

# Biobanking of Breast Cancer: Ultimately leading to prevention of brain metastases



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# Content.

- Introduction:
  - > need to optimize current treatment options for brain metastasized breast cancer patients
- Challenges.
- South-East Netherlands Biobanking Project.
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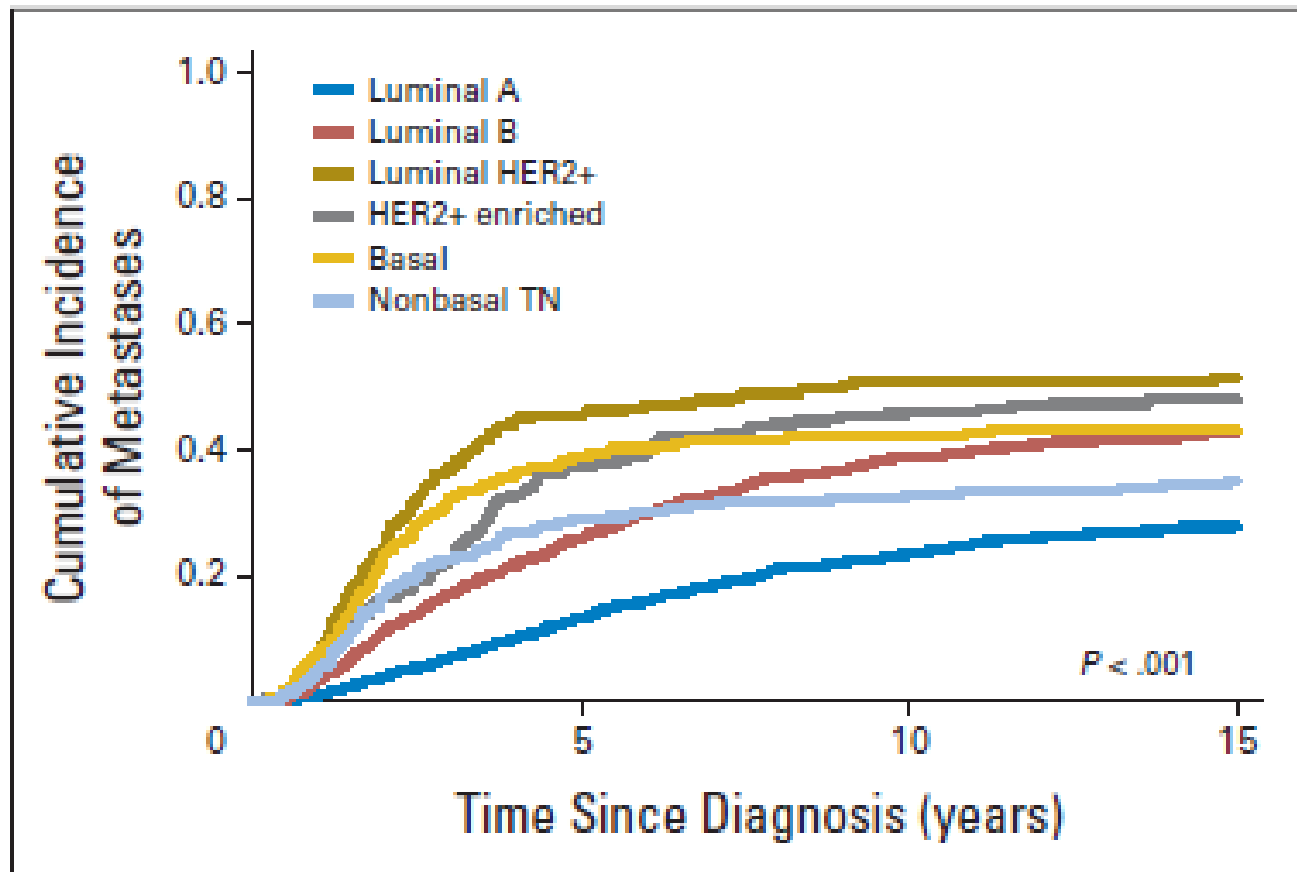
# Introduction.

Breast cancer: heterogeneous disease: molecular subtypes.

	ER	PR	Her2	Other
Luminal A	+	+/-	-	Ki-67<14%
Luminal B	+	+/-	-	Ki-67>/=14%
Luminal-Her2	+	+/-	+	
Her2 enriched	-	-	+	
Triple negative, basal like	-	-	-	CK5/6 +; EGFR +/-
Tripe negative, non-basal	-	-	-	CK5/6 -; EGFR -

# Introduction.

## Cumulative incidence of First Distant Metastasis by Breast Cancer Subtype



# Introduction.

Metastatic breast cancer: relative risk of site of first recurrence

**N = 1389**; Triple Negative N=480; Her2+ N=373; Luminal (ER+) N=536

	Triple Negative vs ER+		Her2+ vs ER+	
Site	OR (95% CI)	p	OR (95% CI)	p
Distant vs locoregional	1.32 (1.01, 1.74)	0.045	1.12 (0.83, 1.51)	0.45
Lung vs other	2.17 (1.47, 3.21)	<0.001	1.73 (1.13, 2.66)	0.012
<b>Brain vs other</b>	<b>3.5 (2.1, 5.85)</b>	<b>&lt;0.001</b>	<b>3.97 (2.35, 6.72)</b>	<b>&lt;0.001</b>
Bone vs other	0.26 (0.19, 0.36)	<0.001	0.39 (0.29-0.54)	<0.001
Liver vs other	1.09 (0.74, 1.61)	0.67	1.58 (1.07, 2.33)	0.021

# Introduction.

Metastatic breast cancer: Her2 enriched versus triple negative breast cancer.

Feature	Her2+	TN
Time from metastastatic disease to CNS event	~ 1 year	< 6 months
Control of extracranial disease at time of CNS event	~50%	uncommon
Median overall survival from time of CNS event	Up to 1-2 years	3-5 months
Cause of death	Up to 50% due to progression CNS metastases	Rarely due to CNS PD alone

CNS event: increase in mortality and morbidity in Her2+ metastatic breast cancer

# Introduction.

Metastatic breast cancer: systemic treatment of brain metastases (BM):  
**selected prospective trials.**

Study	Agent(s)	CNS objective response rate
Rivera et al., 2006	Capecitabine + TMZ	18% (> half of patients no prior radiation therapy)
Franciosi et al., 1999	Cisplatin + etoposide	38% (no prior RT allowed)
Christodoulou et al, 2005	Cisplatin + TMZ	40% (in subset of 15 patients with breast cancer)

# Introduction.

**Metastatic Her2+ breast cancer: systemic treatment of brain metastases (BM):  
selected prospective trials with capecitabine + lapatinib.**

Trial	N	Prior RT	CNS ORR	TTP/PFS
Lin et al., CCR 2009	50	100%	20%	3,6 m
Boccardo et al., ASCO 2008	138	NR	18%	Median time on study 2,6 m
Gutherland et al., BJC, 2010	34	94%	21%	5,1 m
Metro et al., Ann Oncol, 2011	22	86%	32%	5,1 m
Lin et al., J. Neuro-oncol, 2011	12	100%	38%	NR
Bachelot et al. <b>LANDSCAPE</b> Lancet Oncol, 2013	44	0%	67%	6,0 m

Time to brain radiation therapy: 8,3 months



# Challenges.

## Systemic treatment of BM of different molecular subtypes of breast cancer.

- Which treatment is most effective?
- Which dose (heterogeneity of blood-tumor barrier permeability in BM) ?
  - > Window of opportunity trials.
- Timing?
  - > Prevent BM (might be difficult due to early seeding/homing)
  - > Prevent development of macrometastasis

## Challenges 2:

- Should we screen for asymptomatic brain metastasis in high risk breast cancer patients?
  - therapeutic relevance: druggable targets in BM and TME
- Understand mechanism of the development (macroscopic) BM in breast cancer patients
  - identify a brain metastasis gene signature
  - elucidate the role of tumor microenvironment (TME)

Setup biomaterial bank for primary and metastatic breast cancer

# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- 10 participating hospitals.
- Paraffine embedded and fresh frozen tissue samples of:
  - primary breast cancer (to allow future 'matched analysis')
  - breast cancer metastasis (if possible BM biopsy)
- Blood samples (CTCs, ctDNA)
- Linked with prospective clinical pathological treatment response and survival data of the patients included in the biomaterial bank.

# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- **Planned analysis:**
  - Genomic and epigenomic profiling:  
identifying copy number alterations, loss of heterozygosity, mutation screening, promotor methylation.
  - High throughput tissue microarray (TMA):  
identifying deregulated cancer pathways

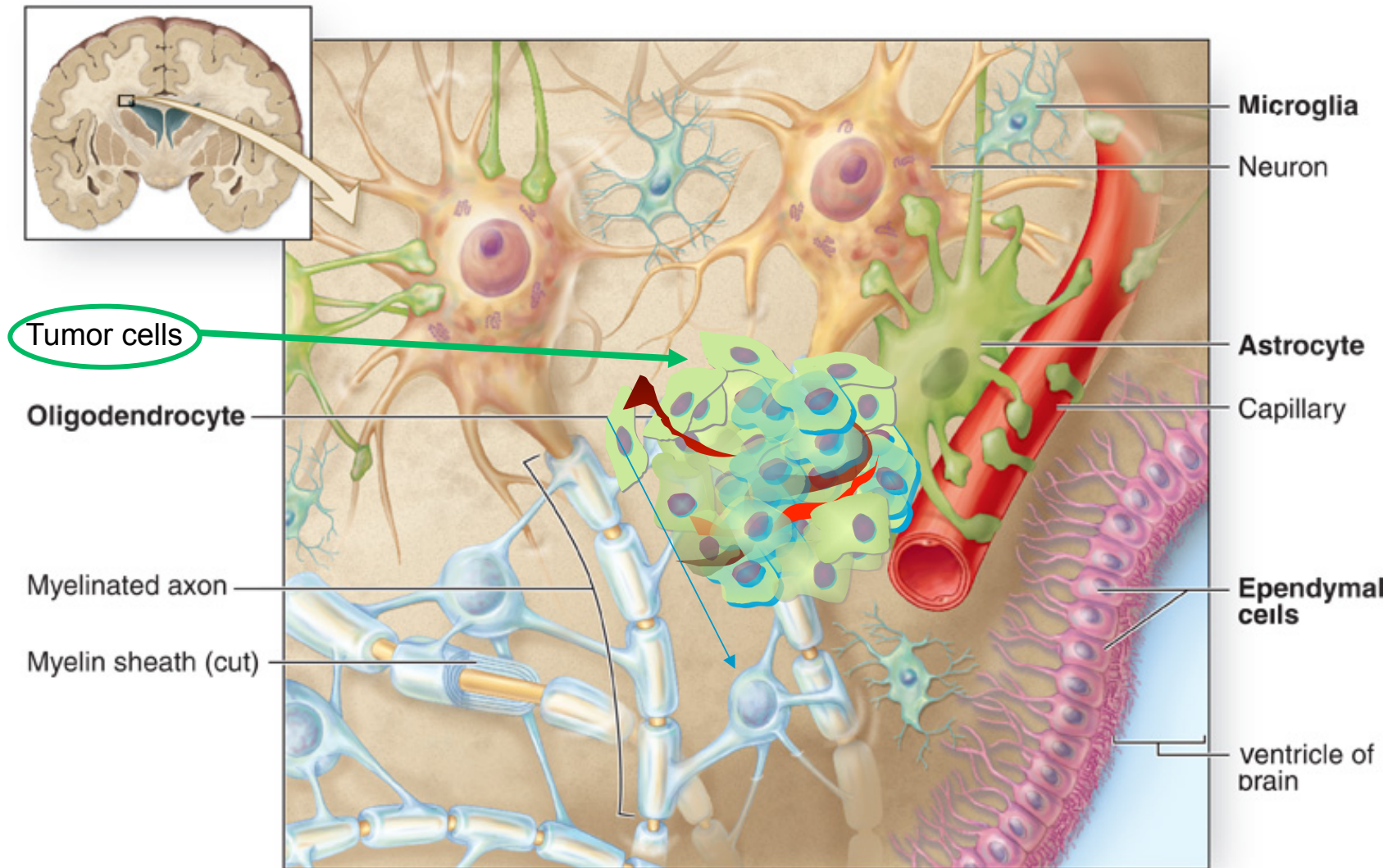
# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- Develop and validate **brain metastasis gene and protein expression signature**:

## **Ultimate goal:**

identify **druggable targets** to prevent the development of macrometastatic disease in the brain. (Her2 + breast tumors)

## Brain metastasis gene and protein expression signatures: target tumor cells



# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

Brain metastasis gene and protein expression signatures: target **tumor cells**

BM compared to unlinked primary breast tumors:  
published gene expression profiles

*Palmieri et al.* (1): differential expression in BM of *BMP1*, *PEDF*, *LAMγ3*, *SIAH*, *STHMN3*,  
*TSPD2* and *HK2*

*Bos et al.* (2): differential- and overexpression in BM of *COX2*, *HBEGF* and *ST6GALNACS*

*Salhia et al.* (3): Overexpression in BM of *ATAD2*, *BRAF*, *DERL1*, *DNMRTB* and *NEK2A*.  
Hypomethylation of *KRT8*

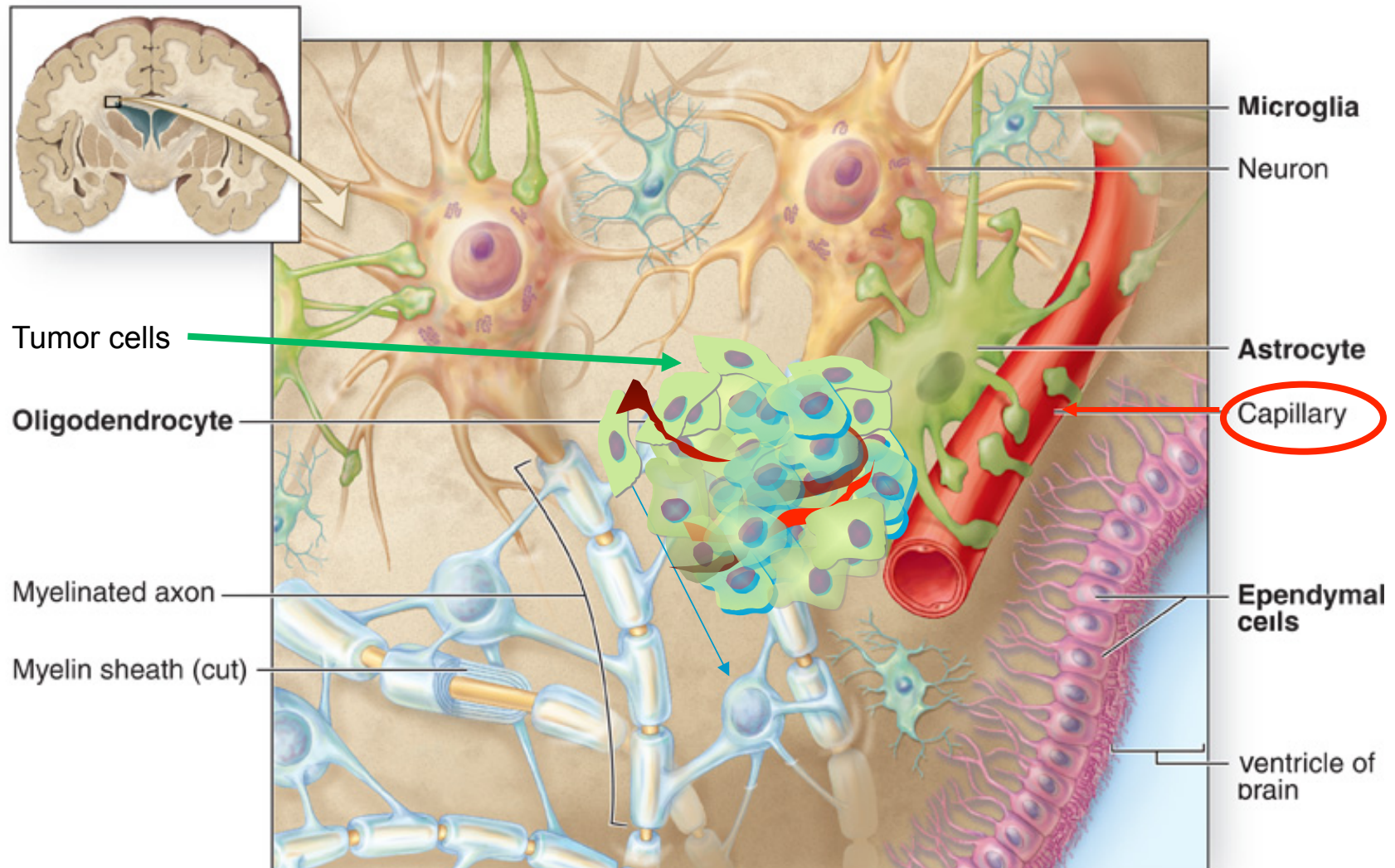
(1) Palmieri et al., Mol Cancer Res, 2009, 7, p 1438-1445

(2) Bos et al., Nature, 2009, 459, p. 1005-1009

(3) Salhia et al. Plos One, 2014, 9, p. 1-13



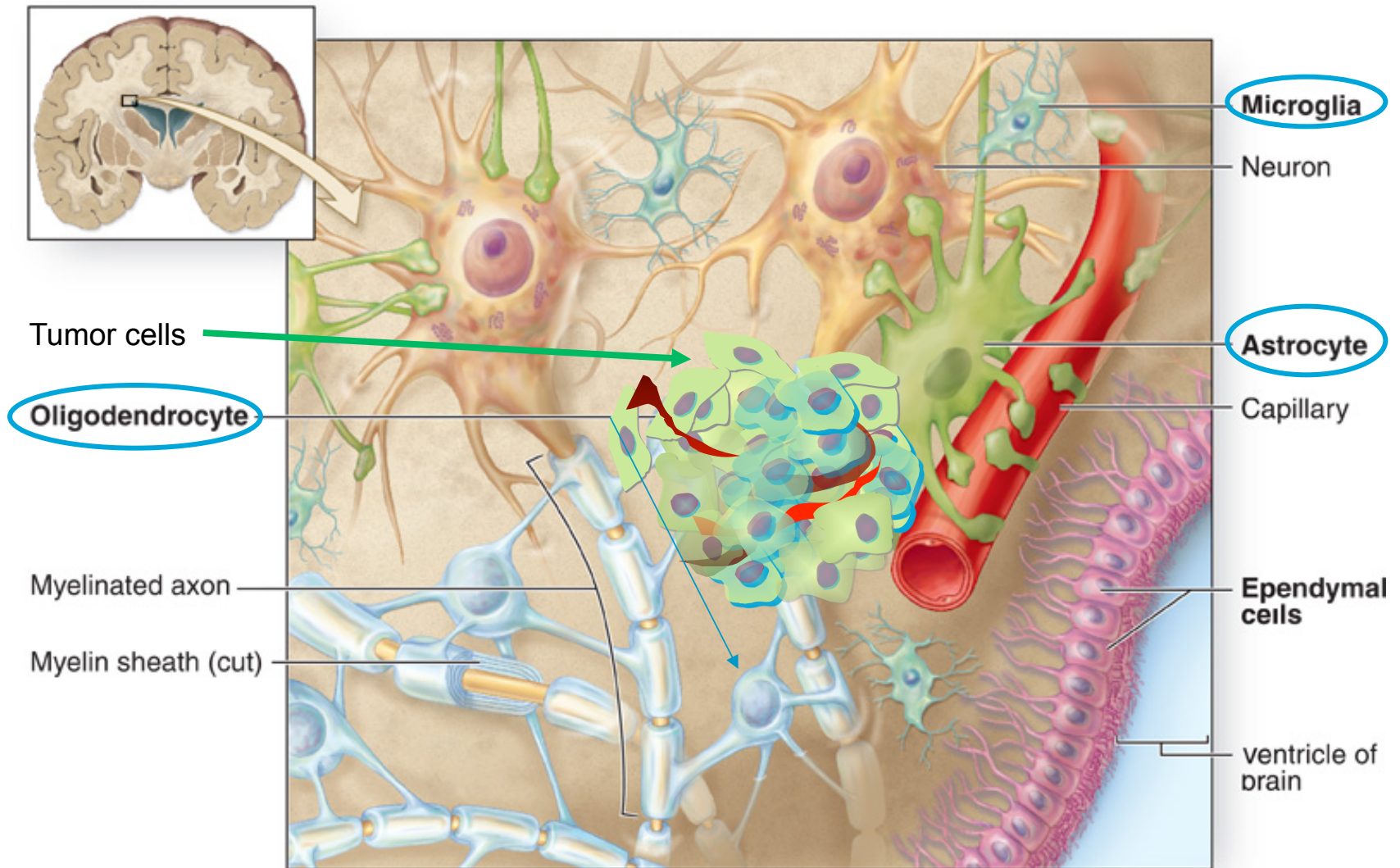
## Brain metastasis gene and protein expression signatures: target blood vessels



- Anti-angiogenic treatment
- Modify blood-tumor barrier: therapeutic intratumoral dose of systemic treatment: inducing dormant micrometastases



## Brain metastasis gene and protein expression signatures: target tumor microenvironment



Identify pro-survival effects of tissue microenvironment on tumor cells:  
induce dormancy of micrometastases

# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- Identify pro-survival effects of tumor microenvironment (1, 2):
  - functional characterization of genes/proteins differentially expressed in activated astrocytes, infiltrating BM, compared to non-activated glial cells.
  - target neuro-inflammatory response?

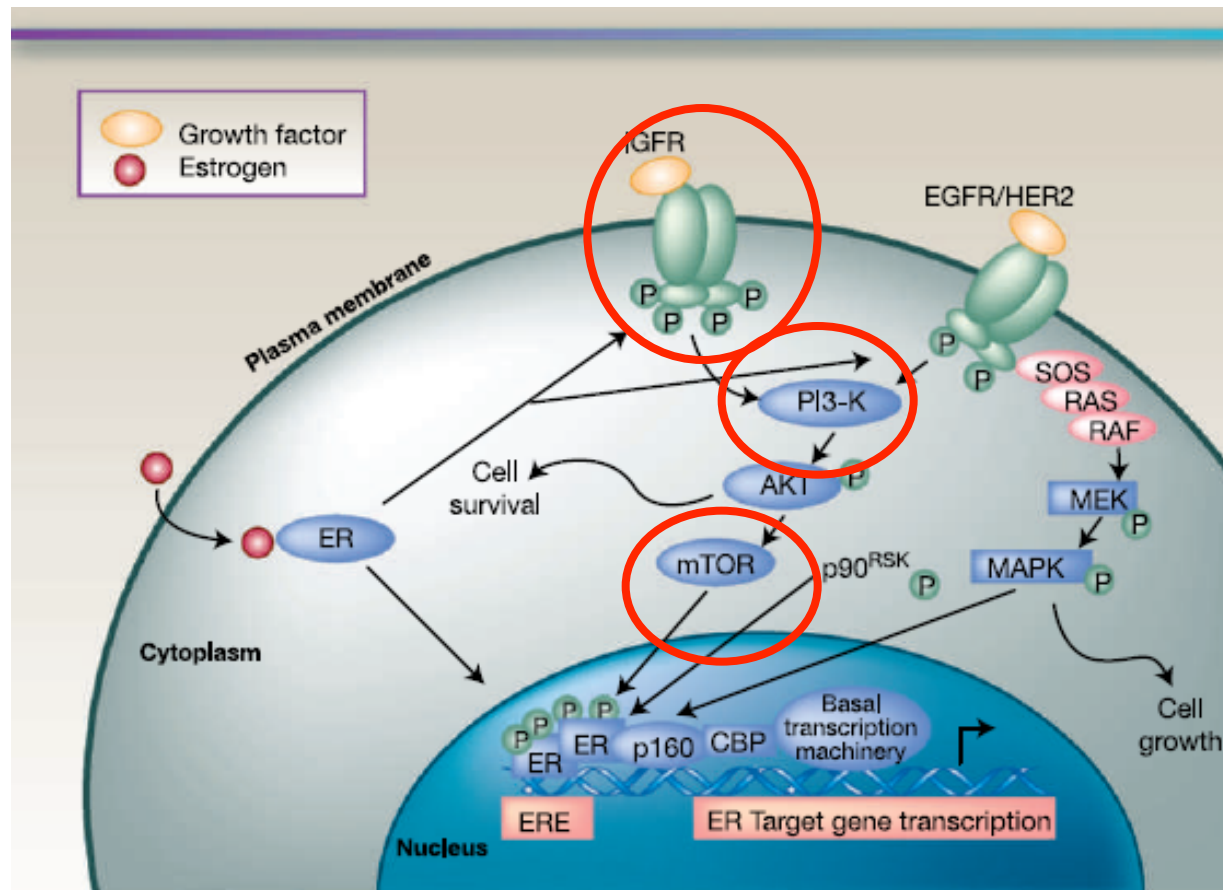
(1) Kim et al., Neoplasia, 2011, 13, p 286-298

(2) Fidler et al., Mol. Cells, 2012, 30, p 93-98

# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- Development of **biomarker guided trials** in metastasized breast cancer patients:
  - **genotype based targeted therapy** compared to biomarker guided chemotherapy and standard of care.

## Activated signalling pathways in Breast Cancer



# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- Development of **biomarker guided trials** in metastasized breast cancer patients:
  - including **neuro-imaging** to identify occult BM
- ➡ which systemic treatment can prevent (/delay) the development of macrometastases in the brain?

# Biomaterial bank from primary and metastatic breast cancer: the **South-East Netherlands Biobanking Project**.

- Create a **database of drug response**.
- **Design algorithm to predict response to novel drugs** and standard chemotherapeutics, based on the molecular profile of the BM.

# Conclusions.

- Biobanking of primary and metastatic breast cancer will provide a huge pool of data
  - address clinically relevant questions
  - elucidate underlying mechanisms of different metastatic profiles of specific subsets of breast cancers.
  - identify druggable targets and direct targeted agents to genetic profile of tumors.
  - understand differences in drug response between different subsets of metastasized breast cancers.
  - ...

# Conclusions.

- BUT....  
since the quality of biobanked tumor tissue/blood samples/  
DNA/RNA needs to meet high standards
  - finances!  
(infrastructure to store and analyze tissues, personel,...)
  - intense and structured coordination (academic – satellite clinical centers)
  - standardization, quality control and validation

highly motivated team of clinicians and researchers