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Untangling the functional roles of a large HERC1 E3-Ubiquitin Ligase in Dictyostelium and Leukemic Cells.

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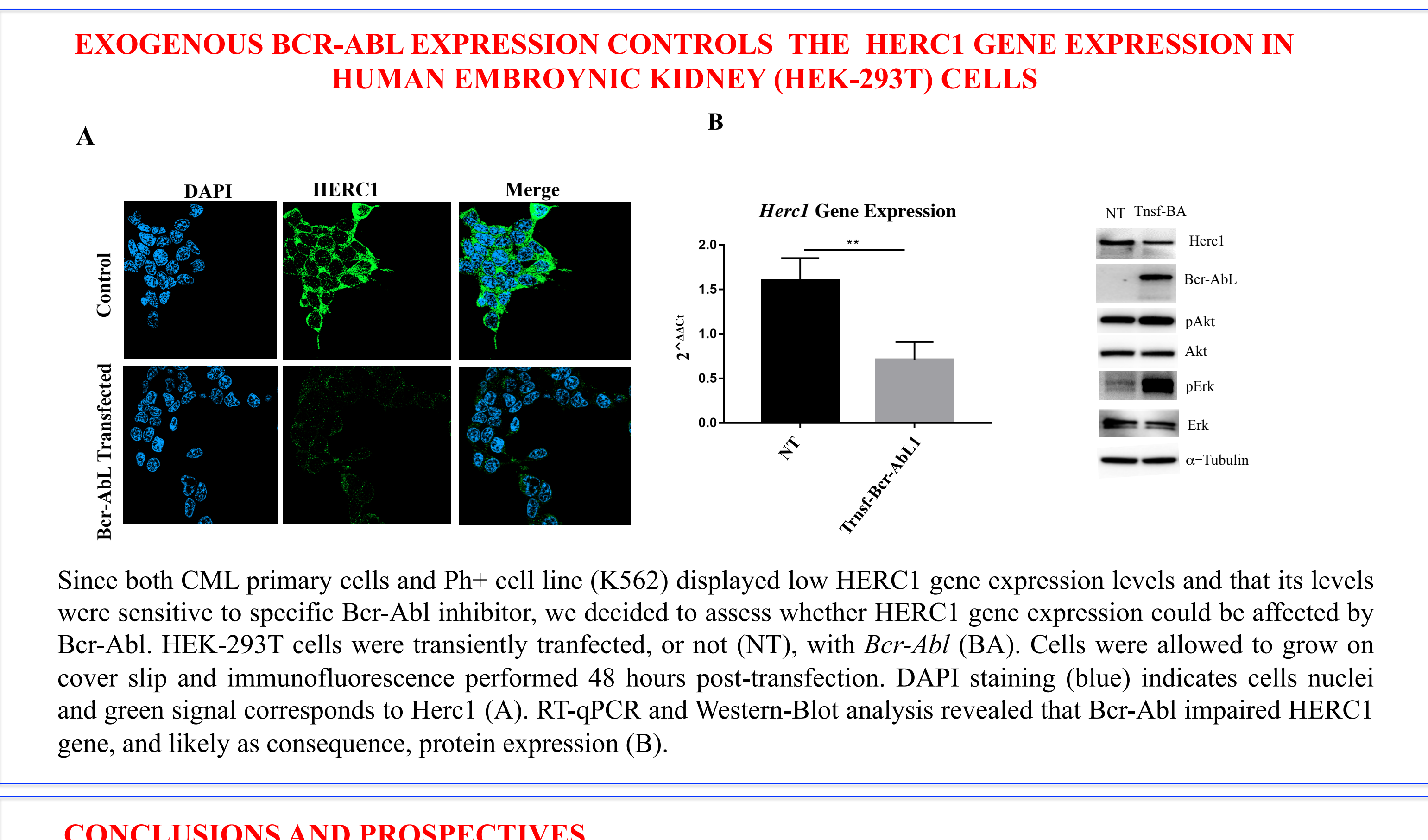
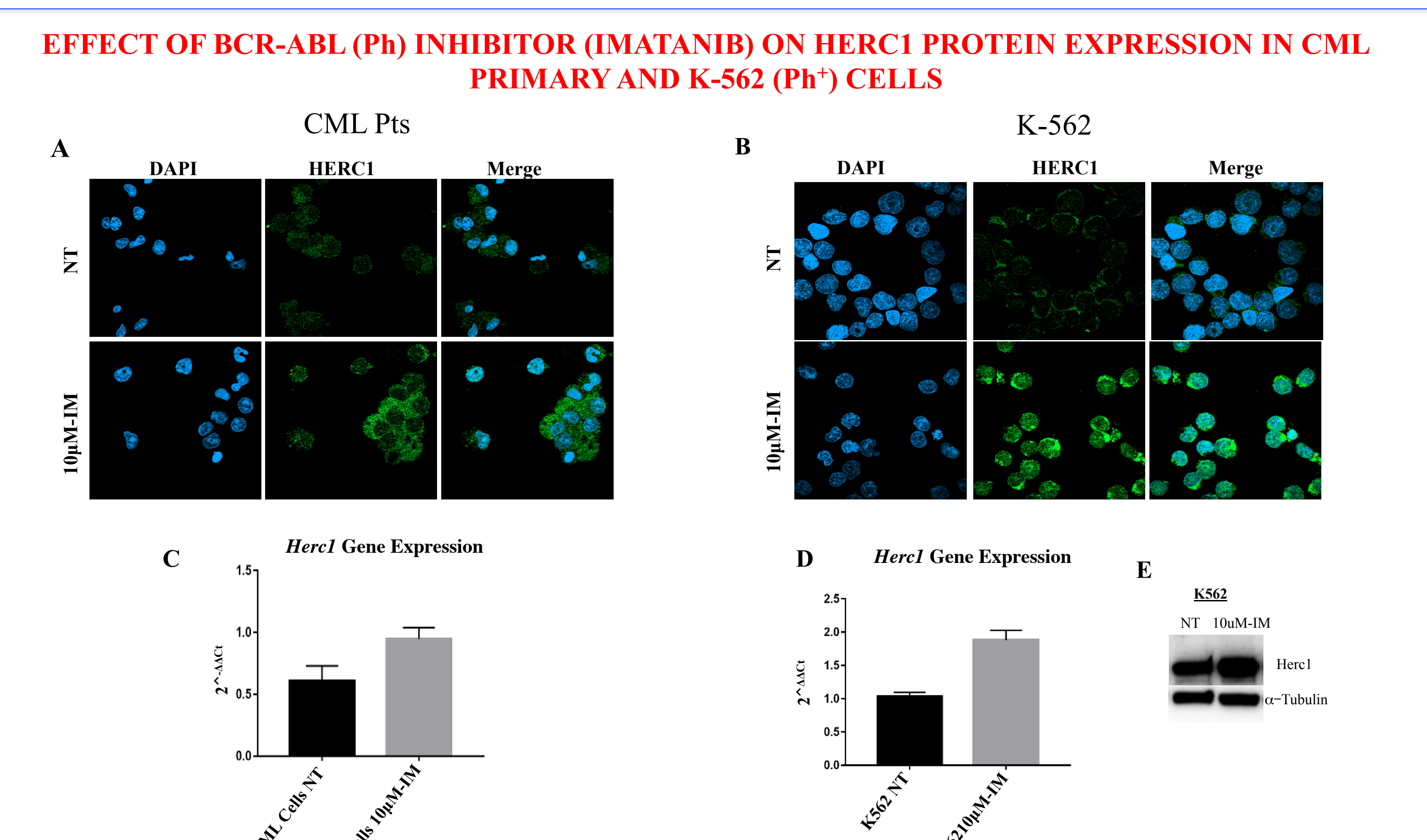
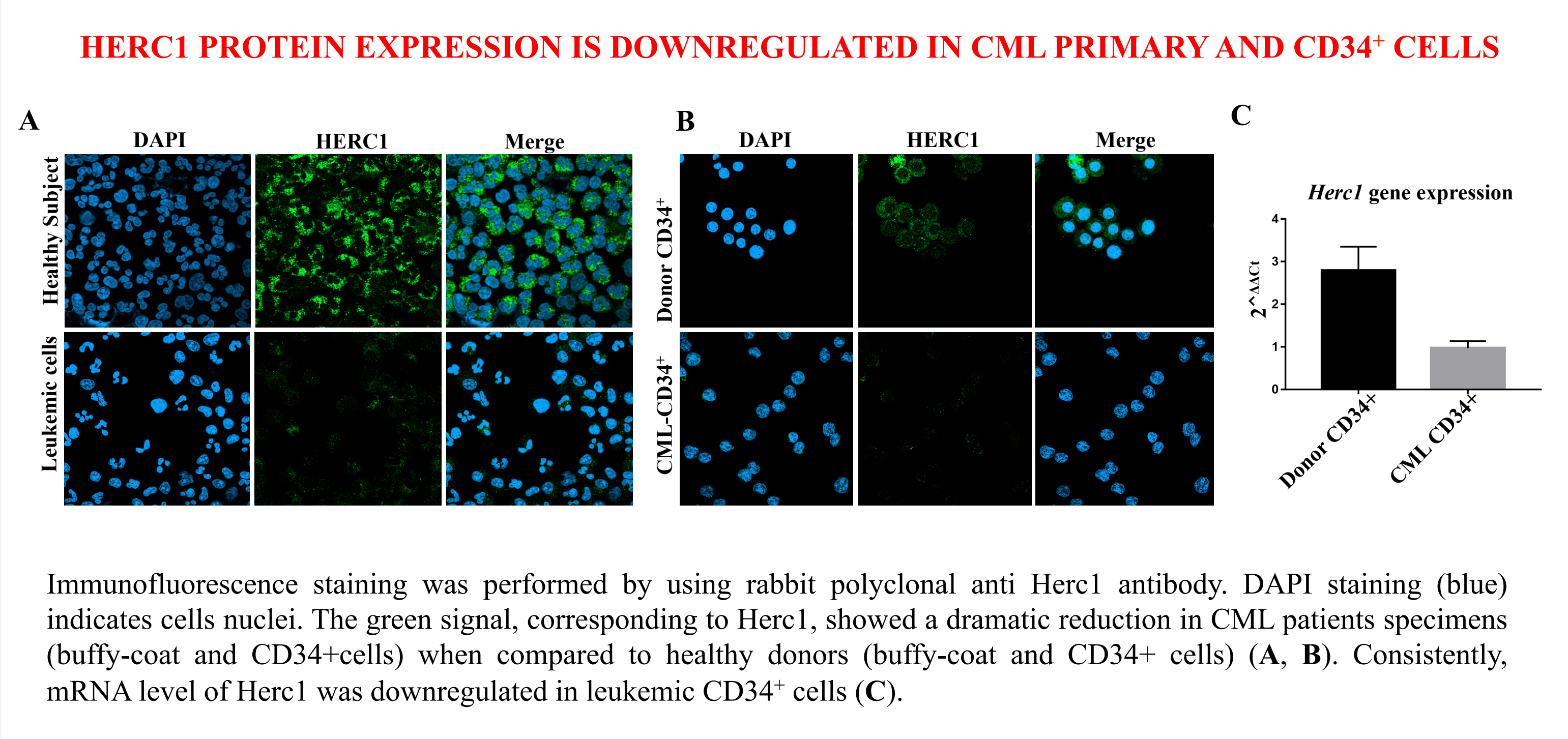
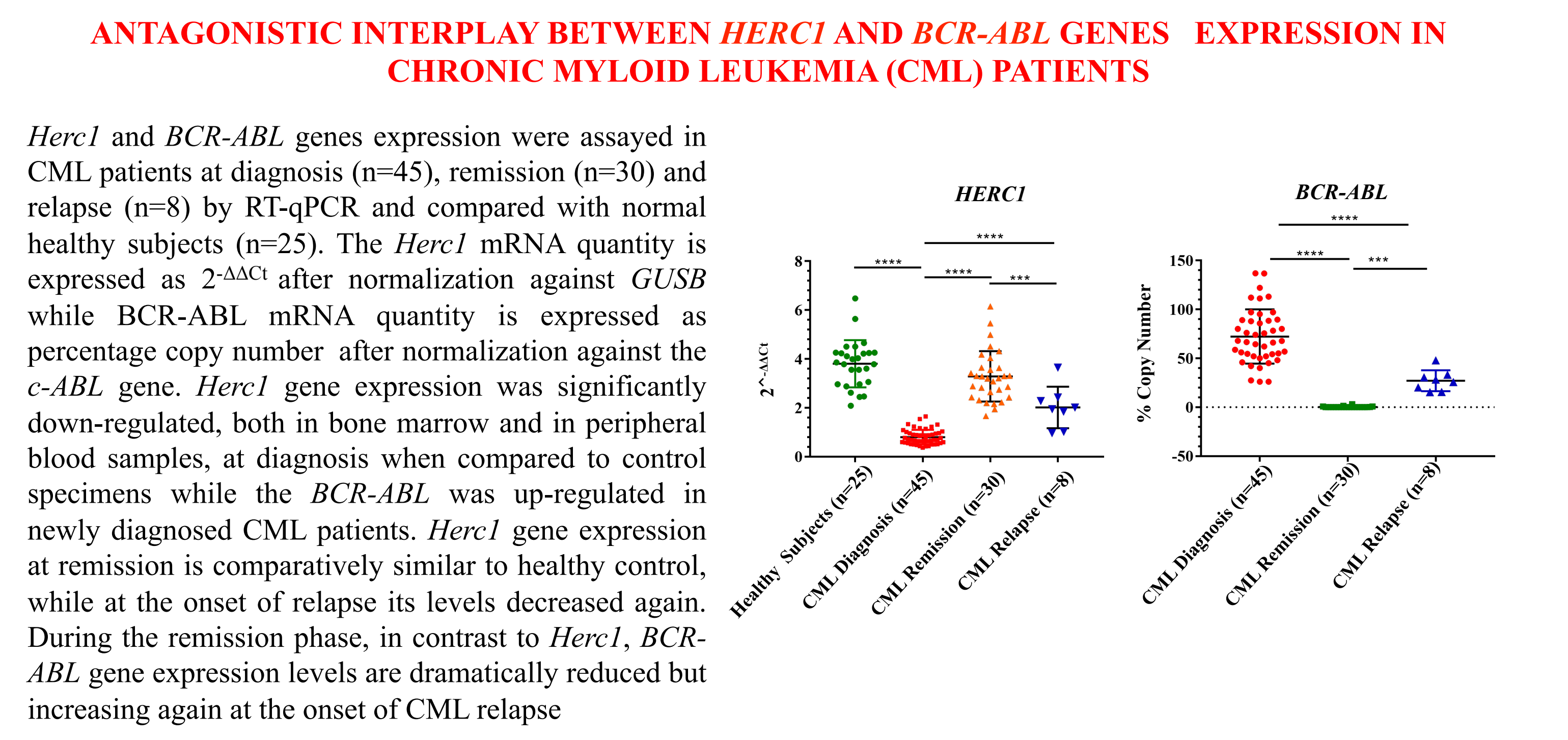
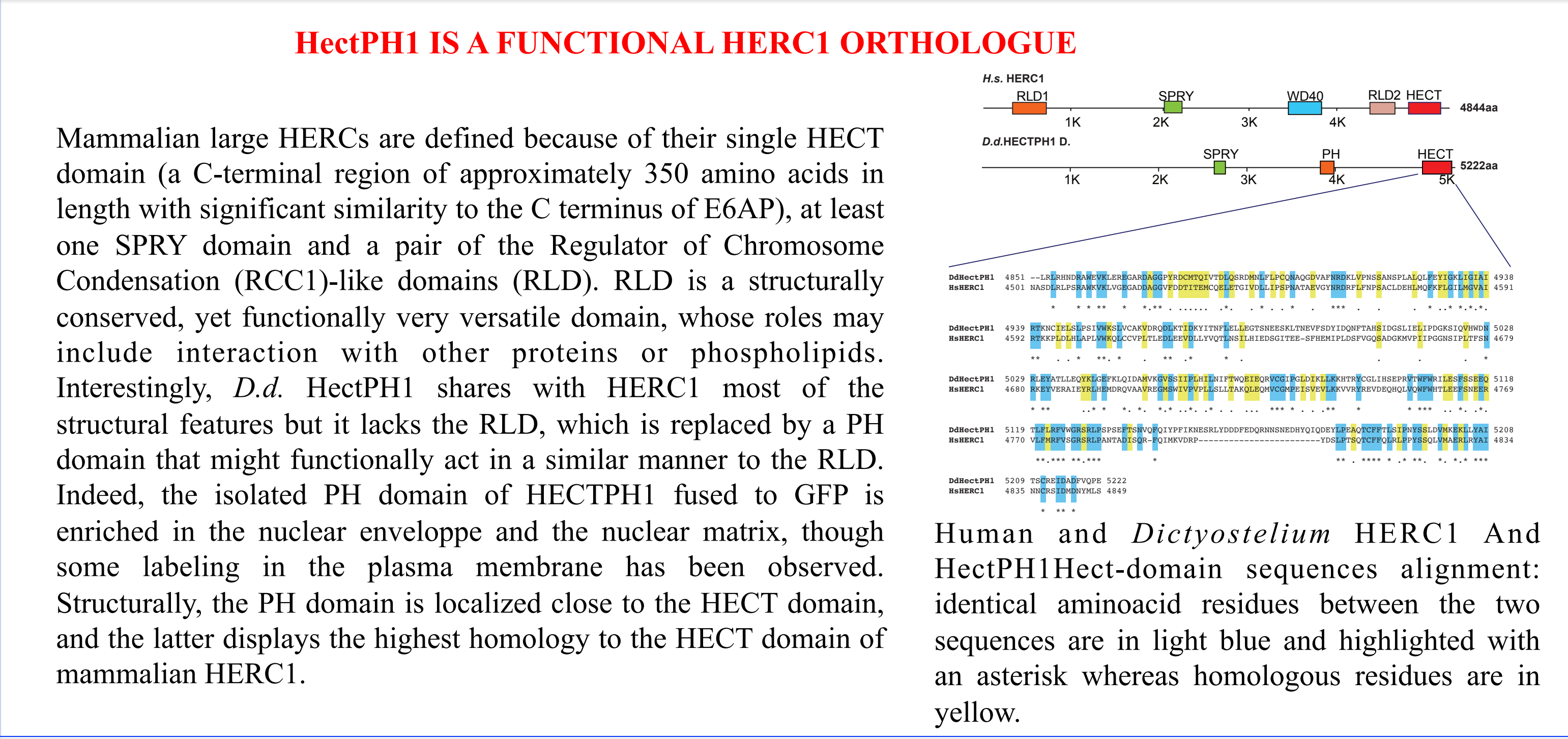
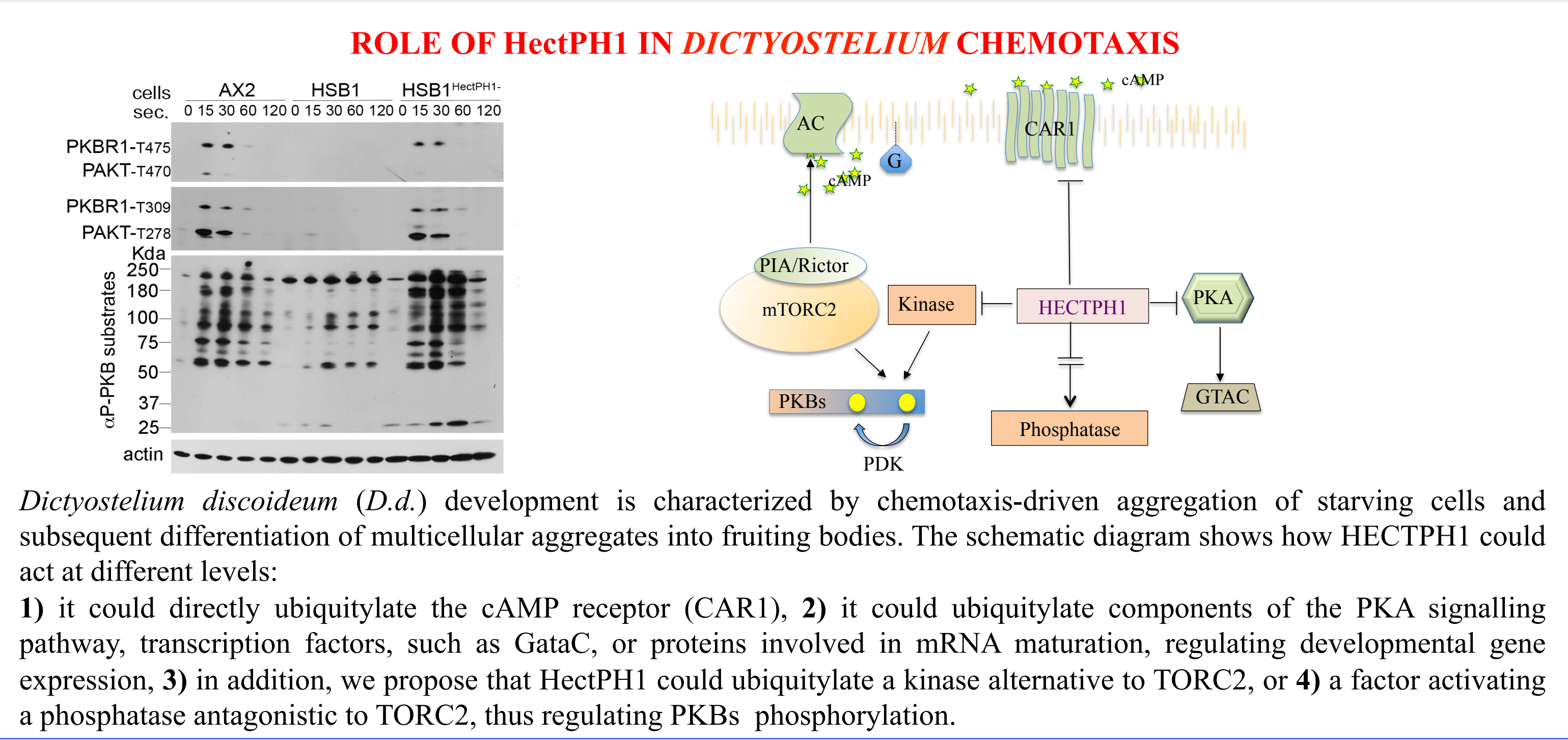
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(Article begins on next page)

Ali M. Shahzad*, Panuzzo Cristina*, Lo Iacono Marco*, Cilloni Daniela*, Giuseppe Saglio*, Bracco Enrico^o and Pergolizzi Barbara*
 *Department of Clinical and Biological Sciences and ^oDepartment of Oncology, University of Turin, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Italy.

The understanding of the physiological relevance of the HERCs E3-Ubiquitin ligases has recently started to emerge, though it remains still poorly investigated. Accumulating evidence show that HERC family proteins are key components of a wide range of cellular functions including pivotal roles in cancer-related pathways. By using a simple model organism, such as the social amoeba *Dictyostelium discoideum*, we identified a novel E3-Ubiquitin Ligase (HectPH1) that the mTORC2-dependent activities. Due to the highest sequence homology of the HECT domain with human *Herc1* counterpart, to the size and structural motifs composition the protein, HectPH1 can be considered a non-conventional large HERC subfamily member. Currently, the molecular mechanisms, by which HectPH1 suppresses the TORC2 deficiency are unknown. We hypothesized that HectPH1 could act either at receptor- or to at different intracellular signalling levels. To properly address these issues it is required to identify the up- and down-stream effectors, but what is/are the regulator/s and the substrate/s of large HERC proteins is currently poorly known, both in animal and other organisms. By means of a proteomic approach, we have recently attempted to fill these gaps. Besides the roles played by *Herc1* in the nervous system of higher organisms like mammals, in the past few years it has emerged that few hematological neoplasms harbor somatic mutations affecting the *HERC1* locus in different kind leukemia. However, the roles played by *HERC1* in blood cells, under physiological and pathological conditions, currently remain unknown. Hence, we have recently started to assess whether *HERC1* might be, or not, associated with a specific pathological condition, namely Chronic Myeloid Leukemia (CML). An in-silico survey carried out on different human neoplasia revealed that most of HECT members act as prognostic markers strengthening the hypothesis that many of them must be therapeutically targettable.



Immunofluorescence and Western-Blot were performed by using rabbit polyclonal anti *Herc1* antibody after treating, or not (NT), the K562 cell line and primary CML leukemic cells with Imatinib (IM) for 48 hours. DAPI staining (blue) indicates cells nuclei and green signal corresponds to *Herc1* (A, B). Similarly, cells treated with Imatinib showed an increase in *Herc1* at both mRNA (C and D) and protein (E) levels. Tubulin was used as loading control.

