

GlioLighT Workshop

1st-2nd September 2026

VINČA Institute of Nuclear Sciences, Belgrade, Serbia

Introduction to brain tumour biology

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**JOHANNES GUTENBERG
UNIVERSITÄT MAINZ**



What is a cancer cell ?

- Deregulation of cell cycle
- Genetic alterations
- Chromosomal instability

How does cancer develop ?

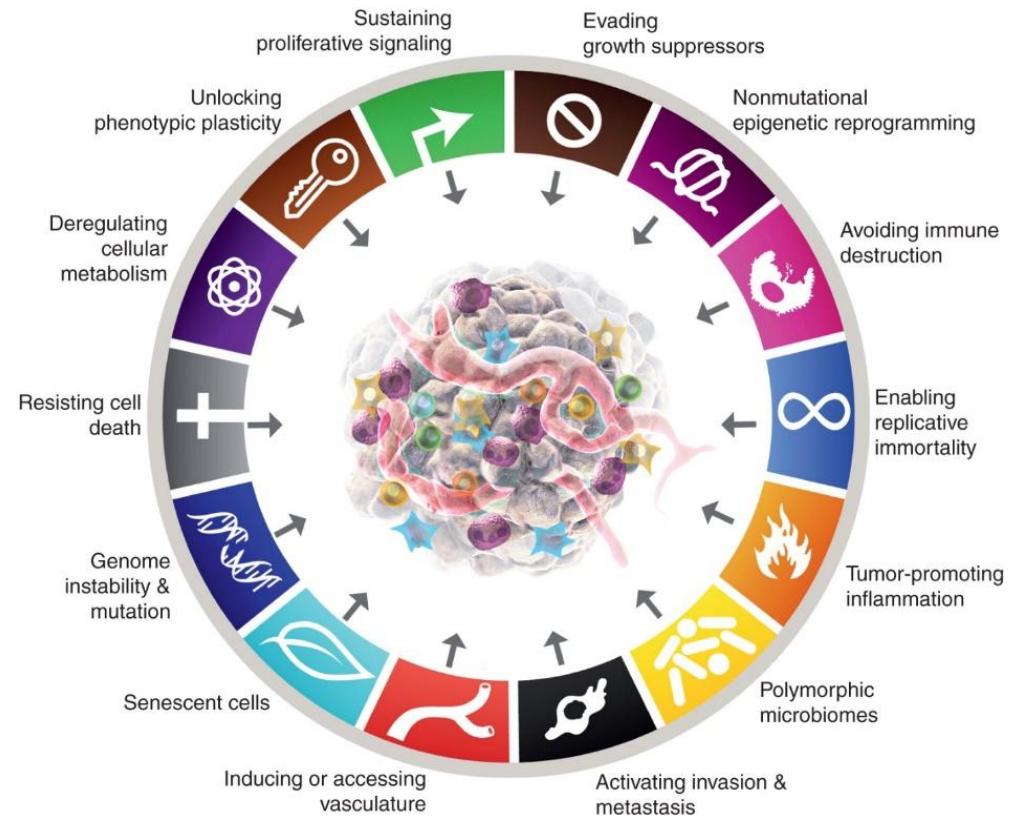
- Hypoxia /metabolic changes
- Metastasis / EMT
- Cellular heterogeneity / tumor initiating cells

Why can cancer develop ?

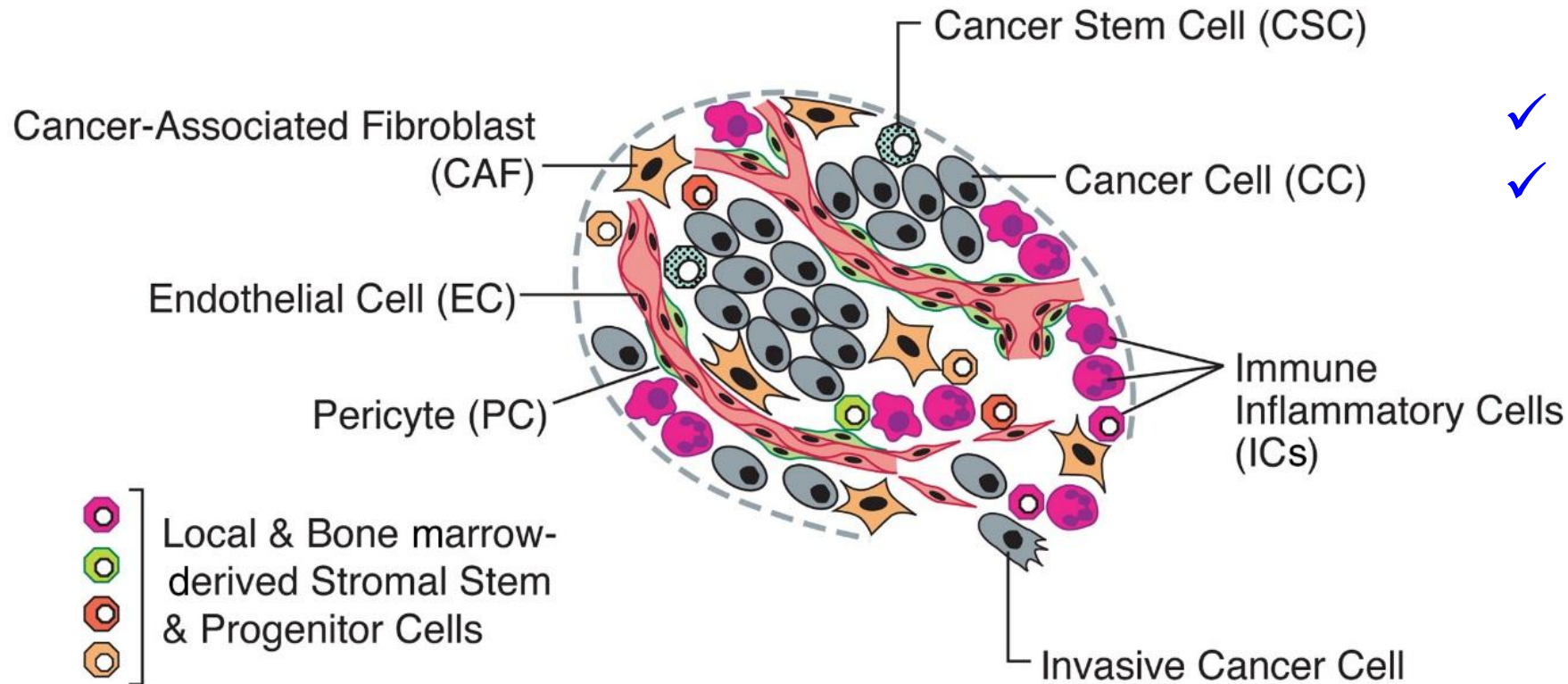
- Immune dysfunction / immunosuppression

The hallmarks of cancer

"A set of functional capabilities acquired by human cells as they make their way from normalcy to neoplastic growth states"
(Weinberg and Hanahan)



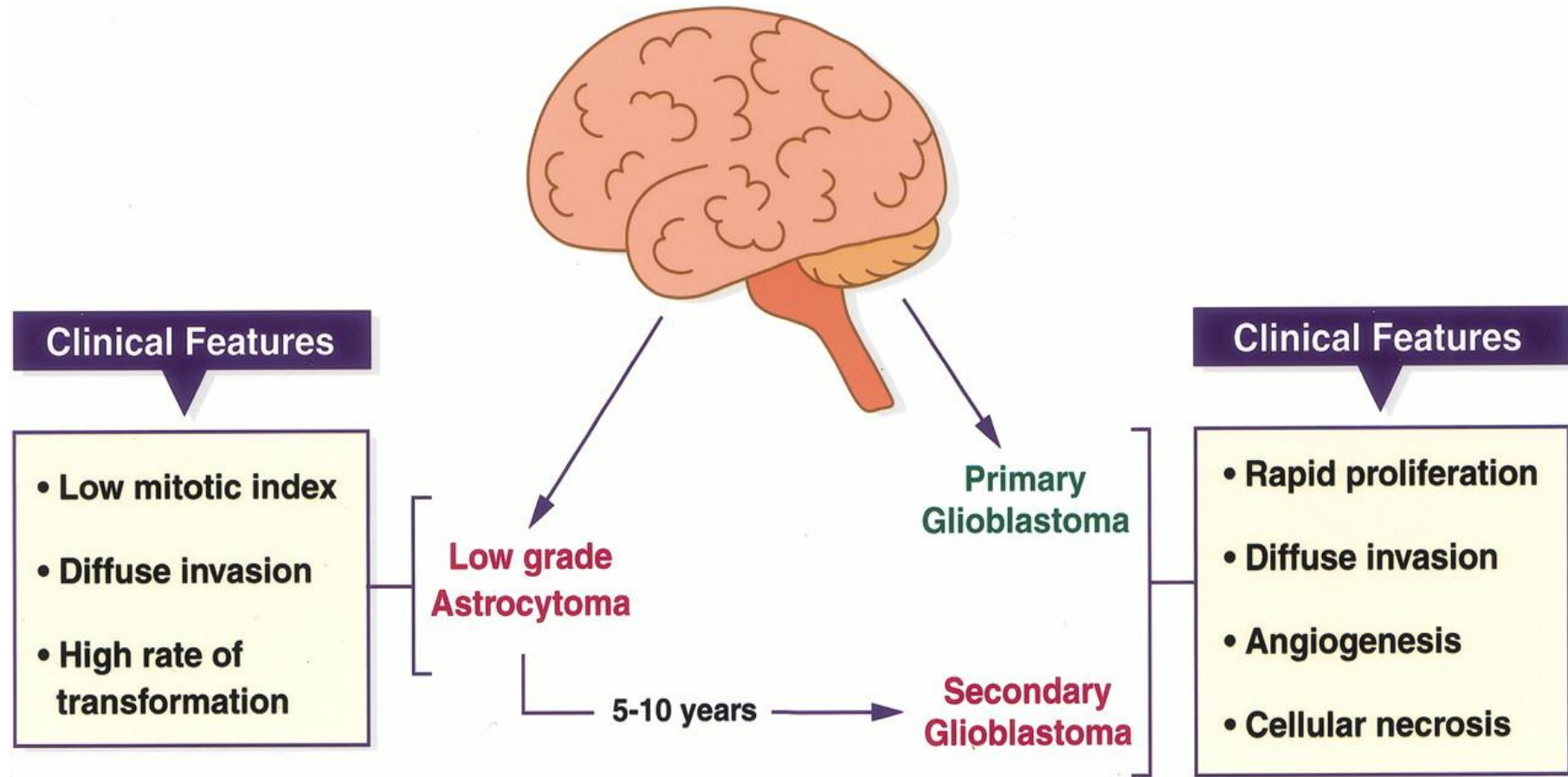
Tumours can be compared to tissues



- ✓ cellular heterogeneity
- ✓ tumour microenvironment

Therapy: what cell type(s) should we target?

Brain tumours (Glioma)

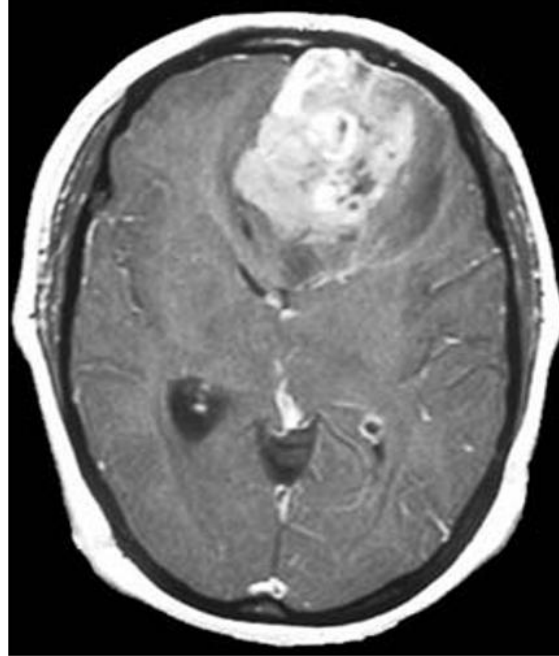


Glioblastoma features and therapy

diffuse, infiltrative

highly vascular tumour

microglia/macrophages
(30-40%)



wikipedia

✓ Surgery

Diffuse infiltrative nature

Recurrent tumour (*tumor stem cells*)

✓ Radiotherapy

Skull; radioresistance

✓ Chemotherapy

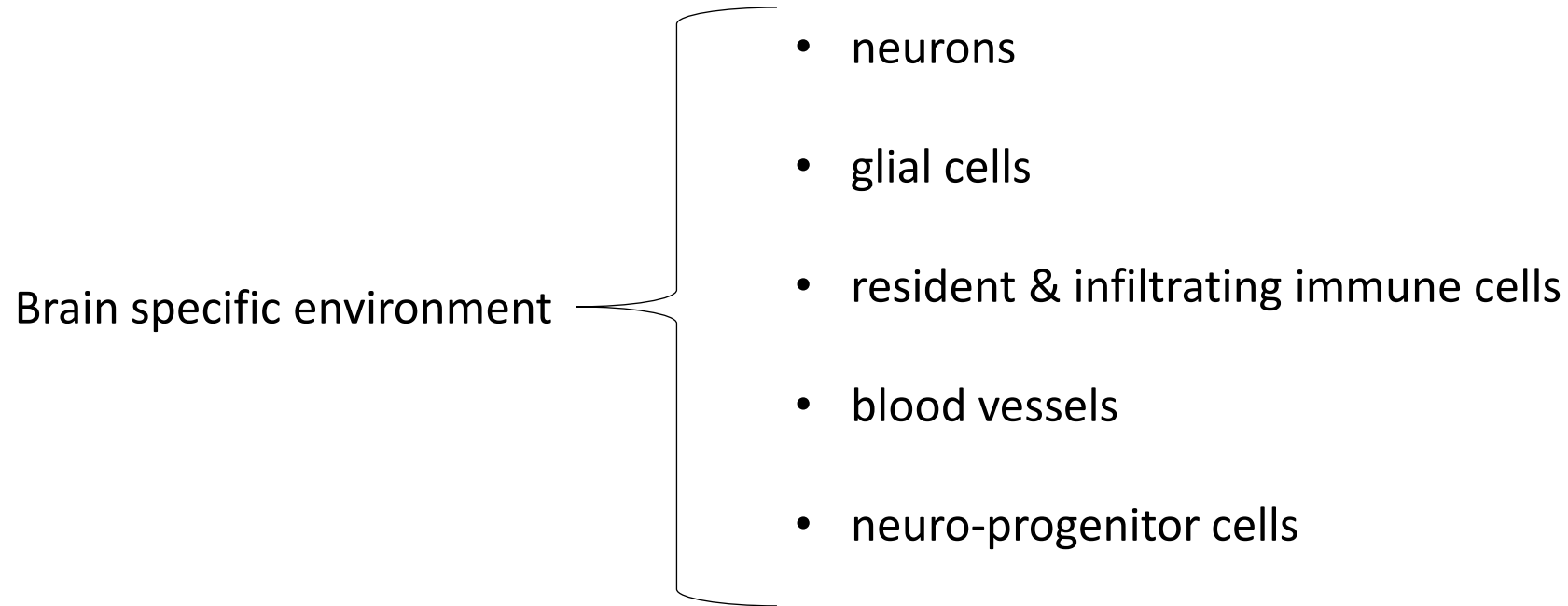
Blood-brain barrier; chemoresistance

Novel / alternative therapies ?



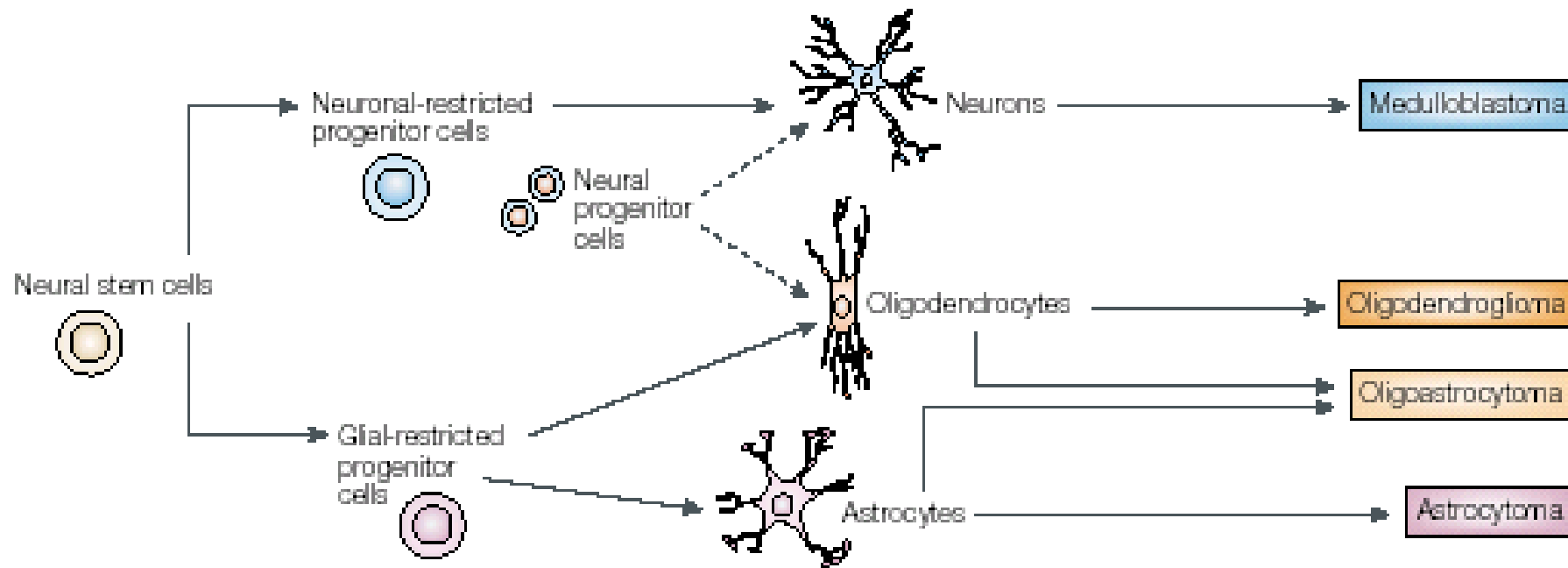
Better understanding of tumour biology

The tumour niche



Origin of brain tumour

➤ Cells of the nervous system:

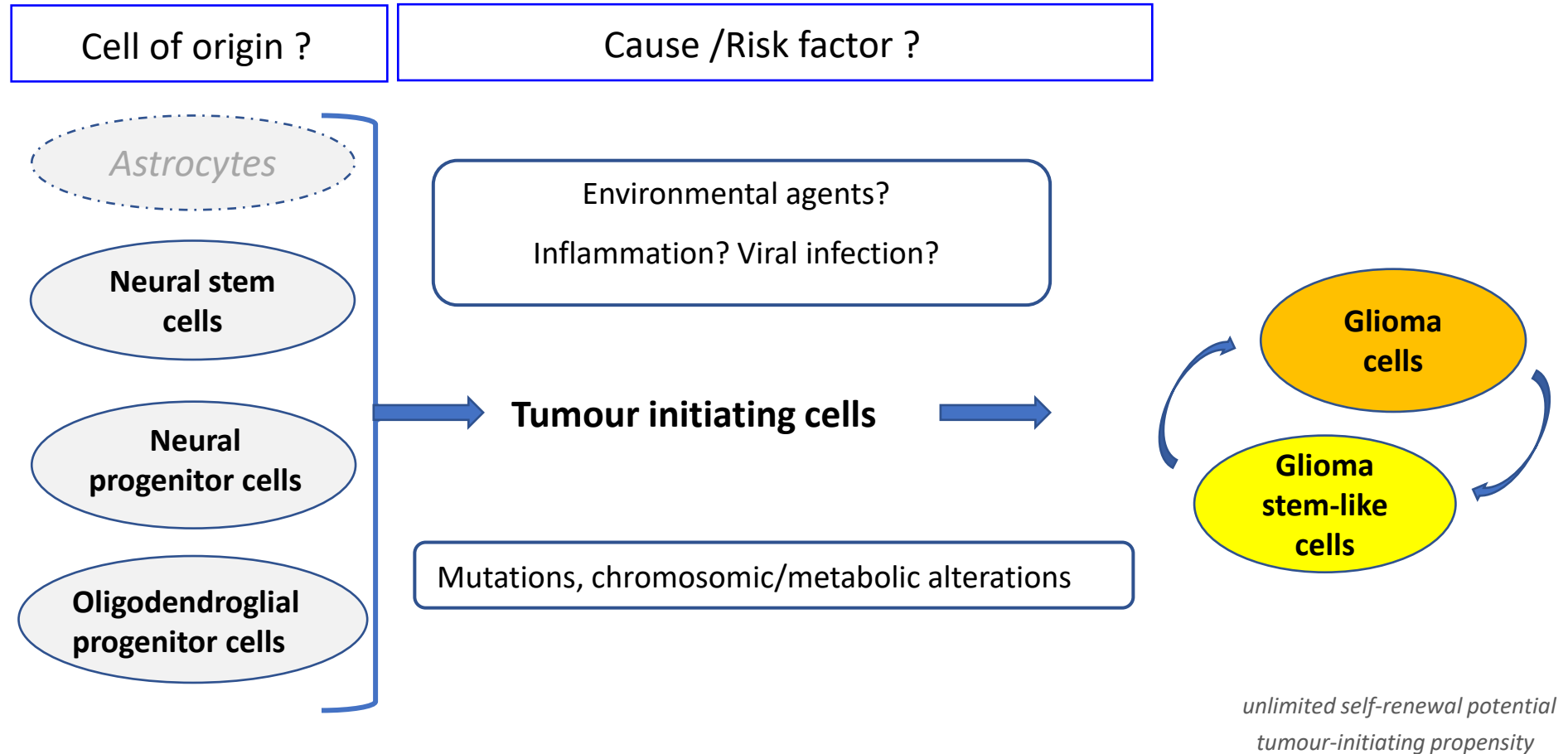


Genes Dev. 2001 Jun 1;15(11):1311-33. doi: 10.1101/gad.891601

➤ Metastasis of tumour cells:

- Breast, colon, kidney, melanoma

Initiation of primary brain tumour



Incidence of gliomas by anatomic location

86 % in cerebral lobes
(highest blood flow)

6,4 % in deep structures of cerebrum

2,2 % in ventricles

1,5 % in cerebellum

4,1 % in brain stem

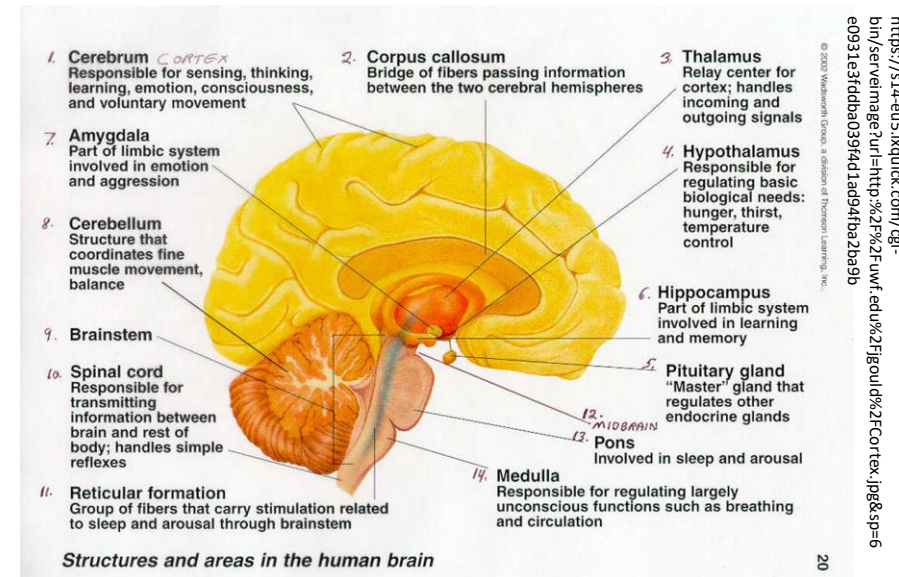
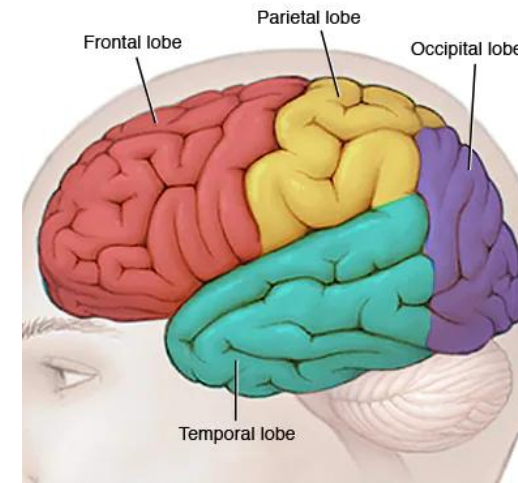


Table 2. Number and frequency of gliomas relative to tissue volume by cerebral lobe

Location of Glioma	Frequency (No. of Gliomas)	Relative Volume ^a	Frequency/Volume ^b	Frequency: Volume Ratio Relative to Occipital Lobe ^{c*}
Frontal lobe	107	3	36	4.5
Temporal lobe	77	2	39	4.8
Parietal lobe	37	2	19	2.3
Occipital lobe	8	1	8	1.0

Neuro Oncol. 2007;9(3):319-325. doi:10.1215/15228517-2007-016



The diversity of the brain tumours

World Health Organization (WHO) Classification:

Grades I to IV:

Morphology
Cytogenetics
Molecular genetics
Immunologic markers

	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	*			
Pilocytic astrocytoma	*			
Piloxyoid astrocytoma		*		
Diffuse astrocytoma		*		
Pleomorphic xanthoastrocytoma		*		
Anaplastic astrocytoma			*	
Glioblastoma				*
Giant cell glioblastoma				*
Gliosarcoma				*
Oligodendroglial tumours				
Oligodendroglioma		*		
Anaplastic oligodendroglioma			*	
Oligoastrocytic tumours				
Oligoastrocytoma		*		
Anaplastic oligoastrocytoma			*	
Ependymal tumours				
Subependymoma	*			
Myxopapillary ependymoma	*			
Ependymoma		*		
Anaplastic ependymoma			*	
Choroid plexus tumours				
Choroid plexus papilloma	*			
Atypical choroid plexus papilloma		*		
Choroid plexus carcinoma			*	
Other neuroepithelial tumours				
Angiocentric glioma	*			
Chordoid glioma of the third ventricle		*		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	*			
Ganglioglioma	*			
Anaplastic ganglioglioma			*	
Desmoplastic infantile astrocytoma and ganglioglioma	*			
Dysembryoplastic neuroepithelial tumour	*			

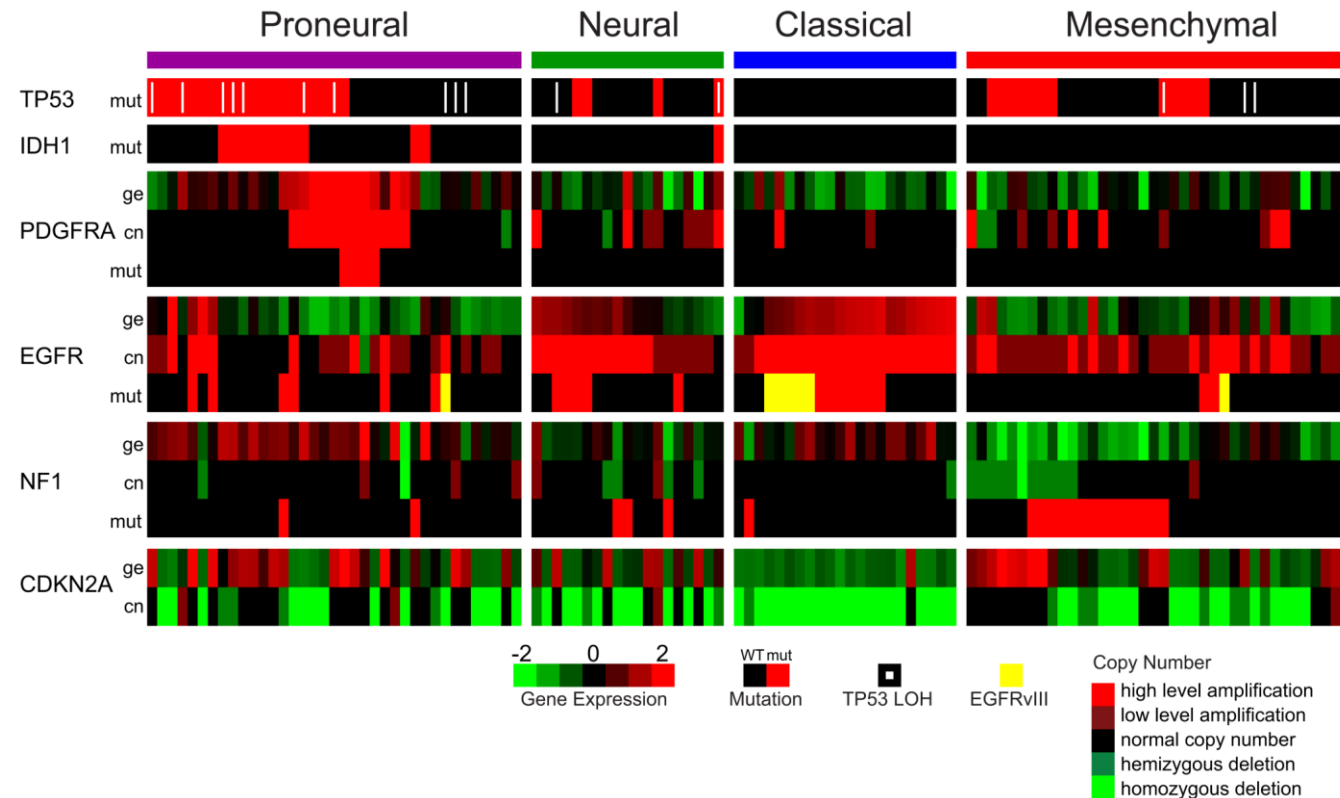
	I	II	III	IV
Central neurocytoma				
Central neurocytoma		*		
Extraventricular neurocytoma		*		
Cerebellar liponeurocytoma		*		
Paraganglioma of the spinal cord	*			
Papillary glioneuronal tumour	*			
Rosette-forming glioneuronal tumour of the fourth ventricle	*			
Pineal tumours				
Pineocytoma	*			
Pineal parenchymal tumour of intermediate differentiation		*	*	
Pineoblastoma				*
Papillary tumour of the pineal region		*	*	
Embryonal tumours				
Medulloblastoma				*
CNS primitive neuroectodermal tumour (PNET)				*
Atypical teratoid / rhabdoid tumour				*
Tumours of the cranial and paraspinal nerves				
Schwannoma	*			
Neurofibroma	*			
Perineurioma	*	*	*	
Malignant peripheral nerve sheath tumour (MPNST)		*	*	*
Meningeal tumours				
Meningioma	*			
Atypical meningioma		*		
Anaplastic / malignant meningioma			*	
Haemangiopericytoma		*		
Anaplastic haemangiopericytoma			*	
Haemangioblastoma	*			
Tumours of the sellar region				
Craniopharyngioma	*			
Granular cell tumour of the neurohypophysis	*			
Pituitaryoma	*			
Spindle cell oncocytoma of the adenohypophysis	*			

The diversity of the brain tumours

Molecular signature and classification in the age of Next Generation Sequencing et al.

The Cancer *Genome* Atlas (TCGA) classification of **Grade IV Glioblastoma (GBM)**

2010 - Transcriptomes of 200 GBM samples : 4 signatures = 4 subtypes

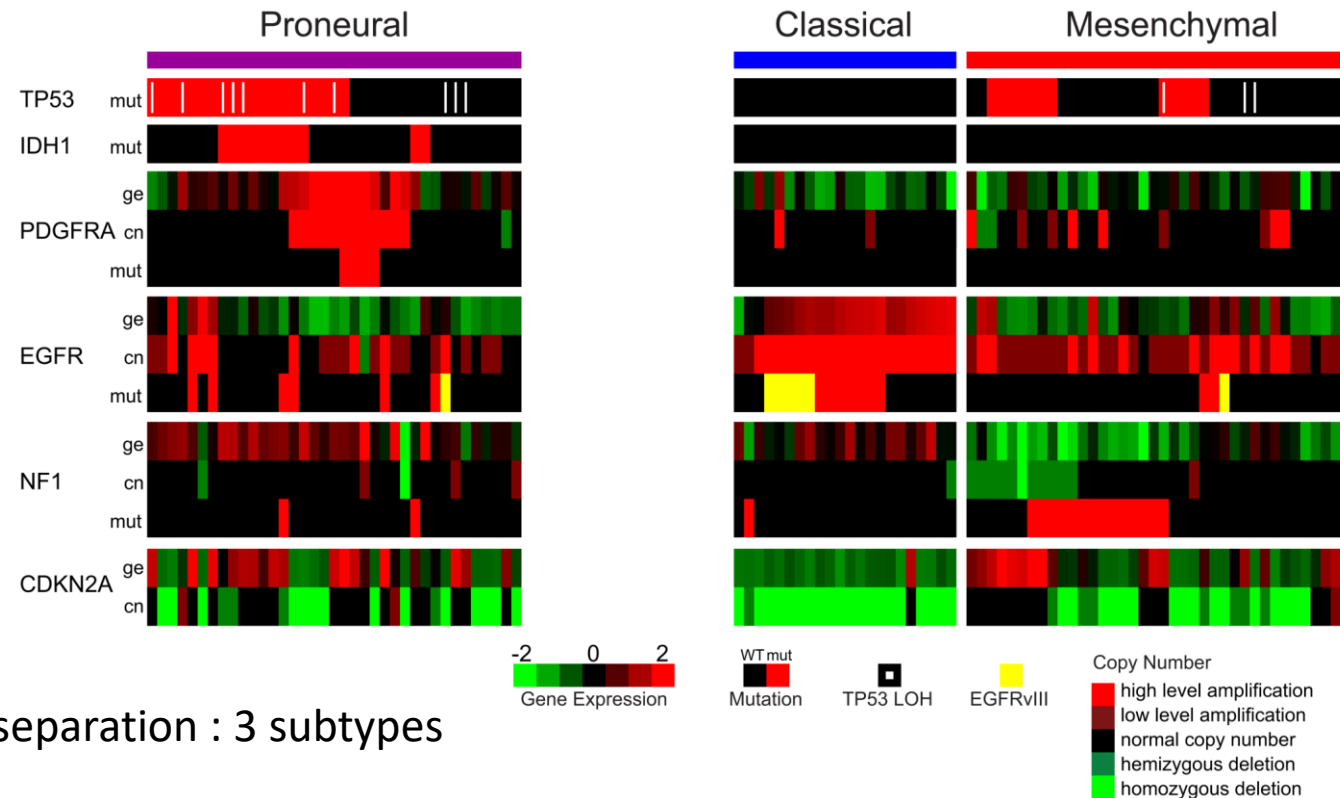


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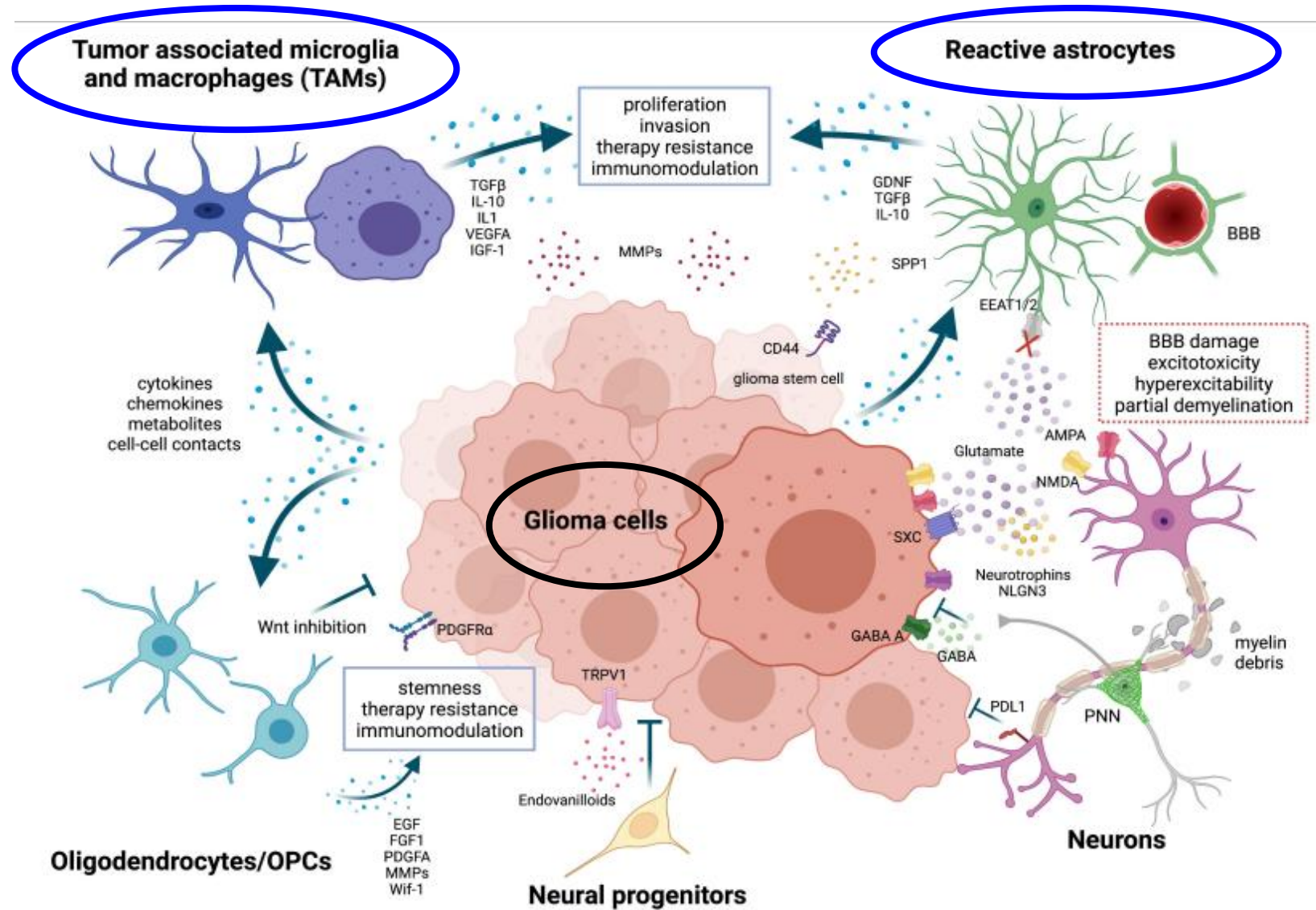
The Cancer *Genome* Atlas (TCGA) classification of **Grade IV Glioblastoma (GBM)**

2010 - Transcriptomes of 200 GBM samples : 4 signatures = 4 subtypes



2017 - More stringent separation : 3 subtypes

Therapeutic target = which cell type(s) ?



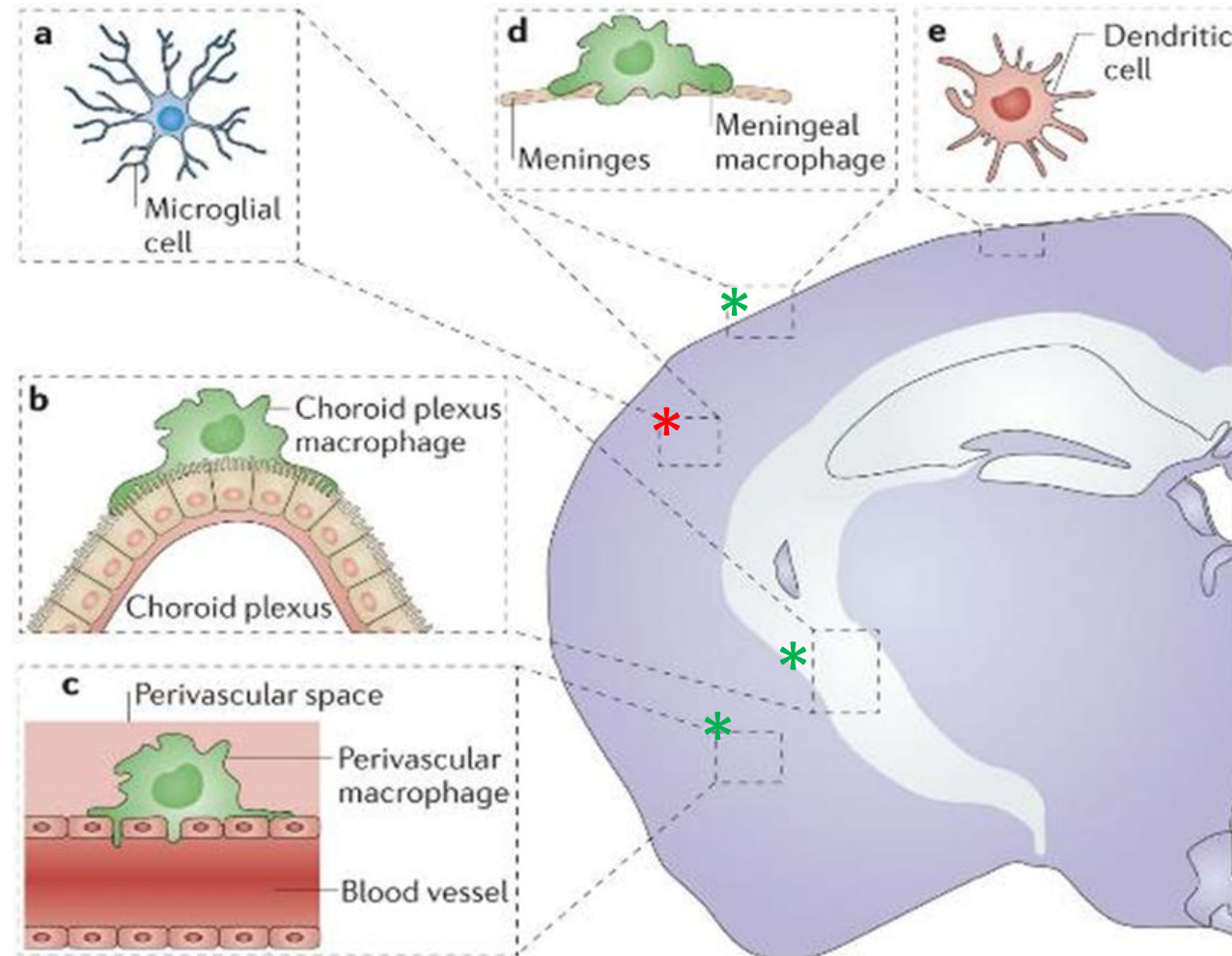
Distribution of microglia and infiltrating macrophages in the adult brain

Microglia*

- *Resident*
- Self-renewed
- Long life expand
- Parenchyma

Macrophages*

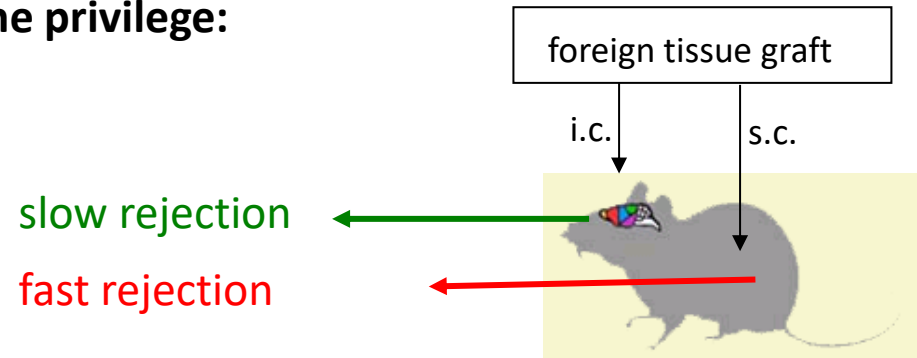
- *Infiltrating*
- Bone marrow
- Blood
- Border associated regions



Microglia/macrophages, targets for glioblastoma (*immuno*)therapy ?

Inflammation and immune response in the brain ?

❖ Immune privilege:



❖ Lack of lymphatic drainage

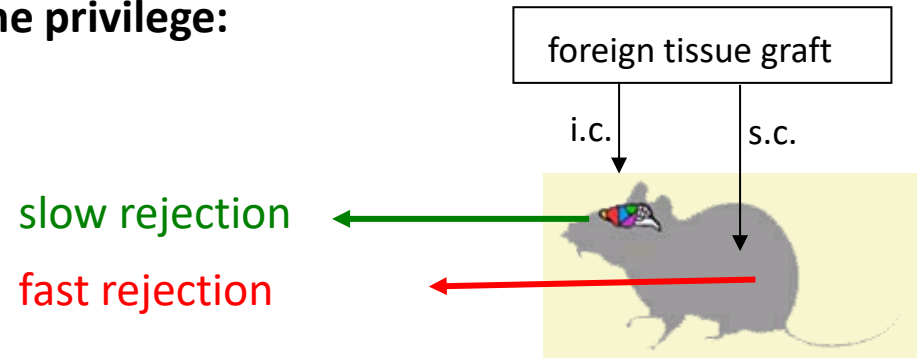
❖ Restricted access by the Blood Brain Barrier

- A „deficient“ immune system as a result of the strong control to maintain homeostasis?

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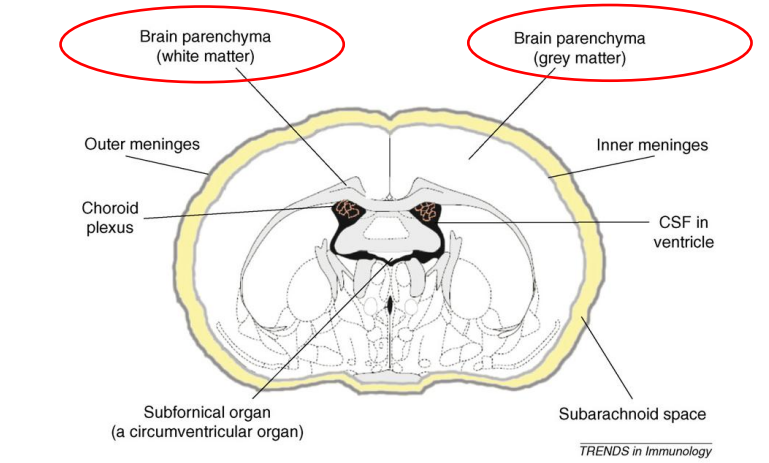


❖ Lack of lymphatic drainage

❖ Restricted access by the Blood Brain Barrier

- A „deficient“ immune system as a result of the strong control to maintain homeostasis?

✓ Immune privilege is compartmentalized



✓ Lymphatic drainage is present in the brain

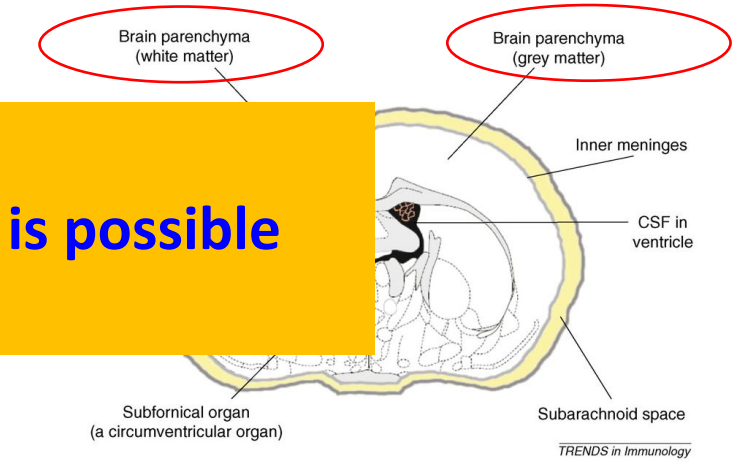
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Immunosuppression in the tumour environment

By infiltrating lymphoid cells:

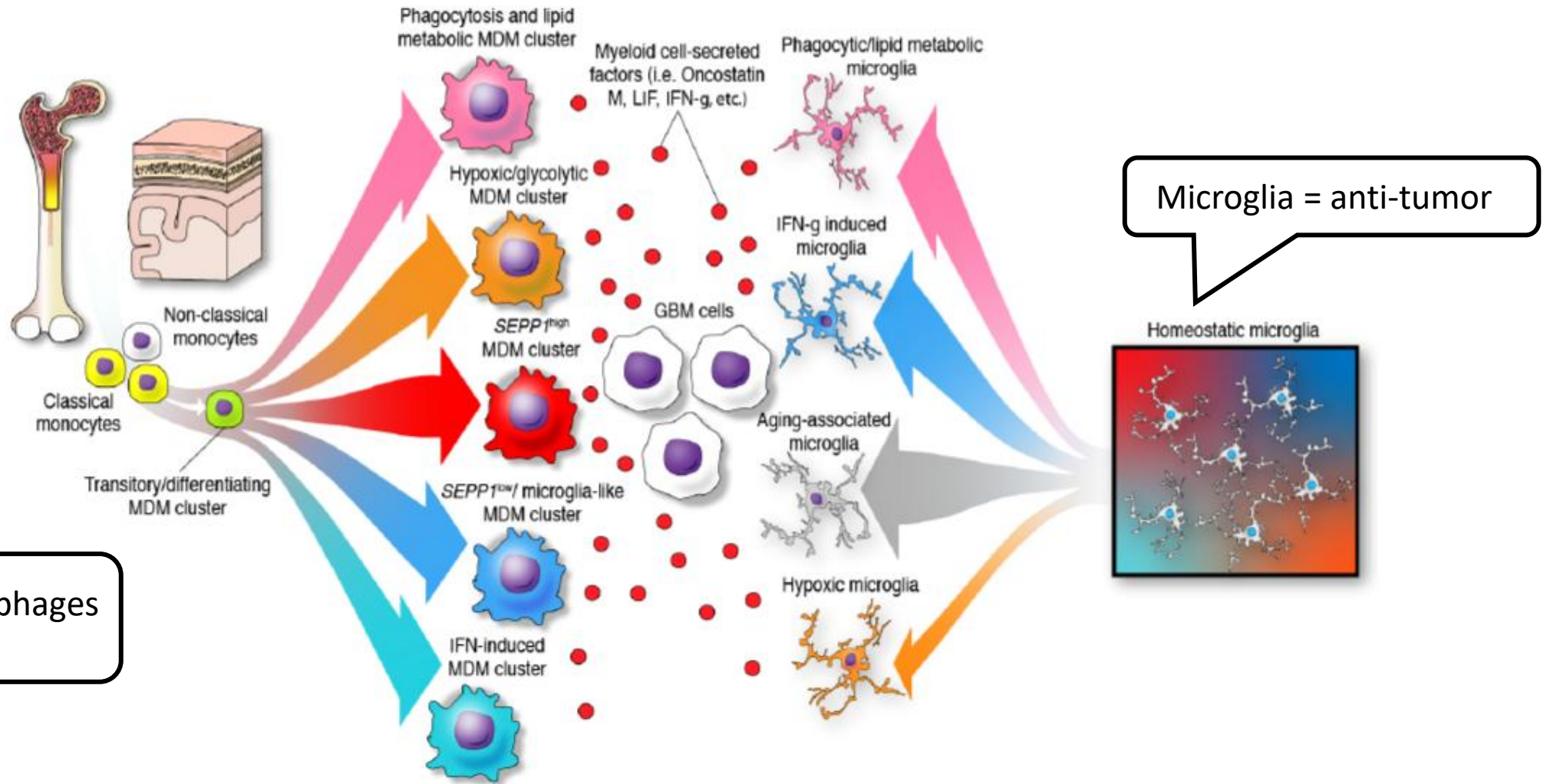
- regulatory T cells:
 - Suppression of adaptive immune cells (B and T cells)
 - Suppression of innate immune cells (cytotoxic activity of Natural killer cells or macrophages)
 - Secretion of immunosuppressive factors: IL-10, TGF β

By infiltrating myeloid cells:

- tumor-associated microglia/macrophages:
 - release of pro- and anti-inflammatory molecules

Microglia versus macrophages in brain tumor

A variety of macrophage clusters is revealed by single-cell RNA-seq analysis



Microglia/macrophages, targets for glioblastoma (immuno)therapy

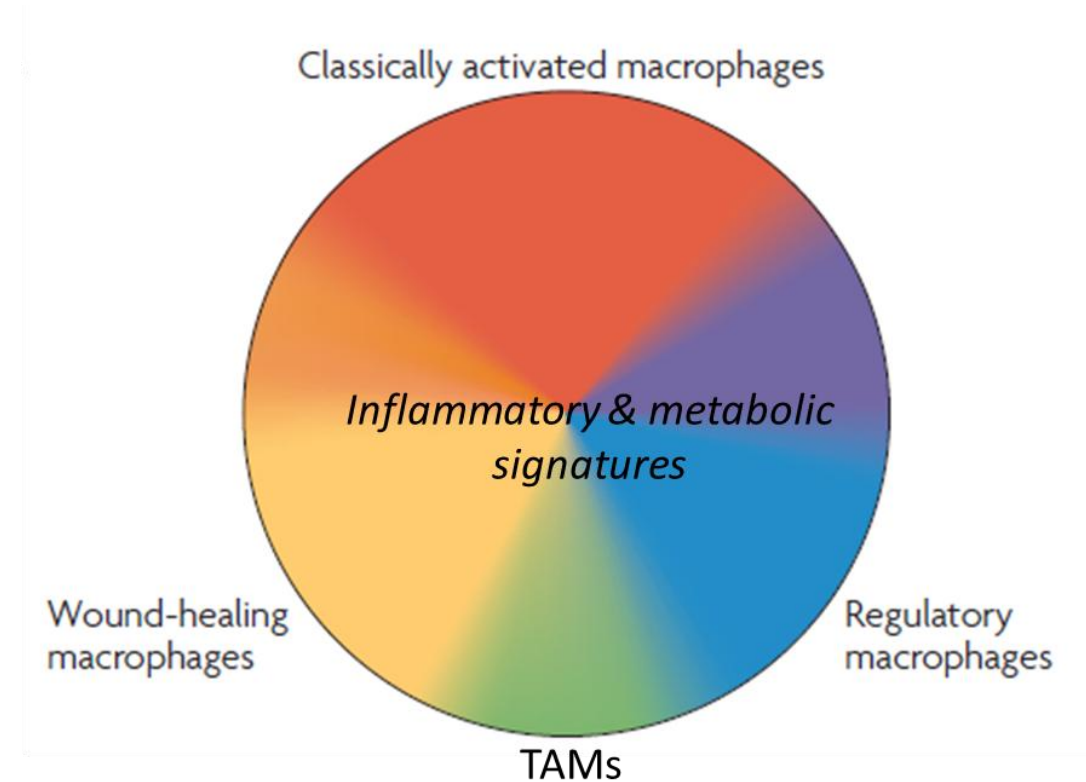
TAMs (tumor-supportive)



Targeting metabolic and inflammatory status



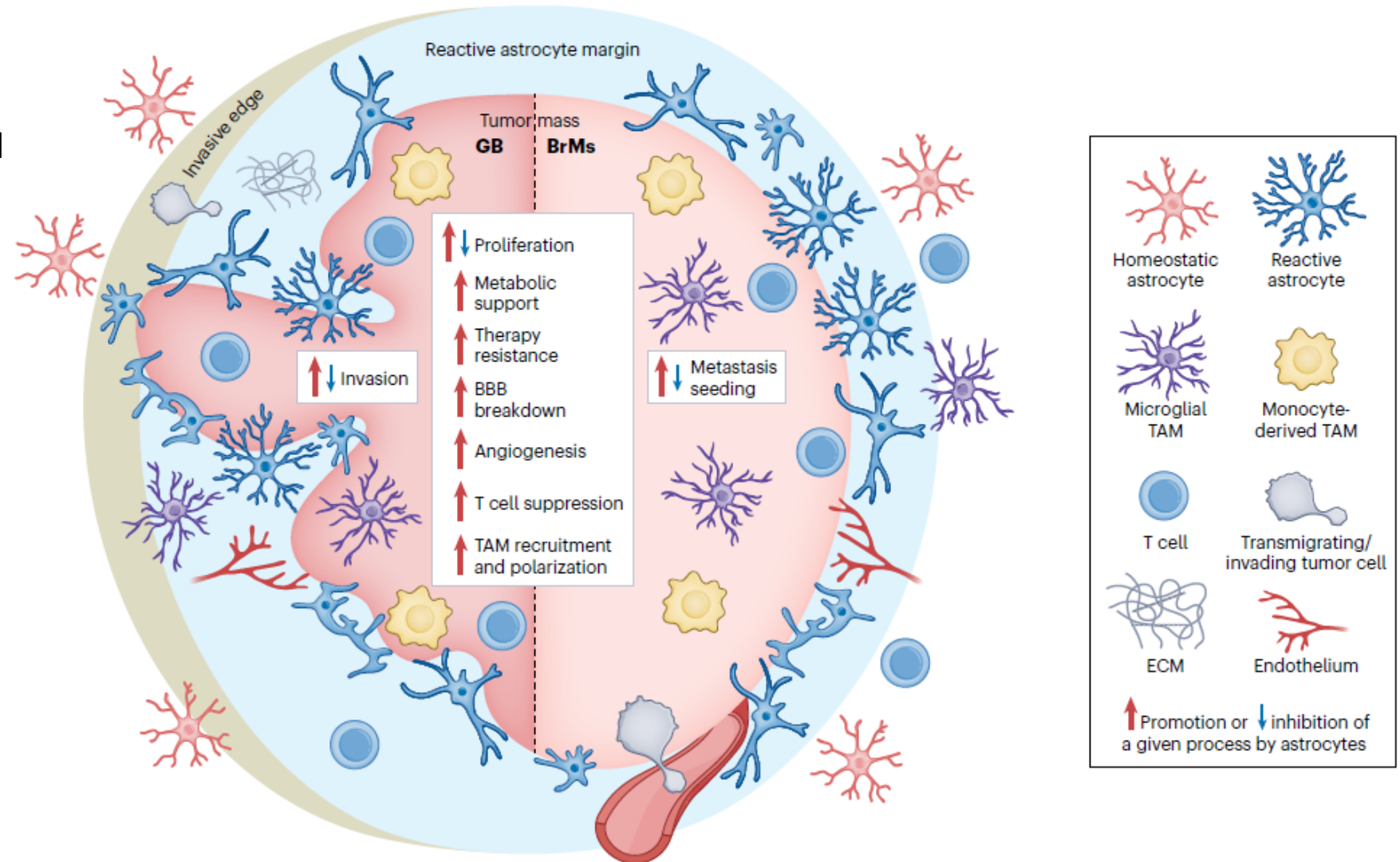
TAMs (anti-tumor)



Nat Rev Immunol 2008 <https://doi.org/10.1038/nri2448>

Tumour associated-astrocytes: Another central component of the brain tumour microenvironment

- ✓ Mostly localized in peritumoral tissue
- ✓ Support proliferation
- ✓ Support invasion

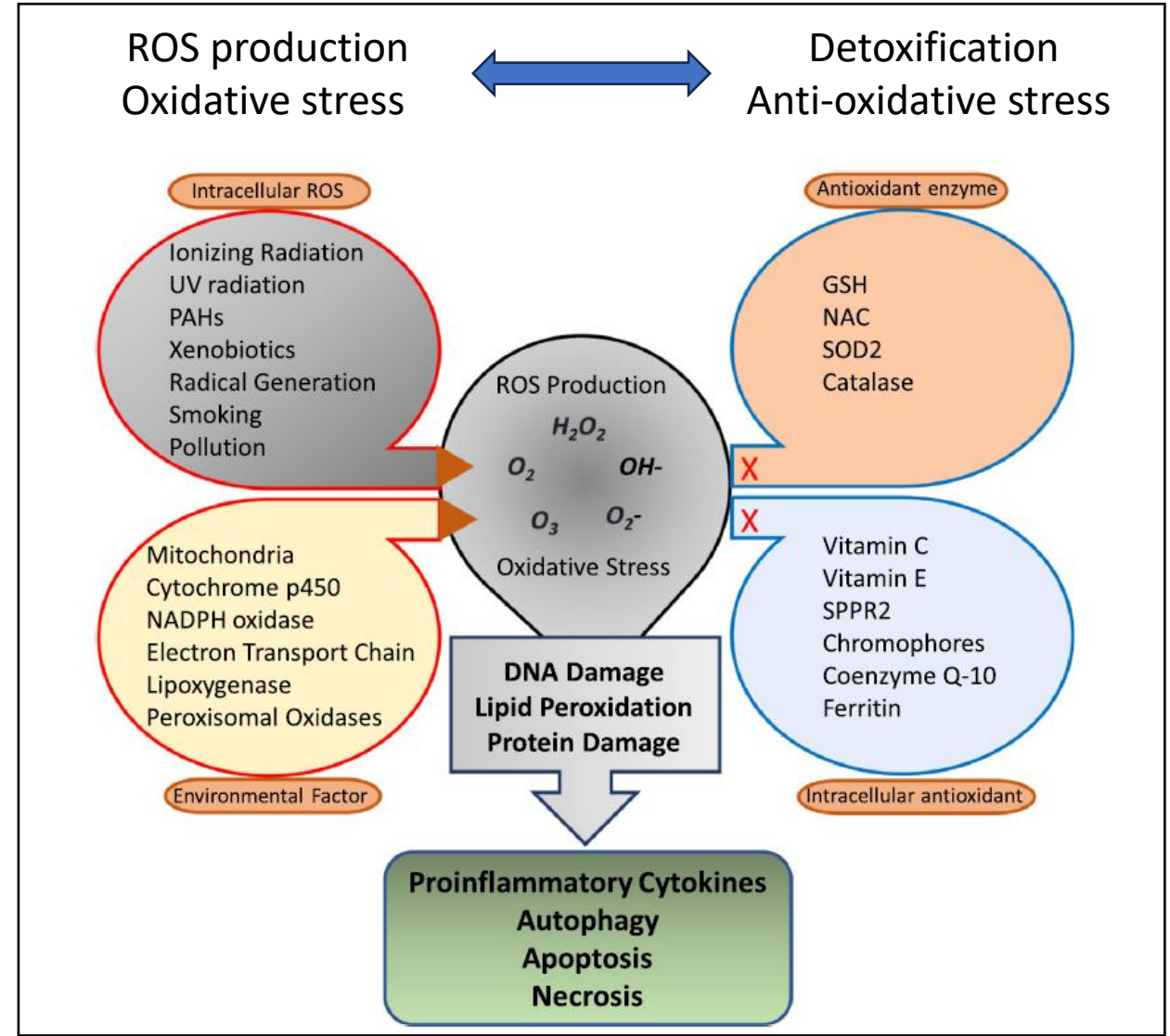


GB: glioblastoma
BrMs: brain metastasis

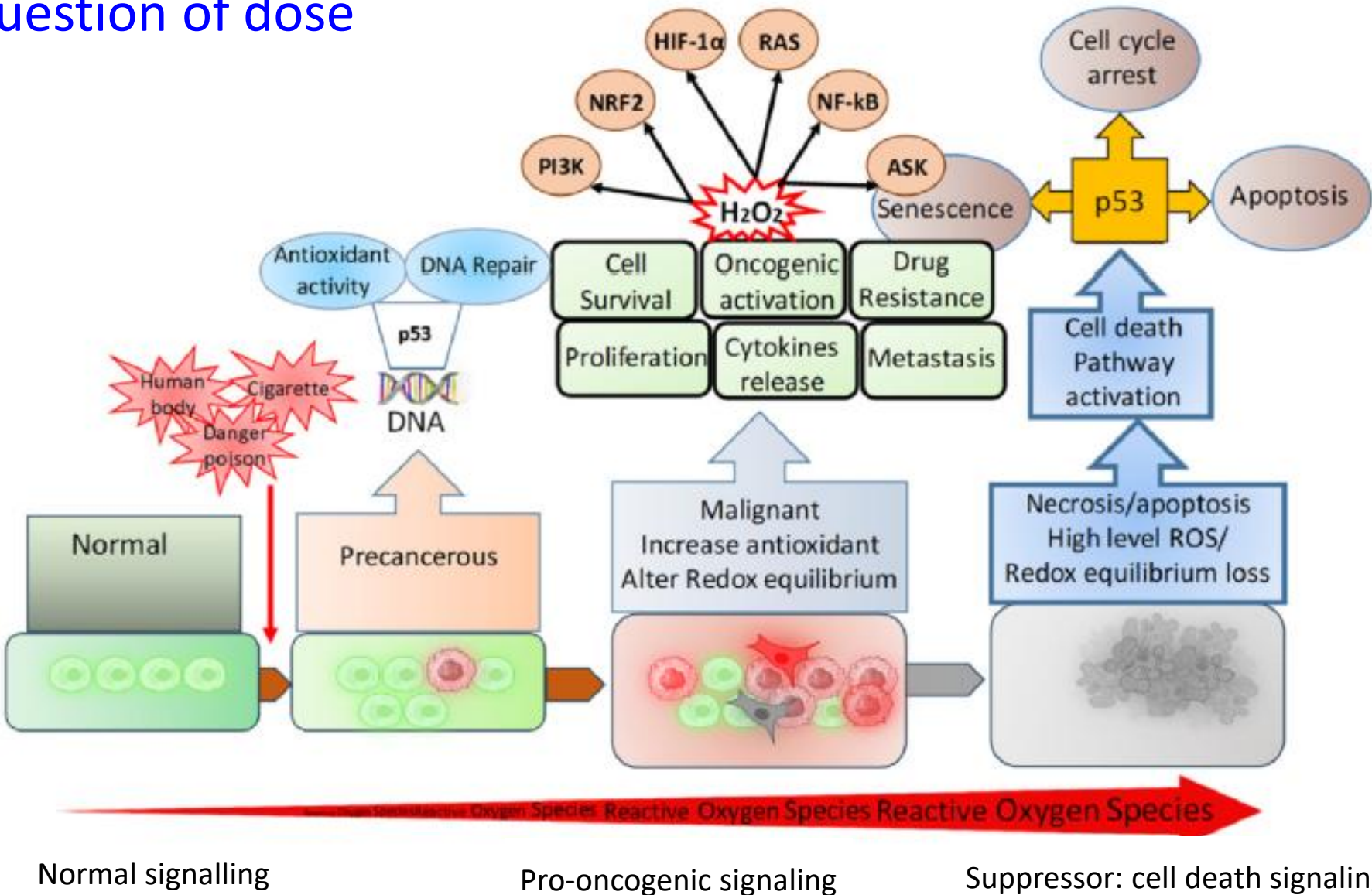
Reactive oxygen species in health and disease: a complex issue

Reactive oxygen species:

- by-products of aerobic respiration
- second messengers
- pro-oncogenic signaling
- cell death signaling



ROS in cancer: a question of dose

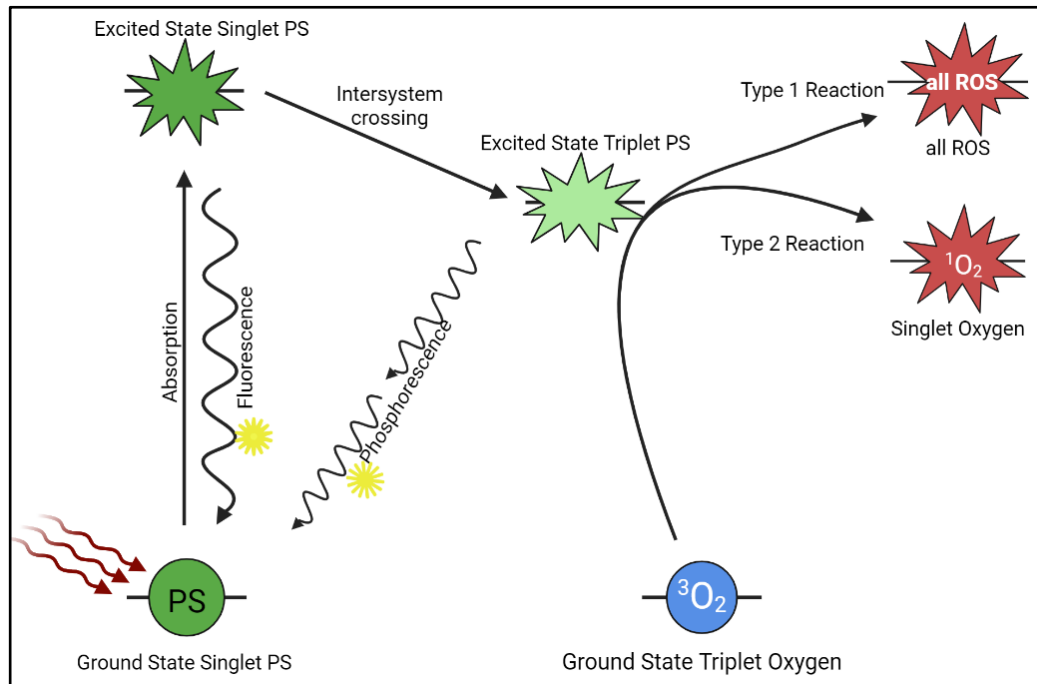


Therapies based on increased ROS production

Photodynamic therapy

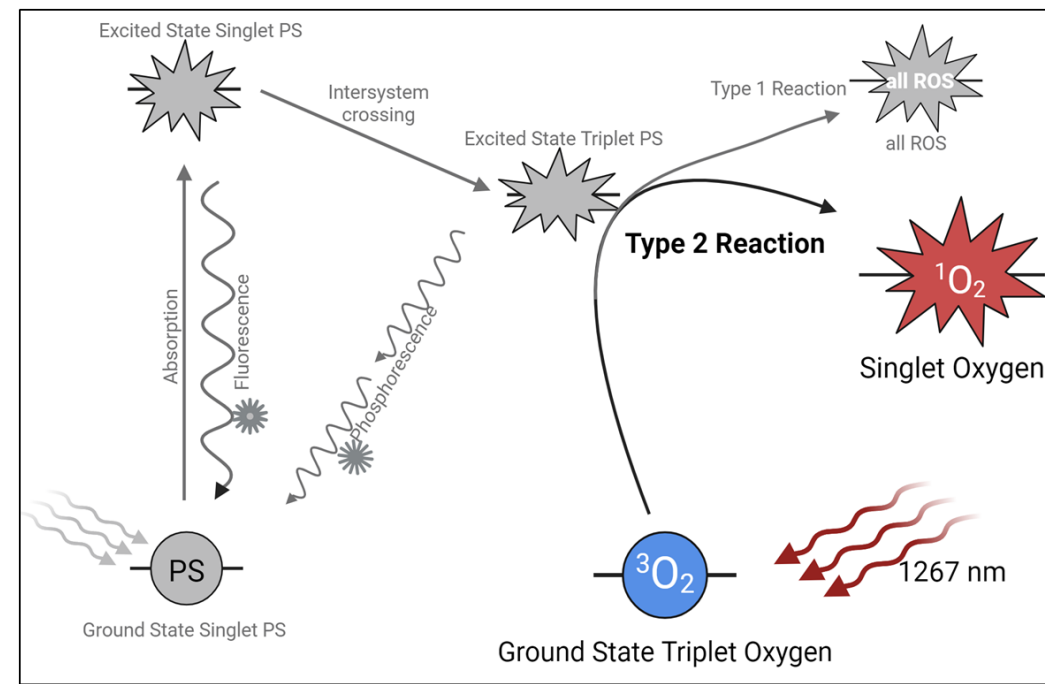
- Indirect generation of ROS via photosensitizers (PS)
- Wave length (600-850 nm/visible light)

Toxicity of PS



Direct Light therapy

- Direct generation of ROS (mainly singlet oxygen)
- Longer wave length (near infrared light) without PS



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- Aston University (UK)
- University of Barcelona (Spain)
- University of Mainz (Germany)
- University of Munich (Germany)
- Modulight Corporation (Finland)
- VINCA, University of Belgrade (Serbia)
- Modus Research and Innovation (UK)

Next Generation Glioma Treatments using Direct Light Therapy

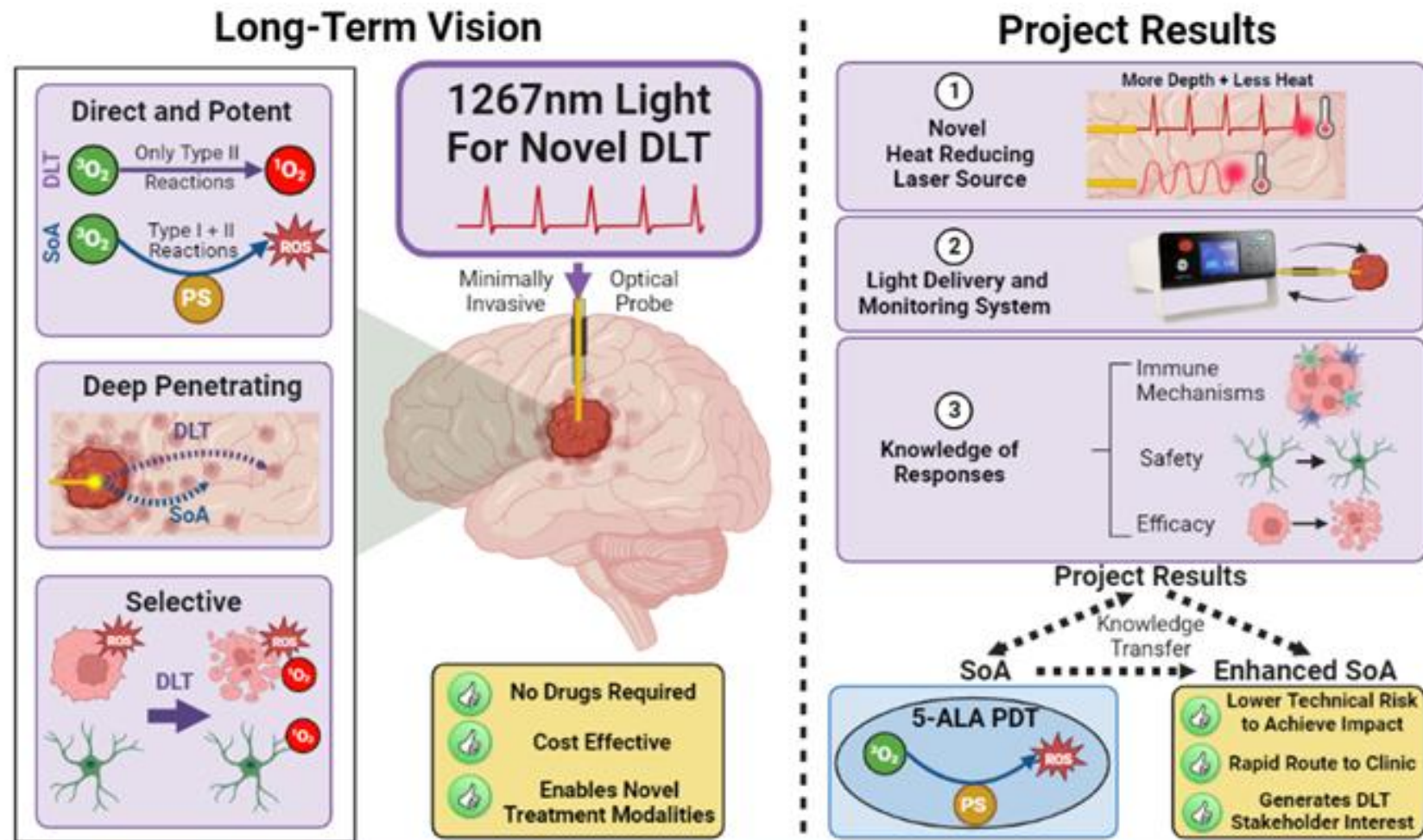


Figure 1. Developing Direct Light Therapy (DLT) as a novel glioma treatment (left), through the GlioSight project (top right) which simultaneously improves State of the Art (SoA) 5-ALA Photodynamic Therapy (PDT) (bottom right)

Reading recommendations...

