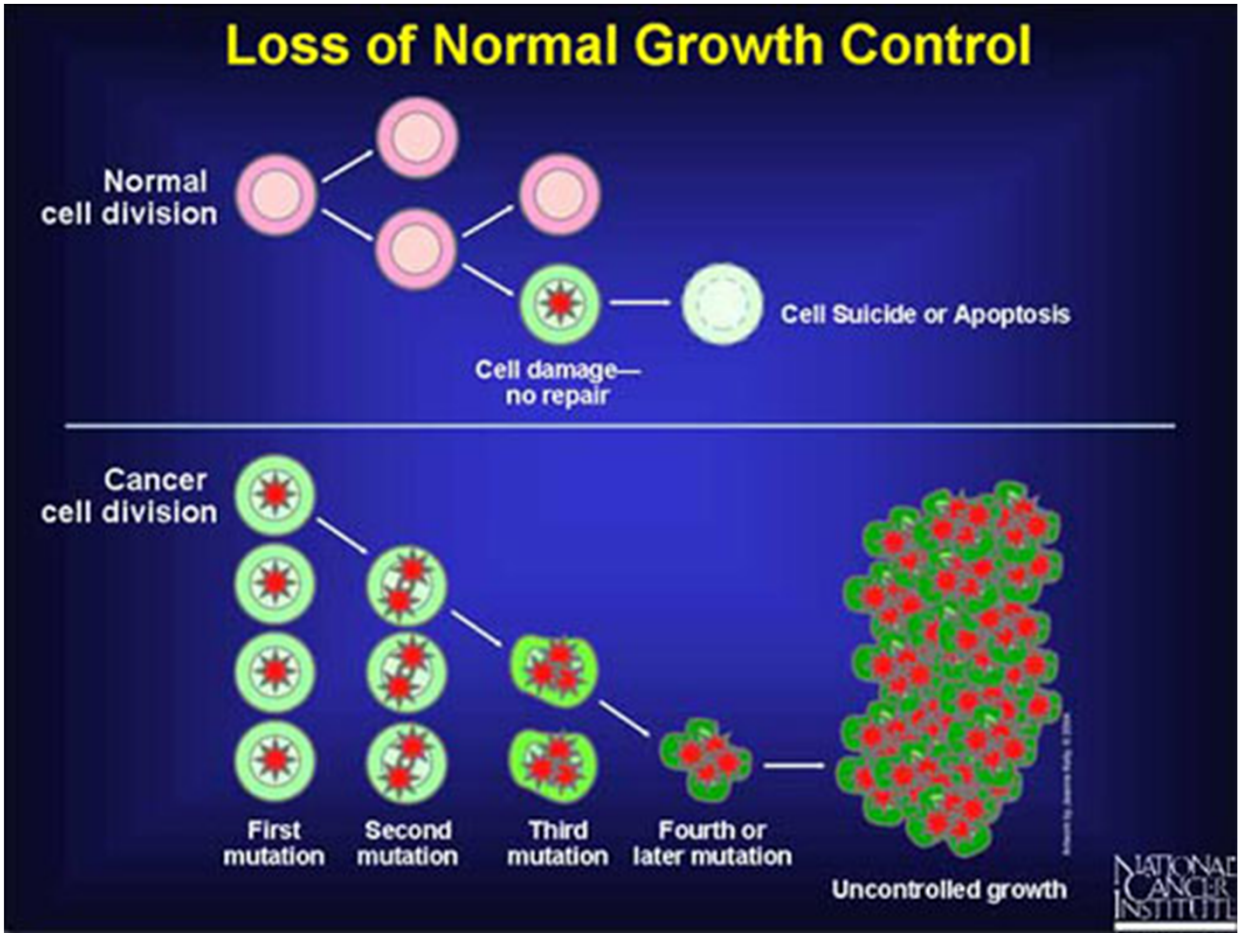
Cancer Pain

- What is cancer?
- Role of nervous system in cancer biology
  - Pain generation – neurogenic inflammation
  - Perineural invasion and metastasis
- What is cancer pain?
  - neuropathic
  - Inflammatory
  - Neither inflammatory or neuropathic
  - Antineoplastic treatment –CIPN, radiation, surgery
- Animal models for human cancer – are they useful?

What is cancer?

From the NCI: Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph system (and via the peripheral nervous system for visceral cancers)



Types of Cancer

•**Carcinoma -** cancer that begins in cells of epithelial origin; e.g., in the skin or in tissues that line or cover internal organs. - **Painful**

•**Sarcoma -** cancer that begins in cells of mesenchymal origin; e.g., bone, cartilage, fat, muscle, vasculature. These are relatively rare (most bone cancers are not 1° bone cancers). - **Painful**

•**Leukemia -** cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood. – **Not Painful**

•**Lymphoma and myeloma -** cancers that begin in the cells of the immune system. **-Not Painful**

•**Central nervous system cancers –** cancer that begin in the tissue of the brain or spinal cord. **Painful in the end**

Factors that increase cancer risk

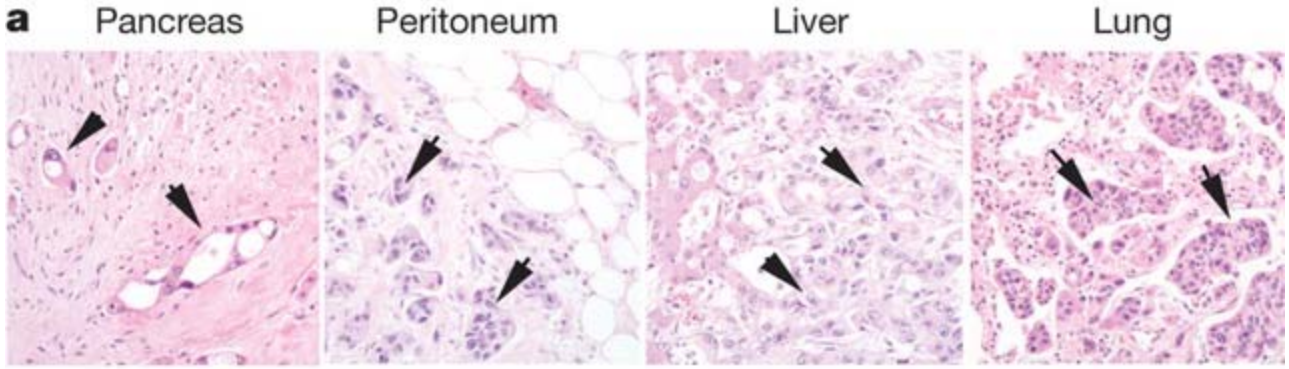
- Chemicals - smoking (50 known carcinogens)
- Diet – high salt (Japan, gastric cancer), high fat (US, colon cancer)
- Infection – usually viral (HPV), Hep B,C, helicobactor
- Radiation – UV, radon -
  - 2007 NCI study – CT scans conducted in 2007 will cause 29K excess cancers cases and 14.5K deaths
- Heredity – BRCA1&2
- Physical agents – asbestos
- Hormones – estrogen
- **AGING – comes with its own pain**

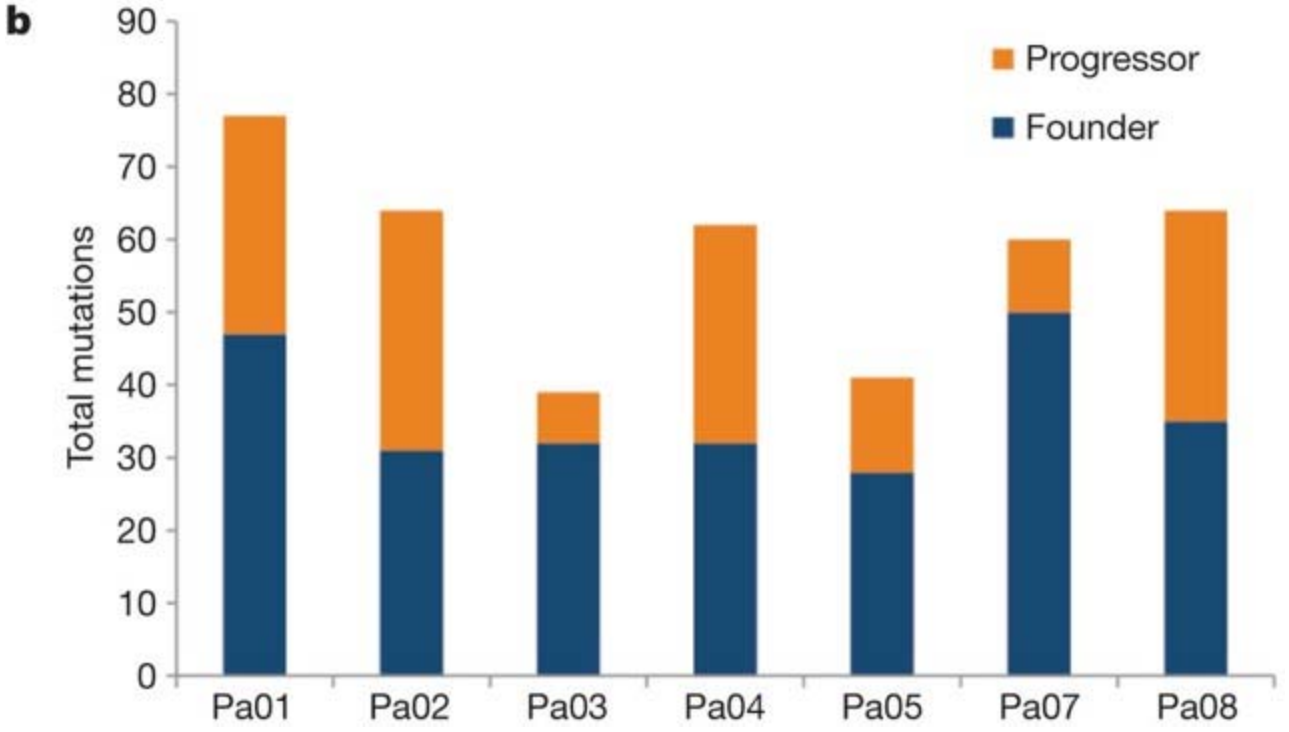
All risk factors lead to genetic changes
Pancreatic ductal adenocarcinoma (PDAC)

In 7 PDAC patients, with 24 different tumors, whole exome sequencing showed:

426 somatic mutations

388 different genes were involved

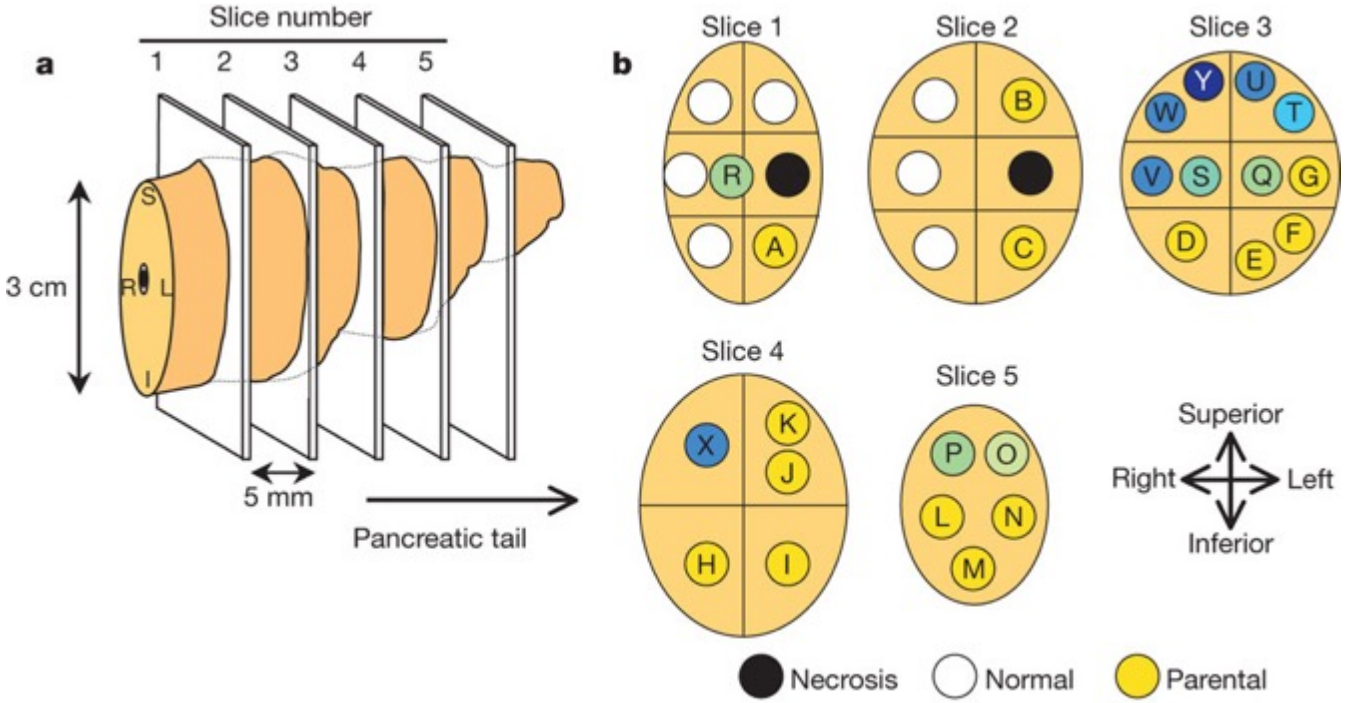




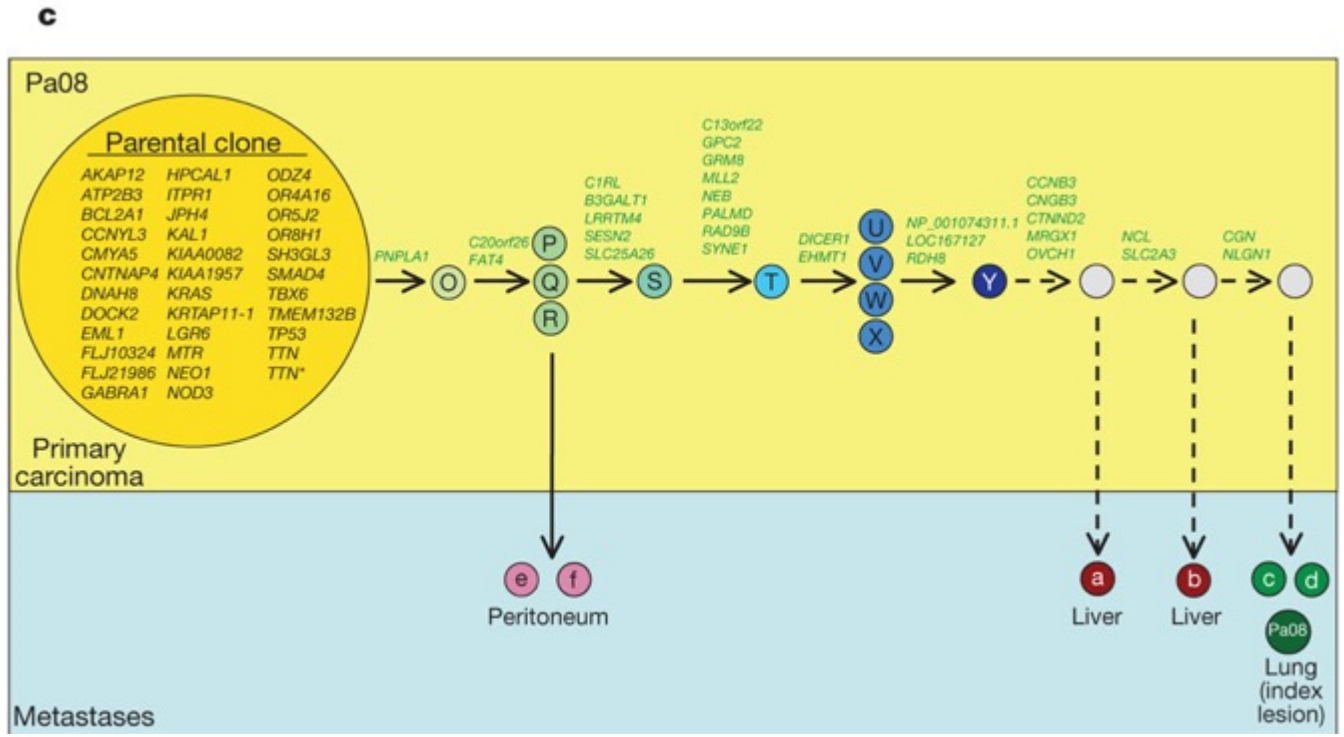
S Yachida *et al. Nature* **467**, 1114-1117 (2010) doi:10.1038/nature09515

nature

Geographic mapping of metastatic clones within the primary carcinoma and proposed clonal evolution of Pa08.



Most of these genetic lesions were missense with some silent single base substitutions (no change in coded amino acid)



S Yachida *et al. Nature* **467**, 1114-1117 (2010)
doi:10.1038/nature09515

Conclusion from Yachida et al

- Clonal populations that give rise to metastases are present in primary tumor
- These clones are genetically evolved from original non-metastatic clone
- 10 yrs between original mutation and non-metastatic parental clone
- 5 yrs more before metastasis
- 2yrs more until death
- **What does this mean for cancer pain? It may be masked or compensated for until it's not.**

Who gets cancer pain?

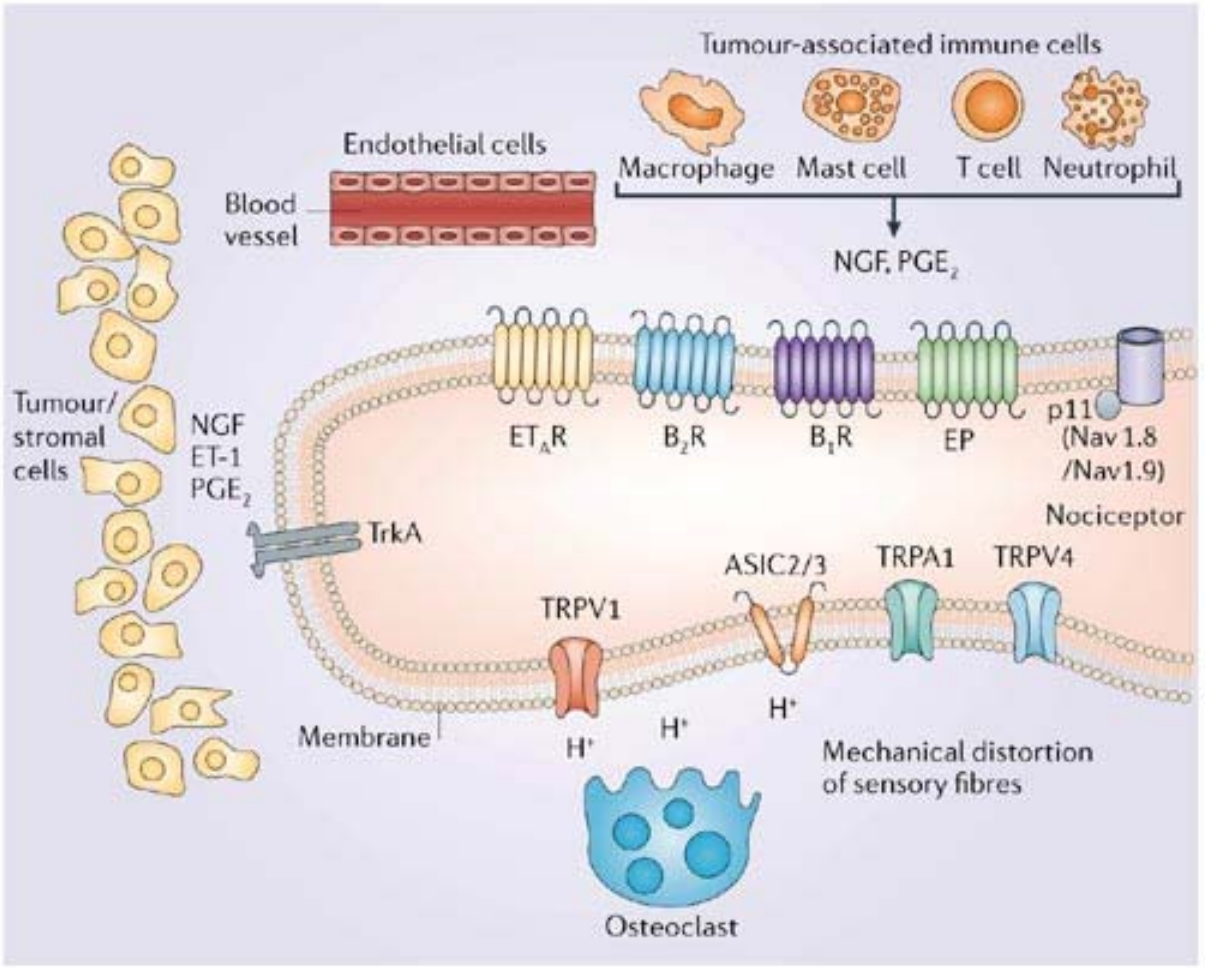
- > ten million people are diagnosed with cancer each year. (this does not include skin cancer. By 2020 15M people will be diagnosed each year).
- ~ 30% of adults receiving treatment and 66% with advanced malignant disease experience pain.
  - Head and neck (67-91%)
  - Prostate (56-94%)
  - Uterine (30-90%)
  - Genitourinary (58-90%)
  - Breast (40-89%)
  - Pancreatic (72-85%)
- Are all cancer pains the same?

What is cancer pain?

- Pain caused by the cancer itself (3/4 of patients):
  - Inflammatory pain
  - Neuropathic pain
    - » Destruction of endings –e.g. in bone cancer
    - » Changes in neuronal environment – pH, tumor derived sensitization (GFs), neuroma formation
    - » Perineural invasion
- Pain Cause by treatment (1/4 of patients)
  - Chemotherapeutic Induced Peripheral Neuropathy (CIPN)
  - Radiation induced
  - Surgical pain
  - Opioid paradoxical pain

Inflammatory aspects of cancer pain

- Local and systemic inflammatory response; pro-inflammatory molecules facilitate pain transmission.
- Tumor and associated immune cells release endothelin, cytokines, prostaglandins, TNF-α, growth factors (NGF) and protons, which excite primary afferents.
- Hematopoietic colony-stimulating factors (G-CSF, GM-CSF); IL6/gp130 signaling.
(Schweizerhof et al., 2009; Andratsch et al., 2009)



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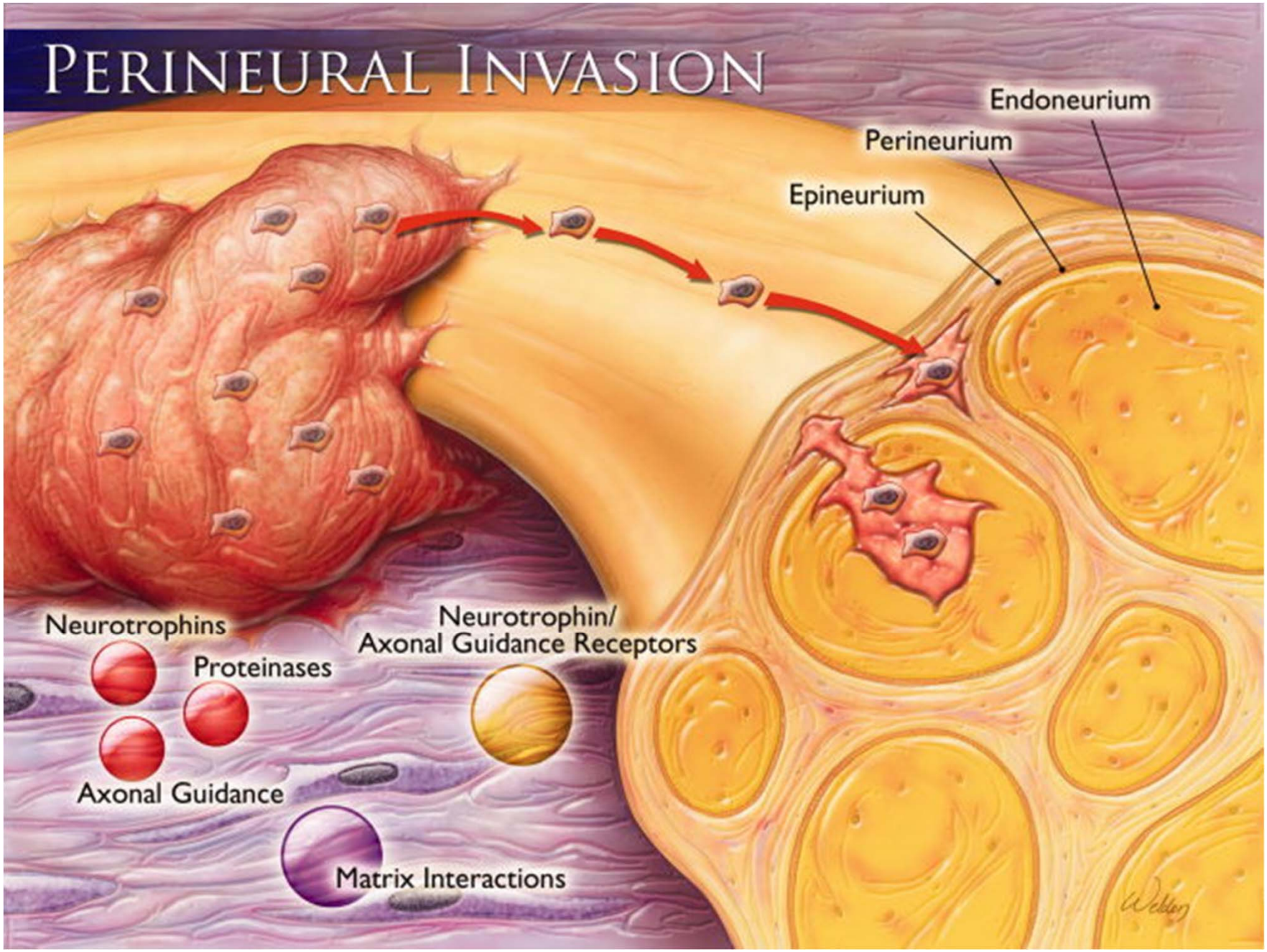
Neuropathic Aspects Cancer Pain

- Invasion of endoneurium and perineurium
- Destruction of nerve fibers
- Distortion of anatomical structures – e.g. periosteum (connective tissue covering bone)
- Sprouting of sensory fibers
- Abnormal interactions between sympathetic and sensory fibers

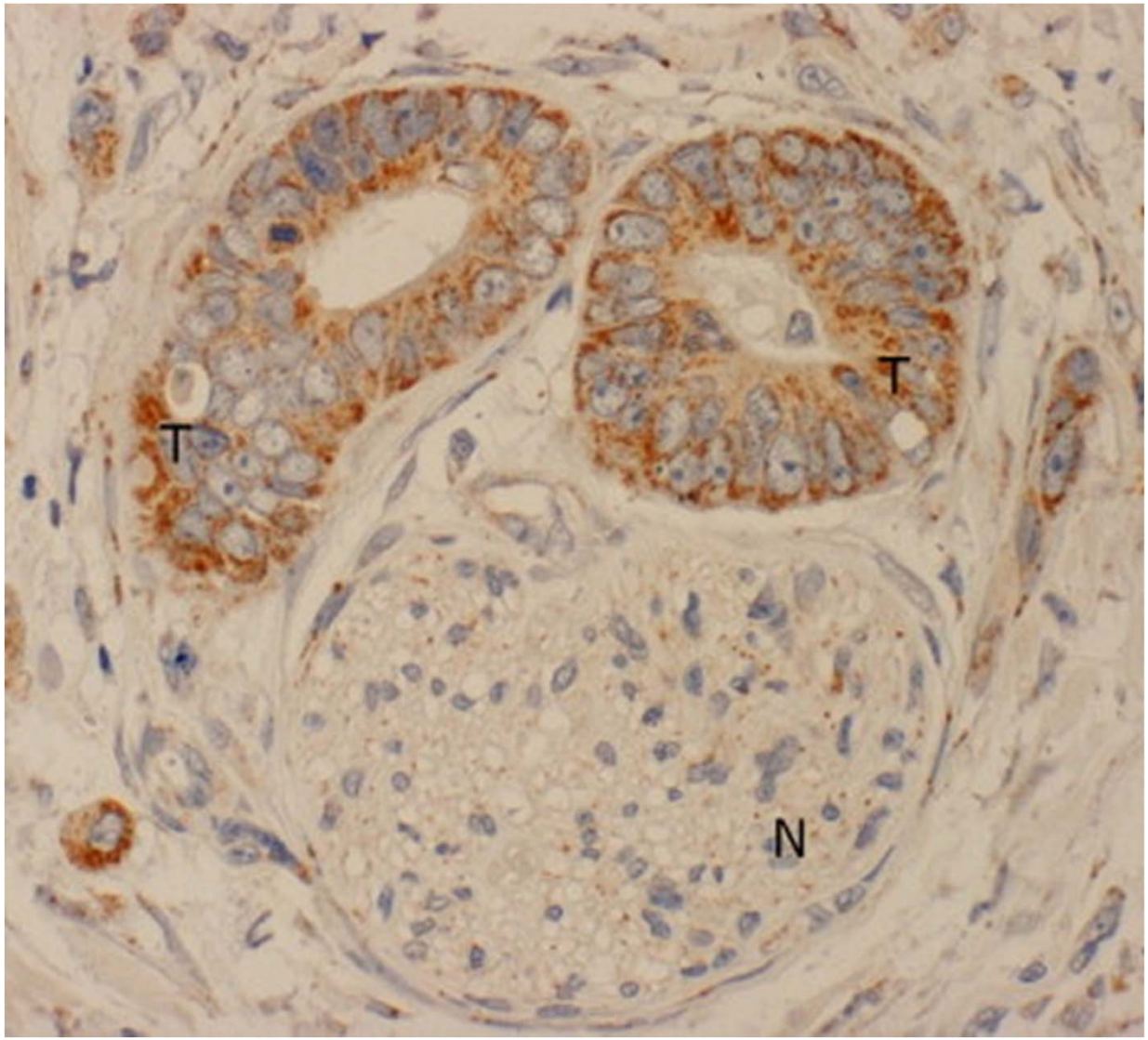

PERINEURAL INVASION
Endoneurium
Perineurium
Epineurium
Neurotrophins
Proteinases
Axonal Guidance
Neurotrophin/
Axonal Guidance Receptors
Matrix Interactions

Cancer type	Incidence of perineural invasion (%)	Refs
Pancreatic cancer	Up to 100	6,11–13
Head and neck cancers	Up to 80	2,9,21,23
Squamous cell carcinoma	2.5–14	9,21,24
Basal cell carcinoma	0.2–10	21
Prostate cancer	75–80	2,9,14–16
Colorectal cancer	9–33	2,17–19
Breast cancer	3–38	2,9,20
Biliary tract cancer	~80	9
Stomach cancer	50–60	2,9,22,25
Cholangiocarcinoma	75–85	2,9,26,27

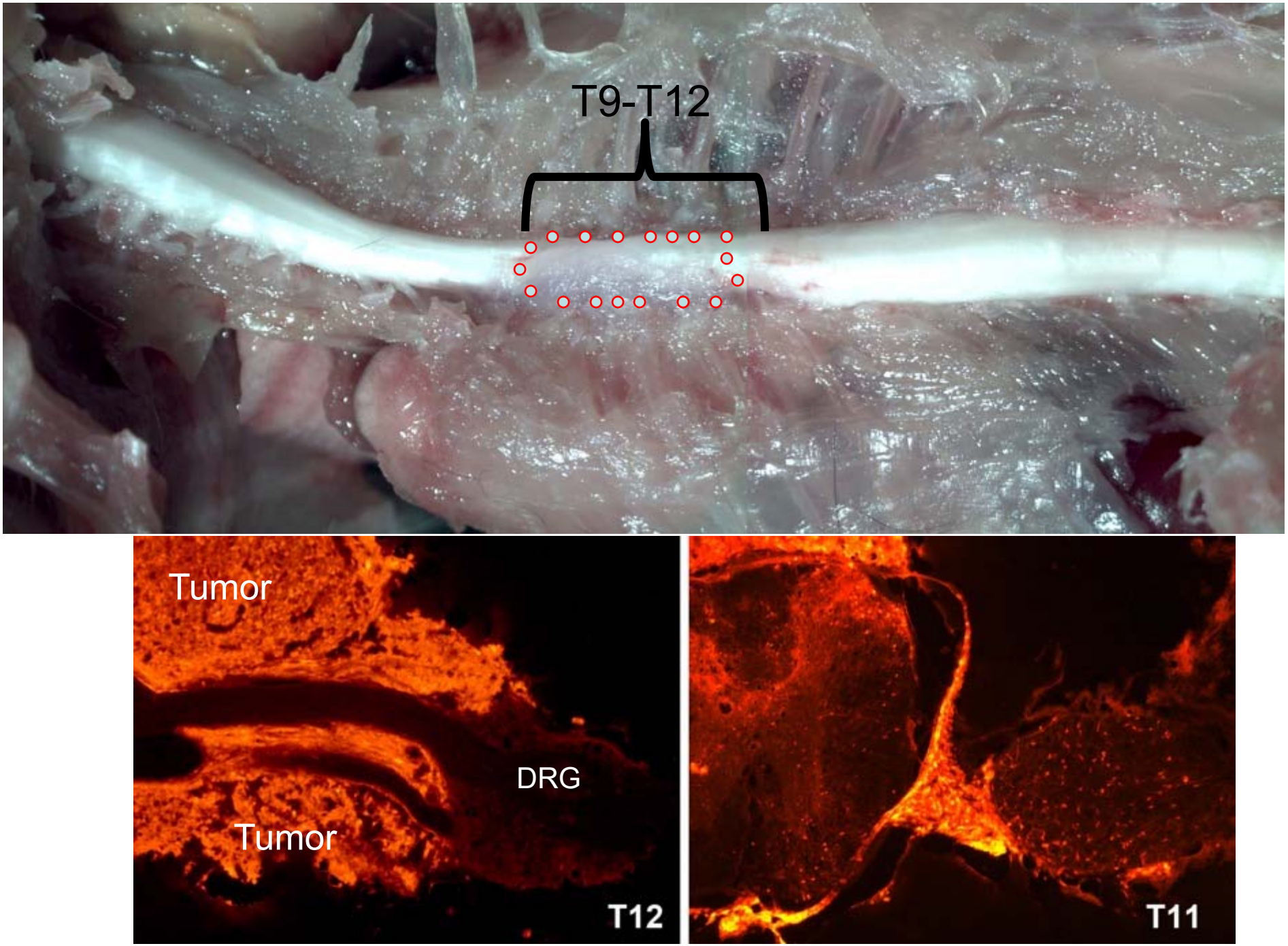
Bapat et al., 2011, Nat. Cancer. Rev. **11:**695

Pancreatic Cancer – Perineural invasion

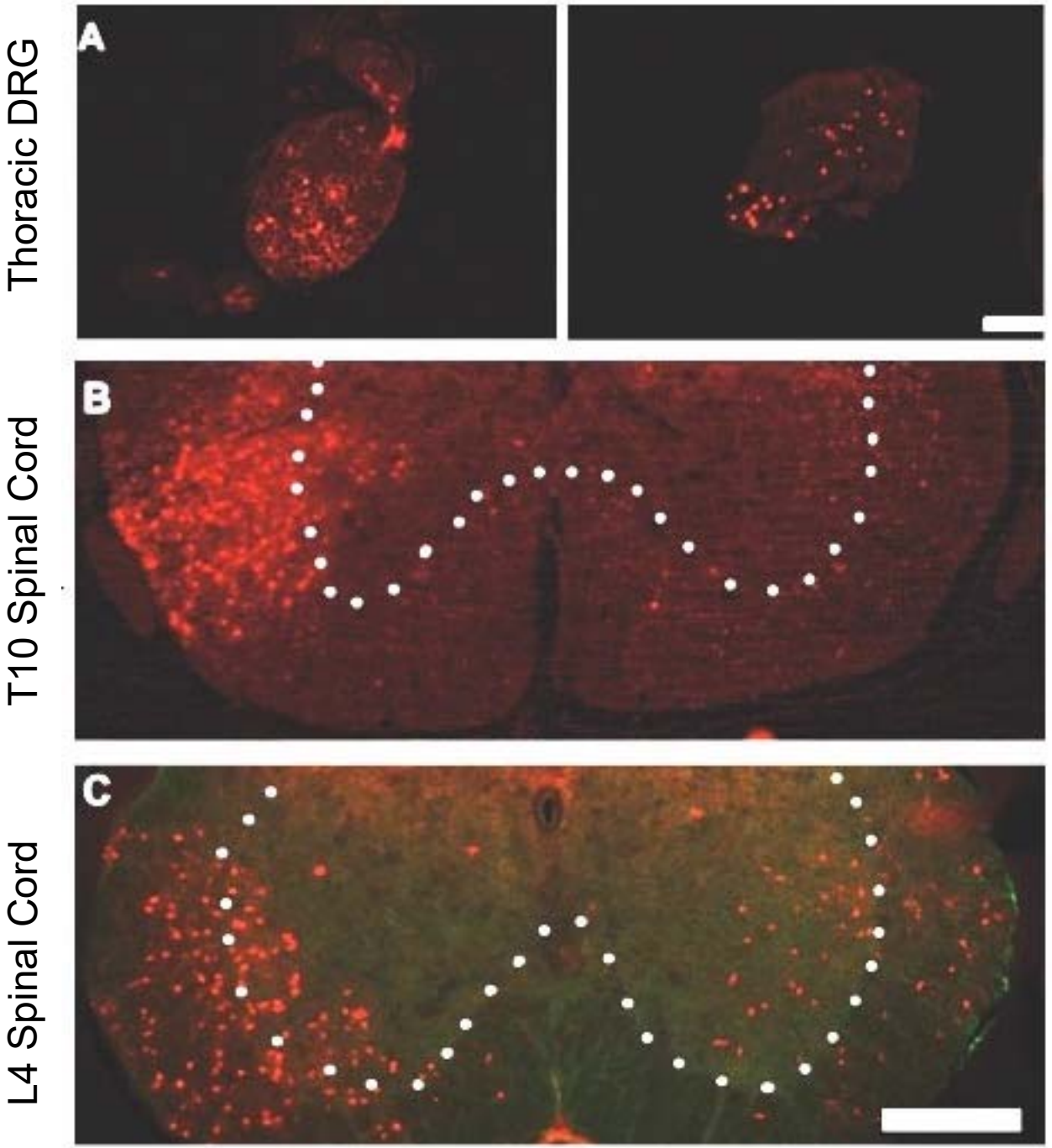
Histological section of pancreatic cancer (T) invading the perineural space (N). Immunoreactivity with an anti-CX3CR1 (fractalkine rec) depicts pancreatic tumor cells.



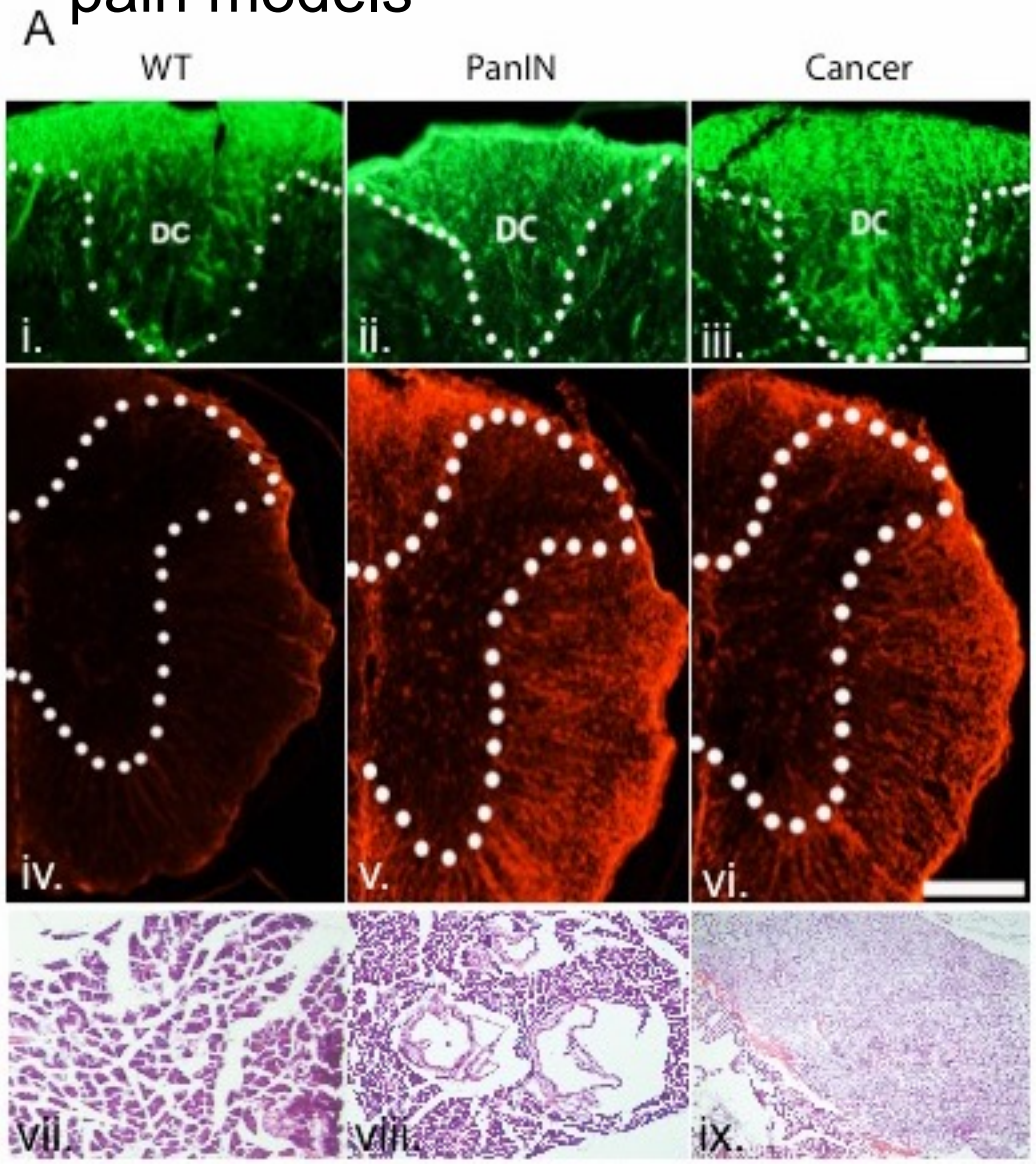
From Marchesi et al. 2010

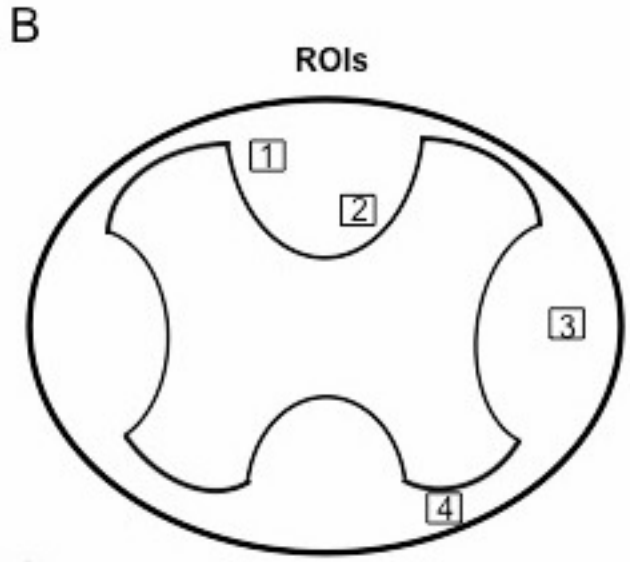

T9-T12
Tumor
DRG
Tumor
T12
T11

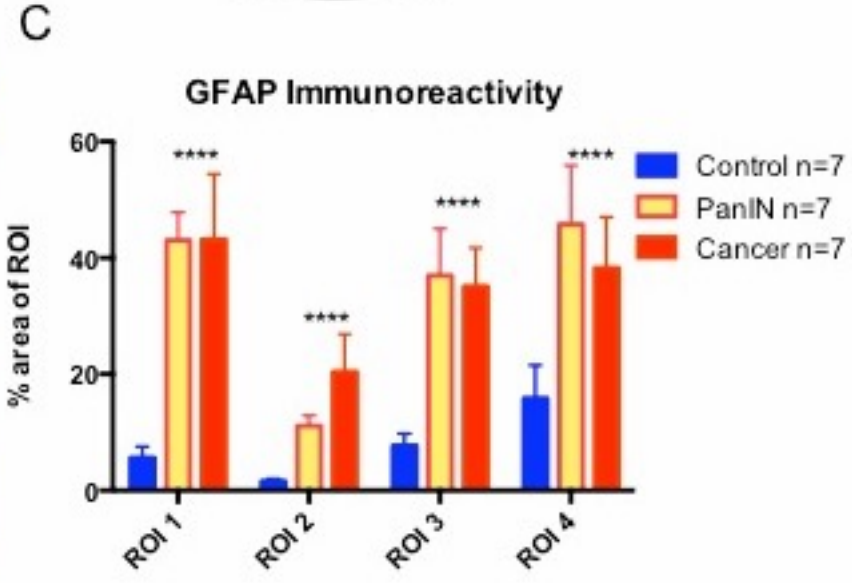
Even at the precancerous stage stage in PDAC (**PanIN**) mice, disseminated pancreatic cells can be found in the sensory ganglia and spinal cord, leading to inflammation in the CNS



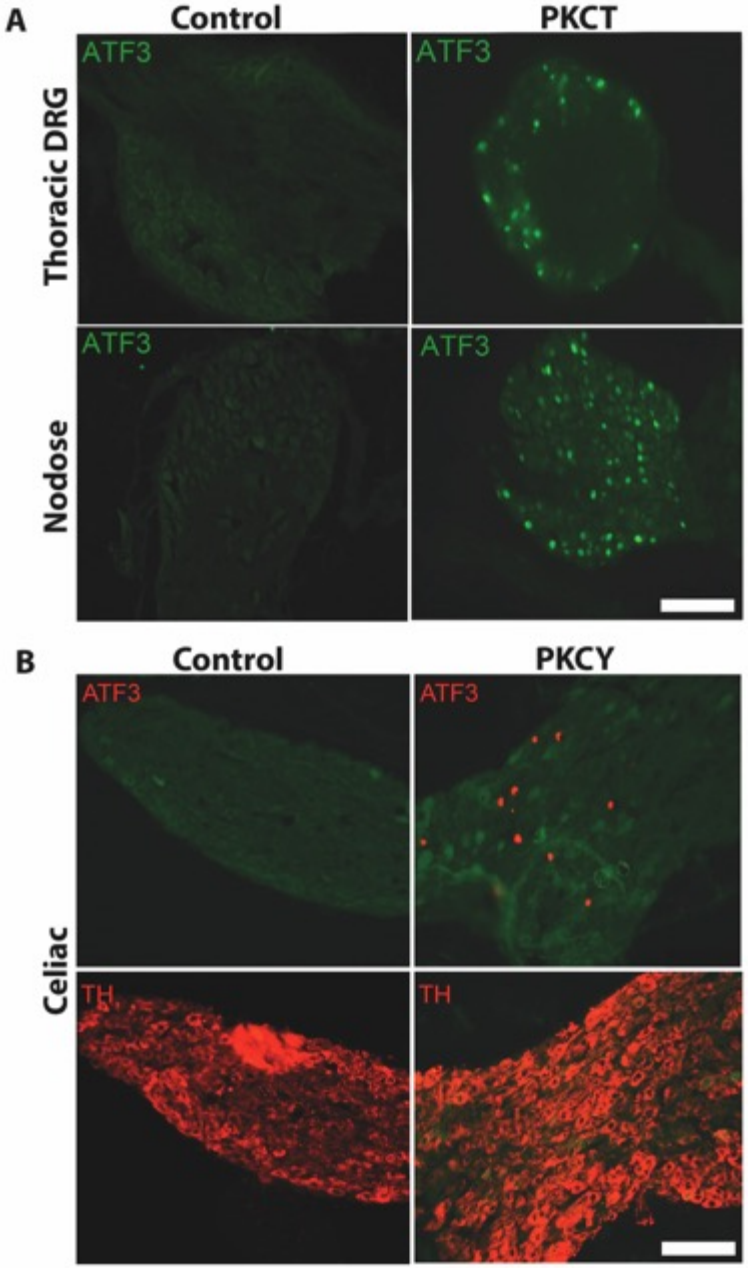
PanIN stage PDAC pancreas induces activation of spinal cord astrocytes – a feature of both neuropathic and inflammatory pain models

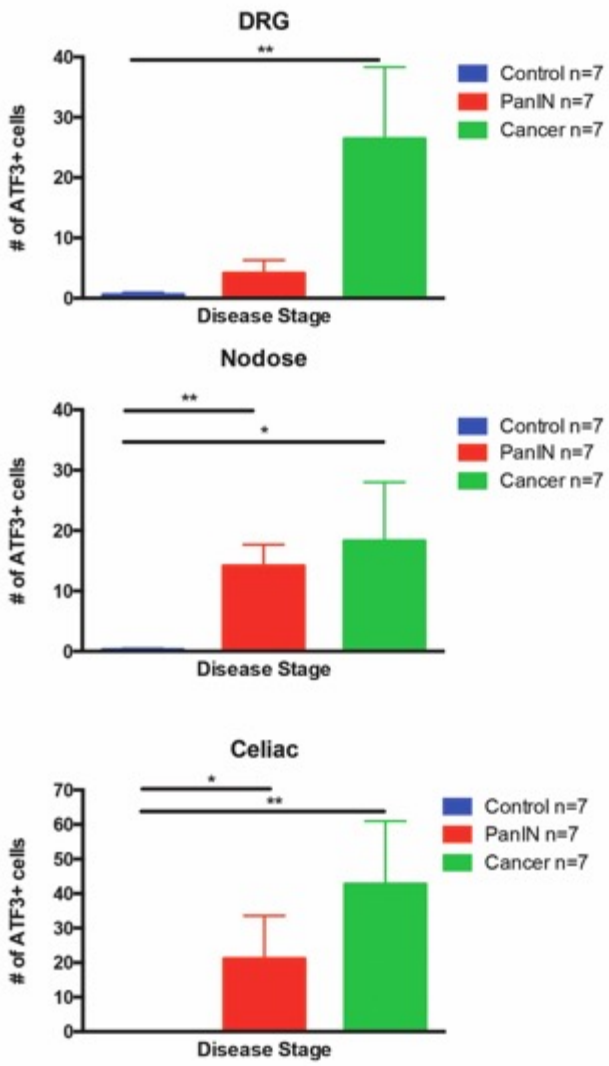




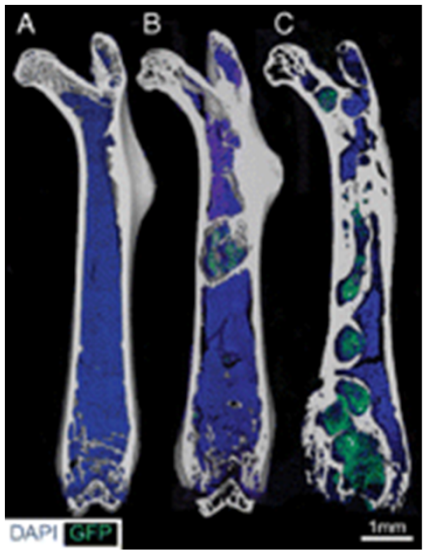


ATF3 (marker of nerve injury) is expressed at PanIN stage in PDAC mice (typical in neuropathic pain models)





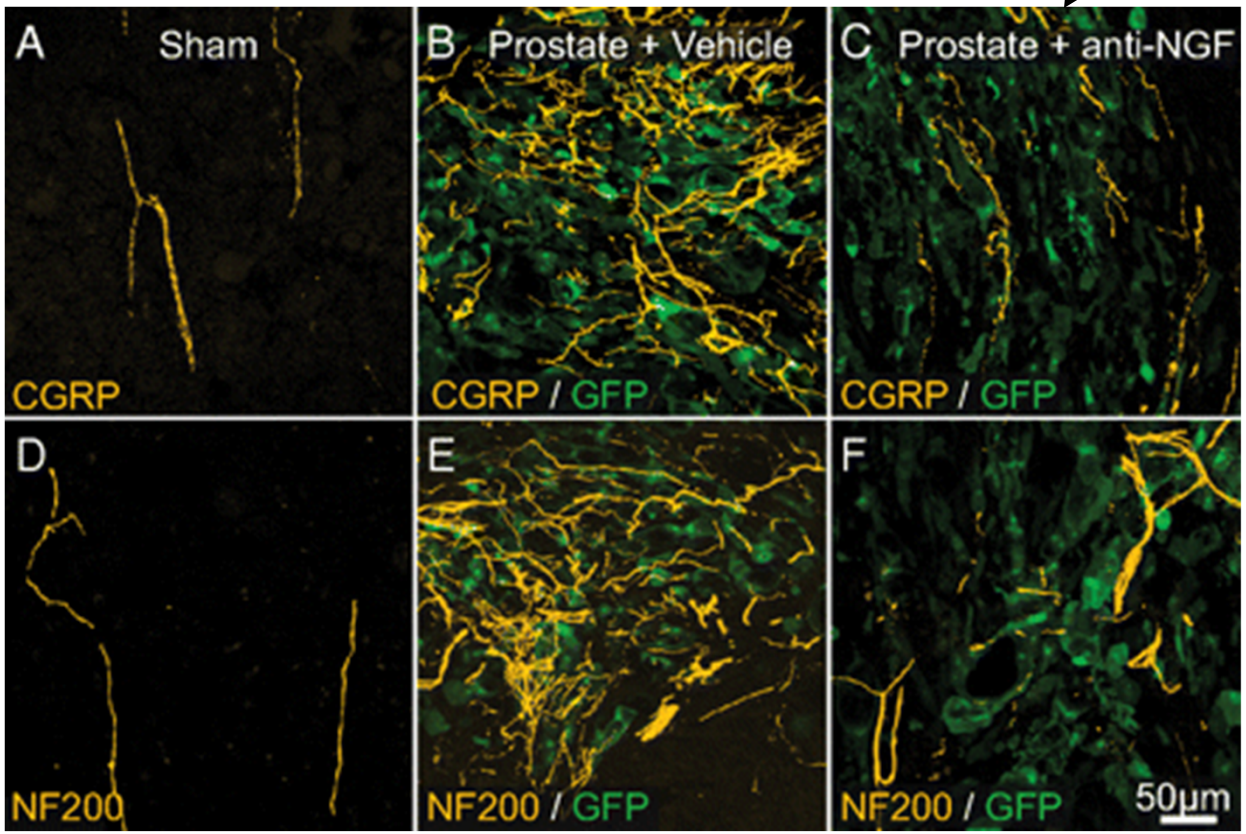
Anatomical changes contributing to PNI and pain – sprouting



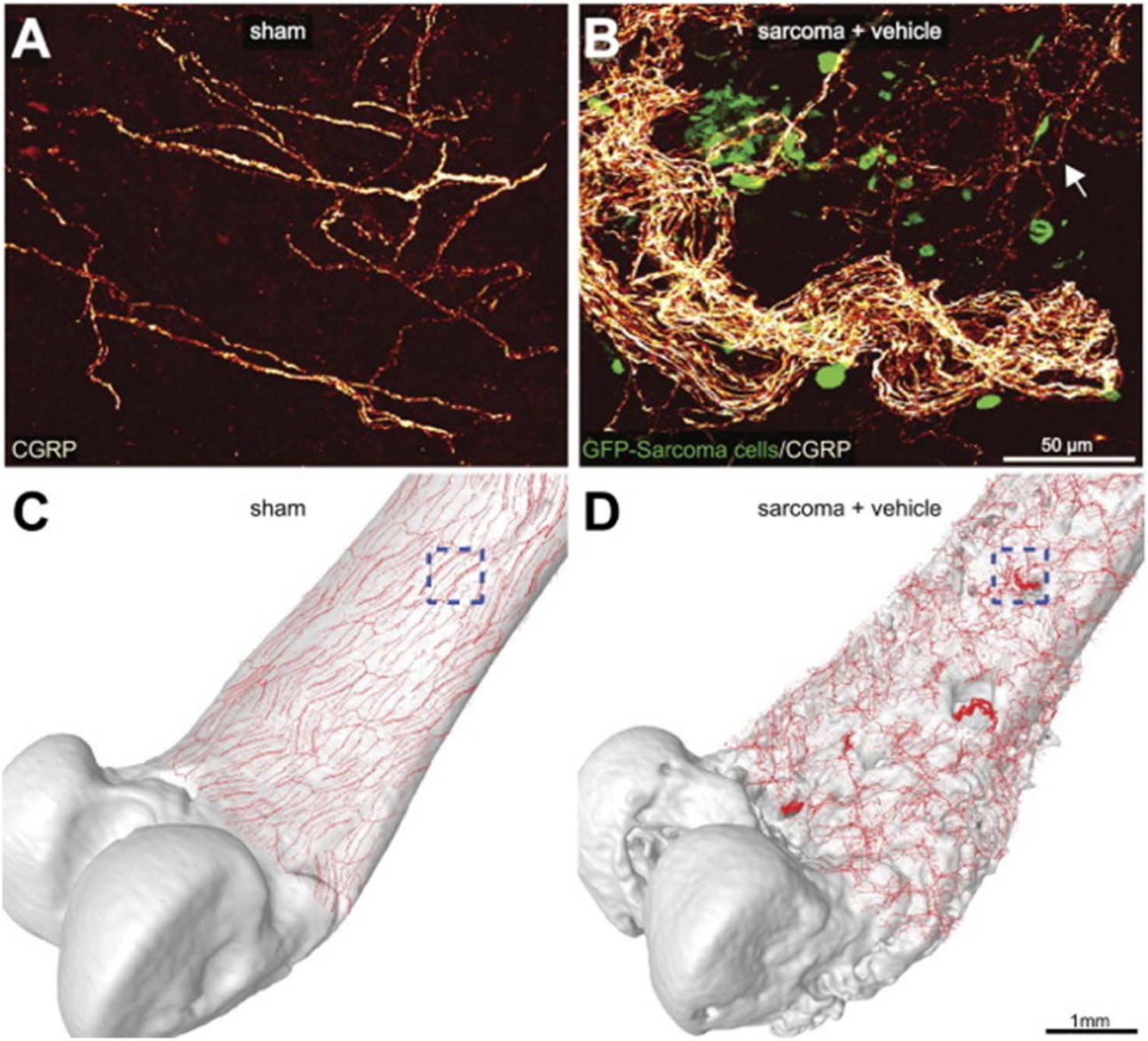
Sham Early Late (<26d)

Canine prostate injected in mouse femur; tumor cells express GFP. (From Jimenez-Andrade et al. 2010

Sprouting fibers are both CGRP and NF200 positive – and responsive to anti-NGF (arrow)



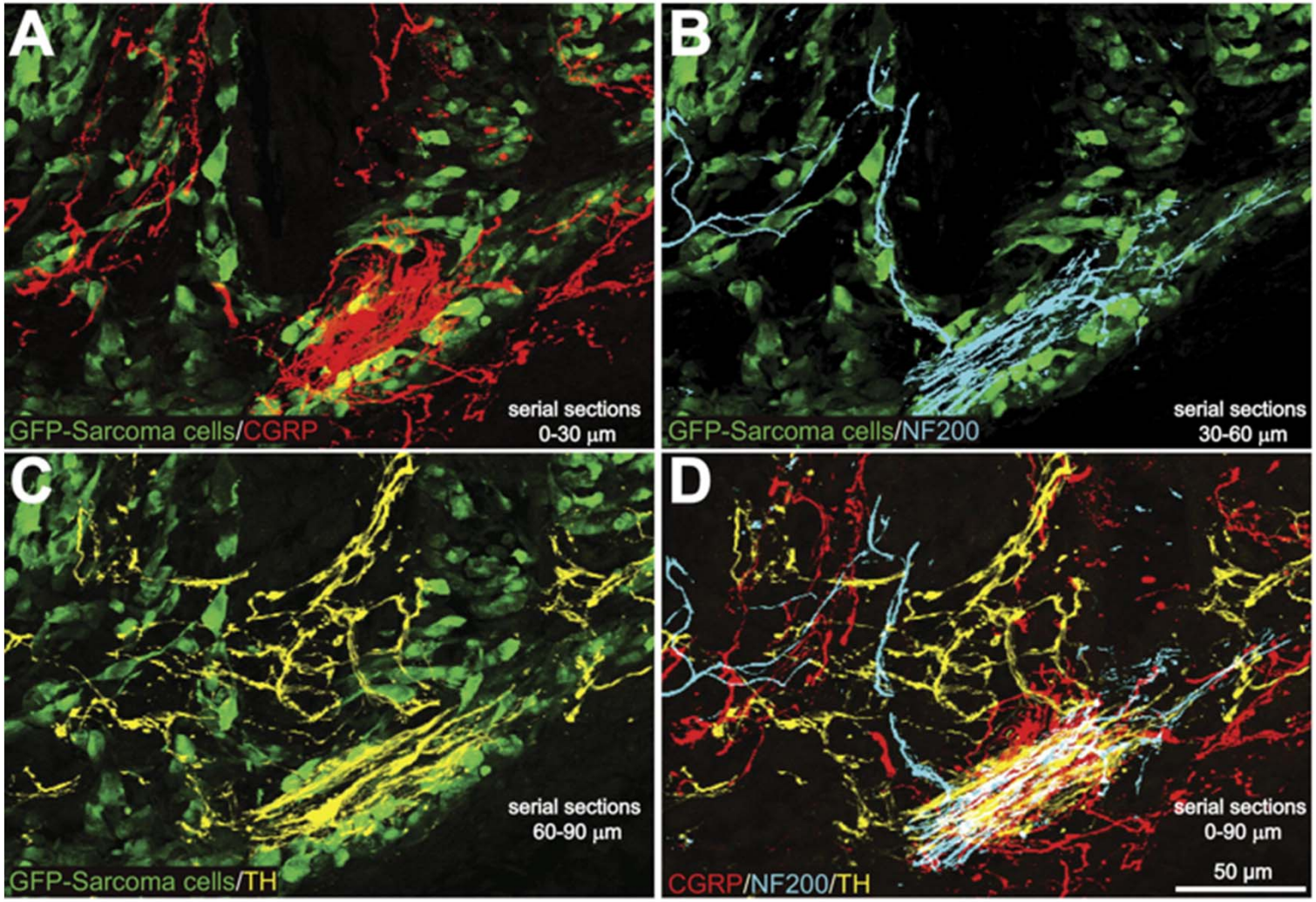
Neuroma in mouse model (<26d)



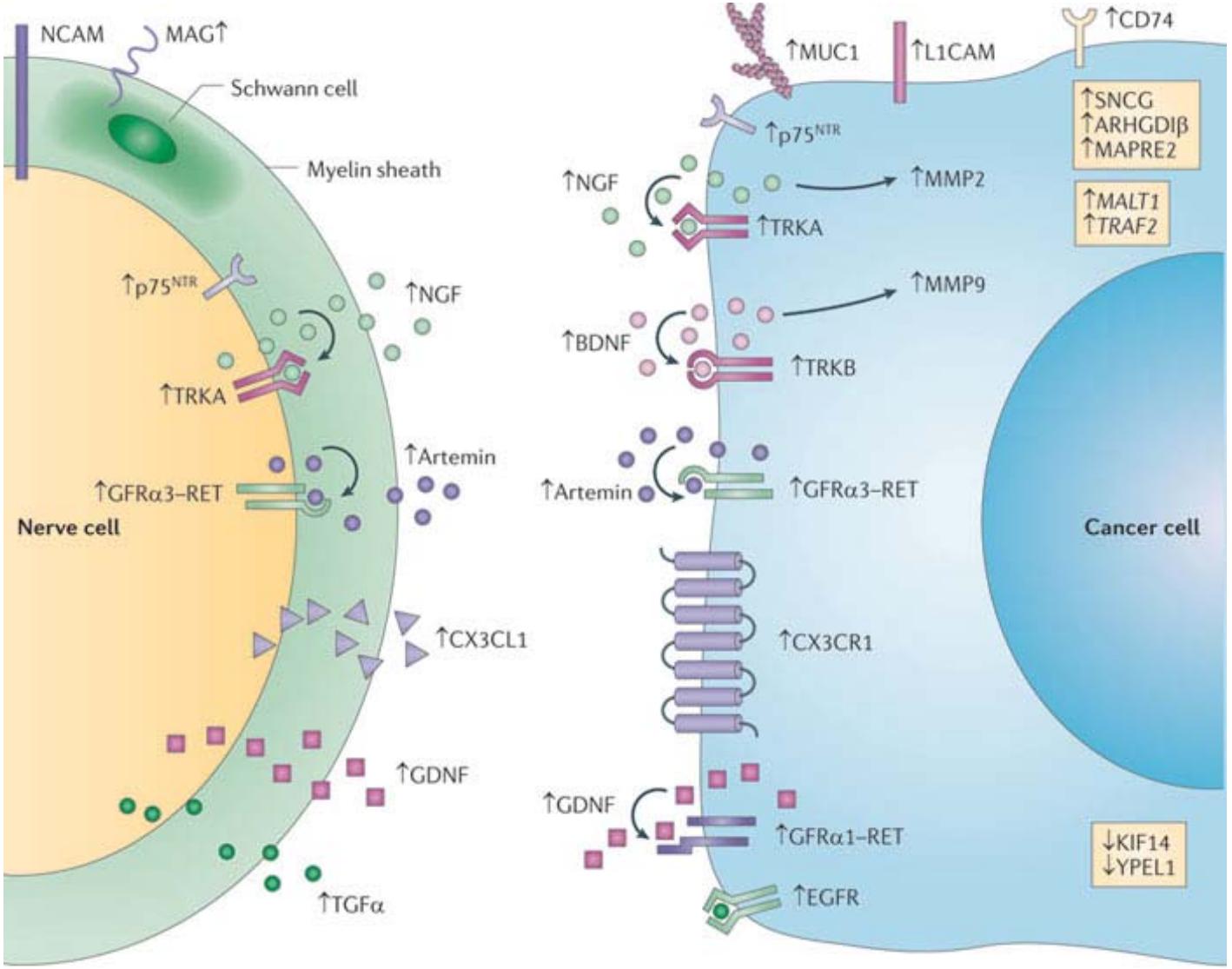
•Sympathetic (TH+) and sensory fibers (CGRP+) are intermixed in periosteal neuromas; 1-2/femur are typical.

•These develop within 21d following injection of cancer cells

•NF 200 staining indicates some of these guys are myelinated



Growth factors/cytokines produced by tumor have autocrine and paracrine functions that drive PNI via sprouting & hypertrophy



Nature Reviews | Cancer

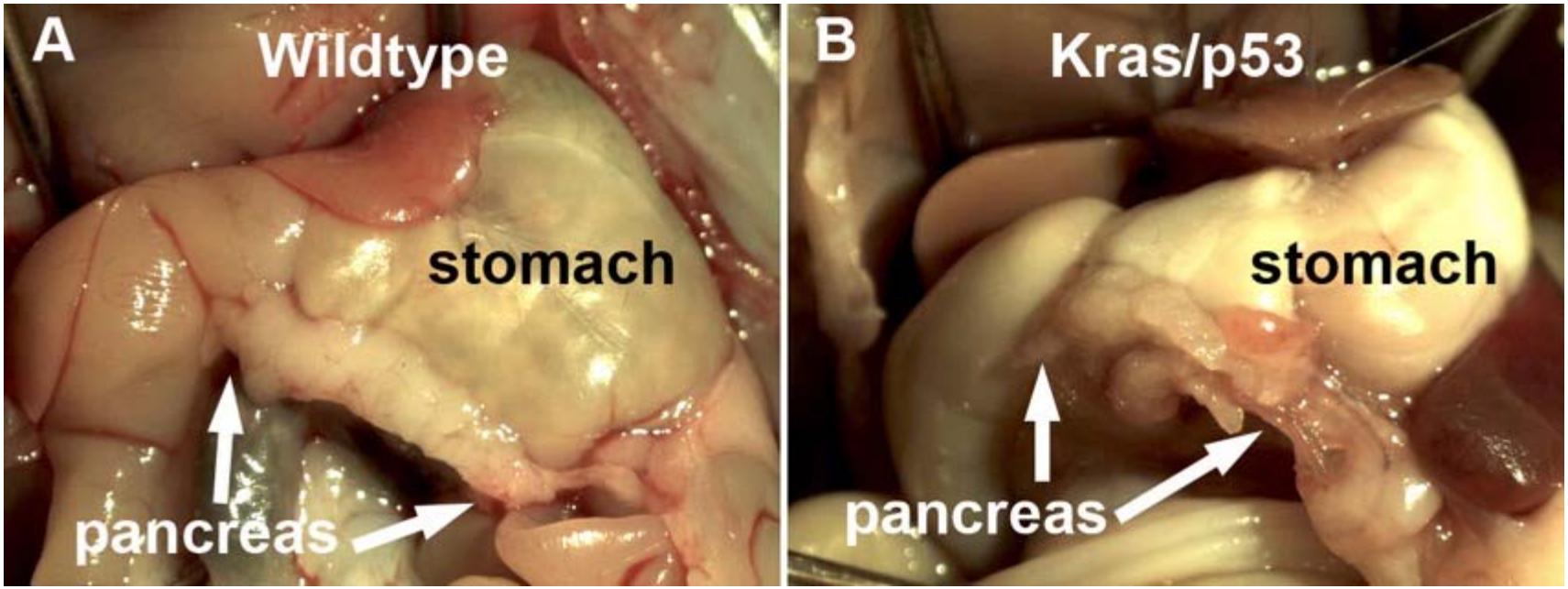
Animal models for cancer/cancer pain

- Until recently most models relied on implantation of cell lines. Death occurred with days-weeks. Not very human-like. (e.g. Mantyh bone cancer)
- Recent models use genetic replication of human disease – still relatively fast (months to year) but includes many/most hallmarks of the disease including precancerous lesions and metastasis. (DePinho, Tuveson pancreatic cancer)
- Carcingens have also been used. (Brian Schmidt, oral cancer)

Pancreatic Ductal Adenocarcinoma (PDAC)

- DePinho/Tuveson – took advantage of most common genetic defect and pair it with KO of tumor suppressor gene
- Depending on p53 (het or homozygous KO) cancer develops 8-21 weeks.
- Mice can live for at least 8 months
- Compare to Mantyh bone cancer – 3wk post tumor cell injection pushes survival limit

Kras/p53 model of pancreatic cancer – Growth factors and sprouting



•These mice express the most common form of the Kras mutation found in human pancreatic ductal adenocarcinoma combined with deletion of p53.

•Like human PDAC, mouse tumors exhibit a 9.8 fold increase in NGF mRNA, a 5.2 increase in trkA mRNA and a 6 fold increase in artemin mRNA. (smells like inflammatory pain)

Science AAAS

Autonomic Nerve Development Contributes to Prostate Cancer Progression
Claire Magnon *et al.*
Science **341**, (2013);
DOI: 10.1126/science.1236361

Science Translational Medicine AAAS

Denervation suppresses gastric tumorigenesis
Chun-Mei Zhao *et al.*
Sci Transl Med **6**, 250ra115 (2014);
DOI: 10.1126/scitranslmed.3009569

Article

Cell Stem Cell

Basal Cell Carcinoma Preferentially Arises from Stem Cells within Hair Follicle and Mechanosensory Niches

Peterson et al., 2015, Cell Stem Cell *16*, 400–412
April 2, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.stem.2015.02.006

Shared features of all 4 cancer studies:

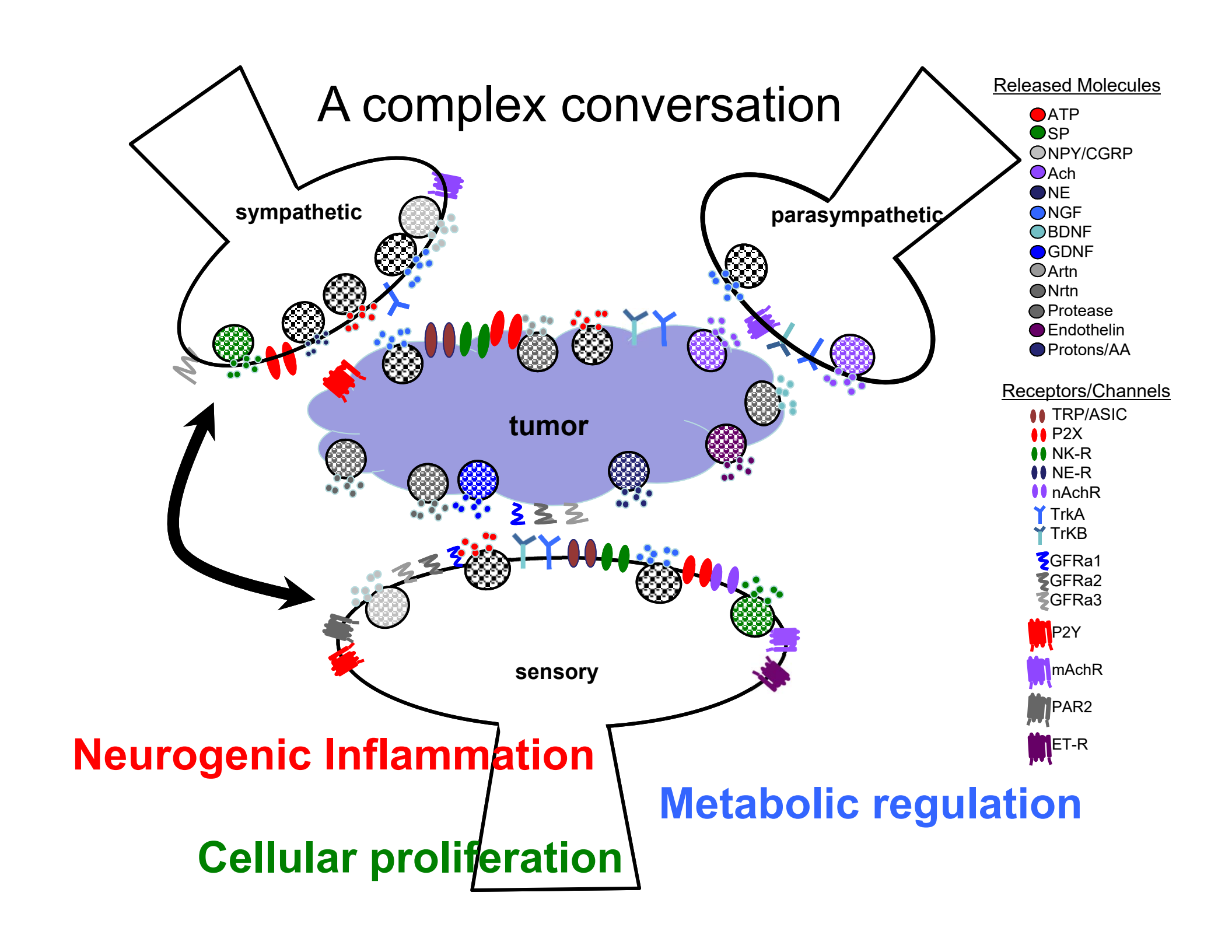
1) Employed naturalistic GEMM

2) Ablated sensory neurons

3) Decrease precancerous and/or cancer lesions

Tumor Type	Models Employed			Nerves Affected by Treatment			Age of Effective Intervention			Outcomes		
	GEMM	Xeno	Chem	Symp	Parasymp	Sensory	Neonate	Juvenile	Adult	Reduced precanc lesions	Reduced tumor growth	Reduced metastasis
Prostate	✔	✔	~	✔	(✔)	✔	✔	✔		✔	✔	✔
Stomach	✔	~	✔	~	✔	✔	~		✔	✔	✔	✔
PDAC	✔	~	~	~	~	✔	✔	~		✔	✔	ND
BCC	✔	~	~	(✔)	~	✔	~	✔		ND	✔	ND

Saloman et al., TIN, (2016), 39:880


A complex conversation
sympathetic
parasympathetic
tumor
sensory
Released Molecules
ATP
SP
NPY/CGRP
Ach
NE
NGF
BDNF
GDNF
Artn
Nrtn
Protease
Endothelin
Protons/AA
Receptors/Channels
TRP/ASIC
P2X
NK-R
NE-R
nAchR
TrkA
TrkB
GFRa1
GFRa2
GFRa3
P2Y
mAchR
PAR2
ET-R
Neurogenic Inflammation
Metabolic regulation
Cellular proliferation

CIPN

(Chemotherapy-induce peripheral neuropathy)

- Cancer therapy is often limited by side effects of drugs
  - Nausea
  - Vomiting
  - Cognitive deficits
  - CIPN – usually sensory, motor symptoms are less common. Stocking and Glove. Autonomic defects also occur. Sensory defects incld.:
    - Paraesthesia
    - Dysesthesia
    - Proprioceptive deficits
    - Allodynia – mechanical and thermal (cold, most often)

CIPN drugs

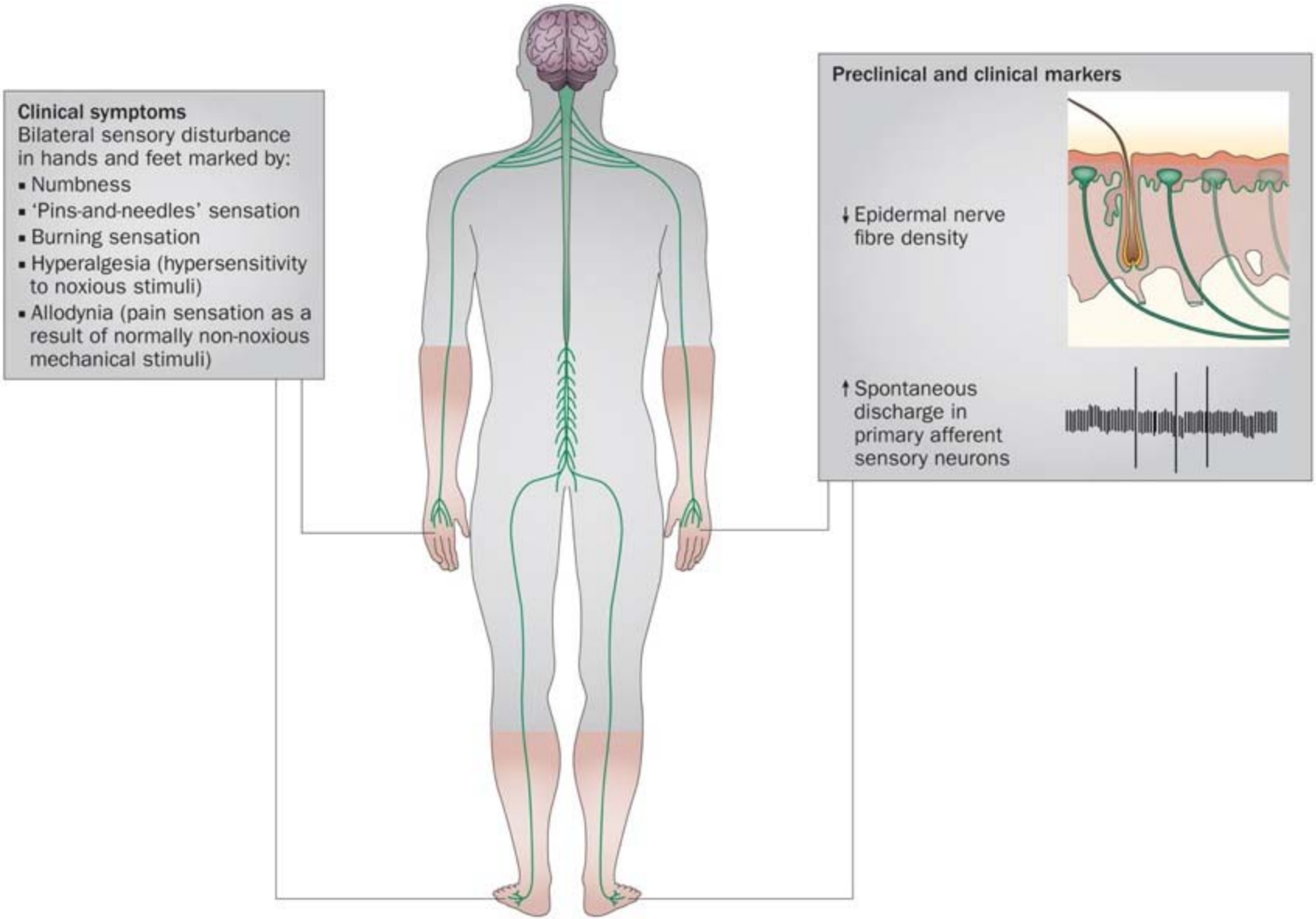
- **Taxanes** (e.g. paclitaxel and docetaxel) – alkaloids based on taxol, natural product from bark of Pacific Yew. Stabilized MTs and prevents separation of chromosomes during anaphase.
- **Vinca alkaloids** (e.g. vincristine) – derived from periwinkle, block tubulin from joining MT, blocking cell division.
- **Alkylating agents** (e.g. oxaliplantin, cisplantin (plantinium-based compounds)) alkylated nucleophilic groups modifying DNA and preventing chromosomal duplication.
- **Immunomodulatory** (thalidomide) – blocks angiogenesis via blocking TNFα.
- **Proteosome inhibitor** (Bortezomib) – binds the 26S subunit of proteosome – may block degradation of proapoptotic proteins. Very effective for some multiple myeloma patients.
- **Gemcitabine** - nucleotide analog, block replication, low neuropathy rate (ca. 10%). Go to for visceral cancers – not very effective by itself

CIPN – drugs that keep on giving

Chemotherapy	Incidence	Onset time (coasting)[a]	Duration/recovery after stopping	Comments
Cisplatin	40%	From 1 month, at most 3 months (+)	Some recovery in 80% patients over some months/years	Carboplatin less CIPN (10–20%)
Carboplatin	Mostly small fibres Pain common		28% patients symptomatic after some years More severe less recovery	
Oxaliplatin	Acute 90% cold induced Chronic 30%	Acute occurs within an hour	Acute 2–3 days 20% limited recovery	Chronic CIPN similar to cisplatin
Vincristine	30–40% Lower limb more common	Within 3 months (+)	In most, some recovery after 3 months More severe, less and slower recovery	30% CIPN at 2 years
Paclitaxel	30–50%	Maybe after single dose, >50% after second dose (+)	75% some recovery after 6 months	Less common now due to changed dosing
Docetaxel	Most sensory modalities affected			Docetaxel less CIPN

CIPN, chemotherapy-induced peripheral neuropathy. Data taken from [6,35••,36,39].
[a] (+) denotes presence of coasting.

CIPN is shares features with other peripheral neuropathies



Bennett, G. J. *et al.* (2014) Mitotoxicity in distal symmetrical sensory peripheral neuropathies
Nat. Rev. Neurol. doi:10.1038/nrneurol.2014.77

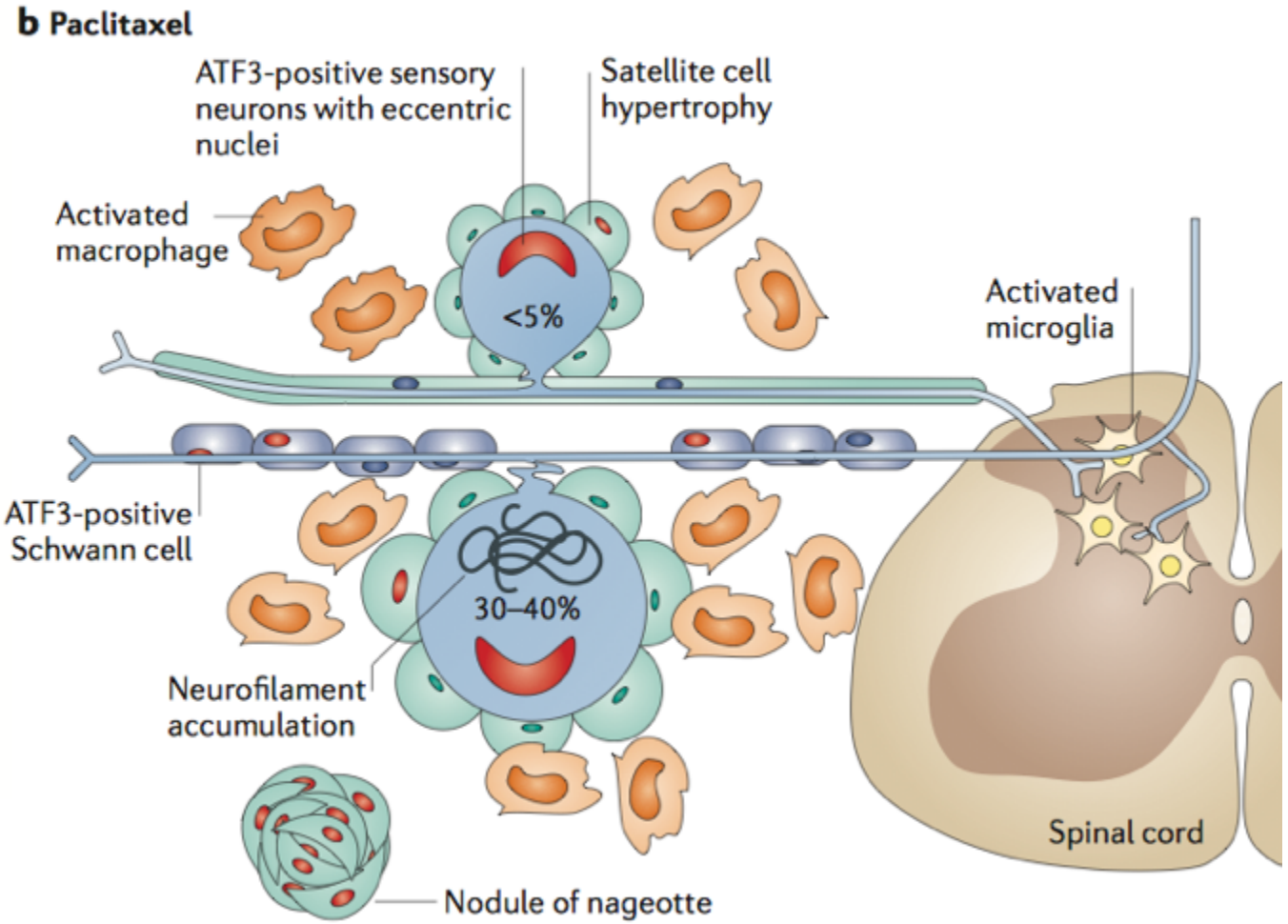
CIPN -MT dysfunction

- Canonical explanation – Chemo disrupts afferent fiber microtubules (MT)
- But – in animal models pain is not always accompanied by MT damage
- Motor axons often not affected
- Some drugs cause pain without MT damage (e.g. bortezomib a highly neurotoxic protease inhibitor).
- Oxaliplatin cause pain before any MT damage is seen.
- Colchicine (not a chemo drug), a classic MT disrupter, is painless.

The "tombstones" of CIPN – evidence of neuronal death

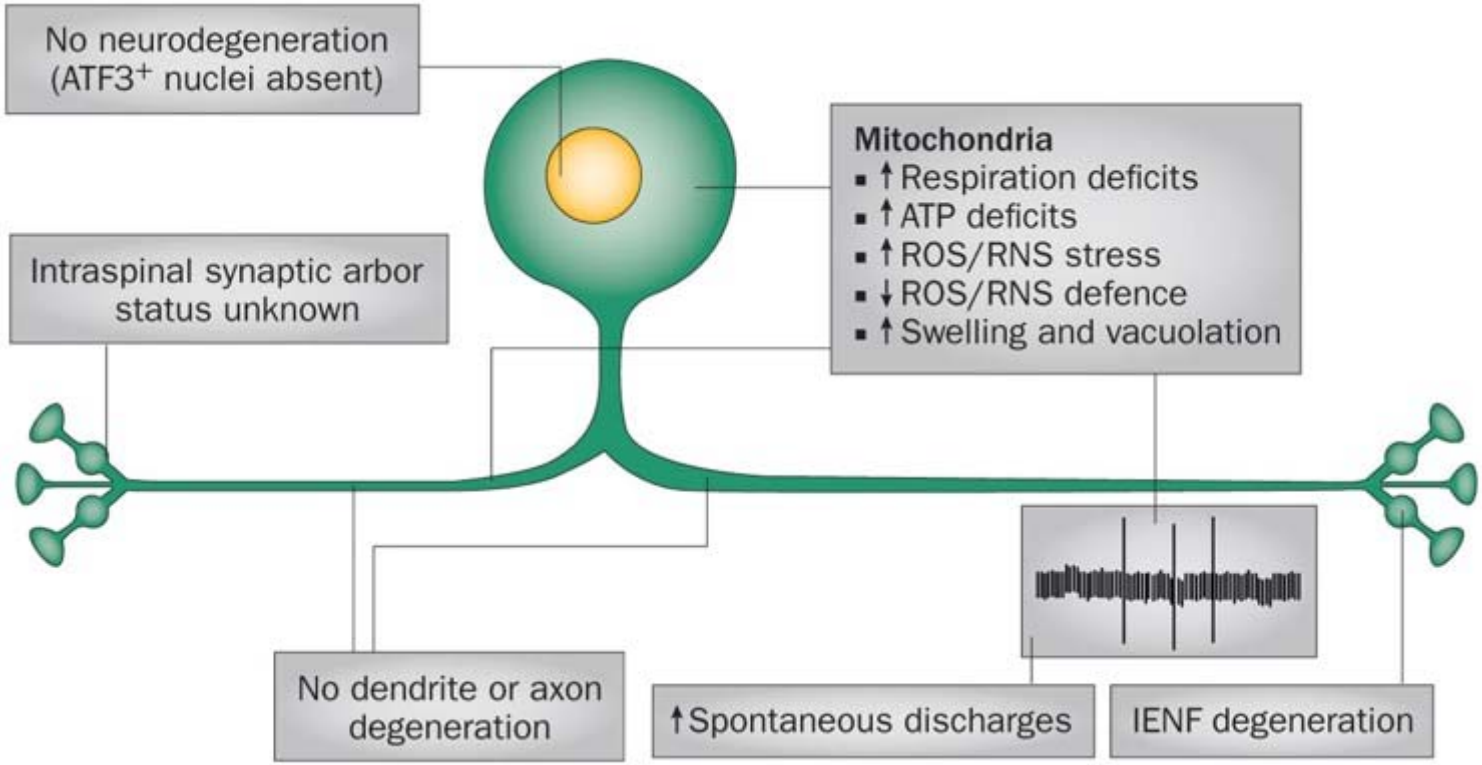
Chemotherapy induced peripheral neuropathy - damage is cumulative and multifactorial.

Nodule of Nageotte- remains of neuron and satellite cells. Found in human as well.



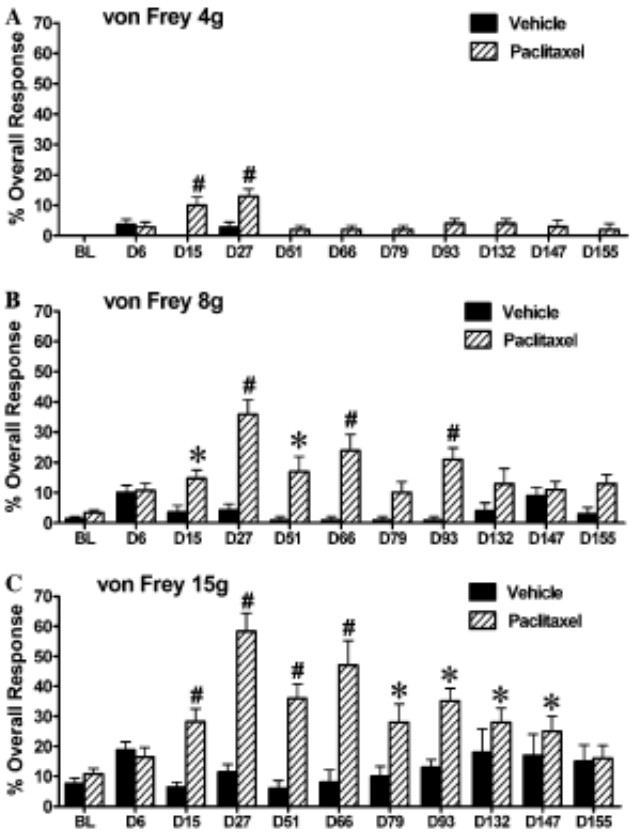
From: Mantyh Nat. Neurosci. Rev. 2006

Other proposed mechanisms of the development of distal symmetrical sensory peripheral neuropathy (including CIPN)

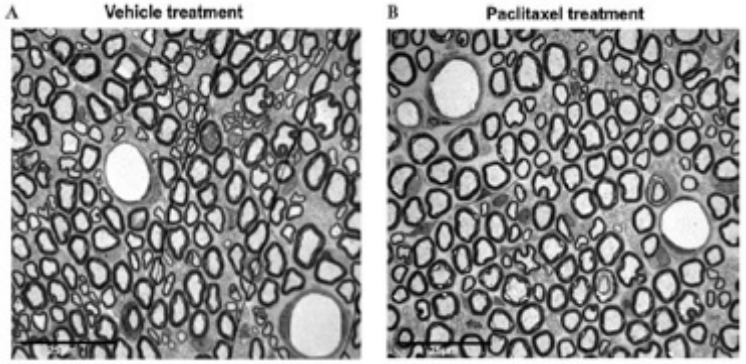


Bennett, G. J. *et al.* (2014) Mitotoxicity in distal symmetrical sensory peripheral neuropathies *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.77

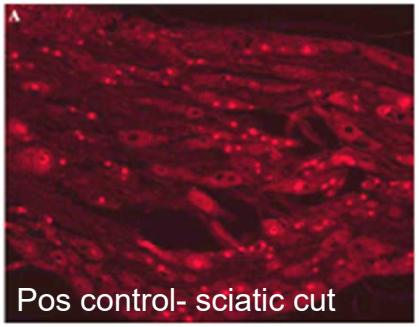
Bennett group - taxol induced neuropathic pain is due to mitochondrial damage that damages distal endings.



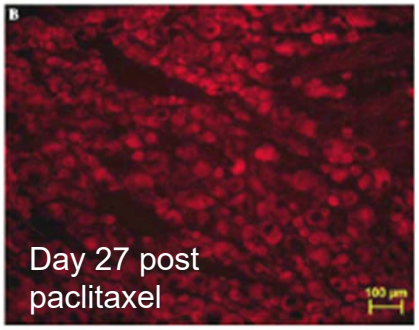
Mechanical sensitivity (allodynia, hyperalgesia) develops.

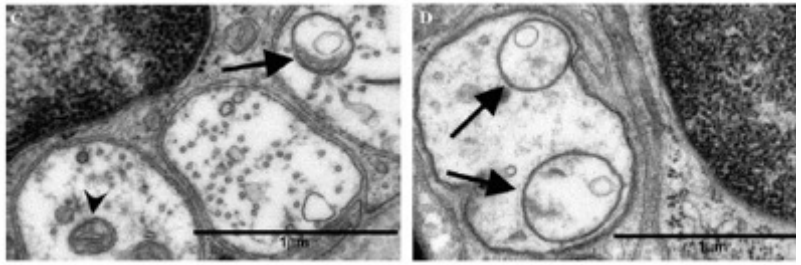


Saph.nerve and number of microtubules ok.



No ATF3 expression.

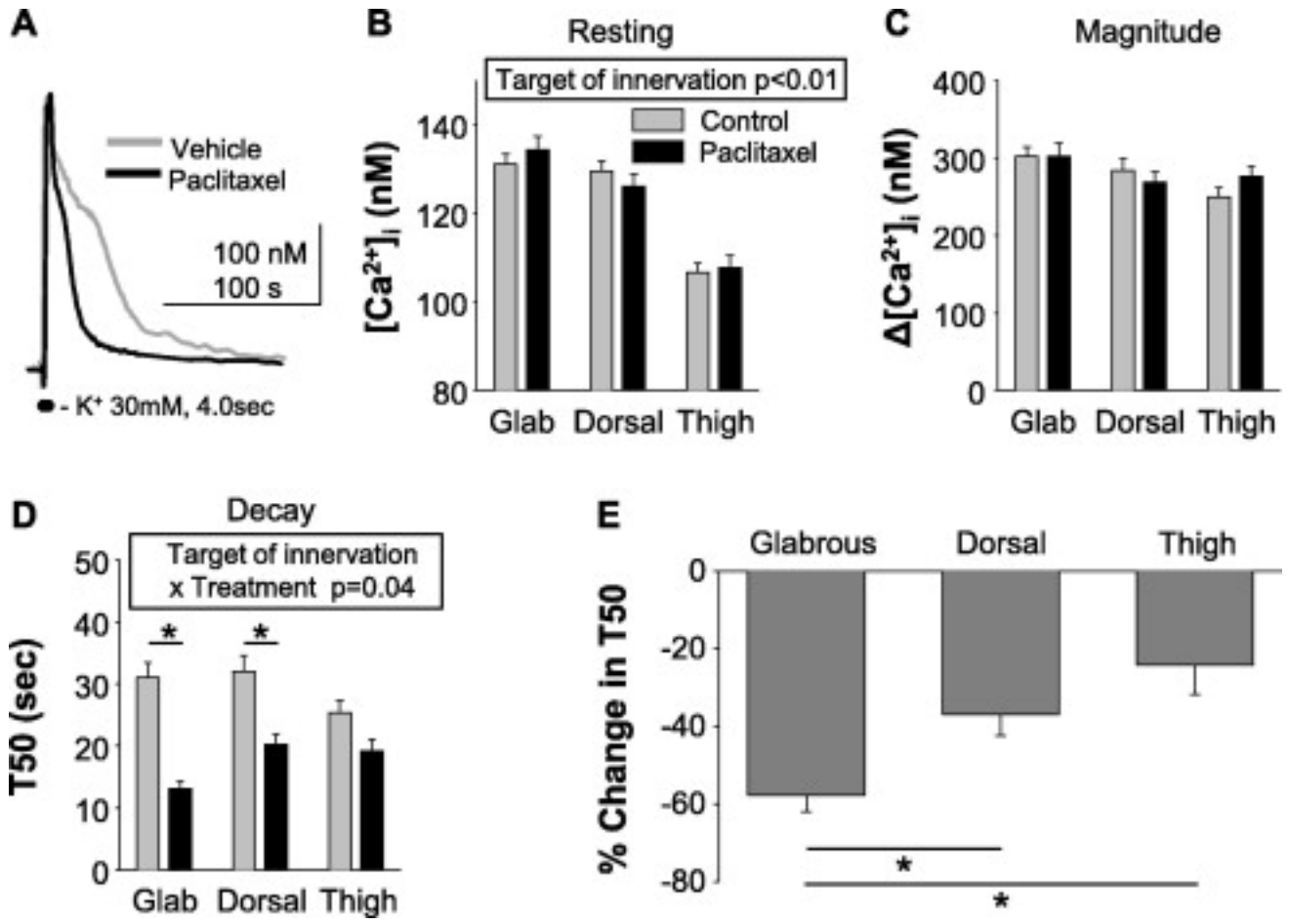




Mitochondria in c fiber and myelinated fibers were swollen and vacuolated - effect may be through Ca^{++} dysregulation.

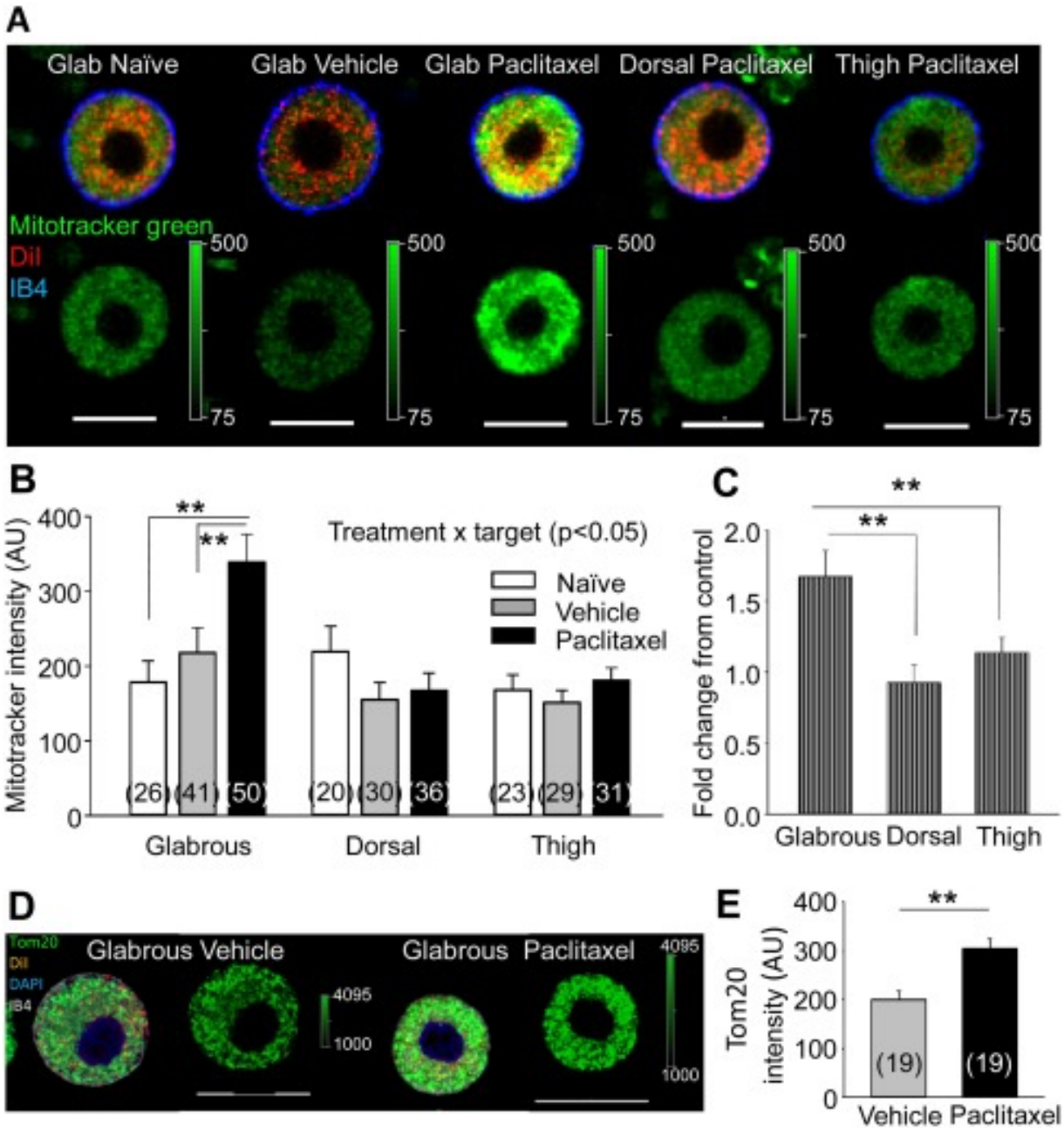
This milder phenotype compared to the Mantyh study may be due to route of drug delivery – Mantyh (i.v.) – Bennett (i.p.)

Further evidence of mitochondrial dysregulation



Yilmaz 2015, Neurosci, 300:210

Mito # and size are increased; but function is not (see paper)



Yilmaz et al., 2017, Cell Calcium 62:16

Conclusions

- Don’t get cancer
- Cancer pain combines the worst aspects of inflammatory and neuropathic pain.
- Sensory (and other peripheral nerves) may not be passive bystanders in tumorigenesis.
- Treatments for cancer pain can have long lasting negative consequences - CIPN
- We can’t wait for a cancer cure before dealing with these pain issues.