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Clinical progress and pharmacology of small molecule bromodomain inhibitors

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Bromodomains have emerged as an exciting target class for drug discovery over the past decade. Research has primarily focused on the bromodomain and extra terminal (BET) family of bromodomains, which has led to the development of multiple small molecule inhibitors and an increasing number of clinical assets. The excitement centred on the clinical potential of BET inhibition has stimulated intense interest in the broader family and the growing number of non-BET bromodomain chemical probes has facilitated phenotypic investigations, implicating these targets in a variety of disease pathways including cancer, inflammation, embryonic development and neurological disorders.

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Introduction

As a result of the understanding that a failure to appropriately control gene expression may underlie most human diseases, epigenetics and the potential of epigenetic therapeutics has rapidly grown into one of the most promising and fertile areas of drug discovery [1]. Bromodomains, a critical component of epigenetic regulation, selectively recognise acetyl lysine (KAc) residues present in both histone and non-histone proteins. The dysregulation of these protein reader modules have been implicated in the development of a large variety of diseases which make them attractive targets for drug discovery. Since the first disclosure in 2005 that a small molecule was capable of binding to a bromodomain [2], the number of reported inhibitors has expanded dramatically, particularly in the past six years, with the disclosure of a large number of small molecule bromodomain chemical probes. The profound and broad pharmacology of bromodomain inhibition, especially that associated with targeting the BET family of bromodomains (BRD2, BRD3, BRD4 and BRDT), has led to the progression of a number of small molecule assets into the clinic. Herein, we discuss the exciting progress of BET bromodomain inhibitors currently undergoing human clinical trials and the emerging pharmacology associated with the less mature field of chemical probes targeting bromodomains outside of the BET family.

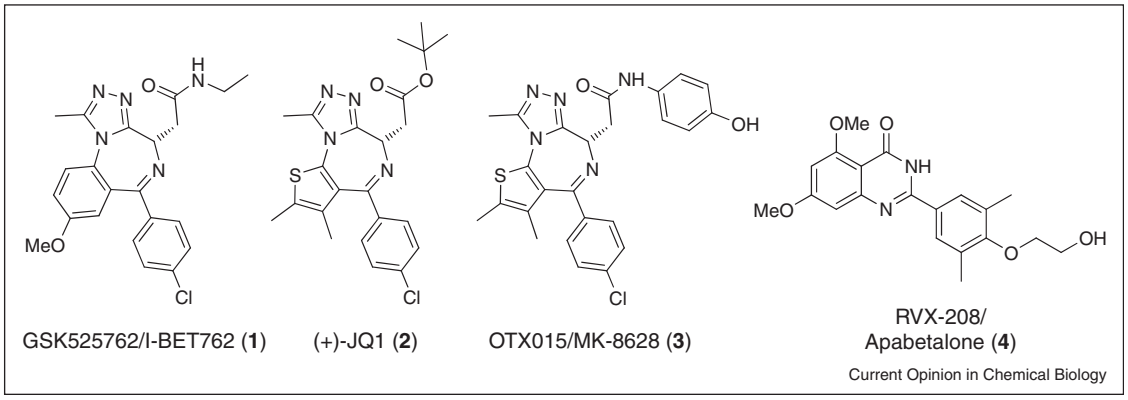
BET bromodomain inhibitors in clinical trials

There has been significant interest in the BET family of bromodomains due to their potential as therapeutic targets for a number of diseases including cancer, inflammation and cardiovascular disease. The first inhibitors reported for the BET family of bromodomains were structurally related I-BET762 (**1**) [3••,4,5] and (+)-JQ1 (**2**) [6••] reported by GlaxoSmithKline (GSK) and the Structural Genomics Consortium (SGC) working with the Dana-Faber Cancer Institute respectively (Figure 1).

This disclosure and ready availability of high quality small molecules such as I-BET762 (**1**) and (+)-JQ1 (**2**) stimulated academic and industrial research in the field. The development of a wide number of BET bromodomain chemical probes, including I-BET762 (**1**) and (+)-JQ1 (**2**) and their biological effects has been widely reported in a number of reviews [7•,8–14]. Indeed, the constantly growing numbers of patents and BET inhibitors in reported pre-clinical and clinical development highlights the substantial interest and investment in the potential of BET bromodomain inhibition for improving human health. As of January 2016, there are 14 small molecule BET inhibitors registered as undergoing clinical trials in a total of 20 studies (Table 1).

The vast majority of BET inhibitors undergoing human clinical trials are initially being investigated in an oncology setting and due to the ongoing nature of most of these clinical studies, there are limited data available (Table 1). However, OncoEthix (acquired by Merck in 2014) have completed a Phase I trial in patients with acute myeloid leukemia (AML) and other haematological malignancies

Figure 1



Chemical structures of BET bromodomain inhibitors I-BET762 (**1**), (+)-JQ1 (**2**), OTX015 (**3**) and RVX-208 (**4**).

with OTX015/MK-8628 (**3**) [15•,16–18]. This orally available molecule is well tolerated up to 80 mg once a day (QD) with diarrhoea/fatigue and reversible thrombocytopenia observed as the dose limiting toxicity in patients with AML and other haematological malignancies respectively. Trough plasma concentrations at 80 mg QD reached the GI_{50} concentration of 500 nM for sensitive tumor cell lines *in vitro* and clinically meaningful activity was seen in AML and lymphoma patients.

Constellation have reported a preliminary analysis of an ongoing Phase I trial with CPI-0610 (structure not disclosed at time of writing) in lymphoma patients [19]. The compound, like OTX015/MK-8628 (**3**), is well tolerated in patients and the principal toxicity was reversible thrombocytopenia. The maximum decline of platelets occurs around day 14 of QD dosing, with subsequent recovery over a 1–2 week dosing holiday. Expression of the BET target gene chemokine C–C motif receptor 1 (CCR1) was suppressed at 170 mg and 230 mg QD, associated with plasma CPI-0610 concentrations $\geq$3 μM and anti-lymphoma activity has been observed in patients with 80–230 mg QD doses.

Tensha Therapeutics (acquired by Roche in 2016) has reported tolerability and partial clinical responses in a small number of NUT-midline carcinoma (NMC) patients with subcutaneous QD dosing of TEN-010 (structure not disclosed) for three weeks in a four-week cycle [20]. The compound and dosing regimen was tolerated with reversible irritation of the injection site, increases of bilirubin and anorexia reported. This observed response in two NMC patients with TEN-010 provides preliminary hope that BET inhibition may provide a treatment for this rare and clinically aggressive cancer.

There are ten other companies progressing BET bromodomain inhibitors in oncology clinical trials for both solid and haematological malignancies (Table 1). However, of note is the Peter MacCallum Cancer Centre in Australia who have entered *N*-methyl-2-pyrrolidone (NMP) into human trials for cancer. It has been reported that this common laboratory solvent can act as a weak affinity, broad spectrum bromodomain inhibitor with binding demonstrated to multiple bromodomains including BET. In a mouse model of myeloma, treatment with NMP demonstrated antineoplastic and immunomodulatory activity consistent with BET inhibition [21].

Outside of oncology, the most advanced bromodomain inhibitor undergoing clinical trials is RVX-208 (**4**), also known as Apabetalone. This compound, independently identified *via* an ApoA1 upregulation phenotypic screen [22], is 8–23 fold selective for the second BET bromodomain (as determined by isothermal titration calorimetry) [23] and has completed Phase II clinical trials for a number of cardiovascular diseases including coronary artery disease, type II diabetes mellitus and atherosclerosis [24]. A *post hoc* analysis from two pooled Phase II trials (NCT01423188 and NCT01067820) demonstrated that patients with cardiovascular disease had a statistically significant decrease in major adverse cardiovascular events (MACE) when given RVX-208 (**4**). As such, this compound has recently entered a Phase III trial titled 'BETonMACE' aiming to reduce MACE in high-risk type II diabetes mellitus patients with coronary artery disease and low high-density lipoprotein [25].

Non-BET bromodomain chemical probes

It is of note that the discovery of the first known inhibitors for the BET family of bromodomains occurred following phenotypic screens where the molecular target was unknown [5,6••]. The small molecule probes that resulted have been pivotal in realising the importance and therapeutic potential of BET bromodomain inhibition. With comparatively little known about bromodomains outside of the BET family, high quality chemical probes are an important tool for unravelling the biological role of these