SUPPLEMENTARY INFORMATION

Supplementary Method 1| **Protein_biotinylation.pdf**

Protocol for protein biotinylation. A protocol for the chemical biotinylation of target proteins for affinity-based selections.

Supplementary Software 1| **DECL_selection_5w_KF.msz**

KingFisher program file. It may be adapted upon import into the BindIt software. The BindIt software runs the program on the KingFisher magnetic particle processor.

Supplementary Data 1| **DECL_protocol_report.pdf**

Example of a KingFisher protocol status report. After the KingFisher program ran successfully, the BindIt software provides a protocol status report file, summarizing the course of the run.

Supplementary Figure 1| **DECL_oligonucleotide_sequences.pdf**

DECL oligonucleotide sequences. Scheme detailing how two PCR steps introduce selection-specific codes as well as the Illumina TruSeq adapter sequence. The example sequences show the ESAC library.

Supplementary Software 2| **count.cpp**

Code of the C++ program "count". "Count" processes HTDS data using information provided in the structure file and the code lists.

Supplementary Software 3| **structure.txt**

Example of a structure file. The structure file provides the C++ program with information about the HTDS data, the code lists as well as the constant regions of the DECL (see **Box 2** for further information).

Supplementary Software 4| **codelist1.txt**

Example of a code list. The code list contains all the

different sequences used in one of the four coding positions.

Supplementary Software 5| **MATLABscript_2BB.docx**

MATLAB script 2BB. Selection number and cut-off may be chosen in the highlighted positions. This script provides a 3 dimensional plot for the display of a 2-building block library. Z-axis represents sequence counts.

Supplementary Software 6| **MATLABscript_3BB.docx**

MATLAB script 3BB. Selection number and cut-off may be chosen in the highlighted positions. This script provides a 3 dimensional plot for the display of a 3-building block library. Dot colour and size represent sequence counts.

Supplementary Method 2| **Ethanol_precipitation.pdf**

Protocol for ethanol precipitation. A protocol for the ethanol precipitation of DNA for purification purpose. Performed before the DNA sample is submitted to Illumina HTDS.