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New drugs for children and adolescents with cancer: the need for novel development pathways

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Despite major progress in the past 40 years, 20% of children with cancer die from the disease, and 40% of survivors have late adverse effects. Innovative, safe, and effective medicines are needed. Although regulatory initiatives in the past 15 years in the USA and Europe have been introduced, new drug development for children with cancer is insufficient. Children and families face major inequity between countries in terms of access to innovative drugs in development. Hurdles and bottlenecks are well known—eg, small numbers of patients, the complexity of developing targeted agents and their biomarkers for selected patients, limitations of US and EU regulations for paediatric medicines, insufficient return on investment, and the global economic crisis facing drug companies. New drug development pathways could efficiently address the challenges with innovative methods and trial designs, investment in biology and preclinical research, new models of partnership and funding including public–private partnerships and precompetitive research consortia, improved regulatory requirements, initiatives and incentives that better address these needs, and increased collaboration between paediatric oncology cooperative groups worldwide. Increased cooperation between all stakeholders—academia, parents' organisations and advocacy groups, regulatory bodies, pharmaceutical companies, philanthropic organisations, and government—will be essential.

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Introduction

Although childhood cancer represents less than 2% of human cancers, it is the most common cause of death from disease in children older than 1 year. Nowadays, with the routine use of intensive, multimodality treatment, established through prospective clinical trials by cooperative groups of the global paediatric oncology research community, 20% of children and adolescents with cancer will still die from their disease, and more than 40% of survivors will have late effects that adversely affect their adult lives.[1] Innovative, effective, and safe new treatments for children with cancer are needed to increase the cure rate, diminish the acute toxic effects associated with existing treatment, and minimise the long-term risks for survivors.

These innovative treatments will come from a variety of approaches. We need improved understanding of the biology underlying childhood cancers and to identify relevant targets and pathways for treatment interventions—knowledge that researchers can use to develop new drugs with novel mechanisms of action and to build on existing treatments. Personalised medicine should be developed through implementation of novel technologies and risk-based algorithms. Optimisation of new radiotherapy and surgery techniques that can spare normal tissue more effectively would reduce treatment-related effects, and using innovative imaging technologies would help to identify patients who are most likely to benefit from specific treatments. A cornerstone for progress, and the focus of this paper, is the development of new anticancer drugs for children (figure 1).

For some adult cancers, targeted agents have transformed outcomes. These agents have offered new approaches for effective treatments in various diseases, including renal cancer, melanoma, chronic myeloid leukaemia, and lung cancer.[2–5] The development of new oncology drugs for adults has also underscored the need for biomarkers. As knowledge of the molecular underpinnings of cancer increases, the common adult cancers—eg, breast, lung, colon, and prostate—will become clusters of rare diseases defined by specific molecular profiles and associated biomarkers. Similar changes are happening in childhood cancers. However, splitting already rare childhood cancers into ultra-rare populations of patients,[6] as most paediatric cancers are divided into several molecularly defined subtypes, means that fewer patients will be available to

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Figure 1: **Innovative drug development for childhood cancers is urgently needed**

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participate in clinical trials of relevant biomarker-directed targeted treatments.

In view of scientific advances, increased investment in childhood cancer research would be timely. However, many challenges are associated with progressing from cytotoxic treatments. To identify relevant targets, biology needs to be linked to outcome. A biomarker for disease cannot always be equated with a drug target, and probably only a small proportion of targets identified will be suitable for drug treatment with present technologies. In addition, the costs associated with research and development are prohibitive for drugs to treat rare and ultra-rare diseases. Support for such development solely in the private sector is unlikely and public–private partnerships will be needed as new drug development pathways for children with cancer are explored.[7]

Challenges and opportunities in early-phase cancer trials

With more than 800 oncology drugs in the development pipeline, and a range of potential targets and pathways, new drugs for paediatric cancer need to be prioritised so that the most relevant and innovative medicines can be fast-tracked. Additionally, the capacities and activity in early-phase clinical trials in children need to be substantially increased. Such studies not only benefit children with relapsed or refractory disease, but will guide advances for front-line trials.

Innovation in trial designs and drug development strategies

For more than 40 years, the development of new and often cytotoxic cancer drugs has followed a linear pathway, beginning with phase 1 single-agent assessment with a traditional 3+3 dose-escalation design. In 1998, an international consensus on the running of phase 1 trials in children was reached.[8] Single-group phase 2 trials generally follow two-stage designs, with the proportion of patients achieving an objective response (ie, complete or partial responses) as the primary endpoint to establish efficacy. These single-group studies are designed on the basis of historical controls. In the past 20 years, this approach in paediatric oncology trials has not yielded many new drugs, and the few novel agents discovered have had little effect on children with cancer. The most notable success—the identification of imatinib for patients with Philadelphia-chromosome-positive leukaemias—marked the start of the investigation of drugs in patients with identifiable biomarkers related to the drug target.[5]

New agents in the development pipeline are likely to be used in combination with classic cytotoxic drugs or other targeted agents. Therefore, early-phase drug development needs to move on from single-agent assessment to give experience with combination treatments,[9] which will need to be validated in phase 2 trials. For phase 2 trials, the selection of patients on the basis of biomarkers could become commonplace. However, our knowledge of pathways and targets is evolving, and the design of early-phase trials with a restricted population could be counterproductive. Late-stage trials (eg, phase 3 trials) could become more efficient as our knowledge of biomarkers, and hence selection of patients, improves. Efforts to explore biomarkers in all phases of clinical trials might accelerate research efforts. Most of these trials will require global international collaboration.

Efforts to shorten the dose-determination phase of trials should continue. The rolling six method[10] is an important step in this direction; it has been successful in phase 1 trials in children, including trials with targeted agents.[11,12] Other designs derived from the continual reassessment method have been developed to avoid waiting lists.[13,14] Some designs take into account several types and grades of adverse events, which could be more efficient for dose-finding trials of targeted agents.[15] Others use mixed criteria (ie, toxicity and efficacy),[16] which might be useful to define the optimum biological dose of a targeted agent. All these designs will eventually accelerate the dose-finding phase. For phase 2 trials, Bayesian approaches can be further explored with efforts to make better use of pharmacokinetic and pharmacodynamic data from adult trials in paediatric studies. Such extrapolation could become routine when a drug is explored in children in the same cancer as in adults—eg, thyroid cancer, melanoma, and some types of acute myeloid leukaemia.

Response criteria need to be harmonised. The International Neuroblastoma Response Criteria programme, the Response Assessment in Paediatric Neuro-Oncology project, and the 2010 international consensus conference on assessment in acute lymphoblastic leukaemias[17] have addressed response assessment harmonisation for these diseases. The use of categorical endpoints (complete and partial response) for phase 2 trials should be reassessed, and response data should be considered as continuous variables with waterfall plots. Additionally, prolonged stable disease for some targeted treatments could be considered as an endpoint in paediatric oncology. Although the costs for such trials are greater than for traditional phase 2 trials, the information might be more valuable for paediatric drug development than data from more traditional designs.

Biological specimens will form the foundation for discovery, and will increasingly be used to guide treatment. Most biopsy samples, with few exceptions, are routinely obtained in newly diagnosed patients. Even for diseases in which biopsy has not traditionally been done because of the associated procedural risk (eg, in children with brainstem gliomas), emerging evidence suggests that such procedures can be safely undertaken in certain circumstances, and that they provide valuable information.[18] At first relapse, biopsy is usually clinically indicated because the implications of relapse are so important prognostically. However, apart from children with relapsed leukaemia, ethical and regulatory issues might continue to restrict the ability to take repeated

	Target	Adult disease	Paediatric disease
Same target and disease			
Vemurafenib,[3] dabrafenib[25]	V600E BRAF	Melanoma	Melanoma
Ganitumab,[26] figitumumab,[27] R1507[28]	IGF-1R	Ewing's sarcoma	Ewing's sarcoma
Not yet developed	PARP	Ewing's sarcoma[29]	Ewing's sarcoma[29]
Imatinib,[5,30] dasatinib,[31] nilotinib[32]	BCR-ABL	Chronic myeloid leukaemia/Philadelphia-chromosome-positive acute lymphoblastic leukaemia	Chronic myeloid leukaemia/Philadelphia-chromosome-positive acute lymphoblastic leukaemia
Brentuximab vedotin[33]	CD30	Hodgkin's lymphoma, anaplastic large-cell lymphoma	Hodgkin's lymphoma, anaplastic large-cell lymphoma
Crizotinib[12]	ALK	Anaplastic large-cell lymphoma	Anaplastic large-cell lymphoma
Rituximab[34]	CD20	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
Midostaurin[35]	FLT3	Acute myeloid leukaemia	Acute myeloid leukaemia
Blinatumomab[36]	CD19	Acute lymphoblastic leukaemia	Acute lymphoblastic leukaemia
Same target but different disease			
Crizotinib	ALK	Non-small-cell lung cancer[4]	Neuroblastoma[12,37]
Vemurafenib, dabrafenib	V600E BRAF	Melanoma[3,25]	Glial tumours,[38] histiocytosis[39]
Dalotuzumab, ganitumab, figitumumab, R1507	IGF-1R	Breast, prostate, lung[40]	Wilms' tumour, neuroblastoma[22,41]
Everolimus	mTOR	Kidney,[42] breast,[43] pancreatic neuroendocrine tumours[44]	Subependymal giant-cell astrocytoma associated with tuberous sclerosis[21]
Vismodegib	Hedgehog pathway	Basal-cell carcinoma[45]	Medulloblastoma[6,46]
Sorafenib	FLT3	Renal-cell carcinoma,[47] hepatocellular carcinoma[48]	Acute myeloid leukaemia[49]
Specific paediatric target and disease			
ch14.18,[50] ch14.18/CHO[51]	GD2	..	Neuroblastoma
Not yet developed	N-MYC[52]	..	Neuroblastoma
Not yet developed	PAX3/7-FOXO1[53]	..	Rhabdomyosarcoma
Not yet developed	EWS-FLI[54]	..	Ewing's sarcoma

All drugs, except figitumumab and R1507, are in clinical development or marketed.

Table: **Anticancer drugs for children, adolescents, and adults as defined by common underlying biological targets**

tumour samples from children undergoing treatment. Approaches that are minimally invasive, such as analysing circulating tumour cells,[19] or novel imaging techniques might represent relevant alternatives to repeated biopsies. Indeed, using information on tumour evolution gained repeatedly during treatment could become a cornerstone of biomarker-directed treatment for the individual child.

Invest in biology and preclinical research

Biomarker-driven studies are an established approach to cancer drug development. Two recent studies in adult solid tumours have confirmed the approach shown to be effective more than 10 years ago with imatinib:[5,20] the sonic-hedgehog pathway inhibitor vismodegib in basal-cell carcinoma,[21] and the ALK inhibitor crizotinib in non-small-cell lung carcinoma with *EML4-ALK* translocation.[7] Although cancer types differ substantially between adults and children, different cancer histologies can depend on similar pathways or biological systems, such as IGF-1R,[22] mTOR,[23] and PARP[24] (table). Different alterations of the same gene have been recorded. *ALK* is translocated in anaplastic large-cell lymphoma, lung cancer, and inflammatory myofibroblastic tumours, whereas *ALK* is mutated or amplified in neuroblastoma.[37,55] Therefore, the potential biological role of cancer drugs developed for adult cancers in paediatric cancers needs to be fully explored. Irrespective of whether the target is altered, its presence and functional validation, and evidence of preclinical antitumour activity (if possible), might be necessary to justify clinical drug development in children.

In parallel, a more comprehensive understanding of the biology of paediatric cancers is essential to identify key drivers of tumour progression and dissemination. This challenge is formidable, because the preliminary results of whole-genome sequencing of paediatric tumours[56] suggest that mutations are not frequent in paediatric tumours, and that other mechanisms, such as epigenetic modifications, might be more important. To this end, the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) programme, funded by the US National Cancer Institute, was established to facilitate the identification of potential treatment targets for childhood cancers; however, greater investment of resources will be needed to close the current knowledge gap.

Finally, improved preclinical models of childhood cancers are needed to prioritise agents in the clinical development pipeline. The Paediatric Preclinical Testing Programme[57] funded by the US National Cancer Institute provides one approach, and allows the study of new drugs in well characterised in-vitro cell lines and in-vivo xenografts. However, the predictive reliability of these models for targeted new agents remains unknown. New

models, including orthotopic, transgenic, and ex-vivo three-dimensional approaches,[58] need further investment and investigation. The reinforcement of basic science and predictive, innovative, preclinical evaluation should be a major part of new oncology drug development for children.

Prediction and prevention of late effects of new anticancer drugs

Paediatric oncologists have, for the past 40 years, tried to increase cure rates and minimise the long-term effect of treatment on survivors of childhood cancer. In 2007, the results of the FAB/LMB96 international collaboration between French, UK, and US cooperative groups suggested that treatment could be reduced in some children with Burkitt's non-Hodgkin lymphoma without affecting the probability of cure.[59] Much progress has been made in the avoidance of radiotherapy in children—especially for the CNS, which can greatly affect neurodevelopment in young children—and lead to secondary cancers. Intensification of chemotherapy is commonly used to decrease or eliminate the need for radiotherapy. Despite these efforts, survivors suffer treatment-related adverse effects throughout life, even when use of chemotherapeutic drugs—eg, cardiotoxic anthracyclines—is restricted. The acute toxic effects associated with chemotherapy have also been lessened, notably through the use of haemopoietic growth factors for children at high risk of neutropenia, by an expanded armamentarium of anti-emetic drugs, and with more effective use of analgesic medicines. However, almost every organ system is at risk from existing treatments: anthracyclines adversely affect the heart,[60,61] platinum compounds can damage the ears,[62] and alkylating agents impair fertility.[63] Furthermore, secondary malignancies can be induced.[64] Academic programmes are in progress in the EU and the USA for researchers to prospectively study survivors, in order to propose adapted care for adults suffering from long-term effects after cancer in childhood. We should emphasise that targeted agents are not necessarily non-toxic. Rather, their toxicity profiles differ from those of classic cytotoxic drugs. Generally, dose-limiting haemopoietic toxicity is less likely with targeted agents than with classic cytotoxic drugs, and skin toxicity is more common (EGFR and BRAF inhibitors). Some agents interfere with biological pathways (IGF-1R, angiogenesis, sonic hedgehog) that are physiologically important for growth and development of children. The long-term toxicity of antibodies used in leukaemia as naked antibodies (eg, rituximab) or targeted delivery (eg, gemtuzumab ozogamicin) is still unknown.

Long-term follow-up of patients who are given new targeted agents will prospectively explore potential late effects, and provide corrective or preventive measures. These long-term follow-up measures, which are often required by the paediatric committee at the European Medicines Agency, cannot be done on a drug-by-drug basis and with industry solely responsible for data collection. Long-term follow-up by childhood cancer survivorship programmes would be a better approach. Academic programmes do not yet have the structure, focus, and resources to set up prospective long-term safety assessments of new drugs, but they do offer an excellent asset to build on and could fill this void.

For the **Medicines for Malaria Venture website** see http://www.mmv.org/

New models of partnership and funding

The timelines for cancer drug development need to change in response to the pace of scientific discovery. Strong public–private partnerships involving all stakeholders—academia, the pharmaceutical industry, parents, regulatory agencies, public health agencies, research-funding agencies, and philanthropic organisations—will form the foundation of drug development for childhood cancer. Patients and families—especially through advocacy organisations—will have an increasing role in the development process. With information widely available on the internet, most parents of a child with a life-threatening disease will demand innovative treatments. The economic model for rare and ultra-rare diseases is a large hurdle,[65] but the pharmaceutical industry will face similar challenges in medical oncology as knowledge of the heterogeneity of common adult cancers increases.

Paediatric oncologists recognised long ago that institutional boundaries need to be crossed to advance, and for more than 50 years have developed collaborative networks for clinical and translational research. The return of investment on these collaborative efforts has been remarkable. Experience and commitment to the extension of these collaborations are increasing worldwide, and paediatric oncologists are ready to forge important new international partnerships, which will become the standard for research into rare disease populations. This growing infrastructure, and the expertise gained, will be a valuable asset to the biopharmaceutical industry. Moreover, expansion of high-quality biobanking for the various distinct types of childhood cancer will be an important undertaking for future treatment development.

As the biopharmaceutical industry copes with changing regulations and incentives, an improved approach is needed to coordinate research efforts and potentially competing or conflicting requirements. One difficulty is the small number of children who are potentially eligible to participate in research for any particular disease. Research cannot be prioritised solely within the biopharmaceutical industry or indirectly through requirements set forth by regulatory agencies. Instead, the academic community, with the support of patients' and parents' advocates, needs to lead the way. A major factor will be the development of public–private partnerships.[66] The Medicines for Malaria Venture is one successful example; it is a not-for-profit public–private partnership that was established as a foundation in 1999. The aim of the scheme is to reduce the burden of malaria in disease-endemic countries through discovery, development, and delivery of new, effective, and affordable antimalarial drugs. In this model of research and development

applicable to neglected disease, product development partnerships use public and philanthropic funds to engage the pharmaceutical industry and academic research institutions.

Early-phase development of paediatric cancer drugs differs substantially between the USA and Europe, in terms of regulatory requirements, structures, and governance. The US National Cancer Institute, through its Cancer Therapy Evaluation Programme, funds a 21-site consortium focused on paediatric phase 1 cancer trials that has supported trials directly, and also trials by industry collaborators. In Europe, an integrated research network of 42 centres in nine countries was created in 2003 to run early-phase trials sponsored by industry and academia and a target evaluation programme.[67] The Innovative Therapies for Children with Cancer consortium runs new drug trials through project funding from industry, national grants, and philanthropic organisations, but no sustainable European funding for infrastructure is available. This difference in public funding largely explains why almost ten times more early-phase trials are done in children in the USA than in Europe. Fiscal restrictions and limited access to early-phase trials are common in other regions such as Asia and Oceania. As a result, outside the USA, most children and adolescents with relapsed or refractory cancer do not have access to early clinical trials investigating innovative compounds. Some families travel to the USA so that their children can participate in clinical research, which can create enormous personal and financial burden.

The National Cancer Institute has funded programmes that support the Children's Oncology Group research platform, including the Paediatric Preclinical Testing Programme and the TARGET initiative. In Europe, the sixth and seventh framework programmes have funded some biology research into childhood cancers (eg, European embryonal tumor pipeline, KidsCancerKinome, and ChildHope), and a 4-year European Network for Cancer Research in Children and Adolescents. Research tools are becoming more powerful, and investment in discovery research is needed worldwide. The European Commission and other international agencies need to make sustainable funding for paediatric oncology research a priority.

Improvement of regulatory requirements and initiatives

Regulatory changes made in the past 15 years in the USA and Europe have changed the environment for paediatric drug development.[68] In the USA, key legislative changes were enacted in 1997 and have now become The Best Pharmaceutical for Children Act and the Paediatric Research Equity Act.[69] The 2007 Paediatric Medicine Regulation in Europe combined some elements of the US approach, resulting in paediatric investigation plans,[40] which are based on incentives and requirements for the pharmaceutical industry. The aim of US regulation is to provide relevant information in their summary of products characteristics for the use of medicines in children, whereas the aim of European regulation is the approval of drugs for marketing authorisation for use in children. Despite the differences in approaches, one important overarching result has been a substantial increase in interaction and dialogue between the biopharmaceutical industry and the childhood-cancer clinical research community. The consideration of childhood cancer in the development of new drugs for adult indications is increasingly being integrated into industry drug-development strategies. The lessons learnt from these important legislative initiatives should be extended worldwide to other international regulatory jurisdictions.

However, these legislative initiatives have limitations and unintended consequences. One important limitation is that legislation only addresses how cancer drugs developed for adults should be studied in children. Industry does not pursue first-in-children indications because of a lack of incentive. To that end, in 2012, the Creating Hope Act was enacted in USA.[69] The Act creates an incentive—a priority review voucher at the Food and Drug Administration—that is transferable to another drug developed and submitted to the Administration by the same company, and partly unlinks the economic limitations of drugs for rare and ultra-rare conditions from the development investment.[69] In the past 20 years, only two drugs have been first approved in children for the treatment of leukaemia: clofarabine and *Erwinia* asparaginase. Had the 2012 Creating Hope Act been in place at the time of the submission of these drugs to the US regulatory authority, the companies would have received and benefited from a priority review voucher.

For more on the **Creating Hope Act** see http://www.childhoodcancer-mccaul.house.gov

Another major limitation is that drugs are labelled for cancer on the basis of a pathological indication, even though the drug target for a common adult cancer might be highly relevant to a pathologically distinct paediatric cancer.[70] Therefore, the Paediatric Research Equity Act has no effect on development of childhood cancer drugs because companies routinely receive waivers so that they do not need to investigate drug effectiveness in children. Similarly in Europe, insufficient early-phase clinical cancer trials are done, and drugs are waived for development in a paediatric cancer that is different from the adult cancer. In the USA and Europe, a major unintended consequence of paediatric investigation plans is a delay in the initiation of early-phase clinical trials by companies. Paediatric investigation plans require review and approval of a complete development plan—sometimes including phase 3 trials—before any paediatric clinical data are available. Commitments to plan phase 3 and beyond before the drug has been tested in children are counterproductive because the early-phase clinical data determines whether a drug should be fully developed, and, if so, how. As a result, companies delay initiation of phase 1 investigation while trying to develop complex phase 3 development plans without key data and waiting for paediatric investigation plans to be approved. An overarching concern is that the

For more on the **sixth framework** see http://cordis.europa.eu/fp6/support.htm

For more on the **seventh framework** see http://cordis.europa.eu/fp7/health/

For the **European Network for Cancer Research in Children and Adolescents** see http://www.encca.eu/

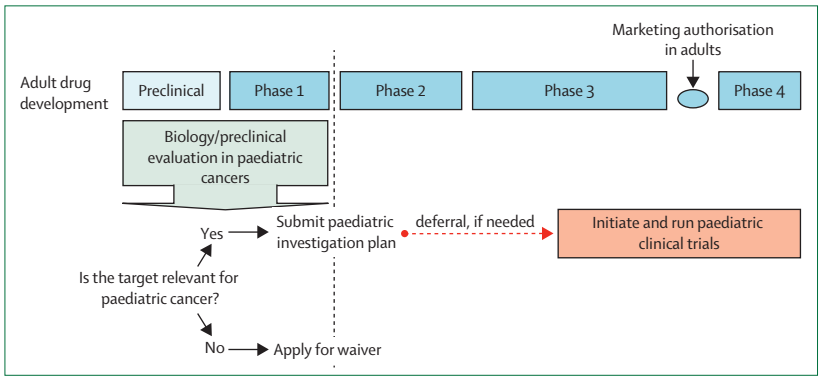

***Figure 2*: Proposed scheduling of an EU paediatric drug-development pathway**
Preclinical assessment and phase 1 studies in adults, with target exploration, validation, and experimental treatments in paediatric tumour models, should answer the question: is the target relevant for a paediatric cancer? At the end of the phase 1 study in adults, if the answer is yes, a paediatric investigation plan is submitted (at the appropriate time required by the regulation), if the answer is no, a waiver for paediatric development should be applied for. The start of the paediatric development can be deferred (dashed line) if additional safety data in adults are needed before paediatric studies.

incentives and requirements put in place generally happen in isolation, with each drug assessed independently. Thus, paediatric investigation plans for different compounds are approved for the same indication, and the feasibility of simultaneous drug trials in these rare-disease populations is disregarded. Prioritisation of clinical research studies by the paediatric oncology research community, including essential input from cooperative group programmes, is absent from the process. It takes 5–7 years to run a phase 3 trial of a paediatric cancer; therefore, in Europe, only one phase 3 trial in a given cancer can be run every 5–7 years.

What changes should be made to the US and EU regulations, and what guidance should be given to address limitations? A waiver should be issued on the basis of the mechanism of action or target of a new drug rather than the pathological adult indication (figure 2). Paediatric investigation plans should limit development proposals to phase 1 and 2 clinical research, and defer any discussion of phase 3 trials until the necessary early-phase paediatric data are available to inform such discussions. To identify requirements for industry, a more disease-centred or target-centred approach rather than a drug-centred approach is needed. Finally, cooperation between the global childhood cancer community, regulatory agencies, and pharmaceutical companies should be pursued to prioritise new drug studies.

For the **TransCelerate BioPharma website** see http://transceleratebiopharmainc.com/

***Panel:* Key messages**

- Innovate new drug development designs and strategies
- Invest in basic science, preclinical evaluation, and translational research
- Develop precompetitive research, public–private consortia, and worldwide collaboration of cooperative groups, with a model joining sources from biopharmaceutical industry, regulatory agencies, public health authorities, advocacy groups (parents' and patients' organisations), and philanthropic organisations
- Harmonise and improve the implementation of both the US and EU paediatric medicine regulations to better address the needs of children, and extend elements of these regulations to other international jurisdictions
- Propose new incentives for specific oncology drugs against targets that are specific to childhood cancers
- Improve and develop platforms for academic collaboration for long-term follow-up and intervention
- Increase cooperation between all stakeholders

Increased cooperation

Low numbers of patients when diseases have been subdivided based on molecular characteristics mean that phase 3 trials will need increased collaboration worldwide. The paediatric cancer research community is aware of this change and several consortia committed to early-phase drug development have formed: the Innovative Therapies for Children with Cancer European Consortium; the Children's Oncology Group phase 1 Consortium; the Paediatric Oncology Experimental Therapeutics Investigators' Consortium; the Therapeutic Advances in Childhood Leukaemias and Lymphomas consortium; the New Approaches for Neuroblastoma Therapies consortium; the Pediatric Brain Tumour Consortium; the Canadian C17 network; and the Australian Children's Cancer Trials group. However, the biggest challenge for the research community is not phase 1 studies, but is in phase 2 trials, for which randomised designs will become increasingly used, and also for phase 3 trials in biomarker-selected patients. The limitations to drug development can be overcome by collaboration, and investigators and consortia in the paediatric oncology community routinely work together. Furthermore, rethinking global collaboration in paediatric oncology research might help to facilitate access to innovative drugs in countries where these drugs are not yet available, such as countries in South America, central Europe, Asia, and Oceania. However, the main challenge is to warrant access to standard curative treatments and validated anticancer drugs worldwide, and in particular in countries of low and middle income. Shortages in drug supplies are a major concern in countries with limited resources.[71]

The idea of precompetitive research[72] and open innovation is entering drug development.[73,74] Drug companies should address paediatric oncology non-competitively and precompetitively, especially with compounds that act on the same targets or those that complementarily affect the same pathway. Some initiatives, such as the European Innovative Medicines Initiative incentivise the creation of precompetitive, public–private consortia addressing bottlenecks in drug development.[37] Another example of innovative precompetitive partnering is the TransCelerate BioPharma initiative,[46] which is a joint effort by ten large pharmaceutical companies. Founding members combine financial and in kind resources to solve industry-wide challenges in a collaborative environment. Outcome-oriented goals are defined as well as guidance for sharing information and expertise.

Search strategy and selection criteria

We searched PubMed with the following search terms: "paediatric" OR "pediatric" OR "child" OR "children" AND "oncology" OR "cancer" OR "malignancy" AND "new drugs" OR "phase I" OR "regulations" OR "public-private partnership" or "precompetitive". The search included only papers published in English from Jan 1, 1965 to Dec 31, 2012. The results were supplemented with the authors' files and the papers referred to in the references retrieved. References are illustrative of the authors' major points and not meant to be exhaustive.

Conclusions

Large-scale collaborative clinical research in paediatric oncology began more than 50 years ago. This cooperation and collaboration led to a substantial improvement in 5-year survival for many childhood cancers. To speed up the development of much needed innovative treatments, this experience should be extended to engage the biopharmaceutical industry, regulatory agencies, public health authorities, advocacy groups, and philanthropic organisations (panel). New pathways, including innovative partnerships and new models for research and development, could efficiently address the challenge of introducing safe, effective, innovative medicines into the standard care of children and adolescents with cancer.

Contributors

All authors prepared the paper and reviewed and approved the final version. GV and PCA did the literature search.

Conflicts of interest

We declare that we have no conflicts of interest.

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