Symposium on Academic Drug Discovery: Challenges and Perspectives
Imperial College, 31 March 2011

Drugging the cancer genome: The challenges of professional drug discovery in an academic environment

Paul Workman
Cancer Research UK Cancer Therapeutics Unit
Institute of Cancer Research/Royal Marsden Hospital
Sutton, Surrey SM2 5NG UK
ian.collins@icr.ac.uk
Disclosure Information

• Consultant for: Novartis, Piramed Pharma (acquired by Roche), Chroma Therapeutics, Avalon Pharmaceuticals

• Grant/Research support from: Vernalis, Piramed, Chroma, Antisoma, AstraZeneca, MerckSerono

• Stockholder in: Chroma (founder), Piramed (founder), Avalon

• Programme IP licensed to: Vernalis/Novartis, Piramed/Genentech/Roche, Astex/AstraZeneca

• I will not discuss off label use and/or investigational use

• Technology collaborations with MesoScale Discovery, Cell Biosciences and BellBrook Labs
Exploiting cancer biology and the cancer genome
Algorithm: Drugs and biomarkers

Disease genes

Diagnostics, prognostics, biomarkers

New therapeutic agents

Biggest impact has been on personalized cancer medicine
Key roles for academia and pharma

Personalised diagnosis and treatment
Personalized cancer genome-based medicine

A Bitter Pill

Is big pharma prepared to swallow a new business model?

Words: Mark Henderson
The old blockbuster pharma model is failing

This is due to:

- Patent expiry on blockbusters for big markets like statins, antidepressants, ulcer drugs and painkillers
- Pressures on pricing from healthcare providers
- Pressures from regulatory authorities
- Risks of serious side-effects
- High failure rates in clinical trials
- Escalating R&D costs
- Declining productivity – fewer drug approvals
- Science (genomics) taking us in a different direction
Personalized or stratified medicine is the way forward

• Individualized treatment replacing one size fits all
• Targets the patients or patient groups most likely to respond
• In tune with the direction of the science
• Means smaller, faster and cheaper trials can yield positive outcomes
• This results in higher approval rates
• Now shown to be compatible with a viable business model
• Can still yield billion dollar drugs
• Exemplified by Gleevec, Herceptin and other cancer drugs
• But mitigating technical and biological risk is a key issue for pharma
Cancer drug development is still expensive and risky

- Leading the way in personalized medicine
- But only around 15% of cancer drugs entering clinical trial get approved
- Many fail in expensive Phase III trials
- Some projects never reach the clinic
- There are both technical and biological challenges in drugging the cancer genome
- Cost of taking a cancer drug to market is above US $1 billion

Things are changing but…
Mitigating risk in innovation is a key factor for industry
Trends we need to consider for our approach

- Drugs will need to be licensed to companies for patients to benefit
- Pharma has made the seismic culture change committing to the new model
- Tighter big pharma budgets but with more outsourcing
- Big appetite for late stage projects which attract good valuations
- Variable appetite for riskier early stage projects which suffer from lower valuations
- Major differences in risk tolerance between different companies
- Pharma looking to share the early risk
- Demise of biotech provides challenges and opportunities
- This varied and volatile market offers opportunities if we are nimble and flexible
The Iressa experience: Exploiting EGFR addiction with a kinase inhibitor

Catalogue of somatic mutations in the lung cancer cell line NCI-H2171

EGFR-Mutation Positive

ISEL study (2005)
Gefitinib vs placebo in NSCLC

Gefitinib vs 1st line chemo

EGFR mutation: RR 38%
EGFR wild-type: RR 3%
Who/what are we?

- Large drug discovery group – 165 staff
- Academic / industry-hybrid model – aiming to combine the best of both worlds
- Derisking new target approaches to accelerate patient benefit
- Extensive collaborations with biotech and pharma
- Builds on strong basic cancer research at ICR and elsewhere
- Integrated relationship with Royal Marsden Hospital forming Europe’s largest comprehensive cancer centre
- Major long term programme grant support from Cancer Research UK – providing continuity and freedom to operate a portfolio of projects
- Originators of approved cancer drugs: chlorambucil, melphalan, busulphan, carboplatin, raltitrexed – important cultural/scientific history
- Since 1997 the focus has been on small molecules acting on new molecular targets
People: Cancer Therapeutics Team Leaders
Technical enablers

- In-house molecular biology and target validation capability
- High-throughput screening for hit generation
- Fragment screening
- High-throughput crystallography
- Modern state of the art medicinal chemistry function
- Strong integrated PK-PD-efficacy axis
- Mechanistic molecular pharmacology
- New computational biology and chemogenomics team
- Strong focus on biomarkers – proof of mechanism and predictive
- Integration with clinical development, including GCLP PK/PD lab
Less obvious enablers

- Strong culture of partnership – with speed (of quality molecule) to the clinic as the main driver
- Integration and joined-up thinking
- High level diplomacy requirement
- Postdocs and students doing exploratory research around drug discovery projects, e.g., chemical biology
- Training element, including Wellcome Trust PhD programme in Mechanism-Based Drug Discovery (30 students over 5 years)
- Rigorous project management and portfolio review process
- Ten year horizon: 5 years of technology and culture change, 5 years to deliver
Encouraging interactions
Recent achievements

- Five drugs now in the clinic at the Royal Marsden
- Abiraterone on track for approval in prostate cancer
- Thirteen preclinical development candidates in last five years
- Many discovery programmes licensed to companies, including Genentech, Novartis, AstraZeneca, MerckSerono, Astex, Vernalis, Antisoma
- Two spin out companies: Piramed and Chroma
- Portfolio of interesting early stage new target projects
Abiraterone acetate in metastatic castrate resistant prostate cancer

- Designed and synthesized by Mike Jarman’s team in 1991
- Three phase I trials with PK/PD under Ian Judson published in 2004
- Key biological insights into disease biology and safety profile by Johann de Bono in 2005
- Worldwide Phase II trials PK carried out in the Cancer Therapeutics Unit by Flo Raynaud
- Phase III trial in metastatic castrate resistant prostate cancer showed a 4 month increase in survival
- J&J to file approval applications in the US and Europe 4Q10
Five drugs in clinical trials at the Royal Marsden

- HSP90 inhibitor NVP-AUY922 – with Vernalis/Novartis
- PI3 kinase inhibitor GDC-0941 – with Piramed/Genentech
- HDAC inhibitor CHR-3996 – oral class I selective, with Chroma Therapeutics
- Alpha folate receptor targeted thymidylate synthase inhibitor ONX-0801 – with Onyx Pharmaceuticals
- AKT/PKB inhibitor – with Astex Therapeutics/AstraZeneca
Integrating drug discovery science

Collins and Workman Nature Chemical Biology 2 689-700 2006
Drug discovery and development: Four critical elements

- Selecting the best targets
  We have enhanced our target selection strategy

- Identifying high quality hit matter
  We have implemented multiple hit discovery options

- Selecting the optimal candidate
  We have delivered candidates and developed our capabilities for the future

- Designing the right clinical trial
  We have developed and implemented the Pharmacological Audit Trail (example later)

We are taking on targets with technical OR biological risk but not both
HSP90 ATPase inhibitor

From natural product tools to HTS to clinical trial

NVP-AUY922
VER-52296
Stress is now included in extended hallmarks of cancer

Stress support systems are targets for tumour-selective therapy
Mode of action of HSP90 inhibitors: An open and shut case

Mode of action of HSP90 inhibitors: An open and shut case


- HSP90 inhibitors block the ATP-driven chaperone cycle, driving client breakdown
- Blocks signal transduction and causes cell cycle arrest and apoptosis
### Combinatorial effects of 17-AAG in human melanoma cell lines

**SKMEL 28 cells**

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- HSP72
- C-RAF
- CDK4
- ERBB2
- Phospho ERK
- Total ERK
- GAPDH

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- Phospho AKT
- Total AKT
- GAPDH

**Geldanamycin**  
- $R = OCH_3$
- $R = NHCH_2CH=CH_2$
- $R = NHCH_2CH_2N(CH_3)_2$

**Swee Sharp**

- Combinatorial depletion of clients
- Hierarchy of client dependence
- Proof of concept
- Limitations with geldanamycins as drugs
Biomarkers for 17-AAG Pharmacologic audit trail

Banerji, Judson, Workman et al JCO, MCT
Taking an early risk on HSP90: Situation in 1997-2000

- Unconventional target – validated scientifically by chemical biology with natural products

- No serious interest from pharma – unprecedented, high risk, different from a single kinase target, concern about toxicity

- Early risk mostly adopted by non-profit labs

- We began high-throughput screening at ICR in 2Q 2001

- We initiated a structure-based design collaboration with Laurence Pearl at ICR

- We learned from the experience of studying 17-AAG in the lab and in the clinic
HSP90 collaborative drug discovery at ICR

- Learning from experience with HSP90 inhibitor 17-AAG in the lab and the clinic – from 1997 to 2000
- In-house molecular pharmacology and structural biology expertise on HSP90
- Aim: To discover improved, synthetic small molecule inhibitors overcoming the limitations of the natural products
- Initial work at The Institute of Cancer Research – HTS 2Q 2001
- Collaboration with RiboTargets/Vernalis – established March 2002
- Subsequent collaboration and development by Novartis
- Two preclinical development candidates nominated – 1st IV agent in December 2005 and 2nd oral agent in December 2006
- First drug NVP-AUY922 entered Phase I trial 2007; Phase II 2010
Chemical probes and drugs for HSP90

Geldanamycin \( R = \text{OCH}_3 \)

17-AAG \( R = \text{NHCH}_2\text{CH} = \text{CH}_2 \)

17-DMAG \( R = \text{NHCH}_2\text{CH}_2\text{N(CH}_3)_2 \)

IPI-493 \( R = \text{NH}_2 \)

IPI-540
Radicicol

NVP-AUY922

KW-2478

AT13387
HTS: Malachite green screen for new HSP90 ATPase inhibitors

- Inexpensive and amenable to automation
- Measures ATPase reaction by inorganic phosphate release
- Used yeast Hsp90
- Subsequently tested on human HSP90 activated by AHA1
- Adapted to 384-well plate format for high-throughput screening
- 50,000 compound library screened
- Diaryl pyrazole resorcinol series identified – CCT018159
- Also found in cell-based screen*

Rowlands, Newbatt, Aherne et al
Analytical Biochemistry 327 176-183 2004

*Hardcastle, Aherne et al
Mol Cancer Ther 6 1112-1122 2007

CCT018159
Crystallography to understand binding

Radicicol

CCT018159

Roe et al, J Med Chem 42 260-266 1999
Cheung et al, Bioorg Med Chem Lett 15 3338-43 2005
Multiparameter evolution of NVP-AUY922

Starting point
HTS hit
CCT018159
FP IC\textsubscript{50} = 280nM
GI\textsubscript{50} = 6000nM

5-amides
Potency breakthrough
VER-49009
FP IC\textsubscript{50} = 25nM
GI\textsubscript{50} = 260nM

Solubiliser, isoxazole
Cell potency
VER-51047
FP IC\textsubscript{50} = 21nM
GI\textsubscript{50} = 83nM

Development candidate
PK/PD, xenograft efficacy
NVP-AUY922/VER-52296
FP IC\textsubscript{50} = 9nM
GI\textsubscript{50} = 14nM

GI\textsubscript{50} in HCT116 colon cell line

Dymock et al J Med Chem 48 4212-4215 2005
Brough et al J Med Chem 51 196-218 2008
Potency & selectivity of NVP-AUY922: Improved probe and drug

HSP90-related properties

- Competitive binding FP IC$_{50}$ 21±16 nM
- Mean GI$_{50}$ in a panel of human cancer cells 10.8 nM
- Ki 9 ± 5 nM
- Kd 1.7 ± 0.5 nM
- Enthalpy -12.24 kcal/mol
- Entropy 0.19 cal/mol/K
- Most potent small molecule HSP90 inhibitor yet described

Selectivity properties

- 5-10 fold selective versus HSP90 family members GRP94 ($K_\text{i}$ 108 nM) and TRAP-1 ($K_\text{i}$ 53nM)
- No inhibition of structurally related Topoisomerase II ATPase or HSP72 ATPase at 10µM
- Little or no inhibition in a representative panel of 13 kinases
- In a further panel of 14 additional enzymes and 67 receptors, NVP-AUY922 showed >50% inhibitory activity at 10µM against only 7 targets, and 50-fold selectivity against these
Efficacy of NVP-AUY922 in human breast cancer xenografts

BT474 human breast carcinoma ERBB2+ ERα+

50mg/kg NVP-AUY922 daily for 23 days

5/12 regressions

Phase I study of NVP-AUY922: Response in an ERBB2+ breast cancer patient

- Multiple phase II studies have been initiated
  - Single-agent in HER2-positive or ER-positive advanced or metastatic breast cancer
  - Combination with docetaxel or irinotecan in advanced gastric cancer
  - Single-agent and with bortezomib (Phase Ib/II) in relapsed/refractory multiple myeloma
Effects of NVP-AUY922 in breast cancer: Lab to clinic

BT474 human breast carcinoma ERBB2+, ERα+

- ERBB2 client protein is highly dependent on HSP90
- Rapidly and extensively depleted by NVP-AUY922 in ERRB2+ve BT474 breast cancer cells
- BT474 breast tumour xenograft is highly responsive to the drug
- PR seen in ERBB2+ breast cancer patient and also in an ER+ patient
- PD and predictive biomarkers have transferred usefully to the clinic

Breast cancer patient ERBB2+

Pre-treatment 4 months
Timeline of HSP90 inhibitors in the clinic
Success in derisking the target

- Natural product analogue trail-blazers
- Subsequent rise of the small molecules

Modified from Trepel, Seeon, 2010
So what’s next?

Dual Targeting of HSC70 and HSP72 Inhibits HSP90 Function and Induces Tumor-Specific Apoptosis

Marissa V. Powers,¹ Paul A. Clarke,¹ and Paul Workman¹,*
¹Signal Transduction and Molecular Pharmacology Team, Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, Haddow Laboratories, Sutton, Surrey SM2 5NG, UK
*Correspondence: paul.workman@icr.ac.uk

SUMMARY

Heat-shock protein 70 (HSP70) isoforms contribute to tumorigenesis through their well-documented anti-apoptotic activity and via their role as cochaperones for the HSP90 molecular chaperone. HSP70 expression is induced following treatment with HSP90 inhibitors, which may attenuate the cell death effects of this class of inhibitor. Here we show that silencing either heat-shock cognate 70 (HSC70) or HSP72 expression in human cancer cell lines has no effect on HSP90 activity or cell proliferation. However, simultaneously reducing the expression of both of these isoforms induces proteasome-dependent degradation of HSP90 client proteins, G1 cell-cycle arrest, and extensive tumor-specific apoptosis. Importantly, simultaneous silencing of HSP70 isoforms in nontumorigenic cell lines does not result in comparable growth arrest or induction of apoptosis, indicating a potential therapeutic window.
PI3K lipid kinase inhibitor

From screen to probe to clinical trial via spin-out

PI-728
GDC-0941
PI3 kinase signalling and cancer hallmarks

Mutations are very common at multiple points in the pathway …

… driving the hallmarks of cancer

Modified from Garcia-Echevria and Sellers Oncogene 27 5511–5526 2008
PI3K collaborative drug discovery

- Supporting academic drug discovery through formation of a spin out company
- Collaboration between Yamanouchi Pharmaceuticals (Astellas), Peter Parker (CRUK LRI), Mike Waterfield (Ludwig Inst) & Paul Workman (ICR) identified PI3K inhibitors
- IP from the collaboration spun out to Piramed, founded by Parker, Waterfield & Workman – 2003
- Collaborative drug discovery between Piramed and ICR identified a candidate that was licensed to Genentech – GDC-0941 – Phase I started 2008
Three series of PI3K inhibitors identified by high throughput screening

4-Morpholino-2-phenylquinazolines
Hayakawa M Bioorg Med Chem 14 6847 2006

\[ p110\alpha IC_{50} = 1.3 \mu M \quad p110\alpha IC_{50} = 0.0020 \mu M \]

Imidazopyridines
Hayakawa M Bioorg Med Chem 15 403 2007
Hayakawa M Bioorg Med Chem 15 5837 2007

\[ p110\alpha IC_{50} = 0.67 \mu M \quad p110\alpha IC_{50} = 0.0028 \mu M \]

Pyridofuropyrimidines
Hayakawa M Bioorg Med Chem Lett 17 2438 2007

\[ p110\alpha IC_{50} = 1.4 \mu M \quad p110\alpha IC_{50} = 0.0036 \mu M \text{ PI-103} \]

Workman et al Cancer Res 70 2146-2157 2010
Properties of the clinical candidate GDC-0941

- IC$_{50}$ p110$\alpha$ 3nM
- IC$_{50}$ p110$\beta$ 33nM
- IC$_{50}$ p110$\delta$ 3nM
- IC$_{50}$ p110$\gamma$ 75nM
- >200 fold selective vs Class II, III and IV PI3K
- Highly selective in broad kinome screening
- Equiactive with wild type on both E545-K helical domain and H1047-R C-term kinase domain mutants of p110$\alpha$
- Competitive inhibitor with Ki for p110$\alpha$ 10nM
- EC$_{50}$ P-AKT Ser$^{473}$ in U87MG glioblastoma cells is 46nM
- GI$_{50}$ in U87MG glioblastoma cells is 0.95$\mu$M
- Good oral bioavailability
- Oral therapeutic activity in several human tumour xenograft animal models

Folkes et al J Med Chem 51 5522-32 08; Raynaud et al Mol Cancer Ther 8 1725-38 09; Workman et al Cancer Res 70 2146-57 2010
Activity of GDC-0941 in IGROV-1 ovarian cancer xenografts

- PTEN negative
- PIK3CA mutant
- Prolonged growth arrest
- Dose-dependent effects
- Biomarkers consistent
- Well tolerated

Raynaud et al Mol Cancer Therapeutics 8 1725-38 2009
GDC-0941: Clinical Activity #2 Ovarian cancer

- 49 y/o female with ovarian cancer; liver & peritoneal disease
  - PTEN negative by IHC
  - 5 prior chemotherapies; Dx 2004
  - 100 mg QD GDC-0941 with AUC ~6.7 μM.hr
  - Best Response-SD, continues on-study >61 days
  - FDG-PET: 30% decrease in mean SUV\textsubscript{max} end of C2

36% decrease SUV\textsubscript{max} in perihepatic disease

Baseline: SUV\textsubscript{max} = 10.7

End C2: SUV\textsubscript{max} = 6.8

CA125 Response Observed

Serum CA125 (IU/ml)

Study Day

ULN
**PI3 kinase inhibitors: From PI-103 to GDC-0941**

**GDC-0941 (PI-728)**

- **PI-103**
- **GDC-0941**

**Response of PTEN null U87MG glioblastoma xenograft**

- Solvent control p.o. daily
- ▲ 25mg/kg p.o. daily
- ▼ 50mg/kg p.o. daily
- ● 100mg/kg p.o. daily
- ● 150mg/kg p.o. daily

**Response of GIST (liver mets) patient assessed by FDG PET**

- **Baseline**
- **Cycle 2**

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*Genentech*  
*IN BUSINESS FOR LIFE*
Potential predictive biomarkers for PI3 kinase inhibitors

- ERBB2/HER2 overexpression/amplification
- PIK3CA mutation
- PTEN loss
- HER2/PTEN or PIK3CA/PTEN combinations especially sensitive
- Wild type KRAS (combine with MEK inhibitor for mutant cancers)
- Gene expression signature
- Note also: ‘Indirect’ effects on angiogenesis, host cells etc

Raynaud et al Mol Cancer Ther 8 1725-38 2009; Workman et al Cancer Res 70 2146-57 2010
PKB inhibitors

From fragments to leads to candidates
Structure-guided fragment elaboration

- Collaboration with Astex Therapeutics for fragment screening on PKB
- Multiple series progressed using crystallography to grow weakly active fragments to potent and PKB-selective compounds
- Orally active lead series developed
- IP licensed to AstraZeneca and candidates identified

McHardy et al J Med Chem 53 2239 2010
Caldwell et al J Med Chem 51 2147 2008
Donald et al J Med Chem 50, 2289 2007
Davies et al Curr Topics Med Chem 9, 1705 2009
Properties of the oral PKB inhibitor CCT129254

- IC\textsubscript{50} PKB 2 nM
- Selective in broad kinome screening with some activity at other AGC kinases
- EC\textsubscript{50} P-GSK3β in U87MG glioblastoma cells is 0.93 μM
- Good oral bioavailability
- Oral therapeutic activity in U87MG human tumour xenograft animal model

Systematic target assessment: canSAR

http://cansar.icr.ac.uk
canSAR
Integrated cancer-focused drug discovery resource

• Comprehensive data
  – >11M experimentally derived measurements
    Gene Expression data
    RNA interference data
    Chemical screening data
  – >560,000 bioactive compounds
  – >1000 cell lines
  – Annotated molecular targets representing entire human genome
    Model organism orthologues
  – Protein interaction networks (ROCK-BCFG)
  – 3D structures, binding sited
    >65,000 structures
    >10,000 ligands

• Internal and public data
• Web-based user friendly interface
• Public release summer 2010

http://cansar.icr.ac.uk

Bissan Al-Lazikani
80% of CGP targets have significant structural annotation
46% have their own structure or very close homologue solved
CGP targets are more druggable than average
Provides modelling and docking opportunities

http://cansar.icr.ac.uk  Bissan Al-Lazikani
Conclusions

• Successful drug discovery science is possible in the non-profit academic environment
  – Critical role in derisking projects for industry
  – Speed to patient benefit is the major driver
  – Builds on strong basic research, professional
  – Validated by multiple drugs in the clinic
  – Strong discovery pipeline and new target portfolio
  – Associated publications and training

• HTS and fragment-based approaches for hit generation
  – Many programmes benefiting from structural biology

• Medicinal chemistry optimization to probe compounds and drug candidates

• Collaboration with other academic groups, biotech and pharma partners to bring new agents to the clinic
  – Several different partnering and licensing models have been successful

• Developing relevant drugs with companion biomarkers

• Moving to personalized/stratified molecular cancer medicine
Cancer genomes to cancer drugs: Lessons learned

- Adopting perceived high risk targets early
- Employing a range of hit finding strategies
- Value of chemical tools and structural biology
- Importance of PK-PD-efficacy audit trail – no biomarker no project
- Continually bringing in new technologies
- Strong project management and portfolio review process
- Good interactions with CRT and ICR Enterprise Unit
- Working in partnership with biotech and pharma, as well as academia
- Moving quickly to proof of concept clinical trials and patient benefit
Future challenges and opportunities

- Defining all cancer genes, networks and key nodes
- Expanding the druggable cancer genome
- Developing relevant drugs with companion biomarkers
- Exploiting systems biology and computational tools – importance of informatics
- Implementing personalized or stratified molecular cancer medicine
- Dealing with the funding and commercial environment
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**CANCER RESEARCH UK**

**ICR**

**astex therapeutics**
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