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Advancing precision oncology: insights from C-terminal FGFR2/3 truncations and MYC-driven mTOR inhibitor resistance

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1. Truncation or loss of exon 18 of *FGFR2*, encoding its C-terminal tail, acts as a potent oncogenic driver alteration in cancer.
Chapters 3 and 4 of this thesis.
2. *FGFR3*, unlike its paralog *FGFR2*, requires both C-terminal truncation and fusion to a partner gene that retains the expression of a dimerizing domain to effectively drive oncogenic signaling and tumorigenesis.
Chapter 5 of this thesis.
3. A C-terminal phenylalanine–serine motif mediates binding of the *FGFR2* C-terminal tail to the kinase domain, thereby suppressing kinase activity and explaining how C-terminal truncation activates *FGFR2* to drive tumorigenesis.
Chapter 4 of this thesis.
4. *MYC* activation is a clinically relevant driver of resistance to mTOR inhibition in breast cancer and may serve as a predictive biomarker for patient stratification.
Chapter 6 of this thesis.
5. Not all genomic alterations in cancer driver genes are oncogenic.
6. Large-scale sequencing approaches, particularly whole-genome sequencing, are essential to uncover rare but biologically meaningful genomic alterations that might otherwise remain overlooked.
7. The growing volume of genomic data generated by next-generation sequencing technologies has limited value without robust computational and statistical frameworks for the initial prioritization of candidate alterations.
8. Despite major advances in computational modeling and AI, experimental functional characterization remains the gold standard for distinguishing biologically relevant driver events from neutral alterations.
9. Durable responses to targeted therapies are unlikely without rational combination strategies that account for the broader co-mutational landscapes and adaptive resistance mechanisms.
10. All cancers are alike but they are alike in a unique way.
Siddhartha Mukherjee, The Emperor of All Maladies: A Biography of Cancer, 2010
11. The whack-a-mole game is a perfect metaphor for our attempt at targeted therapies for precision oncology. While monotherapy leads to initial success, resistance often develops.
Groisberg and Subbiah, Clinical Cancer Research, 2021;27(10):2672-2674
12. Chance favours the prepared mind.
Louis Pasteur