THE POWER OF NMR IN DRUG DISCOVERY

Structural biology (SB) provides a critical drug discovery and development tool for accurately identifying and understanding the structure of a target. Alessandro Piai, PhD, Principal Research Scientist at IRBM, describes the company's expertise in nuclear magnetic resonance (NMR) and how it can be leveraged to accelerate the identification of molecules for progression to the clinic.

Can you tell us more about SB and why it is important for drug discovery?

SB is the study of the molecular structure and dynamics of all biological macromolecules, for example proteins and nucleic acids. Proteins have traditionally been the most popular targets for drug discovery, for example in pathologies or other diseases where proteins malfunction or cease to function. SB can provide a way to figure out the molecular mechanisms behind these non-physiological behaviours and suggest strategies by which to selectively target a protein of interest.

How does NMR complement other techniques such as X-ray crystallography (XRC) and cryo-electron microscopy (cryo-EM)?

XRC is the traditional method used in drug discovery, where a crystal structure provides information on where a ligand/molecule binds to its target and offers potential insights on how to further develop a candidate molecule. Despite the many advantages, the main limitation of this technique is that some proteins cannot be crystallized. In addition, this technique reveals only a snapshot of a protein in its crystallised state, which sometimes can be significantly different than its native state.

Conversely, NMR allows us to study the protein of interest in solution, which is closer to its natural, physiological environment. Considering that proteins can be flexible and can have different domains that may change conformation upon binding, it's the combination of structural and dynamic information provided by NMR that gives a more accurate picture of what is going on.

Single particle cryo-EM can unveil the structure of incredibly large proteins or complexes, but currently does not provide enough resolution to be useful for most drug discovery applications.

What are the advantages of using NMR in drug discovery?

An advantage of screening compounds by NMR is that not just strong, but also weak binders can be detected. This is useful, especially at the beginning of the drug discovery process, when a candidate molecule still has to be optimized. You can also use this technique to determine where the actual interaction/binding site is located at atomic resolution, obtaining valuable information that can be used to further optimise candidate molecules.

NMR is very versatile, allowing us to study small molecules, peptides, and proteins that have a molecular weight below the detection limits of this technique. You can study a vast array of molecular interactions and can customize experiments so that they can be tailored to the properties/requirements of a given sample, for example, to measure protein-protein interactions in a particular sample format or environment.

Another important advantage of NMR is that it is suitable for studying particular classes of proteins that could potentially provide important drug targets but have always been difficult systems to tackle by other techniques. This includes, for example, intrinsically disordered proteins, a class of flexible and dynamic proteins that are not folded like most other proteins, as well as transmembrane and juxtamembrane domains of membrane proteins.

How useful is NMR for developing RNA therapeutics?

NMR is perfectly poised to be used in the RNA therapeutics field. To date, RNA remains more or less untargeted in conventional drug discovery because RNA molecules are by nature very unstable and thus difficult targets. However, the growing awareness that many proteins involved in harmful disease processes cannot be targeted by conventional approaches is promoting the expansion of RNA therapeutics. Here, the idea is to target such proteins at the RNA level, exploiting the fact that RNA nucleotides often have a three-dimensional ordered structure that, similarly to proteins, is critical for their functioning and can thus become drug targets. NMR can be used to understand these structures as well as study drug candidate-RNA interactions to help identify new RNA-focused therapeutics.

What sets IRBM apart in NMR?

At IRBM our NMR team's breadth and depth of experience, combined with IRBM's passion for science, means that we take a collaborative, consultative approach to our work, and we believe that this differentiates our offering. Having expertise in NMR within different areas, including small molecules, peptides and proteins, we have the ability to ask 'atypical questions' that can bring significant value and make a difference to projects in the longer term. Constantly updating our state-of-the-art instrumentation also helps to ensure the highest possible quality when conducting experiments. As a general rule, we always try to go beyond standard services or assays, designing and conceiving the best experiments based on the research needs and goals of our clients.

About IRBM

IIRBM is an innovative Contract Research Organization (CRO) that works across all aspects of drug discovery and early development. It fosters collaborations with pharmaceutical and biotech companies, investors, as well as non-profit and academic sectors to accelerate drug discovery.

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