Detect Early-Stage Cancers From the Blood T cell Repertoire

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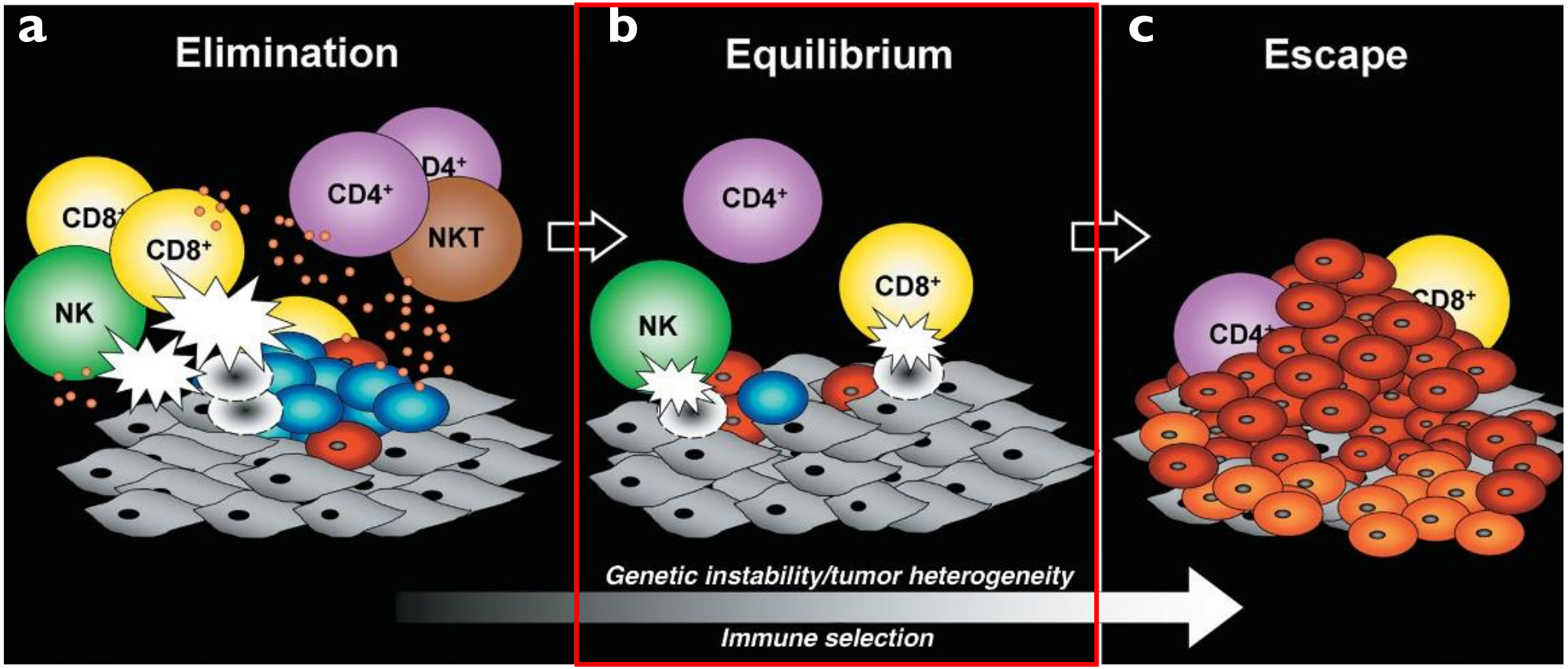
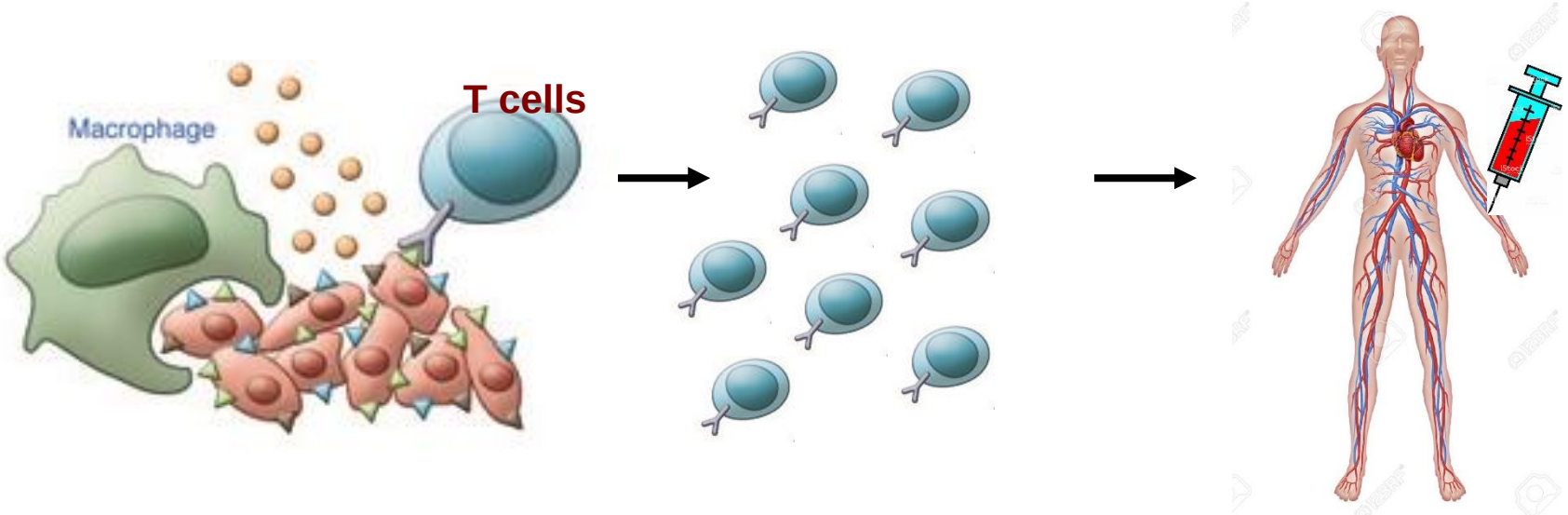
Basis of using the adaptive immune system as an early cancer reporter

Immunoediting: Sustained caner-specific immune responses since early-stage



Dunn et al., 2002, Nature Immunology

T cell proliferation upon cancer-specific recognition



Cancer sensing

T cells sensing the early-stage cancer cells

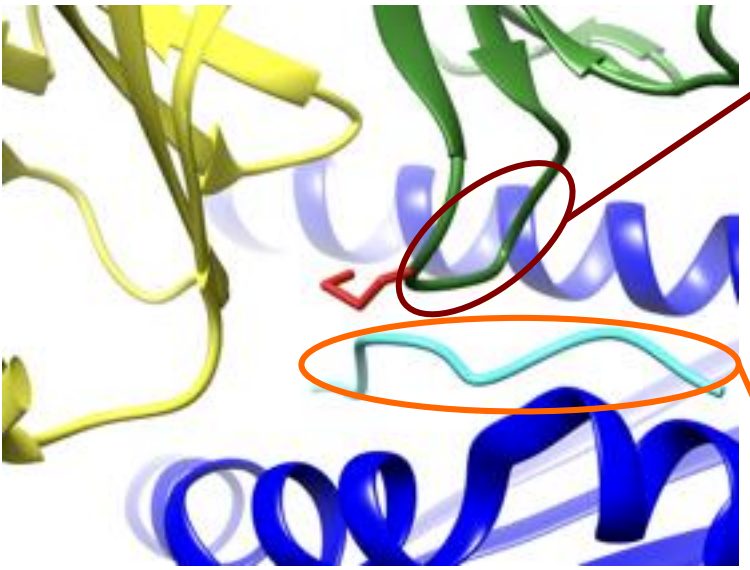
More T cells made

Many copies are made of the T cells that recognize cancer cells

Altered T cells now in the blood

T cells that recognize cancer cells can be detected in blood sample

A major challenge: To recognize cancer-associated TCRs in the blood repertoire



TCR CDR3

Tumor antigens

CASSLKLAGPDTQYF
CASSLGSGTAQGYEQYF
CASTLGQTPKTQYF
CASSLGTGIRTDTQYF
CASSLGTSLGQETQYF
…

Somatic mutations
Frameshift indels
Tissue-restricted genes
De novo ORF
Post-translational modification
Translated ‘non-coding’ genes
…

T cell repertoire with over 100M clones

CASSYSENEQFF
CASRSYVASSNEQFF
CASTQWYGGGTPPYF
CASSLTTGVFSQPQHF
CATSPYSVTTFANTIYF
CAGMTVTEAFF
CASSLKLAGPDTQYF
CASSLGSGTAQGYEQYF
CASTLGQTPKTQYF
CASSLGTGIRTDTQYF
CASSLGTSLGQETQYF
CASSQALLAPSTDTQYF
CASSEGGIGELFF
CASSQDTDGRMFF
CASSEAPGTSVGGLFF
CASTTGDGLGAFF
CASSQDIGNFEQFF
CASSGTGGYSGANVLTF

DeepCAT: A potential solution to de novo detect cancer-associate TCRs for diagnosis

Peripheral blood from unknown individual

TCR repertoire data

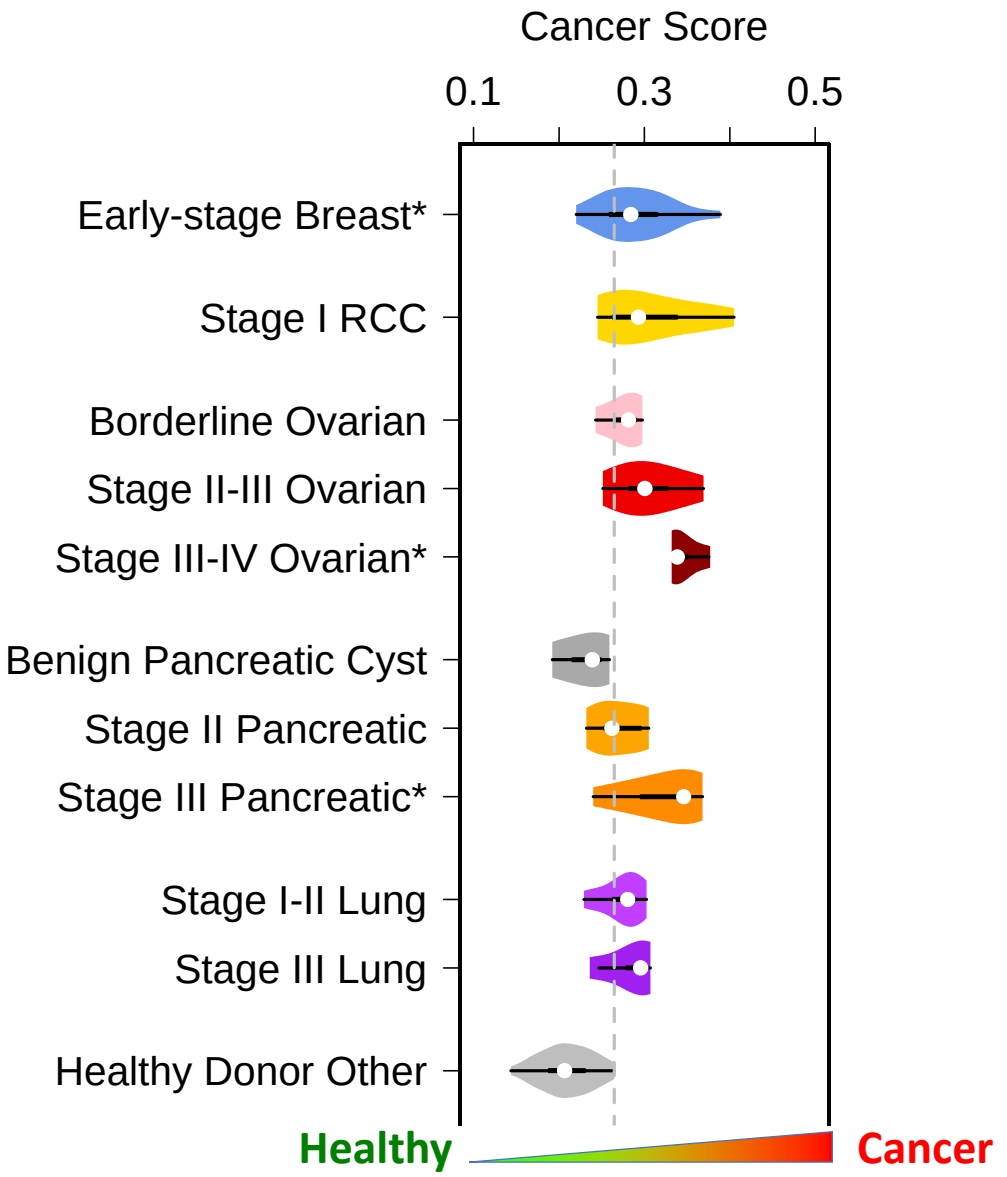
Cancer-associated TCRs from TCGA

Non-cancer TCRs from healthy donors

DeepCAT Classifiers

*P*rediction of cancer-associated TCRs in the blood repertoire

Cancer Score



Advantages of TCR-based detection method

- Non-invasive
  - Blood TCR repertoire is easy to obtain
- Sensitive early detection
  - T cell proliferation at early stage amplifies cancer signals
- Low cost
  - Targeted TCR repertoire sequencing is cheap (~$100 sequencing cost per sample)
- Easy to combine with most of methods based on liquid biopsies
  - Use of PBMCs instead of plasma

Potential caveats of TCR-based detection method

- Difficult to detect cancer localization
  - TCRs are not linked to cancer types due to unknown antigens
- Unknown confounders of other immunologic conditions
  - Autoimmune disorders, chronic infections, pregnancy, etc may change the immune repertoire and affect the predictions
- Potentially longer assessment time
  - Library + Next generation sequencing may take 1-2 weeks
- Requirement of exclusive computational analysis
  - TCR repertoire is very difficult to analyze. Our effort remains one of the very few attempts in this field.

Future directions

- Collection of more TCR-seq samples from cancer patients and healthy individuals
- Improve the performance of DeepCAT for better prediction accuaracy (current AUC=0.95, aim to increase it to 0.99)
- Develop new computational methods to distinguish cancer localizations with blood TCR repertoire
- Conduct a prospective clinical study to evaluate cancer score as a novel diagnostic marker

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