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Eva Maria Huber

Structural and Functional Characterization of the Immunoproteasome

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To my family

Supervisor's Foreword

Curing diseases is the primary long-term goal of contemporary scientific research. However, developing new drugs and bringing them to application demands for enormous efforts and staying power of both academia and pharmaceutical industry. Often the structural analysis of a target protein and its understanding at the atomic level form the foundation of such a long-lasting process. This proved true also for the 20S proteasome core particle (CP), a protease of 720 kDa and 28 single subunits.

In 1995, the first X-ray structure of a 20S proteasome, namely that of the archaeon *Thermoplasma acidophilum* has been elucidated by Löwe and coworkers [1]. Only, 2 years later, the structure of the proteasome from baker's yeast—the first eukaryotic proteasome—was solved [2]. This milestone in proteasome research stimulated the development of the multitude of inhibitory compounds that is known today. Many of these drugs have been structurally analyzed in complex with the yeast 20S proteasome and the obtained X-ray data served as intermediate and validation steps in the drug design development process. Up to now, two proteasome inhibitors have made their way from bench to bedside: Velcade® and Kyprolis®. Since the proteasome is essential for many cellular processes including cell cycle progression, both compounds are applied to patients suffering from blood cancer. However, recently, a novel therapeutic application of proteasome inhibition has been discovered. The compound ONX 0914 (formerly PR-957)—identified in high-throughput screenings—was shown to be of therapeutic benefit in animal models of autoimmune diseases such as rheumatoid arthritis and lupus erythematodes [3, 4]. Remarkably, despite its pronounced structural similarity to other proteasome inhibitors, ONX 0914 selectively targets only the 20S immunoproteasome, a specialized version of the proteasome known in vertebrates.

The immunoproteasome selectivity of ONX 0914 fascinated me as a chemist and formed the starting point for the Ph.D. thesis of Dr. Huber. Her work culminated in the first X-ray structure of an immunoproteasome. Finally, apo and ligand complex structures of the immunoproteasome with ONX 0914 provided an explanation for its selectivity. The structural results described herein represent a valuable contribution for modeling and designing novel proteasome-type selective and subunit-specific inhibitory compounds. Apart from the immunoproteasome structure described herein, Dr. Huber conducted yeast mutagenesis experiments which

aimed at imitating all three 20S proteasomes types of vertebrates in yeast: the constitutive proteasome, the immunoproteasome and the thymoproteasome. Together, the topic and the results of this thesis will definitely inspire further efforts in academic research as well as in medicinal chemistry.

Munich, June 2013 Prof. Michael Groll

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