Annual Inspire2live, September 15th

Out in the City to Dutch NCI

Introduction to immunotherapeutics- Henk van Kranen

Already in the 80th's, long before the recent succes of immunotherapy, Rene Bernards and others noted the importance of MHC & cancer (1)

- One of the papers in RB's PhD thesis was about the difference in oncogenic properties of Adenovirus 5 (not oncogenic) versus Adenovirus 12 (highly oncogenic)
- Jumping to 2020, Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I, Yamamoto et al. 2019

> Immune evasion is a major obstacle for cancer treatment. Common mechanisms of evasion include impaired antigen presentation caused by mutations or loss of heterozygosity of the major histocompatibility complex class I (MHC-I), which has been implicated in resistance to immune checkpoint blockade (ICB) therapy
>
> However, in pancreatic ductal adenocarcinoma (PDAC), which is resistant to most therapies including ICB4, mutations that cause loss of MHC-I are rarely found.
>
> despite the frequent downregulation of MHC-I expression.
>
> Here we show that, in PDAC,MHC-I molecules are selectively targeted for lysosomal degradation by an autophagy-dependent mechanism that involves the autophagy cargo receptor NBR1. PDAC cells display reduced expression of MHC-I at the cell surface and instead demonstrate predominant localization within autophagosomes and lysosomes. Notably, inhibition of autophagy restores surface levels of MHC-I and leads to improved antigen presentation, enhanced anti-tumour T cell responses and reduced tumour growth in syngeneic host mice. Accordingly, the anti-tumour effects of autophagy inhibition are reversed by depleting CD8+ T cells or reducing surface expression of MHC-I. Inhibition of autophagy, either genetically or pharmacologically with chloroquine, synergizes with dual ICB therapy (anti-PD1 and anti-CTLA4 antibodies), and leads to an enhanced anti-tumour immune response. Our findings demonstrate a role for enhanced autophagy or lysosome function in immune evasion by selective targeting of MHC-I molecules for degradation, and provide a rationale for the combination of autophagy inhibition and dual ICB therapy as a therapeutic strategy against PDAC

MHC & Cancer summary (2)

- In summary for many cancers the correct and precise expression of MHC antigens in T cells is one of the important factors to prevent immune evasion.

- Mutations, decreased expression, degradation of MHC by autophagy and others are among the known mechanisms.

A few ways of helping our immunesystem

- Checkpoint Inhibitors (en.m.wikipedia.org/wiki/Checkpoint_inhibitor)

- Neo-antigen derived personalized vaccin's

- CAR-T cell therapy

- Combinations of CAR-T & Checkpoint inhibitors??

Sonntag et al.J Transl Med 2018

Sonntag et al. J Transl Med (2018) 16:23
https://doi.org/10.1186/s12967-018-1382-1

Journal of Translational Medicine

RESEARCH Open Access

Immune monitoring and TCR sequencing of CD4 T cells in a long term responsive patient with metastasized pancreatic ductal carcinoma treated with individualized, neoepitope-derived multipeptide vaccines: a case report

Katja Sonntag[1], Hisayoshi Hashimoto[1], Matthias Eyrich[2], Moritz Menzel[3], Max Schubach[4], Dennis Döcker[3], Florian Battke[3], Carolina Courage[5], Helmut Lambertz[6], Rupert Handgretinger[1], Saskia Biskup[3] and Karin Schilbach[1,7*]

Sonntag et al. (3)

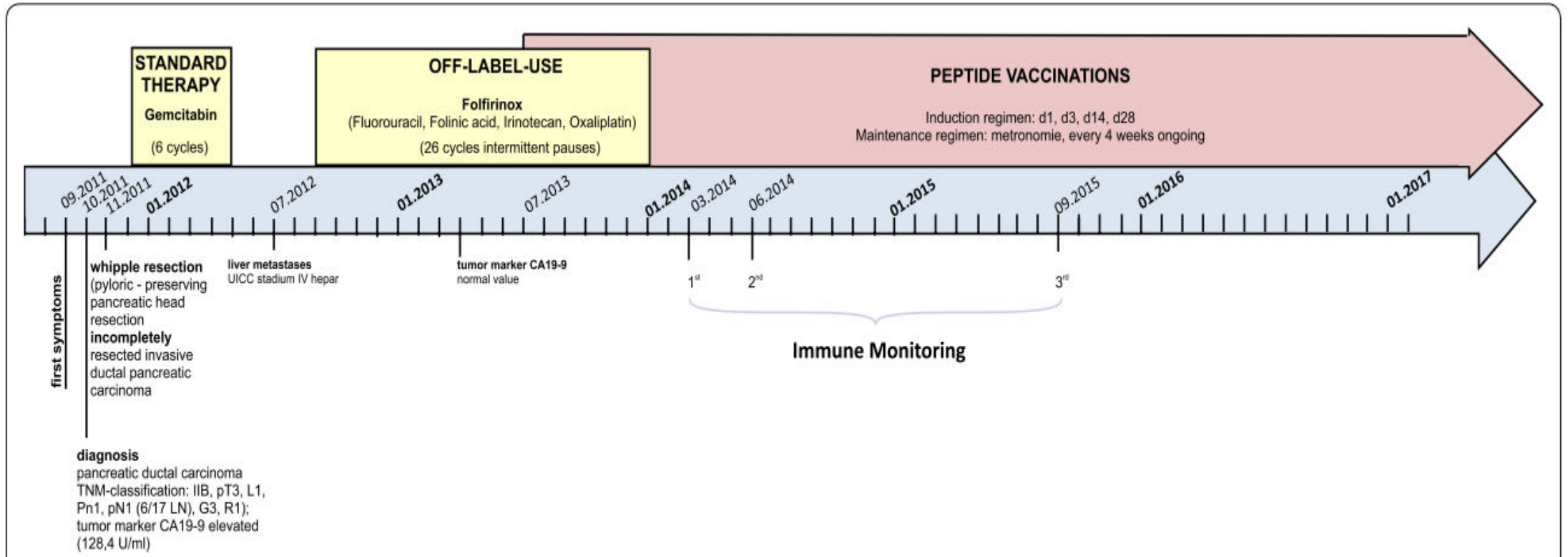

Fig. 1 Clinical course of patient's disease: time line of diagnoses and tumor staging, begin of treatment initiation (yellow block: polychemotherapy, red block: anti-tumor peptide vaccine) and time points of immune monitoring

Sonntag et al. (2)

Abstract

Background: Cancer vaccines can effectively establish clinically relevant tumor immunity. Novel sequencing approaches rapidly identify the mutational fingerprint of tumors, thus allowing to generate personalized tumor vaccines within a few weeks from diagnosis. Here, we report the case of a 62-year-old patient receiving a four-peptide-vaccine targeting the two sole mutations of his pancreatic tumor, identified via exome sequencing.

Methods: Vaccination started during chemotherapy in second complete remission and continued monthly thereafter. We tracked IFN-γ^+ T cell responses against vaccine peptides in peripheral blood after 12, 17 and 34 vaccinations by analyzing T-cell receptor (TCR) repertoire diversity and epitope-binding regions of peptide-reactive T-cell lines and clones. By restricting analysis to sorted IFN-γ-producing T cells we could assure epitope-specificity, functionality, and T_H1 polarization.

Results: A peptide-specific T-cell response against three of the four vaccine peptides could be detected sequentially. Molecular TCR analysis revealed a broad vaccine-reactive TCR repertoire with clones of discernible specificity. Four identical or convergent TCR sequences could be identified at more than one time-point, indicating timely persistence of vaccine-reactive T cells. One dominant TCR expressing a dual TCRVα chain could be found in three T-cell clones. The observed T-cell responses possibly contributed to clinical outcome: The patient is alive 6 years after initial diagnosis and in complete remission for 4 years now.

Conclusions: Therapeutic vaccination with a neoantigen-derived four-peptide vaccine resulted in a diverse and long-lasting immune response against these targets which was associated with prolonged clinical remission. These data warrant confirmation in a larger proof-of concept clinical trial.

Keywords: Pancreatic carcinoma, Therapeutic vaccines, Neoepitope-derived peptides, T-cell responses, CDR3 sequences

FRAMES Therapeutics (is now Cure-Vac Netherlands)

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causes a track of novel amino acids (neoantigens) to be expressed in a protein.

The left side of figure 1 below shows a point mutation (A changes into T) in the DNA, which may cause a single amino acid change in the protein. The right side shows that a deletion of a DNA letter (A) results in a 'Frame shift' and a completely novel stretch of amino acids that follow the deletion, providing a strong antigenic target. The novel stretch of amino acids is termed Frame.

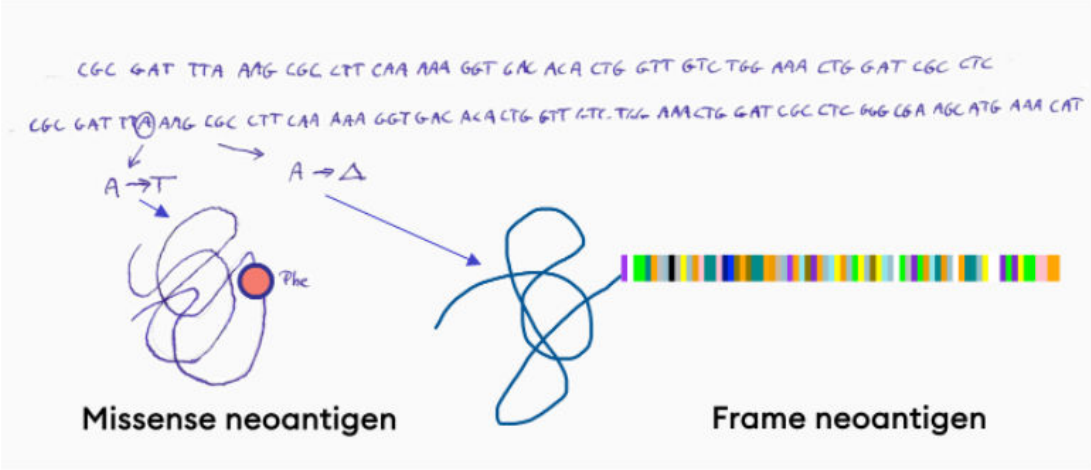

Figure 1: Point mutation (left) resulting in a single new amino acid and Frame shift (right) resulting in a stretch of novel amino acids (termed Frame).

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Frames Therapeutics

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Hidden Frames are the major source of neo-antigenicity

Using FramePro, we have discovered a novel source of neo-antigenicity of tumors, termed Hidden Frames. Hidden Frames are derived from a combination of a structural genomic variation (SV) and splicing of a transcript that covers the SV junction (Figure 3). For many cancer types, Hidden Frames represent a major part of the tumor neo-antigenicity.

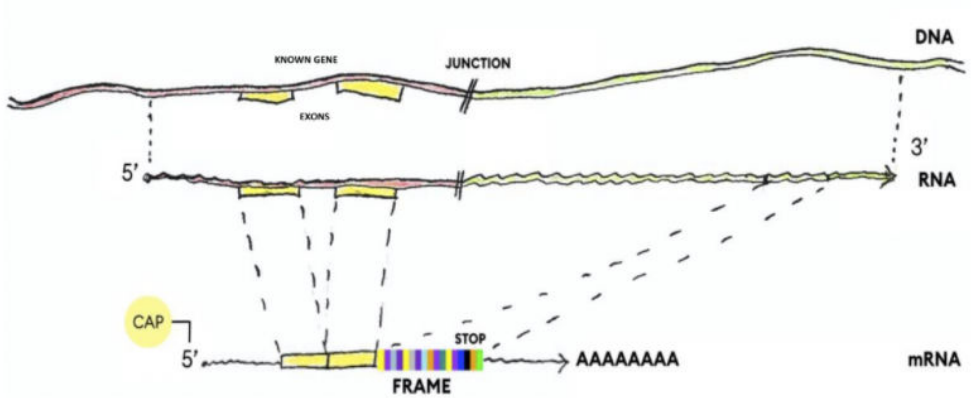

Figure 3: Identification of Hidden Frames that are caused by SV's in the tumor DNA. Using FramePro we are able to discover that novel spliced transcripts result from genomic structural variations in the tumor genome. These transcripts bring a non-coding DNA sequence into frame, and thus encode for a neoantigen.

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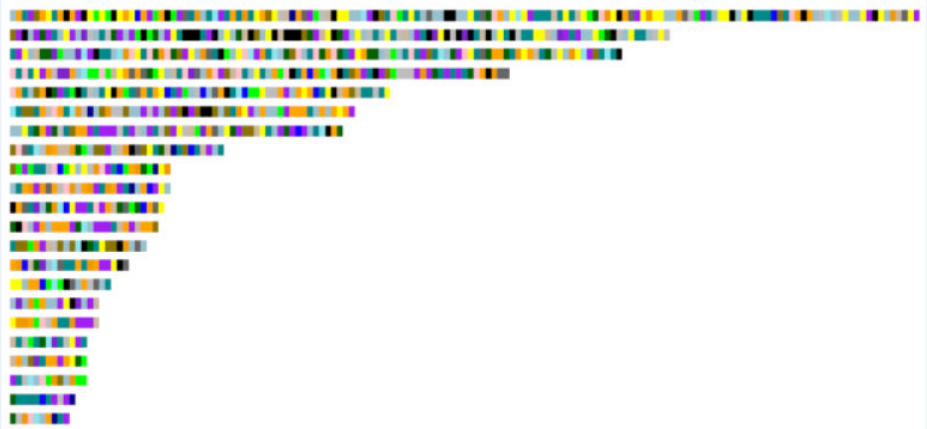
Whole Framome: fully personalized

With our FramePro pipeline we identify all the Frames present in a tumor sample, including those that are a result of short indels and large genomic SVs. The entirely collection of Frames expressed by a tumor is termed the Whole Framome of the tumor. A Whole Framome immunotherapy (e.g., a cancer vaccine) targets the bulk of the antigenicity of the tumor. As a first therapy, Frame Therapeutics is currently developing a Framome personalized cancer vaccine for patients with lung cancer.

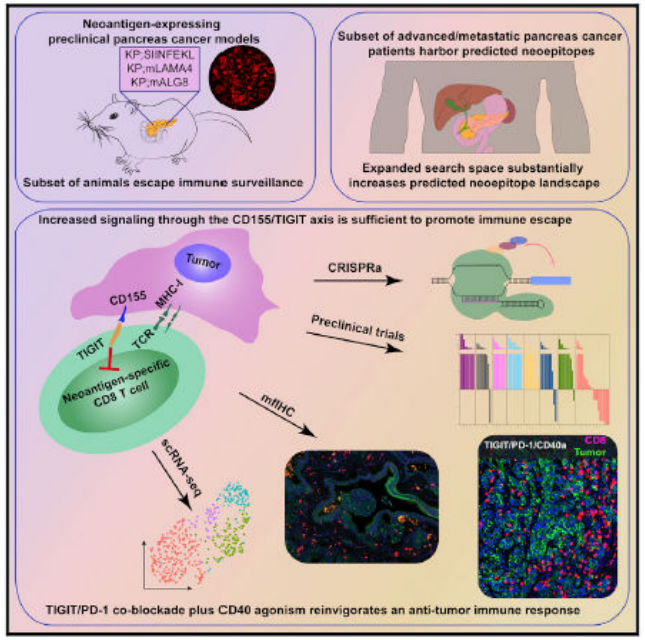
Figure 4 shows an example of a Framome. Every horizontal sequence represents a Frame. Each color represents an amino acid. This lung tumor expresses many Frames, that altogether represent almost 1000 novel amino acids. Each of these Frames can be represented in a cancer vaccine.



Feed-Pastor et al. 2021 Cancer Cell

The CD155/TIGIT axis promotes and maintains immune evasion in neoantigen-expressing pancreatic cancer

Graphical abstract



Highlights

- A subset of neoantigen-expressing pancreas cancer evades immune surveillance
- Markers of T cell exhaustion typify pancreas cancer tumor-infiltrating lymphocytes
- The CD155/TIGIT axis promotes immune evasion in pancreas cancer
- TIGIT/PD-1 co-blockade plus CD40 agonism reinvigorates tumor-reactive T cells

Authors

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In brief

Freed-Pastor et al. identify the CD155/TIGIT axis as a key driver of immune evasion in pancreas cancer. Neoepitope prediction reveals a subset of human pancreas cancer patients with predicted high-affinity neoepitopes and functional interrogation using preclinical models identifies a combination immunotherapy approach (TIGIT/PD-1 co-blockade plus CD40 agonism) capable of eliciting profound anti-tumor responses.

Feed-Pastor (2)

SUMMARY

The CD155/TIGIT axis can be co-opted during immune evasion in chronic viral infections and cancer. Pancreatic adenocarcinoma (PDAC) is a highly lethal malignancy, and immune-based strategies to combat this disease have been largely unsuccessful to date. We corroborate prior reports that a substantial portion of PDAC harbors predicted high-affinity MHC class I-restricted neoepitopes and extend these findings to advanced/metastatic disease. Using multiple preclinical models of neoantigen-expressing PDAC, we demonstrate that intratumoral neoantigen-specific $CD8^+$ T cells adopt multiple states of dysfunction, resembling those in tumor-infiltrating lymphocytes of PDAC patients. Mechanistically, genetic and/or pharmacologic modulation of the CD155/TIGIT axis was sufficient to promote immune evasion in autochthonous neoantigen-expressing PDAC. Finally, we demonstrate that the CD155/TIGIT axis is critical in maintaining immune evasion in PDAC and uncover a combination immunotherapy (TIGIT/PD-1 co-blockade plus CD40 agonism) that elicits profound anti-tumor responses in preclinical models, now poised for clinical evaluation.

Explaining T-Cell Immunotheraypy against mutant KRAS for Pancreatic Cancer by Cees Melief

EDITORIALS

The Science behind the Study
E.G. Phimister, M.B. Hamel, S. Morrissey, and E. Rubin

2138

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M. Schatz

2139-2140

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T-Cell Immunotherapy against Mutant KRAS for Pancreatic Cancer
C.J.M. Melief

NEJM editorials, explaining the Science 2022

Key Concepts

T-cell lysis

'tē 'sel 'lī-səs

A process by which cytotoxic T cells recognize and kill other cells, such as infected or tumor cells. Recognition is mediated by the T-cell receptor (on the T cell) and "foreign" or mutant peptides presented by the HLA class I molecule (on the infected cell or tumor cell).

Chimeric antigen receptor (CAR) T cells

kī-'mer-ik 'an-ti-jən ri-'sep-tər 'tē 'selz

Engineered T cells that target a specific cell-surface antigen, such as one expressed by a tumor cell. The specific targeting is mediated by a chimeric antigen receptor (CAR), so called because it combines the specificity of an antibody (the extracellular part) with the T cell–activating function of a T-cell receptor (the intracellular part). Its forced expression on the surface of the T cell (through genetic means) augments specificity, function, and metabolism.

Human leukocyte antigen (HLA) class I

'hyü-mən 'lü-kə-sīt 'an-ti-jən ('āch-el-'ā) klas 'wən

A type of molecule expressed on the surface of most human cells. Human leukocyte antigen (HLA class I) forms a complex with and "presents" (to T cells) peptides that are present inside the cell. It is therefore a key component in triggering T-cell immunity to infected or tumor cells.

KRAS signaling

'kā-ras 'sig-nə-liŋ

A process in which KRAS, a cytoplasmic molecule, acts like a switch in a cell-proliferation pathway that begins at the cell surface with the binding of growth factors (or other proteins) to receptors and ends with the activation of specific genes that promote cell proliferation. Oncogenic variants in the gene *KRAS* result in versions of the KRAS protein that are permanently switched "on," resulting in uncontrolled cell proliferation and cancer.

An expanded illustrated glossary is available at NEJM.org

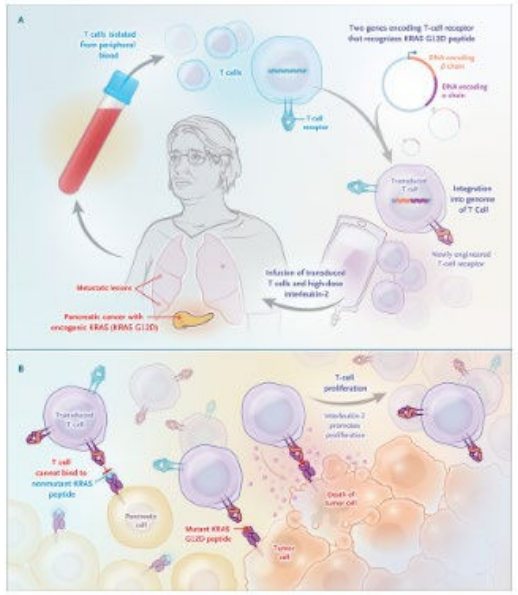

Figure 1.

Neoantigen T-Cell Receptor (TCR) Gene Therapy in Pancreatic Cancer

Leidner et al. NEJM June 2022 TCR & Pancreatic cancer

NEJM June 2022 TCR & Pancreatic cancer

SUMMARY

A patient with progressive metastatic pancreatic cancer was treated with a single infusion of 16.2×10^9 autologous T cells that had been genetically engineered to clonally express two allogeneic HLA-C*08:02–restricted T-cell receptors (TCRs) targeting mutant KRAS G12D expressed by the tumors. The patient had regression of visceral metastases (overall partial response of 72% according to the Response Evaluation Criteria in Solid Tumors, version 1.1); the response was ongoing at 6 months. The engineered T cells constituted more than 2% of all the circulating peripheral-blood T cells 6 months after the cell transfer. In this patient, TCR gene therapy targeting the KRAS G12D driver mutation mediated the objective regression of metastatic pancreatic cancer. (Funded by the Providence Portland Medical Foundation.)

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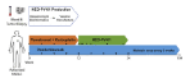

Combining personalized neoantigen vaccination with chemotherapy and anti-PD-1 to treat NSCLC

Carol Sze Ki Leung, Benoit J. Van den Eynde

In this issue of *Cancer Cell*, Awad et al. report a phase 1b clinical trial combining a personalized vaccine NEO-PV-01 with chemotherapy and anti-PD-1 pembrolizumab in first-line metastatic non-squamous NSCLC. They demonstrate that this treatment regimen was well tolerated and induced neoantigen-specific $CD4^+$ T cell responses with effector phenotype.

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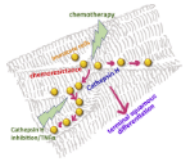

Targeting lineage plasticity overcomes chemoresistance

Seishi Ogawa

In this issue of *Cancer Cell*, Wang et al. reveal that chemoresistant muscle-invasive bladder cancer is associated with partial squamous differentiation. Targeting of Cathepsin H overcomes this chemotherapy-induced semi-squamatization and promotes terminal squamous differentiation and tumor suppression.

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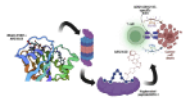

Getting a handle on KRAS inhibitor resistance with hapten-mediated anti-tumor immunity

William A. Freed-Pastor, Andrew J. Aguirre

Covalent inhibitors of oncogenic $KRAS^{G12C}$ have demonstrated impressive clinical responses; however, therapeutic resistance has been commonly observed. In this issue, Zhang and colleagues demonstrate that small molecule $KRAS^{G12C}$ inhibitors can generate haptenated major histocompatibility complex (MHC) class I:peptide complexes, which represent attractive targets for immune-based therapies to combat pharmacologic resistance.

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Many thanks for your attention.

Any questions?