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Only anti-CD133 antibodies recognizing the CD133/1 or the CD133/2 epitopes can identify human renal progenitors

To the Editor: Ivanova *et al.*[1] describe the expression of CD24 and CD133 in developing human kidneys. Their study is based on our previous reports, showing the existence of a CD24 + CD133 + renal progenitor population in human kidney.[2,3] In agreement with our results, they show that CD24 is a reliable marker to detect and purify human renal progenitors, whereas they are unable to obtain a further enrichment of human renal progenitors using CD133 as an additional marker, as we previously reported.[2,3] However, Ivanova *et al.* used anti-CD133 polyclonal antibodies, which stained diffusely differentiated epithelial structures in embryonic, as well as adult kidneys.[1] By contrast, we used anti-CD133 monoclonal antibodies recognizing CD133/1 (clone AC133) or CD133/2 (clone 293C3) epitopes, which selectively recognized renal progenitors.[2,3] It is common knowledge in the stem-cell field that only anti-CD133/1 or anti-CD133/2 antibodies can be used to detect and purify stem cells in several human tissues, whereas other anti-CD133 antibodies show expression in differentiated cells.[4] Recent studies have clarified this apparent discrepancy.[5] Indeed, different tertiary structures of the CD133 molecule justify the diverse accessibility of the CD133/1 or CD133/2 epitopes in undifferentiated versus differentiated cells.[5] Differential recognition of CD133 mRNA variants has also been suggested.[4] Consistently, double-label immunofluorescence performed with anti-CD133 antibodies used by Ivanova *et al.* and anti-CD133/1 or anti-CD133/2 antibodies, confirmed that only the latter recognized human renal progenitors (Figure 1). Thus, we recommend the usage anti-CD133/1 or CD133/2 antibodies to detect or purify human renal progenitors.

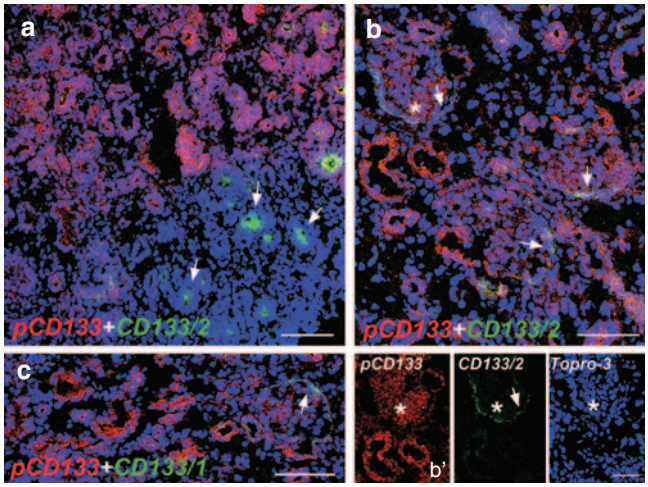

Figure 1 | Only antibodies recognizing the CD133/1 or CD133/2 epitopes can identify human renal progenitors. (**a**, **b**) Double-label immunofluorescence performed with the anti-CD133 polyclonal antibody used by Ivanova *et al.* (pCD133, red) and the anti-CD133/2 monoclonal antibody (green) in embryonic human kidneys. The anti-CD133 antibody used by Ivanova *et al.* poorly stains primary vesicles, comma-shaped bodies and S-shaped bodies, while it extensively stains differentiated tubular cells as well as the differentiating ureteric bud (red). By contrast, the anti-CD133/2 antibody (green) selectively stains condensed mesenchyme-derived primordial structures, primary vesicles, comma-shaped bodies, S-shaped bodies and, in maturing glomeruli, the urinary pole of the Bowman's capsule (arrows). In (**b**), asterisk indicates a maturing glomerulus. Merged areas appear in yellow. Topro-3 counterstains nuclei (blue). Bar 100 μm. (**b'**) Split image of the maturing glomerulus identified by the asterisk in (**b**). The arrow indicates the urinary pole of the Bowman's capsule. Bar 50 μm (**c**) Double label immunofluorescence performed with the anti-CD133 polyclonal antibody used by Ivanova *et al.* (pCD133, red) and the anti-CD133/1 monoclonal antibody (green) in embryonic human kidneys. Only CD133/1 antibody selectively stains human progenitors of the Bowman's capsule (arrow). Merged areas appear in yellow. Topro-3 counterstains nuclei (blue). Bar 100 μm.

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The Authors Reply: We thank Dr Angelotti *et al.*[1] for their comments regarding our paper defining the ontogeny of CD24 in the human kidney,[2] and for their suggestions for the use of anti-CD133 monoclonal antibodies to the CD133/1 and CD133/2 epitopes for the selection and purification of renal progenitor cells. We would like to emphasize that the purpose of our report was to define, using high quality immunohistochemical analyses of human fetal kidneys, the precise spatial and temporal localization of CD24, so as to suggest potential roles of this cell-surface antigen in normal and abnormal human kidney development.

We of course defer to views of Dr Angelotti *et al.* regarding the best technique of isolation of kidney progenitor cells, but we would disagree with their interpretation of our results on CD133 expression. In fact, although CD133 expression using our polyclonal antibody was less restricted than theirs, we did in fact show co-localization of CD133 and CD24 in early developing nephron epithelial structures, which, given postnatal CD133 (or prominin) expression, not surprisingly express this antigen.

Finally, although the CD133/1 and CD133/2 epitopes may be more specific to renal progenitors, we suspect that some of the differences seen in our work and theirs, may have more to do with immunohistochemistry technique, sample collection, and tissue fixation, on the basis of the details of their included photomicrographs.

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Paraproteinemia-associated pseudohypercreatininemia across different analytical methodologies

To the Editor: The case reported by Rudofsky *et al.*[1] illustrated that clinicians and laboratorians need to be cautious of potential analytical interference secondary to paraproteinemia. Recently, we encountered an 81-year-old man with history of IgM κ myeloma and elevated creatinine concentration of 6.5 mg/dl (normal: 0.7–1.2 mg/dl), determined using the modified Jaffé method by Roche (Mannheim, Germany) DP Modular Analytics analyzer. Considering patient's poor premorbid status, conservative and supportive management of renal failure was decided.

The discrepant urea to creatinine ratio and all along normal potassium concentrations were noticed by the chemical pathologist. Distorted reaction curve was noted upon data retrieval. Serial dilution of patient specimen with quality control material showed the creatinine concentration was only 2.1 mg/dl. Creatinine level was measured as 1.7 mg/dl by enzymatic method with J&J Vitros (Raritan, NJ, USA) dry chemistry analyzer. Serum cystatin C was 1.17 mg/l (normal: 0.50–1.00 mg/l). Physicians were contacted and findings explained.

Paraproteins interfering with Jaffé method for creatinine determination have been reported.[2] Analyses of numerous clinically important analytes and electrolytes can be interfered by paraproteins in an extremely unpredictable manner, affecting different methodologies of automated assays. There is poor correlation between the subtype and level of paraproteins and the likelihood of *in vitro* interference.[3] Enhanced clinical alertness helps picking up false results and prevents patient damages, including anxiety and medication underdosing. From the laboratory's perspective, proper procedures in handling specimens with paraproteins should be in place and appropriately documented. Platforms with alternative methodologies should be readily accessible in processing doubtful cases. Interpretation and authorization of abnormal results by chemical pathologists can further minimize reporting misleading results directly from automated analyzers. Finally, the importance of effective communications between physicians and chemical pathologists cannot be overemphasized.

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The Authors Reply: Short time after our report of a patient with pseudohypercreatininemia due to Waldenström's macro-