A QUEST TO FIND CURES FOR PAEDIATRIC CANCERS
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Cancer mortality among children ages 0-19 declined from more than 5 per 100,000 children in 1975 to about 2.1 per 100,000 between 2010-2014. Some cancers, such as acute lymphoblastic leukaemia go into remission in 98% of cases and have a 90% cure rate, defined as more than 10 years of remission. Most childhood cancers are not inherited but are primarily the result of DNA changes that occur early in the child’s life, sometimes even before birth. Although the odds of a child developing cancer by the age of 19 are only 1 in 330, cancer is second only to accidents as a cause of death in children. Because of major treatment advances in recent decades, more than 80% of children with cancer now survive 5 years or more. Overall this is a dramatic increase since the mid-70s, when the 5-year survival rate was about 58%, but nevertheless survival rates vary depending on the type of cancer. Cancers that develop in children include leukaemia, brain and spinal cord tumors, neuroblastoma, Wilms tumor, lymphoma, including Hodgkin and non-Hodgkin lymphomas, rhabdomyosarcoma, desmoplastic small round cell tumor (DSRCT), retinoblastoma, and bone cancer, including osteosarcoma and Ewing sarcoma.

Starting from the premise that no child should die of cancer, we have built a pediatric cancer research program designed to overcome many of the factors that limited progress in paediatric cancer treatment in the past. Much of pediatric cancer therapy was designed based on our understanding of adult cancer biology. However, paediatric cancers diverge from adult malignancies in several ways. Perhaps most importantly, they harbour far fewer genetic mutations than their adult counterparts. In some cases, single mutational events, such as fusion genes generated by reciprocal chromosomal translocations, drive paediatric cancer pathogenesis providing potentially unique therapeutic targets. However, the study of paediatric cancer biology has been challenging for several reasons. First, paediatric cancers, particularly solid tumours, are rare, rendering the abundance of primary material far lower than that of most adult cancers. Second, modelling of paediatric cancers in genetically modified mice has met with mixed results and has been unsuccessful for numerous malignancies. Although established cell lines from most solid paediatric cancers are available, they have adapted to in vitro culture for years and may no longer display the properties of tumour form which they originated.

To circumvent these limitations we are recruiting primary paediatric cancer material from multiple centres around the world and are using primary human mesenchymal cells from which many paediatric sarcomas originate. Although this is a far more complicated approach than working with mouse models and cell lines, it directly addresses the biological properties of the tumours themselves as well as the mechanisms implicated in the transformation of primary human cells that lead to the formation of these same cancer types. In the process of establishing our program, we have acquired a unique expertise in handling rare pediatric cancers and in exploring their biological properties. This has led us to identify a number of properties that we would not have identified had we relied on mouse models or established cell lines.
We have established a paediatric cancer-training program to which we recruit MD-PhD candidates whom we provide with intensive research training prior to their clinical residency. The candidates compete for fellowships within a highly competitive MD-PhD program and we select the most motivated students who have a genuine desire and drive to become physician scientists. The students engage in a 4-year research program at the end of which they obtain their MD-PhD. They are then hired in the paediatric residency program which provides them with 20% protected time for research during their clinical training. They can thus participate in lab meetings and be involved in the continuation of their research projects. At the end of their clinical training in paediatric oncology, they can select their career path: 80% research and 20% clinical activity; or 80% clinical activity and 20% research. The training of MD-PhDs will provide a unique staff in paediatric oncology composed primarily of physician-scientists who bring essential questions from the clinic into the laboratory and conversely, bring into the clinic an analytical approach provided by a scientific mind. The end result will be a fusion between clinical and experimental medicine that will provide a powerful foundation for translational medicine at its best.

Our focus is on solid paediatric malignancies. We want to understand how primary cells undergo transformation in response to oncogenic events, some of which are specific for paediatric cancers, including a number of reciprocal chromosomal translocations that give rise to Ewing sarcoma, synovial sarcoma and alveolar rhabdomyosarcoma, to name but a few. These events are probably not limited to occurring in children but the cells that are permissive for their transforming ability are most likely far more abundant in children than in adults. These cells may display a higher degree of plasticity and pluripotency than their adult counterparts. Indeed, we have shown that mesenchymal stem cells (MSCs), which are a heterogeneous population of stromal cells that can differentiate into a variety of lineages are the most likely cells of origin of several childhood sarcomas. However, MSCs are also present in adult tissues, suggesting that there may be specific MSC subpopulations in children that become depleted in adults and that are particularly permissive for the expression and function of aberrant oncogenic fusion proteins. We have in fact shown that the single fusion gene responsible for the generation of Ewing sarcoma has a far more potent effect on paediatric than on adult MSCs. One of our quests is to characterize these putative subpopulations and determine their biological properties, which should lead to an understanding as to why they are particularly permissive for oncogenic events toward which other MSCs are prohibitive.

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Sarcomas are notorious for relapse following treatment and for dissemination. One underexplored area of sarcoma biology is the interaction of sarcoma cells with the stroma. In carcinomas, this is an intensely investigated field that has shown that the stromal, “wound healing” response to cancer growth conditions cancer cell behaviour, helping sustain their survival, division and dissemination. In sarcomas, the interaction with the host tissue stroma is virtually unexplored. Given that sarcomas are in a sense a malignant stroma, the obvious question is to what extent the normal stroma contributes to sarcoma dissemination. This is an area of investigation in our lab, focusing on the role of normal MSCs and other stromal cells including activated fibroblasts as well as haematopoietic cells in promoting sarcoma dissemination.

Finally, our goal is to address sarcoma heterogeneity. Cancer heterogeneity arises by several mechanisms, including clonal evolution, where different cancer cell clones arise as a result of
the accumulation of novel mutations. Some of the novel mutations confer growth advantage whereas others may inhibit growth. The emergence of different clones shapes the identity of the tumour, which is determined by clones that have the greatest survival and proliferative advantage. These clones also display variable behaviour in response to therapy and some of them may be responsible for resistance to cytotoxic drugs. Because of the relative genetic quiescence of paediatric cancers, clonal evolution may not be the primary determinant of heterogeneity. Another mechanism of heterogeneity is the establishment of a cellular hierarchy, which mimics, albeit in aberrant fashion, hierarchies that are established during normal tissue development. At the apex of the hierarchy are poorly differentiated cells that display pluripotency and give rise to heterogeneous progeny, most of which is not tumorigenic. These cells have the ability to self renew and to initiate tumour growth and are commonly referred to as cancer stem cells (CSCs). We have shown that Ewing sarcoma behaves according to the CSC model and have identified CSCs in these tumours. We are currently addressing tumour cell heterogeneity in a series of other solid paediatric tumours. Cancer stem cells are most likely a major component of the driving force in these tumours and need to be targeted therapeutically. They usually display resistance to conventional cytotoxic drugs, which typically eliminate rapidly dividing bulk tumour cells.

Most paediatric malignancies develop and behave in ways that differ from those of adult cancers, largely due to genetic and epigenetic differences. In contrast to the majority of adult cancers, which develop years to decades following transformation of a single cell, paediatric cancers, particularly those that occur in the first few years following birth, emerge far more rapidly. As already discussed, genetic analyses have shown that whereas most adult cancers accumulate numerous genetic mutations, paediatric cancers are for the most part genetically “quiescent”. Many mutations can contribute to adult cancer growth and different mutations may drive progression of any given cancer at different stages of its evolution. It may therefore be difficult to determine which mutation(s) is/are driving an adult cancer at the time of diagnosis. In contrast, mutations responsible for paediatric cancer development are easier to identify, which facilitates exploring the pathogenesis of these tumours and obtaining clues as to potential therapeutic targets and options.
Although genetic mutations have long been thought to play the key role in the pathogenesis of cancer, it is becoming increasingly clear that in many malignancies, posttranslational and epigenetic modifications may play an equally important role, sometimes even dominating that of the genetic mutations. “Epigenetics” was originally coined to describe heritable changes in a cellular phenotype that were not due to alterations in DNA sequence. It is most commonly used to describe chromatin-based events that regulate DNA-templated processes such as gene expression. Chemical modifications, such as methylation, of DNA within gene promoters and of histones (acetylation and methylation), which are proteins intimately associated with DNA, provide mechanisms that control gene expression. Histone modifications determine whether DNA segments assume a compact or relaxed structure. Activating histone marks are associated with relaxed DNA that is accessible to transcription factors, allowing expression of genes within the corresponding DNA segments. Repressive histone marks induce DNA compaction rendering it inaccessible to the transcriptional machinery and resulting in the silencing of genes located in the corresponding DNA segments. As the genes in question may control cell division, growth and survival, regulation of their expression by epigenetic modifications may be a key determinant of cancer development, behaviour and response to treatment.

Increasing evidence suggests that epigenetic changes play a critical role in the development of paediatric sarcomas. The fusion proteins encoded by fusion genes that arise from unique chromosomal translocations, which provide a diagnostic signature for these particular types of cancer, are responsible for their pathogenesis. In the majority of cases, the fusion proteins behave as aberrant transcription factors or transcriptional regulators. They alter the gene expression repertoire of the cells, augmenting the expression of genes that promote cell survival and growth and silencing those that induce differentiation and quiescence. To execute their functions, these aberrant transcription factors may form complexes with chromatin-modifying enzymes and instruct them to reconfigure DNA structure, opening domains that in normal cells remain compact and therefore inaccessible to transcription, while condensing domains that are open in normal differentiated cells. Chromatin modification may thus contribute to critical changes in the gene expression profile of the cells, rendering them more susceptible to uncontrolled division, inhibiting their differentiation and maintaining them in an undifferentiated, pluripotent, state, which resembles that of stem cells. Aberrant transcription factor-driven chromatin modification may therefore recapitulate a developmental state and establish a cellular hierarchy within the tumour, which mimics that of normal developing tissues, albeit in an aberrant fashion. It may also ensure cell plasticity, such that the tumour cells may oscillate between a CSC a more differentiated state, possibly switching from one to the other in response to a variety of stimuli including cytotoxic drugs. Such phenotypic plasticity may be one factor that renders effective therapeutic targeting so difficult.

Our quest is to understand the mechanisms that underlie paediatric cancer formation and to identify those that may be targetable from a therapeutic standpoint. We are focusing on paediatric sarcomas whose pathogenesis is driven by unique fusion proteins described above. We have begun to understand how the fusion proteins associated with defined paediatric sarcomas transform MSCs and to unravel the mechanisms whereby they drive tumour development and progression. Because they are unstructured proteins, the aberrant transcription factors that underlie sarcoma pathogenesis cannot be readily neutralized by specific drugs. It is therefore essential to identify the downstream events that they initiate, which could be amenable to drug targeting. To that end, we have identified some of the key posttranslational and epigenetic mechanisms induced by the fusion proteins that underlie transformation and tumour progression and are now exploring approaches to target these particular mechanisms and develop new and effective ways to treat these tumours.
Dr Miranda Fidler from the International Agency for Research on Cancer highlights the burden of cancer and the need for prevention, diagnosis, and care…

Cancer is a major cause of morbidity and mortality across all age groups in both developed and transitioning countries. Although substantial research on cancer in children and older age groups has been undertaken, the burden of cancer among young adults (20-39 years) has rarely been studied in depth, often being overlooked by cancer researchers and policymakers alike. With an increasing need of international research investigating the specific issues unique to this age group of cancer patients to improve cancer-related outcomes, a recent report sought to assess the scale and profile of young adult cancers globally.

Analysis
Although it is broadly accepted that the age range for childhood and adolescent cancer is 0-14 and 15-19 years, respectively, the age range for young adult oncology is less clear as there is no uniform opinion on the upper age limit for this group. In the study by Fidler et al, young adult cancers were defined as those that occur between the ages of 20 and 39 years, which is in line with that suggested by the Adolescent and Young Adult Oncology Progress Review Group.

Using the International Agency for Research on Cancer (IARC)’s GLOBOCAN database, the study authors estimated the number of new cancer cases and cancer-related deaths for all cancers combined (excluding non-melanoma skin cancer), as well as by 27 specific cancer sites. Variations in the cancer burden among young adults were assessed at the country and regional level, as well as by the Human Development Index (HDI), which uses life expectancy, education and gross national income to give an indication of socioeconomic development.

Global burden and cancer profile
In total, an estimated 975,000 new cancer cases and 358,000 cancer-related deaths occurred among young adults globally in 2012. Of these, 65% of all new cancer cases and 54% of cancer-related deaths occurred in women.

The cancer profile among young adults was observed to bridge between pediatric and adult oncology. Common tumour types in children and adolescents, including leukaemia and cancers of the brain/nervous system were among the higher-ranking cancers at ages 20-39. However, common epithelial tumours such as breast, cervical, and colorectal cancer were more frequently observed among young adults than children or adolescents, though still to a lesser extent than that observed in older ages.

Breast or cervical cancer was the most common cancer type in young adults for most countries in terms of incidence and mortality and together...
accounted for about 302,000 (31%) of the total estimated new cases and about 77,000 (21%) of the total estimated cancer-related deaths. Other frequently diagnosed cancers included thyroid cancer, leukaemia, and colorectal cancer. In terms of deaths, leukaemia, liver cancer, and brain/nervous system tumours were large contributors to the burden in addition to breast and cervical cancer.

Global variations
Variations in the cancer burden among young adults were evident when the data were stratified by the HDI. Breast and cervical cancer were ranked the first and second most common cancers, respectively, in the low, medium, and high HDI levels, whilst at the very high HDI level these cancers ranked first and fifth, respectively. In general, cancers associated with infection, such as liver cancer and Kaposi sarcoma, were more frequent in countries indexed within the low HDI level, whilst thyroid cancer, skin melanoma, and testicular cancer were highly frequent in very high HDI regions.

Such differences in the distribution of cancer types, with more fatal cancers generally more prominent in low HDI settings, was in turn partially responsible for the poorer cancer outcomes noted among young adults from these regions. Fractured health infrastructures, the detection of cancers at a later stage and poor access and availability of treatment also likely relate to the worse outcomes in less developed regions.

Moving forward
With nearly one million cancers occurring among young adults worldwide in 2012, efforts are urgently needed to address the cancer burden in this age group. Particular opportunities for improvement relate to:

- Cancer prevention;
- Early detection and timely diagnosis;
- Access to appropriate and affordable treatment and;
- Expanding the young adult cancer agenda beyond high-income countries.

For example, given the particularly heavy burden of breast and cervical cancers, increasing awareness of cancer in young women at both the public and professional levels as well as timely treatment is of key importance. National human papillomavirus (HPV) vaccination programs, early detection, and, in women older than 30 years, screening, could significantly reduce the global burden of cervical cancer in young women, at a limited cost.

In closing, although cancer is less frequent in young adults than at older ages, its impact remains considerable because these individuals have a large proportion of their expected lifespans remaining, contribute substantially to the economy, and play an important role in caring for their families.

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As young adult cancer patients exhibit a combination of features observed in younger and older patients, it is crucial that progress is achieved through a combination of the methods that led to improvements in these other groups: advancement of risk stratification and treatment protocols through clinical trials in children and implementation of effective prevention and early detection at older ages.


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A Quest to Find Cures for Paediatric Cancers

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