THE CANCER GENOME ATLAS

Genome Characterization of Glioblastoma Multiforme

Cameron Brennan, MD
Assistant Professor, Surgeon
Department of Neurosurgery

Memorial Sloan-Kettering Cancer Center

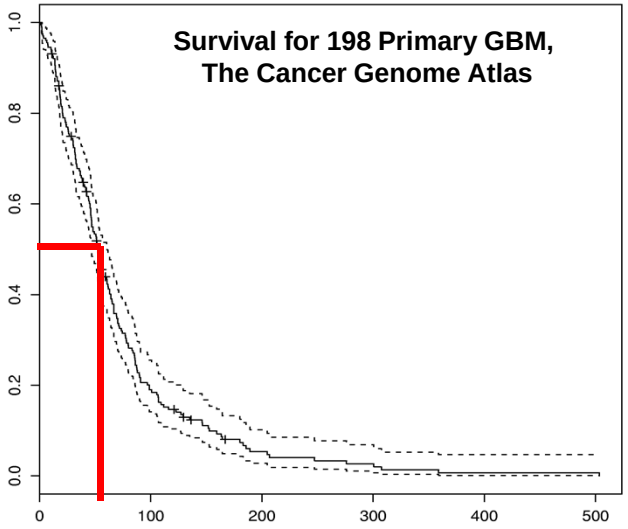
Overview

THE CANCER GENOME ATLAS

- GBM: most common adult brain tumor
- Short survival despite therapy
- High incidence of EGFR mutation (>50%)
- EGFR inhibitors alone unsuccessful

→ Need a clear picture of additional mutations which may abrogate sensitivity to targeted inhibitors in EGFR-mutant tumors

→ Need models, therapeutic targets for non-EGFR-mutant tumors



52wk median survival

The Cancer Genome Atlas Preliminary Analysis

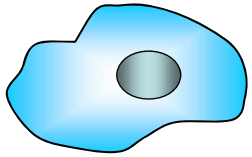
→ Resolving new molecularly-defined subclasses of GBM

→ Subclasses closely associated with mutations in EGFR, PDGFRA, & NF1 with implications for therapy and stratification of patients in current trials.

→ Subclasses mirror known genetically-defined mouse models and give these models new relevance for biologic and preclinical studies

Canonical alterations in Primary vs Secondary GBM

THE CANCER GENOME ATLAS



cells of origin

Primary GBM

EGFR Amplification
Ink4a/ARF loss
PTEN loss

low grade astrocytoma

anaplastic astrocytoma

Secondary GBM

PDGF, FGF2 Overexpression
p53 mutation
CDK4 amplification Rb loss
PTEN loss

GBM **GBM**

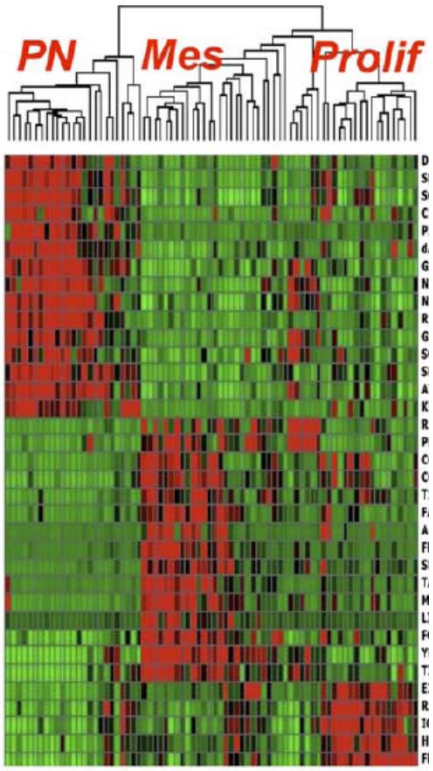
histologically and clinically indistinguishable

Adapted from Holland, Nature Reviews Genetics, 2001

Molecular subclassificaiton of GBM

THE CANCER GENOME ATLAS

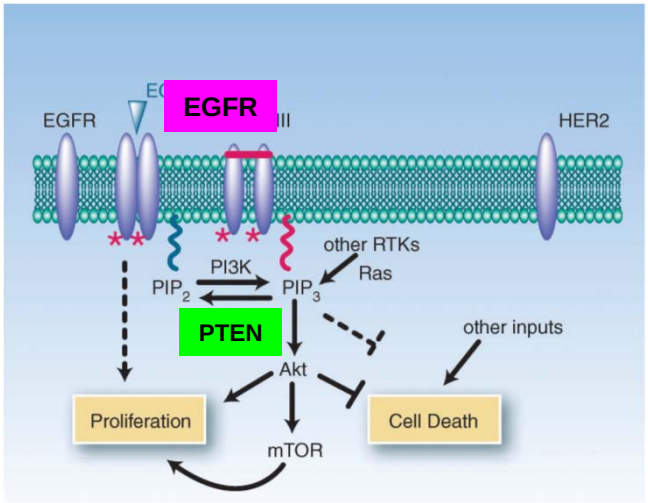
Phillips et al., Cancer Cell. 2006



- Expression clustering of survival-associated genes
- Mixed histology, grade
- Three subclasses:
  - Proneural
  - Mesenchymal
  - Proliferative

→ Unclear difference in survival
→ No new therapeutic targets

Mellinghoff et al., NEJM 2005

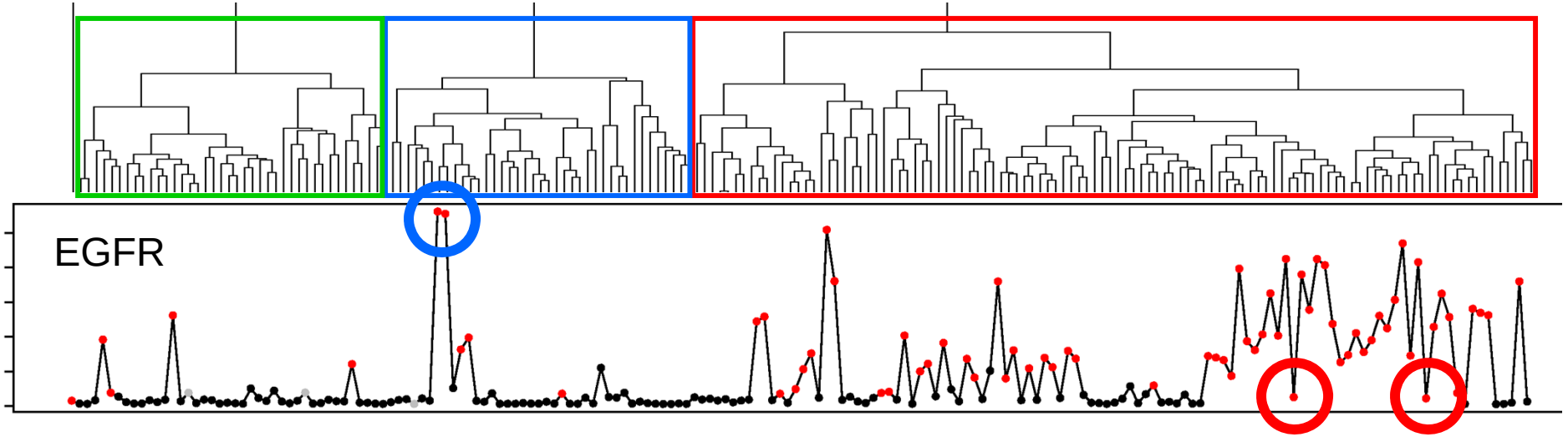


- EGFR-inhibitor trial; retrospective analysis of responders vs. non-responders
- 7/7 responders: intact PTEN expression
- Loss of PTEN predicted response failure even in EGFR-mutant/amplified tumors

→ delay of TTP was small in responders
→ unclear if prospective stratification works

→ established the importance of other mutations as context when treating a "target"

Overlay of array-CGH:
EGFR amplification drives expression



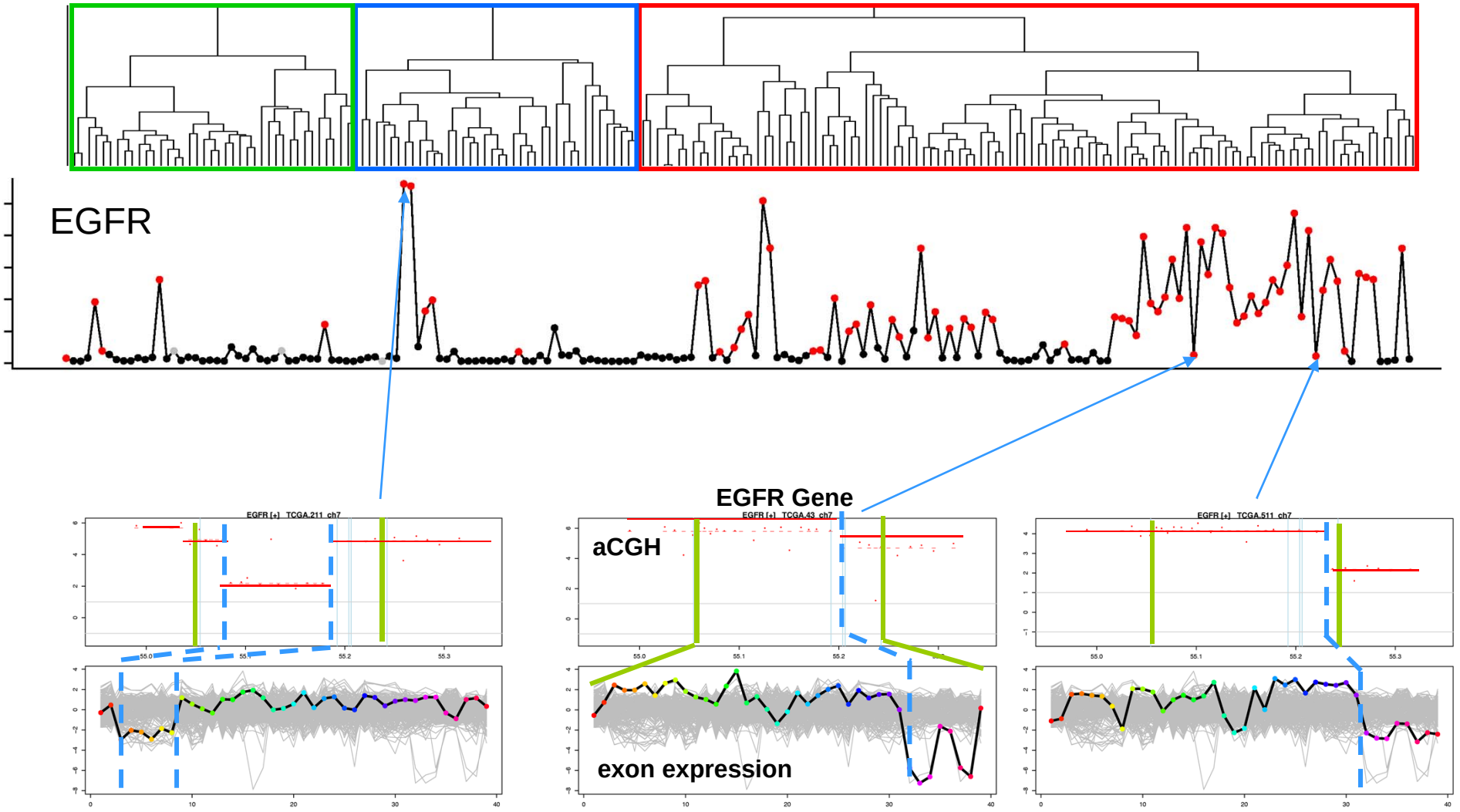
Amplified, not overexpressed?

expression ●, amplification ●

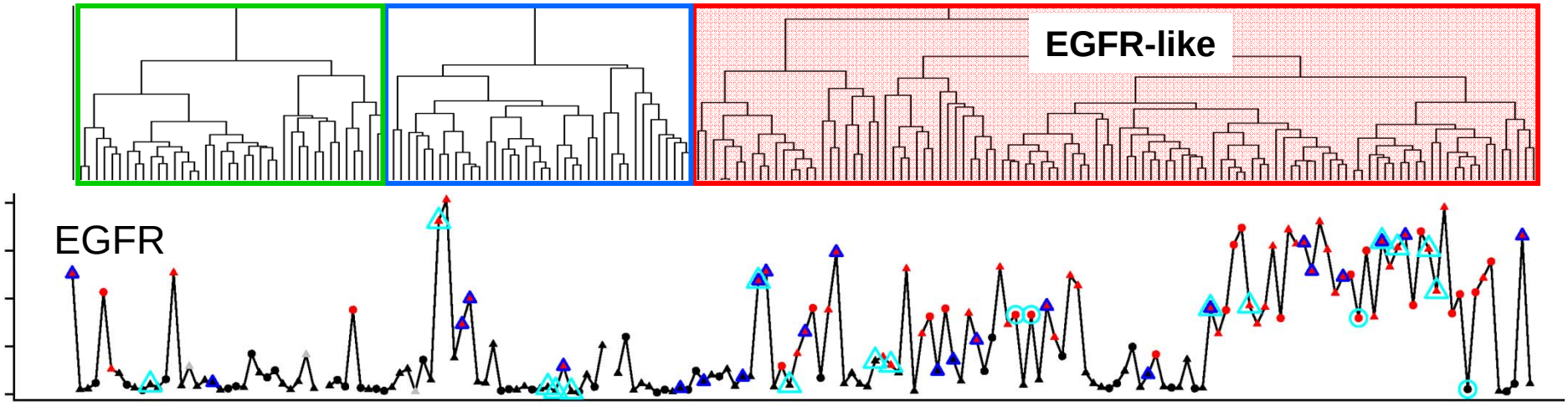
U133 expression, 205 primary GBM

→ At least 3 defined subclasses of tumors

Small intragenic deletions in EGFR account for majority of activating mutations



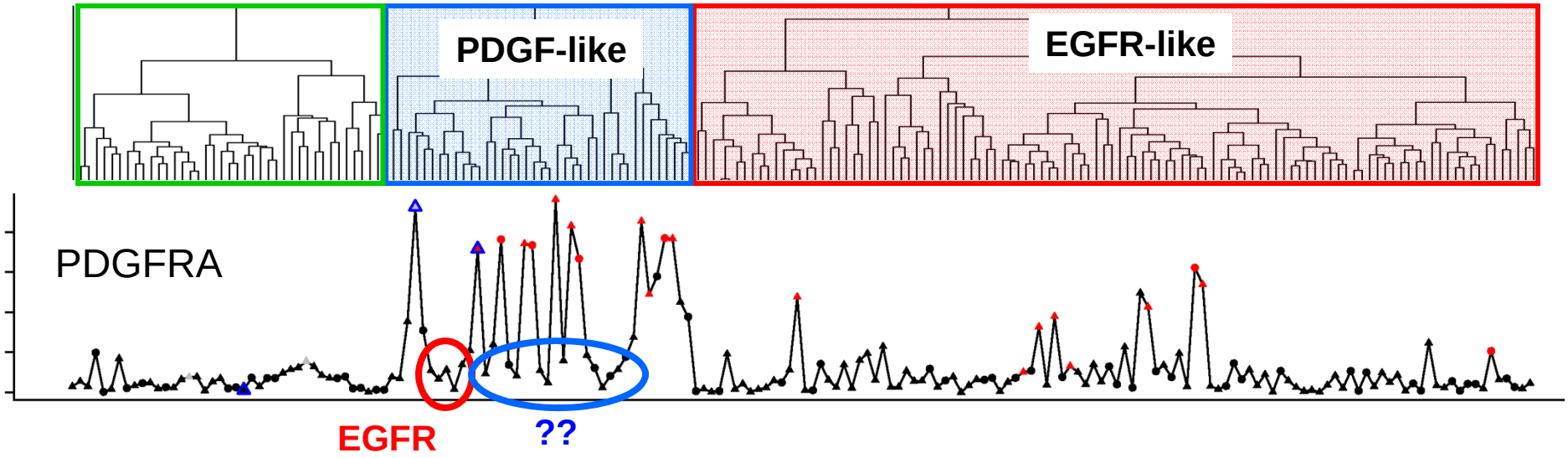
Integration of exon expression, copy number, sequencing defines a subclass with predominant EGFR alteration

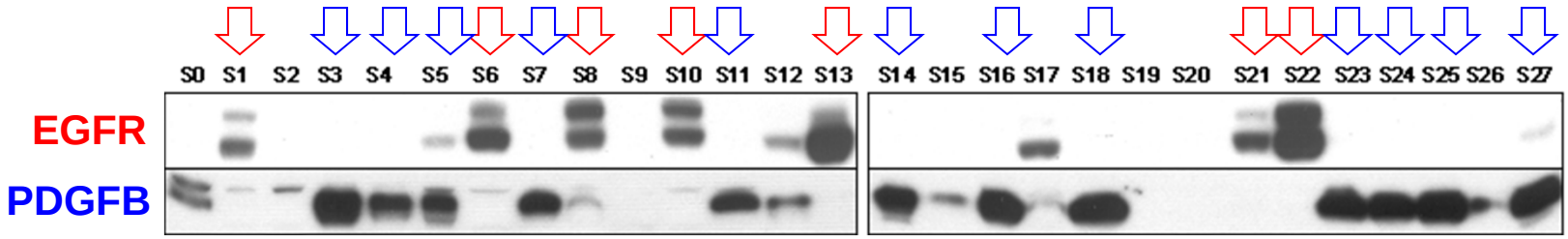


expression ●, amplification ●, deletion ●, mutation by seq ▲ or del △

- 65% EGFR amplified and/or mutated (69/106)
- small % ERBB2, MET mutations
- 20% yet to be sequenced

PDGFRA amplification/mutation: hallmarks of second GBM subclass



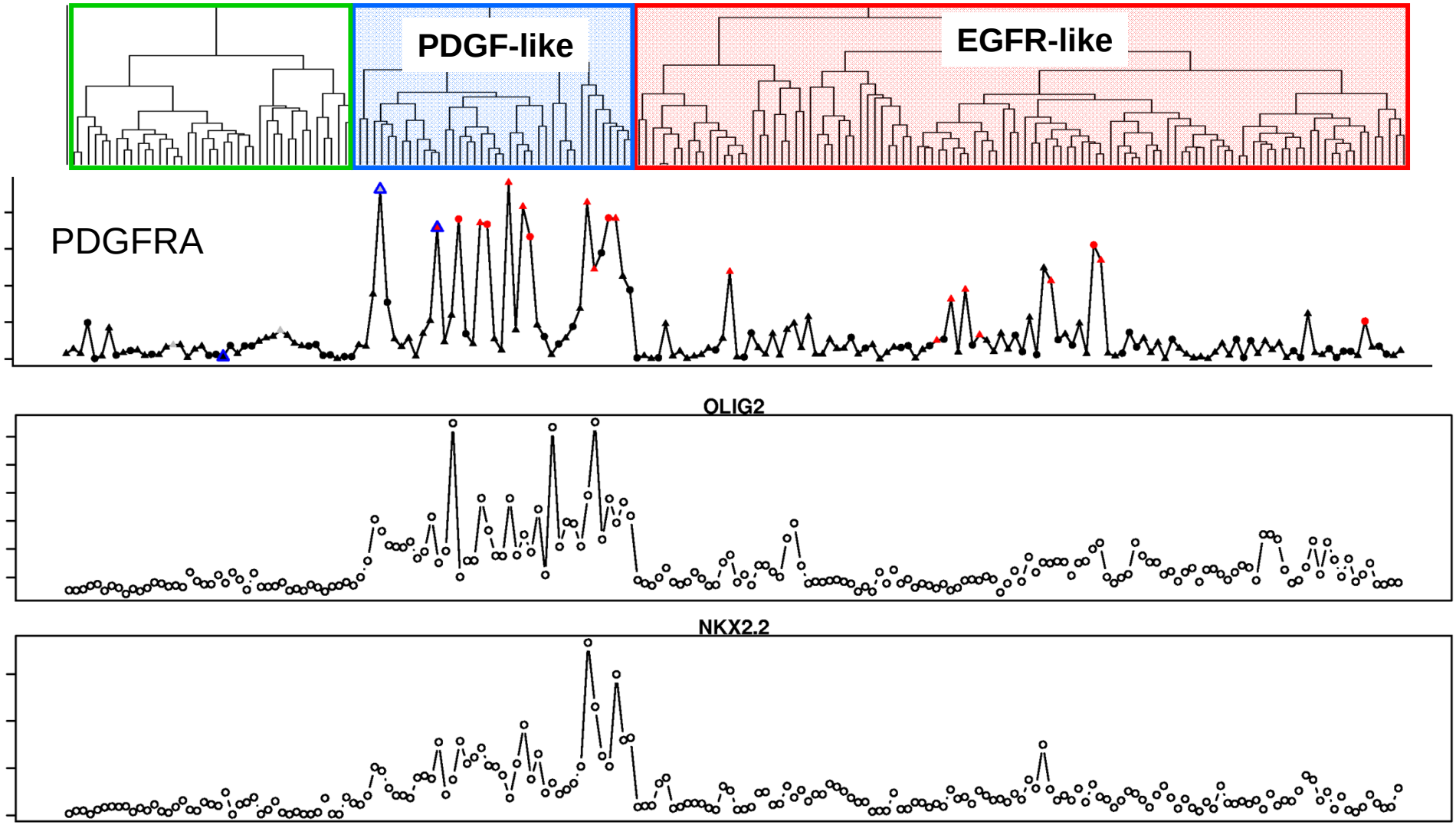


Western for EGFR and PDGFB in 27 high-grade glioma (22 GBM)

→ Significant proportion of GBM have elevated PDGF ligand *not* receptor amplification

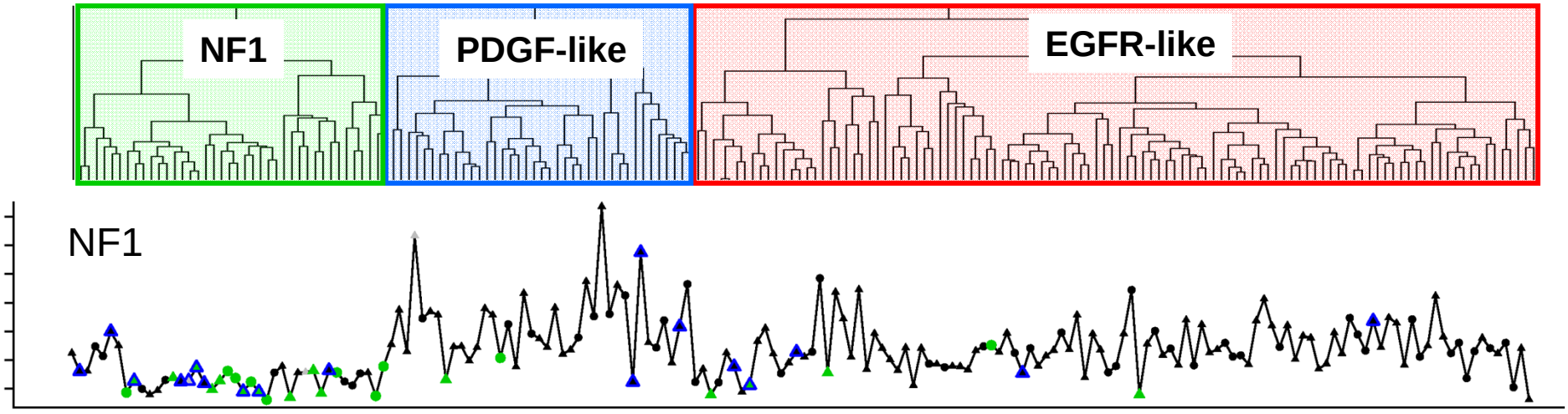
→ PDGF signaling in EGFR-amplified tumors recently described *(Stommel et al, Science 2007)*

PDGF-like class: expression of “proneural” markers associated with PDGF/SHH signaling



→ Olig2 and NKX2.2, associated with PDGF and SHH signaling, are elevated in this group

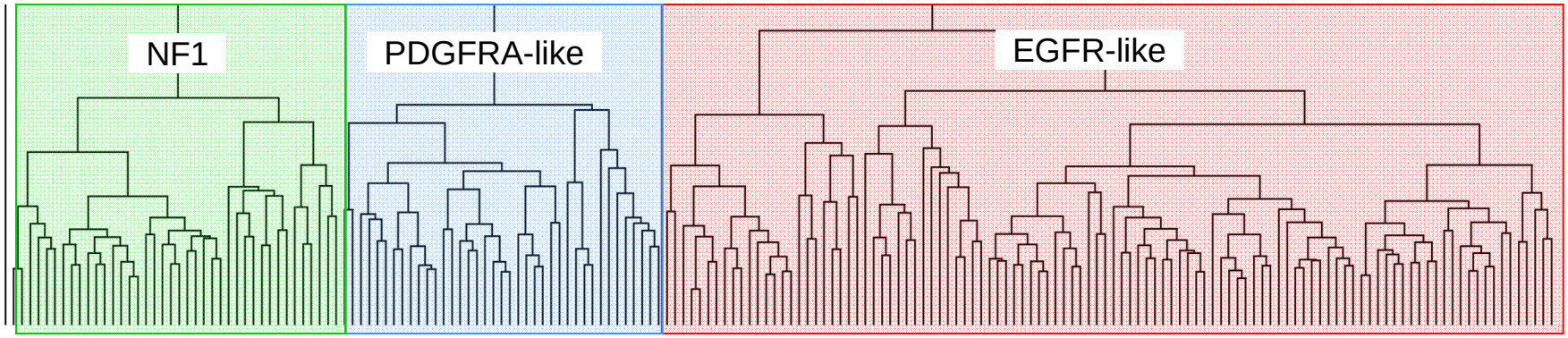
NF1 deletion/mutation: hallmarks of third GBM subclass



expression ●, deletion ●, mutation by seq ▲

- NF1-associated group:
  - Near uniform low expression
  - 63% deleted and/or mutated (24/38)
  - 40% yet to be sequenced

Mouse models exists for each class

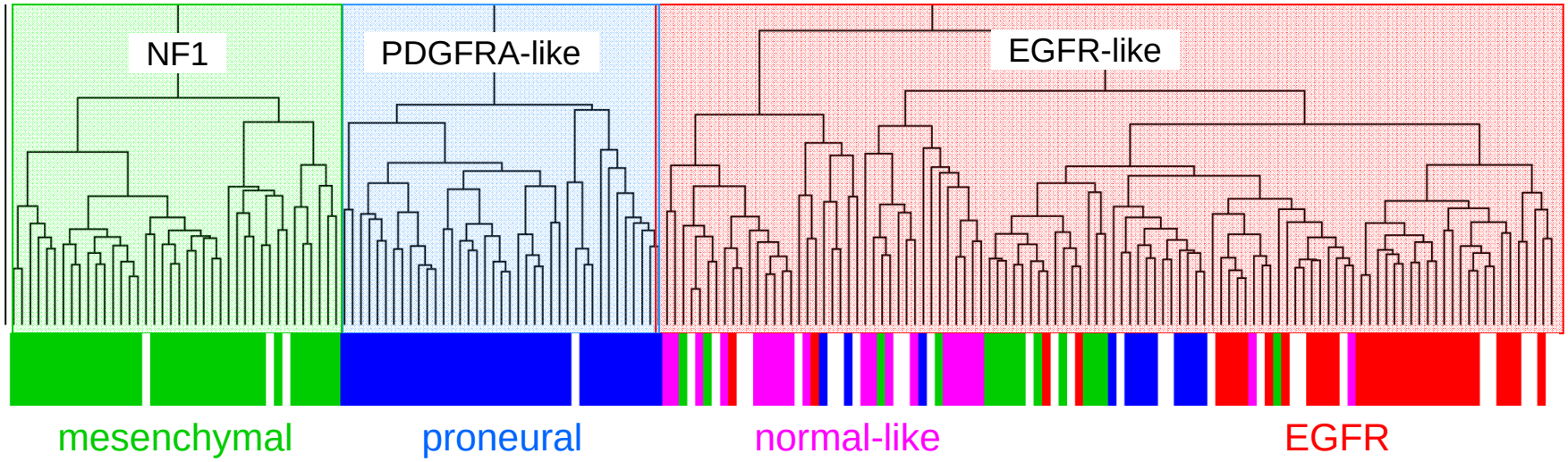


NF1
NF1+p53 / ko
NF1 RCAS-shRNA + $p53^{-/-}$

PDGF-like
RCAS-PDGFB + $Ink4a/ARF^{-/-}$
tet-PDGF / $p53^{-/+}$
Tumor spheres

EGFR-like
EGFRvIII-rv + $Ink4a/ARF^{-/-}$ NSC
rTTA-EGFRmt + $Ink4a/ARF^{-/-}$
Tumor spheres

Summary of results



- Preliminary analysis of TCGA data has revealed at least three subclasses of GBM
- Each associated with mutations of direct therapeutic relevance: EGFR, PDGFRA and NF1
- Deeper analysis of subclasses is underway:
  - integration across expression platforms, miRNA and methylation
  - integration with pathology and clinical variables
  - definition of mutation patterns in each subclass (e.g., Ink4a/ARF, PTEN)
  - there may be a more refined subclassification

  → 4-way clustering to be described by C. Perou, shown above for comparison

Acknowledgements

The Cancer Genome Atlas Network

Memorial Sloan-Kettering Cancer Center

Eric Holland
Dolores Hambardzumyan
Hiro Momota
Ingo Mellinghoff
Marc Ladanyi