MICRODISSECTION BASED GENOTYPING
PLANS FOR PRATT-WHITNEY STUDY

FRANK S. LIEBERMAN, MD
CHIEF, ADULT NEUROONCOLOGY SERVICE
SYDNEY FINKELSTEIN, MD
CHIEF SCIENTIFIC OFFICER, REDPATH, INC.
UNIVERSITY OF PITTSBURGH CANCER INSTITUTE
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
MOLECULAR NEUROONCOLOGY
BASIC PRINCIPLES

• CANCER IS A DISORDER OF GENETIC CONTROLS OF CELL BEHAVIOR
• GENETIC INFORMATION IS ENCODED IN DNA
• CARCINOGENS ACT BY CHANGING DNA
• TUMORS DEVELOP BY ACCUMULATING GENETIC MISTAKES (MUTATIONS)
HOW GENES CONTROL CELL GROWTH
A DELICATE BALANCE

• ONCOGENES
  Signals for cell division
  Signals for cell movement
  Signals for formation of blood vessels

• TUMOR SUPPRESSOR GENES
  – Stop cell division
  – Death signals
MALIGNANT BRAIN TUMORS
MOLECULAR PATHOLOGY

• TYPES OF TUMORS
  – GLIOBLASTOMA
  – MALIGNANT ASTROCYTOMA
  – ANAPLASTIC OLIGODENDROGLIOMA
GENETIC PROFILING
DIFFERENT APPROACHES

• MICROARRAY
  – STUDIES VERY LARGE NUMBER OF GENES
  – REQUIRES FRESH TUMOR; SPECIAL HANDLING
  – CENTRAL DATA BANK AT NCI

• MICRODISSECTION
  – USES STANDARD PATHOLOGY SPECIMEN
  – SMALLER NUMBER OF GENES PROFILED
  – LOOKS AT DNA
GENETIC PROFILING
DIFFERENT APPROACHES

• PROTEOMICS
  – LOOKS AT PROTEINS
  – LOOKS AT LARGE NUMBER OF PROTEINS
MICRODISSECTION GENOTYPING

• MICRODISSECTION OF ROUTINE SPECIMENS
  – STERIOTACTIC BIOPSIES
  – IDENTIFICATION OF REGIONAL HETEROGENEITY
  – READY MADE TUMOR TISSUE BANK
• PCR AMPLIFICATION
• LOSS OF HETEROZYGOSITY
• SEMIAUTOMATED HIGH THROUGHPUT SYSTEM
BRAIN TUMOR GENETIC PROFILING

• PATTERNS OF GENETIC CHANGES
  – ONCOGENES TURNED ON
  – TUMOR SUPPRESSOR GENES BROKEN
  – DIFFERENT TUMOR TYPES-DIFFERENT PATTERNs
    • GLIOBLASTOMA
    • MALIGNANT ASTROCYTOMA
    • OLIGODENDROGLIOMA
MALIGNANT BRAIN TUMORS
GENES THAT ARE INVOLVED

• GROWTH SIGNALING GENES
  – EGFR

• GROWTH SUPPRESSING GENES
  – PTEN; P53; P21; P13

• DEATH SIGNALING GENES
  – P53
MICRODISSECTION GENOTYPING
UPMCC EXPERIENCE

• PROGNOSTICATION
  – 1p deletion: high treatment response
  – Long term survivors: 1p deleted
  – High and low risk low grades
    • Mutational index: mutated/total informative
      – Fibrillary astrocytomas
      – Pilocytic astrocytomas
      – Pleomorphic xanthoastrocytomas
GLIOBLASTOMA MULTIFORME
GENETIC PROFILING

• GENETICS SEPARATE GROUPS
  – CHROMOSOME 1P DELETIONS
  – GROUP 1: NO EGFR MUTATION; MUTATED P53, PTEN LOSS
  – GROUP 2: P53 INTACT; EGFR AMPLIFIED
MOLECULAR GROUPING OF GBMS
WHAT WE KNOW

• Ip deletion group much better outcome
• Group 1: younger patients, arise from low grades
• Group 2: older patients, start malignant
FRACTIONAL ALLELIC LOSS:
# MUTATED MICROsatellites DIVIDED BY
# TOTAL INFORMATIVE MICROsatellites

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MICRODISSECTION BASED GENOTYPING
PRATT-WHITNEY STUDY

• OBTAIN PATHOLOGY SLIDES
• PROFILE TUMOR TYPE
• CARCINOGEN SIGNATURES
  – PATTERNS OF MUTATIONS
    • ANIMAL MODELS
  – MOLECULAR TYPE OF MUTATION
    • CELL CULTURE
    • ANIMAL MODELS
GLIOMA GENETIC PROFILING
TISSUE PROCUREMENT

- BIOPSY OR SURGICAL MATERIAL
- 5 PARAFFIN UNSTAINED SLIDES
- TISSUE BLOCK IF AVAILABLE
- DESIGNED TO PROTECT SPECIMENS
  - ONLY USED IF EXCESS TISSUE
  - IF NO BLOCKS
    - WILL NOT USE SLIDES IF 5 ARE ALL LEFT
    - MAY BE AN ISSUE WITH STEREOTACTIC BIOPSY
GENETIC CHARACTERIZATION
WHAT COULD BE DONE WITH CURRENT CASES

• TUMOR SPECIMENS
  – MICROARRAY STUDIES

• BLOOD SAMPLES
  – PHARMACOGENOMICS
  – SERUM MARKERS
  – CIRCULATING TUMOR CELLS