Scaffold-Based Drug Discovery

Translating Science into Innovation in Healthcare

Peter Hirth, Founder & CEO Plexxikon

NY, NY - October 27-28, 2012
The Three Most Critical Factors for Business Success

- People/Culture
- Capital/Cost
- Technology Products
- Execution

Capital/Cost

Technology Products
Plexxikon Partners in Crime

Peter Hirth  
CEO

Kathy Glaub  
President
Prof Joseph Schlessinger  
Dept. Pharmacology, Yale  
Chairman of the Board, Plexxikon

Prof. Sung-Hou Kim  
Dept. Chemistry, UC Berkeley  
Chairman of the Scientific Advisory Board, Plexxikon
The Plexxikon Technical Leadership
- a Very Experienced Team

Keith Nolop
CMO

Prabha Ibrahim
Non-Clinical

Gideon Bollag
Head, Research
Plexxikonites Wear Multiple Hats!
“Scaffold based Drug-Discovery”

- Co-crystallography as a screening tool
- Mining a different chemical universe
- Leading to broad IP as composition of matter
- Time and cost effective ie. need to make fewer compounds to reach IND stage
- Compounds are built very efficiently (atomic economy)
- Scale-up and development faster and cheaper
- Reduced metabolic liability
- Better oral bioavailability / potential to cross BBB
Advantages of Focus on Target-Rich Families

<table>
<thead>
<tr>
<th>Nuclear Receptors</th>
<th>Kinases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphodiesterases</td>
<td>Aspartyl Proteases</td>
</tr>
</tbody>
</table>

Implications for chemistry and structure

- Defining family-selective chemical scaffolds that provide starting points for optimization of multiple targets
- Exploiting protein structure insight across family members
- Multiple therapeutic opportunities available
- Allows for very capital efficient drug discovery process across multiple therapeutic areas
Exploiting Plexxikon’s Capabilities – Optimized for Innovation

Drug discovery & early development:  
-- Finding innovation – stochastic
  • People dependent
  • Information driven
  • Small organization optimal

Later development & commercialization
-- Statistical results – deterministic
  • Resource dependent
  • Process & rules driven
  • Large scale organization optimal
Plexxikon’s Business Model

• Develop high value NCEs, addressing significant unmet need in any therapeutic area

• Leverage chemistry investment within target families, generating multiple product candidates as well as strong back-up programs

• Execute innovative development strategies:
  -- Minimize cost to failure
  -- Increase probability of success
  -- Accelerate time to market

• Partner aggressively as early as IND stage

• Build profitable, independent business
Plexxikon’s Business Model Is Different

• Inventive and strategic steps in-house

• *We externalize everything else:*
  – Preclinical in vivo models – CROs and academic collaborators
  – Chemistry libraries
  – CMC scale up and manufacturing
  – Specialized consultants – toxicology, clinical specialists, regulatory, quality, toxicology, other advisors, etc.
Same “Chemistry Core” Leading to Several Well Differentiated Clinical Stage NCEs

Example for nuclear hormone receptor targets:

Basis for major strategic alliance with Wyeth

- **PLX204** (pan PPAR; partial gamma activity)
- **PLX201** (alpha-delta PPAR)
- **PLX263** (delta PPAR)

Start of project 2002
FIH 2004
70 cpds made
Fms-Regulated Cell Types

- Macrophage (subset)
- Microglia
- Osteoclast
- Some CANCERS
Same “Chemistry Core” Leading to Several Well Differentiated Clinical Stage NCEs

- **PLX7486**
  - Fms/Trk
  - Perineural invasion
  - Oncology/Pain

- **PLX3397**
  - Fms/ckit
  - Oncology/Pain
  - Metastasis/Bone

- **PLX5622**
  - Fms in CNS
  - Neuro-inflammation

- **PLX9265**
  - Fms in Periphery
  - Auto-immune/inflammation
**PLX3397: First-in-Class Drug for Cancer**
_Targets Fms, Kit & Flt3-ITD mutant_

**Competitive advantage of PLX3397:**
- Oral agent
- Brain permeable
- Delay/prevent tumor growth/metastases
- Overcomes resistance to drugs or radiation
- Reduces bone lysis, fractures, pain

**Target indications:**
- Hodgkin lymphoma
- AML
- Glioblastoma
- Metastatic breast cancer
- Prostate

---

**Taxol only**

**PLX3397+Taxol**

PLX3397+Taxol prevents Breast cancer metastases

Tumor growth/bone lysis prevented with PLX3397
PLX3397 Phase 1 Trial

- **3+3 dose-escalation design**
  - Advanced solid tumors
  - Single agent
  - Sequential dose escalation
  - Continuous dosing in 4-week cycles

- **Current status:**
  - 41 patients treated to date
  - 1000 mg (5th cohort); MTD dose and Ph2 rec. dose
  - Increasing systemic exposure with increasing dose
  - ~20 hour half-life supportive of once daily dosing
  - Bioresponse data indicate exposure in efficacious range
  - Tumor response in few patients
  - Patient benefit in few patients: reduction in pain/narcotics, osteoarthritis symptoms, skin mets/inflammation
Neuro-degeneration
Target Activated Microglia with Fms Inhibitor

Alzheimer’s
MS
Parkinson’s
Dementia
ALS
Ocular Inflammation
PLX3397 Produces Unprecedented Improvement in Memory Performance in Gold Standard Model of Alzheimer’s Disease

Latency to platform localization
(Water maze)

3xTg-AD mice (23 months of age)
Extremely advanced disease

3 month treatment

Lower latency means faster recall, better memory performance

# of Successive Trials
Same “Chemistry Core” Leading to Several Well Differentiated Clinical Stage NCEs

Example for Raf kinase targets:

Basis for major strategic alliance with Roche

PLX4032 aka Vemurafenib V600 BRAF

PLX5568 C-Raf

PLX8394 “paradox breaker” V600 BRAF 2nd Generation
Mutations of the BRAF gene in human cancer

Helen Davies1,2, Graham R. Bignell1,2, Charles Cox1,2, Philip Stephens1,2, Sarah Edkins3, Sheila Clegg1, Jon Teague1, Hayley Wolfenden1, Mathew J. Garnett1, William Bottomley1, Neil Davis1, Ed Dicks1, Rebecca Ewing1, Yvonne Floyd1, Kristian Gray1, Sarah Hall1, Rachel Hawes1, Jaime Hughes2, Vivian Kosmidou2, Andrew Menzies1, Katherine Mould1, Adrian Parker1, Claire Stevens1, Stephen Watt1, Steven Hooper2, Rebecca Wilson2, Hiran Jayatilleke1, Barry A. Gusterson2, Colin Cooper9, Janet Shipley2, Darren Hargrave2, Katherine Pritchard-Jones1, Norman Mantliand3, Georgia Chenevix-Trench3, Gregory J. Riggins1, Darell B. Bigner1, Giuseppe Palmintieri1, Antonio Cassou1, Adrienne Flanagan1, Andrew Nicholson14, Judy W. G. Ho1, Sue T. Yuen1, Barbara L. Weber17, Hilliard F. Seliger1, Timothy L. Darrow1, Hugh Paterson5, Richard Marais2, Christopher J. Marshall2, Richard Wooster1,6, Michael R. Stratton1,6 & P. Andrew Futreal1

1Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, CB10 1SA, UK
2Cancer Research UK Centre for Cell and Molecular Biology, Chester Beatty Labs, Institute of Cancer Research, London SW3 6JB, UK
3Section of Cancer Genetics, 4Section of Molecular Carcinogenesis, and 5Section of Paediatrics, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK
6Department of Pathology, Western Infirmary, University of Glasgow, S11 7NT, UK
7Department of Biology, YCR Cancer Research Unit, University of York, York YO10 5YW, UK
8Queensland Institute of Medical Research, RBH Post Office Herston, Queensland 4029, Australia
9Department of Pathology, and 10Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA
11Institute of Molecular Genetics, C.N.R., Loc. Trammarigli, Alghero 07040, Italy
12Department of Pathology, University of Sassari, Azienda USL1, Sassari 07010, Italy
13Royal Free & University College Medical School, London WC1E 6JB, UK
14Department of Surgery, and 15Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong
16Abramson Family Cancer Research Institute, University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania 19104, USA
17These authors contributed equally to this work

Cancers arise owing to the accumulation of mutations in critical genes that alter normal programmes of cell proliferation, differentiation and death. As the first stage of a systematic genomewide screen for these genes, we have prioritized for analysis signalling pathways in which at least one gene is mutated in human cancer. The RAS–RAF–MEK–ERK–MAP kinase pathway mediates cellular responses to growth signals1. RAF is mutated to an oncogenic form in about 15% of human cancer. The three RAF genes code for cytoplasmic serine/threonine kinases that are regulated by binding RAS1–3. Here we report BRAF somatic missense mutations in 66% of malignant melanomas and at lower frequency in a wide range of human cancers. All mutations are within the kinase domain, with a single substitution (V599E) accounting for 80%. Mutated BRAF proteins have elevated kinase activity and are transforming in NIH3T3 cells. Furthermore, RAF function is not required for the growth of cancer cell lines with the V599E mutation. As BRAF is a serine/threonine kinase that is commonly activated by somatic point mutation in human cancer, it may provide new therapeutic opportunities in malignant melanoma.

Genomic DNA from 15 cancer cell lines (6 breast cancers, 1 small-cell lung cancer (SCLC), 6 non-small-cell lung cancers (NSCLC), 1 mesothelioma, 1 melanoma) and the corresponding matched lymphoblastoid cell lines from the same individuals were screened for sequence variants through the coding exons and intron–exon junctions of the BRAF gene using a capillary-based modified heteroduplex method followed by direct sequencing of polymerase chain reaction products. (Exon 1, containing 135 base pairs (bp) of coding sequence, failed to amplify despite the use of five different primer sets.) Three single-base substitutions were detected. Two were in BRAF exon 15: T1796A leading to a substitution of valine by glutamic acid at position 599 (V599E) in the melanoma cell line Colo-829, and C1786G leading to L596V in the NSCLC cell line NCI-H2087 (Fig. 1). A further mutation was found in exon 11: G1403C leading to G468A in the NSCLC cell line NCI-H1359. None of the three changes were present in the lymphoblastoid cell lines from the same individuals, indicating that the variants were somatically acquired mutations.

Figure 1 Mutations in the BRAF gene. Sequence electropherograms and corresponding comparisons between heteroduplex traces from normal (green) and cancer (red) DNAs from the same individuals. The heteroduplex trace comparisons are generated using proprietary software (see Methods). For each example (NCI-H2087 cell line (a) and ovarian neoplasm (OV180) (b) the cancer trace shows additional peaks and/or differently shaped peaks compared with the normal trace.
Inhibition of $BRAF^{V600}$

Abnormal cellular proliferation

Growth Factors

RTK → Y-P → Y-P

Normal signaling

Membrane

Raf → Ras GTP → MEK → ERK

Other Effectors → Nuclear Translocation

Gene Expression

Abnormal Cellular Proliferation

Oncogenic signaling

B-Raf$^{V600}$ → MEK → ERK

V600 Inhibitor

Rationale: Specific inhibitor against V600 should suppress oncogenic signaling

Arrested

Normal signaling → Abnormal cellular proliferation

Confidential
Personalized Medicine: Plexxikon’s First in Oncology
PLX4032 for Melanoma & Colorectal

**Rationale:**

- Target exclusive to tumors
- Highly selective inhibitor
- Paired drug/diagnostic enables accelerated development
- Therapeutic rationale driven by patient survival outcome data

- Roche Molecular Systems co-developing in vitro diagnostic
- \( \text{BRAF}^{\text{V600}} \) oncology program partnered with [Roche](#)
Scaffold-Based Drug Discovery

Lead Discovered (low nM)
Structural Basis for Selectivity Binding To Only One Protomer Of Asymmetric Dimer
Plexxikon Hallmark Capability
Highly Selective Kinase Inhibitors

Plexxikon Molecules

Sprycel  Tarceva  Gleevec
Sutent  Nexavar  RAF265

Potency (K_i or IC_{50})
- <10nM
- 10-100nM
- 100nM-1uM
- 1uM-10uM

Structure Guided Drug Discovery
Co-Crystallography of PLX4032 with B-Raf$^{V600}$
**Discovery of Game Changer PLX4032**

Test to Select Patients Could Accelerate Development

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
</table>

- PLX4032 discovery
- CoDx deal

Plexxikon

Roche
Vemurafenib Clinical Development Begins
Strong Partner to Increase Probability of Success

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
</table>

- IND filed
- Rx deal

- Plexxikon
- Roche
Optimized Formulation Introduced
First Encouraging Data
Mutation Exclusive to Melanoma Tumors & Moles
Primary Oncogenic Driver in Melanoma

Pre-Treatment 2 Weeks Vemurafenib

Pre-Treatment 2 Weeks Vemurafenib

100% of patients with BRAF^{V600} melanoma achieved an FDG-PET response

PET scans courtesy of Drs. Grant McArthur and Rod Hicks, Peter MacCallum Cancer Centre, Melbourne AUSTRALIA
Phase 2 (BRIM2) & Phase 3 (BRIM3) Initiated in Parallel

PLX4032 Phase 2 Confirms Initial Results

<table>
<thead>
<tr>
<th>Year</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
</table>

![Graph showing Phase 2 (BRIM2) results over years](image)

**Phase 2 (BRIM2)**

- Data trends from 2005 to 2012 are illustrated.
- The graph indicates changes from baseline for each year.
- Phases M1a, M1b, M1c, and No data are represented.

---

*Confidential*
PLX4032 Phase 3 Study Stopped Due to Compelling Efficacy

- Phase 3 (BRIM3) study shows promising results for PLX4032 in BRAF V600 mutation-positive metastatic melanoma
- Market approval filings with FDA & EMA
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,
Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D.,
Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D.,
Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D.,
Antoni Ribas, M.D., Steven J. O’Day, M.D., Jeffrey A. Sosman, M.D.,
John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D.,
Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jian Li, Ph.D., Betty Nelson, M.A.,
Jeanie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D.,
and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*
Vemurafenib Phase 1 Overall Survival
Updated KM Estimates Aug/11

Median OS (month)
- Dose escalation: 25.2
- Extension: 13.8
- WT or subtherapeutic: 4.18

Time since first dose (months)

% Overall survival

V600E dose escalation (n=16)
Extension (n=32)
WT or subtherapeutic exposure (n=33)

1 year – 50%
2 years – 38%

SMR 2011, Hauchild
The Power of Targeted Drug + Companion Diagnostic

- IND filed
- Rx deal

5 years from IND to Launch

1st Launch

2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012

The image shows a timeline with key milestones:
- IND filed in 2005
- Rx deal in 2006
- 1st Launch by 2012
### Selected adverse events (% of patients)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib, n=337</th>
<th></th>
<th></th>
<th>Dacarbazine, n=287</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
<td>Grade ≥4</td>
<td>All</td>
<td>Grade 3</td>
<td>Grade ≥4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>56</td>
<td>6</td>
<td>–</td>
<td>4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>41</td>
<td>9</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
<td>–</td>
<td>35</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>41</td>
<td>4</td>
<td>–</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>↑LFTs</td>
<td>26</td>
<td>10</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>19</td>
<td>19</td>
<td>–</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>–</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>11</td>
<td>10</td>
<td>–</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>–</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>28</td>
<td>&lt;1</td>
<td>–</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>2</td>
<td>–</td>
<td>45</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>–</td>
<td>&lt;1</td>
<td>12</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Discontinuations due to AE: 7% vemurafenib; 2% dacarbazine
8 patients reported new primary melanomas in the vemurafenib group

ASCO 2012, Chapman
PLX4032, *Now ZELBORAF™*

**Game Changing for Patients & Plexxikon**

- **Vemurafenib**
  - Selective for BRAF mutation
  - Target exclusive to tumors & moles
  - Oral agent
- **BRAF mutation market**
  - 50% in melanoma
  - 8% of all solid tumors
- **Companion diagnostic**
  - Accelerated clinical development
  - Potential for premium pricing
- Clinical proof-of-concept established in Phase 1
- FDA approved Aug/2011; approved
- >35 countries worldwide
- First U.S. commercial sales Aug/2011
- First co-approval and co-launch of drug and CoDx in cancer
- Co-promotion in U.S. by Daiichi Sankyo and Genentech; Roche ROW
Further Development of Vemurafenib

- **In Melanoma**
  - Combination with other drugs
    - Signaling inhibitors (e.g. MEKi and PI3Ki)
    - Immunotherapy (e.g. Ipilimumab)
  - Brain metastases
  - Adjuvant treatment

- **Other tumors with BRAF mutations**
  - Papillary thyroid cancer
  - Basket Study (any tumor with activating B-raf mutation)

- Paradox Breaker (to enter clinic in 2013)
## Current Plexxikon Clinical Programs

*Expect New NCEs to Enter Clinic 2012 & Beyond*

<table>
<thead>
<tr>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
</table>
| **PLX4032**
  • Melanoma
  • Melanoma Combos
    – with MEKi
    – with ipi
  • Thyroid
  • Adjuvant Melanoma |
  Phase 1b/2 | FDA Approval | EMA Approval? |
  Phase 1b/2 | Phase 2 | Phase 2 |
| **PLX3397**
  • Hodgkin’s Lymphoma
  • GBM
  • AML
  • Metastatic Breast |
  Phase 1 | Phase 2 |
  Phase 1 | Phase 2 | Phase 1b/2 |
  Phase 1 | Phase 1b/2 | Phase 2 |
| **PLX5622**
  • RA
  • AD |
  Phase 1 | Phase 2 |
  Phase 1 | Phase 2 | Phase 2 |

---

Confidential
Plexxikon as Business

- Financings
- Venture Capital
- Deal Making
- Exit strategy
- Returning Investor Money
Venture Financing History

**Plexxikon Investors**
- Alta Partners
- Astellas Ventures
- ATV Capital
- CW Ventures
- GIMV
- NIF
- Pappas Ventures
- Walden International

**Financing History**
- 2001 Series A ~$8 M
- 2002 Series B ~$46 M
- 2006 Series C ~$13 M
- Total ~ $67 M
## Plexxikon Licensing History Through Oct/2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Program</th>
<th>Upfront $</th>
<th>Ttl $ In</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Genentech</td>
<td>Ret</td>
<td>$2.8</td>
<td>$4.0</td>
</tr>
<tr>
<td>2003</td>
<td>Elan</td>
<td>BACE</td>
<td>$0.9</td>
<td>$0.9</td>
</tr>
<tr>
<td>2004</td>
<td>Wyeth</td>
<td>PPAR/PLX204</td>
<td>$22.1</td>
<td>$42.8</td>
</tr>
<tr>
<td>2006</td>
<td>Servier</td>
<td>Renin</td>
<td>$2.5</td>
<td>$9.5</td>
</tr>
<tr>
<td>2006</td>
<td>Roche</td>
<td>Braf/PLX4032</td>
<td>$46.0</td>
<td>$146.7</td>
</tr>
<tr>
<td>2008</td>
<td>Roche</td>
<td>Craf/PLX5568</td>
<td>$60.0</td>
<td>$62.5</td>
</tr>
</tbody>
</table>

Excludes royalties

$134.3 $266.4
Plexxikon Attractants for Buyout
2010 Licensing Discussions Showcased Plexxikon Assets

• Near commercial asset with co-promote – PLX4032
  – Opportunity to promote high profile first-in-class personalized medicine
    • Remarkable efficacy & safety data
    • High level of publicity, including NY Times, and multiple peer-reviewed journals
  – Economics under Roche collaboration attractive

• Other attractive clinical stage assets
  – Unencumbered next generation BRAF program
  – Additional novel and significant oncology programs
  – Additional novel and significant opportunities outside of oncology
Plexxikon Attractants for Buyout
2010 Licensing Discussions Showcased Plexxikon Assets

• Robust preclinical pipeline:
  – Each opportunity differentiated
  – High science
  – Leverages chemistry investment, faster & more efficient

• Validated discovery platform broadly applicable
  – IND engine

• Novel chemistry approach results in:
  – Long patent terms
  – No royalty stacking

• Team with proven track record
  – Significant credibility accrued with PLX4032 experience
  – Wants to repeat the experiment
Competitive Process
Daiichi Sankyo Buys Plexxikon Apr/11

• **Competing bids led to attractive Plexxikon acquisition:**
  – $805 M upfront – 86% of total deal – plus net cash
  – $30 M near term & probable commercial milestones for PLX4032
    • $100 M milestones – 97% of total deal paid as of Sept/11
    – **Investor returns > 10X**

• **Plexxikon operates as independent at least through April/13**
### Largest Trade Sales of VC-Backed Pharma/Biotech Companies YTD 2011

<table>
<thead>
<tr>
<th>Target</th>
<th>Buyer</th>
<th>Upfront Value ($ million)</th>
<th>Total Deal ($ million)</th>
<th>Estimated Inv. Capital ($ million)</th>
<th>Stage of Lead Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plexxikon (US)</td>
<td>Daiichi Sankyo (Japan)</td>
<td>805</td>
<td>935</td>
<td>67</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Advanced BioHealing (US)</td>
<td>Shire (UK)</td>
<td>750</td>
<td>750</td>
<td>47</td>
<td>Market</td>
</tr>
<tr>
<td>Pharmaswiss (CH)</td>
<td>Valeant Pharmaceuticals (Canada)</td>
<td>478</td>
<td>518</td>
<td>n.a.</td>
<td>Market</td>
</tr>
<tr>
<td>Biovex (US)</td>
<td>Amgen (US)</td>
<td>425</td>
<td>1'000</td>
<td>166</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Calistoga (US)</td>
<td>Gilead Sciences (US)</td>
<td>375</td>
<td>600</td>
<td>120</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Prism (US)</td>
<td>Baxter (US)</td>
<td>170</td>
<td>338</td>
<td>63</td>
<td>Market</td>
</tr>
<tr>
<td>Synosia (CH)</td>
<td>Biotie (Finland)</td>
<td>122</td>
<td>122</td>
<td>85</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Astex (US)</td>
<td>SuperGen (US)</td>
<td>117</td>
<td>117</td>
<td>119</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Taligen (B)</td>
<td>Alexion (US)</td>
<td>111</td>
<td>478</td>
<td>111</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Cellerix (Spain)</td>
<td>TiGenix (B)</td>
<td>86</td>
<td>86</td>
<td>96</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Mpex (US)</td>
<td>Axcan, now Apsalis (Canada)</td>
<td>60</td>
<td>250</td>
<td>100</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
M & A Trends to Milestone Deals

Plexxikon Deal Compares Favorably

1. Average upfront payments

Source: Company press releases and VentureSource
Challenges Plexxikon Met

- Lack of broad investor interest in platform discovery company
- Declining numbers of pharma prospects for partnerships due to M & A
- Increasing volatility/uncertainty among pharma grappling with expiring patents and reduced productivity
- Increasingly difficult financial environment
- Shifting and increasingly burdensome regulatory environment
- Probability of success for any NCE
- Development timelines for any NCE
- Personalizing medicines
Drivers for Plexxikon Success

- Experienced, cohesive team
- New technology capabilities
- Strong investors
- *Disruptive thinking* – *both R & D and business*
- Increasing demand for NCEs that are medical breakthroughs
- Discovery and creation of PLX4032 poster child for personalized medicine
- The gods of good fortune
It still pays to be an innovator!

- Experienced, cohesive team
- New technology capabilities
- Strong investors
- Disruptive thinking – both R & D and business
- Increasing demand for NCEs that are medical breakthroughs
- Discovery and creation of PLX4032 poster child for personalized medicine
- The gods of good fortune
Scientific Insights Gained

**BRAF/PLX4032**

- BRAF MOA – Wistar Inst (Herlyn/Smalley)
- RAF dimerization – MSKCC (Rosen)
- Thyroid, ATC, resistance – MSKCC (Fagin)
- Melanoma resistance – UCLA (Ribas)
- Thyroid crc – MGH (Parangi)
- Glioma & resistance – UCSF (Nicolaides)
- Gene expression & resistance – UCLA (Tap/Slamon)
Scientific Insights Gained

**FMS/PLX3397**
- Melanoma MOA – AECOM (Verma/Stanley)
- Breast crc taxol combo – UCSF (Coussens)
- Pancreatic crc gem combo – Wash U (DeNardo)
- Prostate & ovarian crc – UCLA (Wu)
- MPNST – MSKCC (Tap/Schwartz)
- Prostate, sarcoma crc – U Arizona (Mantyh)
- Flt3-ITD AML – U Penn (Carroll)
- Mesothelioma – UCSF (Coussens/Blakely)

**FMS/PLX5622**
- Alzheimer’s Disease – UC Irvine (LaFerla)
- Progranulin FTD – UCSF (Gan/Ward)
Plexxikon Compounds & Collaborations Generate/Inspire Many Publications
~300 to date
Thank you!

Plexxikon
Scaffold-Based Drug Discovery