MDM2-specific therapy for sarcomas

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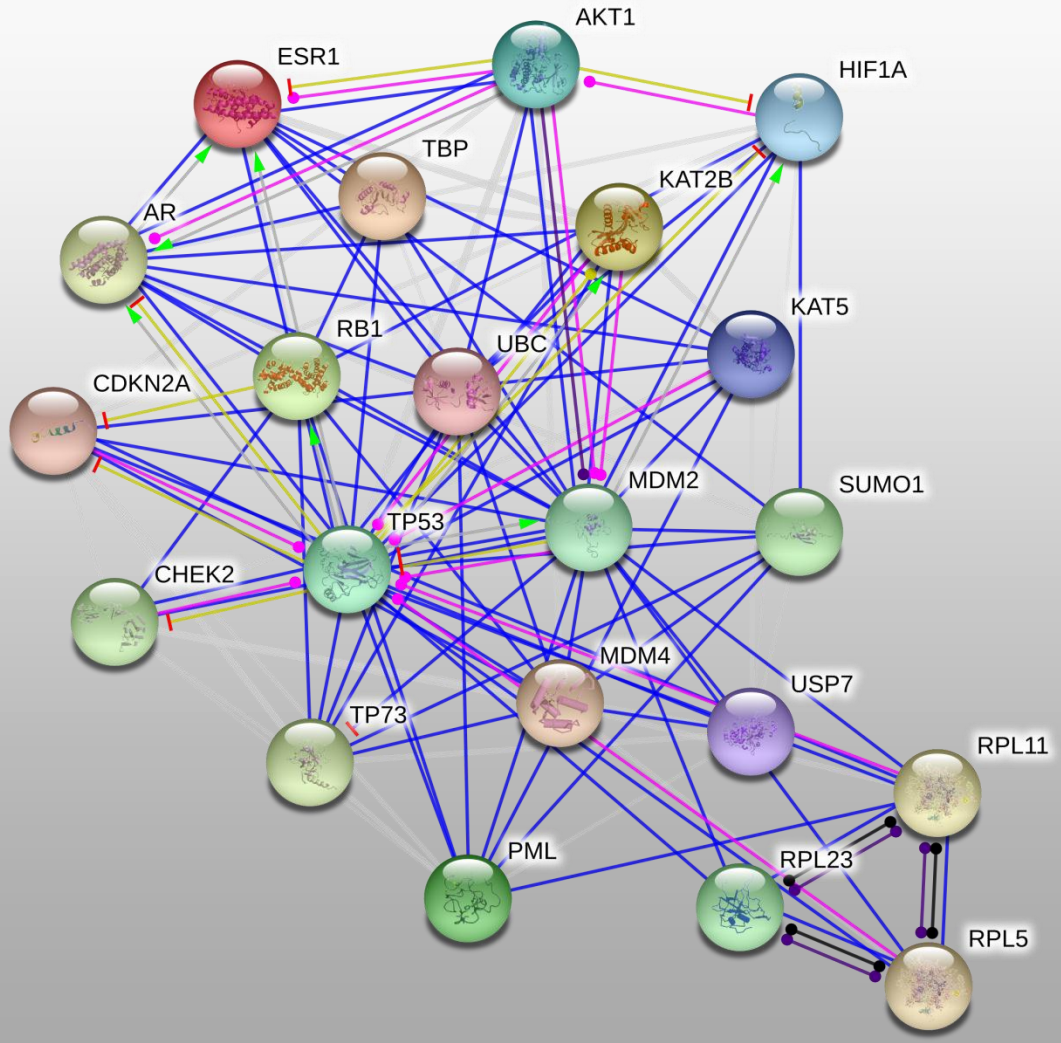
MDM2

- What is it? An E3 ubiquitin ligase, chr 12q15
  - Allows p53 to leave nucleus to be degraded by the proteasome
- Cloned from mouse cells as transforming gene with ras
- Recognizes the N-terminal TAD (transactivation domain) of p53 and inhibits p53 transcriptional activation
- Phosphoprotein—responds to DNA damage
  - Also ubiquitinates itself
- Does not just interact with p53
  - E2F1, p73, MDM4 (MDMX), HDAC1, …

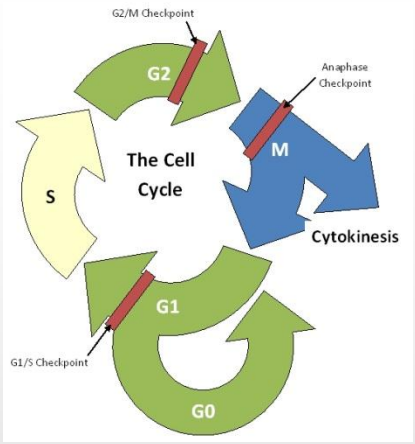
Momand J et al. Cell 1992; 69: 1237

Interactions



String 9.0; http://string-db.org

Simpler pathway



p21

G1-S cell cycle arrest

\+

p53

\+

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MDM2

p14ARF

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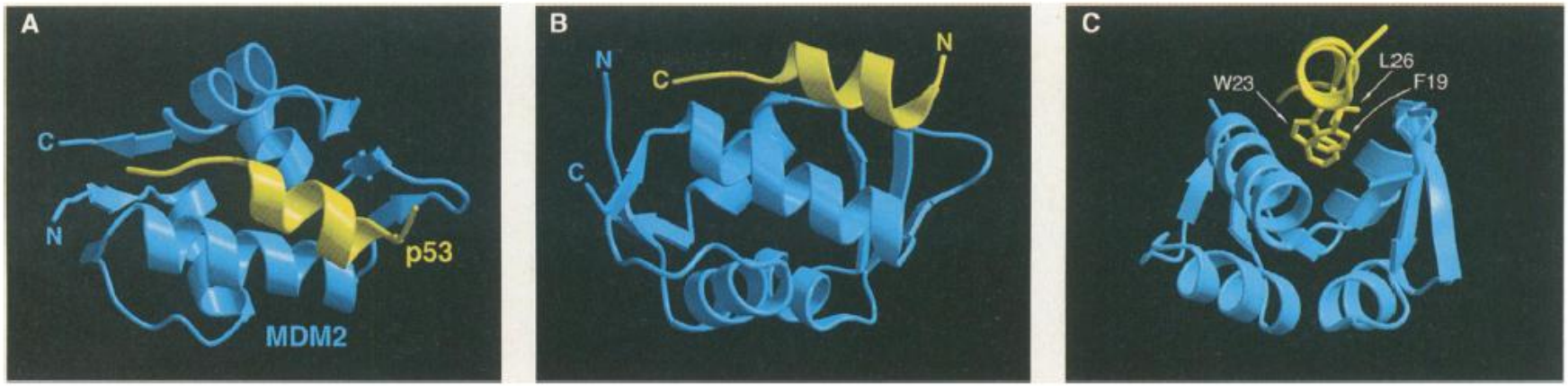
p63

p73

MDM4

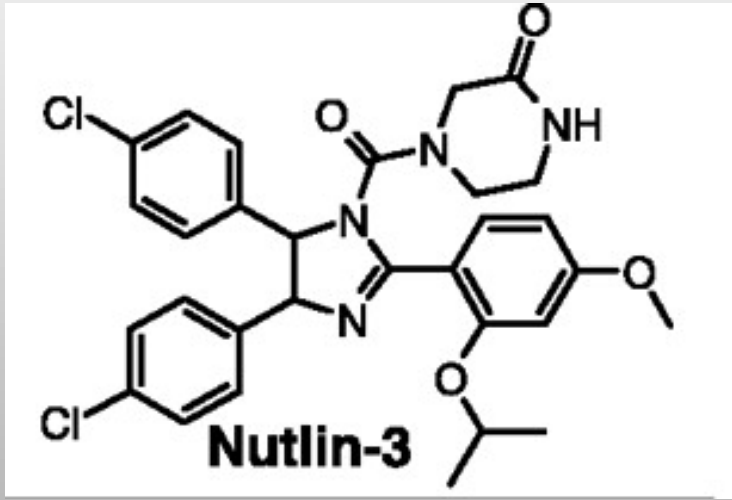
MDM2 & p53

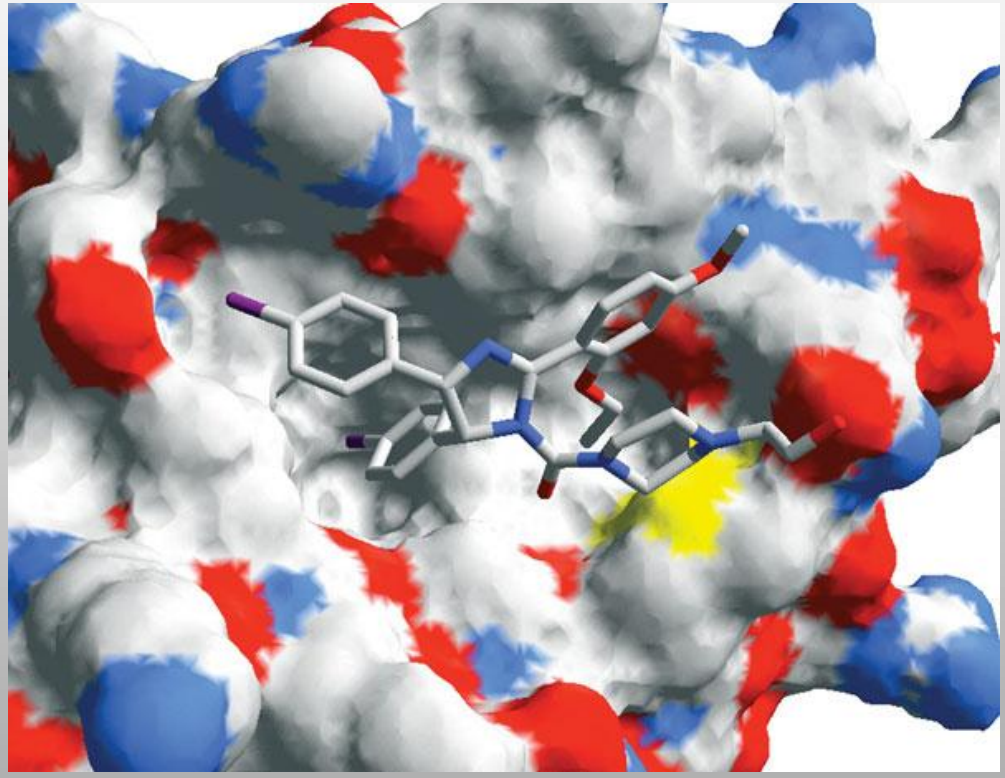


Idea: peptide like molecules that look like p53 could inhibitor p53-MDM2 interaction

Kussie PH et al. Science. 1996; 274:948

Nutlins are born





Vassilev LT et al. Science 2004; 303: 844

Sarcoma side of the equation

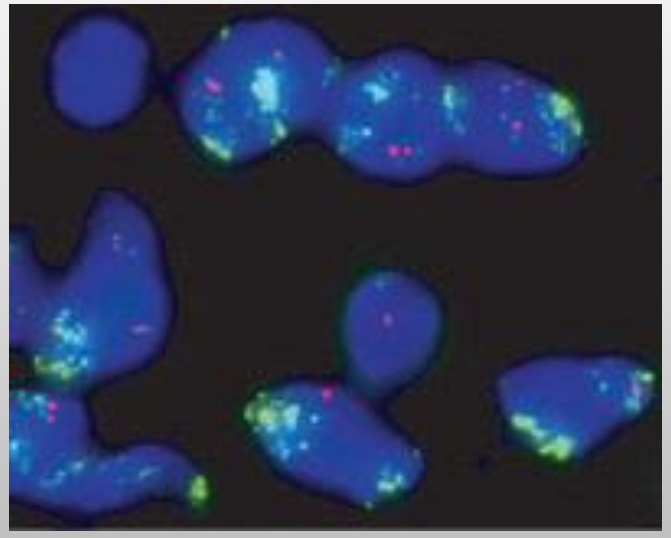
- TP53 mutation and MDM2 overexpression are two means of inactivating the p53 DNA damage checkpoint
- TP53 mutation: common in aneuploid sarcomas
  - Leiomyosarcoma
  - Undifferentiated pleomorphic sarcoma
  - Osteogenic sarcoma
- MDM2 overexpression/amplification: less common
  - Well differentiated-differentiated liposarcoma
  - Parosteal / surface osteosarcomas
  - Other tumors: glioma, neuroblastoma; CRC, H/N, breast…

Pedeutour F et al. GCC 1994; 10:85
Dujardin F et al. Mod Pathol 2011; 24: 624
Duhamel LAE et al. Histopathol 2012; 60: 357

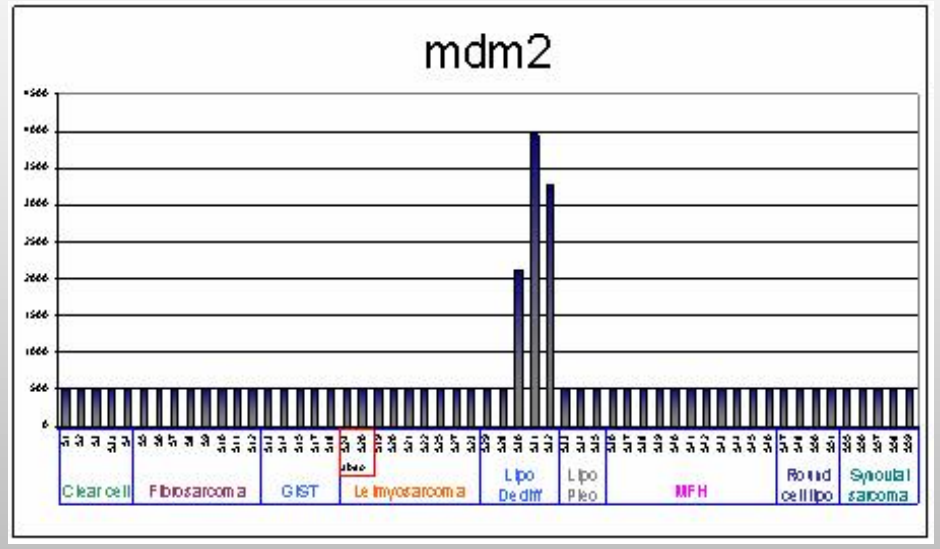
What is being studied?

- Parosteal osteosarcoma
  - Rare
  - Infrequently metastasizes
  - Thus not the focus of MDM2 inhibitor research
- Well differentiated / dedifferentiated liposarcoma
  - More common, ~ 4-5 / million / year
  - High local recurrence risk (peritoneum)
  - Does not often metastasize
- Other *TP53* wild type sarcomas / tumor
  - *MDM2* may not be amplified but such therapies could be useful in ANY tumor with WT *TP53*, at least in principle

MDM2 amplification

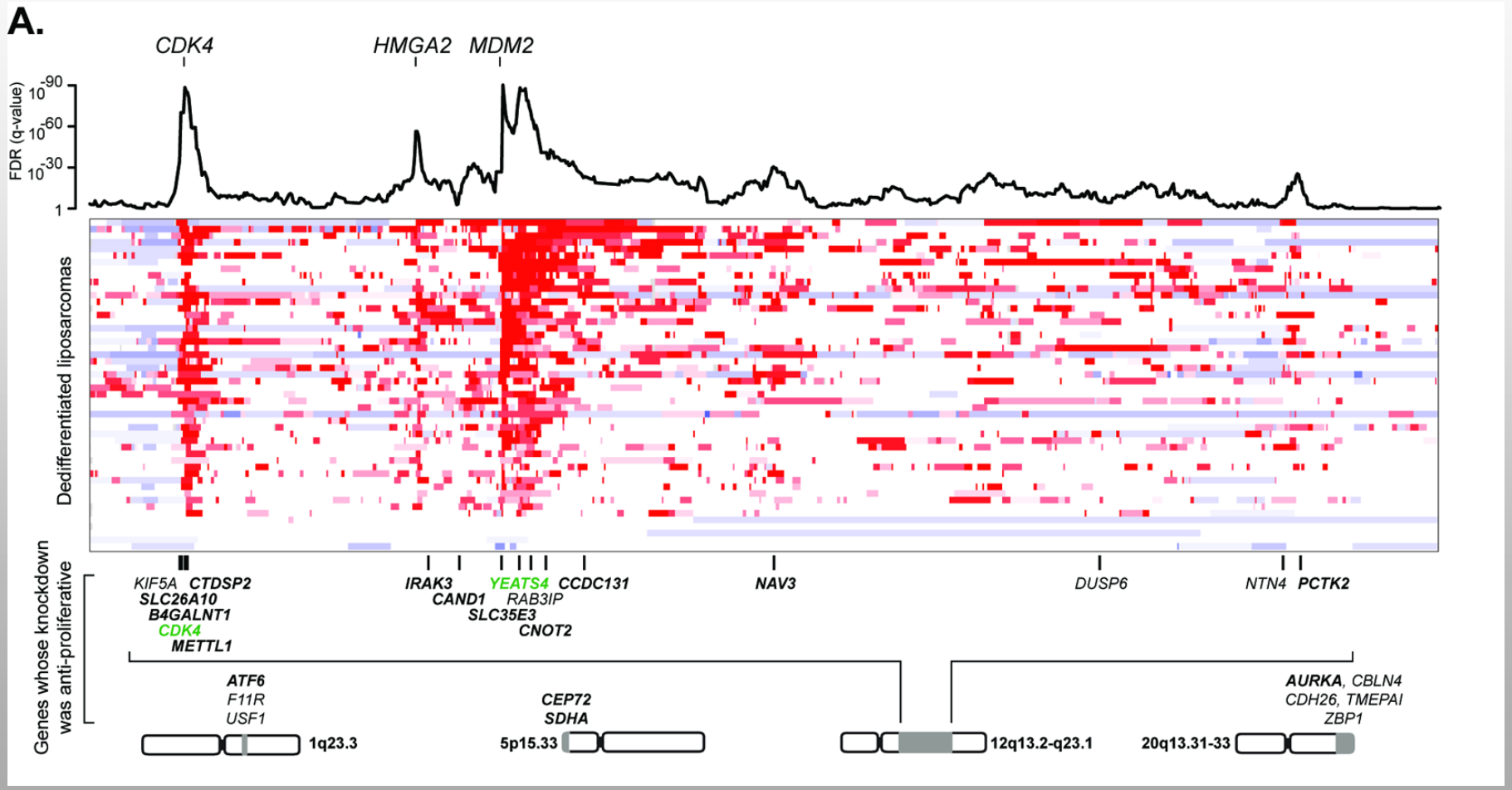


Parosteal osteosarcoma



Dedifferentiated liposarcoma

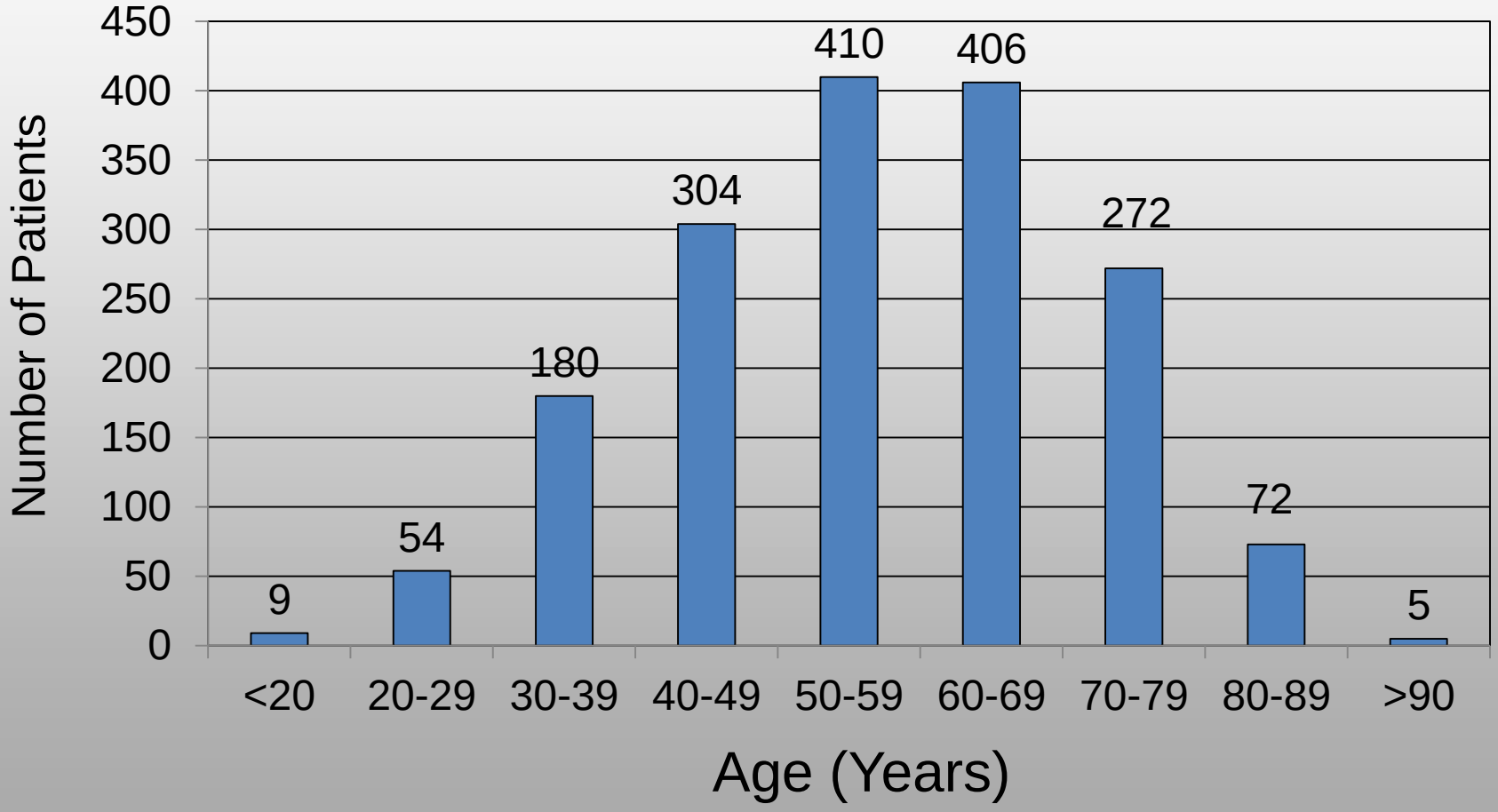
Better look at WD/DD Lipo



Barretina J et al. Nature Genet 2010; 42: 715

Liposarcoma

Distribution by Age

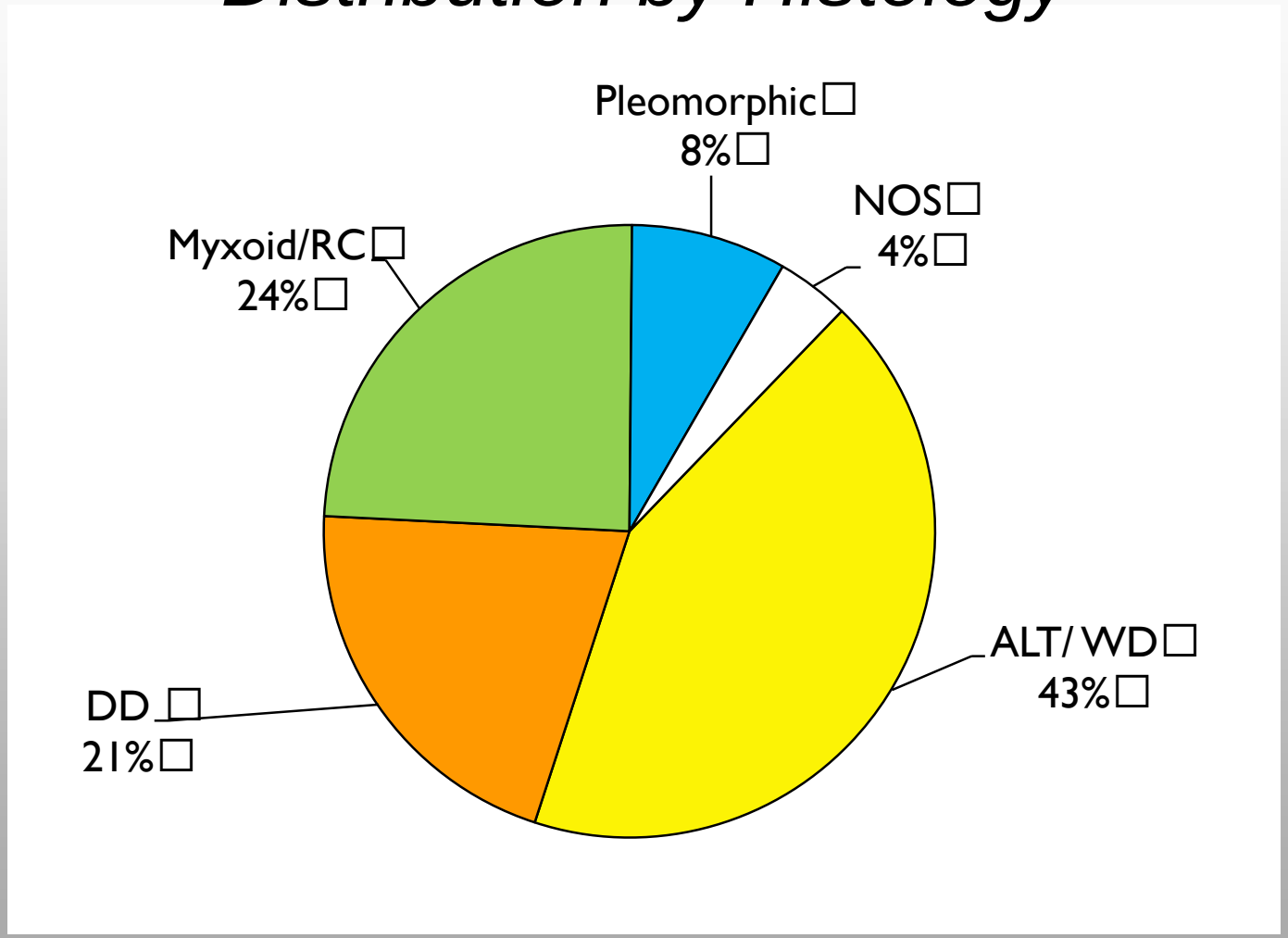


Courtesy of Murray Brennan, MSKCC, 1982-2010, n=1712

Three different biologies

- WD DD liposarcoma
  - Amplification of 12q14-15
    - *HDM2, CDK4, HMGA2,* others
- Myxoid – round cell liposarcoma
  - t(12;16) *FUS-DDIT3 (TLS-CHOP)* most common
- Pleomorphic liposarcoma
  - Aneuploid karyotype, like UPS (MFH)

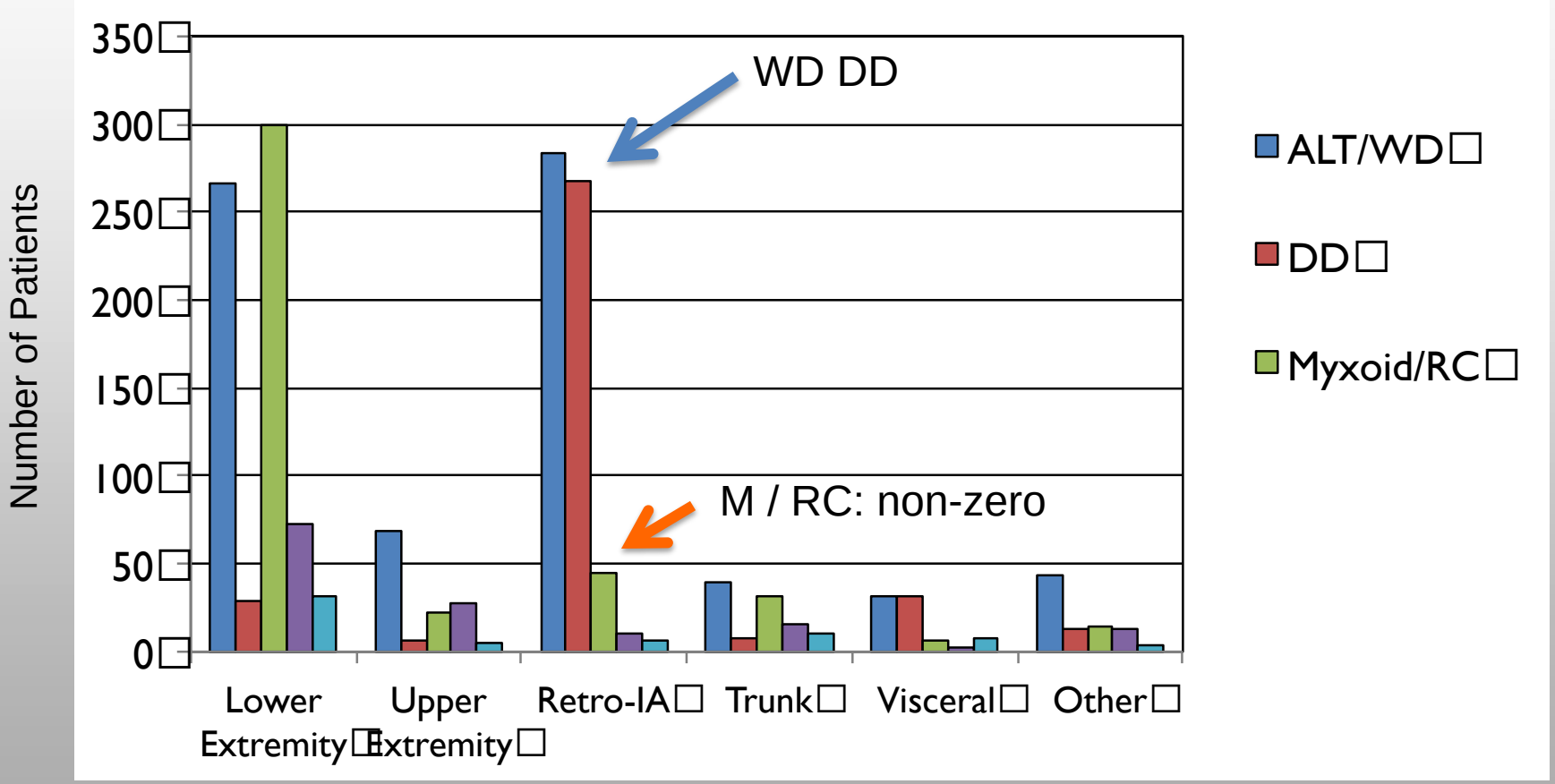
Liposarcoma
Distribution by Histology



Courtesy of Murray Brennan, MSKCC, 1982-2010, n=1713

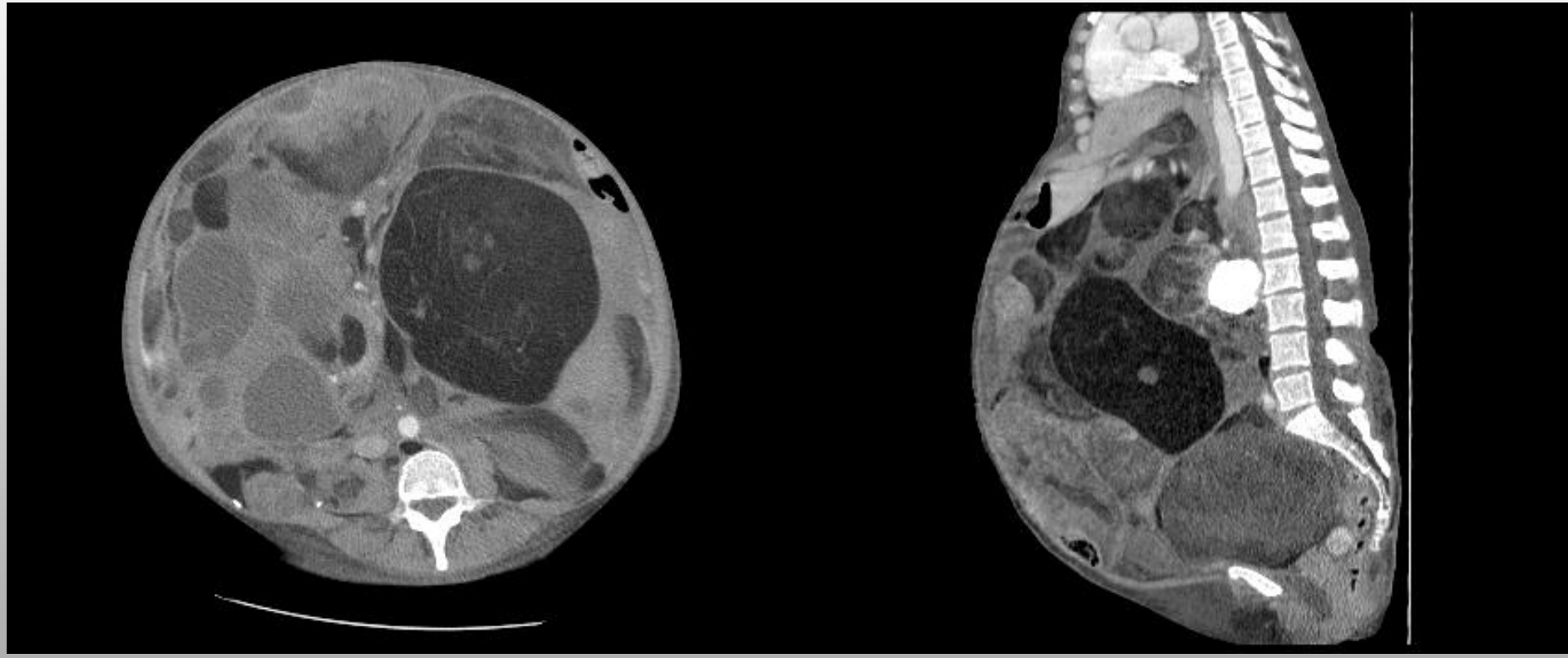
Liposarcoma

Distribution by Site & Histology



Courtesy of Murray Brennan, MSKCC, 1982-2010, n=1712

Well differentiated / dedifferentiated liposarcoma (WD DD LS)



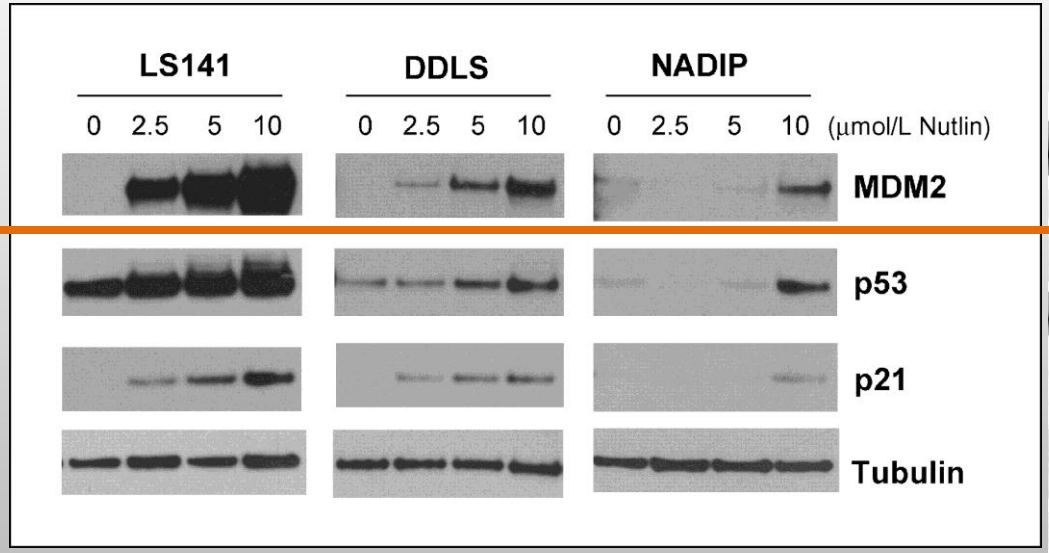
Liposarcoma chemotherapy scorecard

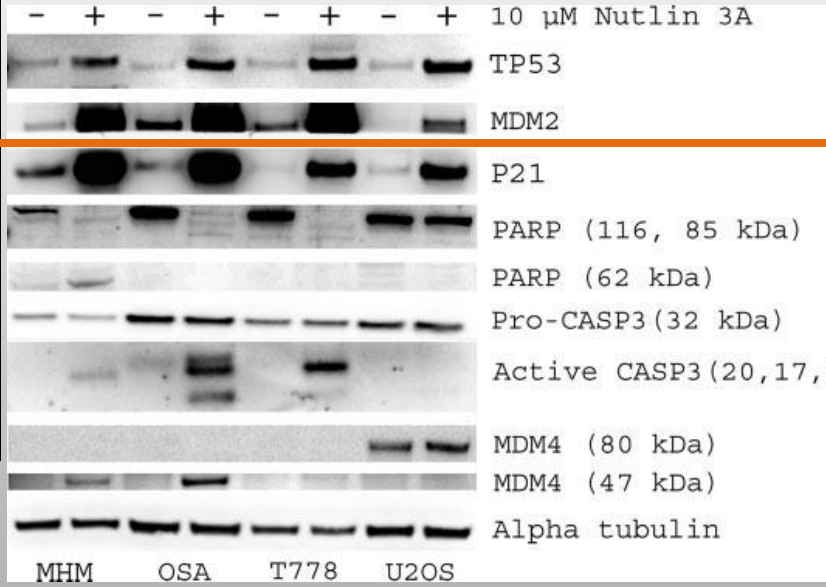
	CR	PR	MR	SD	PD	RECIST RR (CI)
Histology (n)						
Myxoid	0	12	1	4	8	48% (28-69)
Round cell	0	2	2	5	3	17% (2-48)
Well Diff	0	0	3	7	6	0% (0-22)
Dediff	0	3	0	0	9	25% (5-54)
Pleomorphic	1	3	2	2	4	33% (10-65)

Jones RL et al. Eur J CA 2005; 41: 2853

Well, that’s not good. How about MDM2 inhibitors in WD DD LS?

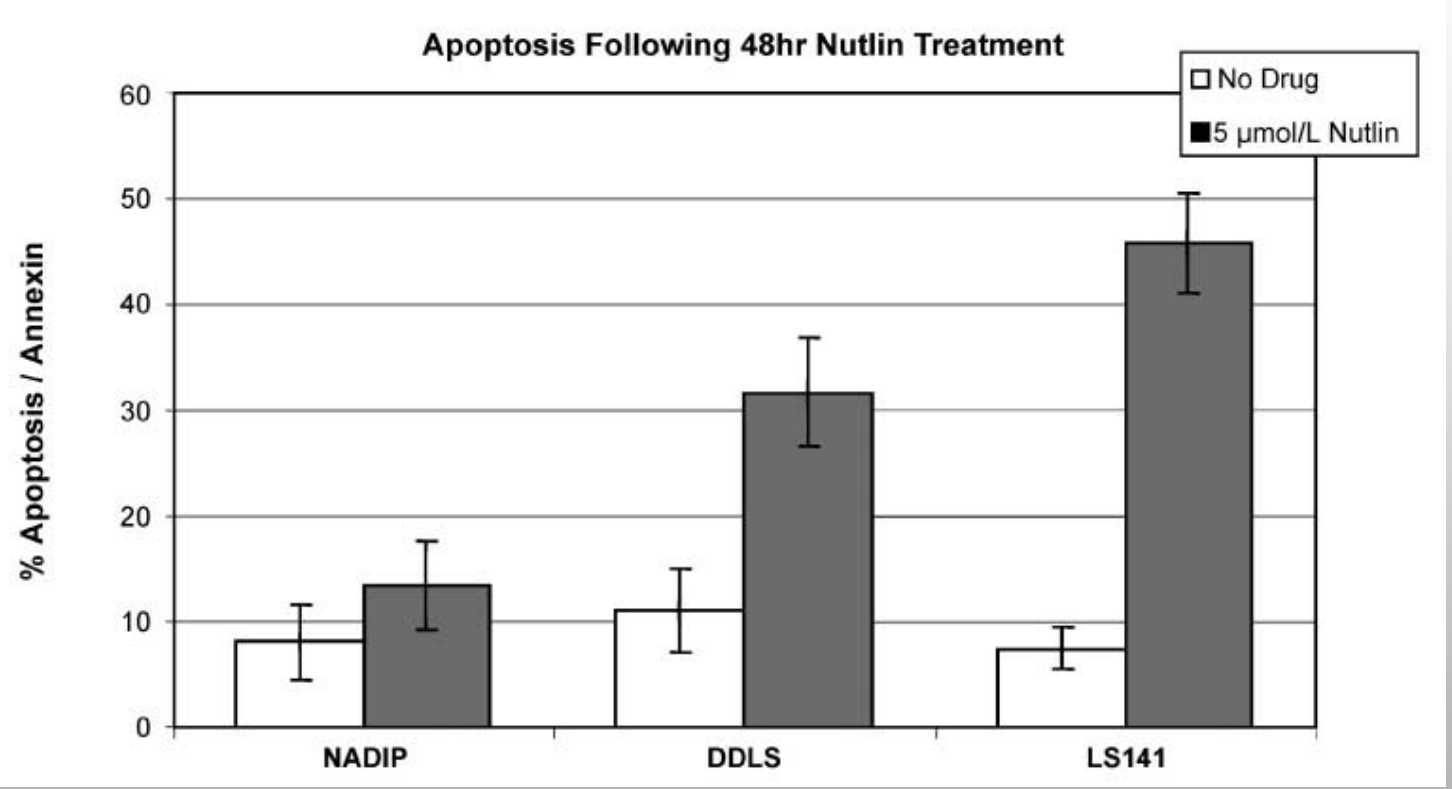
Nutlin vs liposarcoma cell lines





Müller CR et al. Int J Cancer 2007; 121: 199
Singer S et al. Clin Cancer Res 2007; 67: 6626

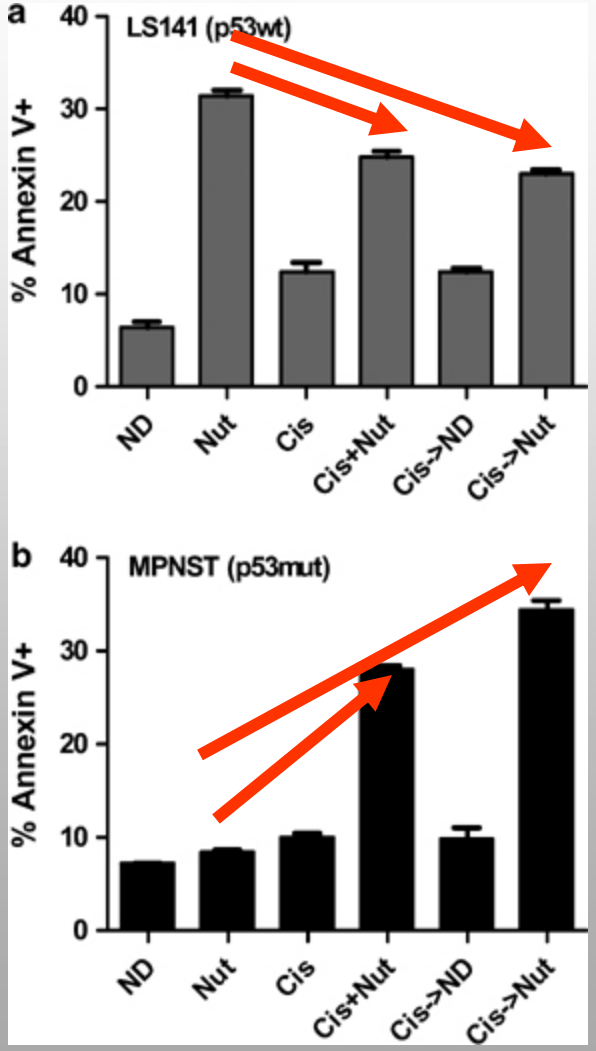
Nutlins affect adipocytes differently than liposarcoma cell lines



Adipocytes Dediff LS cell line 2nd dediff LS cell line

Singer S et al. Cancer Res 2007; 67: 6626

Synergy of nutlin + chemoRx in T*P53* mutant cells

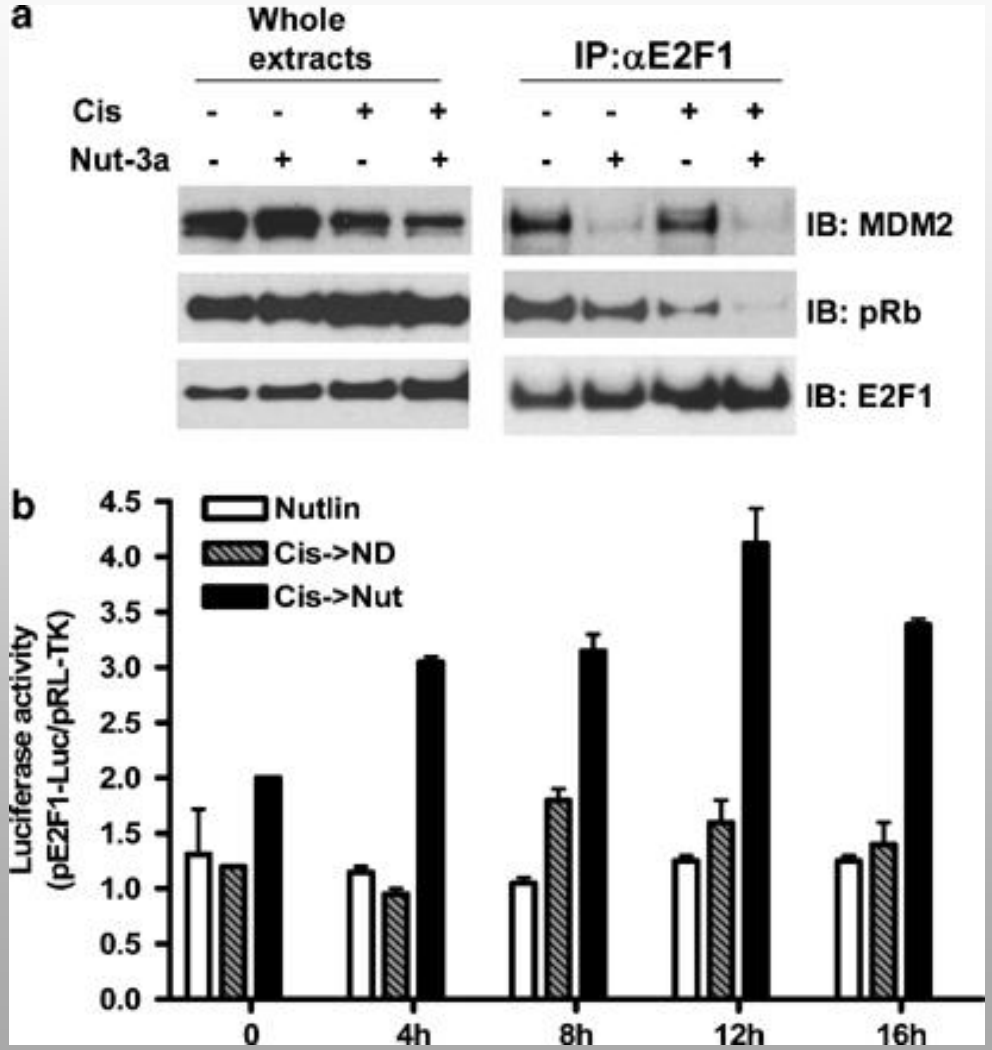


LS141: WT p53

MPNST: mutant p53

Ambrosini G et al. Oncogene 2007; 26: 3473

Nutlin and chemoRx effect may be mediated by (one of the…) E2F1's



Ambrosini G et al. Oncogene 2007; 26: 3473

Can tumors have it both ways?

- If *TP53* WT: Rx nutlin as a single agent
  - Chemotherapy can protect tumor cells from the effect of nutlin in p53 WT cell lines
- If *TP53* mutant: chemotherapy + nutlin is a natural combination to examine
  - May be additive with a number of agents
  - Will kinase targeted drugs and MDM2 inhibitors be less toxic?
    - Synthetic lethality
- Possible problem: heterogeneous tumors that have areas that are *TP53* wild type and *TP53* mutant
- Do patients tolerate these drugs?

Phase I leukemia / solid tumor phase I of nutlin RG7112

- 49 leukemia pts, 76 with solid tumors
  - AML, ALL, CML (blast phase) or refractory CLL/SCLL
- 10 days on every 28 days (QD or BID dosing)
- $\tau_{1/2}$ ~ 1.5 d
- Serum marker MIC1 pharmacokinetic marker
- Clinical outcomes pending

Beryozkina A et al. Proc ASCO 2011; abstr 3039

Phase I solid tumor study of nutlin RG7112

- MTD 1440 mg/m2 daily x 10 q 28 d, $t_{1/2}$ ~ 1.5 d
- 30 sarcoma pts, 106 total pts
- DLT: diarrhea, pancytopenia, hyponatremia
- FLT PET improved on 2 liposarcoma pts
- Extension phase: prolonged heme tox in 6 / 8 pts
- Biopsies: p53, p21, MDM2, TUNEL increased; Ki67 decreased
- No RECIST PR

Kurzrock R et al. Proc ASCO 2012, abstr e13600

Neoadjuvant therapy with RG7112

- n=20, Rx 1440 mg/m^2 daily x 10, q 28 days
- 3 cycles of therapy, then surgery: 1 PR, 14 SD
- 13/14 with *HDM2* amplification; 2/19 *TP53* mutant
- Toxicity
  - Nausea/vomiting: G3-4 in 2
  - Neutropenia: G3-4 in 3
  - Thrombocytopenia: G3-4 in 5 (prolonged, late)
    - Related to AUC and Cmax
- Feasible…but combinable? Stem cell toxin?

Ray-Coquard IL et al. Proc ASCO 2011; Abstr 10007b

Serdemetan (JNJ-26854165) phase I MDM2 inhibitor

- Active against *TP53* wild type cancer cell lines, at uM concentrations
  - Prevents p53/MDM2 destruction by proteasome
  - ?Off target effects: other MDM2 associated proteins could be involved
- Phase I: daily dosing, n=47, 11 dose levels, 4 – 400 mg oral daily
- DLT: QTc increase, rash
- No PR, prolonged stable disease in 3 patients
- PD: p53 up in skin, HDM2 up in tumor, MIC1 increased
- MTD: 300 mg oral daily; 150 BID being tested

Tabernero J et al. Proc ASCO 2009; 27: Abstr 3514

Non-MDM2 p53 inhibitors

- *Pseudomonas aeruginosa* peptide from azurin, 28 amino acids (p28), causes G2/M block by increasing p53 translation in an MDM2-independent fashion
- IV 3 x a week
- MTD > 4.16 mg/kg, rapid distribution
- Objective responses in 8/14 pts

Richards JM et al. Proc ASCO 2011; 29: Abstr 2511

CDK inhibitors—also for WD DD LS

- *CDK4* also has a 12q amplicon in WD DD LS
- CDK inhibitors block more than 1 molecule
  - PD0332991 Pfizer — CDK4/6
  - LEE011 Novartis — CDK4/6
  - P276-00 — CDK1/6
  - Terameprocol — CDK1/survivin
  - AG-024322 — CDK1/2/4
  - Dinaciclib (SCH727965) — CDK1/2/5/9
  - BMS-387032 (SNS-032) — CDK2/7/9
- PD0332991 in phase II in WD DD LS (MSKCC) after evidence of activity in phase I
  - MTD 200 mg oral daily 2 weeks on, 1 week off
  - Neutropenia, thrombocytopenia were DLTs

Schwartz GK et al. Br J Cancer 2011; 104: 1862

Summary

- WD DD liposarcomas and superficial osteosarcomas: MDM2 amplification
- Nutlins are MDM2 inhibitors that may have activity in cancer, especially when *TP53* is wild type, but have significant toxicity
- Combinations with chemotherapy, if feasible, may be approaches to treat *TP53* mutant tumors
- Sarcoma Rx: maybe; treat leukemias?


Connective Tissue Oncology Society
17th Annual Meeting – November 14 - 17, 2012
Alessandro Gronchi, MD - Program Chair • Jay Wunder, MD - 2012 CTOS President
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