INDO SWISS JOINT RESEARCH PROGRAMME (ISJRP)

JOINT RESEARCH PROJECT

FINAL REPORT

Submitted by the Swiss Principal Investigator(s)

Part 1 - General Information

Project Title: Targeted Therapy of hepatocellular carcinoma
Swiss Principal Investigator(s): Prof. Jean-François Dufour
Hepatology
Department of Clinical Research
University of Bern
Project Start: 1.4.2009
Project Duration: 3 years
Indian Principal Investigator(s): Dr. Suvro Chatterjee
AU-KBC Research Centre
MIT Campus of Anna University
Chromepet
Chennai

Part 2 - Scientific Information

A) SYNTHESIS OF THE PROJECT

The goal of this project was to build on the complementary expertise of the 2 principal investigators to investigate in details in vitro and in vivo the potential of sirolimus and sunitinib in combination as antiangiogenic and anti-tumoral therapy. Sirolimus inhibits mTOR a key kinase in cellular proliferation linking energy and nutrient availability to protein synthesis. mTOR pathway is overactive in about 40% of hepatocellular carcinoma. Dufour's laboratory used a syngeneic, orthotopic rat model of hepatocellular carcinoma to show that sirolimus slows the growth of the tumor, prolongs survival and blocks formation of new blood vessels by sprouting. Sunitinib is a multikinase inhibitor blocking signalling though PDGF and VEGF receptors, 2 crucial growth factors in hepatocellular carcinoma biology. Presently, sorafenib is the only systemic targeted therapy registered for hepatocellular carcinoma treatment. Our data revealed that sunitinib treatment blocked the transdifferentiation of primary human HSC (hHSC) to activated myofibroblast-like cells without affecting hHSC apoptosis and migration. In in vitro angiogenic assays, sunitinib reduced endothelial cells ring formation and tube formation and decreased vascular sprouting and angiogenesis in vascular bed of chick embryo. Everolimus treatment blocked the functions of activated hepatic stellate cells without affecting primary stellate cells viability and migration. We also observed that collagen production by activated stellate was inhibited by everolimus treatment. Further experiments confirmed that everolimus treatment attenuated the activation of primary stellate cells to its activated form.
Angiogenesis study demonstrated that everolimus blocks angiogenesis in aortic ring model and inhibits the migration and tube formation of liver sinusoidal endothelial cells. Everolimus treatment reduced the load of activated HSC in a mouse model of HCC. Tumors were smaller in when everolimus was combined with sorafenib and the combination group survived longest. Treated tumors were more hypoxic than control tumors. Vessel sprouting was abundant in control tumors, lower after sorafenib and absent after the combination. Intussusceptive angiogenesis by transluminal pillar formation occurred after sorafenib and the combination, but the process was impaired after the combination when pillars failed to coalesce. In conclusion, these experiments provide insight into the mechanism of action of targeted kinase inhibitors in clinical development for the treatment of hepatocellular carcinoma.

B) RESULTS

Our data revealed that sunitinib treatment blocked the transdifferentiation of primary human HSC (hHSC) to activated myofibroblast-like cells without affecting hHSC apoptosis and migration. In in vitro angiogenic assays, sunitinib reduced endothelial cells ring formation and tube formation and decreased vascular sprouting and angiogenesis in vascular bed of chick embryo. Everolimus treatment blocked the functions of activated hepatic stellate cells without affecting primary stellate cells viability and migration. We also observed that collagen production by activated stellate was inhibited by everolimus treatment. Further experiments confirmed that everolimus treatment attenuated the activation of primary stellate cells to its activated form. Angiogenesis study demonstrated that everolimus blocks angiogenesis in aortic ring model and inhibits the migration and tube formation of liver sinusoidal endothelial cells. Everolimus treatment reduced the load of activated HSC in a mouse model of HCC. Tumors were smaller in when everolimus was combined with sorafenib and the combination group survived longest. Treated tumors were more hypoxic than control tumors. Vessel sprouting was abundant in control tumors, lower after sorafenib and absent after the combination. Intussusceptive angiogenesis by transluminal pillar formation occurred after sorafenib and the combination, but the process was impaired after the combination when pillars failed to coalesce.

C) LIST OF PUBLICATIONS

Publications in reviewed journals

1 manuscript in preparation
1 manuscript submitted
1 manuscript accepted:

Poster presentations

None