FOLATE RECEPTOR 1 ANTIBODIES AND IMMUNOCONJUGATES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. application Ser. No. 14/819,209, filed Aug. 5, 2015, now allowed, which is a divisional of U.S. application Ser. No. 13/800,835, filed Mar. 13, 2013, now U.S. Pat. No. 9,133,275, issued Sep. 15, 2015, which is a divisional application of U.S. application Ser. No. 13/033,723, filed Feb. 24, 2011, now U.S. Pat. No. 8,557,966, issued Oct. 15, 2013, which claims the priority benefit of U.S. Provisional Application No. 61/307,797, filed Feb. 24, 2010, U.S. Provisional Application No. 61/346,595, filed May 20, 2010, and U.S. Provisional Application No. 61/413,172, filed Nov. 12, 2010, each of which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The field of this invention generally relates to antibodies and immunoconjugates that bind to human folate receptor 1, as well as to methods of using the antibodies and immunoconjugates for the treatment of diseases, such as cancer.

SEQUENCE LISTING

[0003] Submitted concurrently on EFS-Web as part of the originally filed subject matter is a sequence listing of amino acid and polynucleotide sequences described throughout the specification. The sequence listing text file concurrently submitted with the specification is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0004] Cancer is one of the leading causes of death in the developed world, with over one million people diagnosed with cancer and 500,000 deaths per year in the United States alone. Overall it is estimated that more than 1 in 3 people will develop some form of cancer during their lifetime. There are more than 200 different types of cancer, four of which—breast, lung, colorectal, and prostate—account for over half of all new cases (Jemal et al., 2003, *Cancer J. Clin.* 53:5-26).

[0005] Folate Receptor 1 (FOLR1), also known as Folate Receptor-alpha, or Folate Binding Protein, is an N-glycosylated protein expressed on plasma membrane of cells. FOLR1 has a high affinity for folic acid and for several reduced folic acid derivatives. FOLR1 mediates delivery of the physiological folate, 5-methyltetrahydrofolate, to the interior of cells.

[0006] FOLR1 is overexpressed in vast majority of ovarian cancers, as well as in many uterine, endometrial, pancreatic, renal, lung, and breast cancers, while the expression of FOLR1 on normal tissues is restricted to the apical membrane of epithelial cells in the kidney proximal tubules, alveolar pneumocytes of the lung, bladder, testes, choroid plexus, and thyroid (Weitman S D, et al., *Cancer Res* 52: 3396-3401 (1992); Antony A C, *Annu Rev Nutr* 16: 501-521 (1996); Kalli K R, et al. *Gynecol Oncol* 108: 619-626 (2008)). This expression pattern of FOLR1 makes it a desirable target for FOLR1-directed cancer therapy.

[0007] Because ovarian cancer is typically asymptomatic until advanced stage, it is often diagnosed at a late stage and has poor prognosis when treated with currently available procedures, typically chemotherapeutic drugs after surgical de-bulking (von Gruenigen V et al., *Cancer* 112: 2221-2227 (2008); Ayhan A et al., *Am J Obstet Gynecol* 196: 81 e81-86 (2007); Harry V N et al., *Obstet Gynecol Surv* 64: 548-560 (2009)). Thus there is a clear unmet medical need for more effective therapeutics for ovarian cancers.

[0008] Three anti-FOLR1 antibodies have been examined as potential anti-cancer drugs. Murine monoclonal antibodies Mov18 and Mov19 were isolated in the late 1980s (Miotti S et al., *Int J Cancer* 39: 297-303 (1987)), confirmed to target FOLR1 (Coney L R et al., *Cancer Res* 51: 6125-6132 (1991)), and tested in pre-clinical studies for their ability to eradicate antigen-expressing cancer cells as conjugates with a cytotoxic ribosome-inactivating protein (Conde F P et al., *Eur J Biochem* 178: 795-802 (1989)).

[0009] Mov19 was tested as a bi-specific antibody targeting cytotoxic T cells and natural killer cells (Mezzanzanica D et al., *Int J Cancer* 41: 609-615 (1988); Ferrini S et al., *Int J Cancer Suppl* 4: 53-55 (1989); Ferrini S et al., *Int J Cancer* 48: 227-233 (1991)), and as a fusion protein of the single-chain Fv (scFv) of Mov19 with interleukin-2 in vivo (Melani C et al., *Cancer Res* 58: 4146-4154 (1998)). Chimeric (murine variable/human constant) anti-FOLR1 antibodies Mov18 and Mov19 have been examined pre-clinically on their ability to mediate cytotoxic immune cell-dependent killing of FOLR1-expressing tumor cells in vitro (Coney L R et al., *Cancer Res* 54: 2448-2455 (1994)), and a chimeric Mov18-IgE was tested in IgE-dependent immunotherapeutic preclinical models (Karagiannis S N et al., *J Immunol* 179: 2832-2843 (2007); Gould H J et al., *Eur J Immunol* 29: 3527-3537 (1999)).

[0010] Mov18 was studied in the form of conjugates with various radionuclides in preclinical studies and then, in early 1990s, in clinical trials (Zacchetti A et al., *Nucl Med Biol* 36: 759-770 (2009)), which ended without any drug being approved for clinical use.

[0011] MORAb003, a humanized form of the murine monoclonal anti-FOLR1 antibody LK26 was evaluated preclinically as a non-modified antibody (Ebel W et al., *Cancer Immun* 7:6 (2007)) and as a conjugate with the ^{111}In radionuclide (Smith-Jones P M et al., *Nucl Med Biol* 35: 343-351 (2008)), and is currently undergoing clinical trials as a non-modified antibody (D. K. Armstrong et al. *J. Clin. Oncol.* 26: 2008, May 20 suppl; abstract 5500).

SUMMARY OF THE INVENTION

[0012] The present invention provides novel antibodies that bind to human folate receptor 1, immunoconjugates comprising these antibodies, and methods of their use. The present invention further provides novel polypeptides, such as antibodies that bind human folate receptor 1, fragments of such antibodies, and other polypeptides related to such antibodies. Polynucleotides comprising nucleic acid sequences encoding the polypeptides are also provided, as are vectors comprising the polynucleotides. Cells comprising the polypeptides and/or polynucleotides of the invention are further provided. Compositions (e.g., pharmaceutical compositions) comprising the novel folate receptor 1 antibodies or immunoconjugates are also provided. In addition, methods of making and using the novel folate receptor 1 antibodies or immunoconjugates are also provided, such as