



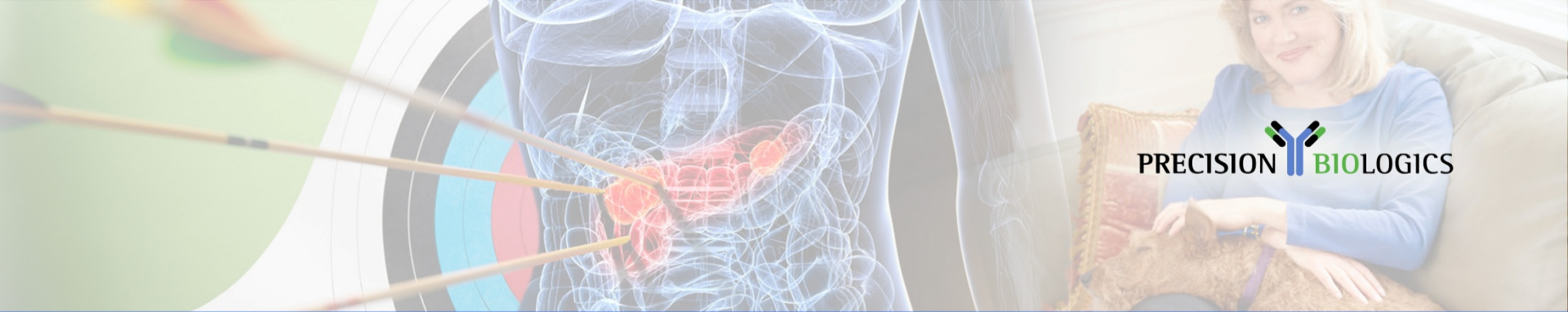
# PRECISION BIOLOGICS

**Discovery And Development Of A Monoclonal Antibody  
Against A Novel Target For The Treatment Of Colorectal Cancer**

**Philip M. Arlen, MD**

16th Drug Discovery Summit and 3rd Discovery Chemistry & Drug Design Congress,  
June 8-9, 2015



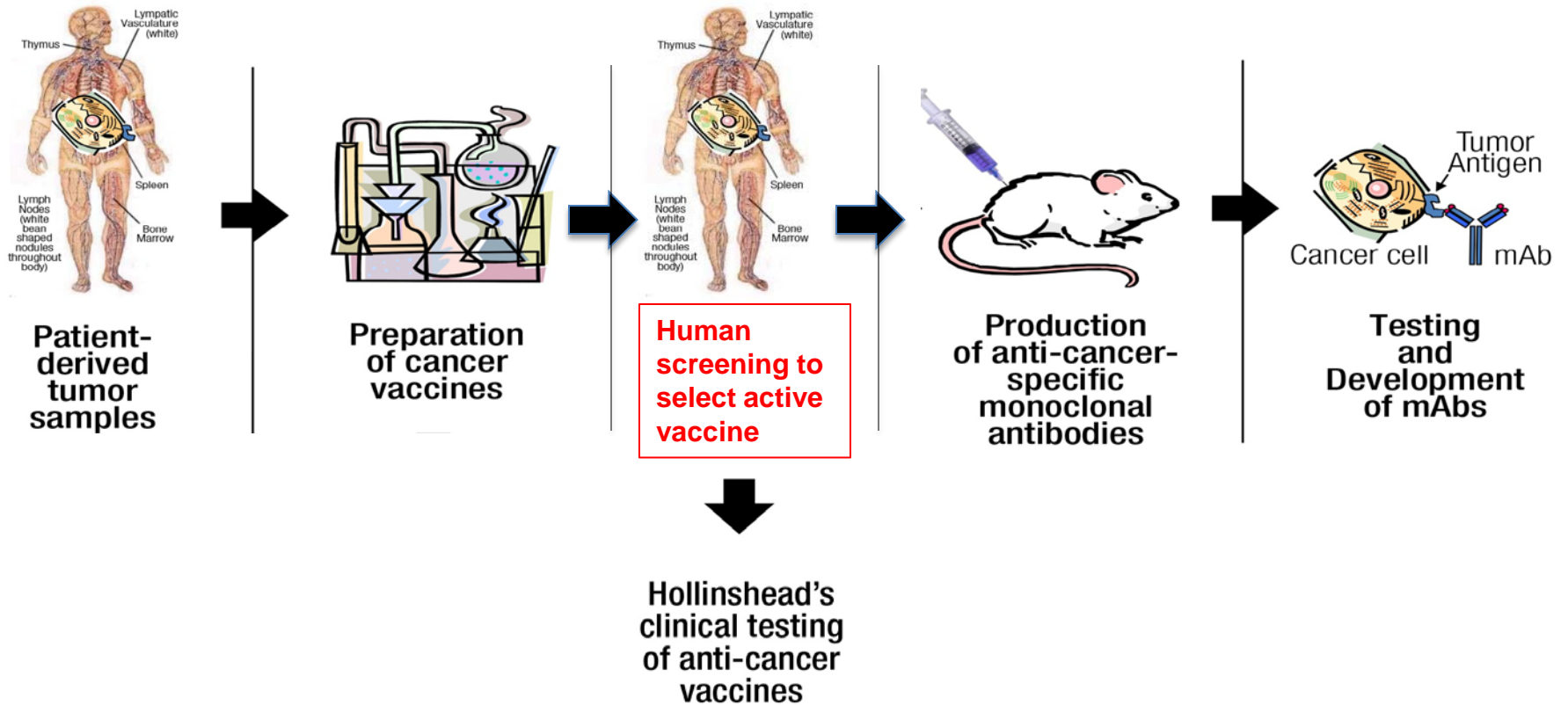


Precision Biologics is a biopharmaceutical company  
developing **tumor-specific**  
**monoclonal antibodies** and  
**companion diagnostics** to  
treat solid-tumor cancers.

# Developing specific monoclonal antibodies to proprietary solid tumor targets

- Unique, proprietary targets isolated from surgically resected human tumor tissue
  - Targets mediating clinical efficacy based on historical tumor-vaccine data
  - Proprietary companion diagnostics -based patient selection
- Targeting solid tumors lacking appropriate treatment
  - **Lead candidate NEO-102: accrual completed-multi-center Phase 2 colorectal cancer study in patients with chemotherapy- refractory disease**
  - **Dose escalation study demonstrated median overall survival of 10.4 months (range 40 days to 615+ days) vs 5.0 historical controls to date**
  - **NEO-102: Orphan drug status for pancreatic cancer**
  - **NEO-102: promising early phase 2 data in pancreatic cancer**
  - Pipeline with two additional novel, proprietary antibodies
- Near term value inflection point
- Highly experienced team: CEO, Medical Oncologist at the NCI, working with leading PI's in US Centers of Excellence (Johns Hopkins University Hospital, Duke University Medical Center, National Cancer Institute, Dana Farber Cancer Institute)

# Only Human Derived & Human Tested Platform to Create Novel Therapeutics



# The Precision Biologics Difference

**PBI's immunotherapeutic cancer drugs differ from other cancer drugs in several important ways:**

- **Most new cancer drugs are developed in a process that starts in the laboratory with previously analyzed, widely available proteins**
  - PB's antibodies are derived from the proprietary cancer vaccines isolated from surgically removed human tumors
- **PBI's therapies operate differently from other biologic and immune therapies, which may attempt either to block growth factors or to produce a general immune-system response**
  - PB's antibodies activate an immune response that specifically targets only tumors
- **Many new drugs appear to be effective in laboratory test tubes and in animals, but fail to achieve comparable success when administered to humans**
  - PBI's drugs, and their predecessors, the Hollinshead vaccines, have shown prolonged survival results with human patients in clinical trials
- **Chemotherapies and biological therapies can poison tumors, but produce significant toxicity as well, and immune therapies often result in development of auto-immune disorders i.e. colitis**
  - PBI's drugs bind only to antigens found exclusively in tumors and do not attack healthy tissue. No significant toxicities have been experienced with PBI's tumor-specific antibody in either laboratory or clinical trials

# Portfolio of proprietary targets and MoAbs

- An extensive library of tumor antigens derived from numerous solid tumors.
- Three novel antibody therapeutic candidates (NEO-102, NEO-201, NEO-301) have been discovered and patented - potential for dozens of more candidates.
- NEO-102 is currently in Phase 2a/2b clinical development: NEO-201 and NEO-301 are preclinical tumor specific monoclonal antibodies ready for development.
- Strong scientific/clinical collaboration network to advance clinical and companion diagnostic programs.
- Parallel program for development of Companion Diagnostic.
- Opportunities to leverage proprietary IP to develop novel products i.e. antibody drug conjugates (ADC), CAR T-cell, Bi-specific t-cell engagers (BiTEs) antibody being discussed





# Medical Need – Colorectal Cancer

- 2014 Estimated new cases: 96,830 (colon) and 40,000 (rectal); Estimated Deaths: 50,310 (colon and rectal combined).
- Greater than \$5 billion spent annually for metastatic colorectal cancer with the majority being spent in the US.
- Current treatment for 1<sup>st</sup> and 2<sup>nd</sup> line therapy includes chemotherapy with Avastin, and Erbitux and Vectibix for patients with EGFR wild type tumors.
- Current experimental compounds include: GDC-0941 and PX-866 (PI3K inhibitors), Mapatumumab (targeting TRAIL-R1) and Apomab (targeting TRAIL-R2), Oblimersen (Bcl-2 inhibitor), as well as several anti-VEGF antibodies.
- **Unlike current and investigational targeted therapies all Precision Biologics TSA antibodies specifically target the tumor.**
- Most patients will progress on 1<sup>st</sup> and 2<sup>nd</sup> line therapy- Regorafenib is FDA approved in 3<sup>rd</sup> line BUT offers minimal (6 week survival) improvement with significant side effects.
- Therefore a significant unmet need exists for our novel antibody drugs that specifically target tumor and spare normal cells with minimal side effects.

# Pipeline

Lead Candidate – NEO-102

- Multicenter Clinical Trials:
  - Phase 2a colorectal and pancreatic ( NEO-102 monotherapy)
  - Phase 2b: pancreatic (randomized Gemzar/Abraxane ± NEO-102)

Product	Indication	Pre-Clinical	Pre-IND/IND	Phase 1	Phase 2	Phase 3
NEO-102	Pancreatic Cancer Phase 2B					
NEO-102	Colorectal and Pancreatic Cancer Phase 2A					
NEO-201	Pancreatic, Colorectal and other Cancers					
NEO-301	Pancreatic, Colorectal and other Cancers					

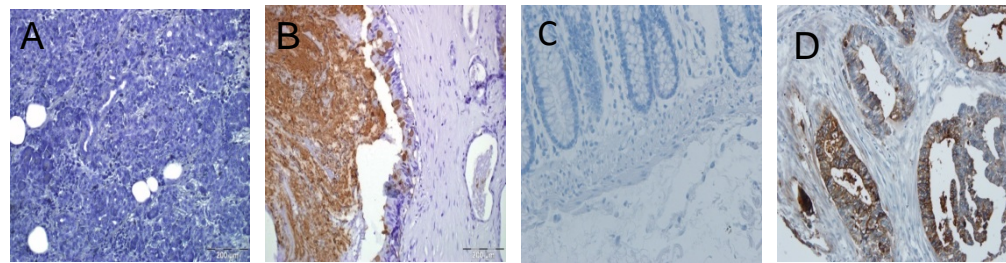
 Active  
 Projected



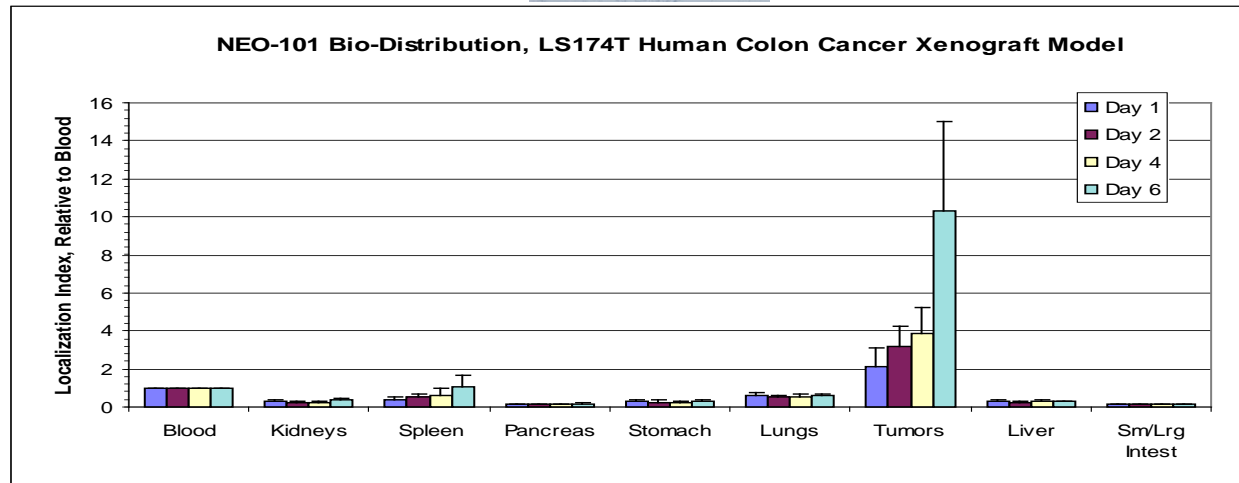
# Ensituximab Highlighted on Cover of Cancer Immunology, Immunotherapy

June 2013

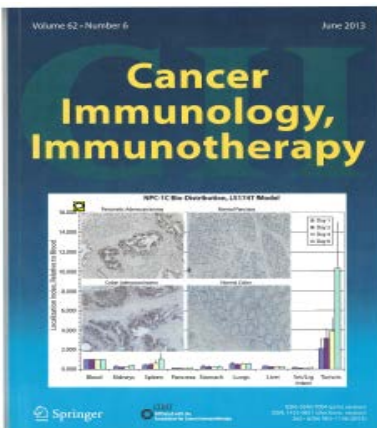
Anti-tumor activity of a novel monoclonal antibody, NEO-102, optimized for recognition of tumor antigen in preclinical models



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



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

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

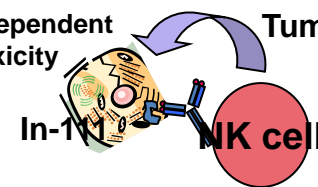
Tumor Cell Line	% Specific Killing ( $\pm$ SEM)		
	Eff/Target Ratio	Control mAb	NEO-101
Colo-205 (Colorectal)	50:1	9.8 $\pm$ 1.9	<b>66.7 <math>\pm</math> 0.6</b>
	25:1	0.8 $\pm$ 1.2	<b>46.4 <math>\pm</math> 1.6</b>
	12.5:1	-0.5 $\pm$ 0.1	<b>32.8 <math>\pm</math> 2.0</b>
SW620 (Colorectal)	50:1	1.6 $\pm$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

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

ADCC:

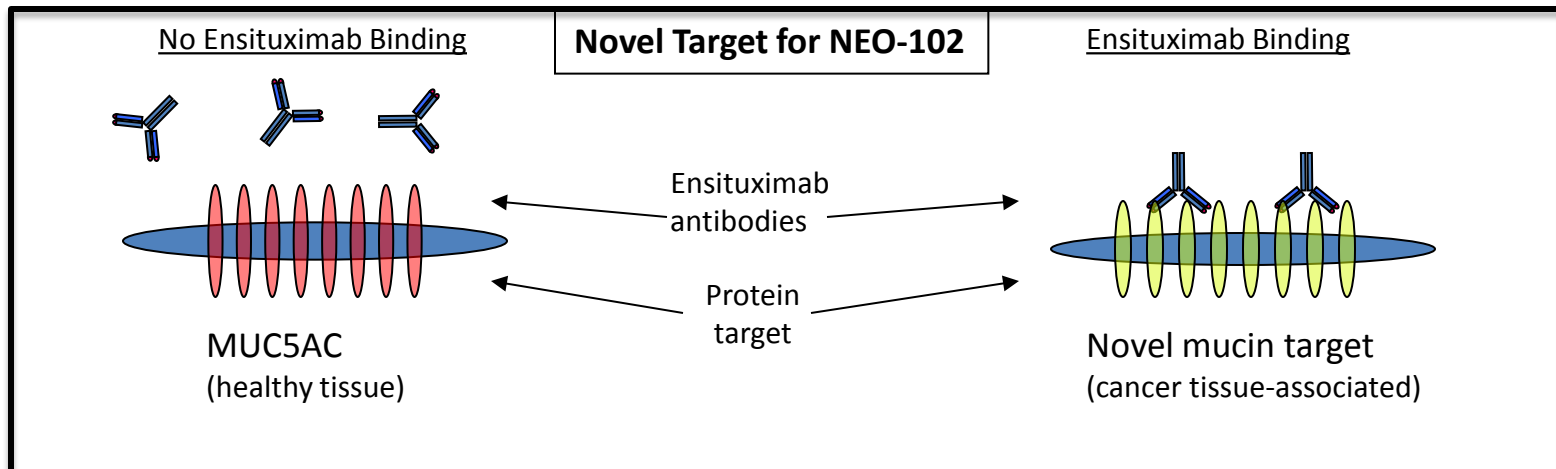
Antibody-dependent  
Cell cytotoxicity

Tumor killing



# 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.



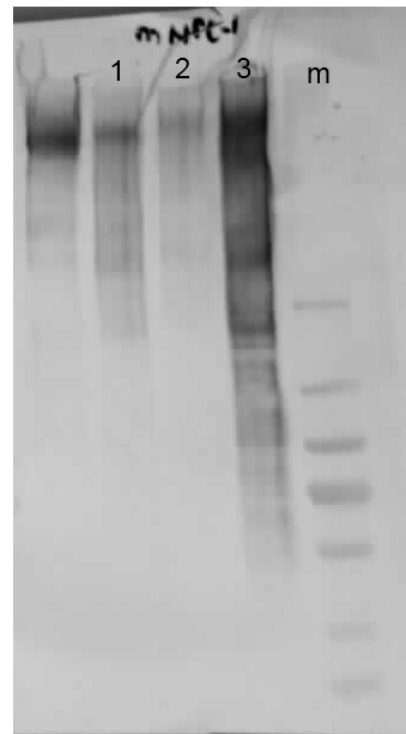
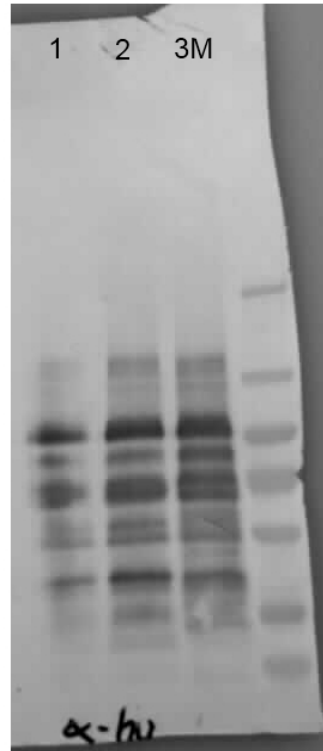
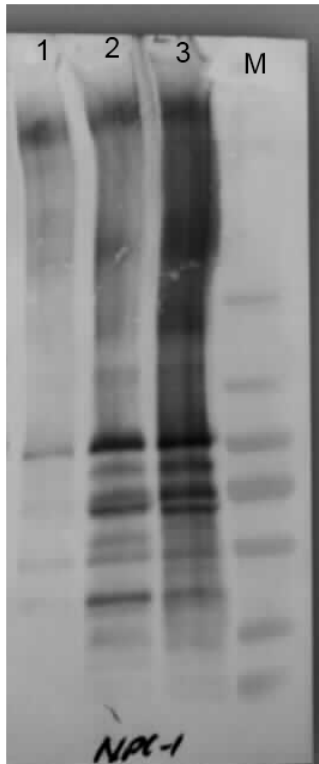
# NPC-1C Antigen and Epitope

## Detection of NPC-1C Antigen in Vaccine Samples by Western Blot

NPC-1C

Anti-H IgG-HRP only

Murine NPC-1



**Lane 1, 2, 3: Aliquots of Hollinshead's colorectal cancer vaccine**

# NPC-1C Antigen and Epitope

## Summary of Cell Lines Tested by Western Blot with NPC-1C Antibody

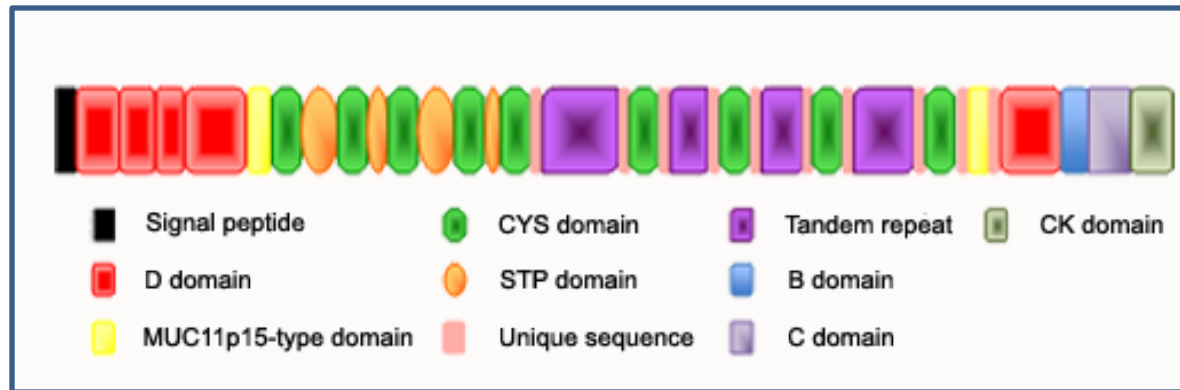
Cell line	NPC-1 antigen
SW1116	negative
SW480	negative
SW1463	negative
COLO	negative
HT226 (lung)	negative
A549 (lung)	Negative
CALU-1 (lung)	Negative
PANC-1	negative
PR-22 (prostate)	negative
HT-29	<b>Positive</b> (MW~550 kDa)
LS174T	<b>Positive</b> (MW~1,000 kDa)
CFPAC-1	<b>Positive</b> (MW~1,000 kDa)
ASPC-1	<b>Positive</b> (MW~1,000 kDa)

## NPC-1C Antigen and Epitope

- Affinity purified antigen from CFPAC-1 cells was run on SDS-PAGE and also on 2D PAGE.
- Bands from both SDS-PAGE and 2D PAGE identified by coomassie brilliant blue staining and western blotting was cut out and sent for Mass Spectrometry (MS) analysis.
- In three separate analysis, the peptide sequences matched closest to MUC-5AC, a glycoprotein belonging to the mucin family.

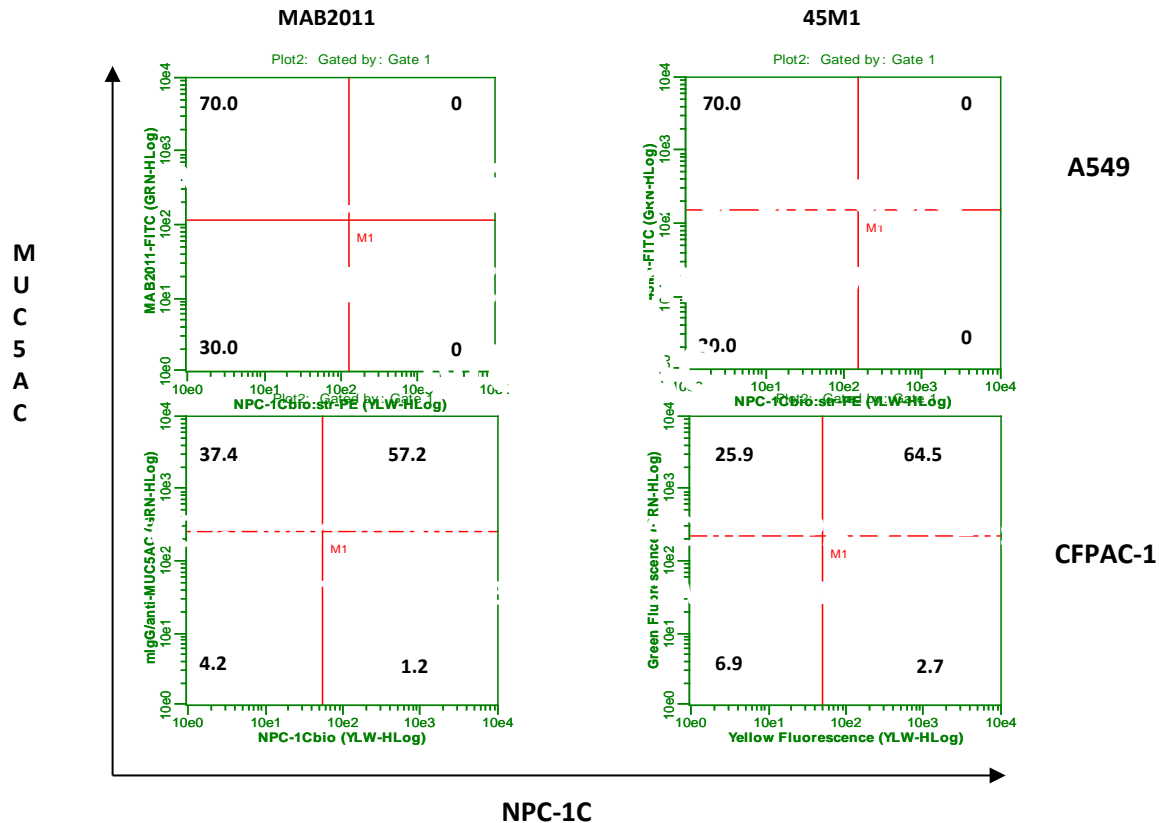
# NPC-1C Antigen and Epitope

## MUC-5AC



- MUC-5AC is a secreted, gel-forming mucin with a high molecular weight (approximately 641 kDa). Up to 80% of the total weight is due to the large number of O-glycosylated chains attached to Thr and Ser residues in the TR sequence.
- MUC-5AC is expressed by *normal* epithelial tissues and secreted into the lumen.
- MUC-5AC can be aberrantly glycosylated in cancer cells.
- In contrast, NPC-1 antigen is tumor specific in the GI tract.

# NPC-1C Antigen and Epitope



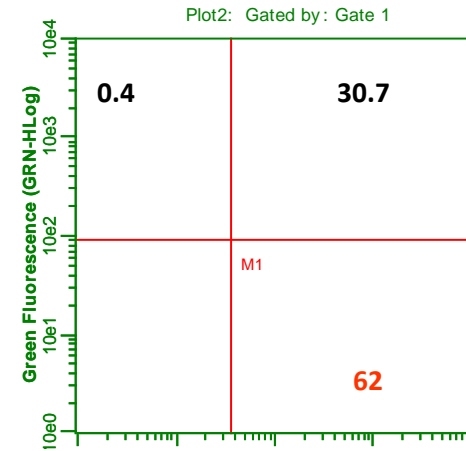
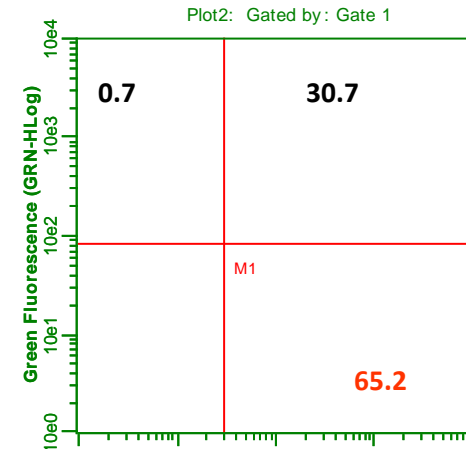
\*Overlays of isotype controls which were used to set gates are shown in the left low corner of the dot plots

**NPC-1 antigen is a unique Mucin with homology to MUC-5AC  
 ~60% overlap with MUC-5AC in CFPAC-1  
 No homology with MUC-5AC in A549 Cells in Flow Cytometry**

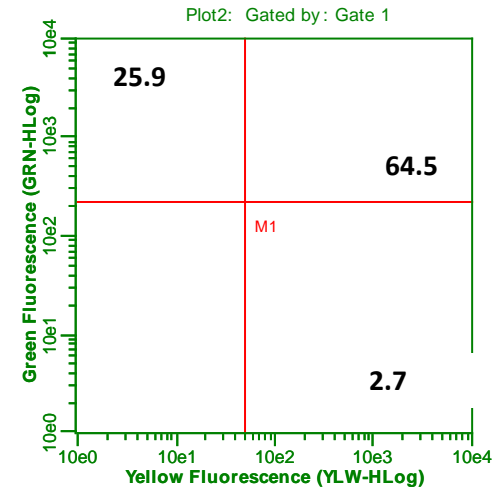
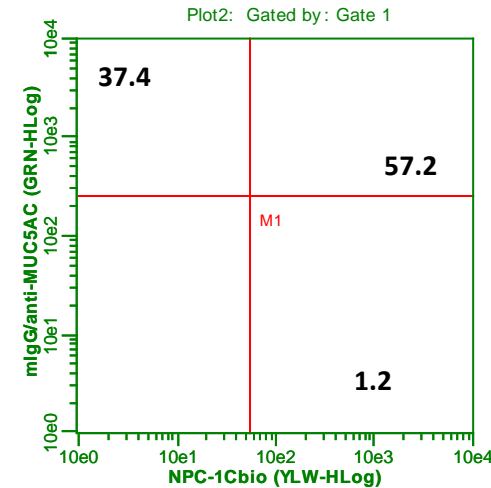


# NPC-1C Antigen and Epitope

MUC-5AC



LS174T



CFPAC-1

NPC-1C

NPC-1 antigen is a unique Mucin

~60% overlapped with MUC-5AC in CFPAC-1 Cells

~30% in LS174T Cells

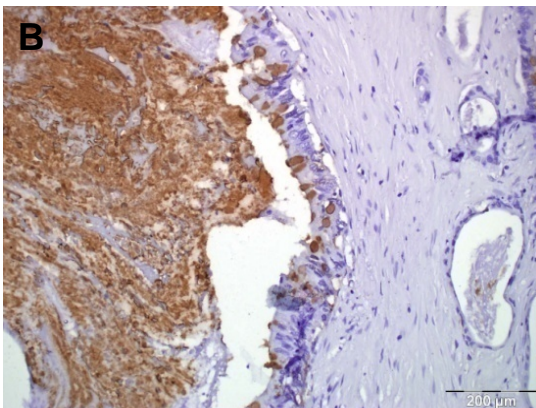
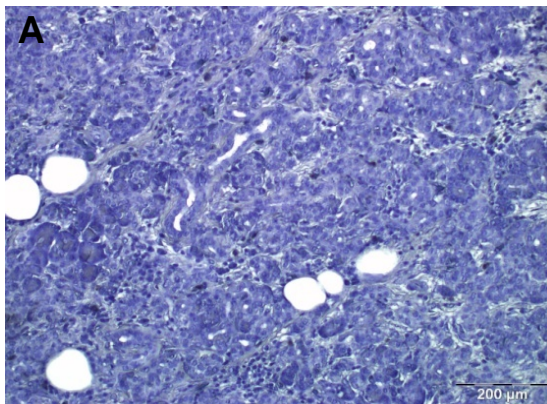
# NPC-1C Antigen and Epitope Summary

## **NPC-1 antigen contains components of MUC-5AC**

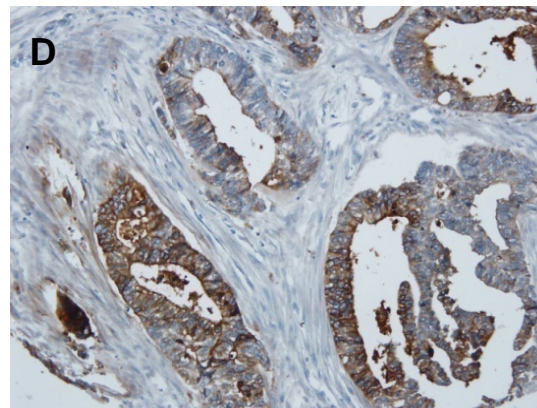
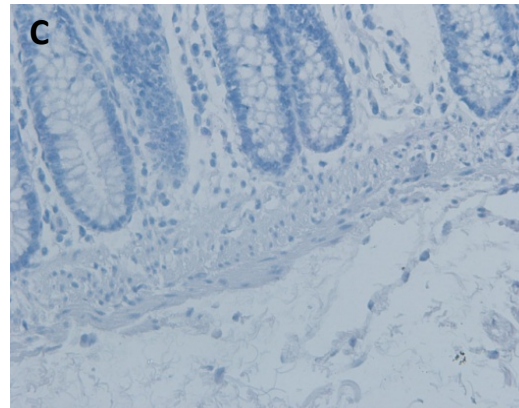
- Peptide sequences from affinity purified NPC1 antigen from CFPAC-1 cells by MS
- Sandwich ELISA with anti-MUC-5AC antibody
- ~60% Overlap with MUC5AC in pancreatic cancer cell line CFPAC-1
- ~40% overlap with MUC-5AC in colon cancer cell line LS174T; **HOWEVER**
- **0% overlap** with MUC-5AC in Lung carcinoma cell line A549

# NPC-1C Antigen and Epitope

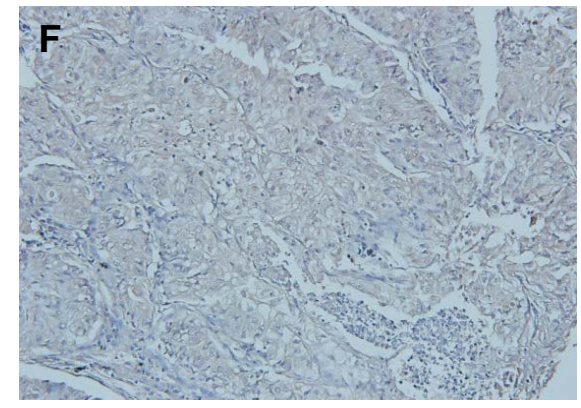
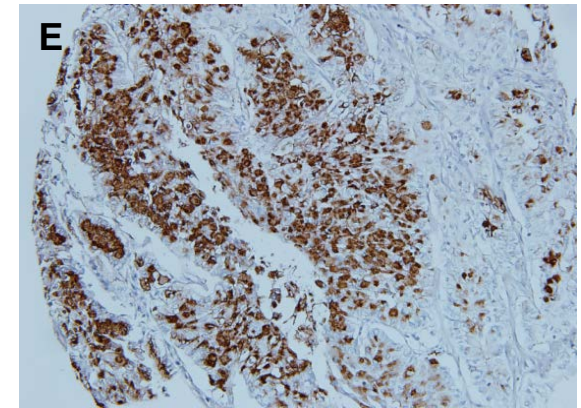
## Tissue-Specific Staining with Ensituximab (NPC-1C)



**A) Normal pancreas**  
**B) Pancreas adenocarcinoma**



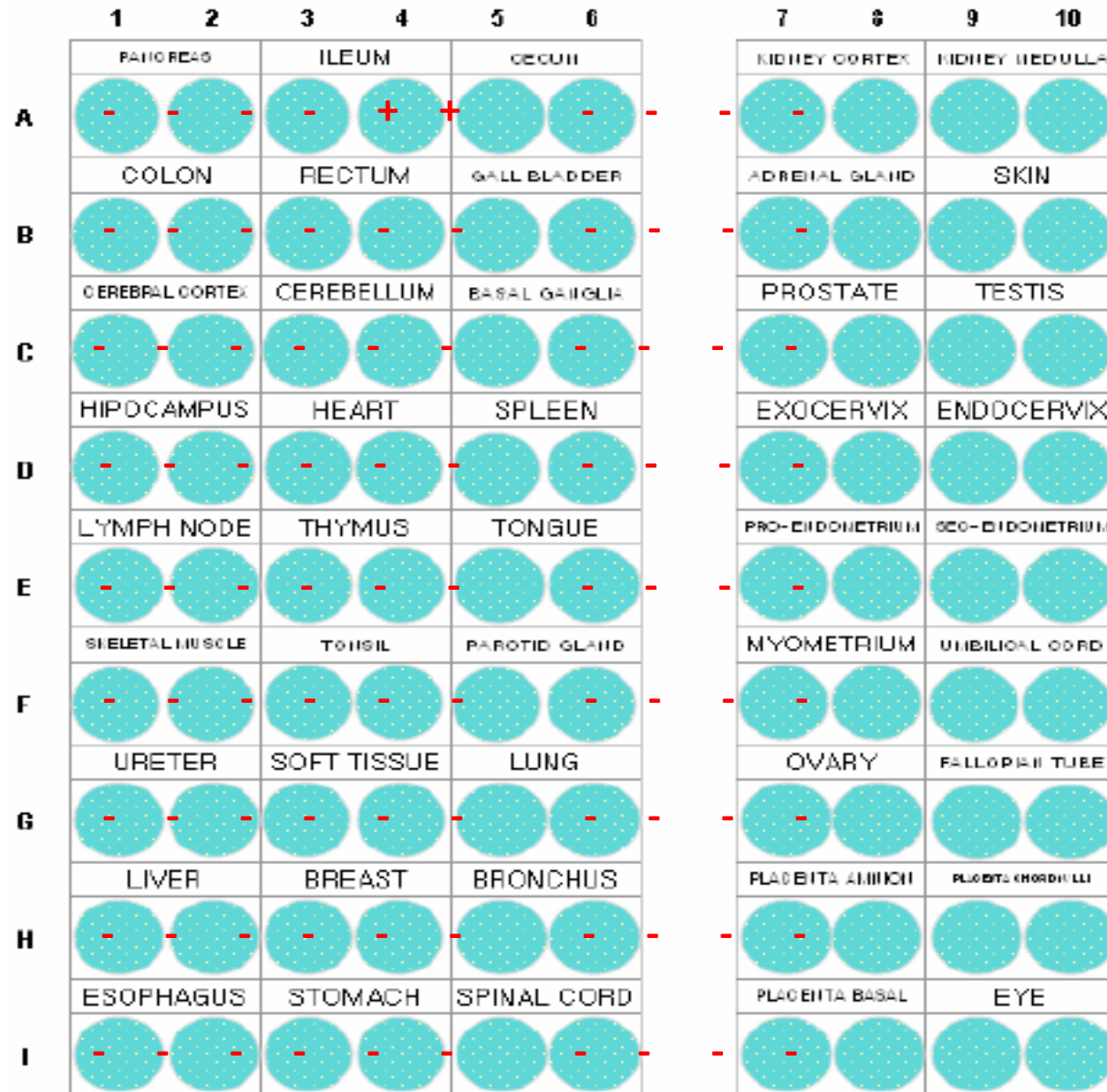
**C) Normal Colon**  
**D) Colon Cancer**



**E) Lung Cancer (anti-MUC5AC)**  
**F) Lung Cancer (NEO-101)**

# NPC-1C IHC Results from Normal Tissue

**NPC-1C IHC Results  
from Various  
Normal Tissue  
Array**

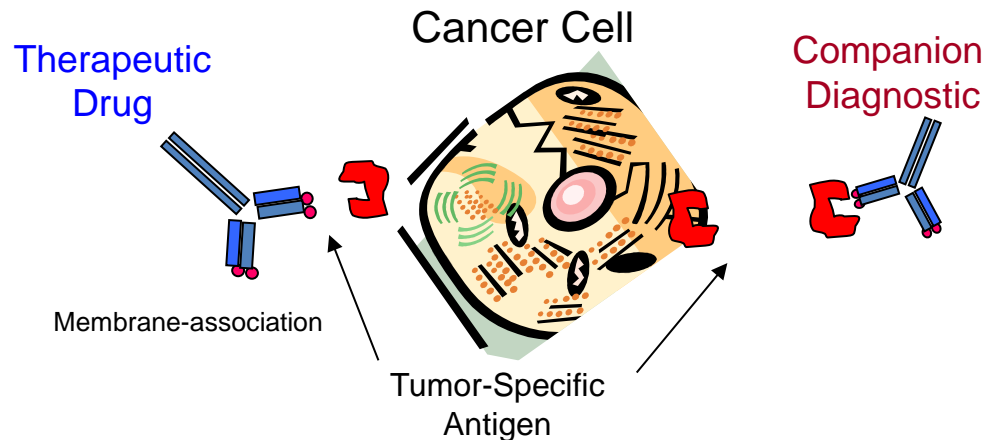


# NPC-1C IHC Results from Normal Tissue

## NPC-1C IHC Staining Results of Normal Colon and Pancreas Tissue

Tissue Type	Positive #/total #	Reactivity
Normal adjacent tissue to colon cancer	1/13	7.69%
Normal colon tissue	1/19	5.26%
<b>Overall</b>	<b>2/32</b>	<b>6.25%</b>
Normal adjacent tissue to pancreatic cancer	0/5	0%
Normal pancreatic tissue	0/17	0%
<b>Overall</b>	<b>0/22</b>	<b>0%</b>

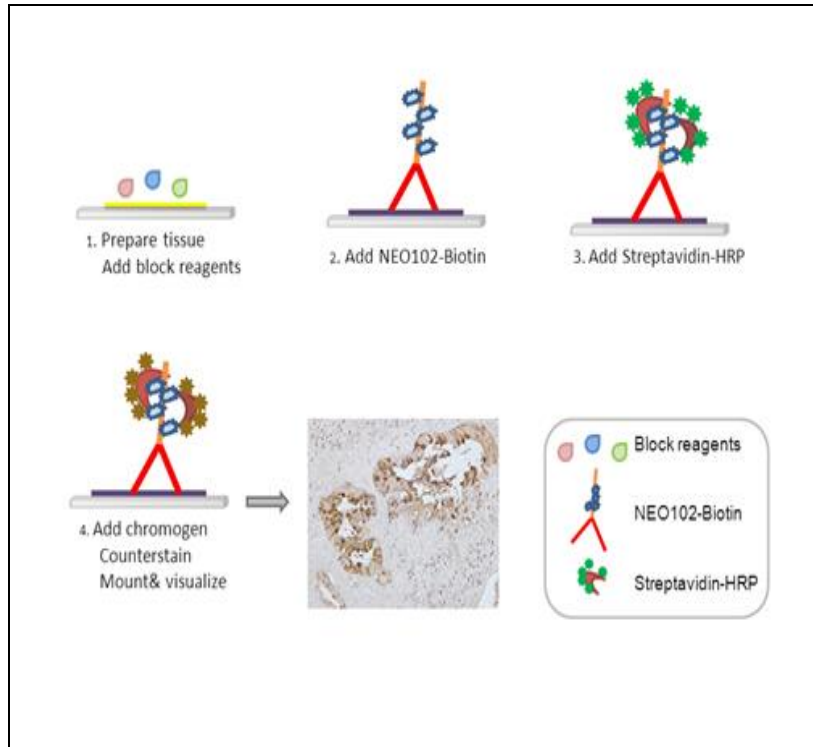
# Identification Tumor-specific Antigen (TSA) in a Companion Diagnostic

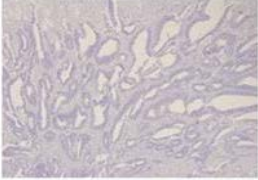
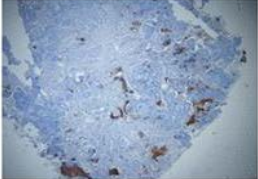
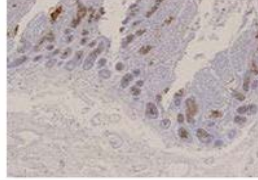


- Tumor-specific antigen detected by companion diagnostic- immunohistochemistry (IHC).
- Herceptin success in breast cancer based on similar concept.
- Companion diagnostic currently used to test formalin-fixed, paraffin embedded (FFPE) tumor tissue to pre-select for clinical trial eligibility.
- Clinical IHC testing is being conducted at the Pathology Department of UT Southwestern, Duke University Medical Center and Johns Hopkins University.
- Eligibility for clinical trial requires IHC staining  $\geq 20\%$  of tissue with at least 2+ intensity positive for NEO-102.
- Pre- IDE package will be presented to the FDA in early 2015.

# NPC-1C IHC Results from Tumor Tissue

## NEO-102 IHC Companion Diagnostic



Intensity	% Stained Colon Tumor Cells	Result	Picture
≥2+	0%	Neg	
<2+	100%		
Background	0%		
≥2+	20%	Pos	
<2+	80%		
Background	0%		
≥2+	45%	Pos	
<2+	55%		
Background	0%		

- In a selection of patients with colorectal or pancreatic cancer screened for NEO-102 IHC staining, 105 out 176 tested positive for IHC (60%).
- In a subset of these patients :
  - 64% of patients with colorectal cancer were positive, and
  - 62% of patients with pancreatic cancer were positive

# NEO-102 Monotherapy - Highlights of Clinical Data for Colorectal Cancer

- Phase 2a, open label, multicenter clinical trial with NEO-102 for patients with refractory pancreatic or colorectal cancer.
- Primary endpoint- overall survival (OS) will be compared with their respective historical controls to determine if there is improvement in OS with administration of NEO-102.
- FDA recently approved Regorafenib for treatment of 3<sup>rd</sup> line colorectal cancer based on Phase 3 data demonstrating an increase in OS from 5.0 to 6.4 months, despite a significant toxicity profile.
- Precision Biologics is targeting this population in a Phase 2 cohort of 47 colorectal cancer patients (accrual completed April 2015) using NEO-102 which has demonstrated a very favorable safety profile; it is statistically powered to compare against the historical control group.
- **Median OS 10.4 months in dose escalation study, compares favorable with historical control of 5.0 months.**
- In addition, a separate cohort of 30 evaluable patients with metastatic, locally advanced, unresectable, or recurrent pancreatic cancer is being evaluated.



# NEO-102 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Overall Survival in Phase I and Phase II

Patient #	Disease	Dose Level	Overall survival days	OS Months
230	Colorectal	1.5	346	12
231	Colorectal	1.5	369	12
232	Colorectal	1.5	650+	22+
233	Colorectal	2	42	1
236	Colorectal	3.0	93	3
237	Colorectal	3.0	311	10
238	Colorectal	3.0	546+	18+
242	Colorectal	4.0	447+	15+
243	Colorectal	4.0	376	13
248	Colorectal	3.0	82	3
249	Colorectal	3.0	142	5
250	Colorectal	3.0	170	6
253	Colorectal	3.0	105	4
255	Colorectal	3.0	206	7
256	Colorectal	3.0	74	2
257	Colorectal	3.0	105	4
258	Colorectal	3.0	209	7
259	Colorectal	3.0	157	5
260	Colorectal	3.0	123	4
262	Colorectal	3.0	184	6
266	Colorectal	3.0	119	4
267	Colorectal	3.0	193+	6+
270	Colorectal	3.0	174+	6+

**Historical control:  
Median OS is 5  
months**

# NEO-102 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Overall Survival in Phase I and Phase II

Patient #	Disease	Dose Level	Overall survival days	OS Months
273	Colorectal	3.0	150+	5+
274	Colorectal	3.0	111+	4+
275	Colorectal	3.0	140+	5+
276	Colorectal	3.0	129+	4+
277	Colorectal	3.0	126+	4+
280	Colorectal	3.0	117+	4+
282	Colorectal	3.0	118+	4+
283	Colorectal	3.0	117+	4+
284	Colorectal	3.0	118+	4+
285	Colorectal	3.0	50	2
286	Colorectal	3.0	111+	4+
287	Colorectal	3.0	115+	4+
288	Colorectal	3.0	112+	4+
289	Colorectal	3.0	112+	4+
291	Colorectal	3.0	112+	4+
292	Colorectal	3.0	105+	4+
294	Colorectal	3.0	104+	3+
295	Colorectal	3.0	102+	3+
296	Colorectal	3.0	98+	3+
298	Colorectal	3.0	91+	3+
299	Colorectal	3.0	96+	3+
302	Colorectal	3.0	91+	3+
303	Colorectal	3.0	89+	3+
304	Colorectal	3.0	88+	3+
305	Colorectal	3.0	80+	3+
306	Colorectal	3.0	88+	3+
308	Colorectal	3.0	75+	3+
311	Colorectal	3.0	67+	2+
313	Colorectal	3.0	54+	2+
316	Colorectal	3.0	45+	2+

Total: N= 53 (34 remain alive)  
 3.0 mg/kg: N= 47 (32 remain alive at 3.0 mg/kg dose)  
 + = Alive

## NEO-102 is well tolerated and convenient for both colorectal and pancreatic cancer patients

- Over 70 patients have been exposed to increasing doses of NEO-102 (ranging from 1.5mg/kg to 4.0mg/kg).
- Infrequent serious adverse events (SAEs) have been reported possibly related to NEO-102 at the MTD of 3.0mg/kg.
- Dose-limiting toxicity in phase 1 was noted at the 4.0mg/kg dose that included Grade 3 transient hyperbilirubinemia and anemia.
- In Phase 2: It is very well tolerated with no grade 3 myelosuppression, skin rashes, GI, renal or cardiopulmonary toxicity.
- Dosing interval is administered IV every 2 weeks.

# NEO-102 Summary

- Promising Phase I/II results in treatment of chemotherapy refractory colorectal and pancreatic patients in monotherapy clinical trial using NEO-102.
  - **Median OS in monotherapy dose escalation study was 10.4 months for colorectal cancer patients, compares favorably to historical control of OS of 5.0 months.**
- Phase I of both the monotherapy and combination studies was completed in less than anticipated time. Enrollment onto phase II of the monotherapy completed.
- IHC companion diagnostic pre-IDE FDA review set for mid 2015.
- Exploring opportunities with new technologies based on NEO-102 such as antibody drug conjugates (ADC), CAR T-cell, Bi-specific t-cell engagers (BiTEs) antibody.



# PRECISION BIOLOGICS

## *Science and Clinical Facility*

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