Medicinal Chemistry with the Fifth Element: Discovery of Arginase Inhibitor AZD0011

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Arginase is an enzyme on the urea cycle that hydrolyzes arginine to ornithine. Because T cells require an arginine concentration of at least 20 μM in order to proliferate, arginase upregulation is one mechanism that tumor cells use to evade the immune response. Thus, arginase inhibition is an interesting target for immuno-oncology. Arginase inhibitors must satisfy an extremely restrictive pharmacophore in the form of a boronic acid warhead distal to an amino acid anchoring group. These polar functional groups are rich in hydrogen bond donors and acceptors, placing arginase inhibitors well outside the rule-of-5 property space, making it difficult to design and synthesize compounds that are both potent and orally bioavailable. As a result, targeting arginase with small molecule inhibitors has been a challenge in the field of medicinal chemistry for over twenty years. In this talk, we will discuss the structure-based drug design that led to the discovery of arginase inhibitor AZD0011, as well as the synthetic and DMPK challenges that had to be overcome along the way.