Proteasome Inhibitor Anticancer Drug Candidate GL101666 (U-74)

Objectives: Seeking a buyer or partnership to further develop novel anticancer drug candidate **GL101666** to fill the gaps of oncology therapeutics.

Description: Novel drug candidate **GL101666** was discovered after multi-round *in vitro* and *in vivo* SAR studies. It exhibited high specificity against the 20S proteasome β5 subunit, >10,000 fold greater in selectivity compared to Bortezomib. In addition to the *in vivo* efficacy against RPMI-8226 human multiple myeloma (MM) tumor, **GL101666** also demonstrated superior *in vivo* efficacy against solid tumors such as colon cancer HCT116, gastric cancer MGC803 and liver cancer BEL7404. In contrast, Bortezomib has not shown promising application on these solid tumors. It is also much safer than Bortezomib. Successful development of this drug will broaden the therapeutic application of the current proteasome inhibitor drugs.

IP: Secure IP position for FTO (free-to-operate) (PCT and CP Applications approved; other country's patent applications are in progress).

Chemistry: Novel urea-mimic dipeptide boronic acid, NCE; ready synthetic process.

Enzymatic activity, selectivity and specificity (IC_{50}, nM): potent proteasome inhibitor with superior selectivity and specificity against 20S proteasome β5 subunit (0.2 pM) comparing to Bortezomib.

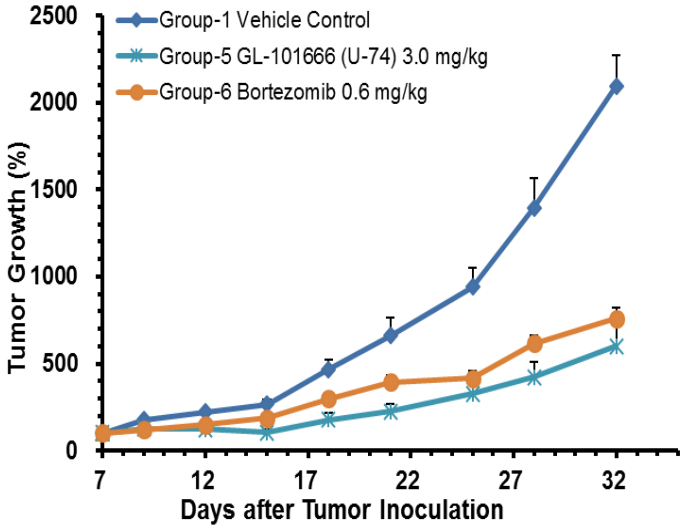
	T-L (β1)	CT-L (β5)	PGPH (β2)
GL101666 (U-74)	2380	0.0002	20
Bortezomib (PS-341)	440	4	30

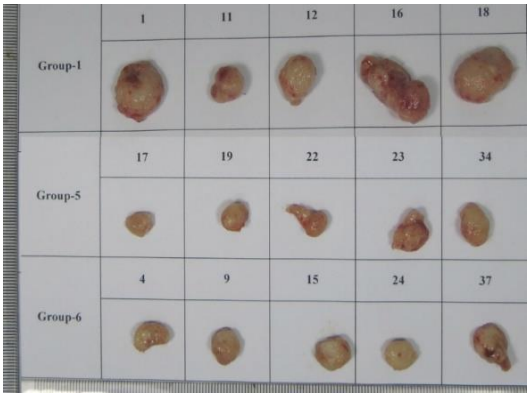
***In vitro* activity: GL101666** demonstrated broad *in vitro* activity against colon, ovarian, breast, leukemia, gastric, liver and other tumor cell lines.

***In vivo* Antitumor Efficacy in Mice: GL101666** demonstrated better *in vivo* efficacy against RPMI-8226 human multiple myeloma tumor than Bortezomib. In addition, it also exhibited superior *in vivo* efficacy against solid tumors such as colon cancer HCT116, gastric cancer MGC803 and liver cancer BEL7404.

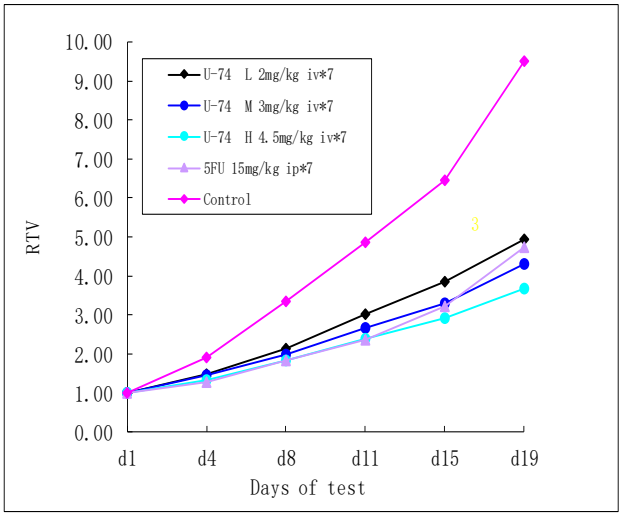
Tumor Models	**GL101666**（U-74）	Bortezomib
Human MM RPMI8226	71.4% (3.0 mg/kg)	63.7% (0.6 mg/kg)
		5FU
Human colon HCT116	61.33%（4.5 mg/kg） 54.79%（3 mg/kg） 48.07%（2 mg/kg）	50.17%（15 mg/kg）
Human gastric MGC803	57.12%（4.5 mg/kg） 45.96%（3 mg/kg) 42.32%（2 mg/kg)	49.84%（15 mg/kg）
Human liver BEL7404	52.65%（4.5 mg/kg） 36.15%（3 mg/kg) 24.46%（2 mg/kg)	43.83%（15 mg/kg）

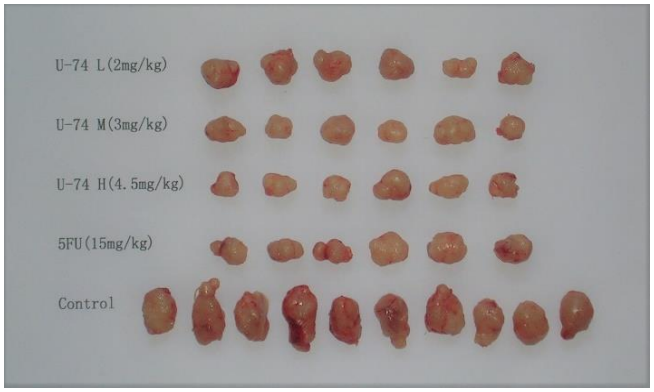
Human Multiple Myeloma RPMI8226 Model



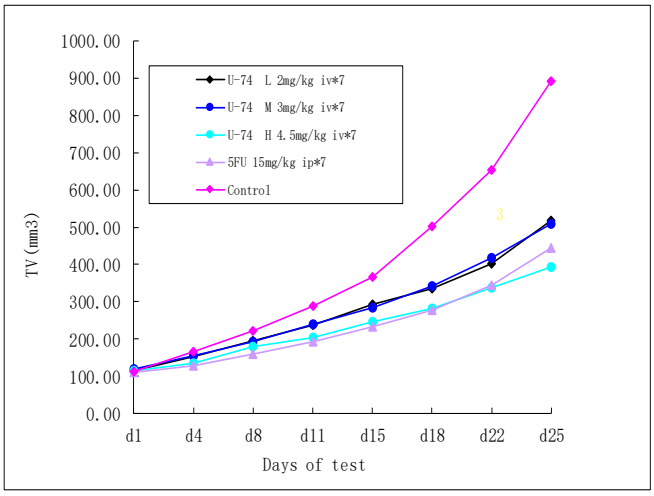


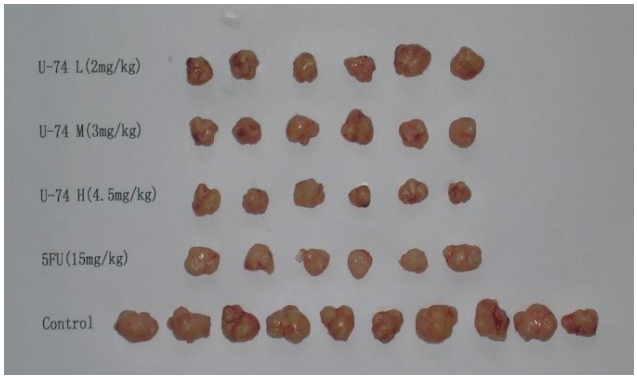
Human Colon HCT116 Tumor Model



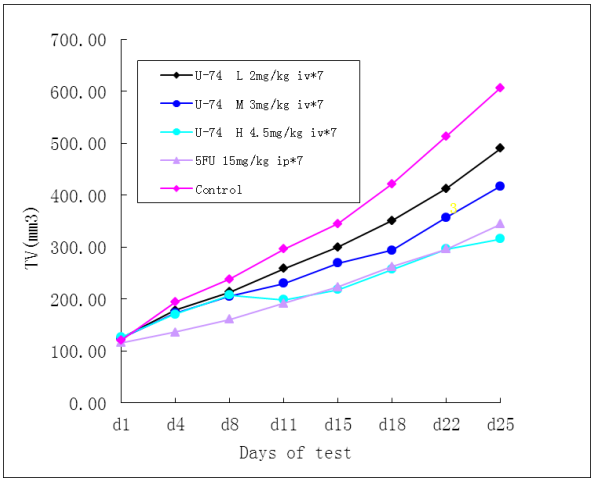


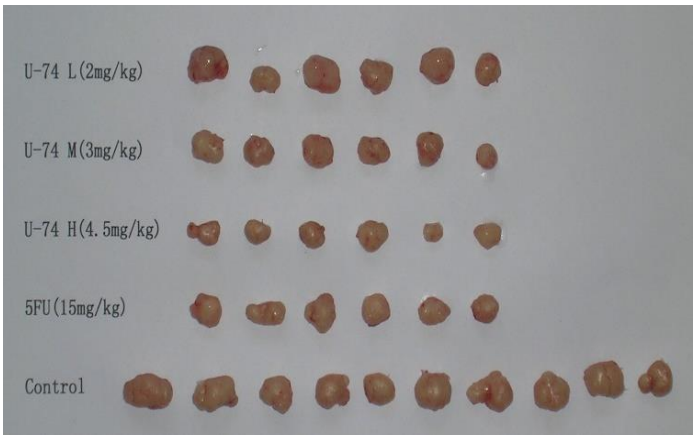
Human Gastric MGC803 Tumor Model





Human Liver BEL7404 Tumor Model





Safety Evaluation: 14-day acute toxicity (*iv* daily; ICR mice) studies at 5.0, 7.5 and 10.0 mg/kg dosages gave promising results: 100% survival rate (no death for all dosages); anatomic, 14 routine blood tests, body weight and others are all normal without obvious adverse effect. The MTD and LD_{50} are expected to be much higher than 10 mg/kg. It is much safer than Bortezomib (all mice died within day 5 at 1.5 mg/kg). Its high selectivity and specificity against 20S proteasome β5 subunit may play an important role on its safety. Further safety evaluation is still in progress.

Group	Dosage (mg/kg)	Death	Anatomic Examination	Body weight	14 routine blood tests
Control	Solvent	0 / 4	-	-	-
GL101666	**5.0**	**0 / 4**	**Normal**	**NSD**	**NSD**
	7.5	**0 / 4**	**Normal**	**NSD**	**NSD**
	10.0	**0 / 4**	**Normal**	**NSD**	**NSD**
Bortezomib	1.5	4 / 4	gastric distention, tail purple	NA	NA

NSD: no significant difference; NA: not available /could not test because of death.

PK Property: GL101666 exhibited favorable PK profile with longer half-life and higher AUC in rats and dogs than Bortezomib.

Animal	$t_{1/2}$ (hr)	AUC_{last} (hr*ng/mL)	V_{ss} (L/kg)	CL (mL/min/kg)
Rats (1 mpk)	5.80	1972	0.825	8.45
Dogs (0.3 mpk)	4.19	1061	1.40	4.55
Bortezomib (rat; 0.8 mpk)	0.80	472	2.4	34

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