新抗原肽个体化纳米疫苗

—临床肿瘤治疗前沿技术—

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南京大学临床肿瘤研究所

治疗型疫苗——肿瘤免疫治疗

William B. Coley
细菌毒素
晚期肉瘤患者肿瘤消退
1893

肿瘤相关抗原:**MAGE1**
1991

1973
树突状细胞（DC）抗原提呈功能

2009
临床试验：**HPV-16**长肽疫苗对外阴上皮内瘤变有效

FDA首个批准的治疗性肿瘤疫苗：
Sipuleucel-T
2010

2015
临床试验：新抗原刺激的**DC**疫苗对黑色素瘤有效

临床试验：
NeoVax, 新抗原长肽疫苗对黑色素瘤有效
IVAC MUTANOME, 新抗原**mRNA**疫苗对黑色素瘤有效
2018

一般组成

疫苗

抗原

1.Tumor-associated

Overexpressed

Tissue differentiation

Cancer-testis

Oncofetal

2.Neoantigen

抗原形式

1.Protein/Peptide-based

2.Nucleic acid-based

DNA

mRNA

3.Cell-based

Whole tumour cells

Antigen-loaded DCs

4.Vector-based

Viral

Bacterial

佐剂

1.TLR agonist

Poly-ICLC

CpG ODN

Imiquimod

2.DC-targeted monoclonal antibody

DEC-205

CD40

3.Saponin-based

4.GM-CSF

5.STING ligands

运载体系

1.Emulsions

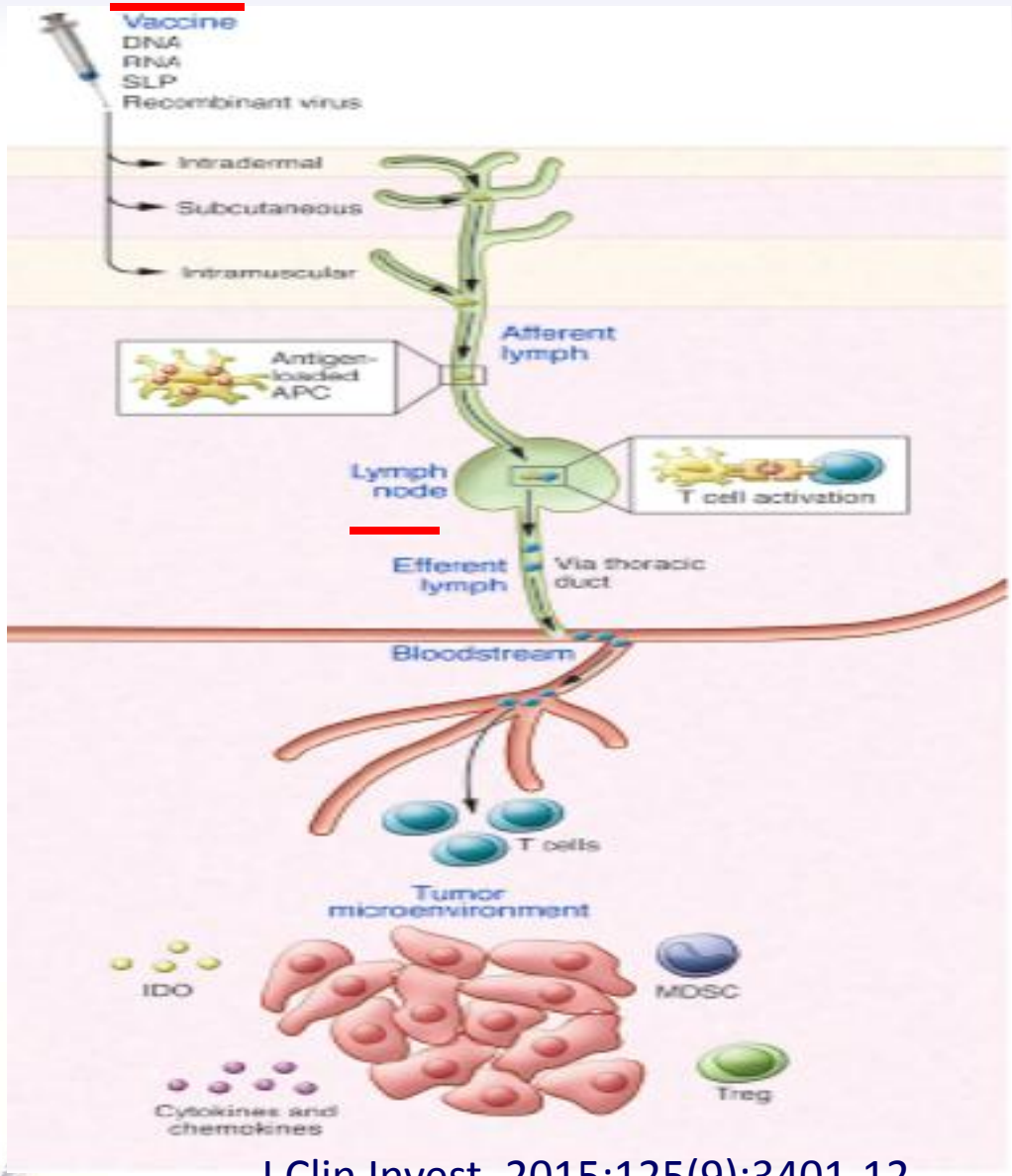
Montaide ISA-51

Montaide ISA-720

2.Liposomes

3.Virosomes

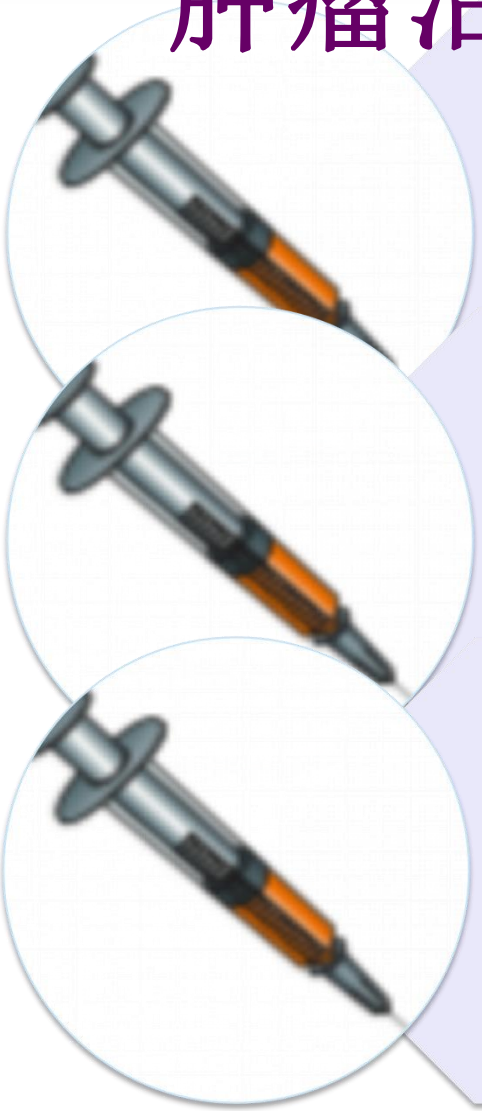
治疗型疫苗起效模式图



J Clin Invest. 2015;125(9):3401-12.

●肿瘤抗原及淋巴结高效富集是影响疫苗疗效的重要因素之一

肿瘤治疗型疫苗



传统模式

最新策略

我们的探索

PROVENGE (sipuleucel-T; Dendreon)

CCR Drug Updates

Clinical Cancer Research

PROVENGE (Sipuleucel-T) in Prostate Cancer: The First FDA-Approved Therapeutic Cancer Vaccine

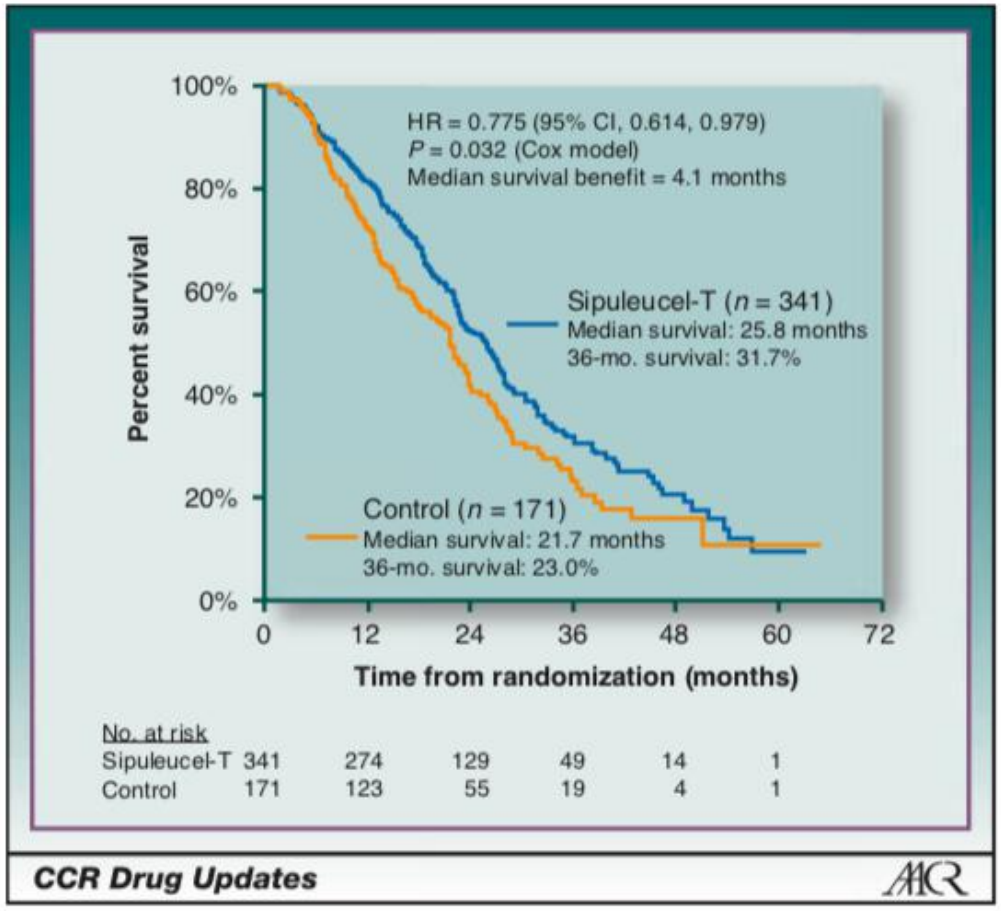
PROVENGE 疫苗的制备：

PAP-GM-CSF 融合蛋白体外与患者自身DC共孵育，40h后去除融合蛋白获得负载目标抗原的DC疫苗。

PAP：prostate acid phosphatase 前列腺酸性磷酸酶

根治性前列腺切除术后，体内主要残留的PAP来源是癌性前列腺组织。

治疗人群：patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC).



中位生存期：延长4.1个月

3年生存率：增高0.5倍

MDX-1379 (gp100 vaccine)

Completed Has Results	MDX-010 Antibody, MDX-1379 Melanoma **Vaccine**, or MDX-010/MDX-1379 Combination Treatment for Patients With Unresectable or Metastatic Melanoma	• Melanoma • Metastases	Phase 3	NCT00094653	September 2004	October 2009

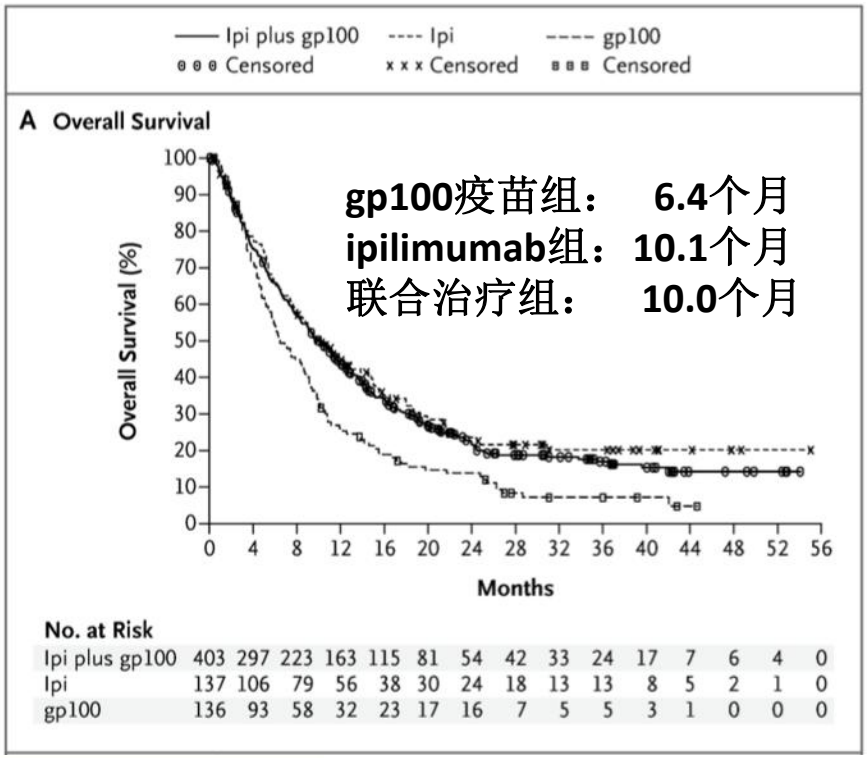
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

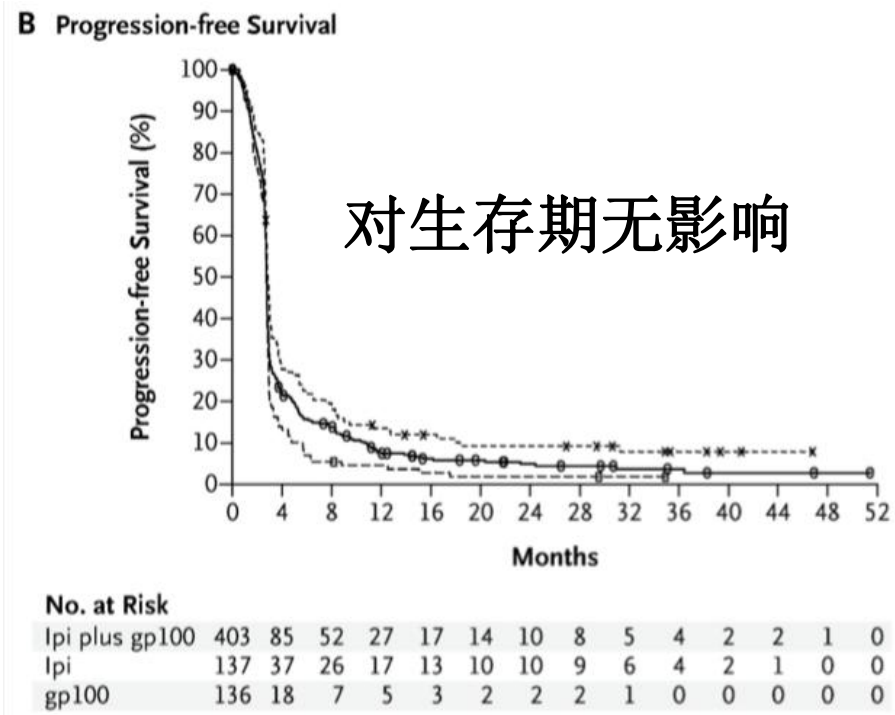
gp100疫苗联合Ipilimumab治疗晚期黑色素瘤患者

总生存期 OS



gp100疫苗组： 6.4个月
ipilimumab组：10.1个月
联合治疗组： 10.0个月

PFS



对生存期无影响

进行到III期的疫苗临床试验多数无进展或被迫中断

Phase 3	Antigen	Study Start	Study Completion	Condition	Intervention
Active, not recruiting	NY-ESO-1	2018.09	2023.06?	Sarcoma	CMB305 (lentiviral vector encoding NY-ESO-1 gene and NY-ESO-1 recombinant protein plus GLA-SE)
Terminated	MUC1	2009.09	2010.08	Breast Cancer	Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine)

Period Title: **Overall Study**

Started	11	5
Completed	1	0
Not Completed	10	5
Reason Not Completed		
Discontinuation of trial by sponsor	10	5

可能的原因

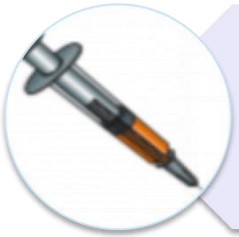
原因

1、肿瘤抗原的选择：胚胎或正常细胞也存在。

2、个体差异：不同个体间免疫学状况的差异。

3、肿瘤免疫微环境抑制：实体瘤微环境中含有很多免疫抑制因素：活化的T细胞会表达抑制性分子PD-1。

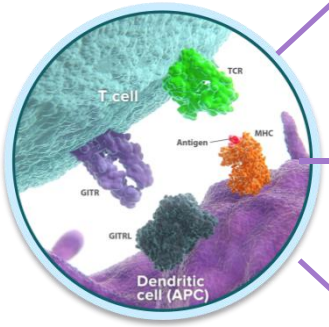
4、抗原难以有效投递：蛋白和多肽。机体的抗肿瘤免疫应答主要在次级淋巴器官中发生，抗原肽需被有效递呈至免疫效应细胞，才能发挥作用。



最新策略

- 新抗原疫苗
- 纳米疫苗
- 联合治疗

肿瘤抗原分类



肿瘤相关抗原

肿瘤组织高表达，正常组织亦表达
例如：EGFR，Her2…

癌睾抗原

肿瘤组织和睾丸组织表达
例如：NYESO-1，MAGE-A1 …

新抗原

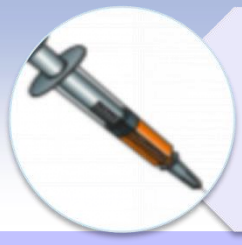
非人类正常基因组来源：
基因突变产物，例如：KRAS G12D …
致瘤病毒整合入基因组，例如：EBV-LMP2A …

◆新抗原（neoantigens）：

①未经胸腺阴性筛选，与T细胞受体（ TCR ）亲和力高，免疫原性强

②不会引起中枢和外周免疫耐受，能诱发强而持久的抗肿瘤免疫反应

③以新抗原为靶点的治疗，不损伤正常组织器官。



新抗原疫苗-DC疫苗

Science 2015

华盛顿大学医学院

A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells.

Row	Saved	Status	Study Title	Conditions	Phase	NCT Number	Study Start	Study Completion
1	☐	Completed	Dendritic Cells (White Blood Cells) Vaccination for Advanced Melanoma	• Melanoma	Phase 1	**NCT00683670**	August 2008	June 2016

生产方式：

1、利用**GM-CSF、IL-4 、irradiated (10,000 rad) GMP-grade CD40L-expressing K562 cells 、IFN-γ 、poly I:C** （TLR3激动剂）、**R848**（TLR8激动剂）

诱导DC成熟。

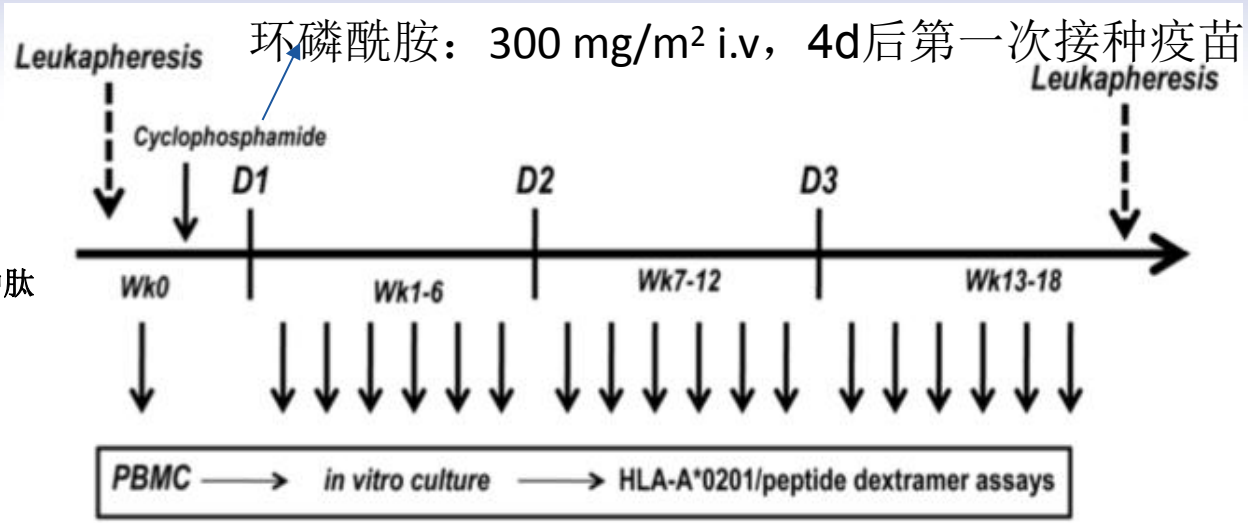
2、成熟DC分别负载**9个新抗原肽和2个gp100抗原肽**（ G209-2M和G280-9V，黑色素瘤高表达的癌睾抗原）。

3、质控：**DC分泌IL-12p70 水平。**

环磷酰胺：300 mg/m² i.v，4d后第一次接种疫苗。

D1：1.35x10⁸ 个DC （每种肽1.5x10⁷ 个DC ）

D2、3：4.5x10⁷ 个DC （每种肽5x10⁶ 个DC ）



3 例 既往接受伊匹单抗治疗的晚期黑色素瘤患者

病人	年龄	肿瘤分期	治疗	结局
MEL21	54	IIIc	3次DC疫苗	SD 9个月后PD
MEL38	47	IIIc	3次DC疫苗	SD 8个月后PD
MEL218	52	IIIc	3次DC疫苗	CR

可提高肿瘤特异性T细胞反应的广度和多样性。

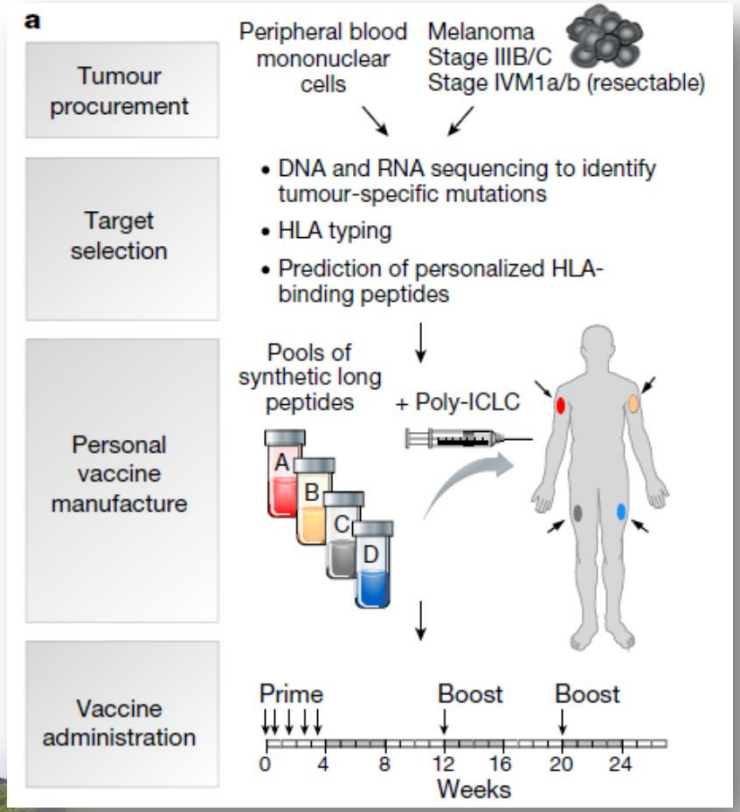
合成长肽疫苗

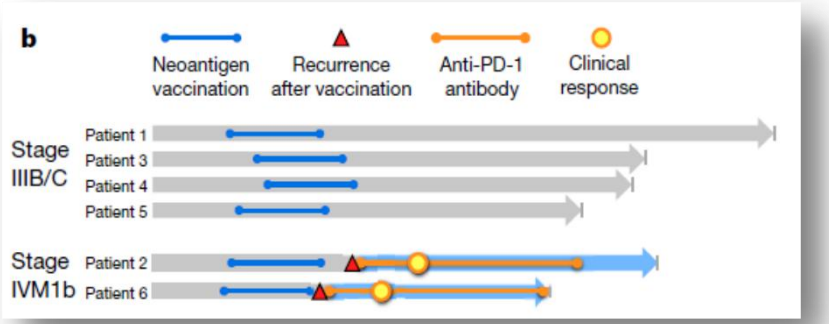
Nature 2017

Dana-Farber Cancer Institute

An immunogenic personal neoantigen vaccine for patients with melanoma.

Row	Saved	Status	Study Title	Conditions	Phase	NCT Number	Study Start	Study Completion
1	☐	Active, not recruiting	A Phase I Study With a Personalized NeoAntigen Cancer Vaccine in Melanoma	• Melanoma	Phase 1	NCT01970358	January 2014	January 2019





测序： WES和RNA-seq

T细胞表位预测： 预测20个长肽，每3-5个长肽一个pool，共计4个pool

疫苗接种： 0.3mg/肽+2mg poly-ICLC 皮下接种
第 1, 4, 8, 15, 22天 (priming phase)
以及第 12 and 20周 (booster phase)

研究对象：

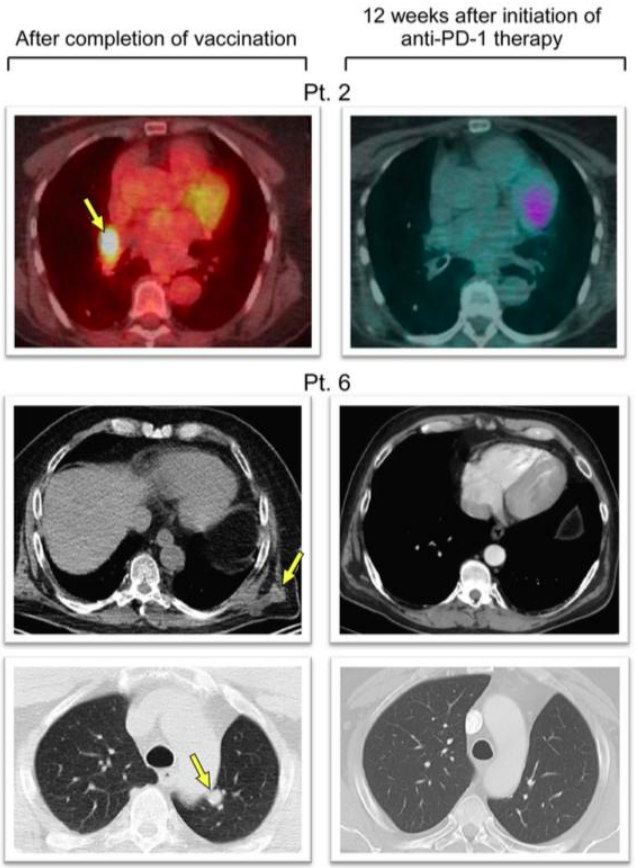
10名黑色素瘤病人：全外显子测序和RNA测序

6名患者注射疫苗，其中4名IIIB/C期，2名IVM1a/b期（肺转移）

安全性及疗效评估：接种日~治疗后36周。

安全性（不良反应记录）：每次接种时及接种一周后，每三个月随访一次。

疗效评估：CT/PET/CT，每6个月一次。



疗效：

4/6名III期患者肿瘤在32个月内无复发；

2/6 IV期患者疫苗接种后复发，在接受PD-1单抗治疗后CR。

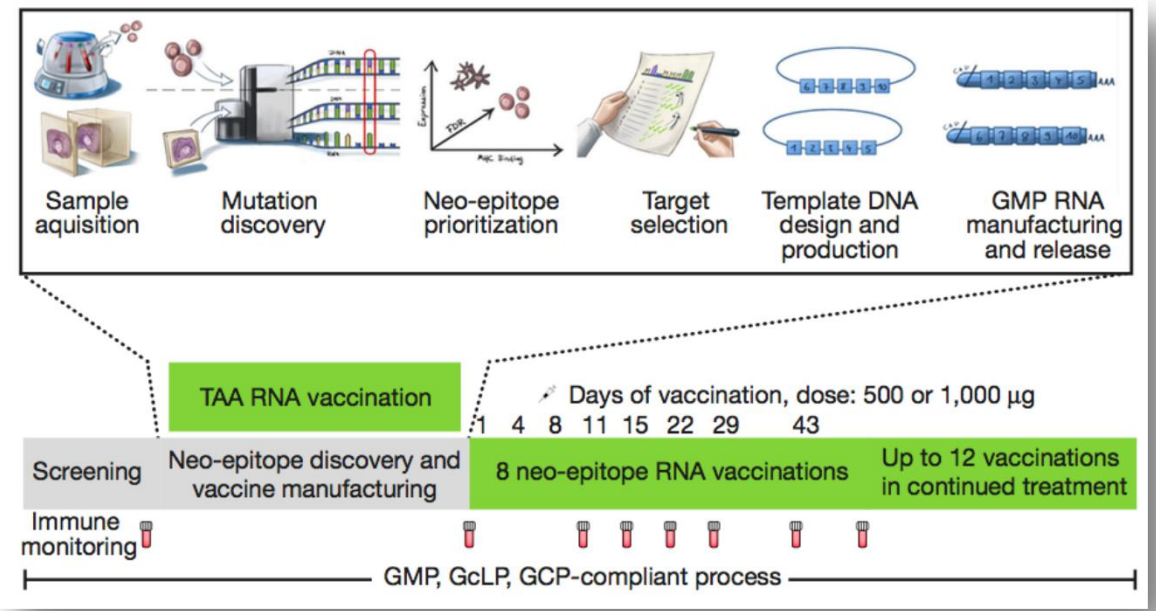
新抗原疫苗-RNA疫苗

Nature 2017

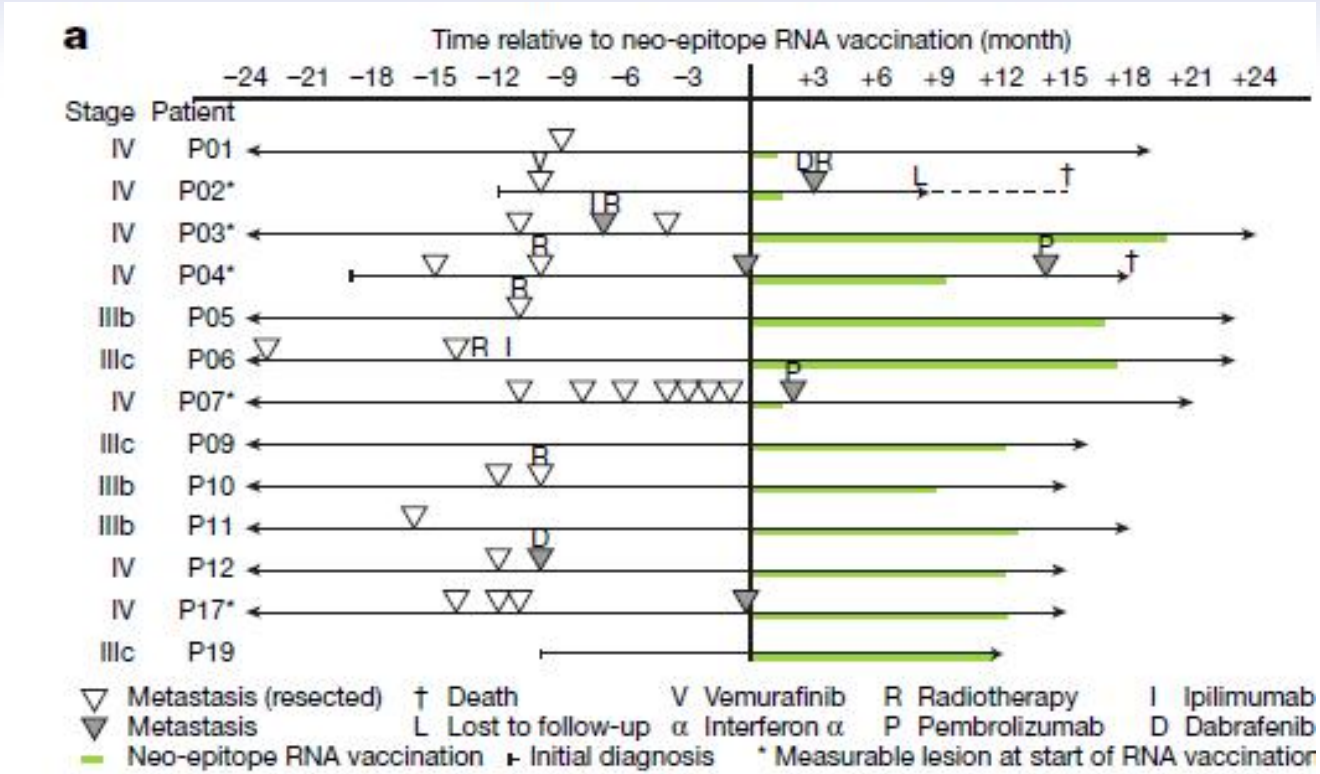
德国

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer.

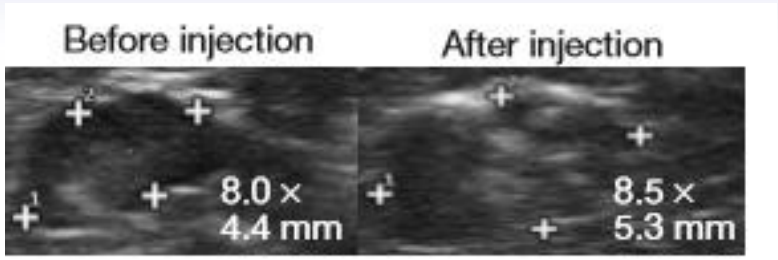
Row	Saved	Status	Study Title	Conditions	Phase	NCT Number	Study Start	Study Completion
1	☐	Active, not recruiting	IVAC MUTANOME Phase I Clinical Trial	• Melanoma	Phase 1	NCT02035956	December 2013	March 2019



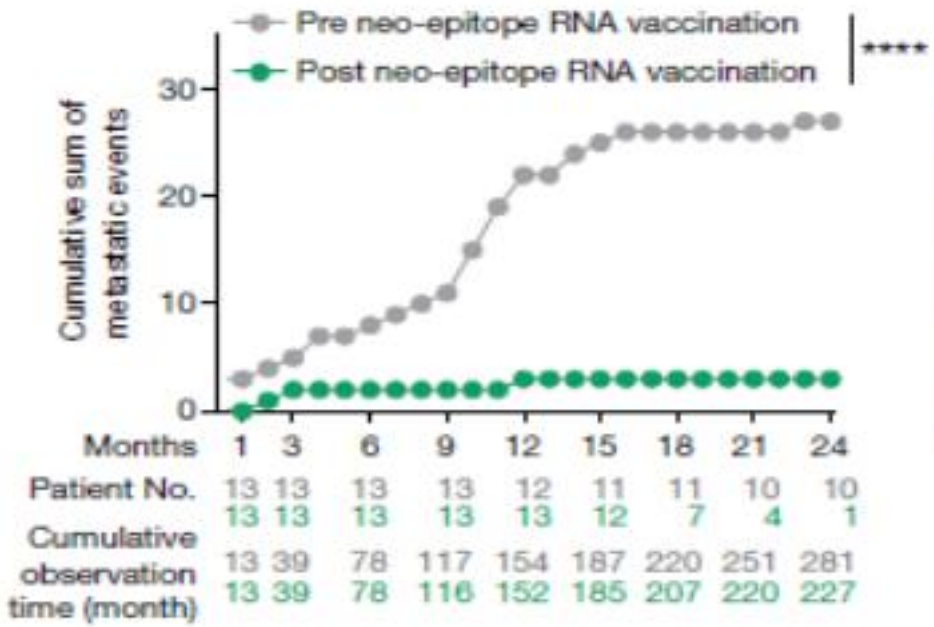
患者进入临床研究前测序筛选neoantigens，筛选设计两个效果好的RNA疫苗。
此外试验中还会用两个肿瘤相关抗原肽RBL001/RBL002，
若肿瘤表达NY-ESO-1/tyrosinase，在RNA疫苗之前使用，否则跳过这一步。

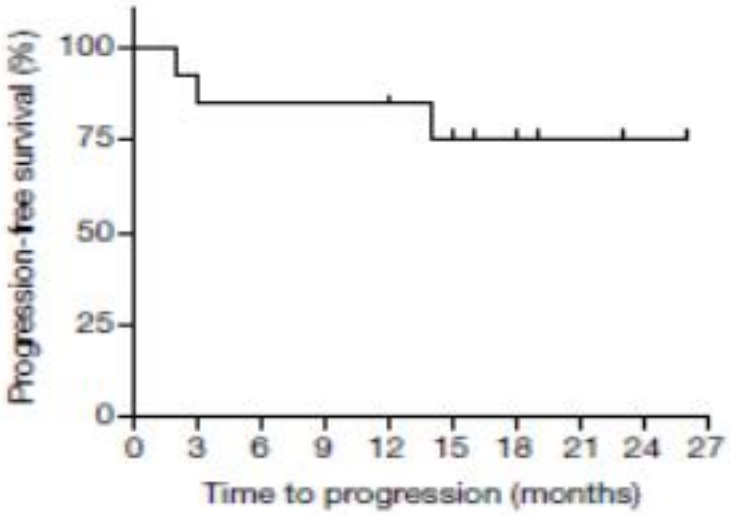


8/13黑素瘤III或IV期患者23月内无复发，
2/5（接种时即有转移）患者病灶缩小，
P04由于出现具有免疫逃逸功能的肿瘤细胞短时间内复发死亡，
P07接受PD-1抑制剂治疗后CR。


Before injection
After injection
8.0 × 4.4 mm
8.5 × 5.3 mm

淋巴结注射


Pre neo-epitope RNA vaccination
Post neo-epitope RNA vaccination
****
Cumulative sum of metastatic events
30
20
10
0
Months 1 3 6 9 12 15 18 21 24
Patient No. 13 13 13 13 12 11 11 10 10
13 13 13 13 13 12 7 4 1
Cumulative observation time (month) 13 39 78 117 154 187 220 251 281
13 39 78 116 152 185 207 220 227


Progression-free survival (%)
100
75
50
25
0
0 3 6 9 12 15 18 21 24 27
Time to progression (months)

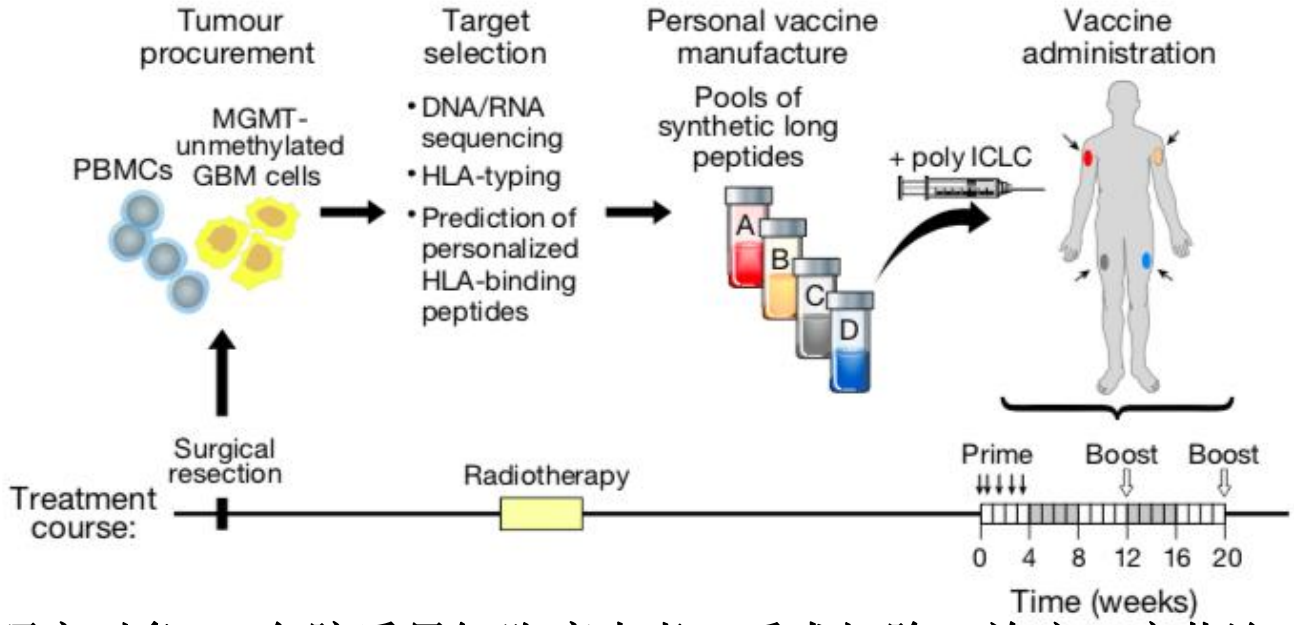
合成长肽疫苗

Nature 2019

Dana-Farber Cancer Institute

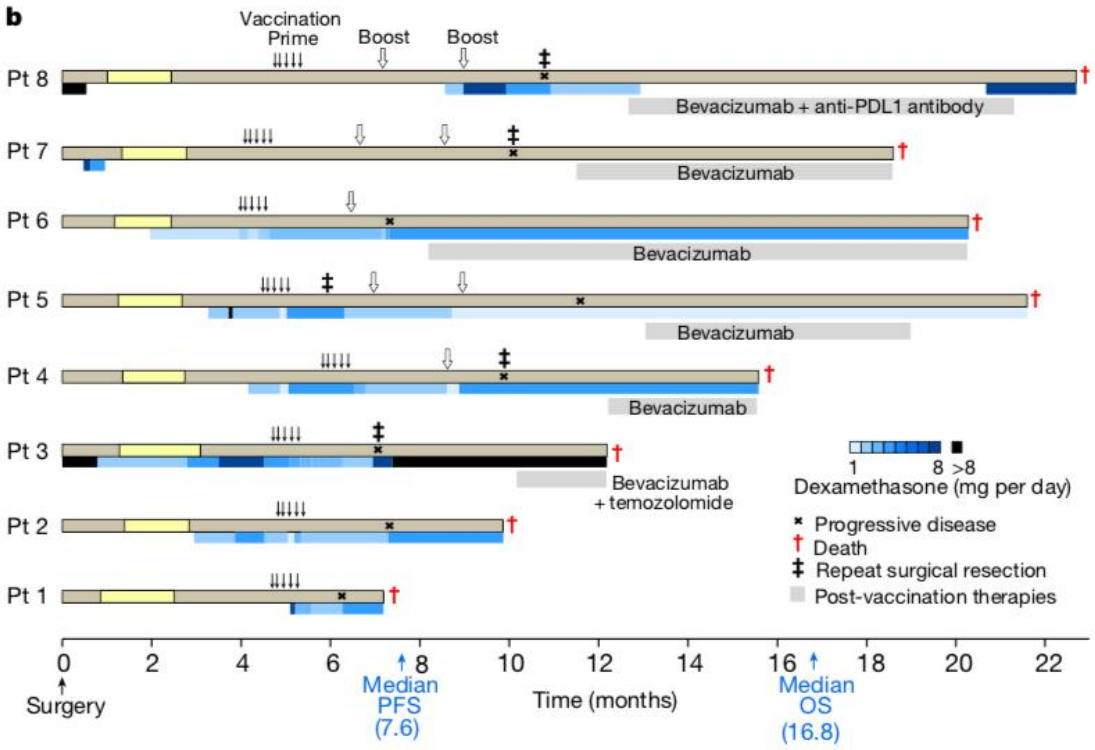
Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial

Row	Saved	Status	Study Title	Conditions	Phase	NCT Number	Study Start	Study Completion
1	☐	Active, not recruiting	Personalized NeoAntigen Cancer Vaccine With RT Plus Pembrolizumab for Patients With MGMT Unmethylated, Newly Diagnosed GBM	• Glioblastoma • Gliosarcoma • Glioblastoma With Oligodendroglial Features • (and 5 more...)	Phase 1	NCT02287428	November 2014	August 2020



研究对象：8名胶质母细胞瘤患者，手术切除、放疗、疫苗治疗。

无进展生存期为7.6个月　总生存期16.8个月

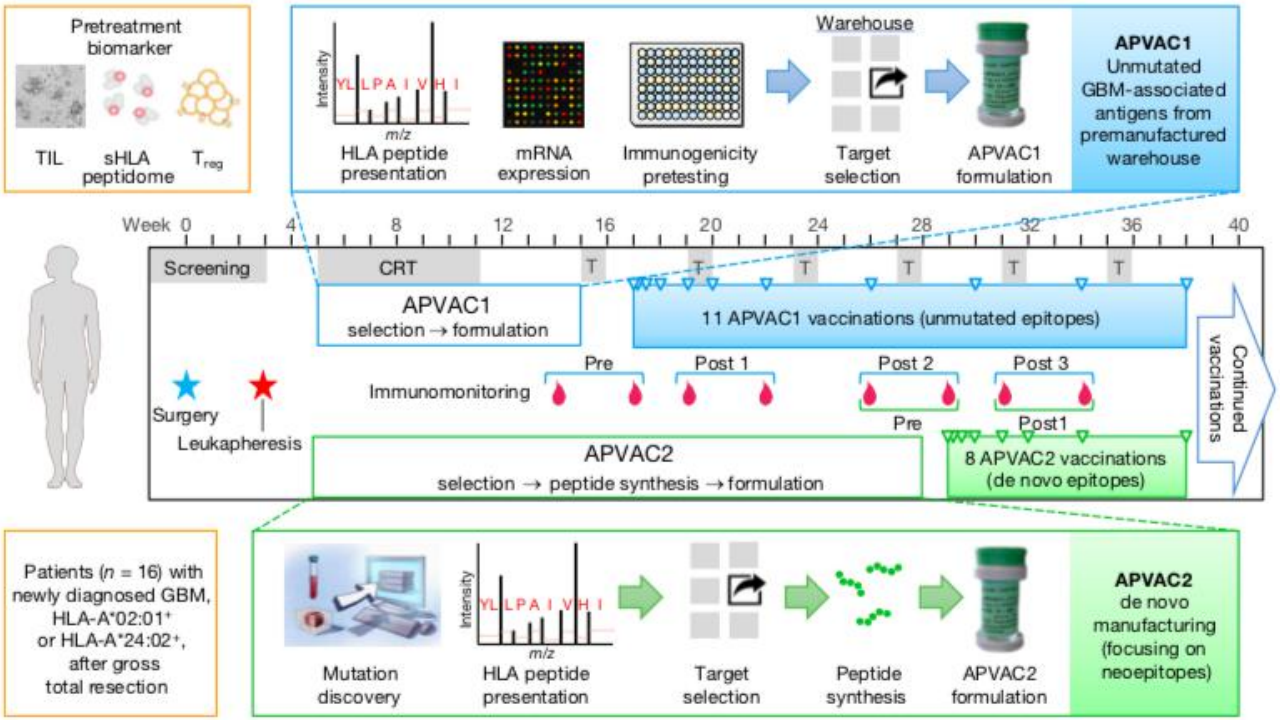


新抗原疫苗-肽疫苗

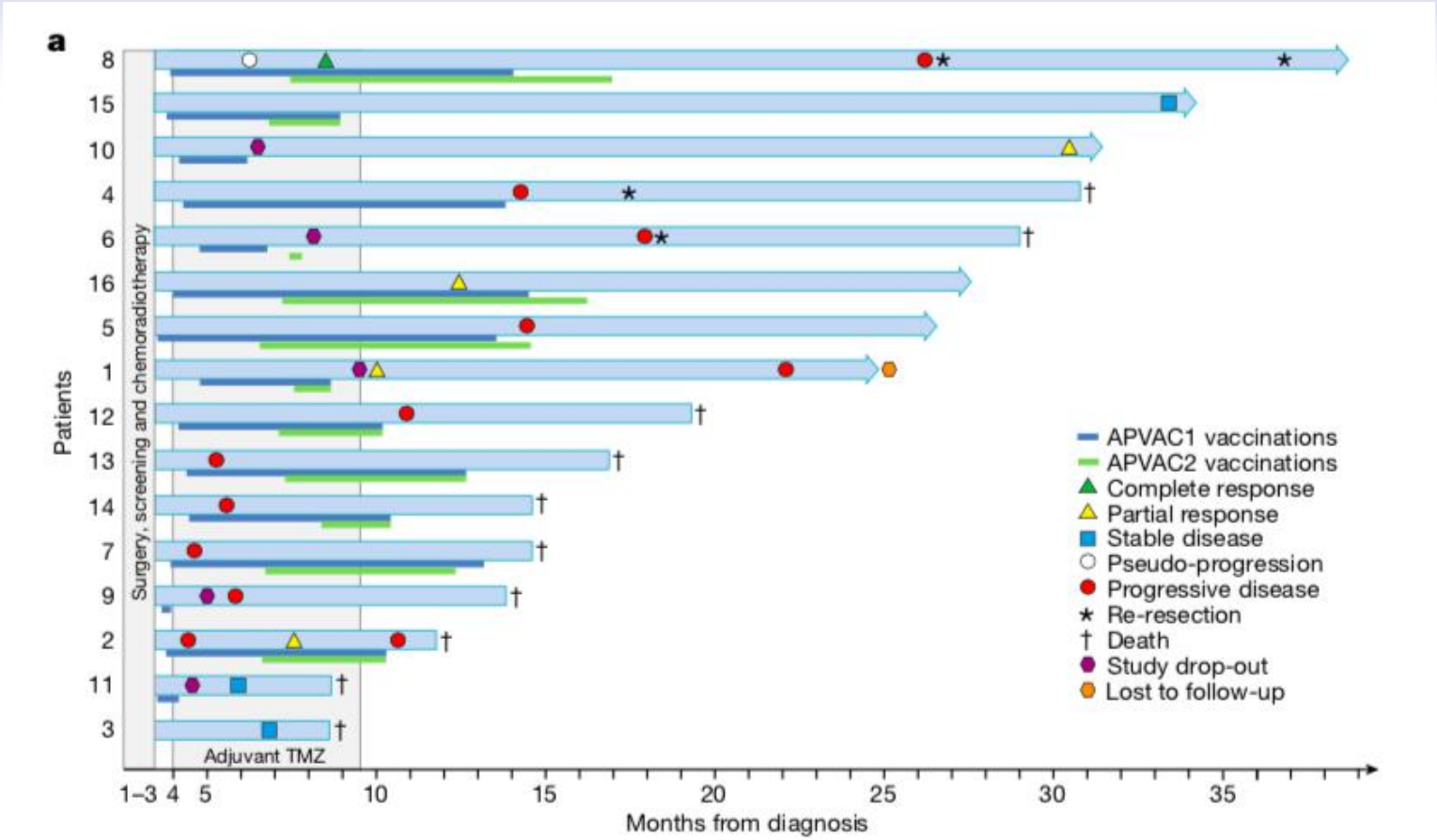
Nature 2019
德 国

Actively personalized vaccination trial for newly diagnosed glioblastoma

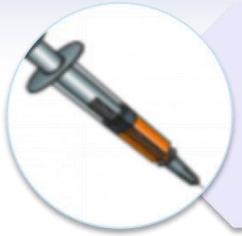
Row	Saved	Status	Study Title	Conditions	Phase	NCT Number	Study Start	Study Completion
1	☐	Completed	GAPVAC Phase I Trial in Newly Diagnosed Glioblastoma Patients	• Glioblastoma	Phase 1	NCT02149225	October 2014	June 2018



APVAC1：非突变抗原肽疫苗　　APVAC2：突变抗原肽疫苗


a
Patients
8
15
10
4
6
16
5
1
12
13
14
7
9
2
11
3
Surgery, screening and chemoradiotherapy
Adjuvant TMZ
1–3 4 5 10 15 20 25 30 35
Months from diagnosis
APVAC1 vaccinations
APVAC2 vaccinations
Complete response
Partial response
Stable disease
Pseudo-progression
Progressive disease
Re-resection
Death
Study drop-out
Lost to follow-up

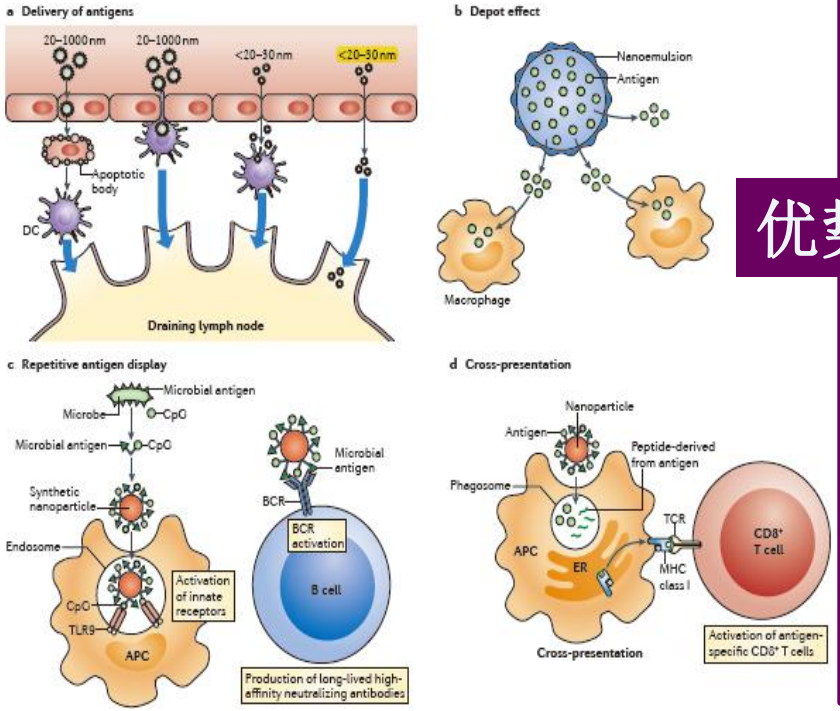
中位生存期16.8个月



最新策略

- 新抗原疫苗
- 纳米疫苗
- 联合治疗

纳米粒子在疫苗治疗中的优势



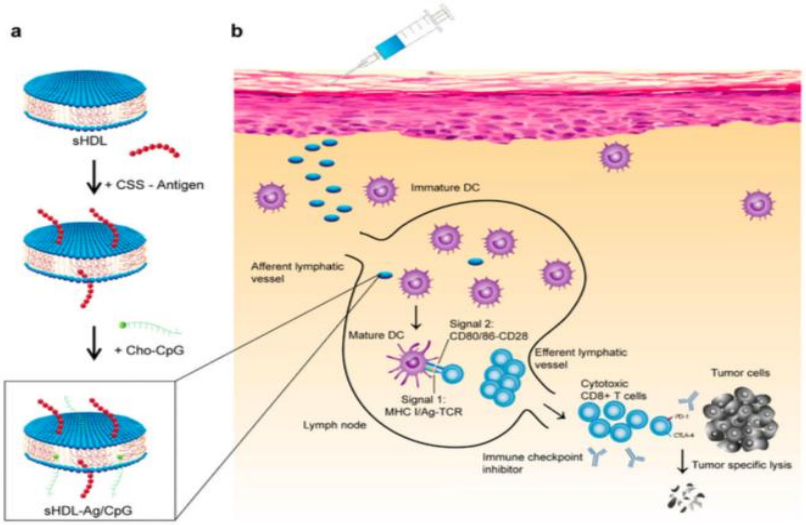
优势

1、纳米粒子容易集中于淋巴结、脾脏等淋巴器官中。（5-100 nm ）

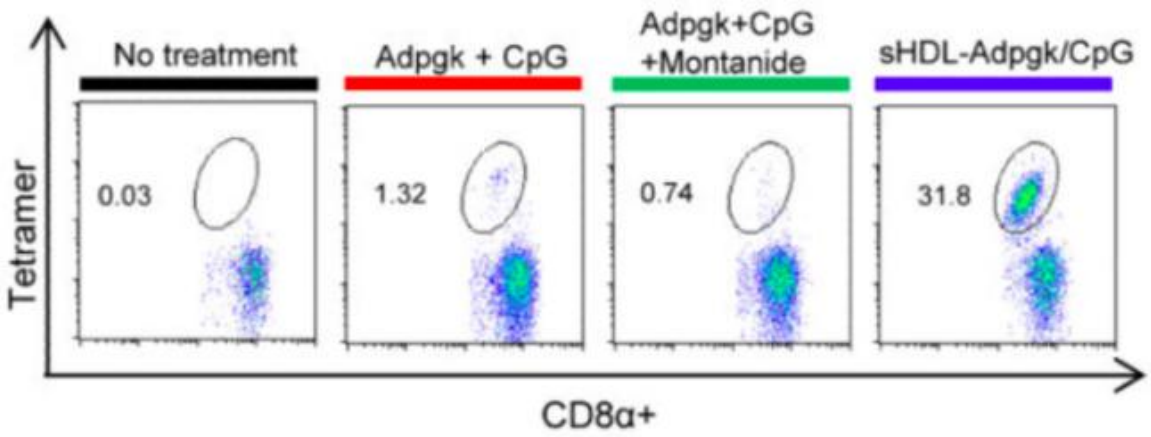
2、可同时负载多种不同药物，在同一时空发挥作用。

3、药物缓释、控释功能，避免抗原被降解，延长所负载抗原的半衰期 。

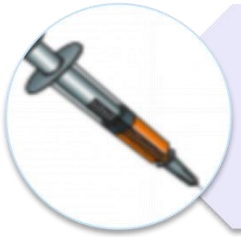
Nat Rev Immunol. 2013;13(8):592-605. Eur J Immunol . 2008;38(5):1404-13.
Vaccines (Basel). 2015 ;3(3):662-85.



与传统裸肽皮下免疫相比，将抗原肽与佐剂采用纳米粒子负载后再进行皮下接种，可将新抗原反应性 T 细胞的数量提高近 30 倍，有效抑制肿瘤生长。



Kuai R Designer vaccine nanodiscs for personalized cancer immunotherapy. Nature materials. 2017; 16: 489-96.



最新策略

- 新抗原疫苗
- 纳米疫苗
- 联合治疗

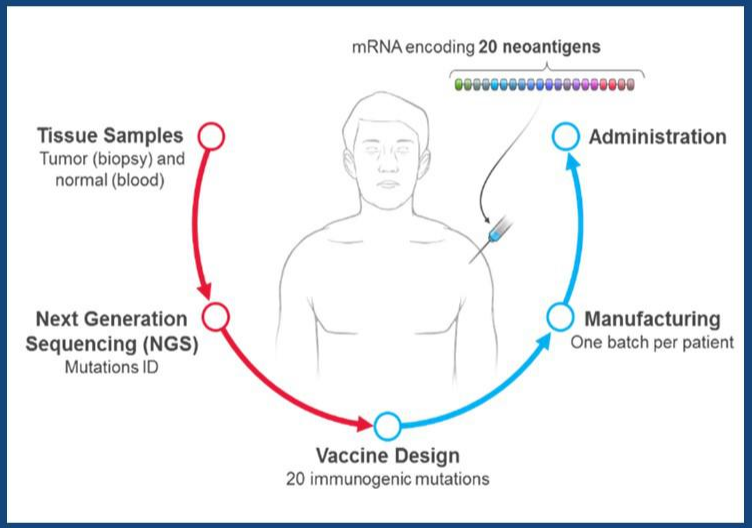
联合治疗

Table 2. Rationale for therapeutic cancer vaccine combinations.

	Rationale
Cytokines (IL, INF, TGF-β)	• Stimulate humoral and cellular immunity • Promote epithelial to mesenchymal transition • Promote differentiation of immature T-cells into Tregs and effectors T-cells • Promote dendritic cell maturation • Chemoattractant for neutrophils and MDSCs
Radiotherapy (External beam and radiopharmaceuticals)	• Enhance destruction of tumor cells via • upregulation of MHC, Fas, ICAM-1 and TAAs • Enhance vaccine-mediated tumor lysis • Increased inflammation and secretion of immunomodulatory cytokines • Sensitize tumor cells to immune-mediated killing
Checkpoint inhibitors (anti-CTLA-4/anti PD-1/PDL-1)	• Immunogenic intensification • Increased inflammation within the tumor • Reduction of Tumor burden • Activation of different T-cell population
Small molecules (TKIs/ HDACi)	• "Off-target" effects on immune cells (i.e., decreasing Tregs, decreasing MDSCs, increasing INF-g producing T-cells, and decreasing IL-4 producing T-cells • Sensitize cells to immune-mediated killing • Increase the protein expression of antigen presenting machinery
Endocrine Therapy	• Inducing thymic regeneration leading to increased production of naive T cells and CD4+ effector T cells. • Decrease Tregs within the tumor
Chemotherapy (including low dose CTX)	• Sensitize cells to immune-mediated killing • Decrease MDSCs and Tregs • Increase immune-supportive M1 macrophages, including CD4+ and CD8+ T-regs • Reduction of tumor burden • Induction of tumor immunsurveillance by NK cells • Enhance immunity by inhibiting Tregs, by enhancing DC maturation and by promoting of a durable T-cell memory response (low dose CTX)

Gatti-Mays ME. Cancer vaccines: Enhanced immunogenic modulation through therapeutic combinations. Hum Vaccin Immunother. 2017; 13: 2561-74.

A Phase 1, Open-Label, Multicenter Study to Assess the Safety, Tolerability, and Immunogenicity of mRNA4157 Alone in Subjects With Resected Solid Tumors and in Combination With Pembrolizumab in Subjects With Unresectable Solid Tumors (Keynote 603)

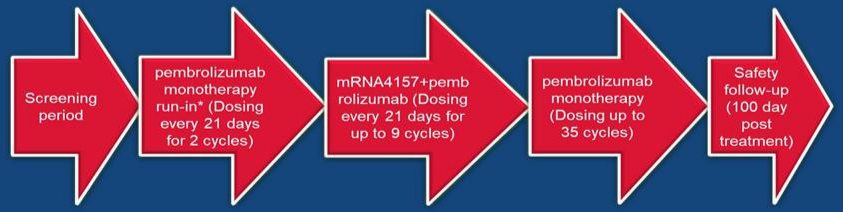


Dose escalation cohorts

Part A (Adjuvant patients): Monotherapy mRNA4157	0.04 mg n=3	0.13 mg n=6	0.39 mg n=3	1.0 mg n=3
Part B (Metastatic patients): mRNA4157 + pembrolizumab	0.04 mg n=3	0.13 mg n=4	0.39 mg n=7	1.0 mg n=5

Histologies in part A and B:

- NSCLC
- SCLC
- Cutaneous melanoma
- HPV negative HNSCC
- Bladder urothelial carcinoma
- MSI high malignancies
- TMB high malignancies



Keynote 603: Safety and PD Correlatives

- Total patients (A+B) n=36
  Part A=13 patients, Part B=23 patients
- Adverse Events (no grade 4/5)
  - Part A: Gr 2 only (limb pain, colitis, fatigue, myalgia)
  - Part B monotherapy: Gr 2 anemia and dyspnea, Gr 3 diarrhea, pancreatic enzyme elevation, AST elevation, GGT elevation
  - Part B combo therapy: Gr 2 fatigue
  - No DLT identified
- Outcomes Part A (n=13)
  - All patients have completed full course (9 cycles)
  - 11/13 remain disease free
- Outcomes Part B (n=23)
  - 20 patients received at least 1 dose
  - CR n=1 (MSI-H CRC), PR n=5 (2/5 patients with PD on prior IO therapy), SD n=7, PD n=6

- PCV based on 20 neoantigens
- Neoantigen-specific T cell responses were evaluated both *ex vivo* (unexpanded; post vaccination) and *in vitro* stimulated (IVS, expanded)
  - Flow cytometry: increase in % frequency of CD8 T cells producing IFNγ 7d post 4th vaccine dose to multiple neoantigens

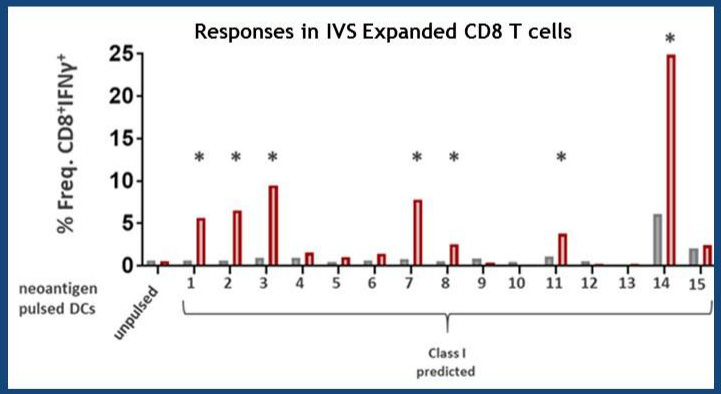


Figure 1-1 Part A: Adjuvant patients receiving mRNA-4157 monotherapy

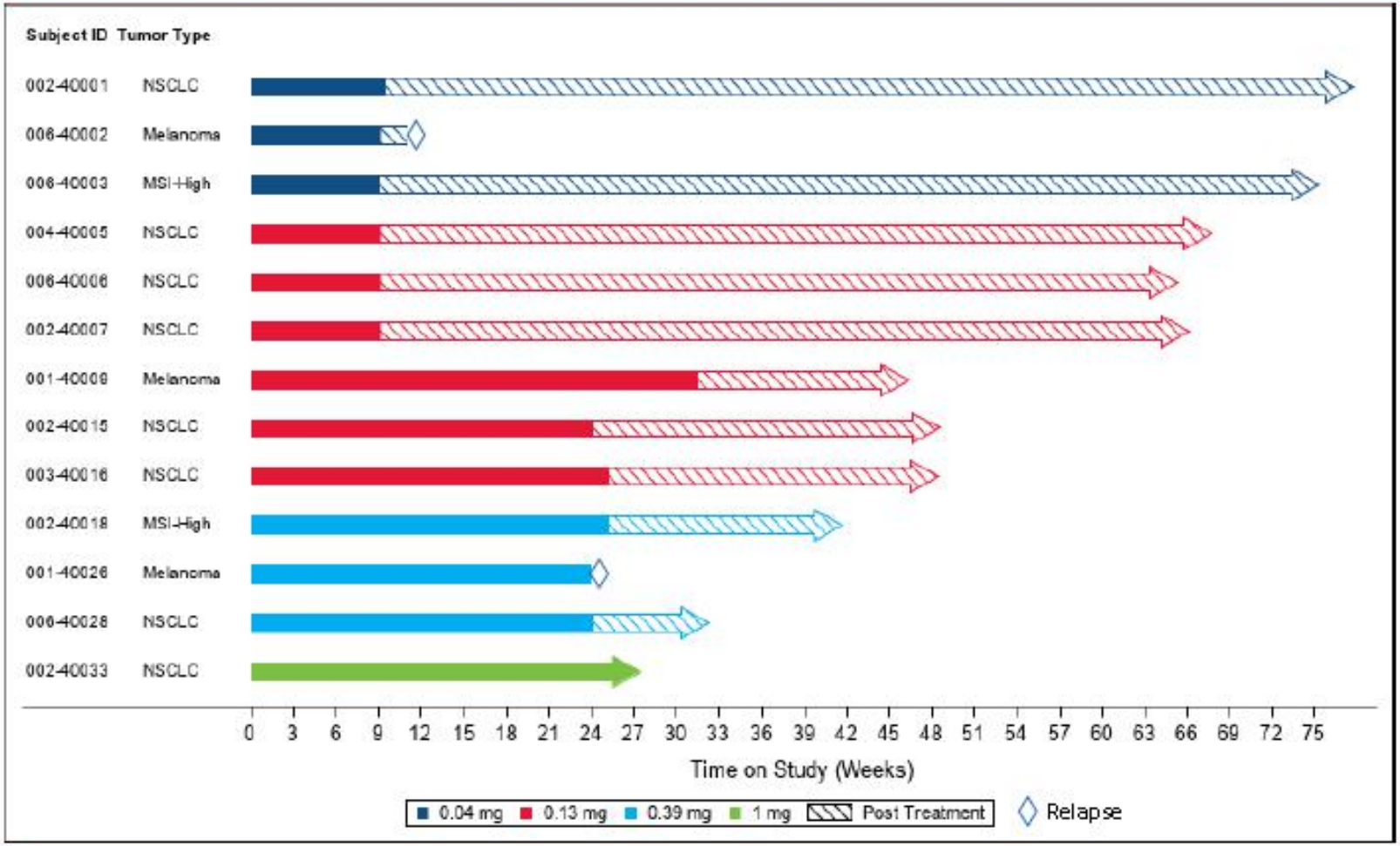
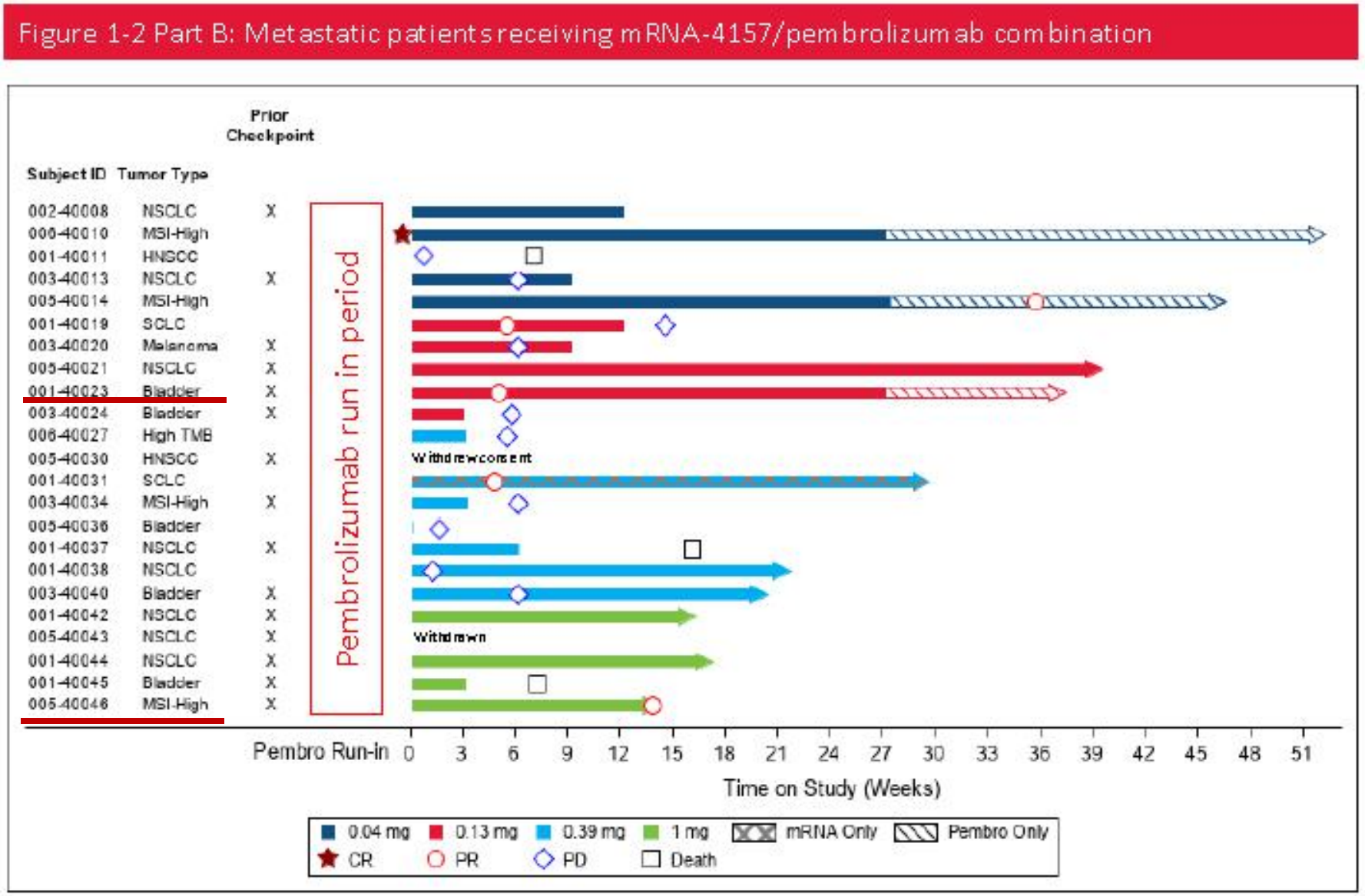
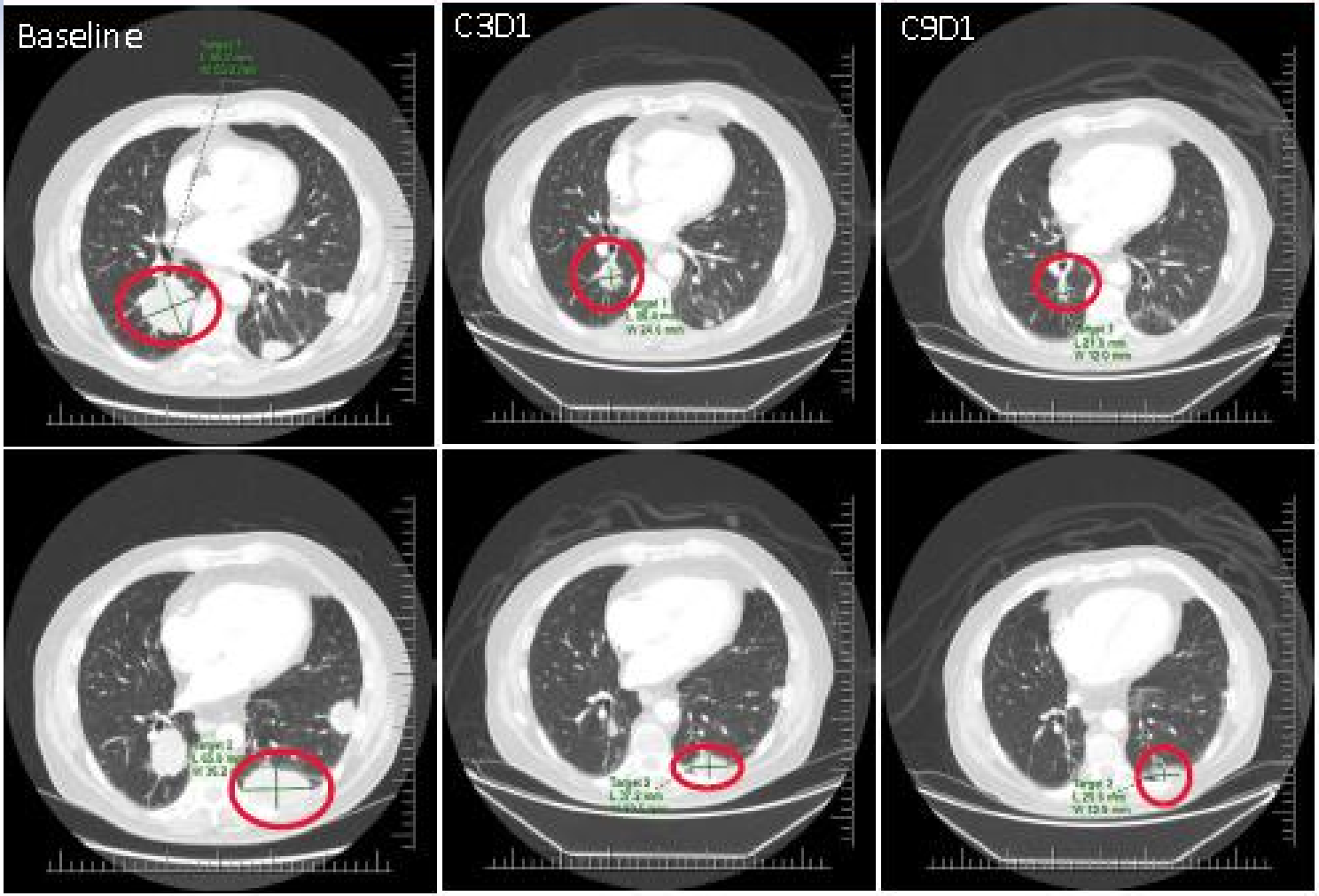


Figure 1-1: 13 adjuvant patients have been treated with mRNA-4157. All 13 patients have completed full course of vaccination per protocol. 11 patients remain disease free up to 75 weeks on study.

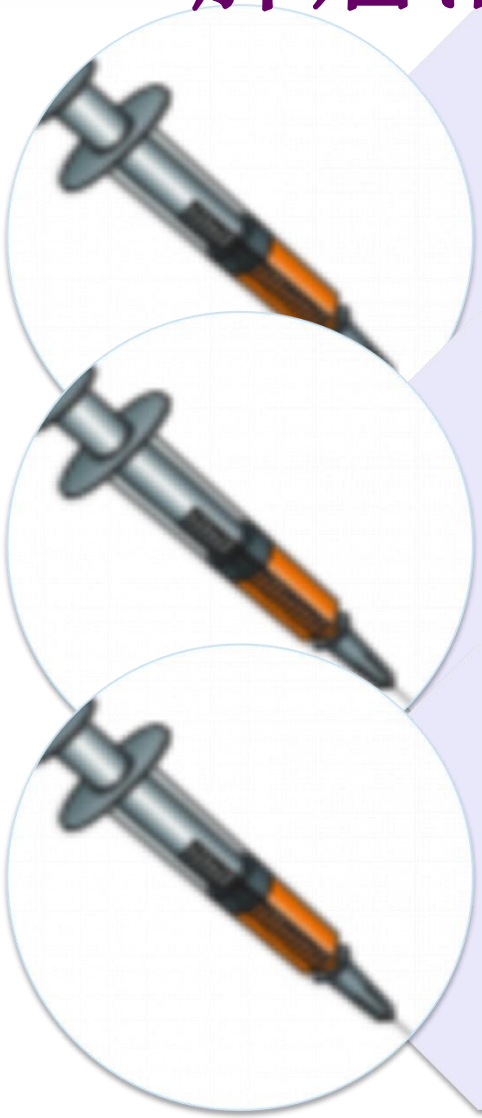


20名患者，有1例达到CR，5例PR，6例SD，8例PD，其中有40023和40046为抗PD-1抗体耐药患者，在接受疫苗后肿瘤再次缩小



Patient 40023 with bladder urothelial carcinoma was previously treated with radical cystoprostatectomy, cisplatin/gemcitabine, HRS7-SN38, four cycles of atezolizumab, and vinorelbine along with a frontal lobe resection with radiation for a brain metastasis. After 2 cycles of monotherapy pembrolizumab and 2 cycles of mRNA-4157/pembrolizumab combination, patient had a partial response and has continued to improve while on study.

肿瘤治疗型疫苗

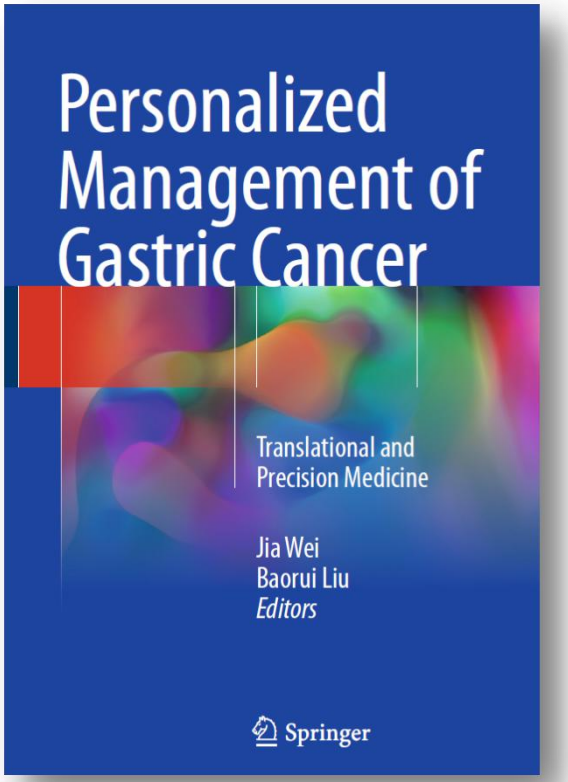


传统模式

最新策略

我们的探索

理论基础


Personalized
Management of
Gastric Cancer
Translational and
Precision Medicine
Jia Wei
Baorui Liu
Editors
Springer


肿瘤个体化与靶向免疫治疗学
刘宝瑞 主编
科学出版社

doi: 10.3872/j.issn.1007-385X.2015.04.019

· 转化医学 ·

胃癌免疫治疗新趋势:个体化肽疫苗

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2018; 8(15): 4238-4246. doi: 10.7150/thno.24387

Review

Personalized cancer neoantigen vaccines come of age

Yanhong Chu#, Qin Liu#, Jia Wei, Baorui Liu✉

The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

#These authors contributed equally to this work.

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工作基础： 新抗原肽库构建及鉴定

新抗原肽库构建

前期已预构建针对胃癌的肽库，体外筛选验证免疫原性

TCGA、CSOMIC 数据库中挖掘出 17 种常见实体瘤突变率>5%的驱动基因

中国各地区骨髓库、血库中证实的高频 HLA-A、B、C 位点

进一步筛选出突变基因中的热点突变（hotspot）

中国人群分布>15%的 HLA 位点

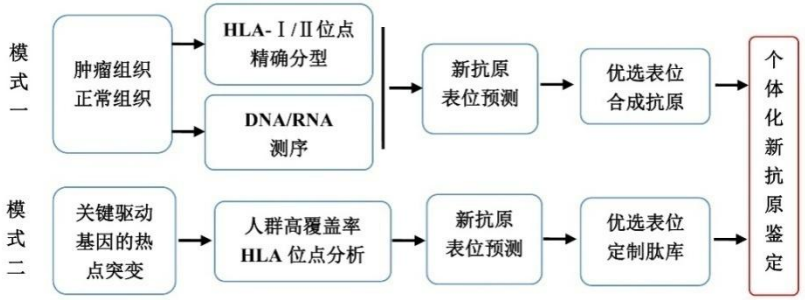
基于肽-MHC 亲和力、稳定性，与 TCR 的相互作用，抗原肽递呈效率和酶切评分等多个方面的免疫信息学工具行多肽表位预测

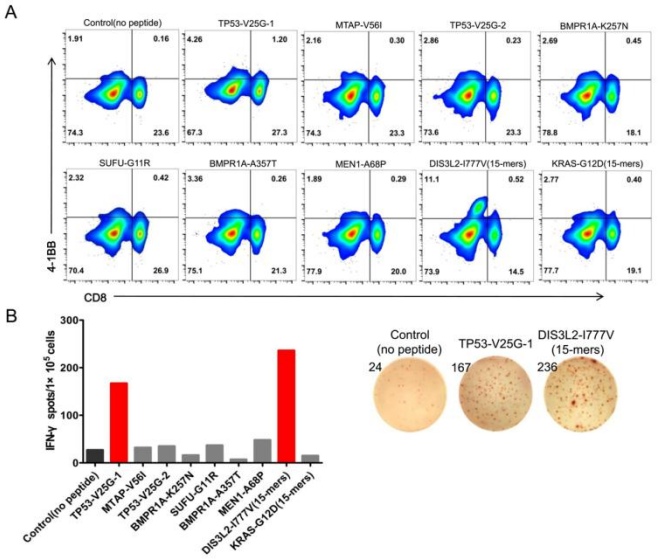
优化出常见实体瘤的驱动热点突变对应的中国人群常见 HLA 分型的最佳表位肽 21 条，合成、鉴定、纯化，并开展抗原筛选的预实验

将针对胃癌中突变率>1%的基因中的热点突变，同时纳入CT抗原、EBV-LMP2A抗原，结合中国人群HLA特征，丰富胃癌肽库至85条肽

不同模式指导下的个体化新抗原鉴定

原创性的构建两种抗原筛选模式，并成熟运用于临床试验中



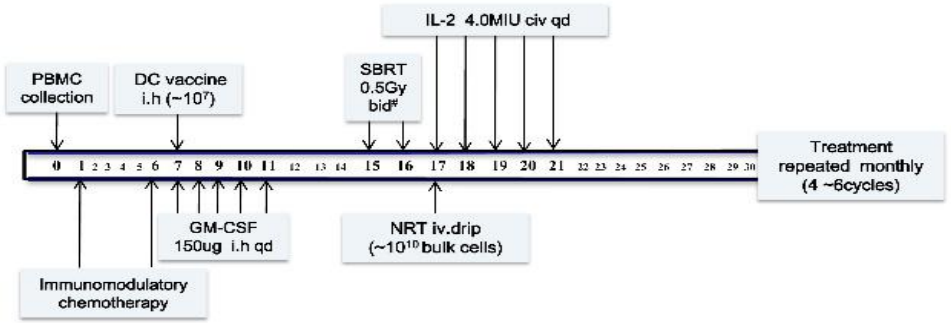


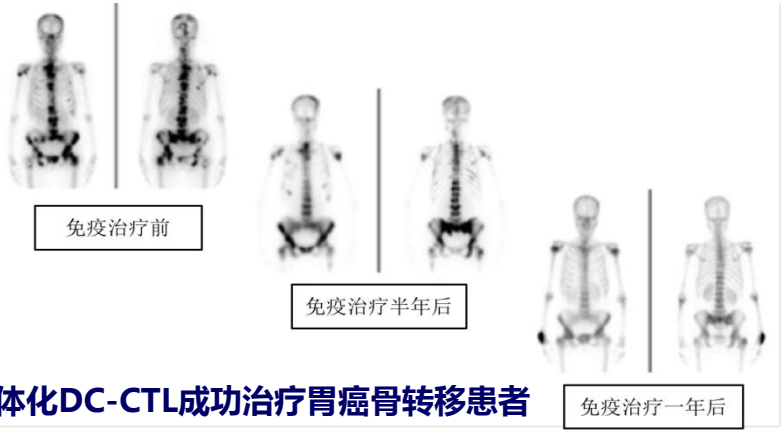
个体化新抗原鉴定(申请者病例-FCM+ELISPOT)

工作基础： 新抗原细胞免疫治疗

国内率先建立不同新抗原筛选模式指导下的精准免疫治疗体系，并已取得预期临床疗效

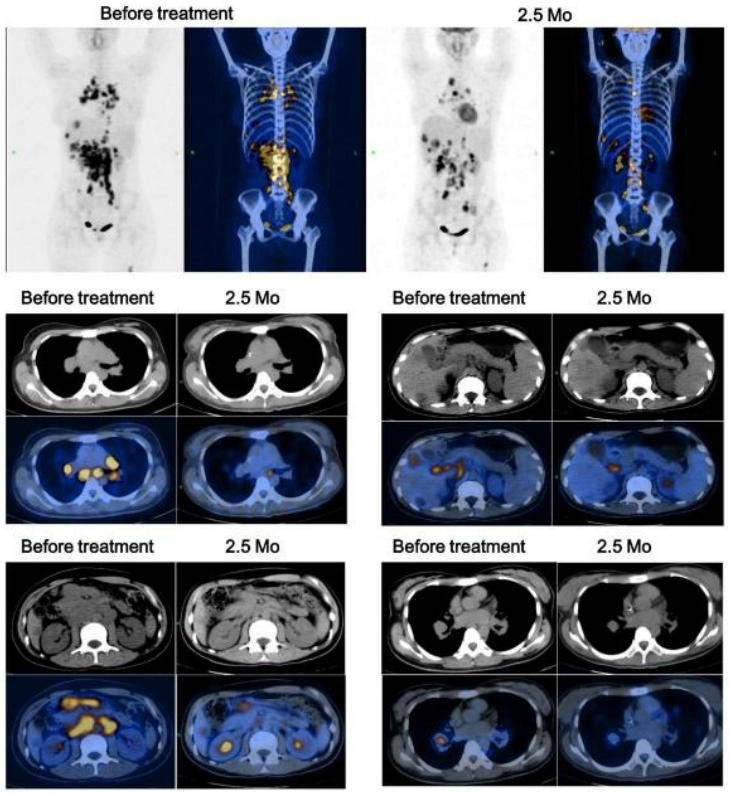
新抗原为基础的精准免疫治疗临床试验治疗流程图





个体化DC-CTL成功治疗胃癌骨转移患者

1例多线治疗失败患者免疫治疗2.5月后的疗效评估



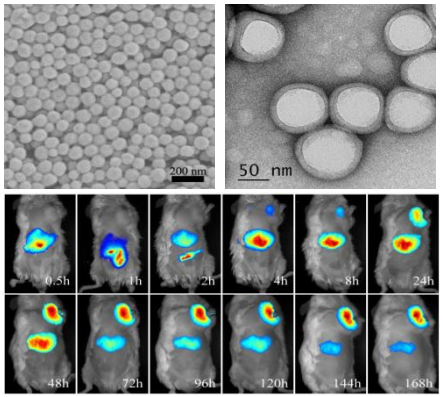
（Data unpublished）

工作基础：纳米药物投递系统研究

纳米载体研究基础

●独立研发明胶酶靶向的肿瘤微环境智能响应型纳米药物载体

●构建多种基于细胞膜的仿生型纳米药物载体



- 多种载体类型（高分子医用材料、天然生物材料）
- 多种治疗药物（化疗药物、基因药物、中药单体）
- 多种给药途径（全身、腹腔、瘤内）
- 多种治疗模式结合（化疗、放疗）

研究成果多次获奖

名称	类别	级别	年份
明胶酶智能靶向纳米药物系统的建立及对胃癌的疗效与机理研究	教育部科技进步奖	二等奖	2016
胃癌靶向纳米药物投递新体系的基础临床研究	中华医学科技奖	三等奖	2015
胃癌靶向纳米药物投递新体系的基础临床研究	江苏省科技进步奖	二等奖	2015
胃癌靶向纳米药物投递新体系的基础临床研究	江苏省医学科技奖	二等奖	2015

发表相关SCI论文50余篇，申请专利3项

获得国家自然科学基金项目10项

最新发表论文 IF 13.25

JCI The Journal of Clinical Investigation

Neoantigen identification strategies enable personalized immunotherapy in refractory solid tumors

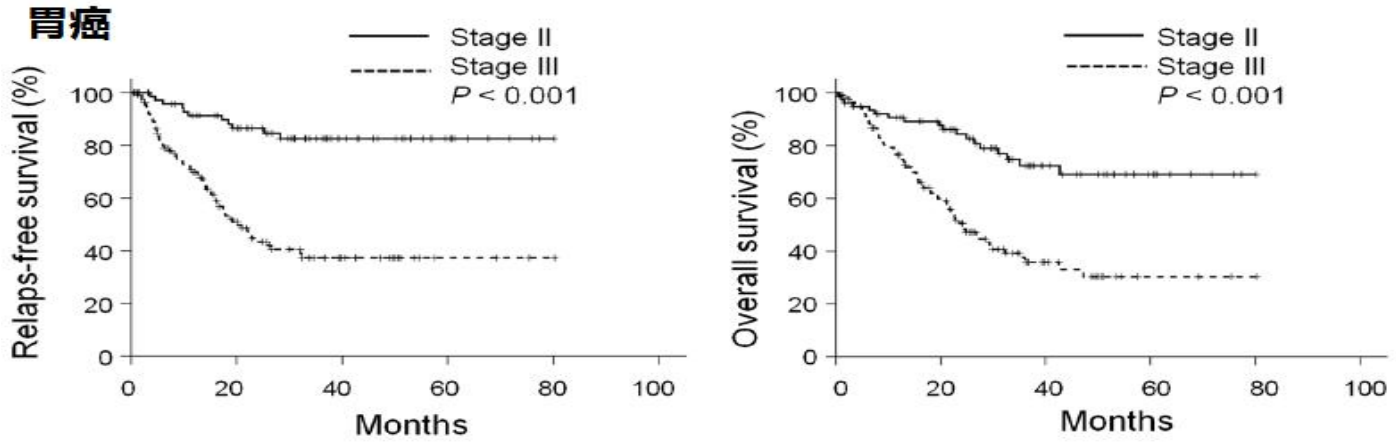
Fangjun Chen, … , Jia Wei, Baorui Liu

J Clin Invest. 2019. https://doi.org/10.1172/JCI99538.

Clinical Medicine In-Press Preview Immunology Oncology

BACKGROUND. Recent genomic and bioinformatic technological advances have made it possible to dissect the immune response to personalized neoantigens encoded by tumor-specific mutations. However, timely and efficient identification of neoantigens is still one of the major obstacles to using personalized neoantigen-based cancer immunotherapy.

胃癌IIIb-c术后辅助治疗后



如何进一步防止复发？

临床转化之一

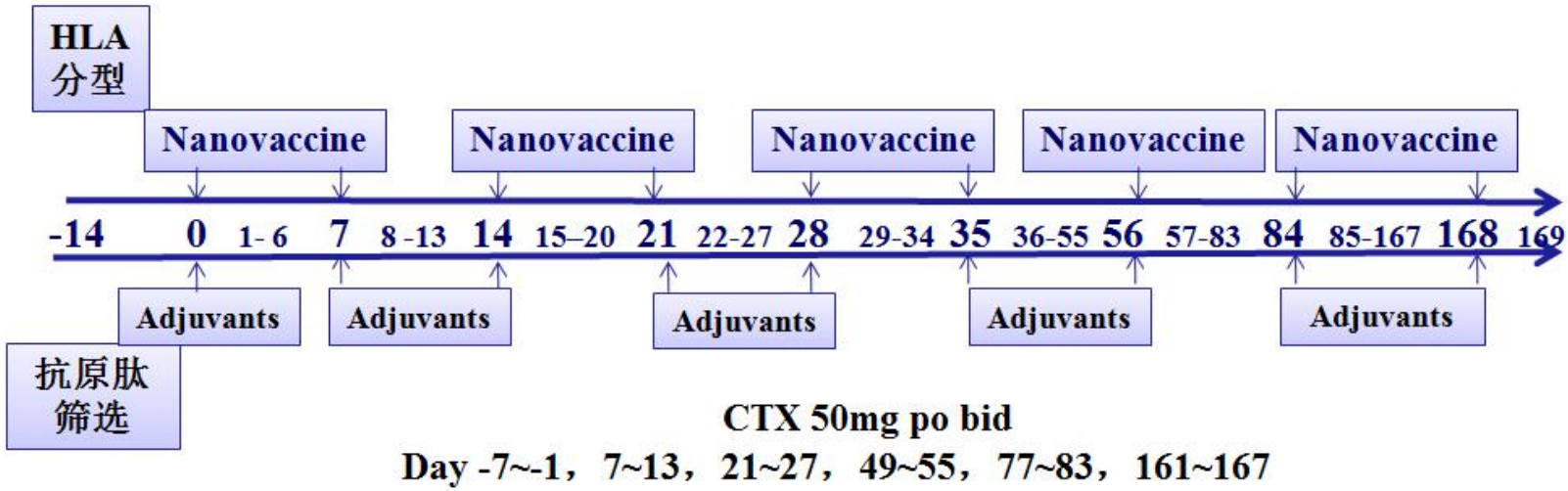
ChiCTR 中国临床试验注册中心 Chinese Clinical Trial Registry

世界卫生组织国际临床试验注册平台一级注册机构

注册号 Registration number	注册题目 Public title	审核状态 State	注册时间 Reg Date
ChiCTR1800017319	个体化新抗原/癌睾抗原肽纳米疫苗辅助治疗高复发风险胃癌/肝癌的临床研究 Personalized neoantigen/cancer testis antigen nanovaccine as ajuvant therapy for high-risk resected gastric cancer/hepatocellular carcinoma patients	通过审核 Successful	2018/7/24 0:00:00

胃癌IIIb-c术后辅助治疗

新抗原肽个体化纳米疫苗



第一例患者简介

男　胃底贲门下低分化腺癌pT4aN2M0 IIIB期

- 2017 行根治性全胃手术，术中探查胃周动脉旁、肝总动脉周围，腹腔干周围、脾动脉周围淋巴结肿大
- PD-L1（1%+）
- 2018-01至2018-07行六周期泰索帝+替吉奥化疗
- 2018-09开始接种个体化新抗原纳米疫苗，已完成9次接种

迄今已经有一些患者陆续接受该技术治疗

突变位点与新抗原肽

Protein	Gene ID	AAChange	MHC Ⅰ	MHC Ⅰ	MHC Ⅱ
PARP4	NM_006437	p.V1219I	WQGEPQEAI	EAIRNQSLL	QEAIRNQSLLASSEW
PALB2	NM_024675	p.P812L	PLIESFTFK	SVPPGTPPL	
BAP1	NM_004656	p.L180F	YVPITGRFF		AFHFVSYVPITGRFF
CTNNA1	NM_001903	p.Q692P	QVASFPEEK		
FLT4	NM_182925	p.S694L	DLLEMQCLV	LLVNVSDLL	TQNLTDLLVNVSDLL

副作用：仅有局部皮肤反应

左上肢

右上肢

胃癌IIIb-c：术后辅助治疗后

新抗原肽个体化纳米疫苗

动态免疫指标检查发现

肿瘤特异性细胞免疫反应显著加强