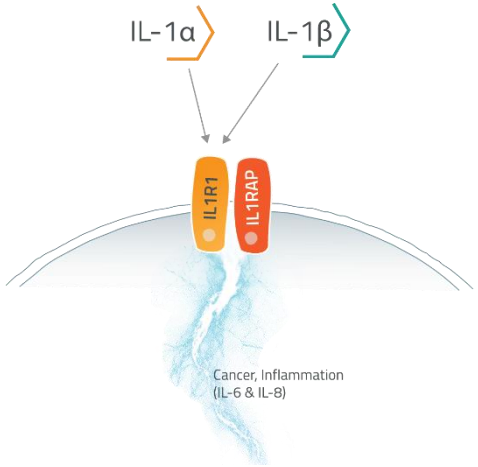


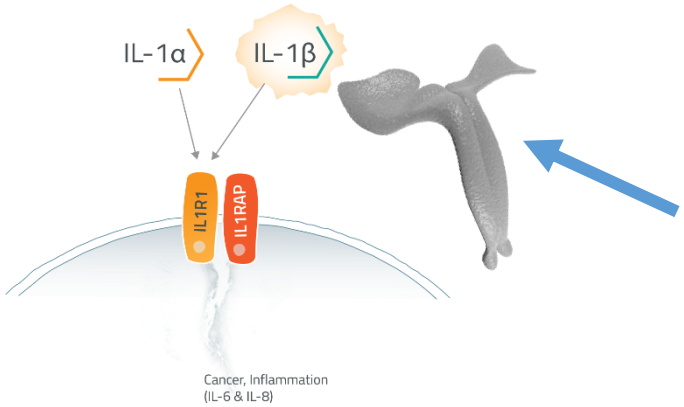
Q4 2018

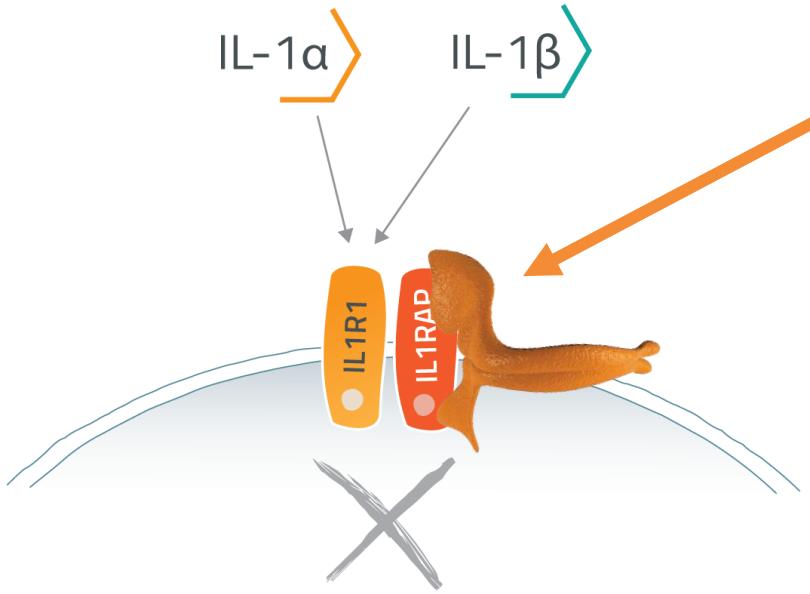
Early 2020

Details on www.clinicaltrials.gov

Receptor blockade vs IL-1β blockade





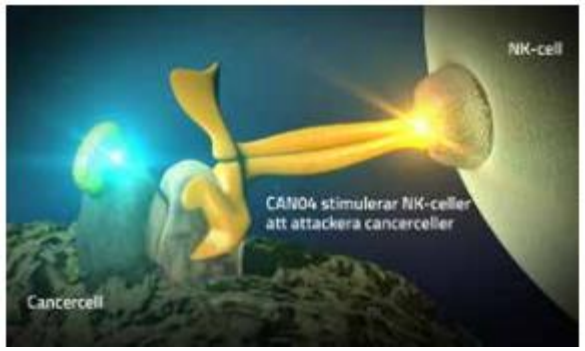


Canakinumab

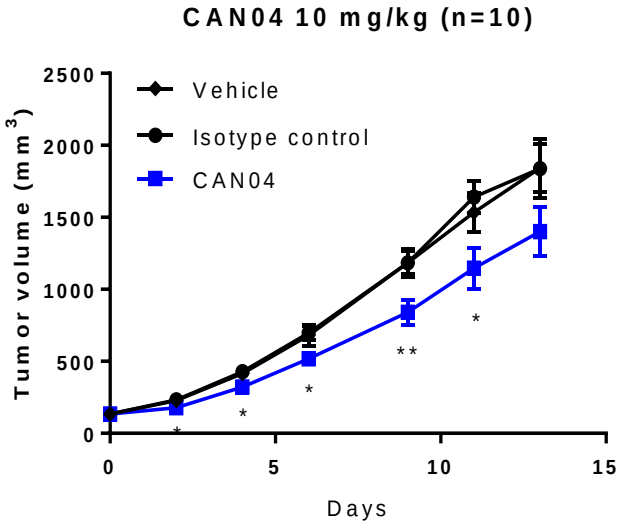
- Antibody directed against one of the two IL-1 ligands, IL-1β

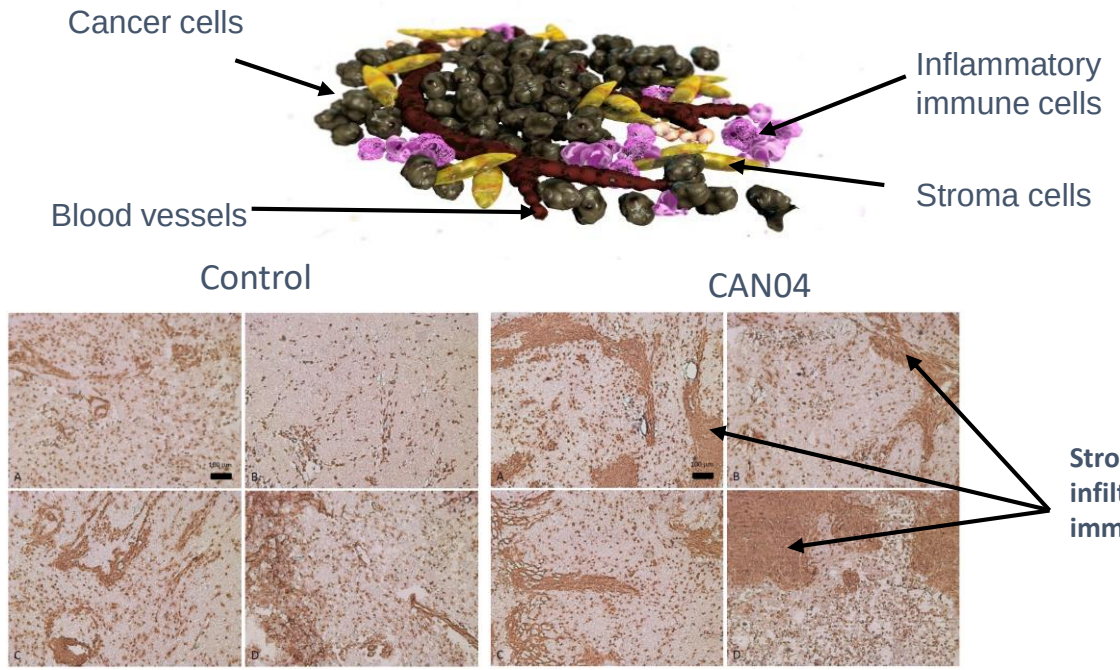
CAN04

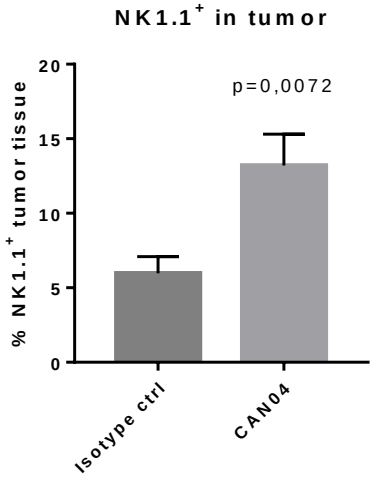
- Binds the common signaling receptor and counteracts both ligands
- Induce killing via the immune system (ADCC)



CAN04 - immuno-oncology mechanism with antitumor effect



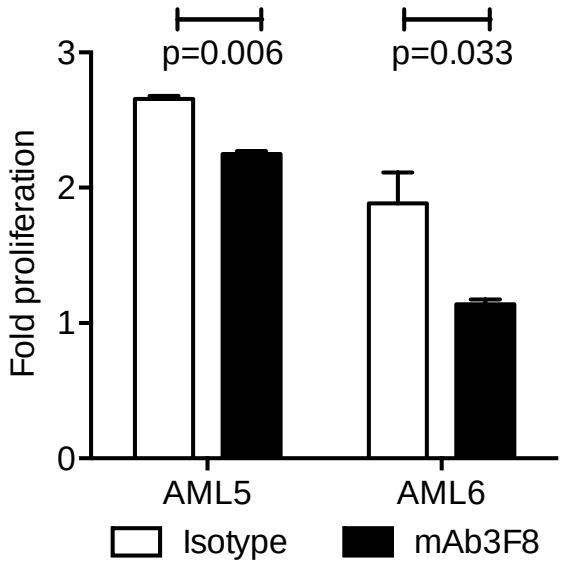




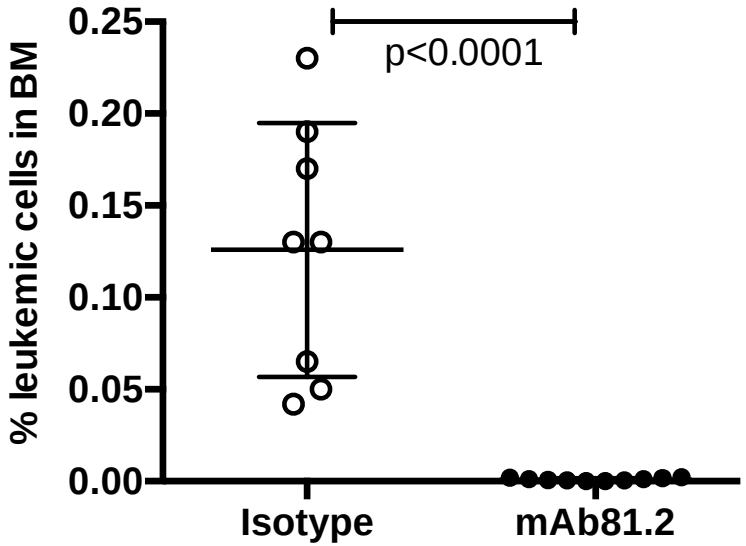
- Antitumor effects in NSCLC PDX models
- CAN04 stimulates immune cells to infiltrate tumor
- (CAN04 not cross reactive with mIL1RAP)

Activity in AML

Blocking proliferation ex vivo

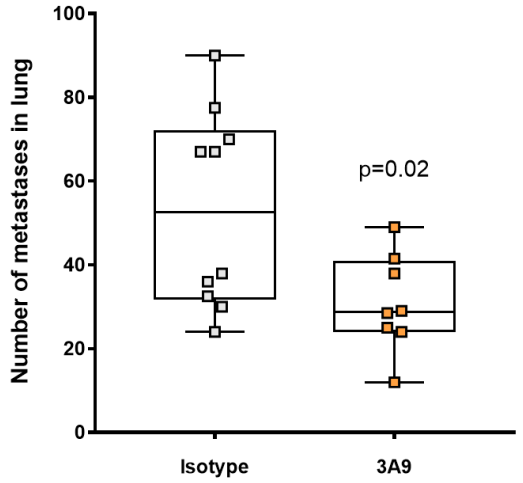


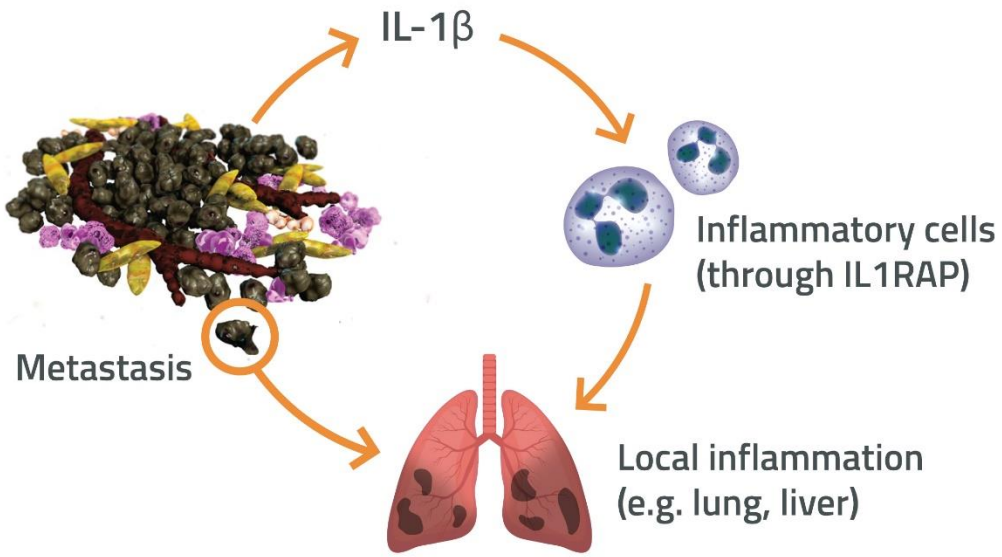
Treating AML (PDX) in vivo



Inflammation and metastasis

- Cancer cells (seeds) needs a good soil to form a metastasis
- The IL-1 system (inflammation) can provide such environment (soil)





A tumor can create its own ”seed and soil”

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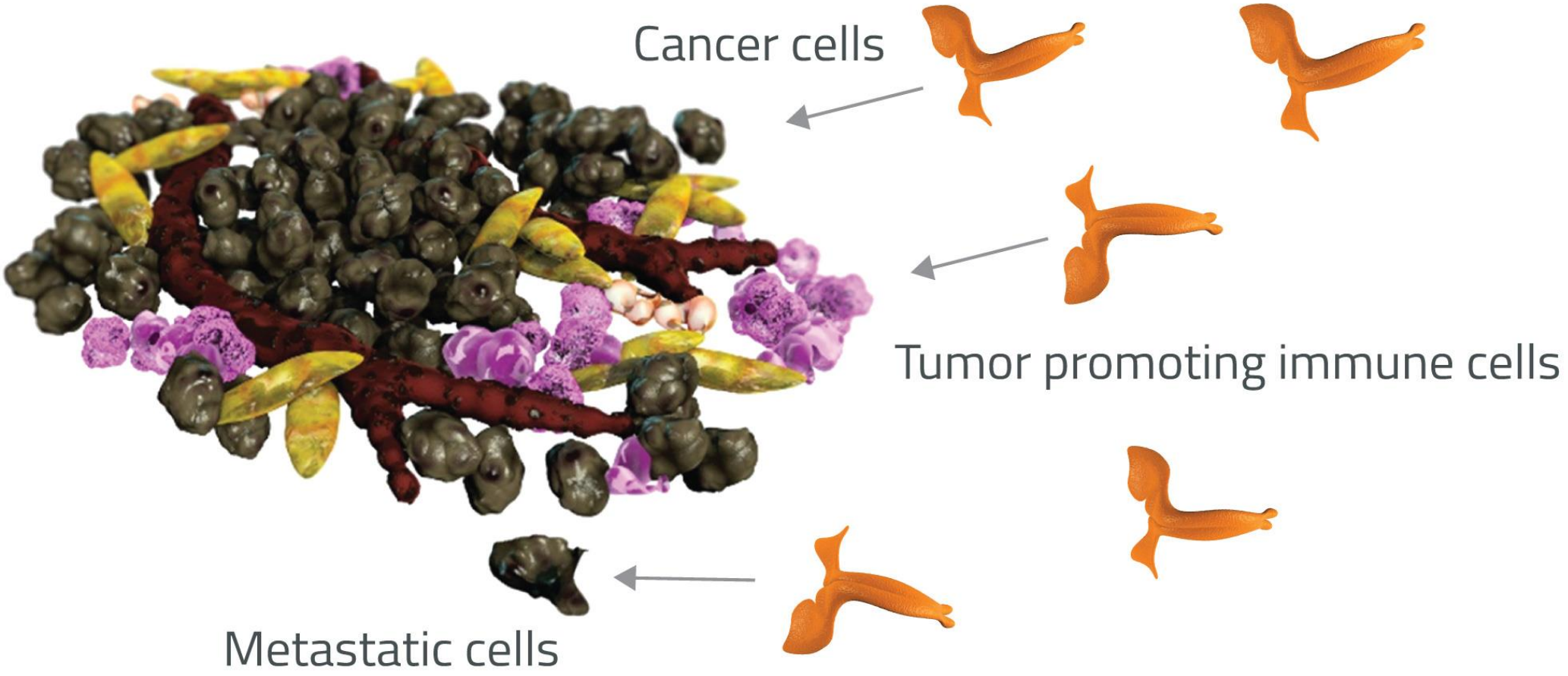
CAN04 attacks several cell types in the tumor



IL-1 and resistance to therapy

Interleukin-1 blockade overcomes erlotinib resistance in head and neck squamous cell carcinoma

Aditya Stanam[1,2], Katherine N. Gibson-Corley[2,5,6], Laurie Love-Homan[2], Nnamdi Ihejirika[3], Andrean L. Simons[1,2,4,5,6]

[CANCER RESEARCH 62, 910–916, February 1, 2002]

Autocrine Production of Interleukin 1β Confers Constitutive Nuclear Factor κB Activity and Chemoresistance i

Alexander Arlt,[2] Jens Vorndamm,[2] Susanne Heiner Schäfer[3]

A Novel Role for the Interleukin-1 Receptor Axis in Resistance to Anti-EGFR Therapy

Valerio Gelfo [1,2,†], Martina Mazzeschi [1,†], Giada Grilli [1], Moshit Lindze Gabriele D'Uva [6], Balázs Győrffy [7,8], Andrea Ardizzoni [1], Yosef Yarden Mattia Lauriola [1,2,*]

Serum levels of IL-6 and IL-1β can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer

S Mitsunaga*[,1,2], M Ikeda[1], S Shimizu[1], I Ohno[1], J Furuse[3], M Inagaki[4], S Higashi[5], H Kato[5], K Terao[6] and A Ochiai[2]

IRAK1 is a therapeutic target that drives breast cancer

Zhen Ning Wee
Puay Leng Lee[1],
Dave S.B. Hoon

Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth

Mélanie Bruchard[1,2,8], Grégoire Mignot[1,2,8], Valentin Derangère[1,2], Fanny Chalmin[1,2], Angélique Chevriaux[1–3], an[1,2], Wilfrid Boireau[4], Benoit Simon[4], Bernhard Ryffel[5], Jean Louis Connat[6], los[7], François Martin[1,2], Cédric Rébé[1–3], Lionel Apetoh[1–3,8] & François Ghiringhelli[1–3,8]

Neutrophil-Derived IL-1β Impairs the Efficacy of NF-κB Inhibitors against Lung Cancer

Allyson G. McLoed,[1] Taylor P. Sherrill,[2] Dong-Sheng Cheng,[2] Wei Han,[2] Jamie A. Saxon,[1] Linda A. Gleaves,[2] Pingsheng Wu,[3] Vasiliy V. Polosukhin,[2] Michael Karin,[4] Fiona E. Yull,[1,5] Georgios T. Stathopoulos,[2,6,7] Vassilis Georgoulias,[8] Rinat Zaynagetdinov,[2,11,*] and Timothy S. Blackwell[1,2,5,9,10,11]

ory cytokines defines resistance of inhibitors

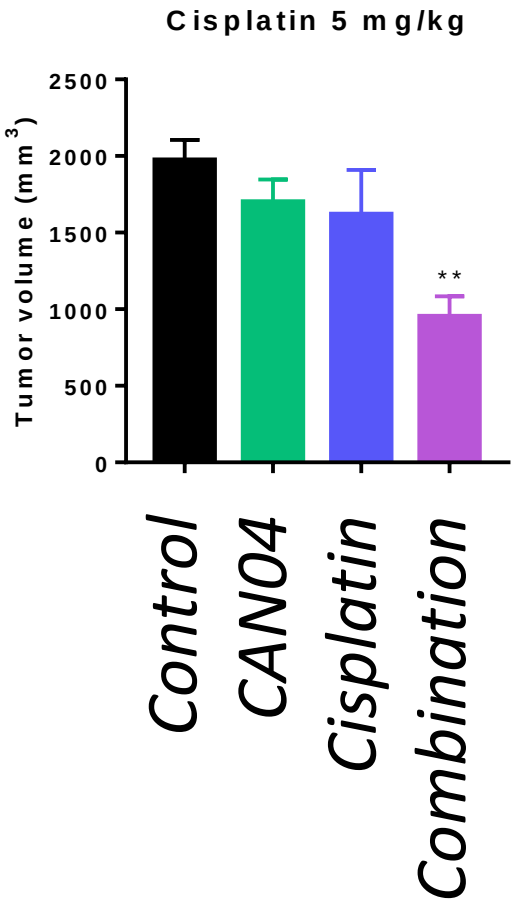
, Maria Teresa Rodia[1,*], Michela Pucci[1], Massimiliano Dall'Ora[1], ,4], Rossella Solmi[1], Lee Roth[5], Moshit Lindzen[5], Massimiliano a Bertotti[6], Elisabetta Caramelli[1], Pier-Luigi Lollini[1], Livio Trusolino[6], Gabriele D'Uva[7,**], Mattia Lauriola[1,2,**]

Constitutive IRAK1 Activation Underlies Poor Prognosis and Chemoresistance in Pancreatic Ductal Adenocarcinoma

Daoxiang Zhang[1], Lin Li[1], Hongmei Jiang[1], Brett L. Knolhoff[1], Albert C. Lockhart[1], Andrea Wang-Gillam[1], David G. DeNardo[1], Marianna B. Ruzinova[2], and Kian-Huat Lim[1]

Cantargia

NSCLC CAN04/Cisplatin combination



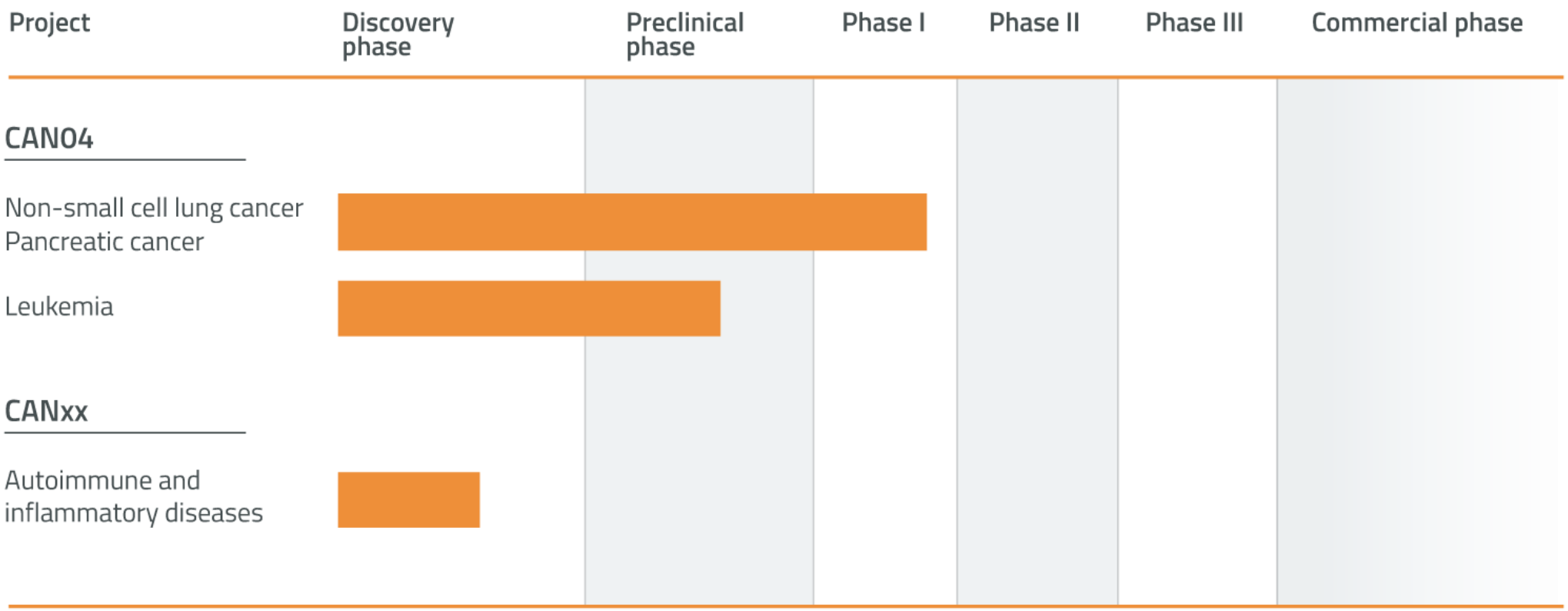
	Control	CAN04	Cisplatin	Combination
Animals withdrawn	20 % (Tumor)	0 %	50 % (Toxicity)	20 % (Toxicity)
Tumor reduction	N/A	14%	18%	52 %
Comment	*Highest tumor burden*	*Best safety*	*Highest toxicity*	*Superior efficacy and reduced toxicity*

Combination CAN04/Cisplatin superior to individual agents

- **Reduction in severe toxicity**
- **Increased efficacy**

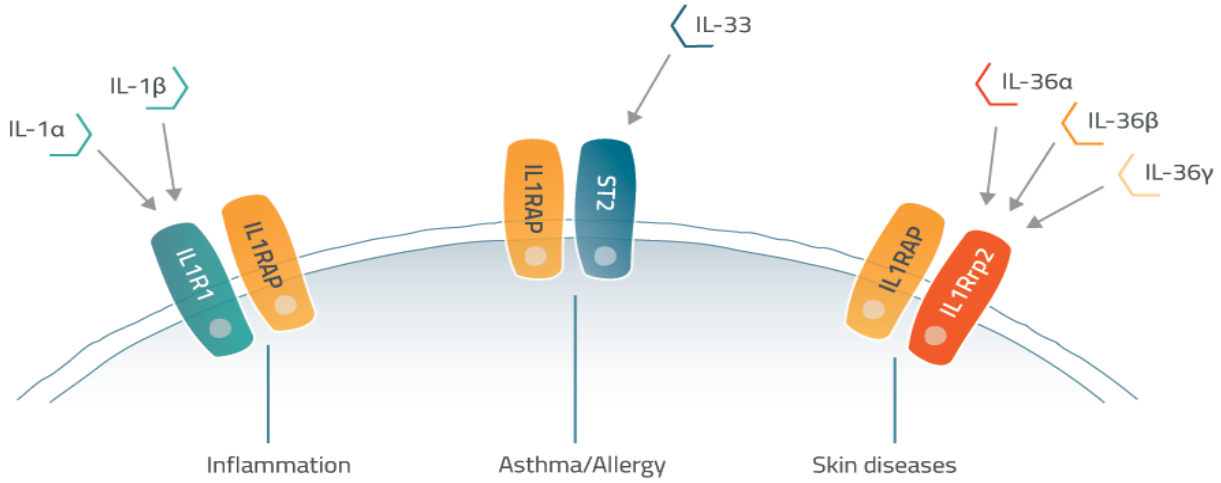
Cantargia

Cantargia pipeline



IL1RAP

- Three different systems signal through IL1RAP
- These systems contribute to various inflammatory diseases
- Can be blocked by antibodies against IL1RAP



Cantargia partnership with Panorama Res Inc (Sunnyvale, CA)

IL1RAP summary

- IL1RAP is a novel target for antibody therapy
- IL-1, IL-33 and IL-36 use IL1RAP for signaling
- IL-1 and IL-33 function through distinct binding
- Generating antibodies blocking various function of these cytokines
- CAN04 is entering phase IIa clinical trials in NSCLC and pancreatic cancer