WIMP-searching liquid-xenon instrument provides striking evidence of the power and versatility of such detectors. However, only four types of double-β decay can be probed by these instruments — namely, the decays of xenon-124, xenon-126, xenon-134 and xenon-136.

From the point of view of nuclear theory, the decay rates of both two-neutrino and neutrinoless double electron capture can be connected to quantities called nuclear matrix elements. Such quantities contain information about nuclear structure that is extracted from nuclear models and can be applied by researchers in the field of nuclear-structure theory. The measured two-neutrino double electron capture will help to test the various nuclear models[8] that are used to calculate rates of double-β decay. Moreover, the acquired half-life data will enable model parameters to be fine-tuned, allowing scientists to more accurately predict the values of the nuclear matrix elements that are associated with neutrinoless double electron capture, as well as neutrinoless double-β decays in general. Finally, all of these factors will contribute to the accurate extraction of neutrino parameters from the data gathered by present and future neutrino experiments. ■

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MEDICAL RESEARCH

Lethal clues reveal tumour vulnerability

Cancer cells often have mutations in anticancer genes that make their survival dependent on other genes. The gene-editing approach CRISPR–Cas9 offers a way to identify such vulnerabilities. SEE ARTICLE P.511 & LETTER P.551

FELIX Y. FENG & LUKE A. GILBERT

Suitable protein targets are needed to develop new anticancer drug-based treatments. Writing in *Nature*, Behan *et al.*[1] (page 511) and Chan *et al.*[2] (page 551), and, in *eLife*, Lieb *et al.*[3], report that certain tumours that have deficiencies in a type of DNA-repair process require an enzyme called Werner syndrome ATP-dependent helicase (WRN) for their survival. If inhibitors of WRN are found, such molecules might be promising drug candidates for further testing.

Imagine a scenario in which scientists could perform an experiment that reveals how almost every gene in the human genome is dysregulated in cancer. Even better, what if such an investigation also offered a road map for how to select a target when trying to develop treatments that take aim at cancer cells, but are non-toxic to normal cells? A type of gene-editing technology called CRISPR–Cas9 enables just that in an approach termed functional genomics. Using this technique, the function of almost every gene in cell-based models of cancer (comprising human cells grown *in vitro* or *in vivo* animal models) can be perturbed, and the effect of each perturbation on cancer-cell survival can be measured.

CRISPR can be used to mutate, repress or activate any targeted human gene[4,5]. In functional genomics, gene function is assessed in a single experiment by growing a large number of cells and then perturbing one gene in each of the cells. The approach is aided by measuring the concentration in each sample of the DNA sequence that encodes an engineered RNA molecule (termed a single-guide RNA; sgRNA) that is needed for the CRISPR gene-editing process. When the DNA that encodes a particular sgRNA is present in a sample of cancer cells in such an experiment, this means that the gene that the sgRNA targets is not required for cell survival. However, if the sgRNA-encoding DNA sequence is not detected, this indicates that the gene targeted by the sgRNA is required for cancer-cell viability, and those cells containing it died, thereby eliminating the sgRNA-encoding sequence from the sample. This approach offers the possibility of systematically searching for genes that are crucial to tumour-cell survival in large collections of cancer cells that are representative of the diversity of tumour types in humans.

Behan *et al.* report their development of an online database that they call Project Score. It is a platform for cancer researchers that amalgamates Behan and colleagues' large-scale data for genome-wide gene editing by CRISPR with previously published genomics information about the cancer models used. The resource consists of data for more than 5 million CRISPR-mediated perturbations undertaken to prevent the expression of individual genes (generating what are known as gene knockouts) in 324 cell-based models of cancer, representing 30 types of cancer in humans. This systematic effort has enabled the identification of genes on which cancer cells depend for survival, as well as those that drive cancer-cell proliferation.

In the database, the authors' integrated analysis of this functional-genomics data is provided together with other data about the samples. For example, there is information about tumour-cell genomes, such as the sequence of the whole genome or that of the genome's protein-coding regions. Also available are the gene-expression profiles for each cell-based cancer model, which reveal vulnerabilities in cancer cells that are associated with the specific tumour-driving alterations that exist naturally in each model. These include mutations in types of gene known as oncogenes and tumour suppressors that, respectively, are associated with promoting or blocking cancer formation. The platform developed by Behan *et al.* complements a similar effort called the Cancer Dependency Map[6,7], and together these resources should accelerate cancer research. For example, these approaches could guide target prioritization for the development of treatments that might be effective in multiple types of cancer.

Many cancers in humans are driven by genetic mutations known as loss-of-function mutations, which inactivate genes so that they no longer encode functional proteins. In cancers, such mutations commonly occur in tumour-suppressor genes. Because these mutations result in the absence of a protein, they do not offer an opportunity for directly targeting an abnormal protein with drugs. However, loss-of-function mutations can render cancer cells dependent on specific genes through a principle known as synthetic lethality[8,9]. Synthetic lethality is a relationship between two genes in which the loss of both gene *A* and gene *B* is lethal, whereas the loss of either gene can be tolerated by cells. If we could understand how the inactivation of tumour-suppressor genes rewires cancer cells to drive tumour progression, this knowledge could be used to implement strategies that enable the specific killing of such mutated cancer cells.

The possibility of synthetic lethality pointing the way to fresh therapeutic approaches is exemplified by studies that demonstrate that combining loss-of-function mutations in the tumour-suppressor genes *BRCA1* or *BRCA2* with the inhibition of a type of enzyme called PARP imparts synthetic lethality[9]. *BRCA1* and *BRCA2* are often mutated in breast, ovarian and prostate cancers, and clinical trials that

enrolled people with *BRCA* mutations have resulted in the approval of three PARP inhibitors for cancer treatment[9]. These and other successes have inspired many efforts to search for synthetically lethal genetic relationships involving commonly mutated tumour-suppressor genes such as *TP53*, *PTEN* and *RB1*. Despite the enormous potential for such efforts to yield drug targets, a challenge remains: how can researchers systematically search for synthetically lethal gene relationships? Now, functional-genomics approaches offer a way to proceed.

The CRISPR knockout data sets from Project Score and the Cancer Dependency Map were analysed by Behan *et al.* and Chan *et al.*, respectively. Both groups found that WRN, a type of helicase that can unwind DNA and is a member of the RecQ family of proteins, is essential in cancers that have a type of genomic alteration called microsatellite instability (MSI). Lieb *et al.* found a similar synthetically lethal relationship between MSI and WRN using a functional-genomics approach involving a technique called RNA interference.

MSI is a common driver of cancer progression in a range of tumour types, including colon, gastric, endometrial and ovarian cancers. It arises when errors occur in a DNA-damage repair system called DNA mismatch repair. Inactivation of a number of different genes, for example, *MLH1* and *MSH2*, can cause a deficiency in mismatch repair. Behan and Chan, and their respective colleagues, found that mutations in genes required for mismatch repair caused synthetic lethality if the gene that encoded WRN was also inhibited. They characterized this synthetic lethality using experiments that measured cellular DNA-repair defects and cell-death mechanisms in cells studied *in vitro* and *in vivo*. This discovery of a strong and specific synthetically lethal dependency represents a major step forward for efforts to develop approaches to treat cancers that have MSI.

The exact molecular mechanisms that underlie the specificity of this synthetically lethal interaction remain to be determined. For example, why does this WRN dependency occur only with tumours that have MSI, and not with tumours that have other forms of genomic instability? Interestingly, this genetic interaction is highly specific; experiments by Behan *et al.*, Chan *et al.* and Lieb *et al.* demonstrated that repression of WRN, but not repression of the four other RecQ helicases that function in the same pathways as WRN, is synthetically lethal in cancers that have deficiencies in DNA mismatch repair. Next-generation functional-genomics approaches promise higher-resolution characterization of individual genetic interactions, which could reveal not only the genes that are involved in a process, but also how those genes function to affect the cell. Such approaches should also enable scientists to elucidate the mechanisms that underlie a particular example of synthetic lethality[10,11].

WRN has both helicase activity and exonuclease activity (the ability to remove nucleotides from a strand of DNA). Behan *et al.*, Chan *et al.* and Lieb *et al.* demonstrate that the disruption of WRN's helicase activity, but not its exonuclease activity, is required for the synthetically lethal effect that they observed. There is a possibility that WRN could be targeted by small-molecule inhibitors. Further studies might enable the development of potent and specific WRN helicase inhibitors that could be tested in cancers that have MSI. These discoveries exemplify how a combined genomics and functional-genomics approach — characterizing the genetic alterations that are already present in cancer models and then assessing the effects of experimentally induced perturbations in further genes — can reveal important cancer-cell dependencies and provide a pathway towards therapeutic innovation. ■

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CATALYSIS

A fresh approach to ammonia synthesis

Ammonia is vital to society, but its manufacture is energy intensive, has a large carbon footprint and requires high initial capital outlays. An intriguing reaction now suggests that energy-efficient alternatives are possible. SEE LETTER P.536

MÁTÉ J. BEZDEK & PAUL J. CHIRIK

Global food production requires ammonia-based fertilizers. The industrial transformation of atmospheric nitrogen gas (N_2, also known as dinitrogen) into ammonia (NH_3) is therefore essential for human life. Despite the simplicity of the molecules involved, the cleavage of the strong nitrogen–nitrogen triple bond (the N≡N bond) in dinitrogen and the concomitant formation of nitrogen–hydrogen (N–H) bonds poses a difficult challenge for catalytic chemistry, and typically involves conditions that are costly in terms of energy requirements: high reaction temperatures, high pressures or combinations of reactive reagents that are difficult to handle and energy-intensive to make. On page 536, Ashida *et al.*[1] demonstrate that a samarium compound mixed with water and combined with a molybdenum catalyst can promote ammonia synthesis from dinitrogen under ambient conditions. The work opens up avenues of research in the hunt for ammonia-making processes that operate under ambient conditions, and raises the question of what an ideal process should be.

Motivated by a looming global fertilizer shortage at the turn of the twentieth century, and later by munitions shortages (ammonia can be used to make explosives), the chemists Fritz Haber and Carl Bosch were the first to demonstrate[2] that dinitrogen could be "pulled from air" and converted to ammonia. In the modern version of the Haber–Bosch process, dinitrogen and hydrogen gas are combined over a catalyst typically based on iron to produce ammonia (Fig. 1a). Today, global ammonia production occurs at a rate of about 250–300 tonnes per minute, and provides fertilizers that support nearly 60% of the planet's population[3,4].

The modern conditions for ammonia synthesis involve temperatures greater than 400 °C and pressures of approximately 400 atmospheres, and are therefore often said to be 'harsh'. This common misconception has motivated chemists to find 'milder' alternatives that use new catalysts to lower the operating temperatures and pressures. In reality, the search for new catalysts should be inspired by the need to reduce the capital expenditure associated with building ammonia plants, and by the requirement to reduce