

MEETING REPORT

NOVEL TARGETS FOR CANCER AND CONNECTIVE TISSUES DISEASES

Coast Coal Harbour Hotel, Vancouver, BC, Canada

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Approximately 45 people attended the recent ICCNS-sponsored meeting in Vancouver. The meeting commenced the evening of September 24, 2011 at the Steamworks Brewpub located on the Vancouver waterfront, with the lights from the Northshore mountains as a backdrop. People were impressed with the beer and wine selection, as well as the quality west-coast food. We were grateful to Springer for sponsoring this welcome dinner.

After a hearty breakfast, the meeting officially started at the Coast Coal Harbour hotel with a session sponsored by the Canadian Institutes of Health Research. Unfortunately, Bernard Perbal (Paris, France) could not attend the meeting due to his move from Paris, nonetheless David Brigstock (Columbus, USA) stepped in at the last minute to provide an excellent overview of the structure and function of the CCN proteins and of the potential use of CCN2 antagonists in liver fibrosis. To continue the theme, Stephen Twigg (Sydney, Australia) and Enrique Brandan (Santiago, Chile) provided strong evidence that CCN2 was essential for controlling the intensity of fibrosis progression in models of diabetes-related non-alcoholic steatohepatitis and skeletal muscular dystrophy, respectively. Chris Overall (Vancouver, Canada) reminded us that the CCN proteins are highly modular, and that matrix metalloproteinases play a key role in modifying the activity of individual CCN molecules and that the function of individual fragments may be quite different. Karen Lyons (Los Angeles, USA) provided strong evidence that CCN1 and CCN2 may be somewhat similar functionally, and suggested that the dosing of these molecules may be important in vivo; deleting CCN1 and CCN2 together had more of an effect on bone development than deleting either protein alone. Thus drugs that target both CCN1 and CCN2 in vivo might have quite different effects than targeting one molecule alone.

After an Italian-themed lunch, the Young Investigator session, sponsored by the Scleroderma Society, started. In this session, Alyssa Charrier (Columbus, USA) and Rohan Samarakoon (Albany, USA) both discussed the link between CCN2 expression and fibrosis, in particular alcohol-induced pancreatic injury and vascular smooth muscle cells, respectively. Taken together, Danilo Janune (Okayama, Japan) and Takashi Nishida (Okayama, Japan) indicated the yin/yang relationship between CCN3 and CCN2 regarding chondrocyte differentiation and/or proliferation. Alex Lambi (Philadelphia, USA) carefully described a heretofore unappreciated phenotype of the whole-body CCN2 knockout mice; namely that these mice possessed cranial defects consistent with impaired intramembranous and endochondral ossification. Finally, the essential role of

matricellular proteins in tissue repair was further emphasized by Chris Elliott (London, Canada) who used the periostin knockout mouse to show that periostin was required for tissue repair, by correlating the role periostin on myofibroblast differentiation to matrix stiffness.

After an afternoon poster session in which Vancouver Chinatown-themed refreshments were served, Brahim Chaquor (Brooklyn, USA) discussed how CCN1 might be used to treat vascular diseases of the eye. CCN1 expression is reduced in response to hyperoxia caused by neovascularization in retinopathy of prematurity (ROP), a leading cause of vision impairment and blindness in childhood. Lentivirus-mediated re-expression of CCN1 enhanced physiological adaptation of the retinal vasculature to hyperoxia and reduced pathological angiogenesis following ischemia. Lester Lau (Chicago, USA) continued with CCN1 theme, and discussed recent data indicating that the CCN1/integrin $\alpha 6 \beta 1$ is important for controlling the kinetics of wound closure (and presumably fibrosis) by altering the accumulation of reactive oxygen species. Hannu Larjava (Vancouver, Canada) and Shoukat Dedhar (Vancouver, Canada) closed the session by discussing the importance of integrin-mediated adhesion to cell physiology by discussing how, in principle, inhibiting integrin $\beta 6$ or integrin linked kinase might be used to control fibrosis or cancer.

The meeting then adjourned until the morning of the 26th. In an interesting morning session, we were reminded by Lynne Postovit (London, Canada) that the surrounding matrix instructs cells to respond to signals; for example, the matrix produced by stem cells or cancer cells are distinct, and can program one cell type to behave like another cell type. Fabio Rossi (Vancouver, Canada) provided fascinating data involving the role of cell adhesion proteins in satellite cell activation during muscle generation. Andrei Thomas-Tikhonenko (Philadelphia, USA) discussed how the p53-responsive miR-194 and inhibits thrombospondin-1 and thus promotes angiogenesis. Ruth Lupu (Rochester, USA) and Chiayeng Wang (Chicago, USA) provided evidence suggesting that CCN1 promotes breast cancer, and that CCN3, by being a target of the a paired-domain-specific PAX3-FKHR transcription factor, promotes survival and motility in alveolar rhabdomyosarcoma cells. Shushanta Banerjee (Kansas City, USA) showed, on the other hand, that CCN5 is anti-oncogenic as CCN5 suppresses twist and then mir-10b, whose expression is increased in metastatic breast cancer cells and elevated cell migration through the suppression of the homeobox D10 (HOXD10) tumor suppressor. The gala dinner, sponsored by the ICCNS, was held in the evening at the extremely vibrant Joe Fortes Restaurant, where delegates dined on locally sourced oysters and seafood.

The final session, on the morning of the 27th, focused on translational research and was sponsored by Actelion. Ron van Noorden (Amsterdam, Netherlands) pointed out that anti-VEGF therapies might not be appropriate to treat diabetic retinopathy given that an elevated CCN2/VEGF ratio correlates with increased fibrosis. Thus dual anti-VEGF and anti-CCN2 therapies need to be considered for this disorder. Chris Denton (London, UK) and Richard Stratton (London, UK) nicely described the autoimmune connective tissue disease scleroderma, and presented data showing that, in spite of much effort, there is no treatment for the fibrosis in scleroderma. Multiple drugs are being considered in clinical

trials for scleroderma, but CCN2 is certainly a marker of fibrosis in this disease and also mediate the ability of scleroderma keratinocytes to promote fibroblast activation in this disease. Satoshi Kubota (Okayama, Japan) provided a highly amusing talk, in which he linked CCN2 expression to nicotine-induced remodeling of periodontal tissues. Finally, Roel Goldschmeding (Utrecht, Netherlands) summed up the meeting by providing exciting data suggesting that anti-CCN2 therapies may be useful to reverse the fibrosis seen in patients with diabetes.

Overall, data was provided that strongly suggested that the CCN proteins, through their ability to modify cellular microenvironments and hence adhesive signaling, appear to be excellent targets for drug intervention in both cancers and connective tissue diseases.