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The Imperial Drug Discovery Centre; enabling translation of academic projects towards commercial reality

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http://www1.imperial.ac.uk/medicine/about/institutes/drugdiscoverycentre/

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Outline

- What is a commercial asset ?
- The growth of academic drug discovery
- An academic virtual biotech
- Challenges

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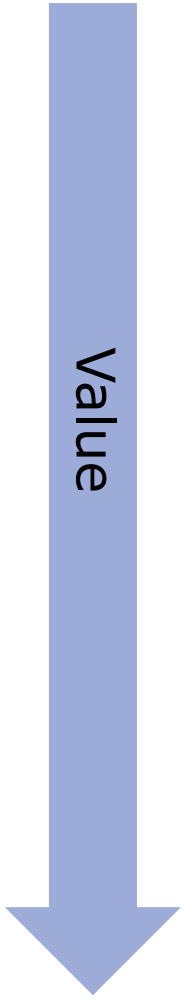
Commercial assets

1. Candidate with human PoC or Phase I safety (IP)
2. Pre- Clinical Candidate with required safety/ toxicology/ pharmacokinetics & efficacy profile (IP)
3. Candidate molecule with defined optimised target profile:

- Optimised drug like molecule- lipinski rule of 5
- Synthetic route with Low COG
- Required PK for route/delivery
- Required level of efficacy (human/ animal models)
- Secure IP
- Defined 'validated' target – OR phenotypic effect?

Documented, robust, reproducible data sets



~Likely to take >2-5y from Target identification

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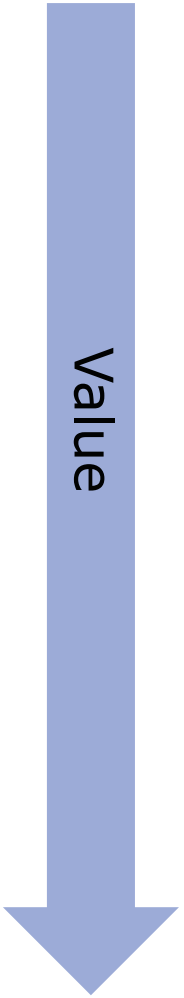
Commercial assets

4. Lead series (+/- backup)
   - Non-optimised drug like molecules
   - Required PK for route/delivery
   - Resonable efficacy (human/ animal models)
   - IP secured or potential
   - target hypothesis OR phenotypic effect?

~2-3 years from Target identification

5. Novel target or effect
   - Linked directly to disease
   - +/- Chemical start point
   - +/- Structural data set



Most academic institutions do not have capabilities or expertise to achieve this alone

Earlier stage projects more likely to gain collaborative or risk-share agreements than licensing deals

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Early phase pharma research in decline

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Pfizer to close UK research site

Drug maker Pfizer is to close its research and development (R&D) facility in Kent, which employs 2,400 people.

The move has raised concerns that the UK is losing highly-skilled jobs and about the private sector's ability to absorb cuts in the public sector.

The Unite union said the roles were "exactly the sort of jobs we need to keep in this country".

Pfizer described the facilities in Sandwich as "excellent"

Business Secretary Vince Cable said the firm's decision was not about the UK as a location for pharmaceutical research.

Pfizer said the majority of staff would be made redundant over the next two years.

But it hopes to transfer several hundred positions to other sites or other companies doing work for Pfizer.

Related Stories

Pfizer plant closure 'body blow'

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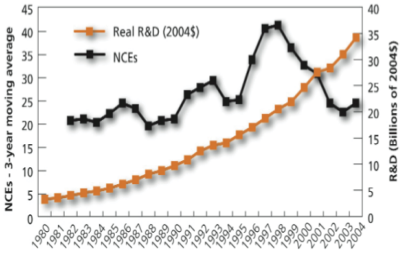
Pharma's recent history…..

- High Throughput science
  - Process displacing the one which made pharma profitable ie phenotypic/pharmacological effect translating to clinical efficacy
- Predicted attrition higher with novel targets
  - Re-focus of efforts to lower risk areas (me-toos, pre-validated targets)
- Single target modulation failed to translate into efficacy
  - inadequate understanding of complex disease
- Dismantling early research capabilities



Source: Tufts CSDD Approved NCE Database; PhRMA

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The Future

Short term

- reduced costs & sustainable portfolio

Longer term

- Fewer more consolidated Large Pharma companies
- Search to in-license the ever-decreasing number of advanced assets
- Limited supply of validated targets & quality candidates
- Focus on low risk assets
- Reduced supply of innovative drugs tackling real un-met need

- Research limited by support for current early projects
- VC/ Biotech funding limited to short-term advanced projects
- Research Council support for early drug discovery very limited despite translational agendas

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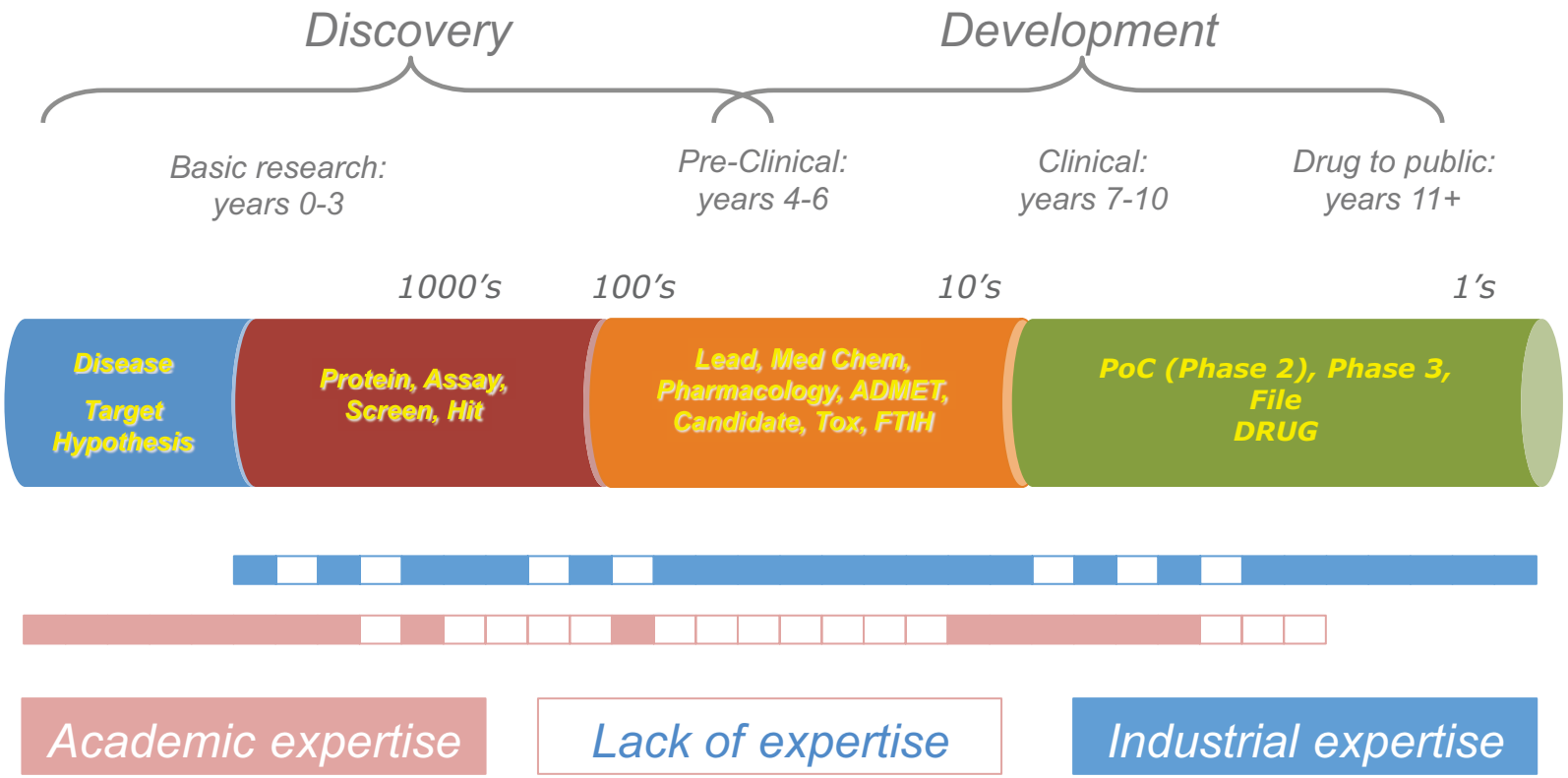
Drug Discovery takes 10 years +



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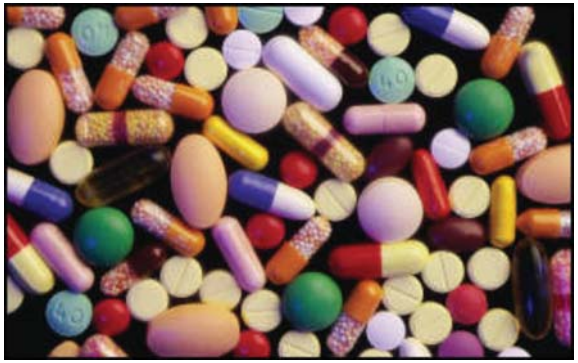
Academic contribution

Academia can help to address the current high-rate of compound attrition

- In depth disease and pathway knowledge across therapeutic areas
- Access to novel technologies
- Clinical expertise
- An innovative environment



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Multi-disciplinary 'Academic' Drug Discovery groups (UK)

University based:

- Dundee Drug Discovery Unit/ Scottish Hit Discovery Facility
- Imperial College London Drug Discovery Centre

Other:

- MRCT Centre for Therapeutics Discovery (Mill Hill London)
- Institute of Cancer Research (Sutton, Royal Marsden London)
- CRUK / Cancer Research Technology (The Wolfson Institute, UCL, London, The Beatson Institute, Glasgow, The Paterson Institute, Manchester)

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Mini-pharma models

Multidisciplinary models including:

- Target validation using SiRNA, KO systems, biological tools, pharmacological tools
- High Throughput Assay development, screening (real/ virtual)
- Compound libraries (purchased, created)
- Synthetic chemistry (tools, novel compounds)
- Structural biology (protein target structures)
- DMPK
- Project management

- ➢ Pharma R&D ‘closed’,
- ➢ skills and tools required ‘in-house’

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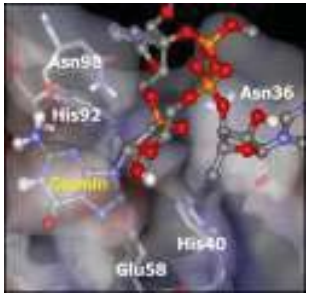
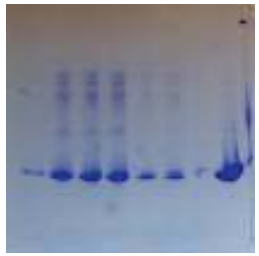
Other linked initiative examples

- Structural Genomics Consortium (Oxford)
  - High throughput crystallography and protein structures
  - Public-private partnership (industry, research councils, charities)
- Kinase Consortium (Dundee)
  - Human Kinase screens
  - Public-private partnership (industry, research councils)
- Strathclyde Innovations in Drug Research
  - Drug Discovery Portal- In silico screening
  - Natural product library access
  - Scottish Universities Life Science Alliance (SULSA)





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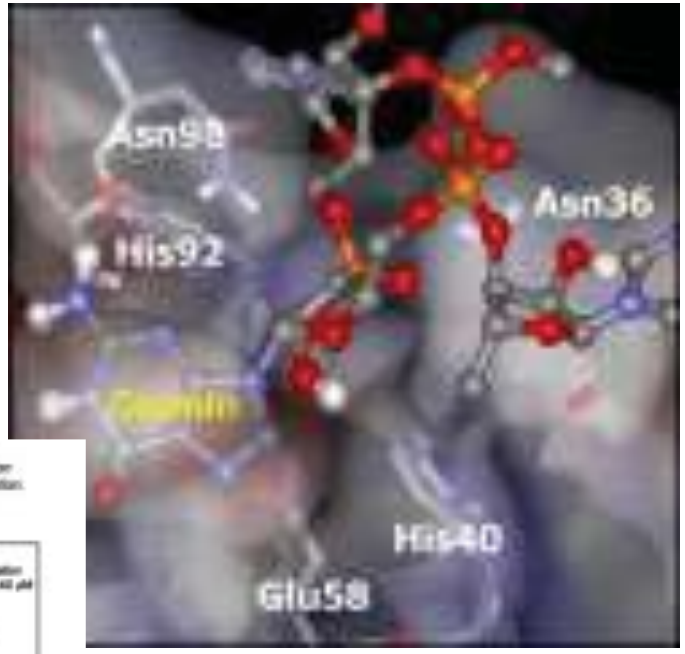
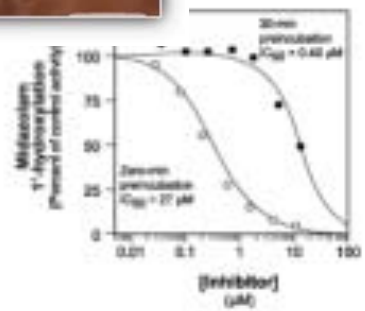
The virtual academic biotech model





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Virtual academic biotech model (Imperial College)

- Pharma R&D ‘still semi-closed’ – opening doors slowly!
- Expertise, skills and capabilities are now available from extensive world-wide array of Contract Research Organisations (CROs)
- Requires multidisciplinary strategic expertise in-house rather than expensive lab capabilities
- Project and outsourcing management are key
- Efficient-flexible model

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Imperial Drug Discovery Centre 'Virtual model'

A flexible, cost-effective "academic virtual biotech"

- Infrastructure: small assay development/screening lab and compound library with supporting chemoinformatic inventory.
- Establishing partnerships with external companies/CROs for flexible compound supply and DMPK.

A core group of scientists to support drug discovery

- Medicinal Chemistry, Molecular Modeling, Pharmacology, Assay Development, Compound Screening, DMPK and "industry-like" project management.

Projects sourced from Imperial's ~2,000+ basic and clinical researchers

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Outputs

The DDC has expertise to

- Create small molecule starting points
- Develop target biology by identifying molecular tools
- Develop robust bioassays to test drug candidates
- Create candidate molecules

We create “Composition of Matter” patents

- the starting point for Industrial Drug Development campaigns

We develop new approaches to drug discovery

- To shorten the 10-15 year timeframe from the bench to the clinic
- Tackle the hard problems - no “low hanging fruit” left
- Create the next generation of drugs

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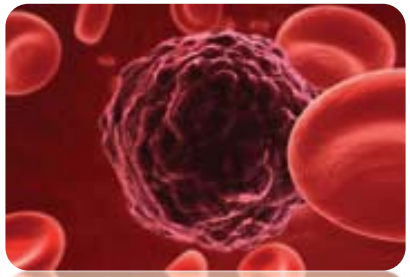
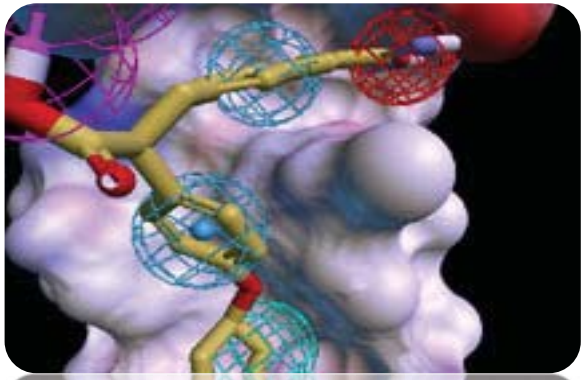
DDC translates academic research towards the clinic





Interesting biology

Drug Candidate

Medicine

Identify novel approaches from academic disease and pathway knowledge

Apply Industry drug discovery expertise and specialist CRO services to achieve quality candidates

Define novel candidate molecules for clinical validation/ licencing etc

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Contract studies- engaging expertise as required

- Synthetic chemistry
- Peptide & protein synthesis
- DMPK ~ *in vitro* and *in vivo*
- Receptor/ enzyme selectivity screens
- HTS

A cost-effective and efficient approach which enables academics to access industry expertise and capabilities

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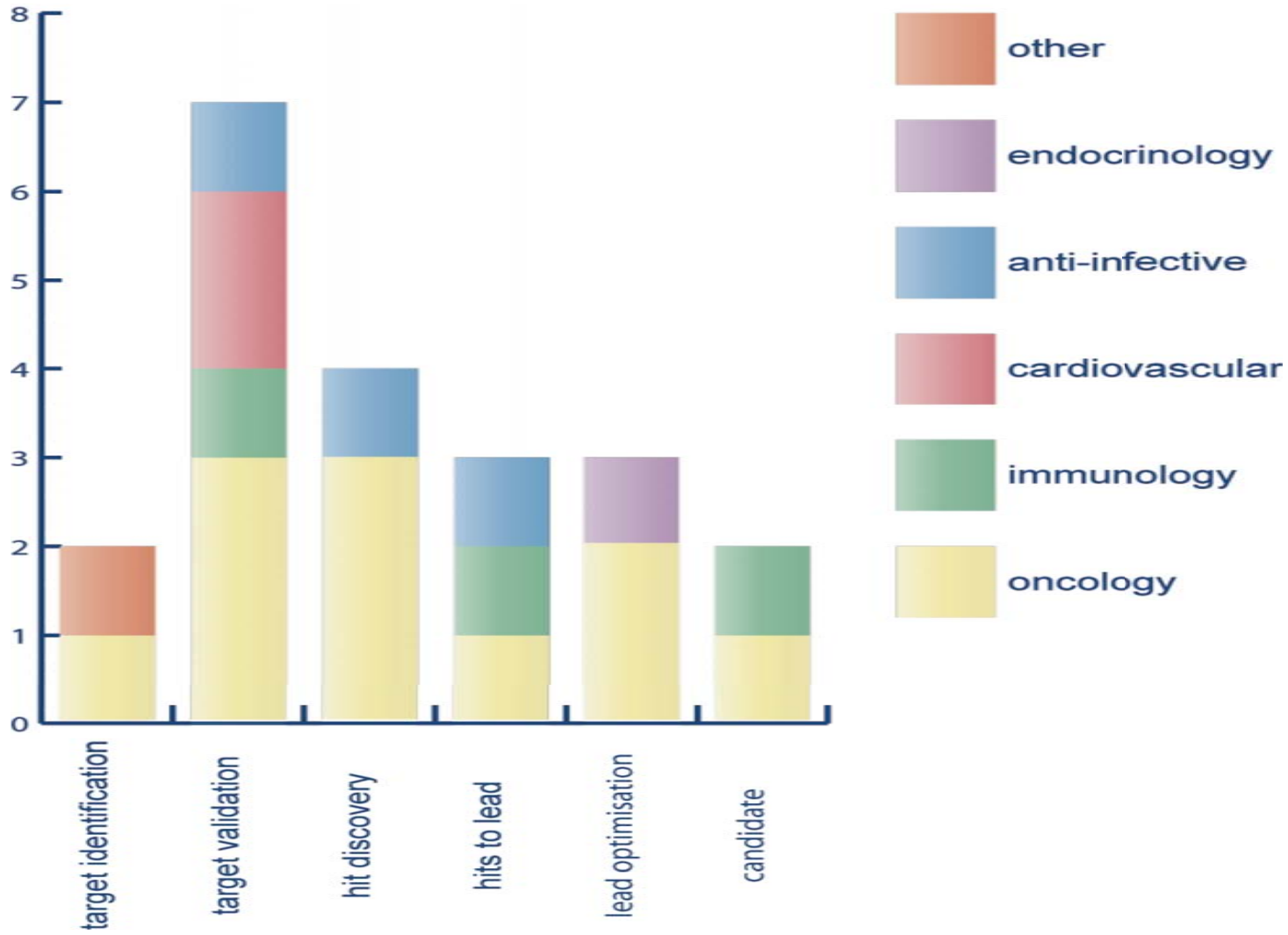
DDC Portfolio by phase Jan 2011



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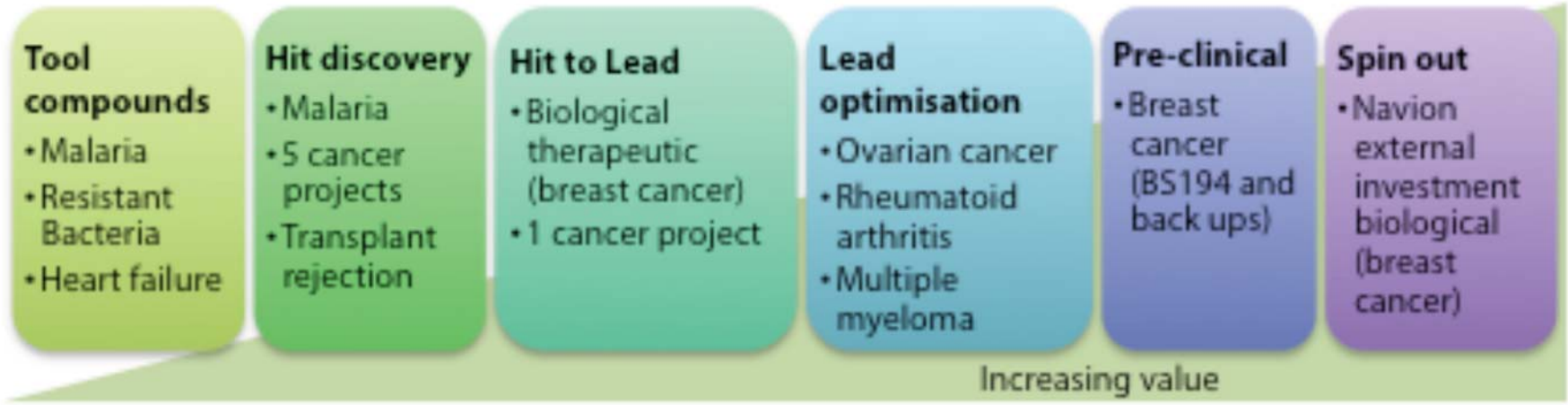
DDC delivery so far



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Oncology portfolio

Therapeutic target	Project Status	Patent status
Breast Cancer	Pre-clinical candidate	Composition of matter patent filed
Metastatic breast cancer	Human cancer cell proliferation inhibiting poly and monoclonal antibodies identified	Patent filed
Multiple myeloma	Lead series of peptides with anti-proliferative activity in human myeloma cell lines	Patents filed
Resistant ovarian cancer	Hit/lead series identified which restore platinum resistance in human ovarian cancer lines	Patents underway
Solid tumours	lead series identified	Composition of matter patent filed

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Non-oncology portfolio

Therapeutic target	Project Status	Patent status
Malaria	Novel *p.falciparum* target identified Hit compounds being optimised	Patents underway
Rheumatoid arthritis	Lead series with activity in human RA synovial model and mouse collagen models	Composition of matter patent filed
Transplantation	Target validation with tool compounds underway	Patents underway
Heart failure	Genetically validated target Assay development and screen underway	
Inflammation	Range of novel anti-inflammatory approaches under investigation	

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Key issues to address in the academic environment

- Assay development & screening
- Data Integrity
- Medicinal chemistry
- Project management

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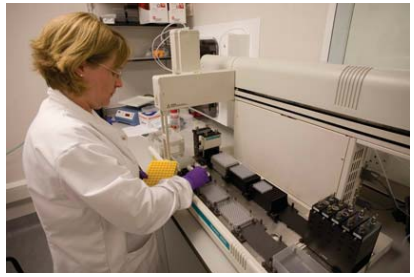
1. Assay Development and Screening

- HTS is the dominant paradigm to identify chemical start points for novel targets
- Academic screening centres are now being established worldwide, such as CRT, CR-UK, MRCT, Scottish Hit Facility, NIH roadmap, EuroScreen etc
- Expensive and skilled activity which requires ‘industrial mindset’
- Centralised not-for-profit facilities accessible to UK academia would be most cost-efficient



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Imperial's approach

Imperial will not run HTS in-house

Assay development group is:

- adapting output of academic experiments into format for screening
- designing /developing robust, reproducible assays for
  - contracted out screening
  - testing of compound sets

Our aim is to find hits/leads using:

- Published compounds/ literature searches
- Virtual screening based upon available structural target or ligand data
- Small-scale screening of focused compound sets e.g. kinases

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2. Data Integrity

- Industry/VCs/investors do not ‘trust’ academic data
  - Data not ‘robust’ and reproducible enough
  - Essential to fully document experimental data
  - Limited access to database systems
    - maintain compound collections & integrate data analysis
- DDC has instituted platform-independant
  - eLab Notebook system
  - Compound registration system and Compound library

3. Medicinal Chemistry

Very limited Medicinal Chemistry expertise and capability in academia

- Medicinal Chemistry is an industry-acquired skill
- Hits from screens are not candidates!

Medicinal Chemistry expertise is crucial to

- unravel SAR,
- design compounds and to
- drive the synthetic chemistry for lead optimisation programs and tool molecules
  - Need Medicinal chemistry expertise to drive strategy
  - Use academic or CRO synthetic capabilities

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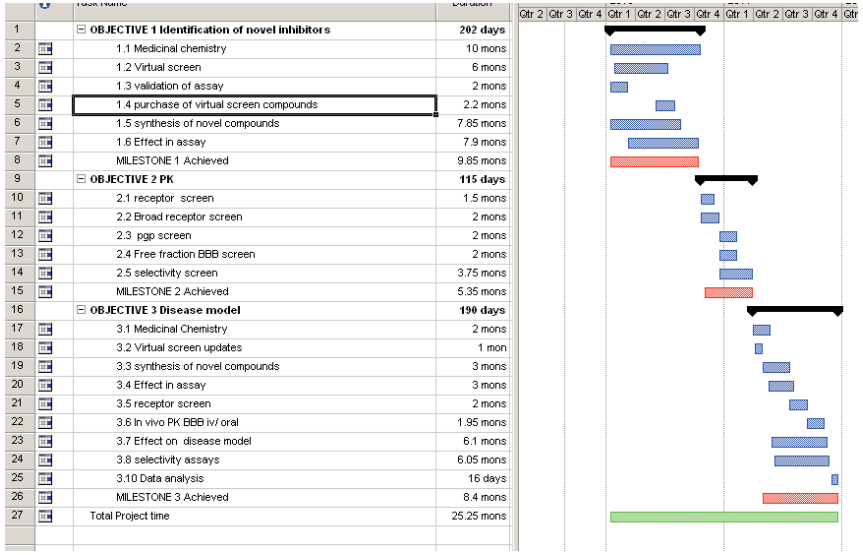
4. Project Management

- Challenging in academia but hugely valuable
- Addressing timelines and milestones has to be done carefully
- Project plans and targets enable efficient decision making
- A requirement for Translational grant schemes i.e. MRC DPFS/ Wellcome Seed Fund/ CRUK DC funding



		Duration
1	**OBJECTIVE 1 Identification of novel inhibitors**	**202 days**
2	1.1 Medicinal chemistry	10 mons
3	1.2 Virtual screen	6 mons
4	1.3 validation of assay	2 mons
5	1.4 purchase of virtual screen compounds	2.2 mons
6	1.5 synthesis of novel compounds	7.85 mons
7	1.6 Effect in assay	7.9 mons
8	MILESTONE 1 Achieved	9.85 mons
9	**OBJECTIVE 2 PK**	**115 days**
10	2.1 receptor screen	1.5 mons
11	2.2 Broad receptor screen	2 mons
12	2.3 pgp screen	2 mons
13	2.4 Free fraction BBB screen	2 mons
14	2.5 selectivity screen	3.75 mons
15	MILESTONE 2 Achieved	5.35 mons
16	**OBJECTIVE 3 Disease model**	**190 days**
17	3.1 Medicinal Chemistry	2 mons
18	3.2 Virtual screen updates	1 mon
19	3.3 synthesis of novel compounds	3 mons
20	3.4 Effect in assay	3 mons
21	3.5 receptor screen	2 mons
22	3.6 In vivo PK BBB iv/ oral	1.95 mons
23	3.7 Effect on disease model	6.1 mons
24	3.8 selectivity assays	6.05 mons
25	3.10 Data analysis	16 days
26	MILESTONE 3 Achieved	8.4 mons
27	Total Project time	25.25 mons

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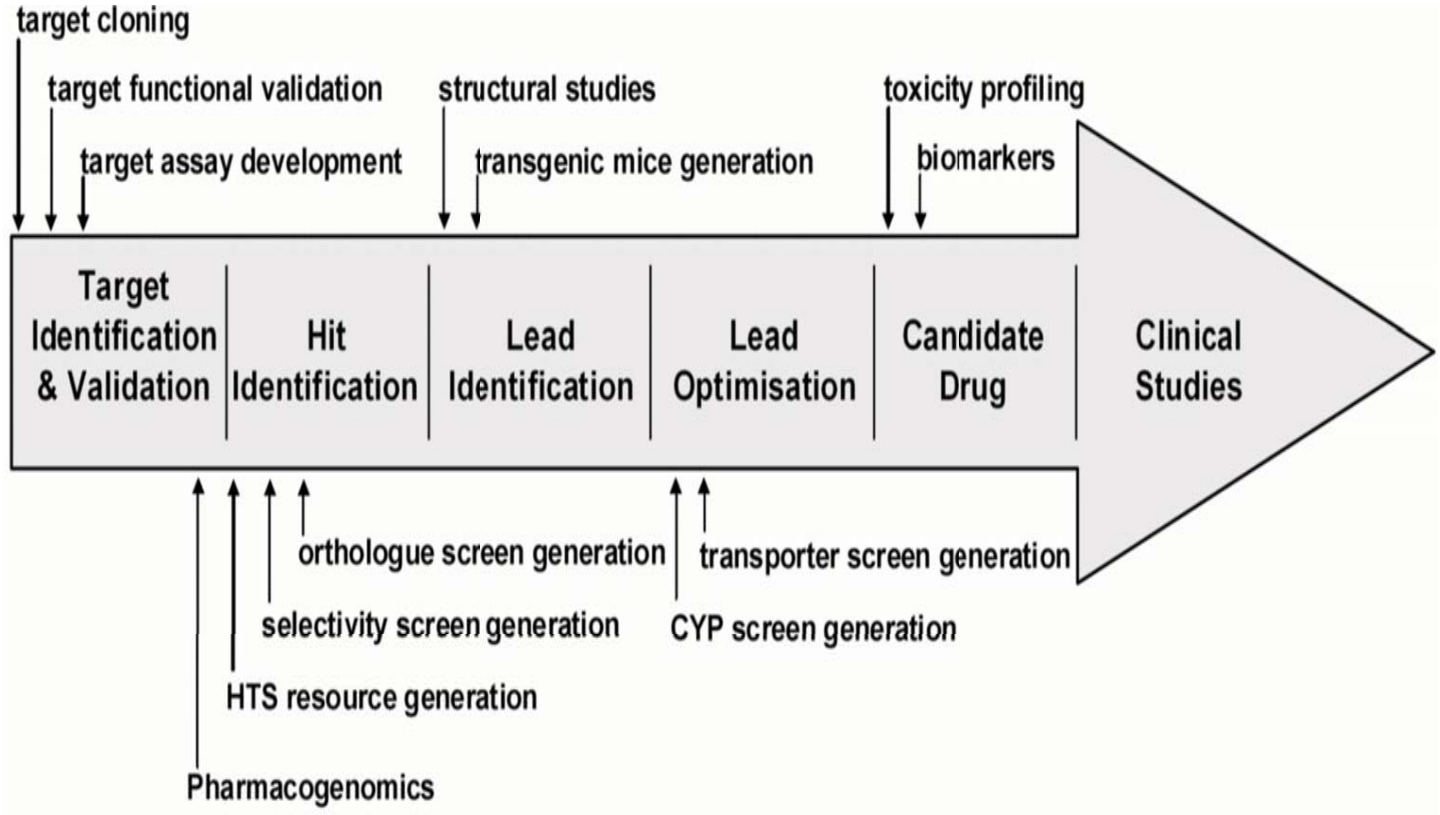
Challenging traditional pharma process



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Learn from past success

- phenotypic assays linked to clinical effect
- In-depth disease understanding
- Traditional medicinal chemistry
- Linked directly to the clinic (early clinical validation)

and

- implement new tools of genetics, genomics, molecular biology, high throughput technologies (biology and chemistry) as appropriate
- to define populations, support target validation, understand mechanisms etc

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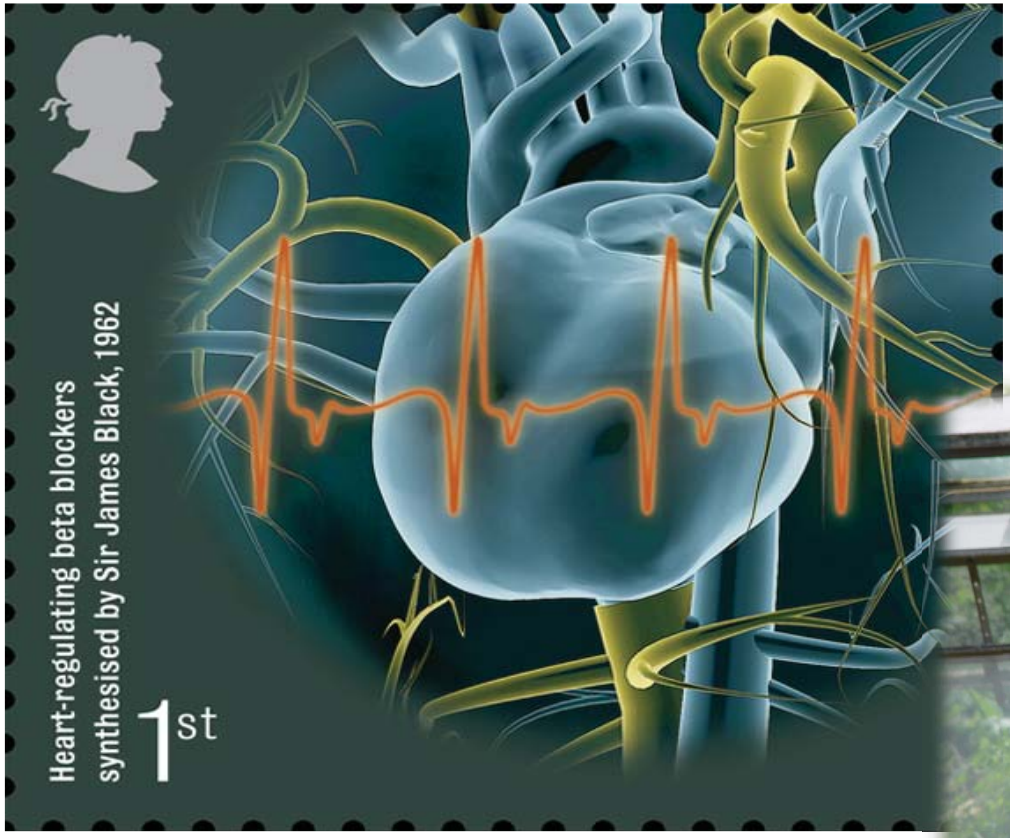
Sir James Black: A first class scientist



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The future

Creative collaborations are key to the progression of academic-industry projects which achieve industry quality robust clinical candidates

Must involve:

- Sharing of expertise & capabilities
- Funding
- Approaches to large and small market un-met need
- Public-Private partnerships to fund early discovery

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Challenges

- Drug discovery is multi-disciplinary and making it work in Traditional Departmentalized University structures is difficult
- Access to large chemical libraries
- Need to publish must be respected
- Academic v translational role debate

- Pharma want to pay for only ‘de-risked’ assets
- Timescale to licencing from Target Identification ~5+ minimum
- Academic funding schemes not ideal for drug discovery

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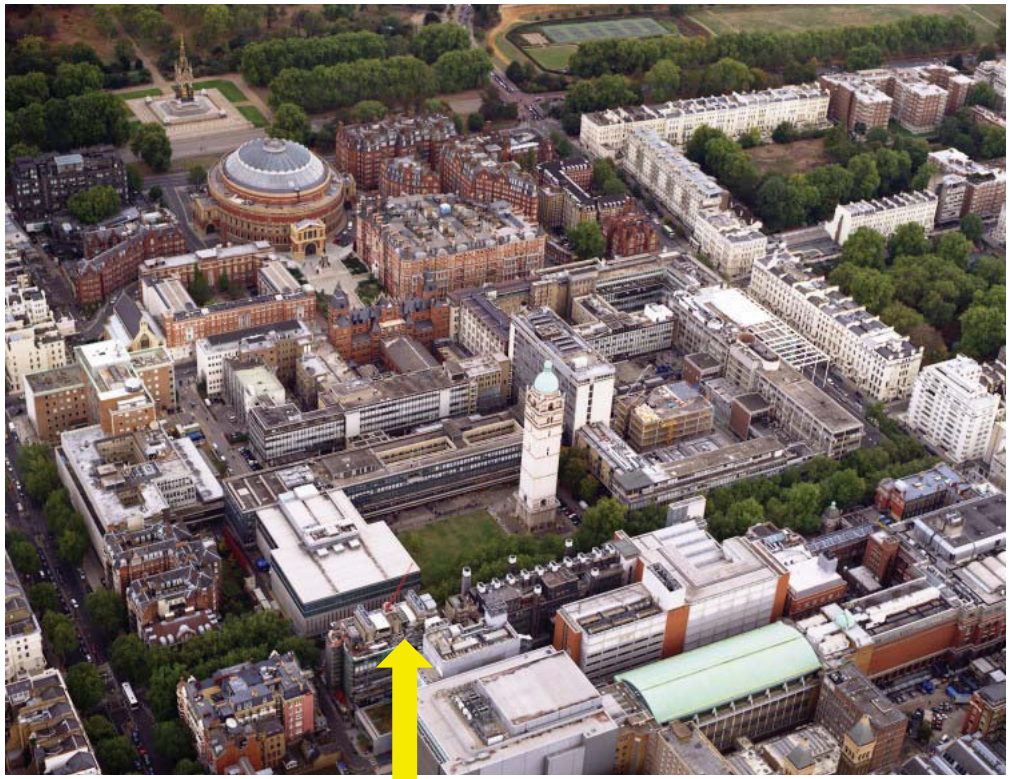

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