

adenosine deaminase (68). The MOA by which cladribine induces apoptosis is not settled, and it is likely to have more than one component. The drug may become incorporated into DNA and inhibit the ongoing “housekeeping” activity of DNA repair, or it may directly inhibit DNA polymerases (69). Cladribine kills lymphocytes, and is thus an effective drug for multiple sclerosis (70,71). Because cladribine kills lymphocytes, it is also an effective drug against cancers involving neoplastic T cells, such as the leukemias (72) and lymphomas (73,74,75).

#### f. Glatiramer Acetate

Glatiramer acetate (“glatiramer”) takes the form of a heterogeneous mixture of polypeptides,

ranging in length from 20 to 200 amino acid residues, with an average length of 60 amino acids (76). The polypeptides are random polymers of four amino acids, glutamate, lysine, alanine, and tyrosine. Glatiramer was designed so that it would include amino acid residues that promote anchoring to MHC class II, and so that it would also include contact residues that promote binding to T-cell receptor during formation of the immune synapse (77).

The mechanism of action of glatiramer, or more accurately, of certain polypeptides in the glatiramer mixture, is described (78). First, the polypeptide binds to MHC class II, and reduces presentation by the MHC class II of peptides derived from myelin-antigens. When glatiramer binds to MHC class II, it is not processed inside DCs. In other words, when

<sup>68</sup>Piro LD, Carrera CJ, Beutler E, Carson DA. 2-Chlorodeoxyadenosine: an effective new agent for the treatment of chronic lymphocytic leukemia. *Blood* 1988;72:1069–73.

<sup>69</sup>Van Den Neste E, Cardoen S, Husson B, et al. 2-Chloro-2'-deoxyadenosine inhibits DNA repair synthesis and potentiates UVC cytotoxicity in chronic lymphocytic leukemia B lymphocytes. *Leukemia* 2002;16:36–43.

<sup>70</sup>Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *New Engl. J. Med.* 2010;362:416–26.

<sup>71</sup>Barten LJ, Allington DR, Procacci KA, Rivey MP. New approaches in the management of multiple sclerosis. *Drug Des. Devel. Ther.* 2010;4:343–66.

<sup>72</sup>Sigal DS, Miller HJ, Schram ED, Saven A. Beyond hairy cell: the activity of cladribine in other hematologic malignancies. *Blood* 2010;116:2884–96.

<sup>73</sup>Blum KA, Johnson JL, Niedzwiecki D, et al. Prolonged follow-up after initial therapy with 2-chlorodeoxyadenosine in patients with indolent non-Hodgkin lymphoma: results of Cancer and Leukemia Group B Study 9153. *Cancer* 2006;107:2817–25.

<sup>74</sup>Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. *Cancer* 2008;113:108–16.

<sup>75</sup>Jaeger G, Bauer F, Brezinschek R, Beham-Schmid C, Mannhalter C, Neumeister P. Hepatosplenic gammadelta T-cell lymphoma successfully treated with a combination of alemtuzumab and cladribine. *Ann. Oncol.* 2008;19:1025–6.

<sup>76</sup>Conner J. Glatiramer acetate and therapeutic peptide vaccines for multiple sclerosis. *J. Autoimmun. Cell Responses* 2014;1:3(2054-989X-1-3) (11 pp.).

<sup>77</sup>Duda PW, et al. Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. *J. Clin. Inv.* 2000;105:967–6.

<sup>78</sup>Firdkis-Hareli M. Design of peptide immunotherapies for MHC class-II-associated autoimmune disorders. *Clin. Devel. Immunol.* 2013;2013:Article ID 826191 (9 p.).