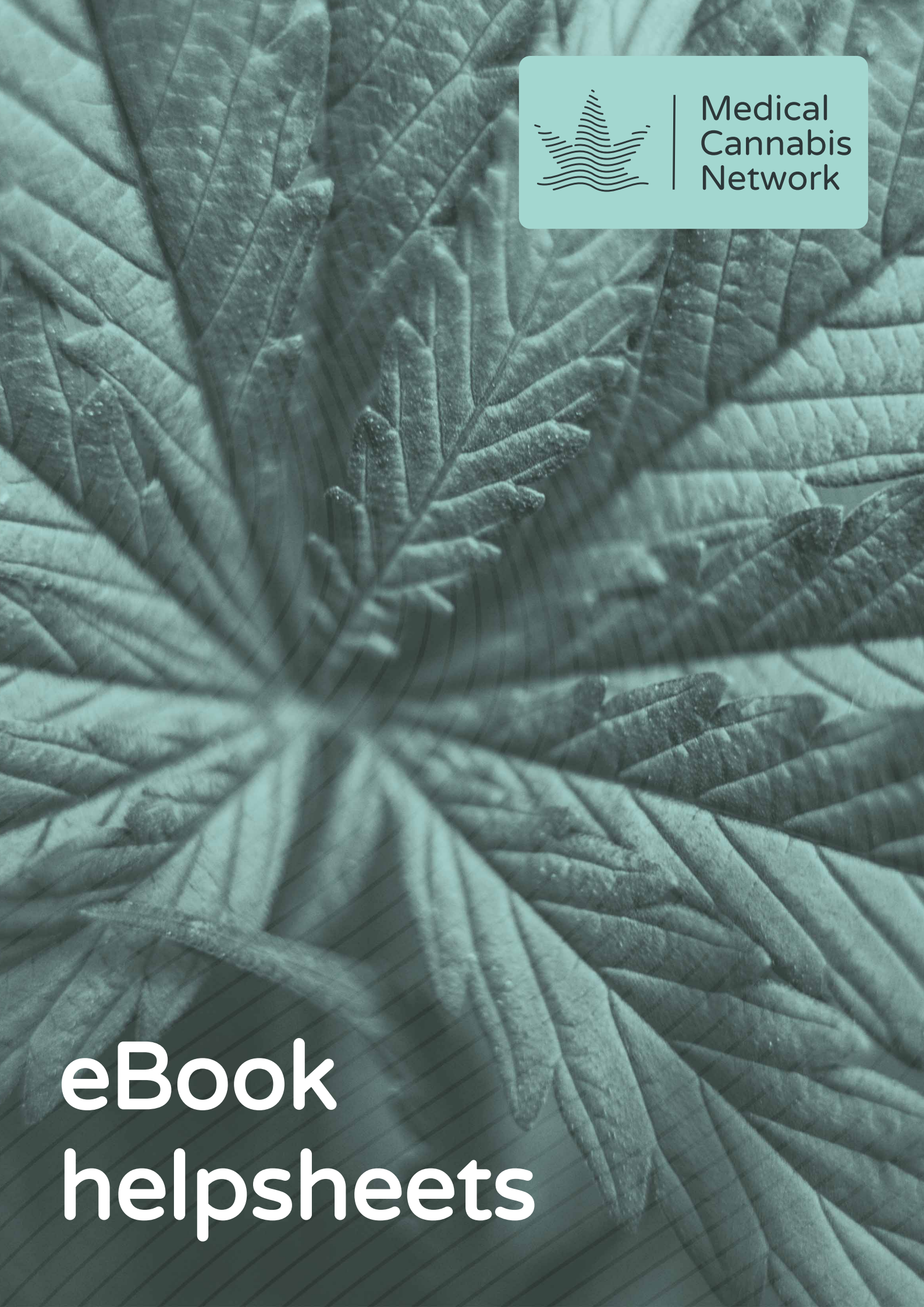
Medical
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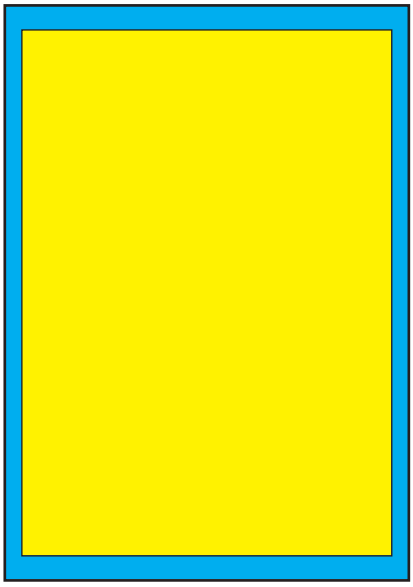
eBook
helpsheets

Page dimensions

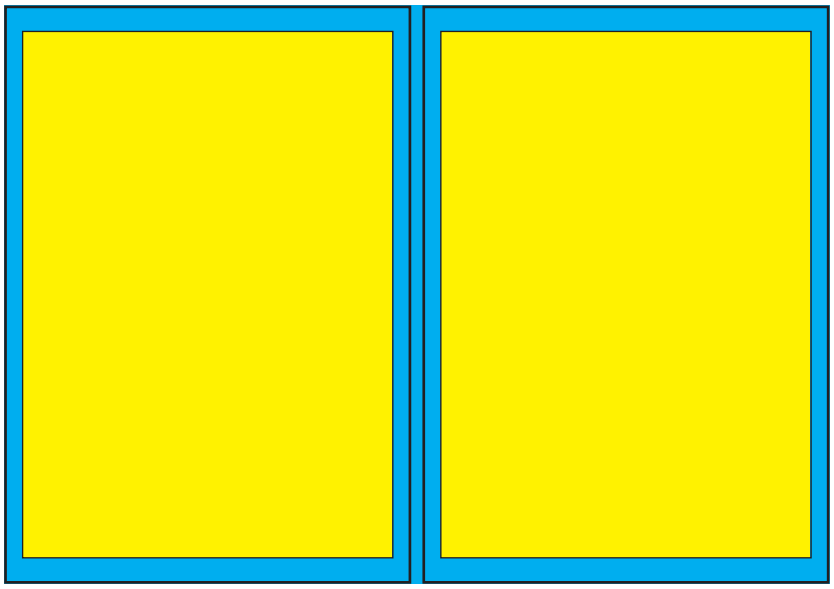


3) Glossary of terms

Trim size:	The finished page size.
Type area:	The maximum area that can be used for type.

1) Full page

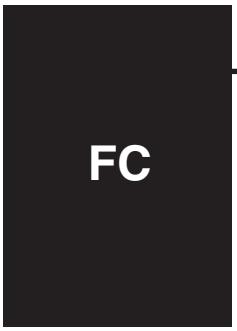
		Height		Width
Trim size:	297mm	x	210mm
Type area:	279mm	x	192mm



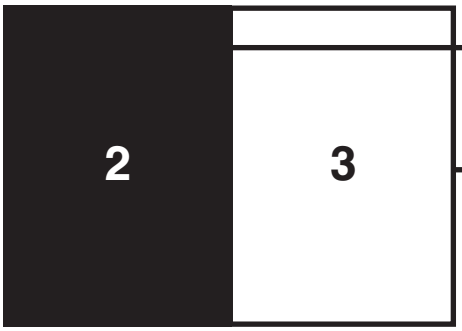
2) Double page spread

		Height		Width
Trim size:	297mm	x	420mm
Type area (each page):	279mm	x	192mm

Suggested page layout

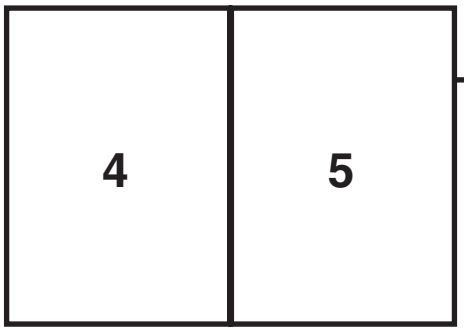


Front cover: Main image, usually with eBook title and company logo.

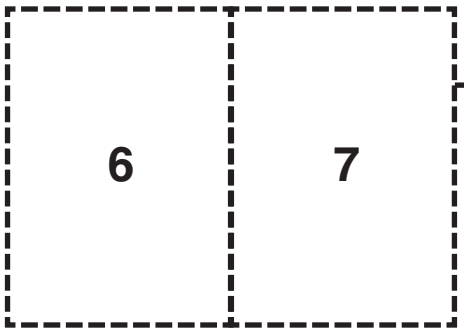


2. Advert: Company advert

3. Introduction: Introduces the eBook, author and eBook subject.



4/5. Main body: The main body of the eBook. Usually including supporting images/figures.

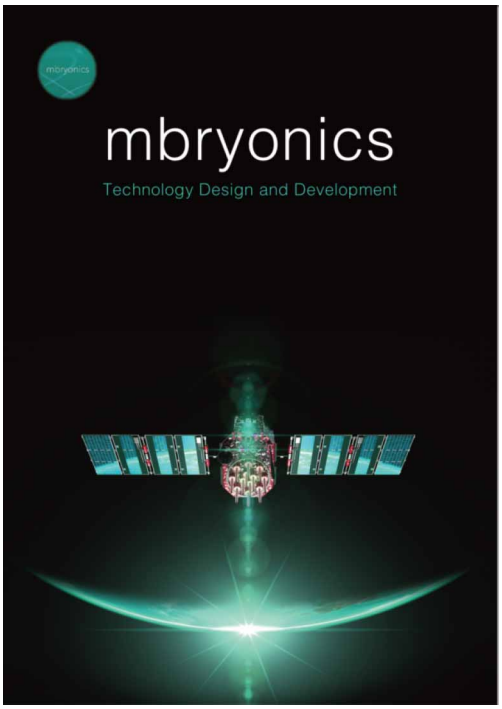


6/7... Extra pages: Any extra spreads beyond pages 4 and 5 are usually an extension of the main body.

Back cover: Can be plain or an image. Includes company logo and contact details.

eBook examples

Front and back cover: Includes title, logo and contact details.
See below example here.



Standard word count: Around 1000 words per spread. Even mixture of image and text.
See below example here.

Text heavy: Around 1800 words per spread. Smaller headlines and font. Few, if any images.
See below example here.

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adhesion via a complex network of target genes. Msi1 expression levels influence both radio- and chemo-resistance and its function are required for the survival of tumor-initiating cells. Msi1 is validated as a critical oncogenic factor, and a small molecule inhibitor that blocks Msi1 RNA binding domains has been identified. (6) Optimisation to improve its potency and pharmaceutical properties is ongoing with the objective of identifying a molecule for use in cancer therapy.

Analysis of several hundred glioblastoma samples compiled by the TCGA (The Cancer Genome Atlas) produced an extensive transcriptomic map, identified prevalent chromosomal alterations and defined important driver mutations. However, as of today, clinical trials based on these results have not improved patient outcome. Therefore, other regulatory routes may play a role in tumour relapse and response to treatment. Alternative splicing affects 90% of the transcriptome and is an essential source for transcript variation and gene regulation. Also, there are numerous genes involved in apoptosis, proliferation, migration, and DNA repair display cancer-specific splicing isoforms with functions distinct from the ones in healthy tissue.

Further, mutations and alterations in splicing factors are highly prevalent in multiple cancers and can act as tumour drivers. Using resources from TCGA and GTex (Genotype-Tissue Expression), expression profiles of splicing regulators in normal and brain tumor tissues have been analyzed, allowing construction of detailed maps of splicing alterations in cancer cells. Current studies will link splicing regulators to oncogenic signals required for transformation, identify critical splicing isoforms and evaluate their contribution to gliomagenesis. (7)

Many studies at Greehey CCRI are directed towards developing new, more efficient and less toxic treatments for childhood cancers. This is being done by employing unbiased high throughput genome-wide functional screens as well as small molecular screens novel targets have been identified that are critical for proliferation, progression and drug sensitivity in medulloblastoma and osteosarcoma. In particular, novel microRNAs that act as potent tumor suppressors in medulloblastoma have been identified. Interestingly, one of these miRNAs sensitises to vincristine as well as radiation response in c-myc amplified medulloblastoma by targeting microtubule dynamics and DNA damage response. (8) Several novel genes including genes associated with translation initiation and DNA repair that act as oncogenes in medulloblastoma have been discovered. Future studies will focus on safety and potency of these candidates' miRNAs as well as inhibitors of the discovered oncoproteins to be developed as novel therapeutics for treating medulloblastoma.

Low-grade paediatric astrocytomas are the most common brain tumours diagnosed in children. Most patients are cured by surgery, but where this is not possible high-dose chemo-radiation treatments are used, with consequent cognitive damage. Activating mutations of the BRAF oncogene are the most common genetic alteration in low- and intermediate grade astrocytoma. Studies by investigators at Greehey GGCR showed that activated BRAF provides a tumor-specific drug target. The activity of targeting downstream of BRAF using a MEK inhibitor, selumetinib, was confirmed in the Paediatric Brain Tumor Consortium 029 phase I trial, and this drug is now in phase III clinical evaluation. These studies will build on exploiting BRAF aberrations to reduce the dose of radiation therapy required for curative activity, and to investigate approaches to prevent the emergence of drug resistance. (9)

Although neuroblastoma is an extracranial tumour of the sympathetic nervous system, the dichotomy between low- and high-risk neuroblastoma raises compelling questions. Researchers at Greehey CCRI are investigating the molecular differences between low-risk and high-risk NB that lead to spontaneous regression in the former and aggressive recurrence in the latter; specifically, whether differentially expressed genes or non-coding RNAs (ncRNAs) shed light on the pathways that are activated or repressed thereby revealing therapeutic vulnerabilities. One focus is to determine whether alteration of specific transcripts selectively kills neuroblastoma cells in response to microtubule-targeting agents. (10) Investigators are developing resources to better understand the roles of non-coding RNAs in cancer etiology, pathogenesis, and pathophysiology, and cell lines are incorporating genome editing machinery as a platform for high-throughput screening to identify loci for which activation or repression selectively kills cancer cells or sensitises them to microtubule-targeting agents.

These investigations are uncovering novel mechanisms of regulating intracellular signalling pathways – through the identification of ncRNAs that have direct therapeutic applications or through the elucidation of pathways that can be targeted through more traditional pharmacological interventions – and providing drug candidates for cancer treatment and non-invasive biomarkers for predicting patient survival and developing personalised therapeutic regimens.

Structural Biology

Recruitment to Greehey CCRI has focused on areas that complement and strengthen existing research in the institute. We have both NMR and X-ray crystallography facilities on campus and have recruited faculty using these techniques that are interested in both fundamental studies of structure, but also in proteins that are critical players in childhood cancers.

Selectively targeting specific protein interactions can be highly beneficial for the treatment of many human diseases such as cancer. One major obstacle in realising the potential of this therapeutic approach is the lack of high-resolution structural details of the macromolecular interaction partners often due to the size, disorder and dynamic nature of the targets. An investigator at Greehey CCRI has developed unique nuclear magnetic resonance (NMR) tools that now allow such structures, even in large complexes, to be resolved. (11) NMR probes the unique chemical environment of every nucleus in a molecule, enabling an atomic picture of the structure and dynamics of biomolecules to be determined. This is particularly advantageous for studying proteins that are too flexible or dynamic to form crystals.

Applying these techniques in conjunction with conventional biophysical approaches, the structural basis of two processes intimately linked to disease progression are under investigation, namely, the structure and intermolecular interactions of the potent oncogenic transcription factor in

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Ewing sarcoma, EWS-FLI1, and the mechanism the chaperone Hsp60 uses to maintain mitochondrial proteostasis and its role in apoptosis. In a general context, these studies will teach us about the fundamental mechanisms of protein interactions, in both healthy and disease states.

Other ongoing studies seek to provide a complete and coherent picture of an emerging area of RNA epigenetics at the molecular and atomic level with a final goal to develop novel anticancer therapeutics targeting the human RNA methylome and other nucleoprotein assemblies in childhood malignancies. By employing cutting-edge structural biology methods such as X-ray crystallography, NMR, cryo-EM in combination with an array of other biophysical and chemical biology tools studies will elucidate structures and mechanisms of large nucleoprotein complexes central to normal homeostasis and cancers. N6-methyladenosine (m6A) is the most prevalent form of internal post-transcriptional modifications in human mRNAs. The m6A marking regulates cellular growth and differentiation programs by modulating localisation, translation, and stability of target mRNA transcripts. These characteristics make the m6A RNA methylome a potential therapeutically exploitable targets in certain cancers. (12)

Genomics and bioinformatics

One goal of ongoing research is to understand the genome of adult and paediatric cancer through the analysis of high throughput data sets including DNA/mRNA/miRNA sequencing, copy number, methylation, etc. Investigators, now at Greehey CCRI, spent more than six years working on brain, adrenal cancer in The Cancer Genome Atlas. A significant research direction is computational telomere biology. Telomeres are the capping structure at the end of each chromosome arm. During malignant transformation, a telomere is progressively shortened due to excessive cellular division, eventually creating a cellular stage called 'crisis.' In this stage, the cell genome becomes inherently unstable, and the vast majority of cells die except minor clones with reactivated telomerase or alternative lengthening of telomeres. Hence, a telomere maintenance mechanism is a fundamental pathway in cancer initiation. Using TCGA resource, this pathway has been interrogated by comprehensively characterising relevant genomic and epigenomic changes including somatic mutations and rearrangements in the TERT promoter region, copy number amplification and deletion of the gene, etc. The same was done to ATRX, a gene known to be associated with alternative lengthening of telomeres. We also estimated telomere length for more than 8,000 cancer samples. (13) The telomere maintenance mechanism is not only relevant in adult cancer but also paediatric cancer. One line of evidence is from high-risk neuroblastoma in which 20% of cases harbour TERT promoter rearrangements, or in Wilms tumor where the WT-1 tumor suppressor functions to suppress TERT gene expression. The modality of reactivation in neuroblastoma has not been described in adult cancers, suggesting paediatric cancer could have reached the same goal via a separate route. However, a comprehensive analysis of paediatric cancer in this regard is lacking. Ongoing studies will use in-house and public TARGET data to explore this question.

A significant new direction at Greehey CCRI is proteogenomics, a new discipline that aims to characterise proteins in the event of genomic changes and to identify new insights into diseases. An exciting example is alternative splicing in cancer. The importance of analysing alternative splicing in cancer is underscored by the possibility that some isoforms could be attractive therapeutic targets. A better understanding of the deregulation of alternative splicing in cancer will potentially reveal a group of biomarkers for tumorigenesis and metastasis.

However, although there is considerable evidence of aberrant alternative RNA transcripts in tumour samples, mainly facilitated by accumulated RNA-Seq data, it is still more difficult to characterise the existing alternative protein isoforms at a global level. (14) The goal is to develop and optimise the alternative isoform detection and quantification workflow in proteomic data, then characterise the proteomic landscape of alternative splicing in cancer and relate the findings to genomic and transcriptomic data. The goal to characterise cancer neoantigens and the adaptive immune repertoires using proteomics data is novel, and accumulating data indicate the significance of anti-tumour immune responses in predicting the prognosis of patients with various types of cancer. This project will investigate the correlation between proteomics profiles and response to immunotherapy, a novel therapeutic modality that shows promise in some cancer types.

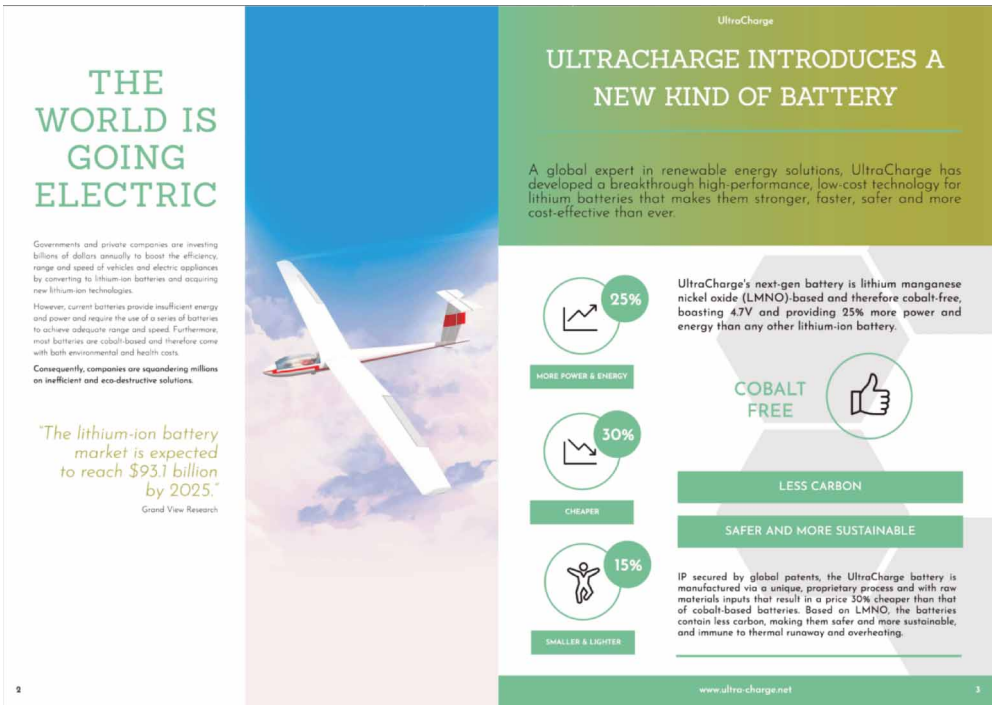
Experimental therapeutics

Investigators at Greehey CCRI have been integral members of both the NCI supported Pediatric Preclinical Testing Program (PPTP) and the current PPT Consortium and have pioneered the use of patient-derived xenografts (PDX) for drug development. These studies have focused on developing genetically representative models of paediatric cancer, and in new approaches to screening new agents and drug combinations. (15) As single agents PARP1 inhibitors have shown promising activity in vitro, but only modest activity in in-vivo models.

These studies showed that low-level damage to DNA by temozolomide (DNA damaging agent) could be potentiated up to 40-fold through inhibition of PARP1 by talazoparib (DNA damage repair enzyme), leading to dramatic tumour regressions in half of Ewing sarcoma xenograft models. These results were used to develop the talazoparib/temozolomide phase I/II clinical trial through the Children's Oncology Group (NCT02116777).

A focus of ongoing studies is to elucidate the mechanism of drug resistance that is developed in animal models and evaluate novel nano-formulations of drug sensitivity modulators, such as PARP inhibitors with the objective of increasing the therapeutic window for these combinations. Another thrust of the program is to identify agents that selectively sensitise tumour cells to ionising radiation. In addition to mouse models, the institute has invested in state of the art zebrafish facility, as a potential model to extend drug discovery and development.

Image heavy: Less than 500 words per spread. Larger headlines, images and added design elements, such as pull quotes.
See below example here.



THE WORLD IS GOING ELECTRIC

Governments and private companies are investing billions of dollars annually to boost the efficiency, range and speed of vehicles and electric appliances by converting to lithium-ion batteries and acquiring new lithium-ion technologies.

However, current batteries provide insufficient energy and power and require the use of a series of batteries to achieve adequate range and speed. Furthermore, most batteries are cobalt-based and therefore come with both environmental and health costs.

Consequently, companies are squandering millions on inefficient and eco-destructive solutions.

"The lithium-ion battery market is expected to reach $93.1 billion by 2025."
Grand View Research

UltraCharge

ULTRACHARGE INTRODUCES A NEW KIND OF BATTERY

A global expert in renewable energy solutions, UltraCharge has developed a breakthrough high-performance, low-cost technology for lithium batteries that makes them stronger, faster, safer and more cost-effective than ever.

25% MORE POWER & ENERGY

30% CHEAPER

15% SMALLER & LIGHTER

UltraCharge's next-gen battery is lithium manganese nickel oxide (LMNO)-based and therefore cobalt-free, boasting 4.7V and providing 25% more power and energy than any other lithium-ion battery.

COBALT FREE

LESS CARBON

SAFER AND MORE SUSTAINABLE

IP secured by global patents, the UltraCharge battery is manufactured via a unique, proprietary process and with raw materials inputs that result in a price 30% cheaper than that of cobalt-based batteries. Based on LMNO, the batteries contain less carbon, making them safer and more sustainable, and immune to thermal runaway and overheating.

Suggested elements

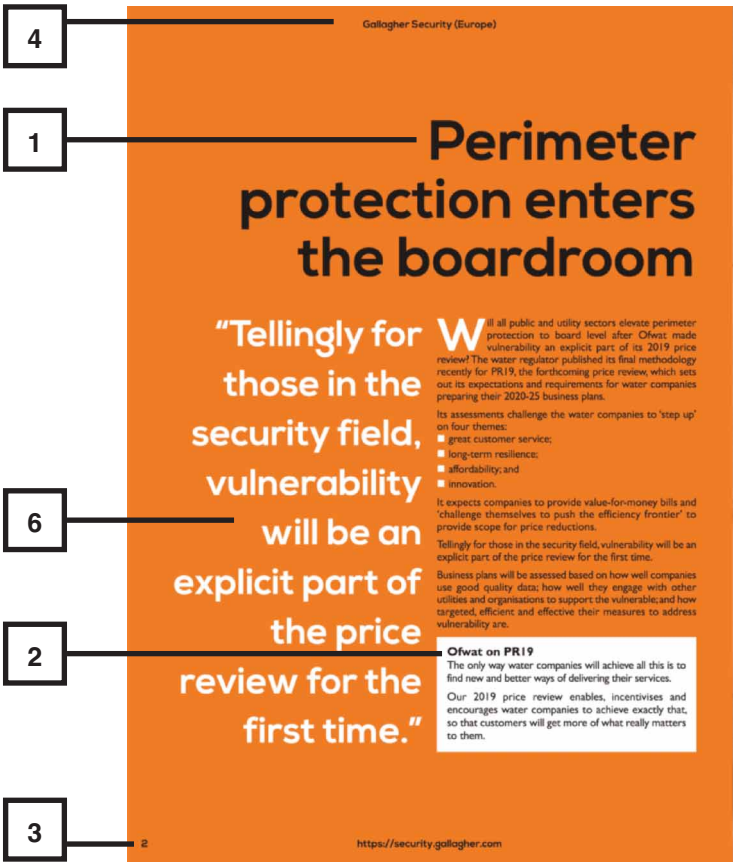
Text elements

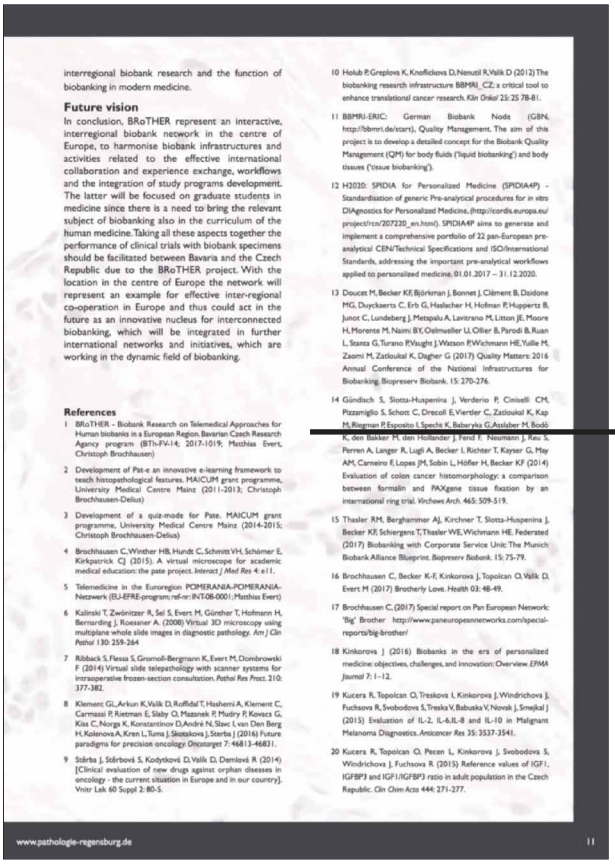
Standard text elements we set all booklets with, unless requested otherwise:

1 Headlines
2 Subheaders
3 Page numbers
4 Headers/footers
5 Contact details (Usually added to back cover)

Other text elements we can include and suggest the client to consider:

6 Pull quotes
7 Standfirst
8 Image captions
9 References





Design elements

Suggested design elements to include:

1 Logo

2 Images

3 Colour - Background, borders, text etc. Often client company colours unless requested otherwise.

4 Graphic elements - Shapes, details, particular layout styles etc. For example, these can be included to mirror the logo or website.

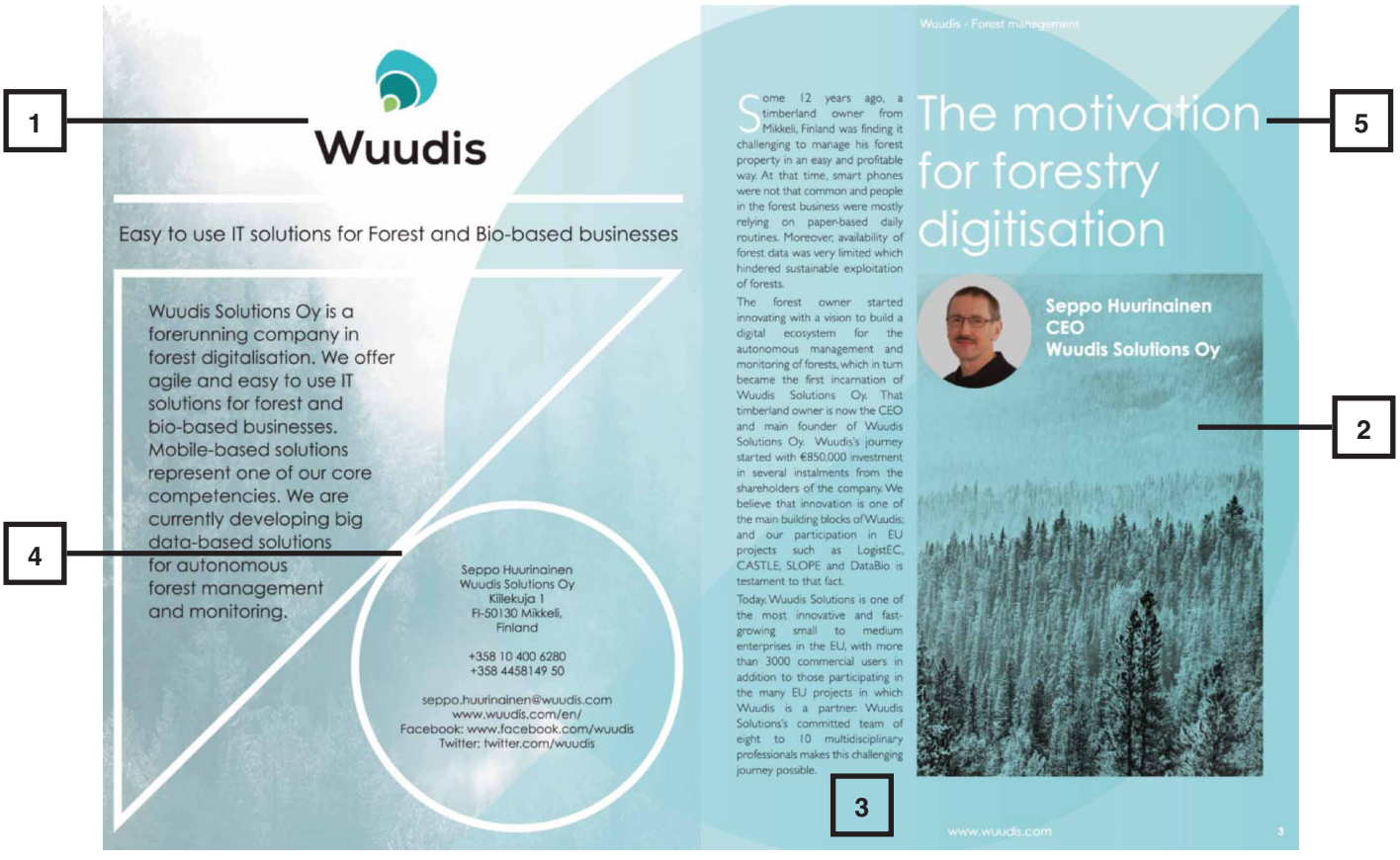
5 Font - Client can request fonts to be used in the eBook. We may request client to send font files if we don't already own them.

Brand guidelines - We are happy to follow any brand guidelines sent to us by the client.

Images
We request all images to be supplied as the original, high quality image file.
eBooks are set to a minimum 300dpi.
If the image quality falls below this we can replace with images from www.istockphoto.com. The client is free to choose any images from iStock they wish.

We request images to be sent in vector or rasterized format - jpg / png / pdf / eps etc.
They can also be supplied as Illustrator or Photoshop files.

Please do not supply images on Word documents or Powerpoint.



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