Highly malignant, invasive, difficult-to-treat primary brain tumor

Frequency: 9,000 cases/year (peak age, 55–65 years)

Recurrence: rapid growth; size may double every 10 days

Median survival: ~1 year
Survival of adult patients with glioblastoma multiforme

Kaplan-Meier Survival Curves

Survival %

0 10 20 30 40 50 60 70 80 90 100

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

Months from Surgery
Pediatric Brain Tumors

Frequency: 3000 cases/year
Pediatric brainstem glioma

- Brainstem location represents 8-15% of all brain tumors in the pediatric population.

- Usually inoperable tumors because of the particular location in the brain.
Survival for Children with Diffuse Pontine Gliomas (CCG 9941)
Tumor cells multiply which results in growth.
Normal growth is controlled
Why do tumor cells grow?

Tumor cells receive the instructions to grow but are insensitive to instructions to stop.
Propagation of neural stem cells

Blue: nucleus
Green: nestin
Nestin: marker of stem cells
Differentiation of neural stem cells in neurons and glia

Blue: nucleus
Green: GFAP astrocytes
Red: β-III Tub neurons
Brain development requires a controlled switch from proliferation to differentiation.
Disruption of pathways essential for neurogenesis have been implicated in childhood and adult brain cancers, for which immature progenitor cells have been proposed as cells-of-origin.
Id proteins: inhibitors of differentiation

Undifferentiated state
- High growth potential
- High amounts of Id proteins

Differentiated state
- Low growth potential
- Low amounts of Id proteins

Iavarone and Lasorella, 2003
Id proteins are antagonists of transcription factors

- **No Id proteins**
  - bHLH heterodimer
  - Activation of transcription and differentiation

- **Id proteins in functional excess**
  - Id2
  - Inhibition of transcription and block of differentiation
The Rb-Id2-bHLH pathway in pediatric tumors
Normal cells

Cancer cells

Cancer cells invade normal tissues

Wild type Rb
Id2 inactive

Mutant Rb
Id2 hyperactive
Id2 loss impairs tumor growth and angiogenesis in tumors from Rb+/- mice
Id proteins are coexpressed with HIF1α in human glioblastoma
Id2 overexpression in neuroblastoma is associated with reduced survival

$P=0.0046$
Id proteins involved in all processes associated with development of neural tumors

- VEGF Signaling
  - Integrons, MMP2
  - Id
  - Metalloproteinases
  - Angiogenesis
  - Anaplasia
  - Tissue Invasion
  - Proliferation

- Lineage Specific bHLH
  - Id
  - Rb, bHLH, Ets, Pax
THE FUTURE: Anti Id2 therapeutics

- Growth arrest
- Differentiation
- Increased cell death
- Inhibition of angiogenesis
Developmental lineages derived from the neural crest and the genesis of neuroblastoma
Underlying challenge: how to control stem cells
Control brain tumor/neural stem cell behavior
Loss of Huwe1 expands the neural stem cell population
Loss of Huwe1 impairs neural stem cell differentiation

**Huwe1^{F/Y}**

- Nestin/DAPI

**Huwe1^{F/Y}Nes**

- Nestin/DAPI

- βIII-tubulin/DAPI

- βIII-tubulin/DAPI
Focal deletions and decreased expression of *Huwel* in GBM

TCGA

Oncomine

Normal brain  GBM
n=23  n=77

P-value: 9.3E-10
Expression of Huwe1 is lost in primary neuroblastomas displaying accumulation of N-Myc protein
Lineage commitment
Differentiation
Cell cycle arrest
Growth arrest
Maturation
Tumor growth
Tumor stem cell

Growth factors
N-Myc
Huwe1
CD2
p27

Neural stem cell
N-Myc
Growth factors
A cancer example: Single target therapies fail because they only modulate a single node of one subnetwork that is involved in the pathogenesis of the disease.
Malignant gliomas invade the normal brain
The mesenchymal signature of high-grade glioma

Unsupervised clustering of 76 high grade tumors by expression of 108 genes that are positively or negatively associated with survival reveals 3 tumors classes - Proneural (PN), Mesenchymal (Mes) and Proliferative (Prolif).

Malignant gliomas belonging to the mesenchymal sub-class express genes linked to the most aggressive properties of glioblastoma (migration, invasion and angiogenesis) and mark the worst clinical outcome.
The mesenchymal network of six major hubs of transcription factors in high-grade gliomas

Mesenchymal genes
Activator
Repressor
STAT3 and C/EBPβ inhibit neuronal differentiation and induce mesenchymal transformation in neural stem cells.

**Panel:**
- **Vector**
  - Tau
  - SMA
  - Tau/SMA/Dapi
- **Stat3C/CEBPβ**
  - Tau
  - SMA
  - Tau/SMA/Dapi

**Gene Expression:**
- **Vector**
  - FN1
  - Ctgf
  - Olig2
  - βIII Tubulin
  - βactin
- **Stat3C/CEBPβ**
  - FN1
  - Ctgf
  - Olig2
  - βIII Tubulin
  - βactin

**Untreated vs. 20 days:**
- **Vector**
- **Stat3C/CEBPβ**
Knockdown of Stat3 and C/EBPβ cooperates to inhibit tumor cell invasion and angiogenesis.
Loss of Stat3 and C/EBPβ in human glioma cells inhibits tumorigenesis in the mouse brain.
The combined expression of Stat3 and C/EBPβ correlates with the poorest outcome of glioma patients.

$p < 1 \times 10^{-3}$
Glioblastoma
From systems biology to prognosis to personalized therapy

Mesenchymal Signature Of High Grade Glioma

ARACNe Regulatory Network

Stat3 and C/EBPβ are Master Regulators
Stat3 and C/EBPβ are Transforming Oncogenes of Neural Stem Cells
Stat3 and C/EBPβ are Predictors of Negative Clinical Outcome