1.1: Different Avenues of Drug Discovery

Medicinal chemistry synergizes applications in cellular and molecular biology with pharmaceutical and organic chemistry to intercept natural processes in the human body. Modern drugs have emerged from different facets of discovery including astute observation from repeated use of natural products, serendipity, as well as hypothesis-driven rational- or targeted- chemical design.

For example, the discovery of the widely used analgesic drug, acetaminophen (also referred to as **Tylenol** or paracetamol) occurred through what was published as 'a fortunate accident'. In 1884, Prof. Adolf Kussmaul (University of Strasbourg) had two assistants who were evaluating different agents against intestinal worms in parallel to their effects on patients. One of their compounds, 'naphthalene' was shown to have unexpected antipyretic effects. However, as is the often the response when obtaining unanticipated results, the dataset and experimental protocols were examined with a deeper level of scrutiny, and it was revealed that the dispensing pharmacy supplied the patient with acetanilide (in error) as opposed to naphthalene. Acetanilide and other derivatives such as phenacetin were further investigated over several years. Each analog had different benefits and toxicities associated with it (some toxicities were associated with metabolites of the compounds, while others were found to be contaminants in the synthesis and/or purification steps). Eventually, the molecule, paracetamol, was identified. In 1955, it was marketed as Tylenol Elixir and was heavily promoted through unique branding campaigns as an over-the-counter medication for bed-ridden sick children.

Other drugs have been identified through more rational and target-based design approaches such as the 'miracle drug', **Gleevec** (imatinib), which is the prototype kinase inhibitor. In the 1950s, two researchers, Peter Nowell and David Hungerford, were analyzing cells from different blood cancer patients. In a specific sub-type of blood cancers, called chronic myeloid leukemia (CML), they identified an unusually small chromosome present in these patients (named the 'Philadelphia chromosome'). Following more than a decade from this discovery, cytogeneticist, Janet Rowely, was able to recognize that the Philadelphia chromosome results from a translocation event between chromosome 9 and 22. Across the span of another decade, researchers were able to identify this translocation specifically results in the fusion of two genes (ABL and BCR from chromosome 9 and 22 respectively), leading to a new gene-product called BCR-ABL. Under normal conditions, ABL is an important kinase protein that is responsible for accelerating cellular growth, especially in white blood cells. The new fusion protein, BCR-ABL decouples ABL kinase from its conventional regulatory controls, leading to highly proliferative cell growth. Oncologist Brian Druker was focussed on developing a molecule that could bind the active site (ATP-binding site) of BCR-ABL and effectively shut-down the protein. His team used computational models to predict chemical structures that could engage in appropriate interactions, and these compounds were synthesized and screened against CML cancer cell lines, *in vitro*. After ~2 years, the top compound, ST1571 (renamed Gleevec) was evaluated in a Phase I clinical trial with all 31 patients demonstrating complete remission. Gleevec was approved by the US FDA in 2001 and shown to have a >95% complete response rate over 60 months. The approval of Gleevec represents a convergence of multiple learnings across distinct disciplines including cancer biology, structural biophysics, organic chemistry, and clinical sciences. Since the discovery of Gleevec, there have been many drugs developed through the iterative pipeline of building on biology-enabled pharmaceutical chemistry.

Regardless of the path towards innovative drug design, the goal for any drug is to maximize therapeutic benefits and while minimizing off-target interactions, which can help maintain the safety window of the drug. There are >13,000 drugs available in Canada for many different indications. Here, we aim to provide an overview of some of the more commonly prescribed drugs and their relationship within the chemical and biological origin, as well as some of the common themes in medicinal chemistry between different drugs.