



New treatment approaches in hereditary cancer: The route towards personalized care

Eduardo Vilar, MD, PhD

Assistant Professor

Department of Clinical Cancer Prevention

THE UNIVERSITY OF TEXAS

**MD Anderson
Cancer Center**

Making Cancer History®

Disclosure

I have no conflicts of interest

Outline

- 1. Hereditary Cancer as a model for Drug Development**
- 2. Targeted Therapies in Hereditary Cancers**
- 3. NSAIDs and COX-ibs as models of Targeted Therapies**
- 4. FAP and COX-2 inhibitors**
- 5. Lynch Syndrome and Targeted Therapies**

From Clinical Cancer Genetics To Targeted Therapy in Sporadic Cancers

Hereditary Cancer
Syndromes

VHL



Sporadic Cancer

RCC

From Clinical Cancer Genetics To Targeted Therapy in Sporadic Cancers

Clinical observations – Phenotype

Retinal and cystic cerebellar hemangioblastomas, RCC

Hereditary Cancer Syndromes

von Hippel-Lindau

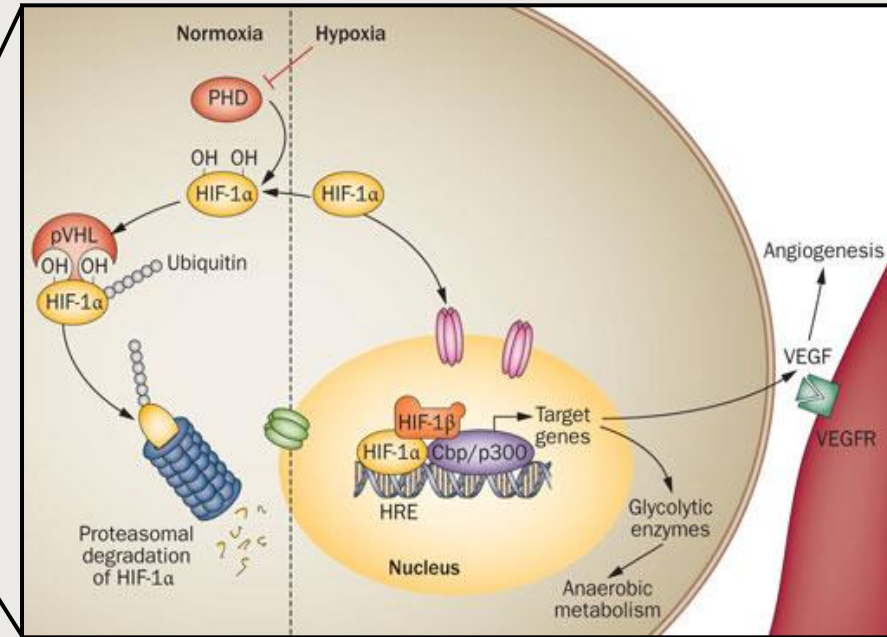
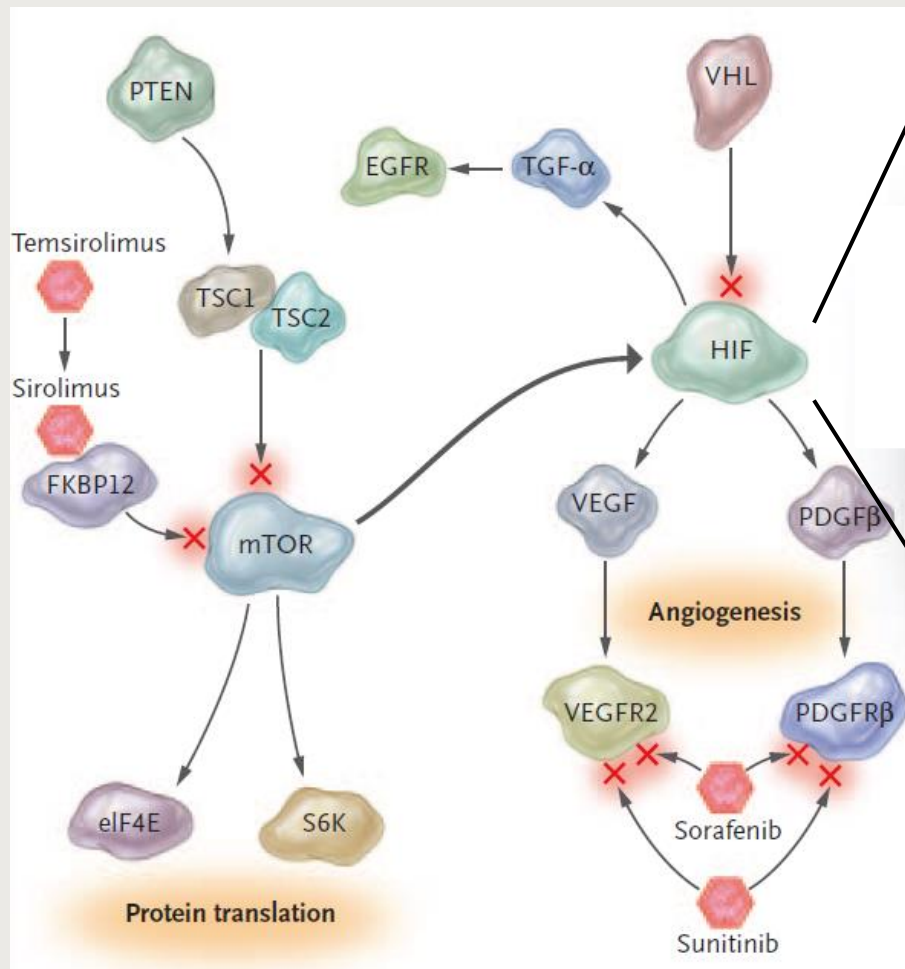
Germline Genetic Defect

Linkage studies map 3p25 – VHL gene

Description of Molecular Pathways

HIF1 α Hypoxia Pathway

From Clinical Cancer Genetics To Targeted Therapy in Sporadic Cancers



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Description of Molecular Pathways

HIF1 α Hypoxia Pathway

Sporadic Malignancies

VHL ~60% RCC

Development of Targeted Therapies

Sorafenib, Sunitinib, Temsirolimus – FDA approved for RCC

Hereditary Cancer Syndromes

Targeted therapies

Hereditary Cancer Syndrome Tumor Type	Genetic Defect	Drug	Target	Evidence
HBOC – Breast Cancer	<i>BRCA1/2</i>	PARPi Platinum Mito-C Others	PARP1/2 DNA add DNA add	Phase I CT Preclinical Preclinical Preclinical
HBOC – Ovarian Cancer	<i>BRCA1/2</i>	PARPi Carboplatin	PARP1/2 DNA add	Phase I/II CT Retrospective
Hereditary Pancreatic Cancer	<i>BRCA2</i> <i>PALB2</i>	PARPi Cisplatin Mito-C	PARP1/2 DNA add DNA add	Preclinical Phase I/II (on going)
Medullary Thyroid Cancer (MEN2A, MEN2B, FMTC)	<i>RET</i>	Vandetanib	VEGFR EGFR RET	Phase III CT
Tuberous Sclerosis – Renal angiomyolipoma Subependymal giant cell astrocytoma	<i>TSC1/2</i>	Everolimus	mTOR	Phase II (RPC)

Fong P *et al*, *NEJM* (2009); Tutt A *et al*, *Lancet* (2010); Audeh MW *et al*, *Lancet* (2012); Imyanitov EN *et al*, *Hereditary Cancer in Clinical Practice* (2011); Thornton K *et al*, *CCR* (2012); *clinicaltrials.gov*

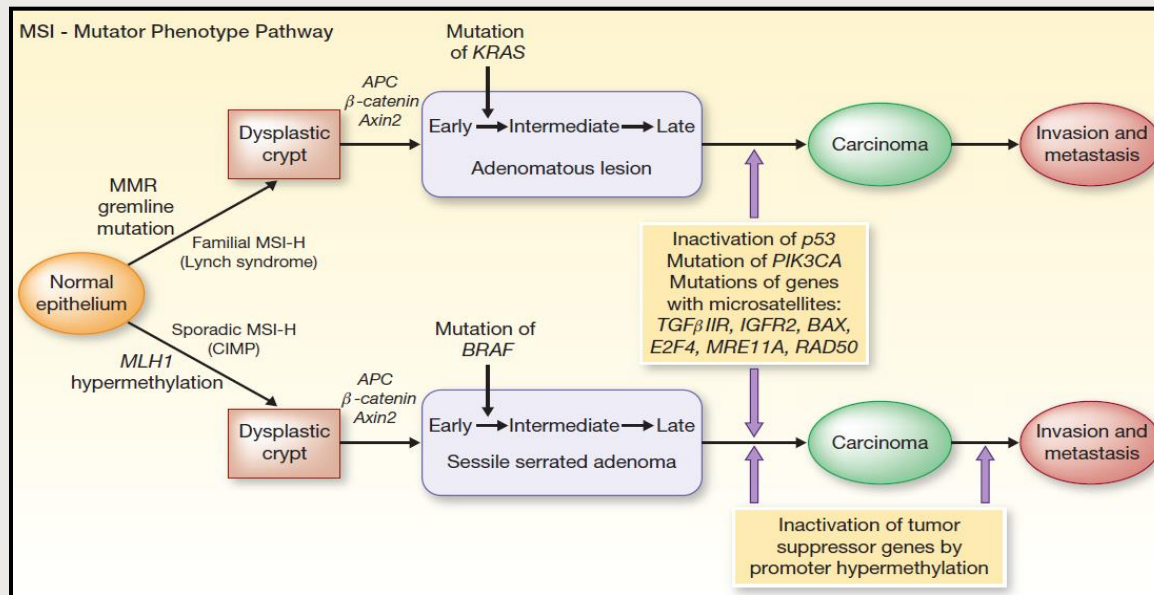
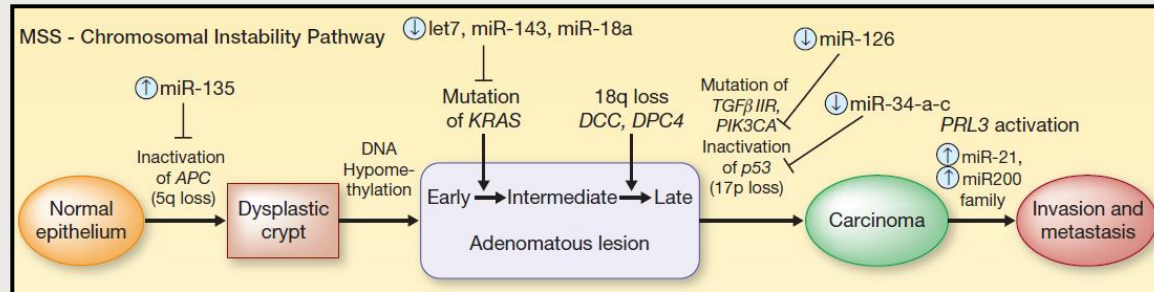
Hereditary **GI** Cancer Syndromes

Targeted therapies

Hereditary Cancer Syndrome Tumor Type	Genetic Defect	Drug	Target	Evidence
FAP – Polyps	<i>APC</i>	Celecoxib, Sulindac	COX-2	RCT RCT
FAP – Desmoid tumors	<i>APC</i>	Sulindac Imatinib SERMs	COX-2 PDGFR α ER	Case series
Lynch Syndrome – Polyps	<i>MLH1, MSH2, MSH6, PMS2, TACSTD1</i>	Aspirin	COX?	Phase III
Lynch Syndrome – Colon cancer	<i>MLH1, MSH2, MSH6, PMS2, TACSTD1</i>	5-FU Irinotecan PARPi	DPD Topo MRE11	Retrospective Retrospective Preclinical
Peutz-Jeghers Syndrome	<i>LKB1, STK11</i>	Rapamycin Everolimus	mTOR	Phase II (terminated) Preclinical
Cowden Syndrome	<i>PTEN</i>	Rapamycin	mTOR	Phase II Preclinical

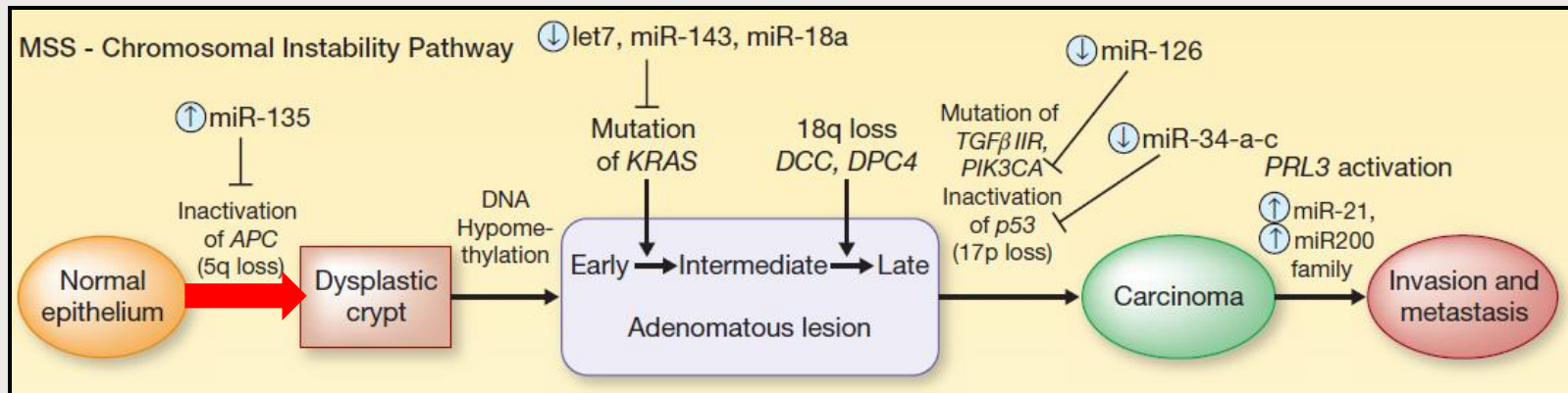
Steinbach G *et al*, *NEJM* (2000); Philips R *et al*, *Gut* (2002); Giardiello F *et al*, *NEJM* (2002); Burn J *et al*, *Lancet* (2011); Vilar E *et al*, *NRCO* (2010); Sargent D *et al*, *JCO* (2012); Sinicrope F *et al*, *JNCI* (2012); Wei C *et al*, *Cancer Lett* (2009); clinicaltrials.gov

Molecular Biology CRC



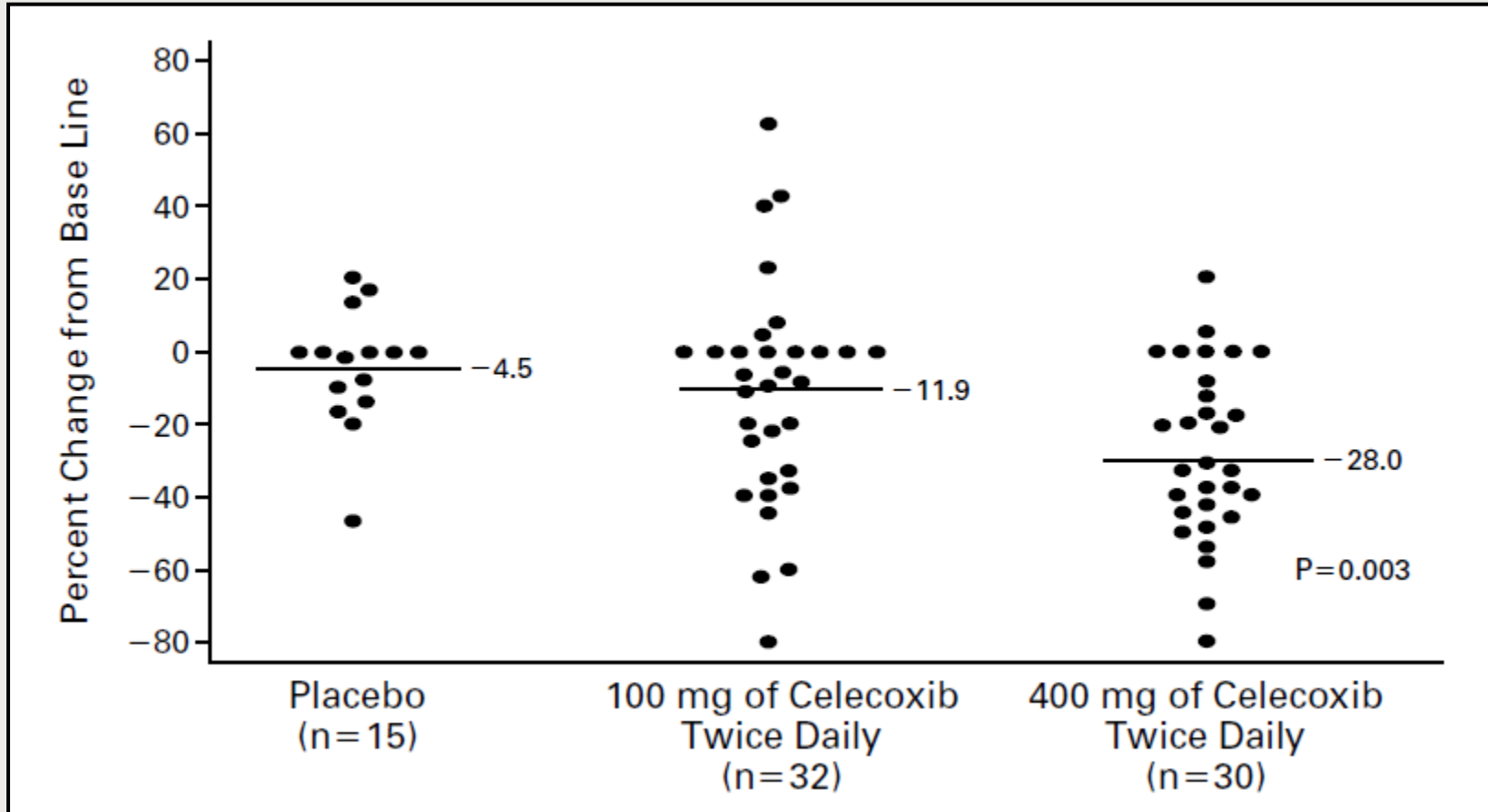
FAP

Chromosomal Instable CRC



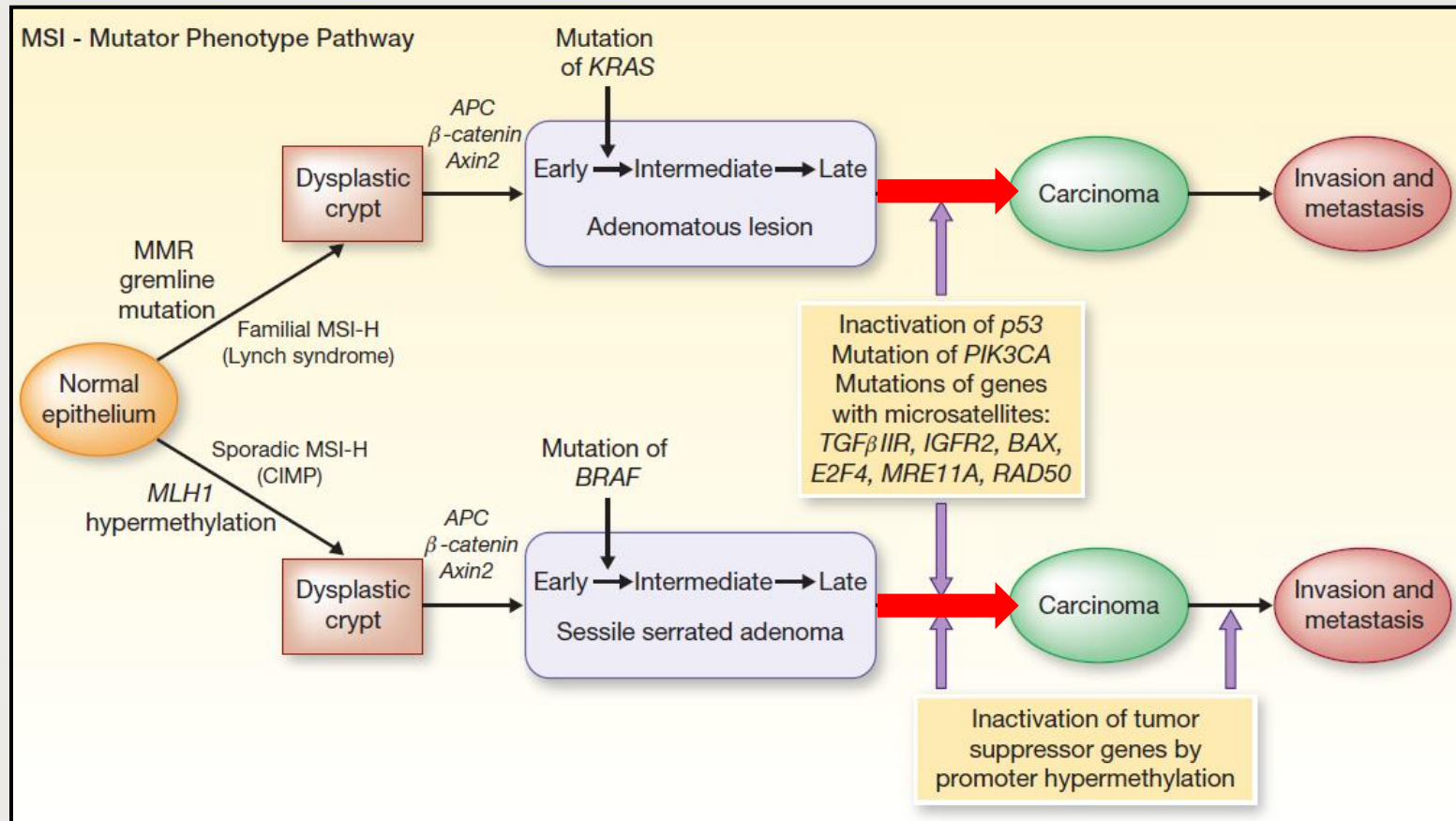
Celecoxib

Chemopreventio and Treatment in FAP

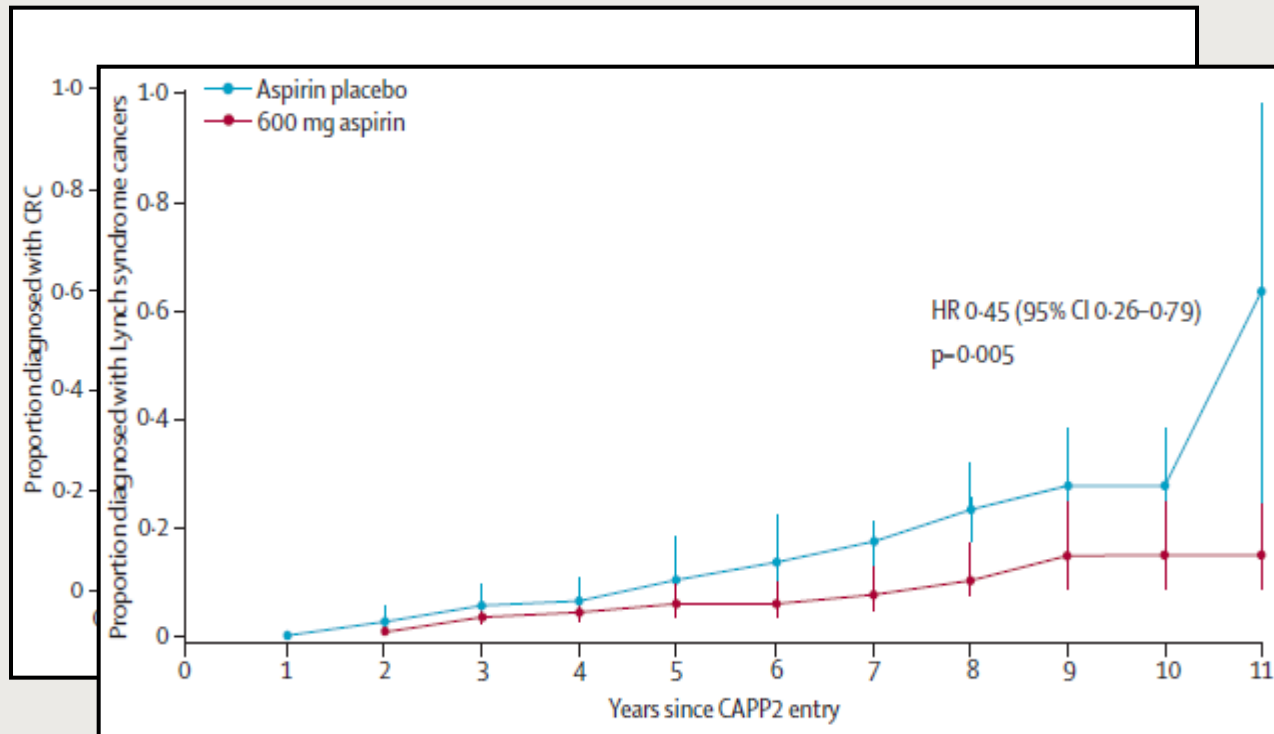


Lynch Syndrome

Microsatellite Instable CRC



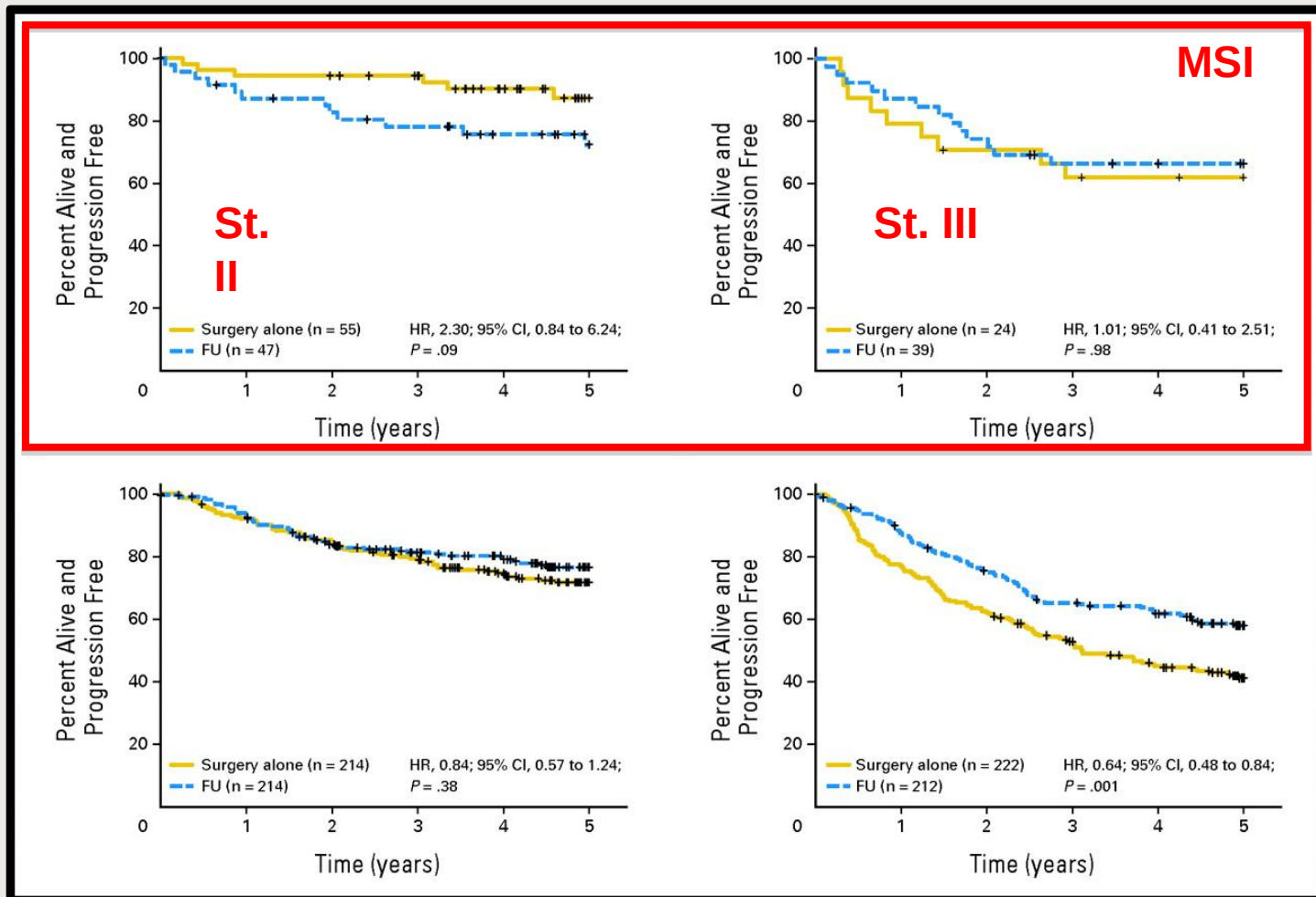
CAPP2 Study – Aspirin in Lynch Sd Colon Cancer Risk



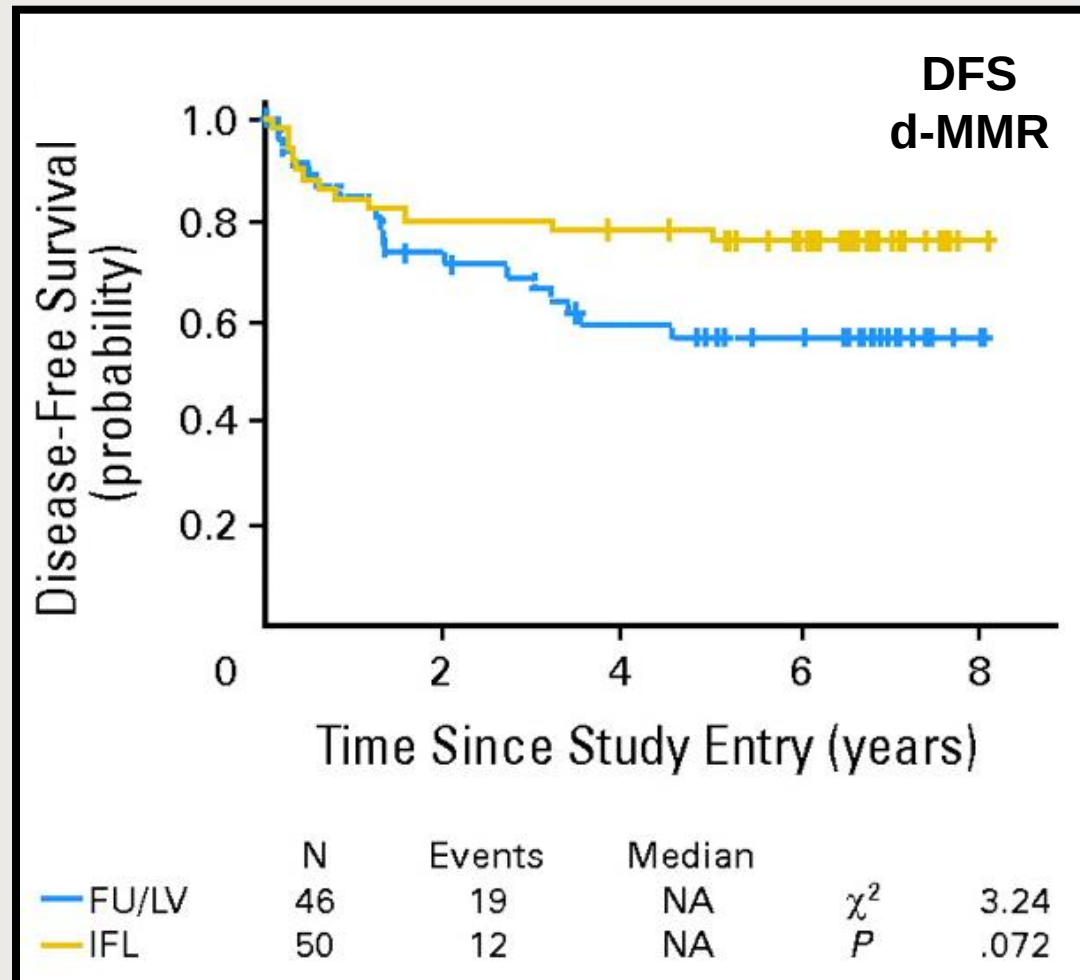
MSI as Predictive Factor: 5-FU

Reference	Type of study	Number of patients	Stage	MSI-H (%)	Duration of follow-up (months)	Stratification	5-FU effects	Primary end point	Chemotherapy regimen
Elsaleh <i>et al.</i> (2000) ⁶⁶	R	656	III	8.5	54	MSI-H	Benefit	5 year OS	5-FU + LEV
Hemminki <i>et al.</i> (2000) ⁶⁷	P NR	95	III	12	31	MSI-H	Benefit	3 year DFS	5-FU + FO 5-FU + MTX 5-FU + LEV 5-FU
Liang <i>et al.</i> (2002) ⁶⁸	P NR	244	IV	21.3	–	MSI-H	Benefit	mOS	5-FU + FO high dose
Ribic <i>et al.</i> (2003) ⁶²	R from RCT	570	II–III	16.7	88.8	CT	Detriment	5 year OS/DFS	5-FU + FO 5-FU + LEV
Carethers <i>et al.</i> (1999) ⁶⁵	R	204	II–III	17.6	43.7	CT	No benefit	mOS	5-FU based
Benatti <i>et al.</i> (2005) ⁶⁹	R	1,263	All stages	20.3	64	CT	No benefit	5 year OS	5-FU based
Jover <i>et al.</i> (2006) ⁷⁰	P NR	754	All stages	8.8	24.3	CT	No benefit	mDFS/ mOS	5-FU based
Lamberti <i>et al.</i> (2007) ⁷²	P NR	416	All stages	12.5	32.9	MSI-H	No benefit	mOS	5-FU based
Kim <i>et al.</i> (2007) ⁷¹	R from RCT	542	II–III	18.1	60	CT	No benefit	mDFS/ mOS	5-FU based
Sargent <i>et al.</i> (2008) ⁷³	R from RCT	1,027	II–III	16	60	CT	Detriment	mDFS/ mOS	5FU+FO
Des Guez <i>et al.</i> (2009) ⁷⁴	MA	3,690	II–III	14	–	MSI-H	No benefit	DFS/OS	5-FU based

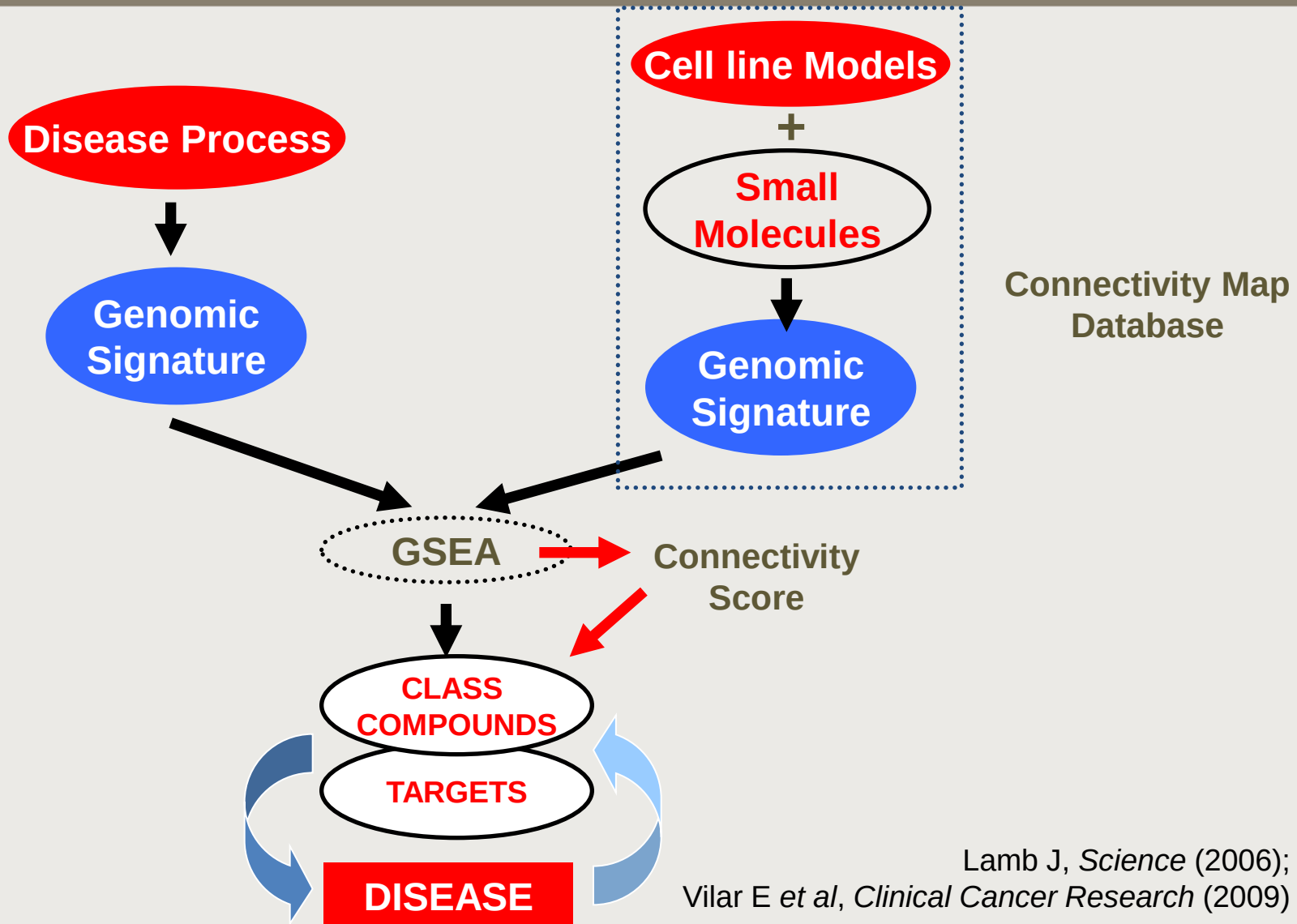
MSI as Predictive Factor: 5-FU



MSI as Predictive Factor: Irinotecan



Connectivity Map



Gene expression profiling studies

MECC DATA SET

Population based study

2000 cases/controls

Northern Israel

51 CRC frozen tumors

13 MSI-H (2 *MSH2* mut)

38 MSS

AFFY - Hu6800

Approximately 6000 probe-sets

T-Test MSI vs MSS

71 probe-sets ($p < 0.0001$)



Vilar E et al, *Clinical Cancer Research* (2009)

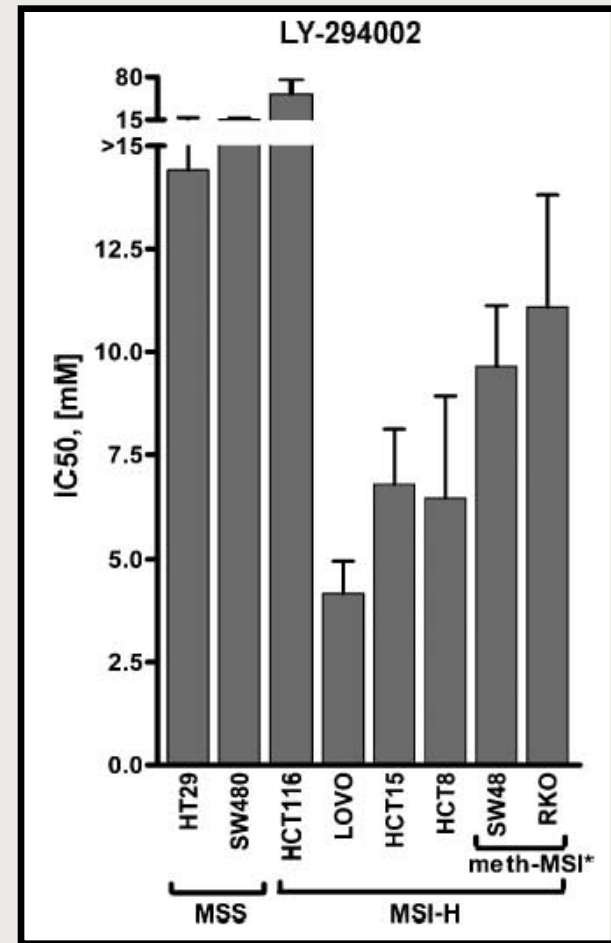
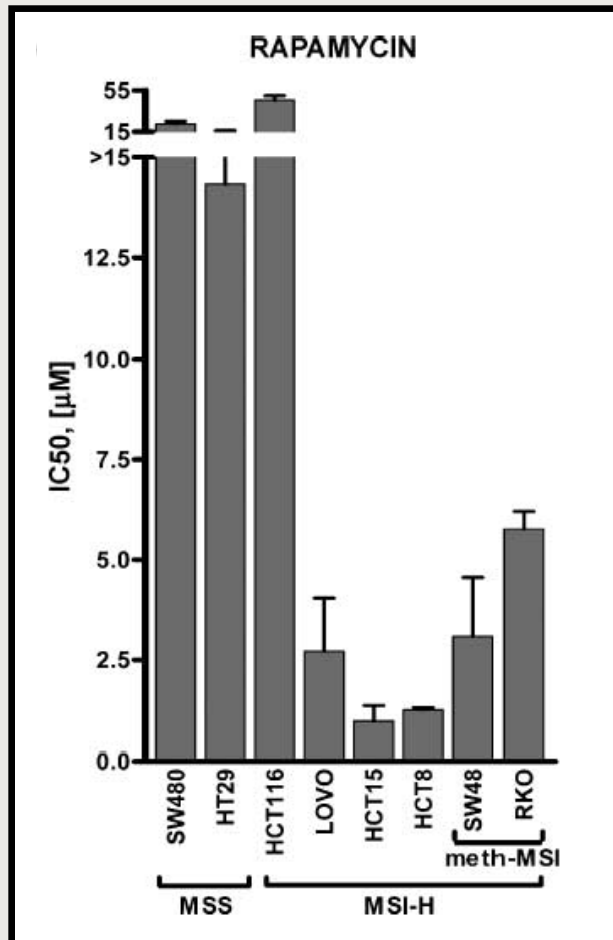
CMAP

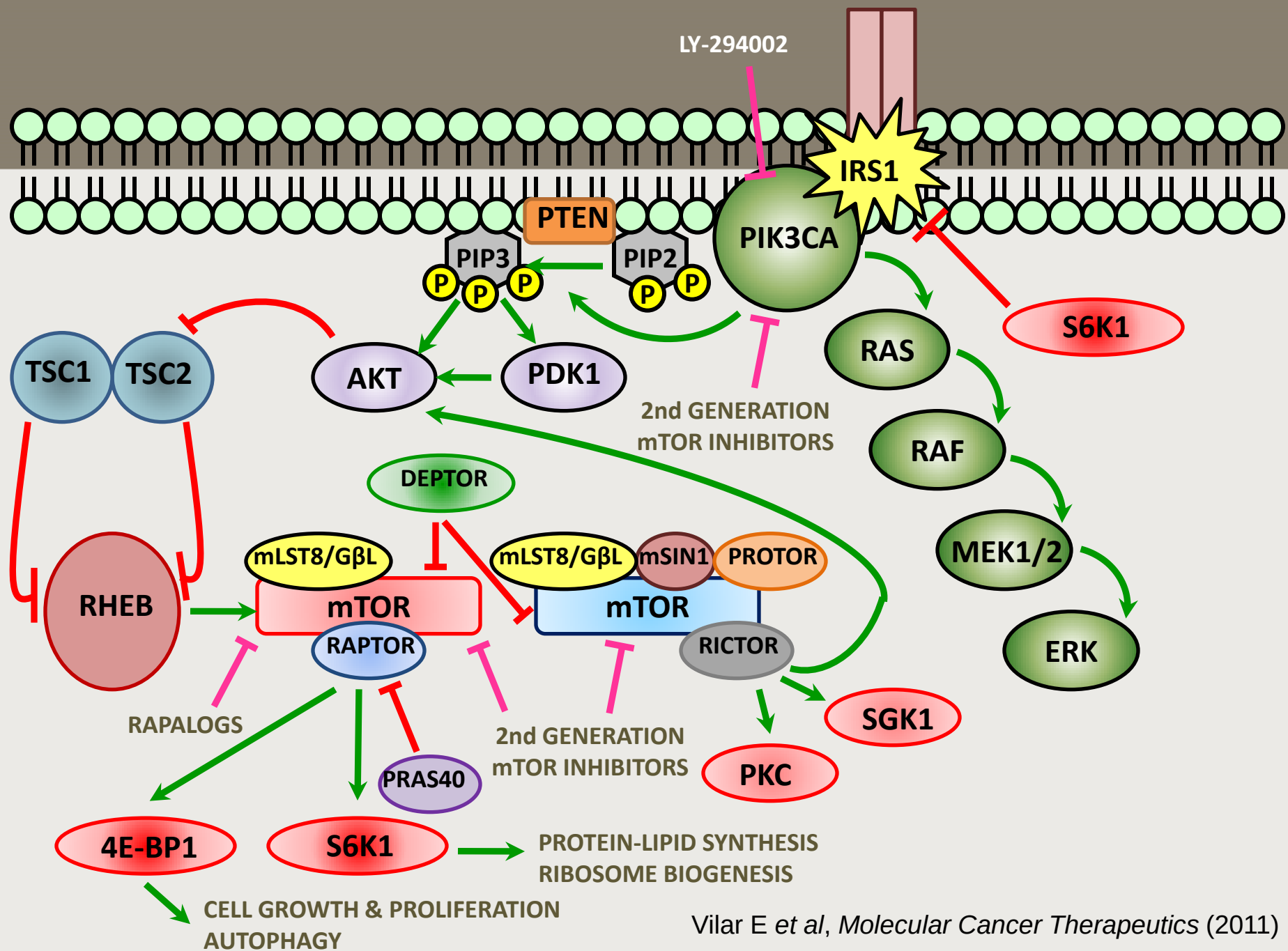
Small molecules targeting MSI

Table 1. List of 27 ranked compounds from discovery set

Rank	Compound
1	LY-294002
2	17-AAG
3	Trichostatin A
4	17-Dimethylaminoethylamino-demethoxy-geldanamycin
5	5224221
6	Geldanamycin
7	Trifluoperazine
8	Monorden
9	Resveratrol
10	Prazosin
11	Rapamycin
12	Haloperidol
13	SC-58125
14	Calmidazolium
15	Valproic acid
16	→ 15-Δ-Prostaglandin J₂
17	Fluphenazine
18	Raloxifene
19	Monastrol
20	Tretinoin
21	Fulvestrant
22	→ Rofecoxib
23	Wortmannin
24	α-Estradiol
25	→ Celecoxib
26	Tetraethylenepentamine
27	Genistein

PI3K & mTOR inhibitors





Conclusions

- 1. Tumors arising on a genetic background serve as a model for therapeutic development in sporadic cancers**
- 2. COX-ibs and NSAIDs as an example of the first targeted intervention in Hereditary GI syndromes**
- 3. Aspirin is a chemopreventive option in Lynch Syndrome patients**

Conclusions

- 4. CRCs in Lynch Syndrome patients has a different sensitivity to standard chemotherapy drugs**
- 5. Further investigation of targeted therapies in Lynch Syndrome patients is warranted.**

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