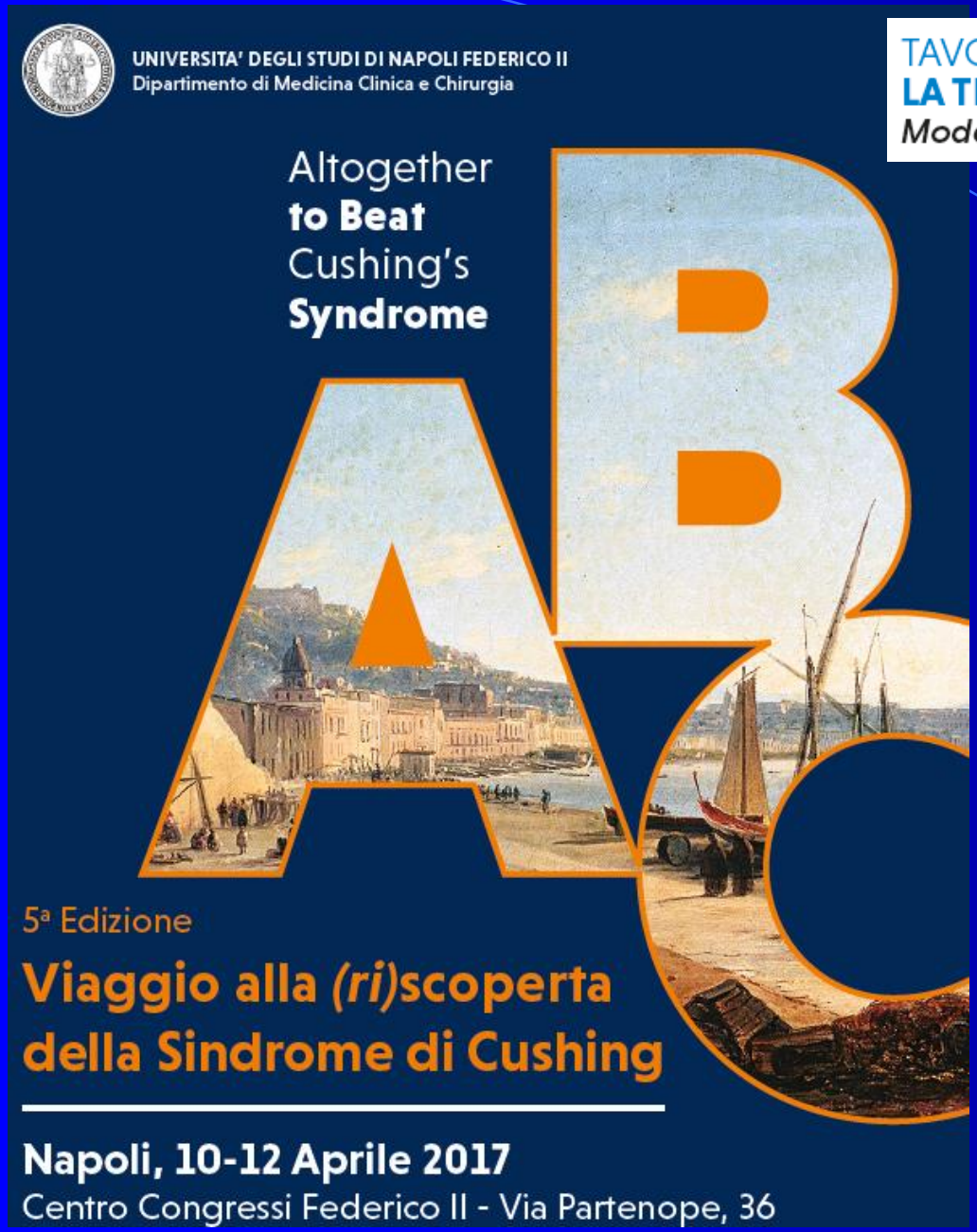


TAVOLA ROTONDA

LA TERAPIA MEDICA NELLA SINDROME DI CUSHING

Moderatori: Annamaria Colao, Marco Boscaro

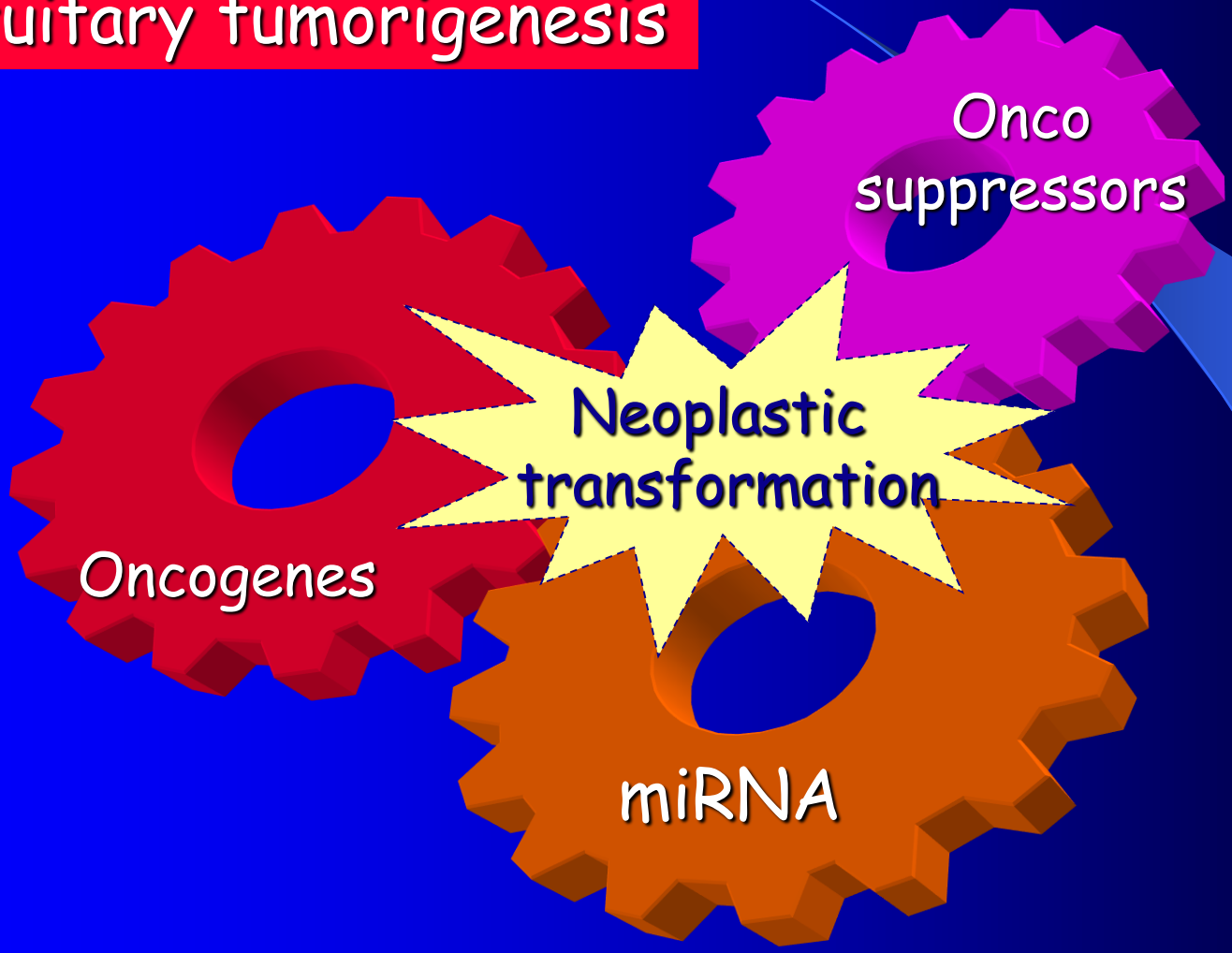
PROSPETTIVE FUTURE

Maria Chiara Zatelli

Section of Endocrinology
& Internal Medicine
Department of Medical Sciences
University of Ferrara

Future perspectives in medical therapy

pituitary tumorigenesis



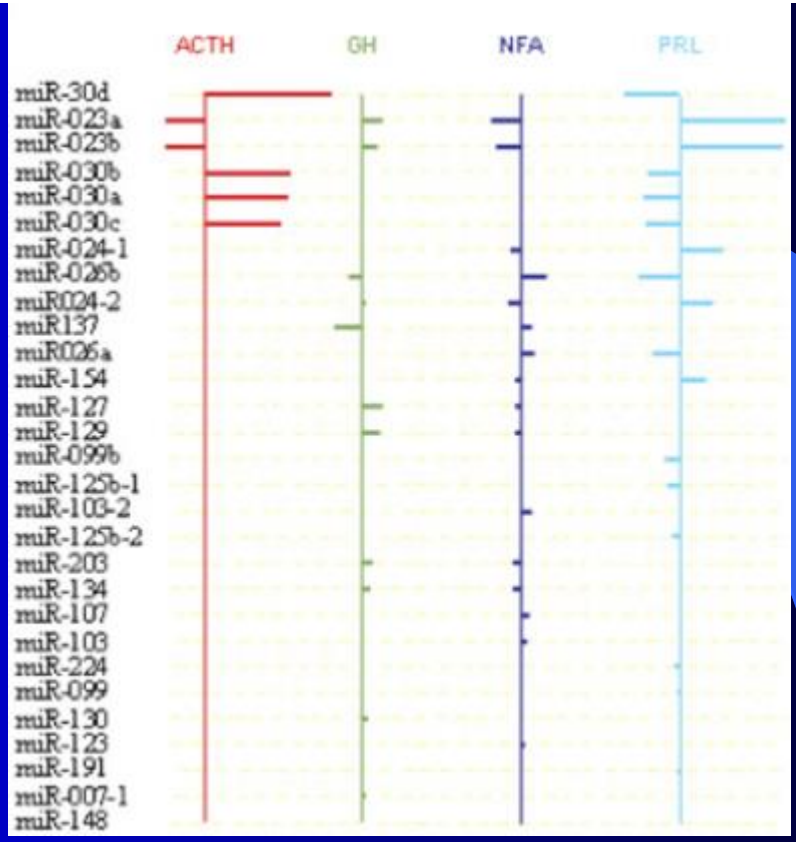
Future perspectives in medical therapy

J Cell Physiol. 2007 Feb;210(2):370-7.

Identification of differentially expressed microRNAs by microarray: a possible role for microRNA genes in pituitary adenomas.

Bottoni A[1], Zatelli MC, Ferracin M, Tagliati F, Piccin D, Vignali C, Calin GA, Negrini M, Croce CM, Degli Uberti EC.

Name	ACTH score	GH score	NFA score	PRL score
miR-030a	1.3854	0	0	−0.5646
miR-030c	1.3075	0	0	−0.5137
miR-030b	1.1469	0	0	−0.475
miR-023b	0	0.0164	−0.2938	0.9632
miR-030d	0.8822	0	0	−0.5742
miR-023a	0	0.0044	−0.3229	0.7999
miR-026b	0	−0.1057	0.3131	−0.4223
miR-137	0	−0.3224	0.1141	0
miR-024-1	0	0	−0.151	0.2571
miR-154	0	0	−0.093	0.2461
miR-129-1/2	0	0.239	−0.0361	0
miR-127	0	0.2353	−0.0766	0
miR-026a	0	0	0.1769	−0.202
miR-024-2	0	0	−0.1688	0.0936
miR-103-2	0	0	0.1617	0
miR-107	0	0	0.1358	0
miR-203	0	0.0865	−0.1239	0
miR-134	0	0.0486	−0.1207	0
miR-099b	0	0	0.0349	−0.1109
miR-103-1	0	0	0.1049	0
miR-125b-1	0	0	0	−0.1026
miR-200a	0.0947	0	0	0
miR-224	0	0	0	−0.0684
miR-007-1	0	0.0675	0	0
miR-125b-2	0	0	0	−0.0546
miR-123	0	0	0.0444	0
miR-148	0	0	−0.0374	0
miR-130a	0	0.0316	0	0
miR-213	−0.0163	0	0	0



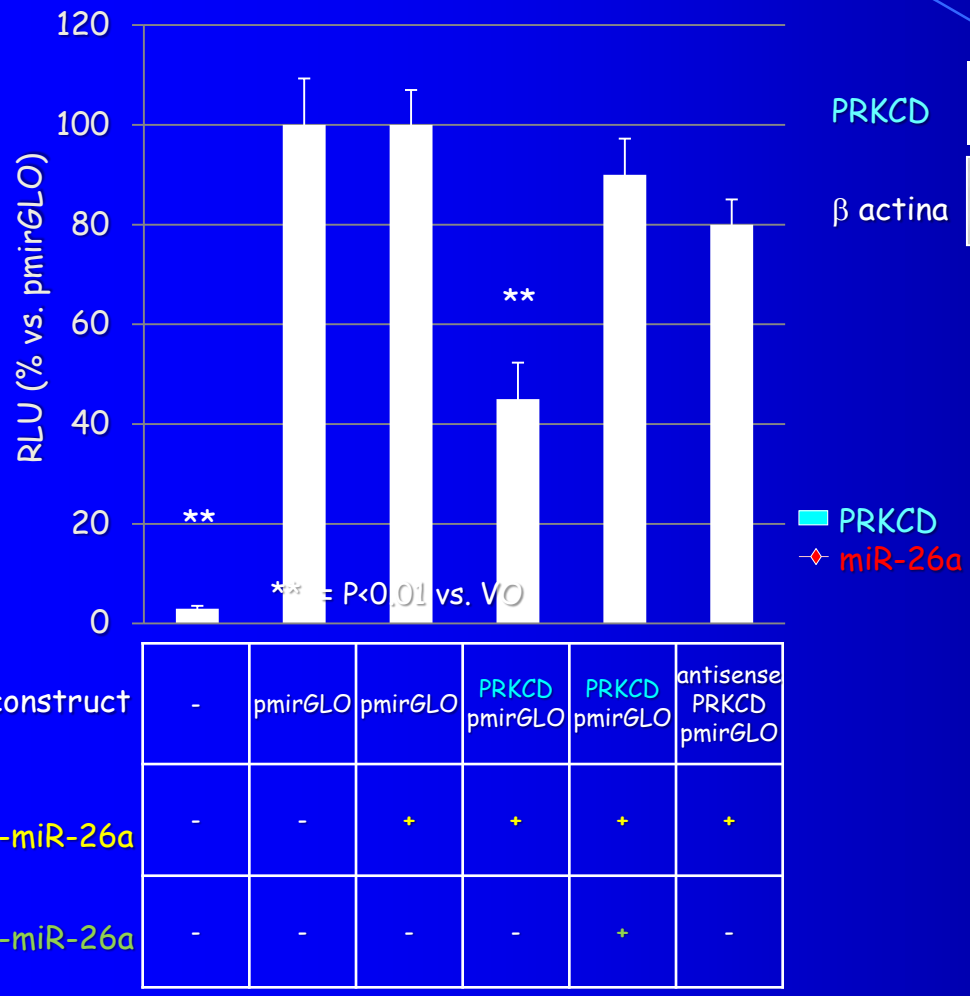
miRNAs predictive of pituitary adenoma subtype

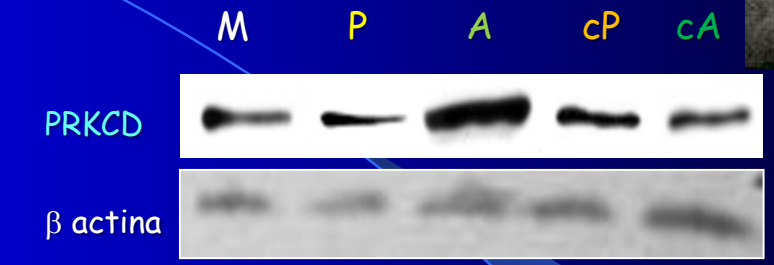
Future perspectives in medical therapy

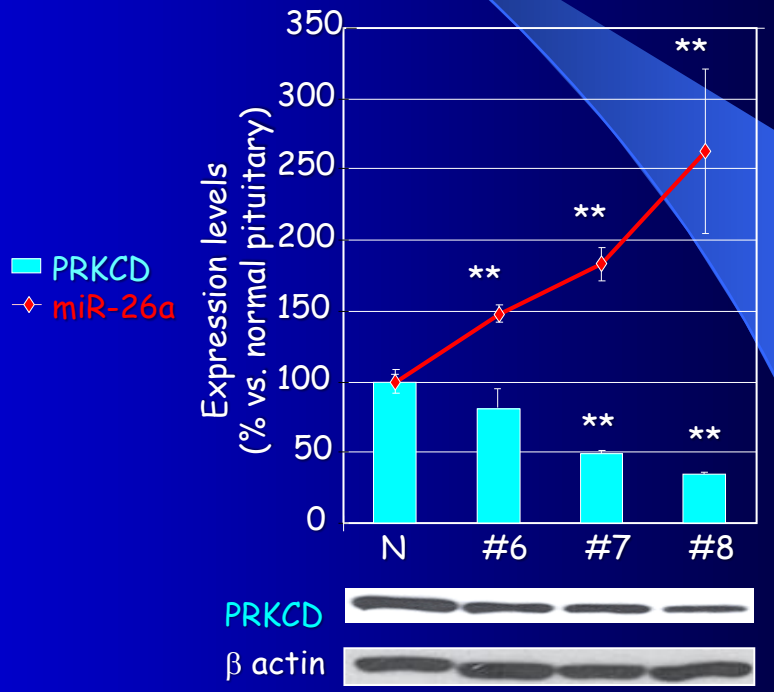
Study	Tumor	Aberrant microRNA expression	Affected gene or clinical correlation
Bottoni et al. 2005	10 GH; 10 PRL	miR-15a and miR-16-1 ↓ in adenomas vs. NP	Inverse correlation with tumor size
Bottoni et al. 2007	17 NFA; 5 PRL; 4 ACTH; 6 GH	30 miRNAs differently expressed between adenomas and NP. 29 miRNAs predict tumor type	6 miRNAs correlated with tumor size in NFA. 3 miRNAs up- and 3 down-regulated in NFA treated with dopamine agonist in comparison with non-treated ones
Qian et al. 2009	98 adenomas	Let-7 ↑ in tumors with low HMGA2 expression	HMGA2
Amaral et al. 2009	14 ACTH	↓ of miR-145, miR-21, miR-141, miR-150, miR-15a, miR-16, miR-143 and let-7a in adenomas vs. NP	miR-141 levels directly correlated with chance of disease recurrence
Stilling et al. 2010	8 ACTH; 2 ACTH carc	188 miRNAs ↑ and 160 miRNAs ↓ in ACTH vs. NP; 98 miRNAs differently expressed in ad vs. carc	
Butz et al. 2010	27 NFA; 15 GH	miR-20a, -128a ↑ in NFA. miR-93 and -55 ↑ in GH and NFA	WEE1
Mao et al. 2010	21 GH	23 miRNAs ↑ and 29 miRNAs ↓ in GH vs. NP	9 miRNAs differently expressed in micro vs. macro; 13 differently expressed in lanreotide treated vs. surgery alone 7 differently expressed in lanreotide r vs. nr
Butz et al. 2011	8 NFA	70 miRNAs ↑ and 92 miRNAs ↓ in NFA vs. NP	18 miRNAs inversely correlated with tumor size
Palmieri et al. 2011	14 PRL; 9 GH; 18 NFA	miR-15, -16, -26a, -196ab and Let-7a ↓ in adenomas vs. NP	HMGA1 and HMGA2
D'Angelo et al. 2012	18 GH	miR34b, -326, -374b, -432, -548c-3p, -570, -603 and-633 ↓, and miR-320 ↑ in GH vs. NP	HMGA1, HMGA2 and E2F1
Palumbo et al. 2012	12 GH	5 miR… …H vs. NP	PTEN and BMI1
Trivellin et al. 2012	10 GH; 7 NFA		AIP
Liang et al. 2013	10 NFA; 10 LH/FSH	25 miR… …FA vs. NP; 16 miRNAs ↑ and 13 miRNAs ↓ in LH/FSH vs. NP	
Gentilin et al. 2013	3 ACTH	miR-26a ↑ vs. NP	PRKCD
Leone et al. 2014	15 GH; 21 NFA	miR-23b and miR-130b ↓ in adenomas vs. NP	HMGA2; CCNA2

miR-26a

Future perspectives in medical therapy







PRKCD is a target of miR-26a

Gentilin, Zatelli et al. Endocrinology 2013

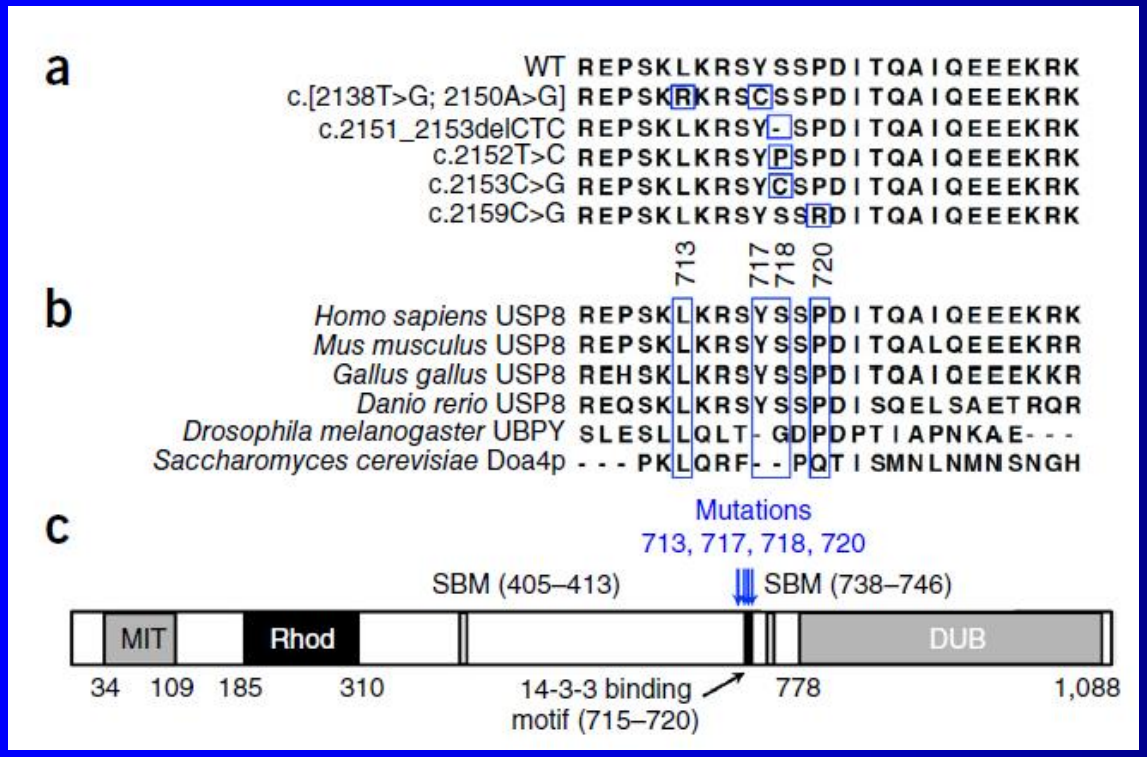
EFE 2017

Future perspectives in medical therapy

Mutations in the deubiquitinase gene *USP8* cause Cushing's disease

Martin Reincke[1,13], Silviu Sbiera[1,2,13], Akira Hayakawa[3,13], Marily Theodoropoulou[4,13], Andrea Osswald[1], Felix Beuschlein[1], Thomas Meitinger[5–7], Emi Mizuno-Yamasaki[3], Kohei Kawaguchi[3], Yasushi Saeki[8], Keiji Tanaka[8], Thomas Wieland[5], Elisabeth Graf[5], Wolfgang Saeger[9], Cristina L Ronchi[10], Bruno Allolio[2,11], Michael Buchfelder[12,13], Tim M Strom[5,6,13], Martin Fassnacht[1,2,10,13] & Masayuki Komada[3,13]

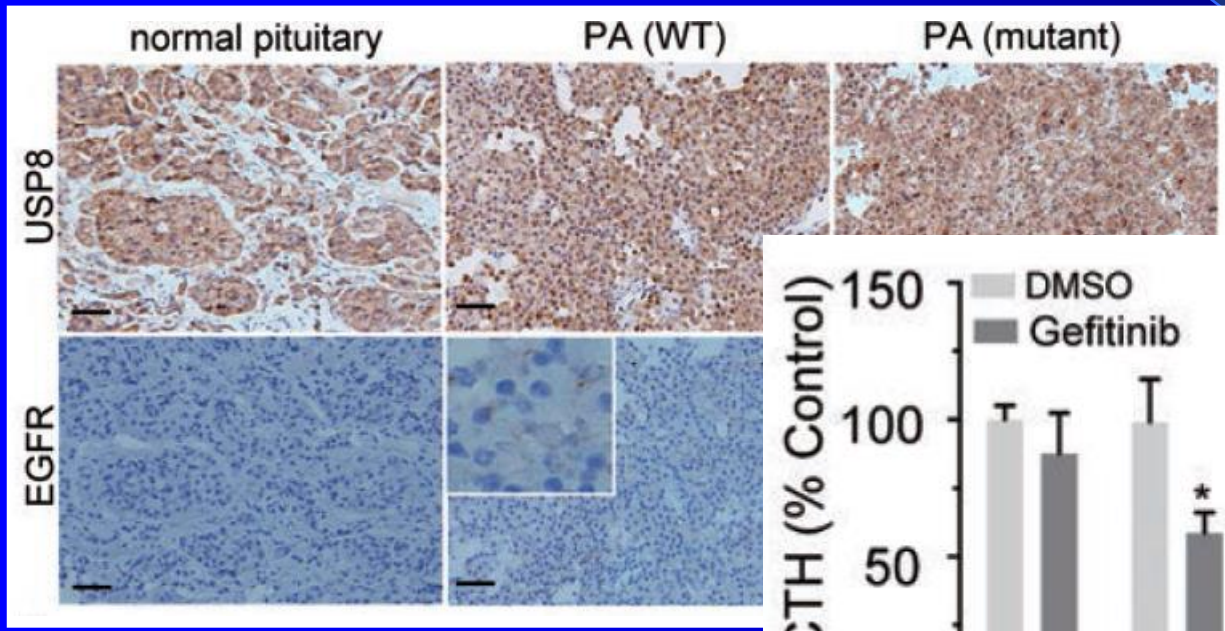
nature genetics

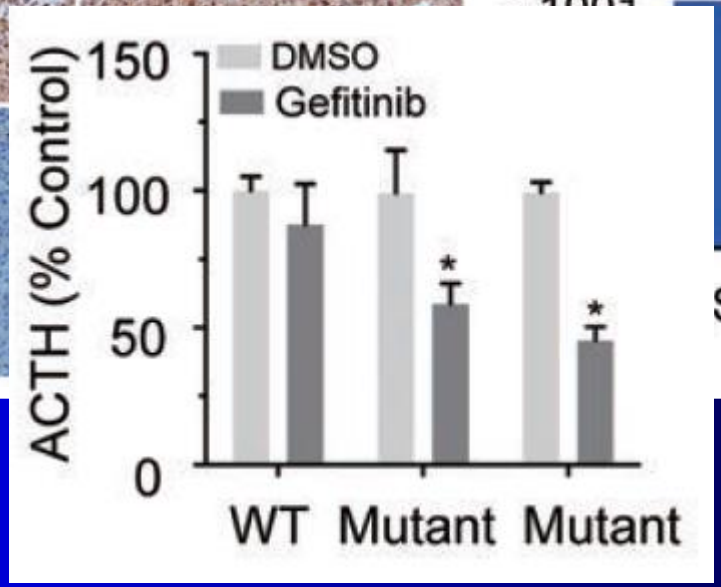


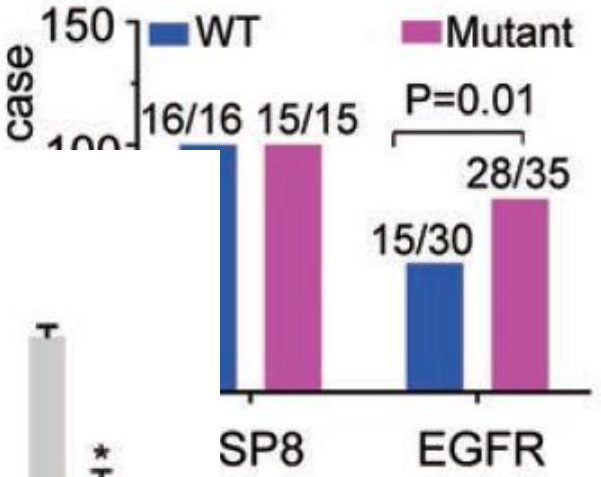
USP8 mutations in 4 out of 10 ACTH secreting pituitary tumors analysed (exome sequencing)

Future perspectives in medical therapy

USP8 mutations in 75/120 ACTH-omas (none in other 150 pituitary tumors)







Ma et al. Cell Research (2015) 25:306-317

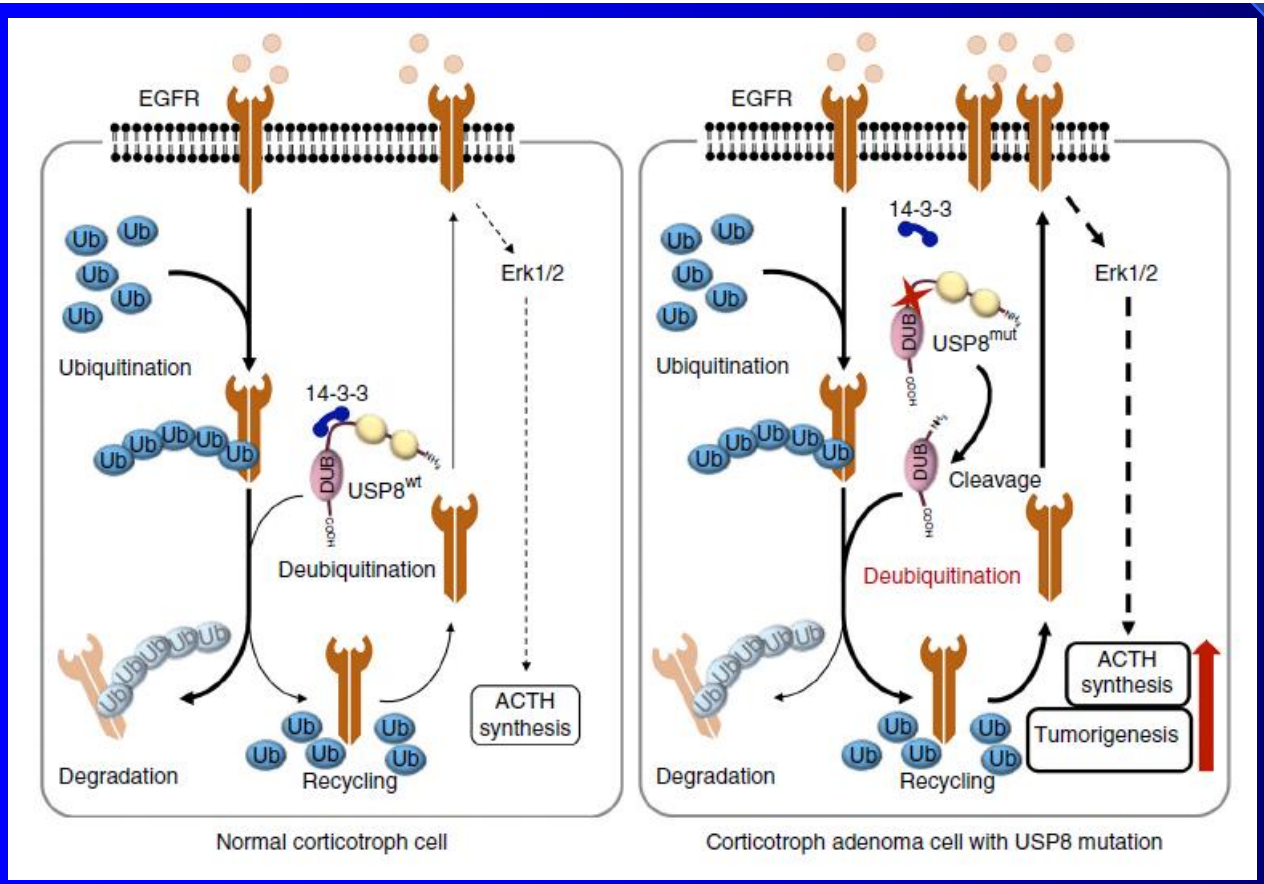
USP8 gene mutations in 33-66 % of patients with CD

Hayashi K, et al. Eur J Endocrinol. 2016;174(2): 213–26

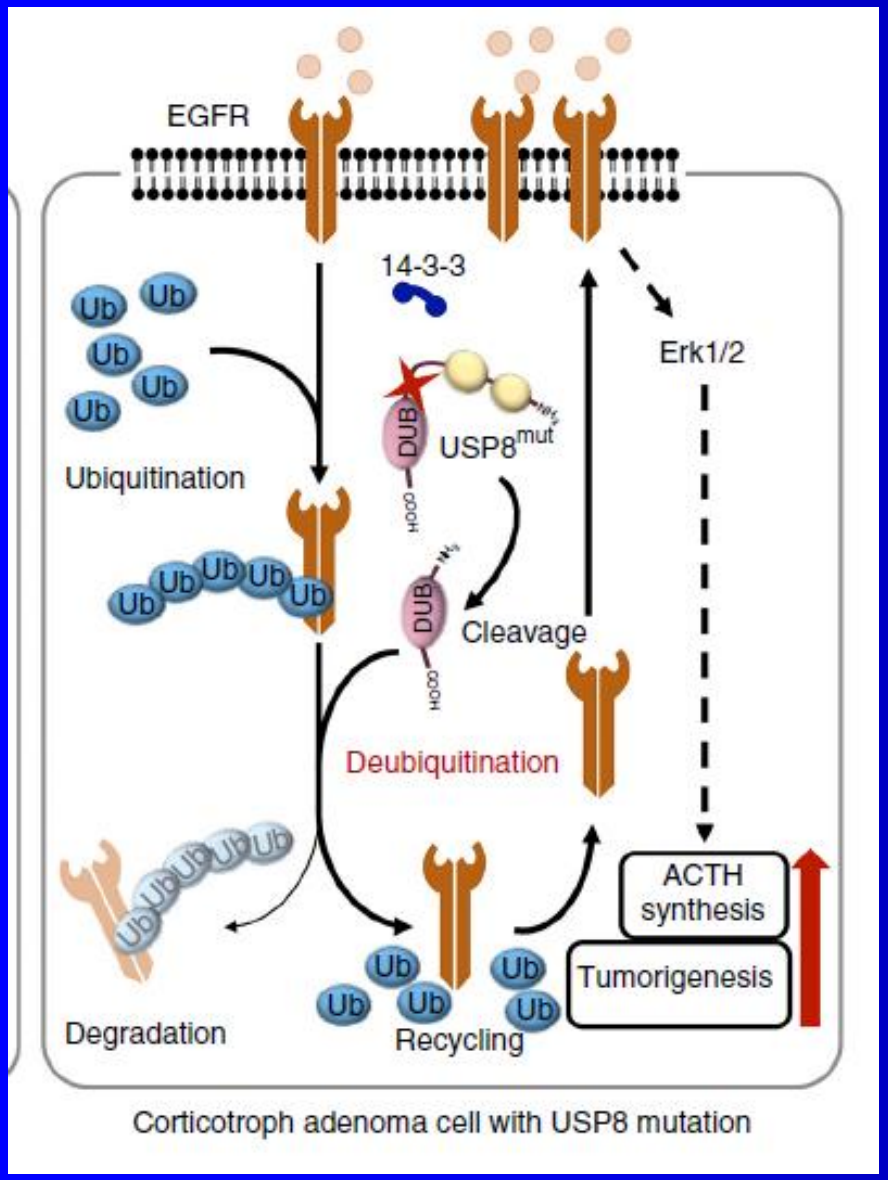
Future perspectives in medical therapy

Mutations in the deubiquitinase gene *USP8* cause Cushing's disease

nature genetics



Future perspectives in medical therapy



Corticotroph adenoma cell with USP8 mutation

USP8 mutations at the catalytic domain

↓

EGFR deubiquitination

↓

↓EGFR degradation
↑ EGFR activity

→ ↑ACTH secretion

↓

↑ SSTR5 expression

↓

↑ sensitivity to pasireotide

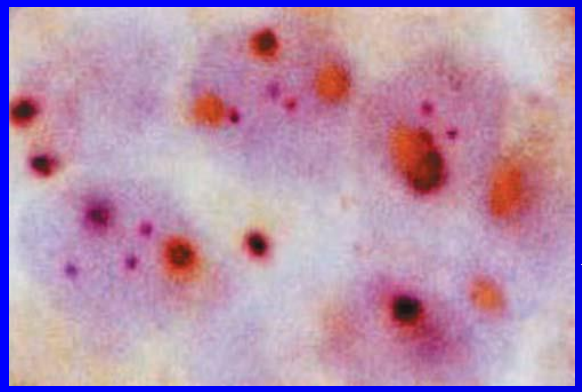
Future perspectives in medical therapy

Epidermal Growth Factor

Expressed both in normal pituitary and in pituitary adenomas

Ezzat et al. Clin Endocrinol 1997;46:599

Lack of gene amplification or activating mutations

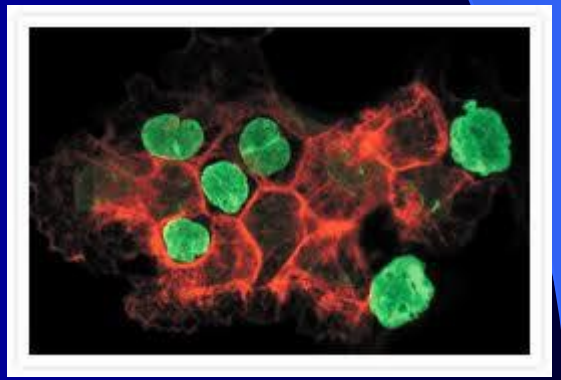


Roncaroli et al. J Neurosurg 2003;99:402

Low-level amplification in pituitary carcinomas and related metastases

EGF-R cytoplasmic staining in 40% of invasive adenomas vs. 1.2% non invasive adenomas

Nose-Alberti et al. Endocr Pathol 1998;9:53



↑ EGFR expression in ACTH secreting pituitary adenomas

Future perspectives in medical therapy

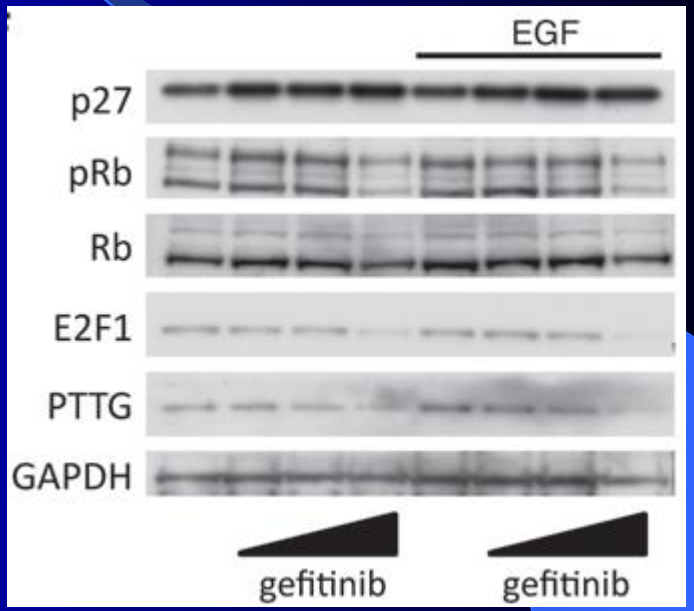
Epidermal Growth Factor

↑ EGFR expression in ACTH secreting pituitary adenomas

gefitinib

↓ p27kip1

↑ cell growth

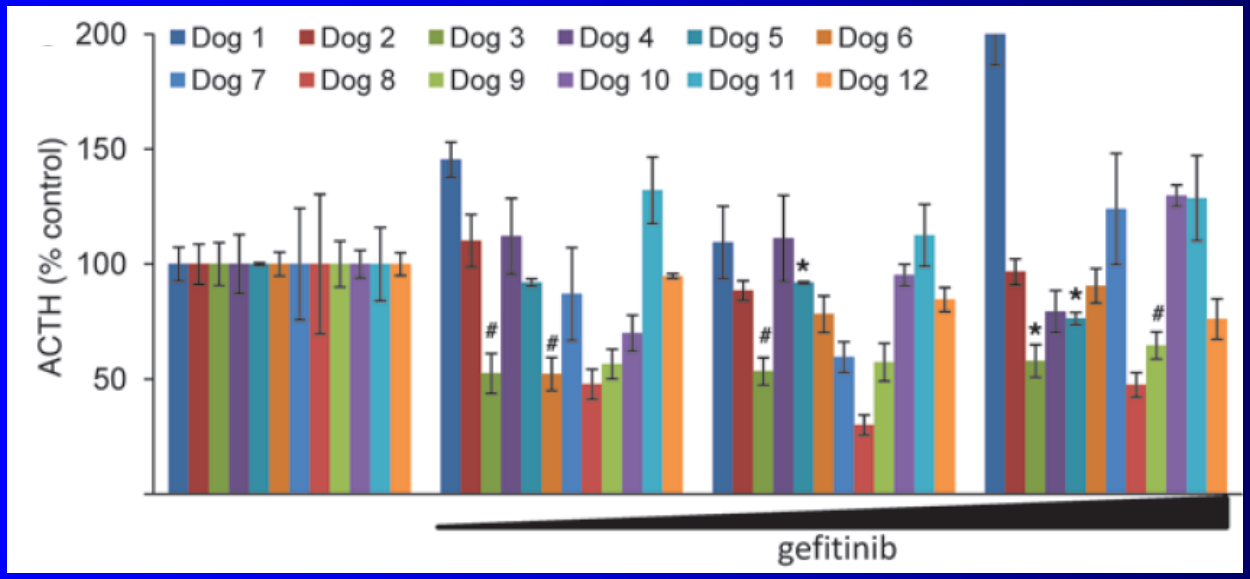


Fukuoka et al., J Clin Invest. 2011;121(12):4712–4721

Future perspectives in medical therapy

Gefitinib

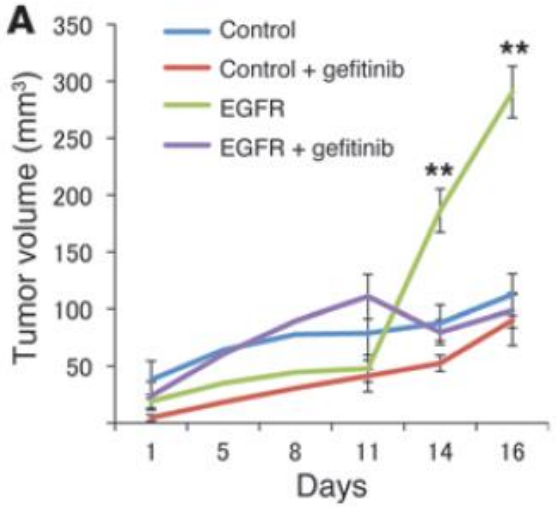
EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas

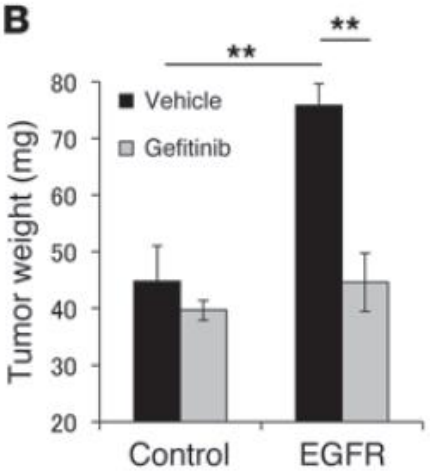


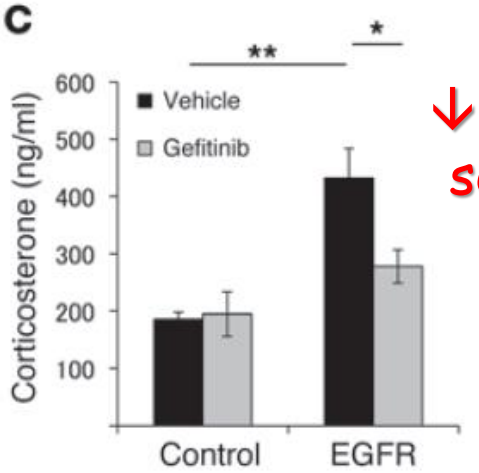
Fukuoka et al., J Clin Invest. 2011;121(12):4712–4721

Future perspectives in medical therapy

Gefitinib

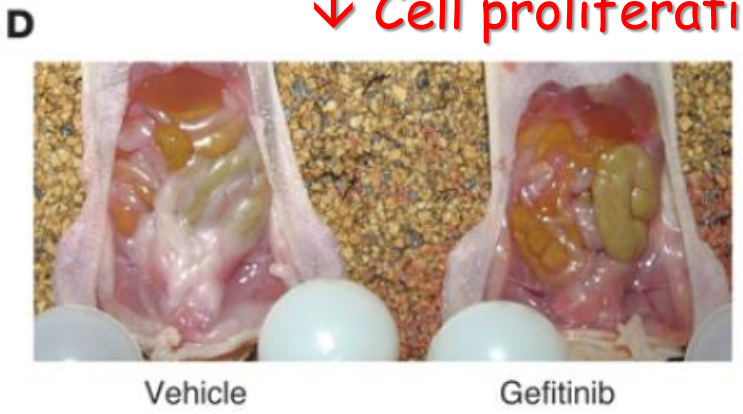


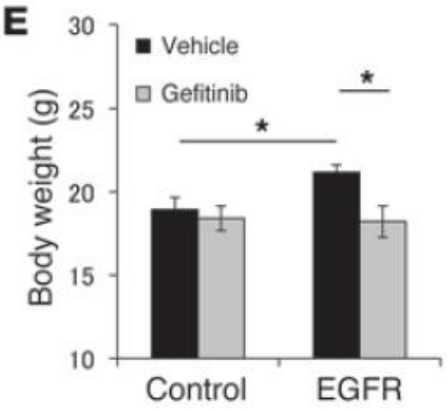


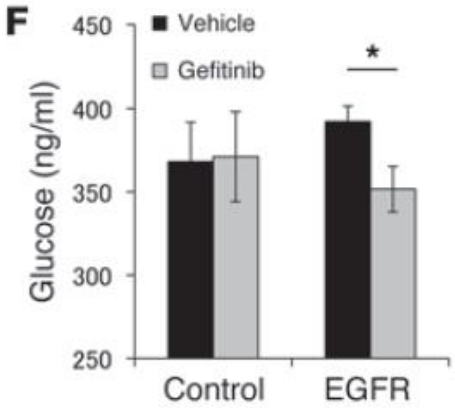


↓ hormone secretion

↓ Cell proliferation







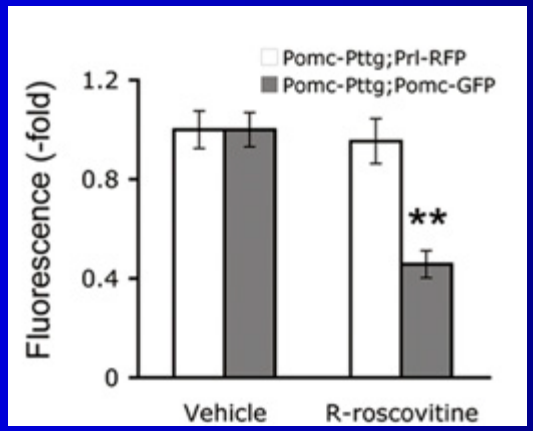
Fukuoka et al., J Clin Invest. 2011;121(12):4712–4721

Future perspectives in medical therapy

Roscovitine cyclin-dependent kinase (CDK2/cyclinE) inhibitor

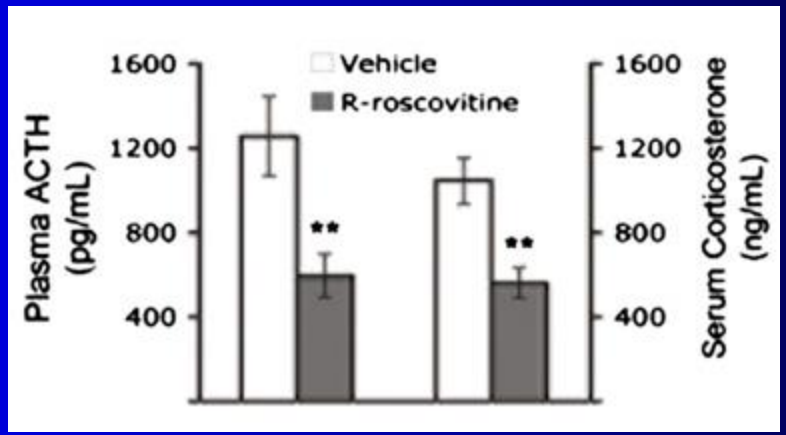
↓ tumor growth

zebrafish xenograft embryos



↓ ACTH
↓ corticosterone

mouse model of ACTH-secreting pituitary tumor



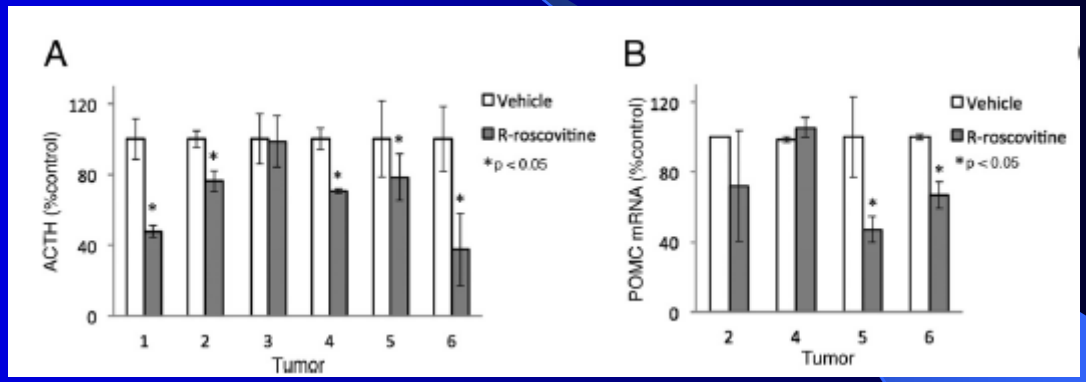
Liu et al. Proc Natl Acad Sci U S A. 2011

Future perspectives in medical therapy

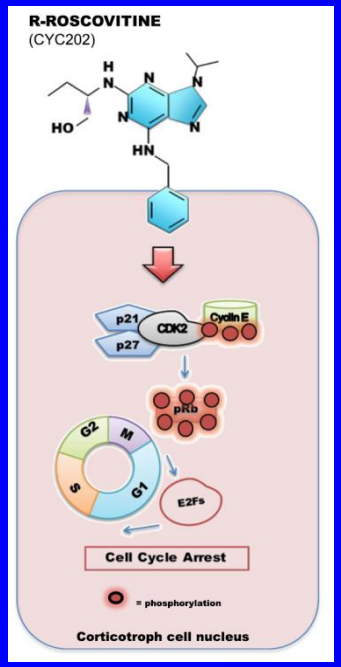
Roscovitine

↓ ACTH
↓ POMC expression

human ACTH-secreting pituitary tumor



Liu et al. J Clin Endocrinol Metab. 2015 Jul;100(7):2557-64.



Phase I and II clinical trials for NSCLC
Concerns on safety profile

Benson et al. J Cancer. 2007;96(1):29-37
Le Tourneau et al. Eur J Cancer. 2010;46(18):3243-3250

Phase II study ongoing for CD patients

Treatment of Cushing's Disease With R-roscovitine. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT02160730

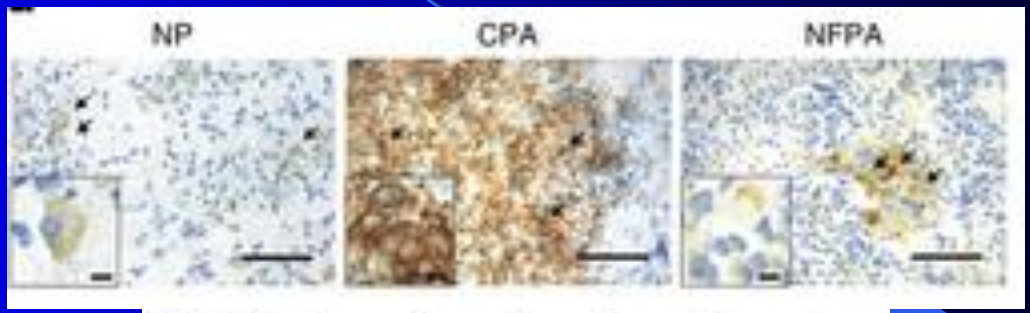
Future perspectives in medical therapy

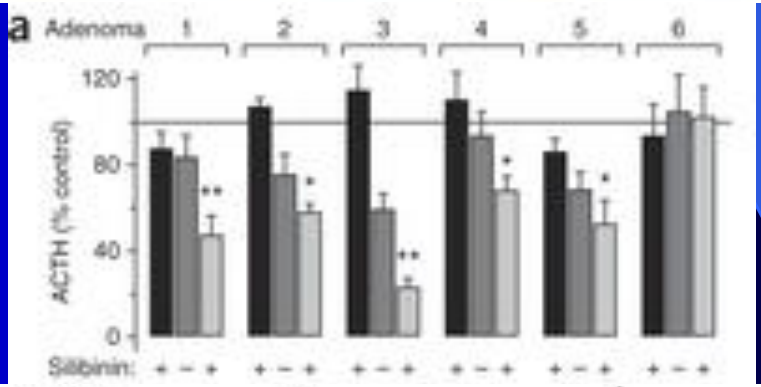
Silibinin HSP90 inhibitor

↓ AtT-20 cell proliferation

↑GR activity
↑ glucocorticoid sensitivity

↓ ACTH production





Riebold et al. 2015 Mar;21(3):276-80.

Future perspectives in medical therapy

ACTH antagonists

melanocortin-2 receptor (MC2R) agonists

↓ ACTH production

HEK 293 cells co-expressing MC2R and MRAP

↓ corticosterone production

rodents

High selectivity
over other MCR (types 1, 4, and 5)
to avoid dysregulations of
energy homeostasis,
pigmentation, lipid metabolism, and
sexual behavior

Halem et al. Endocrine Society, Boston: 2016. OR29-26.

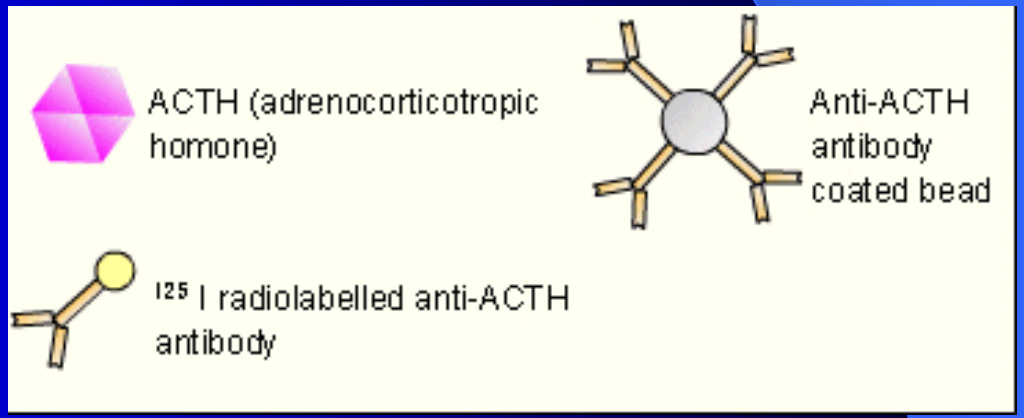
Future perspectives in medical therapy

ACTH antibody

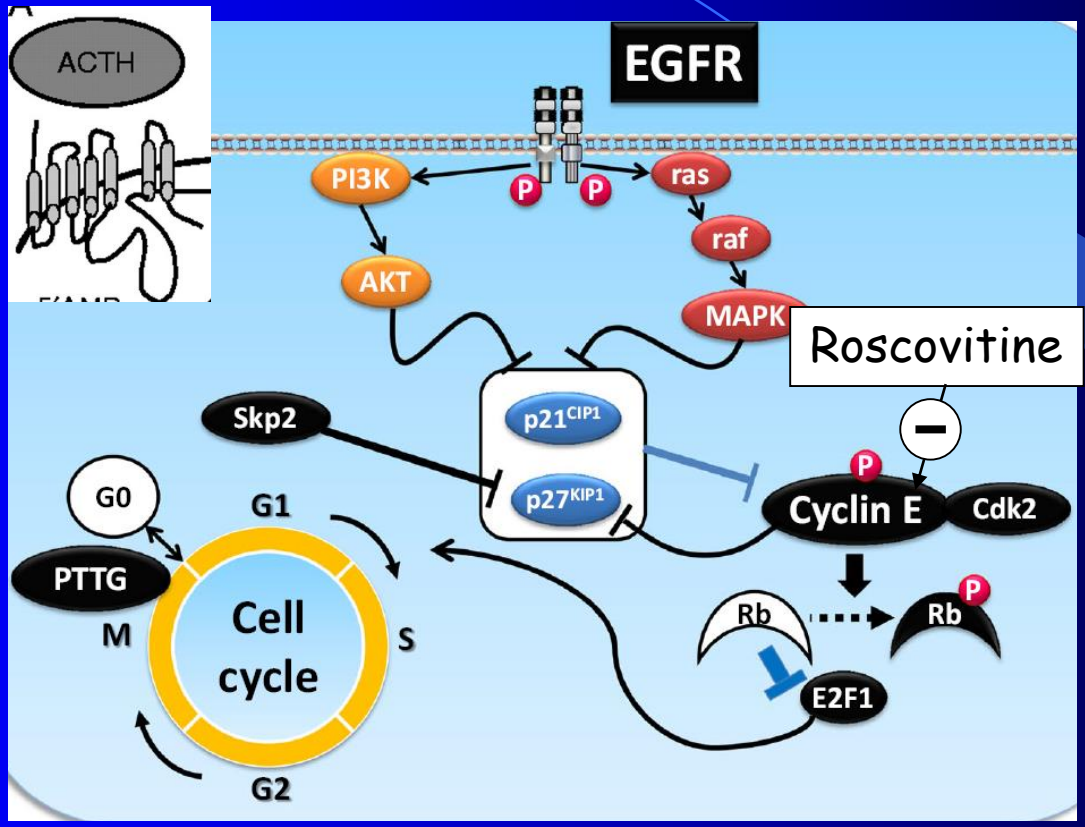
High affinity binding to human ACTH (1–39)
Absent or very low binding to α-MSH and CLIP

↓ ACTH-induced MC2R signalling

↓ ACTH-induced cortisol secretion



Future perspectives in medical therapy



Modified from Fukuoka, Pituitary (2015) 18:274–278

Future perspectives in medical therapy

! Clinical trials are needed !

Clinical practice

Future perspectives in medical therapy

bedside

In vivo studies

In vitro models

bench

Future perspectives in medical therapy

Translational studies

Clinical trials

Clinical approach

Drug availability

Personalized medicine

THANKS

Section of Endocrinology & Internal Medicine
Dept. of Medical Sciences
University of Ferrara