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## **Precision modeling of breast cancer in the CRISPR era**

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## Propositions

Belonging to the thesis

“Precision modeling of breast cancer in the CRISPR era”

- To disentangle tumor’s complexity and pinpoint which molecular perturbations are crucial to hijack the cellular machinery and lead to tumorigenesis and drug resistance, functional studies are needed in model systems that faithfully and comprehensively recapitulate all the salient aspects of their cognate human counterparts (*this thesis*).
- To keep pace with the overwhelming amount of hypotheses that warrant *in vivo* testing, continuous refinement of current breast cancer models and implementation of new technologies is crucial (*this thesis*).
- The unprecedented ease at which endogenous loci can be perturbed with different CRISPR-CAS9 based technologies has opened myriad possibilities for somatic *in vivo* modeling of alterations observed in human malignancies (*this thesis*).
- Individual tumors are mosaics of multiple clones of neoplastic cells, each characterized by a distinct genetic makeup and differential responses to the selective pressures to which they are exposed, making the tumor mass not static but continuously shaped by a branching evolutionary process resembling Darwinian evolution (*this thesis*).
- The overall poor clinical predictability of conventional preclinical *in vivo* tumor models based on xenotransplantation of established human cancer cell lines in immunocompromised mice emphasizes the need for more advanced preclinical *in vivo* models with better predictive power (*Sharpless NE & Depinho RA, Nature Reviews Drug Discovery, 2006*).
- The story of how a mysterious prokaryotic viral defense system became one of the most powerful and versatile platforms for engineering biology highlights the importance of basic science (*Lander ES, Cell, 2016*).
- Rather than studying DNA taken out of the context of the genome, researchers can now directly edit or modulate the function of DNA sequences in their endogenous context in virtually any organism of choice, enabling them to elucidate the functional organization of the genome at the systems level, as well as identify causal genetic variations (*Hsu PD et al., Cell, 2014*).
- In addition to potential off-target activity, the potent immune responses to CAS9 are also a point of concern for *in vivo* application of CRISPR-mediated gene-editing (*Tian X et al., NPJ Precision Oncology, 2019*).

- Nature is the source of all true knowledge. She has her own logic, her own laws, she has no effect without cause nor invention without necessity (*Leonardo da Vinci*).
- Talent wins games, but teamwork and intelligence win championships (*Michael Jordan*).