Bleomycin sulfate, USP
PRODUCT DATA SHEET

issue date 01/06/2020

Product Name:	Bleomycin sulfate, USP
Product Number:	B005
CAS Number:	9041-93-4
Form:	Powder
Appearance:	White or off-white crystalline powder
Source:	*Streptomyces verticillus*
pH:	4.5 - 6.0
Storage Conditions:	2-8 °C
Description:	Bleomycin sulfate is a chemotherapeutic agent commonly used for Hodgkin's lymphoma. Bleomycin is a mixture of Bleomycin A2 and Bleomycin B2. The approximate composition of A2:B2 is 2:1. The compound is water soluble.

TOKU-E also offers:

- Bleomycin (B053)
- Bleomycin A2 sulfate (B019)
- Bleomycin A5 hydrochloride (B004)
- Demethylbleomycin A2 sulfate, EvoPure® (D023)

Mechanism of Action:

The exact mechanism of action Bleomycin sulfate is not well defined; however, it is thought to chelate metallic ions which decreases enzyme activity and stability. This effect is believed to cause the enzymes to react with oxygen, producing free radicals which create single stranded breaks in deoxyribose sugar.

Bleomycin's anticancer activities include the increase of caspase-3 and p53, and the inhibition of telomerase activity leading to apoptosis. The anti-cancer properties derives from its ability to effect DNA cleavage in cancer cells.

Cancer Applications

Bleomycin contains a disaccharide moiety composed of 2 unusual sugars, L-gulose and 3-O-carbamoyl-D-mannose. Bleomycin could be regarded as a modular system composed of a tumor-targeting agent (the dissacharide moiety) and a tumoricidal agent (deglycobleomycin). The disaccharide moiety is responsible for the tumor cell targeting properties of bleomycin. Bleomycin analogs were prepared, the glycosylated analogs were more cytotoxic to cultured DU145 prostate cancer cells. These findings establish a role for the bleomycin disaccharide in tumor targeting/uptake and suggest that the disaccharide moiety may be capable of delivering other cytotoxins to cancer cells. Cytotoxicity testing with DU145 human prostate cancer cells *in vitro.* (Schroeder et al, 2014).

Bleomycin is used in combination with other antineoplastic agents in studying lymphomas, testicular carcinomas, and squamous cell carcinomas. In this report, we found that the human L-carnitine transporter (hCT2) is involved in bleomycin-A5 uptake. NT2/D1 human testicular cancer cells which highly express hCT2 are very sensitive to Bleomycin-A5. Data suggest that hCT2 can mediate the uptake of Bleomycin A5 (Aouida M et al, 2010).

In cell culture experiments with Bleomycins and BLM carbohydrates conjugated to microbubbles it has been demonstrated that Bleomycins are tumor-seeking molecules. Biotinylate bleomycin A5 was attached to microbubbles, and a conjugate-containing solution was passed over a monolayer of MCF-7 cells. The microbubbles adhered to the MCF-7 cells. The conjugate did not bind to a normal breast cell line or to matched noncancer cell lines. No binding occurred if the microbubbles lacked conjugated bleomycin A5 or if the microbubble lacked the carbohydrate moiety (Chapuis et al, 2009).

A well-known characteristic of tumor cells is the Warburg effect, that is the propensity of tumor cells to produce increased ATP via glycolysis rather than by mitochondrial oxidative phosphorylation . The shift to glycolysis is accompanied by upregulation of glucose transporters to provide the greater amounts of glucose needed to support increased glycolysis. If authors treated two normal cell lines (normal lunch WI-38 cells and normal kidney CCD-1105 KIDTr cells) with the inhibitor rotenone , (a mitochondrial complex 1 inhibitor), this forced these cells to use increase glycolysis in the same fashion as tumor cells and this resulted in an enhanced ability to incorporate BLM-Cy5. The finding implies that the BLM saccharide moiety may be able to deliver other cytotoxins selectively to tumor cells (Mobasheril, 2005).

References:

Aouida M, Poulin P and Ramotar (2010) The human carnitine transporter SLC22A16 mediates high affinity uptake of the anticancer polyamine analogue Bleomycin-A5. J. Biol. Chem. 285:6275-6284.

Aszalos A, Crawford J, Vollmer P, Kantor N and Alexander T (1981) High-performance liquid chromatographic determination of components of bleomycin preparations. J. Pharm. Sci 70(8):878-880 PMID 6171636

Burger RM, Paisach J, and Horwitz SB (1981) Mechanism of bleomycin action: *In vitro* studies. Life Sci. 28(7):715-727 PMID 6164898

Chapuis J, Schmaltz RM, Tsosie KS, Belohlavek M and Hecht SM (2009) Carbohydrate dependent targeting of cancer cells by bleomycin-microbubble conjugates. J. Am. Chem. Soc. 131(7):2438-2439

Dorr, RT (1991) Bleomycin Pharmacology: Mechanism of Action and Resistance, and Clinical Pharmacokinetics. Semin. Oncol. 19(2): 3-8. PMID 1384141

Fujiwara Y and Kondo T (1973) Strand-scission of HeLa cell deoxyribonucleic acid by bleomycin *in vitro* and *in vivo*. Biochem. Pharmacol 22(3):323-333. PMID 4119868

Kross et al. (1982) Structural basis for the deoxyribonucleic acid affinity of bleomycins. Biochem. 21: 3711-3721 PMID 6180763

Kross et al (1982) Specificity of deoxyribonucleic acid cleavage by bleomycin, phleomycin and tallysomycin. Biochem. 21:4310 PMID 6181807

Mobasheril, A, Richardson S, Mobasheri R, Shakibaei M, Hoyland, J. (2005) Hypoxia inducible factor-1 and facilitative glucose transporters GLUT1 and GLUT3: Putative molecular components of the oxygen and glucose sensing apparatus in articular chondrocytes. Histol. Histopathol. 20(4):1327-1338 PMID 16136514

Schroeder BR et al (2014) The disaccharide moiety of bleomycin facilitates uptake by cancer cells. J. Am. Chem Soc. 136(39):13641-13656

Takita T et al (1972) Chemistry of bleomycin. IX. The structures of bleomycin and phleomycin. J. Antibiot. (Tokyo) 25:755-757 PMID 4119701

Yang L, Yang S, Tai K, Chou M and Yang J (2004) MEK inhibition enhances bleomycin A5-induced apoptosis in an oral cancer cell line: Signaling mechanisms and therapeutic opportunities. J. Oral Path. and Med. 33(1):37-45