

Preface

The history of poly ADP ribose polymerase (PARP) research dates back more than 50 years to the first identification of the polymer in 1963. One might argue that the connection of PARP to cancer therapy goes back even further to the 1950s when the first cytotoxic agents the nitrogen mustards and other DNA alkylating agents inhibited glycolysis by depleting the cell of NAD. Of course, as some of these publications preceded or coincided with the discovery of DNA, the mechanism of alkylating agent cytotoxicity was thought to be through inhibition of glycolysis.

When inviting contributions for this volume, we were exceptionally fortunate to receive acceptances from two authors who were there in those early days of the discovery of the ADP-ribose polymer, the biochemical reaction, the enzyme that catalysed it and the development of the first benzamide inhibitors to elucidate its cellular function. Their insight into how the exploration of fundamental biology underpins future discoveries, which are presented in the first chapter of this volume, is enlightening.

A major step in PARP research came with the creation of knockout mice that led to the discovery of the second DNA damage-activated PARP, swiftly followed by the identification of a superfamily of PARP enzymes, identified by sequence homology with the catalytic domain. Some of these have turned out not to have *poly* ADP-ribosylating activity. The leading researchers on the PARP super-family contributed to Chaps. 2–4. The family as a whole is comprehensively described in Chap. 2 with the *bona fide* PARPs, the DNA damage-activated PARPs and the tankyrases, being described in more detail in Chaps. 3 and 4. In the following two chapters, other international research leaders describe the significance of PARP enzymes in maintaining health. Chapter 5 is a comprehensive review not only the roles of the PARP enzymes, but also PAR and PARG in cell death and carcinogenesis. In Chap. 6, the complex role of PARP in ageing and age-related diseases is elegantly untangled and visually represented.

PARP inhibitors were originally developed to determine the cellular function of PARP, but the early discovery of its role in DNA repair and the enhancement of alkylating agent-induced and radiation-induced cytotoxicity immediately highlighted

their potential as chemosensitisers and radiosensitisers. This was the initial push to develop more potent cellularly active inhibitors. Chapters 7 and 8 are written by two senior medicinal chemists who worked on the synthesis of PARP inhibitors in the pharmaceutical industry. They provide unique insights on the evolution of the classical benzamide inhibitors into the different series of PARP inhibitors using conventional structure-activity relationships (Chap. 7), and the application of structural biology to direct the synthesis (Chap. 8).

In the following section of the volume, data from preclinical studies with the newer more potent and specific PARP inhibitors as chemo- and radio-sensitisers are described. This section begins with a contribution from the groups at AbbVie (who made ABT-888/veliparib) and Pfizer (AG14361, AG014699/rucaparib) describing the advanced preclinical evaluation of these and other leading PARP inhibitors (Chap. 9). An in-depth evaluation of the mechanisms underlying chemosensitisation of topoisomerase I poisons and alkylating agents by PARP inhibitors is given in Chap. 10 by the group that has been probing the process most actively in recent years (Chap. 10). Radiopotentiality by PARP inhibitors through inhibition of both SSB and DSB repair when administered concurrently with radiotherapy, and the potential benefit of adjuvant PARP inhibitor therapy, is appropriately reviewed by the international experts from Institut Curie (Chap. 11). In their chapter, these authors also consider the potential unexpected or undesirable consequences due to the targeting of several PARP isoforms by the inhibitors and genomic destabilisation. This section is completed in Chap. 12 by a description of the unexpected vasoactivity of PARP inhibitors, the proposed underlying mechanisms and the potential for improved drug delivery and radiosensitisation, written by the scientists who first identified this unexpected activity.

Perhaps the most exciting and highly publicised discovery relating to PARP and cancer therapy is the discovery of the synthetic lethality of PARP inhibitors in cancers defective in homologous recombination repair (HRR), e.g. those associated with *BRCA1* and *BRCA2* mutations. In Chap. 13, the author of the first publications of this phenomenon describes the concept of synthetic lethality, DNA DSB repair pathways and the mechanisms underlying the pharmacological synthetic lethality of PARP inhibitors in cells with defects in direct and indirect players in the HRR pathway, along with considerations of the limitations of current understanding and the potential advantages and pitfalls of this therapeutic approach. Tumour hypoxia has long been considered a barrier to therapy but the discovery that it leads to a reduction in HRR capacity has led to the exploitation of this phenomenon using the concept of “contextual synthetic lethality” with PARP inhibitors. This concept is elegantly described by experts in this area in Chap. 14.

Further evaluation of the potential for PARP inhibitors to influence the mode and extent of cell death after irradiation in cells with other DNA damage response defects, and the potential to reduce inflammation, are very nicely explained in Chap. 15 by prominent scientists in the field. The concept of synthetic sickness is explored in the next two chapters. This is where a cellular defect or pathway inhibition alone has only a modest effect on viability, but where two defects/inhibitors are

combined there is a hugely synergistic impairment of viability. The combination of two molecularly targeted agents to achieve this synthetic sickness is a relatively recent concept in tumour biology; both Chaps. 16 and 17 provide excellent examples of such combinations with PARP inhibitors and the underlying mechanisms from the leaders in these areas.

Genomic instability and tumour heterogeneity are major issues in cancer therapy as both can lead to the outgrowth of a resistant population in response to the selective pressure of a therapeutic agent. Resistance to PARP inhibitors can develop in HRR-defective cells by different mechanisms. The acquisition of a secondary mutation in *BRCA1* or *BRCA2* can lead to the re-expression of a functional protein, thereby restoring resistance to PARP inhibitors, as described by the first person to identify this effect in Chap. 18. Other mechanisms of resistance, including the balance between NHEJ and *BRCA1*-independent homology-directed repair, are clearly explained by leading experts in Chap. 19.

PARP inhibitors first entered clinical trials in 2003 as chemosensitisers, but soon afterwards single agent studies in patients with *BRCA* mutations were also initiated. The final chapters of the book are introduced in Chap. 20 by the clinicians who conducted some of the earliest clinical trials and who were also involved in the pre-clinical studies that highlighted the differences in the doses needed for single agent activity compared to combination studies for efficacy without toxicity. An overview and critique of single agent PARP inhibitor clinical trials and the current status of the inhibitors in clinical trial development is provided in Chap. 21 by the clinical experts who were involved in several pivotal studies. The history and current status of trials using PARP inhibitors in combination with cytotoxic drugs, and the highs and lows of such studies, are presented by those involved in many of these studies in Chap. 22. Although there is a strong preclinical rationale for the combination of PARP inhibitors with radiotherapy, clinical trials of this combination have only recently been initiated. The justification for PARP inhibitor + radiotherapy trials is eloquently presented, along with the challenges associated with such studies, by a research champion of these trials and clinical leader in Chap. 23. Finally, the need for predictive and pharmacodynamic biomarkers for patient selection and activity monitoring, and strategies for developing appropriate biomarkers, are described in Chap. 24 by the editors of this volume.

As a final note on behalf of all the contributors to this volume, we all agree that PARP is a beautiful enzyme and the cellular effects can be visually spectacular with fluorescence microscopy. However, few of us will have considered what PARP *sounds* like! We are delighted to provide here links to a work by Ed Carter who has produced a piece of music based on the chemistry of PARP 1. For the amino acid sequence, Ed creatively used a 20-note scale with 1 note per amino acid each of 1 s duration. For its secondary structure, he used sustained notes for β sheets and split notes an octave apart for α -helices. This soothing piece of music, performed by a brass quintet, was composed to accompany Ed's art-work called "Inhibitor" based on the synthetic lethality of PARP inhibitors with HRR defects. Links to this composition and a short documentary on the science and art are given here: <http://>

edcarter.net/home/inhibitor/ alternatively, <https://soundcloud.com/edcarter/inhibitor> and <http://vimeo.com/97666957>.

We are delighted to conclude that PARP is not only bench to bedside, but also bench and bedside to art-form.

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