Understanding Chronic Pain at Its Source: How Small Molecular Changes Drive Pain in Schwannomatosis

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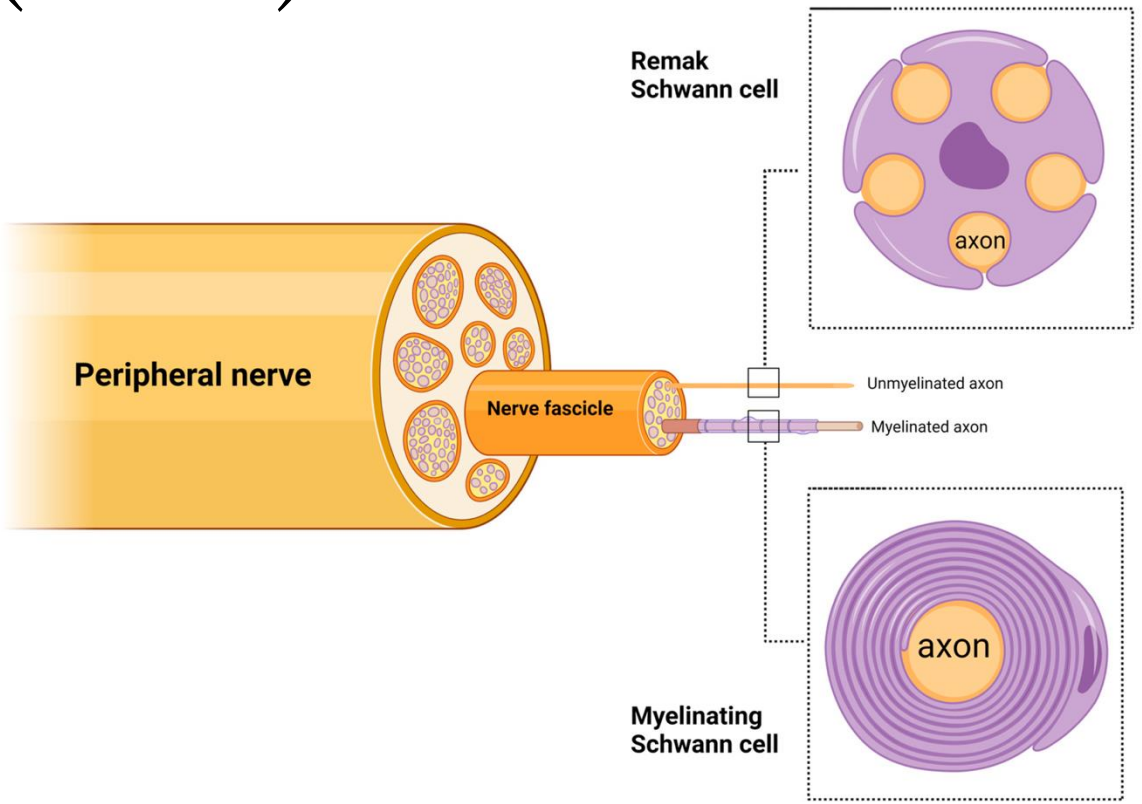
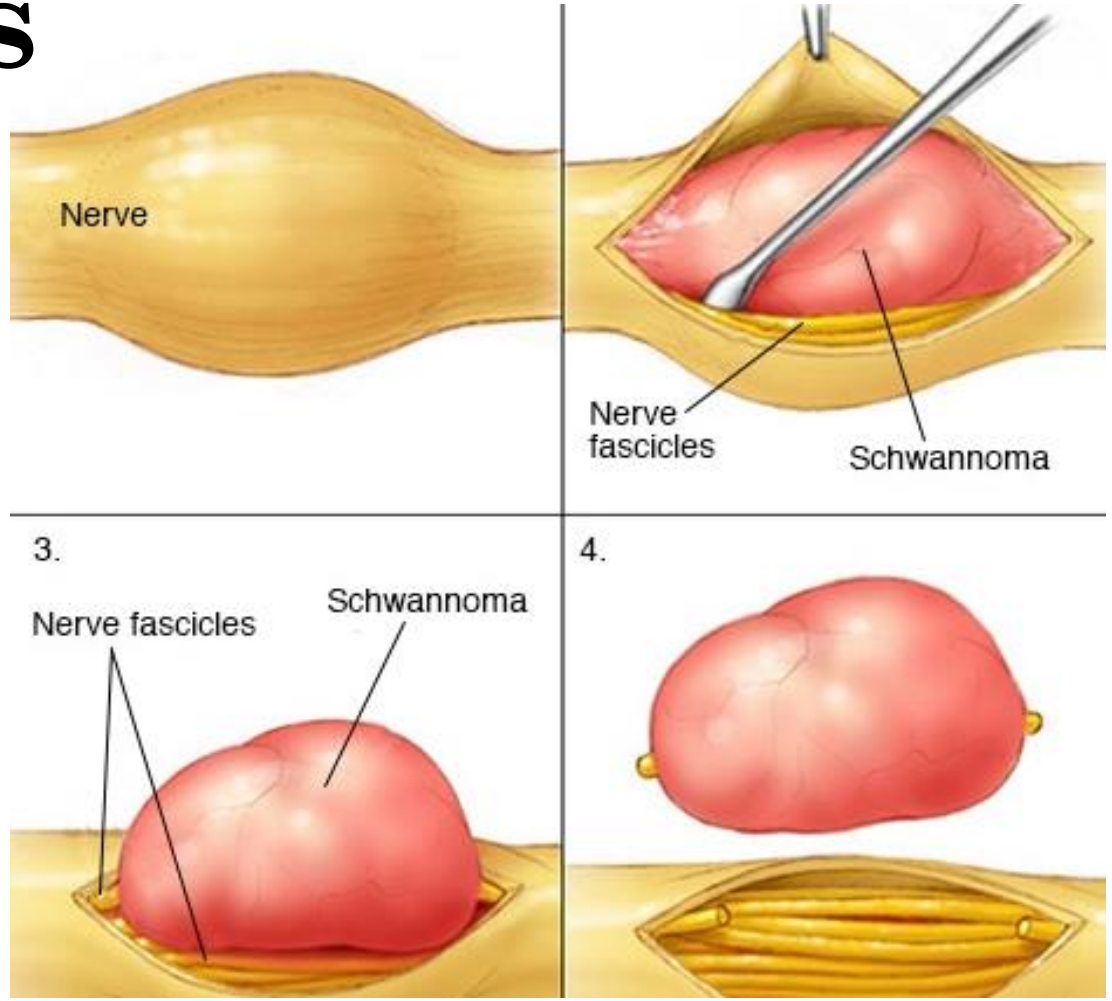
Pain.

Schwannamatosis (SWN)





Schwannomatosis (**SWN**) is a rare genetic disease characterized by the development of multiple benign tumors (known as **schwannomas**) along nerves throughout the body.

To treat pain effectively, we need to understand *why* it persists

(Chen et al., 2020; Rubright et al., 2025;Johns Hopkins, 2022)

The Question Guiding My Research: What is going wrong?

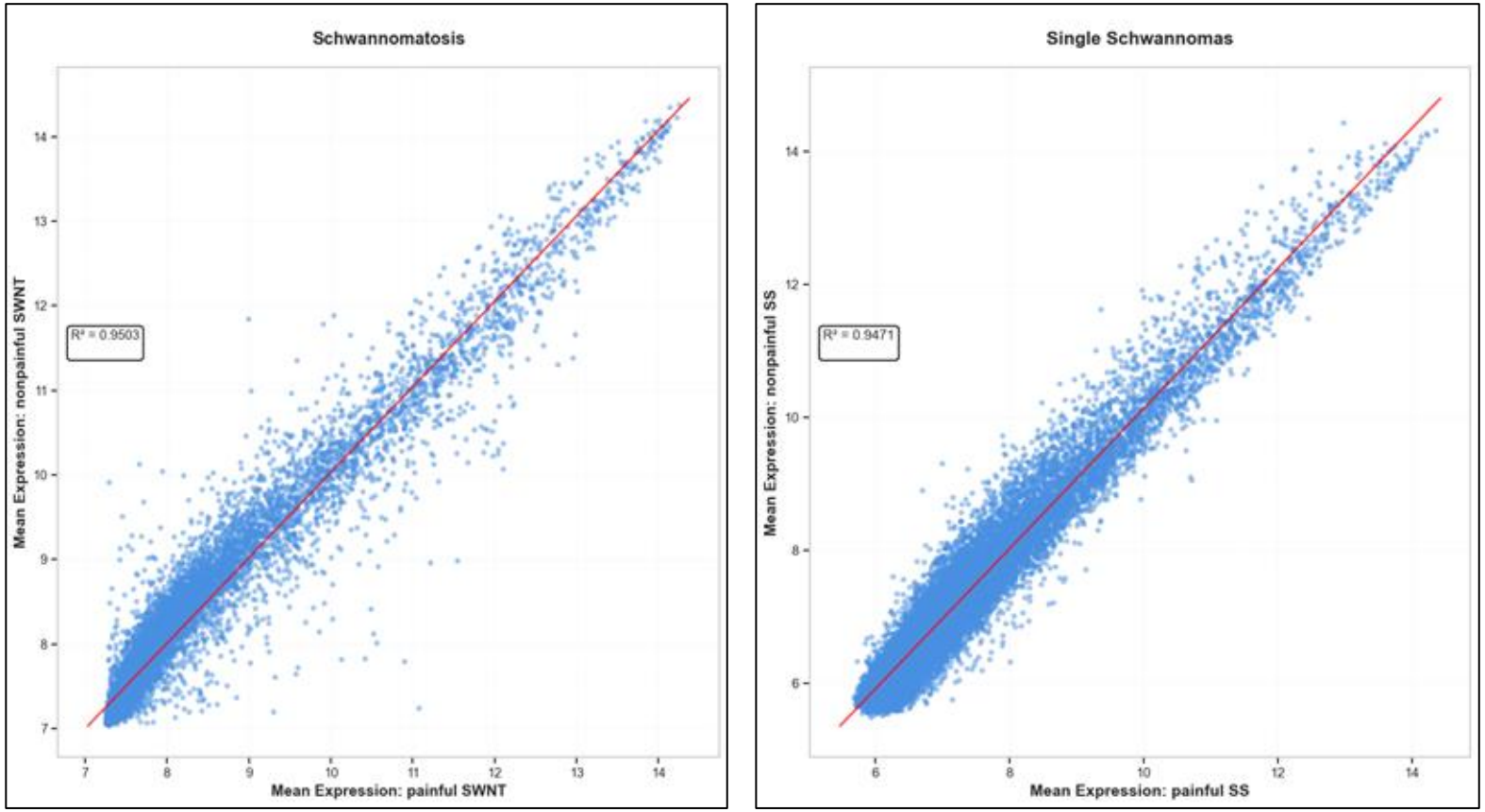
Examined:

(1) Schwannomatosis (SWN) samples: painful vs. nonpainful

(2) Painful schwannomatosis vs painful solitary schwannomas (SS)

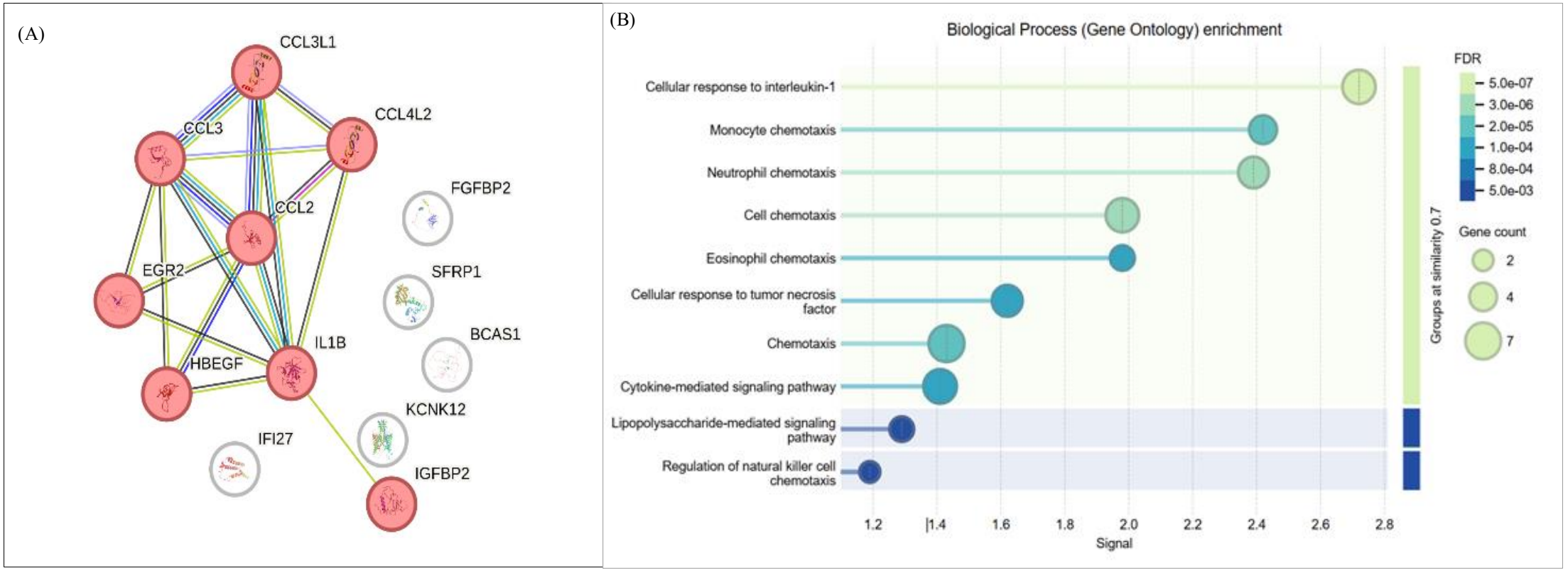
Painful and Nonpainful Tumors

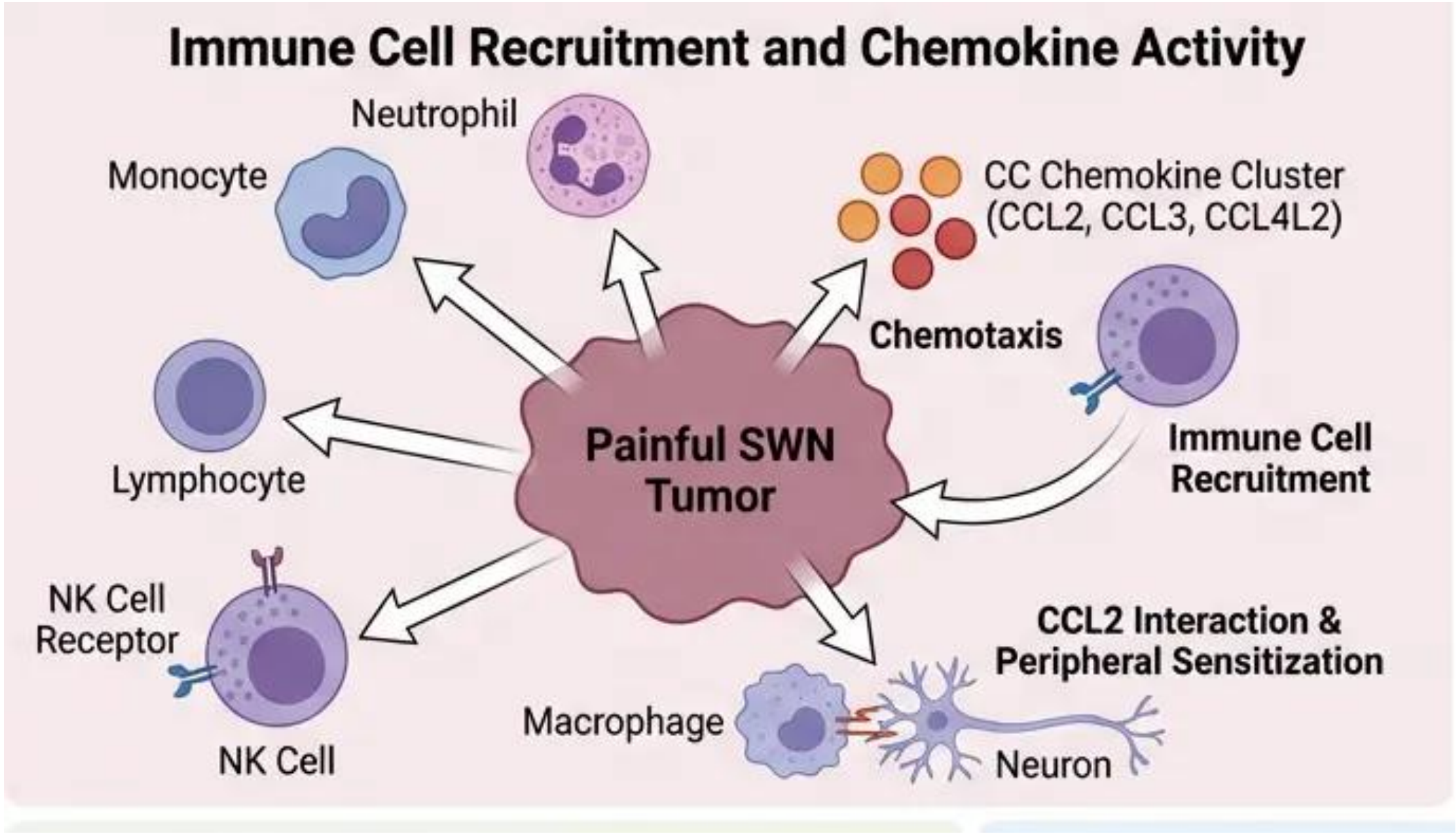
Painful and Nonpainful Samples are Highly Similar in Both Schwannomatosis and Solitary Schwannoma Tumors



Note. The average gene expression of painful samples (x-axis) plotted against the average gene expression nonpainful samples (y-axis) in (A) schwannomatosis tumors (N = 7) (R^2 = 0.9503) and (B) single schwannoma samples (N = 21) (R^2 = 0.9471) for 14,656 common genes.

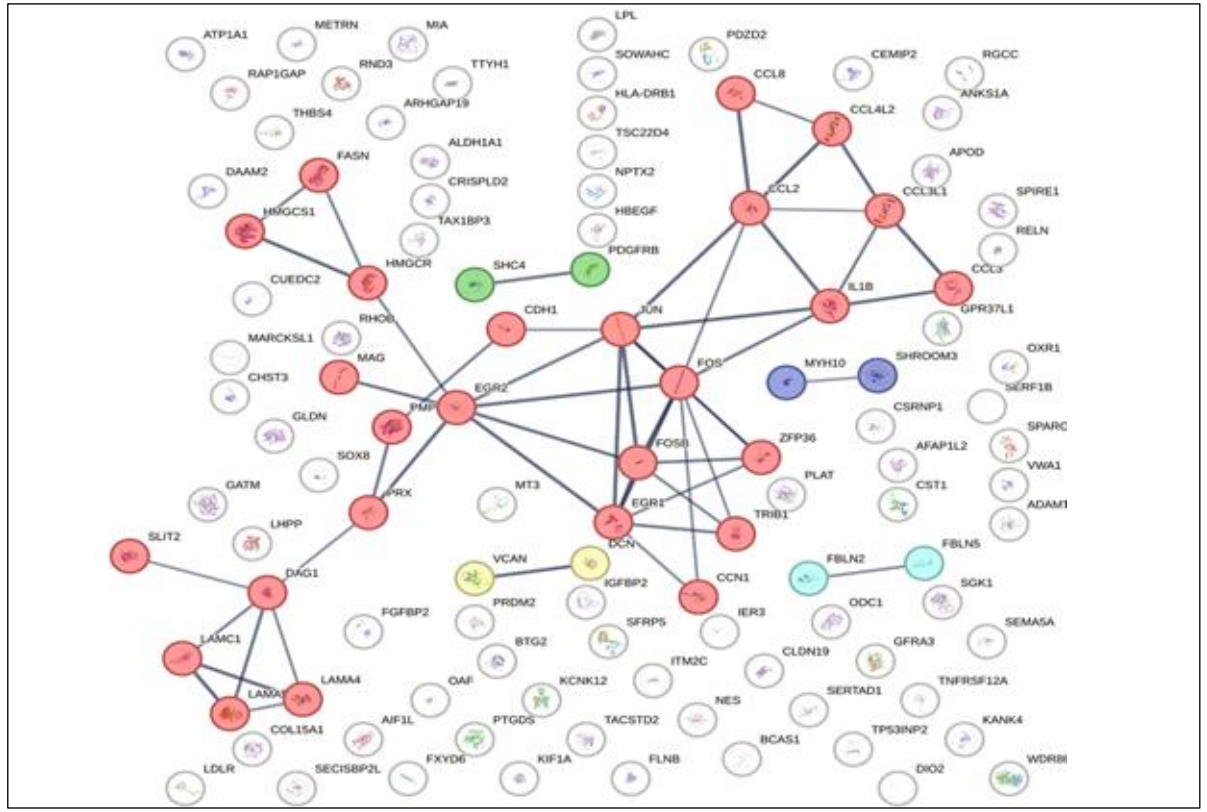
SWN Highest Expressing Pain-Upregulate Genes




Immune Cell Recruitment and Chemokine Activity
Neutrophil
Monocyte
CC Chemokine Cluster
(CCL2, CCL3, CCL4L2)
Chemotaxis
Lymphocyte
Painful SWN
Tumor
Immune Cell
Recruitment
NK Cell
Receptor
CCL2 Interaction &
Peripheral Sensitization
Macrophage
NK Cell
Neuron

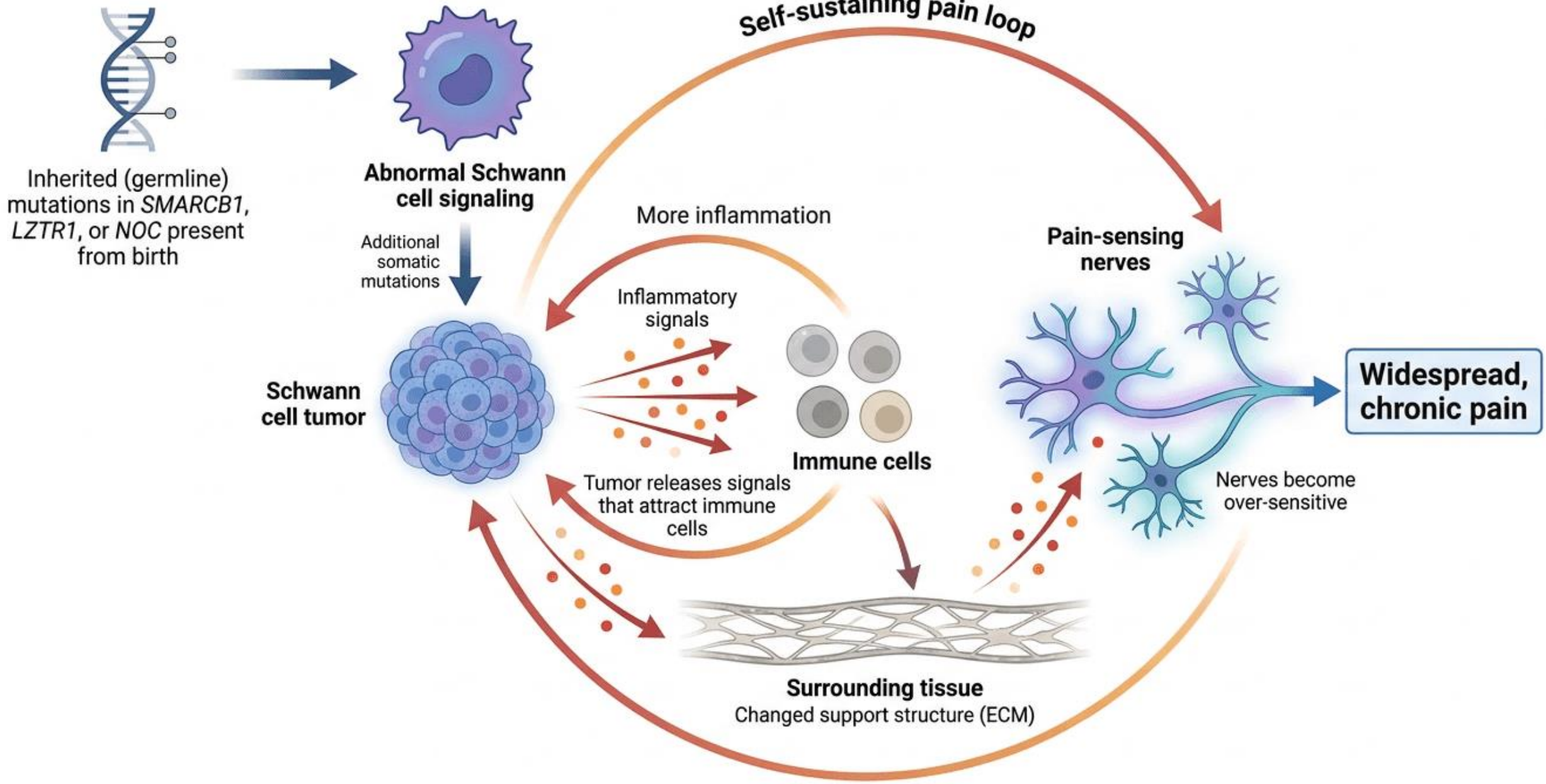
Painful SWN vs Painful SS

Upregulated Painful Schwannomatosis versus Painful Single Schwannomas PPI Networks

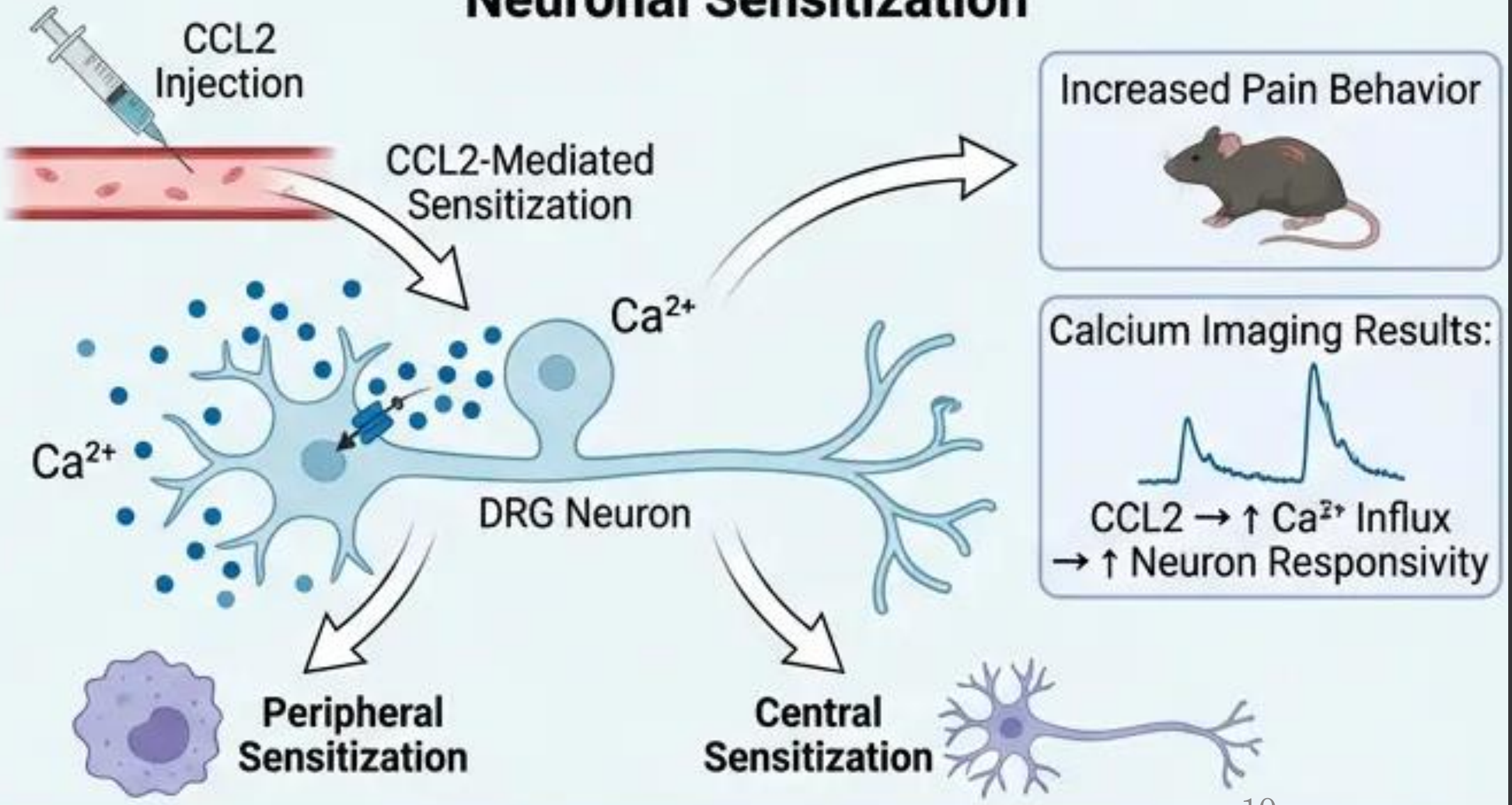


Functionally enriched pathways aligned with the following categories:

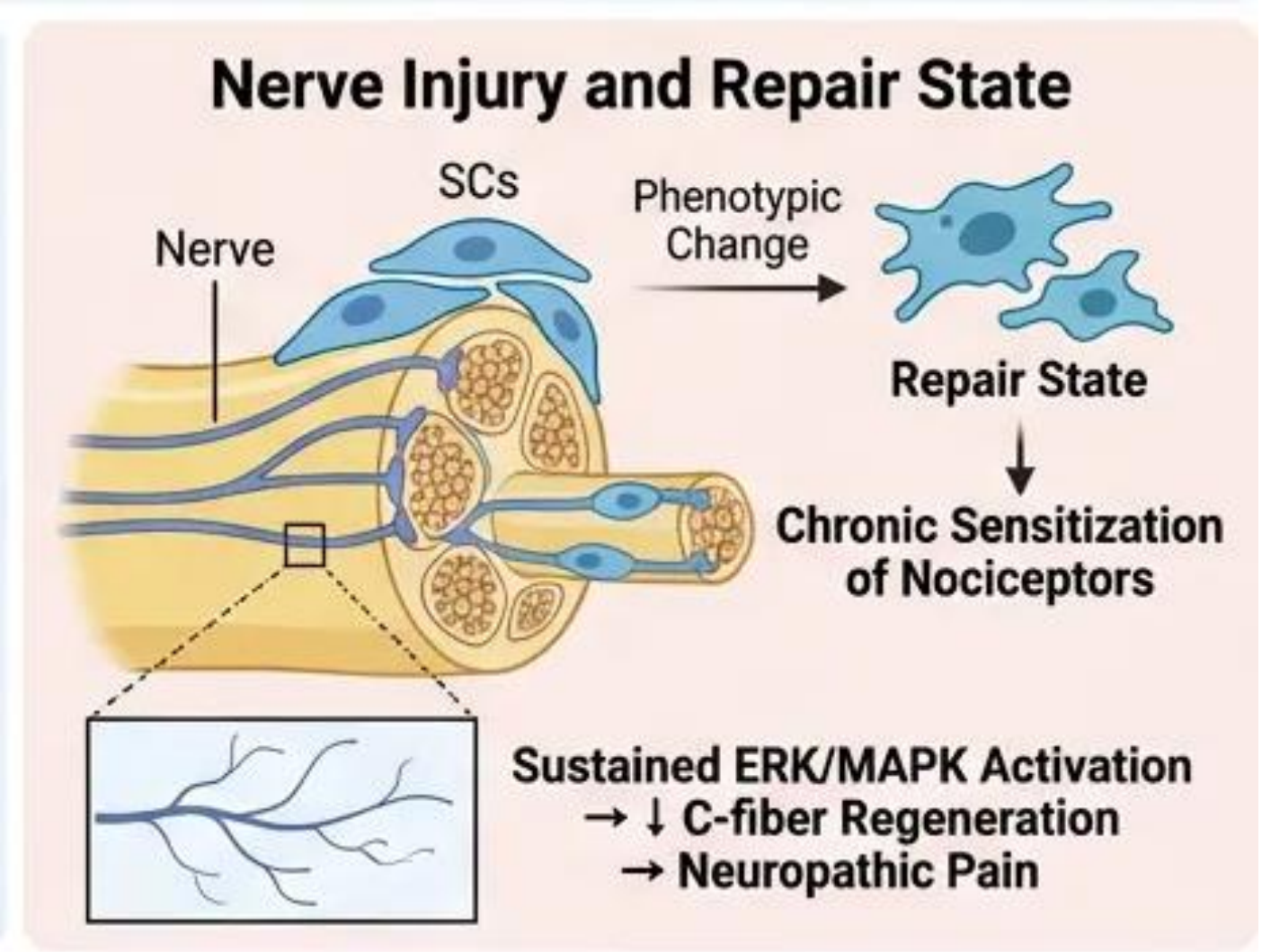
1. **immune-inflammatory** pathways and ERK/MAPK signaling
2. extracellular matrix (**ECM**) **remodeling** and adhesion
3. glial and **Schwann cell** facilitated **repair**
4. neural injury and repair context


Inherited (germline) mutations in *SMARCB1*, *LZTR1*, or *NOC* present from birth
Abnormal Schwann cell signaling
Additional somatic mutations
Schwann cell tumor
Self-sustaining pain loop
More inflammation
Inflammatory signals
Immune cells
Tumor releases signals that attract immune cells
Pain-sensing nerves
Widespread, chronic pain
Nerves become over-sensitive
Surrounding tissue
Changed support structure (ECM)

Neuronal Sensitization



RAS/MAPK Signaling



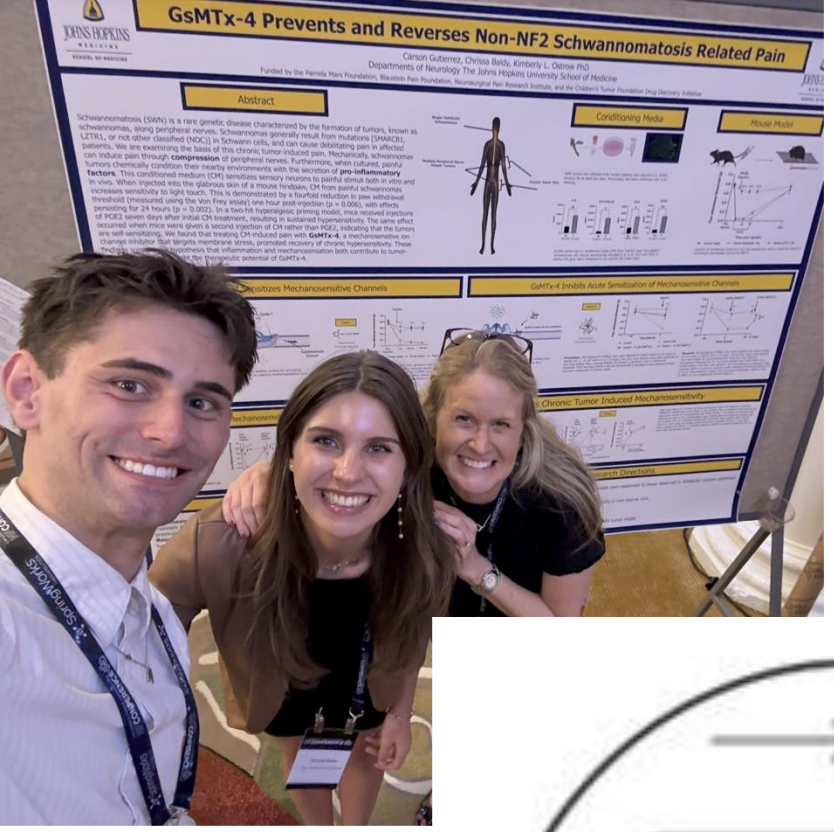
Understanding Chronic Pain at Its Source

Study Findings:

- Painful tumors show heightened inflammatory signaling
- Repair pathways meant to heal nerves can become chronically activated

This mechanistic insight reveals new therapeutic targets, such as CCL2 and RAS/MAPK Signaling

Take-Home Message: By understanding how pain begins at the molecular level, we move closer to treating its cause, not just its symptoms.



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DMV PetriDish
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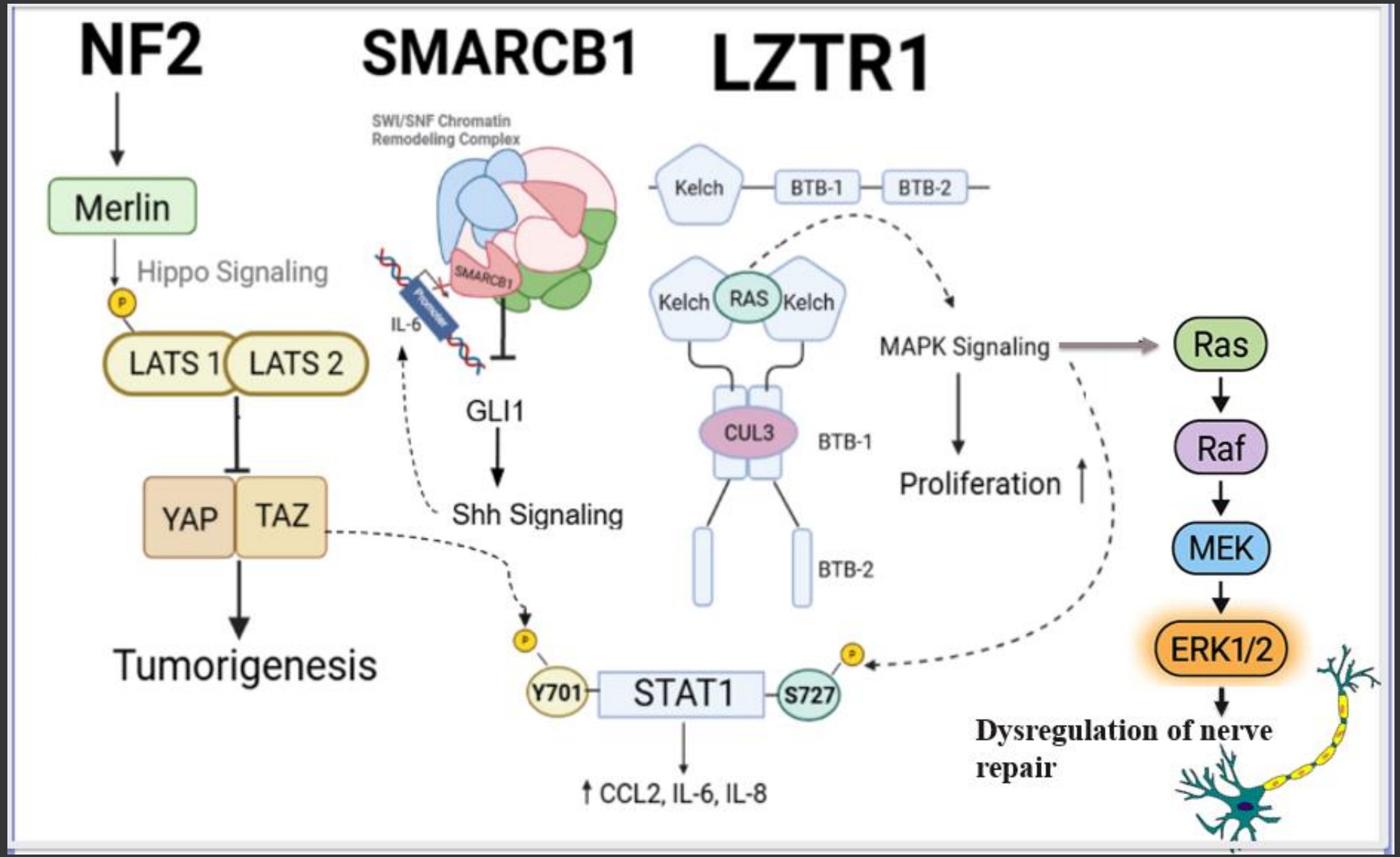
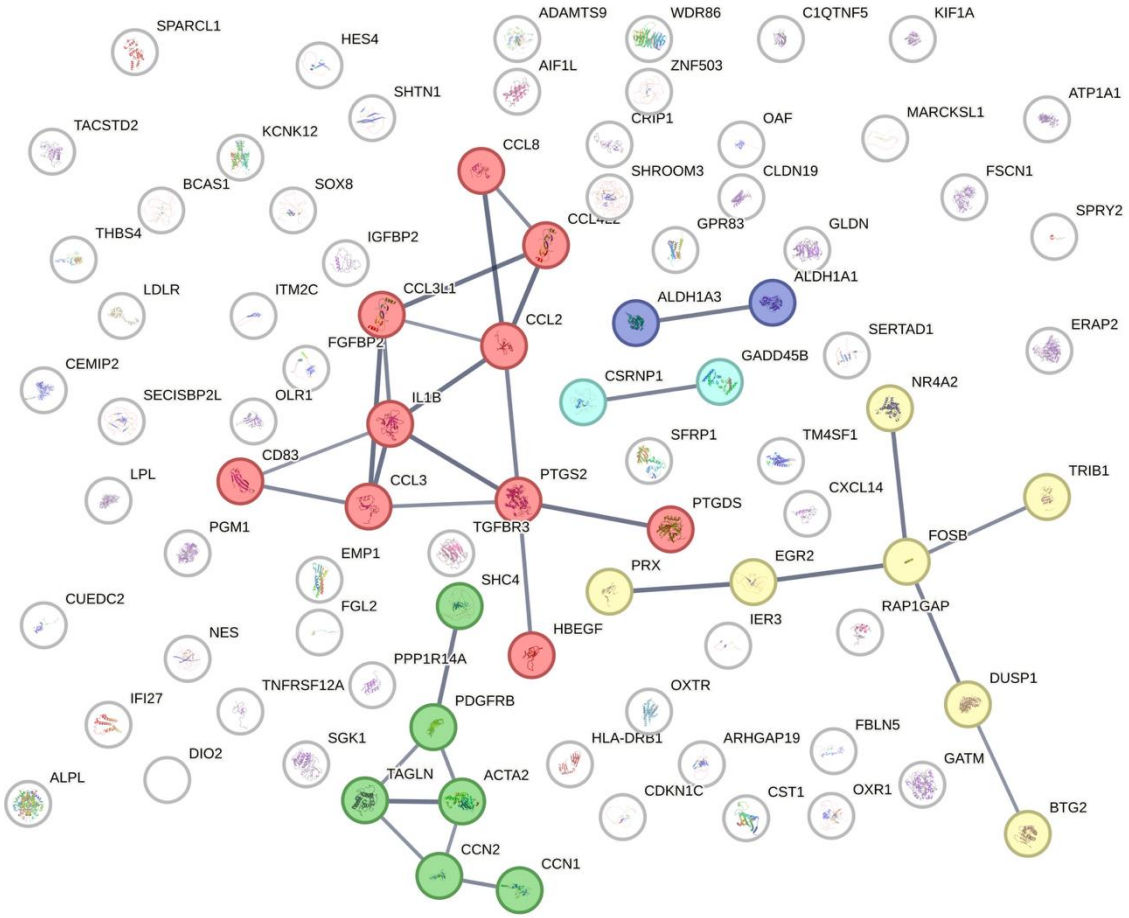
Thank You!

Bonus Slides!


NF2
SMARCB1
LZTR1
Merlin
Hippo Signaling
LATS 1
LATS 2
YAP
TAZ
Tumorigenesis
SWI/SNF Chromatin Remodeling Complex
SMARCB1
IL-6
GLI1
Shh Signaling
Kelch
BTB-1
BTB-2
Kelch
RAS
Kelch
CUL3
BTB-1
BTB-2
MAPK Signaling
Proliferation
Ras
Raf
MEK
ERK1/2
Y701
STAT1
S727
↑ CCL2, IL-6, IL-8
Dysregulation of nerve repair

SWN Pain-Upregulate Genes



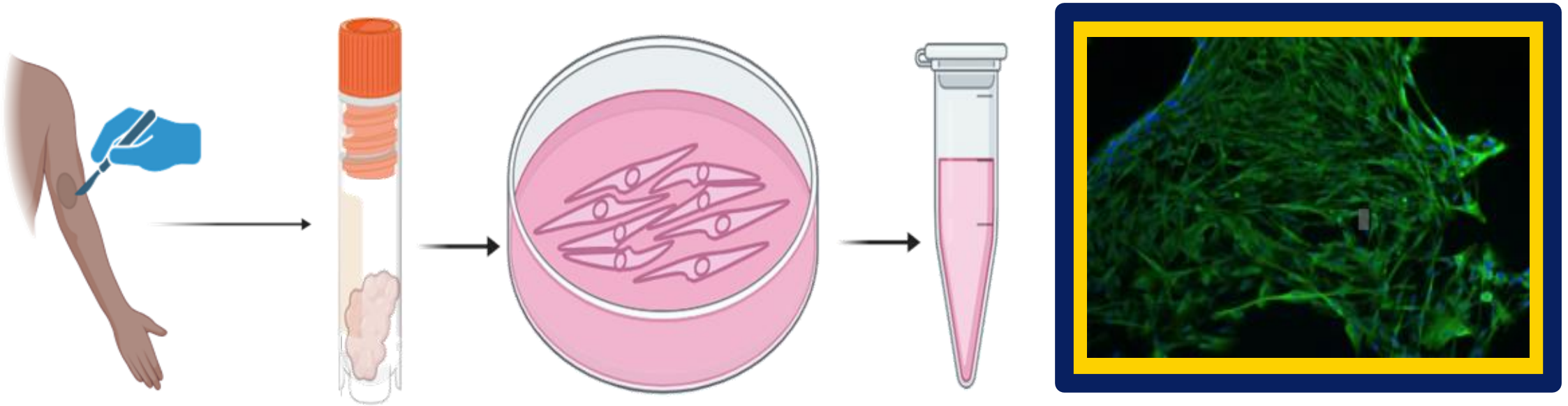
SWN Pain-Upregulated Gene Ontology Functional Enrichment

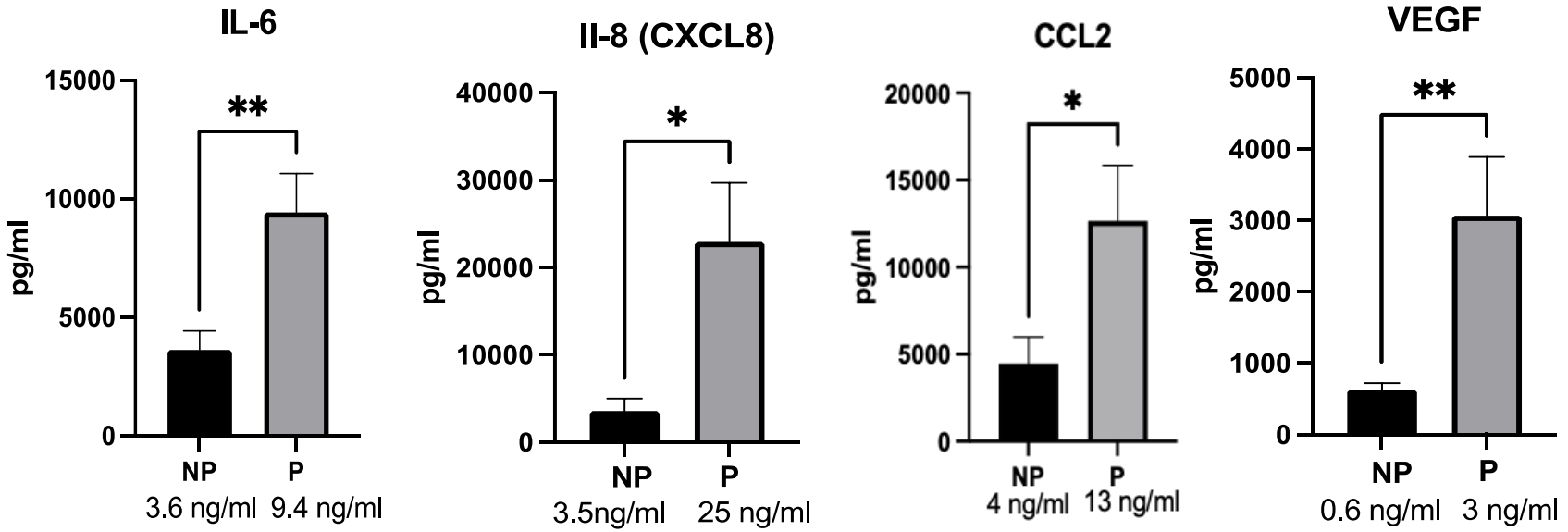
Biological Process (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0002548	Monocyte chemotaxis	5 of 21	1.55	0.99	0.00038
GO:0070372	Regulation of ERK1 and ERK2 cascade	12 of 209	0.93	0.94	6.25e-05
GO:0071347	Cellular response to interleukin-1	7 of 68	1.19	0.91	0.00037
GO:0060326	Cell chemotaxis	9 of 143	0.97	0.82	0.00039
GO:2000501	Regulation of natural killer cell chemotaxis	3 of 5	1.95	0.75	0.0034
GO:0048545	Response to steroid hormone	10 of 211	0.85	0.72	0.00071
GO:0150077	Regulation of neuroinflammatory response	4 of 25	1.38	0.63	0.0068
GO:0032355	Response to estradiol	6 of 82	1.04	0.61	0.0051
GO:0090280	Positive regulation of calcium ion import	3 of 11	1.61	0.57	0.0127
GO:0045933	Positive regulation of muscle contraction	4 of 32	1.27	0.55	0.0120
GO:0051384	Response to glucocorticoid	6 of 103	0.94	0.51	0.0116

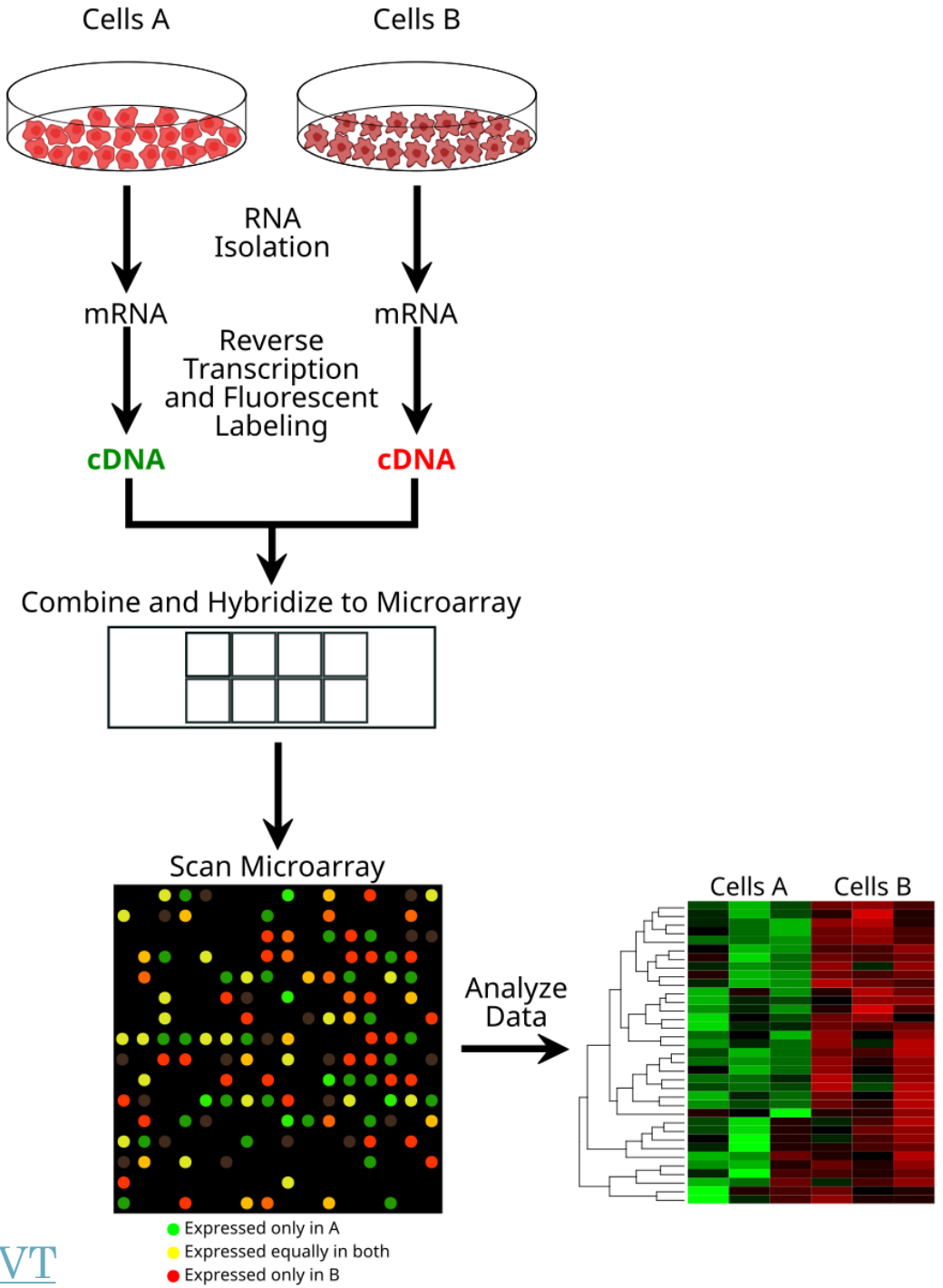
Molecular Function (Gene Ontology)

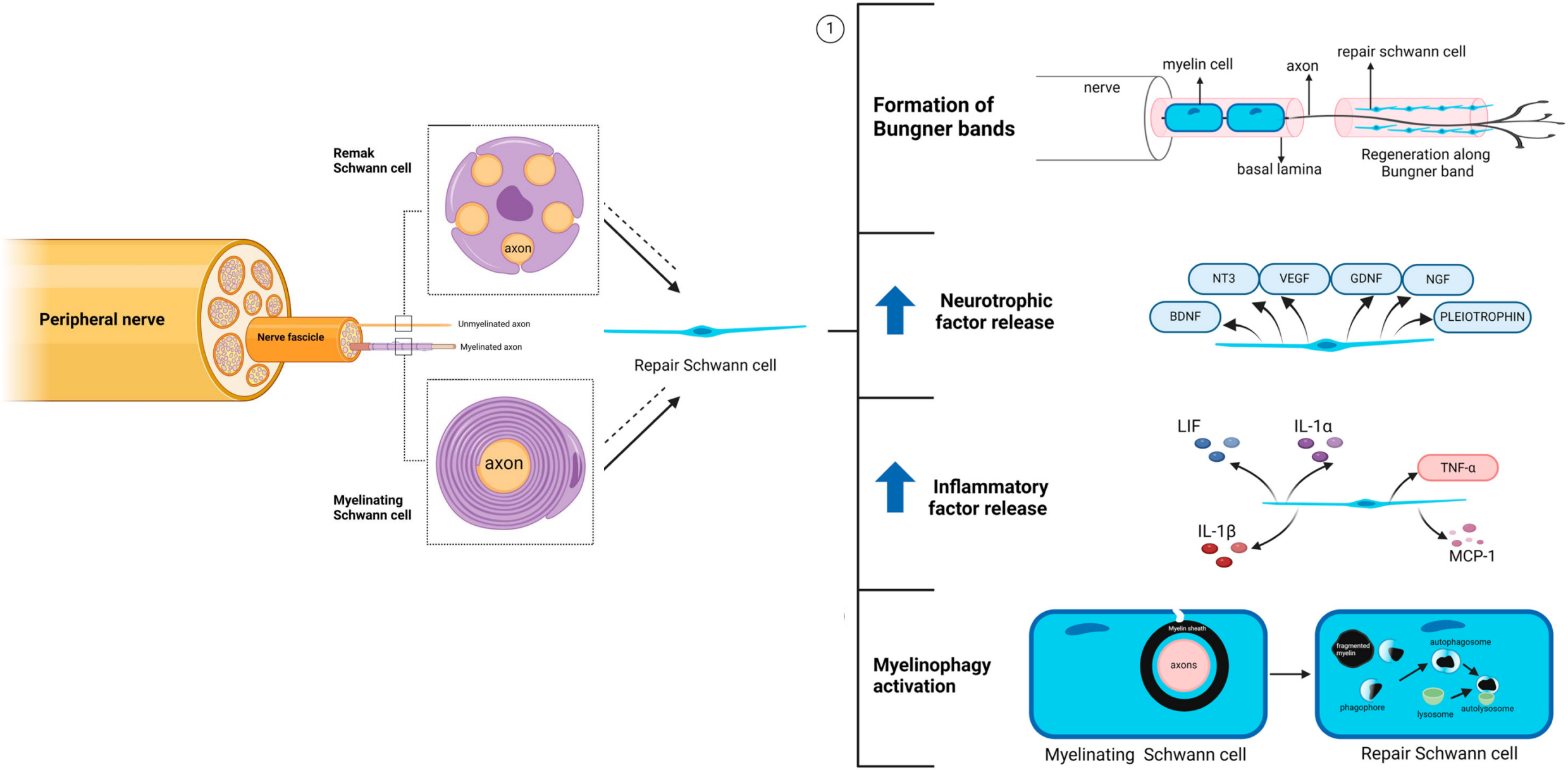
GO-term	description	count in network	strength	signal	false discovery rate
GO:0042379	Chemokine receptor binding	7 of 39	1.43	1.17	5.83e-05
GO:0008201	Heparin binding	8 of 114	1.02	0.77	0.00086
GO:0005126	Cytokine receptor binding	9 of 161	0.92	0.73	0.00092
GO:0005125	Cytokine activity	7 of 107	0.99	0.64	0.0034
GO:0048018	Receptor ligand activity	10 of 232	0.81	0.63	0.0019





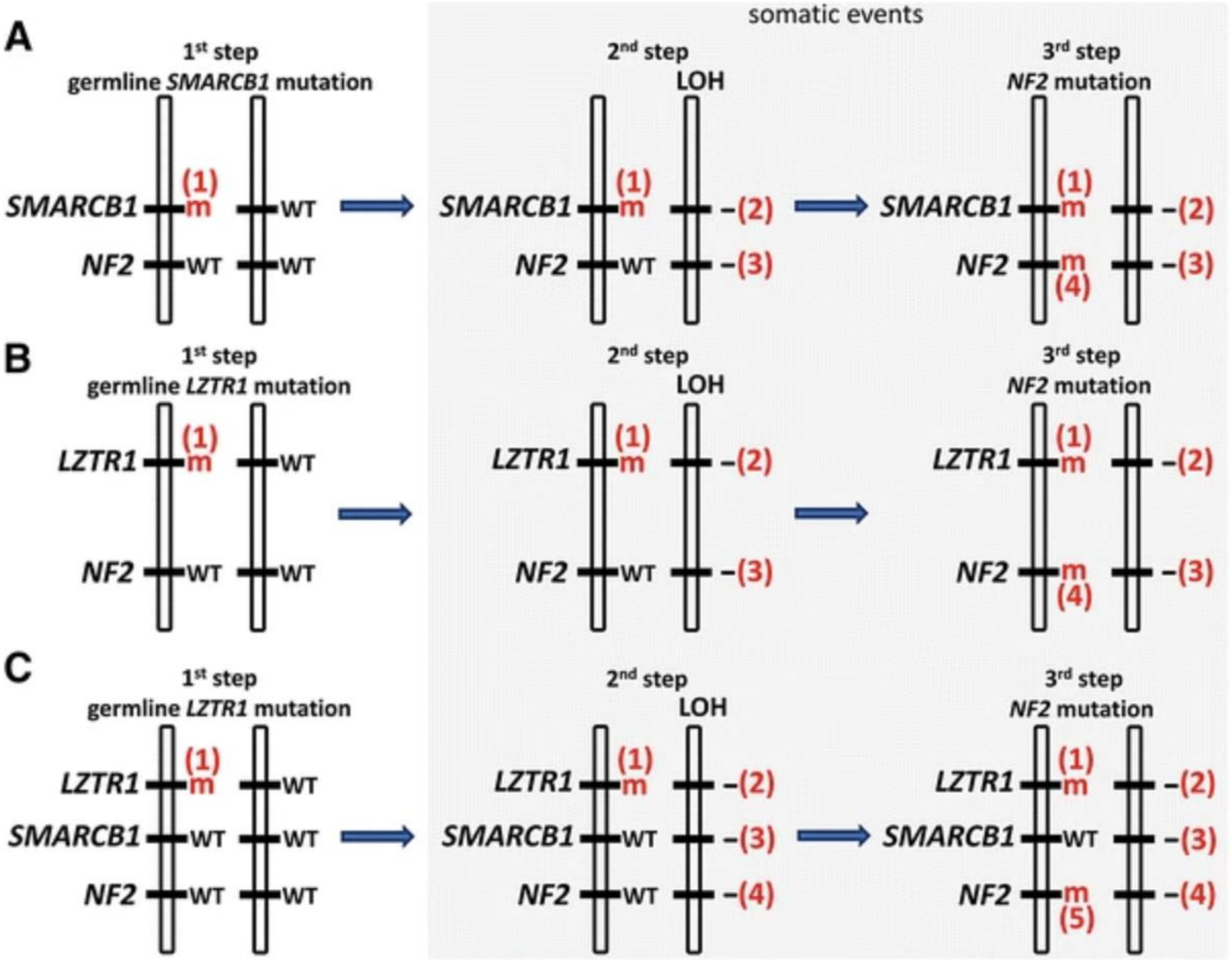
ELISAs performed on conditioned media (CM) from "painful" and "non-painful" Schwannoma cell cultures demonstrate elevated IL-6, IL-8, CCL2 and VEGF in painful CM (grey bars) compared to non-painful CM (black bars).


Cells A
Cells B
RNA Isolation
mRNA
mRNA
Reverse Transcription and Fluorescent Labeling
cDNA
cDNA
Combine and Hybridize to Microarray
Scan Microarray
Analyze Data
Cells A
Cells B
Expressed only in A
Expressed equally in both
Expressed only in B

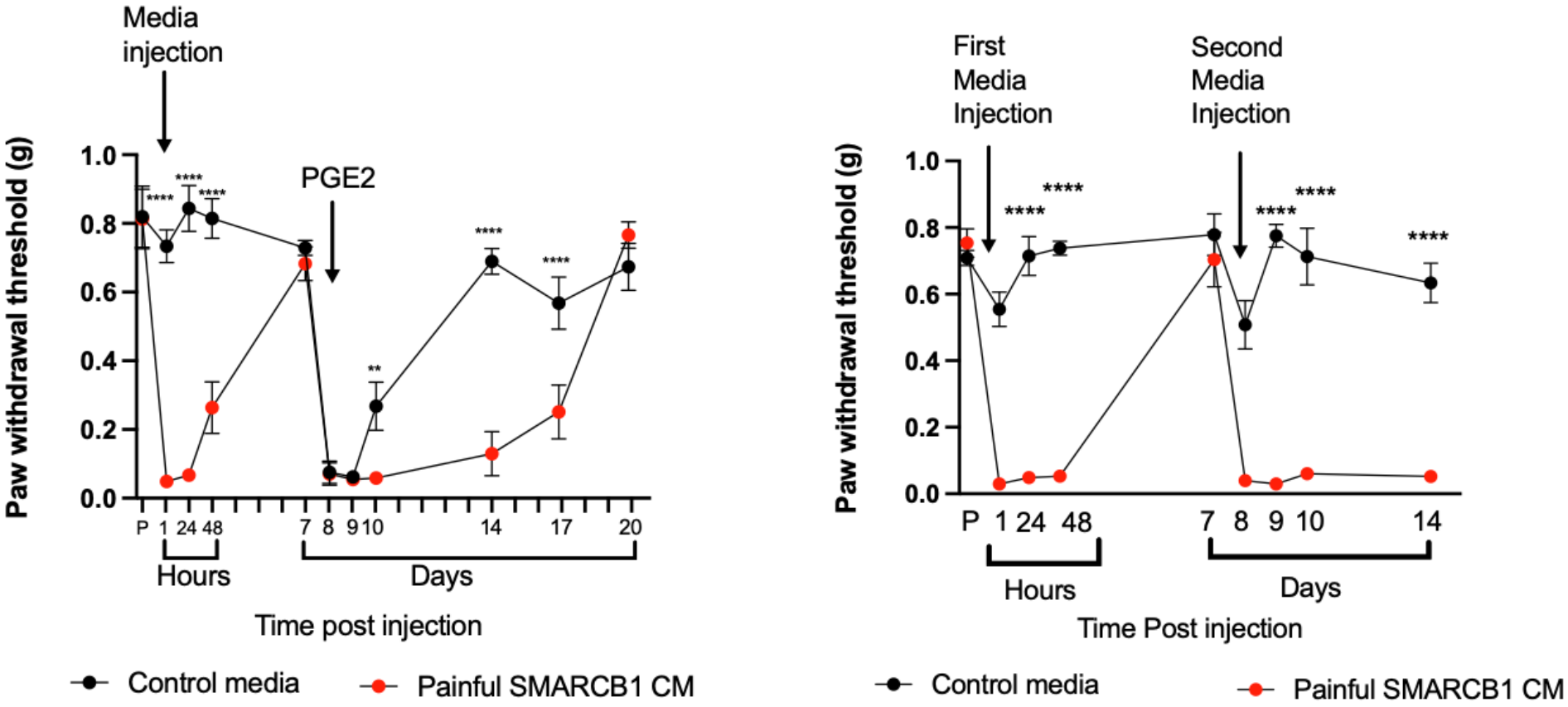


(Abd et al., 2024)

Bonus Slide:


somatic events
A
1st step
germline SMARCB1 mutation
2nd step
LOH
3rd step
NF2 mutation
SMARCB1
NF2
(1)
m
WT
–(2)
–(3)
m
(4)
B
1st step
germline LZTR1 mutation
2nd step
LOH
3rd step
NF2 mutation
LZTR1
NF2
C
1st step
germline LZTR1 mutation
2nd step
LOH
3rd step
NF2 mutation
LZTR1
SMARCB1
NF2
m
(5)

Bonus Slide:



Wild Type Black C57 8-week-old mice received an initial 10ul injection of painful SMARCB1 conditioned tumor media in one hindfoot, the contralateral side received an equivalent volume of unconditioned cell media. One week post injection, both hind paws received a 10ul dose of PGE2 at 100nM. Sustained hyperalgesia in the foot treated with painful CM confirmed that a chronic pain model of SWN was established. Painful phenotypes resolved by day 20 and no significant differences were found in either the male or female versions of the chronic pain model. When the second hit was replaced with an additional CM injection, chronic pain states were still observed regardless of sex.

BIOLOGY OF PAIN: MECHANISMS & TYPES

NOCICEPTIVE PAIN

Throbbing, aching, pressure-like

Forces threatening tissue integrity (thermal, chemical, mechanical).

NEUROPATHIC PAIN

Sharp, shooting, burning, tingling, electric shock-like

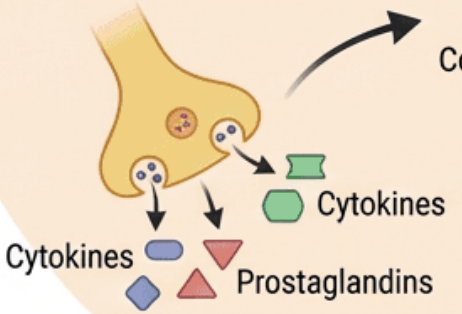
Damage to CNS or PNS (trauma, neurodegeneration, autoimmune, nerve compression, metabolic, viral, chemo)

NOCIPLASTIC PAIN

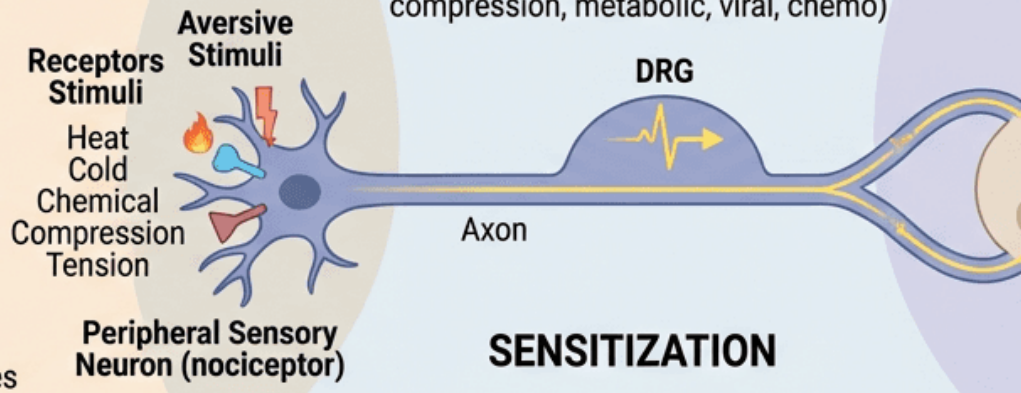
Globally enhanced responsivity, visceral pain, widespread sensitivity

Altered CNS processing (no clear tissue/nerve damage)

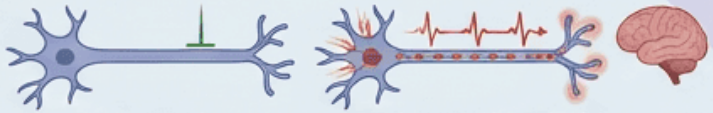
INFLAMMATORY PAIN



Prolonged pain, sensitization of nearby nociceptors.

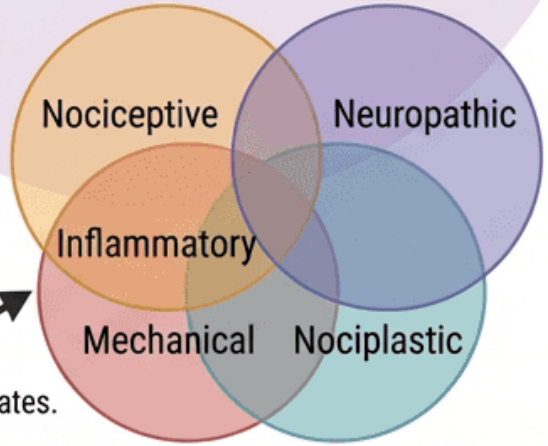


SENSITIZATION



Normal Threshold

Reduced Threshold (Increased Response)



MIXED-PAIN STATES & MECHANISTIC OVERLAP

Pain is a continuum of inter-related mechanisms. Patients may experience mixed-pain states.