DISCOVERING AND DEVELOPING NOVEL ANTICANCER BIOOTHERAPEUTICS: 
THE VIEW FROM CANCER RESEARCH UK

James Ritchie, Drug Development Scientist, Centre for Drug Development (CDD), Cancer Research UK
ELRIG: Research and Innovation 2016
23rd March 2016
Overview

• Scene setting:
  o CRUK
  o Challenges within the cancer drug development landscape
• The Cancer Research UK Centre for Drug Development
  o Capabilities
  o Partnership models in drug development
• Biotherapeutic drug development case studies
• Investing in biotherapeutic drug discovery
  o CRUK-MedImmune Alliance
And an intro to the challenges within cancer drug development landscape
Cancer Research UK (CRUK)

• Largest fundraising medical charity in the world
• Research spend of £430 million in 2014-2015
• Supports over 4000 academic researchers active in basic, translational and clinical research
• **Track record of success in drug discovery and development**
• Invests in infrastructure (cancer research centres) and training
• Provides information on cancer to patients, healthcare professionals and the public
• Work with government on policy initiatives around cancer treatment, prevention and scientific research
• Wholly own Cancer Research Technology (CRT) – CRUK’s commercialisation arm
Some Sobering Facts

• Over 150,000 people die of cancer in the UK every year
• Over 300,000 new cases of cancer are diagnosed every year in the UK
• Someone in the UK is told they have cancer every 2 minutes
• 1 in 2 of people in the UK will develop cancer
• It is predicted that the global incidence of cancer will double over the next 20 years

• Industry has been struggling with cost and attrition is endemic in Cancer R&D
Why the Struggle?

- Increasing pressure from payers (e.g. NHS in the UK, insurance companies in the US) on the price of medicines & health economic assessments increasingly required for reimbursement (e.g. by NICE in the UK)
- Key patents are expiring (the patent cliff)
- Challenges in the global economy

- Unacceptable failure rates in oncology clinical drug development due to lack of sufficient efficacy
Comparison of Attrition Rates

- 7% likelihood of approval on Phase I entry

Michael Hay et al., Nature Biotechnology 32, 40–51 (2014)

Today’s Science, Tomorrow’s Medicine
Outcome

• Proposals to redirect resources from late stage clinical development to deliver more early Phase studies
• Focus on new models to decrease costs and increase efficiency in drug discovery and development
• Calls for greater collaboration amongst all stakeholders (industry, academia, regulators, payers)
• Development of highly networked partnership models for delivery of sufficient numbers of studies

• Role for the non-commercial sector in supporting experimental medicine, working with industry to explore effects of drugs targeting novel mechanisms in the clinic
CRUK Centre for Drug Development

Capabilities & Strategy
Drug Development at Cancer Research UK

- CRUK Centre for Drug Development (CDD) based in London
- Manages preclinical development and sponsors Phase I and II trials of new anticancer agents (currently ~ 30 active projects)
- Small molecule therapeutics, antibodies, cell therapies, gene therapies, imaging agents
- Global partnerships with academia and industry
- Development function established in 1982
- Over 100 agents taken into early phase trials

CRUK Drug Development Infrastructure

- Fully integrated clinical operations function delivering ICH-GCP compliant trials
- Project & study management
- Quality and regulatory affairs
- Preclinical and medical sciences teams
- GMP manufacturing capabilities:
  - Small molecule formulation unit at Strathclyde University
  - Biotherapeutics Development Unit in Potters Bar (£18m investment, 2010)
- Trials conducted via a network of 18 world-class, UK-based Experimental Cancer Medicine Centres (ECMCs; http://www.ecmcnetwork.org.uk)
CDD Focus & Strategy

• Develop novel agents where expertise and/or resources to support further development are not available
  
  o Sourced globally from academic institutes, pharmaceutical and biotechnology companies

• Scientific focus on demonstrating proof of mechanism (target inhibition) and proof of principle (modulation of biology)

• Strategic focus on novelty (first in class) and scientific impact

• Specific Clinical Development Partnerships (CDP) initiative taking forward agents not being progressed by industry

‘Sweet spot’ around translation from preclinical development into FTIH Phase I/II trials
Clinical Development Partnerships (CDP): Business Model

- A joint initiative launched by CRUK in collaboration with its development and commercialisation company Cancer Research Technology Ltd. (CRT)
- Combines CRT’s commercial know-how and the CDD operational capabilities, translational and clinical expertise to bring promising anti-cancer agents, that companies are unable to develop, into clinical trials
  - Targeted at leading pharmaceutical and biotechnology companies
  - Provides a route for companies to develop:
    - Non-core assets (larger Pharma)
    - Core assets where resource or expertise is lacking (small Pharma/Biotech)
  - Provides early clinical development at no up-front cost to the company
  - Studies are performed through the ECMC Network
  - Projects are undertaken on a shared-risk reward basis
## Clinical Development Partnerships (CDP): Business Deals

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TARGET/TECHNOLOGY</th>
<th>COMPANY</th>
<th>INDICATIONS</th>
<th>COMMERCIAL STATUS</th>
<th>DEVELOPMENT STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EXPLORE</td>
<td>PRECLINICAL</td>
</tr>
<tr>
<td>NMI-900</td>
<td>Aurora Kinase B</td>
<td>Nemucore (GSK)</td>
<td>Advanced solid tumours</td>
<td>PARTNERED</td>
<td></td>
</tr>
<tr>
<td>IMA950</td>
<td>Multi-peptide vaccine</td>
<td>immatics biotechnologies</td>
<td>Glioblastoma multiforme</td>
<td>OPTION EXERCISED</td>
<td></td>
</tr>
<tr>
<td>AT13148</td>
<td>Multi AGC-kinase</td>
<td>Astex Therapeutics</td>
<td>Advanced solid tumours</td>
<td>OPTION EXERCISED</td>
<td></td>
</tr>
<tr>
<td>AZD0424</td>
<td>Src</td>
<td>AstraZeneca</td>
<td>Advanced solid tumours</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>AZD3965</td>
<td>MCT-1</td>
<td>AstraZeneca</td>
<td>Solid tumours; Lymphoma</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>DI-B4</td>
<td>CD19 (mAb)</td>
<td>Merck KGaA</td>
<td>Leukaemia; Lymphoma</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>AMG319</td>
<td>PI3K delta</td>
<td>Amgen</td>
<td>Solid tumours</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>BI-1206</td>
<td>CD32b (mAb)</td>
<td>BioInvent International</td>
<td>non-Hodgkin lymphoma</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>AZD2098</td>
<td>CCR4</td>
<td>AstraZeneca</td>
<td>Renal cancer</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>AST-VAC2</td>
<td>Telomerase (iPSC vaccine)</td>
<td>Asterias Biotherapeutics</td>
<td>Lung cancer</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>264RAD</td>
<td>Integrin alpha V beta 6 (mAb)</td>
<td>MedImmune</td>
<td>Pancreatic cancer</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>ATN658</td>
<td>uPAR (mAb)</td>
<td>Monopar Therapeutics</td>
<td>Advanced solid tumours</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
<tr>
<td>MEDI3039</td>
<td>TRAILR2 (recombinant protein)</td>
<td>MedImmune</td>
<td>Advanced solid tumours</td>
<td>UNDER OPTION</td>
<td></td>
</tr>
</tbody>
</table>

As of December 2015

---

*Today’s Science, Tomorrow’s Medicine*
Clinical Development Partnerships (CDP): Completed Programmes

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TARGET/TECHNOLOGY</th>
<th>COMPANY</th>
<th>INDICATIONS</th>
<th>COMMERCIAL STATUS</th>
<th>DEVELOPMENT STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMI-900</td>
<td>Aurora Kinase B</td>
<td>Nemucore (GSK)</td>
<td>Advanced solid tumours</td>
<td>PARTNERED</td>
<td>● ● ● ● ● ● ● ● ● ● ● ●</td>
</tr>
<tr>
<td>IMA950</td>
<td>Multi-peptide vaccine</td>
<td>immatics biotechnologies</td>
<td>Glioblastoma multiforme</td>
<td>OPTION EXERCISED</td>
<td>● ● ● ● ● ● ● ● ● ● ● ●</td>
</tr>
<tr>
<td>AT13148</td>
<td>Multi AGC-kinase</td>
<td>Astex Therapeutics</td>
<td>Advanced solid tumours</td>
<td>OPTION EXERCISED</td>
<td>● ● ● ● ● ● ● ● ● ● ● ●</td>
</tr>
</tbody>
</table>

- **IMA950 multipeptide vaccine**: immunogenic success criteria exceeded in Phase I and immatics entered into license in April 2014 and is currently planning Phase II trial.
- **GSK1070916A (NMI-900) small molecule Aurora Kinase B/C inhibitor**: tumour PD biomarker success criteria met in Phase I and success payment received by CR-UK; GSK opted not to take back into development and CRT successfully licensed agent to Nemucore.
- **AT13148 small molecule Rho kinase inhibitor**: Option exercised Feb 2015 during on-going trial.
Biotherapeutic Case Studies

Developing vaccines to cell therapies
Therapeutic Cancer Vaccine Approach

- Aims to elicit anti-tumour activity by stimulating the immune system to attack tumour cells expressing tumour-selective antigens or antigens over-expressed by tumour cells

- Re-expressed oncofoetal antigens (CEA, AFP)
- Oncogenic viral antigens (EBV)
- Cancer-testis antigens (NY-ESO-1, MAGE)
- Post-translationally modified proteins (MUC1)
- Mutant proteins (fibronectin, TGF-βRII)
- Lineage restricted antigens (PSA, gp100)
- Over-expressed antigens (telomerase, mesothelin, FRα)

**FAILURE**

Immunosuppression, suboptimal adjuvants, loss of single antigen expression, antigens not presented in the right context
IMA950

- Novel GBM specific therapeutic vaccine containing 11 tumour-associated peptides (TUMAPs), identified on human leukocyte antigen (HLA) surface receptors in primary human GBM tissue
- Designed to tackle issues around antigen expression and context

IMA950 ready to enter clinical development but no resources to fund a company-sponsored clinical trial
IMA950 Clinical Trial

- Phase I safety and immunogenicity study of IMA950 plus standard chemo-radiotherapy and adjuvant temozolamide in patients with newly diagnosed glioblastoma
- Eleven intradermal injections plus adjuvant GM-CSF over 24 weeks using two cohorts with different scheduling relative to SoC
- 40 immune evaluable patients recruited
  - 36/40 TUMAP (90%) responders
  - 20/40 multi-TUMAP (50%) responders

**Study success criteria exceeded**

Licence taken by Immatics

BUT further optimisation necessary
# AST-VAC1 Autologous Dendritic Cells Pulsed with Telomerase

- First generation immunotherapy
- AST-VAC1 is Safe and Stimulates anti-Telomerase Immune Responses
- Biomarker Modulation and Signals of Potential Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Phase 1 Prostate Cancer Duke</th>
<th>Phase 2 Acute Myelogenous Leukemia Multi Center Khoury ASH 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td># Treated Patients</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Patients Immunized Against hTERT</td>
<td>95%</td>
<td>55%</td>
</tr>
<tr>
<td>Laboratory &amp; Clinical Impact</td>
<td>• Highly Significant Increase in PSA Doubling Times</td>
<td>• Significant Increase in 12 Month DFS (81%) in High Risk Group (N=11) Compared to Published Historical Controls (45%)</td>
</tr>
</tbody>
</table>

- Up to 32 Doses Administered per Patient
- Long-term Follow-up Data Being Collected
Mechanism of Action: Antigen Presentation

- Migrate to lymph node to present antigen
- Activated in inflammatory environment
- Prime T cells to recognize antigen
CRUK/Asterias CDP Collaboration: AST-VAC2

• Dendritic cells derived from hESCs using cytokine-driven maturation process
• Pulsed with hTERT mRNA

**AST-VAC1 Autologous Immunotherapy Challenges**

• Patient specific production
• Number of doses can be limited
• Availability delayed until product released
• Starting material variability can lead to failures in production or potency
• Difficult quality control
• Higher cost of goods

**AST-VAC2 Improvements**

• Allogeneic immunotherapy
• Adjuvant effects possible
• Limitless amounts of cells ➔ batch production enables “on demand” availability
• Uniform potency
• Standardized quality control
• Lower cost of goods
• Cryopreserved and irradiated (Safety)
• Stimulates naïve antigen restricted T-cells with only a single MHC match (Broad Patient Access)
• Match for approximately 75% of European descent with 2 hESC lines
Anti-cancer Antibodies: IgE First in Class

Development of MOv18 IgE: An Academic Collaboration

<table>
<thead>
<tr>
<th>Ab Class</th>
<th>Serum ½ Life</th>
<th>Tissue ½ Life</th>
<th>Binding Affinity (Kd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>21-24 days</td>
<td>2-3 days</td>
<td>Typically low (10^-7 M) for most FcγRs</td>
</tr>
<tr>
<td>IgE</td>
<td>1.5 days</td>
<td>14 days</td>
<td>High (10^-10 M) for FcεR1</td>
</tr>
</tbody>
</table>

MOv18 is a first-in-class Anti-folate receptor alpha IgE
Efficacy of rMOv18 IgE v rMOv18 IgG in an Immunocompetent WAG Syngeneic Model

A  No. Metastases/cm²

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>PBS</th>
<th>IgG</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lung metastases/cm²</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

B  % Tumour Occupancy

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>PBS</th>
<th>IgG</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Tumour Occupancy</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

C  

- First in world GMP complaint IgE manufacture at CRUK Biotherapeutics Development Unit
- Ready for clinical entry
The CRUK-MedImmune Alliance Laboratory

First in class therapeutic antibodies via academic/industry collaboration
CRUK-MedImmune Biotherapeutic Discovery Alliance

Mission:

- To maximise cancer patient benefit
- To run a collaborative research laboratory focussed on antibody discovery using MedImmune’s proprietary platform technologies, staffed predominantly by CRUK scientists
- To actively engage the oncology research community to elicit proposals for novel biological targets amenable to antibody discovery programmes
- To partner closely with investigators from target identification and profiling through to all stages of drug discovery, bringing together their expertise with the Alliance’s technological capability
MedImmune and CRUK: Core Competencies and Goals

MedImmune

- Biologics Drug Discovery Expertise
- Staff training and knowhow
- Phage libraries and other antibody platforms
- Project specific funding

CRUK and academia

- Novel Targets from PIs
- Biology and oncology expertise
- Disease mechanisms
- Disease Models
- Operational funding and staff

Alliance

- First in Class innovative biologics to oncology targets
- Tools to support oncology research
- Joint IP and publications
CRUK-MedImmune Alliance: Scope, Governance & IP

Alliance activities

Target ID ➔ Lead Identification ➔ Pre-Clinical Proof of Concept ➔ Optimized Therapeutic ➔ Development

Governance:
– Target Selection Committee; Joint Management Committee; Joint Steering Committee: 50/50 representation

IP and exploitation:
– Joint ownership of newly created IP; Academic research rights retained for PIs
– MI has two options
  • Proof of concept in one or more in vivo model
  • Candidate nomination
– Hand back to CRT if MI does not develop
SUMMARY

• Cancer Research UK’s vision is to bring forward the day when all cancers are cured

• Emphasis on delivery through partnerships and collaboration across sectors and across scientific disciplines

• Fuel our ambition is to accelerate progress and see three-quarters of people surviving the disease within 20 years

• Support our key strategic focus of ‘discovering and developing new therapeutics, surgery and radiotherapy treatments, including increased investment in biological therapies’