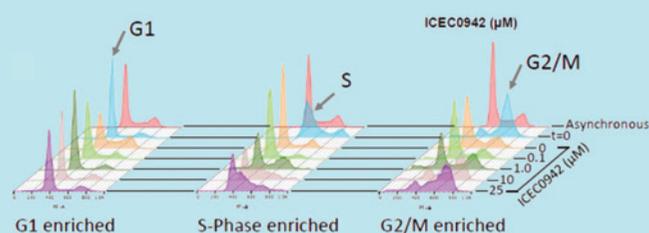


Development of a Clinical Candidate CDK7 Inhibitor

Patel and Periyasamy *et al.* _____ Page 1156

Deregulated cell cycle progression and gene regulation in cancer cells exposes vulnerabilities that can be exploited in developing new therapies. For example, CDK7 is an important protein kinase that controls cell cycle progression through the phosphorylation of cyclin-CDKs and transcription initiation by phosphorylating RNA polymerase II. Here Patel, Periyasamy and colleagues describe a new CDK7 inhibitor, ICEC0942 (CT7001), which effectively inhibits tumour cell growth, both as a single agent and in combination with hormonal therapies in estrogen receptor-positive breast cancer cells. Good pharmacological characteristics, including oral bioavailability, highlight potential for the clinical development of ICEC0942, with Phase I trials now underway (clinicaltrials.gov: NCT03363893).



Silencing Genes in Glioblastoma with Self-Delivering siRNAs

Osborn and Coles *et al.* _____ Page 1251

Glioblastoma is the most common and lethal form of primary brain tumor with a dismal median survival of 14.5 months. Cancer genomics studies have identified a wealth of new genetic targets, many of which amenable to silencing by oligonucleotide drugs, such as small interfering RNAs (siRNAs). Here, Osborn, Coles, and colleagues have demonstrated that administration of metabolically stabilized, cholesterol-conjugated, self-delivering siRNA (hsiRNA) supports widespread tumor distribution and highly efficient gene silencing in established, orthotopic gliomas. Direct delivery of hsiRNAs allows straightforward *in vivo* target validation, a critical step to the development of effective therapeutics for these devastating tumors.

HSP27 and LC3B Identify High-risk Osteosarcoma Patients

Livingston *et al.* _____ Page 1315

Chemotherapy-induced autophagy is a proposed mechanism of chemoresistance and potential therapeutic target in osteosarcoma. Here, Livingston and colleagues report the occurrence and prognostic significance of autophagy and heat shock protein 27 (HSP27) in osteosarcoma patients. Autophagy, as measured by punctate LC3B expression (LC3B+), was increased in post-treatment specimens and highest in osteosarcoma metastasis. Following preoperative chemotherapy, expression of HSP27 was associated with poor survival whereas LC3B+ expression conferred a favorable prognosis. These results identify novel prognostic biomarkers in osteosarcoma and support further investigation into targeting HSP27 or modulating autophagy in osteosarcoma treatment.

A Mechanistic ADC Processing Model

Durbin *et al.* _____ Page 1341

In this article, Durbin and colleagues demonstrate how a mechanistic model can determine key inefficiencies in the processing of an antibody-drug conjugates (ADC) at the cellular level. Using techniques such as imaging flow cytometry and mass spectrometry, the cellular ADC processing steps (i.e., binding, internalization, lysosomal processing, and intracellular drug accumulation) were analyzed and integrated into a novel model. Sensitivity analysis then highlighted parameters that, when modified, would ultimately yield the highest increase in intracellular free drug levels. These outcomes are important for understanding the steps driving ADC uptake and which steps could be improved upon in future rounds of drug development.