

**DEVELOPMENT OF BIOCONJUGATES AND THEIR  
MODUL CONSTRUCTS FOR TARGETED THERAPY  
OF CANCERS WITH HIGH MORTALITY**

Excerpt from the results obtained in frame of the grant

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# **Development of bioconjugates and their module constructs for targeted therapy of cancers with high mortality**

## **Preface**

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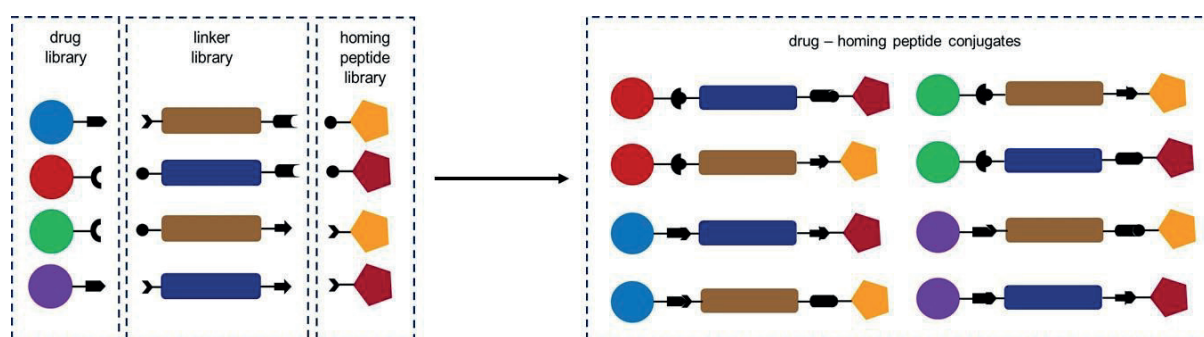
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Cancer is currently the second leading cause of death worldwide. Global cancer statistics estimate over 18 million new cases and close to 10 million deaths for 2018. One of the main therapeutic approaches for cancer is chemotherapy. However, chemotherapy is not always effective and induces severe toxic side effects, as the applied drugs affect not only cancer cells but also normal tissues. To overcome this drawback, targeted therapeutic possibilities have been investigated for increasing tumor selectivity. For this purpose, the anticancer drugs are attached either to antibodies or small molecules like homing peptides that can recognize specifically the tumor-specific or overexpressed receptors on cancer cells. The other advantage of this type of therapy is the avoidance of multidrug resistance. Although some antibody–drug conjugates (ADCs) are investigated to the market for tumor treatment, besides their benefits (*e.g.* high specificity and slow elimination from the circulation) they have some limitations as well (*e.g.* pure tumor tissue penetration and high cost). Therefore, there is increased interest in small molecule drug conjugates (SMDCs) especially in peptide drug conjugates (PDCs). Appropriate homing peptides can recognize tumor-specific or overexpressed receptors on tumor cells with high affinity even if they might not be as selective as ADCs, moreover, they are not immunogen and the preparation of PDC is easier and more cost-effective. However, in many cases, the cell surface components that could be attacked are not well known. In this case, peptides with specific binding properties can be selected by the aid of phage display. The second most important problem is the selection of efficient anti-cancer agents to be bound to the peptide through an appropriate linkage allowing the release of the free drug or its active metabolite in cancer cells. There are several promising peptide-based drug conjugates for targeted tumor therapy in Clinical Trial phases. However, many different types of cancers exist, therefore a few structures of peptide drug conjugates are not enough for the treatment of a broad range of malignant diseases. The recent trend of personalized oncology needs a significant number of versatile drug delivery systems (DDSs)

with high selectivity and efficacy to the special tumor types. Furthermore, a combination of DDSs might increase the therapeutic effect.

In the frame of the project “Development of bioconjugates and their module constructs for targeted therapy of cancers with high mortality” supported by Hungarian National Research, Development and Innovation Office (grant number: NVKP\_16-1-2016-0036) our goal was to develop new peptide drug conjugates for the treatment of different types of tumors especially for the ones that cause high mortality (*e.g.* pancreatic, lung, colon, metastatic melanoma, glioma and HER2 positive breast cancers). For this purpose, three libraries of compounds: a) anticancer agents, b) homing peptides, and c) bifunctional linkers that are suitable for connection of the two previous ones) were developed. The final aim of this project was to prepare appropriate modules that can be combined easily for the development of numerous different DDSs for targeted tumor therapy (Figure 1).



**Figure 1.** Schematic presentation of module libraries and their combination in conjugates

This booklet provides an overview for readers about the results obtained in the frame of the project by the consortium members. The consortium members are Eötvös Loránd University, Institute of Chemistry including the Research Group of Peptide Chemistry, Semmelweis University and ComInnex, Inc. We believe that this concept may provide a new strategy and our results make a stride towards efficient personalized tumor chemotherapy.