

Supplementary Information

Suppression of hepatocellular carcinoma by mycophenolic acid in experimental models and in patients

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Supplementary Table S1. Clinical information of patients using MMF

| No | Age (yrs) | LTx date | Start date MMF | End date MMF | MMF period (weeks) | Recurrence date | Death date |
|----|-----------|-------------|----------------|--------------|--------------------|-----------------|-------------|
| 1 | 58 | 22-May-1992 | 26-Jan-1998 | 21-Feb-2008 | 525 | - | - |
| 2 | 50 | 18-Jan-1998 | 26-Sep-2002 | 04-Feb-2011 | 436 | - | - |
| 3 | 55 | 18-May-2006 | 24-May-2006 | 04-Jul-2013 | 371 | - | - |
| 4 | 53 | 28-Jul-2007 | 13-Aug-2007 | 12-Jun-2013 | 304 | - | - |
| 5 | 60 | 21-Dec-2005 | 25-Jan-2006 | 07-May-2009 | 171 | - | - |
| 6 | 69 | 21-May-2000 | 19-Dec-2005 | 22-Sep-2008 | 144 | - | - |
| 7 | 63 | 05-Sep-2007 | 11-Sep-2007 | 15-Jun-2010 | 144 | - | - |
| 8 | 65 | 20-Nov-2004 | 15-Sep-2005 | 17-Mar-2008 | 130 | 19-Jun-2007 | 18-Mar-2009 |
| 9 | 58 | 01-Jan-2007 | 29-Jan-2007 | 21-Jan-2010 | 155 | - | - |
| 10 | 24 | 09-Feb-2005 | 02-Mar-2005 | 20-Apr-2006 | 59 | - | - |
| 11 | 65 | 23-Aug-2007 | 23-Aug-2007 | 21-Sep-2007 | 4 | - | - |
| 12 | 56 | 22-Jan-2007 | 26-Jan-2007 | 15-Oct-2007 | 37 | - | - |
| 13 | 52 | 27-Mar-2007 | - | - | - | - | - |
| 14 | 50 | 07-Nov-1997 | - | - | - | - | 18-Jan-2001 |
| 15 | 52 | 19-Jul-1997 | - | - | - | - | 09-Dec-2003 |
| 16 | 43 | 02-Mar-1998 | - | - | - | - | 12-Feb-2000 |
| 17 | 55 | 10-Sep-2004 | - | - | - | - | 23-Aug-2005 |
| 18 | 60 | 16-Feb-2000 | - | - | - | - | - |
| 19 | 54 | 22-Mar-2002 | - | - | - | - | 11-Jan-2004 |
| 20 | 63 | 25-Jan-1994 | - | - | - | - | 09-Jun-1996 |
| 21 | 67 | 26-Jul-1998 | - | - | - | - | - |
| 22 | 56 | 25-Apr-2005 | - | - | - | - | 31-Mar-2007 |
| 23 | 42 | 31-Mar-2005 | - | - | - | - | 23-Feb-2006 |
| 24 | 61 | 10-Oct-2006 | - | - | - | - | - |
| 25 | 69 | 05-Apr-2000 | - | - | - | - | 23-Feb-2001 |
| 26 | 55 | 04-Jul-1995 | - | - | - | - | 13-Sep-1998 |
| 27 | 58 | 24-May-2006 | - | - | - | - | - |
| 28 | 24 | 04-Oct-1989 | - | - | - | - | 02-Dec-1990 |
| 29 | 67 | 04-Mar-2007 | - | - | - | - | - |
| 30 | 64 | 17-Sep-2007 | - | - | - | - | - |
| 31 | 53 | 15-Feb-2001 | - | - | - | - | 21-May-2002 |
| 32 | 50 | 03-May-2000 | - | - | - | - | - |
| 33 | 60 | 17-Oct-1999 | - | - | - | - | 05-Dec-2008 |
| 34 | 66 | 06-Aug-2001 | - | - | - | - | 22-Jul-2004 |
| 35 | 48 | 08-Jul-2004 | - | - | - | - | - |
| 36 | 53 | 05-Jan-1990 | - | - | - | - | 26-Jul-1992 |
| 37 | 46 | 14-Apr-2004 | - | - | - | - | 17-Sep-2005 |

| | | | | | | | |
|----|----|-------------|---|---|---|---|-------------|
| 38 | 44 | 01-May-1996 | - | - | - | - | 30-Aug-1996 |
| 39 | 61 | 10-Oct-1999 | - | - | - | - | - |
| 40 | 58 | 16-Nov-2002 | - | - | - | - | - |
| 41 | 57 | 29-Nov-2003 | - | - | - | - | - |
| 42 | 57 | 17-Oct-1996 | - | - | - | - | 10-Jul-2000 |
| 43 | 57 | 12-Jun-2002 | - | - | - | - | - |
| 44 | 66 | 15-Mar-2007 | - | - | - | - | - |

MMF, mycophenolate mofetil.

Note: - no recurrence/no death/no MMF treatment

Supplementary Table S2. Experimental cancer cell models sensitive to MPA

| Tumor type | Name of cell lines | References |
|-------------------------|--------------------|---------------|
| Human T-cell | Jurkat | PMID:19430526 |
| | CEM | PMID:19430526 |
| | A3.01 | PMID:8181860 |
| | Molt-4 | PMID:8181860 |
| Human B-cell | Dab-1 | PMID:19430526 |
| | Daudi | PMID:8181860 |
| Mouse pre-B-cell | RAW117-H10 | PMID:8181860 |
| Multiple myeloma cell | RPMI8226 | PMID:16505121 |
| | RPMI8226-HAMcl1 | PMID:16505121 |
| | ARP1 | PMID:16505121 |
| Human colon | T84 | PMID:8181860 |
| | LS174T | PMID:8181860 |
| | HT-29 | PMID:29848681 |
| Human hepatic | Hep3B | PMID:8181860 |
| | SK-Hep1 | PMID:8181860 |
| Human breast | SKBR3 | PMID:27651367 |
| | MCF-7 | PMID:24294374 |
| Human lung | CaLu-3 | PMID:8181860 |
| Human pancreatic | CaPan-2 | PMID:8181860 |
| | PANC-1 | PMID:24294374 |
| | BxPC-3 | PMID:24294374 |
| Human cholangiocellular | HuCCT1 | PMID:27206490 |
| | TFK1 | PMID:27206490 |
| Human gastric | AGS | PMID:24349619 |
| | Hs746T | PMID:24349619 |
| | NCI-N87 | PMID:24294374 |
| Human intestinal | HCT-8 | PMID:24294374 |
| Human ovarian | A2780 | PMID:24294374 |

MPA, mycophenolic acid.

Supplementary Table S3. Potential anti-malignant effect of MPA in clinical studies

| Functions of MPA | Patient numbers | Type of study | Reference |
|---|-----------------|-------------------------------------|----------------|
| Inhibiting multiple myeloma | 11 | Phase I Clinical Trial | PMID:15623606: |
| MPA is not associated with increased risk of lymphoma or other malignancies post-renal transplant | 6751 | Prospective cohort study of 3 years | PMID:16303010 |

MPA, mycophenolic acid.

Supplementary Figure S1

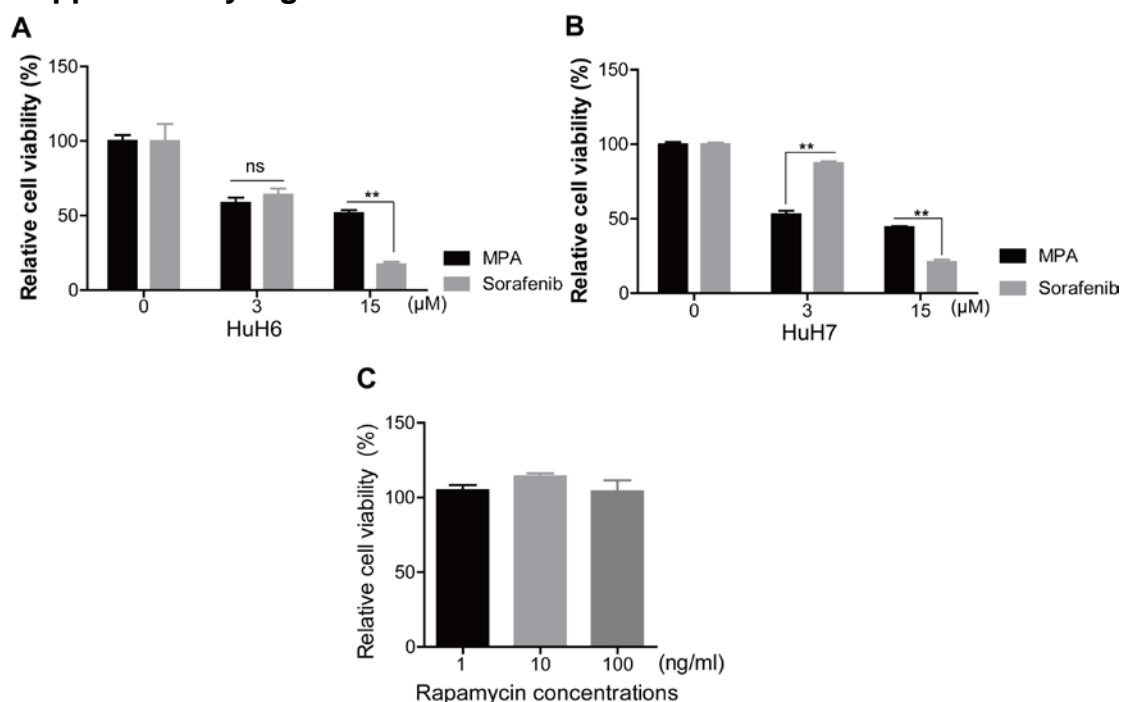


Figure S1. The effects of mycophenolic acid (MPA), sorafenib and rapamycin on HCC cell lines. (A) At the low concentration of 3 μM , the inhibitory effects of MPA and sorafenib have no significant difference, while at the concentration of 15 μM , sorafenib* showed more potent effect in HuH6 cell line; (B) At the low concentration of 3 μM , MPA has stronger inhibitory effect, while at the concentration of 15 μM , sorafenib showed more potent inhibition in HuH7 cell line; (C) The effects of rapamycin (at the concentrations of 1 ng/ml, 10 ng/ml and 100 ng/ml, respectively) were not significant in HuH6 cell line, determined by MTT assay. (mean \pm SEM, $n = 3$, respectively, $**P < .01$, $***P < .001$). MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

*Clinical use of sorafenib is 400 mg twice daily, and the C_{trough} sorafenib average concentration in patients treated with the dose of 400 mg is $8.78 \pm 4.82 \mu\text{g/ml}$ (equivalent to $13.78 \pm 7.57 \mu\text{M}$)