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Drug discovery in paediatric oncology: roadblocks to progress

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Abstract

Approval of new cancer drugs for paediatric patients generally occurs after their development and approval for treating adult cancers. As most drug development occurs in the industry setting, the relatively small market of paediatric oncology does not provide the financial incentives for companies to actively pursue paediatric oncology solutions. Indeed, between 1948 and January 2003 the FDA approved 120 new cancer drugs, of which only 30 have been used in children. This slow rate of development must be addressed in a meaningful way if we are to make progress in the most pressing settings in childhood cancer. In this Viewpoint article, the key opinion leaders in the field weigh in and offer practical advice on how to address this issue.

What are the major drug hurdles in paediatric oncology?

Peter C. Adamson

To understand challenges in childhood cancer drug development better, how all of biomedical research is supported at the national and international levels needs to be considered. In the USA, approximately 60% of funding for biomedical research stems from the private biopharmaceutical sector.[1] The next largest funder is the NIH, which supports approximately 25% of research. For childhood cancers, however, which represent a constellation of more than 100 rare and ultra-rare diseases, the biopharmaceutical sector has an almost negligible investment, resulting in virtually all research funding emanating from the National Cancer Institute (NCI), private foundations and philanthropic sources. This

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limitation of funding and investment from industry impacts all key areas of drug development, spanning target discovery through clinical development.

An ongoing challenge today is defining which agents in development for treating adult cancer have potential therapeutic value for childhood cancers as well. To that end, earlier collaboration between the paediatric oncology research community and the biopharmaceutical industry is needed. Early insight into the development pipeline can foster necessary preclinical research on the potential utility of novel targeted agents for childhood cancers. Currently, industry generally starts considering developing a cancer drug for paediatric patients only when such agents are entering phase II studies for the treatment of adult patients—a time point at which it would be helpful to have preclinical data in paediatric cancers available to inform on drug development. Without such data, drug development for children lags even further behind that for adults, and development plans, including defining which pediatric cancers should be the focus of exploring the potential benefit of a new therapeutic agent, become more difficult to formulate.

Peter J. Houghton

The major problem in paediatric oncology is that drug development focuses on the most frequently occurring adult carcinomas, such as lung, breast, colon and prostate cancers, which are almost nonexistent in children. Childhood cancer is rare, with approximately 12,400 new cases diagnosed ever year in patients under the age of 21 years. Thus the ‘market’ for paediatric cancers is too small for pharmaceutical companies to invest in developing drugs that will specifically target these types of cancer. Furthermore, the genetics of childhood cancers differ markedly from adult cancers, therefore, most agents developed to inhibit specific pathways in adult carcinomas may have little or no benefit in the treatment of childhood malignancies. However, an agent that is active in an adult malignancy can be effective in the paediatric setting. For example, crizotinib shows efficacy for treating adult patients with *EML4–ALK* mutations in non-small-cell lung cancer, but is also active against anaplastic large cell lymphoma, a tumour driven by *ALK* mutation, and in some neuroblastomas that have *ALK* mutations or amplification. A second example is the promising activity of the MEK inhibitor selumetinib for treating low-grade *BRAF*-mutant glioma. Unfortunately, such examples are quite rare, and the duration of response to these treatments developed for adult malignancies for individual patients may be brief. As with many molecularly targeted therapies, there can be rapid onset of resistance. Of note, while an increase in overall survival of a few months might be acceptable for treating some adults, the focus for paediatric oncology is to cure. One strategy to better identify agents that may have broad-spectrum, or histotype-specific activity against childhood cancers is to screen using validated models of specific cancer types, as demonstrated by the Pediatric Preclinical Testing Program (PPTP).[2–4]

Giorgio Perilongo

First, despite changes in the regulations and incentives around drug development, we are still facing difficulties because the process is designed for adult cancers. Second, children deserve their own drugs for treating their diseases. These simple ideas have many important implications, which are frequently underestimated. Currently, most of the innovative

concepts driving new drug development for childhood cancers are derived from adult tumour models—an approach that can be quite misleading. In fact, the emerging data derived from whole-genome sequencing studies suggest that mutations are relatively rare in paediatric cancers, underscoring other possible oncogenic mechanisms, such as epigenetic modifications.[5–7] Considering that this finding is opening a relatively new field of research, a major strategic effort should be planned to address our lack of knowledge. Furthermore, the same gene thought to be central to both adult and childhood tumour development often operates according to different pathological mechanisms in the two age groups. The *ALK* gene, for example, is translocated in some lung cancers or in large-cell anaplastic lymphoma, but mutated or amplified in a subset of neuroblastoma.[8,9] Accordingly, the drugs developed to target specific gene defects in adult tumours are not necessarily efficacious in paediatric tumors. Finally, developing drugs specifically for childhood diseases requires investigation into possible long-term adverse effects, more so than for adult diseases. Indeed, therapies that modify transcriptional pathways, epigenetic functions or the microenvironment have the potential to affect every tissue and might, therefore, have indeterminate long-term effects in still-developing young children.[10]

Kathy Pritchard-Jones

The major hurdle is the lack of access to novel therapies for children with cancer. This lack comprises two main elements: insufficient clinical trials of new agents whose eligibility criteria include the paediatric age group, and insufficient efforts in drug development to generate preclinical information and novel compounds targeted at the unmet clinical needs of children with cancer.[11] Where a potentially relevant targeted therapy is in clinical development, the pharmaceutical industry is generally uninterested or unwilling to support the necessary clinical trials to establish safety and test for preliminary evidence of efficacy in children.

Some companies have dipped their toes in the water, for example, by a planned lowering of the age limit for trial inclusion once initial adult phase I studies have established a biologically effective dose.[12] However, as seen in the case of the insulin-like growth factor I receptor antibodies, these trials were opened too late in each company’s overall development of these agents in common adult cancers. When the latter late-phase trials failed to show efficacy, there was no longer any incentive for the companies to pursue marketing authorization. Hence, the drug supply was no longer available for the already planned trials in the embryonal tumours of childhood and, therefore, could not be taken forward by the academic investigators who had initiated them.[13] Some companies have invested in setting up specific early phase paediatric trials to take advantage of the regulatory incentives to develop new or better drugs for children. However, the costs and complex bureaucracy involved mean that such trials are usually opened at a very limited number of treatment centres and not in every country. This limitation increases the difficulties for clinicians looking after a child with a cancer who has failed to respond to all standard therapy to offer the trial to families.

On the positive side, academic investigators supported by governmental medical research funding have succeeded in running paediatric preclinical testing programmes in childhood

cancers—most comprehensively in the USA,[2] but also in Europe.[14] These studies have provided a rational basis for which drugs are taken forward to trial, as well as trial design, but need to be better connected to and supported by the pharmaceutical industry to be sustainable.

What are the major difficulties in running paediatric oncology trials?

P.C.A

Paediatric oncology is an almost unique medical subspecialty that has evolved for >60 years, in which clinical research is highly integrated with clinical care. Research partnerships with families have taken place consistently for generations of children and, to this day, no other field has a higher degree of participation from patients in clinical research. Although patient accrual in clinical trials is often listed as the primary hurdle in medical research, this drawback is fortunately not a major limitation in childhood cancer research.

There are, however, two overarching challenges regarding clinical trials for childhood cancer drug development. The first challenge is how best to integrate novel therapeutics into treatments that may be effective, but too often carry both severe acute and lifelong adverse effects. The second one is the fact that success of frontline treatment for many childhood cancers results in a decreased number of children potentially able to participate in phase I trials, as such trials are usually conducted in patients with relapsed or refractory disease.

With an increasing number of new targeted agents in the development pipeline, the research community will need to further extend phase II studies to include appropriate populations of children with cancer. Such phase II studies should be considered not only for newly diagnosed patients with high-risk disease or very high-risk disease but also—under certain circumstances—for the intermediate-risk population. For children with disease classified as intermediate risk, 5-year event-free survival in general is in the range of 60–85%. This survival rate should still be considered an unacceptable risk of death from the disease, and for certain new agents, a strong case can be made to conduct phase II investigations of novel agents integrated with frontline standard treatment in children across a spectrum of risk strata.

P.J.H

Cure rates for many childhood cancers exceed 70%, and 5-year event-free survival is approaching 80%. Thus, there are relatively few patients eligible for phase I–II trials and, historically, relatively few new anticancer agents have been adequately tested in children. Furthermore, even patients that ultimately succumb to their disease might have a good initial response to treatment. Most phase II trials enrol patients either at relapse or who are refractory to standard-of-care therapy. These patients might represent a poor ‘signal’ population, because they might have multiple mechanisms of resistance that greatly reduce the activity of the agent, whereas if the agent was tested at diagnosis it may have significant activity.[15] The concept of ‘window’ studies, whereby a novel agent is tested against high-risk patients (those with predicted long-term survival of <20%—such as metastatic sarcoma at diagnosis), has fallen from favour; however, both topotecan and irinotecan were developed in such high-risk diagnosis populations.[16] With the increasing use of molecularly

targeted therapies it is important to match the right drug to the right patient and to develop pharmacodynamic biomarkers as surrogates for early response to therapy. Currently, there is no nationwide network to sequence tumour and normal tissue to identify 'actionable' mutations—such as the *BRAF* mutation in glioma. Also, sequencing data emerging from several sources suggest that the frequency of mutations that 'drive' adult cancer may be very rare in most paediatric malignancies. Moreover, although pharmacodynamic studies are conducted within the Children's Oncology Group (COG) phase I consortium—which usually measure surrogates in blood—a better standard of training is required to ensure that when samples are collected, they can still be analysed and are informative when reaching the assay laboratory.

G.P

Numbers of patients, funding, infrastructure, regulations and, to some extent, ethical issues can be counted as the major difficulties in running clinical trials in paediatric oncology. Not only are cancers in children rare (<1% of cancers),[17] but the progressive refinement of risk-based algorithms according to biopathological characteristics of patients and their tumours are creating even smaller clusters of patients.[18,19] Thus, to collect statistically meaningful cohorts of homogeneous patients, it is becoming crucial to form large modern cooperative efforts in the international community. In this regard, having adequate financial support to run large, international trials is becoming an increasingly relevant problem. Furthermore, the infrastructure to conduct modern clinical trials in paediatric patients with cancers is not available in most countries. This stands particularly true if one considers how entry criteria have increased in complexity—genetic and proteomic data are needed to enrol children into such trials, and the tools to obtain the type and quality of information might not be readily available. Expanding international cooperation also implies harmonization of different regulatory requirements, a process that will further delay the already long procedures for launching clinical trials.[20,21] Furthermore, methods must be implemented to facilitate access to new drugs. Finally, the ethical implications of conducting early drug development research in childhood and adolescent cancers are also under constant debate, and include the need to develop appropriate and reliable information and consent processes.[22]

K.P.-J

Once a supply of a relevant new drug has been secured, several further challenges must be overcome. Due to the low mortality rates from cancer in childhood, the number of children eligible for early phase trials in any one region or country is small and will be made up of a wide range of diagnostic and molecular subgroups.[23] For example, only 2–3 children each year in the UK have multiple-relapsed, high-risk-histology Wilms tumour. Thus, any trial targeted specifically to this group, which itself comprises more than three distinct molecular entities, requires international collaboration and considerable resources. Whilst academic investigators already have long-established collaborative clinical research networks, they face challenges in obtaining grant funding for rare indications and need to compete for the attention of the finite clinical research workforce at the treatment centres.

Trial design is another challenge, since the rare child with an eligible but rapidly growing embryonal tumour might deteriorate whilst waiting for a 'slot' to become available on a

conventional phase I trial. The trial design itself slows recruitment and limits access to new drugs for patients. This obstacle is being overcome with increasingly flexible designs that avoid 'waiting lists'—such as the so-called rolling six design and continuous reassessment methods.[11] In the randomized trial setting, a new drug can be added to similar but nonidentical background therapies (for example, different chemotherapy backbones), a design that accommodates differences in national practice that are not thought to materially affect efficacy.[24] These pragmatic approaches can succeed in accelerating recruitment rates, but also benefit from and increasingly mandate multiple tissue sampling to ensure the drug is acting through the molecular pathway it is believed to target and to provide insight into tumour response.

In this regard, testing noninvasive biomarkers is attractive but poses challenges in small children. Functional imaging through MRI sequences that measure diffusion and perfusion, or spectroscopy, require general anaesthesia, which is logistically difficult, especially if required at several time points. Blood volumes required for circulating tumour cells or DNA extraction might be onerous in a small child and present difficulties in obtaining ethical approval, especially from a nonspecialist review board unfamiliar with the clinical unmet needs of children with cancer. The input of paediatric pharmacology researchers is needed for an adaptive trial design that can move rapidly to a limited sampling technique, based on early analyses.

What is the implication of molecular profiling on running paediatric oncology trials and how can these challenges be overcome at the hospital or group level?

P.C.A

The ongoing molecular characterization of childhood cancers will further subdivide disease classifications into smaller subpopulations, requiring an even greater level of global collaboration to conduct impactful research. Building on existing infrastructures that routinely conduct research in rare diseases, we will have to create new platforms that enable rapid identification of molecular subtypes of cancer at time of diagnosis and at time of relapse, facilitating enrollment in clinical trials specifically designed to explore an array of therapeutic targets. Collaborative research programmes must continue to improve the efficiency with which scientific advances can be translated into well-designed clinical trials. Enthusiasm about molecular profiling of childhood cancers, however, must be tempered given the significant gaps in knowledge that currently exist. Early wins will be further constrained by the relatively quiet mutational landscape of the majority of common childhood cancers, suggesting that identification of key drivers may not primarily derive from genomic sequencing strategies.

With the emergence of a number of commercial genomic sequencing ventures, there is the risk that—without a robust clinical trial platform to investigate rare molecular subtypes of childhood cancer harbouring the identified molecular target—clinical research may devolve into reports of small case series, precluding previous meaningful advances in treatment. Trials of $n = 1$ populations will defy interpretation. Similarly, small studies using

combinations of novel agents with active, cytotoxic regimens will neither be interpretable nor offer conclusive advances. For many targeted new agents, an increasing number of randomized phase II trials will need to be undertaken, with a focus on assuring that designs yield interpretable results.

P.J.H

Molecular profiling will further complicate the design of paediatric oncology trials, and possibly increase the time to complete the trials. Molecular profiling can be valuable for stratification of patients into risk groups, and potentially to stratify patients to receive targeted therapies. This field of clinical research is still in its infancy, but one can predict that subgrouping rare tumours into even smaller groups for testing novel therapies will present complex logistical issues. Identifying these patients and stratifying them to receive a targeted therapy will require significant resource allocation. An alternative approach is to profile each cancer using commercial vendors that report back the mutation status of a panel of cancer-related genes and might contribute to identify actionable mutations. It is important to consider that all data so far indicate that childhood cancers have far fewer mutations than adult cancers, and that mutations common in carcinomas are very infrequent in childhood cancers. Profiling can be valuable in deciding therapy, as certain mutations are associated with hypersensitivity to certain drugs (as in the case of crizotinib in anaplastic large-cell lymphoma); however, the same genetic aberration may or may not predict sensitivity in neuroblastoma. The rapid emergence of resistance to targeted therapies means that profiling should be considered a dynamic process requiring multiple biopsies during the course of the disease. Profiling must ultimately account for changes in signalling pathways that circumvent target inhibition. In my opinion, profiling every child diagnosed with cancer will require enormous resources, with potentially little return. We hope that through profiling we can select the best therapy for each patient; however, at this time there is relatively little data to support this anticipation. Perhaps taking a focused approach—by selecting few patients where there is some rationale to support profiling —and testing whether therapeutic decisions based upon profiling significantly improves outcome, would be a starting point to assess the validity of such an approach.

G.P

Molecular pathology is used to formulate the final diagnosis of many adult and childhood cancers and, subsequently, to stratify patients into specific risk groups and allocate them into specific treatment arms.[25] This strategy stands true particularly for phase I and phase II trials, in which agents selected to target aberrantly activated molecules are expected to work only in patients with tumours harbouring that specific abnormality. Thus, it is essential to have the pertinent biological information available, almost in real time, before entering a patient into a trial. However, obtaining such biomarkers requires modern genetic investigations—for example, molecular gene profiling, exome sequencing, whole-genome sequencing and methylation pattern determination—that use equipment that are expensive, not universally available and have a short lifespan. At the hospital level, this implies expanding the spectrum of the diagnostic tools available to formulate the modern diagnosis and then to acquire all the institutional credentials necessary to participate in the relevant trials. As a consequence, only selected centres can join the research consortia investigating

new compounds,[14,26] limiting access of innovative therapies to few children. For phase III cooperative trials, the solution that is emerging to maximize the trial population is to use well-equipped national or supranational laboratories to circulate biological samples and generate high-quality data for enrollment and monitoring. Concurrently, the appropriate 'language' to share the enormous data generated from the modern sequencing techniques must be also be developed.

K.P.-J

Mortality rates have fallen faster in childhood haematological malignancies, for which molecular profiling has been easier and more revealing of genetic subtypes than in solid tumours.[27,28] However, efforts in this area are essential if new and less-toxic agents are to be introduced to replace conventional cytotoxic therapies, with all their acute and long-term adverse effects in the growing child. Until recently, the leukaemias and lymphomas had the advantage of carrying activating mutations in kinases and other targetable proteins, whereas the solid tumours were mostly characterized by nonactionable mutations (such as fusion gene translocations affecting transcription factors). Whole-exome and whole-genome analyses are now changing this situation quite rapidly, revealing mutations in genes that are also mutated in adult cancers, and for which targeted agents might already be available. This development puts the onus on the paediatric oncology community to run trials that mandate collection of relevant biological material for molecular testing, both to identify predictive biomarkers for response (and toxicity) and to continue to improve understanding of the molecular drivers of the various childhood cancer subtypes. Mandatory companion biomarker studies do not necessarily mean that only those tumours with the predicted relevant molecular abnormality should be eligible. Much information of clinical relevance can be learnt from responses amongst children with molecularly uncharacterized tumour types, providing efforts are made to ensure they have relevant high-quality tissue samples stored for future testing. We do not yet know what 'off-target' mechanisms will become apparent or which biological pathways await discovery in the known subgroups of mutationally silent tumours revealed by 'omics' analyses. Also, having a less-restrictive recruitment arm within a trial expands the portfolio of trials in which a patient would be eligible to participate and, therefore offers families more treatment choices.

What role do non-governmental organizations (NGOs) and not-for-profit research institutions have in this issue?

P.C.A

There will be an increased need for public–private partnerships to develop novel targeted therapeutics for the rare and ultra-rare cancers that occur in children. Almost 10 years ago, the Institute of Medicine (IOM) made recommendations for developing drugs for children with cancer,[29] which included the proposal to create a virtual drug development enterprise that would foster a range of partnerships in the drug development process. These recommendations remain valid and even more necessary today. Although the infrastructure for childhood cancer clinical research exists and is able to conduct the necessary clinical investigations for new agents, clear gaps remain in drug discovery, medicinal chemistry,

biomarker development, and pre-clinical testing. Greater investment to bridge these critical gaps in knowledge is needed.

P.J.H

There are several realities we have to consider. Firstly, the oncogenic 'drivers' for many paediatric cancers are unique, different from adult cancers and, therefore, not a priority for pharmaceutical companies—or even academic investment. The second reality is that many of these 'drivers' are chimeric transcription factors that historically represent 'undruggable' targets. Thus, we have a situation that can be perceived as high-risk and no-gain. Consequently, nongovernmental organizations (NGOs) and not-for-profit organizations might be the only way, short of significant government investment, to support the development of paediatric-cancer-specific drugs. Advocacy groups are starting to play more of a part in drug development (such as in cystic fibrosis), although those focused on childhood cancer tend to fund relatively small projects with restricted periods of funding. Developing a coordinated programme to identify targets, and develop robust screens, will require significant resources and time, as well as input from industry and academia. I believe that with new approaches to drug development, such as fragment-based design, structure–activity relationship by NMR, surface plasmon resonance and high-throughput screening, could make these undruggable targets druggable. Expression of an oncogenic fusion protein as a driver may induce cell death and necessitate suppression of other genes to maintain viability. Alternatively, the function of an oncogenic fusion protein might require activation of specific pathways, such as DNA damage repair, to drive proliferation. In either case, identifying synthetically lethal interactions with the driver mutation can identify novel targets that would be cytotoxic when inhibited or synergistic with conventional therapy (such as PARP inhibitors in combination with temozolomide, for *EWS*/*FLI1*-driven Ewing sarcoma).[30] The development of an infrastructure to enable a concerted effort to identify childhood cancer-specific agents could be facilitated by NGOs, but would ideally benefit from the collaboration with pharmaceutical industries.

G.P

As well as provide funding for research, NGOs must take part in advocacy—to influence the policies regarding paediatric oncology in general and, in this case, the research into new drugs for childhood cancers.[31] More precisely, there is a need for partnerships that involve all possible stakeholders: the philanthropic organisations, parent and patient organisations, research-funding agencies and not-for-profit organisations (including scientific societies other than the public health authorities). In this regard, the International Society of Pediatric Oncology (SIOP) is advocating for the inclusion of childhood cancers into the global health agenda promoted by the WHO, into the programme that seeks to reduce the global burden on noncommunicable diseases.[32,33] Once on the WHO global agenda, it will be easier for NGOs and not-for-profit research institutions to take leading roles in guiding biopharmaceutical industries—as well as policy makers—to favour research in paediatric oncology, which is currently hindered because financial revenues are not as high as in the adult market. This advocacy role must be directed at guaranteeing the greatest access possible to innovative therapies to all children with cancer who need them. Saving life-years

in children by increasing survival from cancer on a global level has an obvious and long-standing benefit for society.

K.P.-J

In most countries, drug discovery in childhood cancer has been largely investigator-driven preclinical research and clinical trials that rely heavily on cancer charities for funding.[34] Such response-mode funding is suboptimal to drive what are long-term strategic goals to address the clinical needs of improving survival rates and quality of survival. Not only must we identify more-effective drugs to continue to improve cure rates, but we must undertake research to ensure new drugs are safe in the long term and to improve supportive-care drugs to make treatment more tolerable. Additionally, the area of drug 'repurposing' is emerging, whereby drugs already licensed for use in children for another indication might have anticancer activities in another setting, dose and schedule. Securing funding for many of these under-researched areas can be difficult, hence a strong partnership between NGOs and investigators can help drive development through a collective vision.

Of course, an extremely important influence here is the parent and patient voice. As members of the public and representing those most affected by childhood cancer, this community ultimately represents the source of funds donated to charities and should be able to influence how these funds are allocated for maximum patient benefit. This influence can go beyond drug therapy, with many NGOs aiming to fund other types of support, such as nursing care and twinning programmes between centres of expertise and those with fewer resources to deliver the complex diagnostics and care that is necessary for the successful treatment of children with cancer and support to the whole family.

What role do pharmaceutical and biotech companies have in this issue?

P.C.A

The biopharmaceutical industry has a central role in the development of novel therapeutics. Whereas target discovery remains largely in the realm of academia, development of a novel therapy requires industry expertise and capabilities. The current challenges that industry are facing regarding childhood cancer drug development include economic factors, the variable but limited effect of regulatory incentives and requirements described below, and too often, an unfounded concern about the risks of conducting clinical research in children with cancer. All these factors contribute to a lack of timely paediatric drug development.

The IOM published a report in 2010 that focused on the market forces that align against industry investment in drug development for rare diseases, alongside a series of recommendations that could begin to address the unfavourable landscape of drug development.[35] Many of the recommendations for rare diseases indeed apply to childhood cancer. The regulatory requirements and incentives that have existed under the US Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), and the European Medicines Agency Pediatric Regulation, have had limited positive impact of the current landscape of childhood cancer drug development, with still too few drugs being evaluated in children with cancer and less than timely introduction of investigational drugs into pediatric development. On the US side, cancer drugs already developed for adults

almost universally receive waivers under PREA, eliminating the regulatory requirement to conduct childhood cancer studies. Although BPCA has catalysed certain paediatric studies, the programme is voluntary and the economic incentive (a 6-month extension of market exclusivity) is delayed until the end of the product lifecycle. BPCA has worked reasonably well for drugs with large market shares, in which a modest investment could result in a delayed but significant return on that investment. However, BPCA incentives might not function as well with drugs developed for smaller markets, as is increasingly occurring with adult cancer drugs. More recently, the Creating Hope Act was enacted, which provides a novel incentive in the form of a priority review voucher at the FDA, for the development of therapeutics for life-threatening paediatric diseases for which development and approval first occur in children.[36] It is too early to know the extent that this welcome incentive programme will have on industry investment in paediatric cancer drug development.

In certain circumstances, the EMA's Paediatric Investigation Plan (PIP) has had unintended consequences for childhood cancer drug development, paradoxically delaying the conduct of select paediatric phase I studies in the USA.[37] One of the reasons for this delay is that PIPs require a complete investigational plan, from phase I through to phase III, before there is actually any paediatric clinical data available to inform such a plan. The consequence of this set up is that companies can be reluctant to initiate phase I paediatric trials prior to having PIP approval, resulting in an overall delay in the whole drug development process.

Lastly, concerns occasionally expressed by biopharmaceutical sponsors that potential adverse events observed in a paediatric trial could result in delaying drug development and approval are not based on fact, as an event in a paediatric trial negatively impacting adult development has, to my knowledge, never occurred. The ability to safely conduct early phase pediatric trials, which almost invariably follow early phase adult trials, is well documented. With cancer remaining the leading cause of death from disease in children in the USA, launching early phase paediatric clinical trials in a more timely fashion must occur.

P.J.H

There are several ways in which the pharmaceutical and biotech industries can be engaged and assist in developing therapeutics for treatment of childhood cancer. At the pre-clinical level, companies could make drugs within their portfolio more readily accessible, as single agents or combinations, for preclinical testing in validated preclinical models of paediatric cancer. At the clinical level, several examples exist of companies interrupting the development of agents because they failed to meet expectations in adult patients. A good example is the recent attrition of antibodies that target the insulin-like growth factor receptor. These antibodies have significant activity against Ewing sarcoma,[38] and possibly other childhood sarcomas, and could be the basis for developing new combination therapies. However, because of failure of adult phase III trials, the development of these agents was discontinued. One company has given their remaining antibody supply to the Cancer Therapy Evaluation Program (CTEP) to allow further evaluation in Ewing sarcoma; however, the long-term prospects for development are unclear unless the antibody-producing hybridoma is made available. A system where agents no longer under

development for adult cancer treatment are made available for paediatric oncology development needs to be implemented and at a reasonable cost. Another issue is combining agents from different companies, both for preclinical evaluation and subsequently for clinical trials. To some extent CTEP has facilitated such trials for adults, but it will require a greater engagement of pharmaceutical and biotech industries for such trials to become routine. With an increasing number of paediatric oncologists leading programmes within industry, there is an increasing realization that childhood cancer should have more internal advocacy. The limitation is, of course, resource availability. Perhaps, this is an area where NGOs and pharmaceutical companies can interact to speed development of novel cancer therapeutics for children.

G.P

By definition, pharmaceutical and biotech companies have an essential role in developing new drugs for childhood cancer. The long and costly (approximately US$1.8 billion per compound[39]) process, which brings the research products from bench to bedside, cannot be completed without them. However, industry has much to gain from collaborating with international research networks, including access to an integrated network of research hubs, the infrastructure of the networks, and the inestimable experience of the stakeholders. More importantly, the international high-quality biobanks that are in development are tremendous assets for industry. On the other hand, the costly technologies required to make considerable advancements in tumour molecular and cell biology will demand biotech companies to have a central role in supporting academic research. However, biomedical enterprises, which should bring rapid and efficient changes to human health, have limitations. The so-called precompetitive collaboration, which implies the wide sharing of information, resources and capabilities early in the drug development pipeline, has been proposed to try to address this problem.[40,41] Obviously, not all these changes can occur without specific interventions at the regulatory level. Indeed, in the past decade or so, important new legislations have come into effect to reset the partnership between the biopharmaceutical industry and paediatric oncology research community, but much more should be done to specifically address the need for new drugs targeted to the unique characteristics of childhood cancers.[42–44]

K.P.-J

The current approach to licensing drugs is based on their pathological indication rather than their mechanism of action, even though the drug target for a common adult cancer, such as *ALK* in non-small-cell lung cancer, can be present and therapeutically relevant in a pathologically distinct childhood cancer, such as neuroblastoma.[45] This reality means that the pharmaceutical industry routinely receives waivers for new targeted agents because the common adult cancers do not occur in children. Accordingly, the relevant paediatric trials either occur very late, with industry support often limited to free drug, or not at all.

To tackle this situation, a ‘therapeutic alliance’ of sorts must be formed between industry, regulators, the clinical research community and patients so that drug development efforts are focused on and proportionate to the clinical unmet needs of children with cancer.[46] Pharmaceutical and biotech companies need to engage with the clinical community at the earliest stage and develop an end-to-end strategy that can be mutually beneficial.

Precompetitive research consortia could support preclinical work on childhood cancer tissues and in genetically engineered model systems to test the therapeutic potential of a range of compounds on relevant tumour subgroups and identify the best schedule for companion biomarker sampling to facilitate trial design. Such preclinical work is best undertaken by researchers who are immersed in the biology and clinical behaviour of the various childhood cancers, based in academic institutions where they can access samples readily. Industry needs to seek advice from multinational clinical trial groups to ensure that the study proposals that are industry-initiated address a clinically relevant unmet need and that trial designs are acceptable to patients and families and feasible in terms of recruitment numbers and geography.

For some childhood cancers, paediatric-specific targets are known that are not yet found in adult cancers. Drug development in this area has been largely investigator-initiated, and then spun out to interested, generally small biotech companies, which has presented some challenges in terms of sustainability around an often single, highly complex product. Again, earlier interactions and mutual planning should mitigate some of these risks.

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Biographies

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