1.7: An Outlook on Medicinal Chemistry

> *"Art is never finished, only abandoned."*
>
> *– Leonardo Da Vinci*

7.1 Modern Medicinal Chemistry

Modern medicinal chemistry is a highly integrative field of science, that embodies nearly all disciplines of physical science in the effort to develop new pharmaceutical agents. Completion of the Human Genome Project in 2003 serves a launch-point for the vast expansion of multi-omics datasets, which, coupled with advances in computational power has begun to open a new era in in drug discovery, driven by collaborative workflow models and information networks. Advances in chemical biology, organic synthesis, and structural biophysics have enabled medicinal chemists to achieve creative, precise molecular intervention at the cellular level. Significant investment in data collection technologies (e.g. mass spectrometry proteomics) and data analysis strategies (bioinformatics/machine learning) have in some ways, "flipped" drug discovery workflows, where compound libraries are screened agnostically against any particular protein/enzyme, often leading to valuable new insights about previously "undruggable" targets in disease-driving pathways. Ultimately, all stages of the traditional pipeline must work in concert in order to bring transformative treatment options to patients and combat emerging disease-strains that are resistant to previous therapies.

7.2 New Technologies are Constantly Created

The integrative workflows of modern medicinal chemistry are back-dropped against a constantly growing toolbox of therapeutic technologies. The creativity of researchers in the field has been on full display over the last two decades, where a vast number of new mechanisms for modulating cellular proteins are emerging. A harmony between organic chemistry and chemical biology, among other disciplines, has engendered breakthroughs that go beyond the traditional ligand/enzyme binding equilibrium model in order to regulate target activity. For instance, the emergence of covalent inhibitors has changed the way medicinal chemists think about the classical concepts of potencies and occupancy, allowing more favourable target inhibition. Such developments are driving research in many challenging areas, such as targeting difficult or previously undruggable sites, such as those of protein-protein interactions. Alternatively, heterobifunctional ligands have recently undergone a massive stage of growth and development, and these technologies are now reaching the point of clinical evaluation. These bivalent molecules employ a clever mechanism of binding with two distinct cellular proteins simultaneously, with a chemical linker connecting the events. Chemists have now demonstrated this concept as a viable approach to affect a wide variety of post-translation modifications (e.g. phosphorylation) through proximity-induction between the target of interest and modifying enzyme. In concert with the rapidly expanding fields of proteomics, metabolomics, and computational biology, researchers are pushing the boundaries of the conventional archetypes in small molecule drug discovery. Guided by the well-established principles of molecular recognition and protein-ligand binding models used by medicinal chemists for over half a century, molecules of increasing complexity in cellular mechanism-of-action are being designed and validated. In the push to rectify high clinical attrition rates in drug discovery and achieve patient specific therapy, these technologies which depart from the traditional mechanisms for target modulation may provide the solution.