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Igniting Ideas, Bridging Minds

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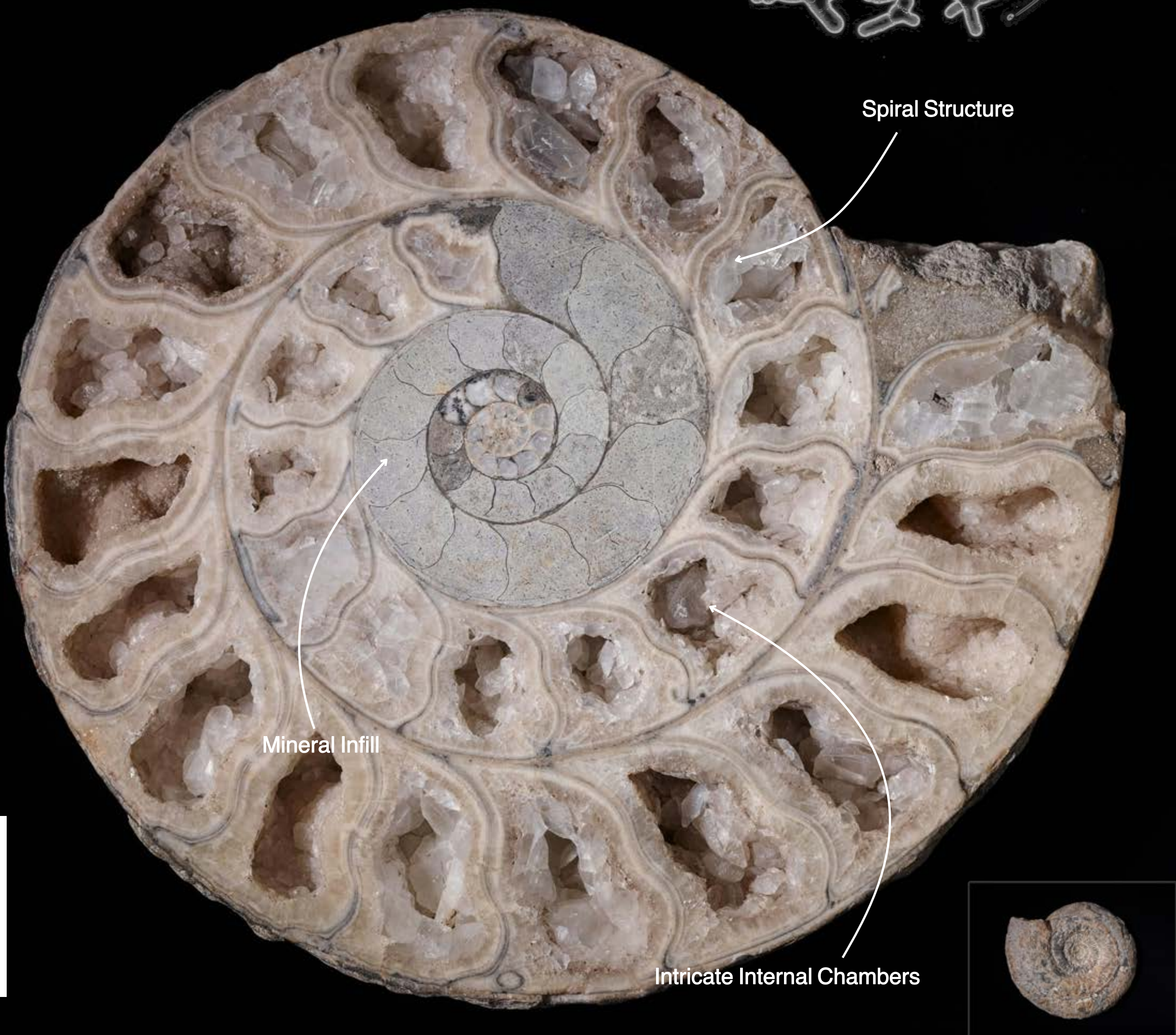

Sectioned Ammonite Fossils by Birmingham Museums Trust

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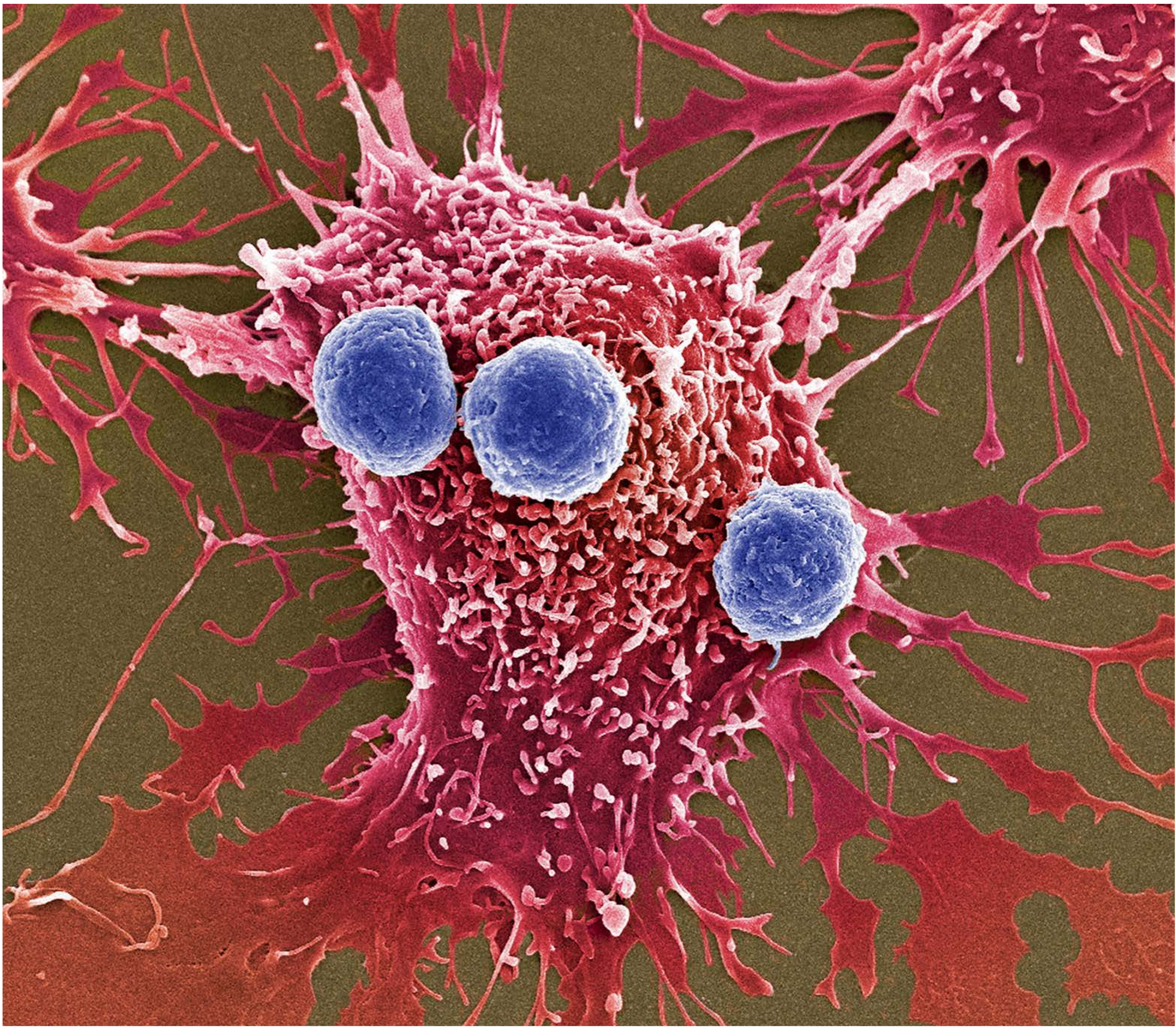
What fossils reveal about Evolution, Extinction, and Future

Ammonites, extinct marine mollusks from over 65 million years ago, leave behind intricately spiraled fossil shells that serve as a visual bridge between biology, geology, and time. Their chambered structures, often echoing the golden ratio, reveal nature's deep, mathematical patterns, uniting life, science, and the ancient Earth.

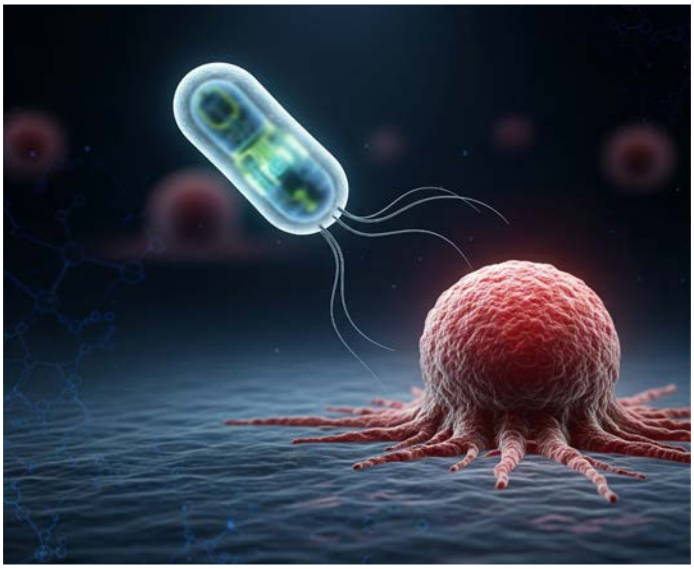


From Tumor Inducing Bacteria to Tumor Fighting Vectors: The Microbial Revolution in Cancer Therapy

FROM TUMOR CAUSERS TO CANCER KILLERS

By Umendra Jayasundara[1,2] & Mahesh Premarathna[1]

Picture a small soil bacterium that is capable of injecting a piece of its own DNA into a plant cell, taking over the cell machinery to form a tumor. Such is the activity of *Agrobacterium tumefaciens*, a plant pathogen that causes "crown gall disease" in numerous plants[1]. Yet, this bacterium's special talent for rewriting plant genetics once created agricultural problems, it's currently motivating researchers to consider how bacteria could be utilized to combat one of humanity's deadliest foes: cancer.



Nature's Genetic Engineer

Agrobacterium tumefaciens is often called nature's genetic engineer[2]. When a plant is wounded, the bacterium detects chemical signals and attaches itself to the damaged cells. It then transfers a specific segment of DNA, known as Transfer DNA (T-DNA), from its own plasmid directly into the plant's genome. This T-DNA encodes genes that trigger uncontrolled growth and production of plant hormones, causing tumors called crown galls. Remarkably, this trans-kingdom gene transfer, from bacteria to plants, has been harnessed for decades to create genetically modified crops.

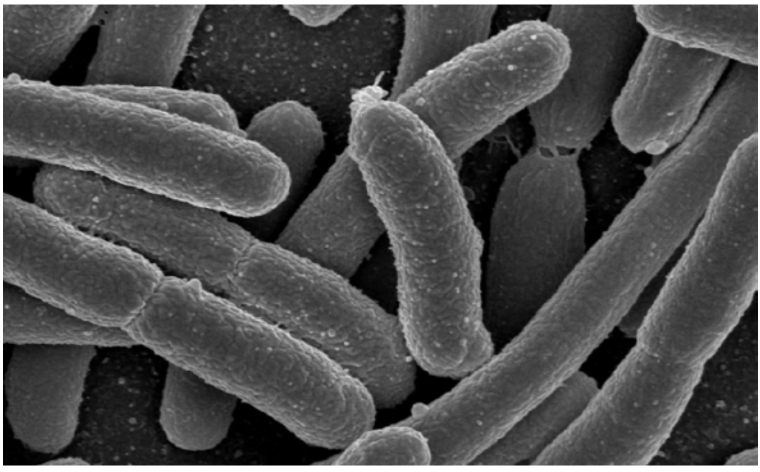
How bacteria could be utilized to combat one of humanity's deadliest foes: cancer...This strategy, often referred to as bactofection, which involves arming bacteria with mammalian-expression plasmids that carry therapeutic payloads...Bacteria, once feared as threats, may soon be among our most reliable allies in detecting, preventing, and curing human disease.

But could this remarkable natural mechanism teach us how to tackle tumors in animals and humans?

Bacteria as Vectors in Cancer Therapy: The Big Picture

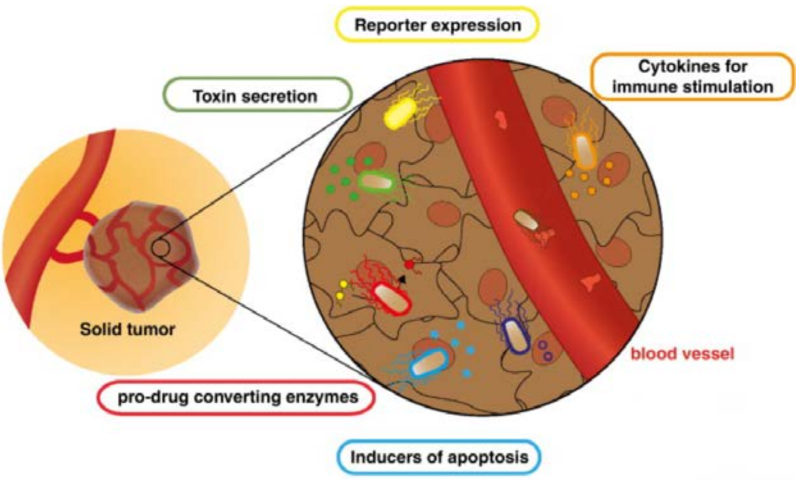
The idea that a bacterium like *Agrobacterium tumefaciens* can transfer its own DNA into another organism's genome isn't just a plant pathology marvel; it's a molecular gateway into the future of gene-based medicine. Though *Agrobacterium* is primarily a plant pathogen, there are multiple laboratory studies have demonstrated its ability to deliver genes into certain human and animal cells under specific conditions[3,4,5]. These kinds of experiments confirm that bacterial machinery can facilitate gene transfer across kingdoms. But the practical challenges, such as immune rejection, delivery inefficiency, and safety concerns, prevent the *Agrobacterium* from becoming a direct gene therapy vector in human medicine.

Nonetheless, *Agrobacterium's* DNA transfer system remains a powerful proof of concept, which shows that bacteria can serve as genetic couriers. This foundational idea has inspired researchers to explore how other bacteria, especially those more compatible with human biology, might be engineered to do what *Agrobacterium* does inside the



plants, by inserting therapeutic DNA to alter cell behavior. But, at this moment, the attention of tumors has moved on towards the organisms that have naturally localized tumors. These organisms, often thriving in low-oxygen environments where immune surveillance is weaker, are being reprogrammed as living vectors to deliver cancer fighting genes directly into tumor tissue.

This strategy, often referred to as **bactofection**, which involves arming bacteria with mammalian-expression plasmids that carry therapeutic payloads[6]. When these bacteria enter to the body, they travel to the tumor site, invade cancer cells, or die, then release their genetic material to uptake by host tissues. Among the pioneers in this space are attenuated strains of *Salmonella typhimurium*, which can home in on tumors and release immune-stimulating chemicals like cytokines or enzymes that activate prodrugs[6]. Similarly, *Listeria monocytogenes*, known for its ability to escape cellular compartments and spread intracellularly, has been re-engineered to deliver therapeutic DNA or cancer antigens[7]. Even the *Escherichia coli*, when equipped with invasion-promoting proteins and phagosomal escape tools like listeriolysin, has shown the capacity to deliver genes to human epithelial cells, with some systems being explored for oral delivery in gut-related conditions[8,9,10].



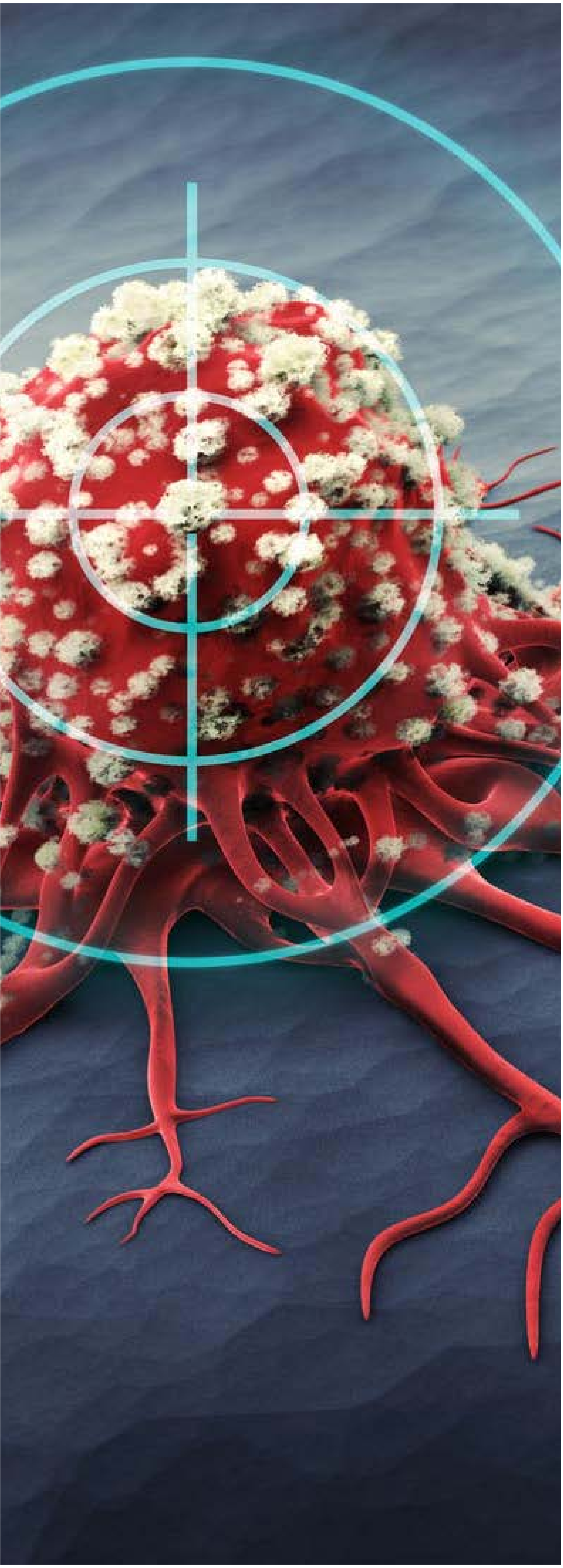
Meanwhile, the obligate anaerobes like *Clostridium novyi-NT* and *C. sporogenes* offer another promising route. These bacteria germinate exclusively within the necrotic centers of tumors, where they have been modified to express prodrug-converting enzymes and immune regulators, minimizing “off-target” effects[11]. In parallel, commensal anaerobes like *Bifidobacterium longum* have been shown to selectively colonize in tumors and they express therapeutic genes *in vivo*[12]. When the rise of synthetic biology, these kind of microbial systems can now be fine-tuned with genetic circuits, safety switches, and tumor-specific promoters to ensure that gene delivery is tightly controlled.

Bacterial Biosensors for Cancer Screening

In addition to therapy, researchers are now engineering bacteria as diagnostic tools. These microbial biosensors are capable of detecting tumor-specific DNA or metabolic markers and responding by producing detectable signals. One such system, involving *Acinetobacter baylyi*, was designed to detect mutant Kristen Murine Sarcoma Virus2 homolog (KRAS) DNA shed into the gut by colorectal tumors. Upon detecting the cancer-specific DNA, the bacteria activated a genetic switch to report the presence of a tumor. Such innovations suggest a future where a capsule of engineered bacteria could both diagnose and initiate treatment in a single pass through the digestive system[13].

Gene Delivery for Other Diseases

Not only for the cancer treatments, but also the potential of bacterial gene delivery extends well beyond oncology. In models of cystic fibrosis, modified strains of *Listeria* and *E. coli* have successfully delivered the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene to airway epithelial cells, showing promising restoration of function. For inflammatory bowel disease, the researchers engineered *E. coli* carrying plasmids for anti-inflammatory proteins like TGF-β1 have been administered orally to mice, reducing inflammation by acting directly on the gut mucosa. In parallel, there are some similar approaches under investigation for autoimmune disorders and metabolic diseases, where localized or systemic delivery of corrective genes could restore physiological balance[6,10].



The Challenges Ahead

But still, the bacterial vector treatments pose many challenges. Foremost is safety; injecting live bacteria into patients comes with the risk of infection or off-target immune responses. It is another challenge to make the bacteria target only tumors and not normal tissues. Finally, efficient delivery of genes and maintaining therapeutic effects over time without toxicity is a delicate balancing act.

Still, clinical trials are underway. For example, attenuated *Salmonella* strains have been tested in patients with advanced cancers[14,15], and spores of *Clostridium novyi* have shown tumor-shrinking effects[16,17]. While the results are preliminary, they offer hope that bacterial vectors could become powerful allies in the fight against cancer.

Looking Ahead: Microbial Symbiosis and Smart Therapies

The next frontier lies in transforming engineered microbes from mere delivery tools into intelligent, symbiotic agents. These future therapeutics may live inside us as part of our microbiome and be programmed to detect molecular signs of disease and respond instantly. Also, they could adjust therapeutic outputs based on local cues, provide long-term protection, or integrate with wearable health monitoring systems. From its origin as a tumor-inducing pathogen in plants, the concept of microbial gene transfer is being reimagined as a cornerstone of precision medicine. Bacteria, once feared as threats, may soon be among our most reliable allies in detecting, preventing, and curing human disease.

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