Introduction: More targeted chemotherapies with improved Therapeutic Index are strongly needed for cancer patient’s treatment. Over the last three decades, antibody drug conjugate-based strategies have resulted in new promising treatments mainly in lymphomas and acute leukemias, however, after two decades of developments, only six compounds have been approved by the FDA and several pivotal clinical phase III trials failed in solid tumors. Some of the limiting factors include but not limited to the narrow therapeutic index and difficulties in CMC production. Over time, methodologies for ADC synthesis were improved. Approximately 60 ADCs are currently in clinical development in nearly 620 clinical trials with some ADCs being close to be approved. Whereas problems with ADC linkers and warheads have been extensively investigated and in part be solved, the question of identifying selective targets and developing the most suitable ABs remains largely unsettled. Except for common targets such as ERBB2, most information is not enough for many novel targets particularly regarding expression in normal tissue that can predict side effects.

FDA Approved ADCs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Target</th>
<th>Approval Status</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mylotarg</td>
<td>CD33</td>
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<td>Kadcyla</td>
<td>HER2</td>
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<tr>
<td>Besponsa</td>
<td>HER2</td>
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In Clinical Development

- **Herceptin**
- **Bexxar**
- **Immuno-chemotherapy**
- **Immunohistological evaluation**

**Studying expression in normal tissues**

- **FOLR1** is highly expressed in several types of normal tissues.
- **DLL3** mainly detected in brain and pharynx.
- **GUCY2C** expressed in normal colon.
- **CIR1** seen in ovary and in amplified samples.
- **CDH1** well expressed in normal tissues.
- Overexpression of **MSLN** significant for pancreas and ovary.
- **CSACAMS** strongly expressed in normal GI.
- **PVRIL** weakly expressed in both normal and tumors, irrespective of types.

**Novel targets?**

Conclusions: Here we showed that our in-Silico platform supports the evaluation and identification of gene target candidates for ADC development. The analyses underline the importance of studying genes in context of tumor heterogeneity as well as for their distribution across normal tissues. We believe that such approach should be more systematically done in ADC development programs. In parallel, data driven screening approaches allow to prioritize novel targets for ADC development.