WORKING GROUP 4:
Setting Up New Business Models and Ways to Invest in Paediatric Oncology Research and Drug Development
WG4 team: patients advocates

Patricia Blanc
Imagine for Margo, FR
Unite2Cure, EU

Sam Daems
Waterland, BE-GER-POL

Delphine Heenen
KickCancer, BE
Unite2Cure, EU

Jean-Charles van den Branden
Bain & Company, WW
KickCancer, BE
Working Group 4 team: industry and academics

Sam Blackman
MavuPharma, USA
CureSearch, USA
Accelerate, EU

Gilles Vassal
Gustave Roussy, FR
ITCC, EU
SIOPE, EU
Accelerate, EU

Raphaël Rousseau
Gristone, USA
CureSearch, USA
Accelerate, EU

Andy Pearson
Ex-Institute of Cancer Research, UK
Ex-Royal Marsden Hospital NHS, UK
ITCC, EU
Accelerate, EU
Drug development in paediatric oncology is frequently deemed not profitable.

- Too long!
- Complex with different age groups
- Expensive and not profitable
- Regulatory issues and uncertainties on reimbursement
- Small population...
We need a new model for paediatric oncology

New drug development is driven by adult diseases and targets (vs. paediatric diseases and targets)

Let’s think differently and start from the children’s needs
Innovation is booming but delayed not for children

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Adults Approved</th>
<th>Children Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase inhibitors (targeted therapies)</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Checkpoint inhibitors</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Antibody-drug conjugates</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>CAR-T cells &amp; BiTEs</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

When it comes to innovation in paediatric oncology, children (usually) come last.

Source: IMS Health, MIDAS, Lifecycle, R&D Focus, IMS Institute for Healthcare Informatics, Dec 2015; US FDA; Blue Ridge Institute for Medical Research
Explosion of new therapies for AML but few approvals for paediatric patients

- **Gilteritinib** (2018): adult patients with r/r AML with FLT3 mutation
- **Glasdegib** (2018): patients ≥ 75y ineligible for induction chemotherapy
- **Ivosidenib** (2018): adult patients with r/r AML with IDH1 mutation
- **Enasidenib** (2017): adult patients with r/r AML with IDH2 mutation
- **Midostaurin** (2017): adult patients with AML and FLT3 mutation
- **Gemtuzumab ozogamicin** (2017): CD33+ AML in adults and children ≥ 2

FLT mutations occur in 15% of pediatric AML (versus 20-35% of adult AML)

IDH mutations occur in 3.5% of pediatric AML [10% with normal karyotype] (versus 16% of adult AML)
CALL TO ACTION
Stars are aligned to do better...

**Strong international networks of professionals**

Parents, academics, pharma industry and regulators already work together to accelerate innovation
Improvements in our understanding of paediatric cancer biology has led to the development of new clinical trial infrastructure

**International precision medicine strategy**

**Whole genome and whole exome sequencing (WES/WGS)**

**Immune profiling (e.g. MSI-H)**
THE ACCELERATOR
Multiple ways to bring innovation to children

The goal: Identify scientifically relevant drugs for paediatric indications and make them:

- available for children
- approved on label for paediatric indications

Accelerating testing of new adult drugs in children

Make sure that clinical trials lead to market authorisation for paediatric use of new drugs earlier

Develop de novo drugs for children for validated targets

Develop drugs where the target is predominant in paediatric tumor biology (e.g. EWS-FLI1)

Retargeting existing or discontinued drugs

Repurpose abandoned molecules in adult oncology based on emerging paediatric cancer biology data
A "portfolio" model for pediatric oncology

Can Financial Engineering Cure Cancer?
Andrew W. Lo, MIT
(based on joint work with Jayna Cummings, David Fagnan, John Frishkopf, Jose-Maria Fernandez, Carole Ho, Austin Gromatzky, Ken Kosik, John McKew, Vahid Montazerhodjat, Roger Stein, Richard Thakor, David Weinstock, Nora Yang)

JAMA Oncology | Review
New Business Models to Accelerate Innovation in Pediatric Oncology Therapeutics
A Review
Sonya Das, Raphaël Rousseau, MD, PhD; Peter C. Adamson, MD; Andrew W. Lo, PhD

OBSERVATIONS Review of published studies of pediatric oncology research and the cost of drug development, as well as clinical trials of pediatric oncology therapeutics at ClinicalTrials.gov, identified 77 potential drug development projects to be included in a hypothetical portfolio. The returns of this portfolio were simulated so as to compute the financial returns and risk. Simulated business strategies include combining projects at different clinical phases of development, obtaining partial funding from philanthropic grants, and obtaining government guarantees to reduce risk. The purely private-sector portfolio exhibited expected returns ranging from −24.2% to 10.2%, depending on the model variables assumed. This finding suggests significant financial disincentives for pursuing pediatric oncology therapeutics and implies that financial support from the public and philanthropic sectors is essential. Phase diversification increases the likelihood of a successful drug and yielded expected returns of −5.3% to 50.1%. Standard philanthropic grants had a marginal association with expected returns, and government guarantees had a greater association by reducing downside exposure. An assessment of a proposed venture philanthropy fund demonstrated stronger performance than the purely private-sector-funded portfolio or those with traditional amounts of philanthropic support.

CLINICAL RELEVANCE A combination of financial and business strategies has the potential to maximize expected return while eliminating some downside risk—in certain cases enabling expected returns as high as 50.1%—that can overcome current financial disincentives and accelerate the development of pediatric oncology therapeutics.
Added value of the Accelerator

1. Covers the whole value chain of development
   - Develop and maintain a list of eligible, prioritized compounds to be developed in children
   - Definition of an integrated development plan for each compound including regulatory, strategy, clinical trial plan & dev costs
   - Execute / project manage / delegate integrated development plan: from drug selection to MA filing

2. Starts from the patients’ needs by target and by disease

3. Focuses development strategy to reach MA faster

4. Helps the industry in paediatric development by acting as strategic partner

5. Cost effective due to expertise in paediatric oncology development
A specific set of criteria will help determine the first candidate molecules

**Demonstrated unmet need**
- Size of patient population
- Low survival rates
- Low QoL from current standard-of-care
- Limited progress/interest to date for target/disease

**Goal is to help children not helped today**

**Probability of launch**
- Strong pre-clinical data
- Success in other studies
- Adult data available
- Success in agents in same class
- Promising results from previous phase
- Diagnostic data / Proof of mechanism in humans
- Clear regulatory pathway

**Goal is to demonstrate capability to bring product to the market**

**Time to value inflection**
- Technically/statistically feasible to prove beneficial impact on short-term endpoints
- Substantial patient pool for trial recruitment
- Limited competing trials
- Dismal survival rate in the near-term

**Goal is to achieve rapid proof-of-concept**
The Accelerator will operate through a delegated model, with specialized team to manage projects:

1. **CONTRACTS**
   - Law firm to negotiate partnerships with the pharma industry & academia

2. **REGULATORY AFFAIRS**
   - Specialist to help determine best regulatory pathway to launch drugs on market

3. **MARKET AUTHORISATION**
   - CRO to prepare filing for MA to EMA

4. **TRIAL EXECUTION**
   - Academia running the clinical trials
Building a viable new company requires solving these problems

- Employees
- Access to molecule (license)
- Capital (investors)
- Team & Molecule
- Capital & Team
- Team & Molecule & Clinical dev path
KEY FINDINGS
Full-time expert team is critical for success

Individuals with significant industry experience
- Target/program hunting
- Getting in the door business development/licensing groups
- Structuring, financing, and executing complex deals
- Designing and executing focused trials
- Agility: If successful, team will need to rapidly initiate clinical development, manufacturing, regulatory interactions

Broad Network
- Global clinical development partners
- Access to sources of capital and programs: VCs/institutional investors, family foundations/HNW individuals; biopharmaceutic BD/L teams

Compensation
- Market for oncology biopharma talent is extremely competitive:
  - Salary, benefits, and equity required to recruit top talent away from other companies or compete against funded startups
What patient/parent representative can bring to the project

**Political network**
- Contact with politicians at national and international levels
- Agenda to improve the regulatory environment in favor of children with cancer

**Patients’ network**
- Access to patients can improve recruitment to trials
- Expert patients can contribute to improved trial design (compliance, tolerability)

**Access to executives**
- Long-standing relationship with several pharmaceutical companies
- Mostly with the top executives, who may help gain access to programs despite BD group’s priorities
Access to pipelines is harder than expected

Companies often do **not have large efforts dedicated to out-licensing**
- Information around discontinued programs is usually not publicly available
- Pharma business development/licensing efforts are laser-focused on **in-licensing**
- High cost for out-licensing assets, including opportunity cost

**Terminal elimination half-life** of discontinued programs is **very short**
- Loss of institutional knowledge
- Loss of manufacturing capability, existing API

**Most out-licensing/partnering deals** to date are **front-ended** (large upfront cash payment)
A new company without capital can usually only do **back-ended deals** (equity, royalties)

Even if successful, new translational/validation data in appropriate models may be required to de-risk hypotheses (e.g. CSF1R)
Unintended consequences: Heisenberg’s Uncertainty Principle

Sharing a new hypothesis about a discontinued program may impact a company’s perception of the value of the program.
Unintended consequences: LOXO FOMO

Eli Lilly to buy Loxo Oncology for about $8 billion in cancer drug bet
Access to significant capital/financing is required

• Capital demands for development more than what private donors can raise
  – $20-50M to value inflection
  – Commercialization/manufacturing

• **Venture returns** are expected by VCs for an ongoing company.

• Competition for investment dollars with many other high-risk/high-reward opportunities.

**Buying and selling at the same time**
- Negotiating for assets and planning clinical development without having capital in hand
- Fundraising without having a full team and/or assets in place.
Conclusions of WG4 and Next Steps

• WG4 concludes that a **novel biotechnology company** is the business model with the highest probability of success across all domains (retaining talent, access to pipelines, ability to raise capital).

• Multiple emerging biotech companies are using this model, but none are focused either primarily or exclusively on new therapeutics for **pediatric oncology**:

  ![SpringWorks Therapeutics](image1.png)  ![Cydan](image2.png)  ![Rallybio](image3.png)  ![bridgebio](image4.png)

• There are **ongoing efforts** to bring forward **not-for-profit** and **for-profit** companies focused on pediatric cancer.

• Time will tell which model will succeed. Most importantly: **the experiment has started**.

**Multiple efforts of all types should be encouraged/supported until the problem is solved**