Syntekabio

Targeting neoantigens for the precision cancer immunotherapy

21 May 2019

Yeojun Yun
MSL Team

NEOANTIGEN

Because neoantigens are only expressed in tumors, they may be the ideal targets of new cancer vaccines and cell therapies.

TISSUE SPECIFIC ANTIGEN

Tissue-specific antigens are specific to the tissue but upregulated in cancer cells, including MART-1, gp-100, TRP-1/gp75.

CANCER-TESTIS ANTIGEN

Cancer-testis antigens are expressed mainly in tumors or testis but have low-level expression in normal tissues and include MAGE-A1 and NY-ESO-1 2017.

OVEREXPRESSED IN TUMOR

Overexpressed tumor antigens are expressed in both tumor cells and healthy cells but have high expression in tumor cells.

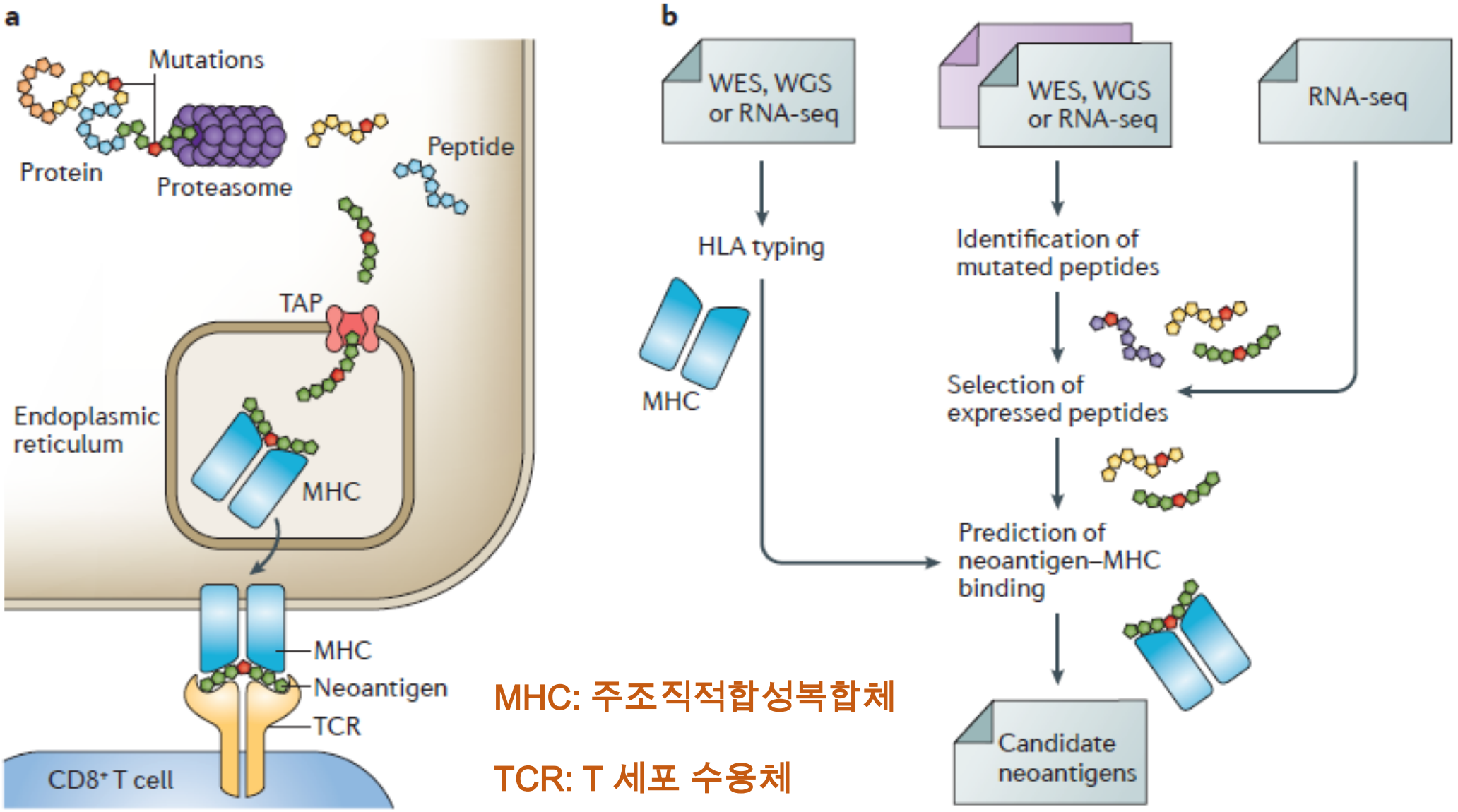
NEOANTIGEN

Neoantigens are new proteins created as the cancer cell goes haywire and mutation rates intensify.

- Expression of antigen in normal tissue
- Expression of antigen in the tumor

- ✓ Only found on tumor cells
- ✓ Arise from mutated genes in the tumor
- ✓ Highly patient specific

NEOANTIGEN



MHC: 주조직적합성복합체

TCR: T 세포 수용체

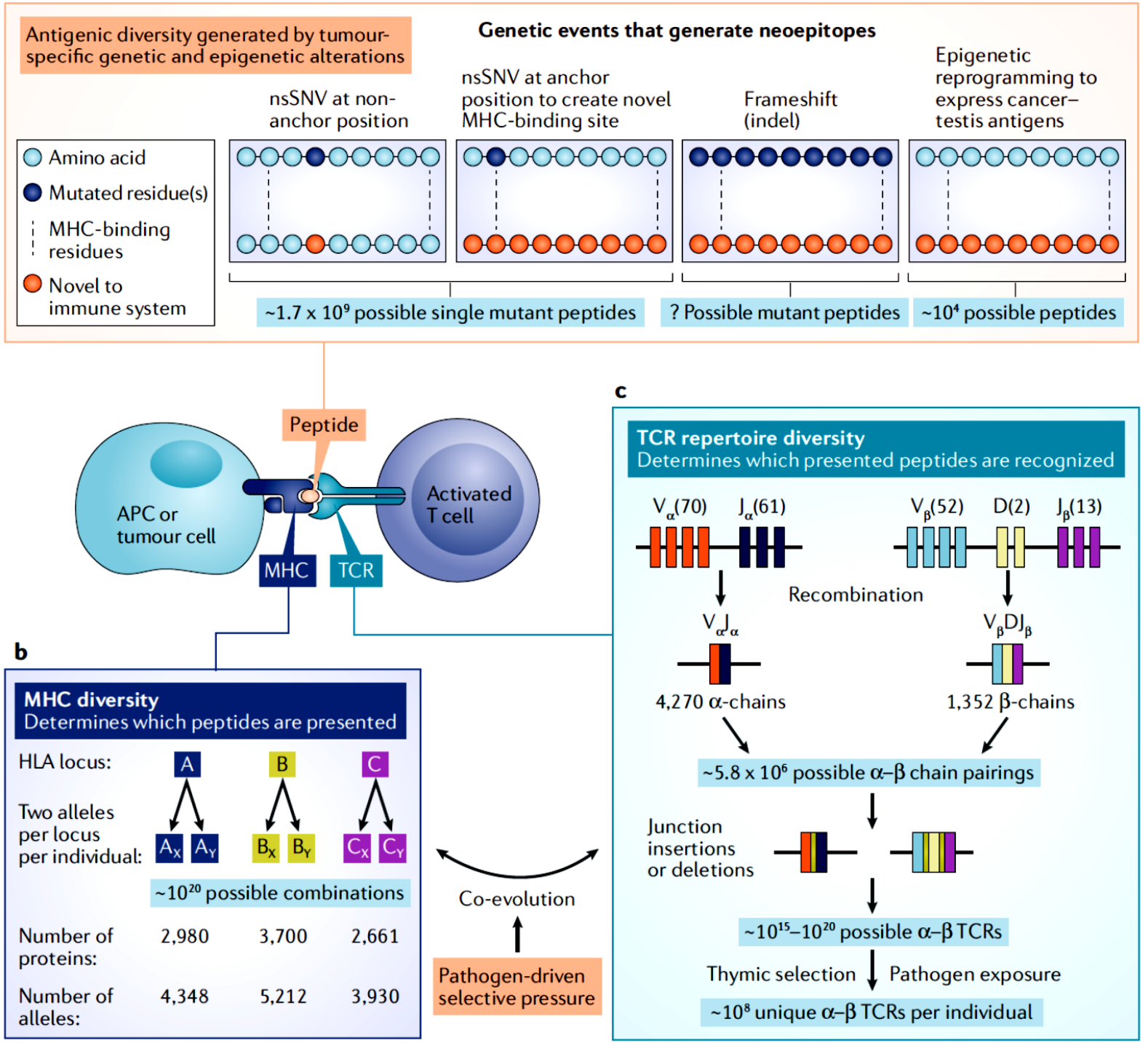
Hackl et al. 2016 Nature reviews genetics

The complexity of neoantigen prediction

HLA diversity

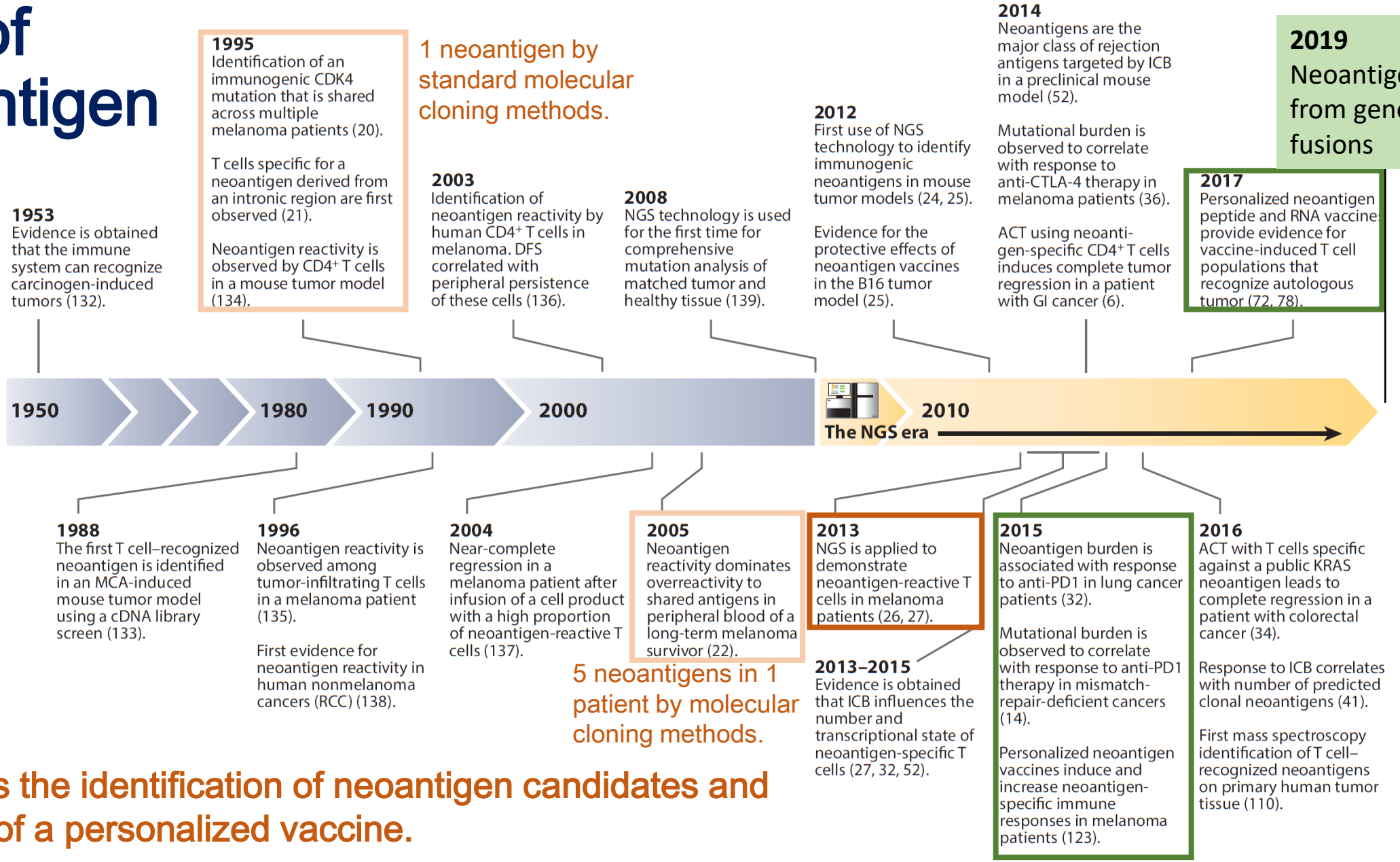
✖

TCR diversity



Havel JJ et al 2019. Nature Rev. Cancer

History of Neoantigen



NGS enables the identification of neoantigen candidates and the creation of a personalized vaccine.

Schumacher TN et al 2019. Annu. Rev. Immunol

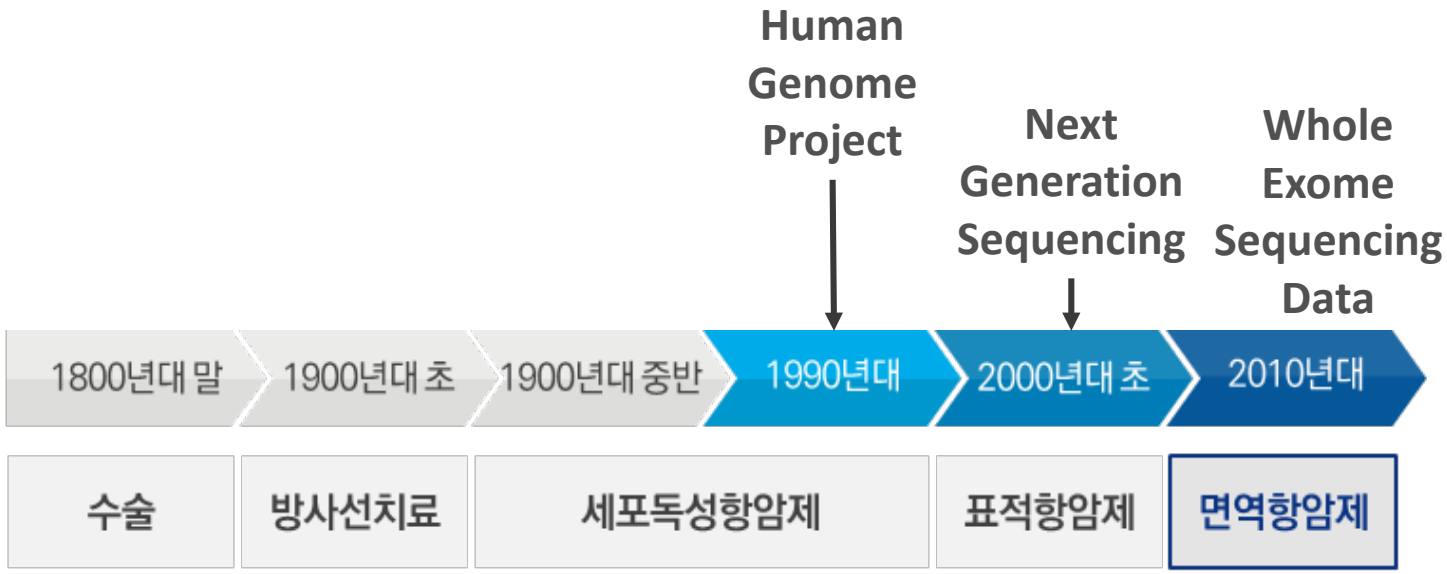
Figure 1

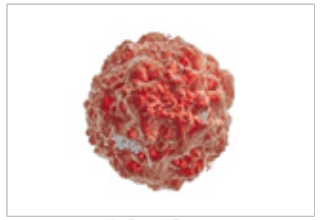
Historical overview of cancer neoantigens. Abbreviations: ACT, adoptive cell transfer; DFS, disease-free survival; GI, gastrointestinal; ICB, immune checkpoint blockade; MCA, 3-methylcholanthrene; NGS, next-generation sequencing; RCC, renal cell carcinoma.

The Rise of Neoantigen

1. 시컨싱 기술의 발전

2. 최근 면역항암제의 성공

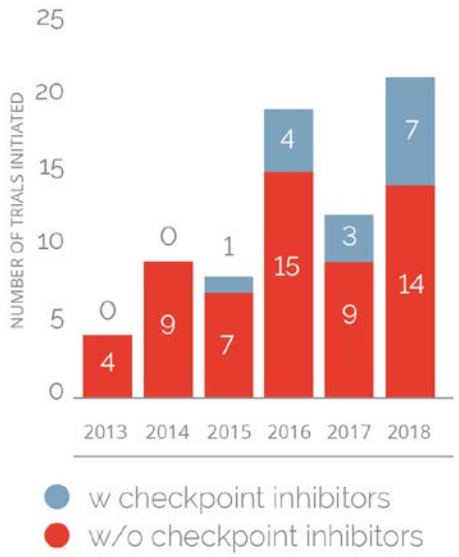




암세포

면역 체계

암세포



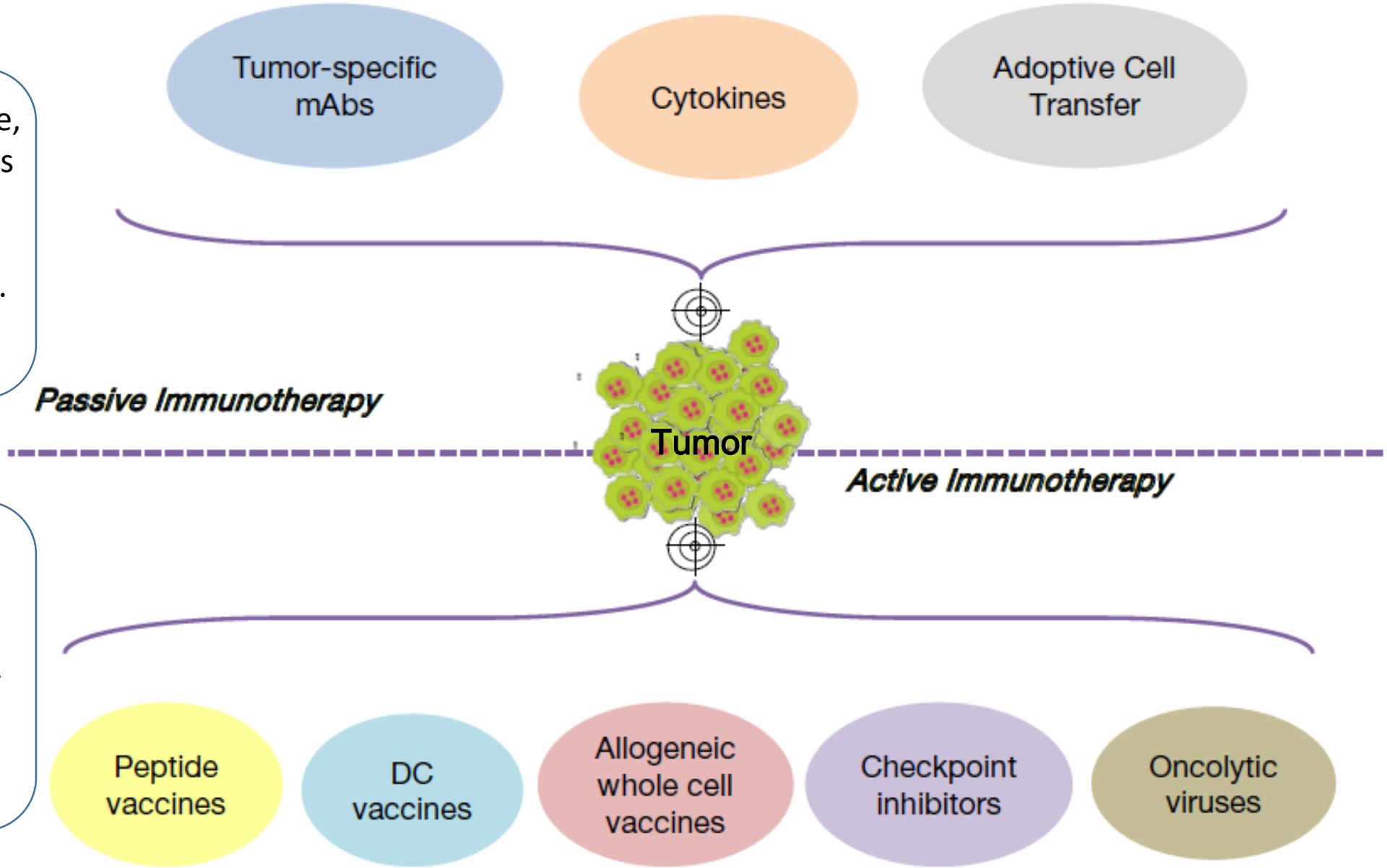
Worldwide neoantigen trials initiated, 2013-2018

Syntekabio

Cancer immunotherapy approaches

weak, unresponsive, low responsiveness immune systems. *ex vivo*-activated cells or molecules.

Memory: No



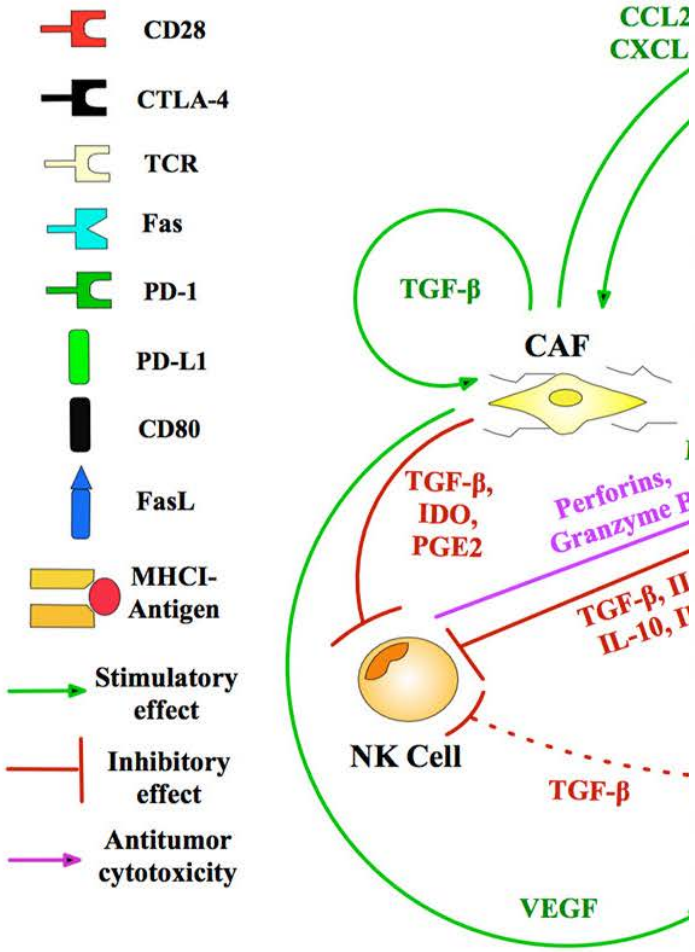
able to respond upon challenge, stimulated stimulate effector functions *in vivo*

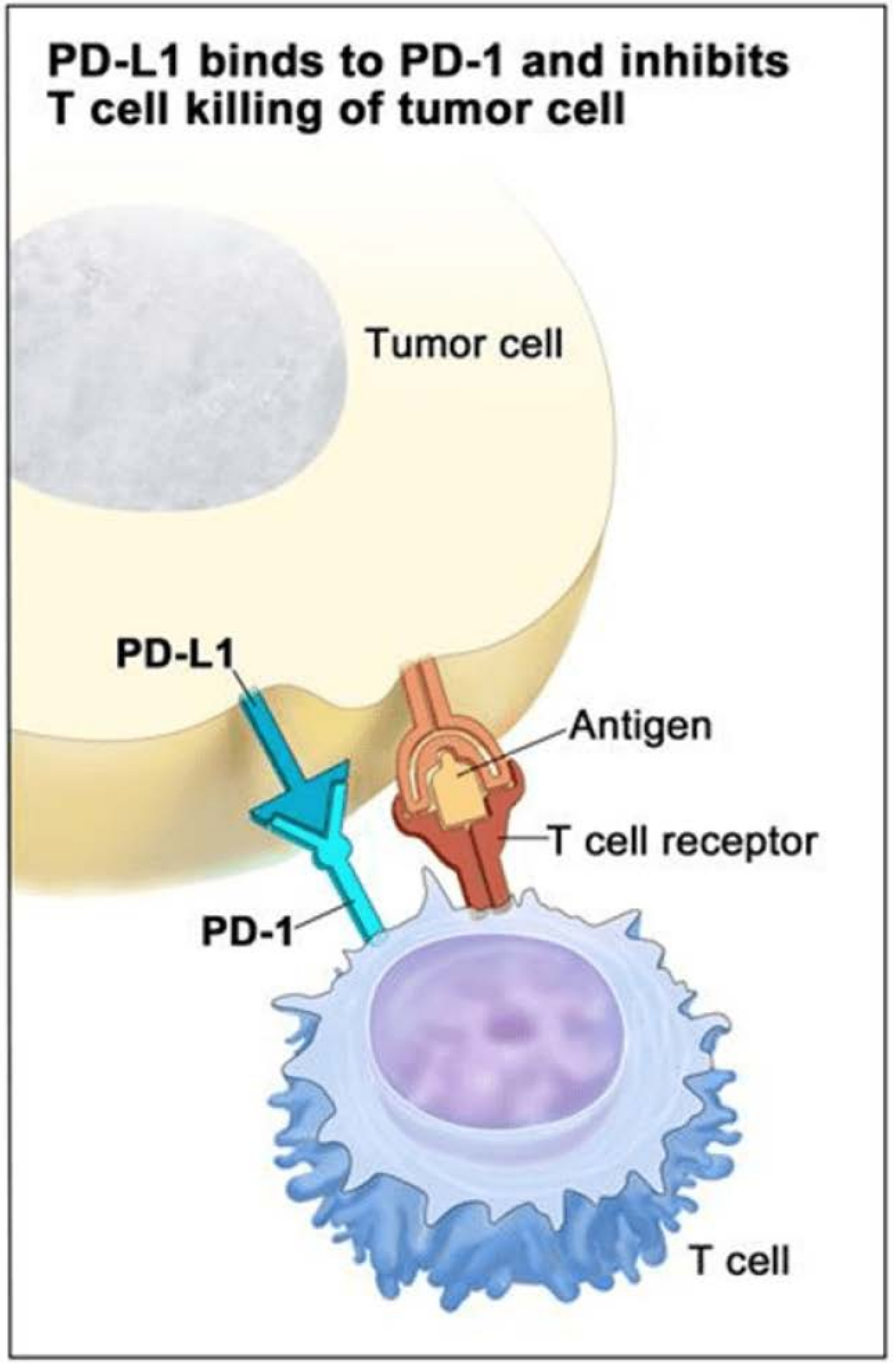
Memory: Yes

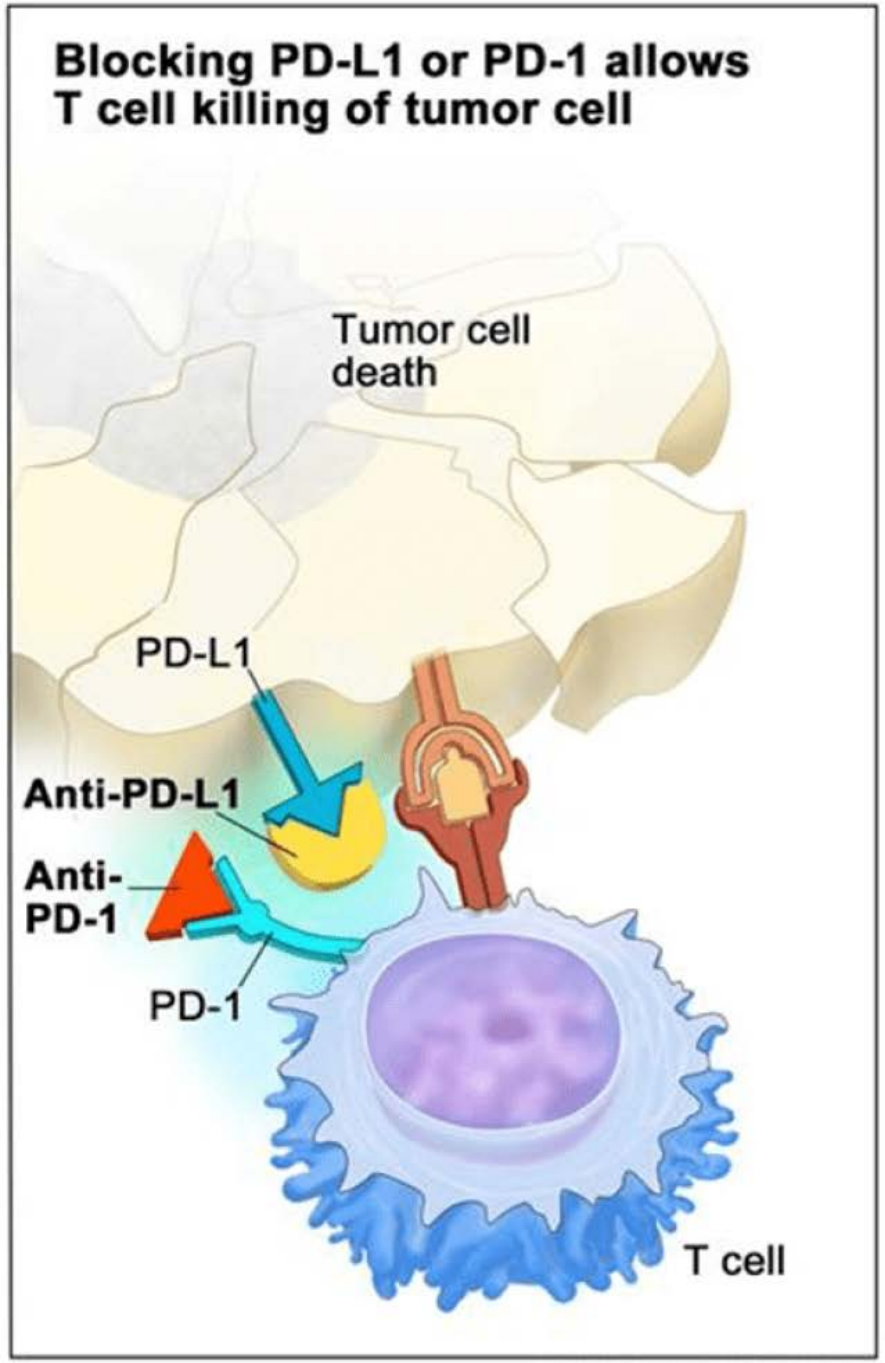
Syntekabio

Papaioannou NE et al 2016 Ann Transl Med

Tumor microenv



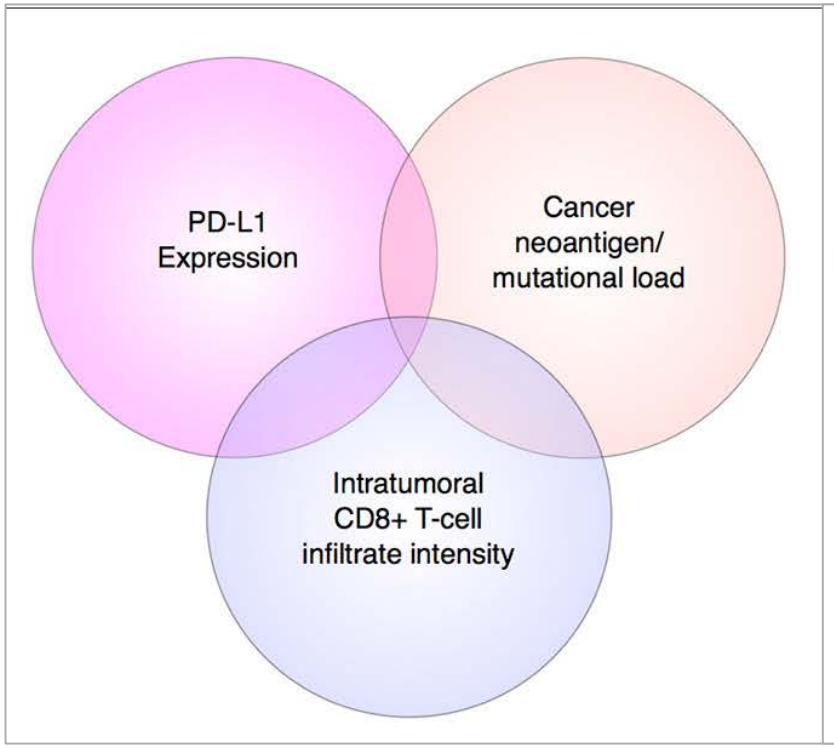


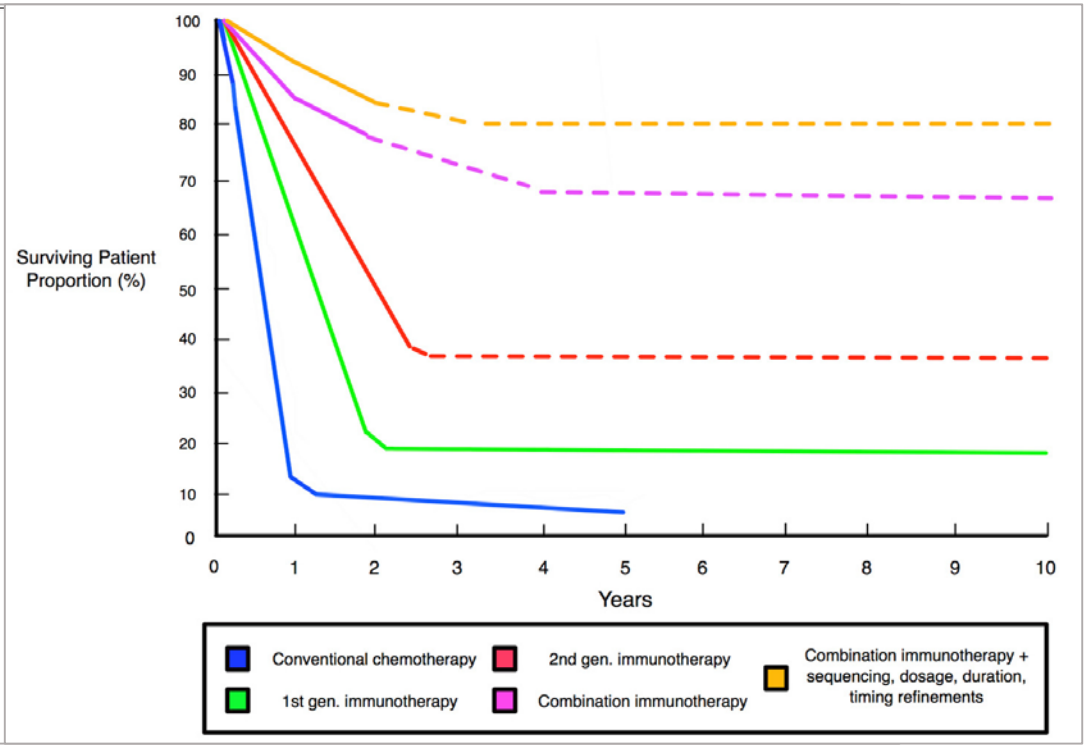


Immuno-Oncology: Emerging Targets and Combination T

Syntekabio

"The neoantigen vaccine is like the steering wheel, to guide the immune response … the checkpoint blockade is removal of the brakes." — Nir Hacohen, Director of the Center for Cancer Immunotherapy, Massachusetts General Hospital in Charlestown





Immuno-Oncology: Emerging Targets and Combination Therapies/ Henry T. Marshall and Mustafa B. A. Djamgoz/ Front. Oncol. 8:315.

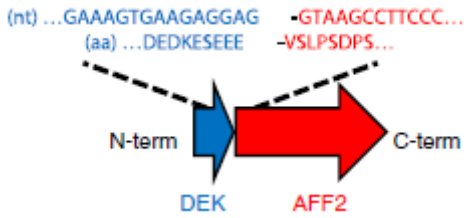
nature medicine

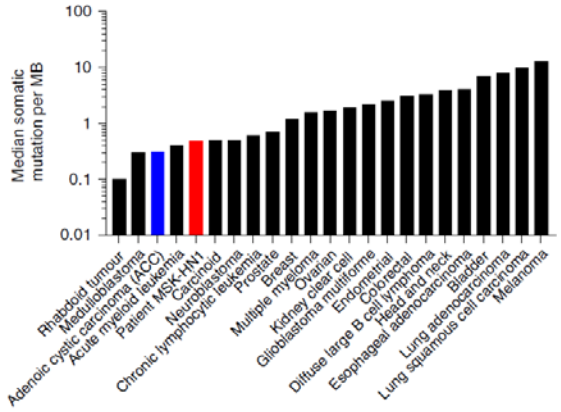
Letter | Published: 22 April 2019

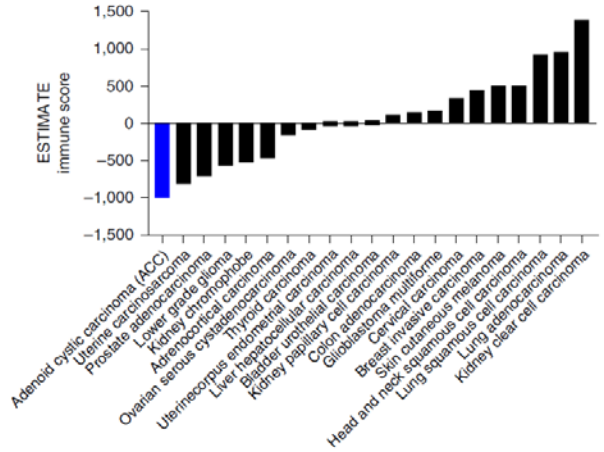
Immunogenic neoantigens derived from gene fusions stimulate T cell responses

Wei Yang, Ken-Wing Lee, […] Luc G. T. Morris

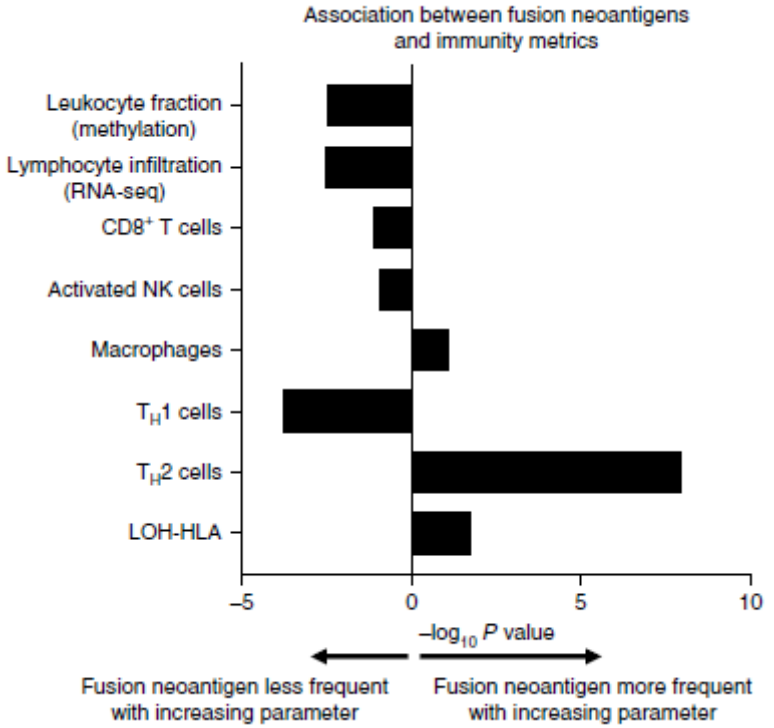
Nature Medicine **25**, 767–775 (2019) | Download Citation



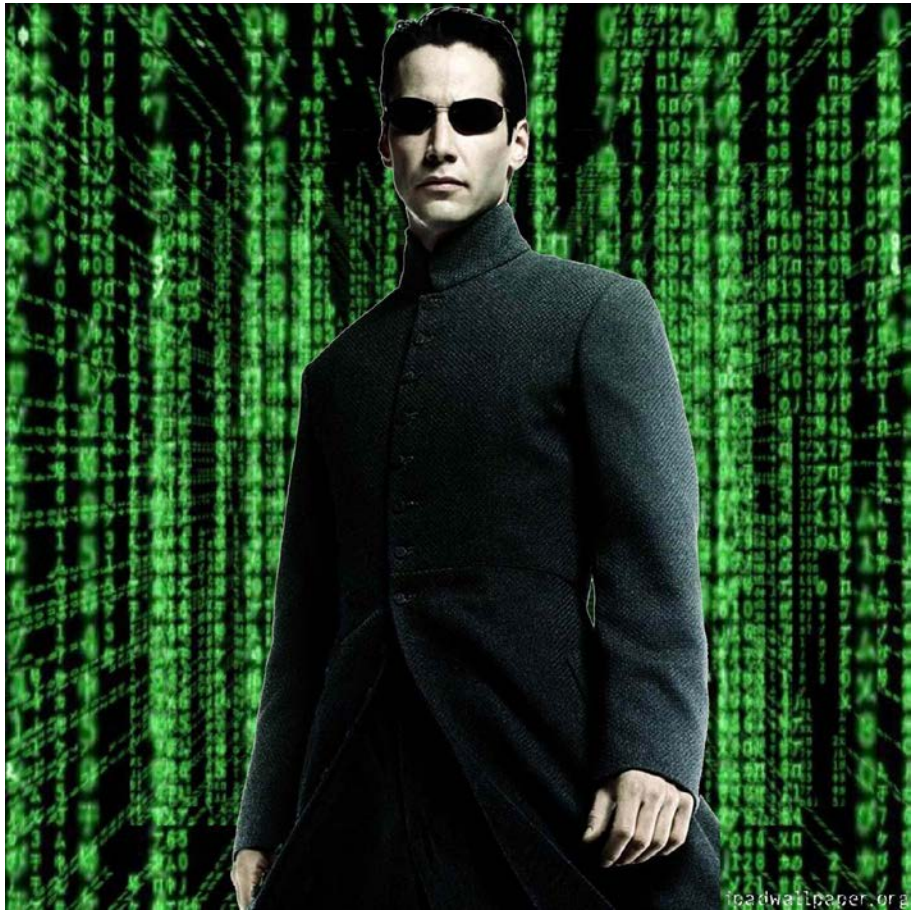




- head and neck tumors with low mutation burden, minimal immune infiltration and prevalent gene fusions, identified gene fusion-derived neoantigens that generate cytotoxic T cell responses.
- RNA-seq data TCGA 30 cancer types: 1,404/5,825 fusion protein, 24% neoantigen predicted to bind to patient-specific HLA
- LOH-HLA was associated with a higher likelihood of a fusion neoantigen being present ($P = 0.018$).
- Fusion neoantigens were more frequent in tumors with more immune-depleted microenvironments or HLA loss.
- Cancers with low mutational load and minimal immune infiltration.



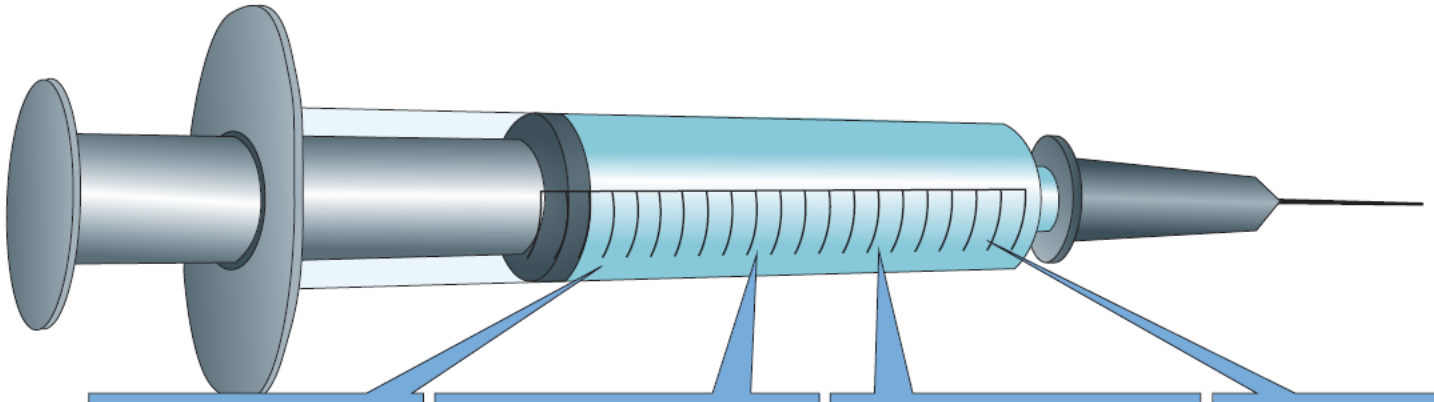
Cancer Wars: a Neo Hope



The Matrix

Kakao Friends

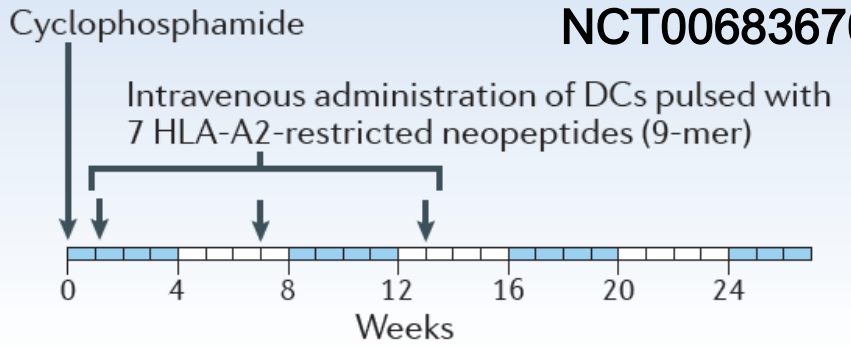
Therapeutic Cancer Vaccine using Neoantigen



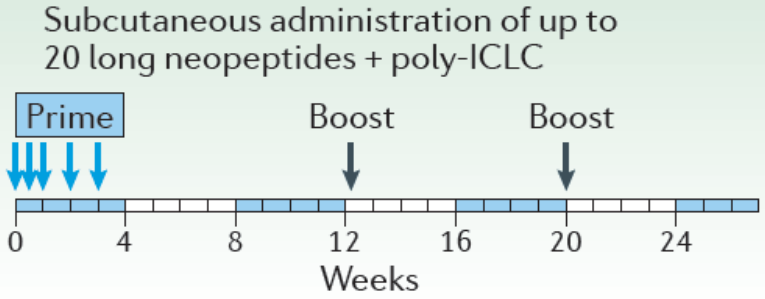
Tumour antigens	Formulations	Immune adjuvants	Delivery vehicles
Tumour-associated • Overexpressed • Tissue differentiation • Cancer–testis • Oncofetal	**Protein-based or peptide-based**	**TLR agonist** • Poly-ICLC • MPL • CpG ODN • Imiquimod	**Emulsions** • Montanide ISA-51 and Montanide ISA-720
Tumour-specific • Oncogenic viral • Neoantigens	**Anti-idiotype antibody-based**	**DC-targeted monoclonal antibody** • DEC205 • Agonistic CD40-specific	**Liposomes**
	Heat shock protein-based	**Saponin-based** • ISCOMATRIX • QS-21	**Virosomes**
	Nucleic acid-based • DNA • mRNA	**GM-CSF**	**Nanodiscs**
	Cell-based • Whole tumour cells • Antigen-loaded DCs	**STING ligands**	
	Vector-based • Viral • Bacterial	**Tetanus or diphtheria toxoid**	

Hu Z et al 2018 Nature Reviews Immunology

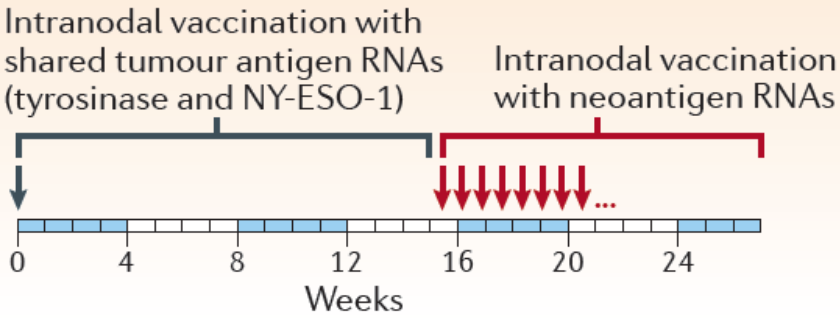
Neoantigen-based DC vaccine
Three patients previously treated with ipilimumab



NeoVax
Six patients
NCT01970358



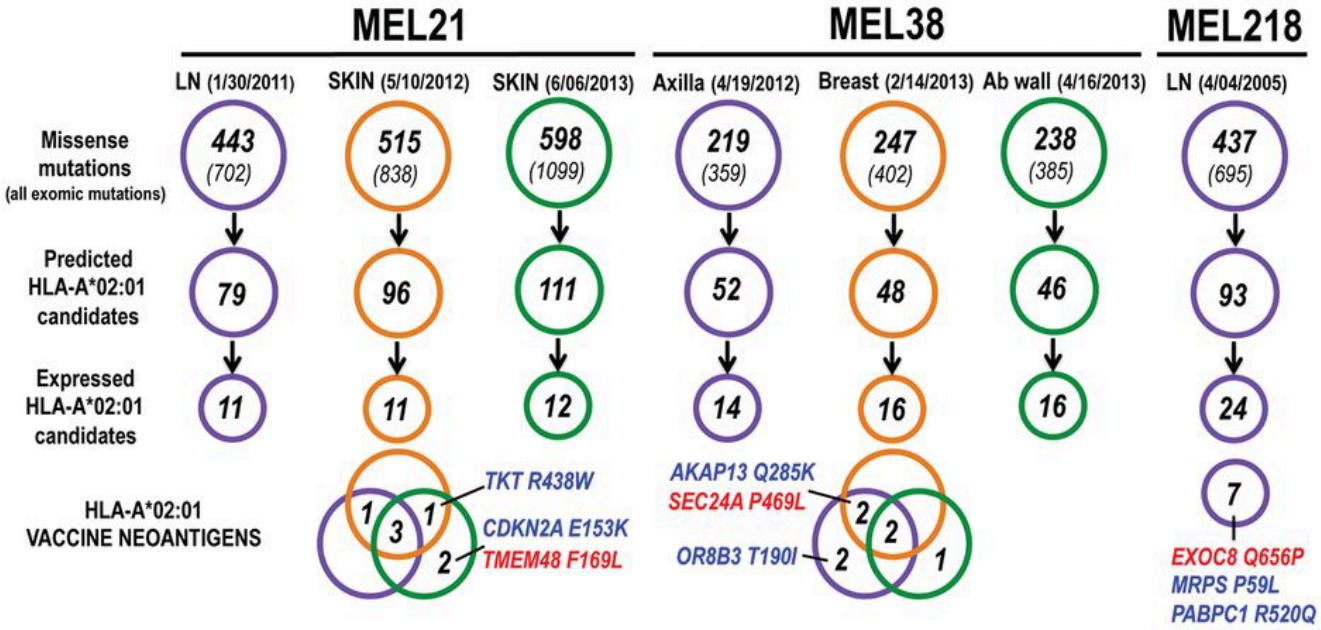
IVAC MUTANOME
Thirteen patients
NCT02035956



Clinical trials using neoantigen vaccines

1. First human clinical trial in 2015
   - 3 melanoma patients, 8-10mer neoantigen peptide for HLA-A*02:01 in human melanoma
   - with dendritic cells as the vaccine platform
   - Gerald P. Linette/ Washington University School of Medicine
   - Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, Ly A, Lie WR, Hildebrand WH, Mardis ER, Linette GP. *Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells.* Science. 2015 May 15;348(6236):803-8.

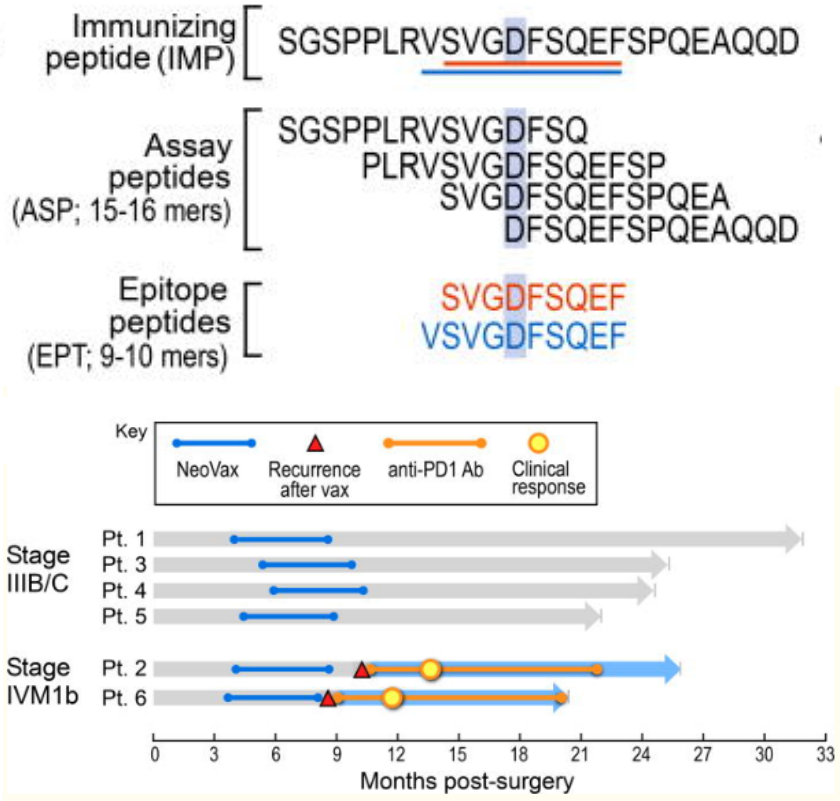
   - High risk of recurrence, a history of surgical melanoma removal. All developed a relapse before the trial began. Treated with ipilimumab.
   - 2 patients (MEL21 and 38): disease progression → MEL21;stable disease, MEL38; 2 month regression of lung metastasis
   - 1 patient (MEL218): complete remission → remain in remission, no evidence of cancer.



Clinical trials using neoantigen vaccines

2. Neon Therapeutics in 2017: NeoVax

- Brigham and Women's Hospital/Dana Farber Cancer Institute
- 15-30mer peptides + poly-ICLC platform
- 20 neoantigens from 6 melanoma patients
- within 2.5 years, 4 of 6 patients → cancer free
- The remaining 2 patients → became cancer free after α-PD-1
- expanding Breast and Bladder cancers….



Ott PA et al 2017 Nature

3. BioNTech in 2017: IVAC MUTANOME

- Germany, Austria
- 13 melanoma patients, a mix of 10 mRNA (8 neoantigens, NY-ESO-1 and tyrosinase)
- Within 12-23 months, 8 patients of 13 patients → cancer free

The Rise of Neoantigen

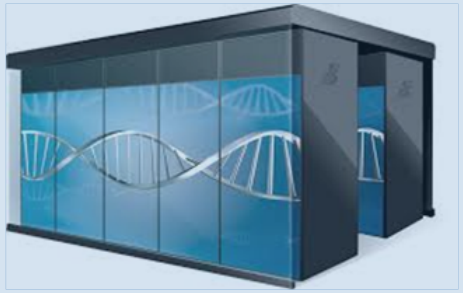
1. 시컨싱 기술의 발전

2. 최근 면역항암제의 성공

3. AI-Big Data 시대

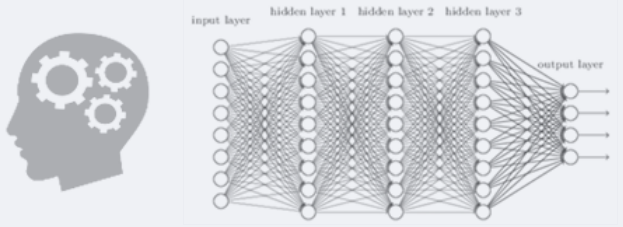
Syntekabio – Who We Are

PMAP™ Genome Bigdata Platform & MAHA supercomputer



\+

A.I. engines Drug development & Clinical decision support



Mission

GAME CHANGING INNOVATION of Drug Discovery & Development

Target discovery → Hit screening → Lead optimization → Preclinical → Phase I → Phase II → Phase III → Approval → Market

PHscan™ & RESIscan™
COMPOUND SCREENING

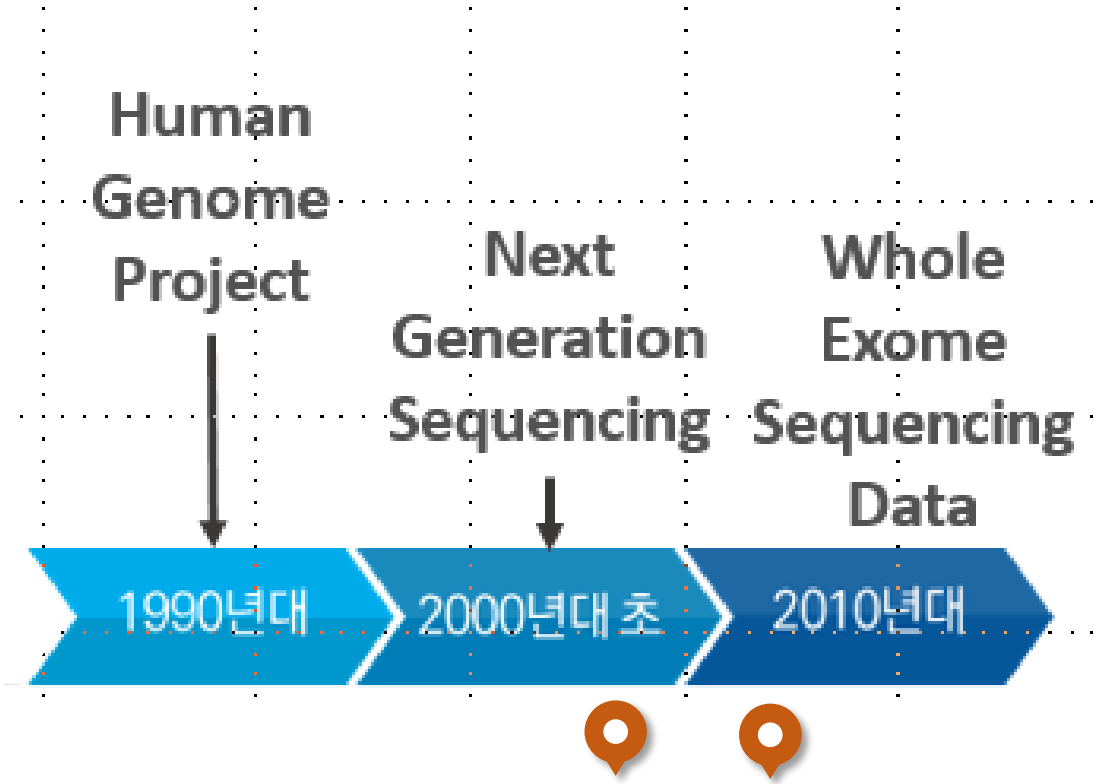
GBLscan™
PREDICTIVE BIOMARKER ID. FOR ONCOLOGY DRUGS

PTscan™
PATIENT STRATIFICATION

PGXscan™
SAFETY MARKER ID.

PHARMA R&D
FASTER,
CHEAPER,
MORE EFFECTIVE

History of Syntekabio



’09 Company Founded

신테카바이오
In silico Biology & Analytics

‘11 Conducted Genomic Data Integration & Analysis of The National Project for Personalized Genomic Medicine

2019

01. J.P. Morgan Conference

2018

04. Naver Cloud Genomics Collaboration MOU
04. JW Pharma Collaboration MOU
04. Yuhan Pharma Collaboration MOU
09. INHA University Medical Center – Oncology Precision Medicine Center Established
12. Yonsei University Severance Medical Center – Rare Disease Precision Medicine Center

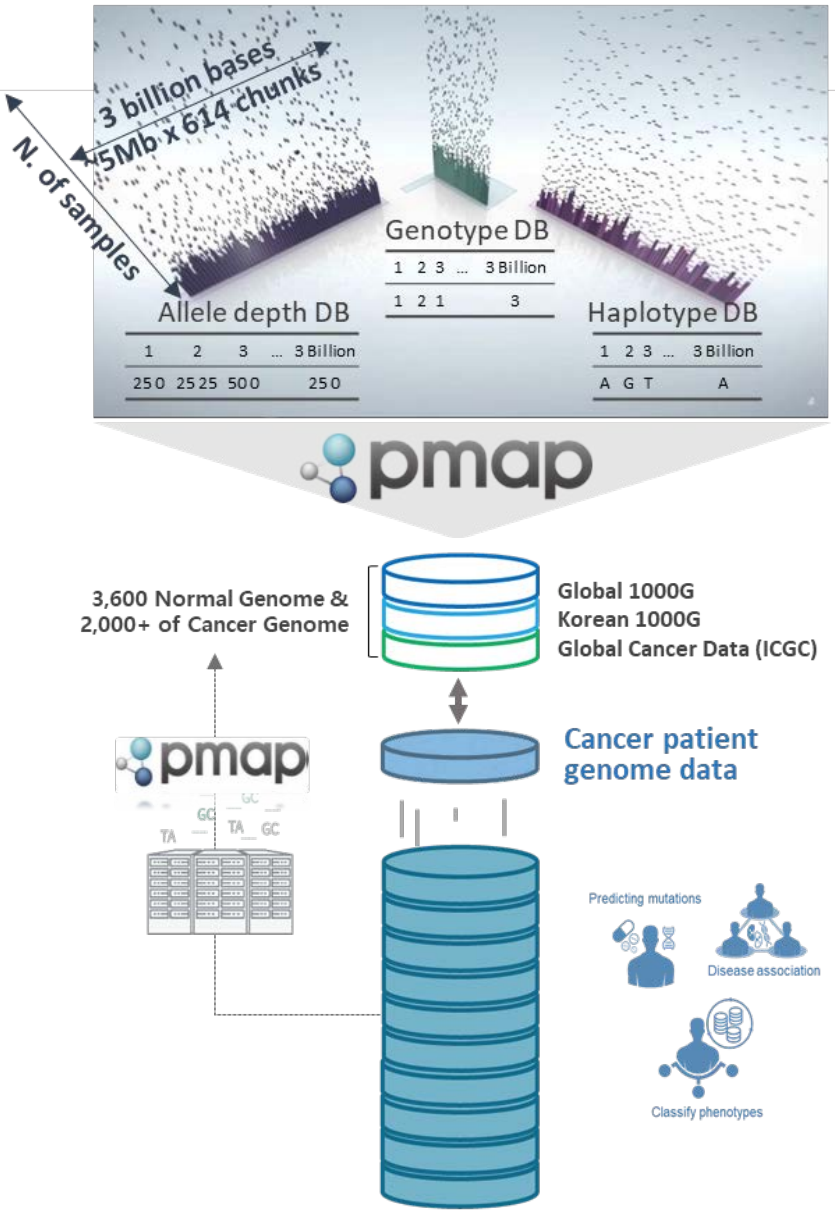
2017

02. INHA University Medical Center, Precision Medicine Center MOU
06. Catholic Medical Center, Dementia & Cancer R&D MOU
08. ASAN Medical Center, DNA Extraction Technology Licensing In.
08. UTAH University, R&D Collaboration MOU
11. Yonsei University Severance Medical Center MOU
12. CJ Healthcare Application of AI for Drug Discovery – Immunotherapy

2016

01. KFDA Certified NGS System Workflow Established
02. Seoul National University, School of Medicine Academia & Industry Cooperative Education MOU
06. Awarded New Excellent Technology(NET)* Certification for Genetic Disease Screening

Genome bigdata platform PMAP™



- ✓ Genome bigdata generation & management
- ✓ Enables integrated analysis and discovery of disease- or drug response-associated genetic marker

Sona *et al. BMC Bioinformatics* (2018) 19:462
https://doi.org/10.1186/s12859-018-2499-1

BMC Bioinformatics

METHODOLOGY ARTICLE Open Access

Integrated genome sizing (IGS) approach for the parallelization of whole genome analysis

Peter Sona[1], Jong Hui Hong[1], Sunho Lee[1], Byong Joon Kim[1], Woon-Young Hong[1], Jongcheol Jung[1], Han-Na Kim[2], Hyung-Lae Kim[2], David Christopher[3], Laurent Herviou[3], Young Hwan Im[3], Kwee-Yum Lee[1,4], Tae Soon Kim[1,5] and Jongsun Jung[1*]

Nucleic Acids Research, 2018 1
doi: 10.1093/nar/gky445

Development of the variant calling algorithm, ADIScan, and its use to estimate discordant sequences between monozygotic twins

Yangrae Cho[1,2,†], Sunho Lee[1,3,†], Jong Hui Hong[1,4], Byong Joon Kim[1], Woon-Young Hong[1], Jongcheol Jung[1], Hyang Burm Lee[2], Joohon Sung[5], Han-Na Kim[6], Hyung-Lae Kim[6] and Jongsun Jung[1,*]

[1]Syntekabio Incorporated, Techno-2ro B-512, Yuseong-gu, Daejeon 34025, Republic of Korea, [2]DFTBA, CALS,

Ka *et al. BMC Bioinformatics* (2017) 18:258
DOI 10.1186/s12859-017-1671-3

BMC Bioinformatics

METHODOLOGY ARTICLE Open Access

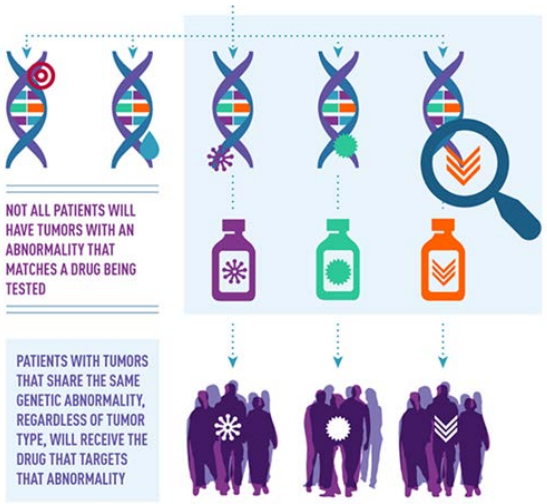
HLAscan: genotyping of the HLA region using next-generation sequencing data

Sojeong Ka[1†], Sunho Lee[2†], Jonghee Hong[1], Yangrae Cho[2], Joohon Sung[3], Han-Na Kim[4], Hyung-Lae Kim[4*] and Jongsun Jung[2*]

정밀의료 기반 암 진단 및 치료

정밀의료 기반 암 진단 및 치료란?

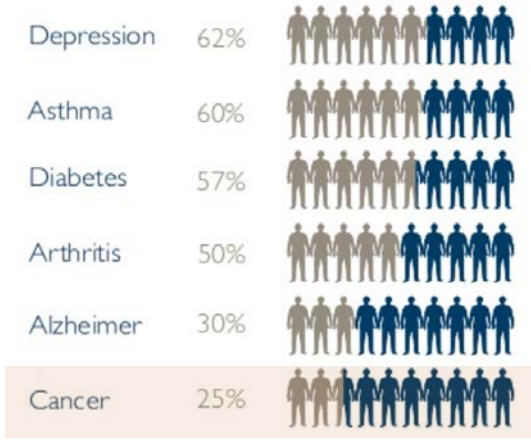
기존 항암치료:
- 환자의 유전 정보와 무관하게 일괄적으로 처방
- 치료 효과 있는 환자 비율 낮음 (~25%[1])



정밀의료 기반 항암치료:
- 환자 암조직의 바이오마커를 바탕으로 표적치료제 선별
- 환자맞춤형 항암제를 처방
- 표적항암치료의 혜택을 보는 환자 비율이 크게 증가

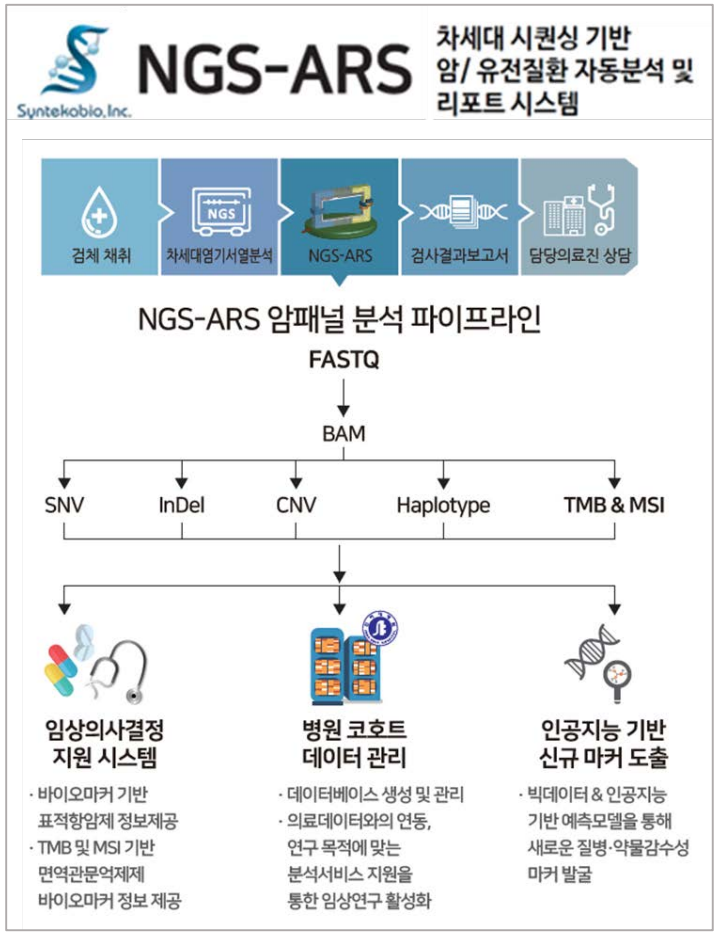
Modified from https://www.cancer.gov/about-cancer/treatment/types/precision-medicine

치료제 비반응군 비율



[1]Spear et al., 2001 *Trends Mol Med*

NGS 기반 암 유전자 검사의 중요성
➔ 다수의 암 유전자를 한번에 검사



암 정밀의료를 위한 인공지능 기술의 적용

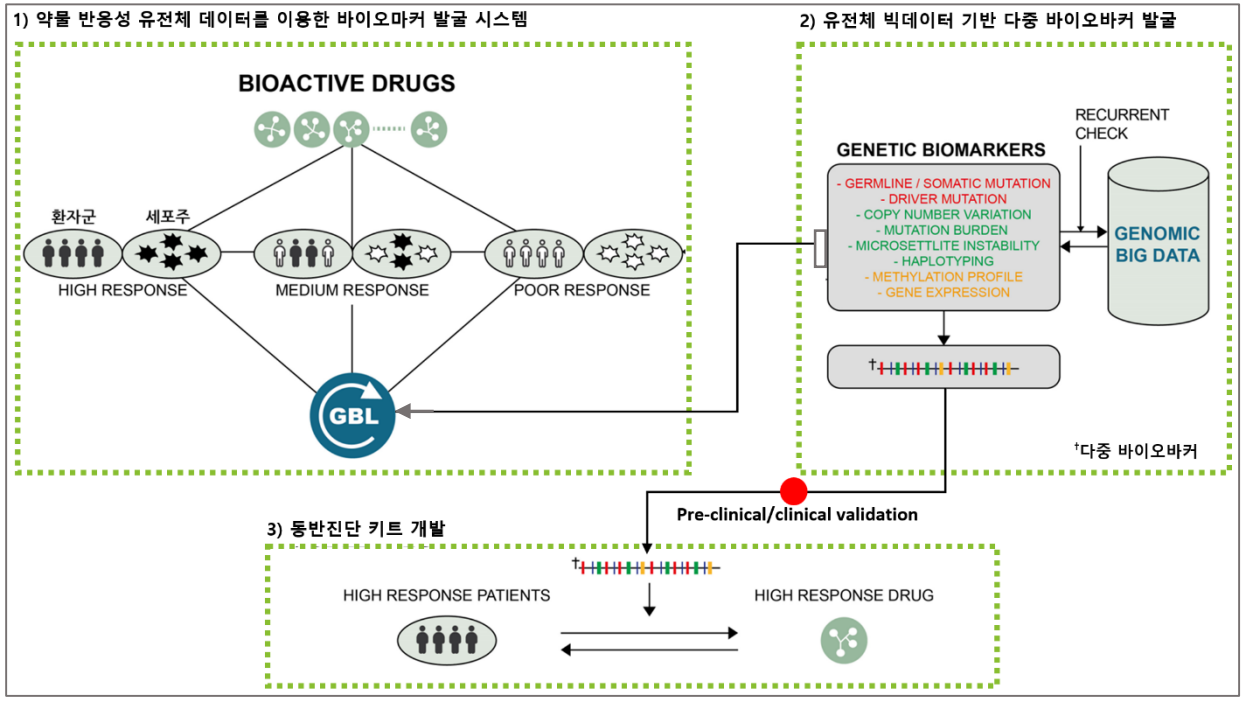
분석 & 리포트 자동화 → 확립된 마커 기반 항암제 정보 제공 → 신규 항암제 바이오마커 발굴 및 종양특이적 타겟발굴을 통한 정밀의료 시대 선제적 대응

✓NGS-ARS™

✓CDRscan™ 환자 암 유전변이 패턴과 화학구조 기반 항암제 반응성 예측

✓GBLscan™ 기존 항암제의 신규 바이오마커 발굴

✓NEOscan™ 종양특이적 타겟 발굴, 항암백신



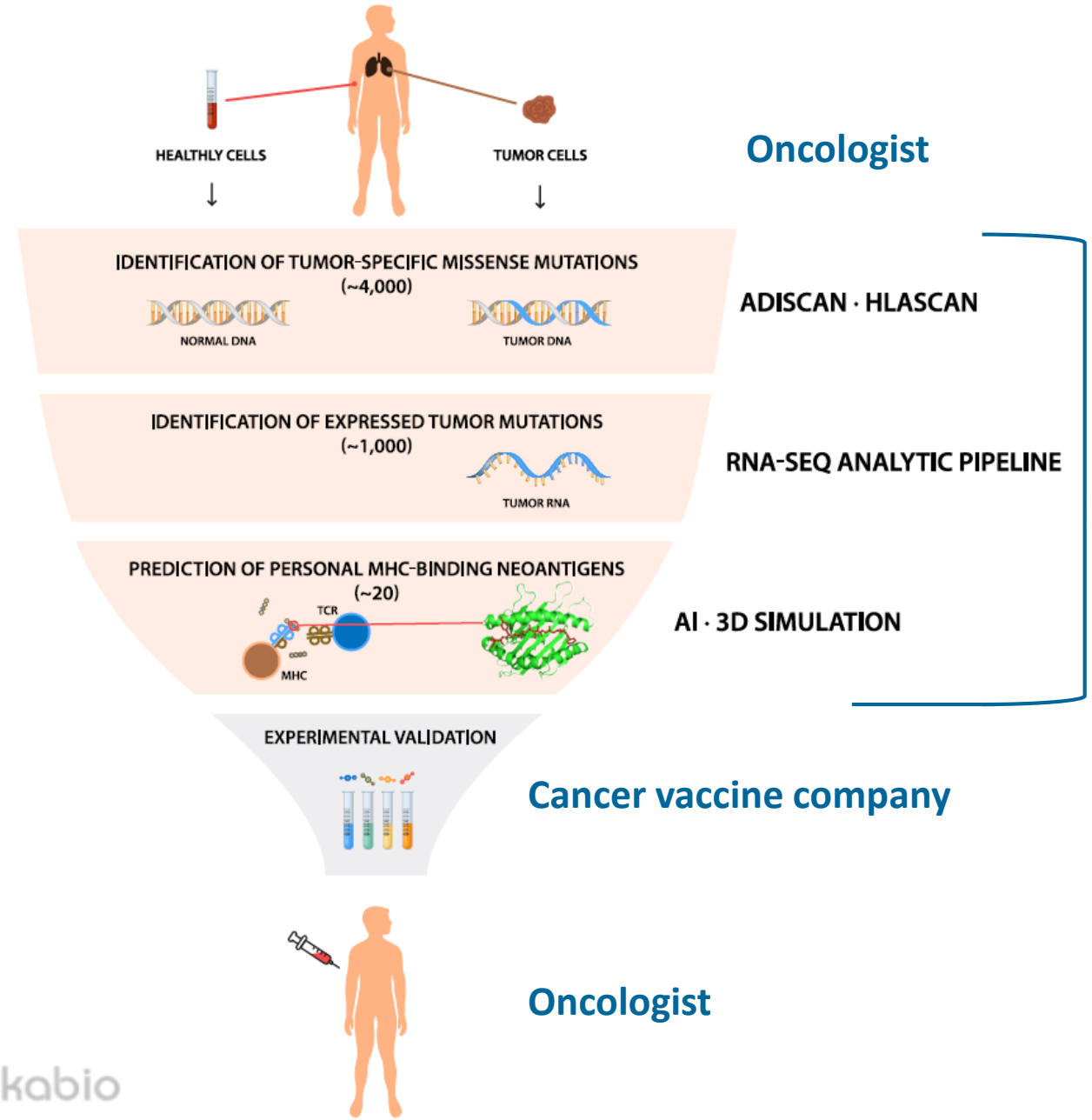
GBLscan 모식도

AI

Syntekabio, Inc.

Syntekabio's AI solutions

NEOscan™ – AI-driven neoantigen identification



AI-Deep Learning based
MD simulation analysis
- Deep-Matching filtering

Bioinformatics analysis &
Precise prediction of
immunogenicity

NEOscan™ – Looking forward to…

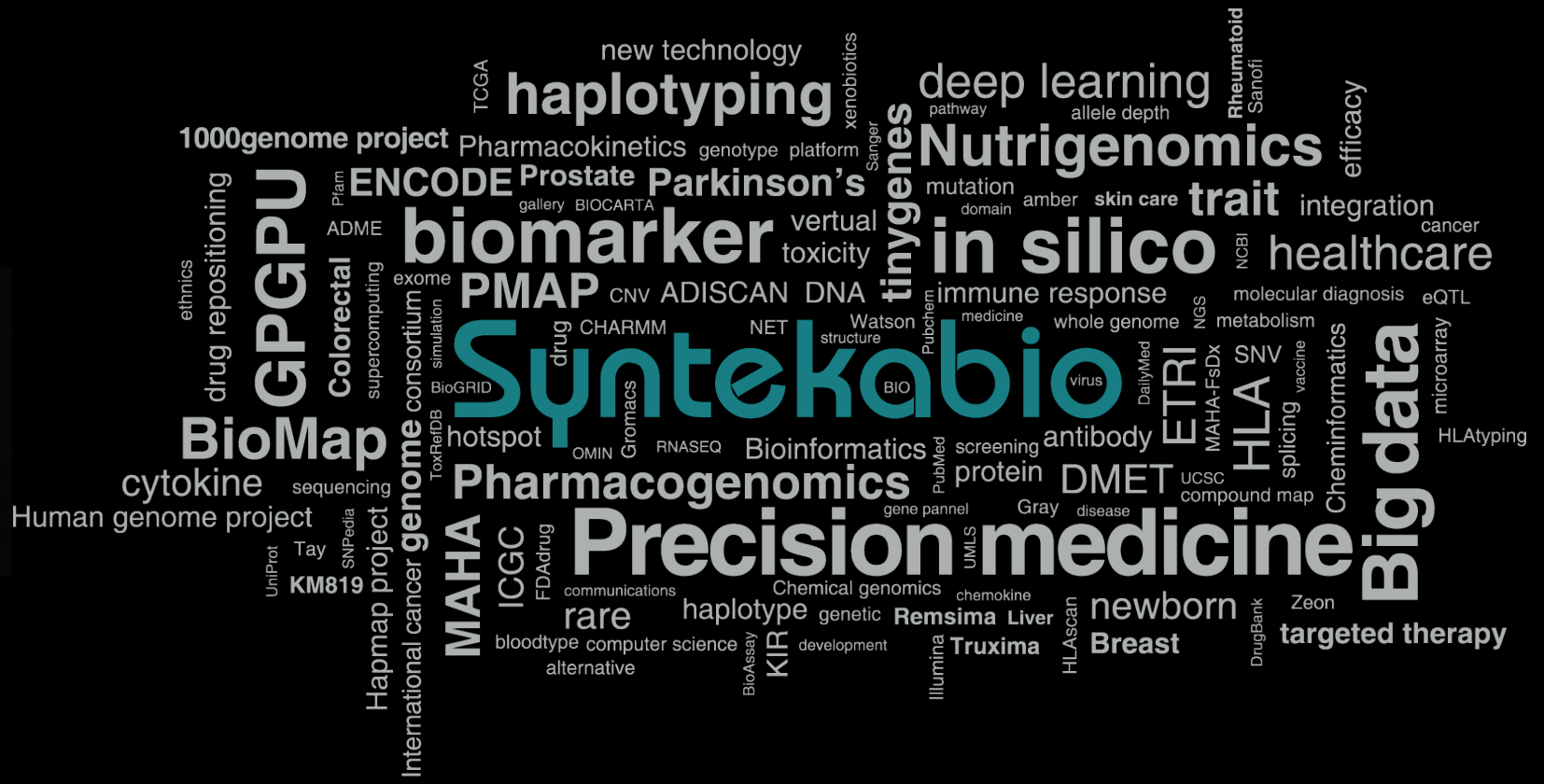
Flying and playing around genomic bigdata…..

Scanning cancer hallmark neoantigens…..

Cancer vaccine development

Winning in the cancer wars…..

Thanks a lot for listening!!!



Contact for Business Development

jaeyeourl.maeng@syntekabio.com