学位論文（要約）

Development and applications of thioether-macrocyclic peptides targeting c-Met–HGF signaling pathway

（c-Met–HGF シグナル伝達系を標的としたチオエーテル大環状ペプチドの開発と応用）

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Abstract

In this thesis, I developed both antagonistic and agonistic peptides targeting the c-Met–HGF signaling pathway to artificially regulate it. Because disruption of the c-Met–HGF signaling pathway causes various diseases such as cancers or intractable diseases, compounds which control its activity will be applicable to potent drugs. To target c-Met and HGF, the Random non-standard Peptide Integrated Discovery (RaPID) system, which is an in vitro peptide screening system recently developed in our laboratory, was utilized and bioactive thioether-macrocyclic peptides were developed. They were applied to human HGF-inhibitory peptides and c-Met agonistic peptide dimers and their drug efficacies, target selectivities and other properties were evaluated.

In Chapter 1, biological information of c-Met and HGF, and significance of targeting their signaling pathway are firstly introduced. Current drug discovery of the c-Met–HGF signaling pathway and its issues are also discussed. Then, properties of the RaPID system and its advantages in drug discovery of the signaling are introduced.

In Chapter 2, development of human HGF (hHGF)-inhibitory thioether-macrocyclic peptides is demonstrated. Using the RaPID system, several human hHGF-inhibitory peptides (HiPs) were identified. Strong hHGF-neutralization effect of HiP-8, one of the HiPs, will be reported.

In Chapter 3, development of novel c-Met-agonistic peptide dimers is reported. First, c-Met-binding peptides were discovered through the screening using the RaPID system and their c-Met-binding affinities, selectivities and stabilities were evaluated. Next, those peptides were dimerized to be c-Met-binding peptide dimers. Bioactivities (induction of c-Met autophosphorylation, activation of signaling pathway and promotion of cellular phenotypic changes) of the peptide dimers will be demonstrated. In addition, establishment of a methodology to improve stability of the
selected peptides will be reported in this chapter. Finally, new insights about target-selectivity of thioether-macrocyclic peptides were discussed in the end of the chapter.

Chapter 4 is the conclusion of the entire thesis. Achievements of the studies and new insights obtained in the thesis are included. Finally, perspective of the antagonists, the agonists and the technologies newly developed in the thesis are discussed.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Table of contents</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>General introduction</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Development of human HGF-inhibitory thioether-macro cyclic peptides</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Results and discussions</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Conclusion</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Materials and methods</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Development of c-Met agonist peptide dimers</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Results and discussions</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Conclusion</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Materials and methods</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>106</td>
</tr>
<tr>
<td>4</td>
<td>General conclusion</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>List of accomplishments</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>Acknowledgement</td>
<td>119</td>
</tr>
</tbody>
</table>
Chapter 1

General introduction
Biology of the c-Met–HGF signaling pathway.

c-Met is one of the receptor tyrosine kinases (RTKs), which are single transmembrane proteins, and also called hepatocyte growth factor receptor (HGFR). It is expressed on the cellular membrane as a receptor of its ligand, hepatocyte growth factor (HGF), which is secreted as a growth hormone. c-Met is a heterodimer protein constructed from a short α-chain and a long β-chain, which includes a transmembrane domain (Figure 1a). Ectodomain (extracellular domain) of c-Met includes a Semaphorin-like (Sema) domain, a cysteine-rich (Cys) domain and four immunoglobulin-like (Ig) domains. The Sema domain is the most N-terminal and constructed by whole α-chain and a N-terminal part of the β-chain. It contains seven β-propellers and is important for interaction with HGF. Two of four Ig domains, Ig3 and Ig4, were reported to be important for binding with HGF. Intracellular region has a juxtamembrane domain, a tyrosine kinase domain and a multifunctional docking site (MDS). All of the domains in the intracellular region include tyrosine residues which can be phosphorylated. Especially, phosphorylation of Y1234 and Y1235 of kinase activation loop of the tyrosine kinase domain has an important role in the early stage of the c-Met–HGF signal transduction. Autophosphorylation of these two tyrosines changes conformation of the tyrosine kinase domain from inactive to active form and enables further phosphorylation of other tyrosines. Various proteins including Grb-2 or Gab-1 (Grb2-associated binding protein 2) proteins, which are related to the signal transduction, recognize phosphorylated MDS and transduce c-Met–HGF signals.

HGF, the ligand of c-Met, is a secreted cytokine and also a heterodimer protein constructed from an α-chain including an amino-terminal (N) domain and four kringle (K1-K4) domains, and a β-chain including a serine protease homology (SPH) domain (Figure 1b). From previous study of the X-ray crystal structure, the SPH domain was revealed to interact with the Sema domain of c-Met. There are other reports that NK1 multidomain of HGF is also important for binding with c-Met.

Detailed binding manner and activation mechanism of c-Met and HGF have not been revealed yet because only partial crystal structures of both c-Met and HGF have been solved. However, one report of the X-ray scattering (SAXS) analysis showed...
that c-Met and HGF hetero-dimerize with 2:2 stoichiometry (Figure 1c,d). In that report, it was revealed that center of the 2:2 dimer structure was the HGF dimer and two c-Met molecules existed at the periphery. As same as other receptor tyrosine kinases, formation of this complex enables intracellular tyrosine kinase domains of c-Met to get

![Diagram](image)

**Figure 1.** Structures of human c-Met and HGF. Domains whose crystal structures have been solved are illustrated by ribbon diagrams. (a) Structure of the human c-Met. It contains an N-terminal Sema domain (PDB: 1SHY)\(^2\) which consists of a pair of α and β chains, a cysteine-rich (Cys) region and four immunoglobulin-like (Ig) domains (ribbon diagrams were referred from previous report\(^5\)) in the extracellular region. It also has a lipophilic transmembrane region and the intracellular region containing a juxtamembrane (JM) domain, a tyrosine kinase domain (PDB: 3RHK)\(^4\) and a multi-docking site (MDS). (b) Structure of human HGF. N-terminal (N) domain and four Kringle (K1-K4) domains are expressed as the α chain (PDB of NK1: 1BHT)\(^3\). A serine protease homologous domain (SPH) is expressed as the β chain (PDB: 1SHY)\(^2\). (c and d) Proposed model of the c-Met–HGF complex with 2:2 stoichiometry reported by Gerardi et al\(^7\). (c) NK1 multi-domain of the HGF binds to the Sema domain of the c-Met. c-Met is shown in blue, NK1 is shown in red and other domains of HGF is in gray. (d) Top view of the c-Met–HGF dimer. c-Met is shown in blue and two HGF molecules are in red or gray.
proximate and phosphorylate each other.

A signal triggered by c-Met and HGF is transduced by sequential phosphorylation of various signaling proteins including Grb2, Gab1, Akt or Erk1/2 (MAPK), which are cytoplasmic kinases (Figure 2). Its activation is known to change various cellular phenotypes, such as cellular proliferation, migration, morphogenesis, scatter, suppression of apoptosis or cytoskeleton change. In our living cells, activation of c-Met–HGF signaling is essential for early development and wound healing of damaged organs. However, abnormal activation of the c-Met–HGF signaling is often observed in various tumors and it causes malignant behaviors of the cancer cells such as their metastasis, growth and immortality. Because of those important functions, c-Met–HGF signaling has been gathering attention as a target of the drug discovery since its first discovery in the mid of 1980’s.

**Figure 2.** c-Met–HGF signaling pathway. The signal is initially stimulated by c-Met–HGF interaction and dimerization of c-Met. Dimerized c-Met gets autophosphorylated and several proteins including Gab1 associates to phosphorylated c-Met to form an active intracellular protein complex. Subsequently, branched downstream signaling pathways (i.e. Akt or Erk1/2 signaling) are transduced to introduce cellular phenotypic changes.
Drug discovery targeting the c-Met–HGF signaling and their current issues.

Regulation of the c-Met–HGF signaling pathway is important for molecular therapy and drug discovery since it regulates various important cellular phenotypes and its disruption causes various diseases\textsuperscript{1,16,17,21}. As previously described, abnormal activation of c-Met triggered by its overexpression or/and that of HGF is known to cause various malignant behaviors of tumors. Moreover, it was recently revealed that secretion of HGF from micro-environment of the tumor activates c-Met–HGF signaling pathway in tumor cells and gives them resistance to RAF or EGFR inhibitors, which are effective anti-tumor drugs\textsuperscript{22,23}. Thus, c-Met–HGF signaling has been gathering attention as a potent drug target for anti-cancer.

Various inhibitors targeting c-Met–HGF signaling have been developed (Table 1)\textsuperscript{24}. Most of the inhibitors are low molecular weight compounds (\textit{i.e.} XL 184, ARQ 197)\textsuperscript{25,26} which inhibit kinase activity of the intracellular tyrosine kinase domain of c-Met and their binding modes and inhibitory mechanisms have been well understood from analysis of many co-crystal structures of the tyrosine kinase domain and small molecule inhibitors\textsuperscript{27}. However, such low molecular weight inhibitors often show side effects, which are crucial problems derived from their small binding surface. Furthermore, most of the c-Met kinase inhibitors show somehow inhibitory activity to other RTKs\textsuperscript{24} resulting mis-regulation of non-selective signaling pathway because tyrosine kinase domains are conserved among RTKs.

Also, protein-based drugs, which inhibit protein-protein interaction between c-Met and HGF, have been developed as selective inhibitors of c-Met–HGF signaling. One of them is c-Met- or HGF-neutralizing antibodies. Targeting the Sema domain of c-Met and SPH domain of HGF, METMab (onartuzumab)\textsuperscript{28} and AMG102 (rilotumumab)\textsuperscript{25} monoclonal antibodies have been developed by Genentech and Amgen, respectively. Another approach is decoy proteins, which are fragments of natural proteins. For example, decoy c-Met (ectodomain of c-Met)\textsuperscript{29} and decoy HGF, represented by NK4 (α-chain of HGF)\textsuperscript{30} developed by Matsumoto’s group, have been developed. However, those biopharmaceuticals generally require high production costs.
In addition, they sometimes cause crucial problems of immunogenicity\(^\text{31}\). Thus, a new class of c-Met inhibitor has been expected to be developed.

On the other hand, c-Met agonists, which turn on c-Met signaling, have also been developed as potent drugs for regenerative medicine\(^\text{32-34}\). Because c-Met–HGF signaling regulates cellular activities, such as cellular proliferation or morphogenesis, which promote development and wound healing of organs, its activation will enable regenerative medicine of various intractable organ diseases such as hepatitis\(^\text{35}\) or spinal injury\(^\text{36}\). As c-Met-activating drugs, recombinant HGF and HGF gene therapy drug (Collategen) have been developed\(^\text{37}\). Furthermore, HGF has recently been utilized to make induced pluripotent stem (iPS) cells differentiate into hepatocytes\(^\text{38}\). If artificial c-Met-agonists which have same agonistic activity as native HGF were developed, they would be powerful tool of substitution of HGF.

### Table 1. Properties of conventional c-Met–HGF antagonists and agonists.

<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Patient population</th>
<th>Phase</th>
<th>Company</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>XL184</td>
<td>Small molecule</td>
<td>Advanced medullary thyroid cancer</td>
<td>III</td>
<td>Exelixis</td>
<td>24</td>
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<tr>
<td>ARQ 197</td>
<td>Small molecule</td>
<td>Non-small-cell lung carcinoma (NSCLC)</td>
<td>III</td>
<td>Daiichi Sankyo</td>
<td>24</td>
</tr>
<tr>
<td>METMab</td>
<td>Antibody</td>
<td>NSCLC</td>
<td>III</td>
<td>Amgen</td>
<td>28</td>
</tr>
<tr>
<td>AMG102</td>
<td>Antibody</td>
<td>NSCLC</td>
<td>II</td>
<td>Genentec</td>
<td>25</td>
</tr>
<tr>
<td>CGEN241</td>
<td>Decoy c-Met</td>
<td>Solid carcinoma</td>
<td>Pre-clinical</td>
<td>Compugen</td>
<td>29</td>
</tr>
<tr>
<td>NK4</td>
<td>HGF fragment</td>
<td>Solid carcinoma</td>
<td>Pre-clinical</td>
<td>Kringle Pharma</td>
<td>30</td>
</tr>
</tbody>
</table>

| HGF        | Recombinant HGF     | Acute renal failure                | I     | Kringle Pharma | 35        |
| Collategen | Gene therapy        | Limb ischemia                      | III   | AnGes MG      | 37        |

In addition, they sometimes cause crucial problems of immunogenicity\(^\text{31}\). Thus, a new class of c-Met inhibitor has been expected to be developed.

On the other hand, c-Met agonists, which turn on c-Met signaling, have also been developed as potent drugs for regenerative medicine\(^\text{32-34}\). Because c-Met–HGF signaling regulates cellular activities, such as cellular proliferation or morphogenesis, which promote development and wound healing of organs, its activation will enable regenerative medicine of various intractable organ diseases such as hepatitis\(^\text{35}\) or spinal injury\(^\text{36}\). As c-Met-activating drugs, recombinant HGF and HGF gene therapy drug (Collategen) have been developed\(^\text{37}\). Furthermore, HGF has recently been utilized to make induced pluripotent stem (iPS) cells differentiate into hepatocytes\(^\text{38}\). If artificial c-Met-agonists which have same agonistic activity as native HGF were developed, they would be powerful tool of substitution of HGF.

**Non-standard peptides and the RaPID system for drug discovery.**

As described above, conventional small molecules and biopharmaceuticals have respective problems. Generally speaking, limitations in selectivity and binding affinity of the small molecules causes side-toxicity. Moreover, it needs great time and labor to obtain inhibitors against certain proteins from conventional small molecule libraries or natural products, whose diversity is limited\(^\text{39}\). On the other hand, biopharmaceuticals have problems in both their production and property. To produce biopharmaceuticals,
facilities for large scale cell culturing and high production cost are required. Furthermore, they sometimes show crucial immunogenicity problems.$^{31}$

As a solution of such problems, peptide drugs have been gathering attention as a new class of drugs. Although peptides have relatively smaller molecular weight (generally, one to several kDa) than large biopharmaceuticals, their unique sequences with 20 proteinogenic amino acids which have varieties of characteristics such as electric charges, hydrophilicity and aromaticity, provides high binding potencies and high target-selectivities to them. Moreover, well-established chemical SPPS (solid phase peptide synthesis) is available for their production, resulting in their easy and cheap production cost than biopharmaceuticals.

Recently, peptides with non-traditional macrocyclic structures including lantipeptides or bicyclics, have been developed.$^{40,41}$ Particularly, those macrocyclic peptides screened by in vitro screening systems have been revealed to have high selectivity, stability and binding affinity which are advantages to utilize them as drugs.$^{42}$ As one of such non-traditional macrocyclic peptides, thioether-macrocyclic peptides, which are ring-closed by thioether linkages, have been developed as a potent scaffold of bioactive peptides. Because thioether linkages are non-reducible, they may be possible

\[ \text{RaPID system} \]
\[ \text{fit system} \]
\[ \text{wPURE system} \]
\[ \text{Flexizyme} \]
\[ \text{Modified mRNA display} \]
\[ \text{FIT system} \]
\[ \text{Modified mRNA display} \]

**Figure 3.** The RaPID system and its peripheral technologies. The RaPID system (pink), which is the primary tool for drug-like peptide discovery is derived from a combination of the FIT system (orange) with a modified mRNA display technique (green). The FIT system itself is derived from a combination of a modified PURE in vitro translation system (blue) with flexizyme technology (tan).
to maintain their macrocyclic structures \textit{in vivo}.

While various novel chemical/biological technologies have been developed to efficiently develop such bioactive macrocyclic peptides\textsuperscript{43}, the Random non-standard Peptide Integrated Discovery (RaPID) system had been developed in Suga’s group as an innovative \textit{in vitro} display system\textsuperscript{44,45}. The RaPID system is a combination of the mRNA display technology\textsuperscript{46,47} and the Flexible \textit{in vitro} translation (FIT) system\textsuperscript{48} (Figure 3). mRNA display is one of the \textit{in vitro} display methods and was originally developed by Yanagawa’s group\textsuperscript{47} and Szhostak’s group\textsuperscript{48}, and the RaPID system utilizes optimized one. The FIT system is a technology of the peptide synthesis, which also had been developed by Suga’s group. It enabled ribosomal synthesis of highly modified peptides containing non-canonical amino acids and/or non-natural peptide scaffolds including thioether-macroyclic structures. The FIT system is an customized \textit{E. coli} reconstituted cell-free \textit{in vitro} translation system (PURE system)\textsuperscript{49} coupled with genetic code reprogrammed by Flexizymes, which are artificial aminoacylation ribozymes\textsuperscript{50}. Using the FIT system deficient of methionine and supplied with N-\textit{O}-(2-chloroacetyl)-aminoacyl-\textit{tRNA}\textsuperscript{Met}_{\text{CAU}} (ClAc-aa-\textit{tRNA}^{\text{Met}}_{\text{CAU}}), which works as an orthogonal initiator aminoacyl-\textit{tRNA}, prepared by Flexizymes, we achieved incorporation of chloroacetyl-amino acids on the N-termini of the peptides. By arranging cysteine on the downstream position of the peptide, a chloroacetyl group reacts with a sulfhydryl group of the cysteine resulting formation of the thioether linkage\textsuperscript{51,52} (Figure 4).

One of the advantages of the RaPID system is that it can use highly diverse (more than $10^{12}$ unique peptides) unique non-standard peptide libraries, such as thioether-macroyclic\textsuperscript{53,54}, warhead-armed\textsuperscript{50} or \textit{N}-methyl peptide libraries\textsuperscript{55}, ribosomally synthesized by the FIT system. From those non-standard peptide libraries, inhibitors against various proteins have been screened by the RaPID system. Both thioether-macroyclic peptide Akt (serine/threonine-specific protein kinase) inhibitors\textsuperscript{53} and warhead-armed thioether-macroyclic peptide Sirt2 (NAD-dependent deacetylase) inhibitors\textsuperscript{50} showed not only strong inhibitory activities but also novel isoform selectivity to their respective target proteins. As ubiquitin ligase E6AP inhibitory
peptides, \(N\)-methylated thioether-macrocylic peptides were selected and they showed extremely high stability against proteolysis \textit{in vitro}\textsuperscript{55}. Recently, thioether-macrocylic peptide inhibitors against a bacterial multi antimicrobial extrusion (MATE) protein were screened by using the RaPID system. Their crystal structures revealed that they had tightly packed macrocyclic structures derived from many intramolecular interactions and deeply stuck to a periplasmic tunnel of the MATE protein\textsuperscript{56}. This conformational advantage might enable them to tightly bind to target proteins.

From these previous achievements, I considered thioether-macrocylic peptides and the RaPID system should be highly suitable for both development of c-Met–HGF signaling inhibitors and activators.

**Development of human HGF-inhibitory thioether-macrocylic peptides (brief introduction of Chapter 2).**

As inhibitors of c-Met–HGF interaction and its signaling, many biopharmaceuticals such as HGF-neutralization antibodies, NK4 (decoy HGF) and anti-c-Met antibodies have been developed. In Chapter 2, I will report the first achievement of the development of thioether-macrocylic peptides which inhibit interaction between human HGF (hHGF) and c-Met (Figure 5a). First, hHGF-binding thioether-macrocylic peptides were screened using the RaPID system. Peptides were further screened by
evaluating following two their inhibitory activities: (i) in vitro inhibitory activity against c-Met–hHGF interaction and (ii) on cell inhibitory activity against c-Met-phosphorylation induced by hHGF. Finally, highly potent hHGF-neutralizing peptide HiP-8 was identified and its inhibitory activity were evaluated in detail.

**Development of c-Met-activating thioether-macrocyclic peptides (brief introduction of Chapter 3).**

In Chapter 3, I aimed to develop novel c-Met-binding peptide dimers which work as low molecular weight c-Met agonists (Figure 5b). In this work, I first developed c-Met-binding thioether-macrocyclic peptides, which tightly bound to c-Met, using the RaPID system. Binding potencies and selectivities of the peptides were evaluated by several in vitro and on cell assays including surface plasmon resonance (SPR) analysis, highly sensitive pull-down assay and fluorescent imaging on live cells. Subsequently, they were chemically dimerized to be c-Met-binding peptide dimers, which have two c-Met-binding motifs in one molecule. Those peptide dimers were revealed to agonize native human c-Met in the same manner as HGF and promote cellular phenotypic changes in quite low concentration (~30 nM). In addition, a novel methodology to improve stability of the screened macrocyclic peptides against proteolysis by N-methylating adequate amino acid residues was established and it will be demonstrated in this chapter.
Figure 5. Overview of the thesis. (a) Development of hHGF inhibitory thioether-macroyclic peptides to inactivate c-Met–HGF signaling is demonstrated in Chapter 2. (b) In Chapter 3, development of c-Met binding thioether macrocyclic peptides and c-Met agonistic peptide dimers to artificially activate c-Met signaling pathway and promote phenotypic changes to cells will be demonstrated.
References

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30. Suzuki, Y. et al. Inhibition of Met/HGF receptor and angiogenesis by NK4 leads to suppression of tumor growth and migration in malignant


Chapter 2

Development of
human HGF-inhibitory thioether-macrocyclic peptides
Chapter 3

Development of c-Met agonist peptide dimers
Chapter 4

General conclusion
In this thesis, I successfully developed not only peptide antagonists but also peptide agonists targeting the c-Met–HGF signaling pathway by screening bioactive thioether-macrocyclic peptides using the RaPID system. As it was achieved without any mimicking of natural ligands (i.e. partial protein fragments, core peptide epitopes), I could demonstrate that it was possible to control (both inactivate and activate) native cellular signaling pathway with completely artificial ligands and the RaPID system was a powerful tool for drug discovery. Furthermore, I could find out various potencies and insights of those peptides through investigations of their bioactivities as follows.

In the study of antagonist development (Chapter 2), I could obtain potent hHGF-neutralizing peptide HiP-8 and revealed that it had quite strong inhibitory activity (IC$_{50}$ <1 nM) against both c-Met–hHGF interaction and the signal to transduction triggered by it. It was a new insight that low molecular weight thioether-macrocyclic peptides screened by the RaPID system could block strong protein-protein interactions with high efficacy comparable to monoclonal antibodies whose clinical investigations are ongoing$^{1}$, and even cellular phenotypic changes induced by hHGF stimulation. Because there are many other membrane receptor proteins including other RTKs, which are also potent therapeutic targets, the methodology used in this study will be applicable for development of strong inhibitors targeting them.

c-Met-binding peptide dimers, which agonized entire c-Met–HGF signaling pathway, were reported in Chapter 3 of the thesis. This study was worthwhile for the first achievement of developing agonistic peptides against endogenous c-Met and its signaling pathway. It demonstrated that we could develop not only antagonists but also agonists by utilizing the RaPID system. As c-Met-binding peptide dimers showed completely the same c-Met activation pattern as recombinant hHGF, it could be a potent substitution of hHGF and a valuable tool for regenerative medicine. In the study, N-methyl scanning was also established as a novel methodology to improve stability of
the peptides. Because kinds of amino acids to be $N$-methyl-modified are not limited in this strategy, it could be a general methodology for post-screening improvement of the serum stability of the peptides. Moreover, it might be more powerful by combining with previously reported screening method of the bioactive $N$-methyl-macrocyclic peptides\textsuperscript{2}.

Also, a new insight about high target-selectivity of the thioether-macrocyclic peptides screened by the RaPID system was revealed in the thesis. Although selectivity of the peptides screened by the RaPID system for different protein isoforms has been confirmed by previous reports\textsuperscript{3,4}, it was confirmed that they have much higher selectivity than expected. In Chapter 3, c-Met-binding peptides were revealed to be able to distinguish c-Met to not only most of the RTKs but also all the membrane proteins and even proteins derived from different biological species through RTK array, proteomic pull-down assay and SPR measurement. With achievements described above, I demonstrated the capability of the RaPID system to develop highly stable, target-selective and bioactive peptide drugs in this thesis. I am confident that the RaPID system will be a promising tool for drug discovery. Also, both antagonistic and agonistic thioether-macrocyclic peptides for c-Met–HGF signaling pathway developed in the thesis will be innovative drugs for cancer therapy and regenerative medicine, respectively.
## References


List of accomplishments

Papers
1. K. Ito and Hiroaki Suga
   Development of macrocyclic peptide inhibitors targeting hepatocyte growth factor receptor c-Met.
   *Peptide Science 2012, 2013, 43-44.*
2. K. Ito, T. Passioura and H. Suga
   Technologies for the Synthesis of mRNA-Encoding Libraries and Discovery of Bioactive Natural Product-Inspired Non-Traditional Macro cyclic Peptides
   *Molecules, 2013, 18, 3502-3528.*

Books
1. 伊藤健一郎、菅裕明
   RaPID システムが創る特殊環状ペプチド創薬
2. 高辻諒、伊藤健一郎、菅裕明
   特殊ペプチドの新規合成法と探索法: RaPID システム
   ペプチド医薬の最前線, シーエムシー出版, 2012.

Awards
1. Research fellowship for young scientists, Japan Society for the Promotion of Science (2010)
2. Best poster presentation award in the 27th Bio-related Chemistry Symposium Young Investigator Forum (Sep. 2012)
3. Poster presentation award in the 9th International Symposium on Aminoacyl-tRNA Synthetases (Oct. 2013)

Patents
1. c-Met protein agonist
   JP 2013/214771
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Kenichiro Ito