FROM BIOMARKERS TO INNOVATIVE THERAPIES IN HIGH-RISK CANCERS

Innovative technological and computational approaches to unravel genetic and epigenetic mechanisms of resistance in the immunotherapy era

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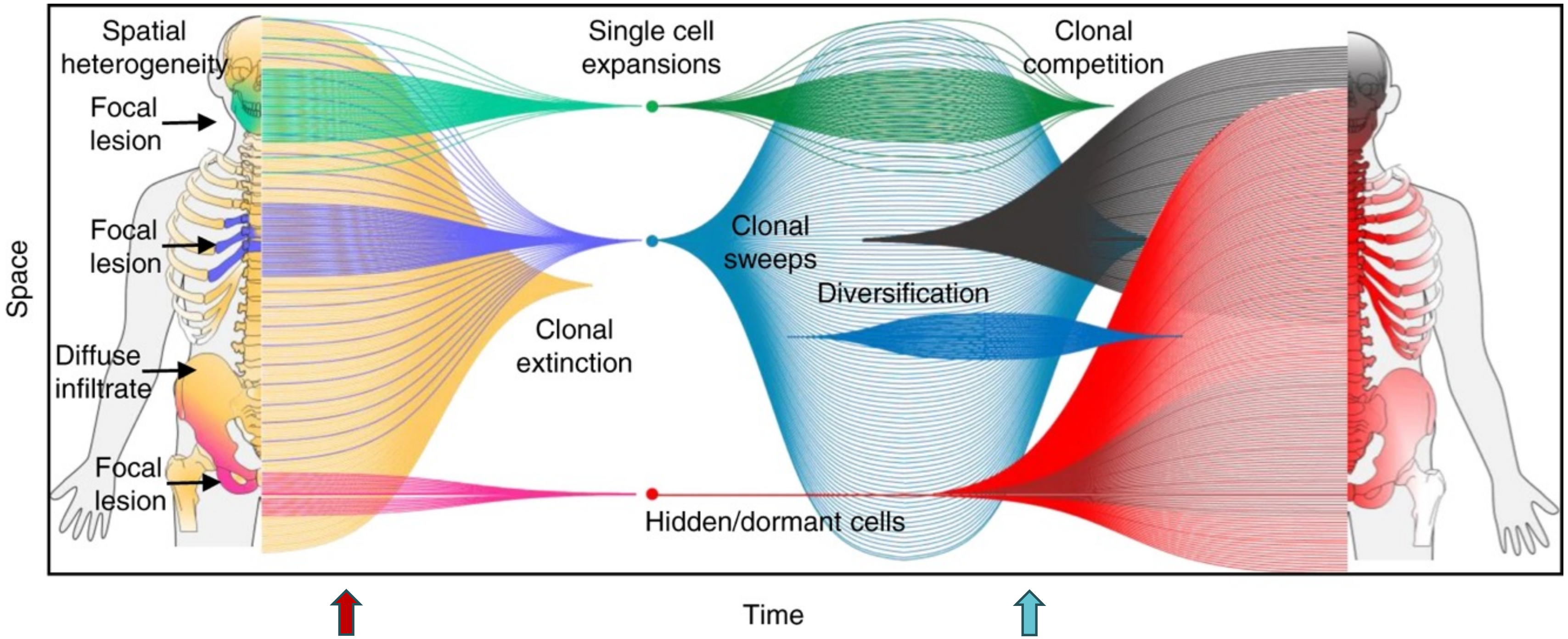
2025-05-27 · JOURNÉES SCIENTIFIQUES Nantes Université · Colloque n°16

Keywords: WGS, scMultiome, clonal evolution, treatment resistance

Multiple myeloma exhibits complex spatio-temporal evolutions



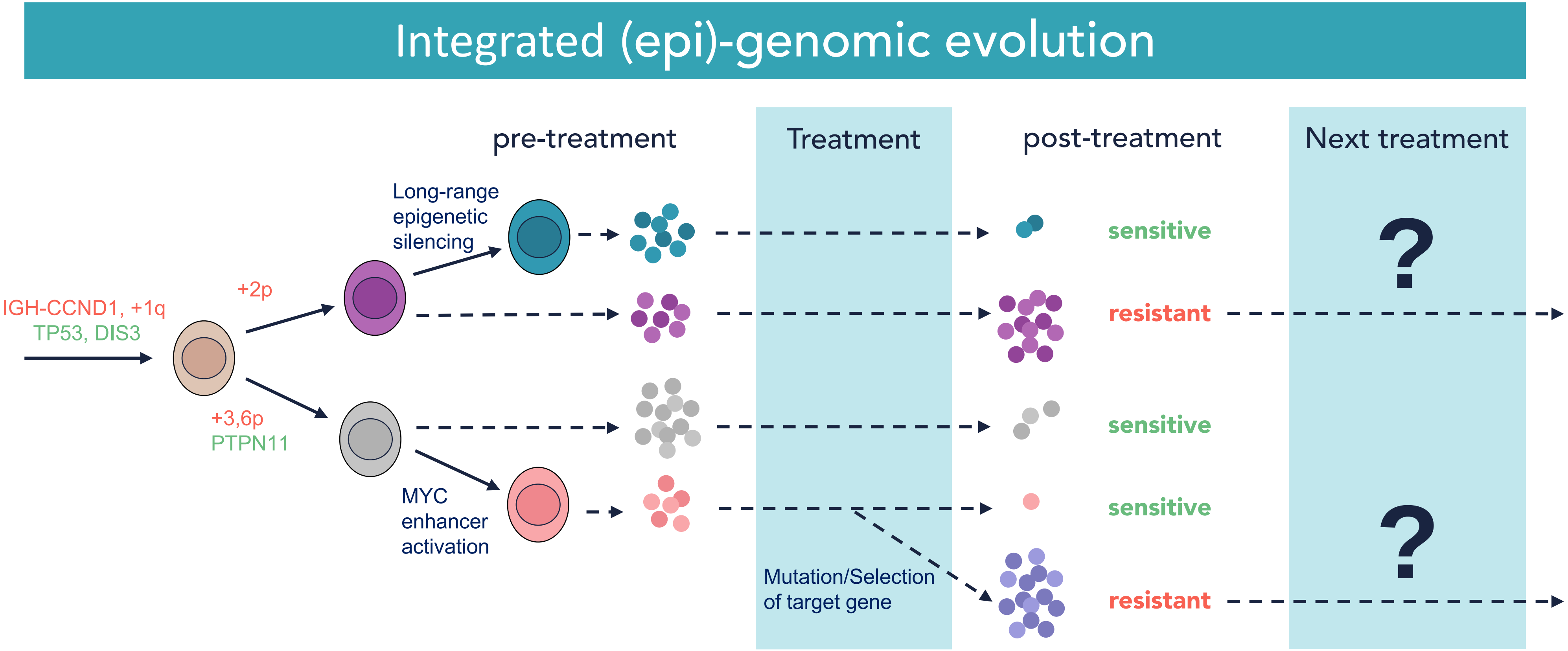
Treatment n

Treatment n+1

Image credit:
Pr Françoise Kraeber-Bodéré, MD, PhD
Head of Nuclear Medecine Department

Rasche et al. *Nat Commun* **13**, 4517 (2022).

Objective: unravel genetic and epigenetic evolution of tumor cells at patient level

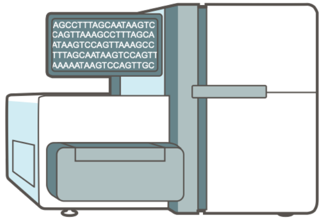


27/05/2025

Leveraging recent advances in sequencing technologies

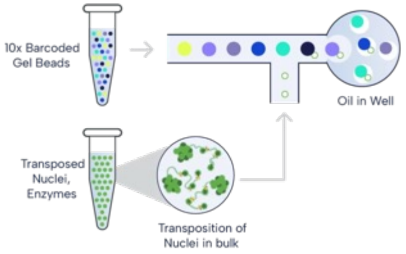
Whole Genome Sequencing:
deep characterization of the tumor at the sample level

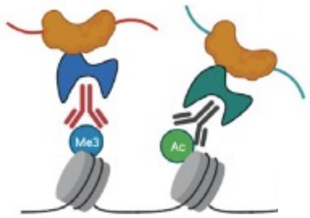
- ✓ mutations, structural variants
- ✓ copy-number estimation
- ✓ sub-clonality estimation



Single-cell sequencing (scMultiome, scCUT&Tag):
functional understanding at the sub-clonal level

- ✓ chromatin accessibility (scATACseq)
- ✓ gene expression (scRNAseq)
- ✓ euchromatin marker (H3K27ac) +
- ✓ heterochromatin marker (H3K27me3) −



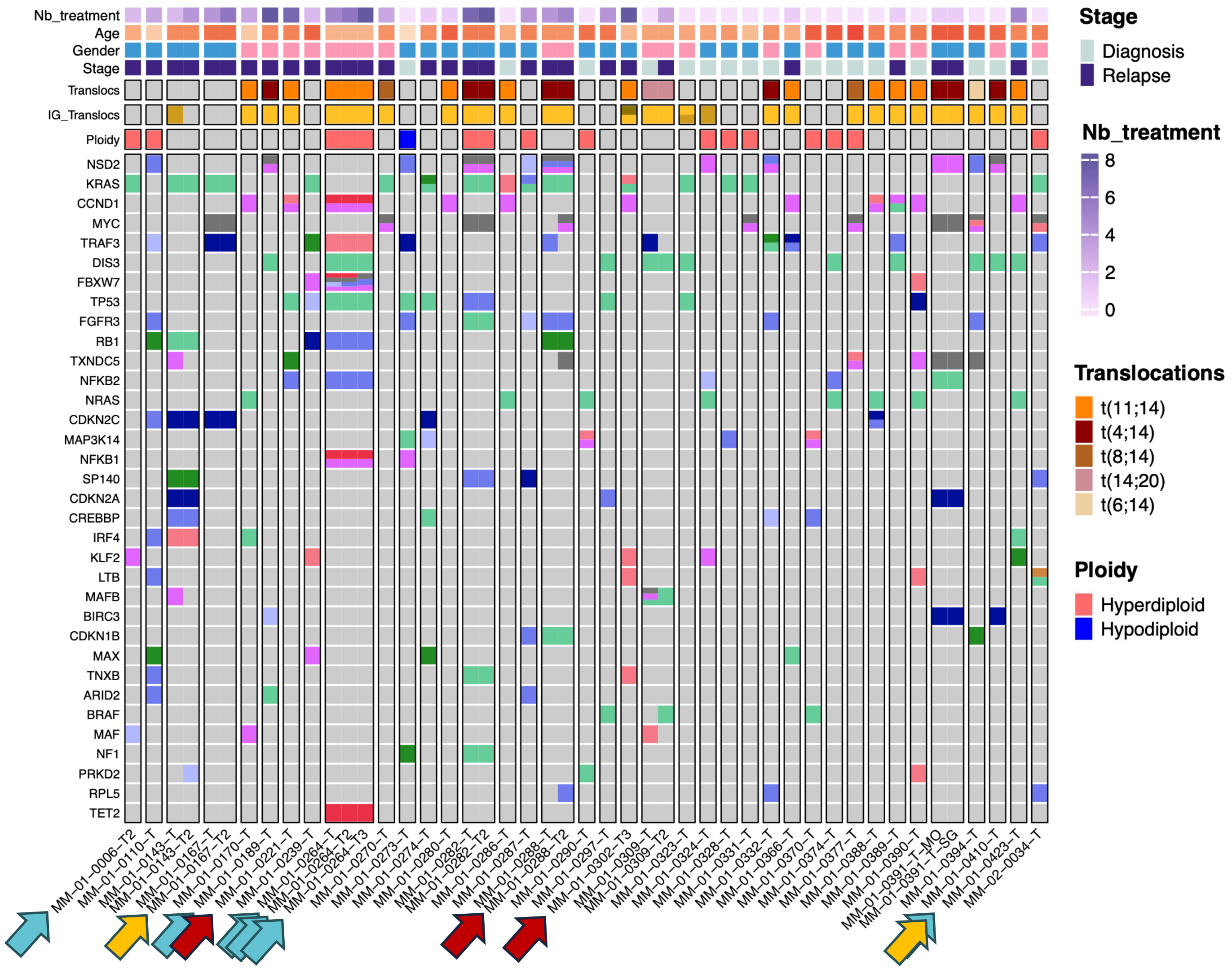


Analyses/Storage on High Performance Computers

- ✓ scalability
- ✓ reproducibility
- ✓ collaboration

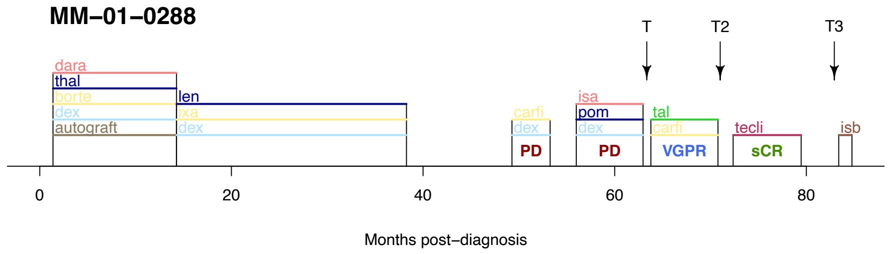
Groupement Ligérien pour le
Calcul Intensif Distribué
(GLiCID)

Cohort of 38 MM patients (46 samples) with multiple omics



MYRACLE cohort: 467 patients (jan. 2025)

→ follow-up and highly detailed clinical timelines



Representative of whole-cohort diversity:

- → 13 t(11;14), 9 t(4;14), 2 t(8;14), 2 t(14;20), 1 t(6;14)
- → 17 hyperdiploid , 1 hypodiploid
- → 6 multi-sample patients

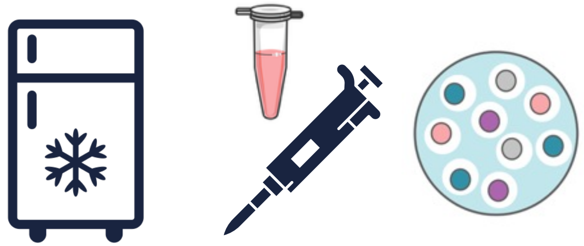
Bispecific T-cell engagers:

- ➚ Elranatamab / Teclistamab (BCMA)
- ➚ Talquetamab (GPRC5D)
- ➚ ISB1342 (CD38)

Systematic reconstruction of patients' tumor evolution

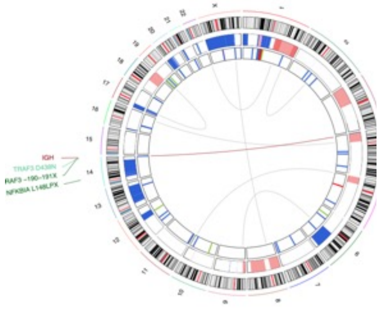
Sequencing and pre-processing

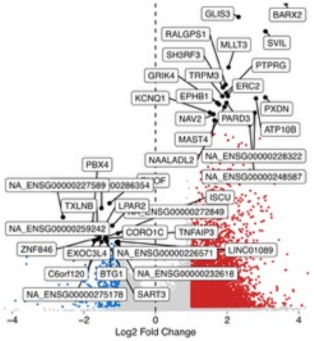
- ✓ Acquisition, storage and selection of biosamples
- ✓ Experiment, Sequencing
- ✓ Pipeline development for automatic quality-control



Patient-level characterization

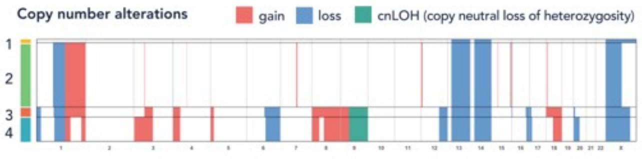
- ✓ Identification of tumor mutations
- ✓ Inference of tumor epi-genetic alterations
- ✓ Detection of gene expression changes

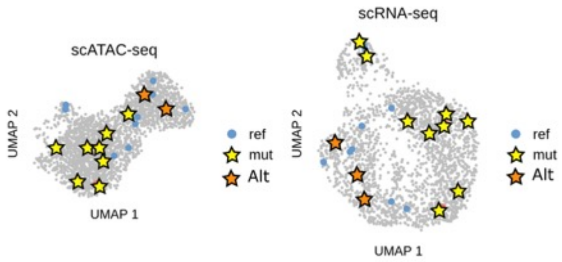


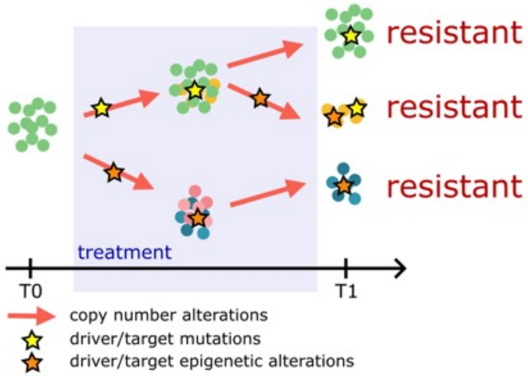


Subclonal-level characterization

- ✓ Multi-omic inference of copy-number alterations
- ✓ Identification of subclones
- ✓ Mapping on subclones of mutations and epi-alterations







Complete phylodynamic reconstruction of clonal evolution

- ✓ Reconstruction of a parsimonous tree
- ✓ Time-assignation of main mutations and epi-alterations
- ✓ Mapping on subclones of mutations and epi-alterations

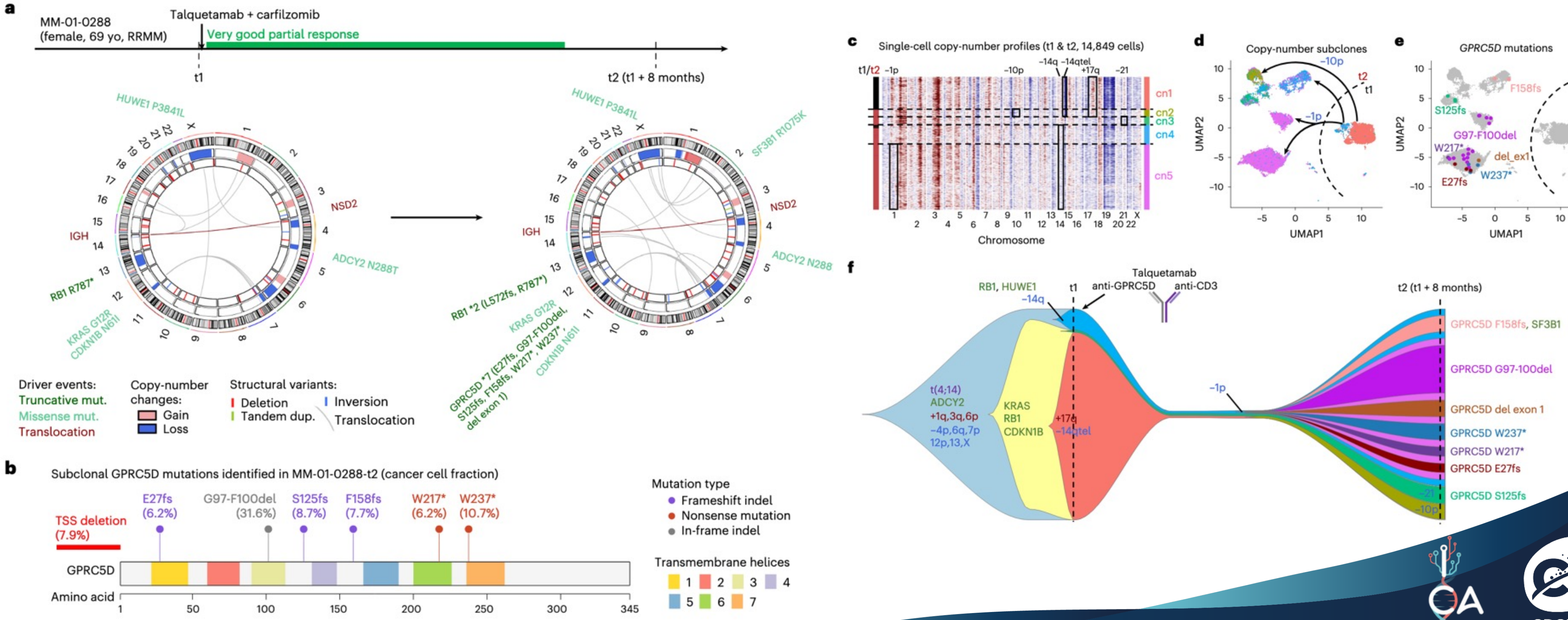
Acquired resistance to a GPRC5D-directed T-cell engager in multiple myeloma is mediated by genetic or epigenetic target inactivation

Jennifer Derrien, Sarah Gastineau, Antoine Frigout, Nils Giordano, Mia Cherkaoui, Victor Gaborit, Rémi Boinon, Elise Douillard, Magali Devic, Florence Magrangeas, Philippe Moreau, Stéphane Minvielle, Cyrille Touzeau & Eric Letouzé

Nature Cancer **volume 4**, pages 1536–1543 (2023)

➡ **Talquetamab (GPRC5D)**

1) Intrinsic resistance through genetic mutation of the target gene (1 patient)



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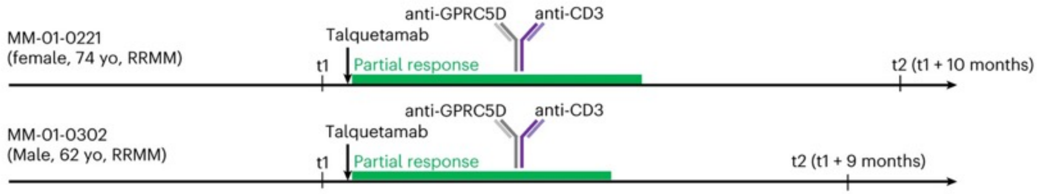
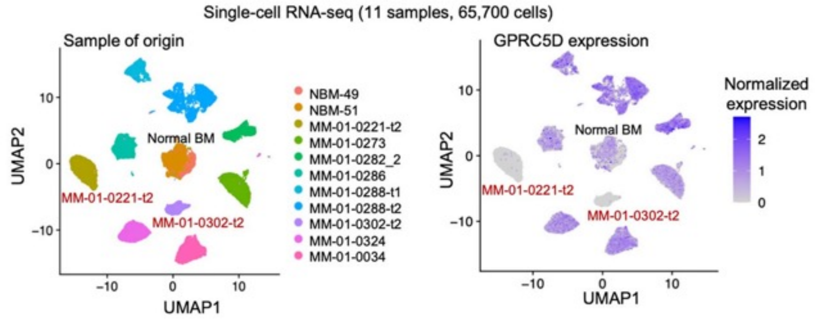
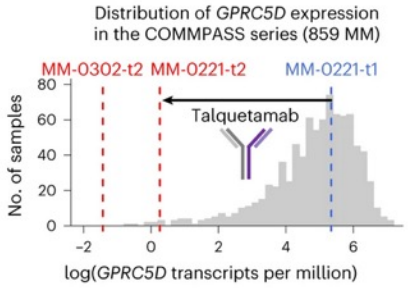
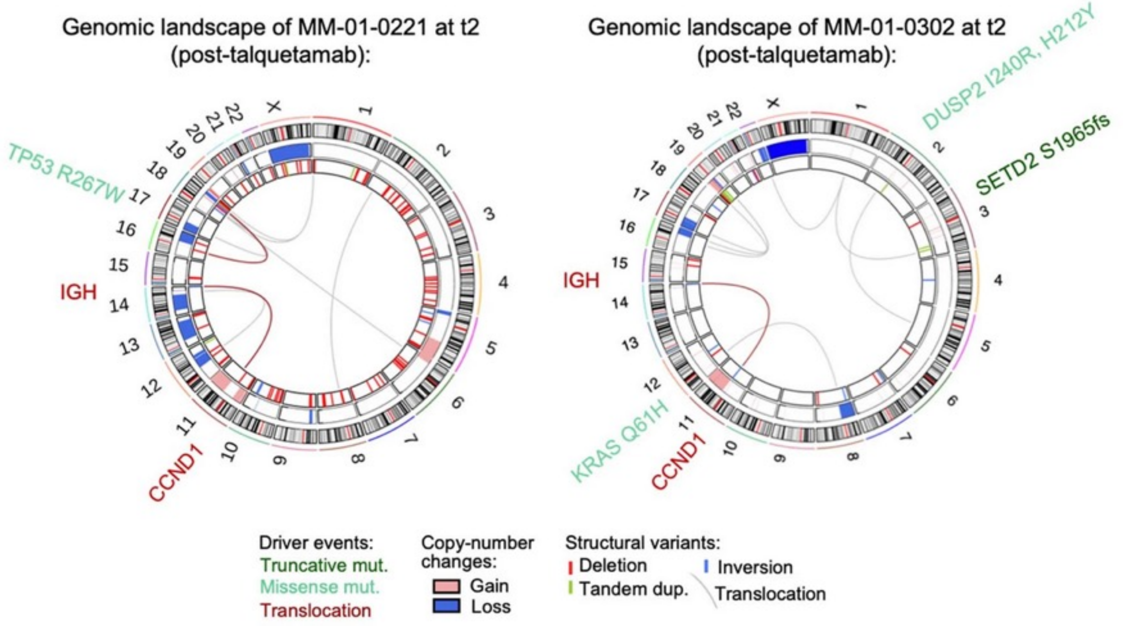
➡ **Talquetamab (GPRC5D)**

2) Intrinsic resistance through epigenetic inactivation of the target gene (2 patients)

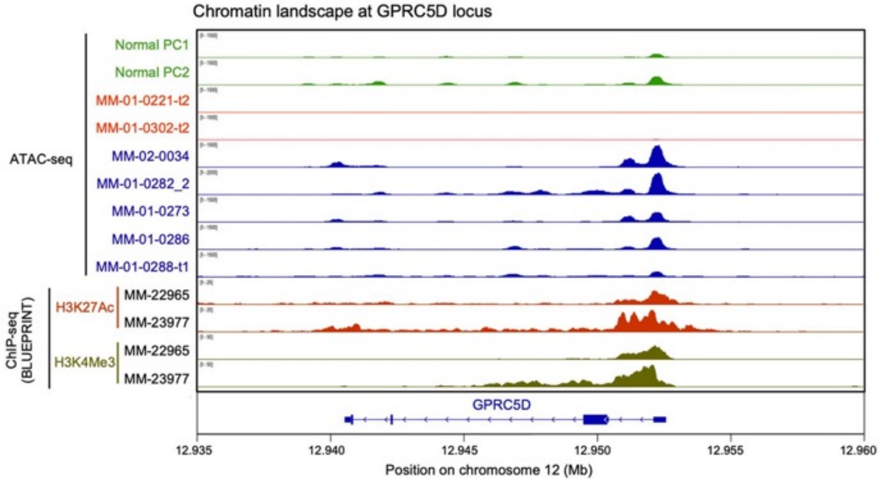



Single-cell RNA-seq (11 samples, 65,700 cells)


Distribution of *GPRC5D* expression in the COMMPASS series (859 MM)


Genomic landscape of MM-01-0221 at t2 (post-talquetamab):

Genomic landscape of MM-01-0302 at t2 (post-talquetamab):


Chromatin landscape at GPRC5D locus

Current developments

Giordano et al, in preparation

Interplay of Genetic and Epigenetic Events in MM Progression

- ✓ Somatic accessibility changes deregulating **driver genes**
- ✓ **Sub-clonal** reconstruction of tumor evolution
- ✓ Role of specific genes on (epi)-driver alterations
- ✓ **Heritability** of genetic and epigenetic alterations
- ✓ Genetic and epigenetic drivers of **drug resistance**

Denoulet et al, in preparation

Innovative Computational Tool for Multiomic Copy-Number Profiling

- ✓ **R package** for copy-number profiling from single-cell multiomics
- ✓ **Integration** strategy of multiple omics
- ✓ **Benchmarking** against current mono-omic tools
- ✓ **Performance** evaluation and limitations
- ✓ **Application** to clonal evolution analysis of multiple myeloma

muscadet

Other examples of bi-specific T-cell engagers:

↗ **4 patients Elranatamab / Teclistamab (BCMA)**
↗ **2 patients ISB1342 (CD38)**

Other immunotherapies (CAR-T cells):

- 5 patients Cilta-cel / Ide-cel (BCMA)

Other innovative treatments:

→ selective inhibitor of nuclear export (N = 2)
→ HDAC inhibitor (N = 2)

Micro-environment available for sequencing

ACKNOWLEDGEMENTS

CRCI^{2}NA
CANCER & IMMUNOLOGY

ICAGEN

CRCI^{2}NA, Team 8, Integrated Cancer Genomics (ICAGEN)

Stéphane Minvielle
Florence Magrangeas
Philippe Moreau
Loïc Campion
Victor Bessonneau-Gaborit
Catherine Guérin-Charbonnel
Céline Chevalier
Eric Letouzé
Marie Denoulet
Mia Cherkaoui
Magali Devic
Elise Douillard
Jennifer Derrien

Projet soutenu par
Fondation de France

SIRIC ILIAD
Nantes - Angers

GLiCID