Simulations offer a "virtual microscope" for drug design

Computer simulations play an increasingly important role in drug design, with new techniques enabling researchers to perform highly accurate calculations. **Professor Vittorio Limongelli**, together with his team at the Limongelli Research Group, develops advanced computational protocols to study pharmacologically relevant systems.

The significant improvement of simulation methods in parallel with increasing computing power is opening up exciting new avenues of investigation in biomedicine, allowing researchers to analyse molecular mechanisms in greater depth than previously possible. Based at the Institute of Computational Science (ICS) of Universitá della Svizzera italiana in Lugano, Professor Vittorio Limongelli is both developing and applying new methods for investigating molecular interactions, work which holds wider relevance to the pharmaceutical sector. "One pillar of my research group is the development of funnel-metadynamics, which is an important new methodology in computational pharmacology, as it allows us to identify new binding modes between ligands, proteins and DNA. It also provides an accurate estimate of the inter-molecular interaction strength through the calculation of the ligand binding free energy," he outlines. A second major pillar of Professor Limongelli's research is the development and application of coarse-grained metadynamics. "This is a new approach through which we are able to observe the formation of protein dimers and oligomers in cell membrane models, as in a virtual microscope," he says.

Molecular interactions

These methods are central to Professor Limongelli's work in a research project dedicated to investigating the molecular interaction between a sheltering complex protein called TPP1 and the telomerase enzyme (TERT), which is instrumental to the design of new anti-cancer drugs. The binary interaction between TPP1 and TERT plays a key role in the telomere maintenance mechanism, the process which protects the ends of the chromosome from degradation and fusion. "The telomere maintenance mechanism can be seen as the biological clock of the cell. This process is enhanced in tumor cells, therefore starving this mechanism leads to an anti-tumor effect," explains Professor Limongelli. Normally telomeres gradually shorten over time, yet in cancer cells the interaction between TPP1 and TERT helps telomeres maintain the same length, an important motivating factor behind the project's work. "The primary goal of this project is to discover the first compounds able to bind TPP1 and to disrupt its interaction with TERT. The novel compounds are designed to interfere with the telomere maintenance process and limit the number of cell cycles that a cancer cell can undergo. If successful, this study will lead to a new generation of anti-cancer agents," continues Professor Limongelli.

In fact, no molecules that bind to TPP1 on the TEL patch – the region of TPP1 which TERT binds to – have yet been identified, so Professor Limongelli and his team are investigating a completely new target. "First we have used high-throughput screening protocols and our in-house technology to identify in-silico potential ligands, then we test them on different cancer cell lines using tools that allow us to assess their activity on telomers," he outlines.

This research holds important implications in terms of the development of anti-cancer drugs, and the long-term goal is to bring the most promising ligands towards applications. This is not an immediate prospect however, and at this stage Professor Limongelli and his collaborator Simone Aureli are focusing on identifying lead compounds and considering questions around their potency, selectivity and toxicity. "We can identify ligands that are able to disrupt mechanisms in the cancer cell lines, but we want to be sure that the new molecules are not toxic for the healthy cells," he continues. Alongside this work, the Limongelli Research Group is also working to develop the first tridimensional model of the binding complex formed by TPP1 and TERT, which will provide solid foundations for further structure-based drug design. "Once we have achieved that, we can proceed with a rational understanding of some diseases involving mutated versions of these proteins, and consequently develop patient-tailored therapies," says Professor Limongelli.

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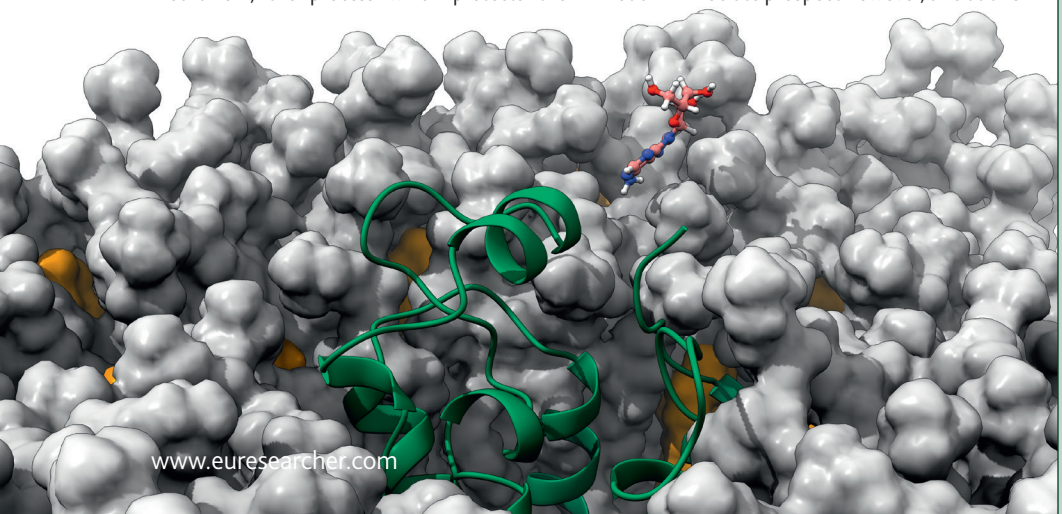

Extensive computer simulations investigate TPP1-TERT protein-protein interaction

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