As best he can remember, says Paul Davies, the telephone call that changed his professional life came some time in November 2007, as he was sitting in the small suite of offices that comprise his Beyond Center at Arizona State University (ASU) in Tempe.

Until then, the questions that animated Davies' research and 19 popular-science books had grown out of his training in physics and cosmology: how did the Universe come to exist? Why are the laws of physics suited for life? What is time? And how did life begin? But this particular call was nothing to do with that. The caller — Anna Barker, then the deputy director of the US National Cancer Institute (NCI) in Bethesda, Maryland — explained that she needed his help in the 'War on cancer'. Forty years into the government's multibillion-dollar fight, said Barker, cancer survival rates had barely budged. The hope now was that physicists could bring some radical new ideas to the table, and she wanted Davies to give a keynote address at an NCI workshop explaining how.

Ummm, sure, said Davies, who until that minute had been only vaguely aware that the NCI existed. "But I don't know anything about cancer."

"That's okay," Barker replied. "We're after fresh insights."

And with that, says Davies, he was hooked. "If it had been just, 'Give us another beam', I wouldn't have been interested," he says, referring to X-rays, particle beams, magnetic resonance imaging and the many other tools that physicists had provided to medicine. But an opportunity to contribute entirely new concepts and ways of thinking — "now that", says Davies, "was exciting".

That excitement explains how the 65-year-old Davies, at an age when most academics are planning their retirement, finds himself embarking on practically a new career. Barker's original workshop metamorphosed into a network of 12 Physical Sciences–Oncology Centers, which launched in late 2009. Davies now finds himself the principal investigator of one such centre, and a major player in the physics-meets-cancer effort as a whole. Cancer gives Davies a new realm in which to exercise what many colleagues regard as his greatest talent: asking 'dumb' questions that provoke fresh ways of thinking about a problem. "Paul is wrong sometimes. But he is not afraid to ask a very naive question that gets at the heart of the matter," says Robert Austin, a biophysicist who heads another of the 12 centres, at Princeton University in New Jersey. Davies' questions have addressed topics ranging from metastasis (when tumour cells come apart and migrate, is it because of some physical change in their stickiness?) to subatomic physics (is cancer influenced by quantum effects inside biomolecules?). "I often joke that my main qualification for cancer research is that I am unencumbered by any prior knowledge of the subject," Davies says.

True, his naivety sometimes makes biologists grit their teeth. ("Aaargh! Physicists!" wrote Paul 'PZ' Myers, a biologist at the University of Minnesota, Morris, in a blog response to Davies' proposal earlier this year that tumours are a reversion to primitive genetic mechanisms that pre-date the dawn of multicellular life.) "But his critics don't appreciate the value of a disruptive agent," says biophysicist Stuart Lindsay, who works closely with Davies at the ASU physics–cancer centre. "It takes someone like Paul, constantly nagging, asking disruptive questions, to get people to take a fresh look at their assumptions."

Davies says that he has been asking questions as long as he can remember. The suburbs of London were a dull place to grow up, he explains, thinking back to the post-Second-World-War austerity that prevailed in the years after he was born there in 1946. "No toys. No money. We made our own entertainment — so we had to use our imagination a lot."

Maybe that's why he became so fascinated with shooting stars and astronomy, he says. "I liked the fact that, just by looking up, you could escape into this wonderland out there." And maybe that's why by the age of ten he had become enthralled with atoms, which seemed to embody a hidden order behind the surface complexity of the Universe. A few years later, he says, "I remember being struck by the fact that the brain is made of atoms, and atoms follow the laws of physics — so how can we have free will?" By age 16, says Davies, his course was set: he would become a theoretical physicist and spend his life trying to answer the "deep questions".

He began to explore one such question — how does quantum theory operate when space and time are curved by gravity? — first as a PhD student at University College London in the late 1960s and later as a lecturer at Kings College London. "It was a connection between the very small and the very large, between quantum mechanics and the whole Universe," Davies explains. He eventually summarized the field's accomplishments as co-author of a classic monograph, *Quantum Fields in Curved Space* (1982). But even then his interests were not easily confined — and he was beginning to develop a parallel outlet for them. In the early 1970s, the British magazine *Physics Bulletin* invited Davies to write a popular article dealing with a long-standing conundrum he had touched on in his PhD dissertation: why does time seem to flow only in one direction — towards the future — even though most physical laws make no distinction? After the article appeared, a publisher asked him for a book on the subject. And yet "I barely scraped through English class!" Davies says.

QUESTIONS IN WRITING

But Davies discovered that he enjoyed popular writing, and had a knack for it. Whereas early titles mirrored Davies' research in pure physics and cosmology, dealing with the physics of black holes, the unification of forces, and quantum theory, later ones have reflected his widening interests. In 1980, he joined the physics department at the University of Newcastle, UK, where half the department was focused on geophysics. So just by osmosis, he began to learn about the long history of life on our planet, and he found himself inexorably drawn to another big question: how is life even possible? How could such complexity arise in a lifeless Universe, purely by the action of natural law? Davies explored the complexity question in popular books such as *The Cosmic Blueprint* (1987), and then — after moving to the University of Adelaide, Australia, in 1990 — went on to tackle the philosophical implications of extraterrestrial life in books such as *Are We Alone?* (1995). At the same time, titles such as *God and the New Physics* (1983) and *The Mind of God* (1992) revealed his willingness to engage in the dialogue about religion and science — efforts that he assumes contributed to his winning the 1995 John Templeton Prize for Progress in Religion and, Davies admits, earned him plenty of criticism from anti-religious scientists.

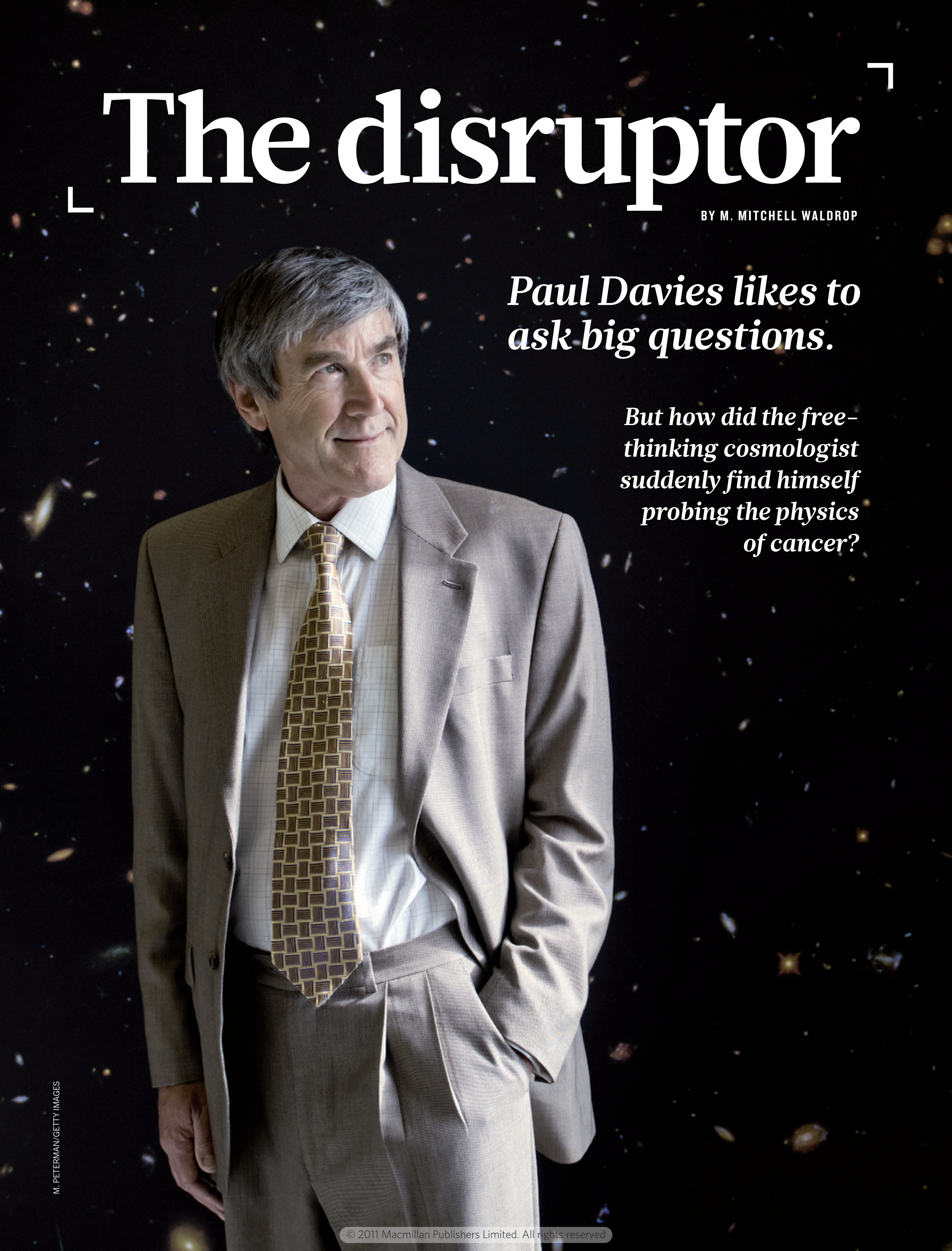
But Davies has never let critics stop him from asking provocative questions. In the 1990s, for example, he began to wonder whether Earth and Mars might share a biosphere. Might chunks of rock blasted loose from one planet by ancient asteroid impacts have carried viable microbes to the other when the rocks fell as meteorites? "Most people dismissed the idea as total nonsense, in rather blunt terms," says Davies. By 2004, he was wondering whether life could have originated on our planet more than once, with each lineage based on utterly different biochemistries, perhaps even without DNA or RNA. Might some of those alien lineages still be alive today? That question has led a number

The disruptor

BY M. MITCHELL WALDROP

Paul Davies likes to ask big questions.

But how did the free-thinking cosmologist suddenly find himself probing the physics of cancer?



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of astrobiologists to search for alternative life forms in harsh environments such as Mono Lake in California. It is also how Davies came to act as an adviser and co-author on last year's highly controversial paper claiming to have found bacteria that break life's rules by using arsenic instead of phosphorus in their DNA (F. Wolfe-Simon *et al. Science* doi:10.1126/science.1197258; 2010).

In 2004, Davies was contacted by Michael Crow, president of ASU, who was looking to overhaul the university's department-based hierarchy in favour of a more interdisciplinary approach (see *Nature* **446,** 968–970; 2007). Davies seemed to be one of those rare thinkers who could shake up the status-quo thinking in academia, says Crow. "Individuals who are polymaths, able to think across different subjects, and who personify 'disruptive thinking'." He contacted Davies at Macquarie University in Sydney, where Davies had helped to found the Australian Centre for Astrobiology in 2001, and offered to set him up in a centre where he could freely pursue all his interests.

It was an offer too good to refuse, says Davies. He moved to ASU to head the Beyond Center for Fundamental Concepts in Science in September 2006. Just over a year later, Anna Barker was on the other end of the phone.

MAKING A LIST

Once Davies had signed up to talk at the physics-cancer workshop, he had to figure out what to say. He knew he couldn't tell experienced cancer researchers how to do their jobs. So instead, he did what he does best: "I made a list of dumb questions."

First was whether physics could contribute anything at all to cancer research. A little reading and talking to colleagues convinced him it could. "To my astonishment, I learned that physical forces can affect gene expression," he says. Stretching, squashing — lots of things would do the trick.

Davies also learned that biologists rarely think about the cell as a physical object. "Look at something as straightforward as 'where does metastasis occur?'" says Davies. Does a tumour tend to seed itself in a second organ simply because blood flows there from the primary site? And what makes tumour cells suddenly break apart and become mobile in the first place, despite all the biophysical forces that tend to stick them together? He added those to the list.

Next, Davies was struck by the fact that biologists can now explore the cell in enormous detail — practically molecule by molecule. But that very power, he says, has often beguiled cancer researchers into focusing on individual genes and all the other pieces that go wrong, instead of how the pieces come together into a complex whole. "It's like trying to run the economy of the United States by measuring every transaction in every commodity and every city," says Davies. Granted, the comparatively new discipline of systems biology has been trying to take a more global view. But even so, says Davies, few cancer biologists are familiar with non-linear systems analysis, network theory or any of the other tools that have been developed by mathematicians and physicists over the past few decades to deal with complex systems.

> **"I worry that there aren't enough Paul Davies around to ask disruptive things."**

The questions, he says, were "all very, very basic. My level of ignorance was embarrassing."

But when the workshop convened in Arlington, Virginia, on 26 February 2008, Davies' talk was a hit. Barker remembers being delighted. "He gave a fascinating perspective, at a level biologists often just haven't thought about." And the cancer researchers in the audience were very receptive, recalls Austin, who also presented at the workshop. Even though many biologists object to the involvement of physicists in their field, "people in the oncology community have been very welcoming", he says. "They know they have a problem."

In December 2008, the NCI outlined its plan to fund the 12 physics-oncology centres at roughly US$2 million apiece over five years, and invited applications to host them. Each one would look at cancer from one of four points of view: physics, evolution, biological-information processing or complex systems.

Researchers at ASU's four-year-old Biodesign Institute spearheaded an application. William Grady, a gastroenterologist with a joint appointment at the University of Washington Medical Center and at the Fred Hutchinson Cancer Center in Seattle, agreed to serve as the senior scientific investigator on the project. But by the NCI's rules, the proposal needed a principal investigator in the physical sciences.

Davies describes himself as a reluctant draftee to that role. "I'm not a natural administrator," he says. But every time he protested "I have no credibility", his colleagues would point to his reception at the workshops and insist "You've got lots." When the NCI announced its selection of the 12 centres in October 2009, ASU was among them.

Since then, Davies has tailored his contribution to his strengths: he runs about three workshops a year for participants throughout the physics–oncology community. The goal is to trigger new collaborations, new experiments, new thinking — and the topics have ranged "all the way from downright crazy to productive", says Lindsay. Quantum effects in cancer might fall in the former category; the latter might include the physics of chromatin, the mass of DNA and protein in the cell nucleus.

"He won't allow people to get into a shoot-out of your theory versus mine. Just lots of critical thinking: 'what does this mean?'," says a frequent participant, oncologist Donald Coffey of the Johns Hopkins University in Baltimore, Maryland. "These are dynamite meetings. I come out incredibly enlightened, with lots of things to think about. And it works because of his personality."

DYNAMITE MEETINGS

What remains to be seen, of course, is whether the multimillion-dollar physics–cancer effort will pay off. The centres are only now starting to produce their first papers, Lindsay says, "and there's nothing earth-shattering yet". Several of the papers, including various studies on the mechanical properties of cancer cells and chromosomes along with a formal write-up from Davies on the idea that irritated Myers, appear in the February 2011 issue of the journal *Physical Biology*. It's early days, agrees Austin — but not too early to fret. "I worry that there aren't enough Paul Davies around to ask disruptive things," he says. "I worry that we'll become conventional — another failed assault on cancer. I really hate the thought that in ten years we'll find we haven't accomplished anything."

Davies isn't worried — and he is happy to keep asking those disruptive questions. "My mother didn't understand science at all," he says, by way of an explanation. In fact, he was the first person in his family to go to university. "But she was fond of saying that she hoped I could do two things with it." One was to build a robot to help with housework — something he'll have to leave to others. But the other was to find a cure for cancer.

"She would be quite thrilled that I'm finally doing something useful." ■

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