Disclosures

- Currently employed by AbbVie Inc.

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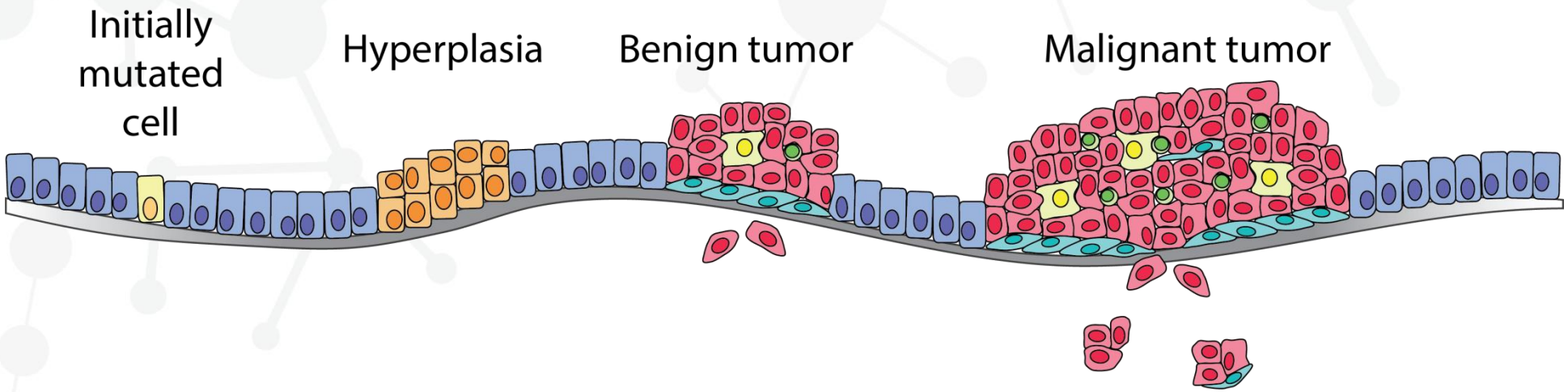
Tumor development requires the acquisition of tumor-cell intrinsic and extrinsic phenotypes, both of which are driven by mutations and alterations in the tumor cell



Effect on tumor cell growth			
Initial disruption of cell-cycle controls	Development of tolerance to anti-growth signals	Metabolic and proliferative adaptations. Possible early metastatic seeding. Initial immunoevasive strategies.	Acquisition of invasive and widespread metastatic potential. Fully established immunoevasive strategies.
Effect on tumor microenvironment			
	Establishment of growth-supportive microenvironment	Engagement of tumor supportive and suppressive immunity. Adaptation of local non-tumor cells.	Erosion of local mechanical barriers. Conversion of distant sites into viable tumor soil. Incapacitation of local and distant anti-tumor immunity.

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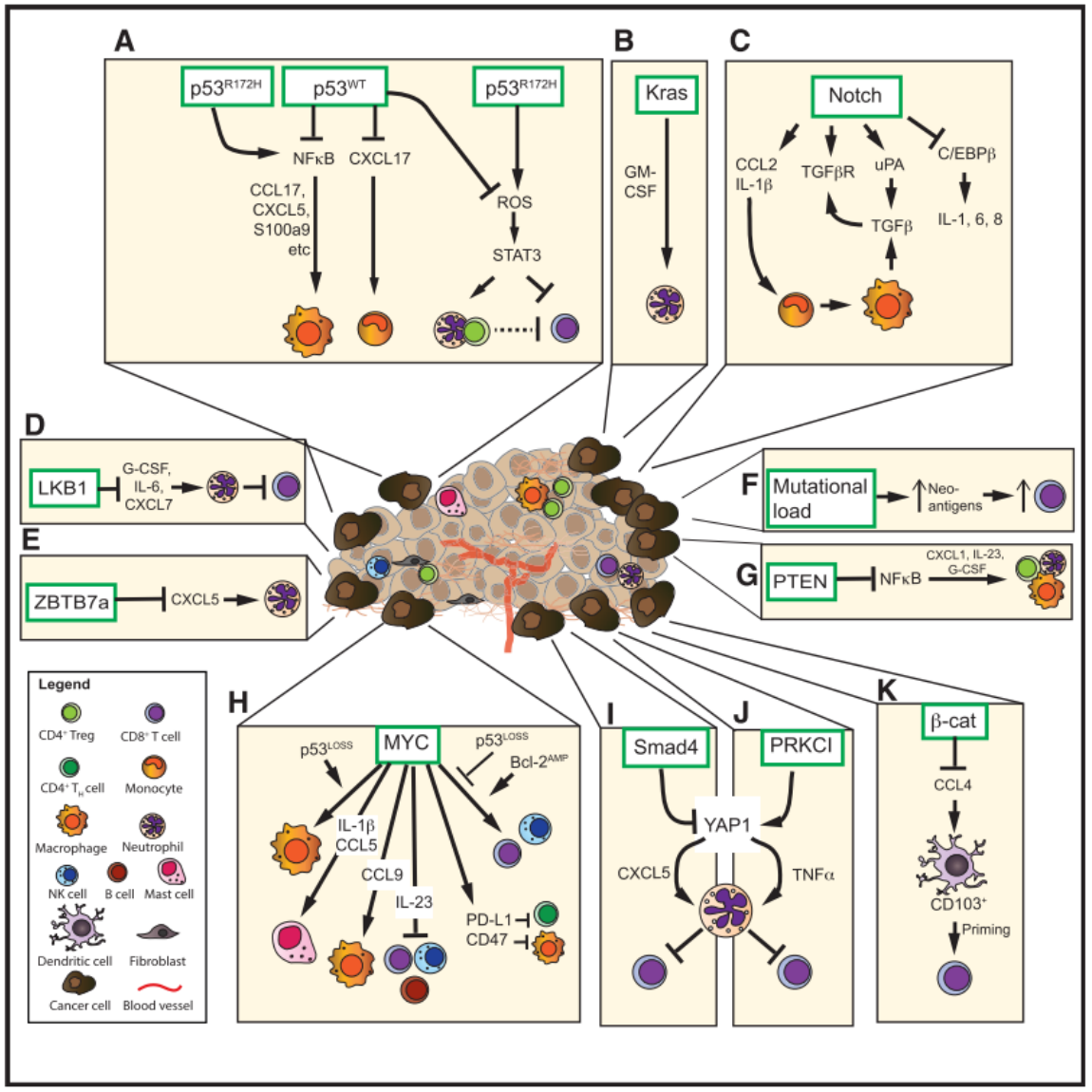
Specific tumor-cell alterations with clear effects on the tumor-immune context and IO response



Types of mutations interacting with the immune context:

Immunogenic drivers
Mutations driving the development of anti-tumor immunity. Includes mismatch repair deficiency, polymerase mutations.

Immunoevasive mutations
Mutations with direct effects on the ability of the immune system to eliminate tumor cells. Includes antigen presentation and processing mutations, PD-L1 amplification, and many others.

Context drivers
Mutations with clear effects on the immune context, but which may not directly impair the ability of the immune system to eliminate tumor cells. Examples include aneuploidy and LKB1/STK11, EGFR, BRAF.

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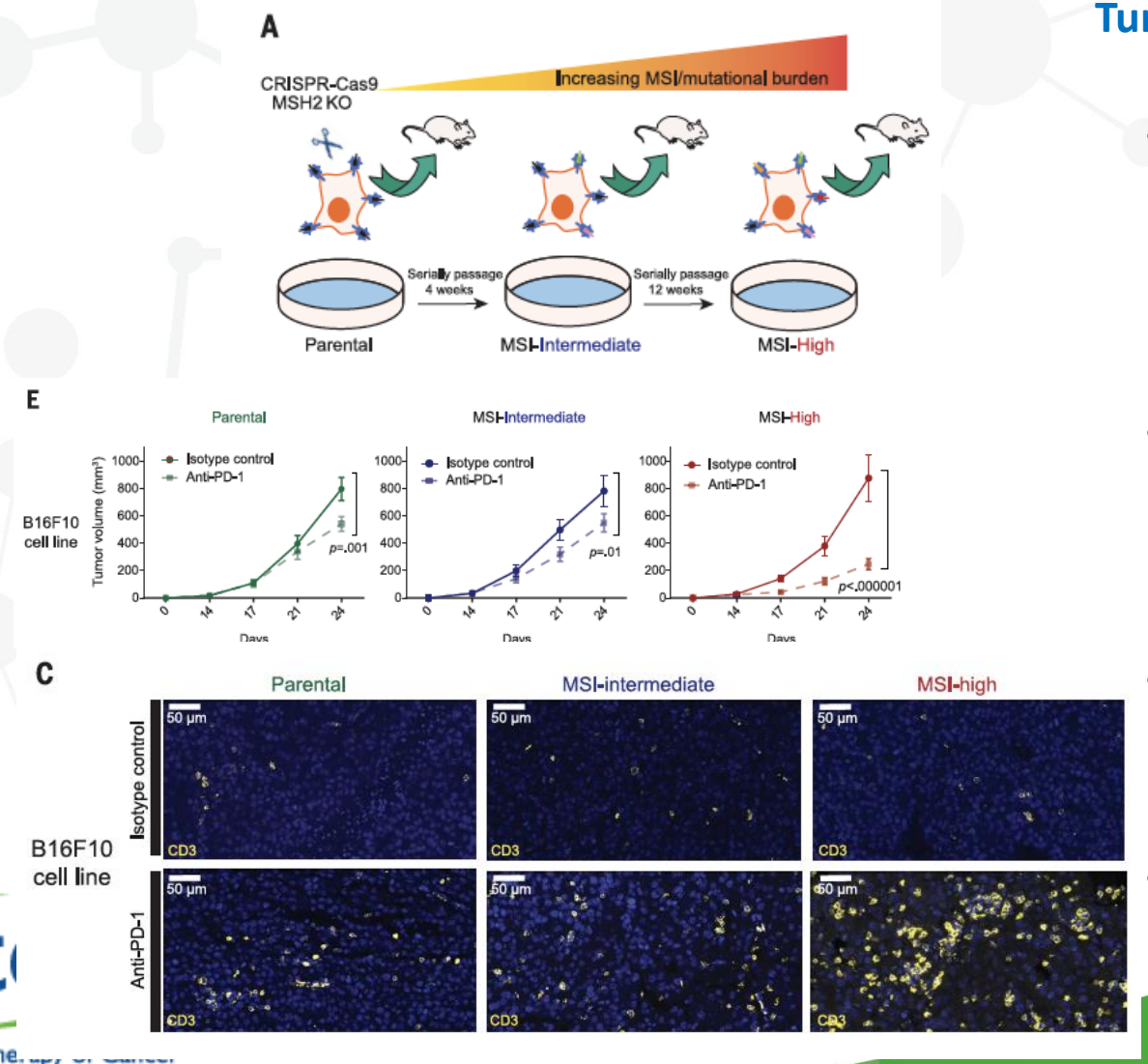
Wellenstein and de Visser, *Immunity*, 2018

Genetic diversity associated with MMR-d influences response to ICI



Tuning MSI severity with CRISPR-Cas9

- Study authors used CRISPR-Cas9 guide RNAs directed to Msh2 to knock out MSH2 in a poorly immunogenic mouse models B16F10, CT26
- Used serial passage of 1 & 4 months to model varying degrees of MSI, MSI-intermediate and MSI-high respectively
- As expected, MSI-high displayed higher non-synonymous SNVs and coding indel mutations
- MSI-high associated with increased anti-PD1 responsiveness and immune infiltration compared with parental and intermediate groups

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Mandal *et al*. Science, 2019

Emerging questions from the breakout session

- How do we deal with the molecular subtypes that define intrinsic resistance to ICI and expand CIR?
- What is the relationship between primary and secondary resistance to ICI
  - What data is available to address this questions?
  - We need data from treated patients? PACT initiative.
- What would we do with this information? Could we leverage it for combinations with targeted therapies or just for exclusion criteria?
- There is a need to develop methodologies to more accurately identify key driver mutations and their connection to CIR.
- What technologies & biomarker development are needed to translate this knowledge into clinical practice?
  - How do we convince the clinicians to use the data?

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