Strengths, weaknesses and bottlenecks in new drug design and validation

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The ambitious research of new chemical entities in the PIRAMID consortium aimed at targeting 5 protein-protein interfaces. Depending on the prior network already existing in each axis, new chemical entity search and validation has required to enhance the activity of existing drugs, to determine the binding mode of new drugs and even to start from scratch new prediction and/or validation methods. This unique collaboration between biologists, chemists and modellers has allowed to obtain for each axis strong modulators of the targeted interfaces based on our deeper understanding of the mechanism of interaction between proteins. This presentation will detail how the drug discovery strategies for Axis 1, proteins RhoA/ArhGEF1, and Axis 2, proteins Bcl-Xl/PUMA, has led to the discovery and validation of innovative inhibitors, altogether with a strong increase in knowledge and know-how for all partners. General recommendations for pursuing new drugs development will be drawn, in perspective of the recent advances attained in both axis.