Guest lecture

Thursday, February 13. from 11.15-12.00
in BMB Seminar room (V18-501-1)

"Splice Switching as Potential Cancer Therapy: Activation of Therapeutic RTK Variants by Splicing Interference"

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The aberrant activity of receptor tyrosine kinases (RTKs), such as EGFR or MET, is implicated in various forms of cancer and have emerged as a both drivers and mechanism of resistance to therapy, thus, making them attractive targets for cancer therapeutics, particularly in lung (NSCLC), colon, and gastric cancer and glioblastoma multiforme (GBM). No effective options are currently available for MET-dependent tumors, whereas in the case of EGFR, current treatments are limited by the almost unavoidable appearance of TKI resistance, especially from secondary somatic mutations in the *EGFR* gene, such as the T790M mutation (>50% of biopsies) in the EGFR kinase domain following erlotinib or gefitinib treatment. Even next-generation T790M-targeted TKIs, such as Osimertinib, are over-seeded by the appearance of resistance-driving EGFR mutations (e.g. C797S). As these tumors are still EGFR-dependent, EGFR remains a prime therapeutic target in NSCLC. We recently described multiple natural soluble decoy isoforms for several RTKs, including EGFR and MET. We employ antisense oligonucleotides (ASOs) to reprogram RTK pre-mRNA processing to increase expression of soluble decoy RTKs (sdRTKs), at the expense of the oncogenic full-length receptor. These alternative splicing isoforms are generated via alternative intronic polyadenylation (IPA) of pre-mRNAs, in a U1-snRNP (U1)-dependent manner. More specifically, we are able to induce the sdEGFR or sdMET variants by using specific ASOs designed to block the upstream U1 binding site and thus activate the appropriate IPA sites. Our novel strategy effectively induces the expression of potent natural inhibitors of EGFR and MET signaling in treatment-refractory lung cancer models *in vitro* and *in vivo*, leading to suppression of downstream pathways and tumor growth inhibition. The ASO-induced natural sdRTK compounds function in a dominant-negative manner and induce dramatic cell death in NSCLC cells harboring multiple activating and resistance EGFR mutations, and thus provides a novel alternative strategy for treatment of refractory NSCLC, to overcome resistance mediated by the EGFR secondary mutations (including T790M, C797S, exon 20, and others), or to target MET-dependent cancers.

Host: Brage Storstein Andresen, BMB