Peptide-Based Individualized Vaccines

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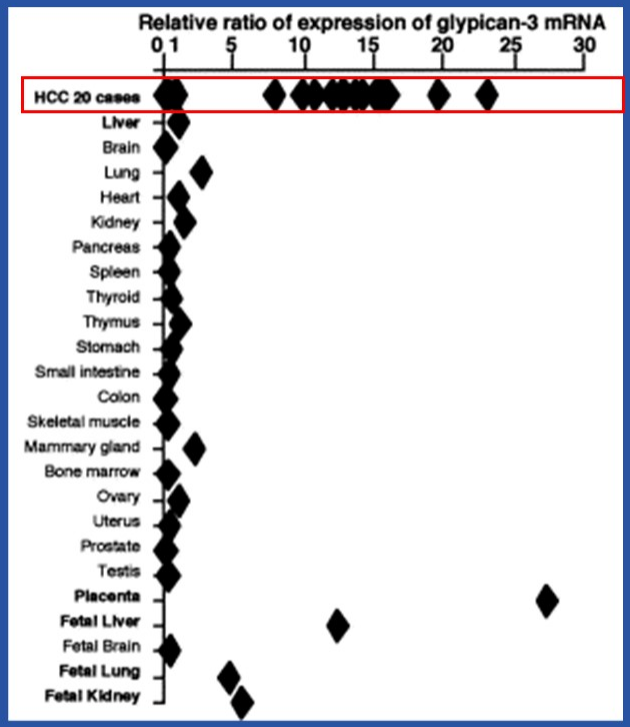
PRESENTED AT: ASCO Breakthrough #ASCOBT19

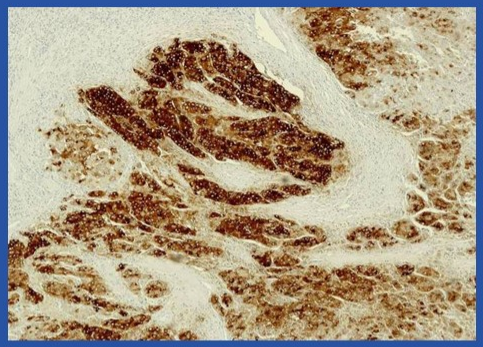
PRESENTED BY: Tetsuya Nakatsura

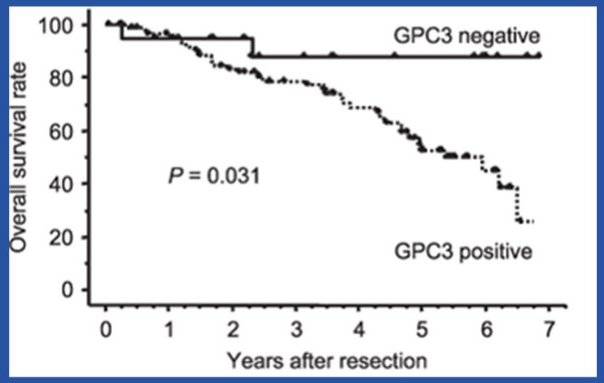
Presented By Tetsuya Nakatsura at 2019 ASCO Breakthrough: A Global Summit for Oncology Innovators

Glypican-3 (GPC3), a carcinoembryonic antigen, is an ideal target of anticancer immunotherapy against hepatocellular carcinoma(HCC)



Nakatsura T et al, Biochem Biophys Res Commun. 2003



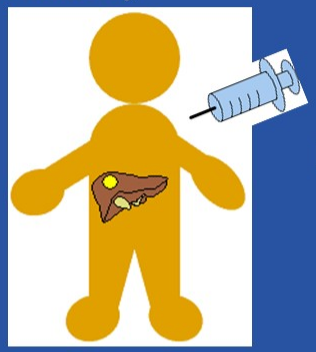


Shirakawa H et al, Cancer Sci. 2009

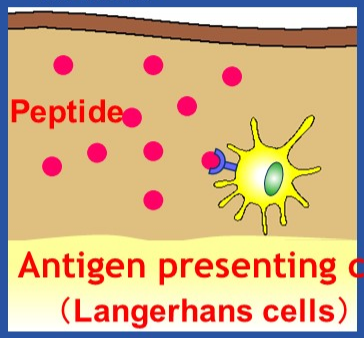
GPC3 is overexpressed specifically in HCC and correlates to a poor prognosis.

Outline of mechanism of action of peptide vaccine therapy

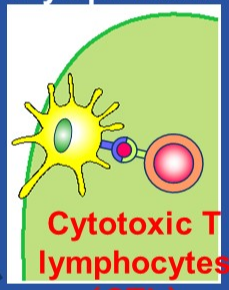
Peptide is injected intradermally or subcutaneously



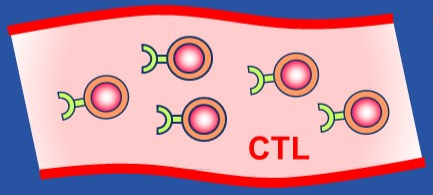
≪Skin≫



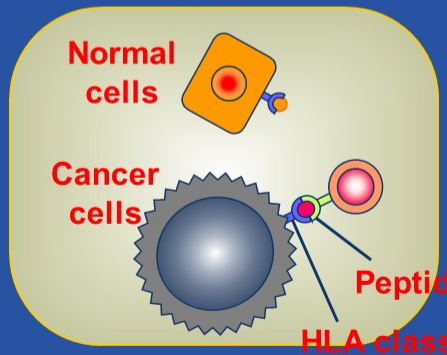
≪Lymph nodes≫



≪Blood vessel≫

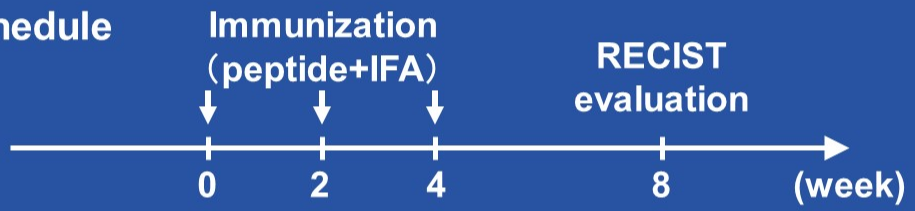


≪ Whole body organization ≫



Phase I trial of GPC3 peptide vaccine for advanced HCC

Treatment schedule



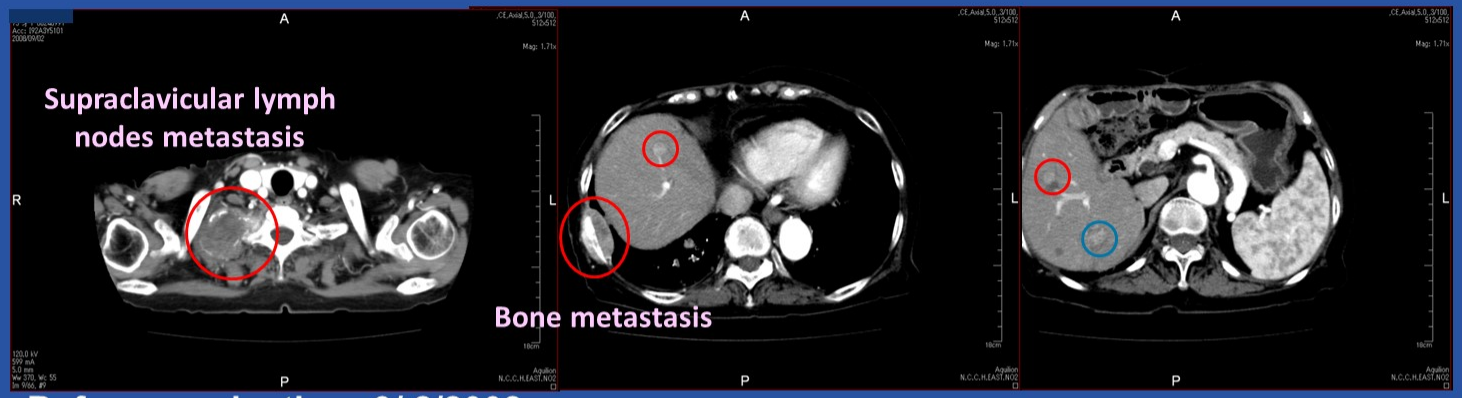
Glypican-3 (GPC3) peptide vaccine

HLA-A2 $GPC3_{144-152}$ (FVGEFFTDV)
HLA-A24 $GPC3_{298-306}$ (EYILSLEEL)

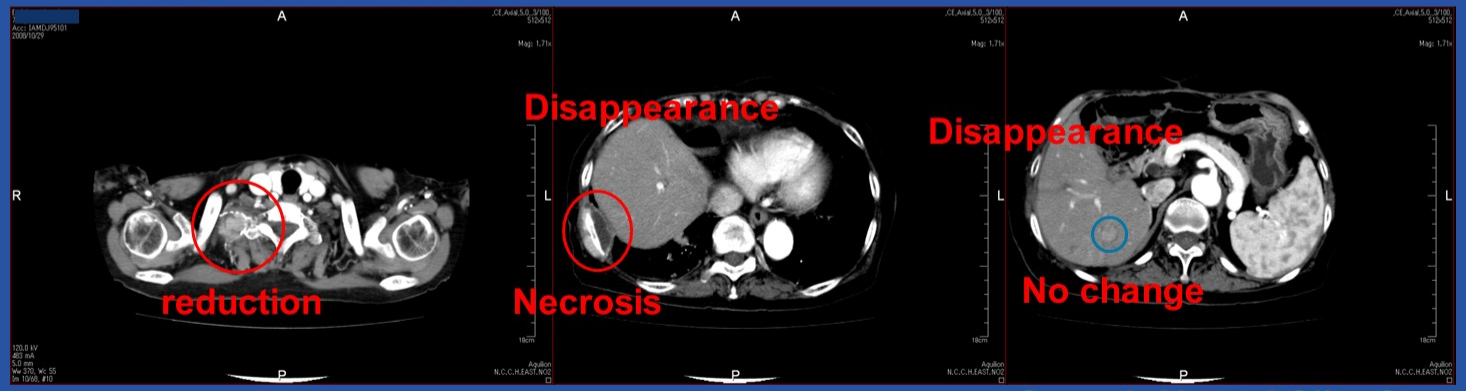
Peptide dose	No. of cases
0.3 mg	8
1.0 mg	6
3.0 mg	6
10.0 mg	7
30.0 mg	6
Total	33

Sawada Y. *et al Clin. Cancer Res.* 2012, Yoshikawa T. *et al Cancer Sci.* 2011

75y F multiple HCC, bone meta, lung meta, LN meta HLA-A*0207/1101
HLA-A2-restricted glypican-3 peptide: 30 mg per body, 3 times vaccination



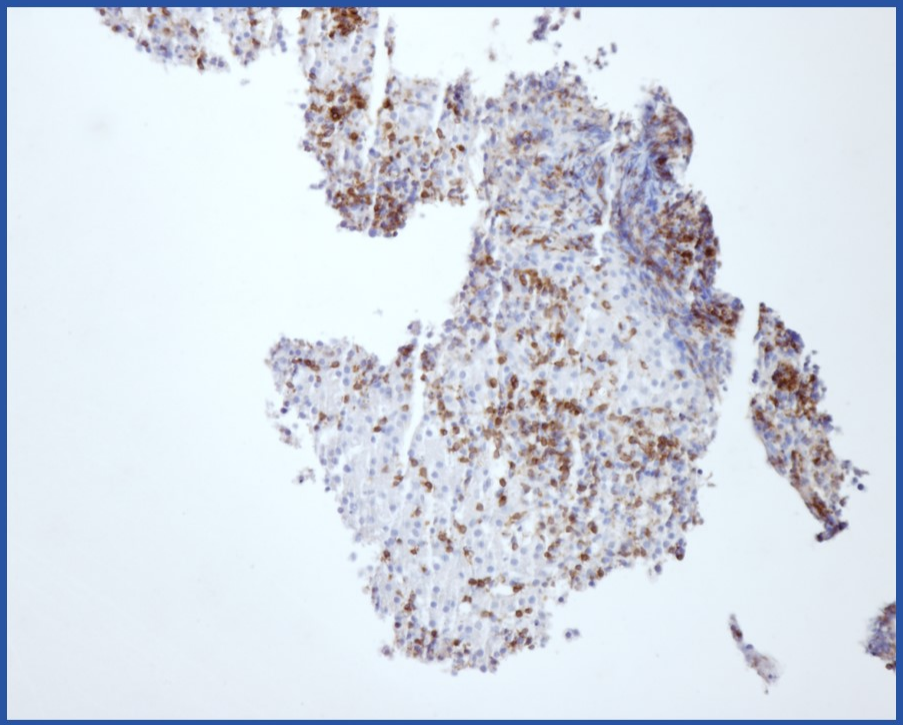
Before vaccination 9/ 2/2008



1 month after 3rd vaccination 10/29/2008

Sawada Y. *et al Clin. Cancer Res.* 2012

Infiltration of a large amount of CD8-positive killer T cells was proved in tumors that did not change in post-vaccine

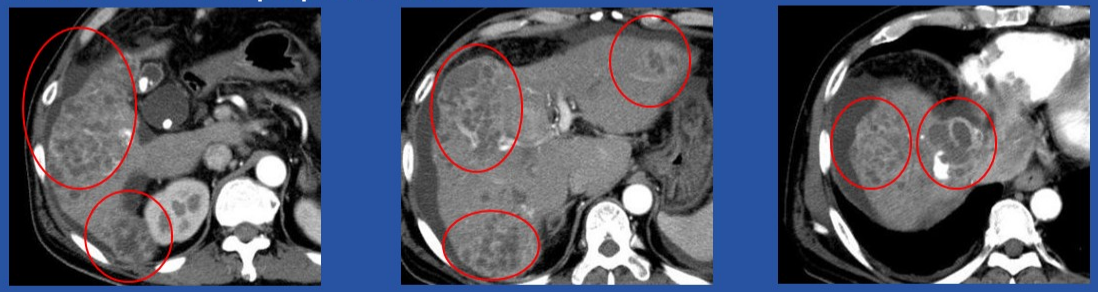


Sawada Y. *et al Clin. Cancer Res.* 2012

A case experienced in clinical trials for advanced cancer

Before administration of GPC3 peptide vaccine

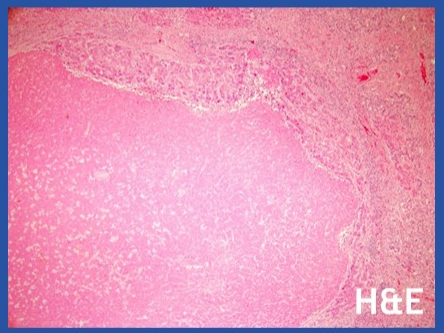
After 2 doses of GPC3 peptide vaccine

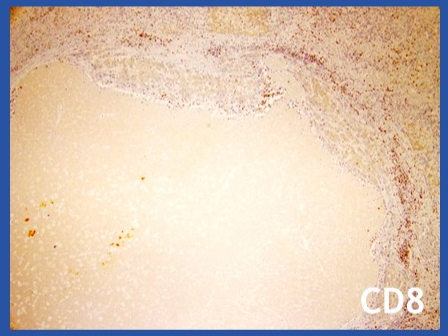


Sawada Y et al. Hum Vaccin Immunother. 2013 :1228-33

A case experienced in clinical trials for advanced cancer

Most of the tumor necroses macroscopically





The majority of intrahepatic tumors are central necrosis. Viable tumor remains at the periphery. CD8 positive lymphocytes observed nearby viable cancer cells.

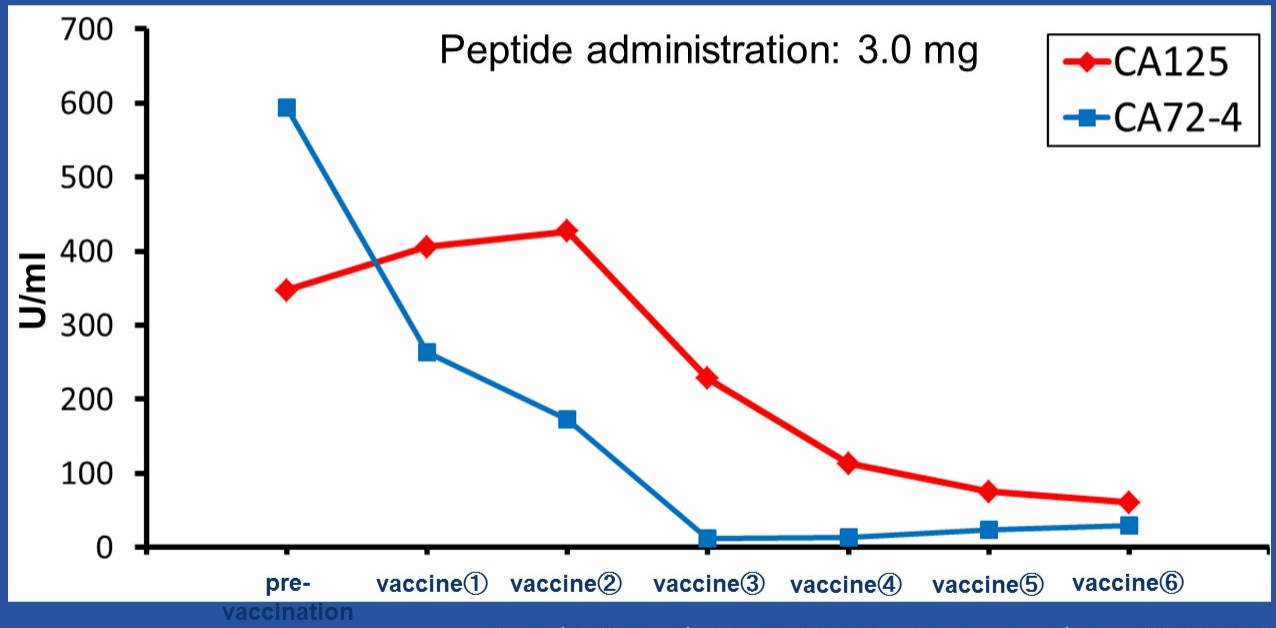
Sawada Y et al. Hum Vaccin Immunother. 2013 :1228-33

Ovarian clear cell carcinoma patient
Received Glypican-3 derived peptide vaccine （HLA-A24）

Patients gloup：advanced　42 YO、stageⅢc
previous treatment：

*HLA-A*24:02, 31:01*

operation（ATH+BSO＋sampling of retroperitoneal lymph node、residual tumor＋）→TC treatment→IDS（PEN+PAN+OM）→CPT-T+CDDP treatment



Suzuki S et al. Hum Vaccin Immunother. 2014 :338-43

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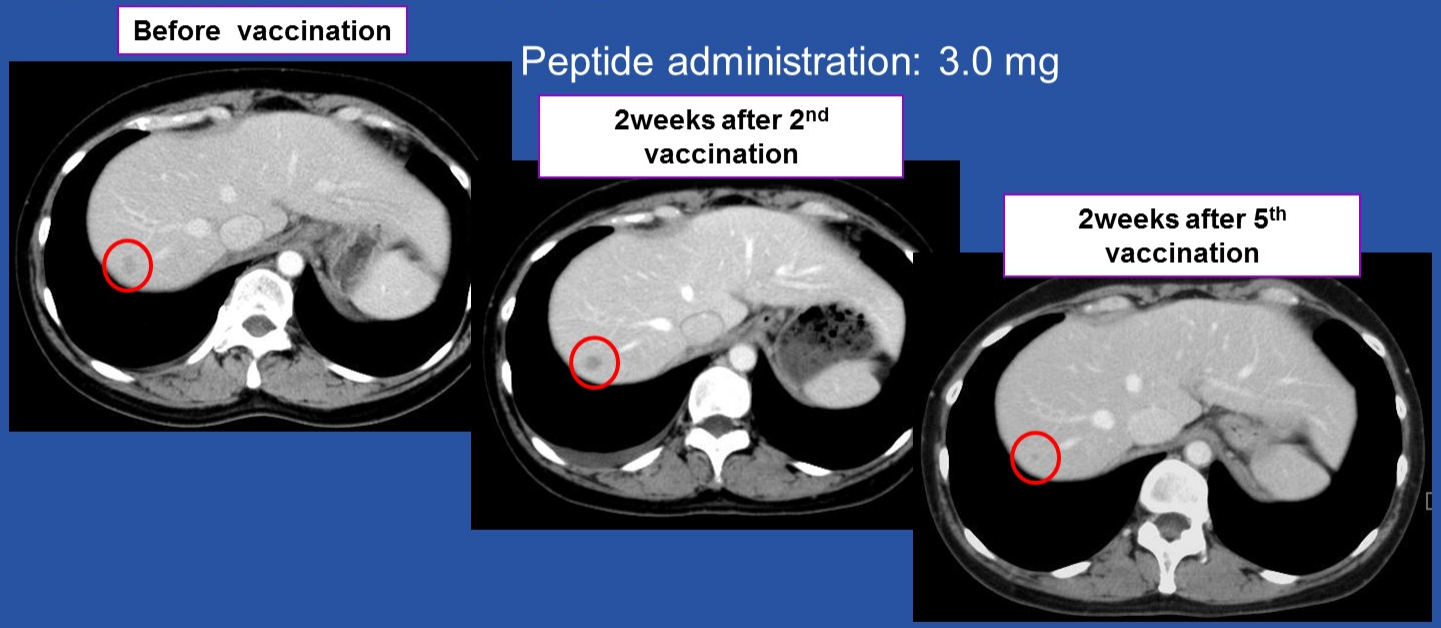
Peptide administration: 3.0 mg



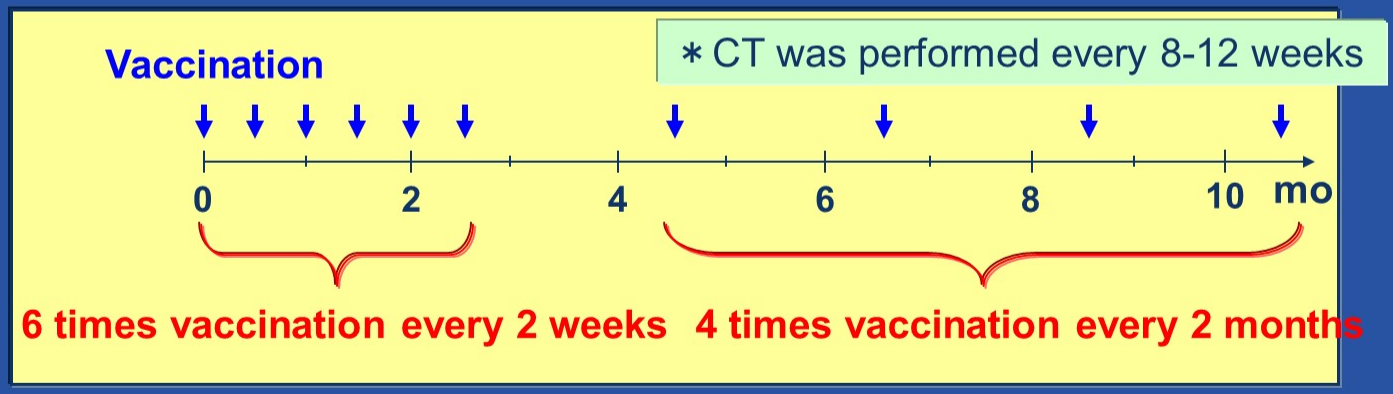
Suzuki S et al. Hum Vaccin Immunother. 2014 :338-43

phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for HCC patients

3.0mg of GPC3 peptide emulsified with IFA (intradermally)

EYILSLEEL peptide for HLA-A24-positive patients
FVGEFFTDV peptide for HLA-A2-positive patients

10 vaccinations are performed for 1 year after curative treatment.

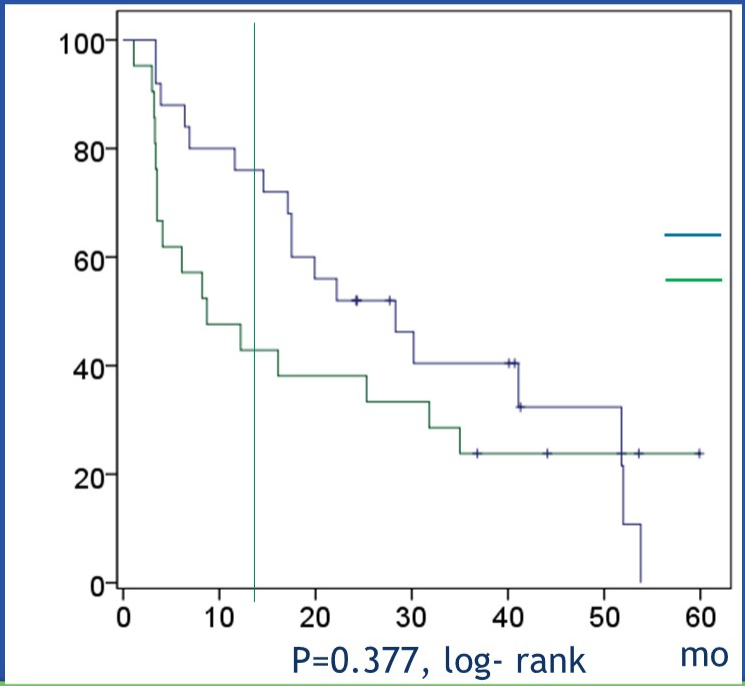


Sawada Y. *et al* *OncoImmunology 2016*

It is expected to recurrence-prevention effect of GPC3 peptide vaccine in GPC3-positive HCC

1-year recurrence rate 24.0% vs 52.4% (*p*=0.047)

Recurrence free survival

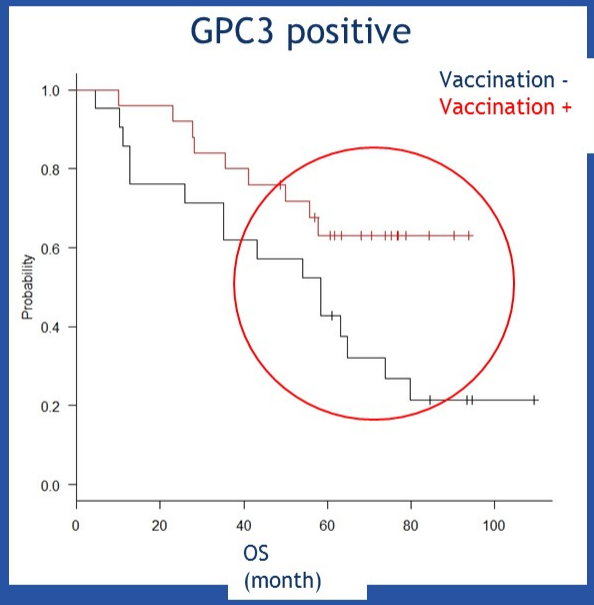


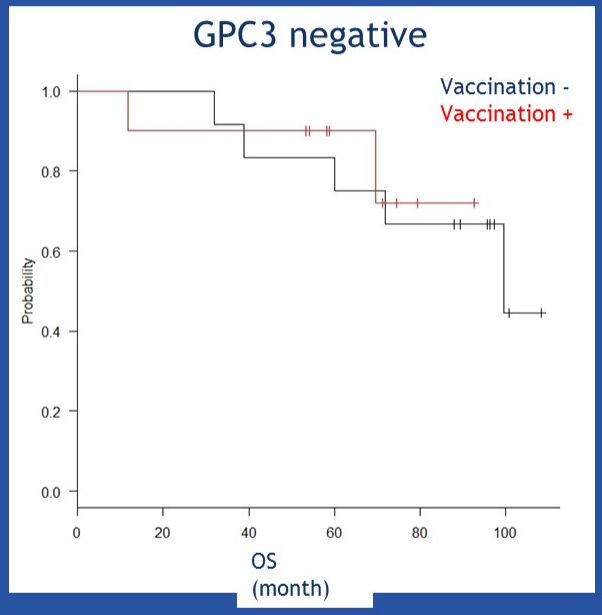
HCC tumor of all these patients showed evident GPC3 expression in immunohistochemical examination

25 patients treated with surgery and the vaccination
21 patients underwent surgery alone in NCCE (control)

Sawada Y. *et al* *OncoImmunology 2016*

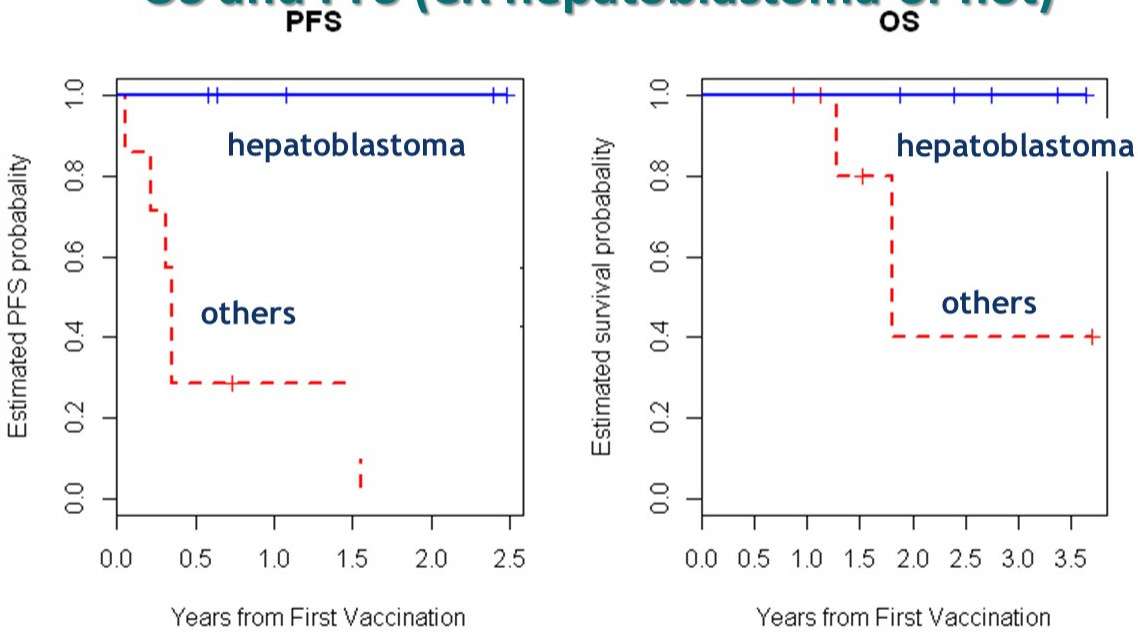
Overall Survival





Phase I study of Glypican-3-derived Peptide Vaccine Therapy for pediatric patients with refractory solid tumors

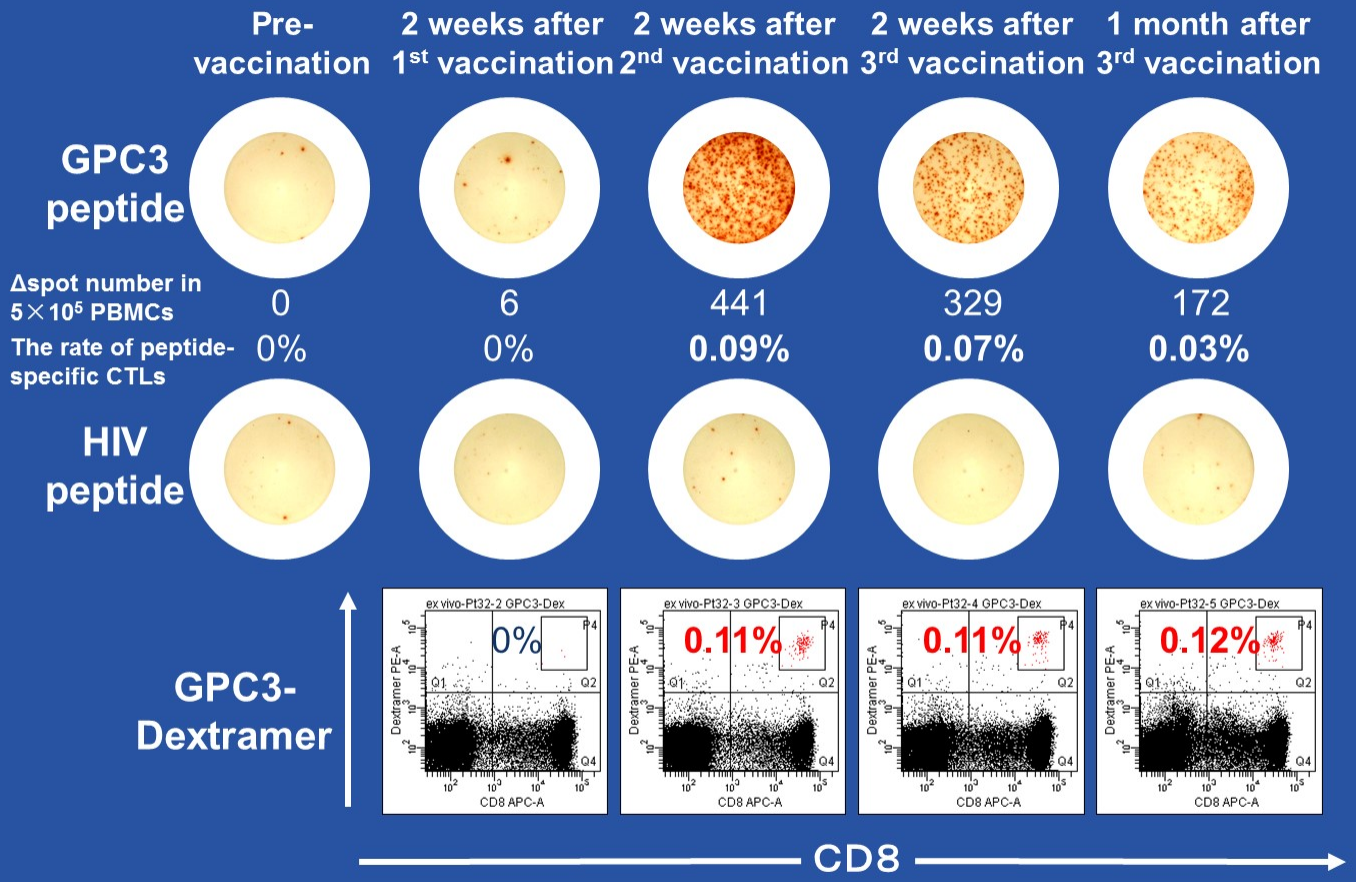
OS and PFS (CR hepatoblastoma or not)



In the remission group at the time of enrollment, all cases of hepatoblastoma remained remission and survival

Monitoring of peptide-specific CTLs in the peripheral blood

Pt. 32 30mg *HLA-A*0201*



Establishment and analysis of GPC3 peptide specific CTL clone

Pt. 32 30mg peptide vaccine *HLA-A*02:01*

ex vivo IFN-γ ELISPOT assay

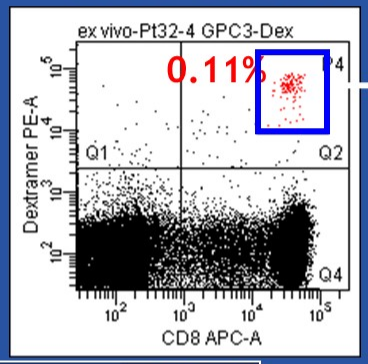
GPC3 peptide

Δspot number 329

The frequency in PBMC 5×10⁵ cells 0.07%

PBMCs at 2 weeks after 3rd vaccination

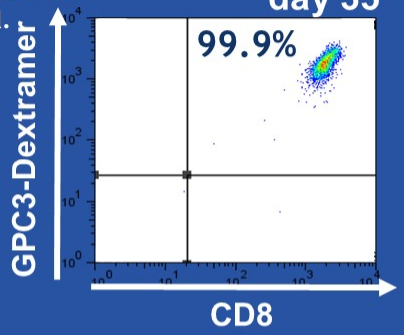
ex vivo Dextramer

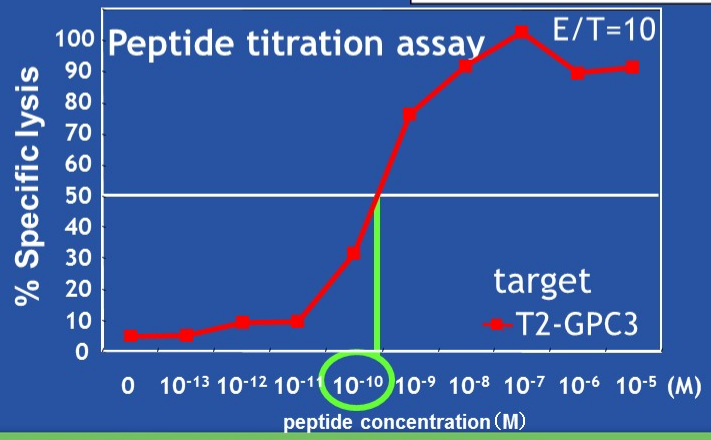


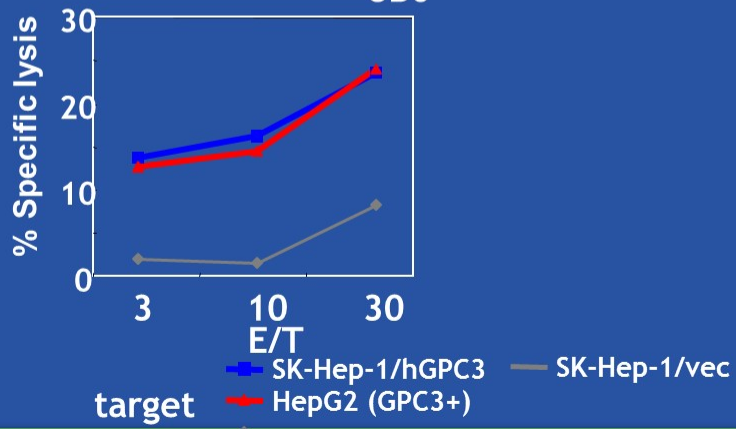
GPC3-Dextramer+ cells were sorted to a single cell.

+ IL-2
+ PHA

ex vivo Dextramer sort clone day 35







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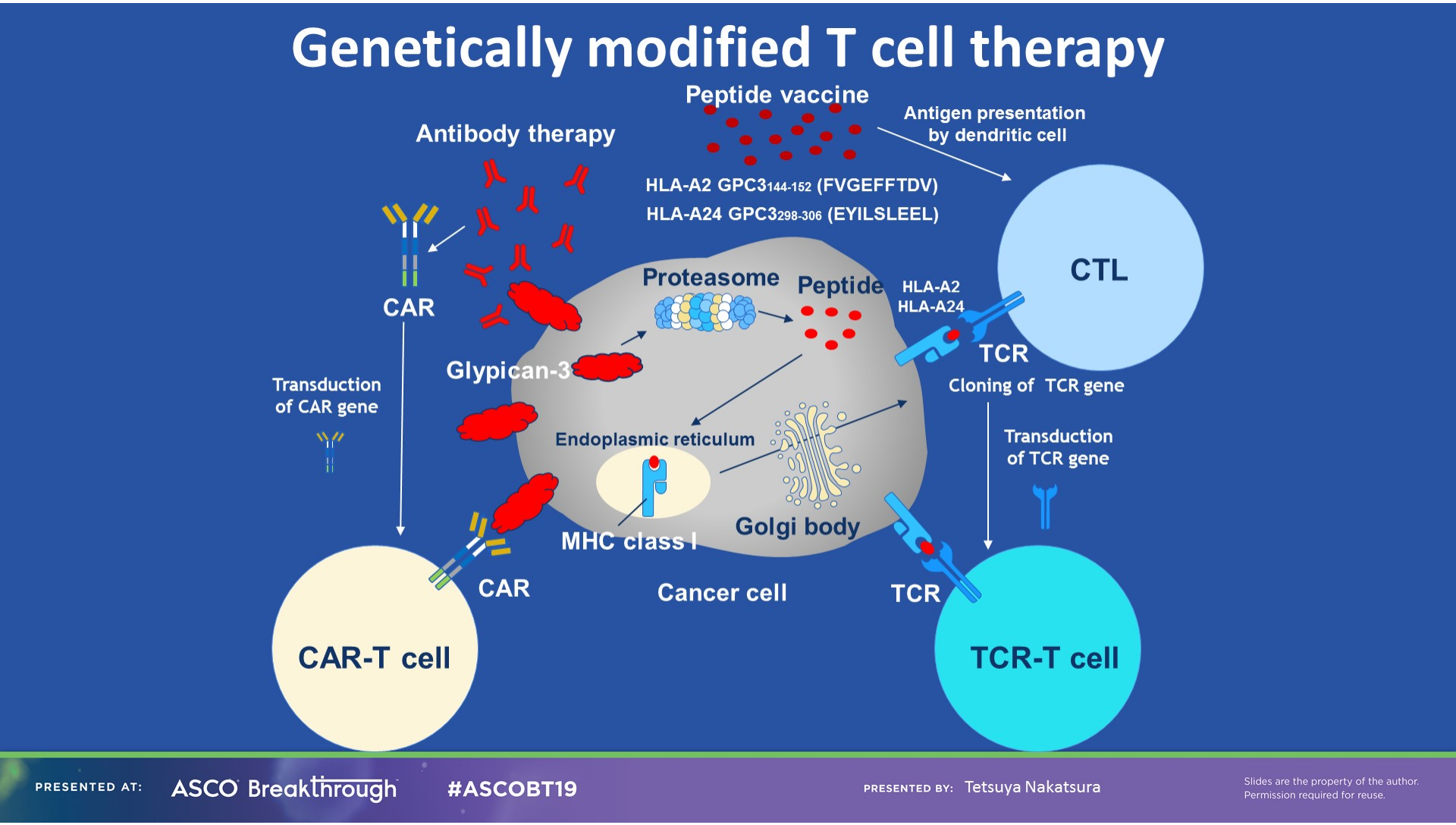
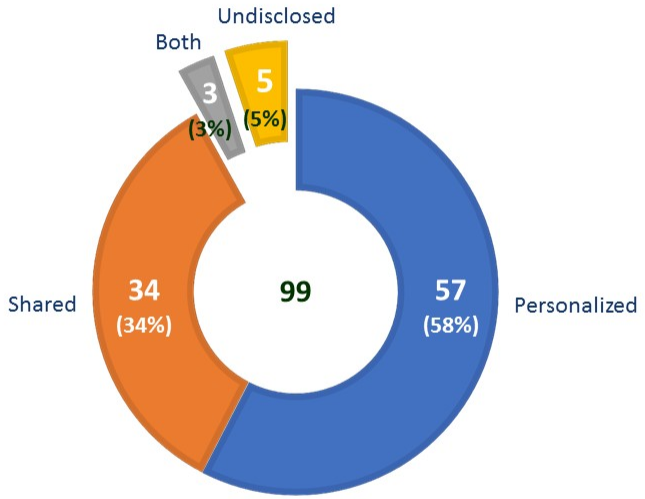
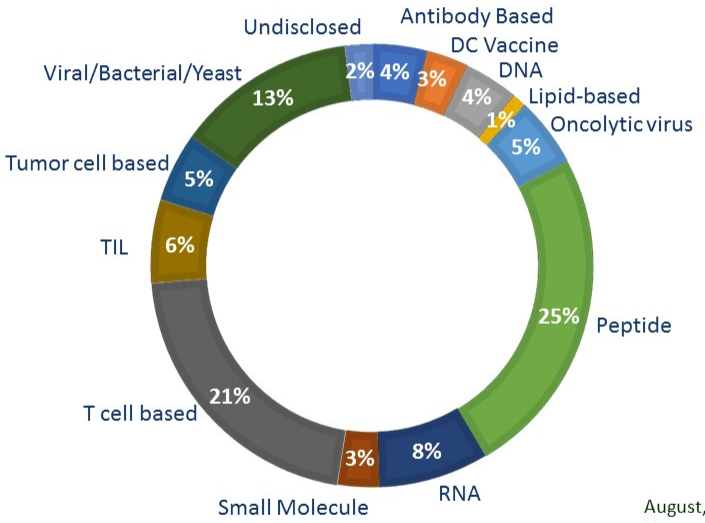


Presented By Tetsuya Nakatsura at 2019 ASCO Breakthrough: A Global Summit for Oncology Innovators

Immunotherapies targeting neoantigens under development





August, 2019
Neoantigen Targeted Therapies
Patent & Deal Analysis
CmaxInsight Market Intelligence

Presented By Tetsuya Nakatsura at 2019 ASCO Breakthrough: A Global Summit for Oncology Innovators

Clinical Studies for Personalized Immuno-oncology Therapies

Sponsor	Region	Target Cancer	Vaccine Platoform	Enrollment	Start Date (Status)	NCT Number
University of Pennsylvania	USA	Melanoma	Peptide-treated DC	17	Aug 2008 (Completed)	NCT00683670
Dana-Farber Cancer Institute	USA	Melanoma	Peptide, poly-ICLC	20	Jan 2014 (Enrollemnt completed)	NCT01970358
Dana-Farber Cancer Institute	USA	Glioblastoma	Peptide, poly-ICLC, Radiotherapy	20	Nov 2014 (Enrollemnt completed)	NCT02287428
Dana-Farber Cancer Institute Oncovir, Inc. Neon Therapeutics, Inc.	USA	Chronic Lymphocytic Leukemia	Peptide, poly-ICLC, Cyclophosphamide	10	Sep 2018 (Enrollment not to start)	NCT03219450
Dana-Farber Cancer Institute	USA	Follicular Lymphoma	Peptide, poly-ICLC	20	Jul 2018 (Enrollment not to start)	NCT03361852
Dana-Farber Cancer Institute Bristol-Myere Squibb	USA	Renal Cell Carcinoma	Peptide, poly-ICLC, Ipilimumab	20	Oct 2016 (Enrollment not to start)	NCT02950766
Neon Therapeutics, Bristol-Myere Squibb	USA	Lung, Melanoma, Bladder	Peptide, poly-ICLC, Nivolumab	90	Oct 2016	NCT02897765
Washington University	USA	Breast (TN)	Polyepitope DNA	15	Jun 2015	NCT02348320
Washington University	USA	Pancreatic	Polyepitope DNA, electroporation	15	Jan 2018	NCT03122106
Washington University MedImmune LLC	USA	Breast (TN)	Polyepitope DNA, electroporation	24	Apr 2018	NCT03199040
Washington University	USA	Breast (TN)	Peptide (poly-ICLC	15	Sep 2015 (Suspended)	NCT02427581
Washington University	USA	Glioblastoma	Peptide, poly-ICLC	10	Nov 2015 (Completed)	NCT02510950
Washington University	USA	Pediatric Brain Tumor	Peptide, poly-ICLC	10	May 2018 (Enrollment not to start)	NCT03068832
Washington University	USA	Follicular Lymphoma	Peptide, poly-ICLC, Nivolumab	20	Jun 2018 (Enrollment not to start)	NCT03121677
Washington University	USA	NSCLC	Peptide, poly-ICLC, Pembrolizumab	0	May 2018 (Discontinued)	NCT03166254
Washington University	USA	Glioblastoma	Peptide, poly-ICLC, ilimumab, Nivolumab	30	Jun 2018 (Enrollment not to start)	NCT03422094
Icahn School of Medicine at Mount Sinai	USA	Solid Tumor	Peptide, poly-ICLC	20	Apr 2016	NCT02721043
Icahn School of Medicine at Mount Sinai NovoCure Ltd.	USA	Glioblastoma	Peptide, poly-ICLC, Tumor Treating Fields (TTF)	3	Mat 2018 (Enrollment not to start)	NCT03223103
Icahn School of Medicine at Mount Sinai Genentech, Inc.	USA	Urothelial Carcinoma, Bladder	Peptide, poly-ICLC, Atezolizumab	15	Jul 2018 (Enrollment not to start)	NCT03359239
M.D. Anderson Cancer Center	USA	Pancreatic, Colorectal	Peptide, IFA	40	May 2016	NCT02600949

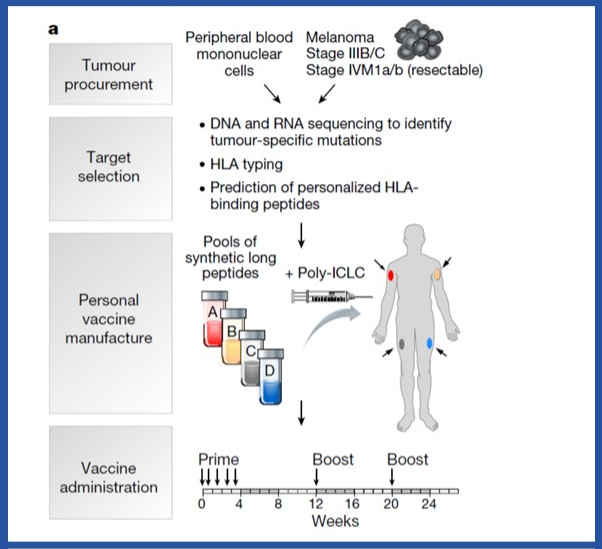
Investigator initiated crinical trials

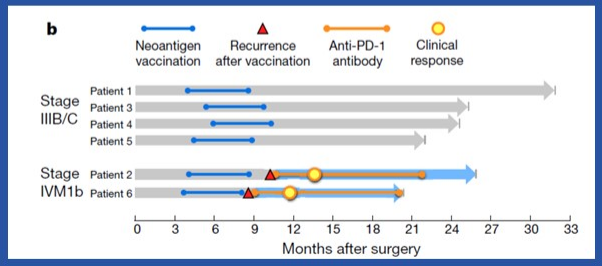
Clinical Studies for Personalized Immuno-oncology Therapies

Drug name	Developer	Format	Stage	Indications
NEO-PV-01	Neon Therapeutics	Peptide	Phase Ib	Melanoma, NSCLC, bladder
GEN-009	Genocea Biosciences	Peptide	Phase I/II	melanoma, NSCLC, SCCHN, Urothelial, renal
iNeo-Vac-P01	Hangzhou Neoantigen	Peptide	Phase I	Pancreatic, solid tumors
AGEN2003, AGEN2017	Agenus	HSP70 peptide	Phase I	Solid tumors
IVAC MUTANOME	BioNTech	mRNA	Phase I, phase II	Melanoma, TNBC, solid tumor
mRNA-4157, NCI-4650	Moderna Therapeutics	mRNA	Phase I	NSCLC, CRC, pancreatic
mRNA vaccine	Stemirna Therapeutics	mRNA	Phase I	Esophageal, NSCLC, Gastric, Pancreatic, CRC
VB10.NEO	Vaccibody	DNA	Phase I/II	Melanoma, NSCLC, bladder, renal, H&N
GNOS-PV01	Geneos Therapeutics	DNA	Phase I	GBM
GRANITE-001	Gritstone Oncology	Viral	Phase I/II	NSCLC, CRC, gastroesophageal, bladder
TG4050	Transgene	Viral	Phase I	Ovarian, H&N
RP1	Replimune	Oncolytic virus	Phase II	Melanoma, skin, bladder
Ruxotemitide	Lytix Biopharma	Oncolytic virus	Phase II	Melanoma, TNBC, breast, H&N, Lymphoma
bLAMP	Aduro Biotech	Bacterial	Phase I	CRC
ADXS-NEO	Advaxis	Bacterial	Phase I	NSCLC, CRC, H&N, melanoma, bladder
YE-NEO-001	NantBioScience	Yeast-based	Phase I	RC, Breast, Melanoma, Pancreatic, Liver, SCCHN
Neoantigen Vaccines	Likang Life Sciences	DC	Phase I	HCC
MDG 1011	Medigene	T cell-based	Phase I/II	AML, MDS, MM
NeoTCR-P1	PACT Pharma	T cell based	Phase Ia/Ib	Solid tumors
PACTN	PersImmune	T cell based	Phase I	Myelodysplastic Syndromes
IMA-101	Immatics	T cell based	Phase I	Solid tumors
IMA-201, IMA-202, IMA-203	Immatics	TCR-T	Phase I	Solid Tumors
TCR Sleeping Beauty	Ziopharm Oncology	TCR-T	Phase I	Solid tumors
Lifileucel, LN-145	Iovance Biotherapeutics	TIL based	Phase II	melanoma, solid tumors
ATL001	Achilles Therapeutics	TIL based	Phase I/II	NSCLC, melanoma

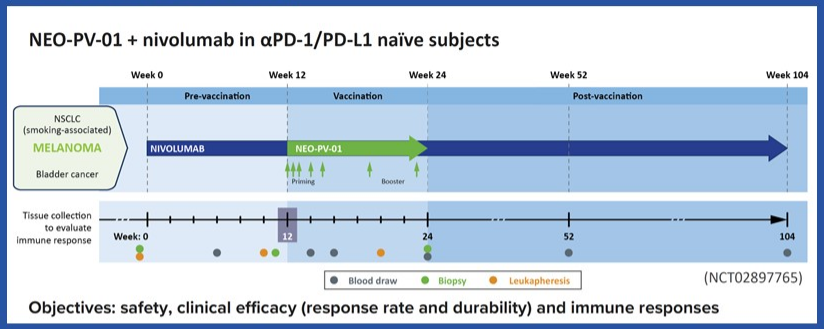
Personalized neoantigen peptide vaccine trial at DFCI and Neon Therapeutics

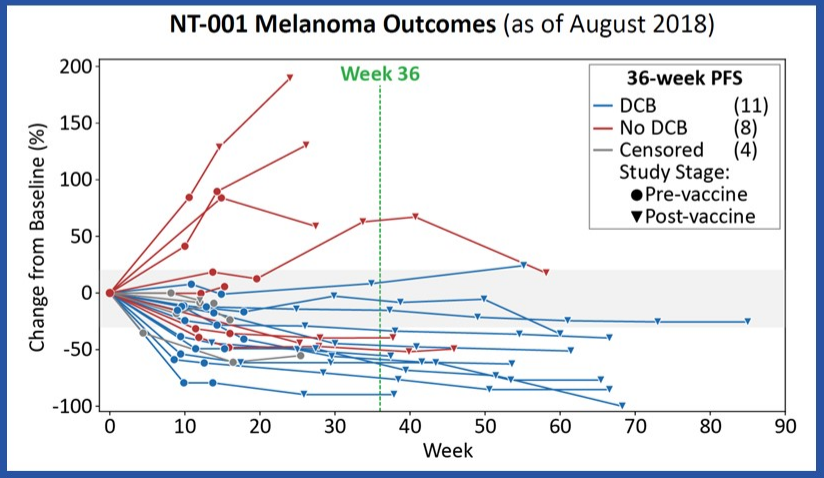
Phase I study (Ott et al., Nature. 2017)



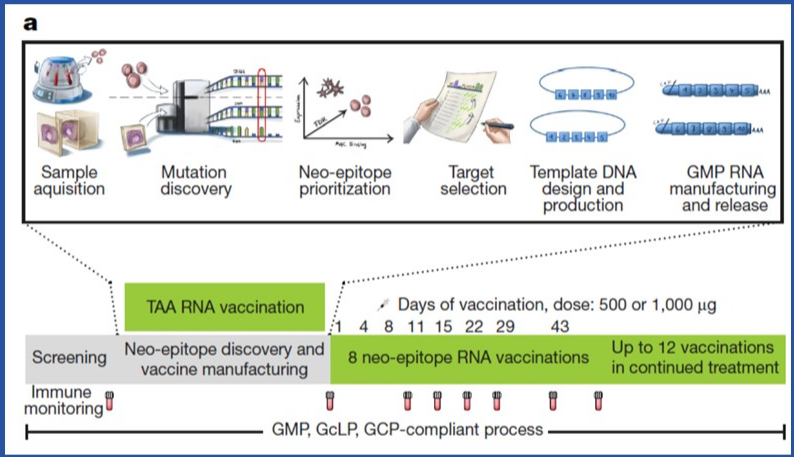


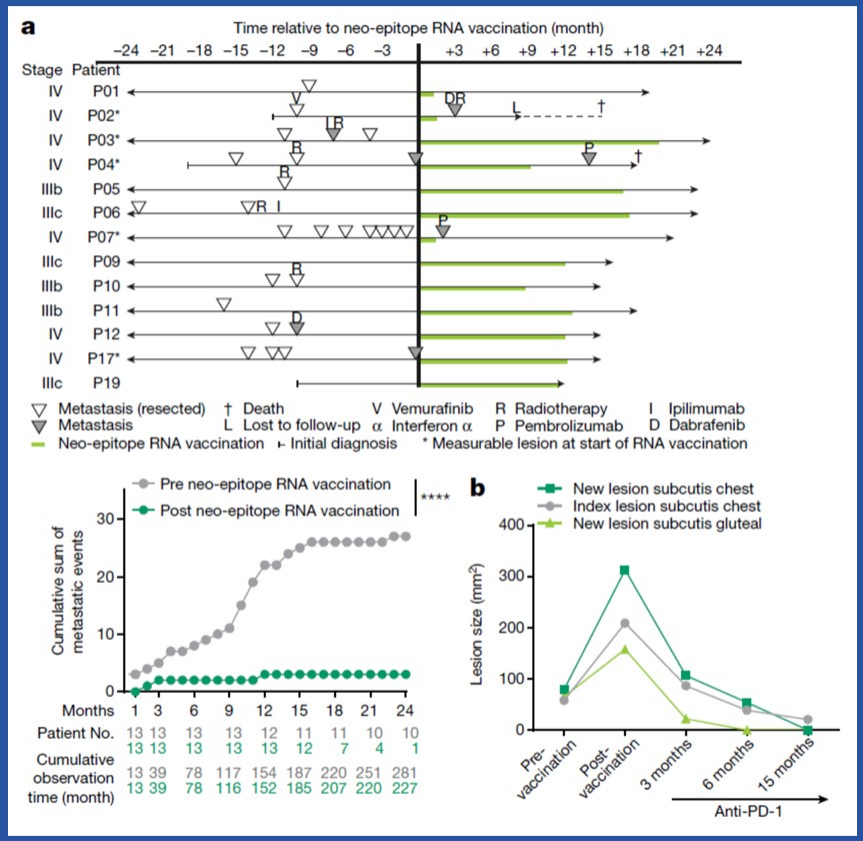
NT-001 Phase Ib study





Personalized RNA vaccine trial by TRON/BioNTech



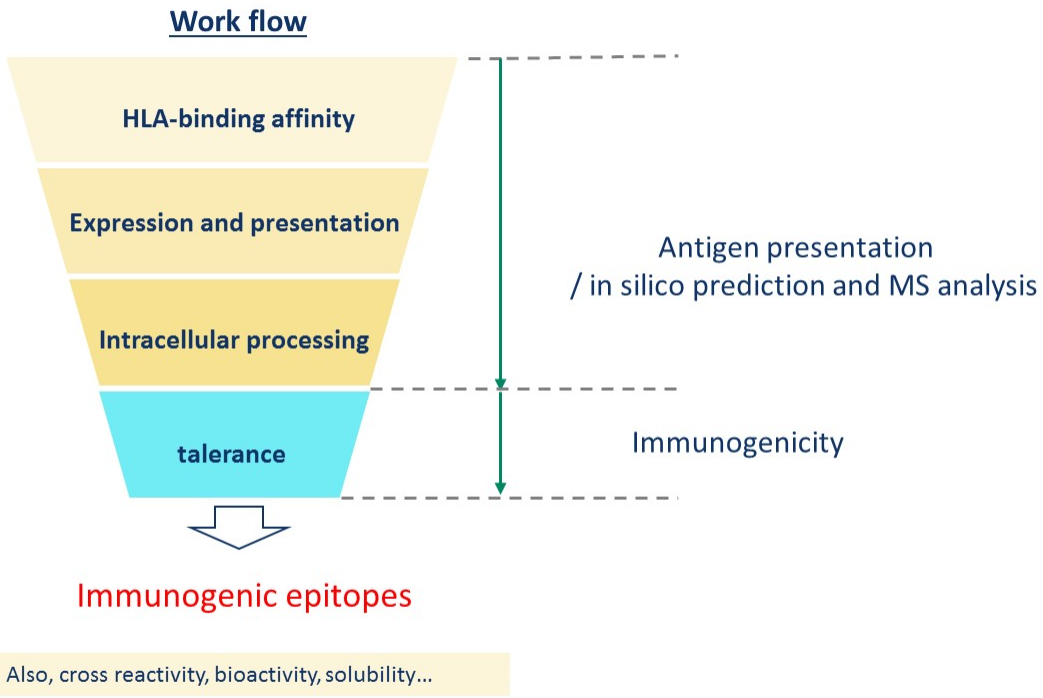


Sahin et al., Nature (2017)

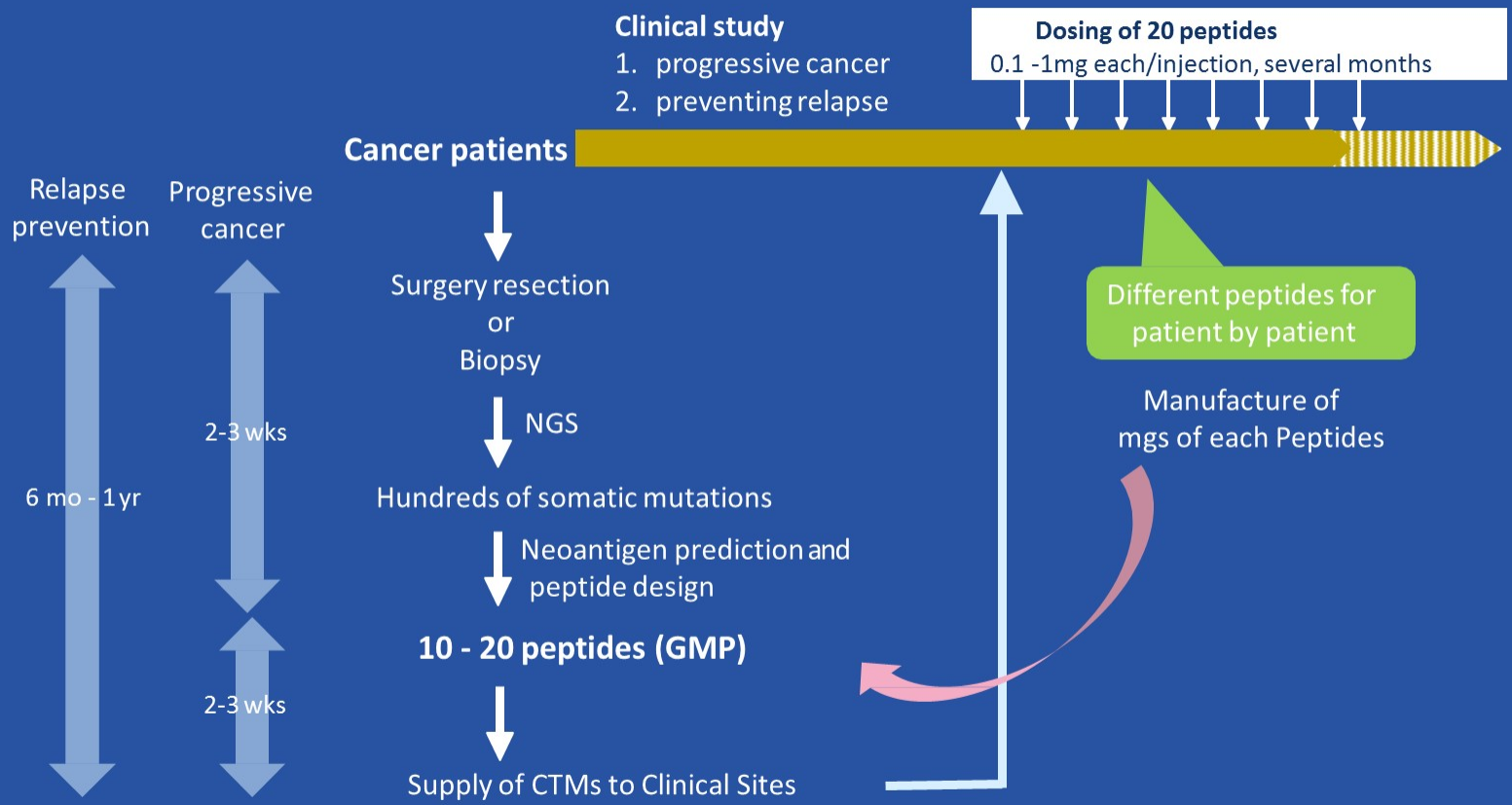
Peptide vaccine development

	Short Peptides / IFA	Long Peptides / PolyIC:LC
Pros	• Potentially earlier IND • Potentially less development cost • No one developing short peptides as a personalized cancer vaccine (Originality)	• Activation of $CD4^+$ T Cells as well as $CD8^+$ T Cells • Precede studies with long peptides showing promising efficacy
Cons	• Need to identify (predict) very peptide sequences to exactly bind MCH Class I • Activation of only $CD8^+$ T Cells ($CD4^+$ T Cells) in which less efficacy might be available	• Potentially higher development cost • To use new adjuvant (not approved yet) -> To require some additional Tox studies

Identification of neoantigens from patients



Personalized Peptide Vaccines from Identification of Neoantigens to their Dosing to Patients



Conclusions/Take-Away

- Immunotherapies targeting neoantigens were developed.
- Many Clinical Studies for Personalized Immuno-oncology Therapies is ongoing.
- We are also planning a clinical trial of peptide-based individualized vaccines in cooperation with Japanese company.