Potent Cyclic Peptide Inhibitors Disrupt the FANCM–RMI Interaction

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"We discovered and optimised peptide inhibitors of a potential new drug target for treating osteosarcomas. Through chemical modification, we improved our peptide inhibitors to bind this new drug target with exceptional strength and interfere with cancer-specific pathways. These peptide inhibitors represent thefirst example of targeting this new drug target in osteosarcomas, towards development of potential new drug candidates."

🧬 What's the study about?

Some cancers use a sneaky trick called **ALT (Alternative Lengthening of Telomeres)** to keep growing. Normally, cells stop dividing when their DNA ends (called telomeres) get too short. But ALT-positive cancer cells bypass this limit, allowing them to live and divide forever.

A key part of this process involves two proteins—**FANCM** and **RMI**—which help repair DNA and keep the cancer cells stable. If you can **block the interaction between FANCM and RMI**, you can potentially **kill these cancer cells** without harming healthy ones.

💊 What did the researchers do?

They created **tiny, circular molecules called cyclic peptides** that can **stick to RMI** and **stop it from connecting with FANCM**. These peptides were discovered using a special technique called **mRNA display**, which helps find molecules that bind very tightly to specific targets.

Three of these peptides—**RMI-L2, RMI-L3, and RMI-L4**—were especially good at:

- Binding to RMI with **very high strength** (in the nanomolar range).
- **Blocking the FANCM-RMI interaction** in lab tests and in cancer cell sample extracts.

🔬 How did they prove it works?

- They used **crystal structures** to see exactly how the peptides attach to RMI.
- They ran **binding tests** to measure how well the peptides compete with FANCM.
- They showed that one peptide, **RMI-L4**, could **completely block the interaction** in cancer cell extracts.
- They confirmed that the peptide is **stable** and has the right shape to fit the target.

🚀 Why is this important?

This is the **first time** scientists have made **valid chemical inhibitors** that can block FANCM-RMI. These molecules could:

- Help researchers understand how ALT cancers survive.
- Lead to **new cancer treatments** that target ALT-positive tumours without affecting healthy cells.

🧠 What's next?

The peptides don't yet work inside living cells, but the team is exploring ways to improve their delivery. Since this breakthrough, the team has discovered new peptide inhibitors that are cell-active and killed the osteosarcoma cells, and their publication about this is imminent. With further development, these inhibitors could become powerful tools for **targeted cancer therapy**.