Targeted therapy using phage technology: A computational and experimental breast cancer study

Franklin L. Nobrega*, Tânia S. Mendes, Mariana Xavier, Vera L. Silva, Joana Azeredo, Lígia R. Rodrigues and Leon D. Kluskens*

franklin.nobrega@ceb.uminho.pt / kluskens@deb.uminho.pt

Centre of Biological Engineering, Universidade do Minho
Campus de Gualtar, 4710-057 Braga, Portugal

Abstract

During the past two decades cancer biology knowledge has widely increased and shifted the paradigm of cancer treatment from nonspecific cytotoxic agents to selective, mechanism-based therapeutics. Initially, cancer drug design was focused on compounds that rapidly killed dividing cells. Though still used as the backbone of current treatments, these highly unspecific targeting drugs lead to significant toxicity for patients, narrowing the therapeutic index, and frequently lead to drug resistance. Therefore, cancer therapies are now based on cancer immunotherapy and targeted agents, whereas novel treatments are strategically combining both to improve clinical outcomes.

Despite the nanotechnology advances dictating the development of targeted therapies in diverse classes of nano-based carriers, virus-based vectors still remain highly used due to its biocompatibility and specificity for the target.

Particularly, bacteriophages are an interesting alternative 'nanomedicine' that can combine biological and chemical components into the same drug delivery system. The great potential of this novel platform for cancer therapy is the ability to genetically manipulate the virus-vector to display specific targeting moieties.

Phage display technology, a general technique used for detecting interfaces of various types of interacting proteins outside of the immunological context, allows the target agents to locate the target (with an increased selection process for the specific binding– termed biopan-

ning) and play their essential role inhibiting molecular pathways crucial for tumour growth and maintenance. Phage display specificity core is related with the binding of small peptides displayed at their coat or capsid proteins, enriched during biopanning. Bioinformatics plays an important role in testing and improving phage display libraries by effective epitope mapping, selecting from a large set of random peptides those with a high binding affinity to a target of interest.

In this work we demonstrate the screening of a manually constructed 7-mer peptide library of M13KE phage particles against MDA-MB-231 and -435 cancer cell lines. Two peptides – TLATVEV and PRLNVSP – with high affinity for the referred cells were identified, respectively. Based on computationally predicted epitopes based on the peptides extracted from this library the linear peptide sequence was docked onto known membrane proteins from the used cell lines and peptides-proteins interactions were mapped. Umbrella sampling studies were performed to predict the binding affinity and to improve future rational design of binding peptides to these cancer cells.

All authors contact details:

franklin.nobrega@ceb.uminho.pt
taniamendes@ceb.uminho.pt
mariana.nx91@gmail.com
vera.7.silva@gmail.com
jazeredo@deb.uminho.pt
lrmr@deb.uminho.pt
kluskens@deb.uminho.pt