

Webinar

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Targeting Minor Splicing Disrupts DNA Repair and Overcomes Therapy Resistance in Prostate and Breast Cancer



Mark A. Rubin, MD, PhD

Guest Speaker



Date

27 November 2025



Time

13:00-14:00 CET



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SPEAKER

**Prof. Mark A.
Rubin, MD**

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Bern, Switzerland



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Abstract:

The minor spliceosome (MiS) is a specialized RNA-processing machinery upregulated in cancer to promote expression of oncogenic genes. Here, we identify its catalytic component, U6atac snRNA, as a druggable vulnerability in prostate and breast cancers. U6atac knockdown triggers R-loop-mediated DNA damage while impairing DNA repair by downregulating key factors such as BRCA1, PARP1, TP53BP1, and CHK1/2, disabling both homologous recombination and non-homologous end joining. This dual effect sensitizes tumors to PARP inhibitors, cisplatin, and radiation, independent of BRCA status. Moreover, we uncover an adaptive resistance mechanism driven by extracellular vesicles enriched in U6atac, which amplify MiS activity and facilitate therapy escape; a process reversed by U6atac depletion. Across multiple in vitro and in vivo models, MiS targeting demonstrates tumor-selective activity with minimal toxicity. These findings position U6atac as a central regulator of genome stability and establish MiS targeting as a promising approach to potentiate genotoxic therapy and overcome resistance.

Bio:

Mark is internationally recognized for pioneering research on the molecular underpinnings of prostate cancer and advancing precision medicine. His landmark discoveries include AMACR and EZH2 alterations; ETS gene fusions; mutations in SPOP, FOXA1, and MED12; and insights into clonal evolution and chromoplexy from whole genome sequencing. He also identified TP53, RB1, and NMYC alterations in advanced disease and revealed novel resistance mechanisms involving epigenetic modifiers such as SWI/SNF and minor intron splicing, reshaping understanding of prostate cancer biology. Prof. Rubin's genomic insights have led to widely used clinical tests and contributed to the WHO tumor classification, shaping global standards for prostate cancer diagnosis and treatment.

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