neoleukin™
THERAPEUTICS

May 12, 2021

Forward Looking Statements

Certain of the statements made in these slides and the accompanying oral presentation are forward looking, including those relating to Neoleukin's business, strategy, future operations, advancement of its product candidates and product pipeline, clinical development of its product candidates, including expectations regarding timing of regulatory submissions and initiation of clinical trials, regulatory requirements for initiation of clinical trials and registration of product candidates, properties of its product candidates, availability of data, the use and sufficiency of its cash resources and other statements containing the words "anticipate," "believe," "expect," "may," "plan," "project," "potential," "will," "would," "could," "continue," and similar expressions. These statements are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, risks and uncertainties related to: whether results of early clinical trials or preclinical studies will be indicative of the results of future trials, the adequacy of any clinical models, uncertainties associated with regulatory review of clinical trials; our ability to identify or acquire additional clinical candidates, our ability to obtain and maintain regulatory approval for any product candidates and the potential safety, efficacy or clinical utility of or any product candidates; further impacts of COVID-19 on our operations; and other factors discussed in the "Risk Factors" section of the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2021 as filed with the Securities and Exchange Commission. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. More information about the risks and uncertainties faced by the Company is contained in its Quarterly Report on Form 10-Q for the quarter ended March 31, 2021, Annual Report on Form 10-K for the year ended December 31, 2020, and subsequent reports, filed with the Securities and Exchange Commission. The Company disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

Leader in Therapeutic Protein Design

First Program: Cancer Immunotherapy

Platform technology: computational protein design methods for creating *de novo* Neoleukin™ cytokine mimetics

NL-201 program: highly potent, non-alpha, combined IL-2 and IL-15 receptor agonist for cancer immunotherapy

2018
FOUNDED

SEATTLE WA

2019
PUBLIC

NASDAQ: NLTX

2020
IND SUBMISSION

NL-201

2021
CLINICAL TRIALS

Systemic
Local

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Functional De Novo Proteins

Better Immunotherapies by Design

nature **2019**

Article | Published: 09 January 2019

De novo design of potent and selective mimics of IL-2 and IL-15

Daniel-Adriano Silva, Shawn Yu, Umut Y. Ulge, Jamie B. Spangler, Kevin M. Jude, Carlos Labão-Almeida, Lestat R. Ali, Alfredo Quijano-Rubio, Mikel Ruterbusch, Isabel Leung, Tamara Biary, Stephanie J. Crowley, Enrique Marcos, Carl D. Walkey, Brian D. Weitzner, Fátima Pardo-Avila, Javier Castellanos, Lauren Carter, Lance Stewart, Stanley R. Riddell, Marion Pepper, Gonçalo J. L. Bernardes, Michael Dougan, K. Christopher Garcia & David Baker

Science AAAS **2020**

CORONAVIRUS Article | Published: 4 December 2020

De novo design of potent and resilient hACE2 decoys to neutralize SARS-CoV-2

Thomas W. Linsky[1*], Renan Vergara[1*], Nuria Codina[1*], Jorgen W. Nelson[1*], Matthew J. Walker[1], Wen Su[2], Christopher O. Barnes[3], Tien-Ying Hsiang[4], Katharina Esser-Nobis[4], Kevin Yu[1], Z. Beau Reneer[5], Yixuan J. Hou[4], Tanu Priya[1], Masaya Mitsumoto[1], Avery Pong[1], Uland Y. Lau[1], Marsha L. Mason[1], Jerry Chen[1], Alex Chen[1], Tania Berrocal[1], Hong Peng[1], Nicole S. Clairmont[1], Javier Castellanos[1], Yu-Ru Lin[1], Anna Josephson-Day[1], Ralph S. Baric[6], Deborah H. Fuller[7], Carl D. Walkey[1], Ted M. Ross[5,8], Ryan Swanson[1], Pamela J. Bjorkman[3], Michael Gale Jr.[4], Luis M. Blancas-Mejia[1], Hui-Ling Yen[2], Daniel-Adriano Silva[1]†

- Scientific founders are world leaders in *de novo* protein design
- Technology originated at University of Washington Institute for Protein Design, led by David Baker, PhD
- Exclusive license obtained for commercialization of NL-201 and other *de novo* protein assets

Neoleukin™ Progress in 2021

- Initiated Phase 1 clinical trial for NL-201
- Announced hiring Priti Patel, MD as Chief Medical Officer
- Occupied new lab and headquarters in Seattle, WA
- ~80 FTE; added expertise in CMC and Clinical

Leadership Team

Jonathan Drachman, M.D.
Chief Executive Officer
Previous: CMO, EVP R&D, Seattle Genetics

Robert Ho
Chief Financial Officer
Previous: Morgan Stanley & Co., DaVita

Priti Patel, M.D., M.S.
Chief Medical Officer
Previous: AstraZeneca, Acerta Pharma

Holly Vance, J.D., Pharm.D.
General Counsel
Previous: Bill & Melinda Gates Foundation

Carl Walkey, Ph.D.
Senior VP, Corporate Development
Previous: Postdoctoral Fellow, UW-IPD

Umut Ulge, M.D., Ph.D.
VP, Clinical Development
Previous: Postdoctoral Fellow, UW-IPD

Samantha Willing
VP, People
Previous: Seattle Genetics, Microsoft

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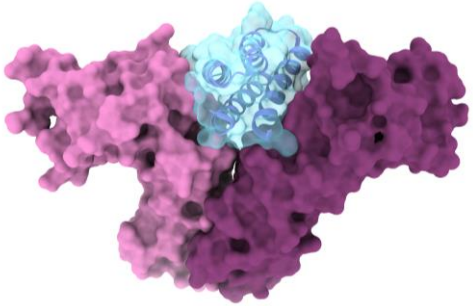
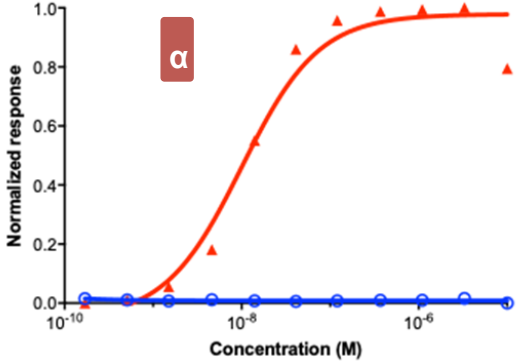
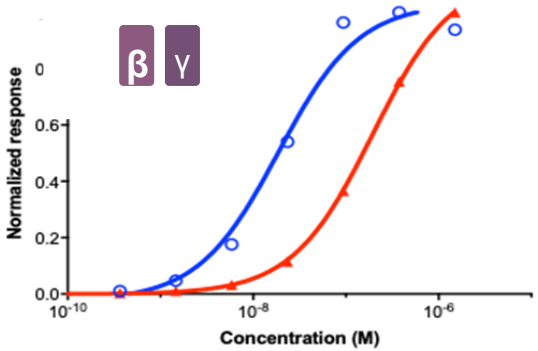
NL-201: *De Novo* IL-2/IL-15 Agonist

Designed to retain benefits of IL-2 without drawbacks

- 100% non-alpha: no residual alpha subunit binding
- No bias toward T-regulatory or endothelial cells
- More potent than IL-2 *and* IL-15
- Activates CD8+ naïve T-cells *and* NK cells
- Hydrophilic, compact, increased thermal stability







Neoleukin-2/15 hIL-2

Source: Silva et al. *Nature*, 565, 186-191 (2019)

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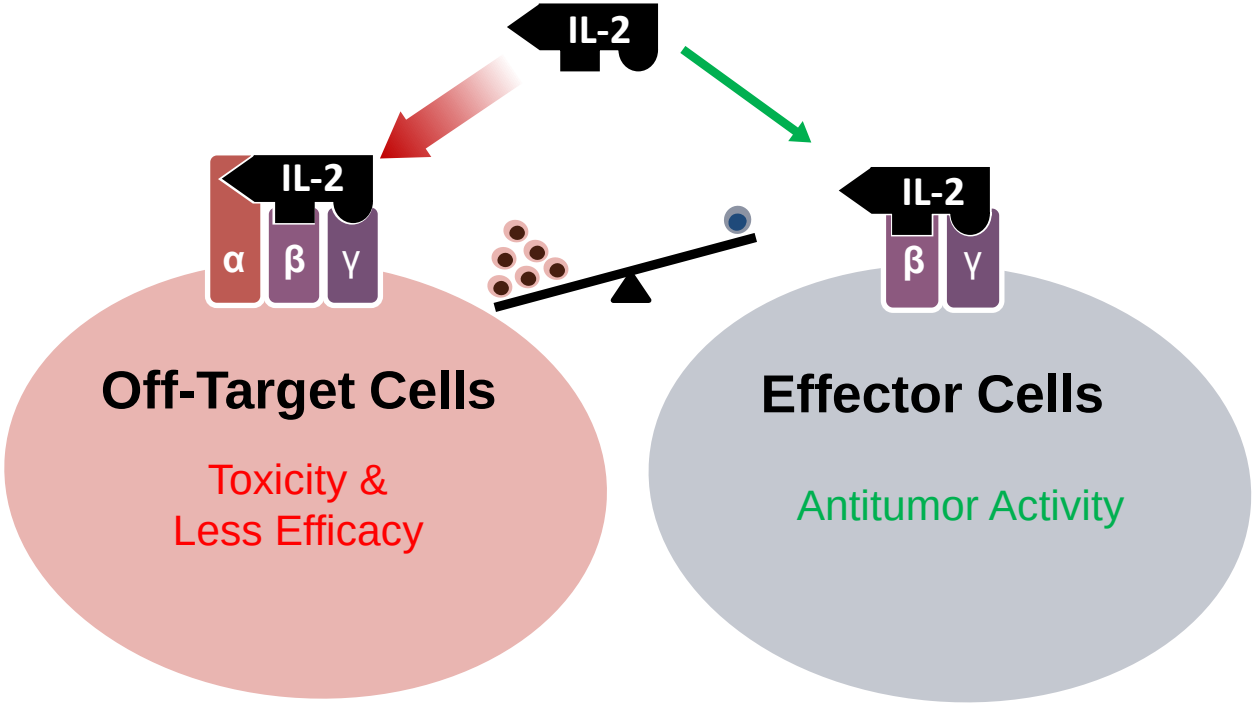
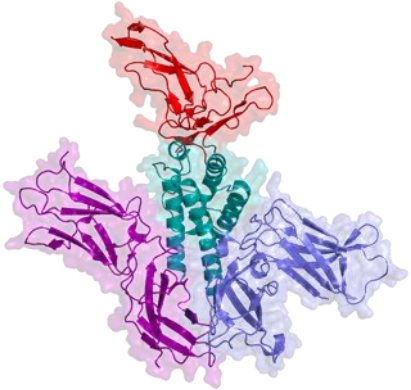
IL-2 Binds Strongly to Non-Target Cells, Causing Toxicity and Limiting Efficacy

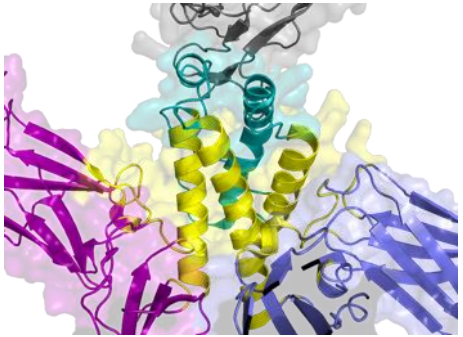


Building a Neoleukin™ Cytokine Mimetic in 4 Steps

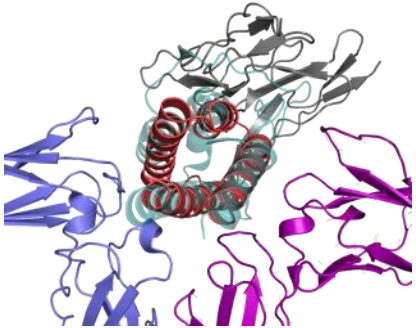
1. Develop an accurate structural model of the target



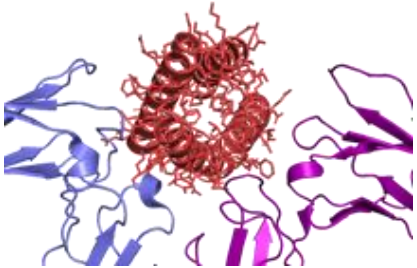
2. Identify regions of intermolecular contact



3. Design an idealized topology



4. Assign optimal amino acid sequence



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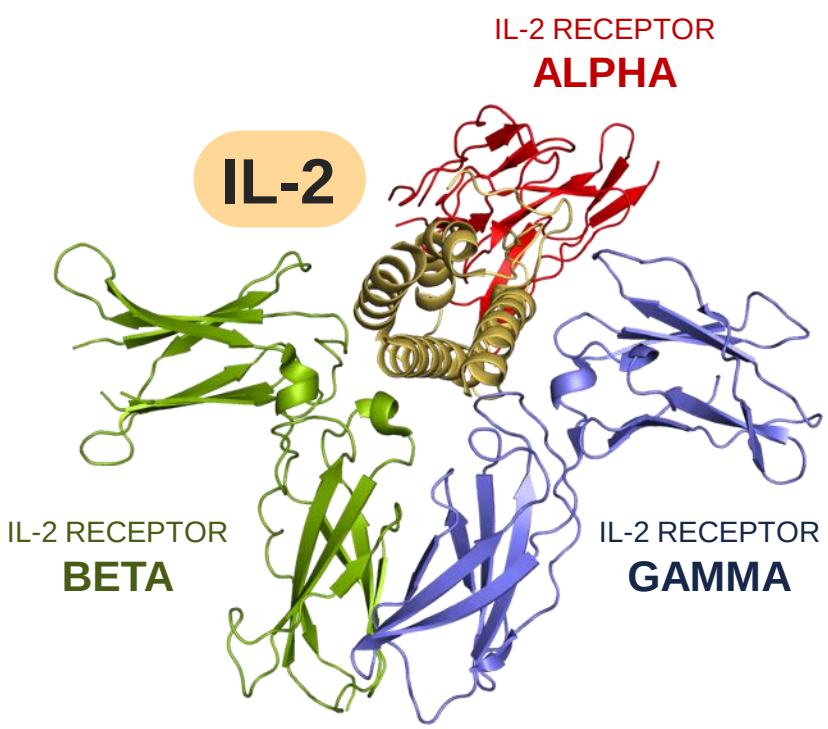
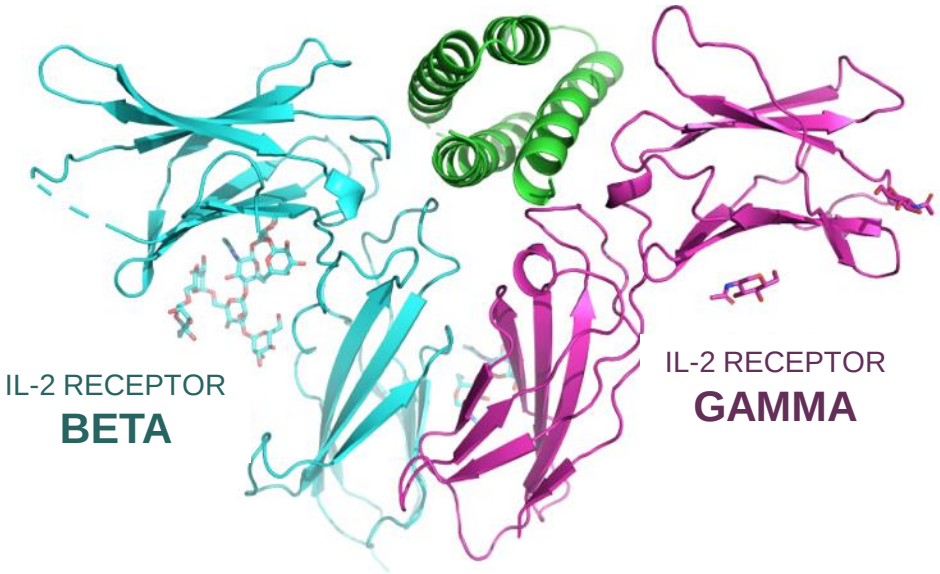
Crystal Structure Shows Neo-2/15 Binding Beta/Gamma as Predicted



14%
conserved sequence

Neo-2/15



Source: Silva et al. *Nature*, 565, 186-191 (2019)

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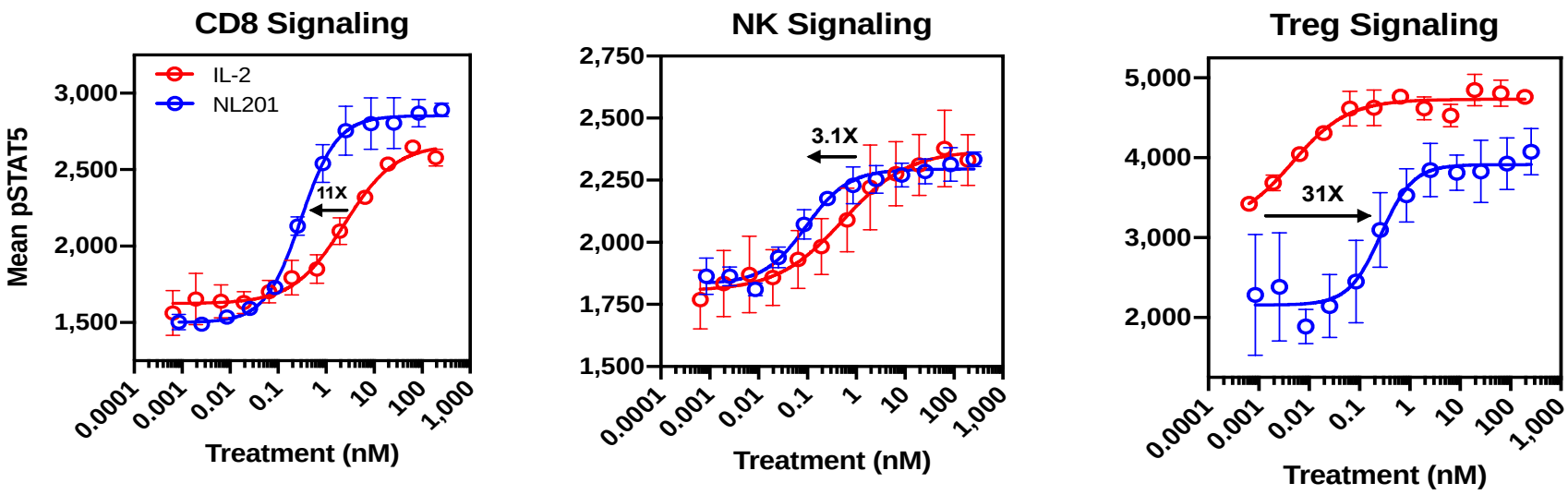
NL-201 Stimulates CD8 Effector T and NK Cells More Selectively Than IL-2



- NL-201 is ~330-fold and ~90-fold more selective for CD8+ T and NK cells (vs. Tregs) than IL-2, respectively

Walkey et. al, AACR Virtual Annual Meeting II, Abstract #4518, June 2020

1) STAT5 phosphorylation in CD8+ T cells, NK cells, and Tregs was measured by flow cytometry using PBMCs from 10 healthy human donors. Proliferation was evaluated using Ki67.

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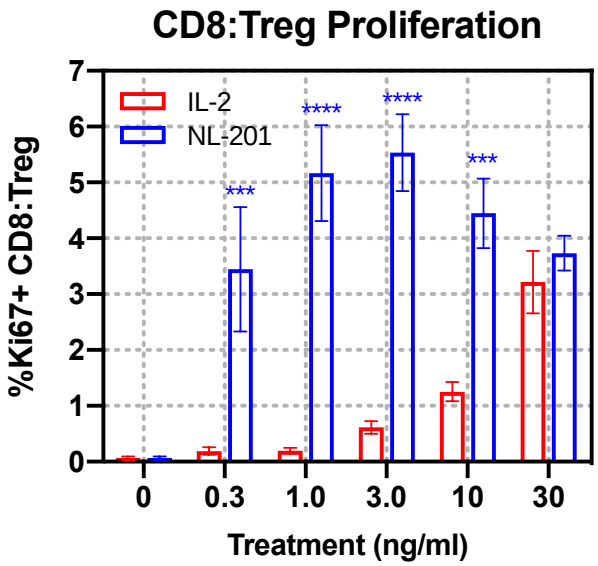
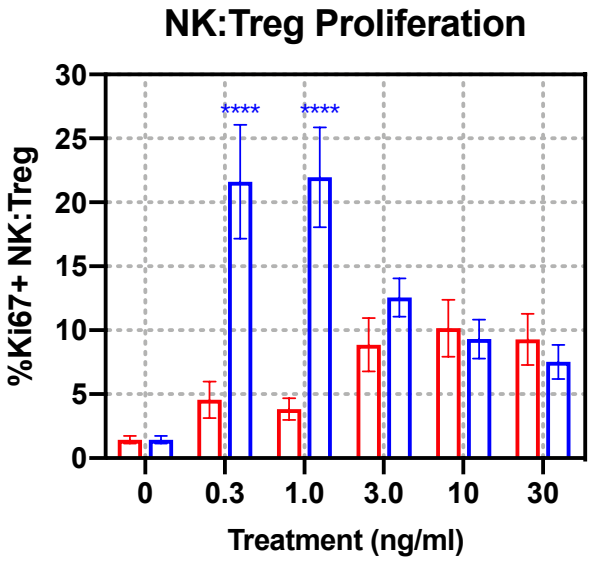
NL-201 Stimulates Dose-Dependent CD8:Treg and NK:Treg Proliferation More Potently Than IL-2





Walkey et. al, AACR Virtual Annual Meeting II, Abstract #4518, June 2020

1) NL-201 vs IL-2: * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

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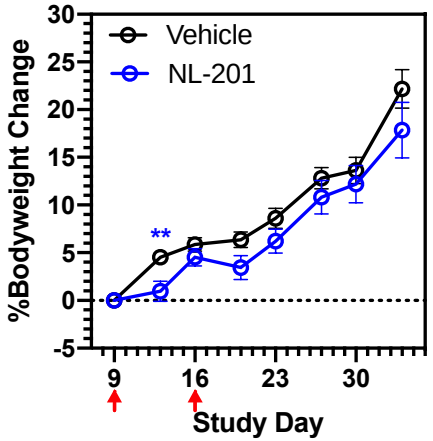
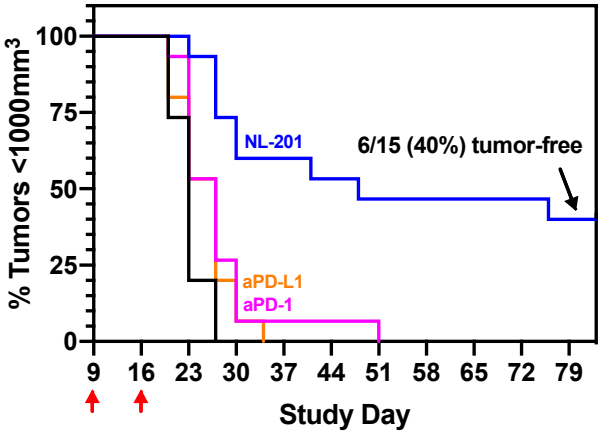
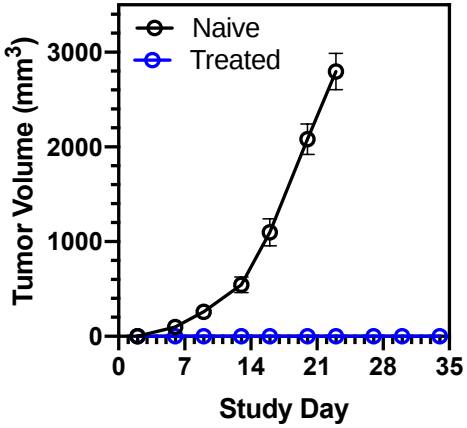
NL-201 is Well Tolerated and Promotes Durable Anti-tumor Activity







- NL-201 is well-tolerated at therapeutic doses
- NL-201 treatment exhibits single-agent activity
- NL-201 promotes durable anti-tumor immunity

Walkey et. al, AACR Virtual Annual Meeting II, Abstract #4518, June 2020

1) Study in a checkpoint inhibitor-resistant CT26 colon cancer murine model.

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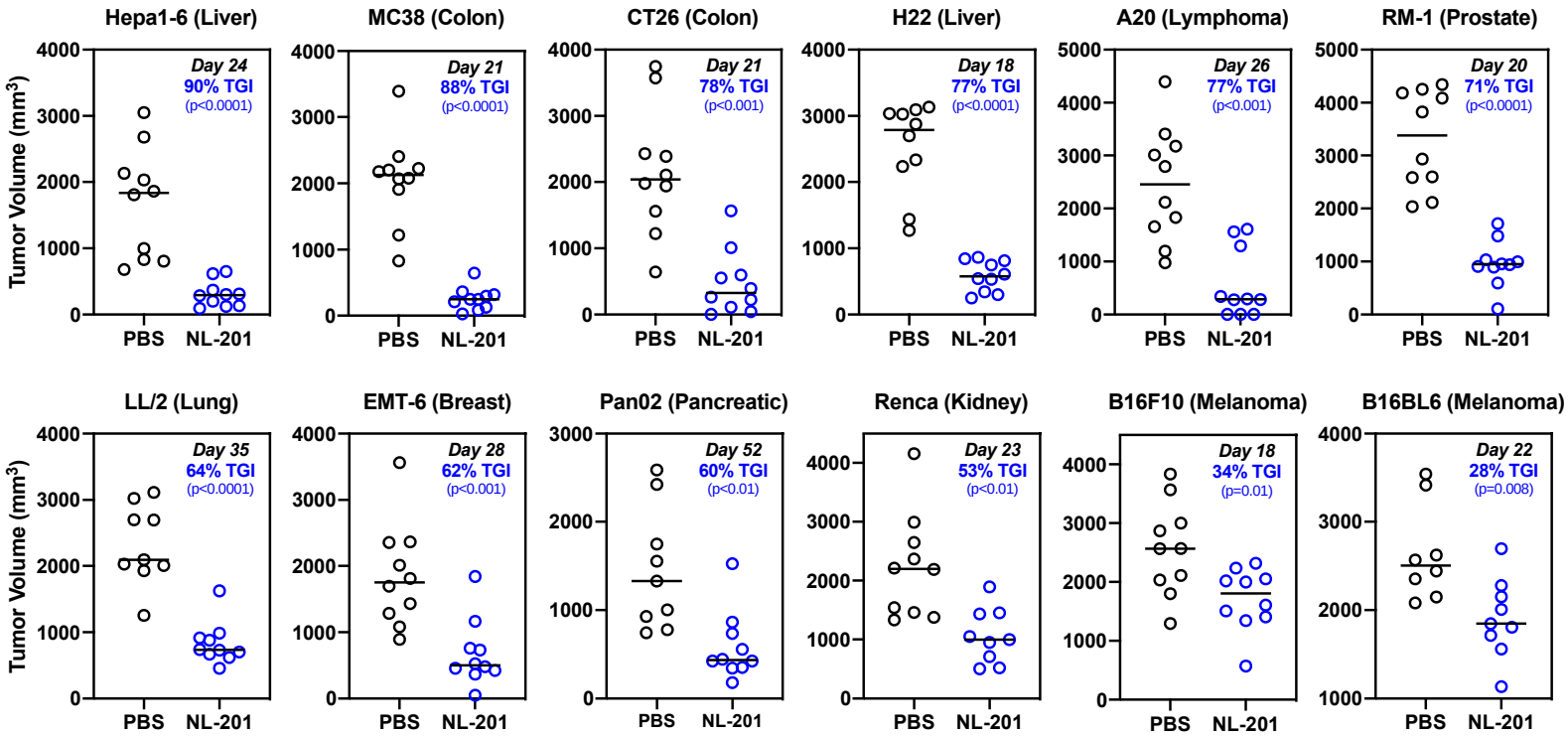
NL-201 Demonstrates Robust Single-Agent Activity in Multiple Tumor Models



1) NL-201 was administered QWx2 when tumors reached ~100mm3. Tumor growth inhibition (TGI) is reported in each graph vs. control.
2) NL-201 treatment inhibited tumor growth in all models: NL-201 significantly inhibited tumor growth in models that are typically refractory to anti-PD-1 checkpoint inhibitors.

Walkey et. al, AACR Virtual Annual Meeting II, Abstract #4518, June 2020

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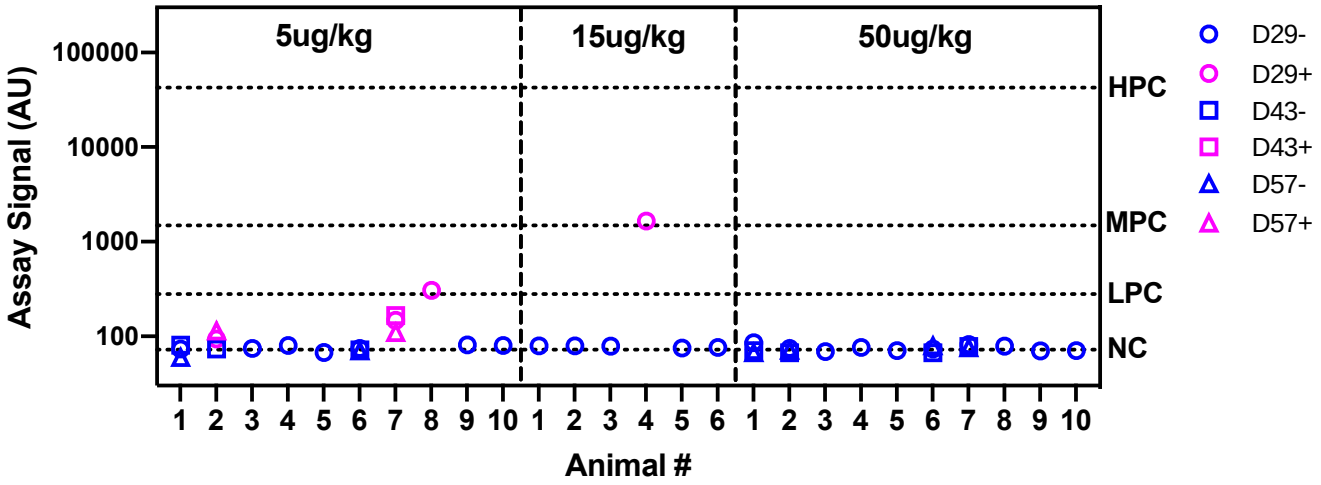
NL-201 Shows Minimal Immunogenicity in NHPs



- ADAs were detectable in: 3/10 NHPs at 5µg/kg; 1/6 NHPs at 15µg/kg; 0/10 NHPs at 50µg/kg NL-201
- 3 of 4 ADA+ NHPs were at or below the low positive control (LPC) level

Abstract #4518, Walkey et. al, AACR Virtual Annual Meeting II, June 2020

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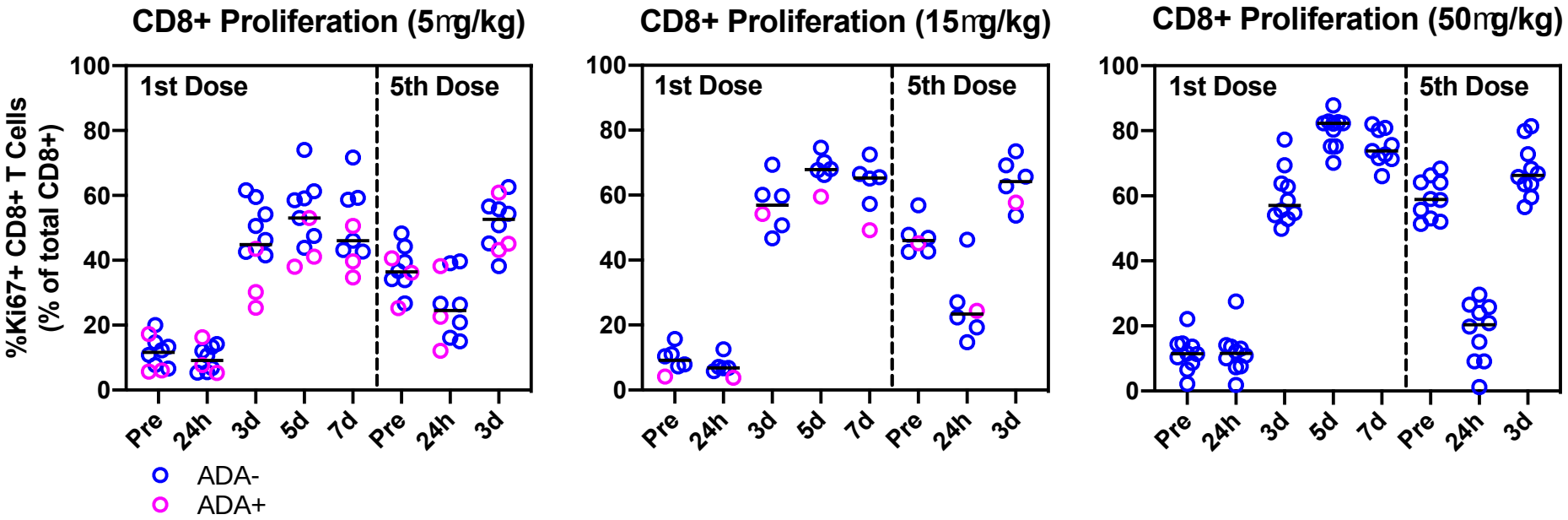
Similar Pharmacodynamics and Tolerability Observed in ADA+ vs ADA- NHPs



Adapted from Abstract #4518, Walkey et. al, AACR Virtual Annual Meeting II, June 2020

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NL-201 Phase 1 Clinical Trials

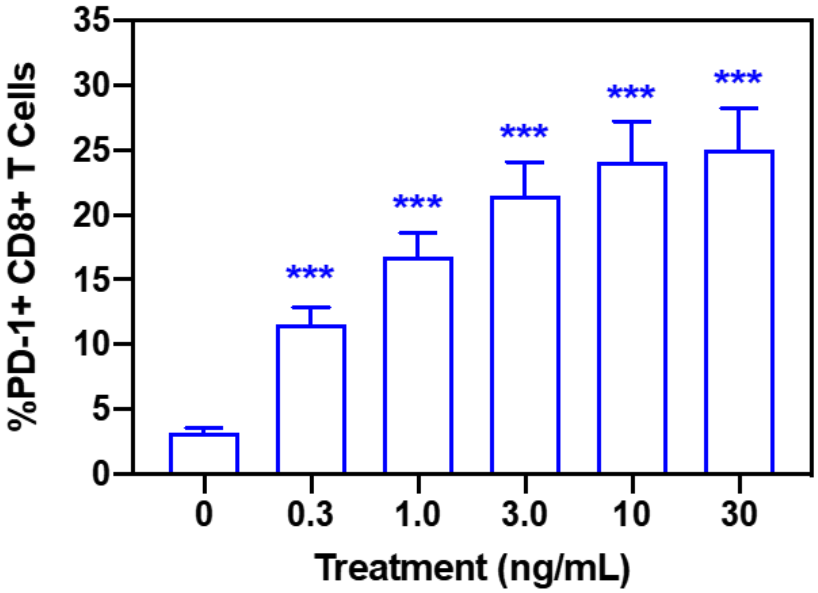
Systemic administration:

- IV, monotherapy in patients with advanced, relapsed or refractory solid tumors
- Multiple schedules and dose levels to assess safety, PK, PD, and antitumor activity
- Indication-specific expansion cohorts, including renal cell carcinoma and melanoma
- Trial will be conducted at multiple sites in Australia and North America
- Targeted enrollment up to 120 patients

Local administration:

- Designed to achieve higher NL-201 concentrations in tumor microenvironment
- Targeted to begin in 2021

NL-201 Upregulates PD-1 Expression by CD8+ T Cells



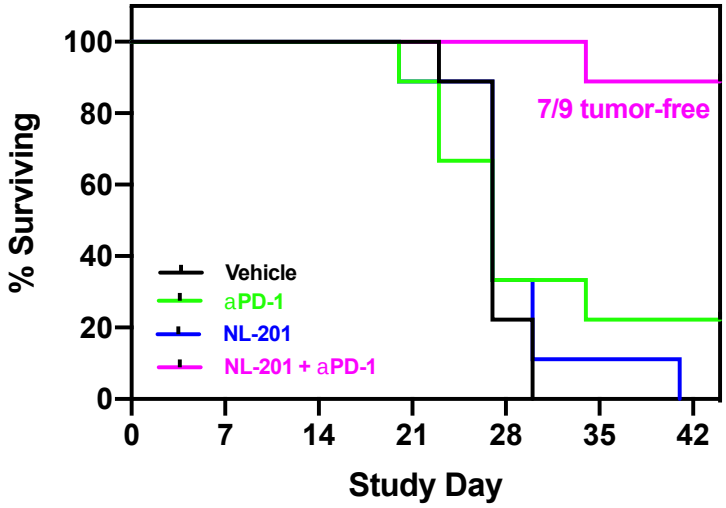
- NL-201 induces concentration-dependent PD-1 expression by CD8+ T cells
- Combining NL-201 with a checkpoint inhibitor may overcome PD-L1 mediated T cell inhibition

Walkey et. Al, SITC 2020, Abstract #576, November 2020

NL-201 Enhances Activity of Checkpoint Inhibitors in Preclinical Models

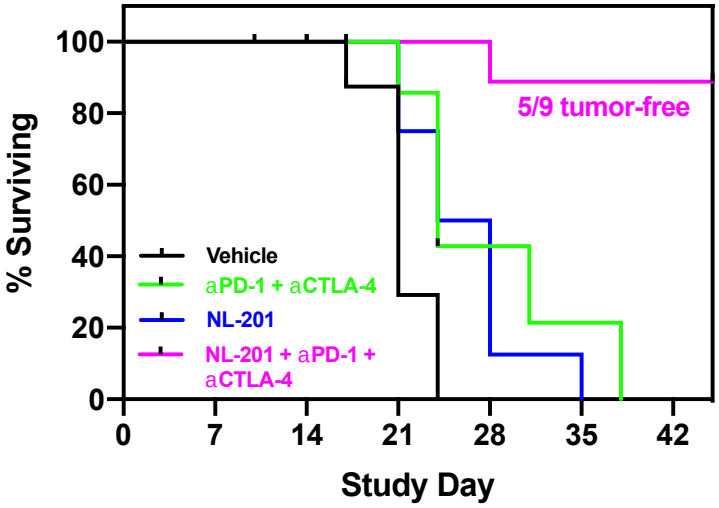
- **NL-201 enhances activity of CPIs in breast and kidney cancer models**
- **Combination with NL-201 beneficial in CPI-resistant syngeneic tumors**

EMT-6 (Breast)



p=0.0029: αPD-1 vs NL-201 + αPD-1
p<0.0001: NL-201 vs NL-201 + αPD-1

Renca (Kidney)



p=0.0001: αPD-1 + αCTLA-4 vs NL-201 + αPD-1 + αCTLA-4
p=0.0006: NL-201 vs NL-201 + αPD-1 + αCTLA-4

NL-201: 90µg/kg QWx2
αPD-1: 10mg/kg BiWx6
αCTLA-4: 10gm/kg BiWx6
Treatment began when tumors reached ~90mm³

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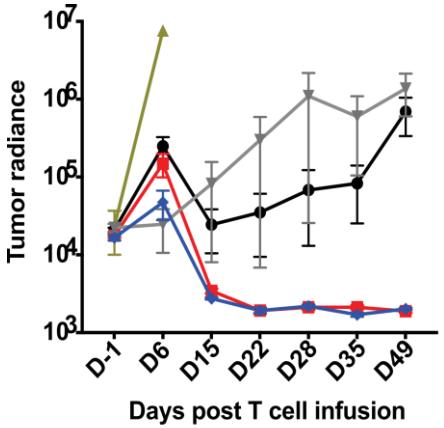
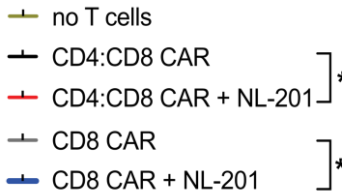
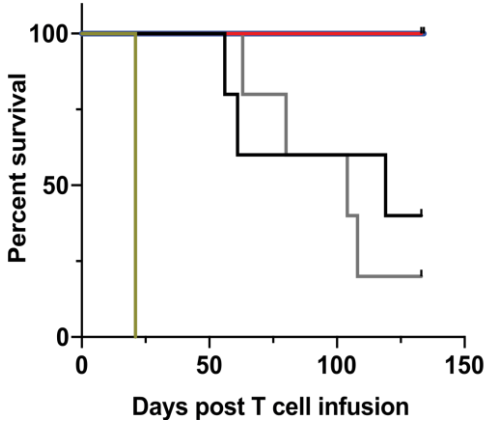
NL-201 Potently Expands CAR-T Cells and Promotes Antitumor Activity

Subcurative doses of CAR-T cells combined with NL-201 induce deep tumor control and achieve 100% survival.

NL-201 greatly enhances intratumoral CD8: Treg ratios (approximately 1000x compared to 50x for IL-2).







Leung et. al, AACR Virtual Annual Meeting II, Abstract #2222, June 2020

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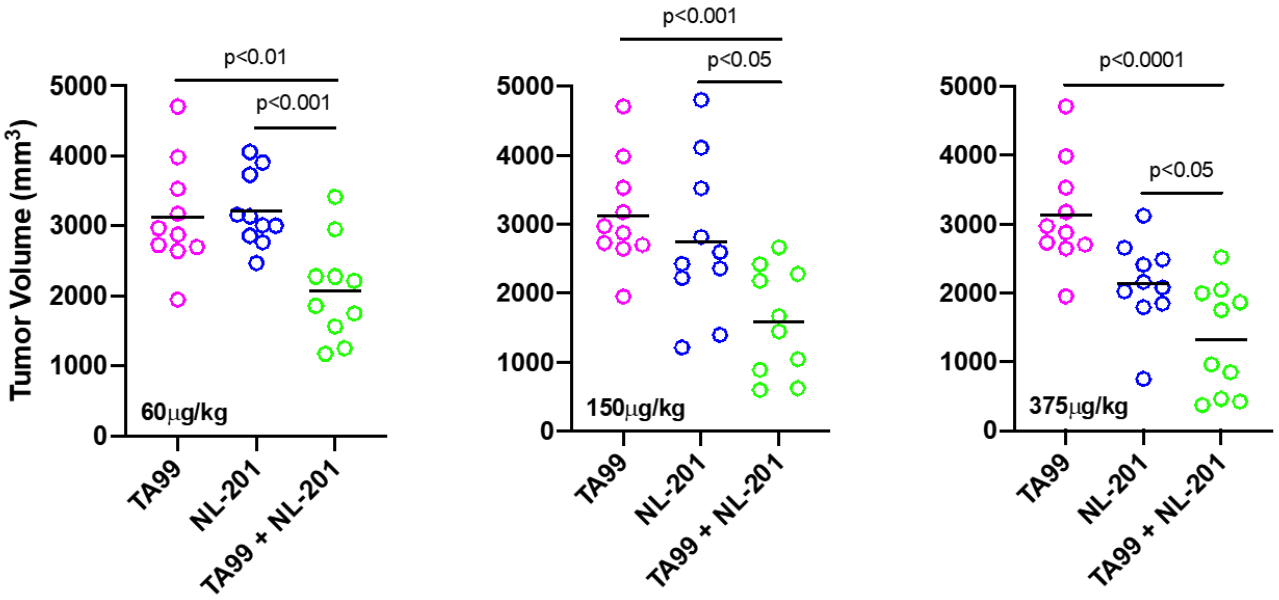
NL-201 Enhances Activity of Tumor-Targeting Antibodies in Multiple Preclinical Models

NL-201 + TA99 significantly improved tumor growth inhibition compared to TA99 or NL-201 alone



Walkey et. Al, SITC 2020, Abstract #576, November 2020

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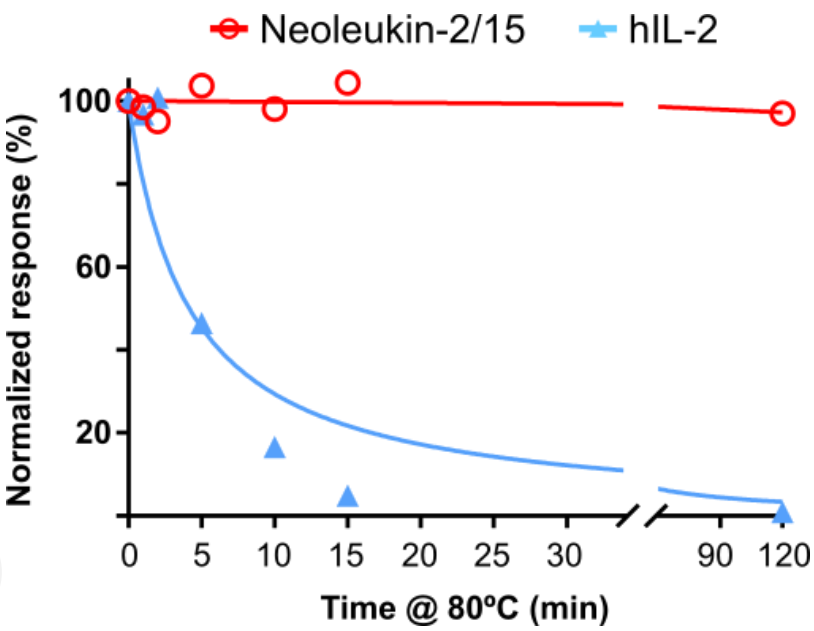
Neoleukin™ Cytokine Mimetics are Hyperstable and Easily Modified

- Able to withstand extreme conditions
- Able to adjust half-life or tune affinity
- Can use with targeting domain to improve biodistribution
- Can be conditionally activated in the tumor microenvironment
- Can be modified to make cytokine antagonists for inflammatory and autoimmune diseases



Source: Silva et al. *Nature*, 565, 186-191 (2019)

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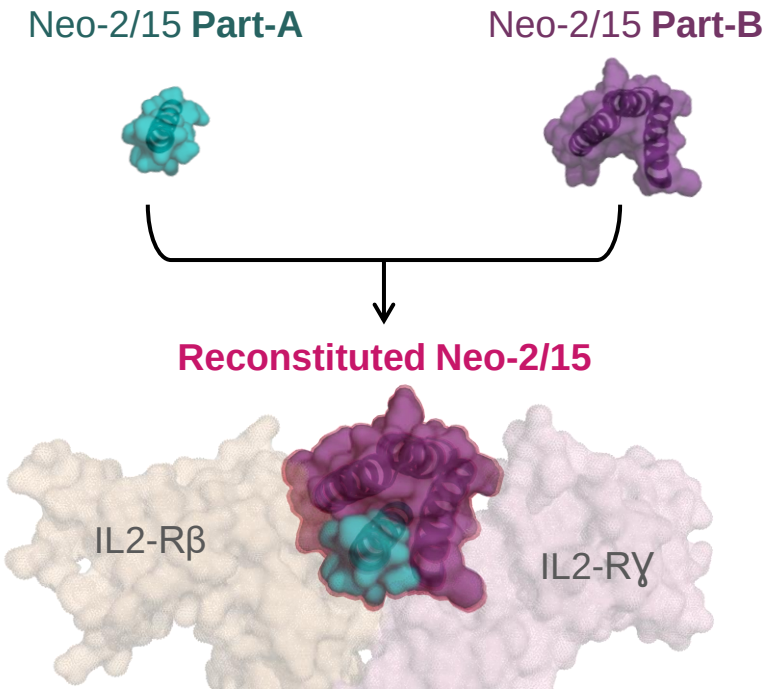
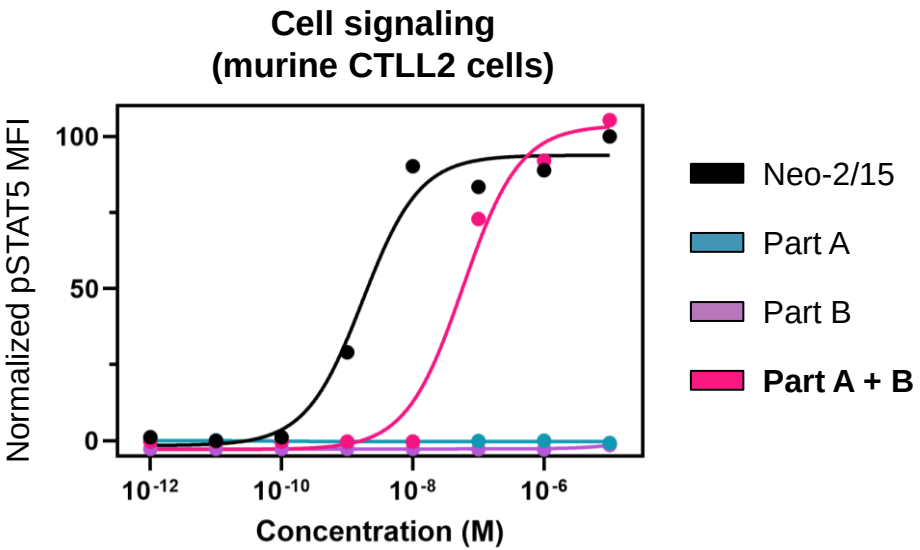
De Novo Split Technology - Conditionally Active IL-2 Mimetic





Quijano-Rubio et. Al., AACR Virtual Annual Meeting II, Abstract #1075, Jun/2020

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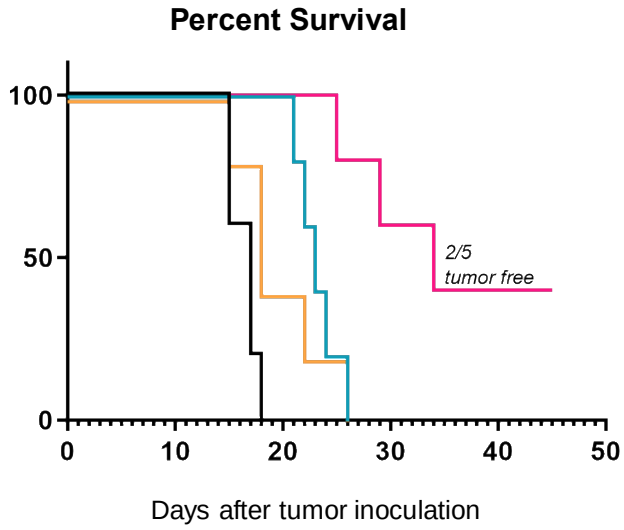
Targeted Split Neo-2/15 Increases Therapeutic Window

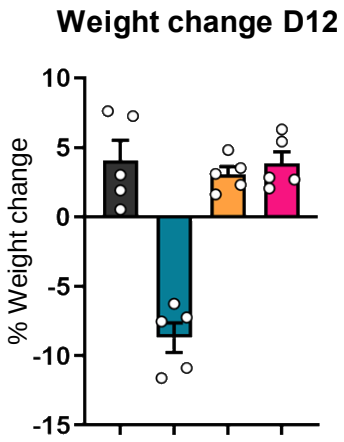


PBS

αPDL1-Neo-2/15 (0.43 nmol)

Untargeted-Part A + Untargeted-Part B (8 nmol)

αPDL1-Part A + αPDL1-Part B (8 nmol)



Notes:

1) C57BL/6J mice bearing B16 PDL1Hi melanoma cells in flank.
2) All groups were co-treated biweekly with Ta99 mAb (150µg/mice)
3) Targeted Neo-2/15 variants and Part-A fusions administered i.p.; Part-B fusions administered s.c. opposite flank of tumor

Quijano-Rubio et. Al., AACR Virtual Annual Meeting II, Abstract #1075, Jun/2020

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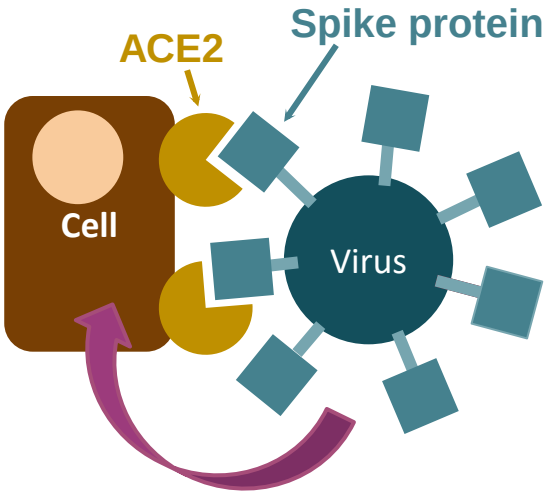
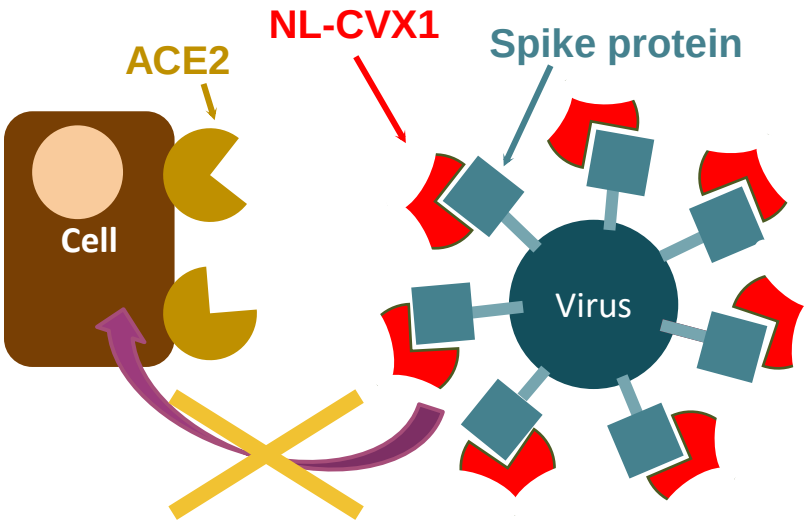
De Novo Platform Potential – COVID-19

SARS-CoV-2 uses **ACE2** as a receptor to gain access to and infect cells



NL-CVX1 - *de novo* ACE2 decoy:

- *Binds to SARS-CoV2 spike protein*
- *Inhibits viral infection in vitro*
- *Designed, tested, optimized in ~10 weeks*



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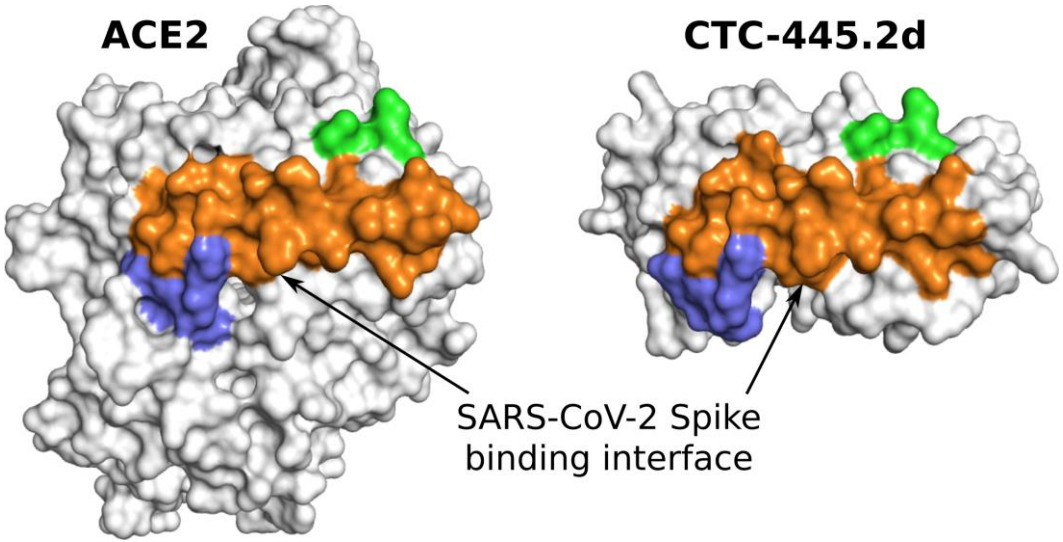
NL-CVX1 – *De Novo* Protein Decoy

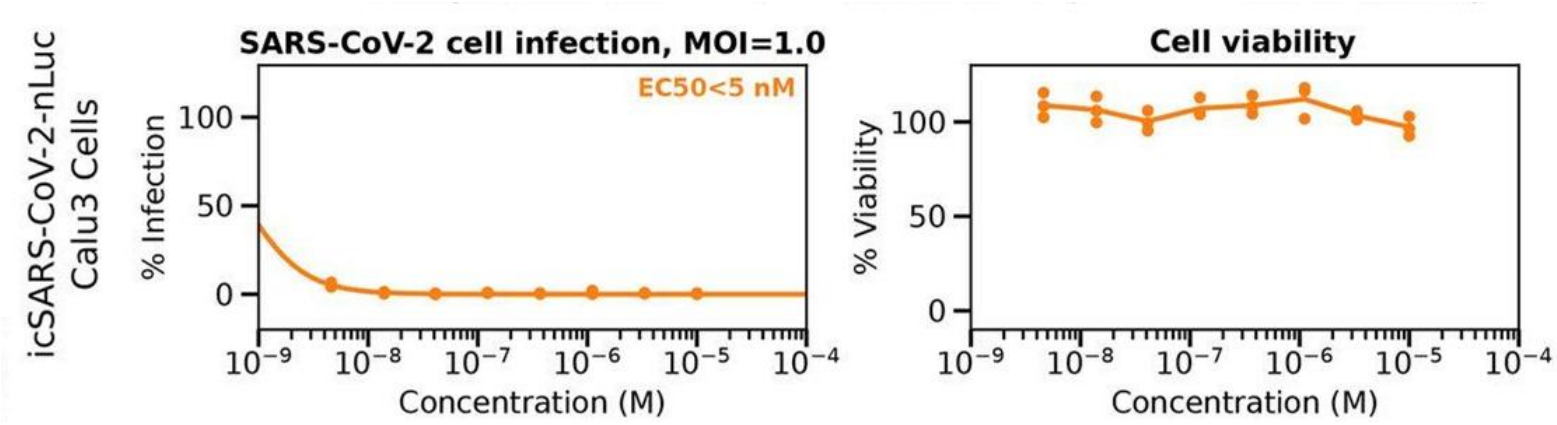
De novo design of potent and resilient hACE2 decoys to neutralize SARS-CoV-2



Science AAAS

T. W. Linsky et. al. Science. 10.1126/science.abe0075 (2020)

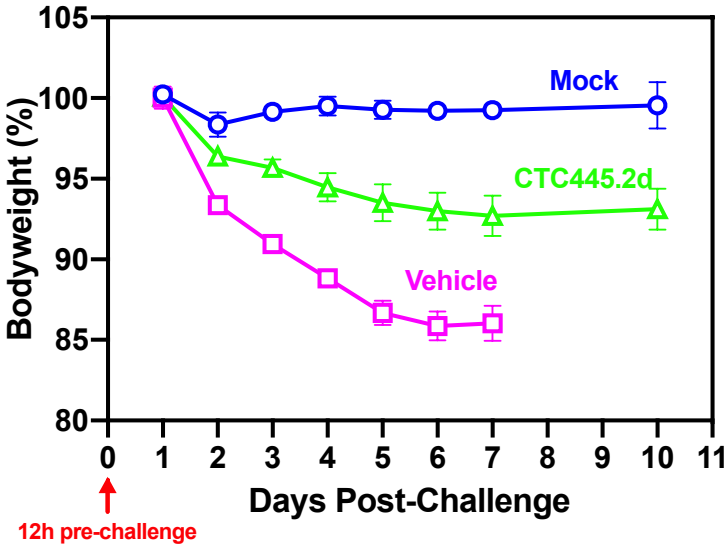
NL-CVX1 Inhibits SARS-CoV-2 Infection of Lung Cells In Vitro

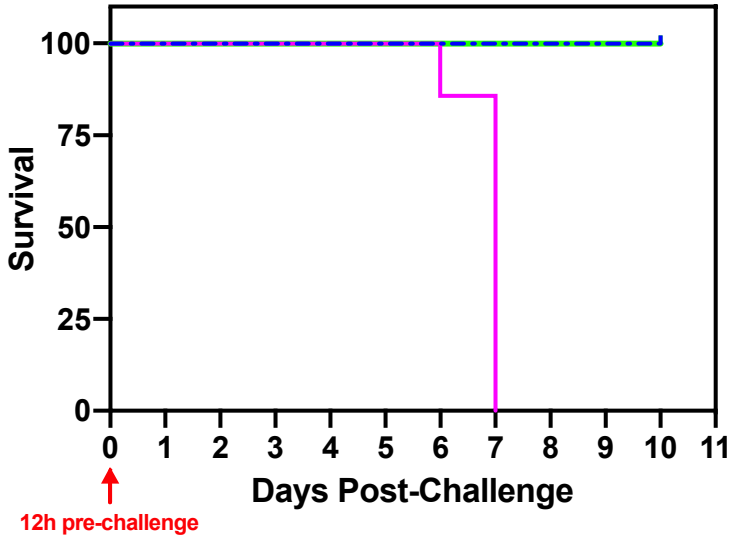


- NL-CVX1 demonstrates potent inhibition of infection by SARS-CoV-2
- No impact observed on cell viability

Linsky et. al. Science. 10.1126/science.abe0075 (2020)

Single Dose of NL-CVX1 Rescues Animals from Lethal SARS-CoV-2 Challenge





- Syrian hamsters received intra-nasal CTC445.2d 12h prior to SARS-CoV-2 viral challenge
- Vehicle group did not receive CTC445.2d
- Mock animals were not infected

Linsky et. al. Science. 10.1126/science.abe0075 (2020)

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Anticipated Milestones

Event	Timeline
Update on NL-CVX1 program	2H2021
Initiation of NL-201 local administration trial	2H2021
Report on *de novo* cytokine mimetic pipeline	2H2021
NL-201 Phase 1 clinical trial: interim data	1H2022

Financial Highlights

- $178.4 million cash & cash equivalents as of March 31, 2021
- Cash and cash equivalents expected to fund operations into 2023
- 42.3M common shares outstanding and 12.7M pre-funded warrants[1]

[1] Warrants to purchase common shares 1:1 with an exercise price of $0.000001 as of March 31, 2021.

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