Weill Cornell Medicine
Meyer Cancer Center

The immune system, cancer and radiation

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NASEM meeting, November 16, 2021

- Methods to study the immune response in cancer
- Application to low dose radiation exposure
- Opportunities and challenges
- Research priorities

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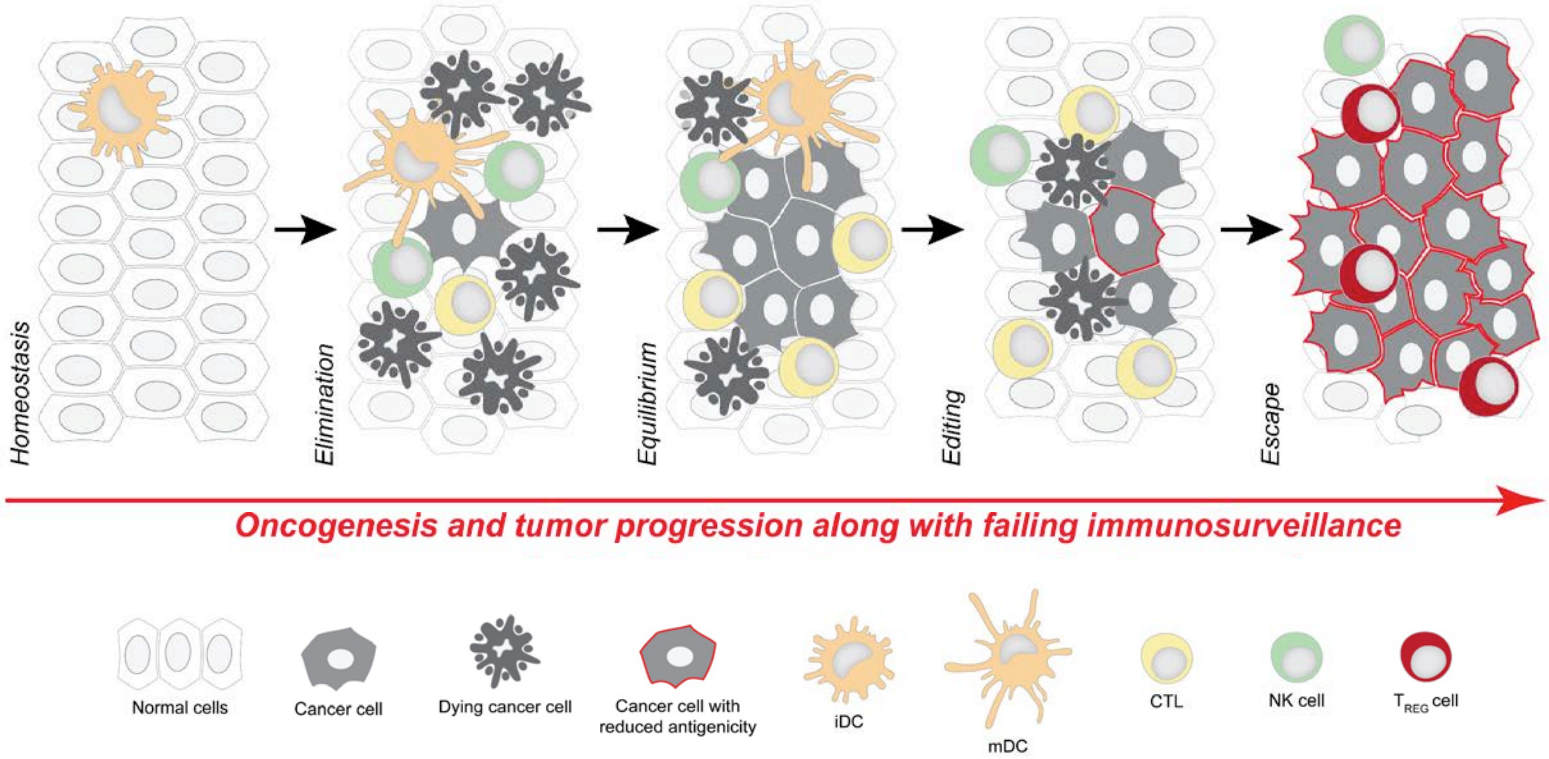
Cancer immunoediting: a framework to study immune system/cancer interactions

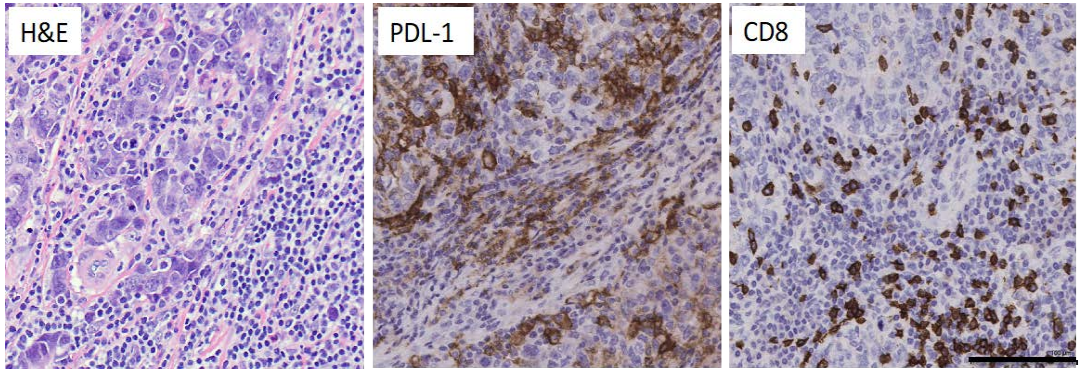


Courtesy of L. Galluzzi

Some patients develop/retain meaningful spontaneous anti-tumor immunity

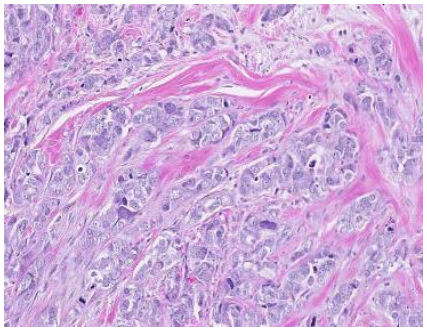
Example of untreated early stage TNBC

Hot tumor



That is

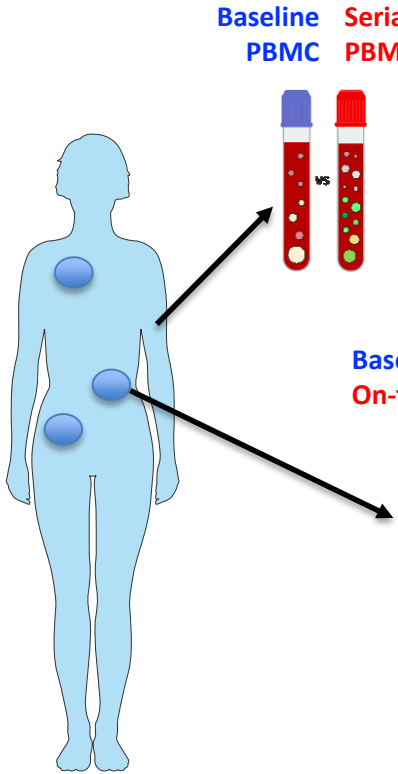
- Prognostic for survival
- Predictive of response to immunotherapy



Cold tumor

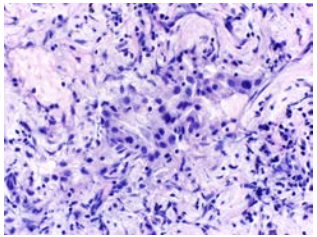
Need to induce anti-tumor T cells:
in situ vaccination (e.g., combination of radiation and immunotherapy)

Comprehensive approach to study immune responses associated with sensitivity and resistance to therapy



Baseline PBMC **Serial PBMC**

Baseline Biopsy +
On-therapy/post-therapy biopsy



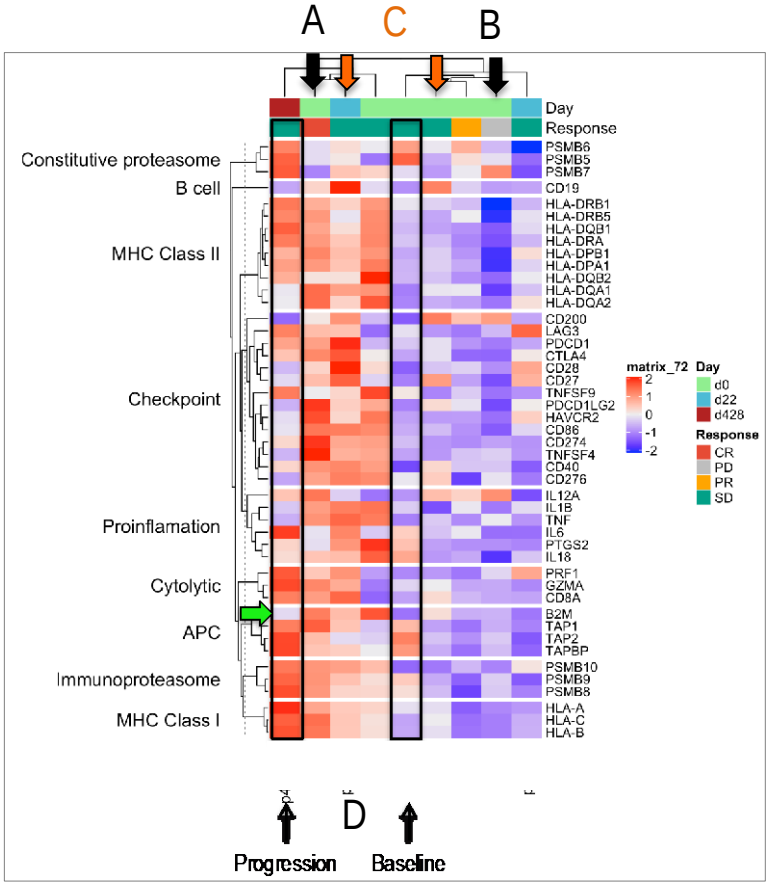
PBMC
- WES (normal tissue control)
- RNAseq
- TCRseq
- Multiparameter flow cytometry
- scRNAseq
- Functional assays (antigen-specific T cells)
- ATACseq

Serum/plasma
- cfDNA (TMB)
- Cytokines & chemokines
- Antibodies
- Soluble receptors (sMICA/B, sCD73, etc)
- Small extracellular vescicles (sEV)
- Proteomics

- WES
- RNAseq
- TCRseq
- Multiplex imaging
- scRNAseq
- Spatial transcriptomics
- ATACseq

Microbiome
Gut
Oral
Organ sites (lung)

Interrogating the TME: an example



RNAseq characterization of the tumor biopsies from 7 patients:
1 CR, 1 PR, 4 SD, 1 PD

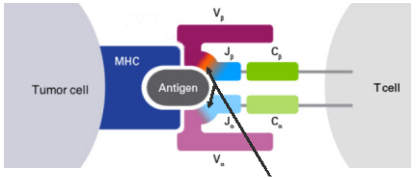
CR (pt#A): hot tumor at baseline
PD (pt#B): cold tumor at baseline

SD (pt#C): cold tumor at baseline, hot at day 22

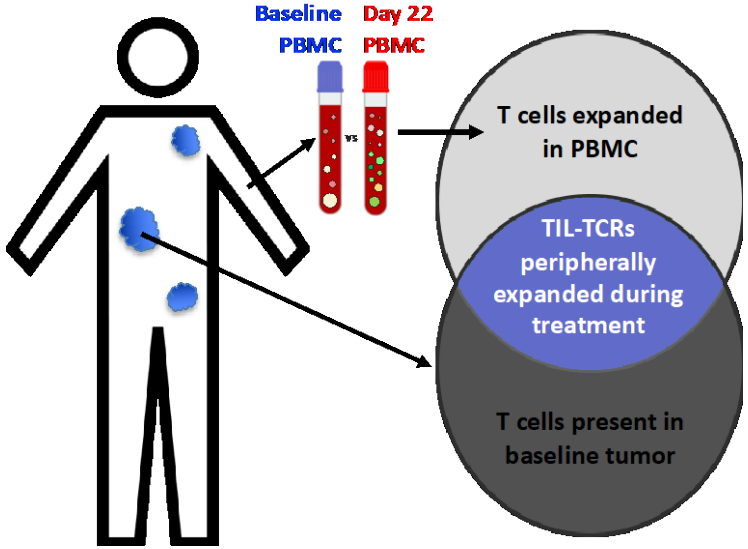
SD (pt#D) >1 year, initially “cold” tumor at progression (day 428) “hot” tumor (CD8A, GZMA, PRF1, and MHC genes), but very low B2M

Unpublished results

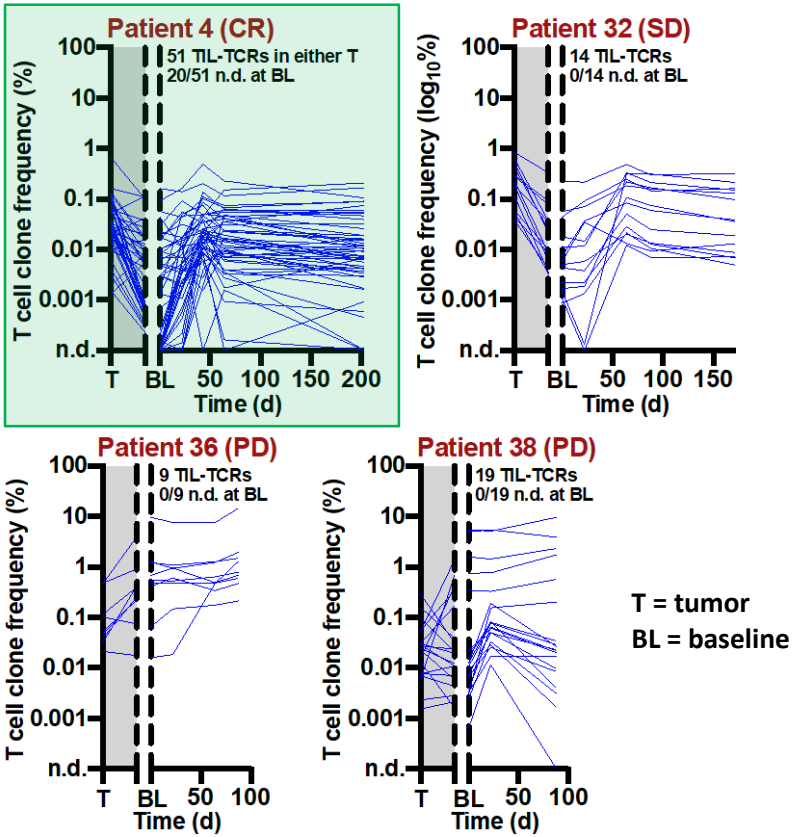
Interrogating the TCR repertoire in tumor and blood



The **CDR3 region sequence** is a functional barcode identifier for a specific T cell clone



Frequency of TIL-TCRs expanding in PBMC

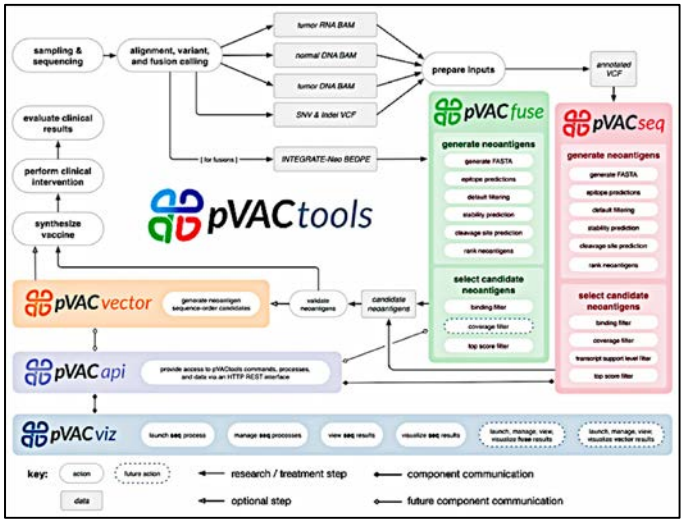


T = tumor
BL = baseline

Formenti et al., Nature Medicine 2018

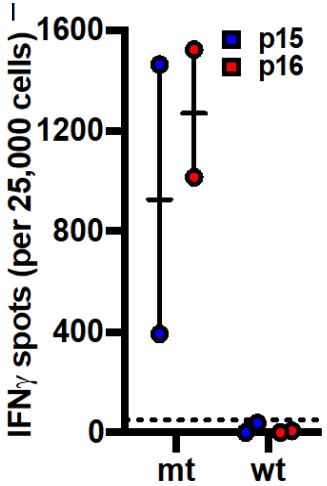
Bioinformatic tools and functional assays to identify tumor antigen-specific T cells

In silico predictions (WES, RNAseq)

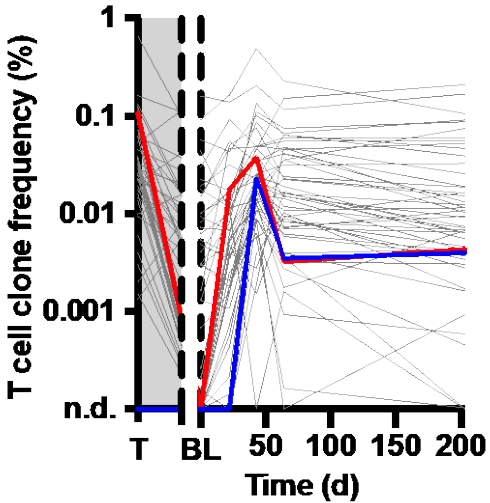


Hundal et al., bioRxiv (501817), 2018

Functional assay (ELISPOT)



TCRseq

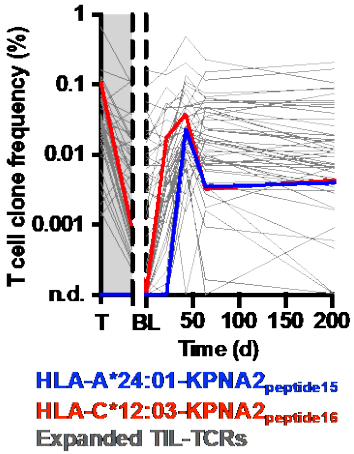


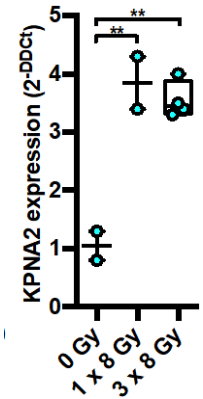
HLA-A*24:02 **p15 *not* detected in pre-tx tumor**
HLA-C*12:03 **p16 detected in pre-tx tumor**

Formenti et al., Nature Medicine 2018

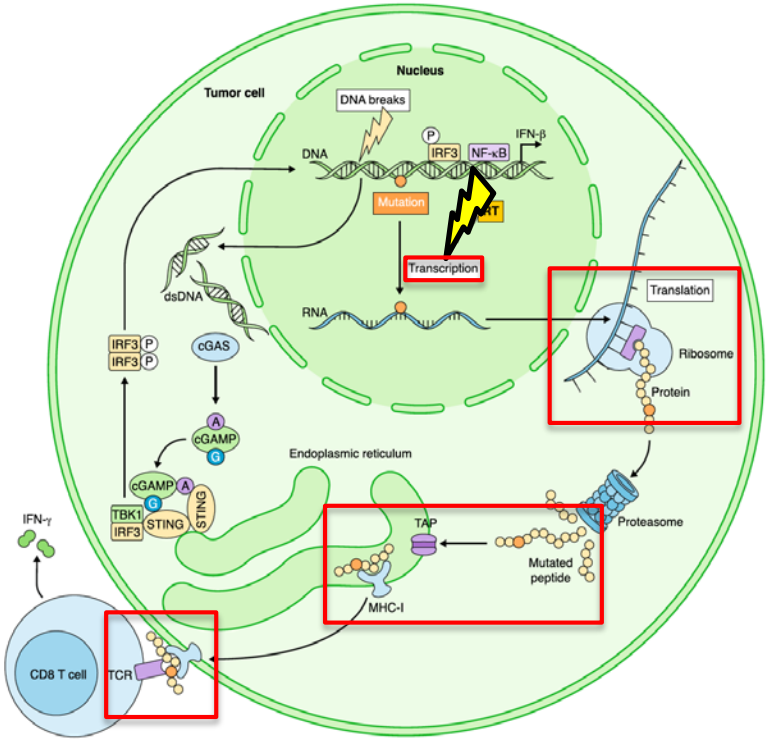
Effects of therapeutic radiation on neoantigen expression

JEM 2006





Formenti et al., Nat Med, 2018



Lhuillier et al. Genome Medicine (2019)

Lhuillier et al. J Clin Invest (2021)

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Environment International 149 (2021) 106212

	Low	Intermediate	High
Dose	<0.1 Gy	0.1-1 Gy	>1 Gy
Settings	Environmental	Environmental /Clinical	Therapeutic

MELODI workshop on non-cancer effects of low dose IR, 2019

ACUTE:
A-bomb survivors (~0.16 Gy) & Cernobyl cleanup workers

- Immune changes similar to ageing (reduced naïve T cells, reduced TCR repertoire, increased inflammation)
- Functional significance unclear: responses to vaccination not impaired

CHRONIC:
Environmental or work-related (uranium)

- Increase in inflammatory cytokines/markers (CRP, IL-1, IL-6, IL-8, TNFα)
- Relative increase in $CD8^+$ T cells, innate immune cell activation
- Functional significance (at least in workers): increase in diseases associated with immune e dysfunction (autoimmune, infectious, allergic)

Anti-inflammatory effects of intermediate dose (0.3-0.7 Gy):
Decreased adhesion of PMN to endothelium – associated with increased TGFβ secretion by endothelial cells (related to modulation of Nrf2 and anti-oxidative enzymes like catalase) – osteo-immunological mechanisms in inflammend joints (radon spa)

Biomarkers of exposure to radiation (X-ray, PET, CTscan): Presence of micronuclei in RBC, γH2AX foci in lymphocytes

Response is NOT linear

? to which degree low dose radiation causes/exacerbates

- **Inflammaging**

- **Senescent immune remodeling (SIR) of adaptive immunity**

and its pathogenesis (aging-associated alterations in stem cell differentiation) [*Denkinger et al., Trends in Immunology, December 2015, Vol. 36, No. 12*]

<u>Use of modern tools to define changes in immune cell subsets</u>

- TCRseq (assess reduction in diversity of T and B cell repertoire)
- Analysis of T_{naive}, T_{CM}, T_{EM}, $T_{SCM,}$ exhausted phenotypes (defined by cell surface markers, transcription factors and epigenetic changes)
- Single cell analyses
- “Liquid biopsies” *may* reflect what is happening in the tissues (cfDNA and extracellular vescicles)

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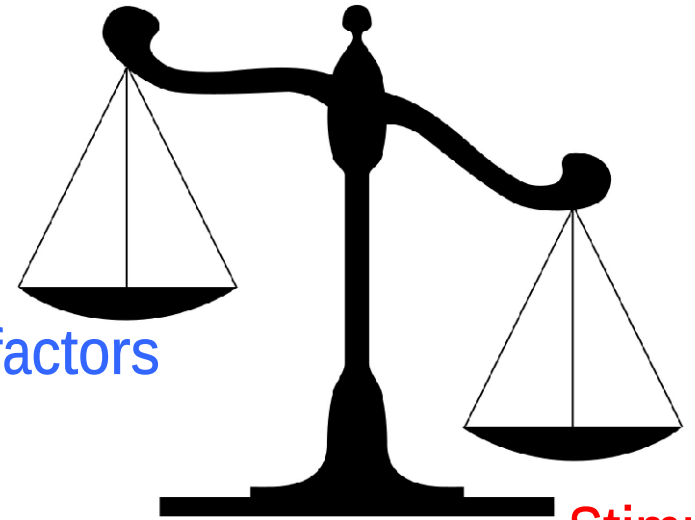
Patient-specific cancer immune-set point

Tumor and host genetics – age – microbiome – concomitant infections, treatments, metabolic conditions, nutrition and stress



Inhibitory factors

Stimulatory factors

Chen & Mellman, Nature 2017

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Use of a holistic approach

The canonical pathways of response to injury & stress are shared: multidisciplinary collaborations with investigators working on tumor immunology, autoimmunity, organ transplant and infectious diseases –

Standardization of assays across different centers

Data sharing