Anti-cancer drug discovery: from bench to bedside

Christian BAILLY, Ph.D.
christian.bailly@pierre-fabre.com

Pierre Fabre CDMO

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"The whole process from ideas to drugs"
Drug Discovery & Development

Drug Discovery

- Biology
- Target selection
- Screening
- Hits
- Lead optimisation
- Extensive Pharmacol.
- Preclinical Dev. Tox.

Early Development

- Phase I trials
- Phase II trials
- Phase III trials
- Registration
- Post-launch Activities

F.i.M.

Clinical Development

- 9-16 years
- cost $~1 billion per successful product

A long, difficult, multidisciplinary and expensive process

Pharmaceutical R&D
High risk, high costs
Target selection and validation
- large panel of biochemical, biological assays
- establish the role of a target in the disease
- addressing the cellular pathway
- and the physiopathology

Screening, hit & Lead compounds
- target-based assays and HTS
- compounds management & selection
- extensive chemistry, SAR
- use of in silico approaches
- ADMET properties
- drug design, back up series
Pharmacology
- Mode of action, target modulation
- in vitro, in vivo activities
- ADMET profile
- Proof of Concept in animal
- Efficacy studies
- drug combinations
- PK/PD, metabolism

Preclinical Development
- Batch synthesis, (salts)
- Formulation, stability
- Toxicology studies: safety profile
- g/kg GMP synthesis, scale up
- complete chemical profile
+ dossiers
- Large panels of patient-derived tumor models (in vitro and in vivo) representing the heterogeneity of the disease
- Extensive data on the characteristics of these tumor models
- Orthotopic models, metastasizing models, imaging models

Translational Research

- Large panels of tumor models (in vitro and in vivo) representing the heterogeneity of the disease
- Corresponding tumor tissue bank
- Genetically engineered models (inducible knock out and knock in models, isogenic models)

- Homogeneous, standardized in vitro tumor models, naturally or genetically engineered with target over or under expression for screening (isogenic models)
- Corresponding homogeneous, standardized in vivo tumor models, natural or genetically engineered, with target over or under expression for pharmacodynamic optimization
- Models for pharmacokinetic/pharmacodynamic correlation studies in different species (mouse, rat and/or non-rodent species)
- Models for evaluation of side effects (toxicology) in correspondence to pharmacodynamic effects
TARGET SELECTION:
Scientific, Medical, Economical, & Strategic Considerations

Picking the right target is key... but confirmed only 10 years later
- by isolating active ingredients from traditional remedies

- by random screening of chemical libraries, including Nat. Prod.

- by rational design: based on understanding the metabolic pathways related to a disease state or pathogen, and manipulating these pathways using chemistry, mol./cell. biology and biochemistry

- by repositioning

- by serendipity…
Serendipitous Drug Discoveries

How an accidental discovery paved the way for the treatment of complicated infantile haemangiomas
A revolution in the management of infantile haemangiomas.
Drug screening & design

- **High throughput screening**: compound libraries, multi-well plates (96, 384, 1536), robotics

- **Knowledge-based rational design**: computer modeling, structural analysis (NMR, X-ray crystal, etc), chemoinformatics…

- Hit optimisation, lead selection, drug candidate
  - iterative cycles of chemistry and biology (cpd MoA, potency, SAR, selectivity, stability…)
  - Physicochemical properties (solubility, purity, complexity…)
  - ADME, DMPK, imaging, in vivo profiling…
  - initial safety assessment (preliminary Tox, predictive Tox)
  - innovation (I.P., patents): breakthroughs target/NCE, 2nd generation, formulation, etc…
  - potential market, time to market (RoI)

  - *Molecular attrition: From « >100,000 » cpds to « 3-5 » pre-candidate*
  - *A major challenge to combine all desired properties into one molecule*
  - *… back-up and follow up programs*
Rational Design: ALK inhibitors

- Search for "oncogenic drivers" and development of targeted therapies.

- Discovery of the EML4-ALK fusion gene in a subgroup (<5%) of patients with NSCLC (2007)

- Accelerated approval of breakthrough therapy-designated drugs
  - Crizotinib in 2011, 2013 (Xalkori, Pfizer)
    [4 years from the discovery of ALK rearrangement in NSCLC to the FDA approval]
  - Ceritinib in 2014 (Zykadia, Novartis)
Structure activity relationship optimization campaign

1 HTS hit $\rightarrow$ 50-300 derivatives $\rightarrow$ 1 optimized Lead
Models to evaluate mechanism of action & antitumor activity

Step 1: from in vitro to in vivo
- Optical imaging (cellular, intravital and whole animal)

Step 2: from in vivo to clinical use
- CT
- PET
- Ultrasound
- MRI
- SPECT

Two-dimensional cell cultures
- CAM assay
- Organoid three-dimensional cultures
- Zebrafish
- Intravital window

Clinical studies
- GEMMs
- Tissue slices

- Cell-line-based, subcutaneous xenografts
- PDXs
- Orthotopic xenografts
Failure: The Reality of Drug Discovery

Historically, the majority of Hit-to-Lead and Lead Optimization programs fail to deliver a preclinical candidate due to:

- Lack of efficacy (in animal models)
- Unexpected toxicity
- Poor pharmacokinetics

If you must fail...

“Fail early, fail cheap”
Preclinical safety studies

- To explore the response at up to maximum achievable doses
- To detect potential hazards and assess risks (general toxicology, geno-tox, carcinogenicity, repro-tox, etc…)
- To assist in dose-selection for initial clinical studies
- To suggest markers to monitor safety in humans
- To guide target-based investigations

- But not
  - to guarantee safety in humans
  - to predict human response
  - to define a mechanism
From molecules to medicines

Drug Substance (API)
- Cost to produce
- Scalability
- Analytical methods
- Stability

Drug Product (Formulated API)
- Cost to produce
- Scalability
- Analytical methods
- Stability
- Packaging and storage

- Chemical Development
- Pharmaceutical Development
CMC: Chemistry, Manufacturing and Controls

- Preformulation / API stress studies
- Formulation: selection of prototype for early clinical studies.
- Process development to select sterilizing method
- Formulation optimization (final strength) for commercial product.
- Scaling-up and process validation
- Long term stability studies

**Formulation development**
- pH solubility and stability profiles
- Additional preformulation studies: sensitivity to light, oxygen, temperature…
- Prototype formulation studies to select the best formulation based on stability studies (minimizing degradation products)
- Choice of the final strength for clinical and manufacturing

**Process development**
- Selection of the sterilisation method.
- Scale-up and process validation
- Manufacturing clinical batches for clinical studies
Clinical Development

USA: Investigational New Drug (IND) application:
• Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
• Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product.
• Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

Europe: Investigational Medicinal Product Dossier (IMPD), for approval of clinical trials by the competent authorities
Phase I: First in Man
- Small group of healthy volunteers or patients
- Determine the active dose or MTD
- Verify the mechanism of action: target modulation
- Determine a safe dose range and identify side effects
- Test potential biomarkers
+ Preliminary information on efficacy

**In general, heterogeneous tumor indications (s.t.)**

Phase II: Efficacy studies
- Larger group of patients (50-300)
- Evaluate activity, efficacy: POC
- Determine effective dose range
- Route and scheme of treatment
- Further evaluate the safety
- Biomarkers
- (Combinations)
Phase III: Comparative studies
- Large group of patients (>500, >>)
- Comparative efficacy vs. used treatments
- Monitor side effects
- Dose range
- Safety
- Biomarker validation

Registration of a new drug
- Compile preclinical and clinical data
- Quality of data (biometry, statistics)
- Manufacturing process
- Submit NDA to regulatory authorities:
  - quality + efficacy + safety
- NDA, from submission to approval:
  → ~2 years (2 months–7 years)
  → Marketing authorization granted
  → Launching, commercialization

Specific tumor indications
- BC, NSCLC, PC, etc…

F.I.M.
- Phase I trials
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**Clinical Development**

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**Phase IV & post-launch activities**
- Drug on the market
- Post-market surveillance
- Continue to monitor and report adverse effects
- Life-cycle management: new indications and/or formulations

*several years after the use in wide population, the risk remains*

*Ex: rofecoxib (Vioxx), unacceptable cardiac side-effects ➔ removed*
R&D productivity over the past 60 years: on decline

- FDA tightens regulation post thalidomide
- FDA clears backlog following PDUFA regulations and perhaps relaxes on HIV drugs
Productivity of the pharma industry

Finding the true cost of a new drug is complex and controversial...

Cost of a new drug in US$ (billions)*

Data: USFDA, PhRMA

* New drug cost and R&D spend could be 30% higher if non-PhRMA members are included
CANCER is an attractive therapeutic field for pharmaceutical companies
- new targets, multiple indications
- high price of drugs « tolerated » (thus far)

But a field with a limited success: *from F.i.M. to registration 90-95% attrition*

Why is cancer drug discovery so difficult?

*Alexander Kamb, Susan Wee and Christoph Lengauer*

*NATURE REVIEWS | DRUG DISCOVERY
VOLUME 6 | FEBRUARY 2007 | 115*
Drug repositioning

De novo drug discovery and development
- 10–17 year process
- <10% overall probability of success

Drug repositioning
- 3–12 year process
- Reduced safety and pharmacokinetic uncertainty

Figure 2 | A comparison of traditional de novo drug discovery and development versus drug repositioning.

(Nat. Rev. Drug Discov. 2004, 3, 675)
Ex: repositioning of anti-depressant drugs

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Repositioned antidepressant drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (MOA)</strong></td>
<td><strong>Original indication (trade name; originator)</strong></td>
</tr>
<tr>
<td>Bupropion (enhancement of noradrenaline function)</td>
<td>Depression (Wellbutrin; GlaxoSmithKline)</td>
</tr>
<tr>
<td>Dapoxetine (SSRI)</td>
<td>Analgesia and depression (N/A; Eli Lilly)</td>
</tr>
<tr>
<td>Duloxetine (NSRI)</td>
<td>Depression (Cymbalta; Eli Lilly)</td>
</tr>
<tr>
<td>Fluoxetine (SSRI)</td>
<td>Depression (Prozac; Eli Lilly)</td>
</tr>
<tr>
<td>Milnacipran (NSRI)</td>
<td>Depression (Ixel; Pierre Fabre Médicament)</td>
</tr>
</tbody>
</table>

**Notes:**
- **dep**ression
- fibromyalgia
vinorelbine (Navelbine®)

Catharanthine + Vindoline \[\rightarrow\] Anhydrovinblastine

Vinorelbine

injectable Navelbine (1989)

oral Navelbine (2001)
Vinflunine (JAVLOR®)

- 1988: HF & vinca-alcaloïdes
- 1991: 50 mg of PM391
- 1994: *in vivo* activity
- 1996: vinflunine
- 1998: Phase I
- 2000: Phase II
- 2003: Phase III
- 2009: EMEA Approval, bladder cancer
VFL: reduced affinity for tubulin dimers

**Table 1. Equilibrium Constants for Vinca-Tubulin Interaction**

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_1(M^{-1})$</th>
<th>$K_2(M^{-1})$</th>
<th>$K_1K_2(M^{-2})$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>$1.4 \times 10^5$</td>
<td>$1.7 \times 10^7$</td>
<td>$2.3 \times 10^{12}$</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>$1.2 \times 10^5$</td>
<td>$5.1 \times 10^6$</td>
<td>$6.1 \times 10^{11}$</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>$1.3 \times 10^5$</td>
<td>$1.1 \times 10^6$</td>
<td>$1.4 \times 10^{11}$</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>$8.8 \times 10^4$</td>
<td>$3.0 \times 10^5$</td>
<td>$2.6 \times 10^{10}$</td>
</tr>
</tbody>
</table>

Abbreviations: $K_1$, affinity of drug for tubulin heterodimers; $K_2$, affinity of liganded heterodimers for spiral polymers; $K_1K_2$, overall affinity for tubulin.

*In the presence of guanosine triphosphate at 25°C.

(Lobert & Puozzo, Sem. Oncol. 2008, 35, S28)
(Lobert & Correia, Methods Enzymol. 2000, 323, 77)

« weak » affinity for tubulin → fewer and smaller spiral filaments → reduced neurotoxicity
VFL: high intra-cellular accumulation

Figure 3. Differential uptake of $^3$H-vinca alkaloids. Uptake of $^3$H-vinflunine (Δ); $^3$H-vinorelbine (○); $^3$H-vinblastine (□); $^3$H-vincristine (●) in P388 murine leukemia cells.

(Lobert & Puozzo, Sem. Oncol. 2008, 35, S28)
Vinflunine activity in bladder cancer

VFL increases lifespan of mice with bladder cancer

Intravesically-implanted murine MB-49 bladder cancer
Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

from Bellmunt et al., J. Clin. Oncol. 2009, August

**Fig 3.** Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.
Vinflunine (JAVLOR®)

- 1991: PM391
- 1994: *in vivo* activity
- 1996: vinflunine
- 1998: Phase I
- 2000: Phase II
- 2003: Phase III
- 2009: EMEA Approval, 1st indication