Pro-inflammatory cytokine lowering anti-inflammatory drugs

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Research Abstract
Tumor necrosis factor- (TNF) is one of the primary pro-inflammatory cytokines synthesized and released by microglial cells. Once TNF is released, it may initiate a self-propagating cycle of unchecked inflammation (Frankola et al., CNS Neurol Disord Drug Targets 10:391-403, 2011). Pharmacological intervention to interrupt this cycle may be of significant benefit in the setting of neuroinflammation-mediated diseases. In 1993, Moreira et al., (J Exp Med 177:1675-80, 1993) described a series of studies showing that the drug thalidomide (THAL) was able to lower TNF protein levels post-transcriptionally by accelerating degradation of its mRNA. Unfortunately

THAL is not a particularly potent TNF lowering agent induces serious teratogenic adverse effects to embryos in utero, sedation and peripheral neuropathy at clinical doses. Nevertheless, the observation of THALs TNF lowering activity gave rise to studies to differentiate these actions, understand THALs TNF structure/activity relationship and develop more potent analogs. In principle, the identification of analogs with enhanced anti-TNF activity and reduced teratogenic and neurotoxic effects may provide a viable treatment strategy for CNS neuroinflammatory and other forms of inflammatory disease. Our medicinal chemistry modifications to the backbone of THAL and newer analogs (namely pomalidomide (POM)) are generating an extensive library of novel agents (successfully issued US patents owned by NIA: 7,973,057 and 8,927,725, and U.S. Patent Application No. 62/235,105 filed September 30, 2015). Our focus is identify well-tolerated drug-like compounds with more potent anti-TNF activity from our generated library and develop these as experimental drugs to characterize the role of the neuroinflammatory component in and to treat Alzheimer's disease (AD) and associated disorders. Problem and Focused Aims: AD is a complex disorder that manifests as progressive dementia with few other symptoms. With a long meandering course, AD is associated with deposits of amyloid- protein (A) as much as 20 years prior to the development of dementia. It also induces intracellular accumulation of the microtubule-associated protein Tau (MAPT) as neurofibrillary tangles (NFTs) that correlate more closely with the extent of dementia (Baranello et al., Curr Alzheimer Res 12:32-46, 2015). NFTs arise some 10 years after A and brain atrophy follows after five further years. However, the resilience and redundancy of the brain protects the affected subject from dementia for around five further years after the detection of atrophy by brain image analysis. Experimental drugs and strategies that reduce the generation of A oligomers and aggregates as well as of phosphorylated-tau have formed, in large part, the basis of treatment strategies thus far developed to combat the development of AD. Whereas these target are considered the initiators of the cascade of events that become self-propagating and then drive AD progression, their toxicity may not be the direct cause of neurodegeneration. This premise may account for the failure of anti-amyloid and anti-tau therapies in clinical AD trials when administered late in the disease course (Becker et al., Nature Rev Drug Discov 13:156, 2014). The presence of soluble and insoluble A and MAPT can induce microglia activation (McGeer & McGeer, Acta Neuropathol 126:479-97, 2013), and direct evidence of neuroinflammation in AD brain has been shown by in vivo PET imaging (Schuitemaker et al., Neurobiol Aging 34:12836, 2013). Notably, levels of pro-inflammatory cytokines are elevated in serum and CSF from AD patients, for TNF by as much as 25-fold (Tarkowski et al., J Clin Immunol 19:223-30, 1999). In MCI subjects that progress to develop AD, a rise in CSF TNF levels correlates with disease progression (Tarkowski et al., J Neurol Neurosurg Psychiatry 74:1200-5, 2003). Paralleling this, elevated expression of TNF is reported within the entorhinal cortex of 3xTg-AD mice prior to the appearance of amyloid and tau pathology, and this increase associates with the onset of cognitive deficits in these mice and later neuronal loss (Janelsins et al. J Neuroinflamm 2:23, 2005). We hypothesize that failure of protein homeostasis leads to accumulation of proteins (e.g., A, APOE and MAPT) that induce microglial activation and a proinflammatory M1 response to instigate their removal. The continuing generation of protein (A, APOE and MAPT) leads to maintenance of a chronic M1 response, an impairment of transition to an anti-inflammatory M2 response (particularly in the aging brain that is already vulnerable to inflammation) with ensuing neuronal impairment observed in the animal models and in preclinical AD that eventually leads to cell death. Proinflammatory cytokines, like TNF, induce vascular changes to allow lymphocyte infiltration that may underpin reported cerebral vasculature leakiness of AD patients and related Tg mouse

models. Moreover, TNF induces A production in cellular and animal AD models, further increasing its accumulation and accelerating the entire cascade. Our focus is to understand the time course of development of neuropathology accumulation of inflammatory cytokines and behavioral deficits in mouse models that may reflect the disease pathology in humans. Our aim is to use these models, together with classical evaluations of pharmcokinetics/dynamics and toxicity evaluations, to aid select out from our agents that potently lower TNF – compounds that can be moved to the clinic to mitigate the neuroinflammatory element in AD and associated disorders. Our studies involve: (i) Synthetic chemistry on the backbones of THAL and POM to generate more potent anti-inflammatory agents that are better tolerated. (ii) Cellular screening for anti-inflammatory actions (Tweedie et al., J Neuroinflamm 9:106, 2012) (iii) Zebrafish and chicken embryo screening for anti-inflammatory, anti-angiogenesis and toxicology screening (Collaborators: Drs. Vargesson, Figg, Beedie) (Mahony et al., PNAS 110:12703-8, 2013; Beedie et al., Oncotarget (Epub ahead of print) 2016). (iv) Pharmacokinetic/dynamic/toxicological evaluations in acute rodent studies. (v) Efficacy evaluations in both acute and chronic rodent models involving inflammation, cognitive impairment and/or AD and related disorders (Russo et al., J Neurochem. 122:11871-92, 2012; Tweedie et al., J Neuroinflamm 9:106, 2012; Belarbi et al., J Neuroinflamm 9:23, 2012; Starke et al., J Neuroinflammation 11:77, 2014; Baratz et al., J Neuroinflamm 12:45, 2015.; Wang et al., J Neuroinflamm 13:168, 2016). In synopsis: Our focus is to use our novel compounds as agents to understand the time-dependent role of neuroinflammation in AD progression in animal models and, concurrently, to select out the most potent with drug-like features as a new treatment intervention for AD and related disorders, creating a preclinical package both on our best agent as well as on the comparator clinically approved cancer drug, POM (as a back up), to support clinical translation. Notably, the drug target in these proposed studies – elevated levels of TNF – has relevance to AD (with the potential to impact acute and chronic neurological endpoints) and to related CNS and systemic disorders driven by inflammation (for independent review see: Tobinick E; Curr Alzheimer Res. 9:99-109, 2012; Ignatowski T et al., CNS Drugs. 28(8):679-97, 2014; Clark & Vissel, J Neuroinflamm ;13:236, 2016).

Further information available at:

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