THE FIGHT AGAINST CANCER: NEOANTIGENS, TUMOUR ESCAPE AND THE TUMOUR MICROENVIRONMENT

A conversation with **JOHN WEST**, CEO of Personalis, Inc. in Menlo, Park, California

Tumours may be initiated by mutations in their driver genes, but their clinical outcomes are strongly influenced by the battle between neoantigens and the immune system's response to them. Checkpoint inhibitors and personal cancer vaccines are rapidly growing areas of pharmaceutical research.

Personalis, Inc. is a provider of advanced genomics solutions for immuno-oncology. The company has developed the ACE ImmunoID Platform, which combines whole exome and transcriptome sequencing with analytics, to help inform clinical and translational research through robust, comprehensive molecular data.

What is the state of immuno-oncology today?
It is now accepted that the immune response to a tumour is driven by neoantigens and that individual neoantigens can have very different HLA binding, levels of expression, and antigenicity. Thus estimates of tumour mutational burden (TMB) fall short because two patients can have the same TMB and yet very different outcomes.

To characterize all the potential neoantigens, we need to examine all of the genes. That is why our field is adopting both exome and transcriptome sequencing, and why we need comprehensive mass-spec data to characterize peptide-HLA binding.

Why do some patients not respond?
Many tumours escape immune attack by down-regulation or mutation of the antigen processing machinery, or by other mechanisms which modulate the immune system. To understand patient response, we need to characterize these mechanisms in the cancer cells, but we also need to characterize the tumour microenvironment — the broad mixture of immune cell types which infiltrate a tumour.

What role does exome sequencing play?
Because neoantigens can exist in almost any gene, we need an assay which captures all the genes. Exome sequencing has been used for that in research for almost ten years now, and exomes have been used clinically since at least 2011. To confidently detect neoantigen variants, which may be present at low allele frequencies, a cancer exome needs uniformly deep sequencing. The newest generation of sequencers have brought down the cost of deep exome sequencing, allowing exomes to replace the panels of the past.

Why do you sequence both the exome and the transcriptome?
With the transcriptome, we can see which neoantigens are actually expressed, and which genes are differentially regulated. The transcriptome is also a powerful tool for detection of gene fusion events. These can be cancer drivers, but they can also be a source of neoantigens, so novel fusions matter.

In addition to cancer cells and background tissue, a tumour sample may contain a wide range of immune cells. RNA is distinctively expressed in different types of immune cells, while the genome sequence of those cells is the same. Thus the transcriptome gives us visibility into the tumour microenvironment that we wouldn't have otherwise. This is key to understanding a given tumour and which therapy may be most effective.

How complete does the sequencing have to be?
From a research standpoint, if you're covering 80 or 90 percent of a gene, that might seem pretty good. But if your goal is to diagnose an individual cancer patient and you miss the key variant because it wasn't in the 80 or 90 percent, that's not OK. We've developed what we call ACE technology. The first part does a conventional exome capture, while the other parts perform a different kind of capture with a biochemistry that has been optimized for difficult sequences. For example, some are optimized for a very high GC-content and we use those to sequence those parts that otherwise would be missing. We combine all of the data into one unified dataset, and that leads to much more comprehensive coverage.

What do you do with all this data?
We're currently developing one of the world's largest databases of peptide and HLA-binding data, which we will use to train our own neural network algorithms. As our database grows, our algorithms will enable us more accurately predict the neoantigens that will bind properly to HLA, and therefore have a higher chance of eliciting an immune response. This is already key to the design of personalized cancer vaccines, but we think it will become central to the assessment of any immuno-therapy.

Do you anticipate any regulatory challenges?
If regulators have difficulty with the technologies described here, it could slow down approvals. Fortunately, that has not been the case. The FDA has been very proactive, embracing the combined potential of genomic information and immuno-oncology. This year they approved Merck's Keytruda, in certain indications, based specifically on a genetic test (MSI). They have also approved multiple clinical trials of personalized cancer vaccines, which integrate deep exome and transcriptome sequencing with the type of analytics that Personalis provides. Personalis has worked actively with our pharmaceutical partners in personalized cancer vaccine development to support the genomic component of these new therapies.

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