Immuno-Oncology I: Attacking Cancer Antigens – Exploiting off-the-Shelf and Personalized Vaccines and Triggering of Immunogenic Cell Death

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Immuno-Oncology I: Attacking Cancer Antigens – Exploiting off-the-Shelf and Personalized Vaccines and Triggering of Immunogenic Cell Death

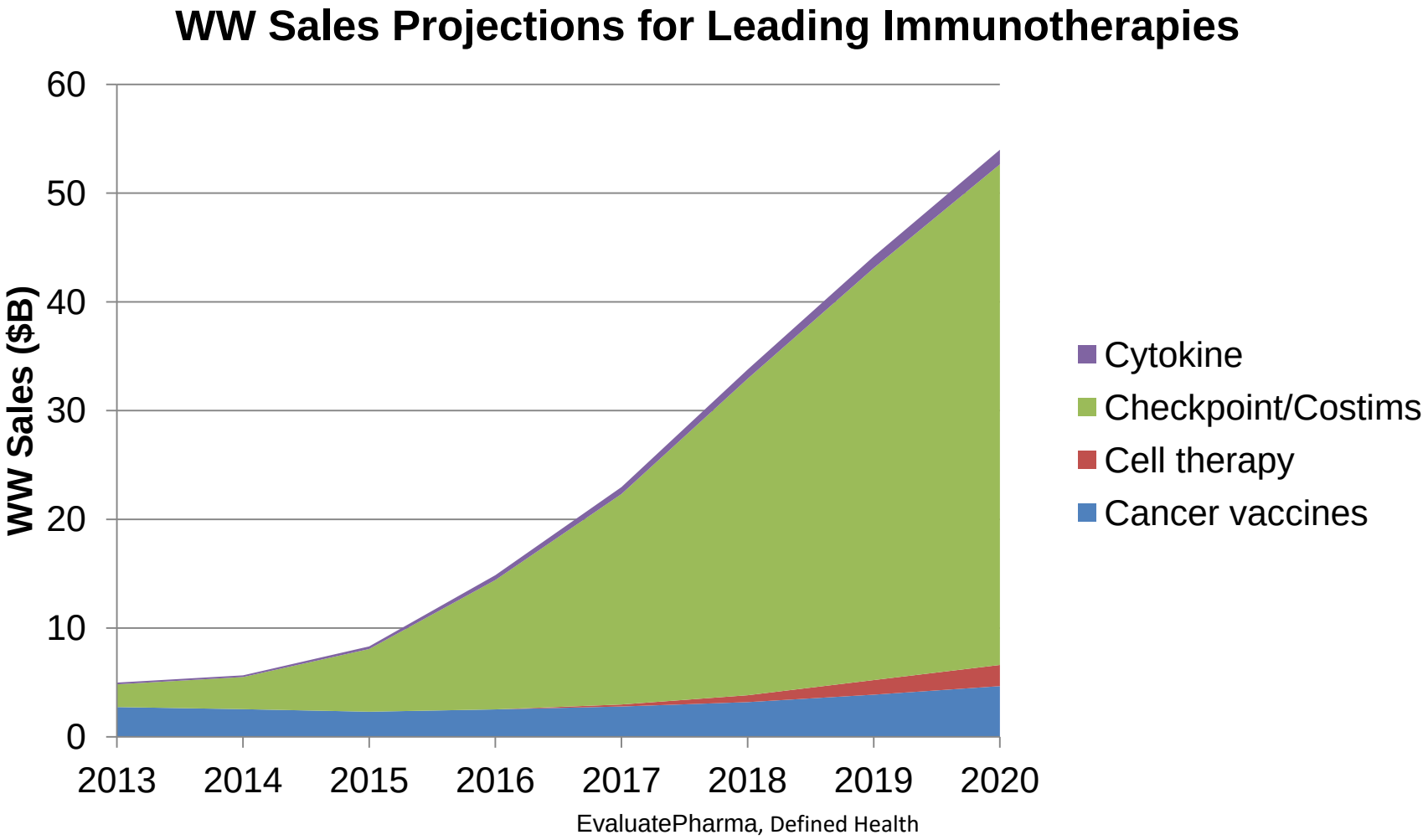
Moderator:

Jeffrey M. Bockman, PhD, Vice President, Defined Health

Panelists:

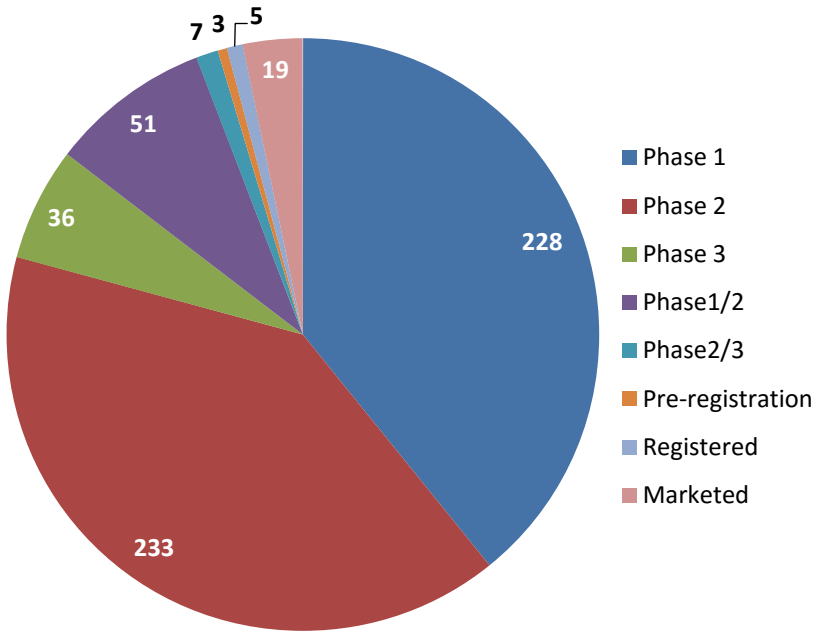
- *Robert Ang, MD, MBA*, Chief Business Officer, Neon Therapeutics
- *Ulrike Gnad-Vogt,* MD, Chief Medical Officer, CureVac AG
- *Taylor H. Schreiber MD, PhD*, Chief Scientific Officer, Heat Biologics Inc.
- *Andrea van Elsas, PhD*, Chief Scientific Officer, Aduro BioTech, Inc.
- *Mai-Britt Zocca, PhD, MSc,* Chief Executive Officer, IO Biotech ApS

Checkpoint Antibodies Are Foundational

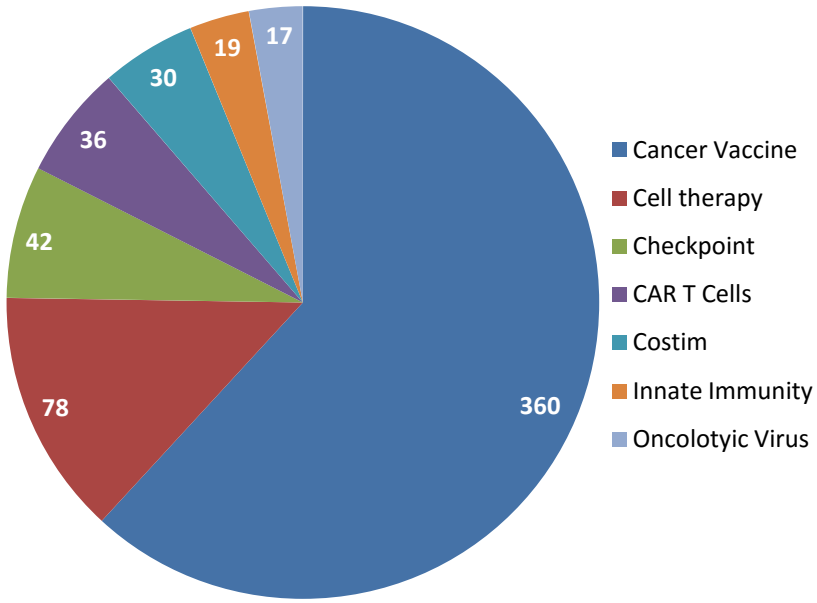


Cancer Vaccines Still Represent a Large Proportion of the IO Pipeline

IO Pipeline by Highest Phase



IO Pipeline by IO Category



Adis R&D Insight, Thomson Reuters Cortellis, Defined Health

Balance of Personalized & Off-the-Shelf, Cell-Based & Peptide-Based Vaccines

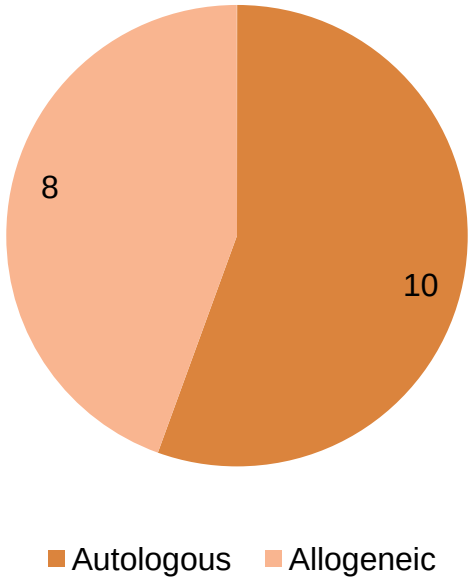
Indications Reflect Technical Risk Such as GBM & Commercial Risk Such as Melanoma

Cancer Vaccines in P3 Development (US) (n=18*)

	Malignant melanoma	Glioblastoma	Renal cancer	Ovarian cancer	Prostate cancer	Pancreatic cancer	Breast cancer	Colorectal cancer	Follicular NHL	Gastric cancer
Dendritic	1	2	1	1	1				1	
Peptide	1	1	1			1	1			1
Tumor Cell	2			1		1		1		
Virus					1					

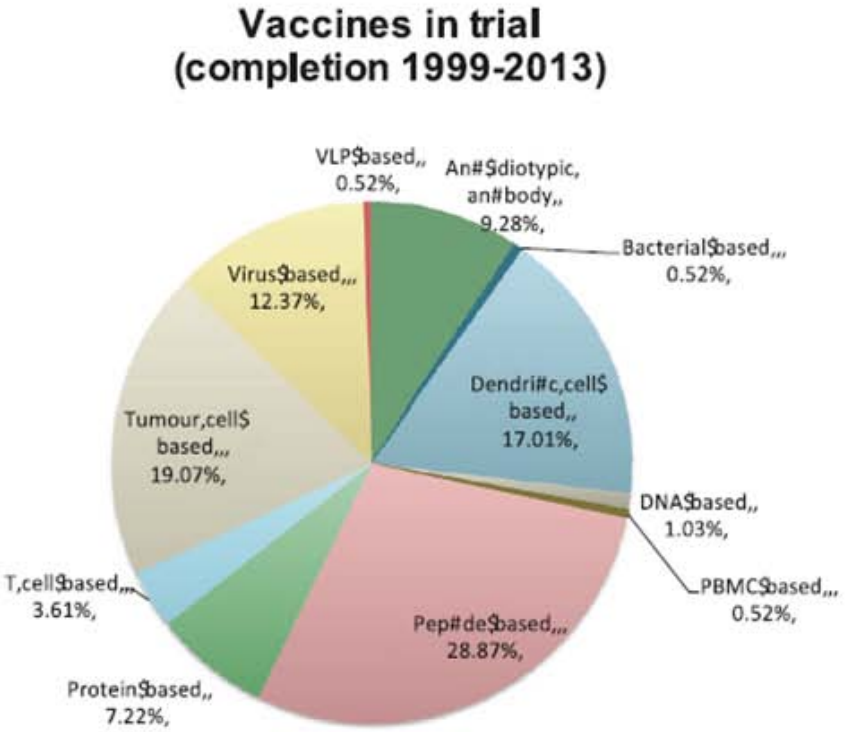
*One vaccine double counted for both Gastric and Pancreatic cancer

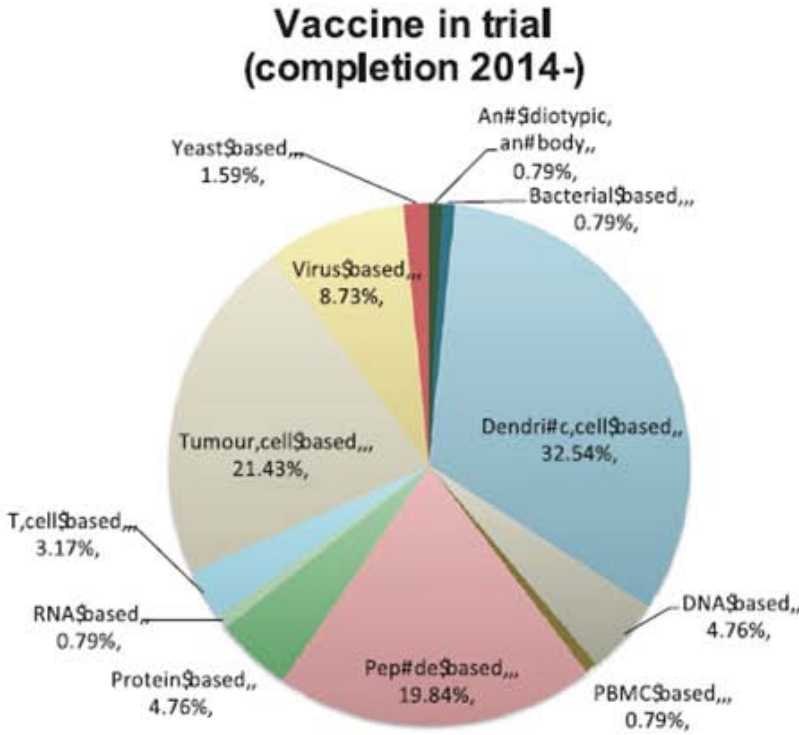
Number of P3 Cancer Vaccines by Type (n=18)



Adis Insight, Thompson Reuters Cortellis

Vaccine Development Over Time





J Immunother Cancer. 2015; 3: 48

Cancer Progress by Defined Health
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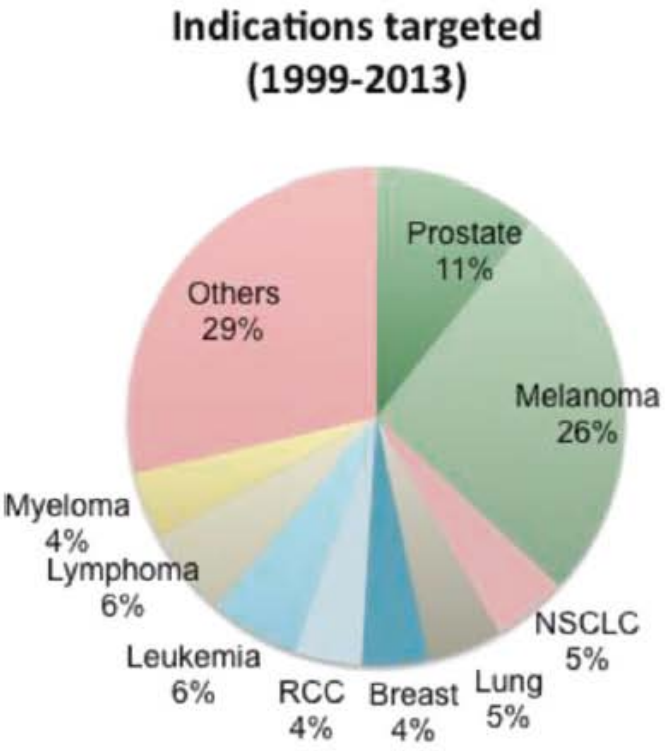

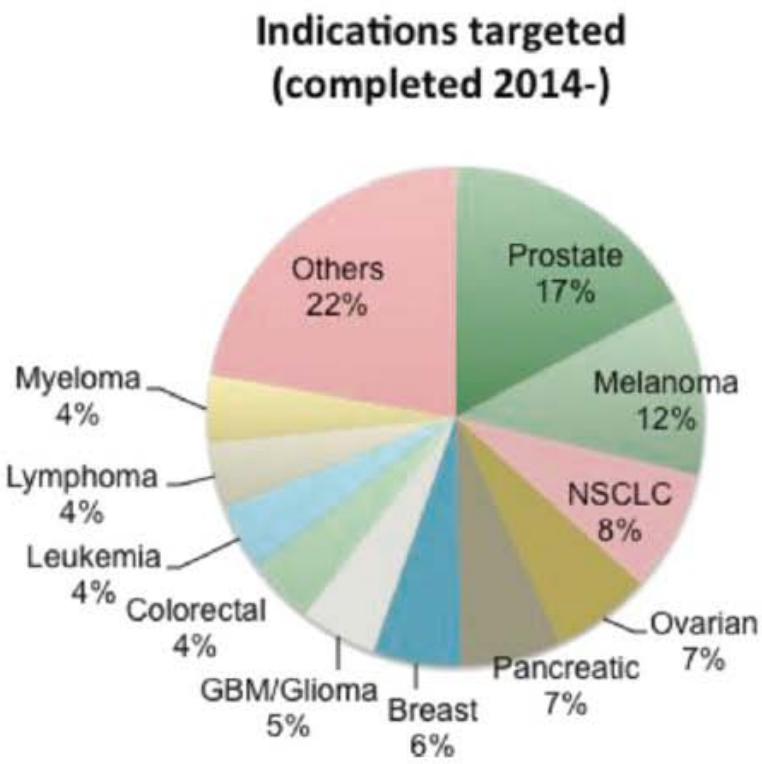

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2013 Update of Cancer Vaccine Status: Advanced Stage Vaccines, Nature Reviews, 2005

Name	Company	Phase	Mode of action	Indications	Class of vaccine
Insegia	Aphton Corp./Sanofi-Aventis	Preregistration	G17-like peptide conjugated to diphtheria toxin	Pancreatic cancer	Antigen specific
PANVAC-VF	Therion Biologics	III	CEA and MUC1-expressing recombinant virus	Pancreatic cancer	Antigen specific
Theratope	Biomira	III	Sialyl-Tn antigen	Breast cancer	Antigen specific
GMK	Progenics	III	GM2 ganglioside	Melanoma	Antigen specific
MDX-1379	Medarex/Bristol-Myers Squibb	III	gp100 melanoma peptides	Melanoma	Antigen specific
IGN-101	Igeneon	III	EpCAM-targeting monoclonal antibody	Breast cancer, NSCLC, colorectal cancer	Antigen specific
FavID	Favrille	III	Anti-idiotype patient-specific protein	NHL	Antigen specific
BIOVAXID	Biovest/Accentia	III	Anti-idiotype patient-specific protein	NHL	Antigen specific
MyVax	Genitope	III	Anti-idiotype patient-specific protein	NHL	Antigen specific
Allovectin-7	Vical	III	DNA plasmid/lipid complex encoding MHC-1 antigen	Melanoma, head and neck cancer	Antigen specific
GVAX	Cell Genesys	III	Allogeneic cell lines	Prostate cancer	Polyvalent
Canvaxin	CancerVax/Serono	III	Allogeneic whole cells	Melanoma	Polyvalent
Oncophage	Antigenics	III	Autologous heat-shock proteins	Melanoma, RCC	Polyvalent
Provenge	Dendreon	III	PAP-loaded dendritic cells	Prostate cancer	Dendritic cell

CEA, carcinoembryonic antigen; EpCAM, epithelial cell-adhesion molecule; G17, gastrin 17; MHC, major histocompatibility complex; MUC1, mucin-1; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; PAP, prostatic acid phosphatase; RCC, renal cell carcinoma.

Nature Rev. Drug Discov. **4**, 623–624; 2005

2013 Update of Cancer Vaccine Status: Advanced Stage Vaccines, Nature Reviews, 2009

Name (company)	Indication (Phase)	Description	Class of vaccine
Abagovomab (Menarini)	Ovarian cancer (II–III)	A murine IgG1 anti-idiotype monoclonal antibody that mimics the structure of a specific epitope on the ovarian cancer tumour-associated antigen MUC16	Antigen specific
Allovectin-7 (Vical)	Metastatic melanoma (III)	A DNA plasmid–lipid complex encoding MHC1 antigen	Antigen specific
Belagenpumatucel-L (NovaRx)	Non-small-cell lung cancer (III)	Allogeneic non-small-cell lung cancer cells transfected with a plasmid containing a TGFβ2 antisense transgene	Polyvalent
BLP-25 (Merck Serono)	Non-small-cell lung cancer (III)	A liposome-encapsulated peptide derived from the MUC1 antigen	Antigen specific
BiovaxID (Biovest/Accentia)	Non-Hodgkin's lymphoma (III)	An anti-idiotype patient-specific protein	Antigen specific
GSK1572932A (GlaxoSmithKline)	Human melanoma antigen A3-positive non-small-cell lung cancer (III)	Human melanoma antigen A3	Antigen specific
MDX-1379 (Medarex/ Bristol–Myers Squibb)	Melanoma (III)	gp100 melanoma peptides	Antigen specific
M-Vax (AVAX Technologies)	Metastatic melanoma (III)	Autologous melanoma cells that have been irradiated and then modified with the hapten dinitrophenyl	Polyvalent
Oncophage (Antigenics)	Renal cell carcinoma (Pre-registration)	Autologous heat shock proteins	Polyvalent
PR1 leukaemia peptide vaccine (The Vaccine Company)	Acute myeloid leukaemia (III)	A 9-amino-acid HLA-A2-restricted peptide derived from proteinase 3	Antigen specific
Sipuleucel-T (Dendreon)	Prostate cancer (Pre-registration)	Prostatic acid phosphatase-loaded autologous antigen-presenting cells	Dendritic cell-mediated
TroVax (Oxford Biomedica)	Renal cell carcinoma (III)	A recombinant modified *Vaccinia ankara* viral vector encoding the 5T4 oncofoetal trophoblast glycoprotein	Antigen specific

gp100, glycoprotein 100; HLA-A2, human leukocyte antigen A2; IgG1, immunoglobulin G1; MHC1, major histocompatibility complex 1; MUC16, mucin 16 (also known as CA125); TGFβ2, transforming growth factor β2.

Nature Reviews Drug Discovery **8**, 685-686 (September 2009)

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Nature Reviews Drug Discovery **8**, 685-686 (September 2009)

Phase 3 Cancer Vaccines (US Only), March 2016: Diverse Platforms & Cancers

Programs in black appear active across multiple sources, those in gray have unclear status

Vaccine	Company Developing/Partners	Platform Type	Autologous/Allogeneic	Lead Indication
AGS 003	Argos Therapeutics	Dendritic	Autologous	Renal cancer
Algenpantucel-L	NewLink Genetics	Tumor Cell	Allogeneic	Pancreatic cancer
Cvac*	CancerVac (Prima BioMed)	Dendritic	Autologous	Ovarian cancer
Dasiprotimut-T*				
DCVax-Brain				
Eltrapuldencel-T				lanoma
ICT 107				
IMA 901				
M Vax				lanoma
Nelipepimut S				r
OncoVAX				ncer
Polyclonal antibody stimulator				creatic cancer
PROSTVAC	Bavarian Nordic/NCI/D	Virus	Allogeneic	Prostate cancer
Rindopepimut*	Celldex	Peptide	Allogeneic	Glioblastoma
Seviprotimut-L	Polynoma (CK Life Sciences)	Tumor Cell	Allogeneic	Malignant melanoma
Stapuldencel-T	Sotio	Dendritic	Autologous	Prostate cancer
Vigil	Gradalis	Tumor Cell	Autologous	Ovary tumor
Zastumotide*	GlaxoSmithKline	Peptide	Allogeneic	Malignant melanoma

March 7, 2016

Data Safety and Monitoring Board Recommends Celldex's Phase 3 Study of RINTEGA® (rindopepimut) in Newly Diagnosed Glioblastoma be Discontinued as it is Unlikely to Meet Primary Overall Survival Endpoint in Patients with Minimal Residual Disease

–Conference Call Scheduled for 8:00 AM ET Today–

HAMPTON, N.J., March 07, 2016 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. (NASDAQ:CLDX) today announced that the independent Data Safety and Monitoring Board (DSMB) has determined, based on a preplanned interim analysis, that continuation of the Phase 3 ACT IV study of RINTEGA® (rindopepimut) in patients with newly diagnosed EGFRvIII-positive glioblastoma will not reach statistical significance for overall survival in patients with minimal residual disease, the primary endpoint of the study, as both the RINTEGA arm and the control arm are performing on par with each other. In the ACT IV study, RINTEGA has performed consistently with prior Phase 2 studies but the control arm has significantly outperformed expectations (Hazard ratio = 0.99; median OS: RINTEGA 20.4 months vs. control 21.1 months). Based on this recommendation, Celldex is discontinuing the study and does not anticipate incurring substantial additional costs related to RINTEGA at this time. All patients on the RINTEGA arm of the ACT IV study, prior Phase 2 studies and existing compassionate use recipients will be offered ongoing access to RINTEGA on a compassionate use basis. Celldex first received the data after market close on Friday, March 4th and is in the process of reviewing the results.

Adis Insight, Thompson Reuters Cortellis, Celldex web site, Defined Health

Phase 3 Cancer Va… Variety of Platforms a…

Programs in black appear active across multi…

Vaccine	Company Developing/Partners	Pla…
AGS 003	Argos Therapeutics	Der…
Algenpantucel-L	NewLink Genetics	Tur…
Cvac*	CancerVac (Prima BioMed)	Der…
Dasiprotimut-T*		
Nelipepimut-S		
OncoVAX		
Polyclonal antibody stimulator		
PROSTVAC	Bavarian Nordic/NCI/D…	Viru…
Rindopepimut*	Celldex	Pep…
Seviprotimut-L	Polynoma (CK Life Sciences)	Tur…
Stapuldencel-T	Sotio	Der…
Vigil	Gradalis	Tur…
Zastumotide*	GlaxoSmithKline	Pep…

BloombergGadfly

Celldex Dims Cancer Vaccine Hopes

By Max Nisen

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A drug failing in Phase III trials has an impact beyond the company developing it.

The latest example is Celldex's Rintega brain-tumor vaccine. The company stopped its final-stage study on Monday due to poor results. The news didn't just cause Celldex shares to collapse 53.72 percent. It also means years of research may go up in smoke, patients will be left without a better treatment option, and an entire approach to fighting cancer looks shakier than ever.

The setback is devastating, but likely not fatal news for Celldex; the New Jersey biotech has a strong research pedigree and other promising (non-vaccine) medicines in the pipeline. But the same can't be said for cancer vaccines, which were already nearly on drug development death watch.

The hope for a therapeutic cancer vaccine is more than a century old. There have been a variety of different approaches, with some tantalizing results, but no real successes.

Dendreon's Provenge is the only such drug to make it to market in the U.S. Approved by the FDA in 2010, it sold so poorly compared to expectations that Dendreon was driven to file for bankruptcy in 2014. The company's assets met a fate that may be, depending on your point of view, worse than death: acquisition by Valeant. Dendreon's vaccine was an unappealing mix of high price, high manufacturing cost and only modest benefit. At its height in 2010, amid blockbuster expectations for Provenge, Dendreon was worth more than $7 billion. Valeant acquired its assets for $495 million in early 2015.

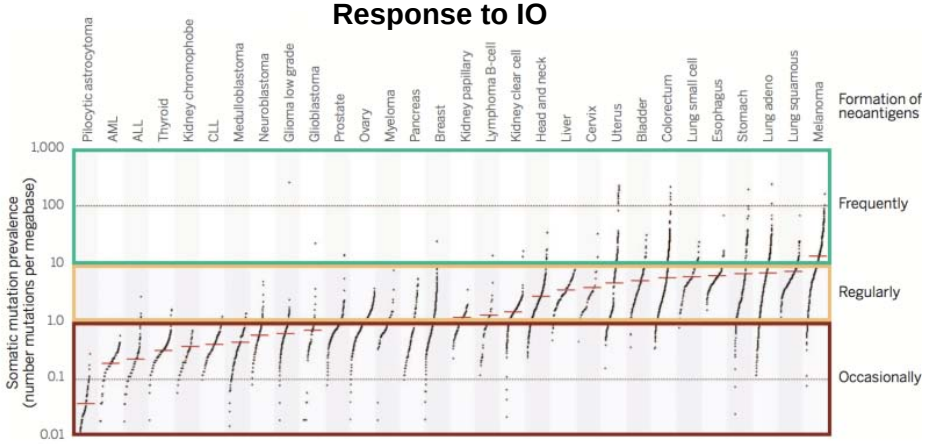
Adis Insight, Thompson Reut…

Cancer Progress by Defined Health
New York, NY | March 8-9, 2016

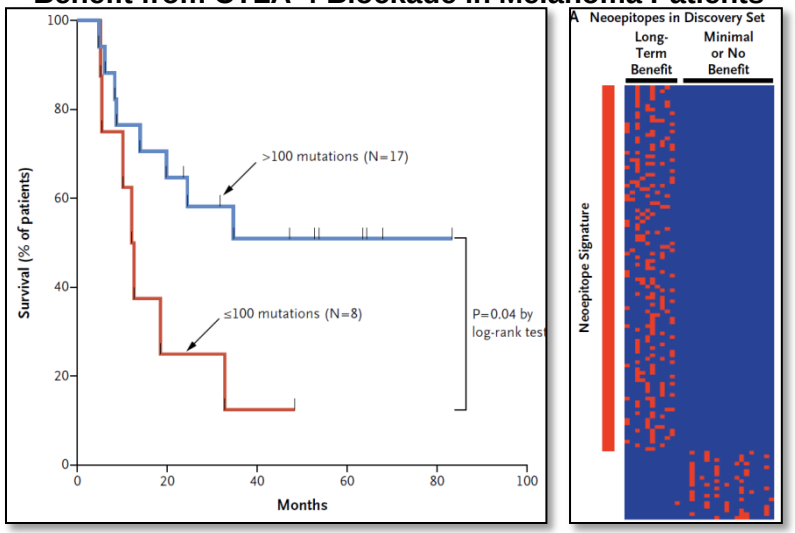
unconventional insight

Neoantigens Are the Latest Cancer Vaccine Approach

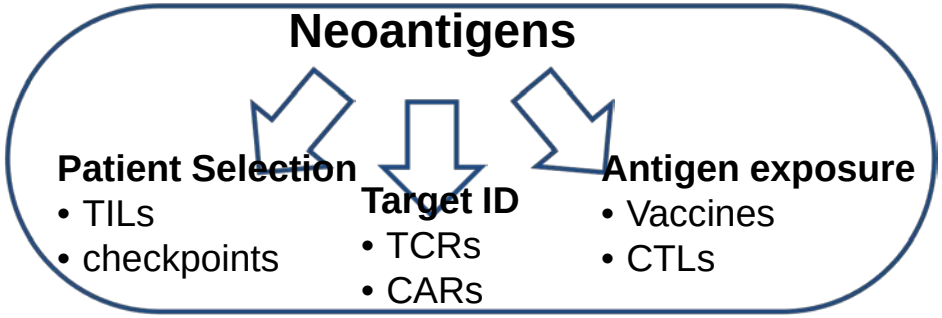
Mutational Burden (and Possibly Tumor-Specific Neoantigen Load) Varies by Tumor Type, Correlates With Antitumor Response to IO



Association of a Neoepitope Signature with a Clinical Benefit from CTLA-4 Blockade in Melanoma Patients



Neoantigens Will Play an Important Role Across the IO Landscape



- Science. 2015 Apr 3;348(6230):69-74.; N Engl J Med. 2015 Jun 25;372(26):2509-20.

Plasticity, Evolution & Acquisition of Resistance

- Acquired resistance: activation of survival signaling pathways and the inactivation of downstream death signaling pathways; epigenetic tumor microenvironment, EMT; and cancer stem cells, which are intrinsically highly resistant to many therapeutic approaches.

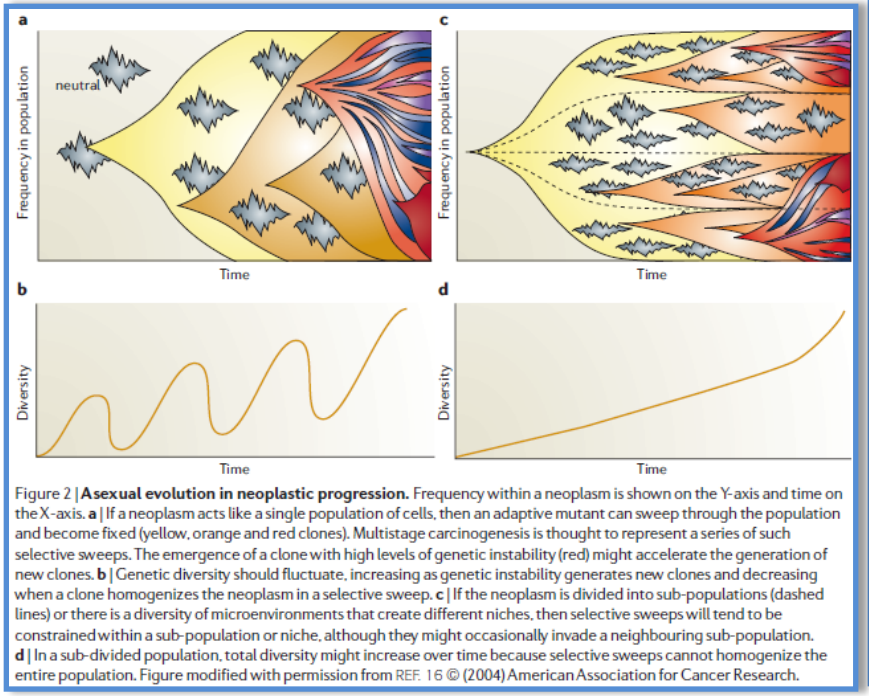
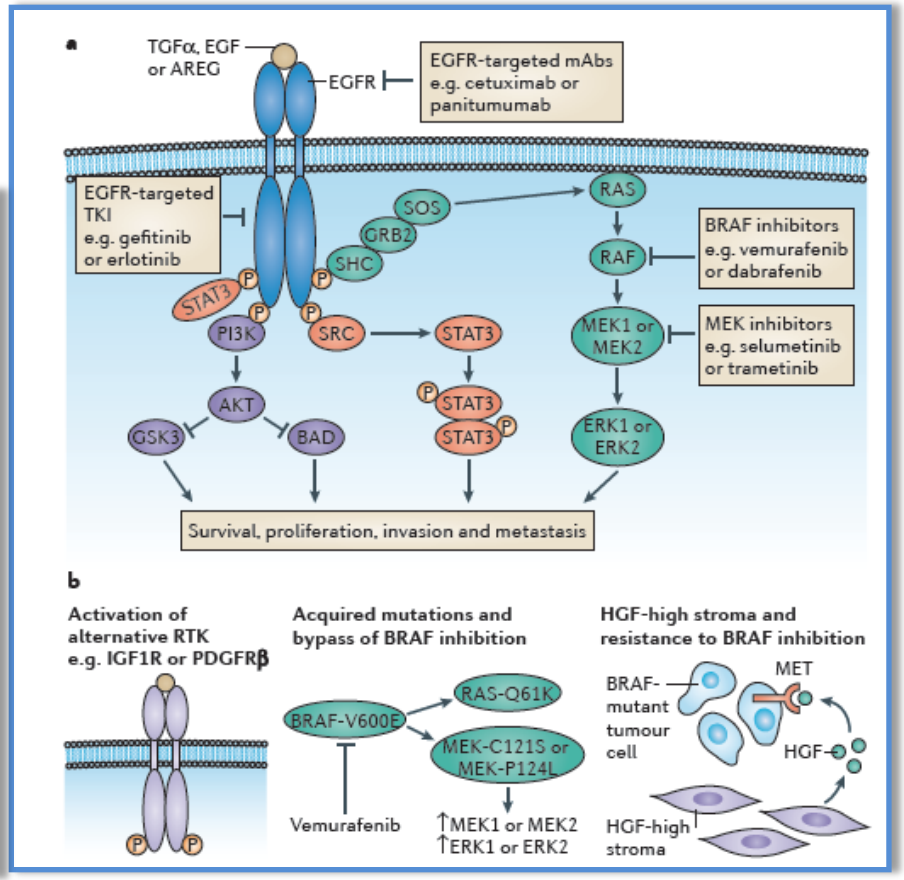


Figure 2 | **Asexual evolution in neoplastic progression.** Frequency within a neoplasm is shown on the Y-axis and time on the X-axis. **a** | If a neoplasm acts like a single population of cells, then an adaptive mutant can sweep through the population and become fixed (yellow, orange and red clones). Multistage carcinogenesis is thought to represent a series of such selective sweeps. The emergence of a clone with high levels of genetic instability (red) might accelerate the generation of new clones. **b** | Genetic diversity should fluctuate, increasing as genetic instability generates new clones and decreasing when a clone homogenizes the neoplasm in a selective sweep. **c** | If the neoplasm is divided into sub-populations (dashed lines) or there is a diversity of microenvironments that create different niches, then selective sweeps will tend to be constrained within a sub-population or niche, although they might occasionally invade a neighbouring sub-population. **d** | In a sub-divided population, total diversity might increase over time because selective sweeps cannot homogenize the entire population. Figure modified with permission from REF. 16 © (2004) American Association for Cancer Research.



Nature Reviews Cancer 6, 924-935; *Nature Reviews Cancer* 13, 714–726 (September 2013)

Cancer Progress by Defined Health
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The Challenge of Diversity

Extremely high genetic
prevalence of non-Darw

Shaoping Ling[a,1], Zheng Hu[a,1], Zuyu Yar
Lihua Cao[a], Yong Tao[a], Lingtong Hao[a],
Wenming Zhao[a], Xiuyun Tian[c], Chunyi Ha
Richard R. Hudson[f], Wen-Hsiung Li[g,2],

Author Affiliations

Contributed by Wen-Hsiung Li, October 10, 201
Jianzhi Zhang)

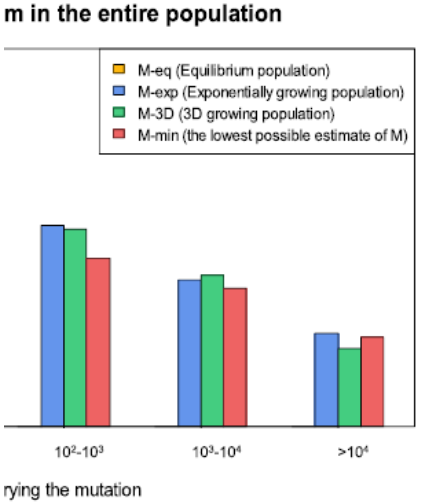
A correction has been published

Abstract | Full Text | Authors & Info

Significance

A tumor comprising many cells can be
amount of genetic diversity reflects ho
evaluated a single tumor by sequenci
data were analyzed by modern popula
region mutations in this unexceptional
the non-Darwinian mode. In contrast,
diversity would be orders of magnitud
probability of drug resistance should

The prevailing view that the evolution of cells in a tumor is driven by Darwinian selection has never been rigorously tested. Because selection greatly affects the level of intratumor genetic diversity, it is important to assess whether intratumor evolution follows the Darwinian or the non-Darwinian mode of evolution. To provide the statistical power, many regions in a single tumor need to be sampled and analyzed much more extensively than has been attempted in previous intratumor studies. Here, from a hepatocellular carcinoma (HCC) tumor, we evaluated multiregional samples from the tumor, using either whole-exome sequencing (WES) (n = 23 samples) or genotyping (n = 286) under both the infinite-site and infinite-allele models of population genetics. In addition to the many single-nucleotide variations (SNVs) present in all samples, there were 35 "polymorphic" SNVs among samples. High genetic diversity was evident as the 23 WES samples defined 20 unique cell clones. With all 286 samples genotyped, clonal diversity agreed well with the non-Darwinian model with no evidence of positive Darwinian selection. Under the non-Darwinian model, M_{ALL} (the number of coding region mutations in the entire tumor) was estimated to be greater than 100 million in this tumor. DNA sequences reveal local diversities in small patches of cells and validate the estimation. In contrast, the genetic diversity under a Darwinian model would generally be orders of magnitude smaller. Because the level of genetic diversity will have implications on therapeutic resistance, non-Darwinian evolution should be heeded in cancer treatments even for microscopic tumors.



Proc Natl Acad