**The molecular basis of how Pradimicin A binds to viral N-glycan, a potential SARS-CoV-2 entry inhibitor**

HIV, Ebola and most recently, COVID-19 viruses have had an enormous impact on our societies world-wide. All these viruses are 'enveloped viruses,' viruses that have an exterior envelope that surrounds them largely composed of its host's cells. This envelope increases the virus's ability to hide from their host's immune system and to access the host's cells. It also, however, gives researchers a target, an opportunity to interrupt viral transmission.

Japanese researchers have been working on the issue of halting viral transmission in these types of viruses. "The development of vaccines and antiviral drugs against COVID-19 has successfully reduced the risk of death, but complete suppression of viral transmission is still challenging. Under such circumstances, we evaluated the potential of naturally occurring pradimicin A (PRM-A) as a new anti-SARS-CoV-2 drug that suppresses SARS-CoV-2 transmission," said Yu Nakagawa, the lead author on the paper and an associate professor in the Institute for Glyco-core Research (iGCORE) at Nagoya University, Nagoya, Japan.

There is strong evidence that PRM-A is a viral entry inhibitor, in other words it stops viruses from entering a host's cells. It does this by binding to N-glycans, which are found on the surface of several types of enveloped viruses including the SARS-CoV-2 virus. However, there is still little known about how exactly PRM-A binds to the viral N-glycans.

Their research was published in *Bioorganic & Medicinal Chemistry* on May 1.

To infect a cell, a virus's envelope uses specific receptors on its surface called spike proteins—which are usually glycoproteins, meaning carbohydrates, specifically sugar (oligosaccharides) attached to proteins—to bind to the cellular membrane of a host's cell, causing a conformational change in the cell membrane which allows the virus to enter the cells. Once there, it uses the cell's resources to replicate its own genome, safe from the host's immune system.

Initially researchers looking at interrupting viral transmission focused on lectins, carbohydrate-binding proteins that are derived from plants or bacteria, which showed strong promise as a viral entry inhibitor. They bind with the viruses' glycoproteins and stop its advance into a cell. However, they are often expensive, easily targeted by the host's immune system, and may be toxic to the host's cells. Lectin mimics have many of the carbohydrate-binding ability of the lectin without the expensive and dangerous side effects.

The Japanese team looked at PRM-A, a naturally occurring lectin mimic. It has shown promise as a viral entry inhibitor as there is evidence it binds to the N-glycans of the viruses' envelope glycoproteins. To determine the molecular basis of the binding, they used molecular modelling and ran binding assays which measure the reactions between PRM-A and N-glycans as they bind. They also carried out *in vitro* experiments to test PRM-A's ability to inhibit SARS-CoV-2.

They found that PRM-A binds selectively to branched oligomannose structures found in high mannose-type and hybrid-type N-glycans on viral spike proteins. Mannose is the specific sugar found in these N-glycans. They also found that PRM-A did inhibit the infectivity of SARS-CoV-

2. In fact, the inhibition occurred through the interaction between the PRM-A and the branched oligomannose-containing *N*-glycans.

“We demonstrated for the first time that PRM-A can inhibit SARS-CoV-2 infection by binding to viral glycans. It is also noteworthy that PRM-A was found to bind preferentially to branched oligomannose motifs of viral glycans via simultaneous recognition of two terminal mannose residues. This finding provides essential information needed to understand the antiviral mechanism of PRM-A,” said Nakagawa.

Nakagawa and their team are already busy working on the next step in their research. “Our ultimate goal is to develop anti-SARS-CoV-2 drugs based on PRM-A. The glycan-targeted antiviral action of PRM-A has never been observed in major classes of the existing chemotherapeutics, underscoring its potential as a promising lead for antiviral drugs with the novel mode of action. Especially, considering that glycan structures are hardly changed by viral mutation, we expect that PRM-A-based antiviral drugs would be effective against mutated viruses. Toward this goal, we are now examining in vivo antiviral activity of PRM-A using hamsters, and also developing PRM-A derivatives that are more suitable for therapeutic applications,” said Nakagawa.

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INSERT BOILERPLATE

Suggested EurekAlert! Summary:

*HIV, Ebola and most recently, COVID-19 viruses have had an enormous impact on our societies world-wide. All these viruses are 'enveloped viruses,' viruses that have an exterior envelope that surrounds them largely composed of its host's cells. This envelope increases the virus's ability to hide from their host's immune system and to access the host's cells. It also, however, gives researchers a target, an opportunity to interrupt viral transmission.*

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Primary Keyword:
Health and medicine

Secondary Keyword:
Infectious diseases,
Antiviral activity,
Bioactive compounds,
Drug development,
Drug targets,
Medicinal chemistry

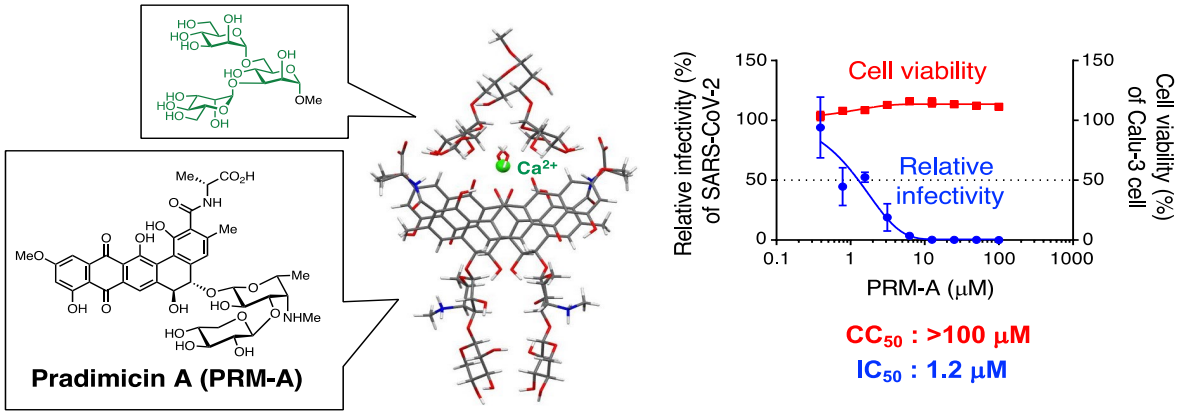


**Image title:** Pradimicin A binding to the branched oligomannose structure and the results of the in vitro experiments on viral infection of SARS-CoV-2 when exposed to PRM-A.
**Image caption**: An illustration of the PRM-A molecule and the branched oligomannose structure found in N-glycans and how they bind with a graphic representation of the resultant decrease in the relative infectivity of the SARS-CoV-2 virus when exposed to PRM-A.
**Image credit**: Yu Nakagawa, Nagoya University
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# 新型コロナウイルスの感染を抑制する天然物質を特定

## ～多様な変異株に有効な革新的抗ウイルス薬の開発に期待～

**【本研究のポイント】**

・糖の一種であるマンノース(Man)に結合する天然物・プラディミシン A が新型コロナウイルス（SARS-CoV-2）の感染を抑制することを発見した。
・プラディミシン A が SARS-CoV-2 表面に存在する糖鎖に結合できることを確認するとともに、プラディミシン A とウイルス糖鎖との結合メカニズムの概要を明らかにした。
・糖鎖構造はウイルスの変異によって変化しにくいことから、プラディミシン A を基にして様々な変異株に有効な革新的抗 SARS-CoV-2 薬を開発できる可能性がある。

**【研究概要】**

名古屋大学糖鎖生命コア研究所の中川 優 准教授、長崎大学高度感染症研究センターの安田　二朗 教授、木下　貴明 助教、櫻井　康晃 助教、広島大学の相田　美砂子 特命教授、赤瀬 大 助教、富山県立大学の五十嵐　康弘 教授、大阪大学大学院理学研究科の伊藤　幸成 特任教授らの研究グループは、放線菌が生産する天然物・プラディミシン A が新型コロナウイルスの表面に存在する糖鎖に結合してその感染を抑制することを新たに発見しました。

近年、新型コロナウイルス（SARS-CoV-2）の表面には多数の糖鎖が付加されていることが明らかにされています。本研究では、SARS-CoV-2 が有する糖鎖にマンノースが多数含まれていることに着目し、マンノース結合活性を有するプラディミシン A が SARS-CoV-2 の糖鎖に結合して細胞レベルでウイルス感染を抑制することを見出しました。さらに、プラディミシン A とウイルス糖鎖との結合メカニズムの概要も明らかにしました。糖鎖構造はウイルスの変異によって変化しにくいことから、これらの知見を基にして様々な変異株に有効な革新的抗 SARS-CoV-2 薬が開発されることが期待されます。

本研究成果は、2024 年 4 月 18 日付化学誌「Bioorganic & Medicinal Chemistry」にオンラインで掲載されました。

**【研究の詳細】**

https://www.nagoya-u.ac.jp/researchinfo/result/upload_images/20240703_igcore.pdf