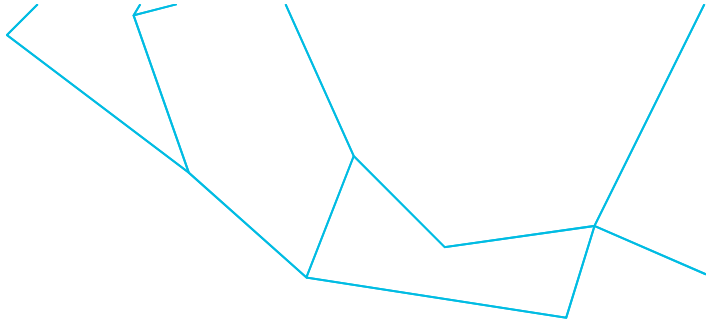
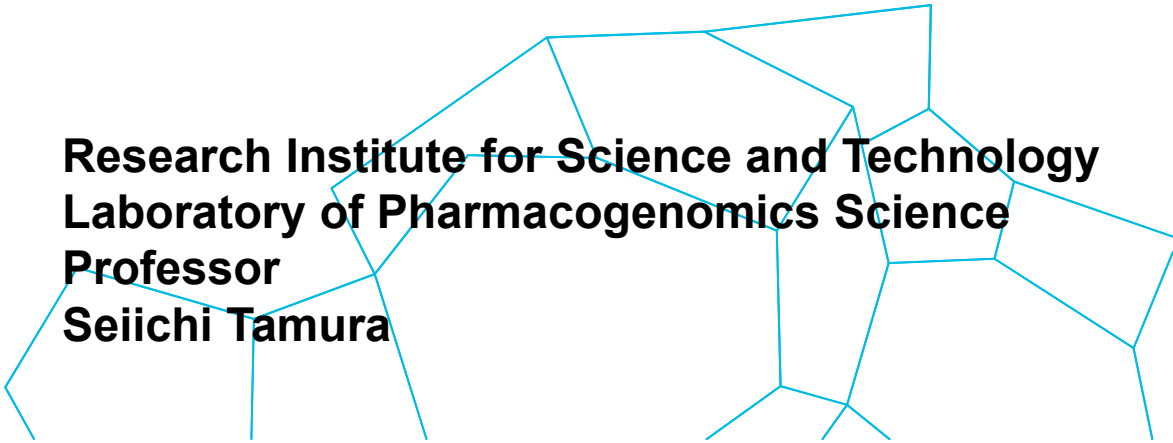


東京理科大学
TOKYO UNIVERSITY OF SCIENCE

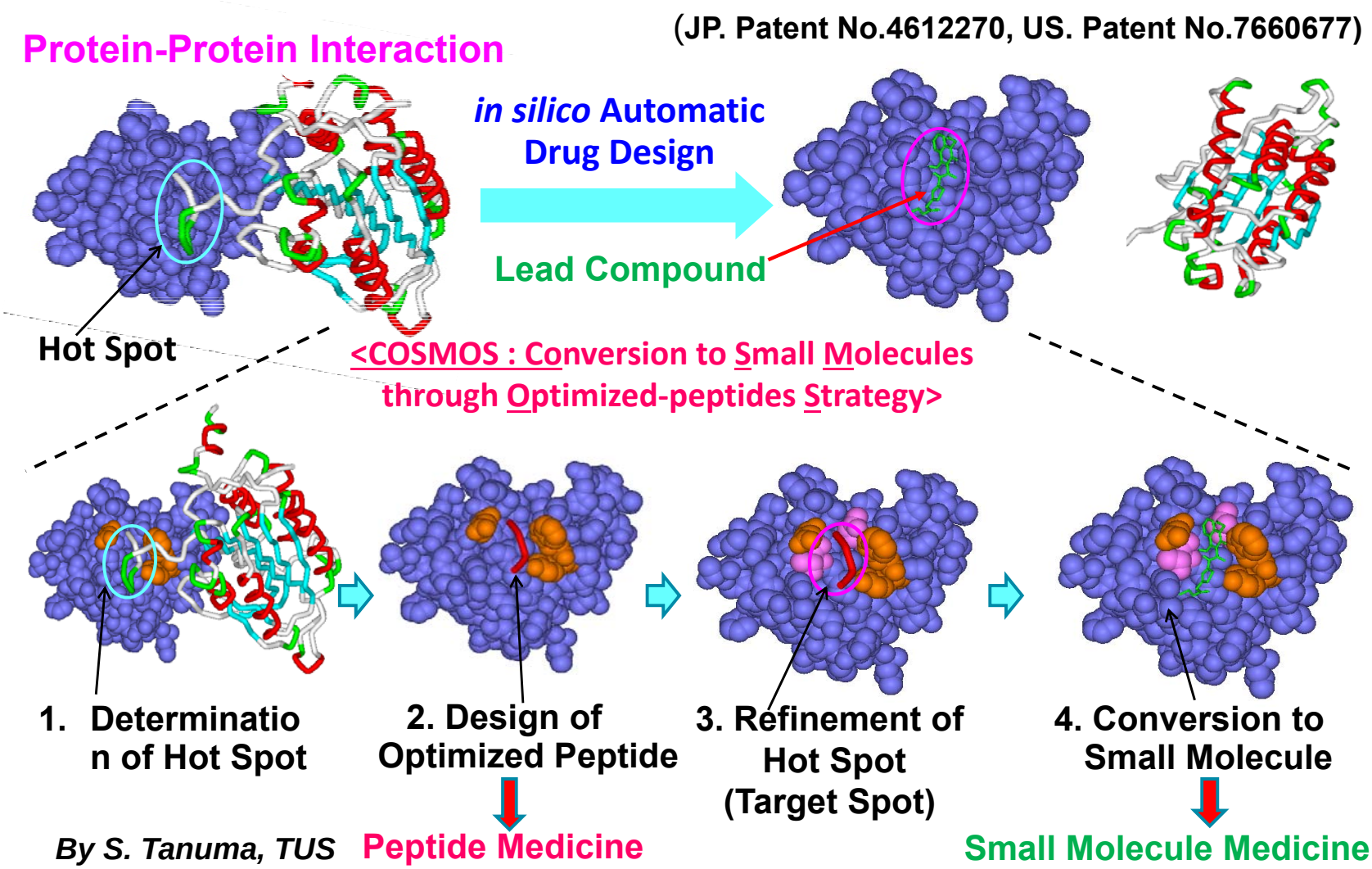
In silico platform for targeting protein-protein interaction, pharmacogenomics “COSMOS”



Research Institute for Science and Technology
Laboratory of Pharmacogenomics Science
Professor
Seiichi Tamura

Scheme of COSMOS Method Targeting of Protein-Protein Interaction

(JP. Patent No.4612270, US. Patent No.7660677)



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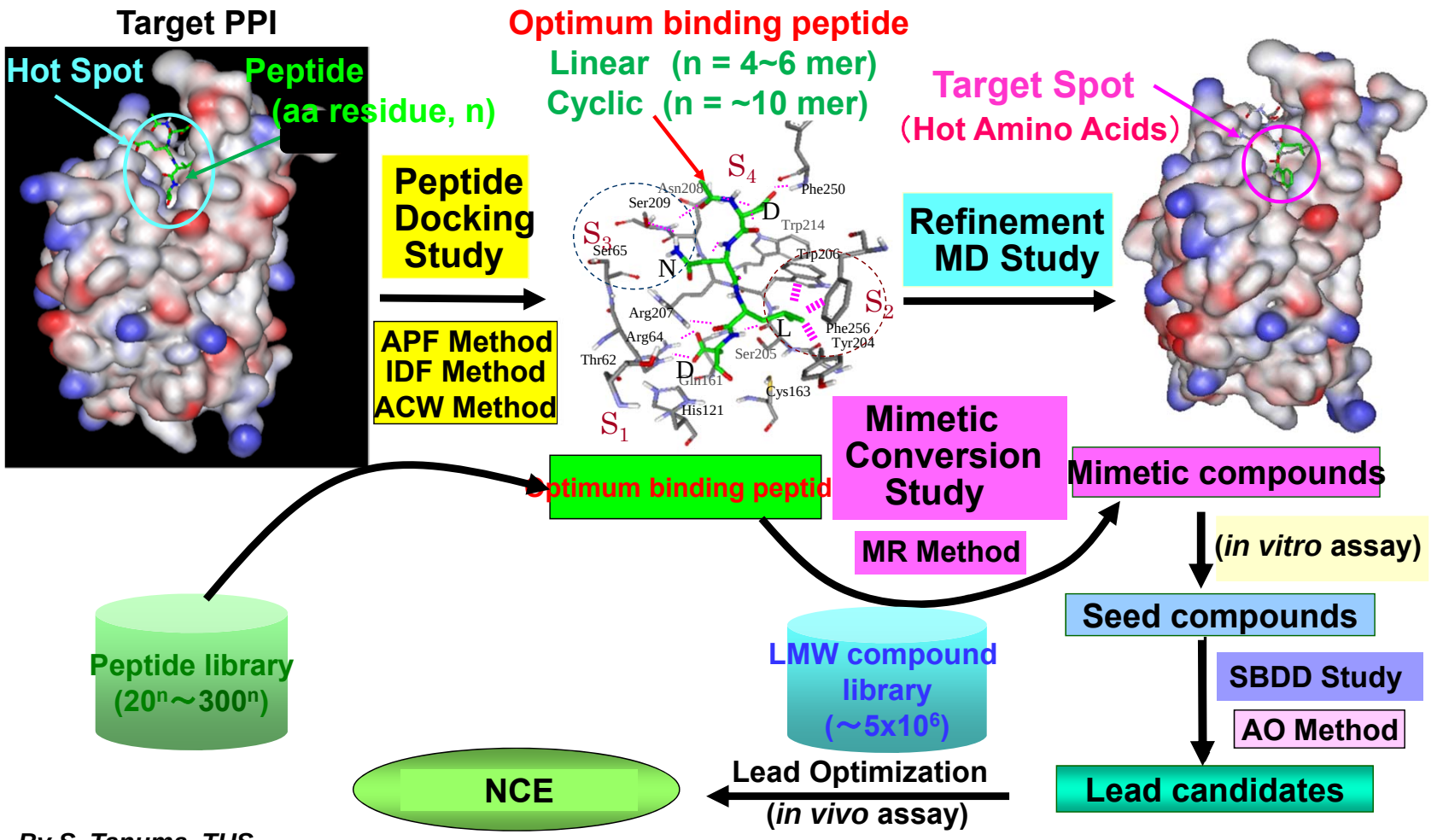
Trial of COSMOS Method

PPI domain (Receptor-Ligand)	Ligand-mimetic Optimized peptide	Conversion molecule	Disease	Patent
β-Sheet (Ligand)	Linear peptide (4~6 mer)	Small molecule		
(Receptor-Ligand)				
○ XIAP – Caspase-9	AVPF (IC_{50} = 99 nM)	New small compounds HCT-116 cells (EC_{50} = 980 nM)	Cancer	
○ Keap1 – Nrf2	XXXX (IC_{50} = 28 nM)	SH-SY5Y-Diff-Neuron (EC_{50} = 440 nM)	Neuronal disorders	
α-helix (Ligand)	Cyclic β-hairpin peptide (8~12 mer)	Small molecule Unnatural amino acid-modified cyclic peptide		
(Receptor-Ligand)				
○ RAGE – HMGB1	Cyclic (PYEIYRIKYp) (IC_{50} = 82 nM)	New small compounds RAW cells (EC_{50} = 330 nM)	Alzheimer's disease Diabetes Sepsis	PCT/JP2019/004760
○ MDM2 – p53	Cyclic (PXXXXXXXXp) (IC_{50} = 0.5 nM)	New small compounds HCT-116 cells (EC_{50} = 18 nM)	Cancer	

COSMOS: Conversion to Small Molecules through Optimized-peptides Strategy

(JP Pat. No.4612270, US.Patent No.7660677)



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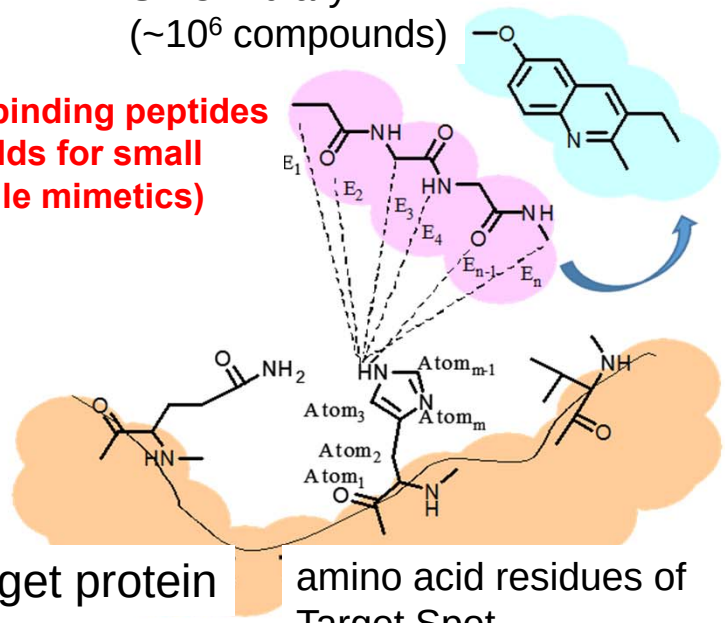
Method for obtaining LMW seeds
— Mimetics Rate method —

SMC* library
(~10^6 compounds)

optimized binding peptides (scaffolds for small molecule mimetics)



target protein — amino acid residues of Target Spot

$$E_n = E_{vdw} + E_{H-bond} + E_{elec}$$

Van der Waals Potential Energy : $E_{vdw} = \frac{C_{12}}{r^{12}} - \frac{C_6}{r^6}$

H-bond Potential Energy : $E_{H-bond} = \frac{C_{12}}{r^{12}} - \frac{C_{10}}{r^{10}}$

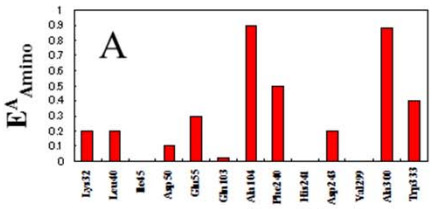
Electrostatic Potential Energy : $E_{elec} = \frac{1}{\varepsilon}\frac{q_1 q_2}{r}$

- $E_{Atom\ i} = E_1 + E_2 + \ldots\ldots + E_n$

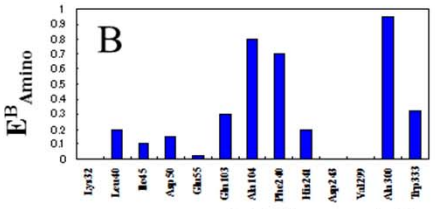
Interaction energy between atoms in amino acid and optimized binding peptide / SMC

- $E_{Amino\ j} = E_{Atom\ 1} + \ldots\ldots + E_{Atom\ m}$

Interaction energy between atoms in amino acid and peptide / SMC

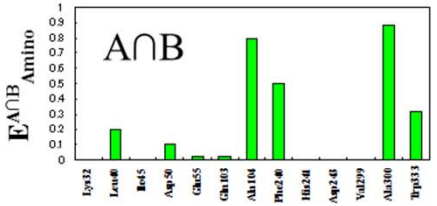


Distribution pattern of E_{amino} in Target Spot and peptides



Distribution pattern of E_{amino} in Target Spot and SMC

- **Mimetic Rate** $= \frac{A \cap B}{A}$



Intersection of pattern A and B

* SMC; small molecule compounds

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