The Role of the p53 Protein in Cancer and New Therapeutic Approaches

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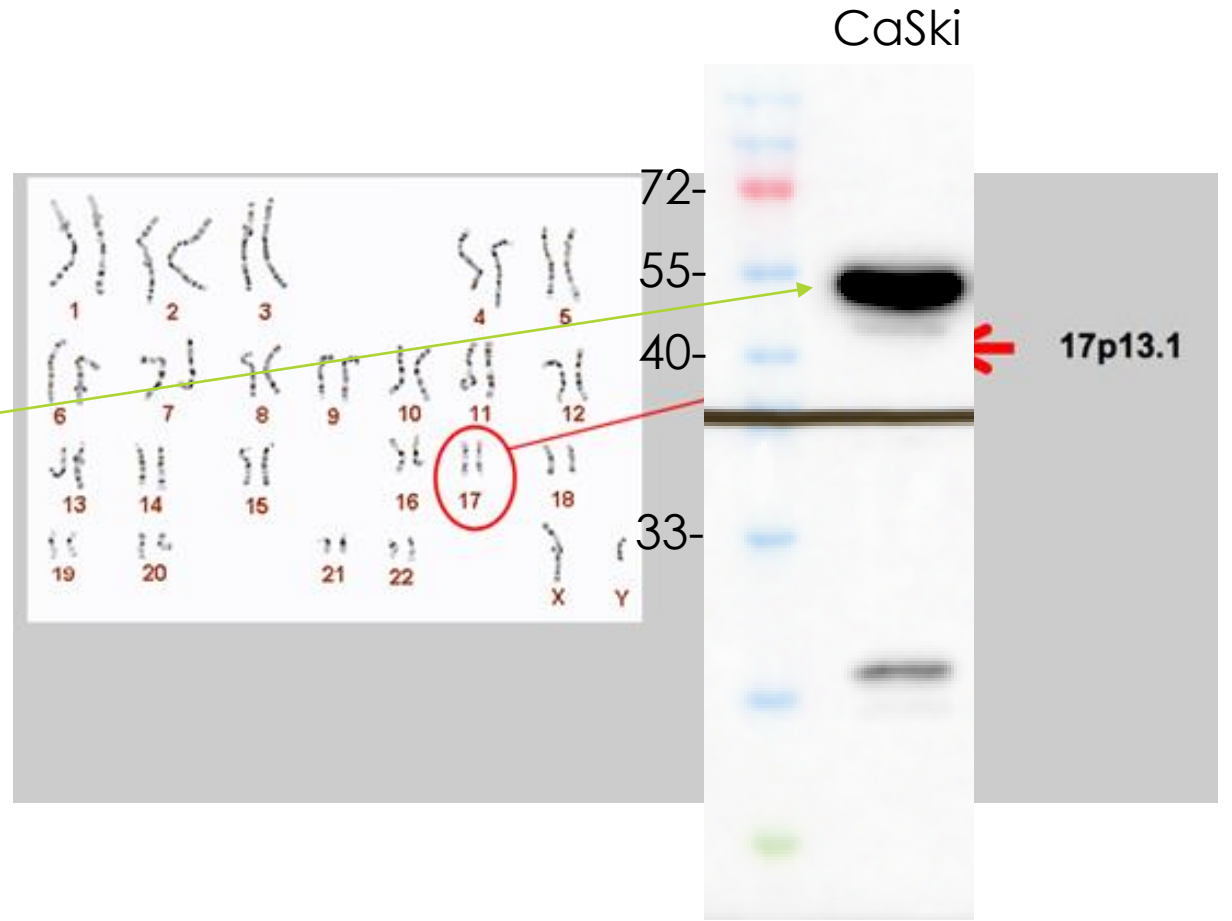
Outline

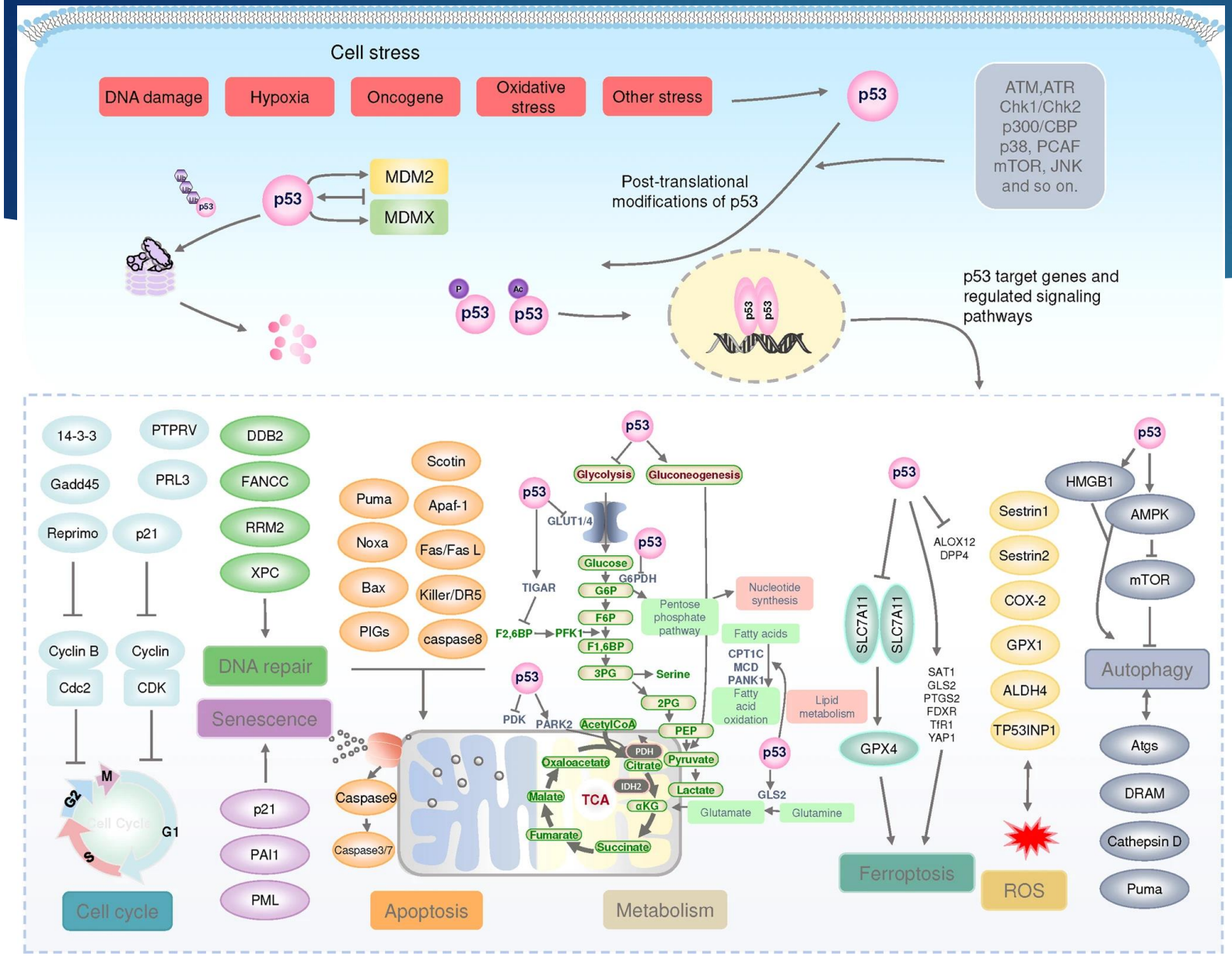
- p53 protein
  - -p53 pathway
  - -p53 mutation
- New developments in p53-targeted cancer therapy
  - -MDM2/MDMX inhibitors
  - -p53 rescue compounds
  - -p53-based immunotherapy
  - -gene therapy
- Challenges and future directions

p53 (Guardian of Genome)

- Encoded by TP53
- located on the short arm of chromosome 17 (17p13.1)
- encodes a protein with 393 aa residues
- Named p53 as the molecular weight ~53kDa in SDS gel
- Actual weight: 43.7kDa
- Initially thought to be an oncogene?



https://p53.fr/



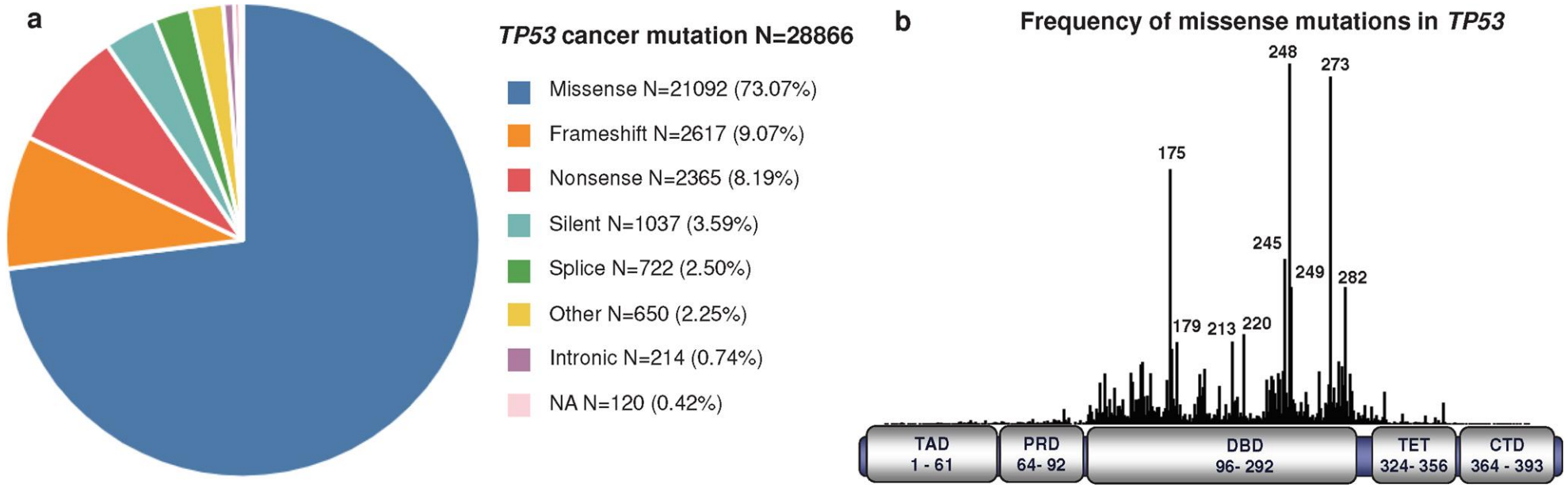
p53 pathway

WANG, H. ET AL. NATURE (2023)

TP53 in cancer

- mutated in most tumor cells
- Genome sequencing of human cancer :

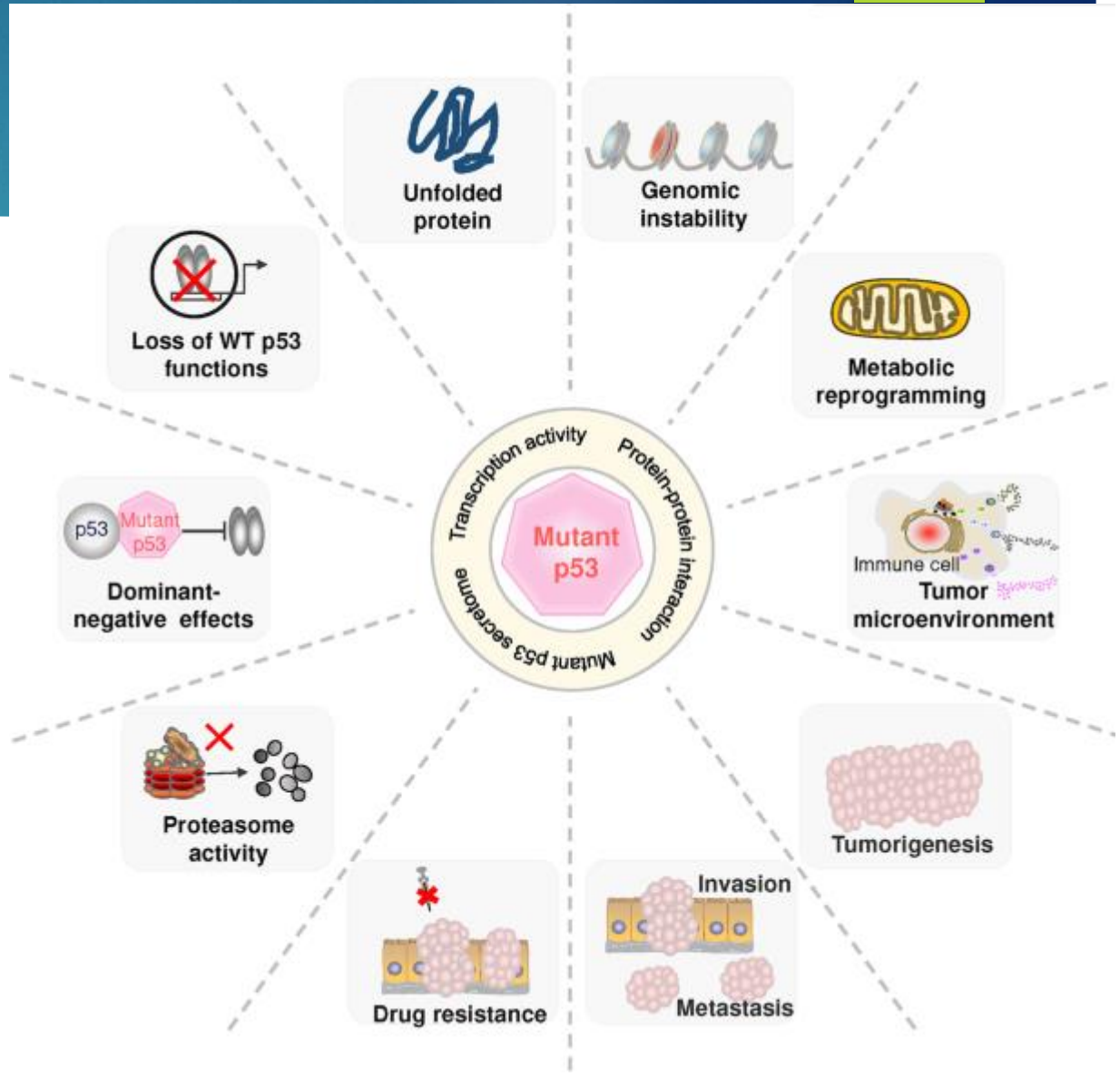
  42% of cases carry TP53 mutations; DBD is the most common mutated region



Wang, H. et al. Nature (2023)

Mutant p53

- cancer cell transformation is unlikely to occur in cells that maintain **normal** p53 function
- TP53 mutations provide a permissive environment for **tumorigenesis**



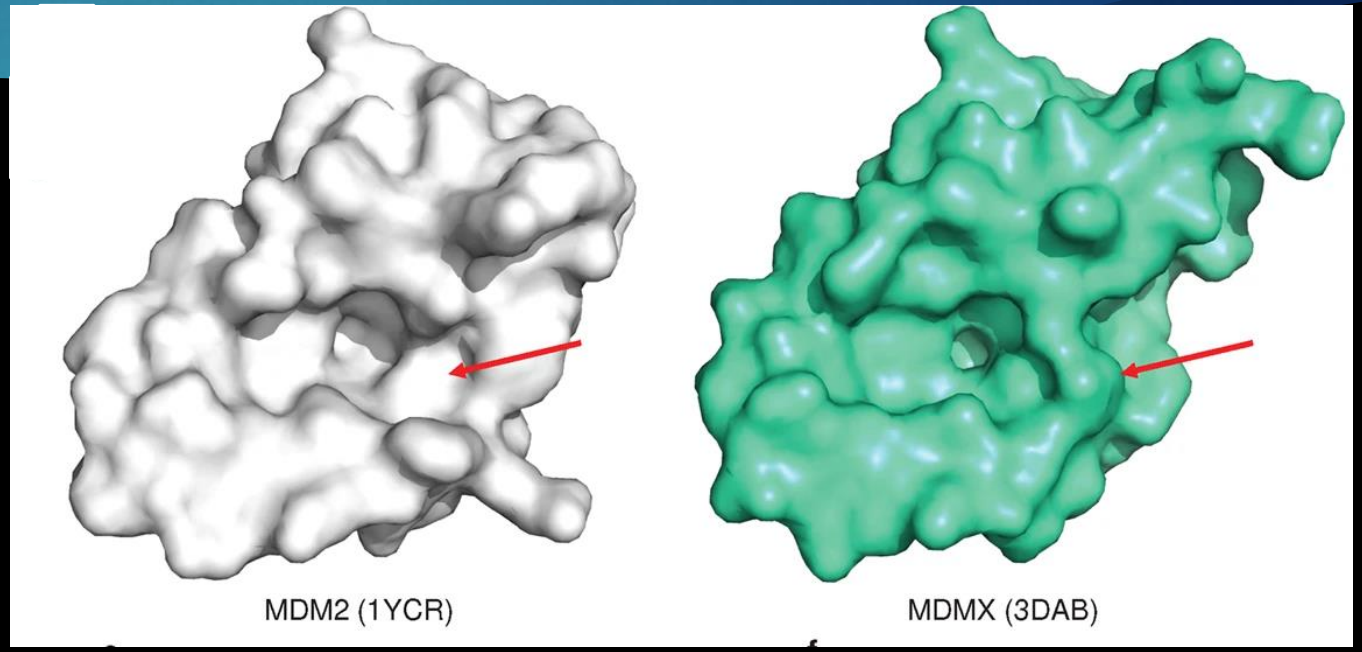
Wang, H. et al. Nature (2023)

Structure-based p53 targeting

- Many **structure–function** and specific regulation of p53 remain to be determined
- with the development of NMR, protein crystallography and cryo-electron microscopy techniques, much structural information has been obtained about the **binding of p53 to ligands**

MDM2/MDMX-p53

- MDM2/MDMX is the **major negative** regulator of p53
- negative feedback regulatory loop
- wtp53 activates the transcription of MDM2
- N-terminal of MDM2 binds to p53-TAD & represses the transcriptional activity of p53



K. Linke. Cell Death & Differentiation (2008)

MDM2-p53 inhibitors

Inhibitors	
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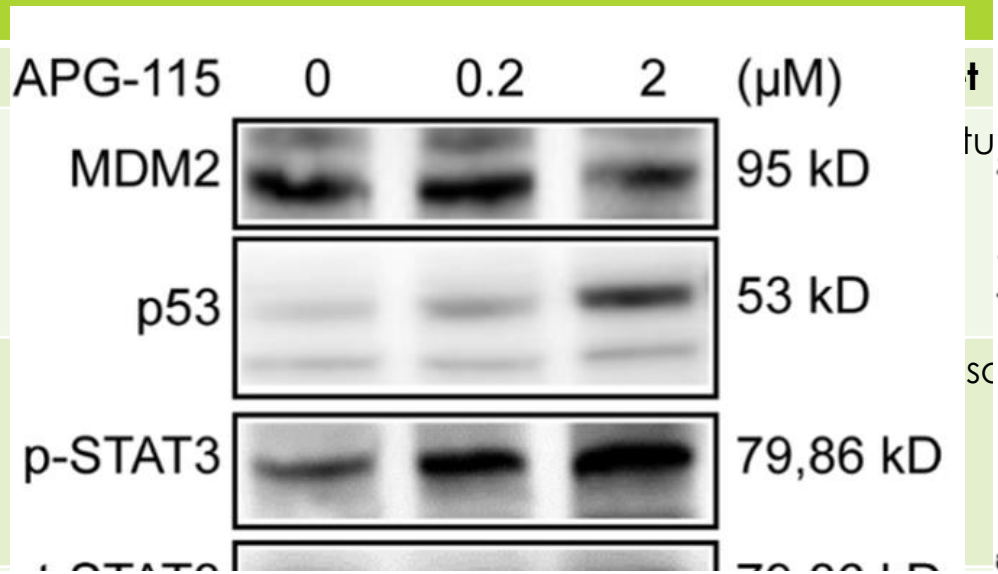
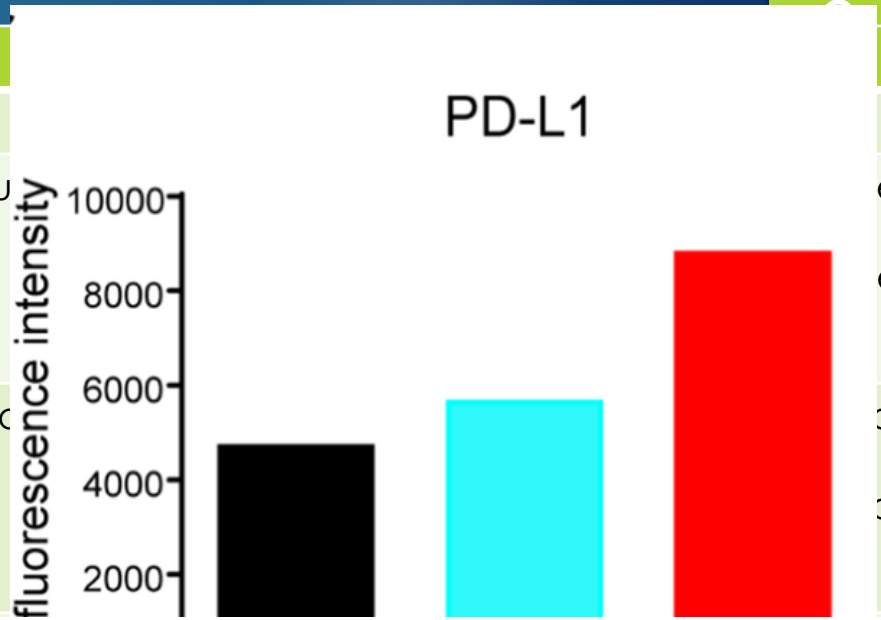
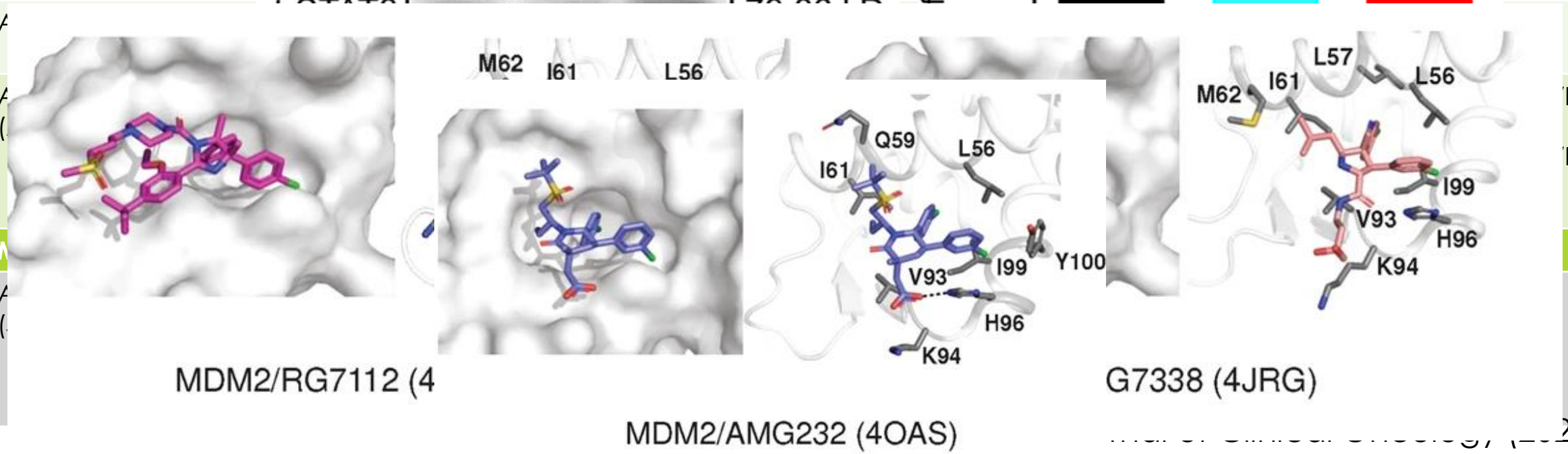






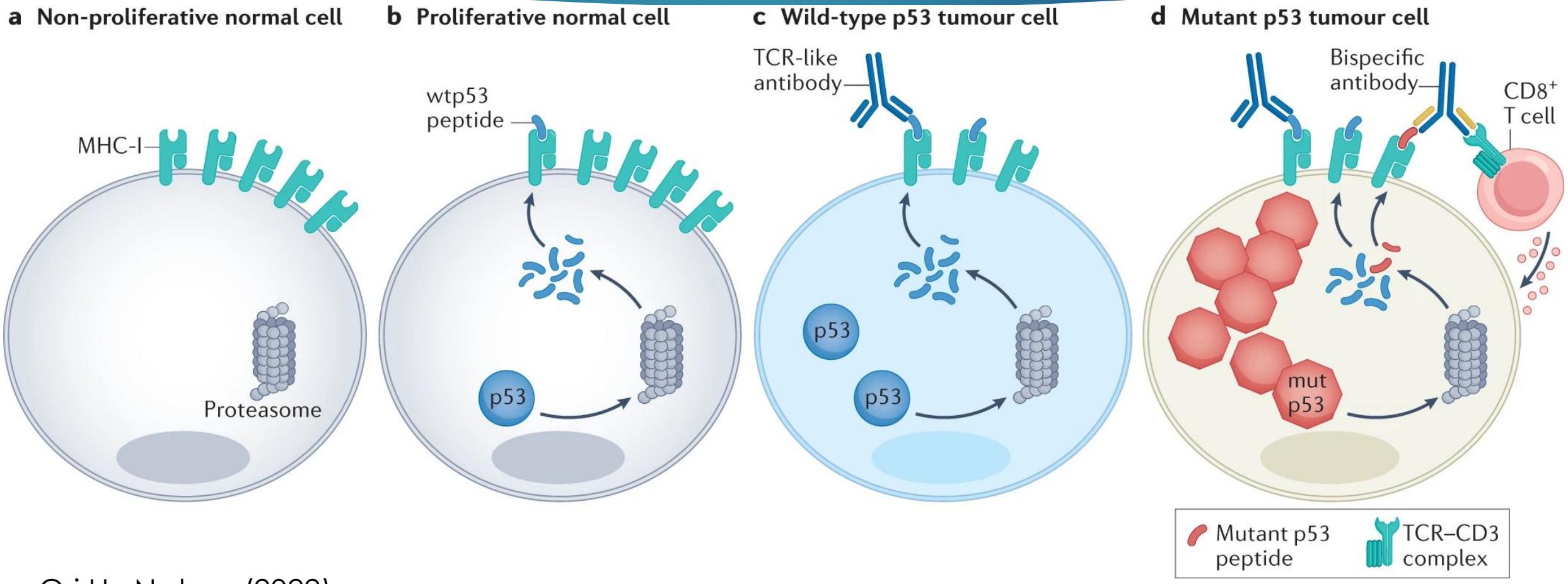
(2022)

Broad-spectrum mutant p53 rescue compounds

- Library screening for **specific DNA binding compounds**
- Screen chemical library, Cell-based/Silico/structure-based/Virtual

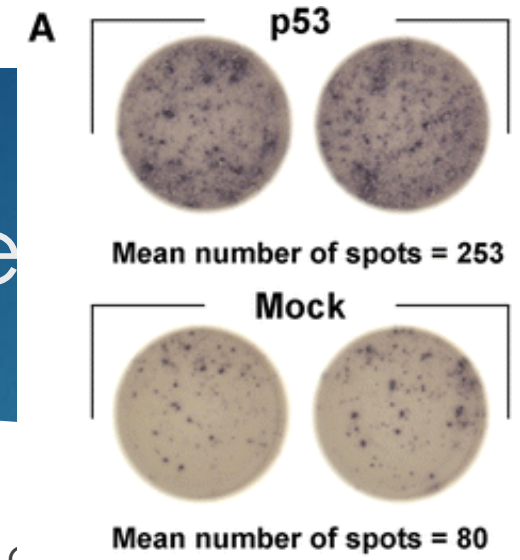
Compound Name	Discovery Method	Clinical Trial
CP-31398	Chemical Library	NA
APR-246 (Eprenetapopt)	Prodrug of a screened compound	NCT03745716 Completed III
Arsenic trioxide (ATO)	Cell-based screening	first-line treatment drug for acute promyelocytic leukemia in clinic
UCI-LC0023	Virtual screening	NA

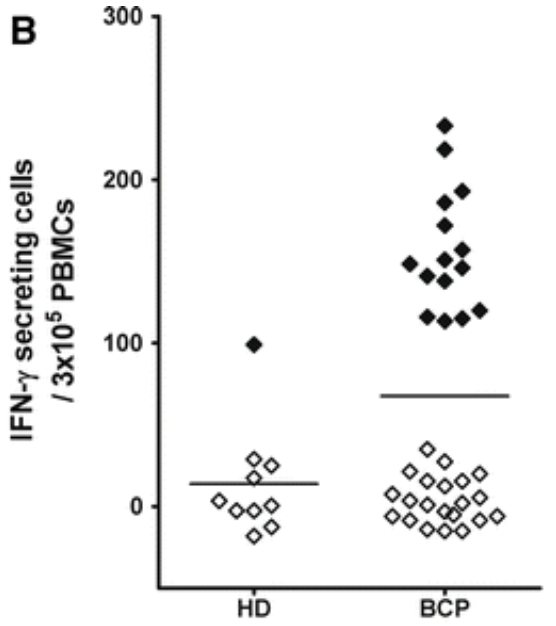
p53-based cancer immunotherapy



Ori H., Nature (2022)

p53-base





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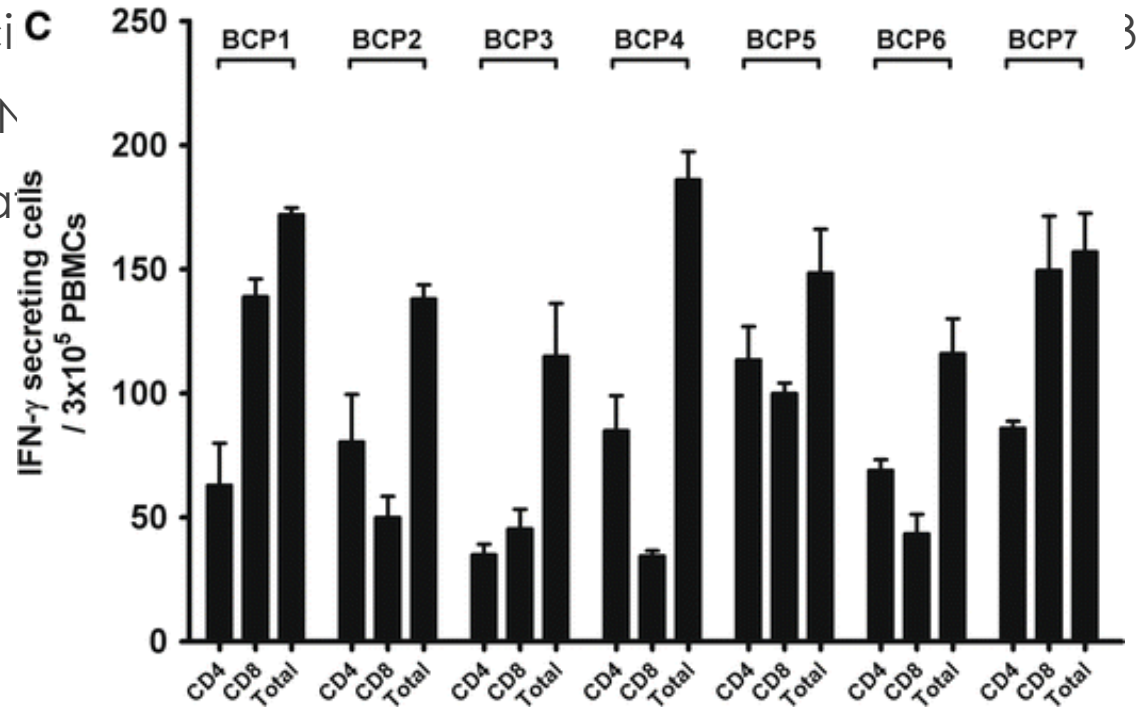
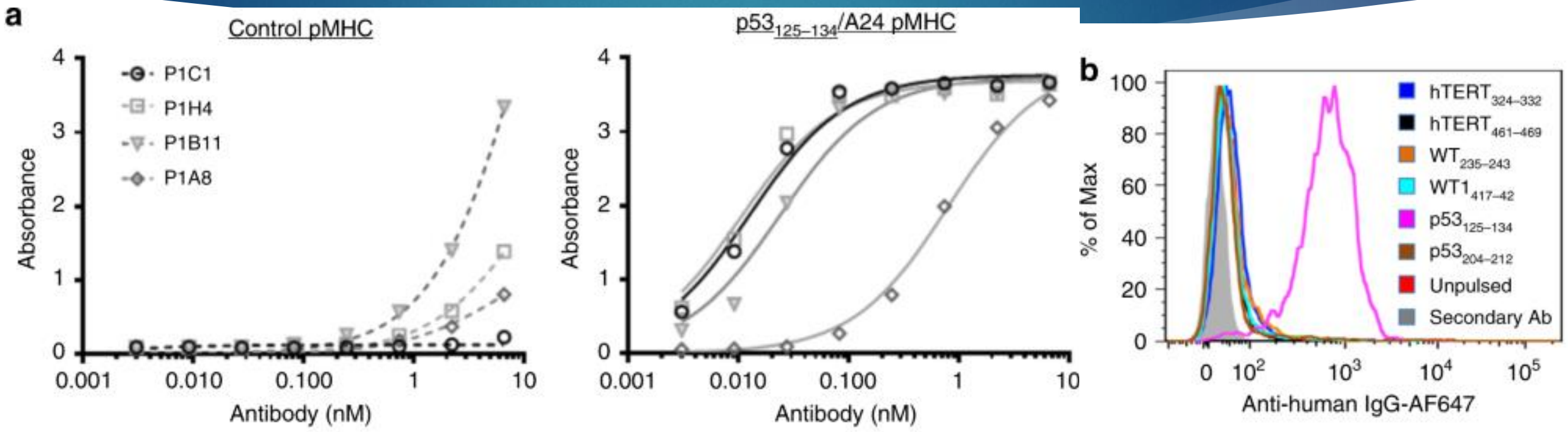
- mRNA vaccina



p53-specific antibodies



Lionel L. Nature Communication (2019)

Gene therapy

- Restore WTp53 lead to tumor regression
- recombinant adenovirus expressing WTp53 (rAd5-p53) (Gendicine™)
- Received approval by CFDA in 2003 for treating HNC

Challenges and future directions

- Is targeting p53 truly a practical approach for treating cancers?
- New targets of p53 are continuously being identified
- E.g. zinc finger matrin-type 3 (ZMAT3), which plays a critical role in p53-dependent tumor suppression
- How do they cooperate in executing p53's tumor-suppressive function?
- Toxicity induced by MDM2 pathway
- Efficacy of p53-based immunotherapy

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Reference

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Thank you