to obtain a cell-level map of the human placenta — specifically, the interface between the fetal placenta and the maternal uterine wall. They used slices of placenta from 66 terminated pregnancies, focusing on those in which placental cells were invading the wall of the uterus — a crucial event that remodels maternal arteries in such a way as to deliver blood to the areas in which maternal and fetal cells interact, without damaging the delicate placenta. Using MIBI enabled the authors to profile multiple samples at different stages of development and to define interactions between placental and immune cells at single-cell resolution.

Through analysis of the maps, the authors identified how maternal immune cells promote a tolerant environment (its niche) in the region in and around the artery, which allows peaceful coexistence between genetically distinct maternal uterine and fetal placental cells. Combined with recent spatial transcriptomics of the placenta[9], Greenbaum and colleagues' discoveries deepen our understanding of the maternal vascular transformation that sustains embryonic development.

Hickey *et al.*[3] (page 572) focused on the intestine — a complex organ that exhibits highly diverse structures and functions along its length. The authors used CODEX and single-nucleus transcriptomics to map eight sites along the intestine, using samples from nine people. The authors discovered drastic shifts in cellular composition and organization between the sites. They found previously unknown subtypes of epithelial cell (the cells that line the intestine), which were arranged in distinct neighbourhoods. They also define immune-cell-rich neighbourhoods where immune cells can be readily activated if required. Overall, the findings reveal that specialized anatomical regions in the intestine are underpinned by highly structured spatial niches, each with unique functions. Such insights could only be gained using spatial methods.

Lake *et al.*[4] (page 585) examined 45 healthy and 48 diseased kidneys. The authors defined the locations of cells that adopt previously unidentified states during acute kidney injury or chronic kidney disease, including maladaptive tissue-repair states that might hinder the formation of kidney tubules after injury. Spatial mapping revealed cell–cell communication between maladaptive cells and other fibrotic (tissue-scarring) and inflammatory cells. The authors also identified transcriptomic signatures associated with a state of cell dormancy, called senescence, that might underlie the progression to kidney failure.

Both Hickey *et al.* and Lake *et al.* complemented their spatial atlases with single-cell 'open chromatin' assays, which provide information about the active transcription factors in a cell. Combining their various approaches enabled the authors to define the transcription factors that mediate cellular identities in different tissue niches. These studies are a powerful example of how incorporating these types of assay with spatial analyses gives a coherent picture of cell identity in context.

Altogether, the three papers demonstrate how spatial methods are empowering scientists to analyse tissues and organs at unprecedented resolution, providing standardized ways to generate cell atlases. The three HuBMAP atlases also have the potential to advance our understanding of disease, by defining the spatial location of cell states linked to disease and by helping to contextualize genome-wide association studies — which can link particular genetic variants to a disease, but provide no spatial context to indicate in what cell type that variant might exert its effect. We anticipate that this work, along with several HuBMAP papers published in other journals (see go.nature.com/3rxansc), will inspire the generation of spatial atlases in other tissues.

Looking to the future, these studies highlight the continued need to advance spatial technologies. The number of assays that can be performed on single-tissue slides must be increased to enhance the ability to study cells at subcellular resolution and begin to move from studies performed in 2D on slides towards true 3D reconstruction. The number of samples analysed must also increase, so that researchers can correlate spatial organization with other information such as body mass index or disease stage. Such correlations could provide clues to how disease progresses in specific locations in the body.

Increasing the breadth and depth of spatial technologies will ultimately establish robust associations between cellular organization and function in health and disease. The current studies provide an outstanding contribution to this aim.

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1. HuBMAP Consortium. *Nature* **574**, 187–192 (2019).
2. Greenbaum, S. *et al. Nature* **619**, 595–605 (2023).
3. Hickey, J. W. *et al. Nature* **619**, 572–584 (2023).
4. Lake, B. B. *et al. Nature* **619**, 585–594 (2023).
5. Ståhl, P. L. *et al. Science* **353**, 78–82 (2016).
6. Rodriques, S. G. *et al. Science* **363**, 1463–1467 (2019).
7. Angelo, M. *et al. Nature Med.* **20**, 436–442 (2014).
8. Goltsev, Y. *et al. Cell* **174**, 968–981 (2018).
9. Arutyunyan, A. *et al. Nature* **616**, 143–151 (2023).

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In retrospect

Proof of the electroweak force 50 years on

Pippa Wells

The discovery of 'weak neutral currents' at Europe's particle-physics research centre CERN 50 years ago was a decisive step towards establishing the standard model of particle physics — a journey that continues to this day.

July 2023 marks the 50th anniversary of one of the greatest discoveries made at CERN, the international particle-physics research centre near Geneva, Switzerland: namely, weak neutral currents. The discovery, made by the Gargamelle experiment, provided key evidence that one of four known fundamental forces in nature, the weak interaction, is inextricably entwined with another, the more familiar force of electromagnetism. That finding opened a path of exploration that led, by way of numerous breakthroughs, to the discovery of the Higgs boson in 2012 — and it is still revealing new and exciting perspectives today.

The influence of the weak interaction is seen most obviously in radioactive β-particle decays. When CERN was founded in 1954, particle physicists' understanding of the interaction was in its infancy. Back then, the best way to study matter and its workings at the smallest scales was to fire high-energy beams of particles into a target and measure what emerged.

In 1959, CERN's Proton Synchrotron accelerator started up. This could produce beams of various particle types, and in the early 1960s, experiments began there with the extremely light particles known as neutrinos — albeit with fierce competition from the higher-energy Alternating Gradient Synchrotron, situated

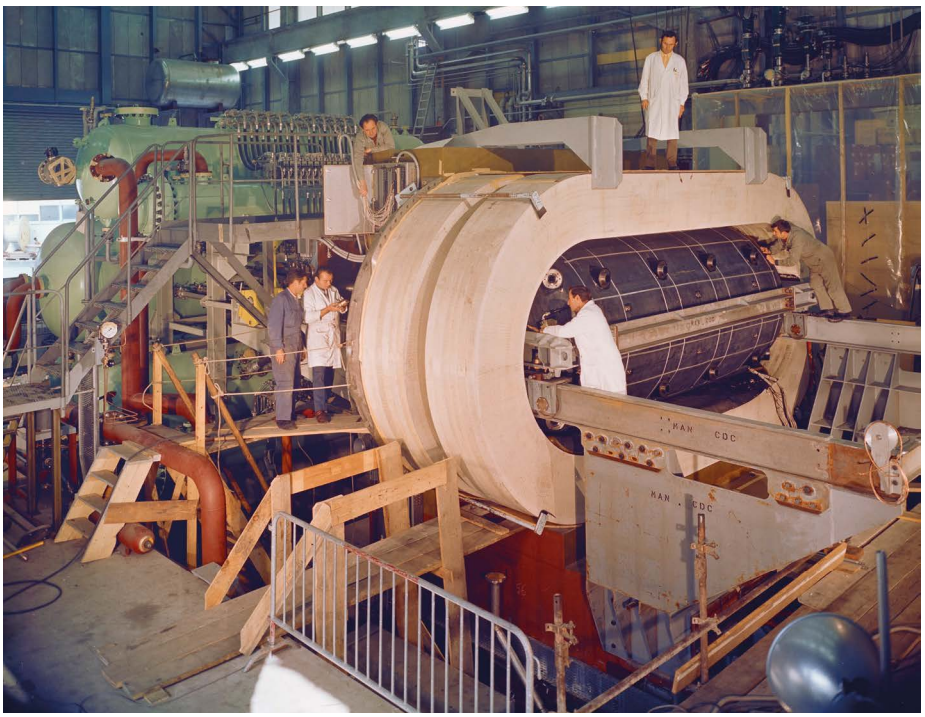
at Brookhaven National Laboratory on Long Island, New York. The CERN and Brookhaven machines both made neutrino beams by colliding protons with a target to make secondary particles such as pions and kaons, which produce neutrinos when they decay. (Protons, pions and kaons are all varieties of hadron, particles physicists now know to be composites constructed from different configurations of elementary particles called quarks.)

The initial CERN configuration yielded disappointingly low-intensity beams. It was the Brookhaven experiments that, in 1962, demonstrated that there were at least two types of neutrino — one produced in decays together with an electron, and another produced together with the electron's higher-mass cousin, the muon.

In 1961, Dutch physicist Simon van der Meer invented a focusing device around the target called a 'magnetic horn', which helped to increase the neutrino-beam intensity. This was a game-changer for CERN. Detecting the resulting interactions using a bubble chamber, in which the paths of ionizing charged particles can be seen as a line of bubbles through a superheated liquid, proved a particularly promising method. This led French physicist André Lagarrigue to propose a larger, 4.8-metre-long bubble chamber — dubbed Gargamelle.

Shortly before Gargamelle started up in 1970 (Fig. 1), the collaborating scientists, based at CERN and at institutions in Belgium, France, Germany, Italy and the United Kingdom, made a list of ten priority measurements. Observations of processes involving weak neutral currents made it only to number eight, merely because previous experiments had set low limits on how often they were expected to occur.

Neutral-current events were nevertheless of great interest because of their role in the electroweak theory. Physicists had successfully described electromagnetic processes through the theory of quantum electrodynamics, in which the particles transmitting the quantum-mechanical force are a type of 'boson', specifically, the familiar massless photon. The researchers wanted to find a similar quantum theory for the weak and strong nuclear forces (the strong force being that which binds quarks together into hadrons). The most promising way to do this was to combine the electromagnetic and weak interactions in a unified description[1–3]. This predicted the existence of three new, heavy bosons in addition to the photon: the neutral Z^0 and the charged W^+ and W^-. The mechanism that was proposed to allow these bosons and other fundamental particles to acquire their mass results in an additional heavy particle with unique properties — the Higgs boson[4–6]. This unified 'electroweak' theory could be combined with the theory of the strong force, quantum chromodynamics, to form what is now known as the standard model of particle physics.



CERN

Figure 1 | Installation of the Gargamelle bubble-chamber experiment at CERN. Commissioned in 1970, Gargamelle discovered its first 'weak neutral current' event in December 1972 — a breakthrough announced to the world on 19 July 1973.

According to the unified electroweak theory, there are two types of neutral-current process, so called because they involve the neutral Z boson: leptonic and hadronic processes. In a bubble chamber such as Gargamelle, the signal of a leptonic process would be a single high-energy electron that would appear after being struck by a neutrino (or its antiparticle, an antineutrino). In a hadronic process, a neutrino would interact with a nucleus in the bubble-chamber fluid, producing a shower of hadrons.

At Gargamelle, photographs of the bubble chamber were taken each time a neutrino pulse went through and were analysed by eye, with potentially interesting events flagged. The frequency of leptonic events was expected to be very low — only a handful of events in a year's data-taking. But the frequency of background processes that could mimic this interaction was also very low, making this the most unambiguous signal of a neutral-current process. Hadronic processes happened much more often, but occurred against a much higher, confounding background.

Gargamelle eventually made the breakthrough in December 1972, finding its first leptonic event. This gave the team an even greater incentive to identify hadronic events and evaluate the expected background rates. So it was that, at a seminar held at CERN on 19 July 1973, the first evidence for both types of weak neutral current was presented. Papers on each were published in the same volume of *Physics Letters B* in September that year[7,8].

This was the first compelling evidence that the electroweak theory was correct. The next challenge was to produce the Z boson, and its charged siblings the W bosons, directly, rather than observing them through their influence on other processes. The decisive step, led by the Italian physicist Carlo Rubbia[9] in 1976, was the realization that this could be achieved by transforming a sufficiently high-energy proton accelerator into a machine to collide protons and antiprotons. CERN's Super Proton Synchrotron saw its first proton–antiproton collisions in 1981. In 1983 — ten years after the observation of neutral currents — the UA1 and UA2 collaborations announced the discoveries first of the W bosons and then of the Z boson. Rubbia and van der Meer shared the 1984 Nobel Prize in Physics for their parts in this discovery.

At that time, preparations were well under way at CERN to build the 27-kilometre-circumference Large Electron–Positron collider (LEP). LEP was designed to make detailed measurements of the properties of W and Z bosons by colliding electrons with their antiparticles, and started operating in 1989. Piece by piece, the experimental evidence in support of today's standard model came together. These included the revelation that there could be three, and only three, light (that is, near-massless) neutrinos — those associated with the electron and the muon, and another neutrino, yet to be discovered, linked to an even heavier lepton, the tau. LEP also demonstrated the validity of subtle

corrections to the electroweak theory, published[10] in 1971, that depended strongly on the mass of the heaviest of the six quarks, the top quark, and also on the mass of the Higgs boson. There was remarkable agreement between the top-quark mass predicted by LEP and the mass eventually measured by the Tevatron proton–antiproton collider at Fermilab near Chicago, Illinois, in 1995.

Eventually, the last missing ingredient of the standard model was the Higgs boson. Experiments at LEP actively searched for the elusive particle, but it became clear that an even more powerful accelerator was needed to produce it. LEP operations ended in 2000, paving the way for the installation of a new proton–proton collider, the Large Hadron Collider (LHC), in the same tunnel. The discovery of the Higgs boson was famously announced in 2012 by two LHC experiments, ATLAS and CMS. Again, its measured mass was in excellent agreement with predictions.

This is by no means the end of the story. In the original electroweak theory, neutrinos were assumed to be massless, but the phenomenon of 'mixing', in which one type of neutrino transforms into one of the other two types, proved this could not be the case. The details of the neutrino masses — which must be very small, but not zero — and the exact nature of these particles are still not known. Next-generation neutrino-beam experiments planned in Japan and the United States will explore these questions in richer detail. An upgrade of the LHC will also continue running until the early 2040s, ultimately aiming to deliver ten times more collisions than the original design.

Meanwhile, a detailed feasibility study of a Future Circular Collider is in progress at CERN. This would replicate the LEP–LHC model in a tunnel with a 90-kilometre circumference: first, an electron–positron collider would be installed to measure the Higgs boson and electroweak processes with even greater precision, and then a hadron collider would explore even higher-energy phenomena, including the production of two Higgs bosons in the same collision, at a much higher rate than that obtained at the LHC. Such experiments should reveal whether the simplest standard-model description of the Higgs boson is correct, or if there is a more complex structure to it — whether there is more than one type of Higgs boson, for example, or whether it interacts with other unknown particles.

This programme might also give clues to the nature of unseen cosmic 'dark matter', for which there is strong evidence from astronomical observations. Just as the LEP measurements were sensitive to the top quark and Higgs boson, precise measurements at future colliders might reveal the influence of as yet unknown, heavier particles. Fifty years after Gargamelle laid the foundations of electroweak interactions, and with it the standard model, a decades-long programme of rich fundamental science still lies ahead.

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1. Glashow, S. L. *Nucl. Phys.* **22**, 579–588 (1961).
2. Weinberg, S. *Phys. Rev. Lett.* **19**, 1264–1266 (1967).
3. Salam, A. in *Elementary Particle Theory: Relativistic Groups and Analyticity* (ed. Svartholm, N.) 367–377 (Almqvist & Wiksell, 1968).
4. Englert, F. & Brout, R. *Phys. Rev. Lett.* **13**, 321–323 (1964).
5. Higgs, P. W. *Phys. Lett.* **12**, 132–133 (1964).
6. Higgs, P. W. *Phys. Rev. Lett.* **13**, 508–509 (1964).
7. Hasert, F. J. *et al. Phys. Lett. B* **46**, 121–124 (1973).
8. Hasert, F. J. *et al. Phys. Lett. B* **46**, 138–140 (1973).
9. Rubbia, C., McIntyre, P. & Cline, D. in *Proc. Int. Neutrino Conf. Aachen 1976* (eds Faissner, H., Reither, H. & Zerwas, P.) 683–687 (Vieweg & Teubner, 1977).
10. 't Hooft, G. & Veltman, M. *Nucl. Phys. B* **44**, 189–213 (1972).

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Medical research

Immune cells aid therapy for Parkinson's disease

Qizhi Tang

Inflammation caused by surgical trauma limits the survival of transplanted stem-cell-derived neurons in rodent models of Parkinson's disease. Co-transplanting immune cells called regulatory T cells improves the therapy's efficacy. **See p.606**

Parkinson's disease is a neurodegenerative disorder characterized by a progressive loss of the neurons in the brain that produce the neurotransmitter dopamine. After decades of research, it is now possible to generate dopamine-producing neurons from human stem cells, and this technology has raised hopes that transplanting such neurons into the brains of individuals with Parkinson's disease might provide a cure[1]. However, to be effective, the transplanted dopamine neurons would need to survive the implantation procedure and avoid immune rejection. Park *et al.*[2] report on page 606 that more than 90% of transplanted dopamine-producing neurons die within two weeks of implantation into animals because of a profound inflammatory response induced by the trauma of the surgery. The authors point to a possible way of tackling this problem.

Park *et al.* show that the inflammation caused by surgery is not only directly toxic to dopamine-producing neurons, but also increases immunogenicity — the 'visibility' of the graft to the immune system. To try to quell the inflammation and reduce immune activation, the investigators turned to a group of immune cells called regulatory T (T_{reg}) cells (Fig. 1). This specialized lineage of T cells is dedicated to suppressing inflammation, constraining immune activation and promoting tissue repair[3]. Park and colleagues found that transplanting T_{reg} cells together with the stem-cell-derived neurons suppressed the local inflammatory response, promoted survival of the neurons and improved therapeutic outcomes in animal models. These results support the idea that Parkinson's disease could be treated with a composite graft that contains dopamine-producing neurons and a person's own T_{reg} cells.

The possibility of treating diseases using stem-cell-based therapies has attracted considerable attention because of the unique ability of stem cells to self-renew and to differentiate into myriad cell types. These cells can be isolated, cultured outside the body and directed to form various cell lineages by mimicking the processes that occur in the body during normal tissue development. Such advances in stem-cell technology have improved the prospect of having cells 'on demand' to replace or repair damaged tissues and organs and thereby treat a wide range of degenerative diseases. However, the immense potential of stem-cell-based therapies in regenerative medicine will only be achieved if the barriers of poor cell survival and immune rejection can be overcome.

Several strategies have been developed to reduce the likelihood of transplanted stem cells being recognized and attacked by the immune system[4]. However, 'immunoengineering' approaches alone will probably have a limited effect, given that 90% of transplanted cells are lost even in the absence of immune rejection, as Park *et al.* show. Poor cell engraftment is a major challenge for many regenerative cell therapies. In Park and colleagues' study, neurons that produce the neurotransmitter GABA had levels of cell death that were comparable to those of dopamine-producing neurons after transplantation. Similarly, the poor survival of stem-cell-derived cells that are generated to