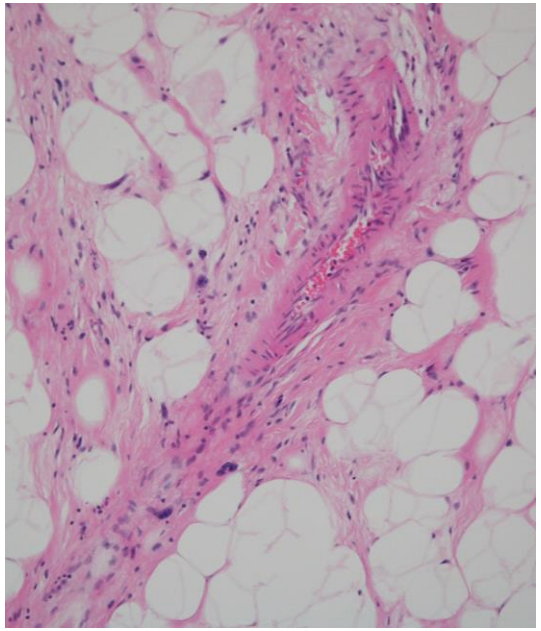
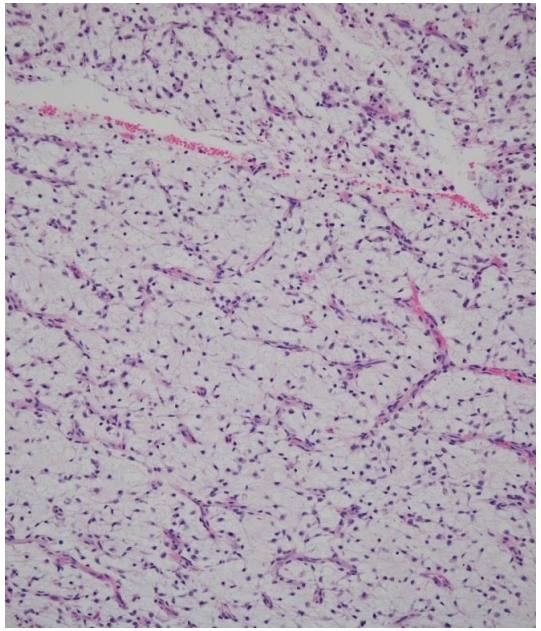
Well differentiated Liposarcoma



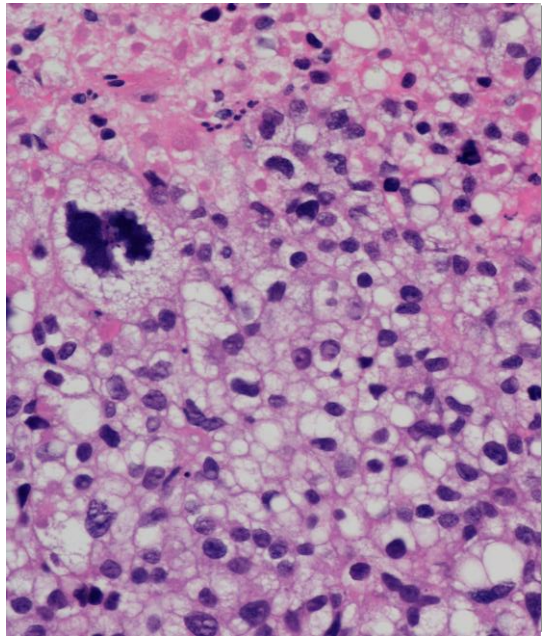
***MDM2 /CDK4* amplification**

Myxoid liposarcoma



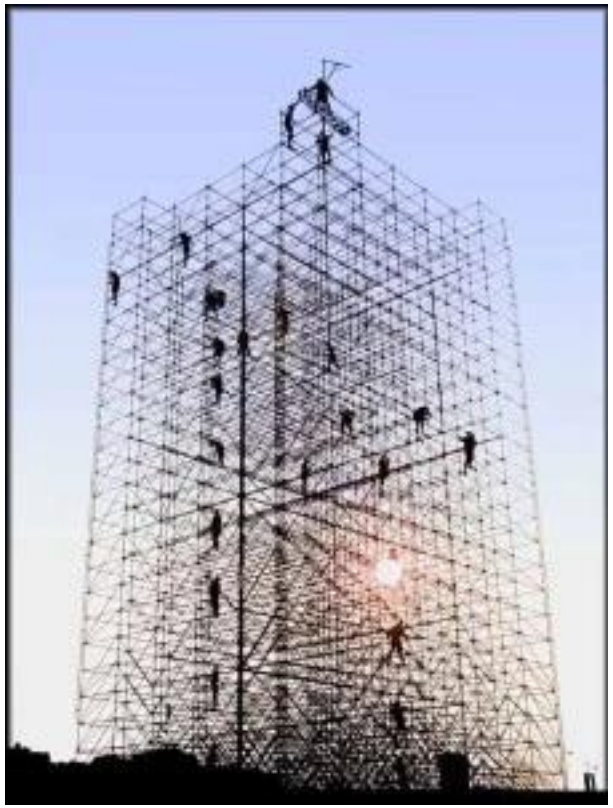
***FUS-DDIT3* chimeric fusion gene**

Pleomorphic Liposarcoma



Complex rearrangements and copy number changes

Mutational catalogues –TCGA, ICGC and others….



- **Bone tumours:** Chondrosarcoma, Osteosarcoma, Chondroblastoma, Giant cell tumour of bone.

- **Soft tissue tumours:** SFT, LGFMS, Angiosarcoma, Radiation induced sarcoma, Leiomyosarcoma, haemangioendotheliomas, MPNST

Output from genome sequencing studies

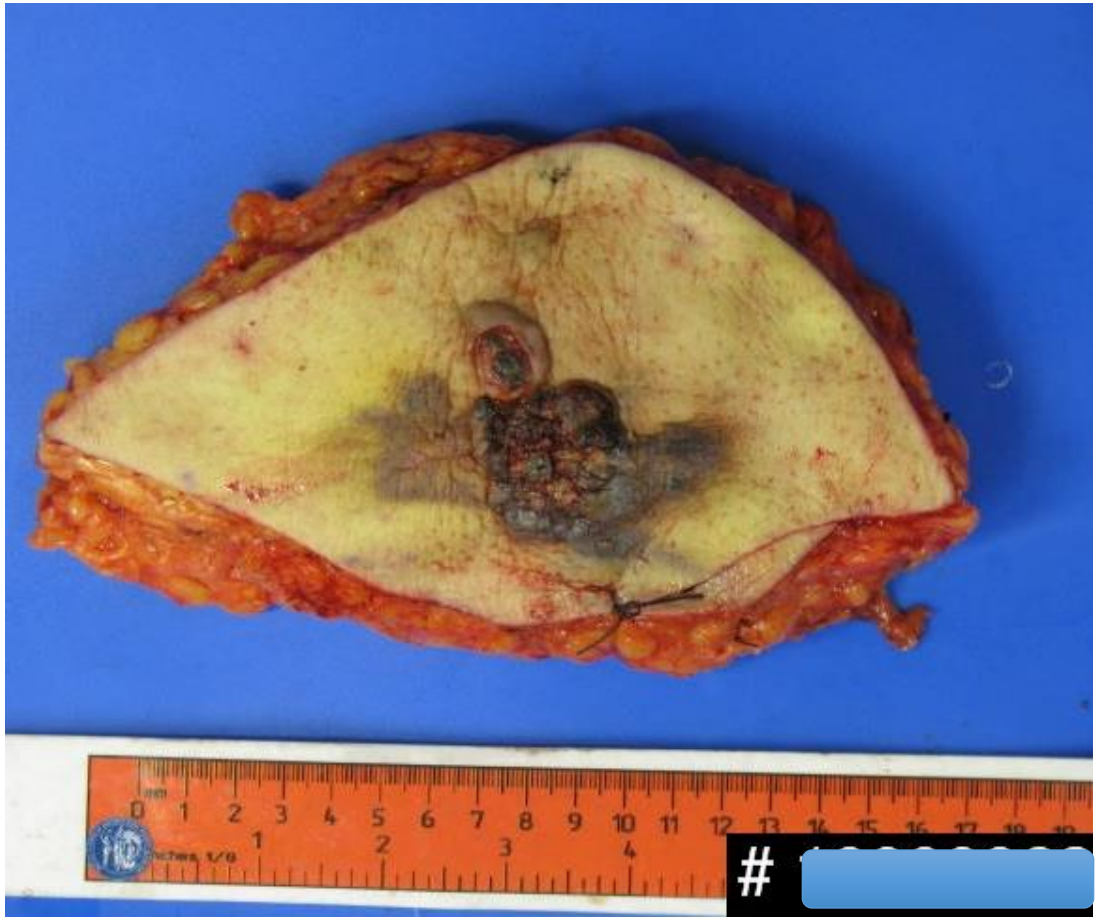
- Biological processes implicated in cancer development.
- Tumour heterogeneity.
- Evolution of metastasis.
- Mutational processes involved in carcinogenesis.
- Identification of drug targets.
- Outcome and response to therapy.
- Identification of new cancer genes.

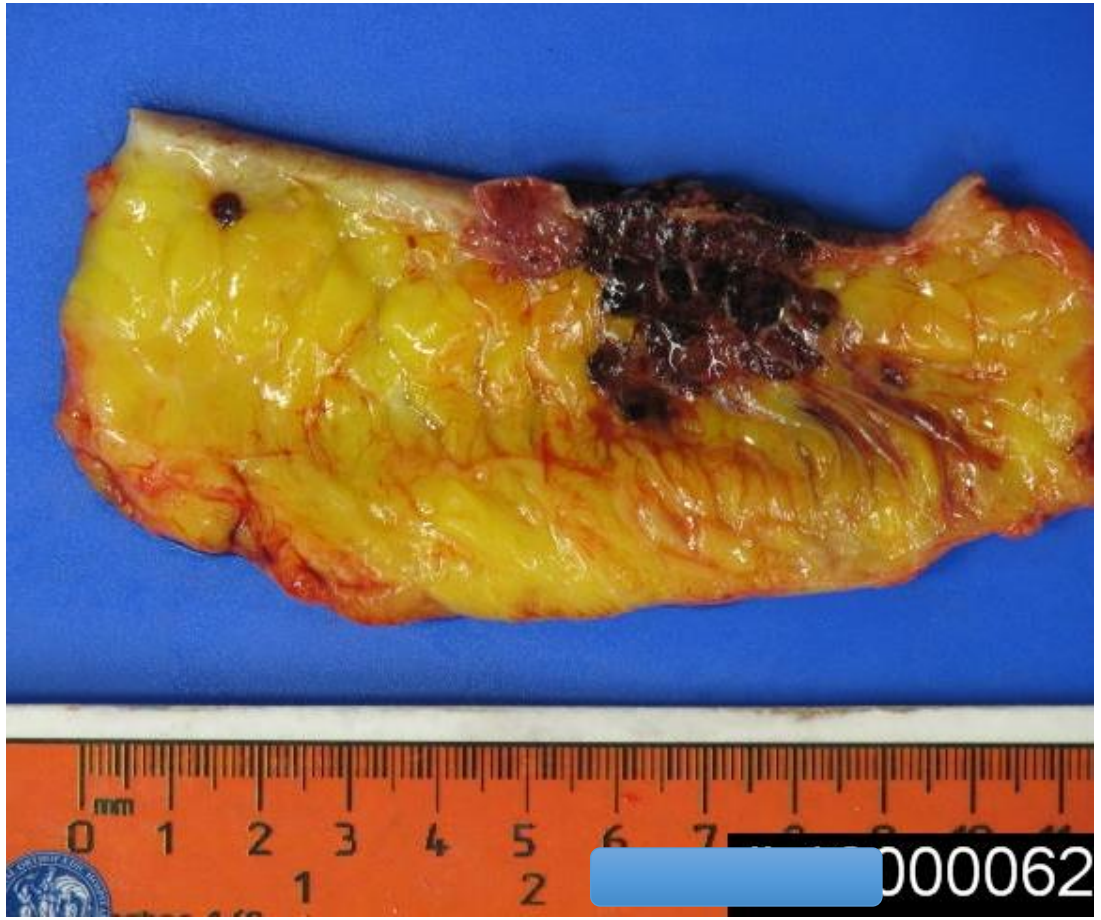
Identifying new biomarkers to delineate high grade sarcomas

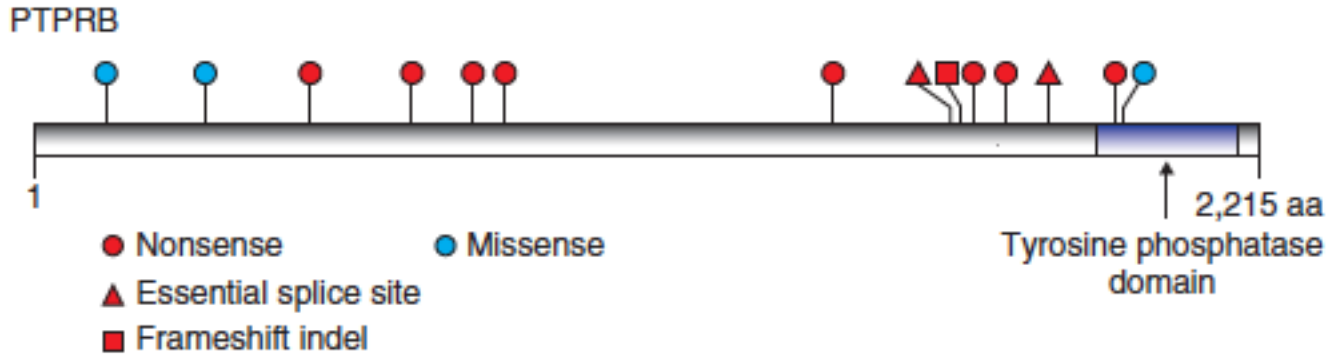
Angiosarcoma

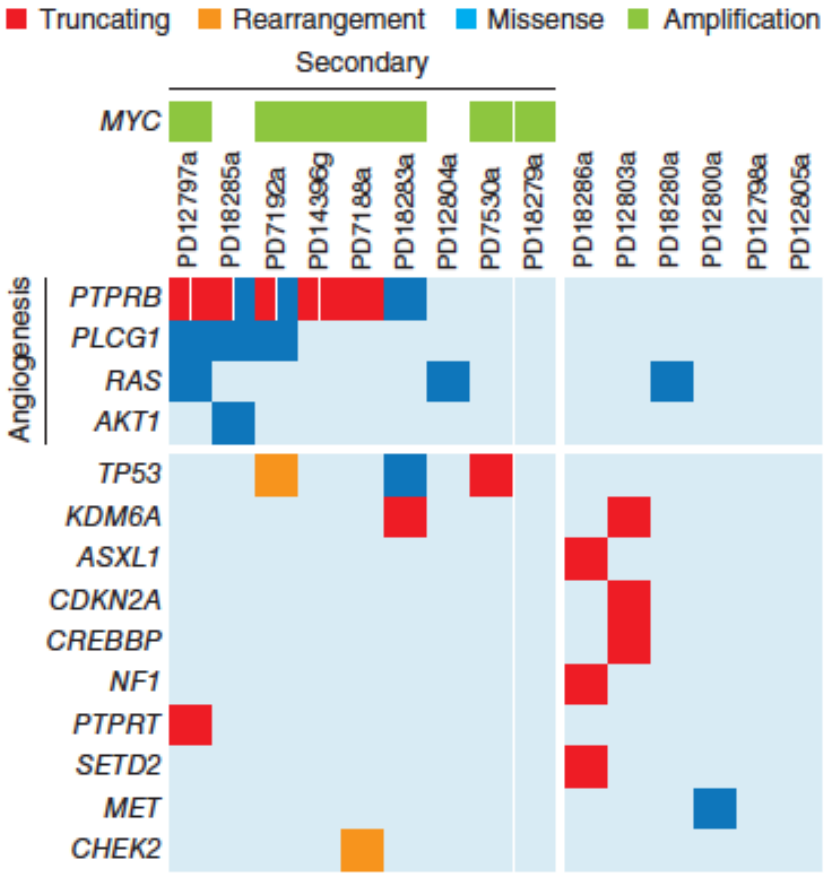
MPNST

Angiosarcoma

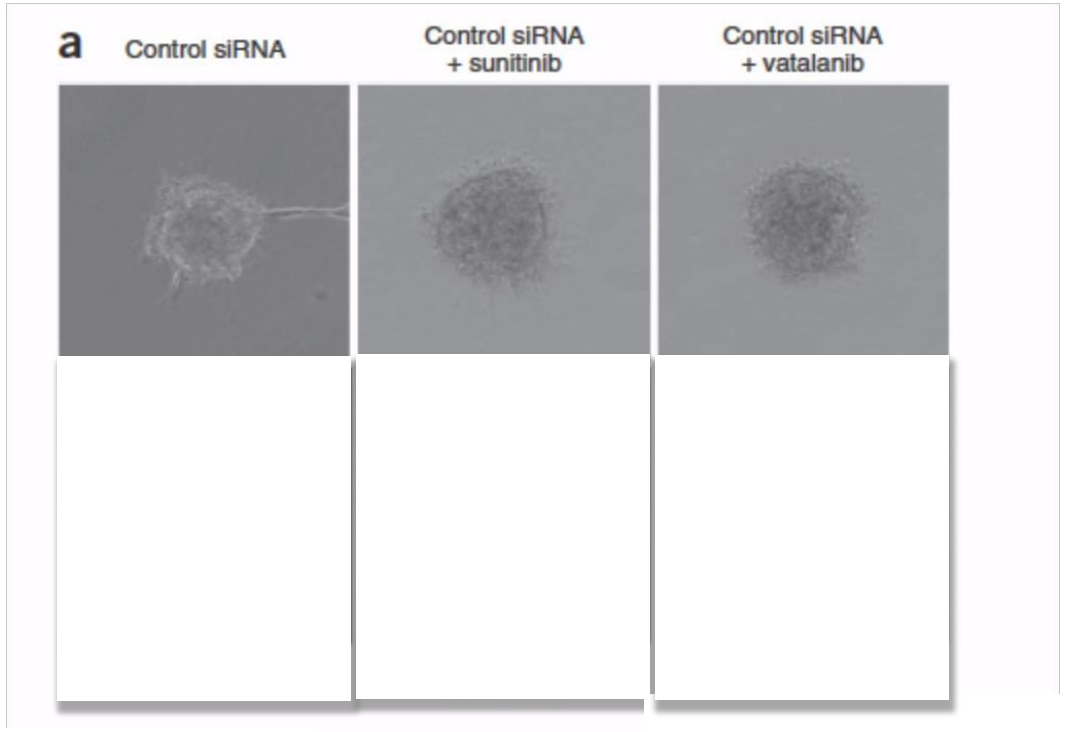


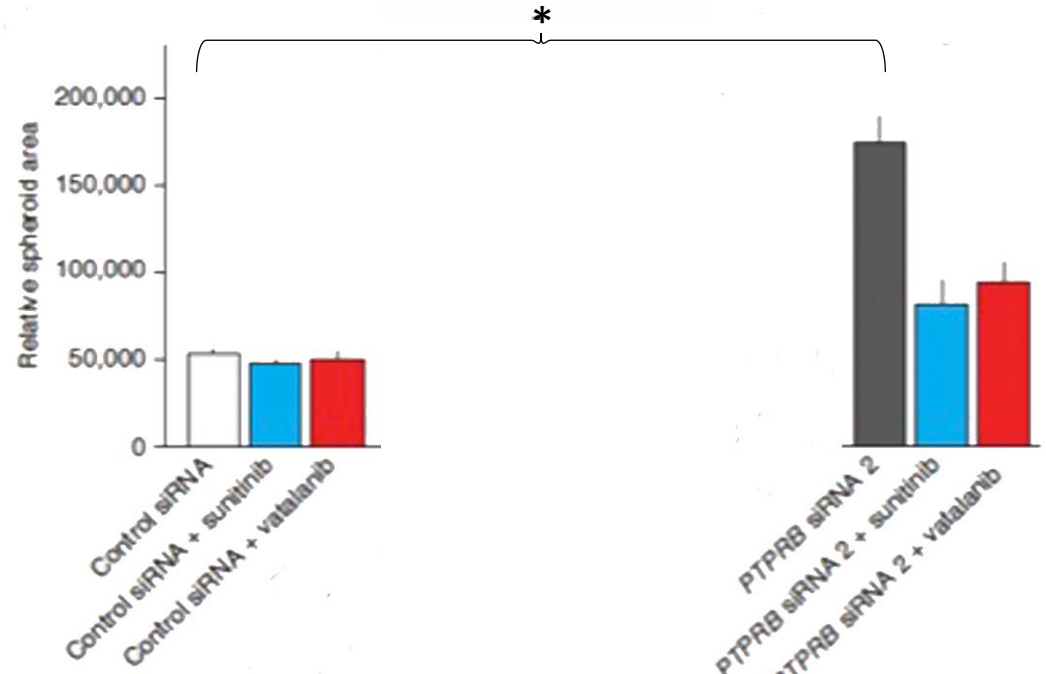






Behjati, S., Tarpey, P.S., Sheldon, H., Martincorena, I., Van Loo, P., Gundem, G., Wedge, D.C., Ramakrishna, M., Cooke, S.L., Pillay, N. and Vollan, H.K.M.et al, **2014. Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nature genetics, 46(4), pp.376-379.**


a
Control siRNA
Control siRNA
+ sunitinib
Control siRNA
+ vatalanib


*
Relative spheroid area
200,000
150,000
100,000
50,000
0
Control siRNA
Control siRNA + sunitinib
Control siRNA + vatalanib
PTPRB siRNA 2
PTPRB siRNA 2 + sunitinib
PTPRB siRNA 2 + vatalanib

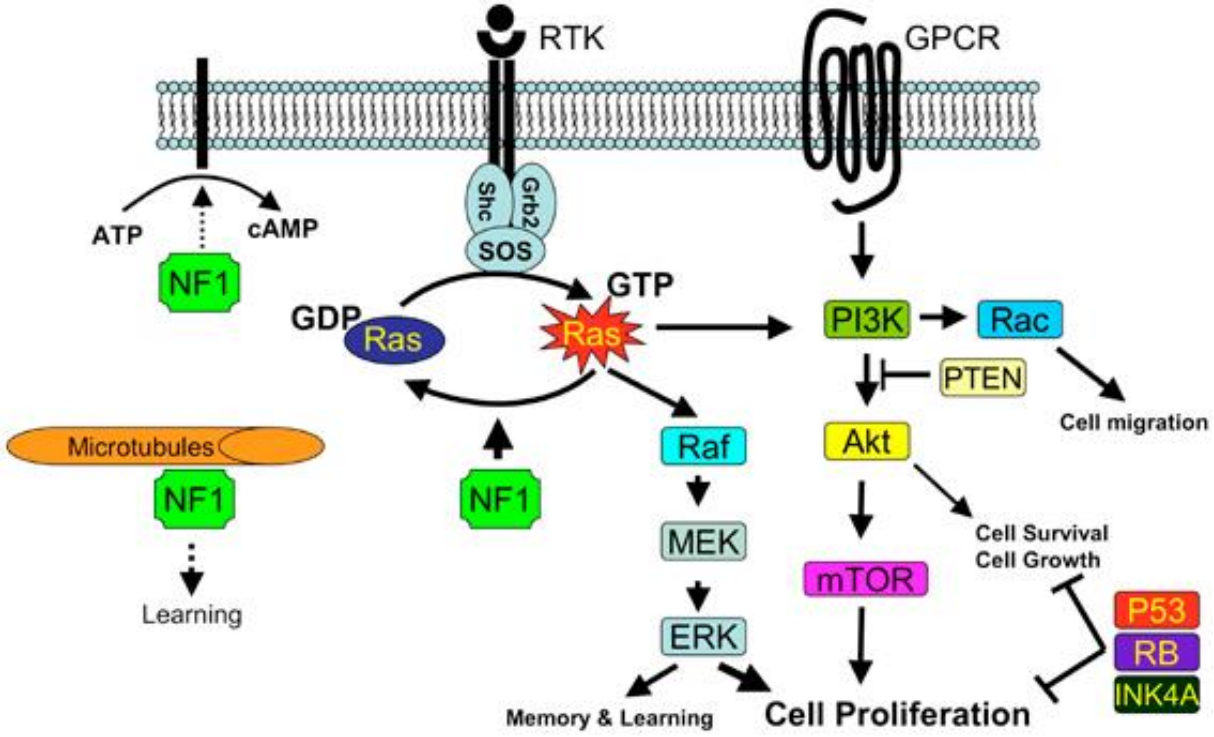
Dramatic increase in our understanding of genomic events that characterise cancer but…

1) Clinical implementation of this knowledge to inform decision making is a major challenge.

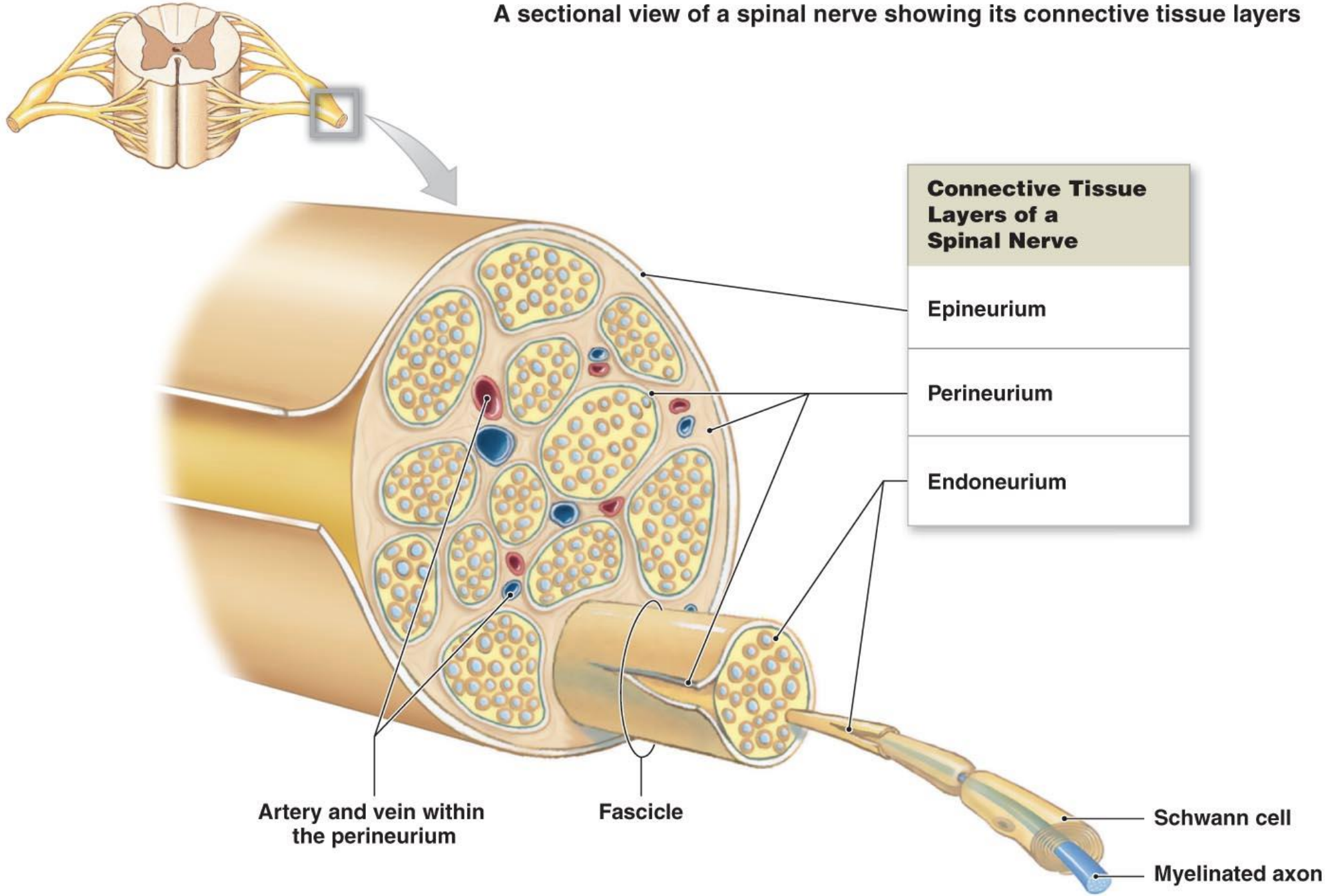
1) Do not fully understand the interaction between molecular therapeutic agents and the genetic mutations they target…

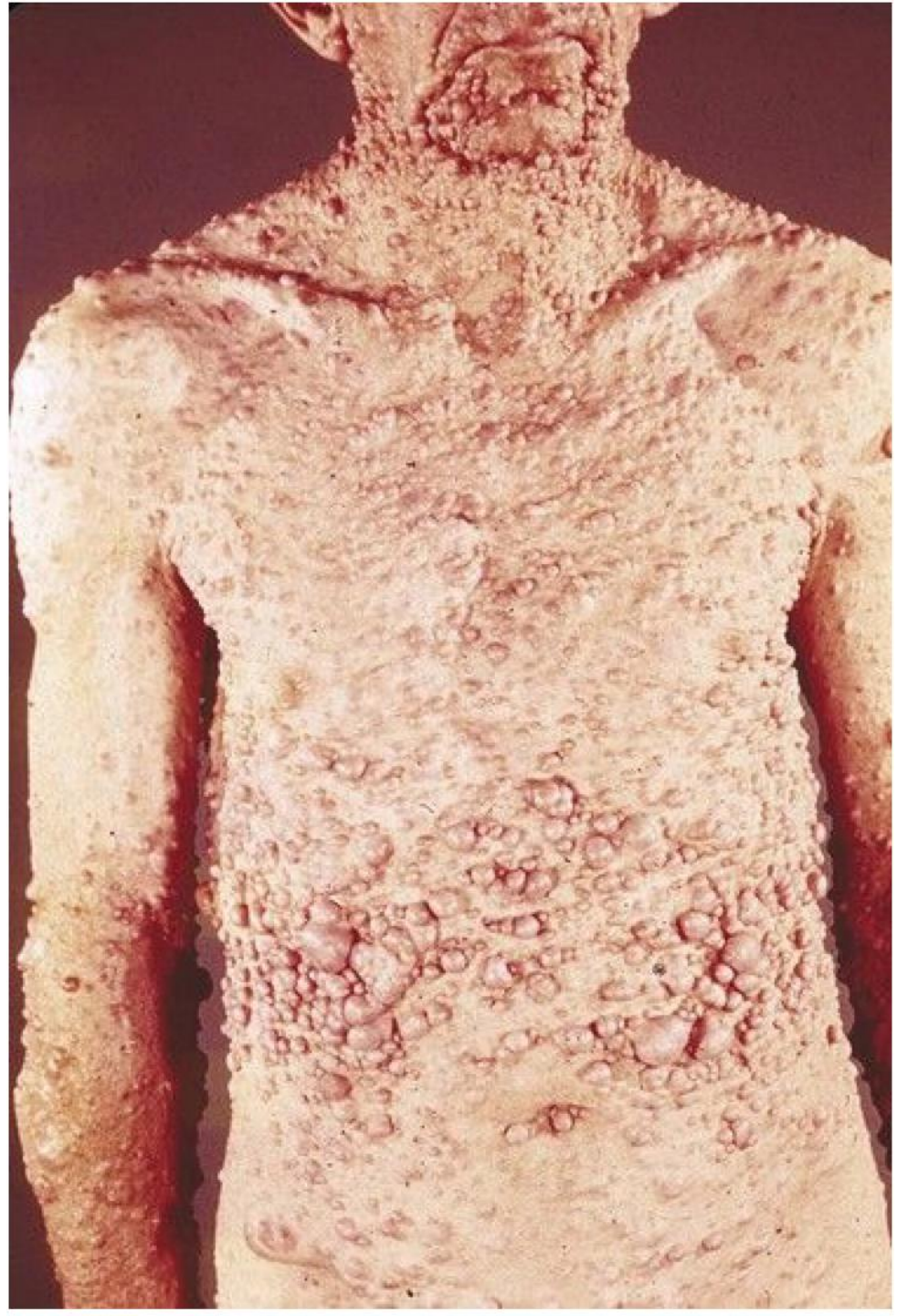
Neurofibromatosis Type I

- Common genetic disease.
- 1 in 3500 people. AD with high penetrance.
- NF1 – deletions, insertions, splice site mutations, mis-sense, non-sense mutations



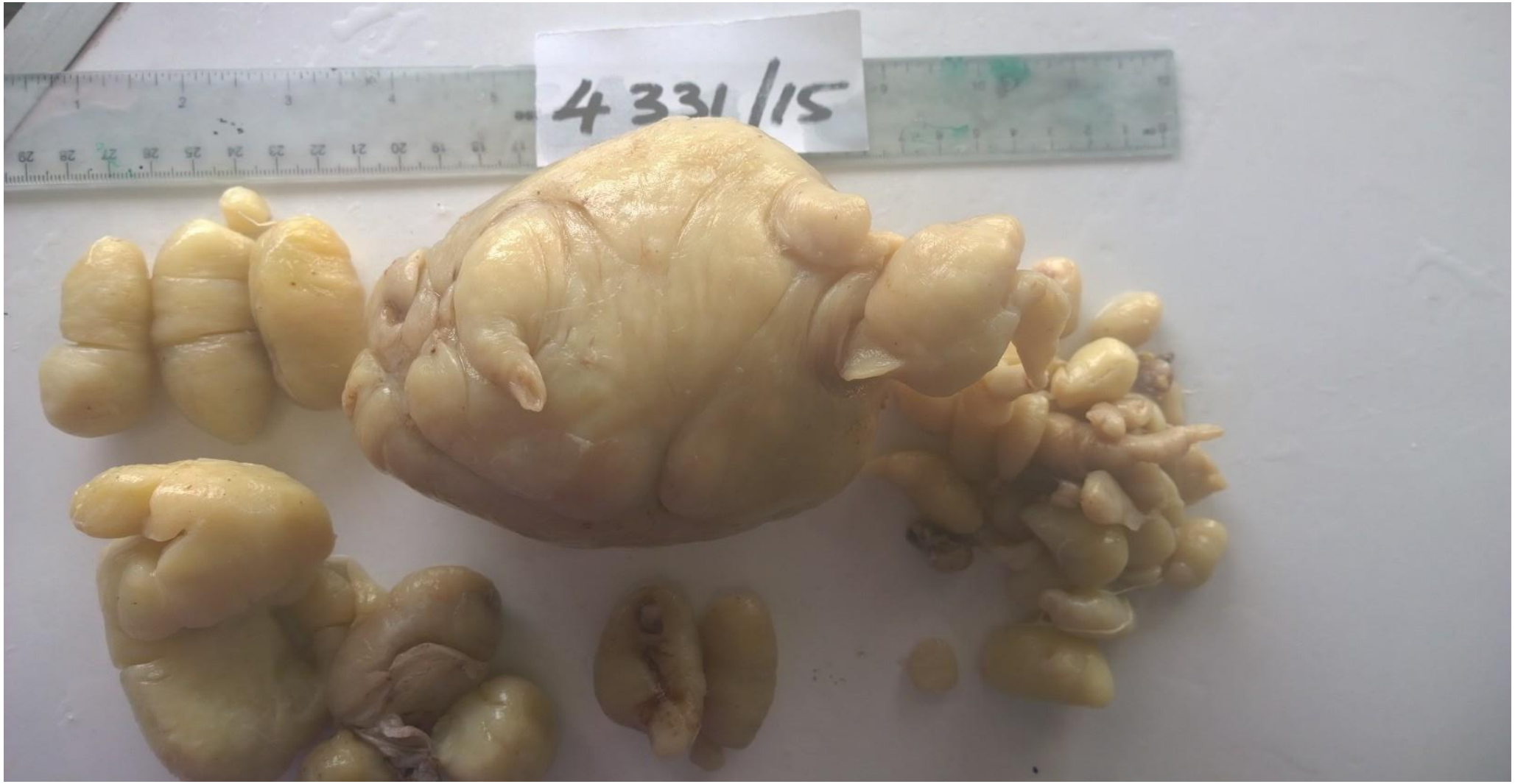
A sectional view of a spinal nerve showing its connective tissue layers

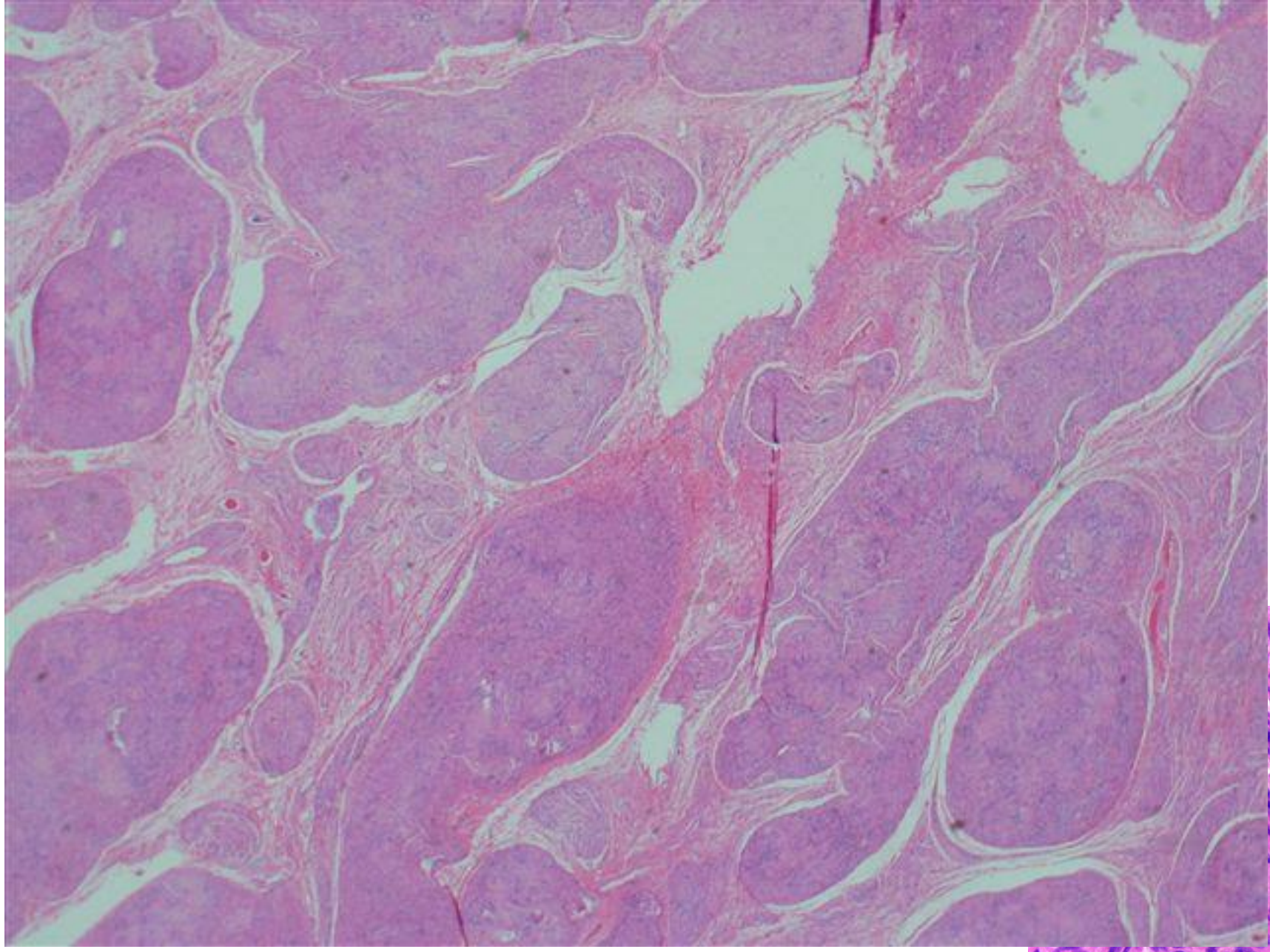


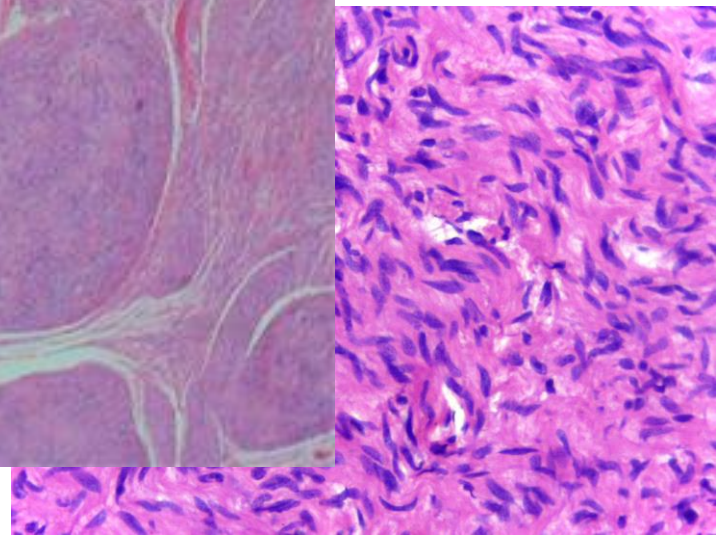


Enzinger and Weiss's Soft Tissue Tumors, 6th Edition

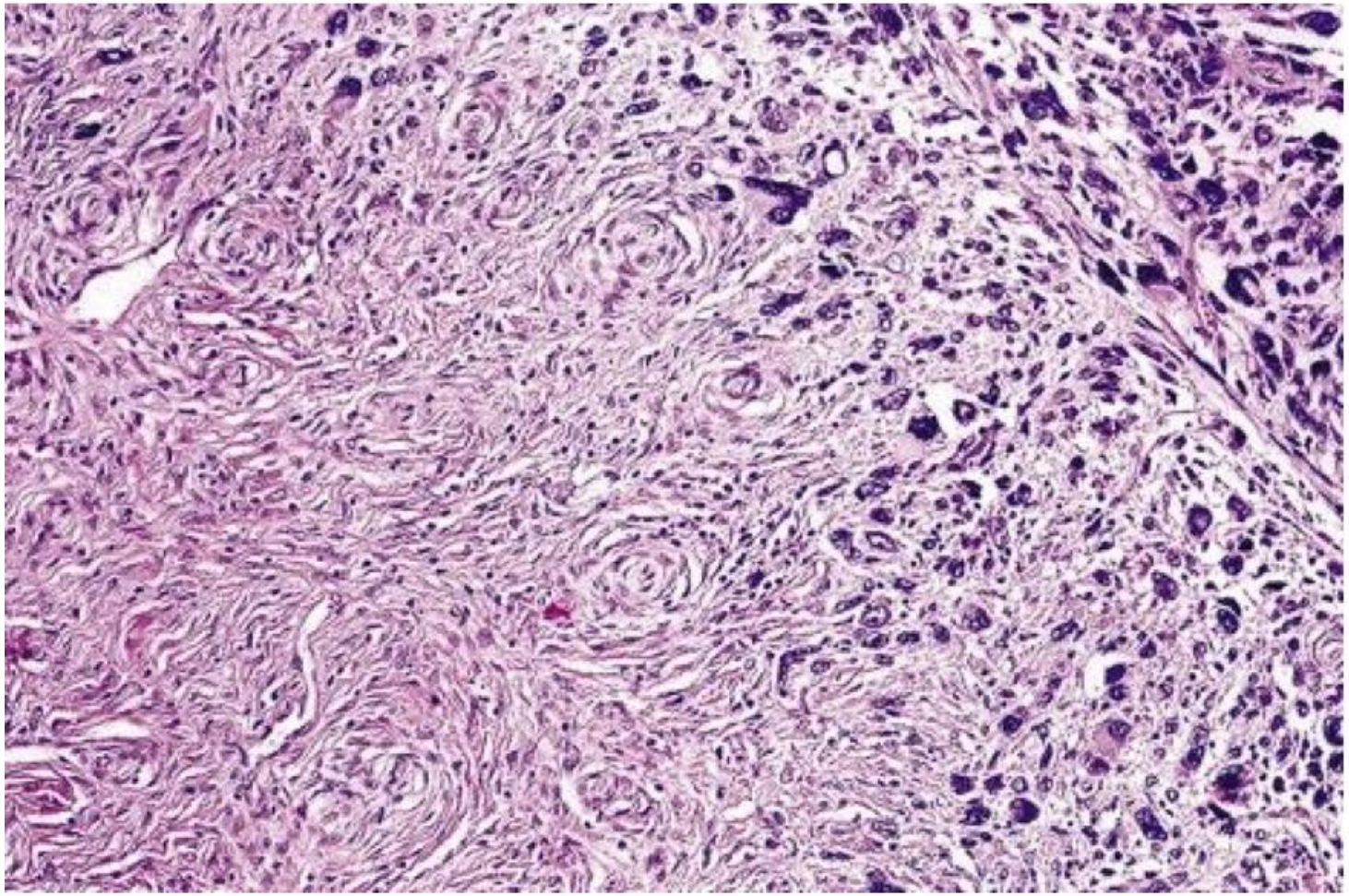
PLEXIFORM NEUROFIBROMA



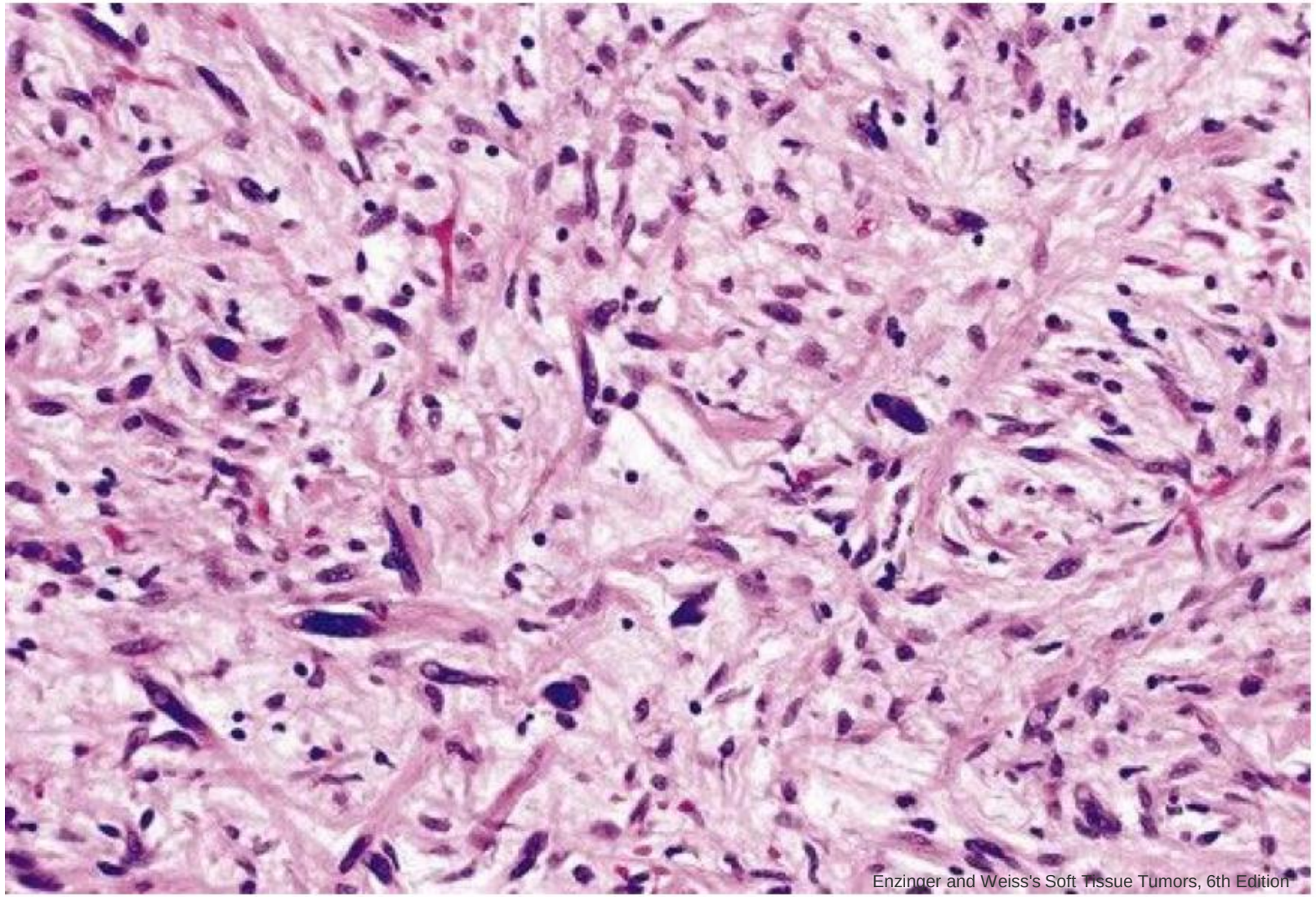




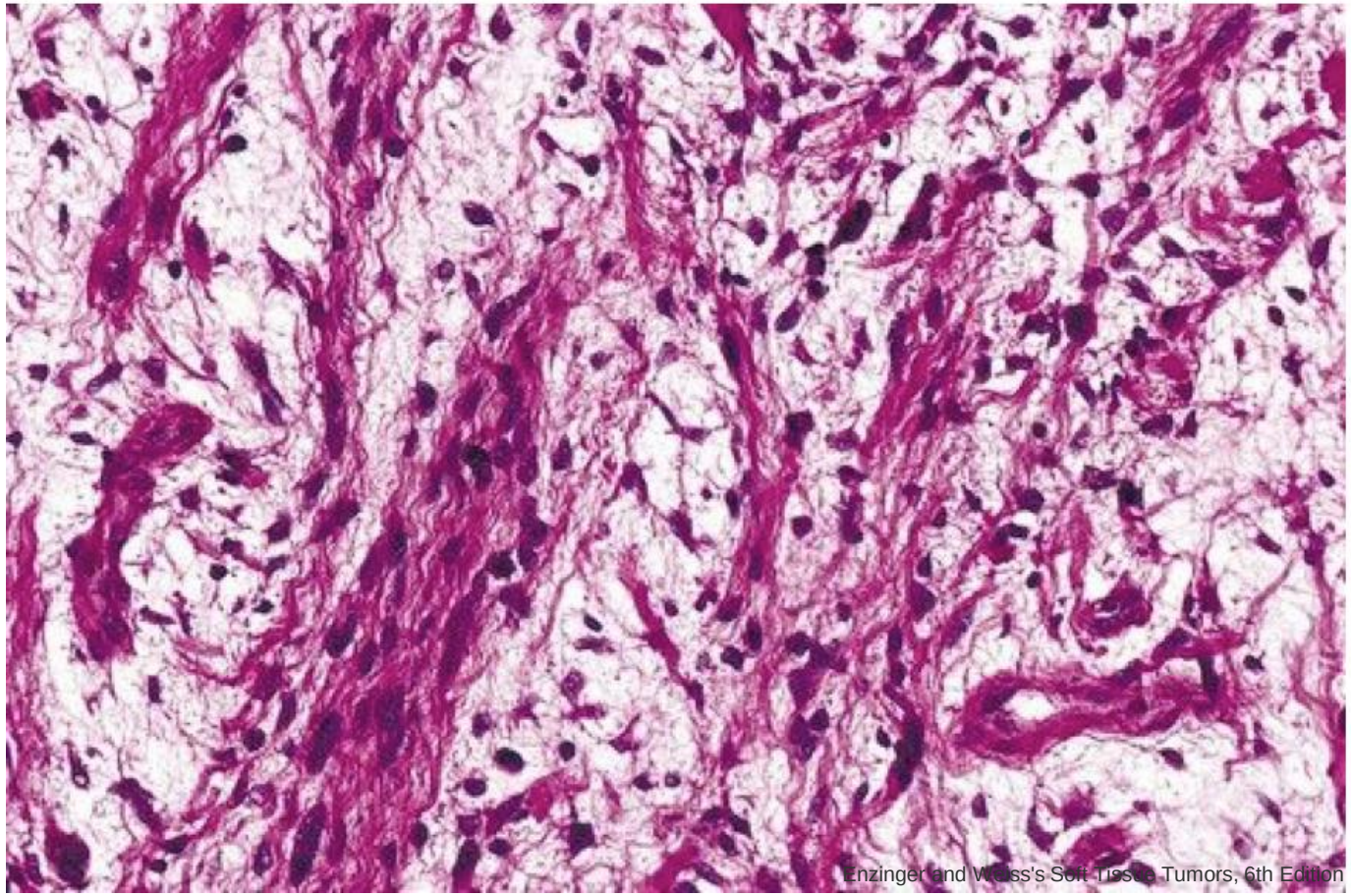
- Distinction between a neurofibroma with atypical features and MPNST Grade 1 is one of the most difficult – histological continuum.



“Atypical” neurofibroma



Low grade MPNST



nature genetics

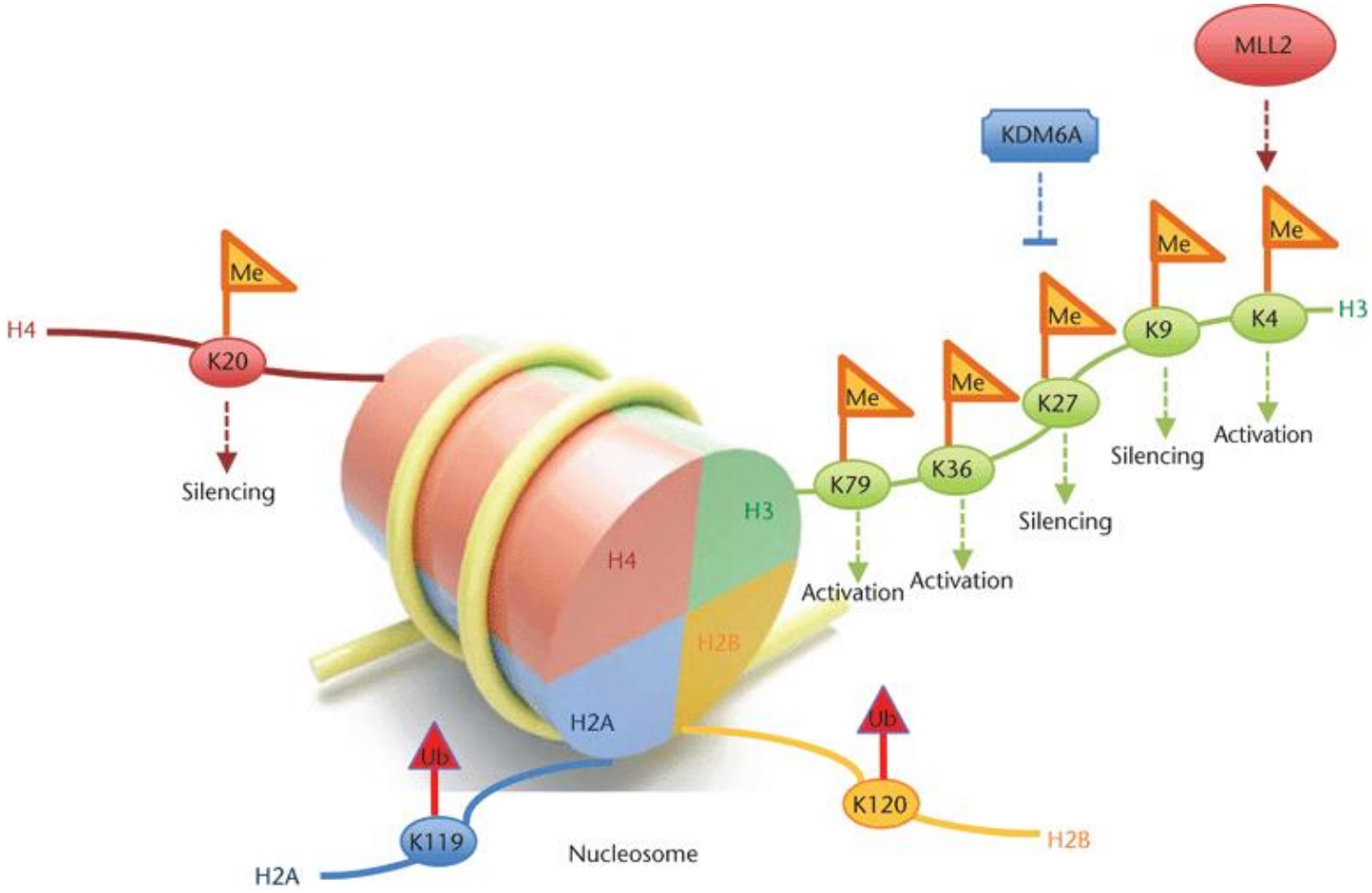
PRC2 is recurrently inactivated through *EED* or *SUZ12* loss in malignant peripheral nerve sheath tumors

William Lee[1,2,17], Sewit Teckie[2,3,17], Thomas Wiesner[3,17], Leili Ran[3,17], Carlos N Prieto Granada[4], Mingyan Lin[5], Sinan Zhu[3], Zhen Cao[3], Yupu Liang[3], Andrea Sboner[6–8], William D Tap[9,10], Jonathan A Fletcher[11], Kety H Huberman[12], Li-Xuan Qin[13], Agnes Viale[12], Samuel Singer[14], Deyou Zheng[5,15,16], Michael F Berger[3,4], Yu Chen[3,9,10], Cristina R Antonescu[4] & Ping Chi[3,9,10]

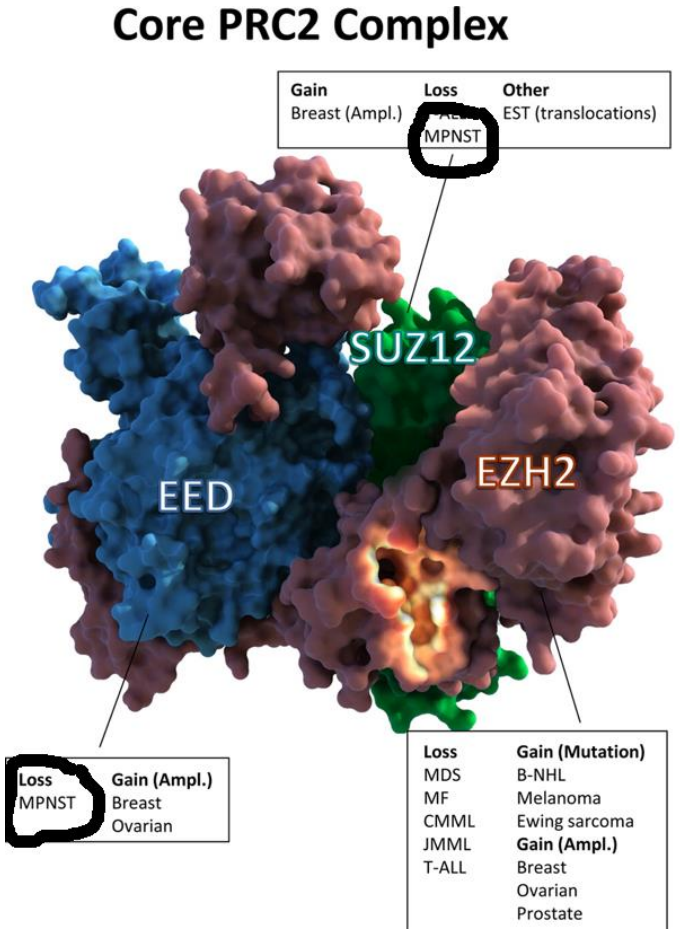
Somatic mutations of *SUZ12* in malignant peripheral nerve sheath tumors

Ming Zhang[1,2], Yuxuan Wang[1,2], Sian Jones[3], Mark Sausen[3], Kevin McMahon[1,2], Rajni Sharma[4], Qing Wang[1,2], Allan J Belzberg[5], Kaisorn Chaichana[5], Gary L Gallia[5], Ziya L Gokaslan[5], Greg J Riggins[5], Jean-Paul Wolinksy[5], Laura D Wood[4], Elizabeth A Montgomery[4], Ralph H Hruban[4], Kenneth W Kinzler[1,2], Nickolas Papadopoulos[1,2], Bert Vogelstein[1,2] & Chetan Bettegowda[1,2,5]

The nucleosome



MPNST have mutations in the PRC2 complex



- H3K27me3
- Transcriptional repression
-

Published in: Cigall Kadoch; Robert A. Copeland; Heike Keilhack; *Biochemistry* **2016,** 55, 1600-1614.
DOI: 10.1021/acs.biochem.5b01191

Loss of H3K27me3 Expression Is a Highly Sensitive Marker for Sporadic and Radiation-induced MPNST

Carlos N. Prieto-Granada, MD,† Thomas Wiesner, PhD,‡ Jane L. Messina, MD,† Achim A. Jungbluth, MD,* Ping Chi, MD, PhD,‡§‖ and Cristina R. Antonescu, MD**

Am J Surg Pathol • Volume 40, Number 4, April 2016

TABLE 2. H3K27me3 Monoclonal Antibody IHC Results of the Different Entities Included in the MPNST Differential Diagnosis and Miscellaneous Tumors

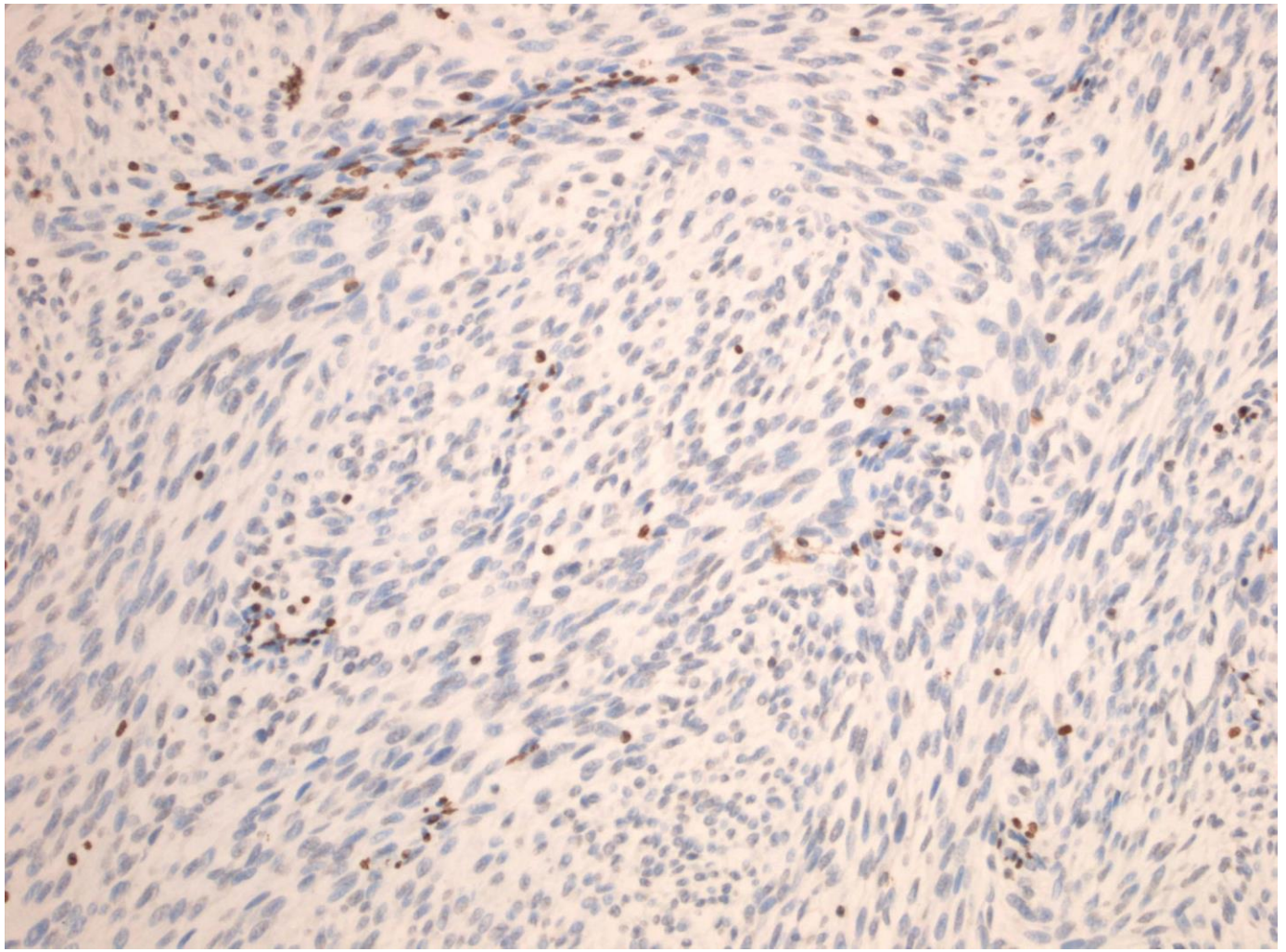
Diagnosis	H3K27me3 IHC Loss/Total Cases
Cutaneous melanoma	
Pure desmoplastic melanoma	0/37
Mixed desmoplastic melanoma	0/11
Spindle cell melanoma	0/5
Synovial sarcoma (MF, BF, and PD)	0/113
GIST	
KIT/*PDGFRA* mutant	0/109
SDHB-deficient WT pediatric and adult	0/13
WT dedifferentiated GIST	0/1
Liposarcoma	
Well differentiated	0/31
Dedifferentiated	0/44
Ossifying fibromyxoid tumor	0/6
Soft tissue myoepithelial carcinomas	0/6
MFS	0/63

In the case of GIST, *KIT* and *PDGFRA* were WT.
BF indicates biphasic; MF, monophasic; PD, poorly differentiated.

H3K27Me3 loss in >90% of MPNST

MPNST Grade 3

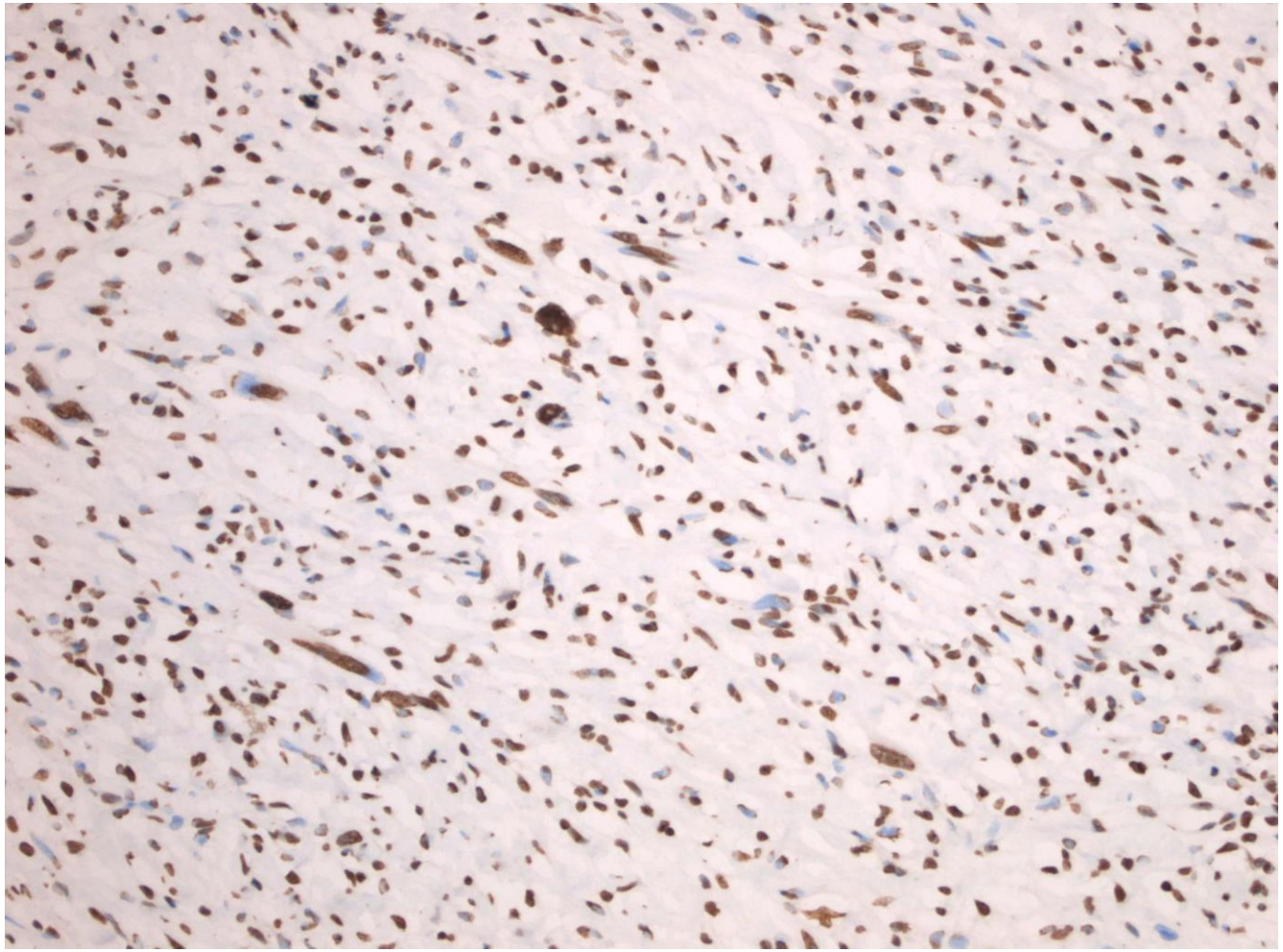
H3K27me3 - immunohistochemistry



Courtesy of Dr. Roberto Tirabosco

Atypical Neurofibroma

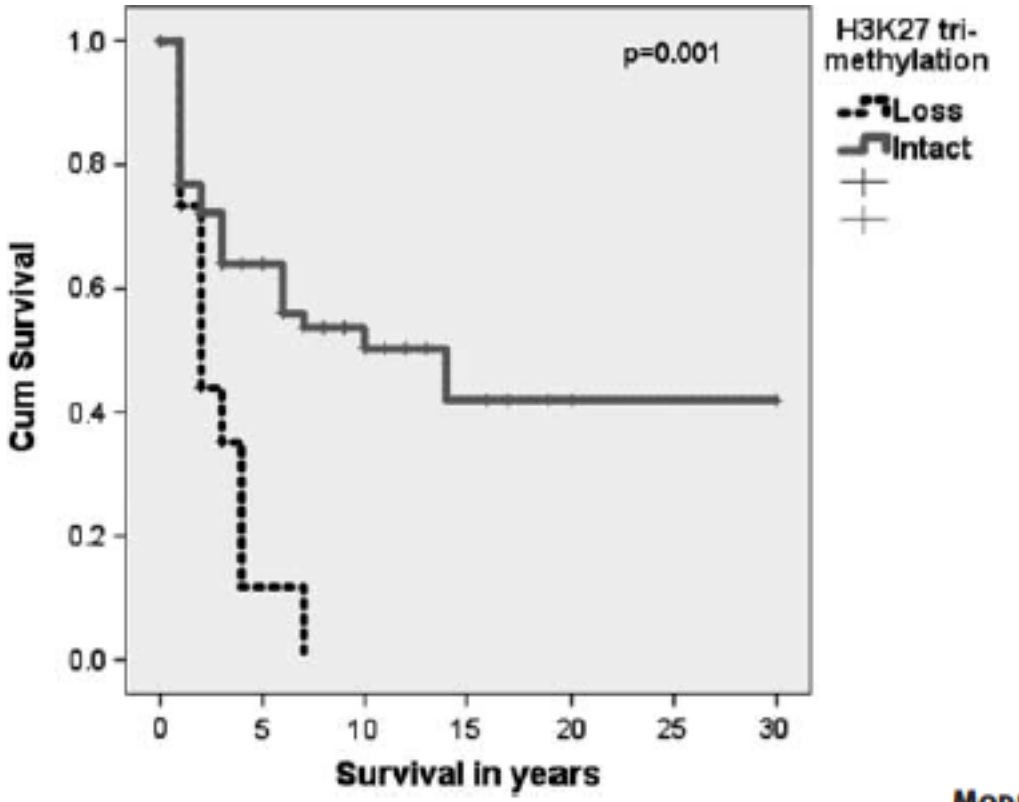
H3K27me3 - immunohistochemistry



Courtesy of Dr. Roberto Tirabosco

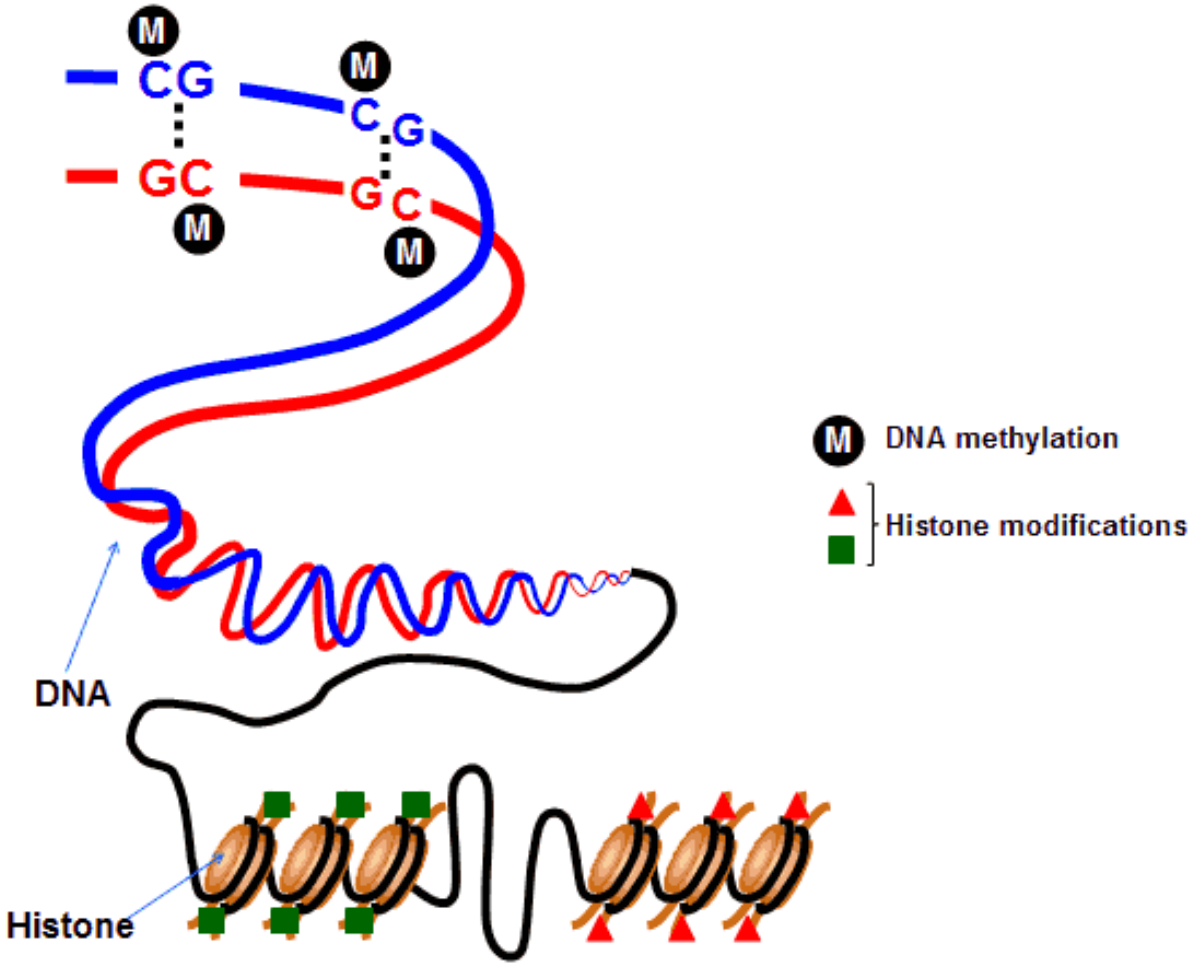
H3K27me3

- Prognostic utility

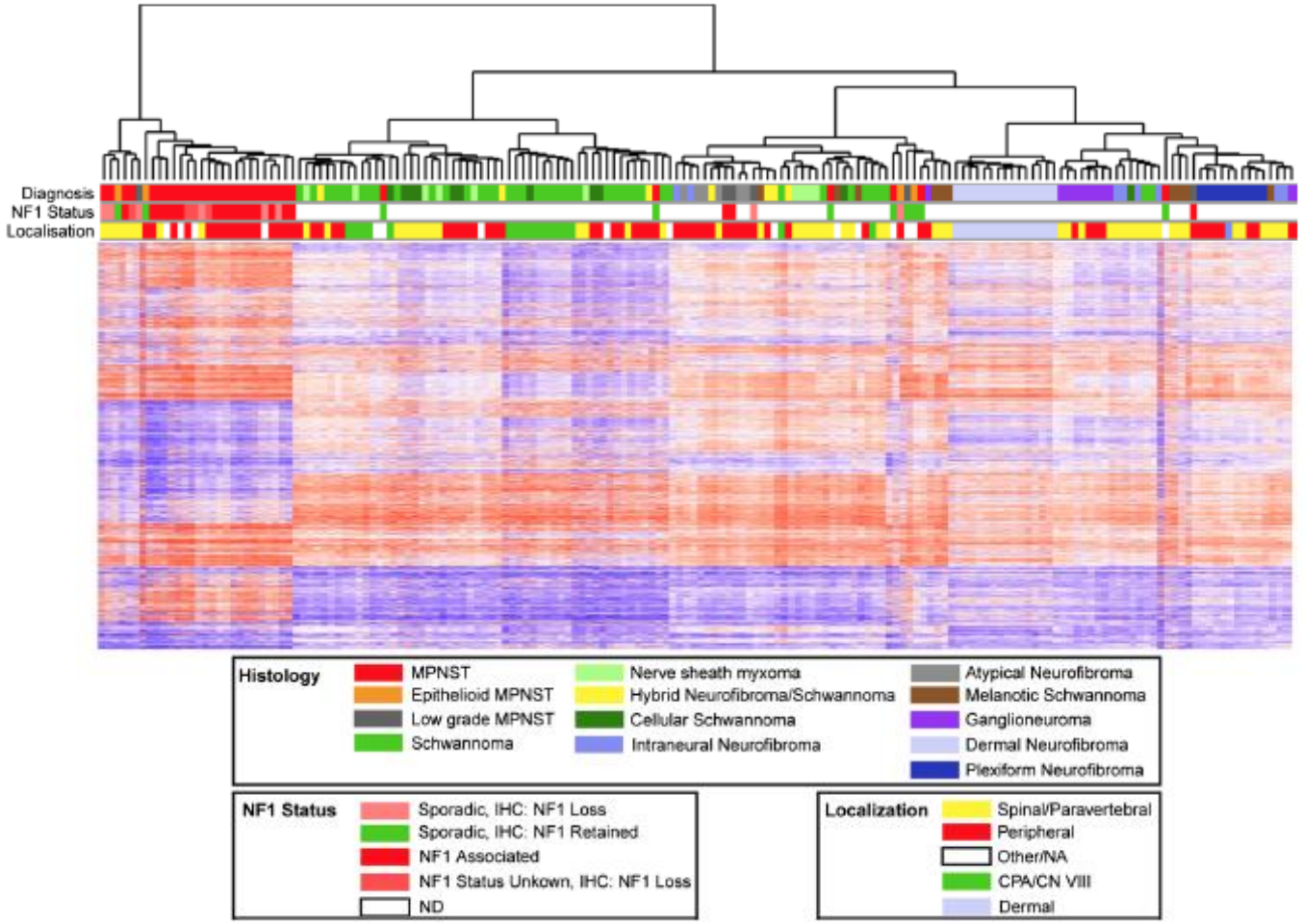


MODERN PATHOLOGY (2016) 29, 582–590

DNA methylation



MPNST



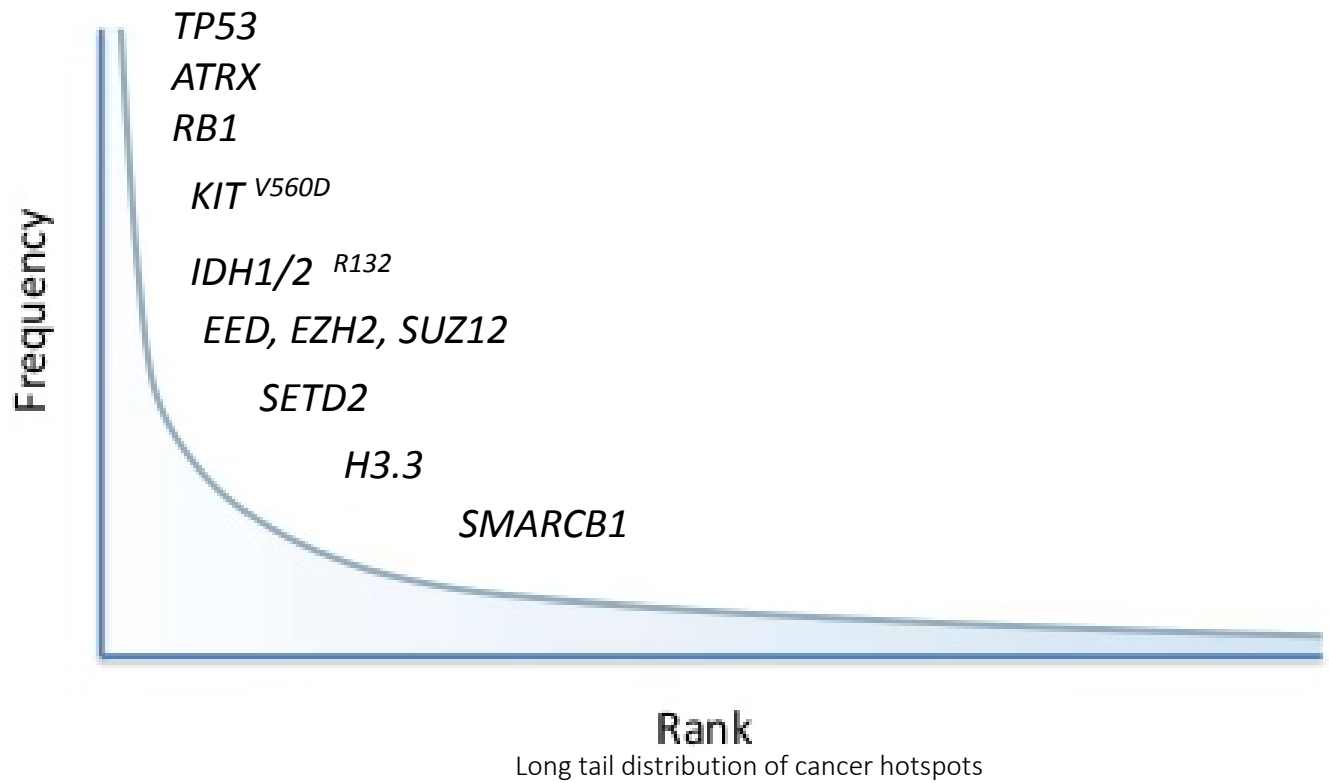
Acta Neuropathol (2016) 131:877–887
DOI 10.1007/s00401-016-1540-6

ORIGINAL PAPER

Methylation-based classification of benign and malignant peripheral nerve sheath tumors

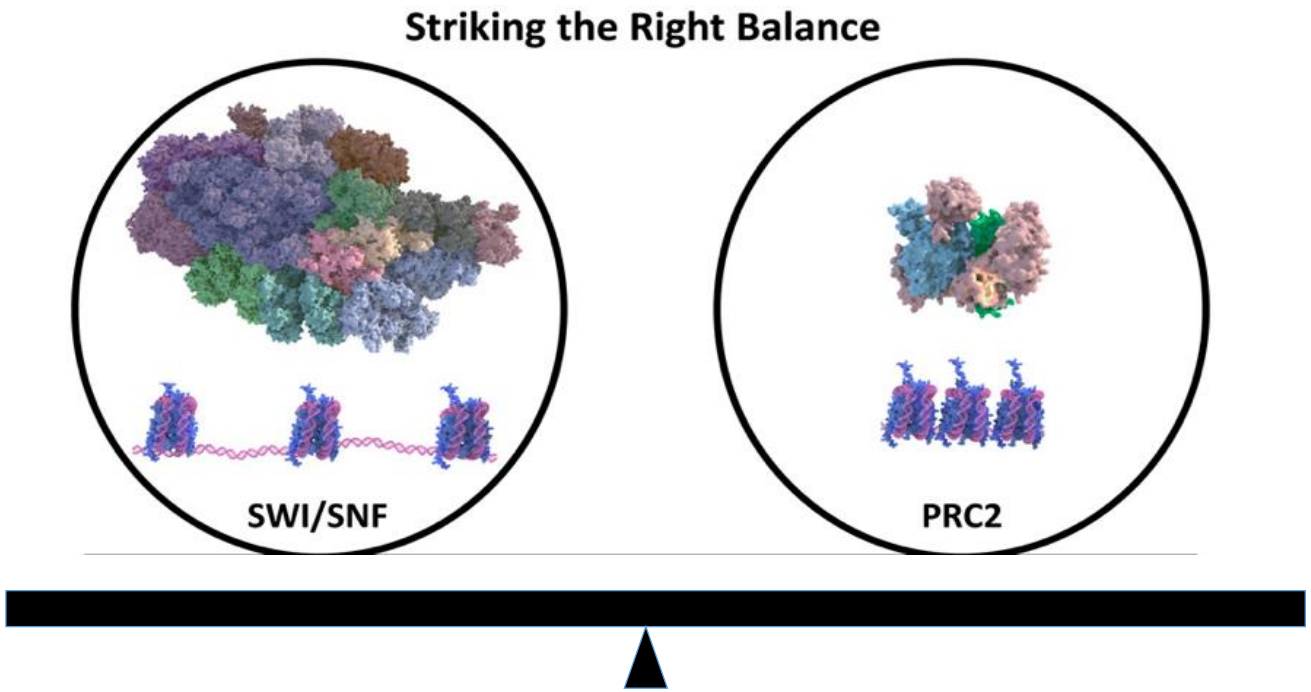
Manuel Röhrich[1,2] · Christian Koelsche[1,2] · Daniel Schrimpf[1,2] · David Capper[1,2] · Felix Sahm[1,2] · Annekathrin Kratz[1,2] · Jana Reuss[2] · Volker Hovestadt[3] · David T. W. Jones[4] · Melanie Bewerunge-Hudler[5] · Albert Becker[6] · Joachim Weis[7] · Christian Mawrin[8] · Michel Mittelbronn[9,10] · Arie Perry[11] · Victor-Felix Mautner[12] · Gunhild Mechtersheimer[13] · Christian Hartmann[14] · Ali Fuat Okuducu[15] · Mirko Arp[16] · Marcel Seiz-Rosenhagen[16] · Daniel Hänggi[16] · Stefanie Heim[17] · Werner Paulus[17] · Jens Schittenhelm[18] · Rezvan Ahmadi[19] · Christel Herold-Mende[19] · Andreas Unterberg[19] · Stefan M. Pfister[4,20] · Andreas von Deimling[1,2] · David E. Reuss[1,2]

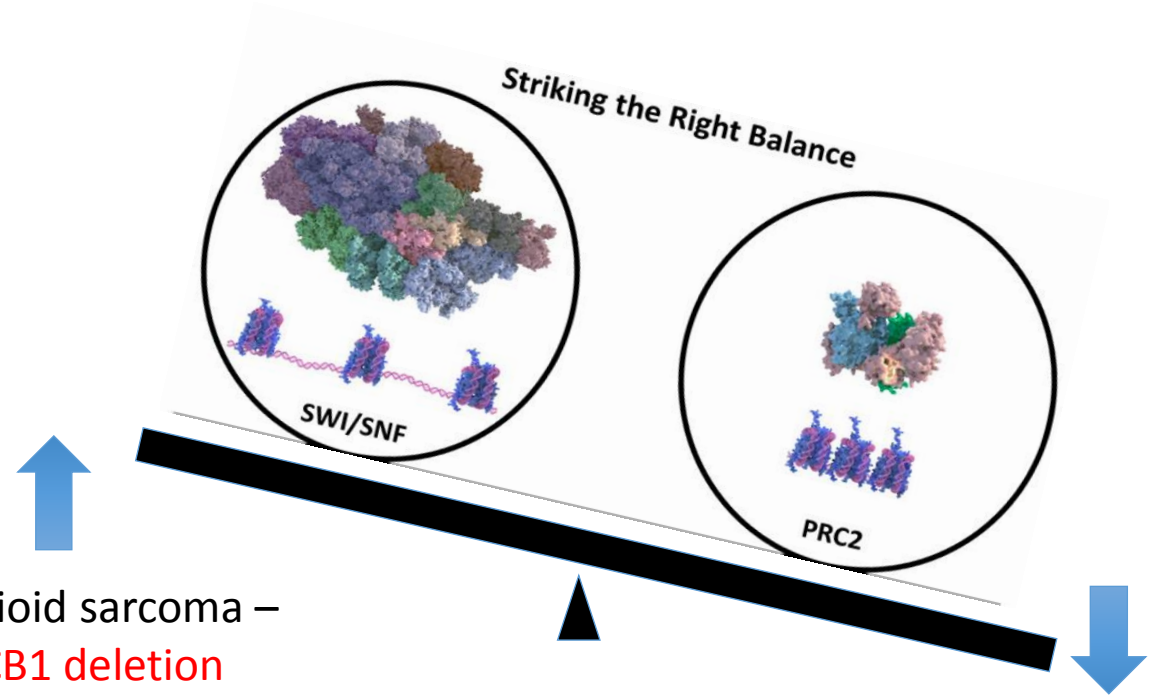
Sarcoma hotspot mutations



Long tail distribution of cancer hotspots

Balance between chromatin remodelling and histone modification has biological implications for sarcomas

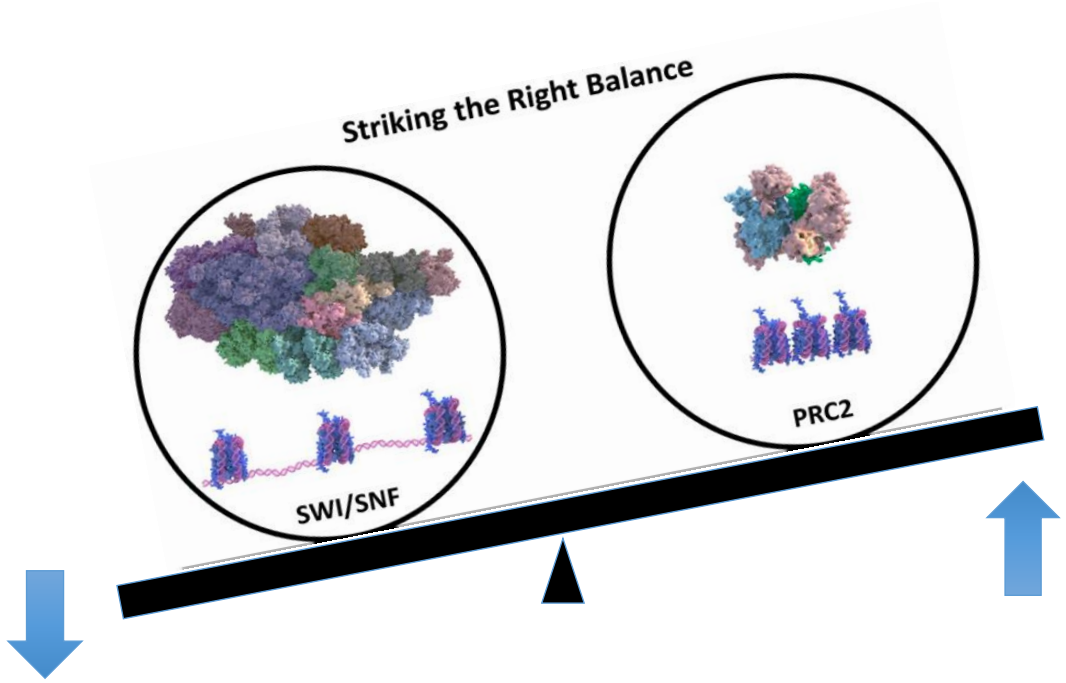




Epithelioid sarcoma – SMARCB1 deletion

Epithelioid MPNST – SMARCB1 deletion

Synovial Sarcoma – SYS-SSX fusion



MPNST – SUZ12, EED, EZH2 loss of function

Take home points

1. Sarcomas are a collection of diverse diseases with different phenotypes, genetics and clinical outcomes.
2. Sarcoma classification – refined by genetics and epigenetics with rapid application in clinical diagnostics.
3. Urgent need to identify more biomarkers and more research is needed – likely to be gains from epigenetic profiling.