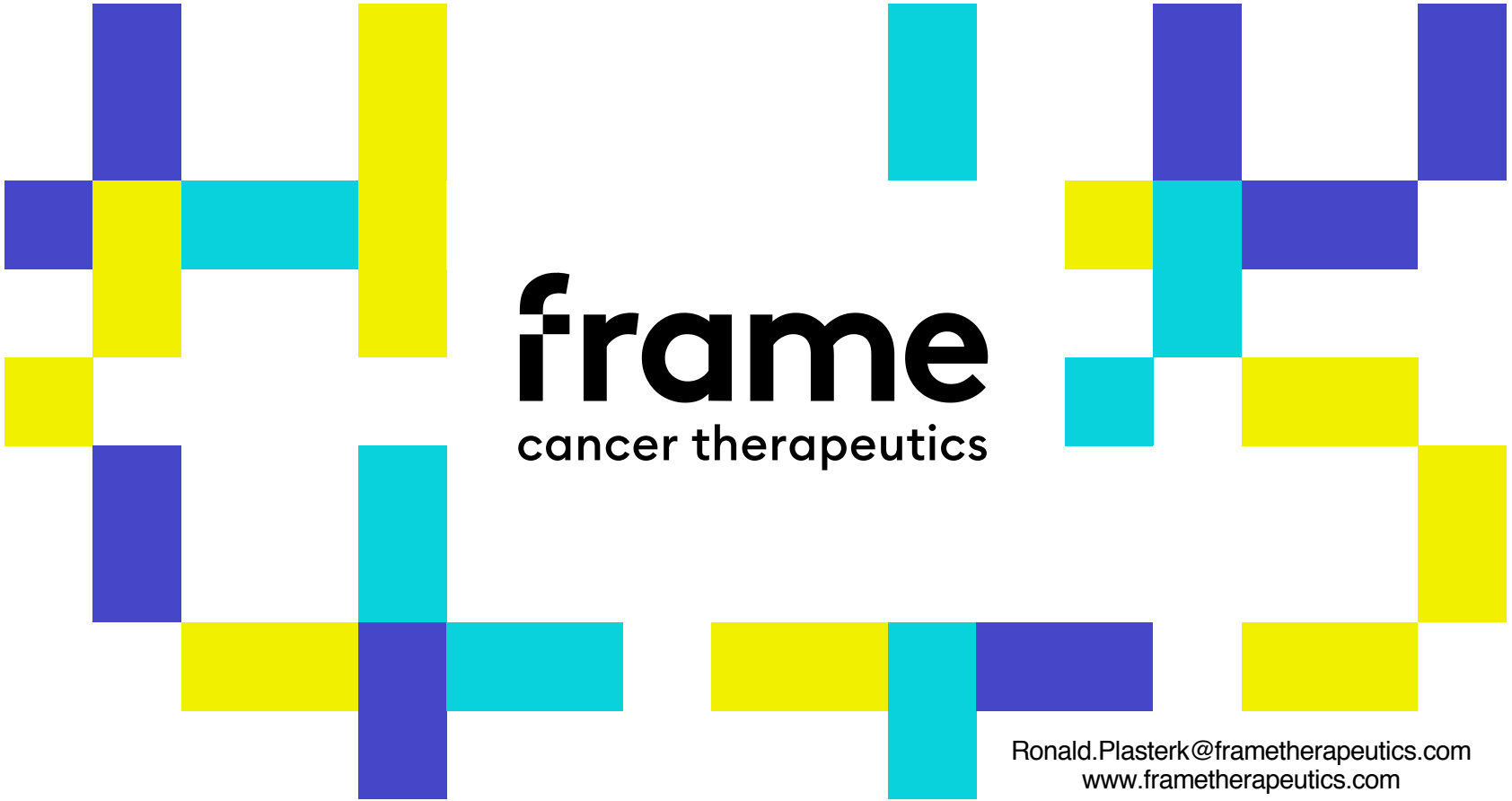

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Founder / CEO

Our goal: personalized cancer vaccine based on DNA sequence

www.frametherapeutics.com

frame
CANCER THERAPEUTICS

Your tumor contains the following Frames:

ORDER A MATCHING VACCINE NOW

For more information on ordering vaccines, click here.

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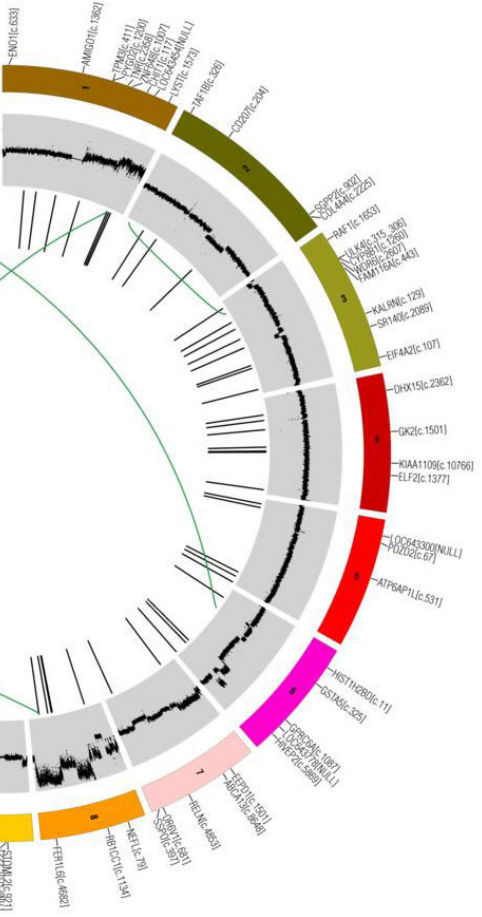

Each tumor can now be DNA- and RNA-sequenced within two weeks

All tumor cells and all mutation patterns are different. With few exceptions, there are really no shared mutations.

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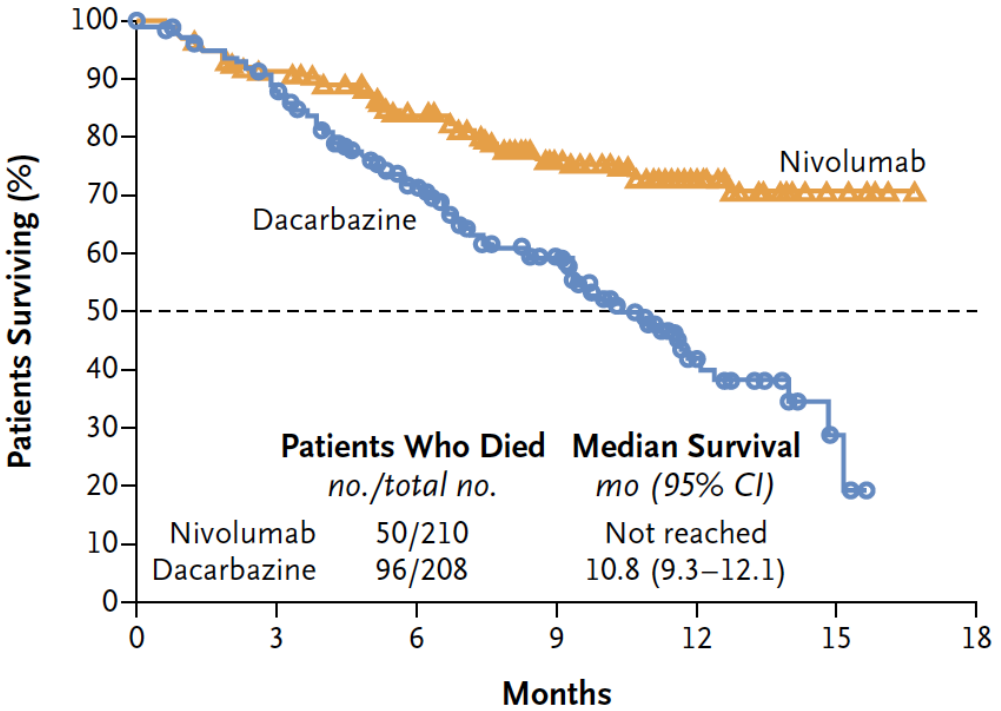
Triggering T cell response improves cancer survival



Robert et al., NEJM 2015

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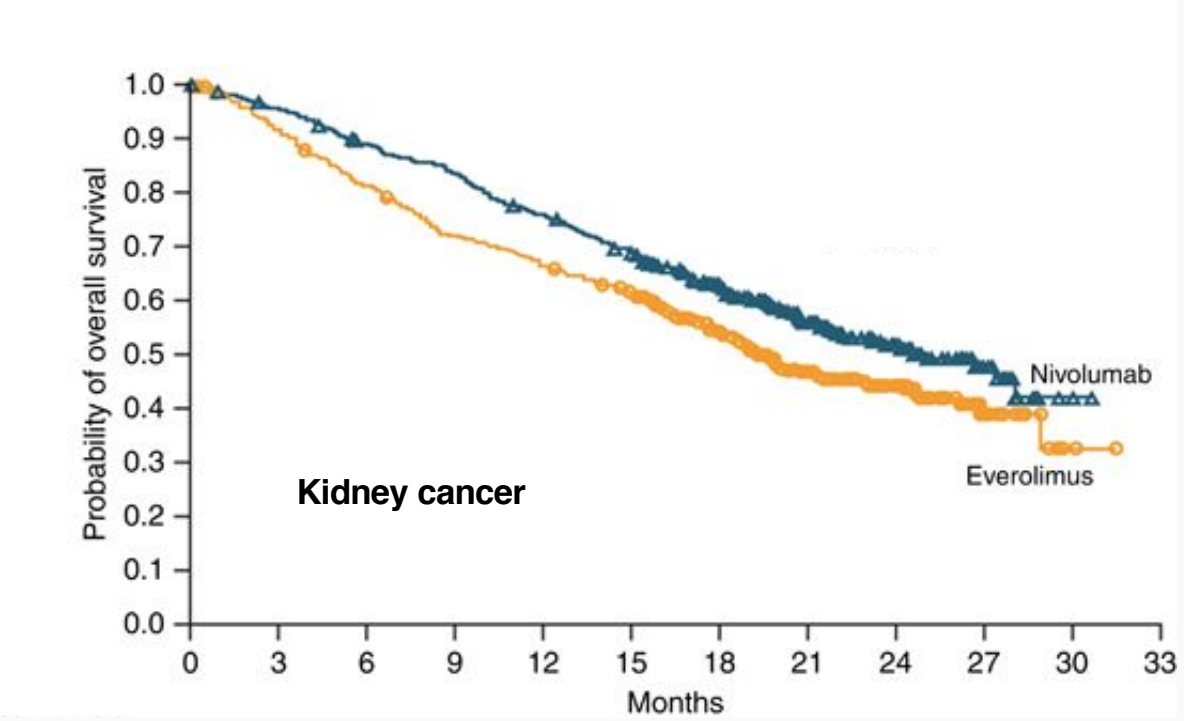
Immunotherapy improves cancer treatment, but not all patients respond



Motzer et al, N Engl J Med **373**: 1803–1813

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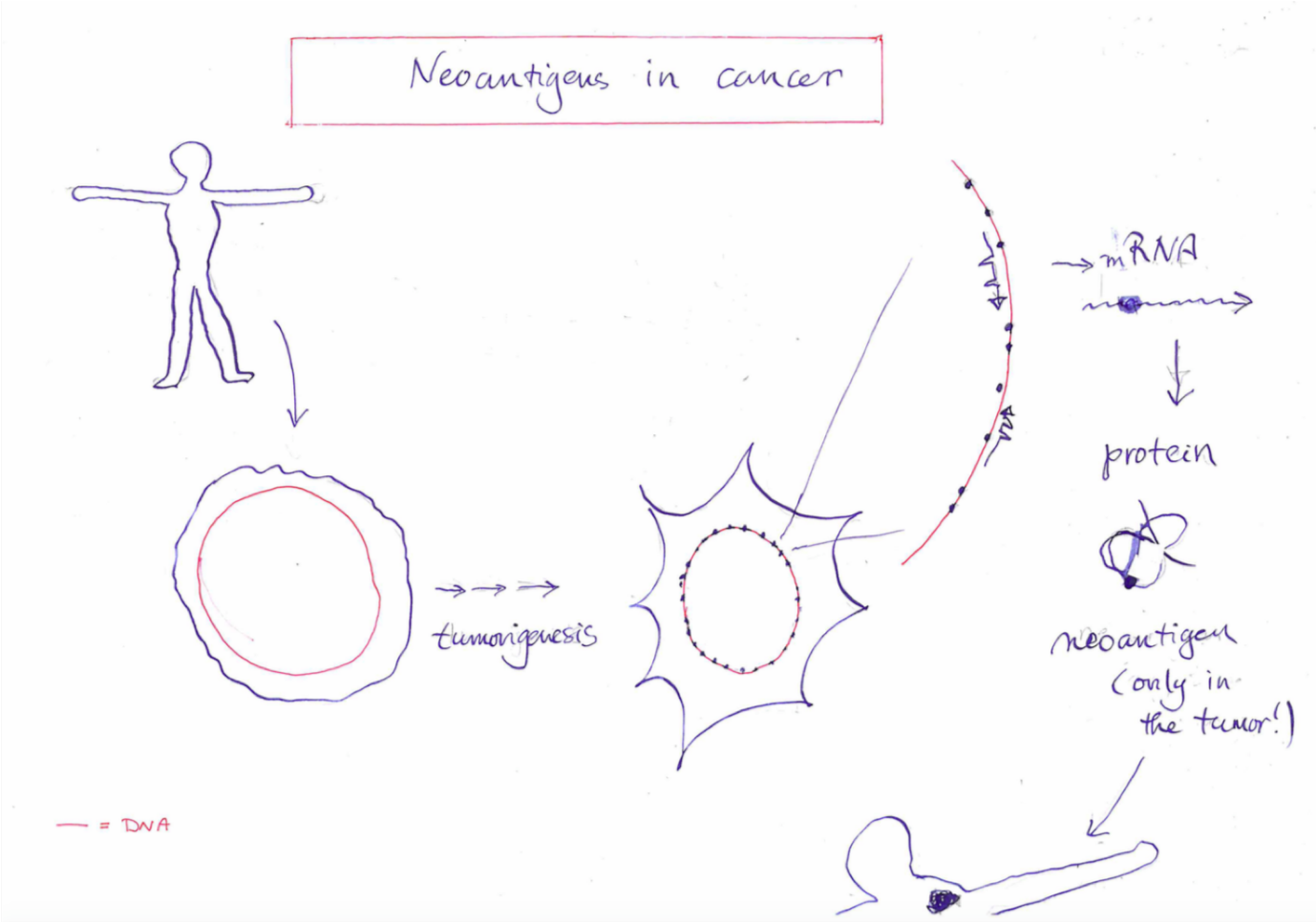
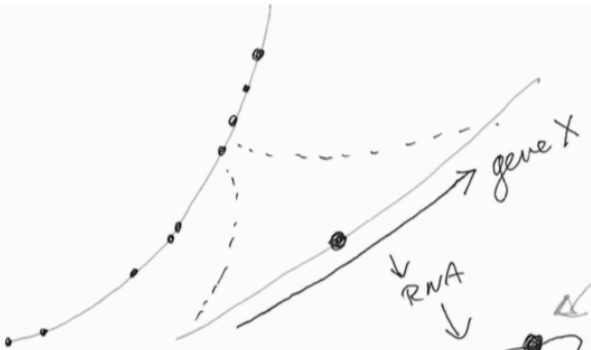


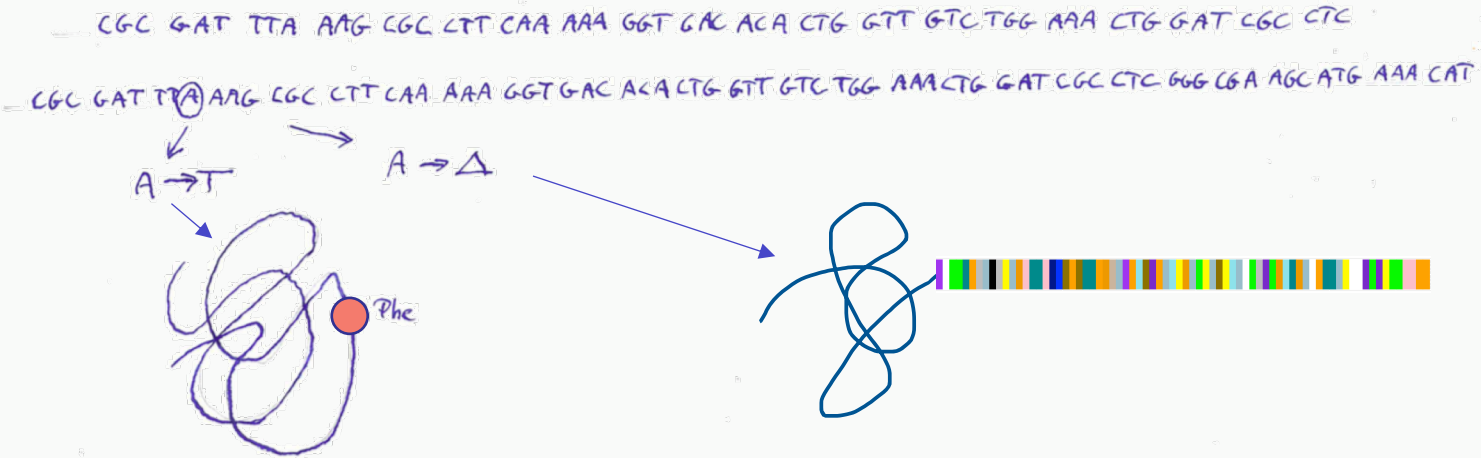
Peptide vaccine for neo-antigen



chemical synthesis of peptide → with neo-antigen (part of protein X)

= vaccine!

Frames are the strongest cancer neoantigens



Missense neoantigen **Frame neoantigen**

DNA sequence from Plasterk et al. PNAS. 1983 Sep;80(17):5355-8.

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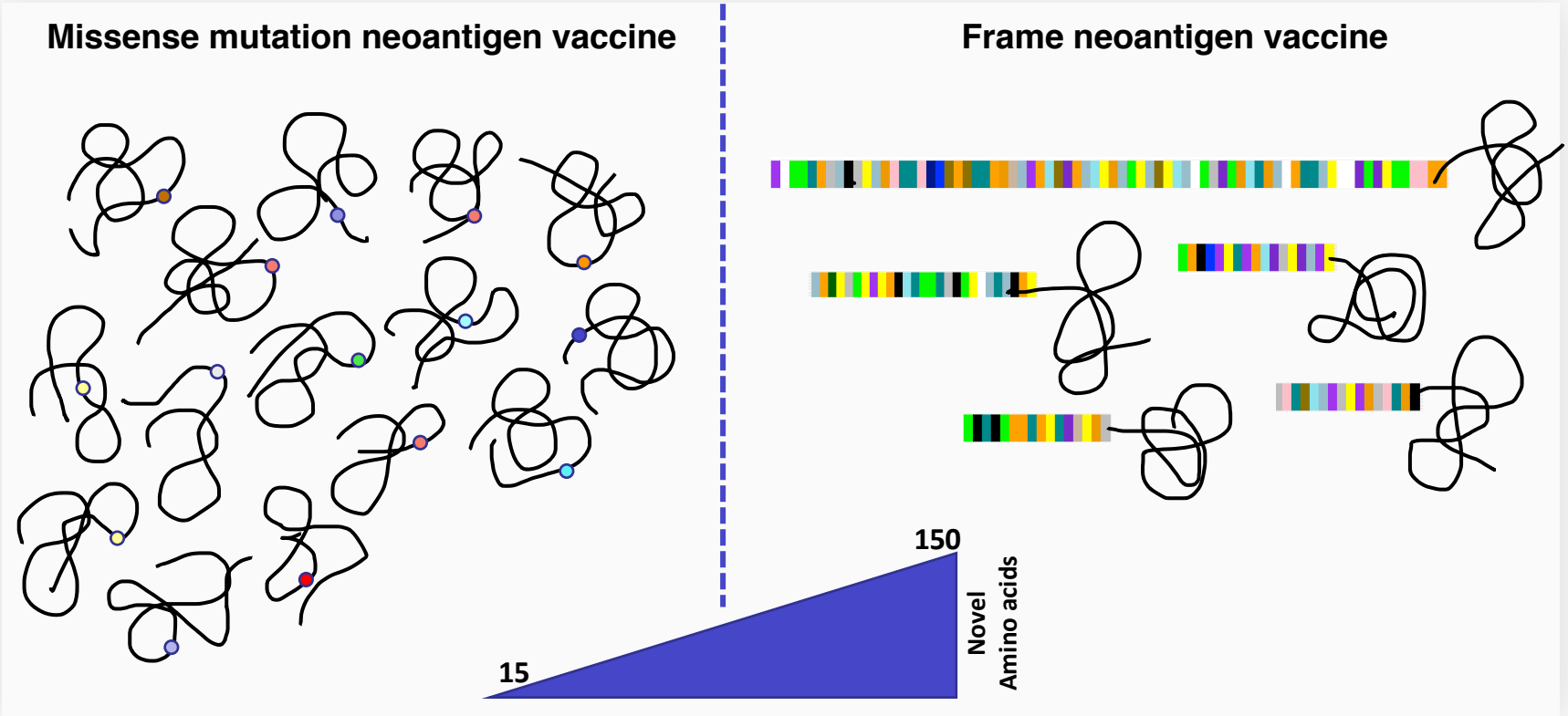
Frame vaccines represent the strongest neoantigens



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Frames are long entirely foreign peptides, just like viral antigens

1. **Frame antigens resemble viral antigens**

Viral antigen (HPV) 

Frame neoantigen 

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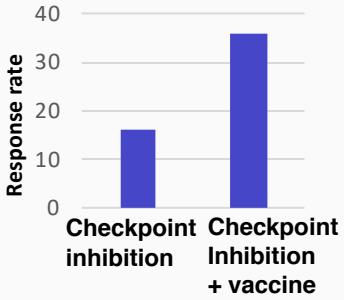
Frames are long entirely foreign peptides, just like viral antigens

1. Frame antigens resemble viral antigens

Viral antigen (HPV) 

Frame neoantigen 

2. Viral antigens are successful for therapeutic cancer treatment



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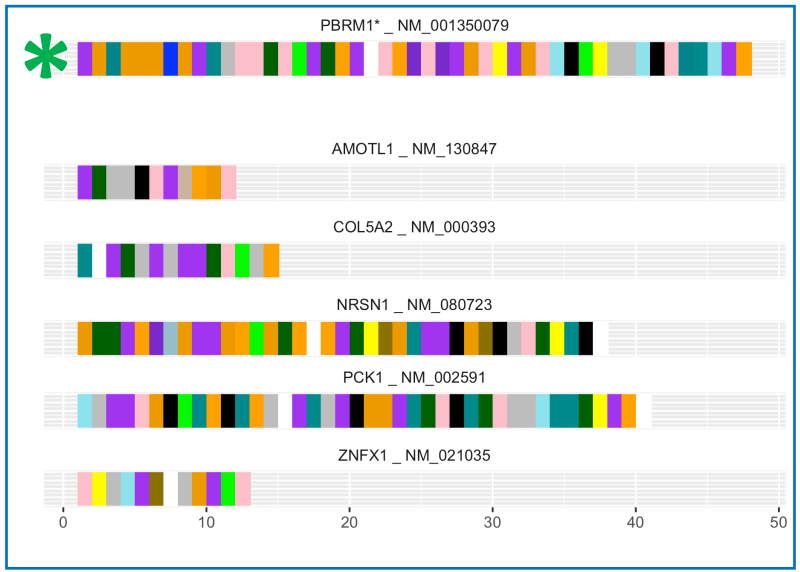
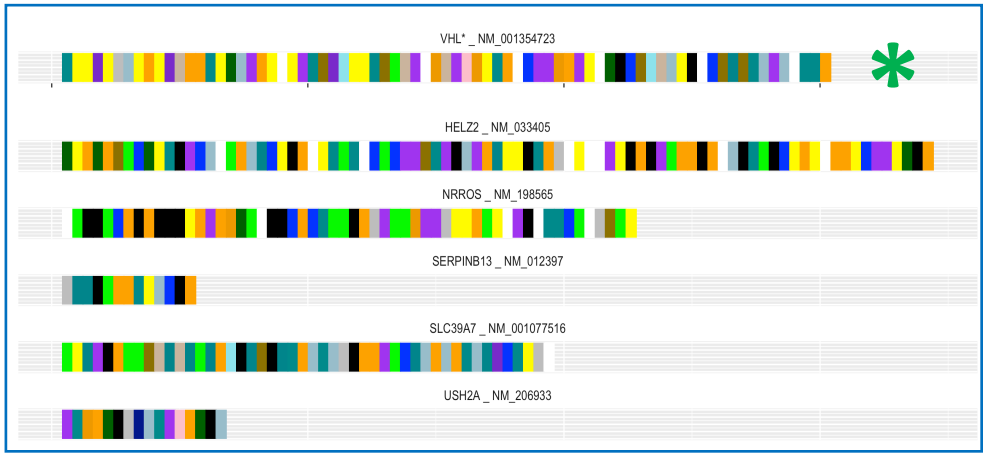
One more thing: personalized yet off-the-shelf frame vaccines

Patient 1



Patient 2



* **Off-the-shelf available vaccine**

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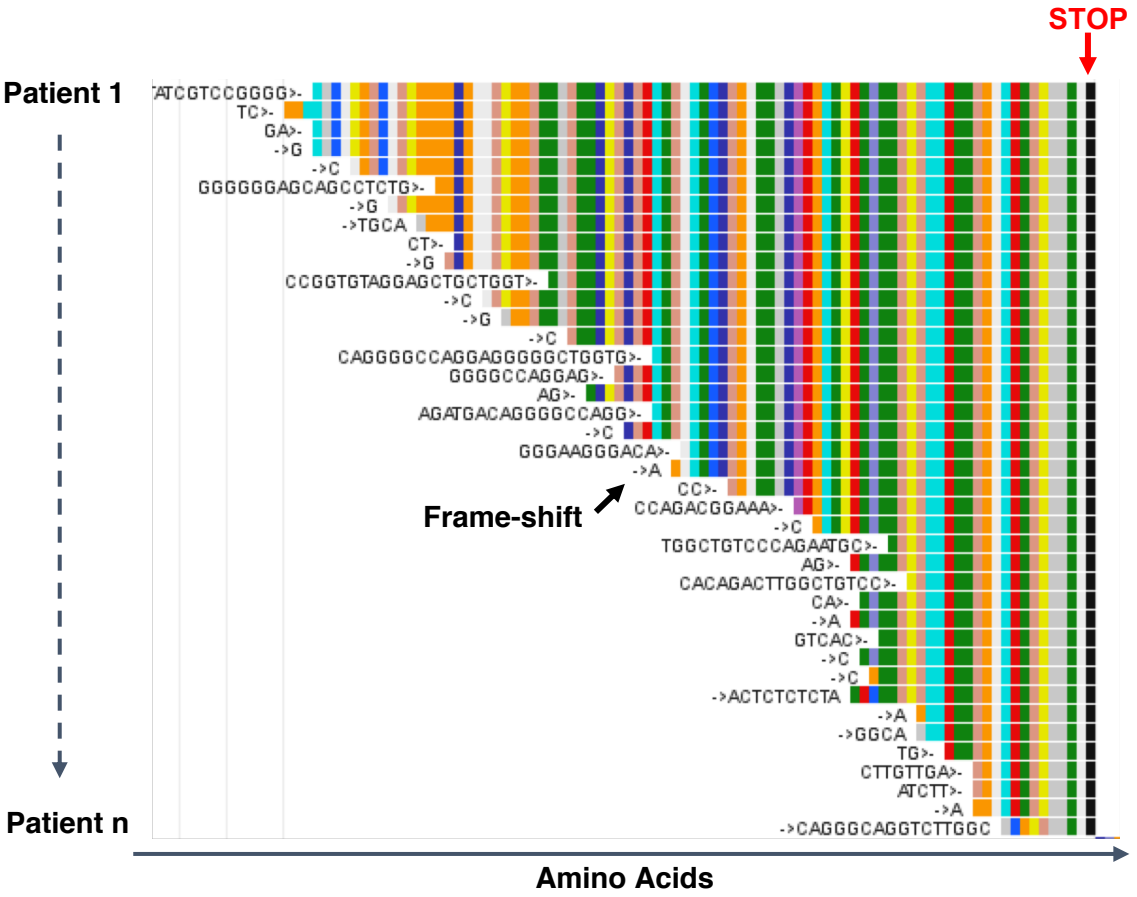
Frame vaccines: personalized yet off-the-shelf



Koster and Plasterk, Nature Scientific Reports, April 2019

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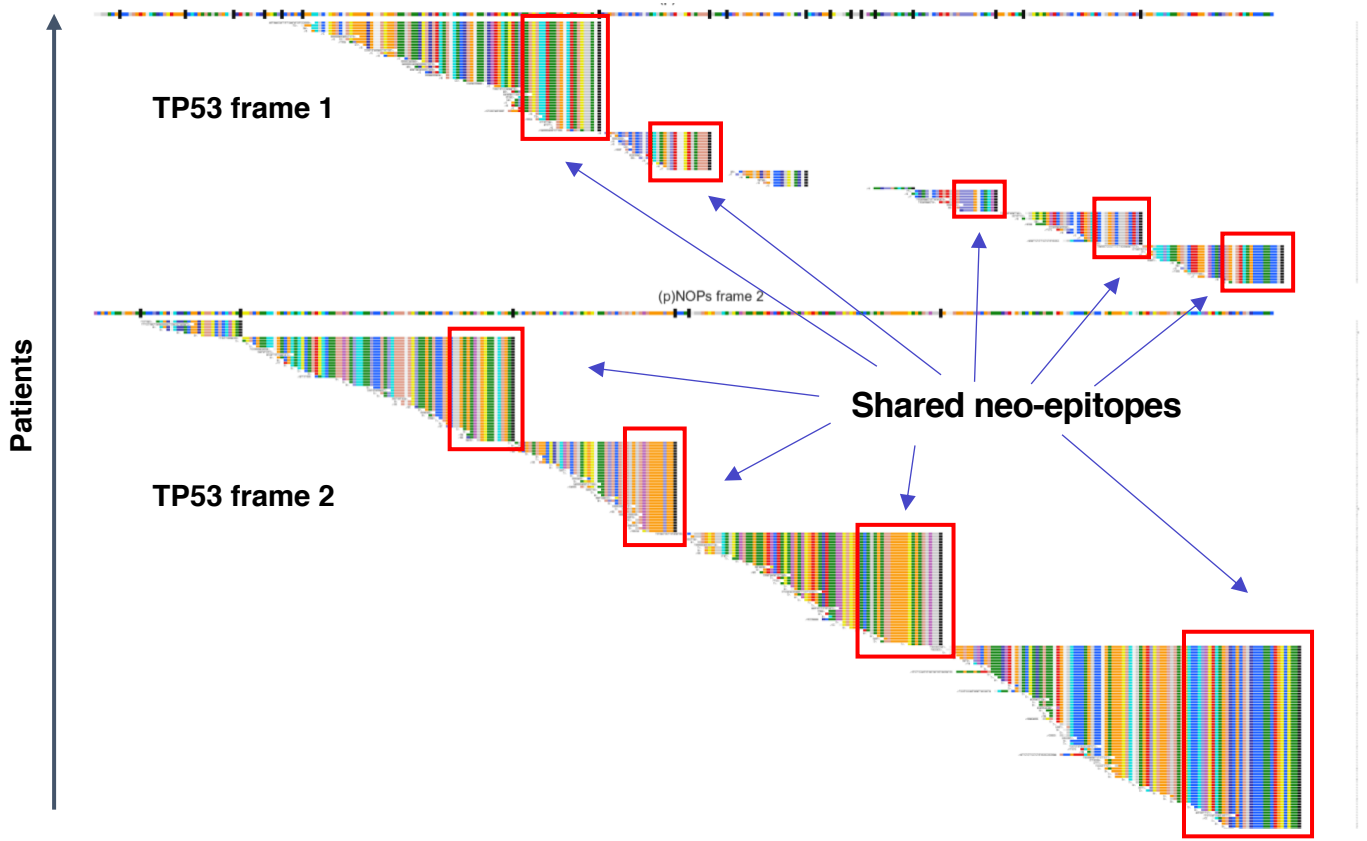
With 9 shared TP53 neo-epitopes 4% of all patients are covered



TP53 tumors have poor prognosis

Koster and Plasterk, Nature Scientific Reports, April 2019

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Shared antigen occur often. Nature Scientif Report Koster and Plasterk 2019

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

A library of Neo Open Reading Frame peptides (NOPs) as a sustainable resource of common neoantigens in up to 50% of cancer patients

Received: 12 October 2018
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Jan Koster[1] & Ronald H. A. Plasterk[2,3,4]

Somatic mutations in cancer can result in neoantigens against which patients can be vaccinated. The quest for tumor specific neoantigens has yielded no targets that are common to all tumors, yet foreign to healthy cells. Single base pair substitutions (SNVs) at best can alter 1 amino acid which can result in a neoantigen; with the exception of rare site-specific oncogenic driver mutations (such as RAS) such mutations are private. Here, we describe a source of common neoantigens induced by frame shift mutations, based on analysis of 10,186 TCGA tumor samples. We find that these frame shift mutations can produce long neoantigens. These are completely new to the body, and indeed recent evidence suggests that frame shifts can be highly immunogenic. We report that many different frame shift mutations converge to the same small set of 3′ neo open reading frame peptides (NOPs), all encoded by the Neo-ORFeome. We find that a fixed set of only 1,244 neo-peptides in as much as 30% of all TCGA cancer patients. For some tumor classes this is higher; e.g. for colon and cervical cancer, peptides derived from only ten genes (saturated at 90 peptides) can be applied to 39% of all patients. 50% of all TCGA patients can be achieved at saturation (using all those peptides in the library found more than once). A pre-fabricated library of vaccines (peptide, RNA or DNA) based on this set can provide off the shelf, quality certified, 'personalized' vaccines within hours, saving months of vaccine preparation. This is crucial for critically ill cancer patients with short average survival expectancy after diagnosis.

The concept of utilizing the immune system to battle cancer is very attractive and studied extensively. Indeed, neoantigens can result from somatic mutations, against which patients can be vaccinated[1–11]. Recent evidence suggests that frame shift mutations, that result in peptides which are completely new to the body, can be highly immunogenic[12–15]. The immune response to neoantigen vaccination, including the possible predictive value of epitope selection has been studied in great detail[8,13,16–21], and there is no doubt about the promise of neoantigen-directed immunotherapy. The quest for common antigens, however, has been disappointing, since virtually all mutations are private. One can derive algorithms that predict likely good epitopes, but still every case is different. Here we report that frame shift mutations, which are also mostly unique among patients and tumors, nevertheless converge to neo open reading frame peptides (NOPs) from their translation products, that result in common neoantigens in large groups of cancer patients.

We have analyzed 10,186 cancer genomes from 33 tumor types of the TCGA (The Cancer Genome Atlas[22]) and focused on the 143,444 frame shift mutations represented in this cohort (see Table S1). Translation of these mutations after re-annotation to a RefSeq annotation, starting in the protein reading frame, can lead to 70,439 unique peptides that are 10 or more amino acids in length (a cut-off we have set at a size sufficient to shape a

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frame cancer therapeutics

No shared mutations but yet shared antigens

While practically all frame shift mutations, like other mutations are unique, the gene products resulting from frame shifts are often shared in cancers.

This is because:

1. They slip into the same frame (only two options, +1 and -1).
2. They are strong loss of function mutations.
3. There are quite many genes, as we find, whose loss of function contributed to the tumorigenesis.

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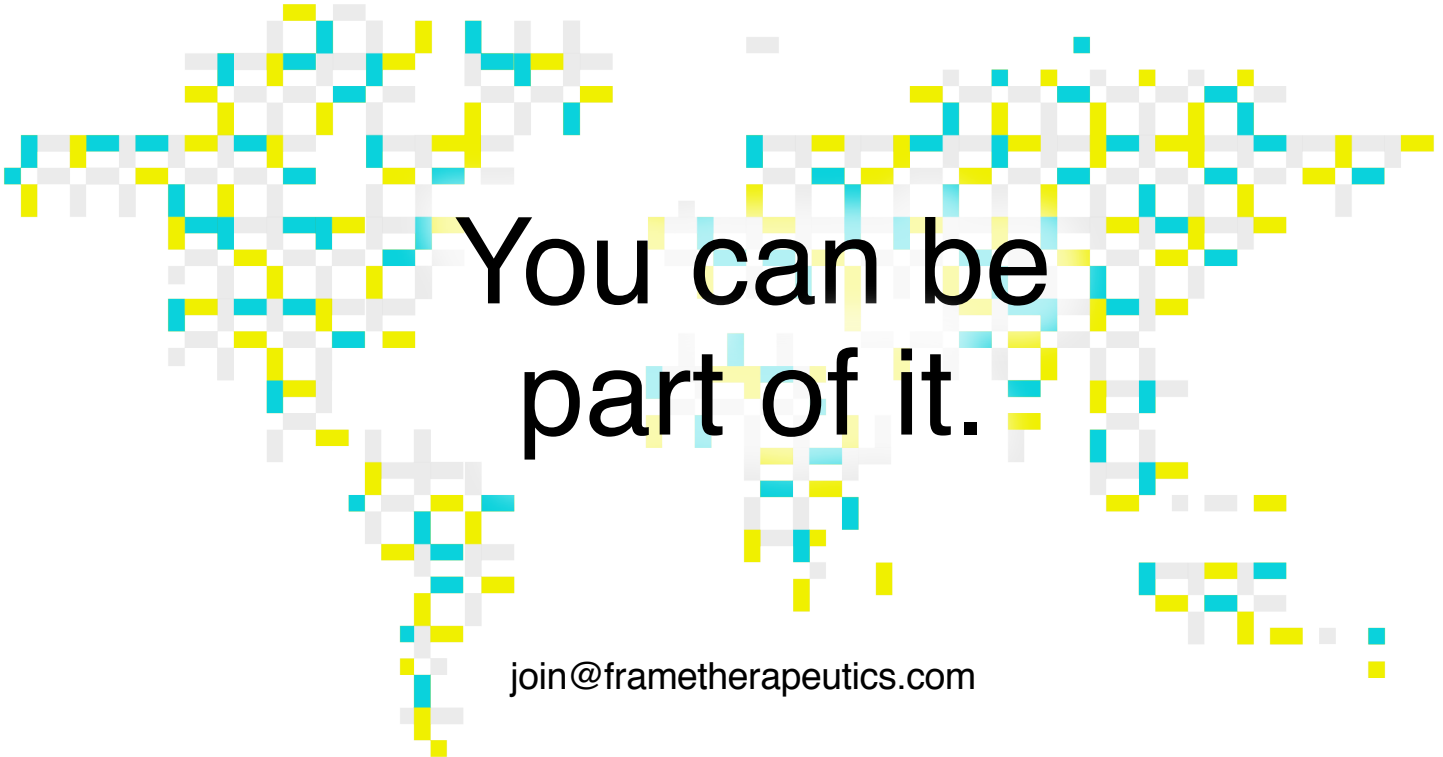

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