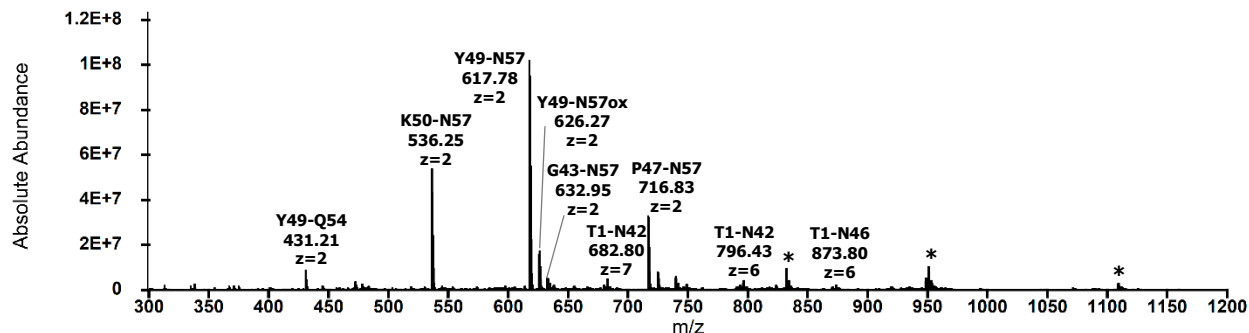


**The Longest Amyloid- $\beta$  Precursor Protein Intracellular Domain Produced with A $\beta$ 42 Forms  $\beta$ -sheet-containing Monomers that Self-assemble and are Proteolyzed by Insulin-degrading Enzyme**

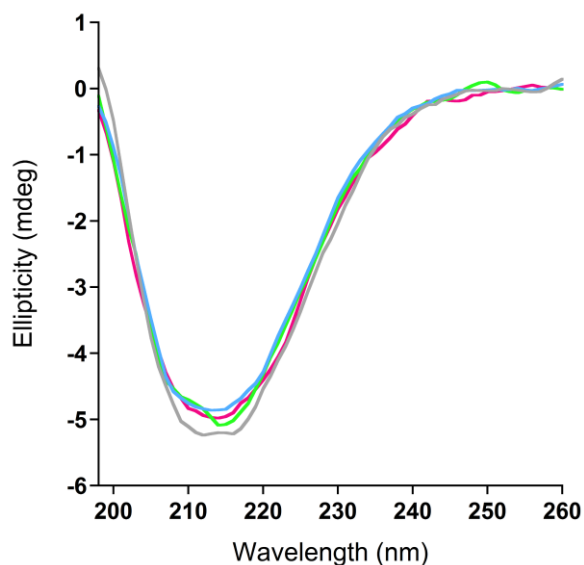
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**Figure S1.** Representative mass spectrum of AICD57 after digestion by IDE for 6 hours showing that the *N*-terminal fragments T1–N42 and T1–N46 are resistant to proteolysis. Peaks of undigested AICD57 are labeled with asterisks.



**Figure S2.** AICD57 contains  $\beta$ -sheet that is resistant to proteolytic attack by IDE. Circular dichroic spectra of AICD57 (20  $\mu$ M in 10 mM phosphate buffer (pH 7.4)) in the presence of IDE recorded immediately after sample preparation (magenta) and after 6 h (green), 22 h (blue), 6 days (gray) of incubation. The substrate to enzyme molar ratio used was 100:1.

**Table S1.** Peaks detected in mass spectra of AICD57 after digestion by IDE for one minute.

<b>Fragment</b>	<b>Observed m/z</b>	<b>Charge</b>	<b>Observed Mass (Da)</b>	<b>Theoretical Mass (Da)</b>	<b><math>\delta^*</math> (Da)</b>
Undigested AICD57	666.15	10	6651.50	6650.70	0.80
	740.05	9	6651.45		0.75
	832.30	8	6650.40		-0.30
	951.06	7	6650.42		-0.28
	1109.57	6	6651.42		0.72
	1331.09	5	6650.45		-0.25
T1-N42	597.58	8	4772.64	4772.60	0.04
	682.80	7	4772.60		0.00
	796.43	6	4772.58		-0.02
G43-N57	632.95	3	1895.85	1896.06	-0.21
	948.92	2	1895.84		-0.22
G43-N57ox	638.28	3	1911.84	1896.06	0.22
	956.91	2	1911.82		0.24
Y44-N57	920.41	2	1838.82	1839.01	-0.19
	613.94	3	1838.82		-0.19
T1-N46	655.47	8	5235.76	5236.05	-0.29
	748.97	7	5235.79		-0.26
	873.80	6	5236.80		0.75
	1048.15	5	5235.75		-0.30
P47-N57	478.22	3	1431.66	1432.61	-0.95
	716.83	2	1431.66		-0.95
P47-N57ox	483.56	3	1447.68	1448.61	-0.93
	724.83	2	1447.66		-0.95
P47-F52	401.71	2	801.42	801.94	-0.52
K50-N57	536.25	2	1070.50	1071.22	-0.72
Y49-N57	617.78	2	1233.56	1234.39	-0.83

\* $\delta$  = Observed Mass - Theoretical Mass

**Table S2.** Peaks detected in mass spectra of AICD57 after digestion by IDE for two hours.

<b>Fragments</b>	<b>Observed m/z</b>	<b>Charge</b>	<b>Observed Mass (Da)</b>	<b>Theoretical Mass (Da)</b>	<b><math>\delta^*</math> (Da)</b>
Undigested AICD57	666.15	10	6651.50	6650.70	0.80
	740.05	9	6651.45		0.75
	832.30	8	6650.40		-0.30
	951.06	7	6650.42		-0.28
	1109.57	6	6651.42		0.72
	1331.09	5	6650.45		-0.25
T1-N42	597.58	8	4772.64	4772.60	0.04
	682.80	7	4772.60		0.00
	796.43	6	4772.58		-0.02
G43-N57	632.95	3	1895.85	1896.06	-0.21
	948.92	2	1895.84		-0.22
G43-N57ox	638.28	3	1911.84	1896.06	0.22
	956.91	2	1911.82		0.24
G43-Q54	761.85	2	1521.70	1522.63	-0.93
Y44-Q54	733.34	2	1464.68	1465.58	-0.90
Y44-N57	920.41	2	1838.82	1839.01	-0.19
	613.94	3	1838.82		-0.19
T1-N46	655.47	8	5235.76	5236.05	-0.29
	748.97	7	5235.79		-0.26
	873.80	6	5236.80		0.75
	1048.15	5	5235.75		-0.30
P47-N57	478.22	3	1431.66	1432.61	-0.95
	716.83	2	1431.66		-0.95
P47-N57ox	483.56	3	1447.68	1448.61	-0.93
	724.83	2	1447.66		-0.95
P47-F52	401.71	2	801.42	801.94	-0.52
N46-N57	773.85	2	1545.70	1546.72	-1.02
K50-N57	536.25	2	1070.50	1071.22	-0.72
Y49-N57	617.78	2	1233.56	1234.39	-0.83

\* $\delta$  = Observed Mass - Theoretical Mass

**Table S3.** Peaks detected in mass spectra of AICD57 after digestion by IDE for four hours.

<b>Fragments</b>	<b>Observed m/z</b>	<b>Charge</b>	<b>Observed Mass (Da)</b>	<b>Theoretical Mass (Da)</b>	<b><math>\delta^*</math> (Da)</b>
Undigested AICD57	666.15	10	6651.50	6650.70	0.80
	740.05	9	6651.45		0.75
	832.30	8	6650.40		-0.30
	951.06	7	6650.42		-0.28
	1109.57	6	6651.42		0.72
	1331.09	5	6650.45		-0.25
T1-N42	597.58	8	4772.64	4772.60	0.04
	682.80	7	4772.60		0.00
	796.43	6	4772.58		-0.02
G43-N57	632.95	3	1895.85	1896.06	-0.21
	948.92	2	1895.84		-0.22
G43-N57 <sub>ox</sub>	638.28	3	1911.84	1896.06	0.22
	956.91	2	1911.82		0.24
G43-Q54	761.85	2	1521.70	1522.63	-0.93
Y44-N57	920.41	2	1838.82	1839.01	-0.19
	613.94	3	1838.82		-0.19
Y44-Q54	733.34	2	1464.68	1465.58	-0.90
T1-N46	655.47	8	5235.76	5236.05	-0.29
	748.97	7	5235.79		-0.26
	873.80	6	5236.80		0.75
	1048.15	5	5235.75		-0.30
P47-N57	478.22	3	1431.66	1432.61	-0.95
	716.83	2	1431.66		-0.95
P47-N57 <sub>ox</sub>	483.56	3	1447.68	1448.61	-0.93
	724.83	2	1447.66		-0.95
P47-F52	401.71	2	801.42	801.94	-0.52
Y49-N57	617.78	2	1233.56	1234.39	-0.83
K50-N57	536.25	2	1070.50	1071.22	-0.72

\* $\delta$  = Observed Mass - Theoretical Mass

**Table S4.** Peaks detected in mass spectra of AICD57 after digestion by IDE for six hours.

<b>Fragments</b>	<b>Observed m/z</b>	<b>Charge</b>	<b>Observed Mass (Da)</b>	<b>Theoretical Mass (Da)</b>	<b><math>\delta^*</math> (Da)</b>
Undigested AICD57	740.05	9	6651.45	6650.70	0.75
	832.30	8	6650.40		-0.30
	951.06	7	6650.42		-0.28
	1109.57	6	6651.42		0.72
	1331.09	5	6650.45		-0.25
T1-N42	597.58	8	4772.64	4772.60	0.04
	682.80	7	4772.60		0.00
	796.43	6	4772.58		-0.02
G43-N57	632.95	3	1895.85	1896.06	-0.21
G43-N57ox	638.28	3	1911.84	1896.06	0.22
	956.91	2	1911.82		0.24
Y44-N57	919.91	2	1837.82	1839.01	-1.19
	613.94	3	1838.82		-0.19
T1-N46	655.60	8	5236.80	5236.05	0.75
	748.97	7	5235.79		-0.26
	873.80	6	5236.80		0.75
	1048.15	5	5235.75		-0.30
P47-N57	478.22	3	1431.66	1432.61	-0.95
	716.83	2	1431.66		-0.95
P47-N57ox	724.83	2	1447.66	1448.61	-0.95
P47-F52	401.71	2	801.42	801.94	-0.52
T1-T48	906.65	6	5433.90	5434.27	-0.37
Y49-N57	617.78	2	1233.56	1234.39	-0.83
Y49-N57ox	626.27	2	1250.54	1250.39	0.15
Y49-Q54	431.21	2	860.42	860.96	-0.54
Y49-M55	496.73	2	992.16	991.46	0.70
K50-N57	536.25	2	1070.50	1071.22	-0.72

\* $\delta$  = Observed Mass - Theoretical Mass