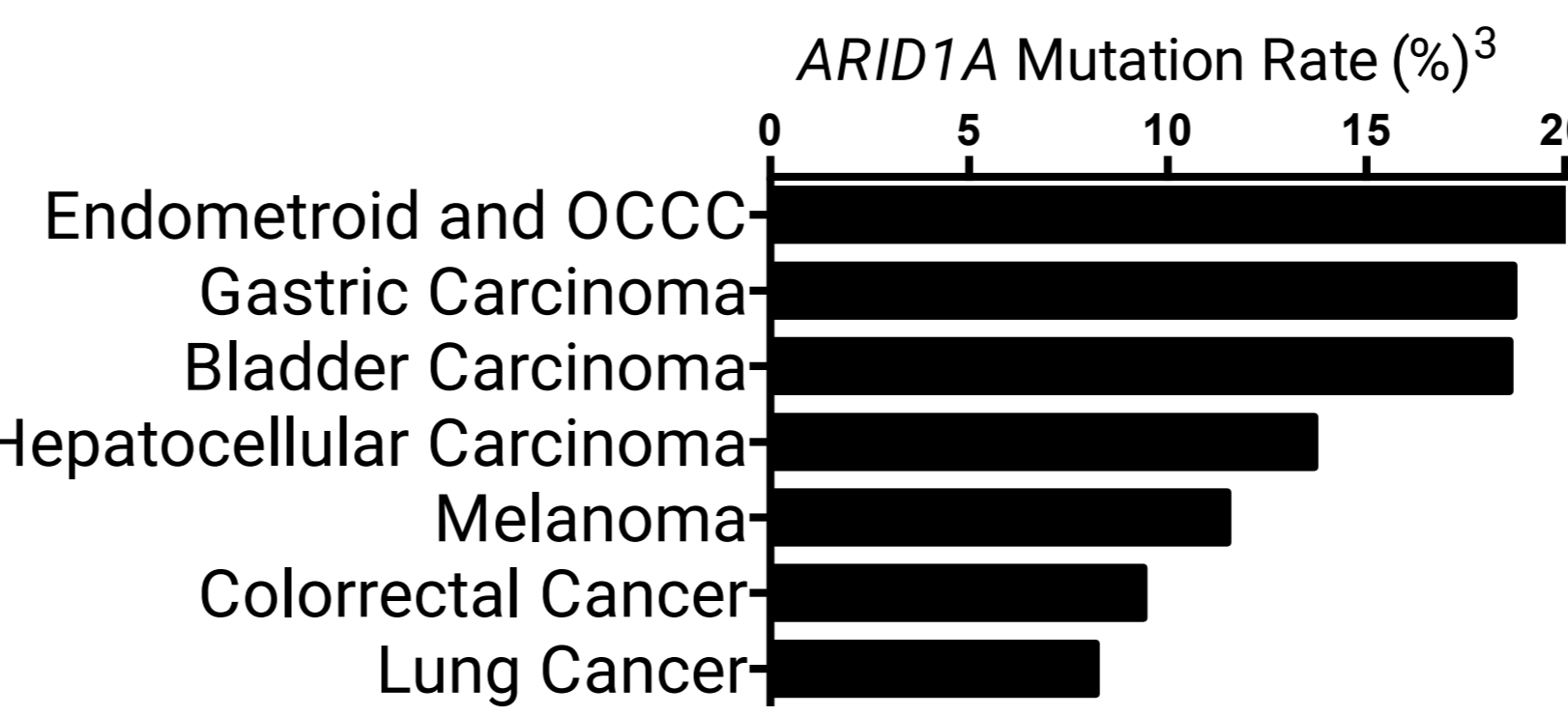
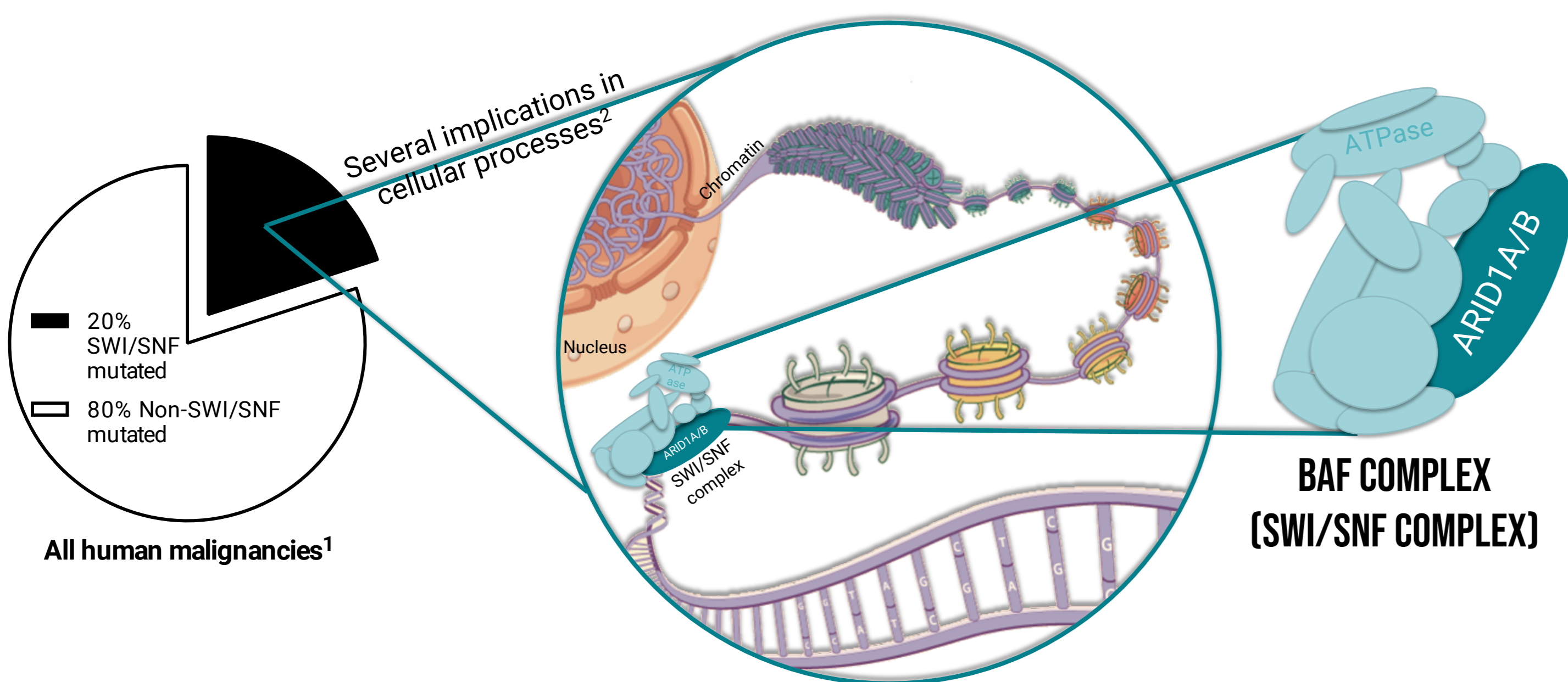


ARID1A: THE GOOD, THE BAD AND THE UGLY

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BACKGROUND AND OBJECTIVES



Mostly, inactivating mutations³

Bona Fide Tumor Suppressor Gene

But... ARID1A is not what it seems...

	Oncogene	Tumor suppressor	Context
Liver cancer	<i>Arid1a</i> inactivation delays tumor onset (in tumor initiation contexts) ⁴	<i>Arid1a</i> inactivation accelerates tumor progression (in tumorigenic contexts) ⁴	TIME-Dependency
Colorectal cancer	<i>Arid1a</i> inactivation blocks cancer in <i>Apc</i> -mutants ⁵	<i>Arid1a</i> inactivation drives cancer in MSI contexts ⁵	GENETIC-Dependency
Ovarian cancer	<i>Arid1a</i> inactivation causes differentiation in <i>Apc/Pten</i> mutants ⁶	<i>Arid1a</i> inactivation drives cancer with <i>Pik3ca</i> mutation ⁷	GENETIC-Dependency

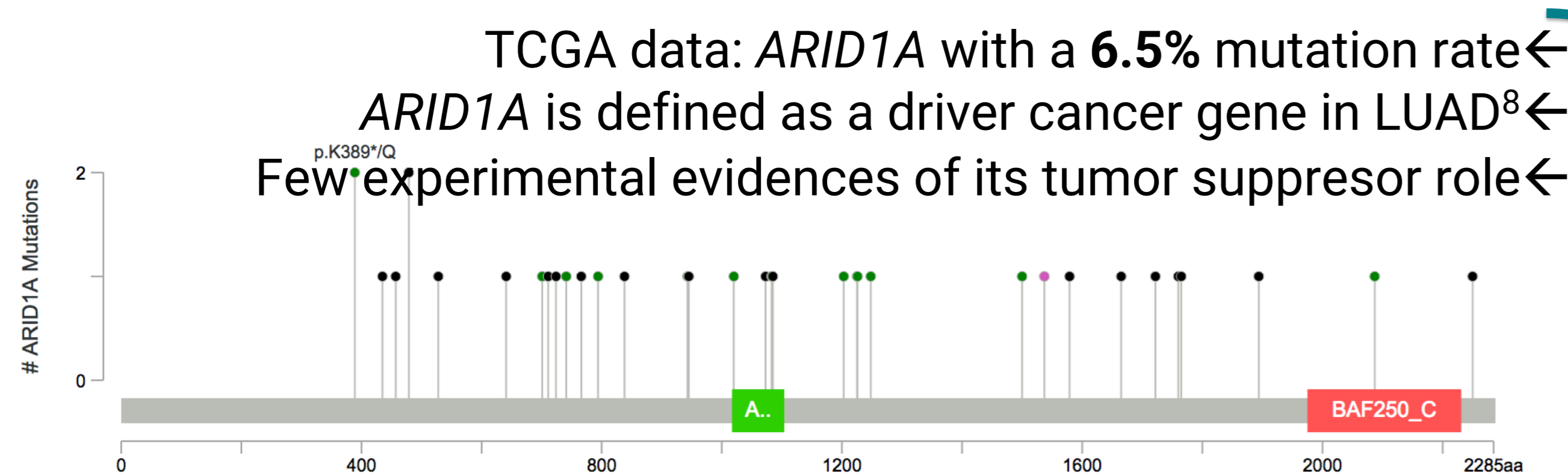
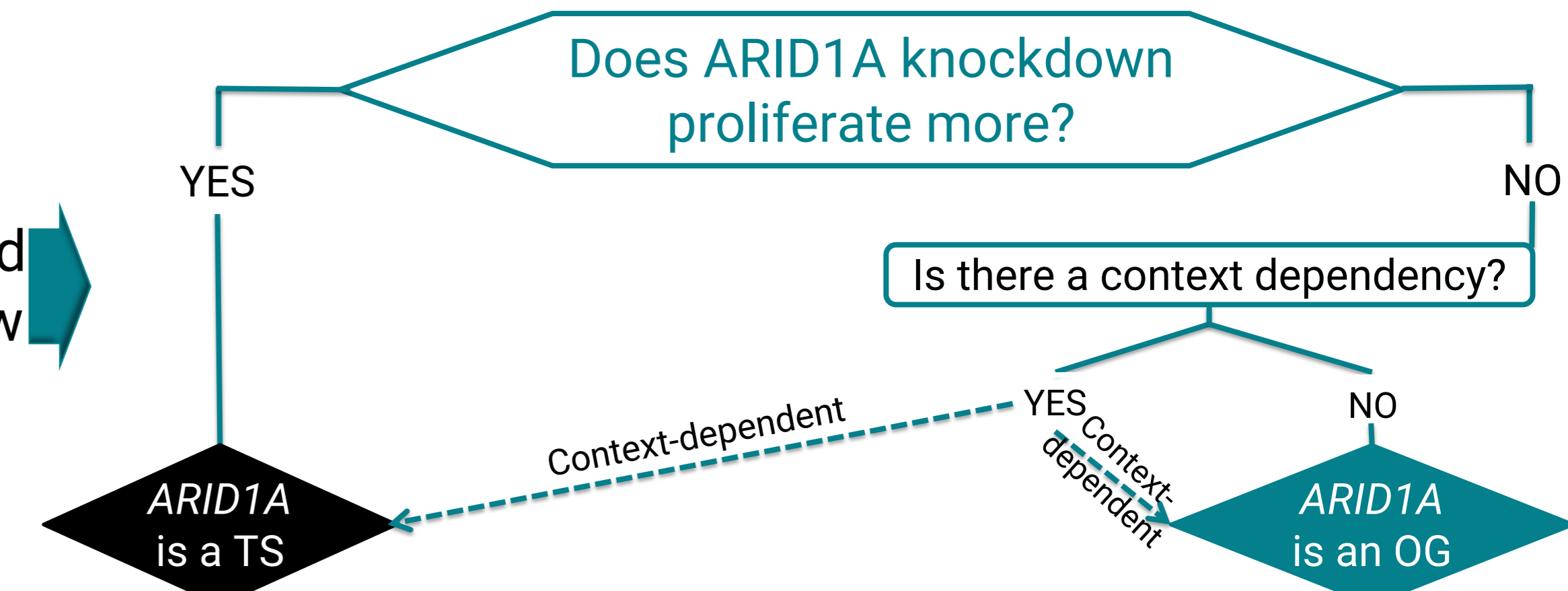


Figure 1: Lollipop representation of all ARID1A mutations found in LUAD patients (TCGA, 2019)

PRELIMINARY RESULTS

LUNG ADENOCARCINOMA

Aims and workflow



A549

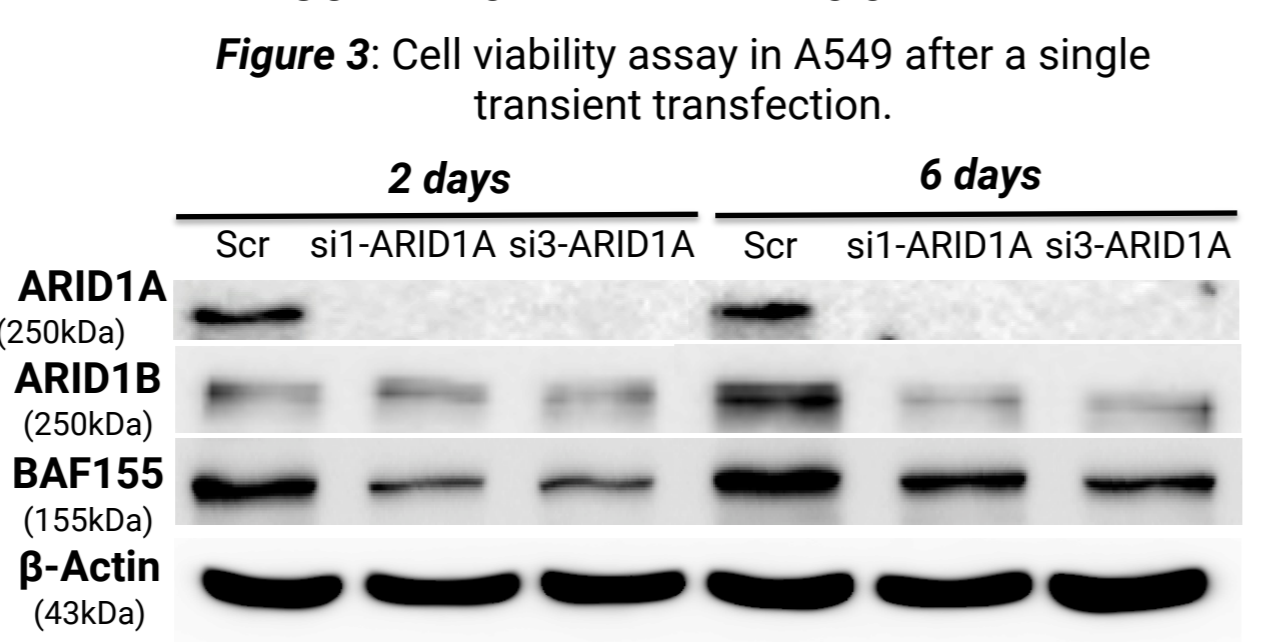
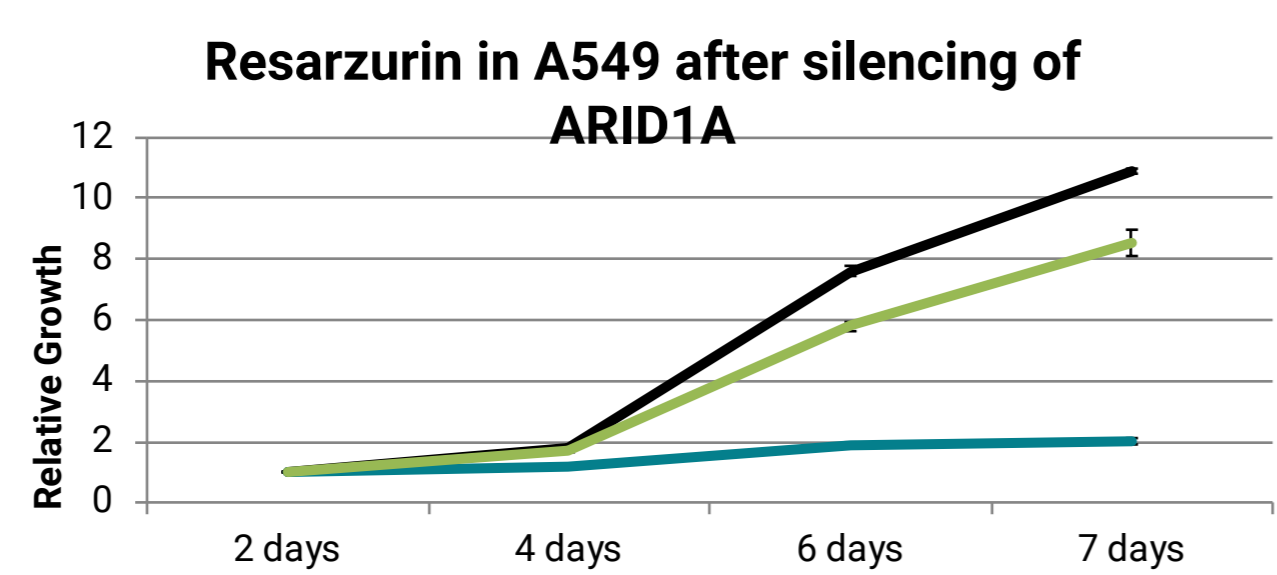
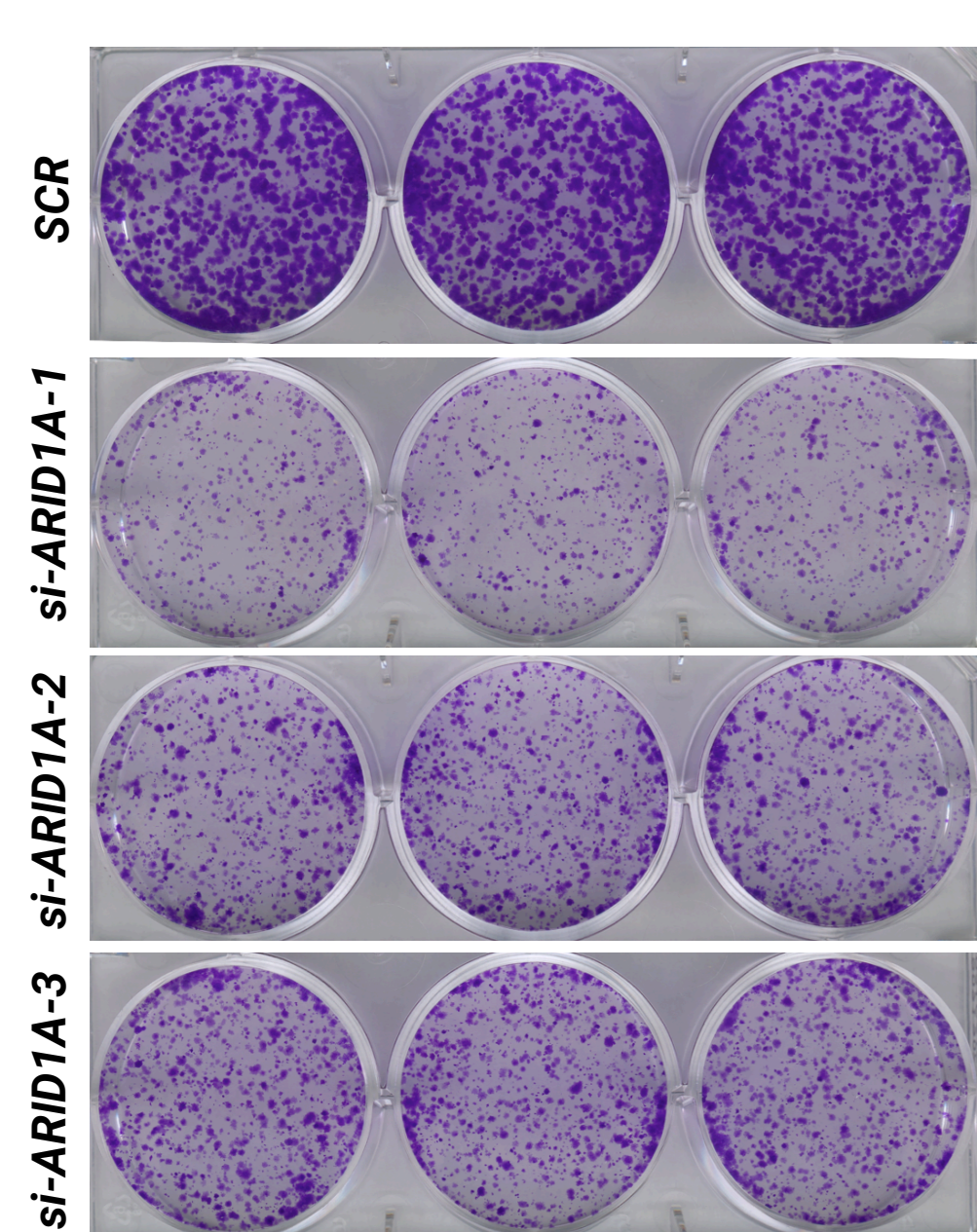


Figure 2: Colony formation assay in A549 cell line with ARID1A-knockdown after 15 days of transfection.

Figure 4: Western Blot of A549 after 2 and 6 days of ARID1A knockdown.

NCI-H2009

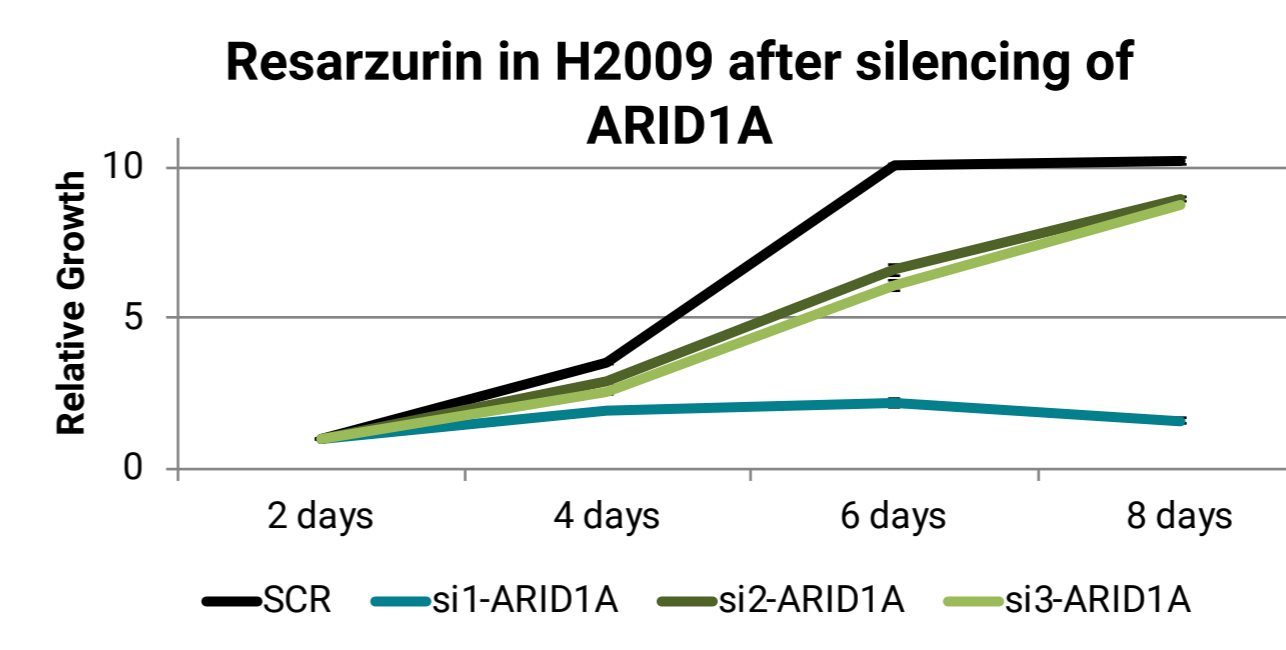
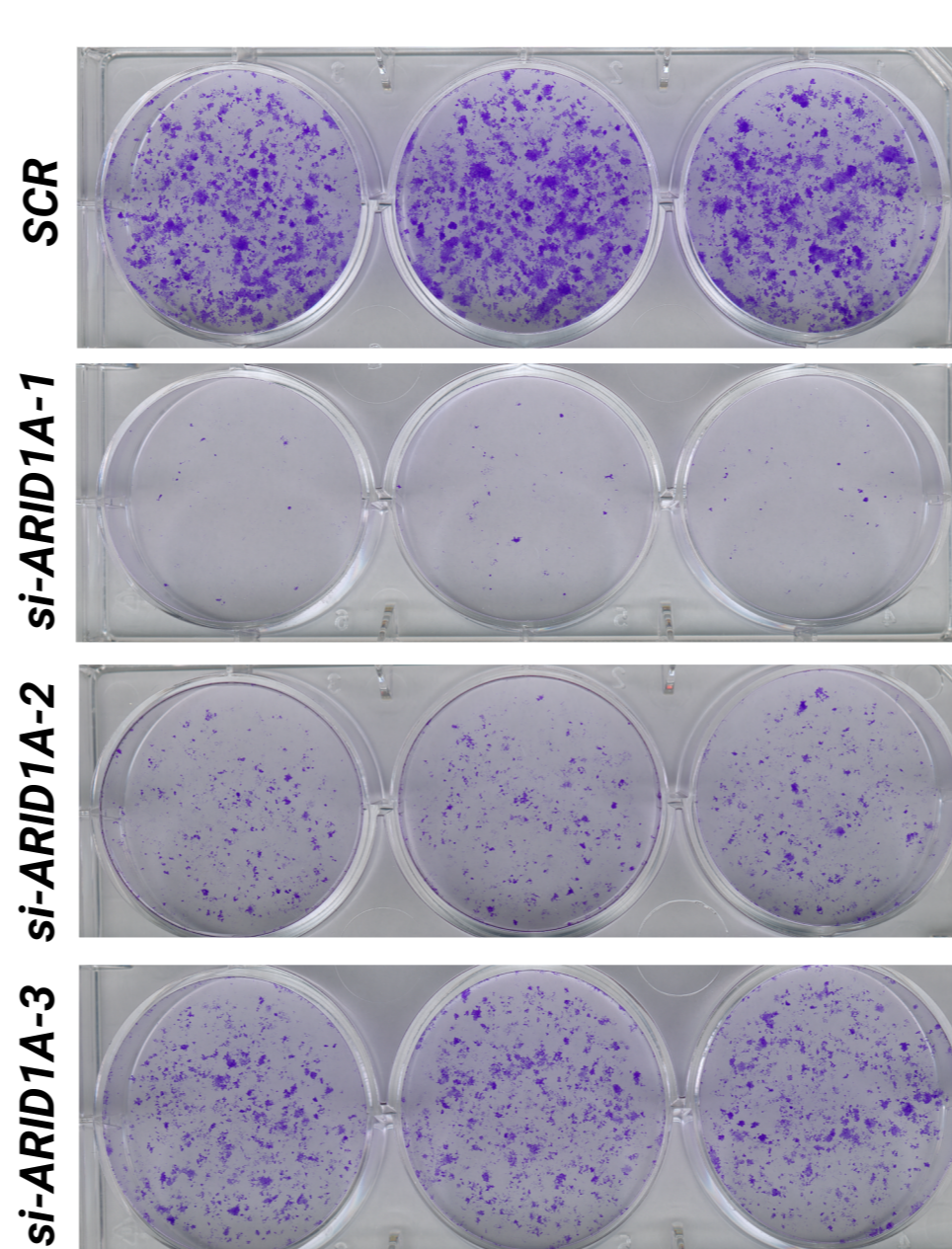


Figure 6: Cell viability assay in H2009 after a single transient transfection.

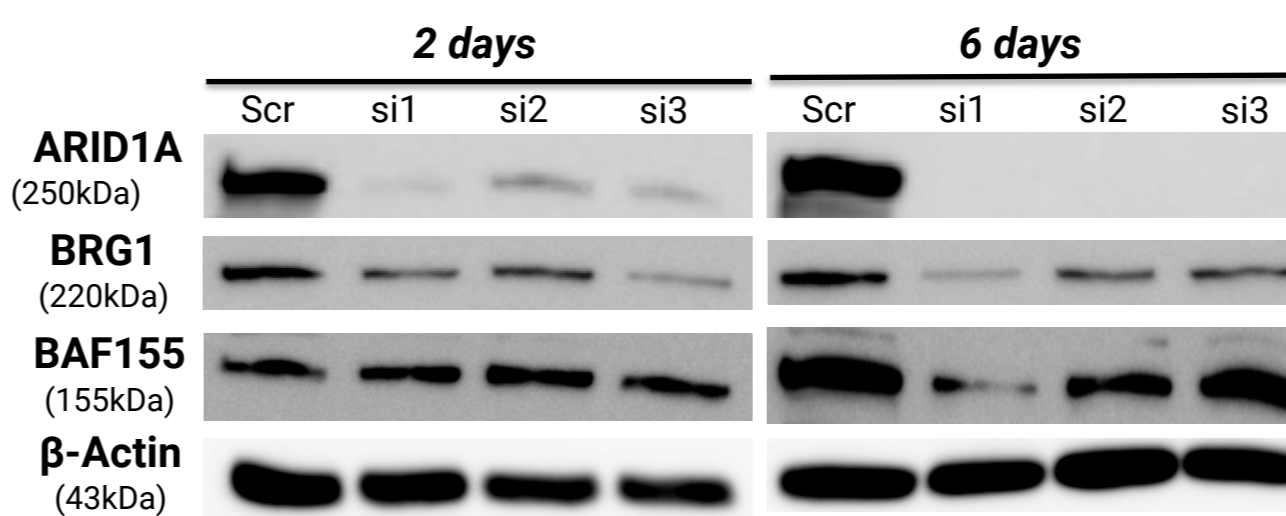


Figure 5: Colony formation assay in H2009 cell line with ARID1A-knockdown after 15 days of transfection.

Figure 7: Western Blot of H2009 after 2 and 6 days of ARID1A knockdown.

NCI-H1373

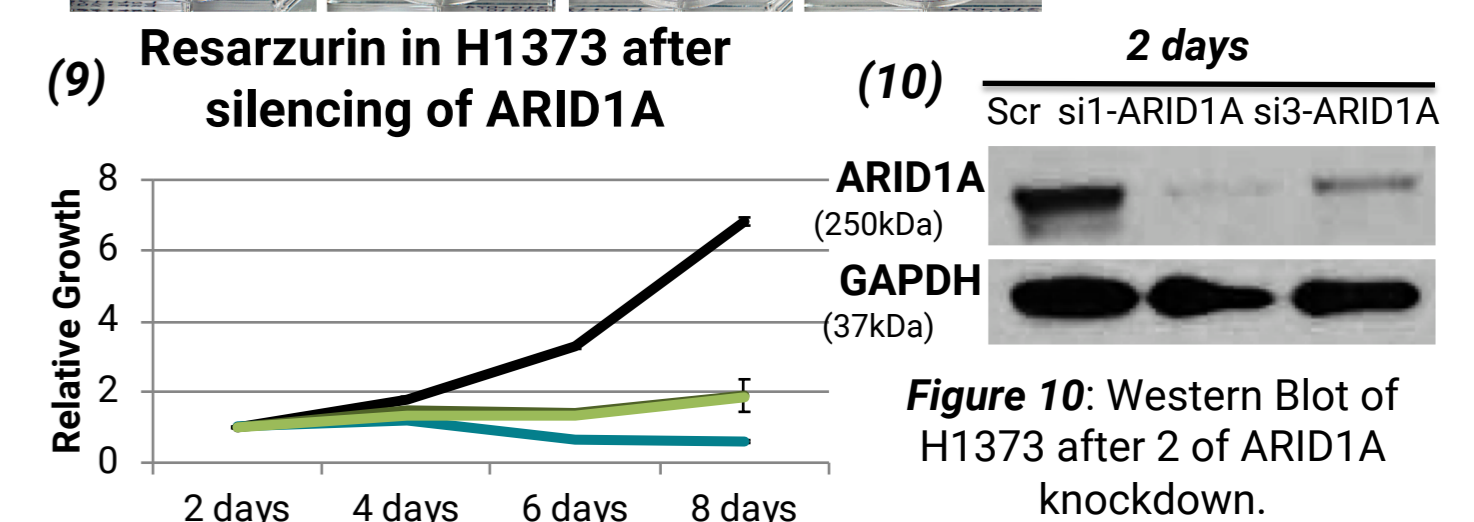
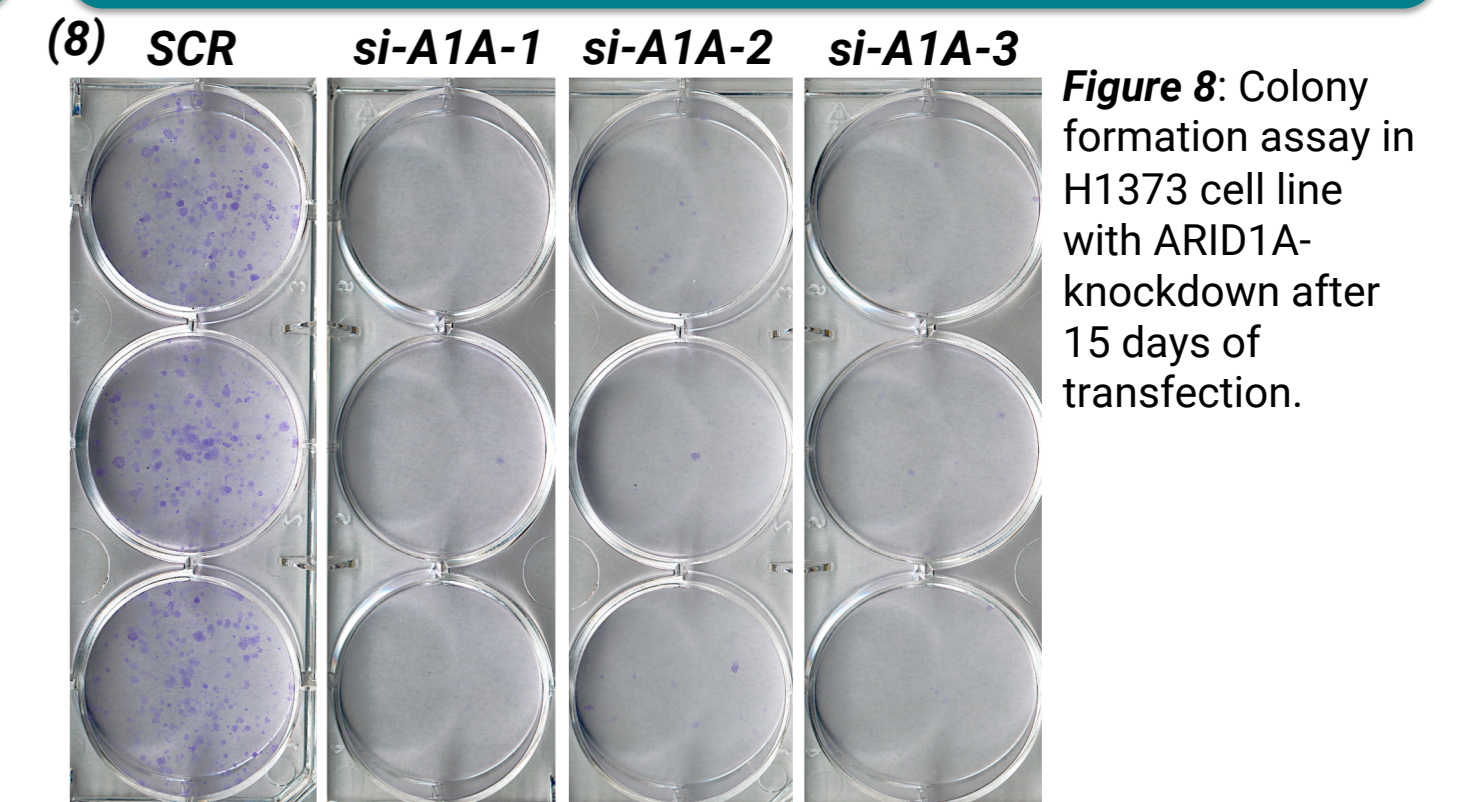
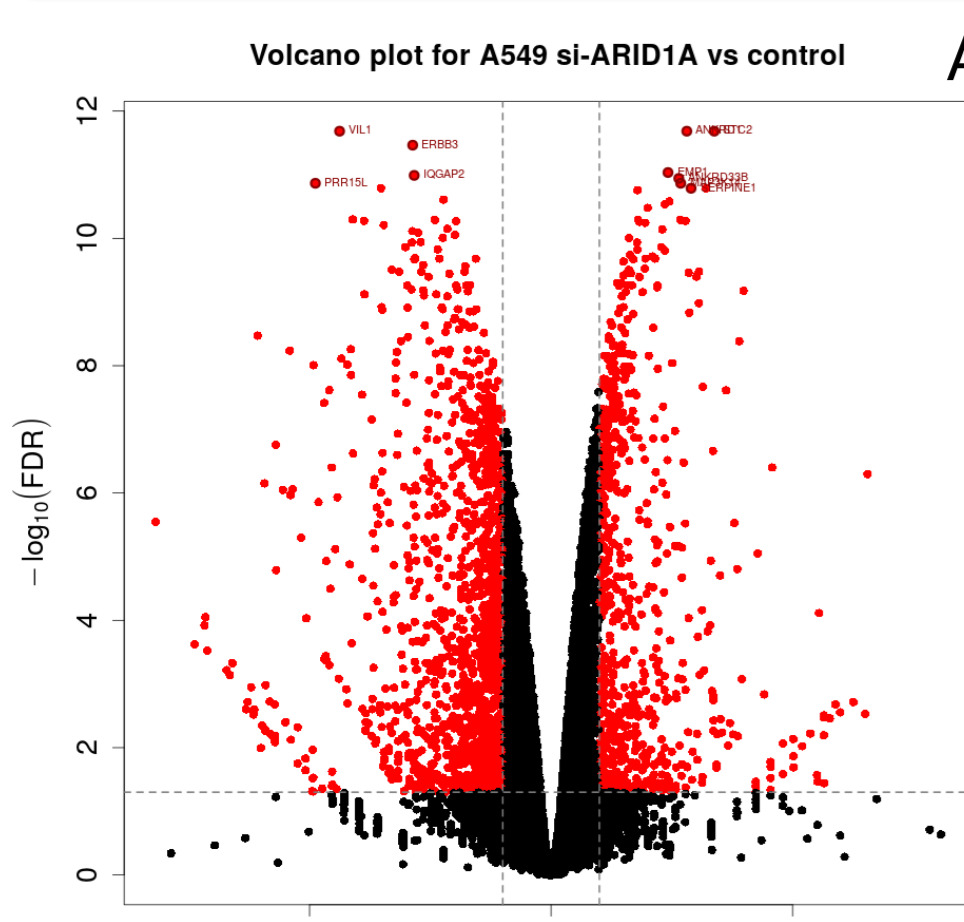


Figure 8: Colony formation assay in H1373 cell line with ARID1A-knockdown after 15 days of transfection.

Figure 10: Western Blot of H1373 after 2 of ARID1A knockdown.

GENETIC-DEPENDENCY: KRAS mutant context



A549, H2009 and H1373 are ARID1A wt and KRAS mutant cell lines. Do KRAS mutants have an ARID1A-dependency?

KRAS-mut → ARID1A inhibition → Cell death
KRAS-wt → ARID1A inhibition → Cell growth

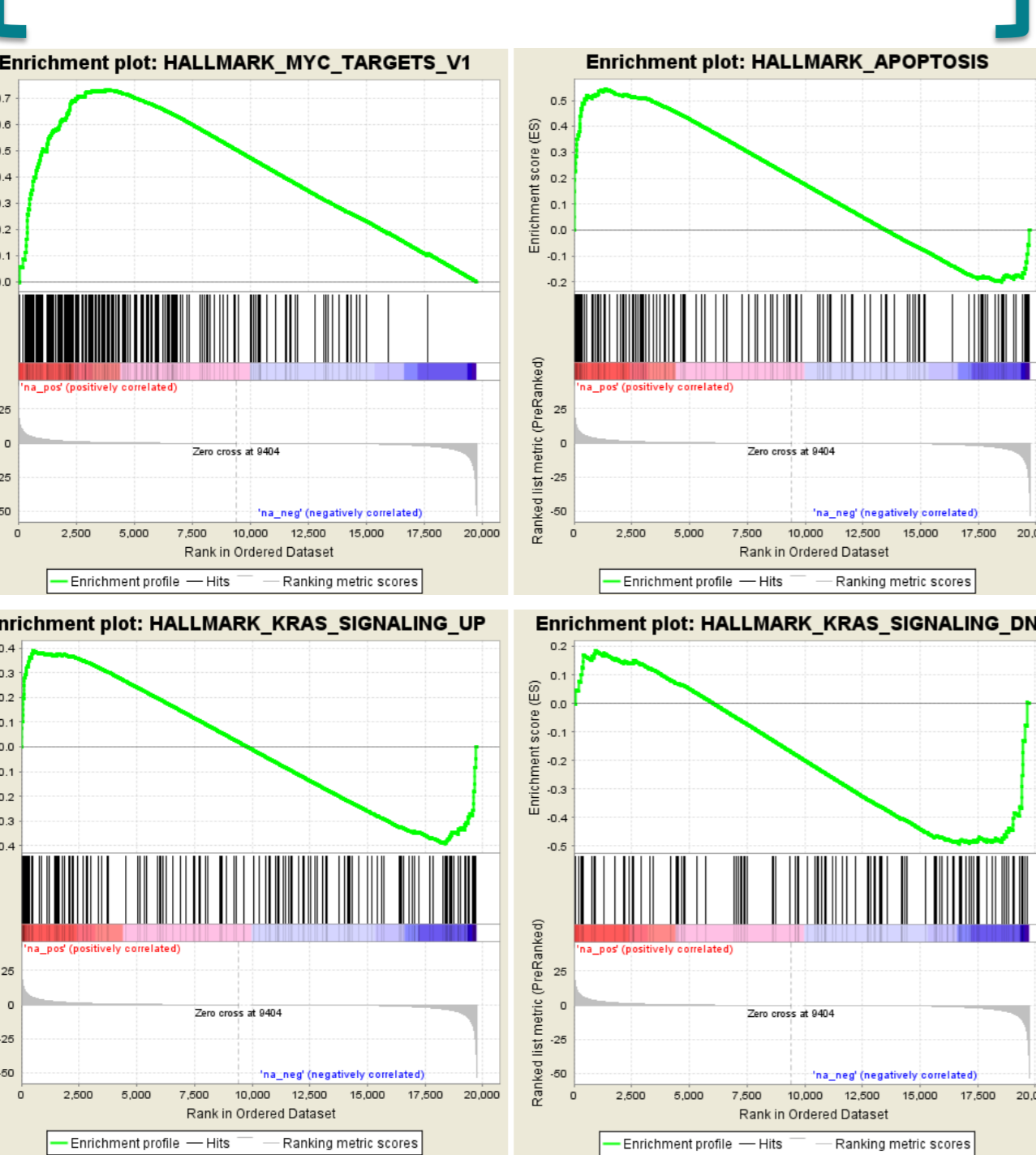


Figure 14: Volcano plot of RNA-seq data in A549 after 6 days of ARID1A knockdown.

Figure 15: Enriched pathways upon ARID1A knockdown in A549.

TIME-DEPENDENCY: Normal and tumor lung cell lines (Dual model)

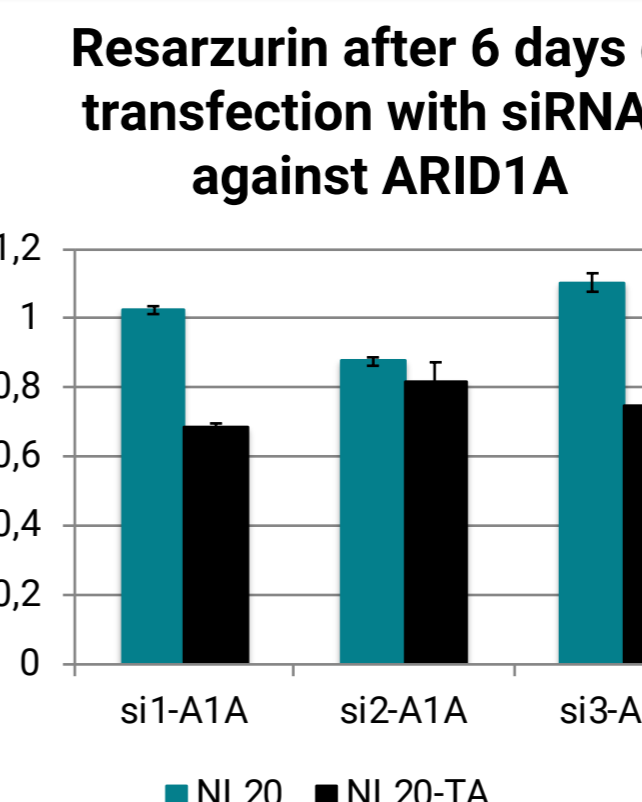
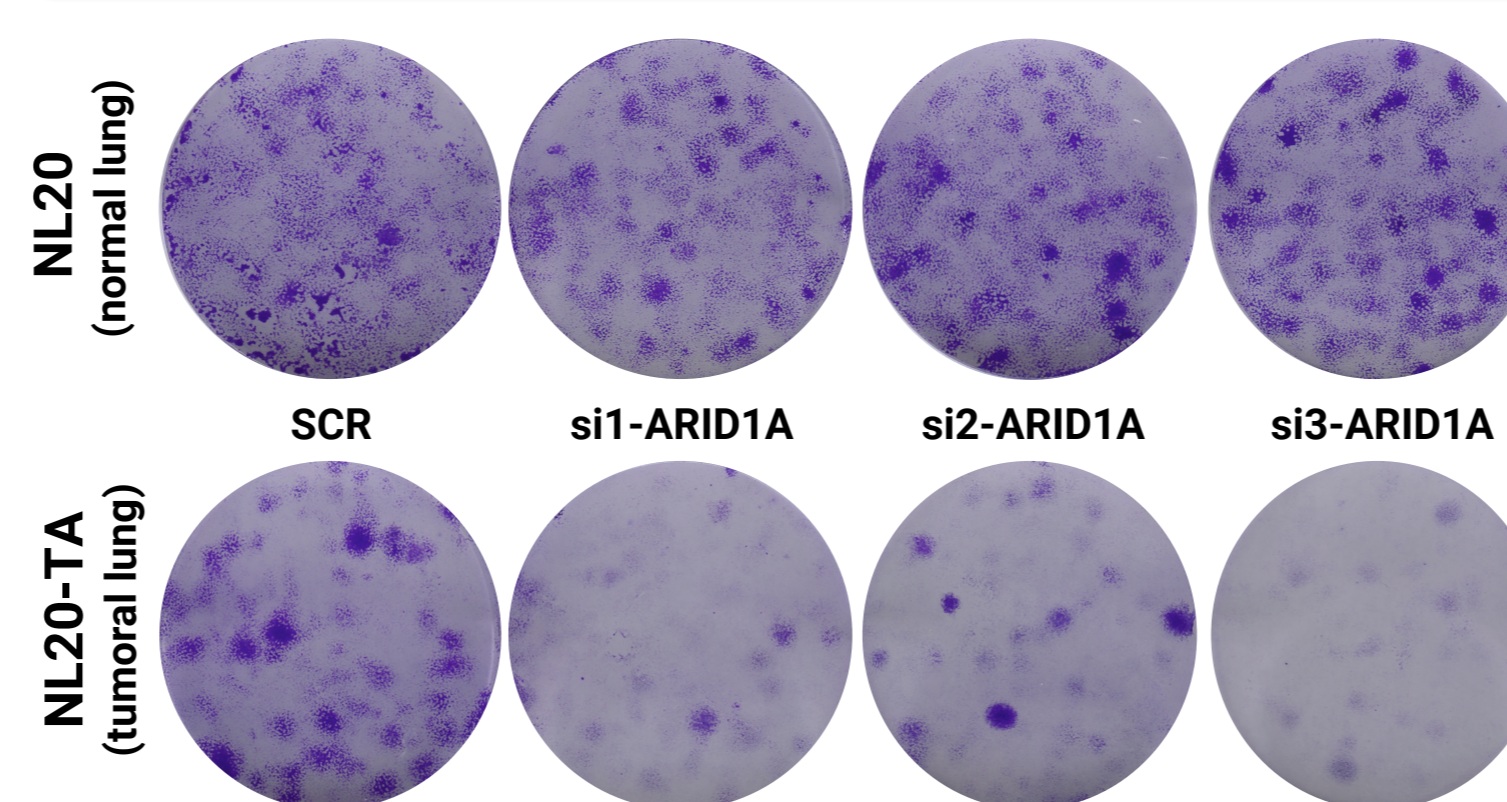


Figure 11: Colony formation assay in NL20 and NL20-TA cell lines with ARID1A-knockdown after 15 days of transfection.

Figure 12: Cell viability assay in NL20 and NL20TA after 6 days of ARID1A knockdown.

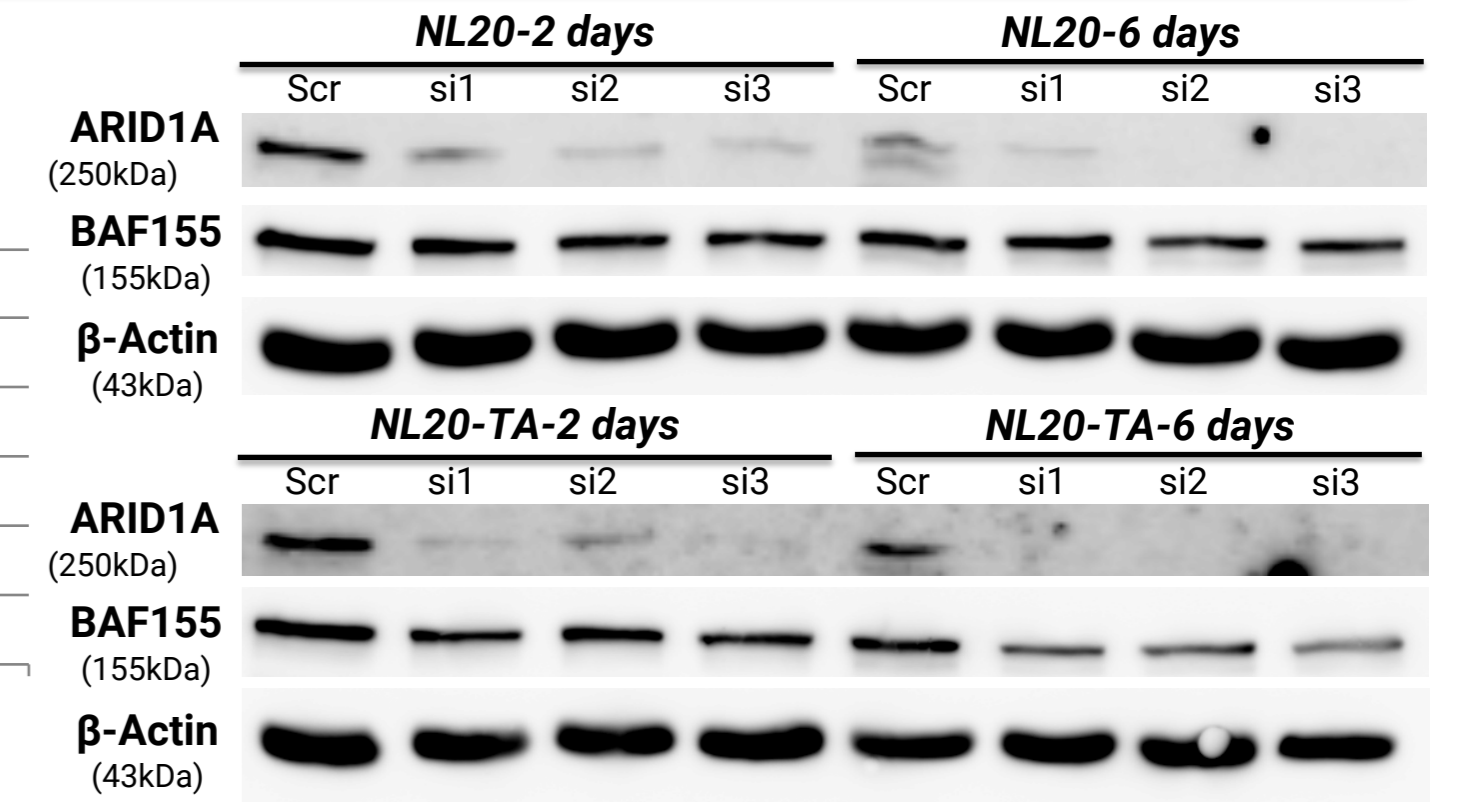


Figure 13: Western Blot of NL20 and NL20-TA after 2 and 6 days of ARID1A knockdown.

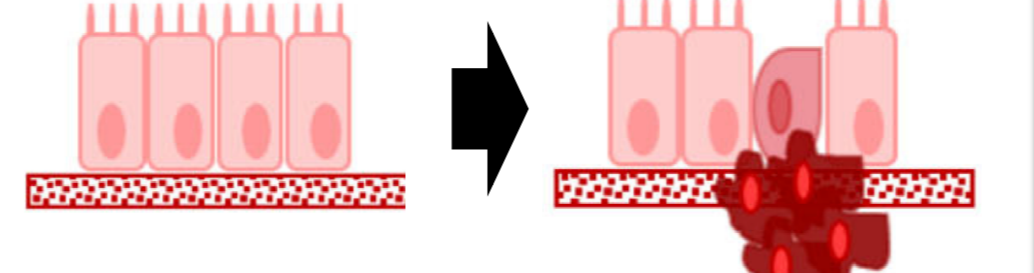
CONCLUSIONS AND CURRENT WORKING MODEL

ARID1A has a context-dependent role in lung adenocarcinoma.

ARID1A, the "good guy"

Normal lung tissue

ARID1A loss



ARID1A, the "bad guy"

Lung cancer cell

KRAS* ARID1A loss

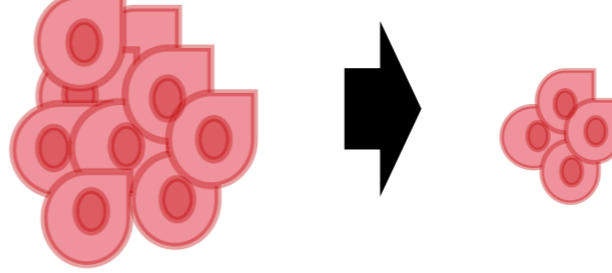


Figure 17: ARID1A context-dependent role as oncogene or tumor suppressor (Adapted from Sen et al.)¹⁰

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