Understanding the Mechanistic Actions & Development of IL-15Rβγ agonist SO-C101 (RLI-15)

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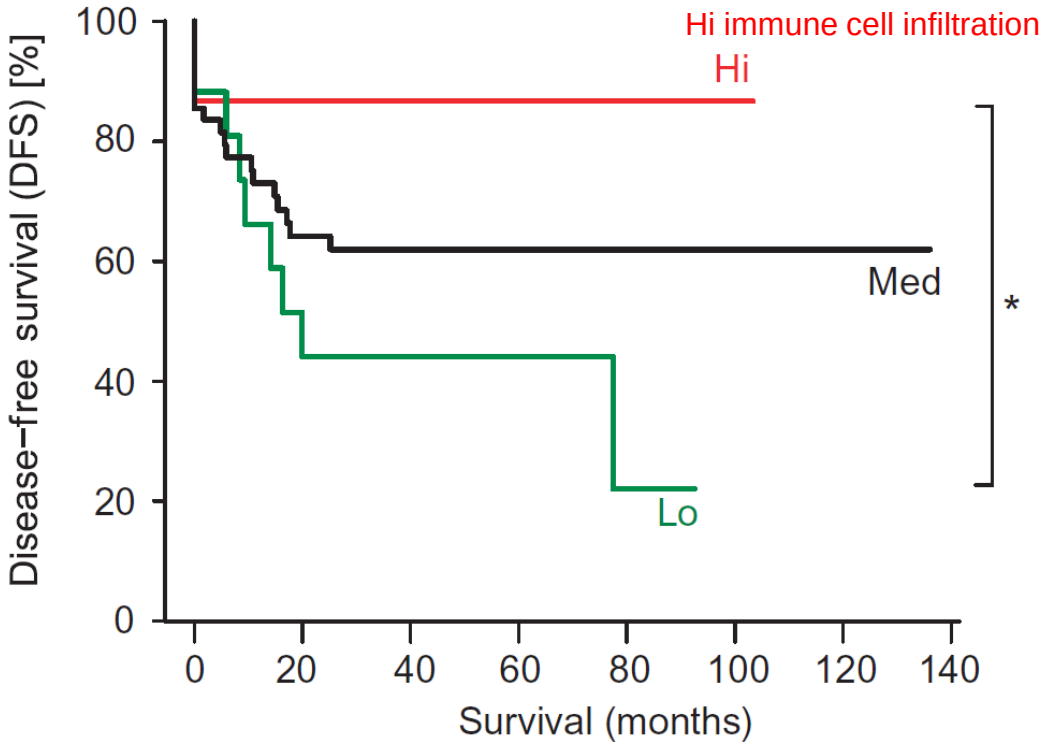
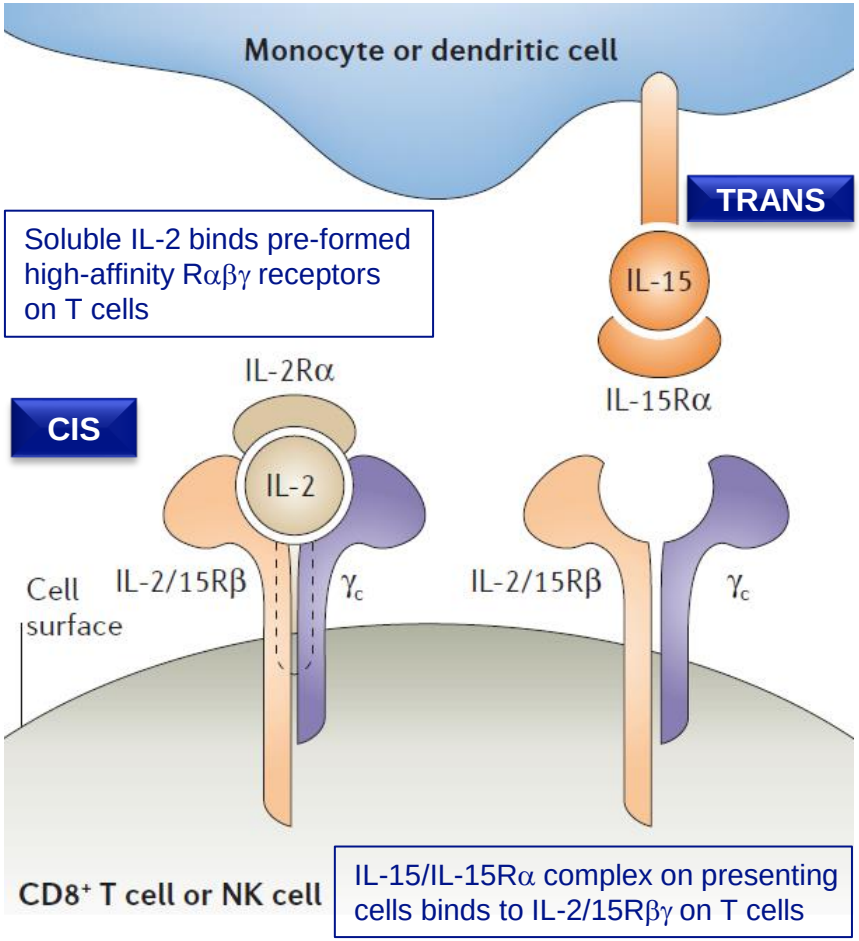
Level of IL-15 tumor expression impacts disease free survival in colorectal cancer patients



IL-15 is the only cytokine with a significant impact on survival, underlining the major role of IL-15 in human anti-cancer immunity

Mlecnik *et al*., Sci. Transl. Med. 2014 Mar 19; 6(228) Vol. 6, Issue 228, pp. 228ra37

IL-15Rα trans-presentation by antigen presenting cells is a prerequisite for proper engagement of IL15Rβγ on NK cells and T cells by IL-15



IL-2 and IL-15 receptors are heterotrimeric

- Common receptor subunit IL-2/15Rβ and the γ chain with intermediate affinity for IL-2 and IL-15
- Distinct receptor α subunit, IL-2Rα or IL-15Rα as the high affinity receptor

IL-15 and IL-2 have distinct high-affinity receptors & binding MOA

- IL-2 and IL-15 have distinct and pivotal roles on the functions of immune cells, due to differential expression of their respective receptor α subunit

KO IL-2 in mice

$CD4^+$ T_{reg} deficiency, autoimmune diseases

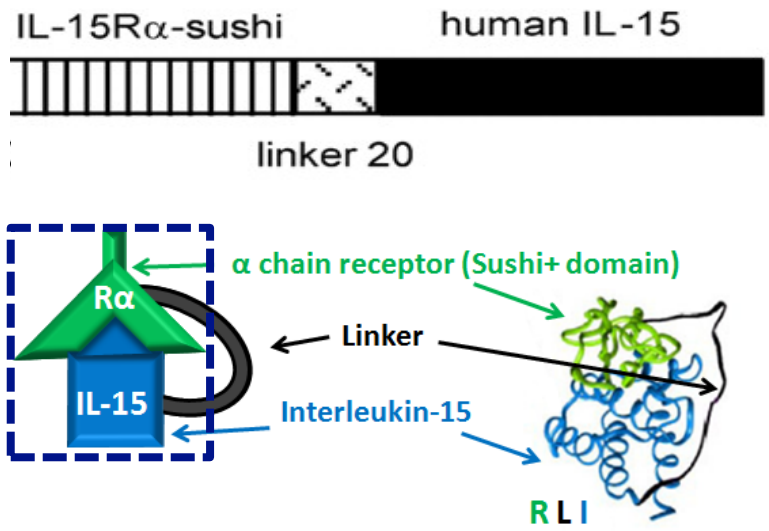
KO IL-15 or IL-15Rα in mice

NK, NKT, $CD8^+$ T, γδT cell deficiency

Adapted from: Waldmann *et al.*, Nature Reviews Immunology volume 6, pages 595–601 (2006)

SO-C101 (RLI-15) ensures optimal IL-15 signaling in NK cells and CD8+ T cells in the absence of IL-15Rα trans-presentation

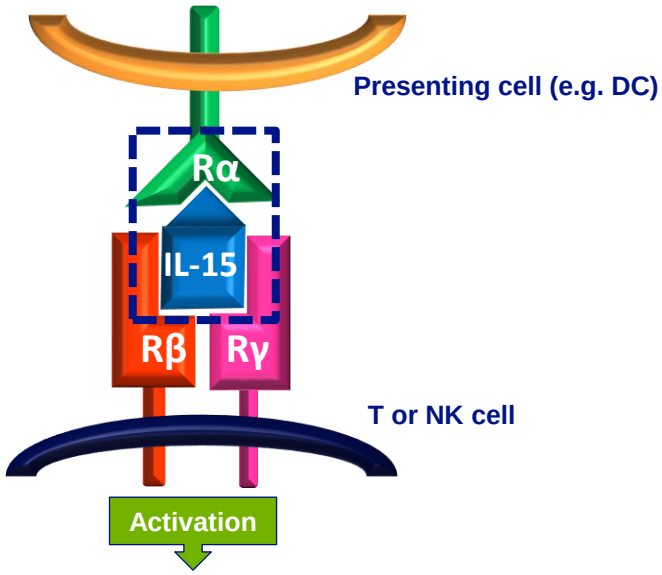
SO-C101 is a fusion protein containing IL-15 and the Sushi+ domain of IL-15Rα



Mortier et al. , JBC 2006

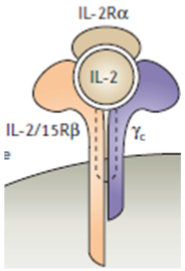
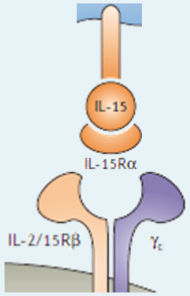
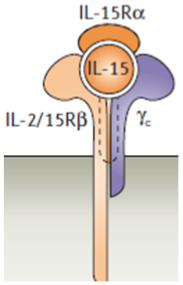
SO-C101 structure

SO-C101 mimics the high-affinity binding of IL-15 trans- presented to its βγ receptor at the immunological synapse



Physiological action of IL-15

Specific targeting of IL-2/IL-15Rβγ by SO-C101 is critical for the stimulation of anticancer immunity and safety

High-affinity IL-2Rαβγ	Mid-affinity IL-2/IL-15Rβγ	High-affinity IL-15Rαβγ	High-affinity IL-15Rα
			
Constitutive expression:			
• CD4⁺ T_{regs} • Lung vascular endothelium	• Resting CD8⁺ T cells • Memory CD8⁺ T cells • NK cells	• T cell leukemia	• Myeloid cells • Macrophages • B cells and neutrophils
Outcome of stimulation:			
• Activation and expansion of CD4⁺ T_{regs} • Activation of lung vascular endothelium	• Activation of CD8⁺ T cells • Activation of NK cells	• Potential risk of expansion of preleukemic T cell clones	• Activation of inflammatory response mediated by the cells of innate immunity
No SO-C101 binding ✗	**SO-C101 binding** ✓	**No SO-C101 binding** ✗	**No SO-C101 binding** ✗

Ongoing SO-C101 phase 1/1b bifurcated trial design

Accelerated dose finding in combination with pembrolizumab

PATIENTS	REGIMEN	END POINTS
EUROPE and US **N= 45-90** patients with relapsed/refractory advanced/metastatic solid tumors 4 centres	**Part A:** SO-C101 monotherapy 3+3 Design	Safety and tolerability of SO-C101 monotherapy • MTD • RP2D
	Part B: SO-C101 combined with pembrolizumab CPI naive + CPI R/R pts	SO-C101 combination • MTD • RP2D

N, number; CPI, checkpoint inhibition; R/R, relapsed/refractory; MTD, maximum tolerated dose; RP2D, recommended phase II dose

PHASE I CENTRES

Dr. Patricia LoRusso, **Yale Cancer Center**, New Haven, CT

Dr. Filip Janku, **MD Anderson Cancer Center**, Houston, TX

Dr. Aurélien Marabelle, **Institut Gustave Roussy**, FR

Dr. Elena Garralda, **Vall d'Hebron**, SP

STATUS

Drug well-tolerated

Recruitment into 7th dose level of Part A completed

Dose level 7 – 15 µg/kg – was defined as MTD

Dose level at 12 µg/kg will be tested

Recruitment into 3rd level of Part B combo with pembro ongoing
Average SO-C101 doses administered = 8

Observed PD activity is consistent with preclinical data

Types of mouse models used for SO-C101 mono/combo studies

Syngeneic mouse with mouse tumors

- Mouse tumor cell lines
- T cell-based models (MC38, CT26)
- NK-cell-based models (RENCA, TC-1, TRAMP-C2)

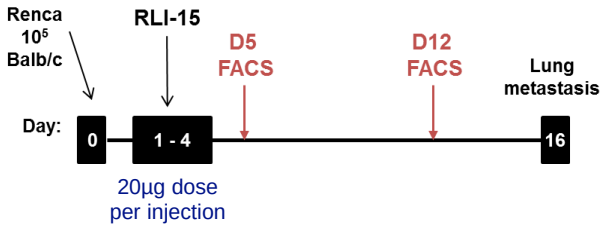
- monotherapy or
- Combination with anti-PD-1 mAb

Mouse with partial or fully competent immune system

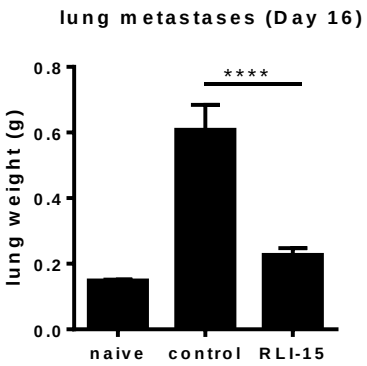
Syngeneic mouse with mouse tumors

- NK cell-based models (monotherapy)

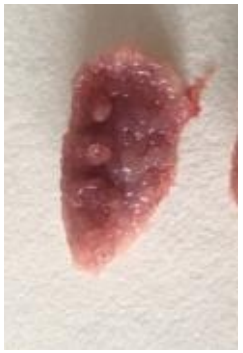
Renca Tumor Model Protocol



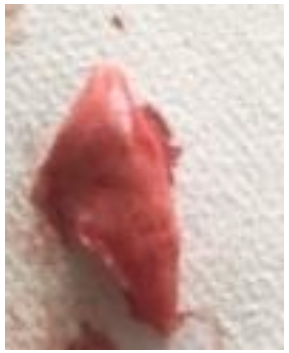
Efficacy



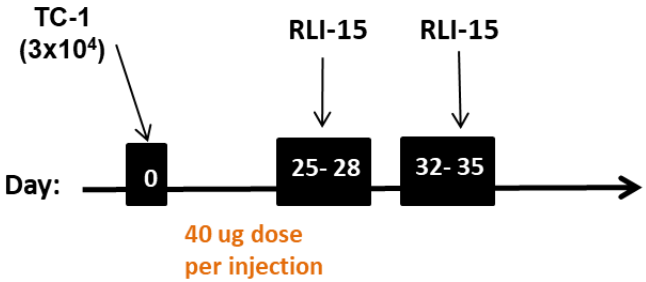
Control

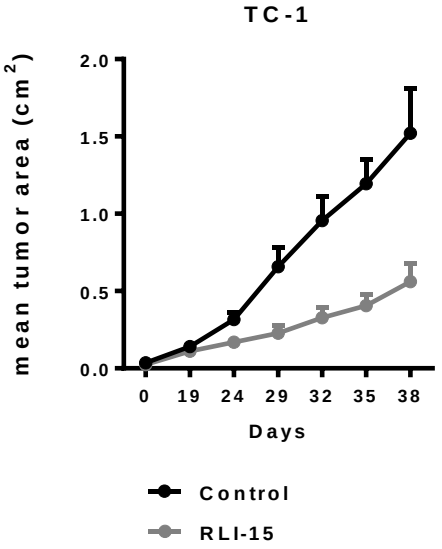


RLI-15



TC-1 Tumor Model Protocol

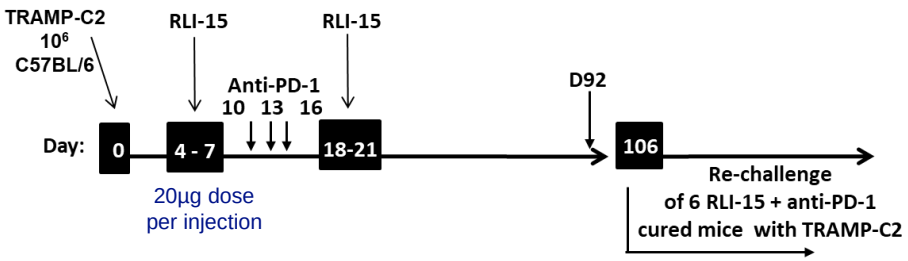


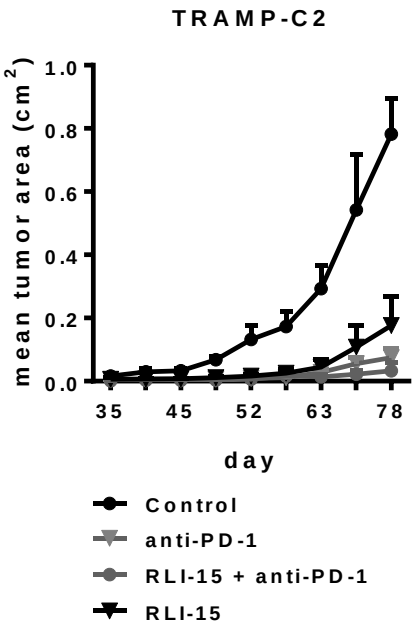


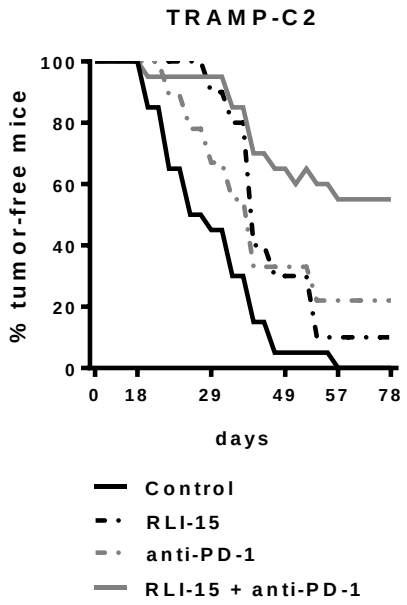
Syngeneic mouse with mouse tumors

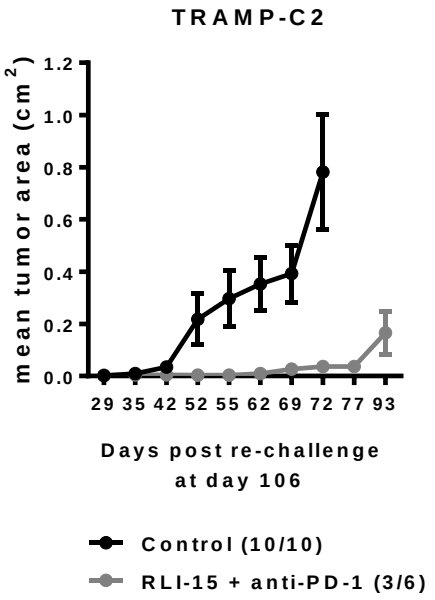
- NK cell-based models (combination with anti-PD-1)

TRAMP-C2 Tumor Model Protocol







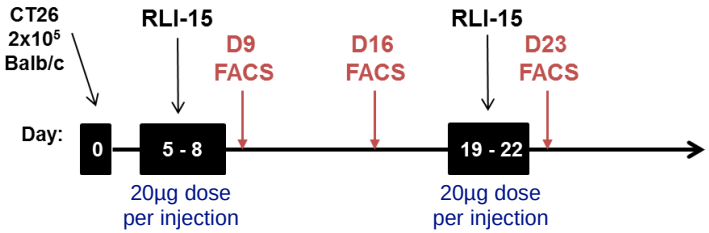


Early treatment with SO-C101/anti-PD-1 mAb combination decreases tumor growth and increases the number of tumor-free mice compared to both single agent effects

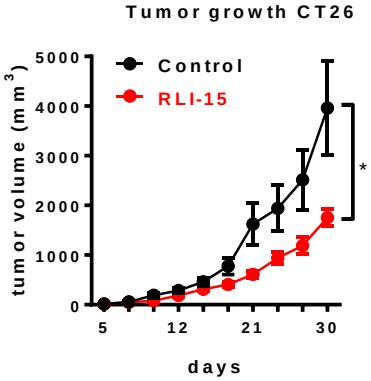
Syngeneic mouse with mouse tumors

- T cell-based models (monotherapy)

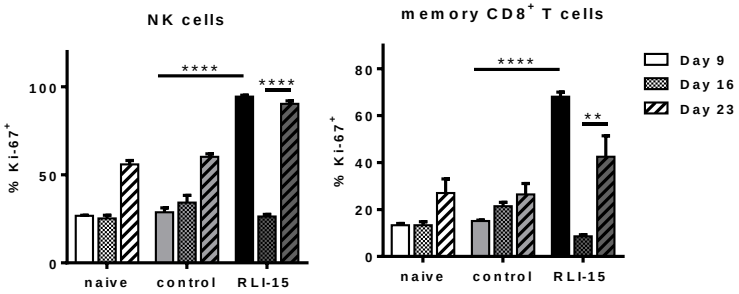
CT26 Tumor Model Protocol



Efficacy

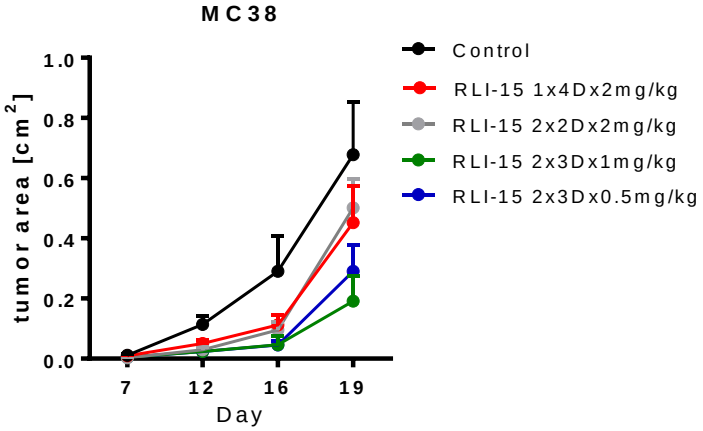


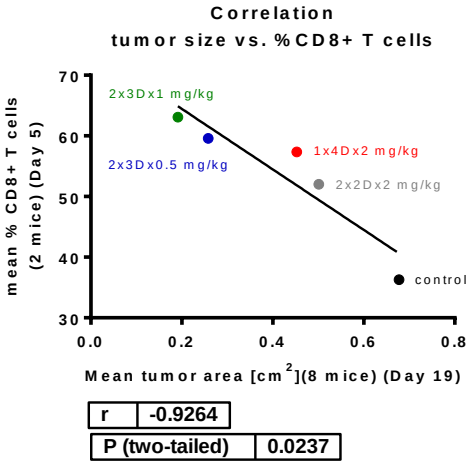
Immune cells activation



MC38 Tumor Model Protocol

Treatment on Day 5, C57BL/6;
10 mice/group
6h between administrations for
2x daily groups

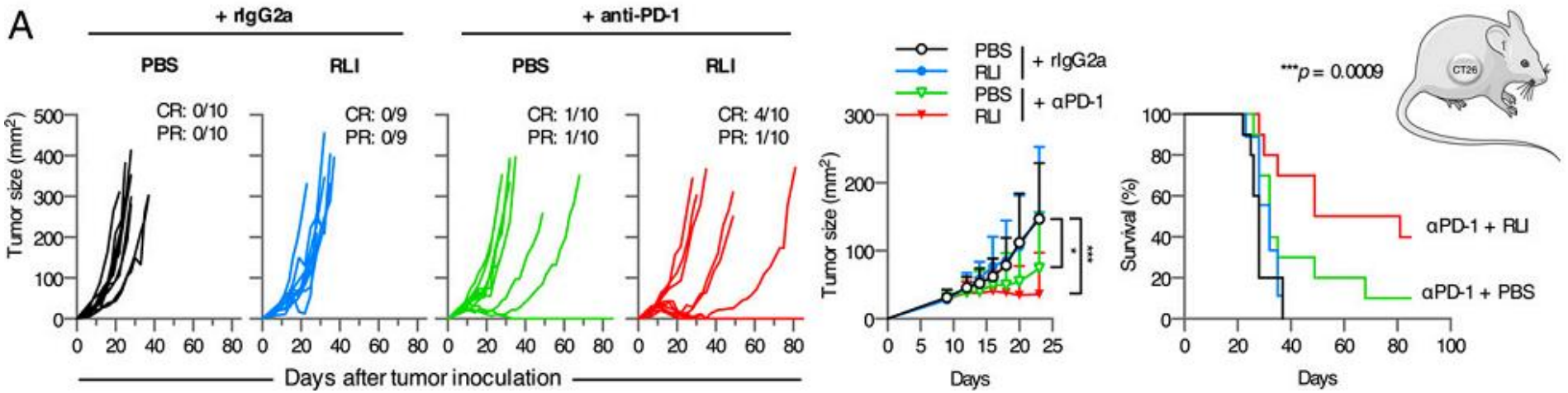




r	-0.9264
P (two-tailed)	0.0237

Syngeneic mouse with mouse tumors

- T cell-based models (combination with anti-PD-1)



Dosing

SO-C101 (2 µg/injection) twice per week from day 13 - 37
anti-PD1 (250 µg, day 9,12 and 15)

SO-C101/anti-PD-1mAb combination significantly decreases tumor growth and increases complete remission rate and long-term survival

Desbois *et al*. J Immunol July 1, 2016, 197 (1) 168-178.

Types of mouse models used for SO-C101 mono/combo studies

Syngeneic mouse with mouse tumors	• Mouse tumor cell lines • T cell-based models (MC38, CT26) • NK-cell-based models (RENCA, TC-1, TRAMP-C2)	• monotherapy or • Combination with anti-PD-1 mAb
Partially immunodeficient with human xenografts	• Human tumor cell lines (RPMI 8226) • NK, NKT cell-based models	• monotherapy or • Combination with anti-CD38 mAb

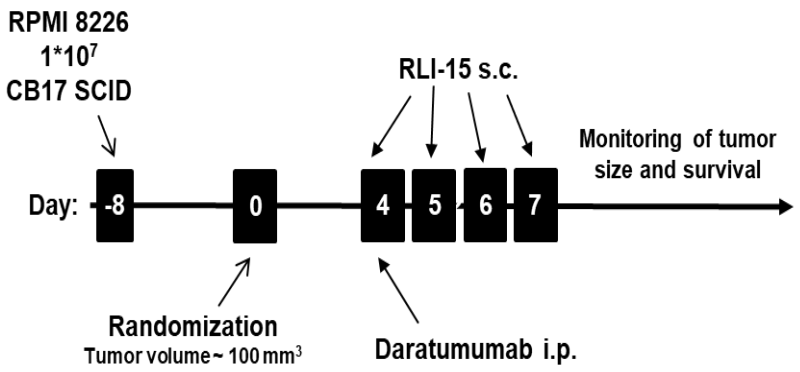
Mouse with partial or fully competent immune system

Partially immunodeficient with human xenografts

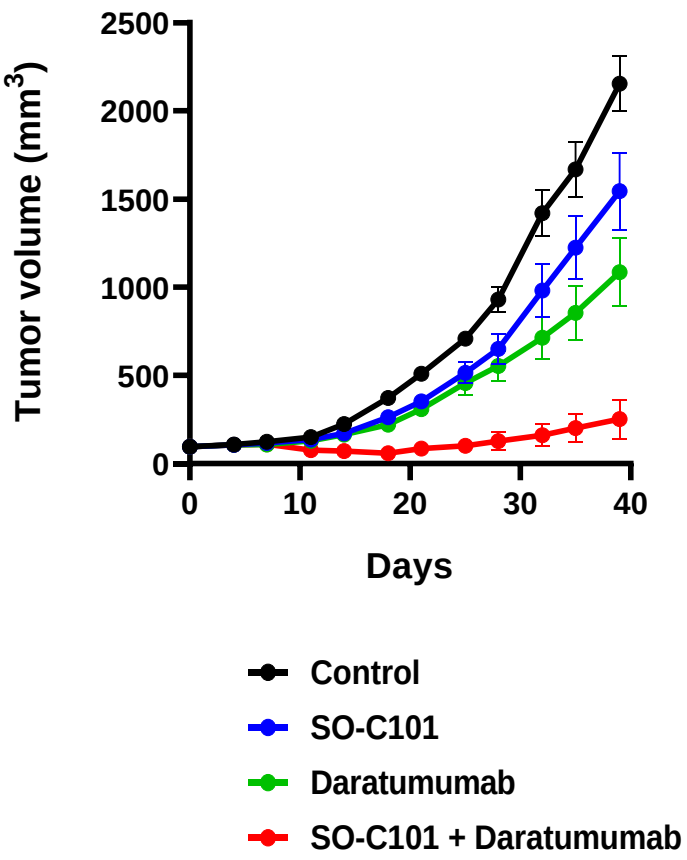
- Human tumor cell lines (RPMI 8226)
- NK, NKT cell-based models

- monotherapy or
- Combination with anti-CD38 mAb

RPMI8226 Tumor Model Protocol



Efficacy



- **Mechanism of action might not reflect fully functional immune system**
- **ADCC mechanism varies between mouse and human**
- **hIgG1 via FcRγIV – ADCP, FcRγIV not in mouse NK cells**

Types of mouse models used for SO-C101 mono/combo studies

Syngeneic mouse with mouse tumors	• Mouse tumor cell lines • T cell-based models (MC38, CT26) • NK-cell-based models (RENCA, TC-1, TRAMP-C2)	• monotherapy or • Combination with anti-PD-1 mAb
Partially immunodeficient with human xenografts	• Human tumor cell lines (RPMI 8226) • NK, NKT cell-based models	• monotherapy or • Combination with anti-CD38 mAb
Immunodeficient mouse with human xenografts and hPBMC	• Human tumor cell lines (A549)	• monotherapy

Mouse with partial or fully competent immune system

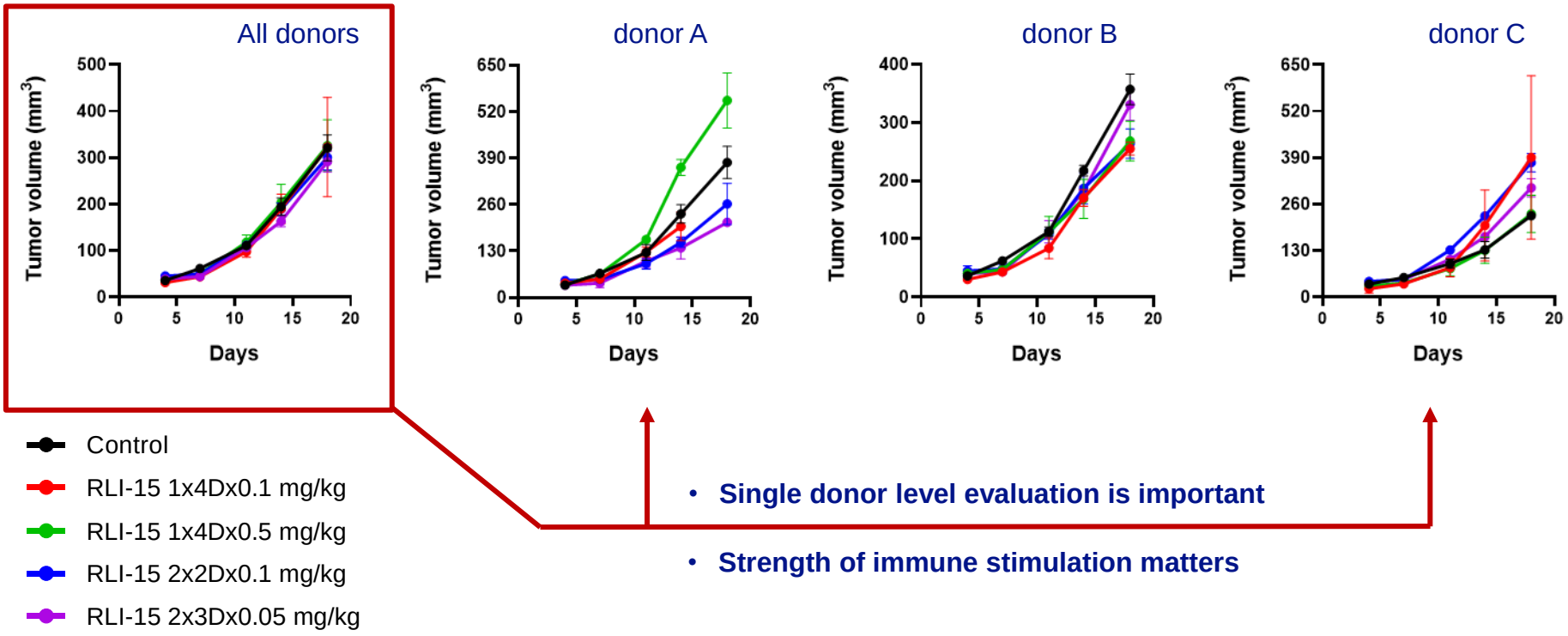
Immunodeficient mouse with human xenografts and hPBMC

- Human tumor cell lines (A549, Daudi)

A549 Tumor Model Protocol

Tumor cell implantation Day 0
PBMC transferred i.p 2h post inoculation
Treatment on Day 2, NCG;
3 donors/3 mice
6h between administrations

Efficacy



- **Single donor level evaluation is important**
- **Strength of immune stimulation matters**

Types of mouse models used for SO-C101 mono/combo studies

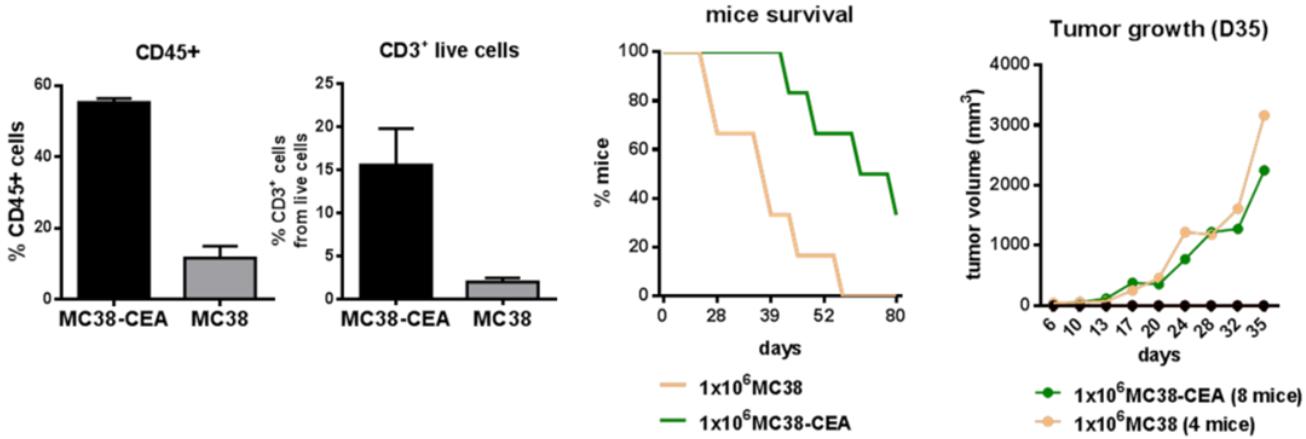
Syngeneic mouse with mouse tumors	• Mouse tumor cell lines • T cell-based models (MC38, CT26) • NK-cell-based models (RENCA, TC-1, TRAMP-C2)	• monotherapy or • Combination with anti-PD-1 mAb
Partially immunodeficient mouse with human xenografts	• Human tumor cell lines (RPMI 8226) • NK, NKT cell-based models	• monotherapy or • Combination with anti-CD38 mAb
Immunodeficient mouse with human xenografts and hPBMC	• Human tumor cell lines (A549)	• monotherapy
Syngeneic mouse with mouse tumors and human antigen	• Mouse tumor cell line carrying human antigen • Transgenic mouse (hPD-1)	• monotherapy

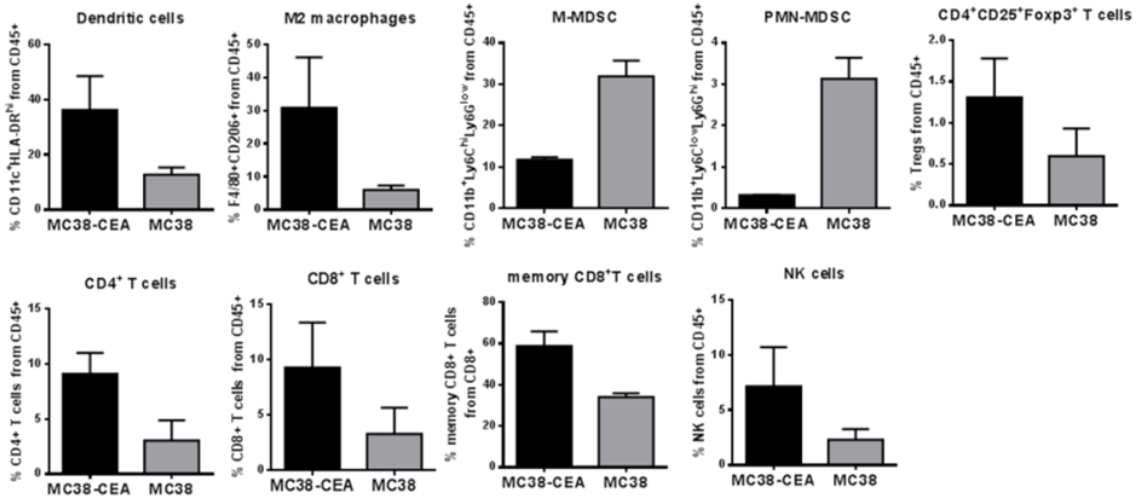
Mouse with partial or fully competent immune system

Syngeneic mouse with mouse tumors and human antigen

- Mouse tumor cell line carrying human antigen
- Transgenic mouse (hPD-1)

MC38-CEA is more immunogenic than MC38, but the tumor growth remains the same





Day 17

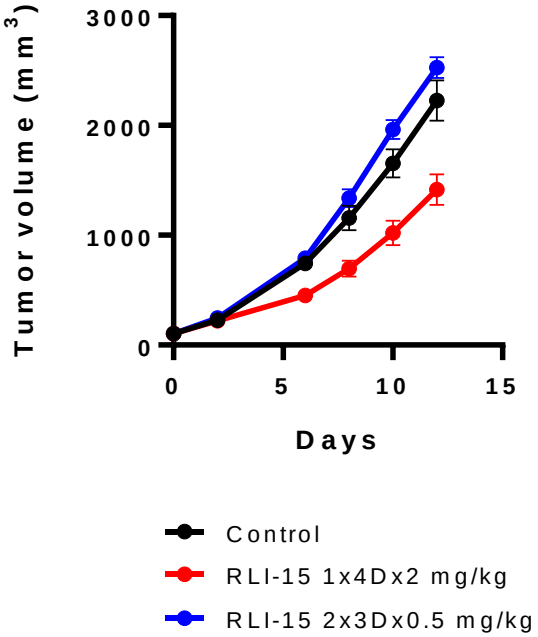
Syngeneic mouse with mouse tumors and human antigen

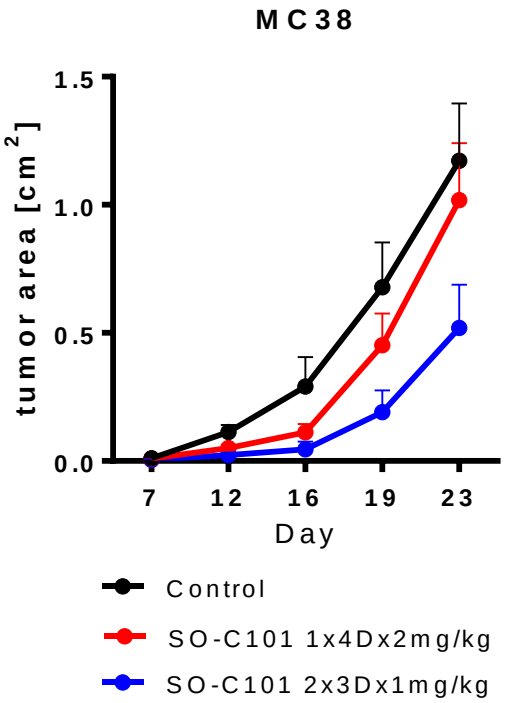
- Mouse tumor cell line carrying human antigen
- Transgenic mouse (hPD-1)

MC38-hPD-L1 in hPD-1 transgenic mouse

Randomization at ~100 mm^3
Followed by RLI-15 treatment
8 mice/group
6h between administrations in 2x3Dx0.5 mg/kg

Efficacy





- **strength of immune cell stimulation is important due to the baseline immunogenicity of the mouse tumor model with human antigen**

Types of mouse models used for SO-C101 mono/combo studies (summary)

	benefits	limitations
Syngeneic mouse with mouse tumors	• Fully competent immune system • good for proof-of-concept of preclinical studies, mechanistical concepts often translatable to humans	• lack of cross-reactivity for testing IO drugs targeting human antigen • Mechanistical interpretation difficult in some cases e.g ADCC
Partially immunodeficient mouse with human xenografts	• Often retained innate immunity compartment (NK, NKT) • Engraftment of human CDX or PDX	• Anti-tumor efficacy mechanisms might not reflect fully competent immune system anti-tumor actions • Mechanistical interpretation
Immunodeficient mouse with human xenografts and hPBMC	• Human immune system (full or partial) • Engraftment of human CDX or PDX	• Short-term models due to GvH • Donor variability • Limited human cell populations
Syngeneic mouse with mouse tumors and human antigen	• Human target antigen in fully immunocompetent mice • Testing of human-targeted IO compounds	• Xenoantigen highly immunogenic • High immunogenicity baseline • Risk of exacerbation of the tumor growth • Price (transgenic mice)

Just because the models are imperfect……

it does not mean they are wrong……

Bob Weinberg

Thanks to:

CrownBio
CONNECTING SCIENCE TO PATIENTS