Monitoring the effect of immunomodulatory treatment on the immune repertoire using the IGX platform

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Immune repertoire sequencing

Lymphocytes form the core of the adaptive immune response. By expressing unique receptors that recognize specific antigens, B and T cells raise specific immune responses that are subsequently remembered by memory responses. The diversity of B and T lymphocytes within a host is called the immune repertoire and represents the total set of receptors that can recognize antigens. Since these receptors are enormously diverse, the nucleotide sequence of the antigen-recognizing part of these receptors can be used as a barcode to identify B and T cell clones (1, 2).

As a result of the high diversity of the immune repertoire, the low-throughput of Sanger sequencing provides only limited visualization of this variability. Next generation sequencing (NGS) platforms are ideally suited to extensively characterize and visualize the complexity and plasticity of the TCR and BCR repertoires (3, 4)

Receptor identification

Obtain receptor sequences to characterize relevant cytoxic T lymphocytes (CTLs) and antibodies

Minimal Residual Disease monitoring

Measuring the level of minimal residual disease in hematological cancers

Cell population dynamics

Monitoring specific lymphocyte populations that display a particular rearrangement in their receptors

Personalized repertoire monitoring

Quantify changes to an individual's repertoire as a result of disease, vaccination, or (immuno-)therapy treatment

The ImmunoGenomiX platform

The ImmunoGenomiX platform (IGX) is an end-to-end immunosequencing data analysis platform designed to process, manage, analyze, visualize, and interpret immune repertoire data. Starting from the raw high-throughput sequencing data, the IGX platform delivers report- or publication-ready figures.

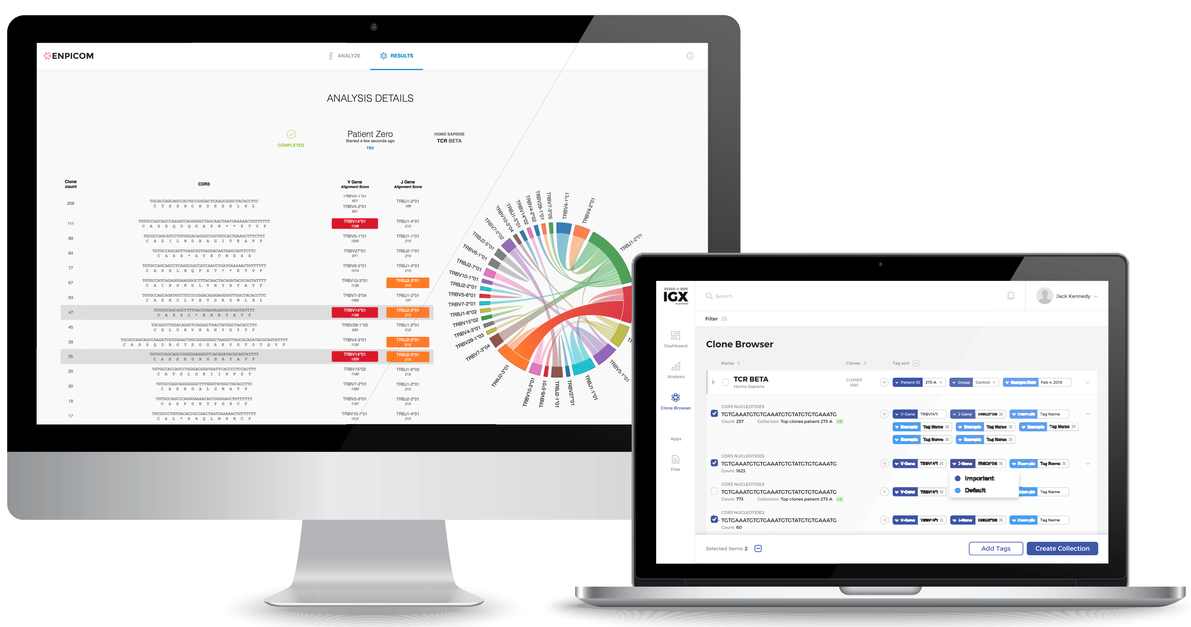
The IGX Platform is founded on innovative bioinformatics methods and has been coded from scratch using rock-solid software engineering. It has a modular structure which hosts multiple application for different repertoire sequencing analyses. Currently, two applications are available for the platform: IGX Profile, for clonotype analysis, and IGX Explore that consist of four different downstream analyses. Additional applications to answer immune repertoire-related questions will be added one-by-one.

Flexible at the frontend
allowing customers to use their own sample preparation protocols and the Next-Generation Sequencing (NGS) technology of choice

IGX Clone Collections
sequencing data, as well as metadata, can be used to perform powerful searches, select and filter clones that can be organized in clone collections for follow-up analysis

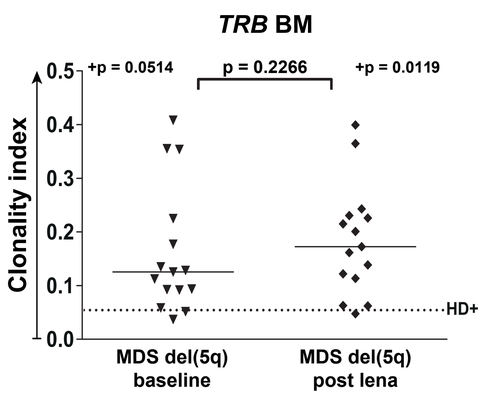
IGX Tags
a powerful, tag-based, annotation system that allows users to extensively annotate repertoire sequencing data with structured metadata at a great level of granularity, including annotations for single clones such as affinity or avidity

Easy-to-use
no skilled bioinformatics staff required, the IGX platform runs in a secure cloud environment and features an intuitive and simple graphical user interface



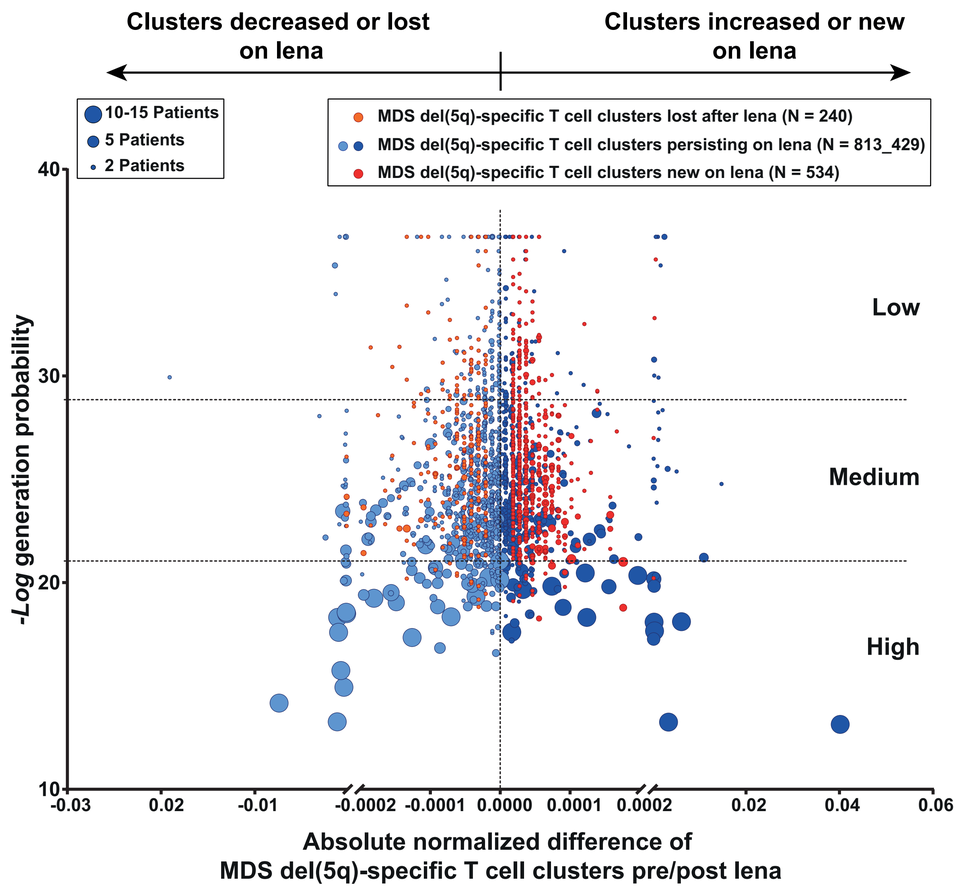
Case study: treatment of myelodysplastic syndrome patients with Lenalidomide

Myelodysplastic syndrome (MDS) are a group of cancers in which mature blood cells are inefficiently generated. In this study (5), we treat the most prevalent subclass, del(5q) MDS patients, with the immuno-modulatory drug Lenalidomide. For 15 patient undergoing Lenalidomide treatment for 12 months, baseline and post-treatment samples were obtained. Several healthy controls were obtained for comparison purposes. TRB V, D, and J rearrangement was established by Illumina sequencing of gDNA from both bone marrow and peripheral blood.



We show that Lenalidomide treatment in del(5) MDS patients leads to an increase in TRB clonality in the bone marrow, while there was no detectable difference in peripheral blood TRB clonality. We applied GLIPH (6) analysis to cluster T cell receptors with similar paratopes, i.e. with similar antigen specificity.

There is induction of new T cell specificity clusters, and more clusters overlap between patients after Lenalidomide treatment than before. The newly-induced clusters tend to have low generation probabilities as computed by IGoR (7), suggesting that these are not generic (or public) clones, but are induced against a specific antigen that is present in the majority of the patients. Taken together, this suggests that Lenalidomide treatment in del(5) MDS patients leads to antigen-specific expansion of T cell clones directed against a MDS-related antigen.



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