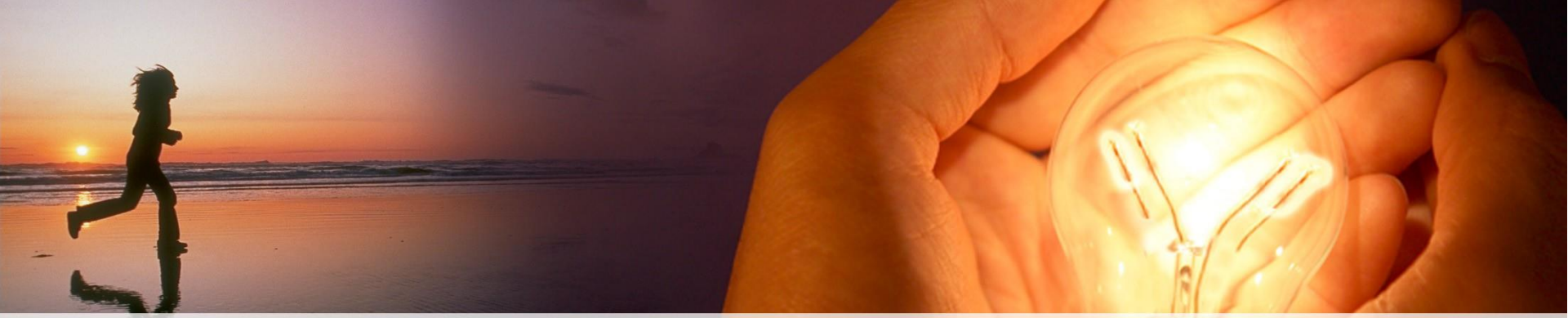


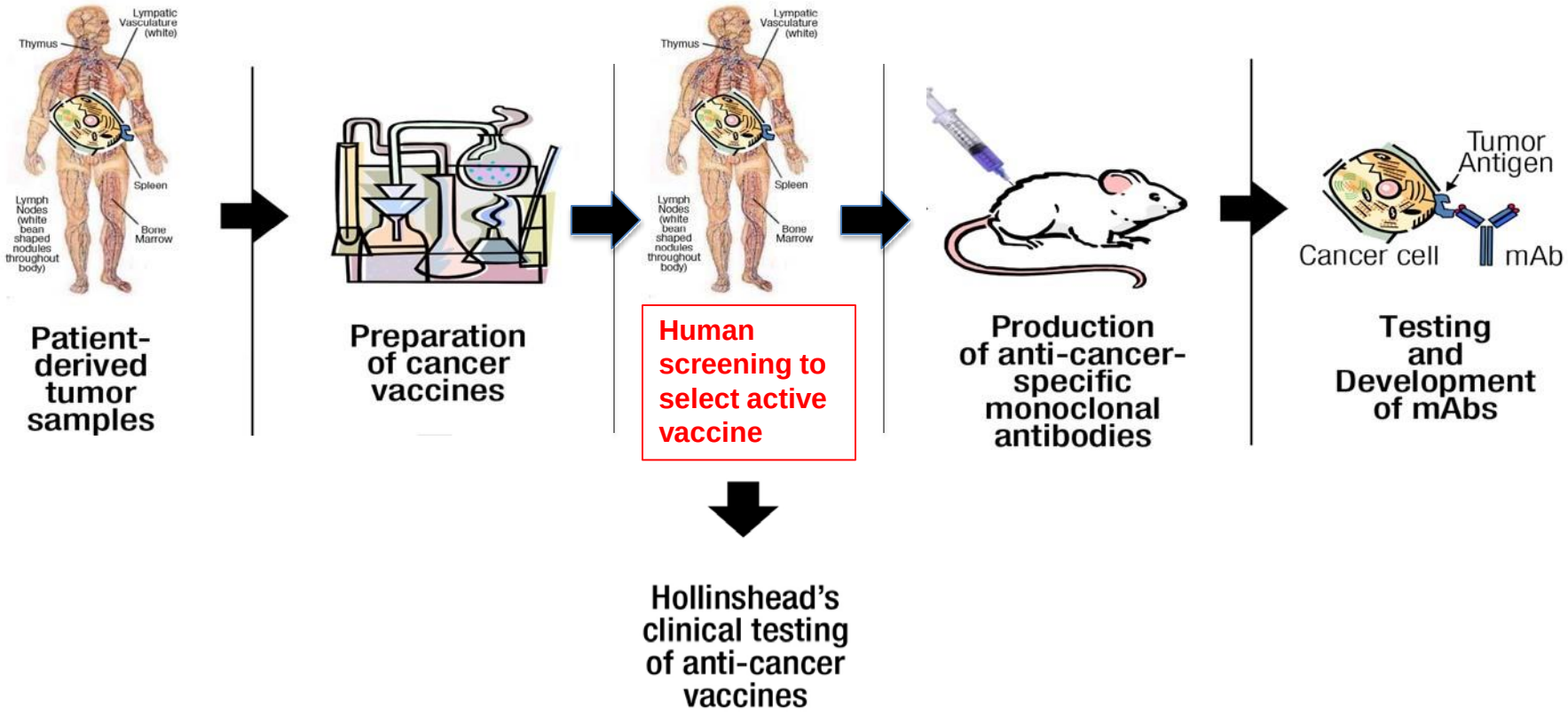
PRECISION BIOLOGICS

Discovery of novel mAbs targeting Solid Tumor Neoantigens

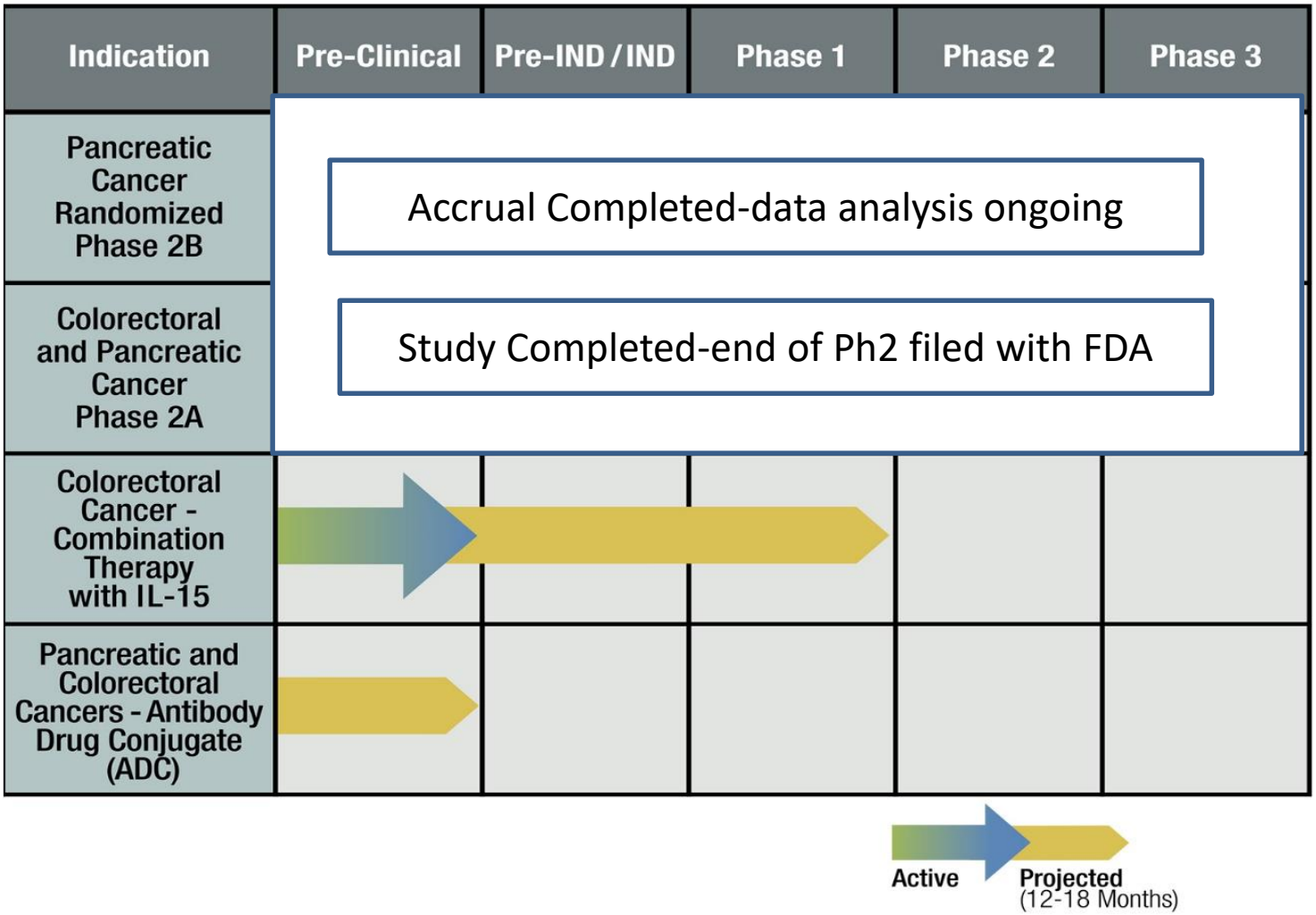
Philip M. Arlen, M.D.

March 3, 2020

Only Human Derived & Human Tested Neo-antigen Platform to Create Novel Therapeutics

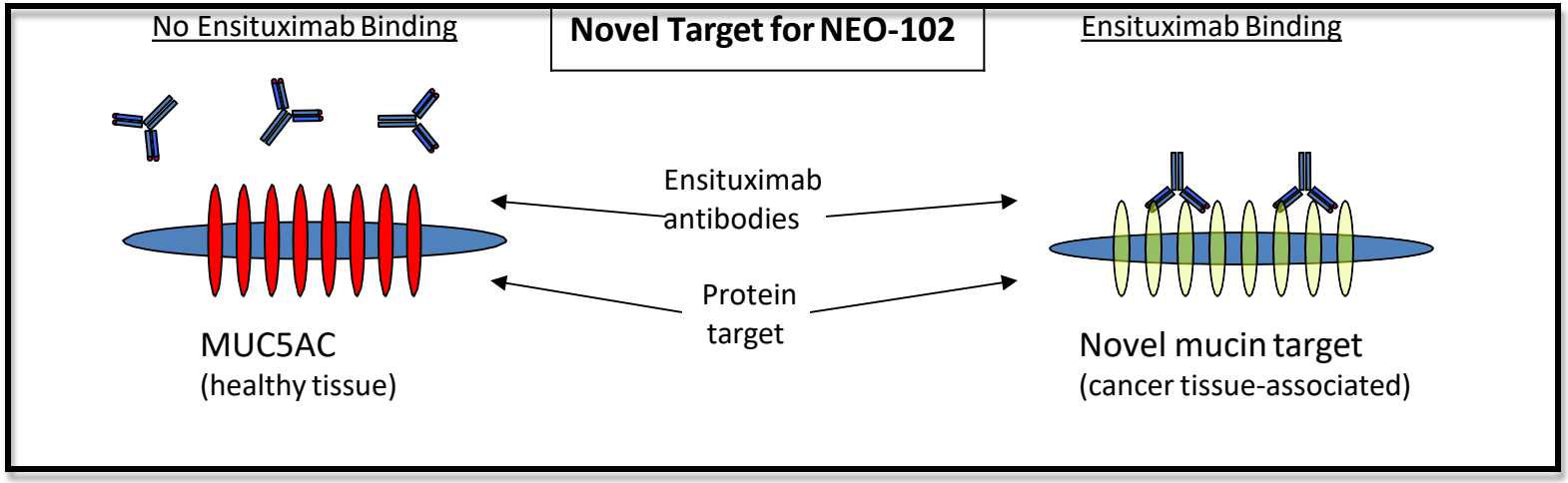


Pipeline for NEO-102



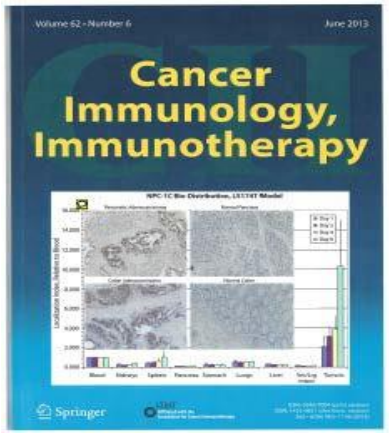
Ensituximab (NEO-102) Binds to *Novel Cancer Target*

- Novel monoclonal antibody that specifically recognizes colorectal and pancreatic cancer.
- Recognizes a novel target which is a member of the mucin family of proteins, similar to BUT distinct from MUC5ac.
- Our novel target is not present in healthy tissues.



Ensituximab Highlighted on Cover of Cancer Immunology, Immunotherapy

June 2013

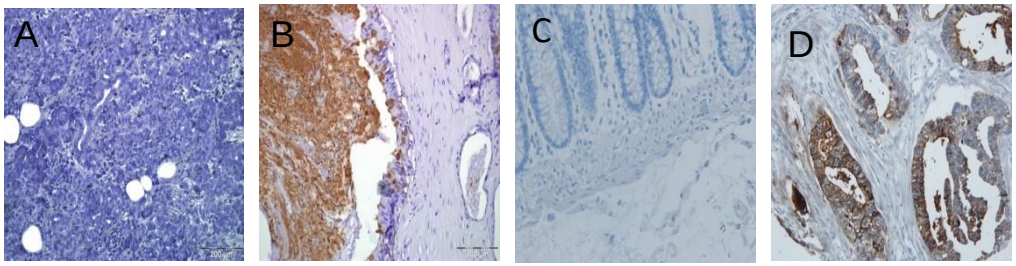


Cancer Immunol Immunother (2013) 62:1011–1019
DOI 10.1007/s00262-013-1420-z

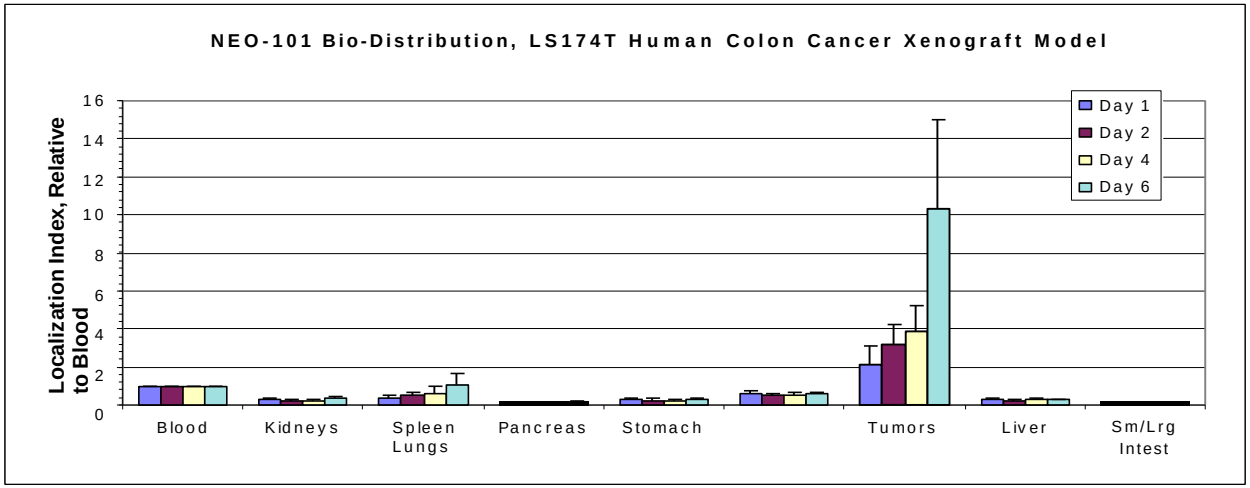
Additional publications:

- J Biomed Biotechnol. 2011;2011:934757
- Curr Drug Deliv. 2012 Jan;9(1):52-6
- Cancer Chemother Pharmacol. 2016 Sep;78(3):577-84
- Future Oncol. 2017 Oct;13(25):2209-2211

Anti-tumor activity of a novel monoclonal antibody, NEO-102, optimized for recognition of tumor antigen in preclinical models



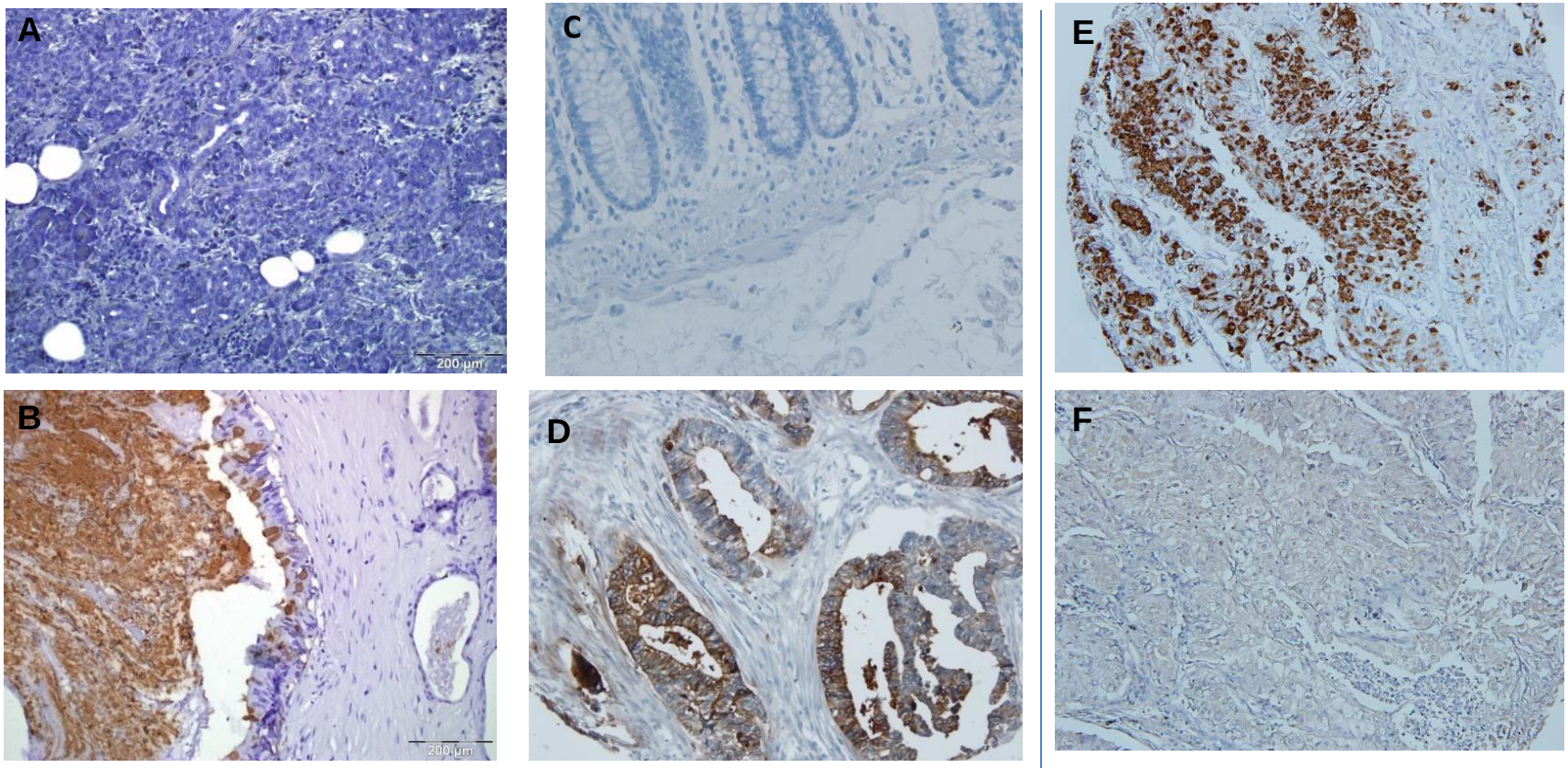
A) Normal pancreas
B) Pancreas adenocarcinoma
C) Normal Colon
D) Colon Cancer



Mice with pre-established human colorectal tumors (LS174T) were injected iv with I-125 labeled NEO-101; mice were sacrificed on the indicated days and radioactivity was measured in selected tissues

1. NPC-1 Antigen and Epitope

Tissue-Specific Staining with Ensituximab (NEO-102)



A) Normal pancreas

B) Pancreas adenocarcinoma

C) Normal Colon

D) Colon Cancer

E) Lung Cancer (anti-MUC5AC)

F) Lung Cancer (NEO-102)

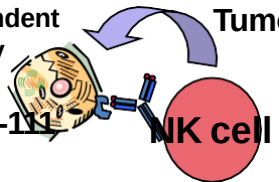
PRECISION BIOLOGICS

Tumor Cell Killing Activity- Antibody Dependent Cell Mediated Cytotoxicity (ADCC) of (NEO-102)

Tumor Cell Line	% Specific Killing (± SEM)		
	Eff/Target Ratio	Control mAb	NEO-101
Colo-205 (Colorectal)	50:1	9.8 ± 1.9	66.7 ± 0.6
	25:1	0.8 ± 1.2	46.4 ± 1.6
	12.5:1	-0.5 ± 0.1	32.8 ± 2.0
SW620 (Colorectal)	50:1	1.6 ± 0.2	63.7 ± 2.9
	25:1	3.5 ± 1.8	61.0 ± 1.8
	12.5:1	0.0 ± 0.3	51.5 ± 0.9
SW1463 (Colorectal)	50:1	0.1 ± 1.1	33.8 ± 1.0
	25:1	-1.3 ± 0.2	25.5 ± 0.6
	12.5:1	-1.2 ± 0.1	17.9 ± 1.7
LS174T (Colorectal)	50:1	-1.2 ± 0.1	26.8 ± 2.9
	25:1	-0.8 ± 0.1	18.5 ± 4.1
	12.5:1	-1.1 ± 0.0	9.5 ± 0.5
AsPC-1 (Pancreatic)	50:1	-0.8 ± 2.9	44.5 ± 6.8
	25:1	-7.0 ± 2.2	36.2 ± 2.6
	12.5:1	-1.2 ± 0.9	26.5 ± 6.7

Tumor Cell Line	% Specific Killing (± SEM)		
	Eff/Target Ratio	Control mAb	NEO-101
CFPAC-1 (Pancreatic)	50:1	-1.2 ± 2.3	26.9 ± 1.6
	25:1	-2.4 ± 0.1	23.2 ± 2.2
	12.5:1	-2.0 ± 0.4	11.1 ± 1.6
PANC-1 (Pancreatic)	50:1	-2.2 ± 0.4	46.8 ± 2.1
	25:1	-2.5 ± 0.4	33.2 ± 3.3
	12.5:1	-3.9 ± 0.3	21.2 ± 0.6
SK-MEL (Melanoma)	50:1	2.7 ± 0.7	4.6 ± 1.1
	25:1	1.5 ± 0.3	3.3 ± 1.1
	12.5:1	1.6 ± 0.4	2.3 ± 0.6
DU145 (Prostate)	50:1	-0.3 ± 0.2	-0.5 ± 0.3
	25:1	-0.7 ± 0.1	0.3 ± 0.8
	12.5:1	-0.2 ± 0.2	-0.3 ± 0.1

ADCC:
Antibody-dependent
Cell cytotoxicity



NEO-102 Phase 1/2 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Compelling Safety Results

Treatment Related Adverse Events seen in more than 2% of partcipants		
Adverse Event	Grade 3 or higher AEs	All AEs
Anemia	8%	32%
Hemolysis		5%
Tachycardia		3%
Constipation		8%
Diarrhea		6%
Nausea		13%
Vomiting		10%
Chills		8%
Fatigue	3%	37%
Fever		8%
Allergic reaction		3%
Blood Bilirubin increased	5%	13%
Weight loss		3%
Decreased appetite		5%
Dizziness		3%
Headache		6%
Dyspnoea		6%
Flushing		13%

NEO-102 Phase 1/2 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Patient Summary

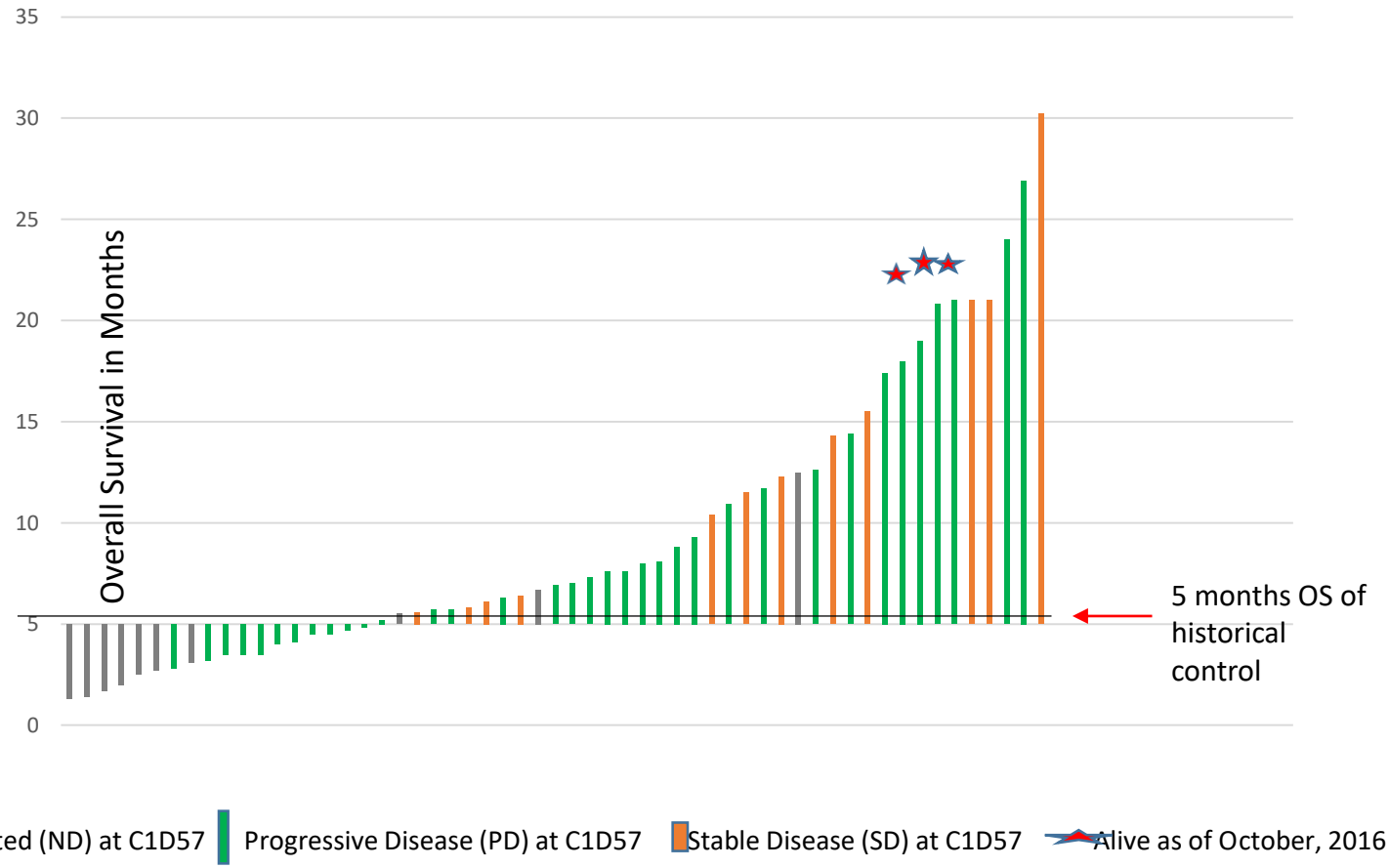
Phase 1 and 2:

- 63 patients with recurrent or metastatic recurrent colorectal cancer received at least 1 dose of NEO-102
- Gender: 35 male (56%), 28 female (44%)
- Age: range 32-83, median 60 years
- Number of Prior Therapies: range 1-9, average 3.7, **median 4.0**
- Number of doses of NEO-102: range 1 – 16, average 4
- Overall survival (OS) of patients with colorectal cancer enrolled in Phase 1/2 who were evaluable for response (57 patients received ≥ 2 doses of NEO-102):
  - ✓ 6.8 months (range 1-30 months after start of therapy)
  - ✓ OS >35% longer than historical control
  - ✓ 15 patients lived greater than 1 year from start of therapy
  - ✓ 3 patients remained alive (20-21 months after start of therapy)

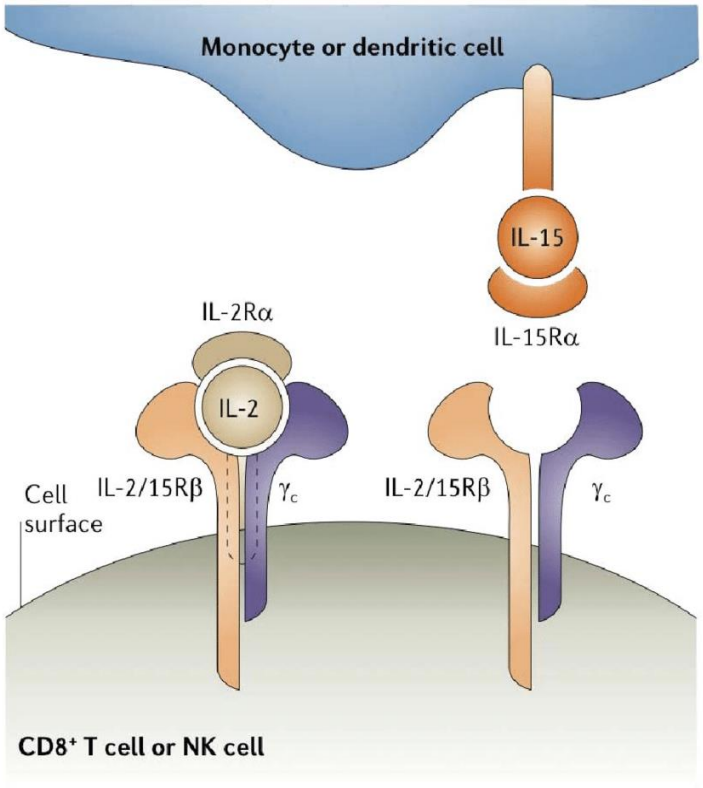
Promising efficacy with Significantly less toxicity than current 3rd line therapies

Overall Survival of Evaluable Colorectal Cancer Patients (≥ 2 doses of NEO-102) in NEO-0901 Compared with 5 months OS in the CORRECT Study (Grothey, et al. 2013)

Impressive OS Tail with 30% patients alive > 10 months



NK cell antitumor activity can be modulated by IL-15



The cytokine interleukin-15 (IL-15) plays a crucial role in the immune system by affecting NK cell development, proliferation, cytotoxicity, and cytokine production.

IL-15 binds to the IL-15Rα present on the surface of monocytes or dendritic cells and is presented to NK and CD8+ T cells where it forms a complex with IL-15Rβ to activate several intracellular signaling pathways.

Cancers **2011**, *3*, 3856-3893

IL-15 enhances NEO-102-mediated ADCC activity

		% specific lysis (SD) (Donor 1)		% specific lysis (SD) (Donor 2)	
Antibody	**E:T ratio**	Untreated	IL-15 superagonist	Untreated	IL-15 superagonist
IgG1	12.5:1	7.7 (1.21)	9.5 (2.5)	1.9 (0.7)	10.9 (1.3)
	6.25.1	-1.1 (1.85)	5.8 (5.5)	-0.6 (3.8)	1.7 (4.6)
NEO-102	12.5:1	14.1 (3.9)	**22.1 (1.4)***	1.6 (4.2)	**19.7 (0.4)***
	6.25.1	7.2 (4.7)	4.3 (4.1)	2.1 (0.6)	**11.4 (1.7)***

NK cells isolated from three normal donors were treated with IL-15 superagonist (25ng/ml) or medium control (untreated) for 48 hours prior to be used as effector cells in a 4h non-radioactive ADCC assay using Celigo Imaging cytometer.

CFPAC-1 (human pancreatic cancer cell line) cells were stained with calcein AM and used as targets at 3,000 cells/well.

Results are expressed in % specific lysis (SD).

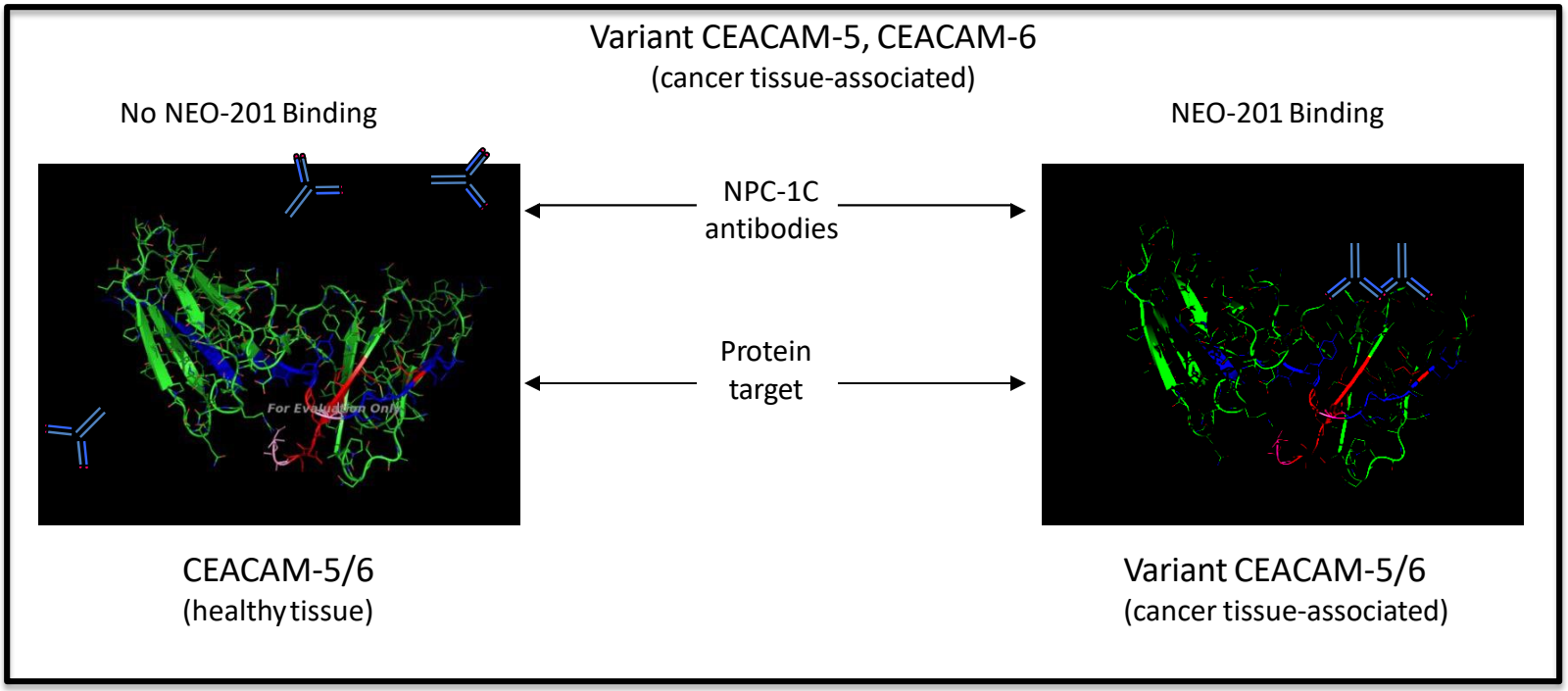
* Statistically significant ($p < 0.05$) by Student's t-test (NEO-102 + IL-15 superagonist vs NEO-102 untreated

NEO-102 Planned Studies

- **Phase 2b Clinical Trial NEO-102 in combination with IL-15** – 3rd line therapy for metastatic colon cancer – 2nd half of 2020
  - Preclinical testing supports combination through enhanced NK killing through ADCC in presence of both IL-15 and NEO-102
  - Clinical Sites: Moffitt Cancer Center, National Cancer Institute (NCI), University Texas Southwestern (UTSW) Medical Center
  - **Data readout late 2021**

- Development of **antibody drug conjugate (ADC)** using NEO-102
  - Affinity maturation studies underway with NEO-102
  - **No off-target** effect of NEO-102 observed in >100 patients treated on clinical trials
  - Outstanding safety profile
  - **File IND and commence Phase 1, 1st half 2022**

NEO-201 Target

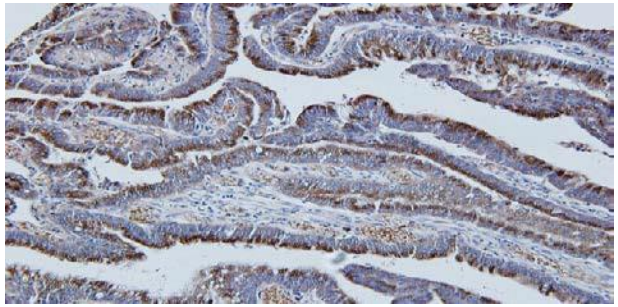


- NEO-201 recognizes tumor-specific variants of CEACAM-5 and CEACAM-6, members of the carcinoembryonic antigen (CEA) family of proteins. These proteins are expressed in normal epithelial tissues, and over-expressed in many solid tumor types (colon, pancreatic, breast, lung, ovarian)
- NEO-201 does not cross-react significantly with healthy tissues that express normal CEACAM-5 or CEACAM-6

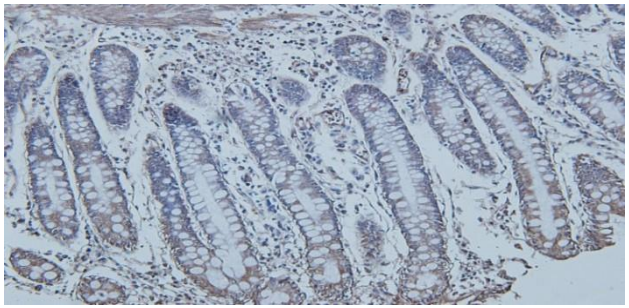
Comparison Binding Specificity of NEO-201 with Commercial CEACAM-5/6 Antibodies by IHC

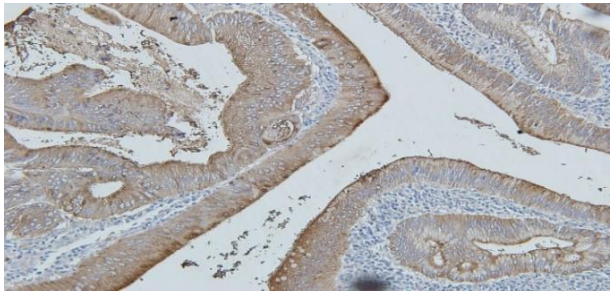
Colon cancer

Normal Colon

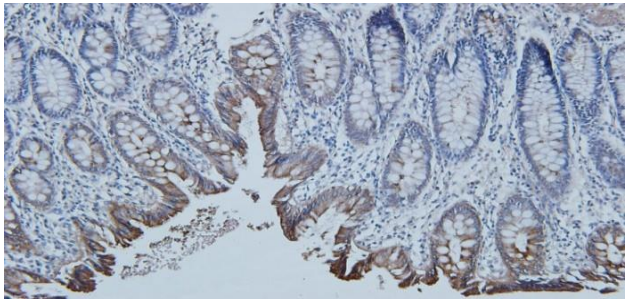


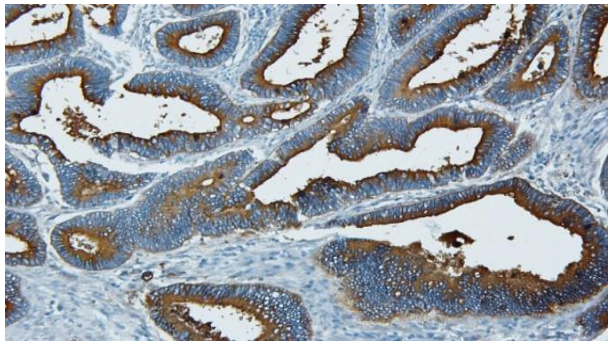
Anti-CEACAM-6
(9A6 from Cell Signal)



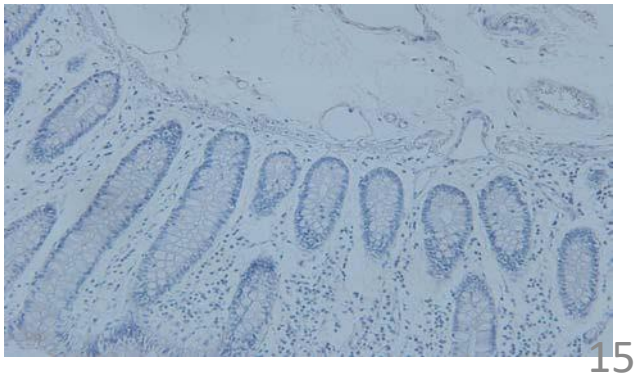


Anti-CEACAM-5
(CB30 from Abcam)



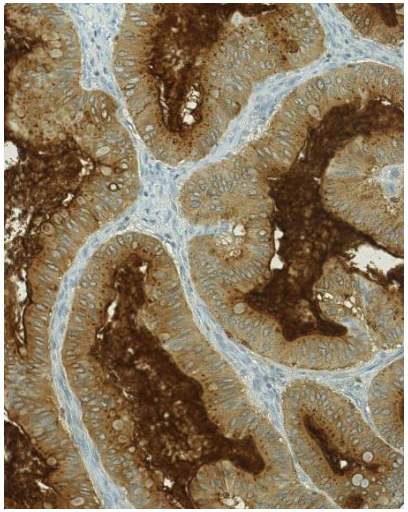


NEO-201

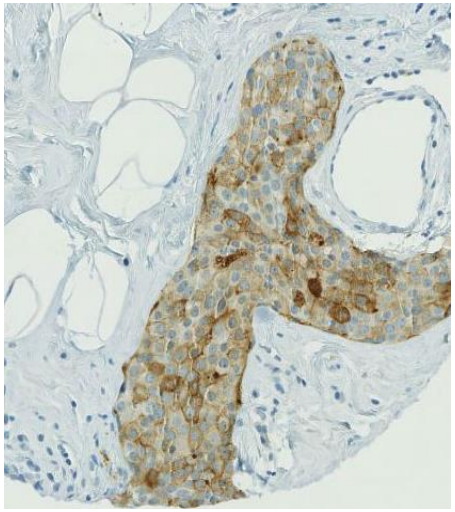


Collaborative Research Project – Precision Biologics and Christina Annunziata, MD, NCI

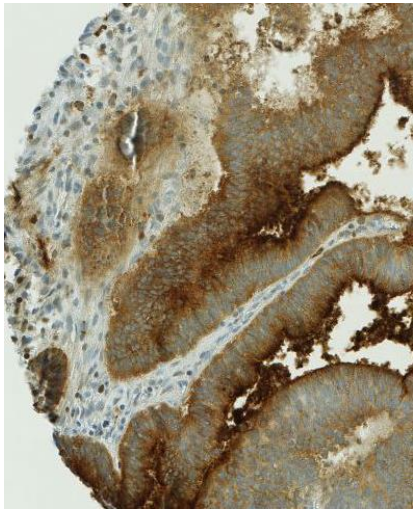
- Binds to tumor-associated antigen
- Minimal binding to healthy tissue



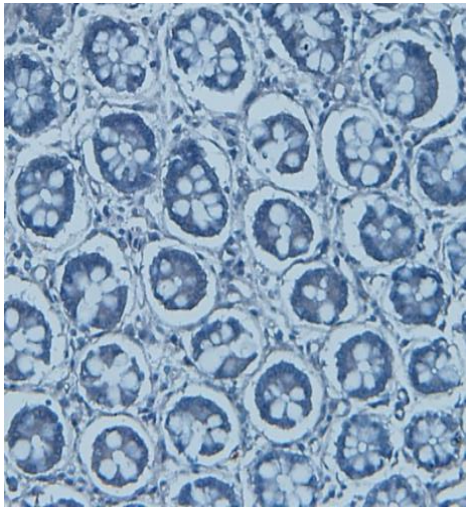
Ovarian Cancer



Breast Cancer



Colon Cancer



Normal colon

Multiple Mechanisms of Action of a Neoepitope-Targeting Antibody NEO-201

Direct Tumor Killing

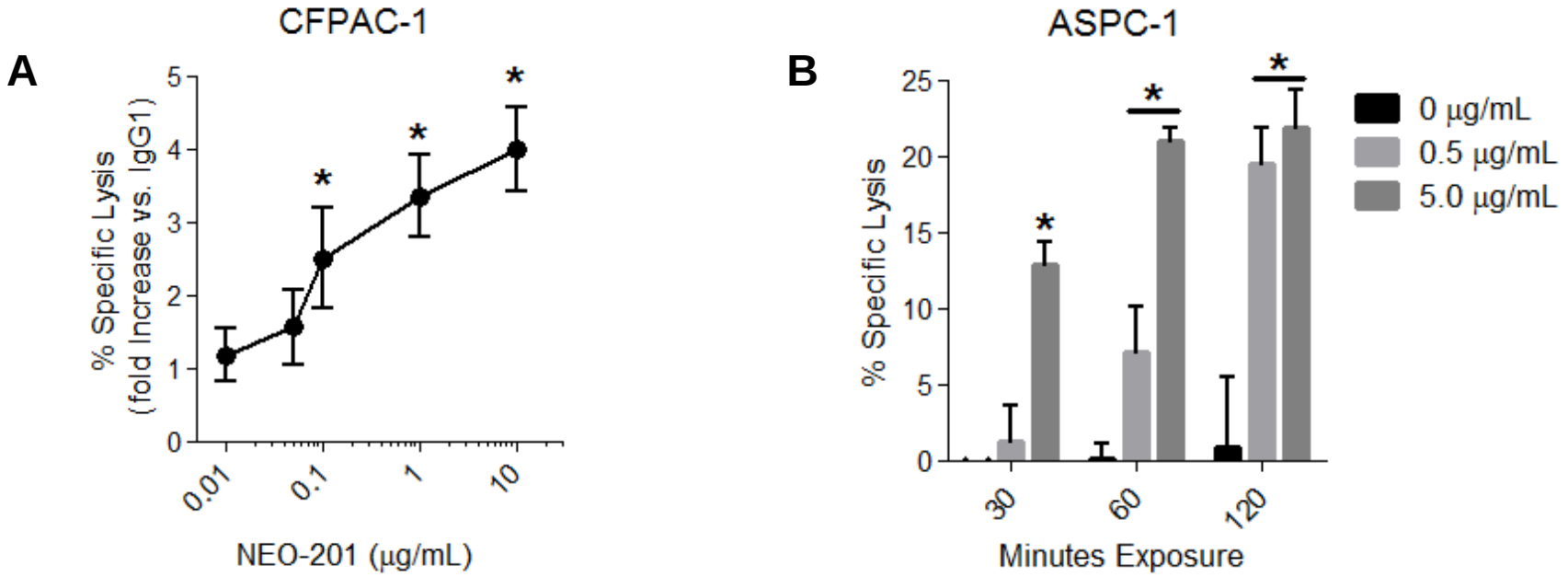
1. Antibody dependent cell-mediated cytotoxicity (ADCC)
2. Complement dependent cytotoxicity (CDC)

Killing through Immune enhancement

1. Enhanced NK tumor killing through CEACAM5/CEACAM1 binding inhibition
2. Binding and killing of human regulatory T cells (Tregs)

- NEO-201 ADCC activity enhanced with IL-15
- Multiple peer review publications available on request

NEO-201 mediates ADCC and CDC against human tumor cells



(A) ADCC assay using CFPAC-1 cells treated with increasing doses of NEO-201. NK cells isolated from a healthy donor were used as effector cells at an E:T ratio of 12.5:1. The graph depicts the fold increase in % specific lysis of NEO-201-treated tumor cells versus that of control cells treated with 10µg/mL human IgG1. (*, statistically significant ($p < 0.05$) by T-test.)

(B) CDC assay using ASPC-1 cells treated with rabbit complement (1:8 dilution) and the indicated doses of NEO-201 for the indicated durations. (*, statistically significant ($p < 0.05$) by T-test.)

NEO-201 mAb enhances NK-92 cell cytotoxicity against CEACAM5+ / NEO-201+ tumor cells

CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 00, Number 00, 2020

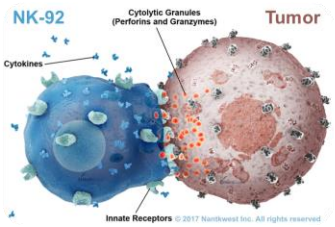
DOI: 10.1089/cbr.2019.3141

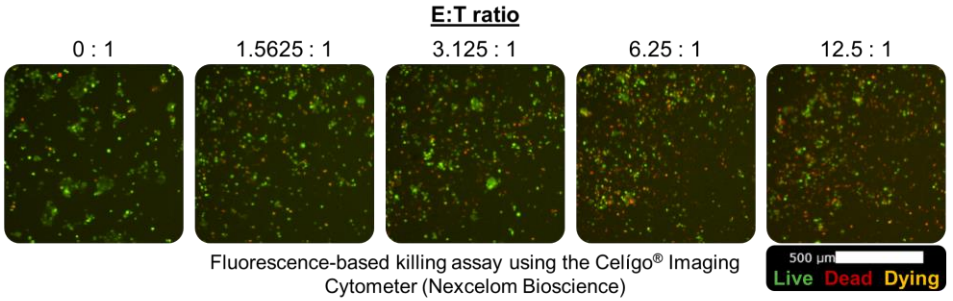
The Monoclonal Antibody NEO-201 Enhances Natural Killer Cell Cytotoxicity Against Tumor Cells Through Blockade of the Inhibitory CEACAM5/CEACAM1 Immune Checkpoint Pathway

Massimo Fantini,[1,*] Justin M. David,[1,*] Christina M. Annunziata,[2] Maria Pia Morelli,[2] Phillip M. Arlen,[1] and Kwong Y. Tsang[1]

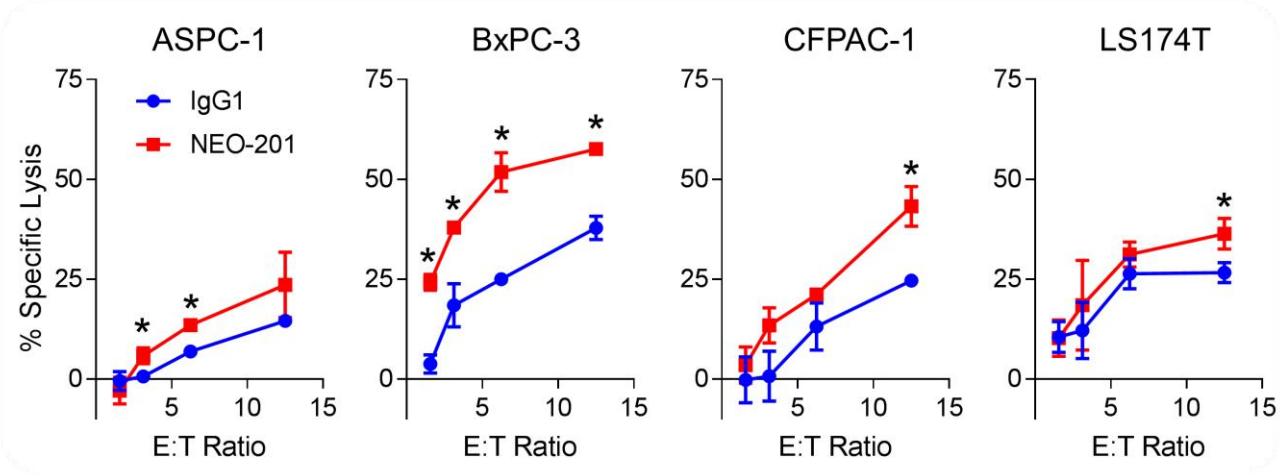
Mechanism of Action: NEO-201 mAb enhances NK-92 cell cytotoxicity against CEACAM5+ / NEO-201+ tumor cells

NK-92 16hr Killing Assay -/+ NEO-201 mAb





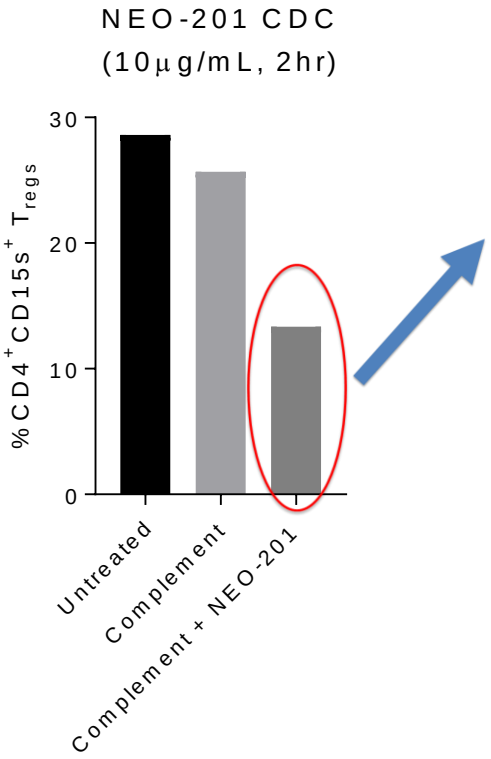
Fluorescence-based killing assay using the Celígo® Imaging Cytometer (Nexcelom Bioscience)



ASPC-1	BxPC-3	CFPAC-1	LS174T
High NEO-201 antigen Low CEACAM5 High CEACAM1	High NEO-201 antigen High CEACAM5 No CEACAM1	High NEO-201 antigen Low CEACAM5 Low CEACAM1	Low NEO-201 antigen Low CEACAM5 No CEACAM1
Poor enhancement of cytotoxicity	Strong enhancement of cytotoxicity	Some enhancement of cytotoxicity	Poor enhancement of cytotoxicity

Mechanism of Action: NEO-201 mediates CDC against human regulatory T-cells as determined by flow cytometry

Treatment	%CD4+CD15s+ Tregs
Untreated	28.60%
Complement	25.68%
Complement + NEO-201	**13.34%**



50 % killing compared to untreated cells

Complement ratio = 1:8, 2hrs
[mAb] = 10μg/mL

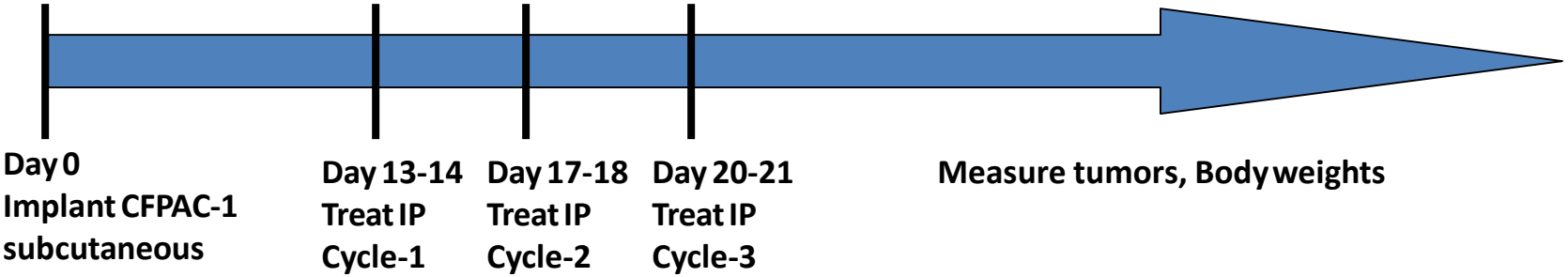
NEO-201 ADCC activity enhanced with IL-15

CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 00, Number 00, 2019
Mary Ann Liebert, Inc.
DOI: 10.1089/cbr.2018.2628

An IL-15 Superagonist, ALT-803, Enhances Antibody-Dependent Cell-Mediated Cytotoxicity Elicited by the Monoclonal Antibody NEO-201 Against Human Carcinoma Cells

Massimo Fantini,[1] Justin M. David,[1] Hing C. Wong,[2] Christina M. Annunziata,[3] Philip M. Arlen,[1] and Kwong Y. Tsang[1]

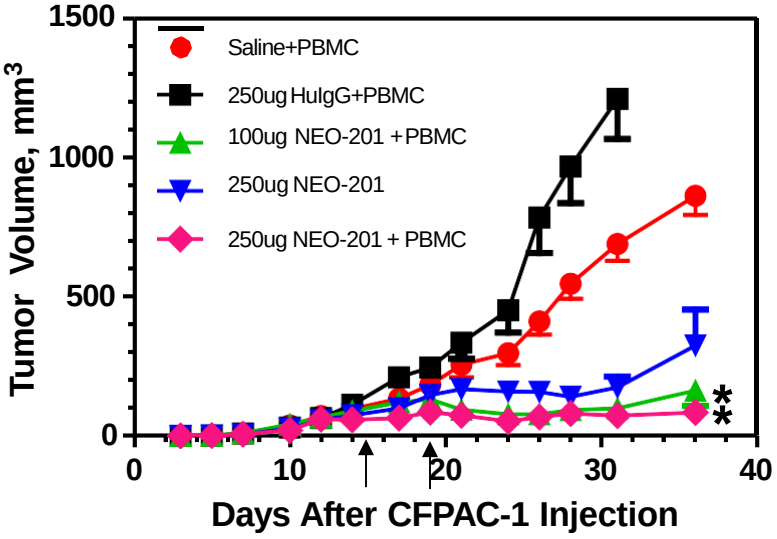
NEO-201(h16C3) Anti-tumor Efficacy in CFPAC-1 Tumor Xenograft Mouse Model



Group (n=10)	Antibody, dose	IL-2 Activated PBMC (NK cells)
1	Saline	~1x10^7
2	Human IgG, 250ug	~1x10^7
3	h16C3, 100ug	~1x10^7
4	h16C3, 250ug	No PBMC
5	h16C3, 250ug	~1x10^7

NEO-201 Anti-tumor Efficacy Results

NEO-201 Treatment of CFPAC-1 Tumor-Bearing Mice

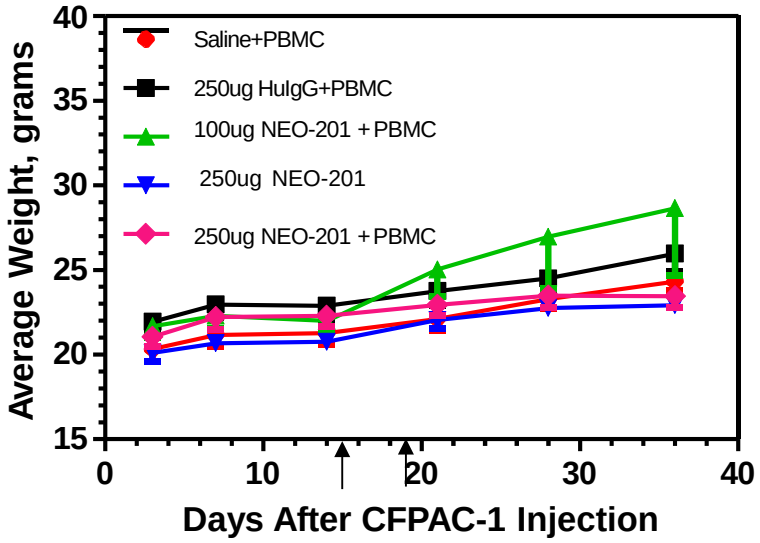


*, indicates $p<0.05$ vs. saline group

NEO-201 injected intraperitoneally on Days 13, 17, 20
PBMC injected intraperitoneally on Days 14, 18, 21

<u>On Day 36:</u>
100ug NEO-201+PBMC, 1/10 mice tumor-free
250ug NEO-201 +PBMC, 4/10 mice tumor-free

Body Weights, CFPAC-1 Tumor-Bearing Mice



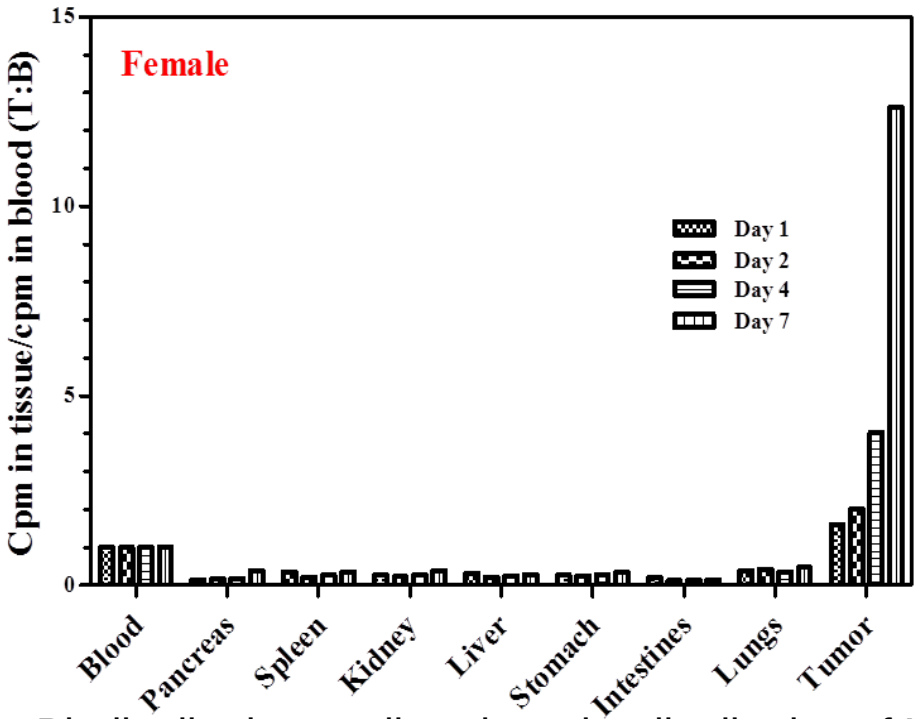
NEO-201 injected intraperitoneally on Days 13,17, 20
PBMC injected intraperitoneally on Days 14, 18,21

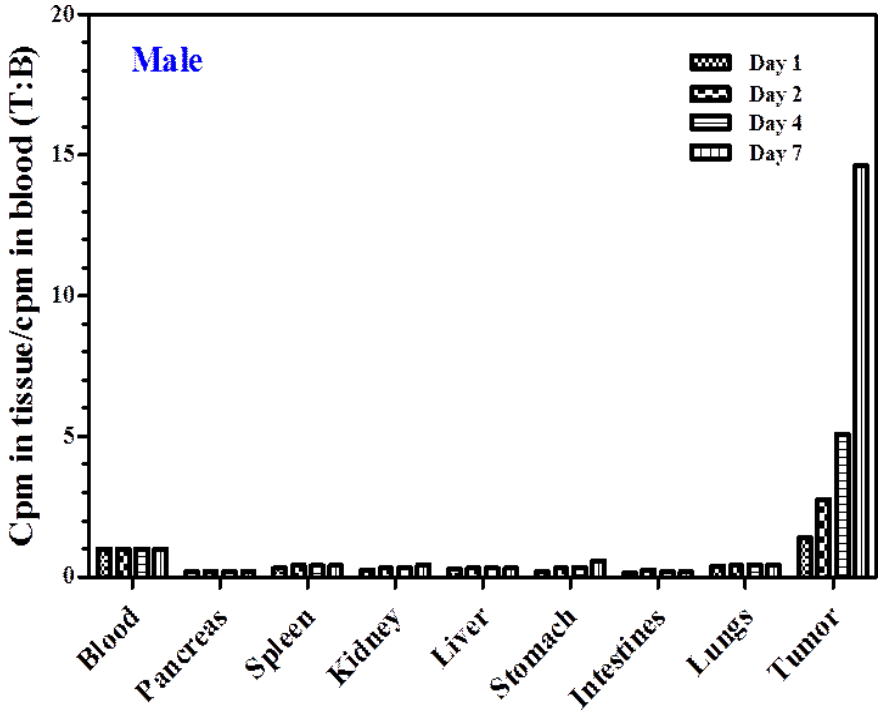
NEO-201 Anti-tumor Efficacy Results

NEO-201 treated mouse

Control/Saline treated mice

NEO-201 Biodistribution Studies



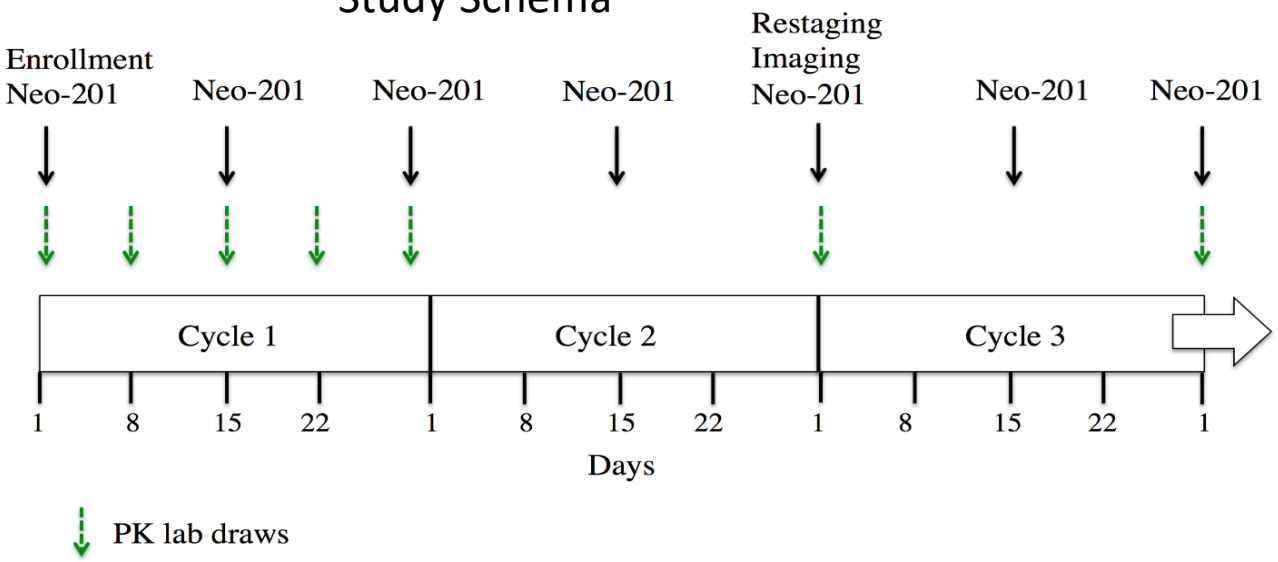


Biodistribution studies show the distribution of NEO-201 in male and female mice with pre-established CFPAC-1 tumors. The mice were injected via tail vein with 20uCi of [^{125}I] labeled NEO-201 monoclonal antibody and necropsied after 1, 2, 4 and 7 days. Blood and tumors were collected. The following organs were removed: lungs, kidneys, liver, spleen, pancreas, intestines, and stomach. All tissues were weighed. Radioactivity in tissues was measured in a gamma counter, and data were calculated as cpm/mg tissue. The data shown above represent the normalization of tissue cpm relative to blood cpm.

NEO-201 Ongoing Study

- NEO-201- 1st in human studies will treat patients with colon ca, pancreatic ca, breast ca, NSCLC, and mucinous ovarian ca, who are no longer eligible for standard therapy .
- Phase I first in human study at NCI, open label, dose escalation study to determine safety and recommended phase 2 dose (RP2D) in patients with refractory cancers expressing NEO-201 antigen. RP2D will be explored in expansion cohorts in several targeted disease states at multiple centers.

Study Schema



NEO-201 Ongoing Study

- Phase I first in human study at NCI:
  - Planned doses:

Dose Escalation Schedule		
Dose Cohorts	**Dose of IND Agent (mg/kg)**	**Number of Subjects planned for enrollment**
Level 1	1	3 - 6
*Level 1.5***	*1.5*	*3-6*
Level 2	2	3 - 6
*Level 2.5***	*3*	*3-6*
Level 3	4	3 - 6
*Level 3.5***	*5*	*3-6*
Level 4*	6	3 - 6
*additional doses may be investigated if no DLTs or clinical activity is observed. ** dose de-escalation cohorts		

  - Correlative studies to include:
    - Cellular immune monitoring assays (phenotype and functional [killing and suppression] assays with NK, Treg and MDSC; CD16 phenotype of NK cells);
    - Humoral immune monitoring assays (multi-plex cytokine and chemokine analysis; soluble factors such as MICA, arginase, soluble PD-1 and soluble PD-L1 and IDO, *in vivo* assay- HAHA analysis)

NEO-201 Planned Studies

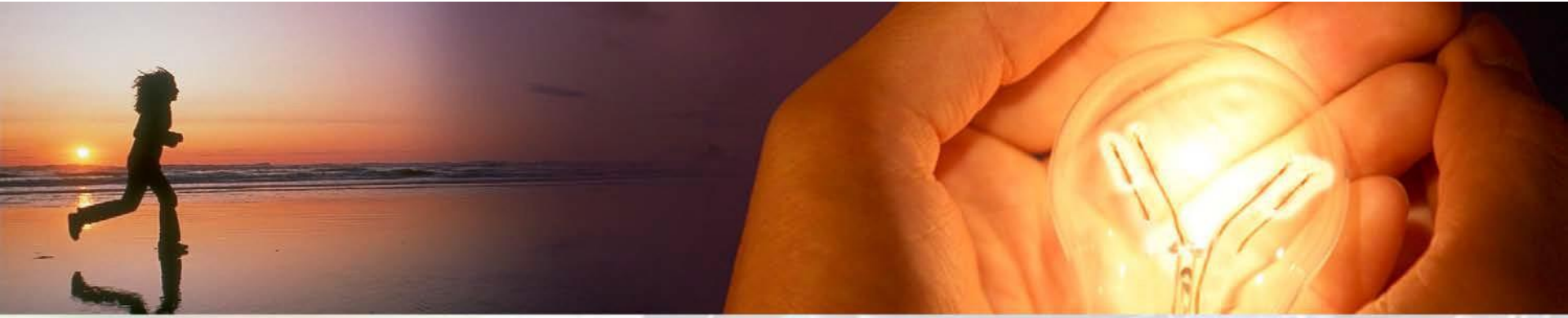
- **3 independent monotherapy Phase 2 Clinical Trials NEO-201 in refractory solid tumors (i.e colorectal ca, pancreatic ca, mucinous ovarian ca) expressing antigen– initiating 2nd half of 2020**

- **Clinical Trial in checkpoint refractory (pembro) NSCLC Phase 1/2b using 2nd line checkpoint (nivo) in combination with NEO-201- initiating 2nd half 2020**
  - Preclinical data/patent supports NEO-201 destruction of Tregs and CEACAM-1/CEACAM-6 interaction blockade
  - Should improve checkpoint activity

- **NEO-201 Phase 2 therapy in refractory Multiple myeloma –initiating 2nd half 2020**
  - Preclinical data supports binding and killing of tumor with NEO-201 antibody

Company Pipeline

Product	Indication	Pre-Clinical	Pre-IND / IND	Phase 1	Phase 2	Phase 3
NEO-201	Solid Tumors ± IL-15					
Checkpoint Refractory NSCLC-Combo NEO-201	Checkpoint Therapy					
NEO-201	Multiple Myeloma					
NEO-102	Colorectoral Cancer - Combination Therapy with IL-15					
NEO-102	Pancreatic and Colorectoral Cancers - Antibody Drug Conjugate (ADC)					



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