FUJIFILM
Value from Innovation

drug2drugs

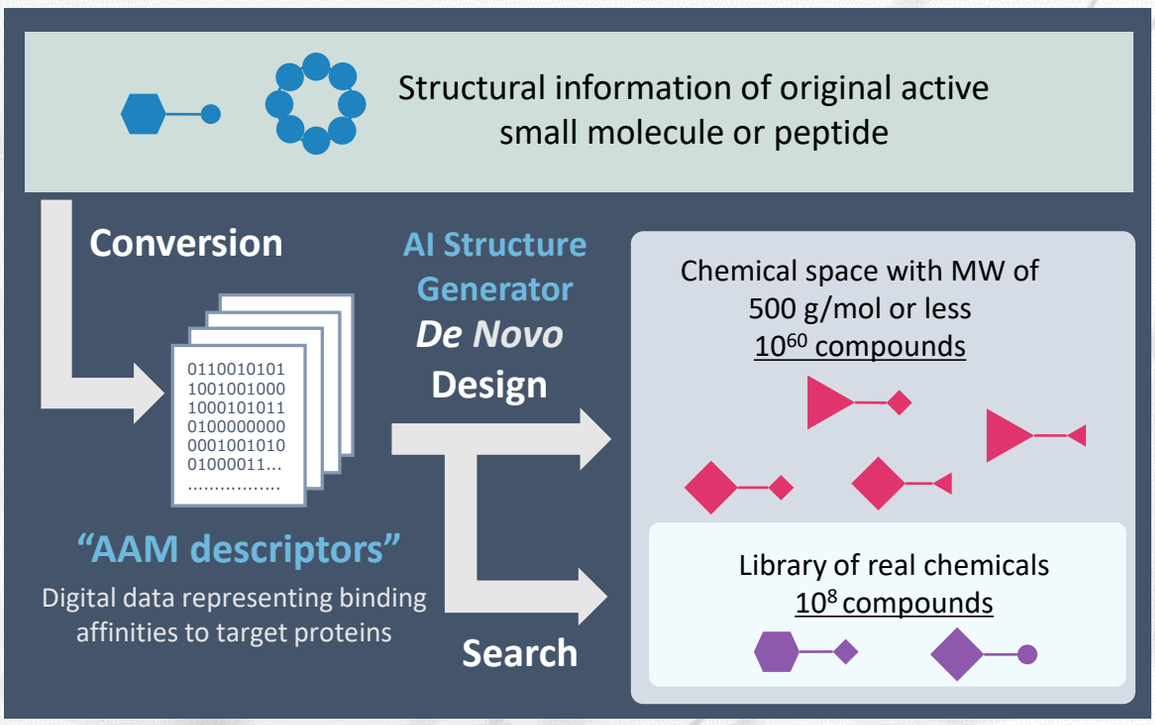
AI and chemical simulation-based drug discovery support service

drug2drugs® is a service to provide you multiple active compounds with different scaffolds from ~~only~~ the structural information of one active compound without knowing the target protein, so that ~~we~~ can increase the success rate in drug discovery.

An active compound is a compound that has the ability to bind to its target protein. Having multiple active compounds with diverse scaffolds ~~is important for improving~~ the success rate in drug development ~~to~~ avoid various problems, such as low solubility, high toxicity or low permeability.

Fujifilm has developed AI-AAM® (AI-Amino-Acid Mapping), a new scaffold transformation method based on AI and chemical simulation, with the aim of increasing the number of active compounds with various scaffolds from one active compound. Scaffold transformation using AI-AAM® requires only the structural information of an active compound, not the information of the target protein.

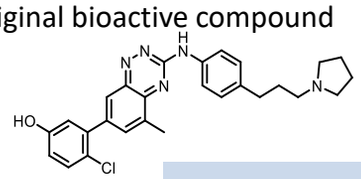
We start drug2drugs®, a service that increases the number of active compounds from active small molecules or peptides by scaffold transformation of AI-AAM®.

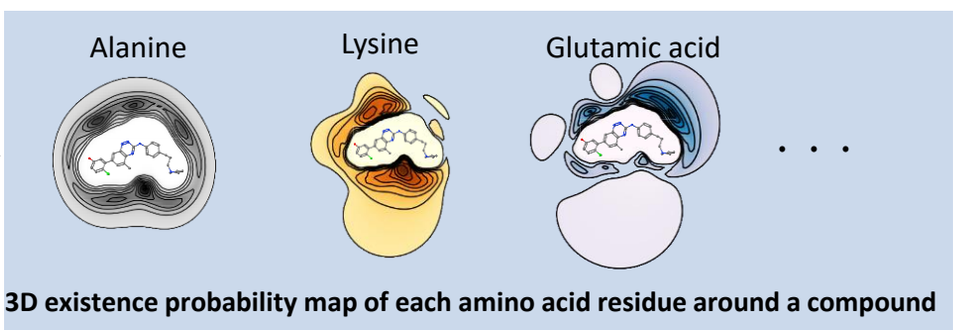


AI-AAM® that consisting of AAM descriptors and AI structure generator

1. AAM (Amino-Acid Mapping) Descriptors[1]

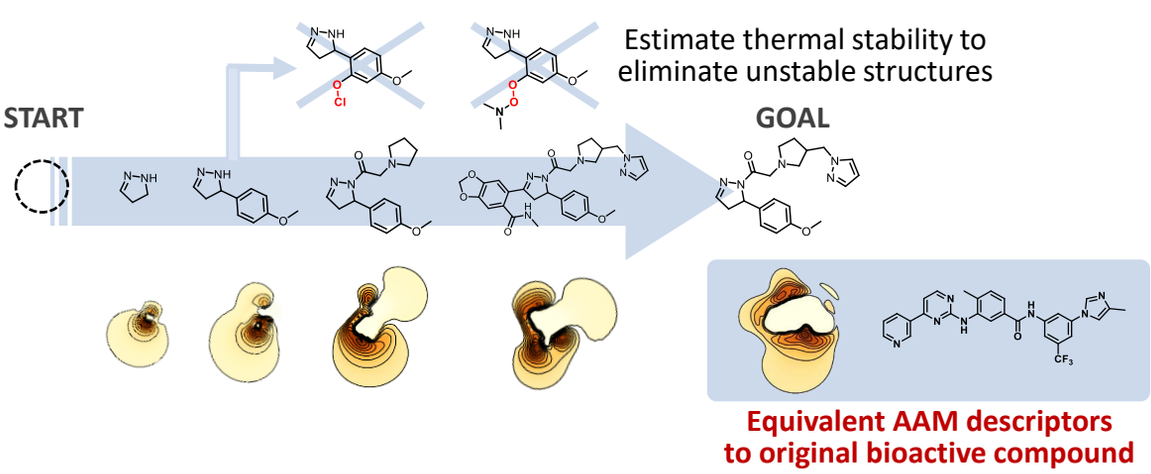
Original bioactive compound





AAM descriptors are the set of the 3D existence probability map of 20 amino acid residues around each compound computed by chemical simulations. Two compounds with the same AAM descriptors but different scaffolds interact with the same amino acid residues and bind to proteins with the same binding pattern.

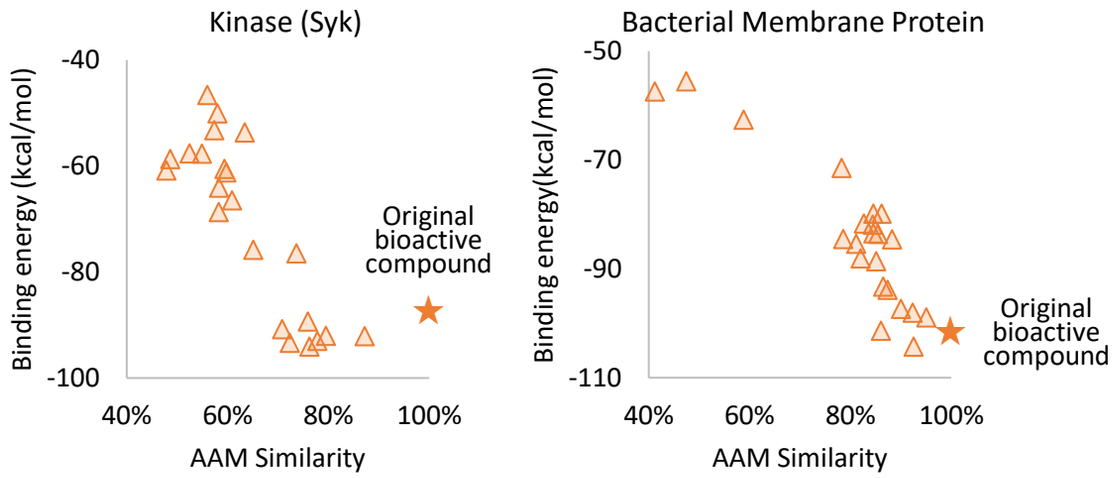
2. *De Novo* Design AI[2]



Our AI automatically designs dozens of chemical structures an atom by an atom with completely different scaffolds but equivalent AAM descriptor with high thermal stability, synthesizability (see validation section 4) and wide structural variety (see validation section 3). ~~We~~ can also modify some parts of active ligands, such as substituents or scaffolds using AI-AAM (see experimental section 1-2&2).

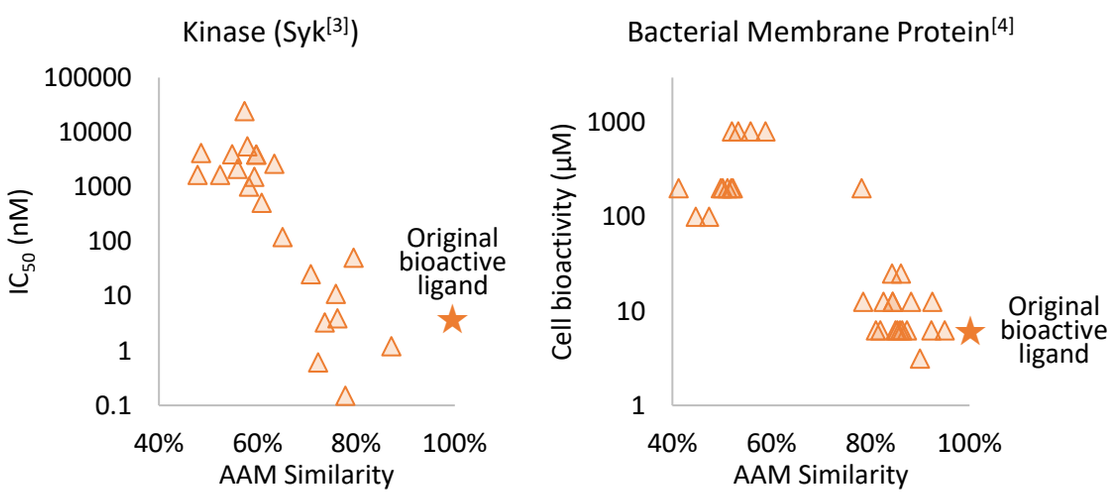
Validation of AI-AAM

1. AAM Similarity vs. Binding Energy (FMO)



We searched for compounds with high AAM similarity to the original bioactive ligands and calculated the binding energy to their target proteins by FMO. Although AAM was not based on target protein information, the binding energy to the targets proteins, a kinase and a membrane protein, could be explained by the descriptors. It was found that AAM could represent binding affinity without using structural information of target proteins.

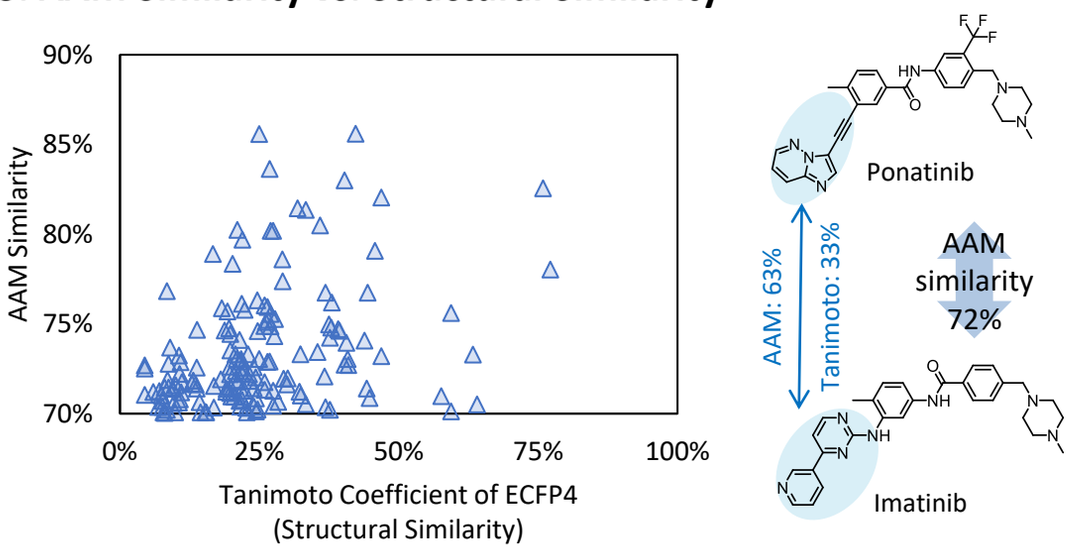
2. AAM Similarity vs. Bioactivity



We compare the AAM similarity and measured bioactivity. It was shown that the binding affinity of the compound to the target proteins, a kinase and a membrane protein, was comparable to that of the original ligand, when we have a compound with high AAM similarity to the original bioactive compound. AAM similarity was found to be a valid indicator for finding a new compound with the equivalent binding affinity to original bioactive ligands.

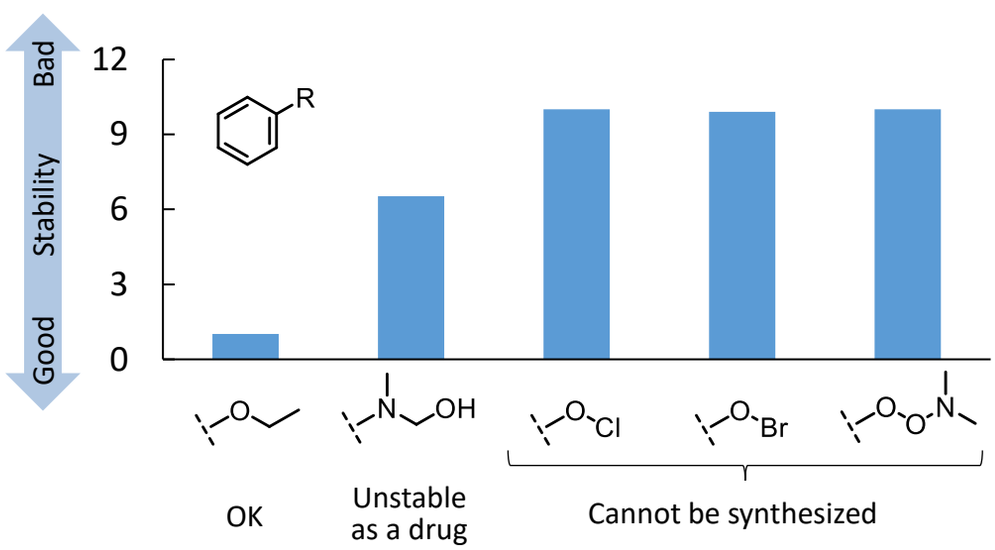
Validation of AI-AAM

3. AAM Similarity vs. Structural Similarity



Most of the compounds with high AAM similarity to the original compound were structurally very different from the original compound. With a combination with our *de novo* design program, we can provide you many promising compounds with various structures. In addition, the AAM similarity of each part is computed to check the influence of structural changes on the interactions with amino acid residue.

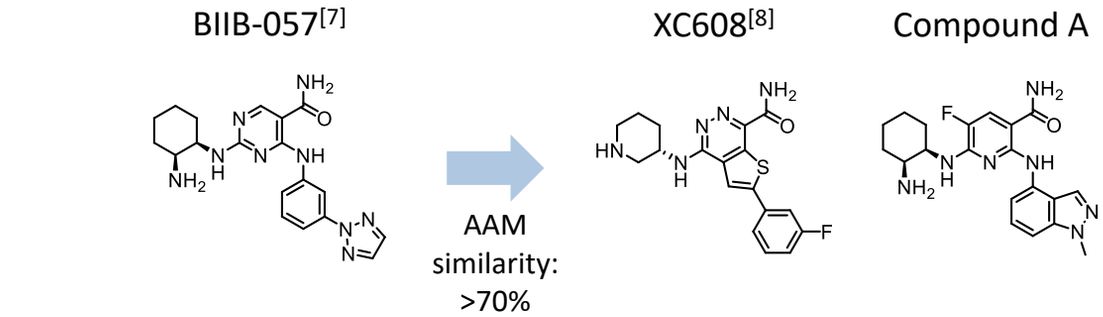
4. Thermal Stability and Synthesizability by *De Novo* Design AI



In our *De Novo* design AI, it is important to predict both stability and synthesizability. We analyzed about 100 million synthesized stable compounds in the world and extracted structural requirements that are important for the compound stability. Based on the requirement, our stability index is computed. The index can correctly predict thermal stability of compounds. Also, the accuracy of the synthesizability of our method was comparable to other common methods[5].

Experimental results of scaffold hopping of active compounds of a small molecule or a peptide using AI-AAM®

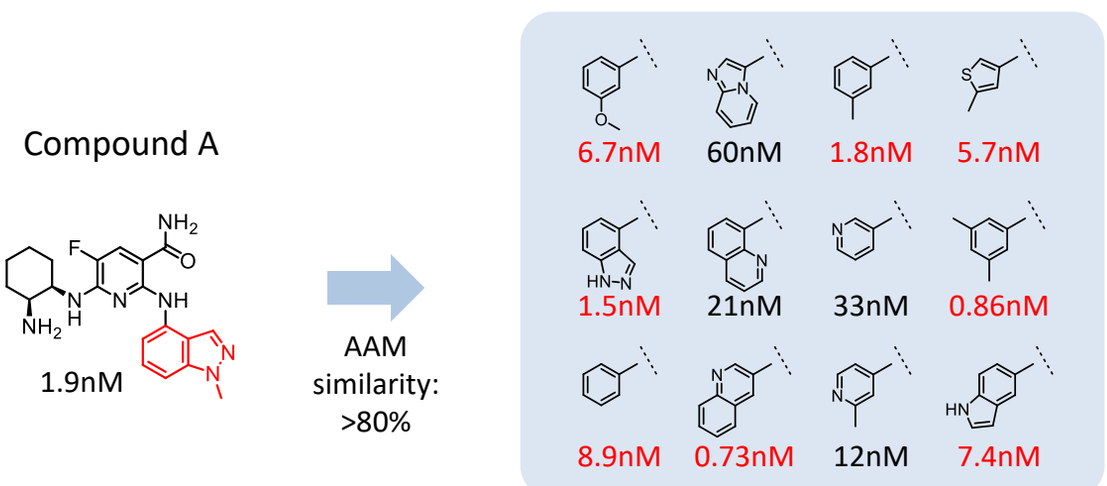
1-1. Scaffold Hopping (Kinase: Syk[6])



	BIIB-057[7]	XC608[8]	Compound A
IC_{50} (nM)	3.9	3.3	1.9

From the structural information of BIIB-057, XC608 was selected as the compound with the most similar AAM from approximately 12 million compounds in commercial compound library within a month. Also, we found another compound, Compound A, from in-house chemical library.

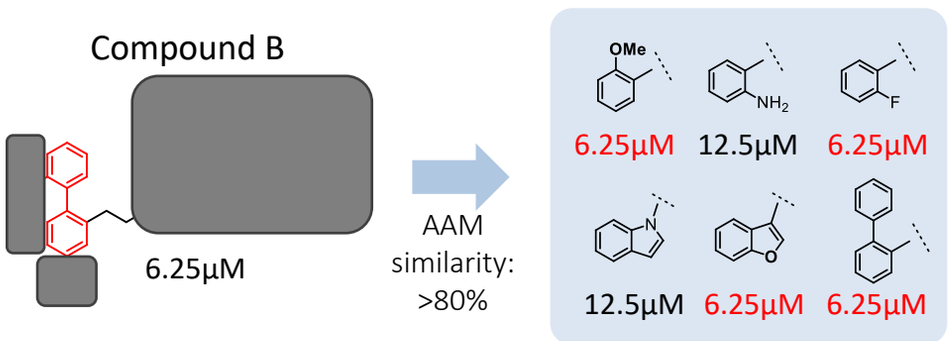
1-2. Partial Modification (Kinase: Syk[3,9])



By AI-AAM, 150 compounds with >80% AAM similarities to the original bioactive ligand were designed with partial modification of the ligand, and 12 of them were selected and successfully synthesized. The enzyme activity of the compounds were evaluated to be 0.73-60 nM[3], which were the same or an order of magnitude weaker bioactivity than the original compound.

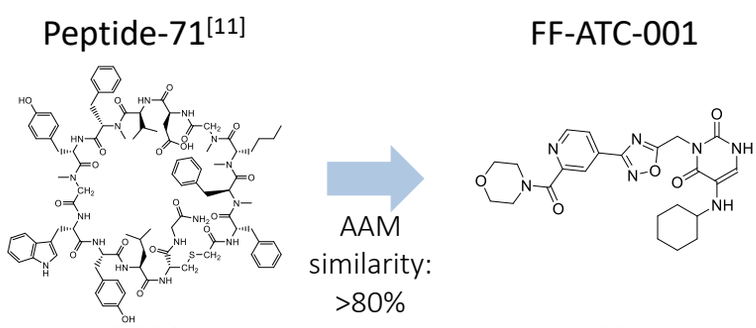
Experimental results of scaffold hopping of active compounds of a small molecule or a peptide using AI-AAM®

2. Partial Modification (Bacterial Membrane Protein[4,9])



By AI-AAM, 332 compounds with >80% AAM similarities to the original bioactive ligand were designed with partial modification of the ligand, and 6 of them were selected and successfully synthesized. The cell bioactivity of the compounds were evaluated to be 6.25-12.5 μM, which were the same or an order of magnitude weaker bioactivity than the original compound.

3. Peptide to Small Molecule (Protein-Protein Interaction: PD-L1[10])

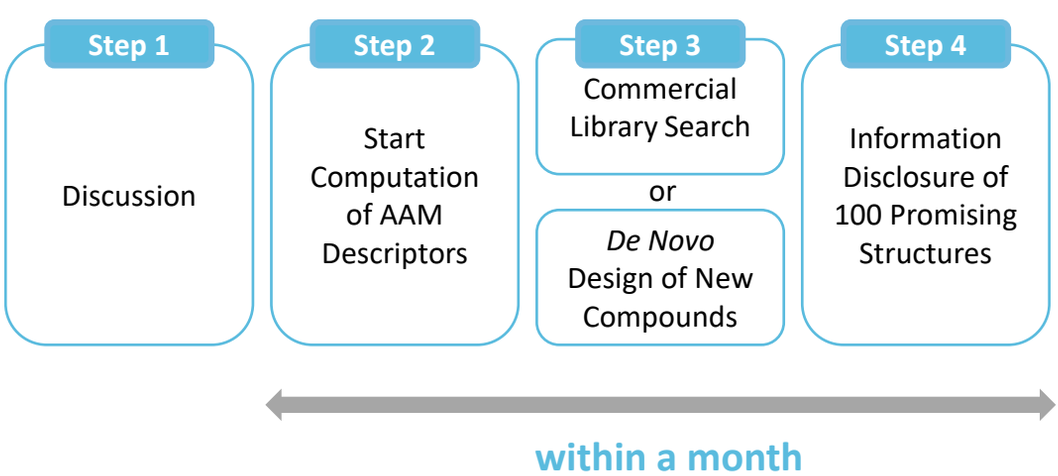


	Peptide-71[11]	FF-ATC-001
K_i (μM)	0.004	39
BEI (pK_i/Mw×10^3)	4.7	9.2
Membrane Permeability (10^{-6}cm/s)	0.08±0.02	11.1±0.8

From the “partial AAM” of the binding conformation of the Peptide-71, the actual parts of the peptide that are physically in contact with the target protein when binding, the small molecule compound FF-ATC-001 was also designed within a month.

drug2drugs®: A service that increases the number of active compounds using AI-AAM®

The content of the service includes (i) scaffold hopping of lead ligands, (ii) hit compound search using bioactive peptides, and (iii) lead-optimization by partial structural modification without using your target protein information. By combining other computational methods, we can present compounds with the required properties (i.e., solubility, predicted safety for the Ames test, and criteria for Lipinski's rules of five).



[1] JP6826672B2. [2] JP7191969B2, JP7190498B2, and JP7116186B2. [3] Enzyme activity was measured by Syk kinase enzyme system and ADP-Glo™ Kinase Assay (Promega, USA). [4] Cell bioactivity was measured by bacterial growth assay. [5] P. Etrl and A. Schuffenhauer, J. Cheminfo. 2009, 1:8. [6]CBI Annual Meeting 2022, P08-14; bioRxiv (2023), doi:https://doi.org/10.1101/2023.07.03.547598. [7] WO 2009/136995. [8] WO 2011/035077. [9] CBI Annual Meeting 2023, P03-07. [10] CBI Annual Meeting 2022, P08-07, Excellent Poster Awards. [11] US20140294898 A1.

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