

Chemical Approaches to the Discovery and Development of Cancer Therapies

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The various branches of chemistry have played a pivotal role in the discovery and development of anticancer agents ever since the serendipitous discovery of the mustard family of agents in the 1940s (generally recognised as the origins of cancer chemotherapy). In this case, the application of *medicinal chemistry* (to sulphur mustard gas) led to agents that are still clinically useful today. However, there has been a shift in emphasis through the years from the use of *synthetic chemistry* to produce molecules, often at random, for screening against cancer cells growing *in vitro* (one of the mainstays of anticancer drug discovery in the latter half of the last century), to the currently favoured approach of the use of *structural chemistry* to elucidate the 3-dimensional shape of a cancer-specific target (usually a protein) in order for it to be used to discover molecules that bind and inhibit its function either through rational design or by screening libraries. This *molecularly targeted* approach has given rise to drugs such as imatinib (Glivec™). Libraries used for these screens are often derived from chemical technologies developed in the 1990s, such as *combinatorial chemistry* and *parallel synthesis*. Similarly, the 3-dimensional structure of a target, as determined by X-ray crystallography or high field NMR, can be used for *in silico* screening against virtual libraries, an approach which relies on recent developments in *computational chemistry*.

Chemical technologies are also important in the discovery and development of anticancer agents from natural sources. For example, the so-called *semi-synthetic* approach to modifying drug leads discovered in plant material has allowed workable quantities of novel agents to be obtained for preclinical studies and even commercial production, an example being paclitaxel. Other types of chemistries important in anticancer drug discovery have included *analytical chemistry* and *electrochemistry* which were crucial in the discovery of cisplatin. Also, with increasing interest in biological agents such as vaccines and tumour-specific antibodies, chemistry is again playing an important role in providing the technologies to stabilise vaccines, antibodies and antibody conjugates, and, in the case of antibody-drug conjugates and other types of prodrugs, in providing the “smart linkers” crucial for allowing active drugs to be released selectively at the tumour site.

Finally, for most classes of anticancer agents, *synthetic* and *medicinal chemistry* play key roles in lead optimisation, and *pharmaceutical chemistry* input is usually required for the development of final versions of new agents (such as salts) suitable for formulation and administration.