Glioblastoma Patient-Derived Mouse Xenografts are Clinically Relevant Models for the Study of Molecular Heterogeneity and Differential Response to Targeted Therapy

KCI Molecular Therapeutics Program
Annual Research Symposium
06/19/13

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Hermelin Brain Tumor Center
Henry Ford Hospital
Outline

• Current treatments for glioblastoma (GBM)
  Temozolomide: standard for newly diagnosed GBMs
  Agents in clinical trials
• “Omics” data and the promise of improved clinical outcomes
  Large scale molecular characterization
  Sub-classification
  Future: targets and biomarkers
• Pre-clinical models and translational value
• Patient-derived xenograft (PDX) models using neurosphere cultures
• Chemoprofiling studies: TMZ, ABT-888, mTOR and multi-kinase inhibitors
  Survival
  Molecular analysis
• Increasing the translational value of PDX: all hands on deck
  PDX collection and molecular heterogeneity: size matters
  In depth molecular characterization
  Understanding molecular changes, testing combinations
Current treatments for glioblastoma (GBM)

Newly diagnosed GBMs: surgical resection, radiation therapy, temozolomide

Temozolomide (Temodar®, Schering-Plough): modest but significant patient survival efficacy (Stupp, 2005)

Epigenetic silencing of the DNA repair enzyme MGMT is a predictive biomarker for response to TMZ therapy
## Table 1. Drugs Targeting Growth Factors and Growth Factor Receptors

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Target(s)</th>
<th>Company</th>
<th>Comments and Status</th>
<th>GBM Trt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa)</td>
<td>EGFR</td>
<td>AstraZeneca</td>
<td>Selective EGFR inhibitor; phase II trials for GBM demonstrated modest if any clinical benefit; FDA approved for NSCLC</td>
<td>Yes</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR</td>
<td>Genentech</td>
<td>Selective EGFR inhibitor; trials indicate minimal efficacy as monotherapy for GBM patients; ongoing trials in combination with other drugs for treatment of GBM; FDA approved for NSCLC</td>
<td>Yes</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>EGFR, ERBB2</td>
<td>GlaxoSmithKline</td>
<td>Dual inhibitor; phase II trials underway for GBM; FDA approved for breast cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>BMS-599626</td>
<td>EGFR, ERBB2</td>
<td>Bristol-Myers Squibb</td>
<td>Dual inhibitor; phase I trials underway for advanced solid tumors</td>
<td>No</td>
</tr>
<tr>
<td>Anti-EGFR antibodies</td>
<td>EGFR</td>
<td>Eli Lilly/ImClone</td>
<td>Chimeric extracellular-binding antibody; small subgroup of patients responded in phase II trial for GBM; trials underway as a combination therapy; FDA approved for colorectal cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>Panitumumab (Vectibix)</td>
<td>EGFR</td>
<td>Amgen</td>
<td>Human extracellular-binding antibody; ongoing phase II trials for various solid tumors; FDA approved for colorectal cancer</td>
<td>No</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>EGFR</td>
<td>YM BioSciences</td>
<td>Humanized extracellular-binding antibody; promising results from early trials; phase II/III trials underway for GBM</td>
<td>No</td>
</tr>
<tr>
<td>Matuzumab</td>
<td>EGFR</td>
<td>Merck</td>
<td>Humanized extracellular-binding antibody; development in question due to poor clinical trial results; may prove effective as a combination therapy</td>
<td>No</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>EGFR</td>
<td>Genmab</td>
<td>Human extracellular-binding antibody; phase II trials for SCCHN in progress</td>
<td>No</td>
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<tr>
<td>IMC-11f8</td>
<td>EGFR</td>
<td>Eli Lilly/ImClone</td>
<td>Fully human extracellular-binding antibody; phase II trial for colorectal cancer in progress</td>
<td>No</td>
</tr>
<tr>
<td>MAb 806 (Ch806)</td>
<td>EGFR</td>
<td>Eli Lilly/ImClone</td>
<td>Chimeric extracellular-binding antibody that preferentially targets EGFRvIII and active EGFR; phase I trial complete</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-ERBB2 antibodies</td>
<td>ERBB2</td>
<td>Genentech</td>
<td>Humanized extracellular-binding antibody; induces glioma cell death in preclinical study; FDA approved for breast cancer</td>
<td>No</td>
</tr>
<tr>
<td>Pertuzumab (Omnitarg)</td>
<td>ERBB2</td>
<td>Genentech</td>
<td>Humanized extracellular-binding antibody; interferes with receptor dimerization; ongoing phase II/III trials for breast cancer</td>
<td>No</td>
</tr>
<tr>
<td>Anti-IGF-1R antibodies</td>
<td>IGF-1R</td>
<td>Amgen</td>
<td>Human extracellular-binding antibody; combined therapy phase I/II trials are starting for solid tumors</td>
<td>No</td>
</tr>
<tr>
<td>IMC-A12</td>
<td>IGF-1R</td>
<td>Eli Lilly/ImClone</td>
<td>Human extracellular-binding antibody; several phase II trials underway for solid tumors</td>
<td>No</td>
</tr>
</tbody>
</table>

Huang, 2009

Targeting growth factors & receptors

Huang, 2009
<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Target(s)</th>
<th>Company</th>
<th>Comments and Status*</th>
<th>GBM Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU11274^{26,29,106}</td>
<td>MET</td>
<td>Pfizer</td>
<td>Selective MET inhibitor effective against several mutant variants of MET; potent antagonist in GBM cell lines</td>
<td>No</td>
</tr>
<tr>
<td>XL880/GSK1363080^{197}</td>
<td>MET, VEGFR2</td>
<td>Exelixis</td>
<td>Multikinase inhibitor that primarily targets MET and VEGFR2; phase I trials for solid tumors; phase II trials for RCC, SCCHN and gastric cancer</td>
<td>No</td>
</tr>
<tr>
<td>XL184^{108}</td>
<td>MET, VEGFR2, RET</td>
<td>Exelixis</td>
<td>Multikinase inhibitor; phase II trial underway for GBM</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PDCFR kinase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel)^{79}</td>
<td>PDCFR, SFKs, BCR-ABL</td>
<td>Bristol-Myers Squibb</td>
<td>Potent inhibitor of many kinases; promising preclinical data; phase I/II trials underway for GBM; FDA approved for CML</td>
<td>Yes</td>
</tr>
<tr>
<td>Imatinib (Gleevec)^{10,113}</td>
<td>PDCFR, KIT, BCR-ABL</td>
<td>Novartis</td>
<td>Multikinase inhibitor; limited antiangioma activity monotherapy; effect in some GBM patients when combined with hydroxyurea; phase II/III trials in combination with other drugs are ongoing; FDA approved for CML and GIST</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>VEGF antibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)^{14,115}</td>
<td>VEGF</td>
<td>Genentech</td>
<td>Humanized VEGF neutralizing antibody; several Phase II trials have reported significant antiangioma activity; many ongoing trials are combining Avastin with other therapeutic agents; FDA approved for previously treated GBM</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>VEGF antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aleibertuzumab/VEGF Trap^{10,21}</td>
<td>VEGF</td>
<td>Regeneron</td>
<td>VEGFR ectodomain/IgG fusion protein; phase II trial found single-agent efficacy in GBM; combined therapy trials imminent</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>VEGFR kinase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cediranib/AZD2171 (Reccetin)^{10,119}</td>
<td>VEGFR, PDGF, KIT, FGFR1</td>
<td>AstraZeneca</td>
<td>Most potent against VEGFR; phase II trial showed promising GBM tumor responses; phase I/III trials are underway in combination with cytotoxic therapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Pazopanib^{120}</td>
<td>VEGFR, PDGF, KIT</td>
<td>GlaxoSmithKline</td>
<td>Multikinase inhibitor; promising phase II/III results for RCC; phase II trials in progress for GBM and other solid tumors</td>
<td>Yes</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)^{21}</td>
<td>VEGFR, c-Raf, B-Raf, PDGF</td>
<td>Bayer</td>
<td>Multikinase inhibitor; combined with other targeted therapies in ongoing phase II trials for GBM; FDA approved for RCC</td>
<td>Yes</td>
</tr>
<tr>
<td>Sunitinib (Sutent)^{21}</td>
<td>VEGFR, PDGF, KIT, RET, FLT3</td>
<td>Pfizer</td>
<td>Multikinase inhibitor; several phase II trials underway for GBM; FDA approved for RCC and GIST</td>
<td>Yes</td>
</tr>
<tr>
<td>Vandetanib/ ZD6474^{12,124}</td>
<td>VEGFR, EGFR</td>
<td>AstraZeneca</td>
<td>Dual inhibitor; phase II trials in progress for GBM; results from other solid tumor trials; candidate for combination therapy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Huang, 2009
“Omics” data and the promise of improved clinical outcomes

Leveraging TCGA data for therapeutic development:

Van Meir, 2010
“Omics” data and the promise of improved clinical outcomes

The Cancer Genome Atlas (TCGA) has assigned GBMs to four transcriptome-based subclasses defined by multi-gene signatures, confirmed by frequency of somatic genomic abnormalities.

**Proneural:**
Primary GBM: PDGFRA amp/mut, expression of NSC markers; TP53 mut lower response to intensive therapy.
Secondary GBM: IDH mut, G-CIMP

**Neural:** expression of markers of differentiated CNS cells; not well characterized

**Classical:** EGFR amp/mut/overexpression, homozygous deletion of CDKN2A, lack of TP53 mutations

**Mesenchymal:** increased expression of mesenchymal genes; NF1 loss; NFκB activity, TP53mut

PTEN loss and MGMT promoter methylation not associated with a particular sub-class

Therapeutic implications are likely
“Omics” data and the promise of improved clinical outcomes

Disappointing results in clinical trials for targeted therapy

e.g., 1st gen EGFR (erlotinib, gefitinib) and PDGFR (imatinib) inhibitors:
Lack of molecular pre-selection and target hit information
Phase II clinical trials have fallen from 28% to 18% in recent years. Insufficient efficacy is the most frequent reason.


**What’s wrong with our cancer models?**

*Alexander Kamb* NatRev Drug Disc, 2005

“Extrapolation from small numbers of ill characterized xenografts is fraught with risk. These experiments seldom illuminate how the xenograft relates to the patient population clinicians should treat.”

Believe it or not: how much can we rely on published data on potential drug targets?

*Florian Prinz, Thomas Schiange and Khursu Asadullah* NatRev Drug Disc, 2011

**Raise standards for preclinical cancer research**

Begley, Nature 2012

Pre-clinical results confirmed: 11%
Pre-clinical models and translational value

- Traditional GBM cell lines cultured for many passages in 10% FBS have provided insights into select GBM signaling pathways, but recent data show that this culture method leads to loss of developmental plasticity, and to genomic and phenotypic deviation from the original tumor limiting its preclinical potential (Lee, 2006)

For patient derived xenograft models:
- patient derived cells that preserve the genomic and phenotypic characteristics of the tumor
- can be cryopreerved
- affordable for large scale amplifications
Patient-derived xenograft (PDX) models using neurosphere cultures

<table>
<thead>
<tr>
<th>Pathology</th>
<th>NS(+) (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed primary GBM</td>
<td>42.0 %</td>
<td>87</td>
</tr>
<tr>
<td>Recurrent GBM</td>
<td>40.5 %</td>
<td>37</td>
</tr>
<tr>
<td>Secondary GBM</td>
<td>0.0 %</td>
<td>1</td>
</tr>
<tr>
<td>All samples</td>
<td>41.6 %</td>
<td>125</td>
</tr>
</tbody>
</table>

deCarvalho, 2010
Patient-derived xenograft (PDX) models using neurosphere cultures

**Implant:**
Neurospheres dissociated into single cells
3x10^5 cells in 5 μl
Free-hand method: injection site manually drilled (25 gauge needle)

**location, location, location!**

- AP 0.0, DV-3.5, lateral +3.0
- AP 1.0, DV -3.5, lateral +3.0

**Toluidine dye**

**Tumor**

Irtenkauf, 2013 in preparation

deCarvalho, 2010
<table>
<thead>
<tr>
<th>GBM neurosphere</th>
<th>Pathology</th>
<th>Verhaak classification</th>
<th>MGMT promoter methylation</th>
<th>Known mutations</th>
<th>Patient age / gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF2587</td>
<td>primary GBM untreated</td>
<td>proneural</td>
<td>methylated</td>
<td>wtTP53, PTEN loss, wt IDH1</td>
<td>56/F</td>
</tr>
<tr>
<td>HF2303</td>
<td>primary GBM untreated</td>
<td>mesenchymal</td>
<td>unmethylated</td>
<td>TP53G245S, PTEN loss, NF1 mut</td>
<td>62/M</td>
</tr>
<tr>
<td>HF2354</td>
<td>primary GBM, Gliadel treated</td>
<td>ND</td>
<td>unmethylated</td>
<td>TP53 V216L, PTEN loss</td>
<td>61/M</td>
</tr>
<tr>
<td>HF2609</td>
<td>recurrent GBM</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>48/F</td>
</tr>
<tr>
<td>HF2927</td>
<td>primary GBM untreated</td>
<td>ND (presumed classical)</td>
<td>methylated</td>
<td>EGFR vIII</td>
<td>55/F</td>
</tr>
</tbody>
</table>
PDX – Temozolomide treatment

1 cycle of TMZ: 5 consecutive days, 40 mg/kg q.d.

U251 GBM serum cultured cell line
Curative!

Neurosphere-PDX: moderate to no increase in survival

<table>
<thead>
<tr>
<th>N</th>
<th>Median survival (days)</th>
<th>Log-rank test vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>85</td>
</tr>
<tr>
<td>Early TMZ</td>
<td>9</td>
<td>106</td>
</tr>
<tr>
<td>Late TMZ</td>
<td>8</td>
<td>104.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Median survival (days)</th>
<th>Log-rank test vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>99</td>
</tr>
<tr>
<td>Early TMZ</td>
<td>9</td>
<td>102</td>
</tr>
<tr>
<td>Late TMZ</td>
<td>7</td>
<td>106</td>
</tr>
</tbody>
</table>
Drug administration by oral gavage, control animals receive vehicle
PDX – Temozolomide

Methylated MGMT

HF2587 survival proportions

Unmethylated MGMT

HF2303 survival proportions

HF2927 survival proportions

HF2354 survival proportions
TMZ treatment induced differential gene expression

**HF2587 xenograft**
- Mouse brains were frozen, and tumor tissue macrodissected for RNA extraction
- mRNA global expression was analyzed by Illumina HT-12v4 array (WSU)
- Analysis of differential gene expression in TMZ treated vs control xenografts (n=3 biological replicates/group), filter: p-value < 0.01, submit gene list to GeneGO
TMZ treatment induced differential gene expression

Network map for the shortest path length (GeneGO)

Blue: upregulated in TMZ
Red: downregulated in TMZ

Target hit

Terminal
Cilengitide/TMZ combination

Cilengitide: integrin αvβ3 and αvβ5 receptor inhibitor
Potentiates radiation therapy in pre-clinical studies

![Survival Proportions for HF 2587fluc and HF2303fluc](image)
Sorafenib (Nexavar®, Bayer HealthCare Pharmaceuticals)
Inhibitor of RAF/MEK/ERK signaling pathway, and VEGFR-2/PDGFR-beta signaling cascade (angiogenesis); FDA approved for advanced renal cell and hepatocellular carcinomas
40 mg/kg q.d.

NVP-BEZ235 (Novartis)Imidazo[4,5-c]quinoline derivative synthesized according to a structure-based design approach. Inhibits PI3K and mTOR kinase activity by binding to the ATP-binding cleft of these enzymes.
30 mg/kg q.d

ABT-888 (Abbot Laboratories) is in clinical trials as potentiator of chemotherapy and as single agent. Inhibitor of poly(ADP-ribose) polymerases (PARP)-1 and PARP-2, nuclear proteins that bind to DNA at the site of damage and mediate base-excision DNA repair.
12.5 mg/kg (bid).
HF2587 survival proportions

HF2303 survival proportions

HF2354 survival proportions

HF2609 survival proportions

Control Rx
TMZ
TMZ, ABT-888
BEZ-235
Sorafenib
Comparison of survival curves for TMZ and TMZ/ABT-888

<table>
<thead>
<tr>
<th>GBM</th>
<th>Median Survival (days)</th>
<th>Log-rank (Mantel–Cox) TMZ vs. TMZ/ABT-888</th>
<th>Significant difference? P &lt; 0.05 (Bonferroni)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMZ</td>
<td>TMZ/ABT-888</td>
<td></td>
</tr>
<tr>
<td>HF2587</td>
<td>172</td>
<td>210</td>
<td>P=0.1544</td>
</tr>
<tr>
<td>HF2609</td>
<td>107</td>
<td>102</td>
<td>P=0.8688</td>
</tr>
<tr>
<td>HF2303</td>
<td>96</td>
<td>107</td>
<td>P=0.0089</td>
</tr>
<tr>
<td>HF2354</td>
<td>73</td>
<td>91</td>
<td>P=0.3345</td>
</tr>
</tbody>
</table>
mTOR: serine/threonine kinase upregulated in a variety of tumors, plays an important role downstream in the PI3K/Akt/mTOR signaling pathway TORC1 and TORC2 complexes

**CC-223:** is an oral, potent, selective, ATP-competitive inhibitor of both TORC1 and TORC2
TORC1-selective inhibitors can induce feedback upregulation of TORC2 and treatment resistance

**CC-115:** oral, dual inhibitor of DNA-dependent protein kinase (DNA-PK) and TORC1/TORC2

Mellinghoff, 2011
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<td>HF2927</td>
<td>primary GBM untreated</td>
<td>ND (presumed classical)</td>
<td>methylated</td>
<td>EGFR vIII</td>
<td>55/F</td>
</tr>
</tbody>
</table>

Confidential data removed
PDX – TORC inhibitors

In vitro screening

Confidential data removed
PDX – TORC inhibitors

Confidential data removed
Cabozantinib (XL184, Exelisys) is a novel inhibitor of MET, VEGFR2, and RET, consequently impairing tumor growth, angiogenesis, and invasion. Cabozantinib is currently in clinical trials for several malignancies, including glioblastoma.

**Treatment groups**

**Control:** vehicle gavage for 4 weeks  
**XL184:** 60 mg/kg q.d. for 4 weeks  
**TMZ:** 40 mg/kg q.d. 2 cycles of 1 week, with 2 week interval  
**XL184/TMZ:** concomitant treatment
PDX – XL184

HF2587fluc

BLI Fold Increase

Days

TMZ 40 mg/kg
XL184 60 mg/kg

XL 184 Target Hit (day 34)
1 h
8 h
24 h
PDX – XL184

HF2303fLuc

- control
- XL184
- TMZ
- TMZ_XL184

BLI fold increase

Days

0 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105
0 50 100 150 200 250 300 350 400 500 600

TMZ 40 mg/kg
XL184 60 mg/kg

XL 184 Target Hit (day53)
1h 8h 24h

HF2303 last BLI measurement

PDX – XL184
**PDX – XL184**

**Survival curve comparison**

<table>
<thead>
<tr>
<th>Survival curve comparison</th>
<th>Log-rank (Mantel-Cox) Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control vs. XL184</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Control vs. TMZ</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Control vs. TMZ/XL184</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>TMZ vs. TMZ/XL184</td>
<td>p = 0.6737</td>
</tr>
</tbody>
</table>

**Median survival (days)**

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>XL184</th>
<th>TMZ</th>
<th>XL184/TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>35</td>
<td>44</td>
<td>85</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>
Increasing the translational value of PDX: molecular validation

GBM

DNA seq
RPPA
mRNA seq
mRNA expers

Methylome

neurospheres

2 mm sections, freeze in OCT macrodissect tumor for molecular analysis

hGBM project:
HFH, MDACC, GMU, VAI

In depth molecular validation of PDX
Increasing the translational value of PDX: the more the better

Large collection of neurosphere-PDX, representative of the heterogeneity encountered in the clinic, aim is to develop and characterize 100 lines

Membership to the JAX ® Human Tumor Consortium for subcutaneous propagation of GBM specimens prior to intracranial implant

Collaborations:
• hGBM
• ABC2, Novartis, Columbia University

Fee per service animal studies: (JAX, TD2)
Increasing the translational value of PDX

- Few PDX lines
  - publications
  - interesting findings
- Validation
  - publications
  - interesting findings
  - biomarker discovery (?)
  - mechanism of resistance
  - drug combination studies
- Large collection of well characterized PDX lines
  - validation
  - publications
  - interesting findings
  - Multi-institutional Consortiums, collaborations
  - clinic
Acknowledgments

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Craig Webb
David Cherba

George Mason University
Chip Petricoin
Claudius Mueller

MDACC
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