Title of Research *
Parf-1A (Partner of ARF isoform 1A) promotes oxaliplatin resistance in tumor cells and is a new marker of survival for resected pancreatic ductal adenocarcinoma patients

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Introduction & Purpose *
Pancreatic ductal adenocarcinoma (PDAC) is an incurable malignancy with ineffective treatments and dismal median survival. The INK4a/ARF locus encodes the alternative reading frame (ARF) tumor suppressor and is commonly inactivated in PDAC tumors. We recently discovered Parf-1A, a novel “Partner of ARF” whose role in ARF signaling and tumorigenesis is unknown. Parf-1A is highly expressed in the normal pancreas and microarray databases suggest Parf expression is altered (both up- and down-regulated) in human PDAC tumors.

Experimental Design *
We generated Parf-1A specific antibodies and examined its protein levels by immunohistochemistry in PDAC tumors from patients who underwent resective surgery.

Results *
Parf-1A expression was altered in 72% of tumors (33% reduced, 39% elevated) compared to adjacent normal ductal tissue. Tumors with the highest Parf-1A levels were significantly associated with poor patient outcome (median survival 5.7 months) while patients with undetectable Parf-1A in tumors had a dramatically extended lifespan (median survival 61 months, p=0.0028). Notably, Parf-1A knockdown in cultured PDAC cells increased the p53-independent growth inhibitory activity of ARF, which was associated with increased ARF accumulation in the nuclear matrix. Parf-1A loss also sensitized PDAC cells to oxaliplatin, a chemotherapeutic agent used in a first-line combination therapy regimen to treat PDAC patients.

Conclusions *
This work identifies Parf-1A as a new inhibitor of ARF p53-independent activity that promotes PDAC chemoresistance in vitro and is a novel prognostic marker of survival in PDAC patients.