Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Rabeximod

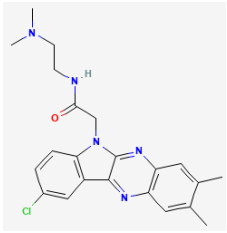
Evidence Summary

Rabeximod may benefit conditions with an autoimmune component. While its narrow mechanism may lead to good safety, it may also limit its clinical utility.

Neuroprotective Benefit: It is unclear whether rabeximod could reduce T-cell-related neuronal damage in neurodegenerative disease, though it may benefit neuro-autoimmune conditions.

Aging and related health concerns: Rabeximod may benefit autoimmune conditions in which antigen-presenting macrophage-derived cells play a prominent role.

Safety: Rabeximod is reported to be well-tolerated in clinical trials, but details are lacking.

Availability: In clinical trials	**Dose**: Not established Administered as oral tablets	**Chemical formula:** $C_{22}H_{24}ClN_5O$ **MW**: 409.9 g/mol  Source: PubChem
Half-life: Not reported	**BBB**: Not reported	
Clinical trials: A Phase 1 (n=80), Phase 2 in rheumatoid arthritis (n=224), and a Phase 2 (n=92) for Covid-19 have been completed.	**Observational studies**: None	

What is it?

Rabeximod (Rob 803) is an immunomodulatory drug that targets antigen presenting cells, and is being developed for autoimmune conditions, primarily rheumatoid arthritis [1]. Jan Bergman developed a series of non-toxic derivatives of ellipticine, a natural alkaloid compound with anti-tumorigenic properties based on its ability to inhibit DNA topoisomerase II [2]. The lead compound B-220 was found to have anti-viral activity, and additional analogs were developed from B-220. Rabeximod is one of these analogs which was found to have anti-inflammatory activity. It prevents the differentiation of monocytes into certain pro-inflammatory subsets of antigen presenting cells, such as macrophages and dendritic cells [3]. Rabeximod was originally developed by OxyPharma, which sponsored a Phase 1 trial in 2006, and a Phase 2 study for rheumatoid arthritis in 2008. Rabeximod was fully acquired by Cyxone in 2018 (Press release). In 2021, Cyxone conducted a trial for Covid-19, and as of 2022 is focusing clinical development on rheumatoid arthritis, with a planned Phase 2b RCT.

Neuroprotective Benefit: It is unclear whether rabeximod could reduce T-cell-related neuronal damage in neurodegenerative disease, though it may benefit neuro-autoimmune conditions.

Types of evidence:

- 1 laboratory study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There is increasing evidence indicating that the adaptive immune system is dysfunctional in dementia patients, and that changes in certain T cell populations are associated with cognitive decline [4]. In dementia patients, there is clonal expansion of certain CD8 and CD4 memory T cell populations within the CNS, which is coupled with an overall decrease in T cell diversity [5; 6]. Clonal expansion of a population of T cells called CD8 T EMRA was seen in the brains of individuals with Alzheimer's disease (AD) [5]. These antigen-trained cells increase with aging, and subsets of them have been shown to display a senescence-associated secretory phenotype (SASP), which drives chronic inflammation [7]. T EMRA cells are highly heterogeneous and typically associated with the immune response to viral pathogens, suggesting their expansion may be related to the presence or reactivation of chronic latent viruses. The presence of these T cells within the CNS is tied to neuronal loss, but the nature of this relationship is not well understood [4]. It could involve an autoimmune type mechanism whereby activated T cells primed with CNS antigens attack neural tissue, and/or neuronal loss could be secondary to prolonged low-grade inflammation stemming from an ineffective primary adaptive immune response. The majority of the evidence to date points to the latter [8], but does not exclude a role for the former.

Antigen presenting cells train and stimulate T cells to either ignore (i.e. induce tolerance to self-antigens), or to mount an attack against that particular antigen [9]. Due to the immune privileged status of the CNS, T cells are trained in the periphery and then migrate into the CNS. The lymphatic/glymphatic drainage of CNS proteins into the cervical lymph nodes provides a source of potential CNS antigens, which could be taken up by antigen presenting cells. The interaction between the antigen presenting cell and the T cell is an important determinant of the ultimate T cell response.

The key question with respect to the potential therapeutic efficacy of rabeximod in this population is whether these detrimental effects to adaptive immune cell function are tied to changes in the antigen presenting cells, and if so, which antigen presenting cell populations are most relevant? Antigen presentation involves the major histocompatibility complex (MHC), which is comprised of human leukocyte antigen (HLA) genes [10]. HLA genes and single nucleotide polymorphisms (SNPs) in genes that regulate HLA genes have been associated with AD [9]. This suggests that altered antigen presentation can promote neurodegeneration. One study found evidence for increased self-antigen load in the brain in the context of AD [11].

Microglia, the resident innate immune cells in the brain, show little antigen presentation capacity under homeostatic conditions [8]. However, in the context of an inflammatory event, they can upregulate MHC proteins and interact with T cells. Microglia typically promote tolerance, but under pathophysiological conditions, these interactions may lead to the induction of a tissue damaging T cell response. While evidence from rodent studies suggests a role for microglia, definite human studies are lacking. As such, the identity of the relevant antigen presenting cells in AD remains unclear. In the context of multiple sclerosis models, it is the infiltrating myeloid cells and dendritic cells, rather than the resident microglia, that appear to act as the antigen presenting cells in the activation of myelin-destroying T cells [12].
There is controversy regarding the contribution and fate of infiltrating myeloid cells, such as monocyte-derived macrophages, in the CNS. Based on the purported mechanism of action for rabeximod, which impacts the differentiation of proinflammatory macrophages and dendritic cells, its potential efficacy is dependent upon the contribution of these cell types to disease etiology. The link for autoimmune and injury-related neurodegeneration is clear, but the relevance for AD is unclear.
There are several outstanding questions. Are infiltrating macrophages and dendritic cells important antigen presenting cells in the brain under physiological conditions? Is this activity increased or decreased in the context of dementia? Do changes in the presence and/or activity of these cells influence the migration or activation status of T cells in the CNS? Are the T cells hyperactive, anergic, or a combination?

For rabeximod to be a viable therapeutic for AD, the uptake of CNS antigens by peripheral monocytes, and the subsequent effect of T cell activity within the CNS needs to be an important mechanism of pathophysiology. Another key consideration is the relevant therapeutic window. Studies in autoimmune disease models indicate that there is a critical window of rabeximod administration for efficacy [13]. This window is associated with the activation of the antigen presenting cells in response to antigen priming. The relevant therapeutic window in the disease course of AD has not been established.

Human research to suggest benefits to patients with dementia:

Rabeximod has not yet been tested in patients with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Traumatic brain injury: UNCLEAR BENEFIT (Preclinical)
In the controlled cortical impact model of TBI in male mice, rabeximod (40 mg/kg i.p.) administered as a single dose 30 minutes following the injury, reduced markers of antigen presentation in the brain without affecting the activation of microglia or astrocytes [14]. The effect was driven by a reduction in the invasion of MHC class II and lysozyme 2 expressing classical dendritic cells (CD11c) with high antigen presenting capacity. Rabeximod didn't impact the overall infiltration of dendritic cells, only the antigen presenting capacity of the infiltrating cells. The length of the therapeutic window for administration following injury has not been established, so the clinical utility is not yet clear. Additionally, neurological outcome measures were not assessed, so it is unclear whether rabeximod has a meaningful impact on neurological recovery.

APOE4 interactions: While the general role of antigen presenting cells in AD is unclear, there is evidence to suggest that they may be particularly relevant in the context of ApoE4. The secretion of ApoE by MHC II expressing (i.e. cells with antigen-presenting capacity) microglia may promote the capture, processing, and presentation of lipoprotein antigens [15]. The cholesterol content of dendritic cell membranes influences the density of receptors involved in antigen presentation, and thus influences the antigen presenting capacity of the cells. The ApoE4 allele is less efficient at transporting cholesterol, which results in dendritic cells with higher cholesterol content and enhanced T cell activating capacity [16]. Consequently, ApoE4 carriers were shown to have higher levels of circulating activating T cells. This suggests that rabeximod may preferentially benefit ApoE4 carriers, though more work is needed to understand the contribution of these cells to the pathophysiology.

Aging and related health concerns: Rabeximod may benefit autoimmune conditions in which antigen-presenting macrophage-derived cells play a prominent role.

Types of evidence:

- 2 clinical trials
- Several laboratory studies

Rheumatoid arthritis: POTENTIAL BENEFIT

Rabeximod has been tested in a Phase 2 RCT (NCT00525213) in patients with moderate to severe rheumatoid arthritis (RA) (n=224). Participants were treated with two capsules per day of rabeximod (Rob 803) or placebo for 12 weeks in combination with a stable dose of methotrexate. The primary outcome was efficacy based on the American College of Rheumatology (ACR) definition of improvement requiring at least 20% improvement on a set of measures (ACR20) at 12 weeks. The trial was completed in 2009, but details from the study sponsor, OxyPharma, are not publicly available. Cyxone, who acquired rabeximod from OxyPharma in 2018 have indicated that the study did not meet its primary endpoint, but a beneficial effect was seen at 16 weeks, suggesting that the original trial duration was too short for efficacy (Cyxone July 2018 Newsletter). As a result, Cyxone has submitted a request for regulatory approval for a Phase 2b RCT testing rabeximod in patients with moderate to severe RA with an inadequate response to methotrexate for 24 weeks (Press release). If approved by European regulators, the trial would begin in late 2022.

Studies in preclinical models indicate that there is a discrete therapeutic window for efficacy, however, in the course of a relapsing condition with periodic inflammatory flare-ups, it is likely that this window of action occurs not only upon disease initiation, but within the course of each inflammatory episode [13]. In the collagen-induced arthritis model in rats, subcutaneous treatment with rabeximod (40 mg/kg) for 14 days, starting the day of immunization (disease induction), modestly slowed the onset of disease and reduced disease severity [17]. The effect was related to a reduction in T cell proliferation in lymph nodes. No effect on disease was seen when administered after the animals reached a clinical score of 2. Similarly, in the collagen antibody-induced arthritis model in mice, subcutaneous treatment with rabeximod (40 mg/kg) reduced disease severity when treatment began between days 3 to 5, but not when administered prior to disease induction or starting after day 5 [13]. The therapeutic window coincides with the period between antigen priming and disease onset. Rabeximod acts on the activation of macrophages downstream of toll-like receptors (TLRs) or other activating stimuli [1]. Cell culture experiments with human monocytes indicate that rabeximod acts specifically on the activation of pro-inflammatory monocyte-derived macrophages and the differentiation of monocyte-derived dendritic cells, without impacting the differentiation or activity of anti-inflammatory macrophages [3]. Rabeximod impaired the ability of the monocyte-derived dendritic cells to take up antigens, without impacting the overall phagocytic capacity of monocytes. Together, these studies suggest that rabeximod has a discrete mechanism of action regarding the differentiation and activation of monocytes into proinflammatory antigen presenting cells which may limit the activation of tissue-damaging T cells in response to autoantigens.

Covid-19: NO BENEFIT

Rabeximod was tested in a placebo-controlled Phase 2 RCT in patients with moderate severity Covid-19, that had difficulty breathing but did not require mechanical ventilation (n=92) (EudraCT Number: 2020-004571-41). Rabeximod was dosed at 15 or 30 mg o.d. with or without oxygen therapy for 14 days. The primary outcome was the proportion of subjects alive and free of respiratory failure at day 28. The majority of patients were alive and free of respiratory failure at the end of the study, with no significant difference across study arms (Press release). Topline results indicated that 100%, 97%, and 97% of patients met this outcome in the 30 mg, 15 mg, and placebo groups, respectively. Based on these results, the development of rabeximod for this indication has been discontinued.

Safety: Rabeximod is reported to be well-tolerated in clinical trials, but details are lacking.

Types of evidence:

- 3 clinical trials
- Several laboratory studies

Rabeximod has been tested in a Phase 1 trial (Single Ascending Dose and Multiple Ascending Dose) in 80 healthy volunteers, assessing safety, tolerability, pharmacodynamics, and pharmacokinetics (Press release). It was also tested in a Phase 2 study in patients (n=224) with rheumatoid arthritis (NCT00525213). These trials were completed in 2006 and 2009, respectively, with OxyPharma as the study sponsor, but other than indications that it was orally available, well-tolerated, and showed a favorable safety profile, details are lacking.

Topline results from a Phase 2 study testing rabeximod in Covid-19 in a trial sponsored by Cyxone indicate that rabeximod was well-tolerated, did not worsen disease, and was not associated with any severe adverse events (Press release).

The main theoretical concern for rabeximod would be the risk for infection due to a blunted immune response. Although the preclinical and clinical studies conducted thus far were too short to provide a clear indication regarding this risk, its narrow activity on particular immune subsets suggests it is likely much safer than broad-acting immunosuppressants, and may not impact global immune function/pathogen control in a clinically meaningful manner.

Drug interactions: Interactions have not been established, but rabeximod may interact with other immunomodulatory drugs.

Sources and dosing:

Rabeximod is under clinical development for rheumatoid arthritis by Cyxone. No clinically efficacious dose has been established. It is administered in the form of oral tablets in clinical trials. Preclinical studies in arthritis models suggest that subcutaneous dosing may be more effective, though this appears to be related to a bioavailability issue, with drug concentrations not necessarily reaching therapeutic levels with oral administration [13; 17]. This could be a function of the animal models used, in which case it may not be applicable to human studies. Presumably, the drug used in clinical trials has been formulated and dosed in a manner where biologically active concentrations are reached with oral administration.

Research underway:

Rabeximod is expected to be tested in a Phase 2b RCT in moderate to severe rheumatoid arthritis starting in 2022.

Search terms:

Pubmed, Google: Rabeximod, Rob 803

- Neurodegeneration, Arthritis, Clinical trial, Safety

Websites visited for Rabeximod:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca

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