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Bladder Cancer and ADCs

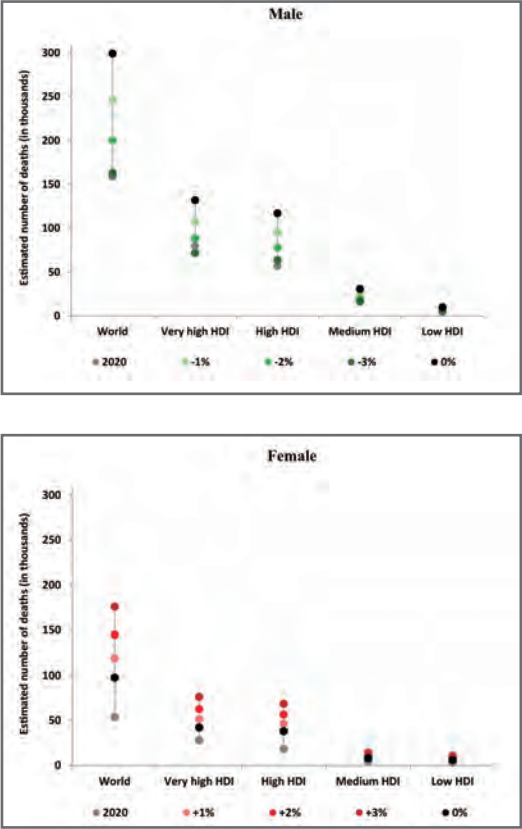
From Understanding the Disease to Unraveling Drug Resistance

International Directed Evolution Competition
(iDEC), 2025 OncoStrat_NMU

Preface


A Hidden Threat to Urinary Health

Bladder cancer, one of the most common malignancies of the urinary system world-wide, is quietly inching its way up the ranks of global health threats. In 2022, it clocked in over 610,000 new cases globally, securing the 9th spot in the cancer hall of fame—or infamy—with over 220,000 lives lost. Projections for 2040 paint a grimmer picture: deaths from bladder cancer could hit 163,000–245,000 in men and 119,000–176,000 in women.



Global mortality rate projection for 2040.

In terms of diagnosis and treatment, traditional chemotherapy often leads to drug resistance in advanced patients, and immunotherapy has limited response rates. However, the advent of Antibody-Drug Conjugates (ADCs) has brought a revolutionary breakthrough in global bladder cancer treatment. In particular, enfortumab vedotin and sacituzumab govitecan have rewritten the rulebook, giving patients precious extra time.

	anti-NECTIN4		anti-HER2		anti-BF-H3		anti-TROP2		anti-DLL3					
	Enfortumab vedotin		Disitamab vedotin *		Trastuzumab deruxtecan		Ifinatamab deruxtecan *		Datopotamab deruxtecan *		Sacituzumab govitecan		Rovalpituzumab tesirine *	
	MMAE				Dxd				SN-38				PBD	
	Microtubule inhibitor				Topoisomerase I inhibitors								DNA crosslinking	

Mechanism of antibody drug conjugates (ADCs) used in urothelial cancer.

Chapter 1

Getting to Know Bladder Cancer

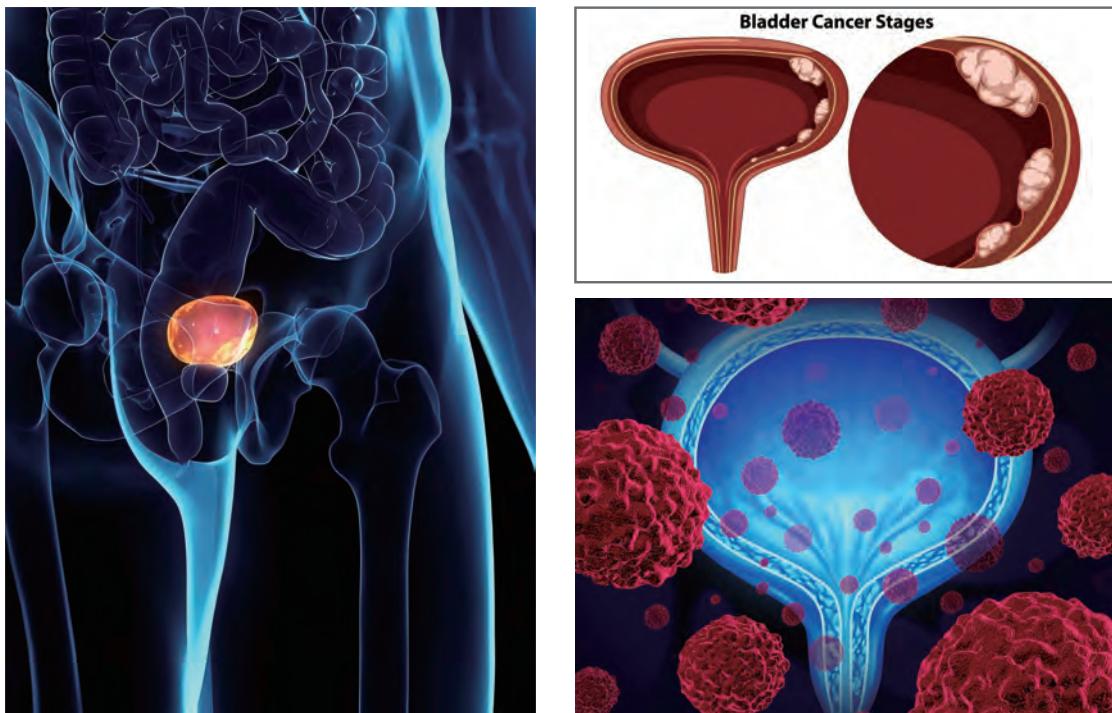
1. What Exactly Is Bladder Cancer?

Think of bladder cancer as a mutiny in your bladder: cells lining the organ, tired of following the rules, start multiplying like uninvited party crashers. The bladder, our body's "urine storage unit", exposes these cells to all sorts of chemicals in urine, making them prone to rebellions (mutations).

Doctors split it into two main types:

Non-muscle-invasive:
The rebels stay near the surface—easier to squelch, better prognosis.

Muscle-invasive:
The mutiny spreads deep into the bladder wall—tougher to contain, needs heavier firepower.

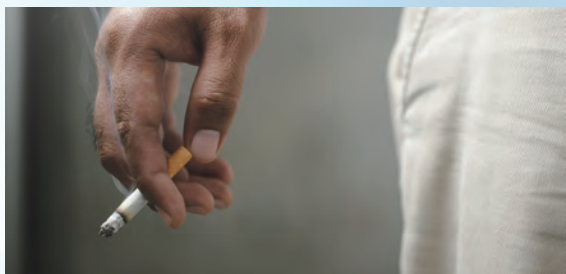


Diagrams of the location of bladder cancer and bladder cancer stages.

2. Who's on Bladder Cancer's Radar?

Smokers

Lighting up doubles to quadruples your risk. Cigarette smoke is basically a cocktail of bladder cell troublemakers.



Cigarette smoker.

Chemistry buffs (unwillingly)

Workers exposed to dyes, rubber, or plastics (think benzidine) are sitting ducks.

Chronic trouble

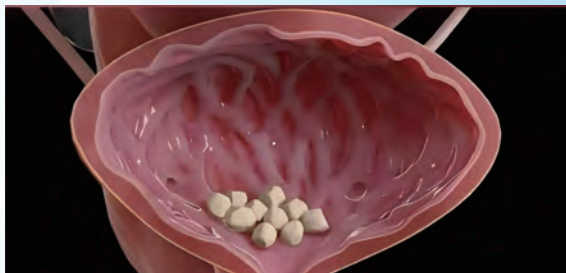
Long-term bladder infections, stones, or catheters keep cells in a bad mood, upping mutation chances.

Dodgy meds

Pills with aristolochic acid? They're like throwing gasoline on a fire for urinary cells.



Chemistry buffs.



Bladder stones.



Pills with aristolochic acid.

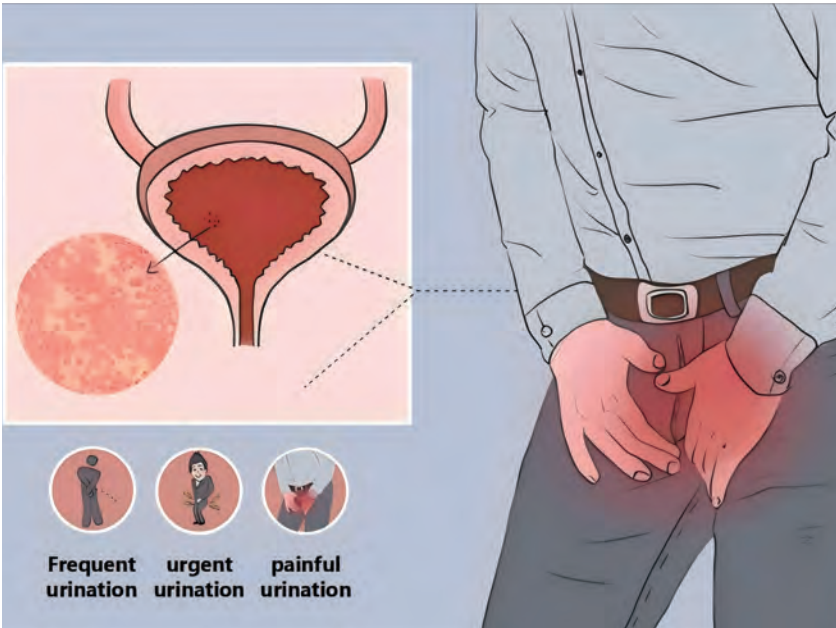
3. Warning Signs: When Your Bladder Sends an S.O.S.

Early red flag: Painless blood in urine (like a burglar leaving a calling card without making a sound).



Blood in urine.

Late-stage chaos: Frequent urination, urgent urination, and painful urination—collectively called "bladder irritation symptoms" along with backaches or unexplained weight loss—your bladder's way of yelling, "Help!" These often indicate advanced disease or spread.



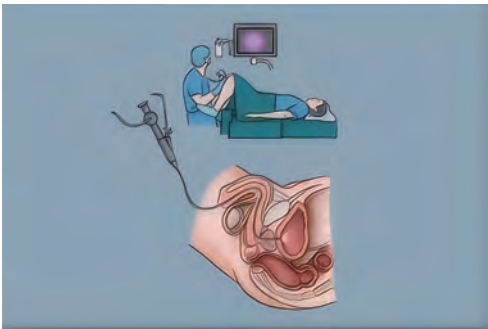
Bladder irritation symptoms.



Backache.



Unexplained weight loss.



Bladder scope.

Pro tip: Blood in urine? Don't brush it off. Bladder scopes and ultrasounds are way better than guessing games.

4. Outsmarting Bladder Cancer: Prevention 101



Quit smoking: This single move slashes risk by 70%—your lungs (and bladder) will throw a parade.



Hydrate like it's your job: Chug 2 liters of water daily. More peeing = less time for baddies to linger in your bladder.



Mask up (if you must): If your job involves chemicals, gear up with gloves and respirators.



Check-ups for high-risk folks: Smokers or industrial workers? Annual bladder ultrasounds could catch trouble early.



Quit smoking.



Drink plenty of water.



Mask up.



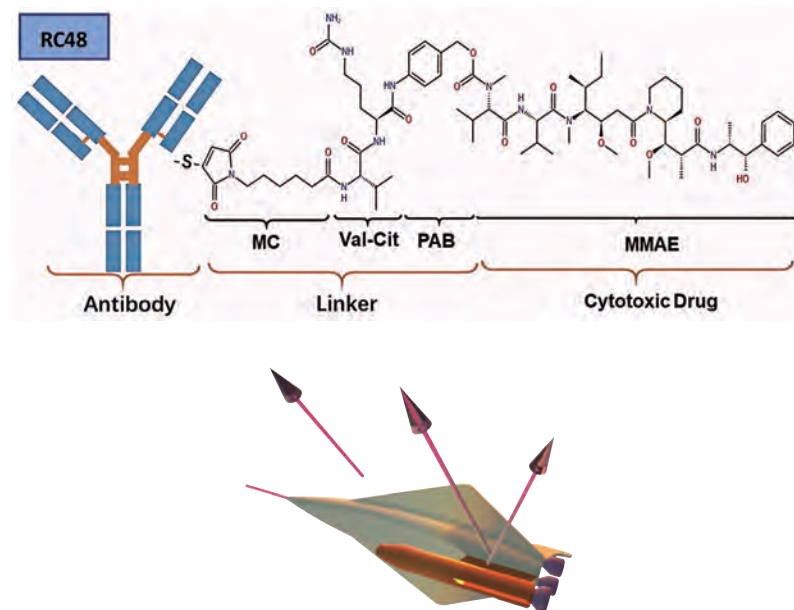
Bladder ultrasound.

Chapter 2

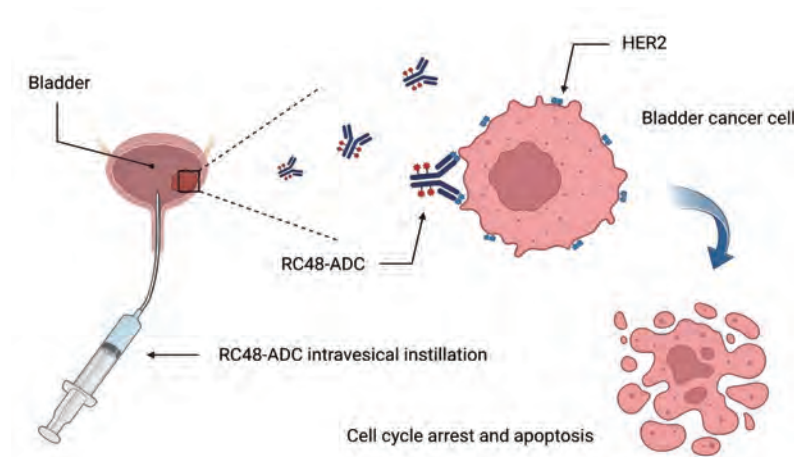
Bladder Cancer Treatment —From Old School to Cutting-Edge

Clinically, bladder cancer treatment has long relied on traditional methods: "surger+ radiotherapy/chemotherapy + immunotherapy." Then, the ADCs was approved, "disitamab vedotin (RC48)" was one of them, offering new hope to bladder cancer patients. It's like a "precision missile"—composed of a "navigation system (anti-body)", a "warhead (cytotoxic drug)", and a "Linker"—capable of accurately targeting cancer cells.

Disitamab vedotin specifically targets bladder cancer with overexpressed HER2 protein and has been designated a "breakthrough therapy" by both the U.S. FDA and China's NMPA. Clinical trials show it can extend the survival of advanced patients with fewer side effects than traditional chemotherapy.



Structure of disitamab vedotin (RC48).



Mechanism of action of RC48.

Chapter 3

The "Roadblock" for ADC Drugs: Drug Resistance

1. Drug Resistance and Its Mechanisms

Just as bacteria "adapt" to antibiotics, cancer cells can also "resist" drugs. ADCs that once worked may become less effective or even completely useless after a period of use—this is "drug resistance." RC48 also faces this issue, which has become a major obstacle to treatment efficacy.

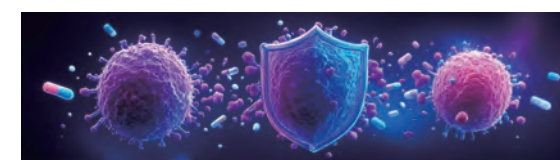
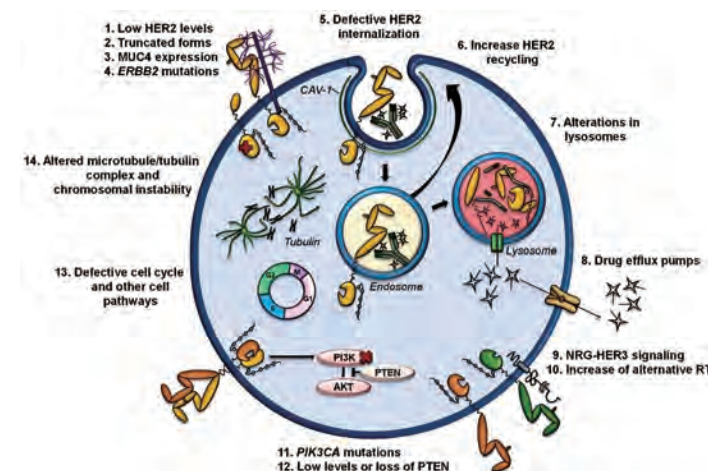
The mechanisms of ADC resistance are not yet fully settled, but preliminary evidence categorizes them into four types:

Antibody-mediated resistance

Cancer cells reduce the number of HER2 proteins on their surface or alter their structure, making RC48's "navigation system" unable to recognize them—like "changing their secret code, leaving the missile lost."

Impaired drug transport:

After ADCs are internalized, they fail to enter lysosomes or the linker cannot break, so the "warhead" can't be released—think of it as "the package gets stuck in the warehouse, unable to be unpacked."



Complex mechanism of ADC offers multiple opportunities for resistance.

Functional disruption

Cancer cells activate signaling pathways like Notch to enhance their survival ability, counteracting the killing effect of MMAE—"putting on a bulletproof vest to avoid bullets."

Payload efflux

Cancer cells "pump" MMAE out of the cell via ABC transporters, reducing its lethality—"the toxin is promptly drained, failing to deliver a fatal blow."

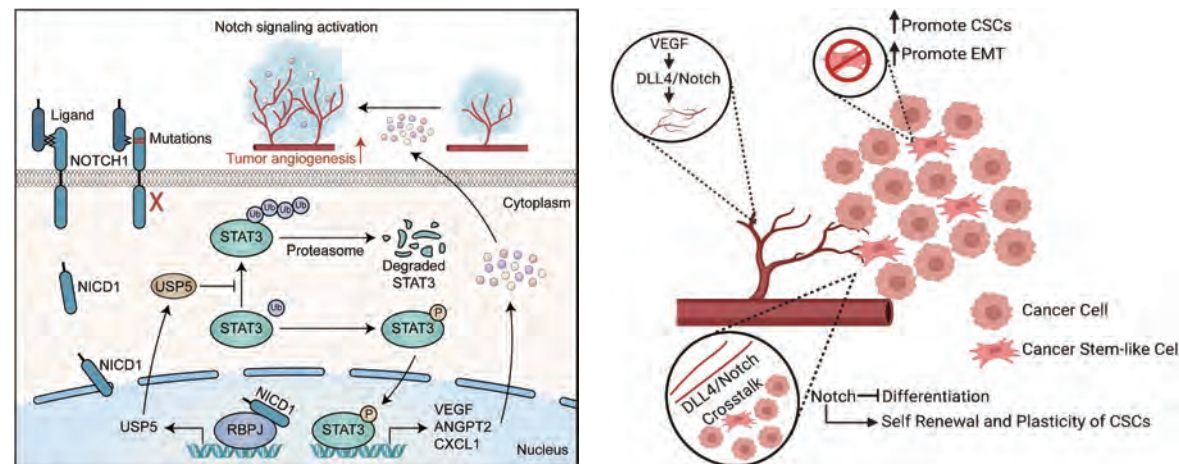
2. Breaking Through Resistance: Our Explorations

Our research team constructed a "drug-resistant cell model" and, combining gene sequencing and protein analysis, identified three characteristics of drug-resistant cells:

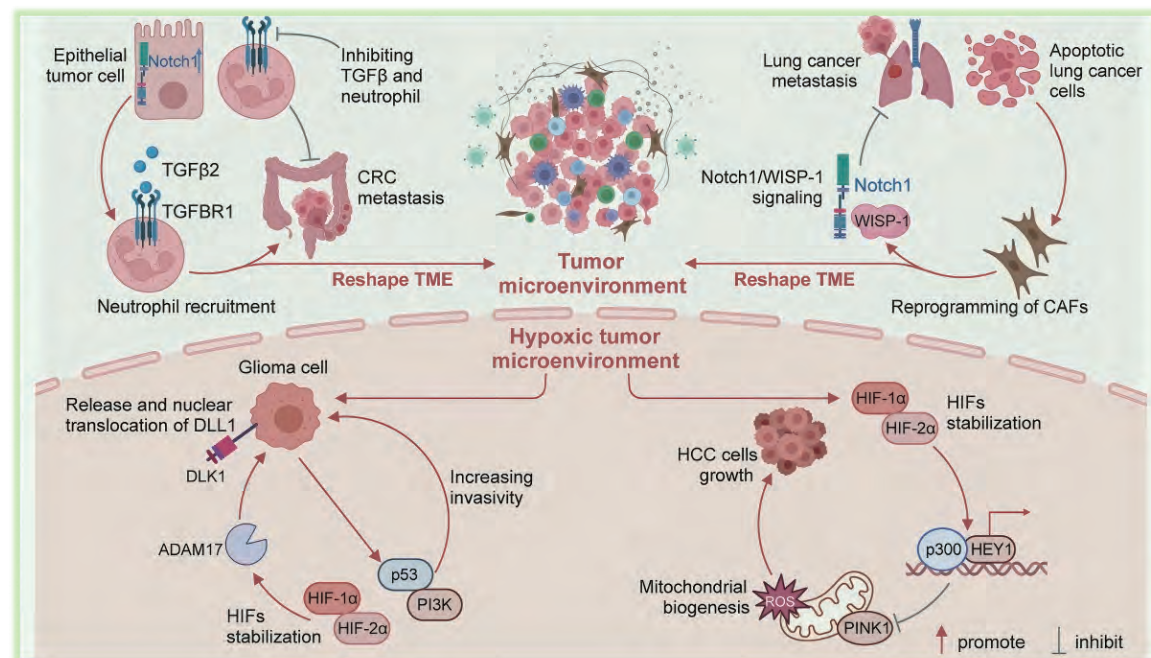
Initial suspected mutations (including HER2) via high-throughput sequencing were ruled out by PCR re-sequencing—no mutations found pre-vs. post-resistance.

Activated Notch pathway: Cancer cells' "survival signals" are strengthened, making them harder to kill.

Elevated PD-L1 and VEGF: PD-L1 helps cancer cells "evade the immune system," while VEGF promotes new blood vessel formation to "deliver nutrients" to cancer cells. Based on these findings, we propose a "combination therapy" approach: using RC48 to attack cancer cells while co-administering a Notch inhibitor (such as a γ -secretase inhibitor) and a PD-1/VEGF bispecific antibody (such as ivonescimab) to block immune evasion, angiogenesis, and hyperactive survival signals simultaneously—leaving drug-resistant cells "nowhere to hide."



Diverse involvement of Notch signaling in angiogenesis and cancer stem-like cells (CSCs).



Notch signaling pathway in tumor microenvironment.

Epilogue

From Lab Benches to Hospital Beds —Hope Marches On

Bladder cancer once trapped patients in a loop of recurrence and resistance, but ADCs have thrown open a window of hope. From RC48's precision strikes to unraveling resistance, every step forward is a victory for science—and for patients. Our work has pinpointed HER2, Notch, and PD-L1 as weak spots in the cancer's armor, lighting the way for new treatments. For you? Know the risks, spot the signs, and stay vigilant—prevention is still our best offense. For patients? Trust in progress, and keep fighting. From lab-grown cells to real-world therapies, from late nights in research labs to brave patients in clinics—we're inching closer to the day we outsmart bladder cancer for good. And that day? It's coming.