PhD in Pharmacology and Toxicology - University of Padua

PhD in Therapeutical Approaches in Oncology - University of Strasbourg

Callerio Foundation Onlus - Trieste

INSERM U682 - Strasbourg

A novel mechanism of action of RDC11: targeting HIF-1 and mTOR pathways

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5eme Canceropole du Grand Est
Strasbourg, 3rd November 2011

METAL-BASED CHEMOTHERAPY → CISPLATIN

- Poor selectivity
- Severe side effects
- Drug-resistance phenomena

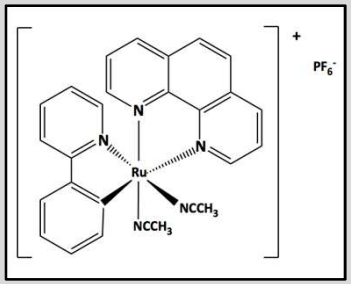
↓

New platinum-free metal-based drugs

RUTHENIUM DERIVATES → RUTHENIUM-DERIVED COMPOUNDS (RDCs)

Synthesized by Prof M. Pfeffer
Unit UMR 7177 (Strasbourg)

RDC11

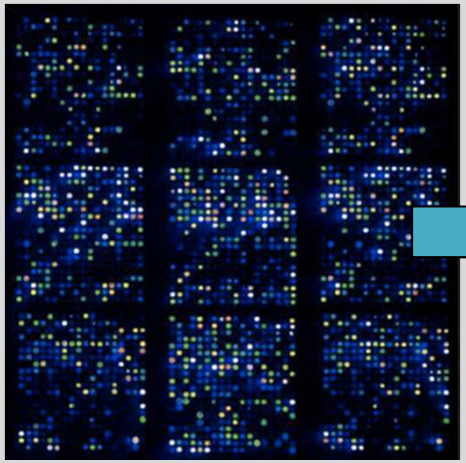


- Interesting anticancer properties *in vivo* and *in vitro*
- No strict correlation between DNA interaction and its activity

→ ALTERNATIVE MODES OF ACTION

INVESTIGATE THE MOLECULAR BASIS OF RDC11 EFFECTIVENESS IN TREATING CANCER

Search for RDC11 direct targets in order to improve its selectivity against cancer cells

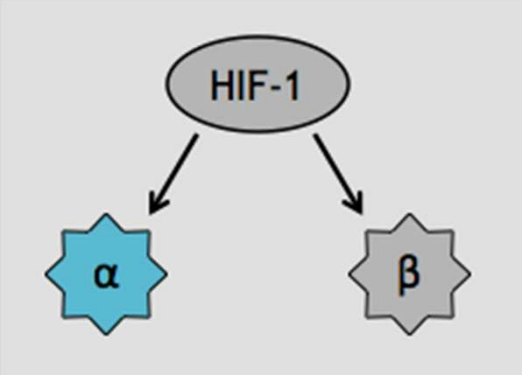


Affimetrix MICROARRAY

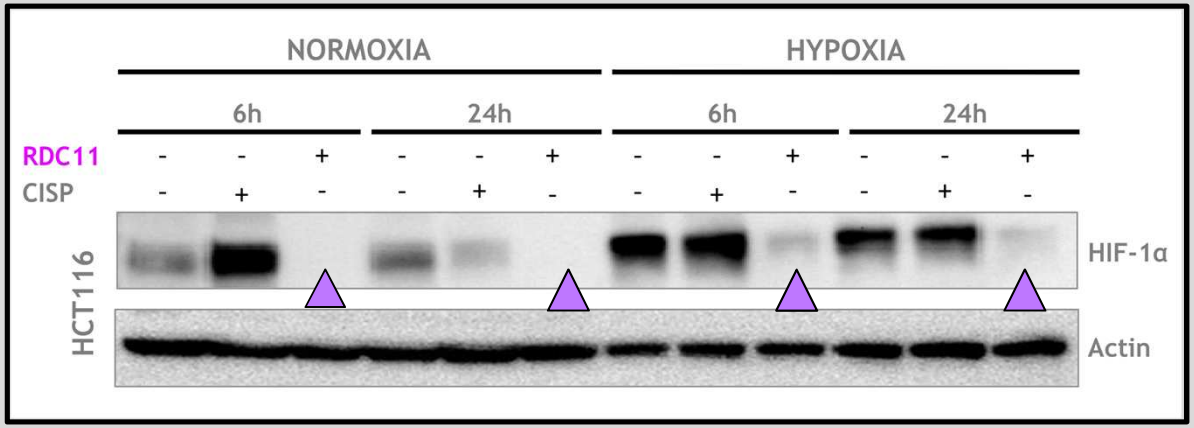
New RDC11-regulated genes

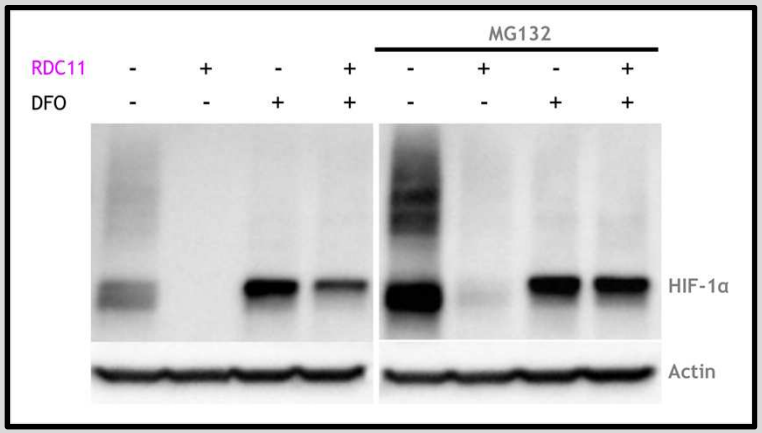
HIF-1 and mTOR pathways

Effect of RDC11 on HIF-1α protein and gene expression



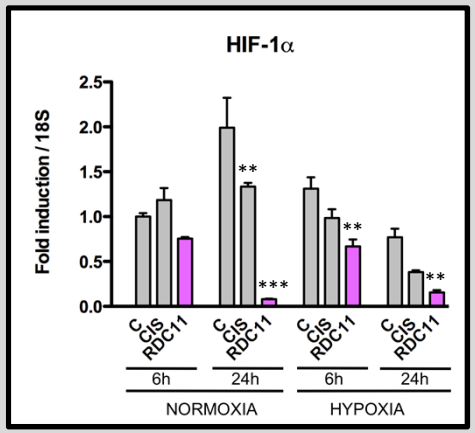
RDC11, cisplatin 5µM corresponding to IC_{50}





Partial reversion of HIF-1α

Proteasome in part involved in HIF-1α degradation

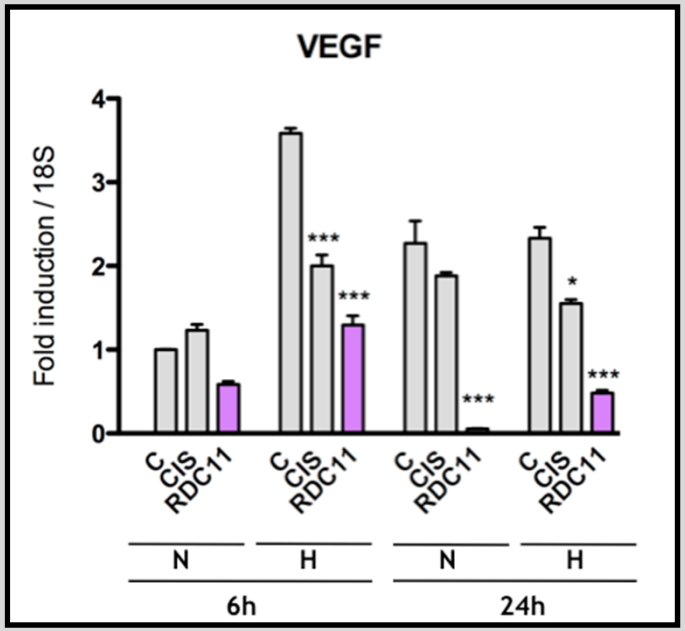


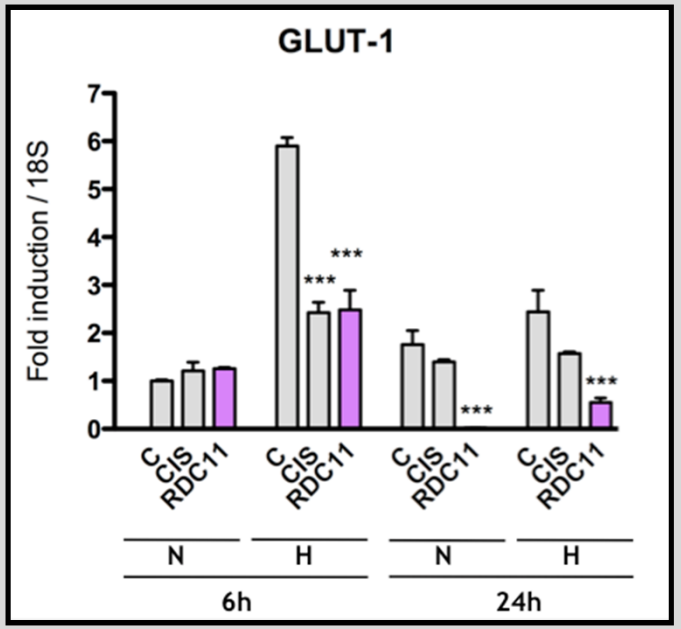
RDC11 decreases HIF-1α protein expression mainly by reducing HIF-1α mRNA level

HIF-1α

ANGIOGENESIS

GLUCOSE METABOLISM



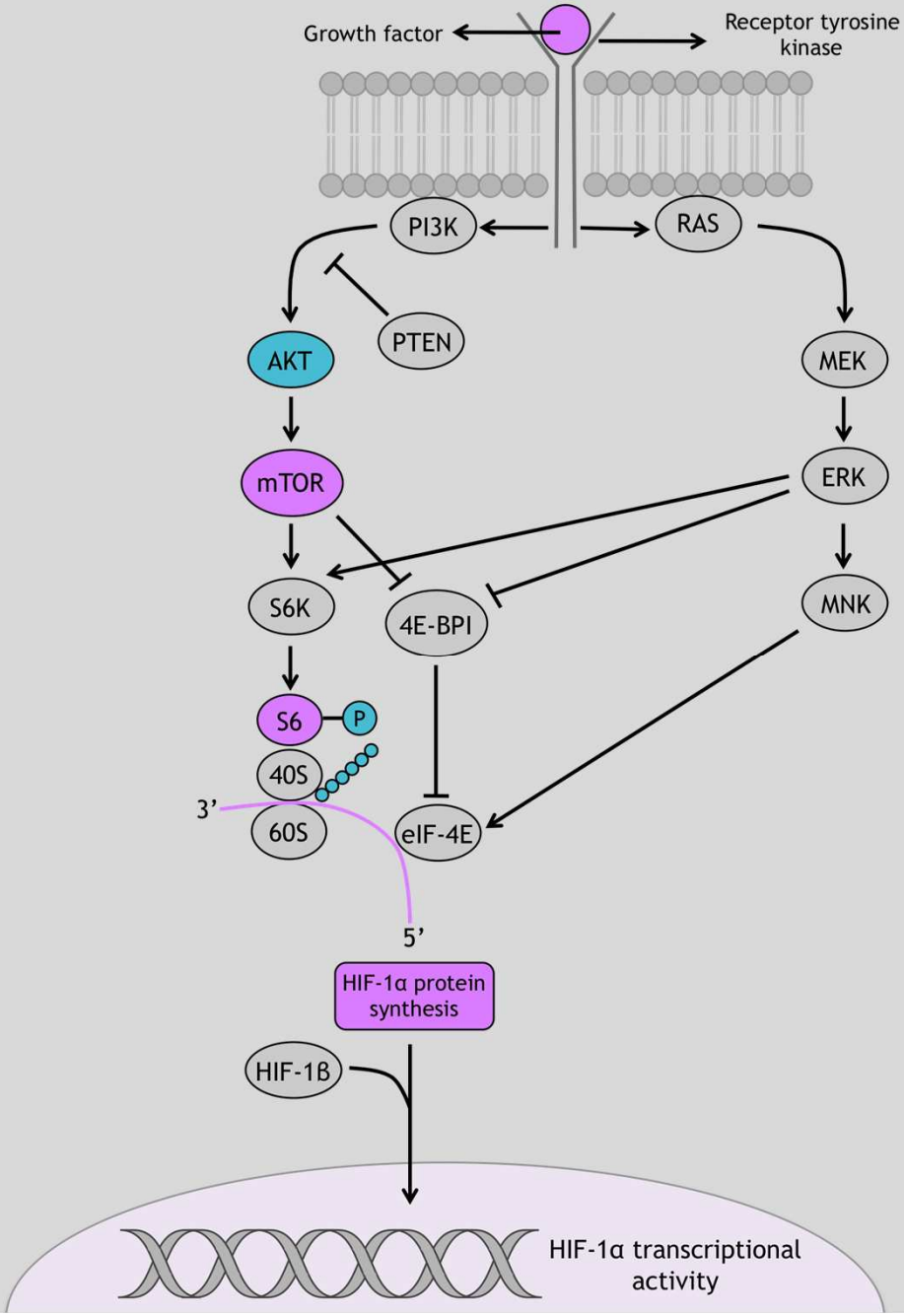


One-way ANOVA + Tukey-Kramer post-test vs corresponding control:
*** = p<0.001; ** = p<0.01

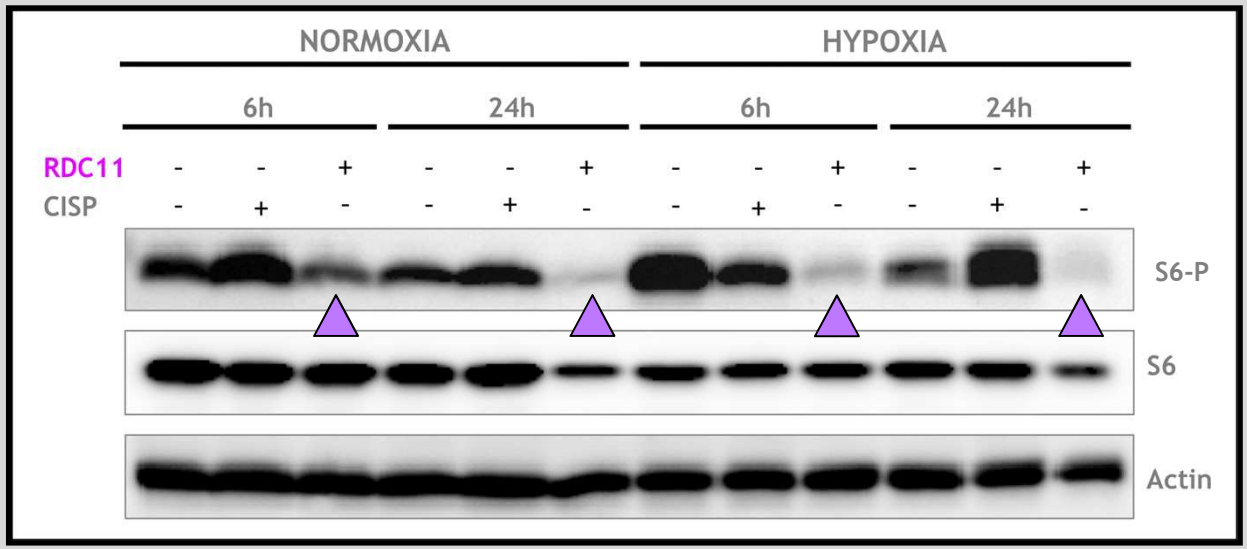
RDC11 reduces *VEGF* and *GLUT-1* mRNA levels

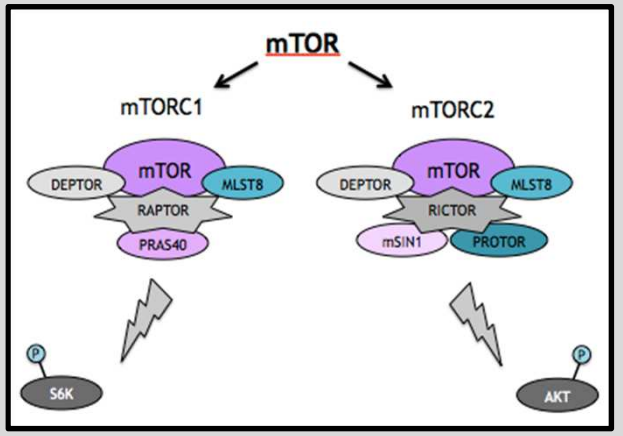
mTOR SIGNALING

RESULTS

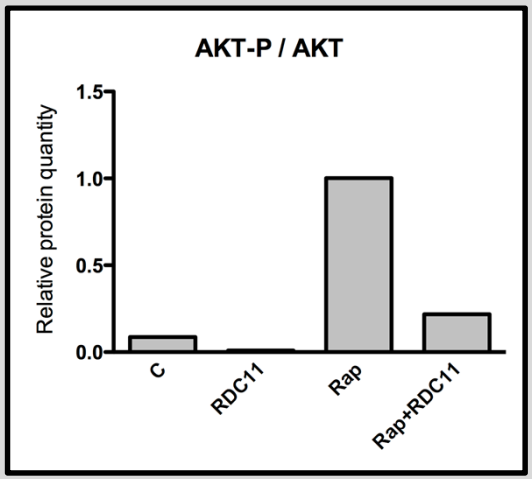


Phosphorylation of the ribosomal protein S6 by S6 kinase is a crucial step in HIF-1α protein synthesis



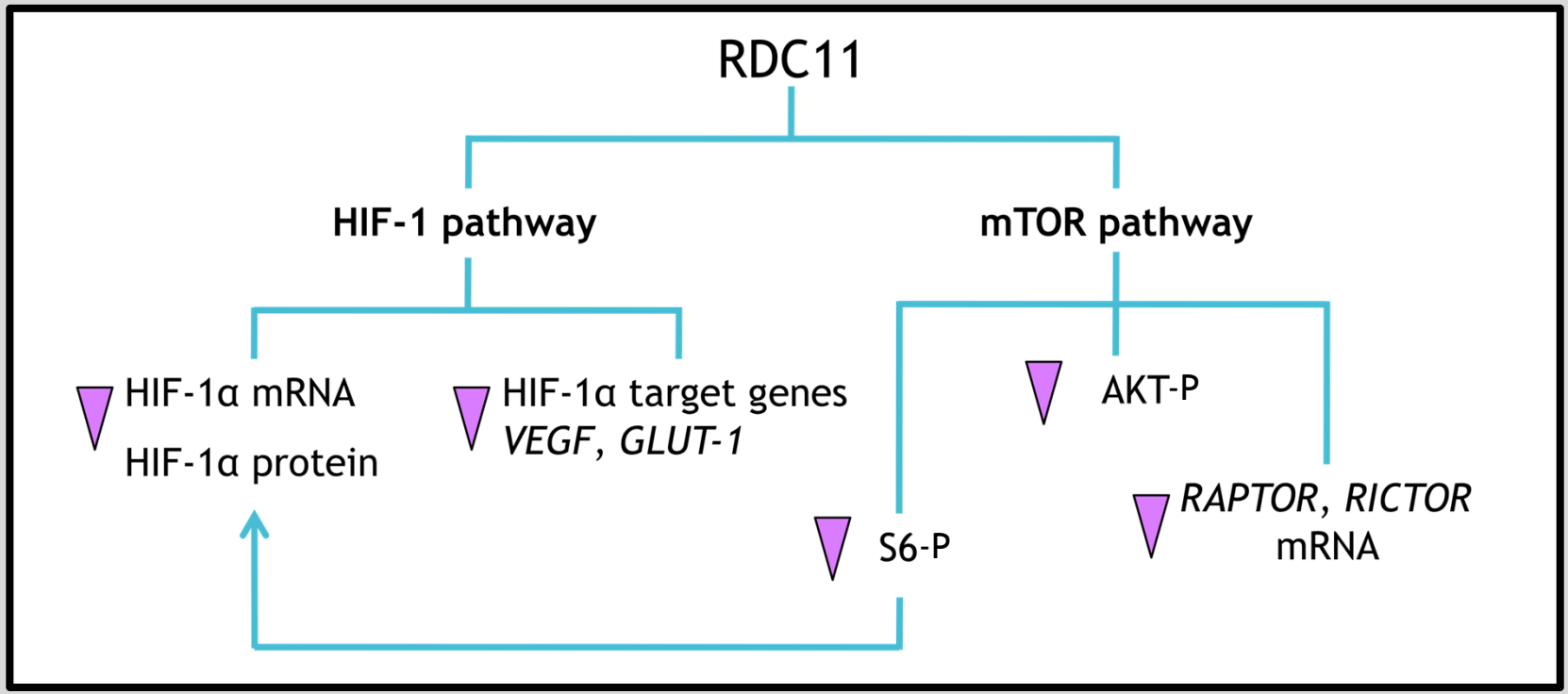


Akt activation by mTOR: most frequent alteration in human cancers



RDC11 reduces S6-P and Akt-P expression

RDC11 affects specific components of HIF-1 and mTOR pathways



UNIQUE CHARACTERISTIC FOR AN ORGANOMETALLIC COMPOUND

Targeted therapy

THE MAIN CHALLENGE OF CANCER CHEMOTHERAPY TODAY

ACKNOWLEDGEMENTS

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Thank you for your attention