Ion Mobility-Mass Spectrometry (IM-MS)

Literature Seminar #3 (2014.9.27)

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§1 Introduction

§2 Basic Information of IM-MS

§3 Application toward Amyloid β Protein (Aβ)

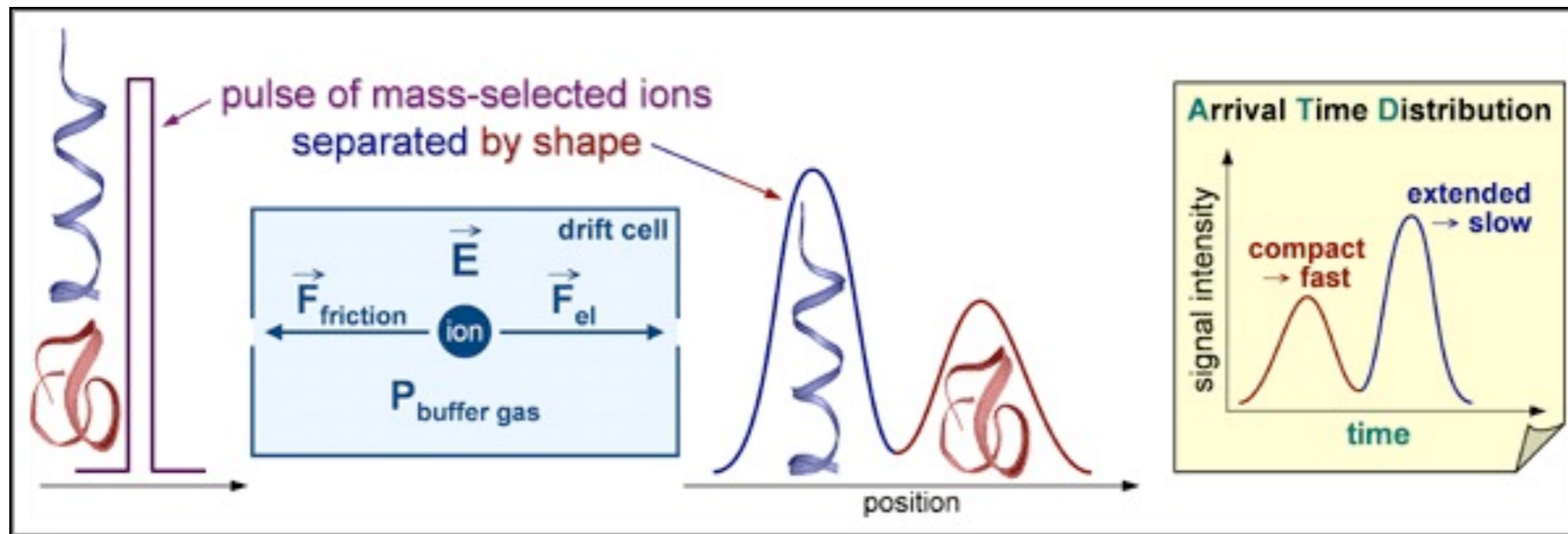§3.1 Why Application toward Aβ is meaningful?

§3.2 Obtainable Data and Their Explanation

§3.3 Oligomerization Analysis

§3.4 Mechanism Analysis of Aggregation Inhibitor

What is Ion Mobility?

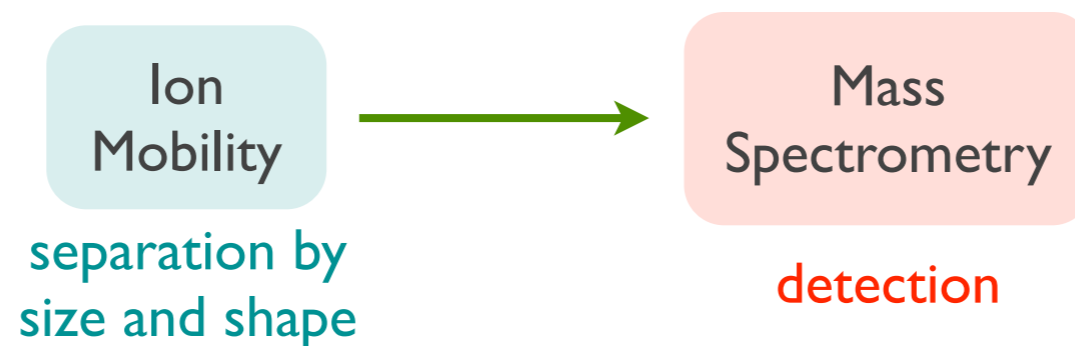- Ion mobility achieves separation of compounds by their **size** and **shape**.

- ○ E = uniform electric field [均一電場]

- ○ $F_{friction}$ = force of friction (caused by collisions of ions with the buffer gas)

- ○ F_{el} = force of elimination

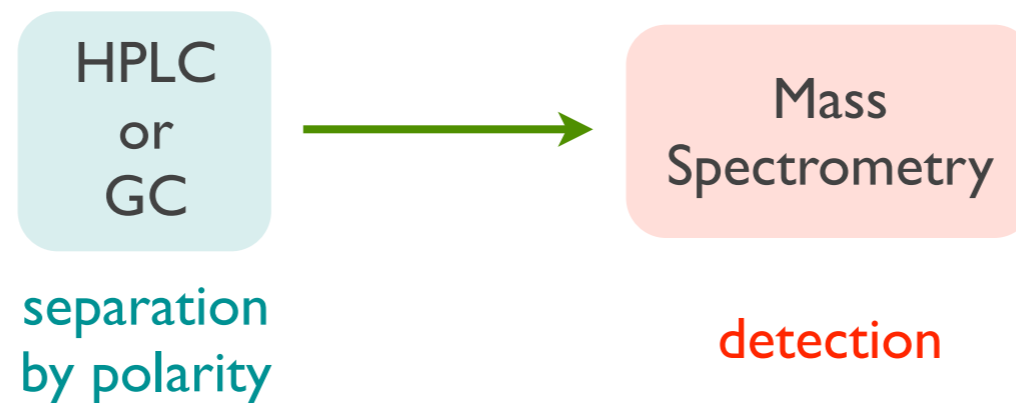- ○ $P_{buffer\ gas}$ = pressure of buffer gas

This figure is cited from Bowers group web page.
(http://bowers.chem.ucsb.edu/theory_analysis/ion-mobility/index.shtml)

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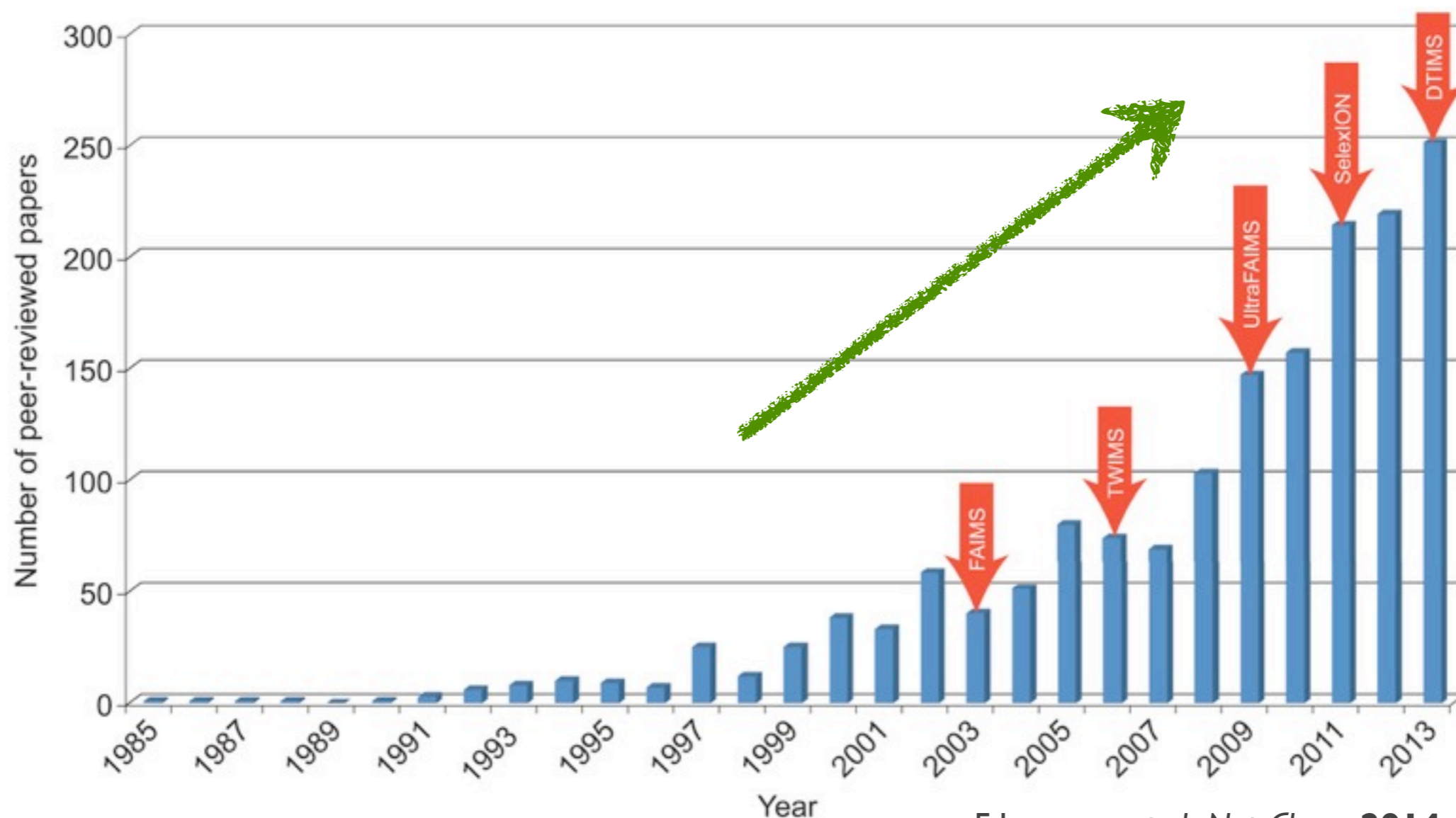# What is Ion Mobility-Mass Spectrometry (IM-MS)?

- conceptual diagram of IM-MS

| Ion Mobility | → | Mass Spectrometry |

separation by size and shape   detection

cf.) How about LC-MS or GC-MS??

| HPLC or GC | → | Mass Spectrometry |

separation by polarity   detection

Recent Explosion in Research Using IM-MS

- number of peer-reviewed papers published annually combining IM and MS

F. Lanucara *et al.*, *Nat. Chem.* **2014**, 6, 281.

○ Especially, the application toward biomolecules is the current hot topic.

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§3.1 Why Application toward Aβ is meaningful?

§3.2 Obtainable Data and Their Explanation

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§3.4 Mechanism Analysis of Aggregation Inhibitor

Three Types of Ion Mobility Spectrometry

a: Drift-Time Ion Mobility Spectrometry (DTIMS)

b: Traveling-Wave Ion Mobility Spectrometry (TWIMS)

c: Field-Asymmetric Ion Mobility Spectrometry (FAIMS)

DTIMS
TWIMS
FAIMS

F. Lanucara *et al.*, *Nat. Chem.* **2014**, 6, 281.
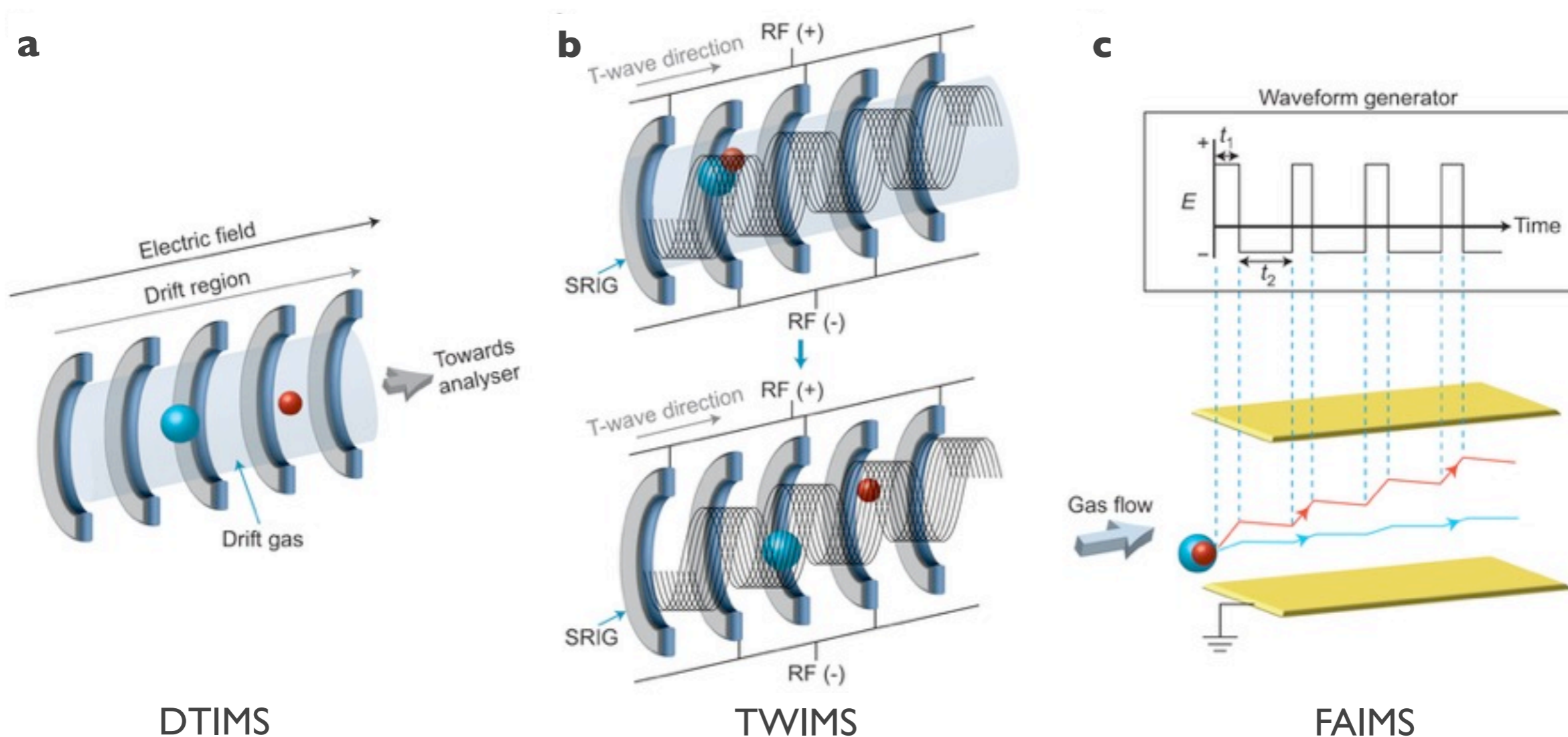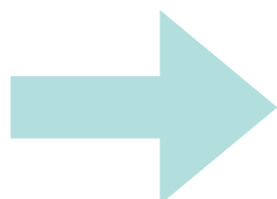
DTIMS (1): System Outline

- Pulse of ions is introduced into a **drift cell**.

  ○ Static uniform electric field is applied.

  ○ filled with drift gas (typically helium)

  ○ Ions travels in the direction of the applied field in uniform motion.
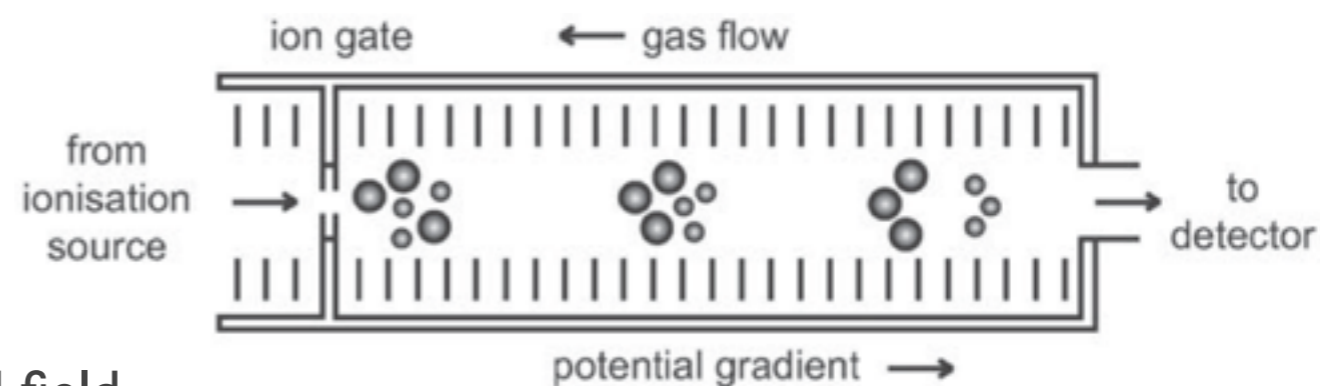
C. Uetrecht *et al.*, *Chem. Soc. Rev.* **2010**, *39*, 1633.

Ions collide with gas and are separated based on its size and shape.
(Small ions travels faster than big ions.)

- The time taken for an ion to drift through the cell (= drift time) is related to its rotationally averaged cross-sectional area (= **collision cross-section (CCS)**).

index of ion size and shape

DTIMS (2): How to Calculate CCS?

- Mason-Schamp equation: provide the **relationship between ion mobility and CCS**

$$K = \frac{v_d}{E} = \frac{3}{16}\frac{q}{N}\left(\frac{1}{m} + \frac{1}{M}\right)^{\frac{1}{2}}\left(\frac{2\pi}{k_B T}\right)^{\frac{1}{2}}\frac{1}{\Omega}$$

$$\left(\text{in the case } \frac{E}{N} \leq 2 \times 10^{-17} \ (\text{V} \cdot \text{cm}^2)\right)$$

K: measured mobility at 273.15 K, 101325 Pa (イオン移動度)
v_d : drift velocity (ドリフト速度)
E: electric field (電場)
q: charge of the analyze ion (分析対象イオンの価数)
N: density of the drift gas (ドリフトガスの密度)
m: mass of the analyte ion (分析対象イオンの質量)
M: mass of the drift gas (ドリフトガス分子の質量)
k_B : the Boltzmann constant (ボルツマン定数)
T: gas temperature (ガスの温度)
Ω : collision cross section (CCS) (衝突(散乱)断面積)

F. Lanucara *et al.*, *Nat. Chem.* **2014**, 6, 281.
C. S. Creaser *et al.*, *Analyst* **2004**, *129*, 984.
T. Sugai, *J. Mass Spectrom. Soc. Jpn.* **2010**, *58*, 47.

**As the recorded drift time of an ion can be easily converted to v_d,
we can calculate CCS using this apparatus!!**

DTIMS (3): Advantages and Disadvantages

- **advantages**

  - ○ **ability to determine CCS**: direct determination of CCS from Mason-Schamp eq.

  - ○ **high resolving power**: An ion with CCS of 100 $Å^2$ can theoretically be separated from an ion with ±1 $Å^2$ difference (= 1% uncertainty).
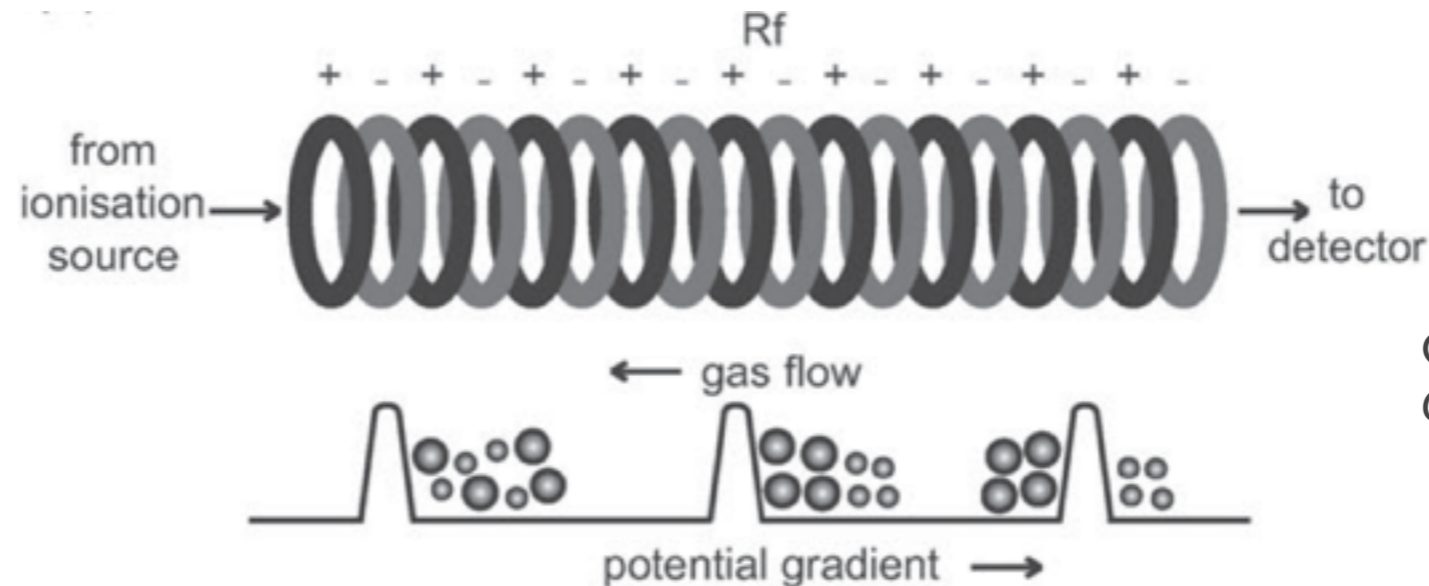
- **disadvantages**

  - ○ **low detection efficiency**: Ions are lost on several devices where entry or exit of ions into the drift cell occurs.

  - ○ **hugeness of apparatus**: Apparatus tend to become huge to provide high resolving power.

F. Lanucara *et al.*, *Nat. Chem.* **2014**, *6*, 281.

TWIMS (1): System Outline

- developed by Waters Corporation (S. Pringle *et al.*, *Int. J. Mass Spectrom.* **2007**, *261*, 1.)

C. Uetrecht *et al.*,
Chem. Soc. Rev. **2010**, *39*, 1633.

- ○ **used for CCS determination**: the condition $\dfrac{E}{N} \leq 2 \times 10^{-17} \ (V \cdot cm^2)$ is met.

- ○ Radio-frequency voltages (高周波電圧) of opposite phases are applied to adjacent electrodes and this voltages consist a sine curve potential barrier which confine the ions.

- ○ Direct current voltage (直流電圧) is applied to each electrode sequentially providing "**traveling waves**" and this "wave" propels ions from cell entrance to the exit.

- Higher mobility ions are carried by the wave, whereas lower mobility ions are trapped by the wave, thus taking longer to move through the drift cell.

TWIMS (2): Advantages and Disadvantages

- **advantages**

  ○ **high detection efficiency**: RF voltages confine ions and prevent their diffusion.

  ○ **ability to determine CCS**: Although drift time calibration with analytes of similar physical and chemical features with known CCS is needed, it is possible.

- **disadvantages**

  ○ **relatively low resolving power**: An ion with CCS of 900 $Å^2$ is theoretically separated from an ion with ±20 $Å^2$ difference at most.

  ○ **limitation of CCS determination**: When system is complex and calibration is difficult, CCS determination is no longer carried out.

F. Lanucara *et al.*, *Nat. Chem.* **2014**, 6, 281.

FAIMS (1): System Outline

- constructed of two electrodes, across which an electric field is established

gas flow →

from
ionisation →
source

to
detector

potential gradient ↕

V

+
0
-
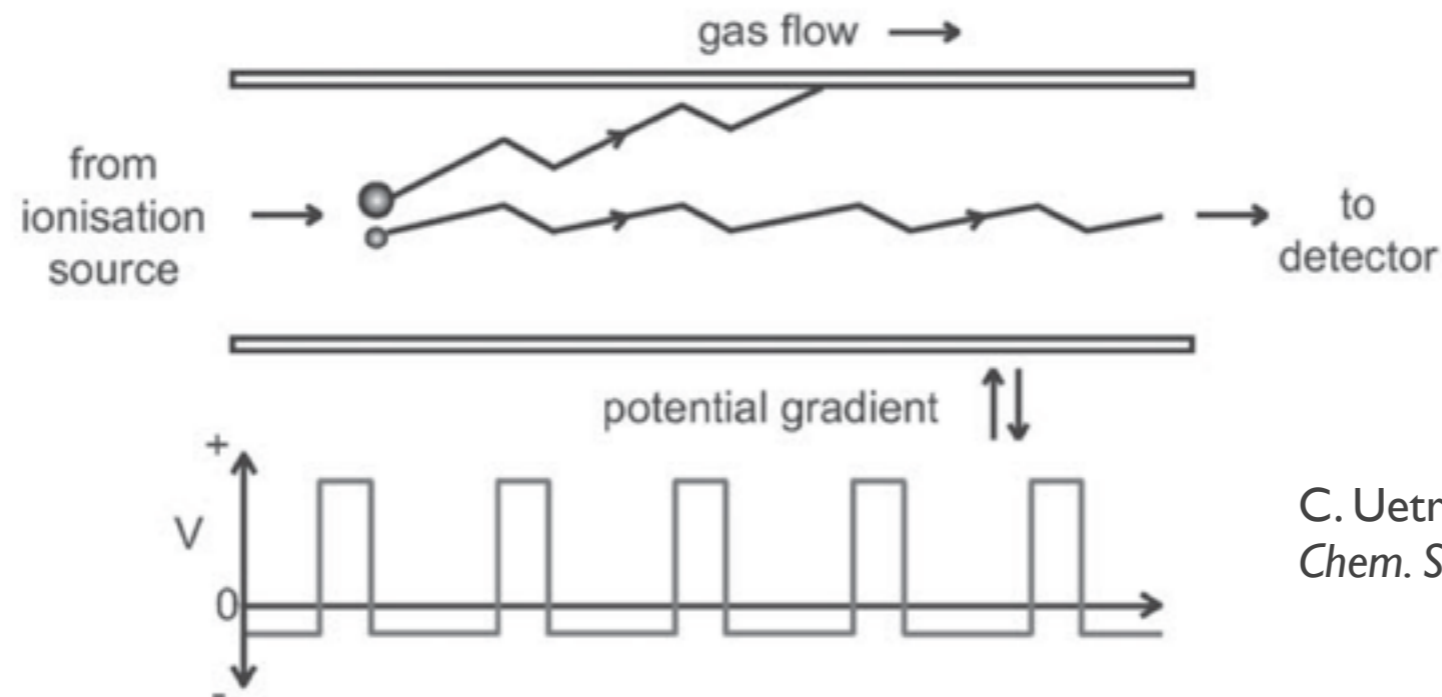
C. Uetrecht *et al.*,
Chem. Soc. Rev. **2010**, *39*, 1633.

○ As $\dfrac{E}{N}$ is greater than 2×10^{-17}, **determination of CCS is no longer possible**.

○ Alternating asymmetric waveform makes ions oscillating and moving toward one electrode.

○ To protect ions of interest from contact with electrode and following neutralization, **the compensation voltage** (補償電圧) is applied.

○ Thus, this apparatus operate as **a mobility filter** to achieve increased selectivity and peak capacity before MS analysis.

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FAIMS (2): Advantages and Disadvantages

- **advantages**

  - **orthogonality toward MS**: As there's no correlation with CCS, FAIMS can be a great filter of undesired ions.

  - **High resolving power** can be achieved by appropriate selection of buffer gas.

- **disadvantages**

  - **CCS can't be determined.**

  - **limitation of application**: limited only to post-ionization separation so far

F. Lanucara *et al.*, *Nat. Chem.* **2014**, *6*, 281.

Short Summary

a DTIMS

b TWIMS

c FAIMS
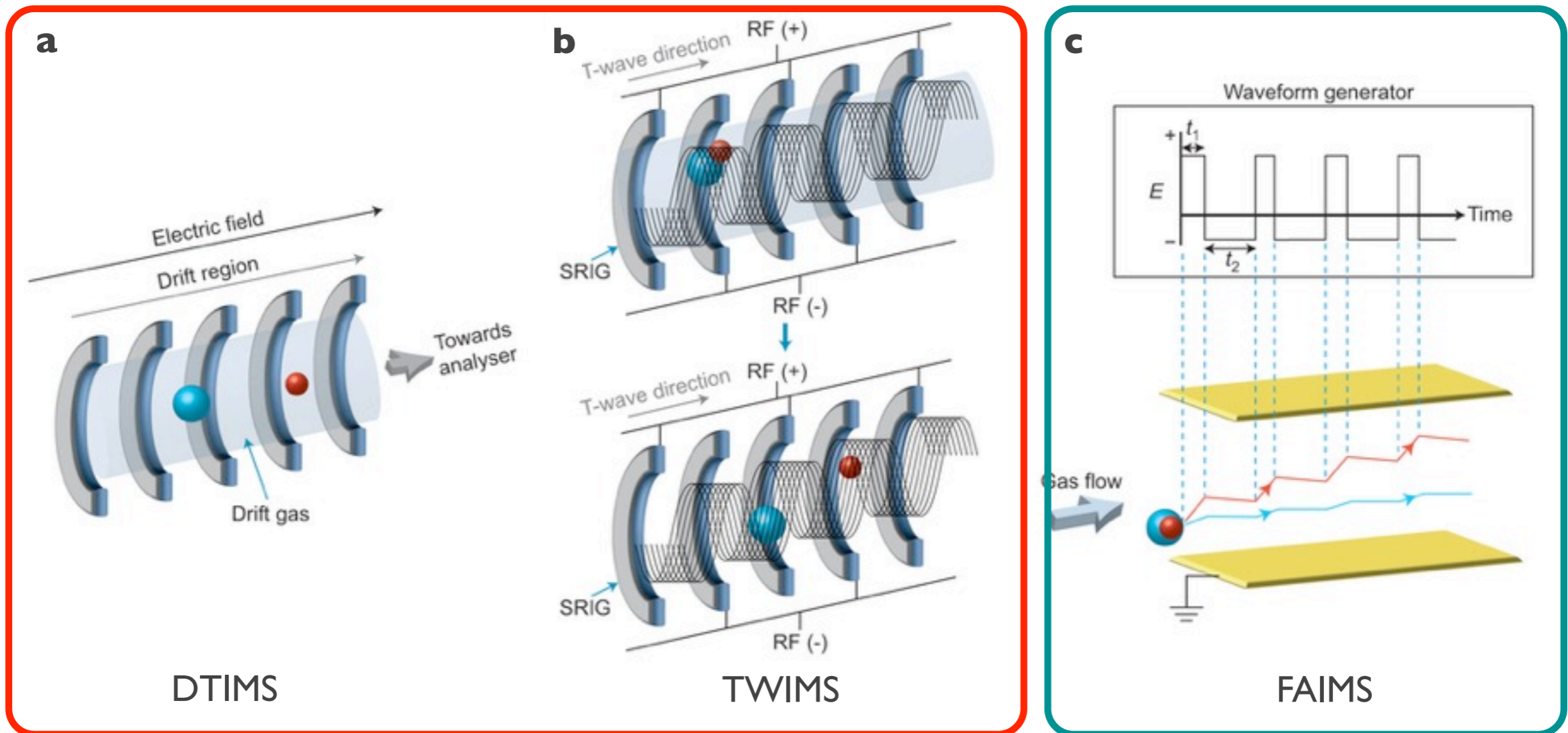
Structural Analysis

Post-Ionization Separation

F. Lanucara *et al.*, *Nat. Chem.* **2014**, 6, 281.

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Current Problem in Aβ Study

1. Ghosh *et al.*, *ChemMedChem* **2007**, *2*, 1674.

major toxic species
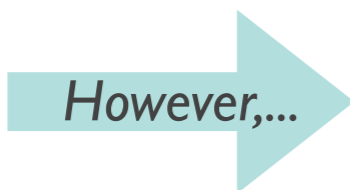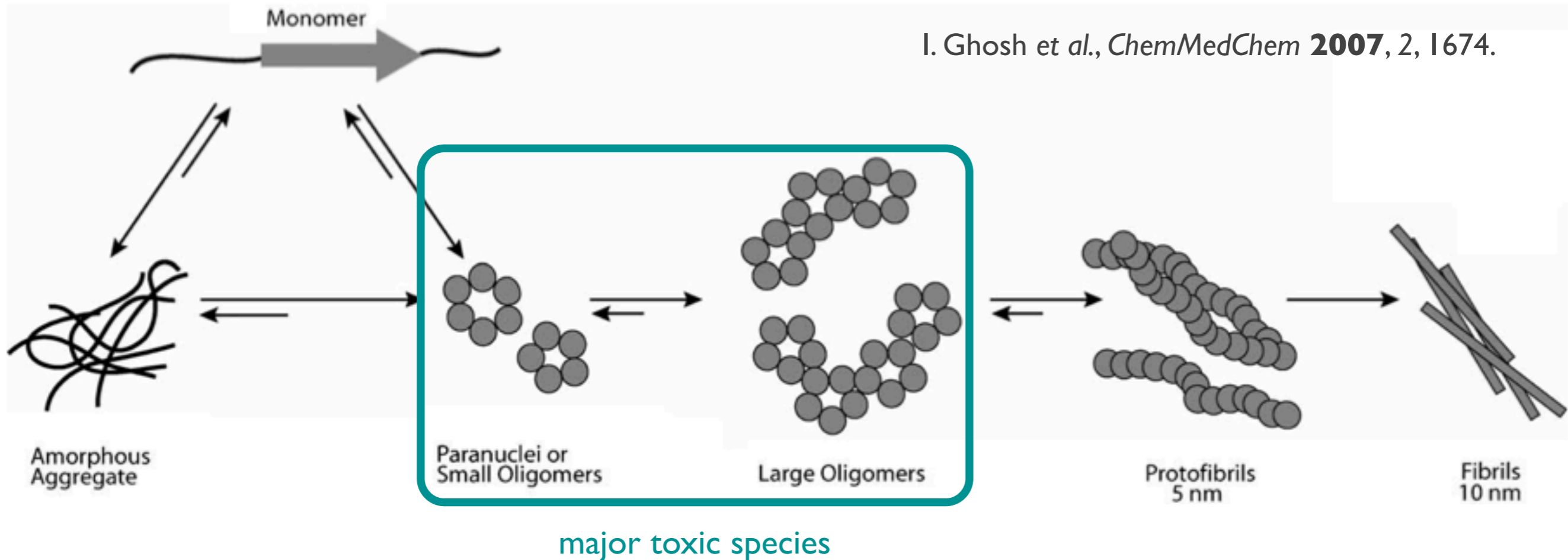
However,... → **oligomer structure hasn't been studied sufficiently.**

∵ Aβ changes its structure dynamically, so that well-established structural study (e.g. NMR or X-ray crystal analysis) which needs pure oligomer can't be conducted smoothly.

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Advantages and Disadvantages of IM-MS Application

- **advantages**

  ○ **quite small sample requirement**: In contrast to NMR or X-ray analysis which require milligrams of sample, IM-MS requires micrograms sample at most.

  ○ **ability to detect intermediates**: Very short analysis time (millisecond time scale) enables the detection of short-living species (e.g. oligomers).

  ○ **no purification requirement**: In contrast to NMR or X-ray, crude sample can be used.

  ○ **ability to determine stoichiometry of complex**: Stoichiometry of complex such as Aβ oligomer and Aβ-inhibitor complex can be determined.

- **disadvantages**

  ○ **requirement of MD simulation for precise structural information**: To obtain detailed structural information such as secondary structure or atomic level information, time-consuming and often challenging MD simulation is necessary.

  ○ **low resolution power**: Compared to NMR or X-ray which give structural information at atomic level, 1% uncertainty in CCS is too big.

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Bowers' Home-Made IM-MS

- Prof. Michael T. Bowers

1962: obtained his B. S. from the Gonzaga University

1966: obtained his Ph. D. from the University of Illinois

1968: joined the University of California Santa Barbara faculty

- classified to **DTIMS** → **Direct estimation of CCS is possible!**
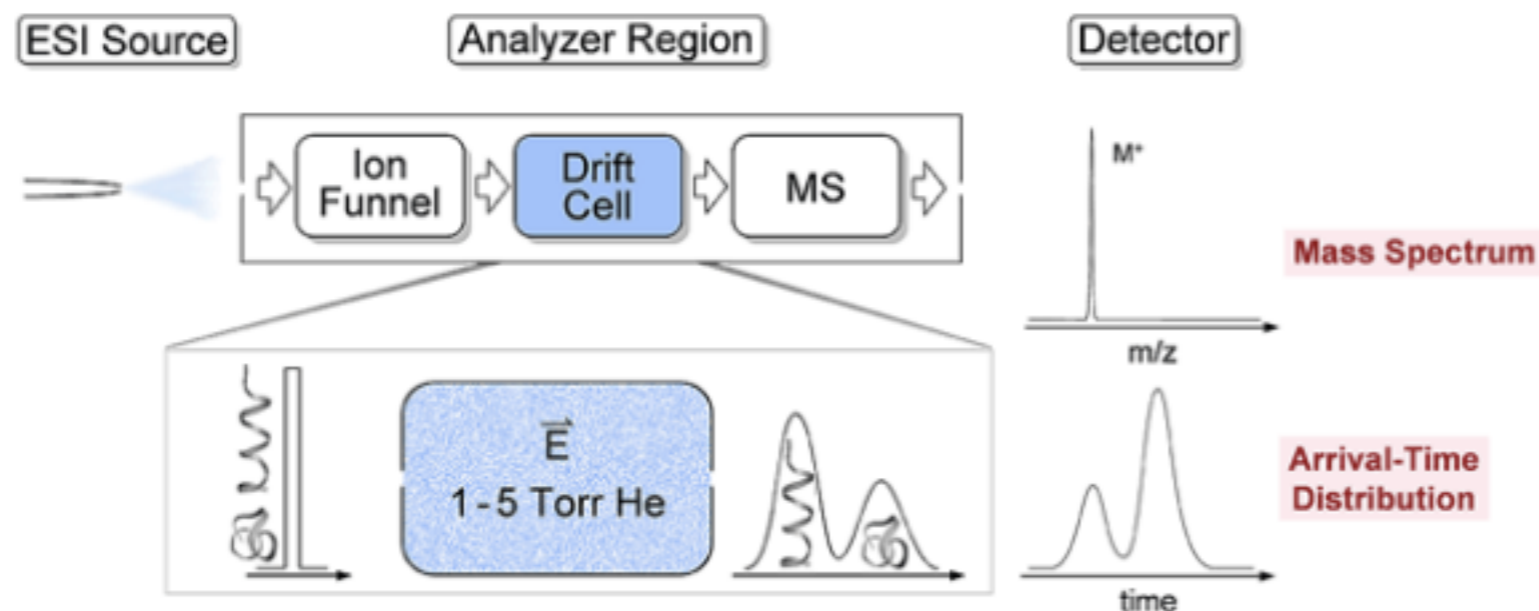
This figure is cited from Bowers group web page and is modified. (http://bowers.chem.ucsb.edu/theory_analysis/ion-mobility/index.shtml)

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Mass Spectrum of [Pro¹⁹]Aβ42

- [Pro¹⁹]Aβ42 (blue: negative charged side chain, orange: positive charged side chain)

  DAEFR HDSGY EVHHQ KLVPF AEDVG SNKGA IIGLM VGGVV IA

- **¹³C isotope distributions** is also shown: show the dominant species of the peak of interest.

  ○ "z/n=−3": Peaks are separated by 0.33 (1÷3) amu.
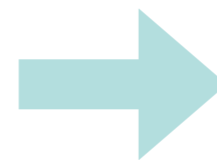
  monomer-dominated

  $$\left(\begin{array}{l} \text{In the dimer-dominated case,} \\ \text{peak will be separated by} \\ 1÷6 = 0.17 \text{ amu.} \end{array} \right)$$

  ○ "z/n=−2": Peak separation is ambiguous...

$$\left(\begin{array}{l} \text{■} = z/n \ (z = \text{charge}, n = \text{oligomer order}) \\ \text{Ex.}) \ z/n = −2 = −2/1, −4/2, −6/3, \ldots \end{array} \right)$$

several species in one peak

S. Bernstein, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 2075.

Collision-Induced Dissociation (CID)

- The "z/n=−2" charge state peak was selected by the quadrupole and subjected to CID.

0.5 amu

S. Bernstein, M. Bowers *et al.*,
J. Am. Chem. Soc. **2005**, *127*, 2075.

CID
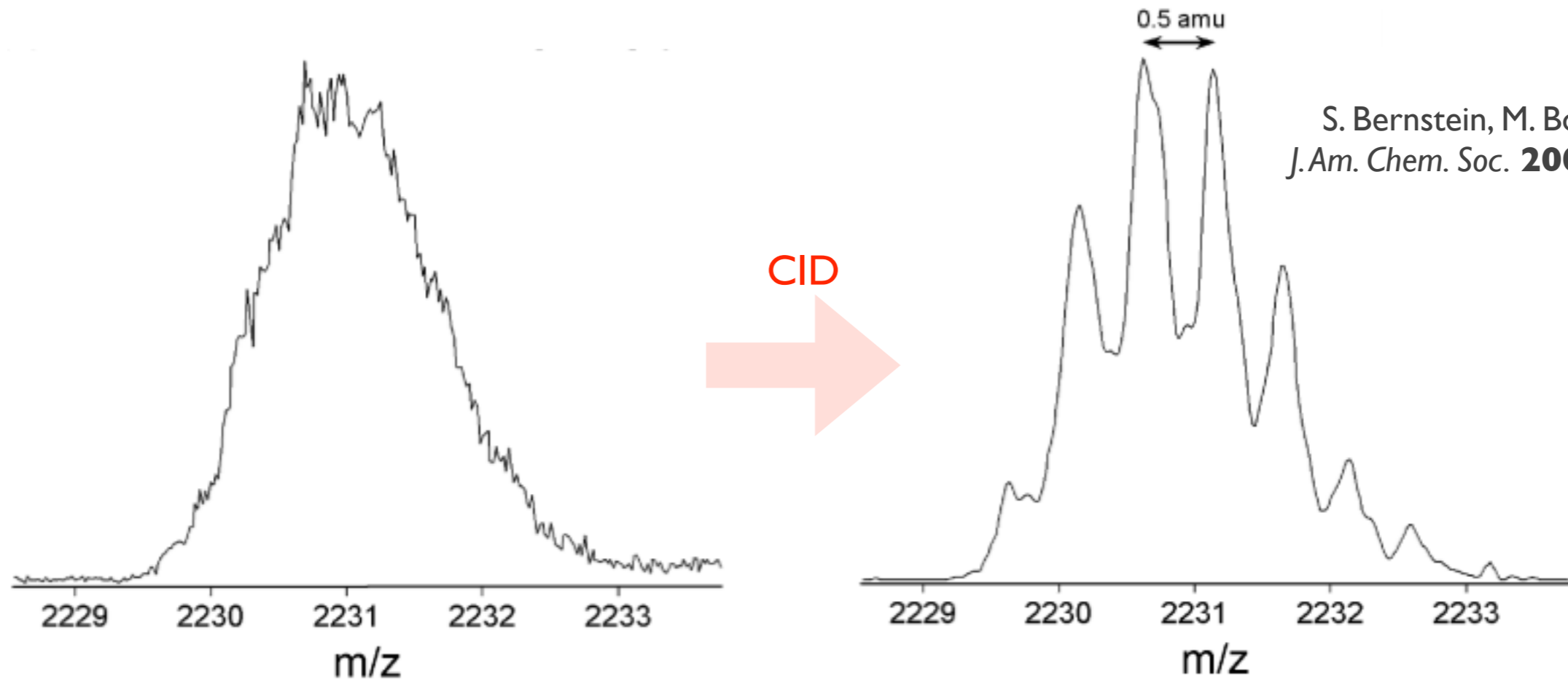
○ Peaks are separated by 0.5 (= 1/2) amu → indicating the monomer generation

○ Small peaks are observed at 0.25 (1÷4) amu, indicating some undissociated dimer remains.

- In summary, **components larger than dimer** construct the "z/n=−2" charge state.

Arrival Time Distributions (ATD)

- In ATD, different compounds which have the same charge state (z/n) can be distinguished.

  ○ Ion mobility can separate ions by their size and shape.

  ○ In "z/n=$-q$" peak of mass spectrum, the following species can be present:
    Monomer^{-q}, Dimer^{-2q}, Trimer^{-3q}, ...

  ○ These species are different in size, so they can be separated using IM.

ATD shows how species with different size and shape are separated.

Assignment of Peaks in ATD (1)

- ATD of "z/n=−3" charge state (injection energy = 40 mV)

  ○ From ^{13}C isotope distributions, this is a monomer-dominant peak.
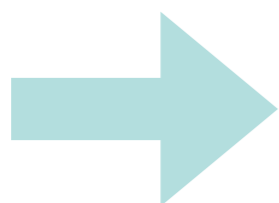
  ➤ These two peaks should be predominantly **monomer**!

m/z 1487 (−3)

drift time (μs)

<caution>
Strictly speaking, to confirm these two peaks are monomer, we need to **calculate the CCS** *from drift times* and *compare them with* **the theoretical CCS** *obtained from modeling* (data not shown).
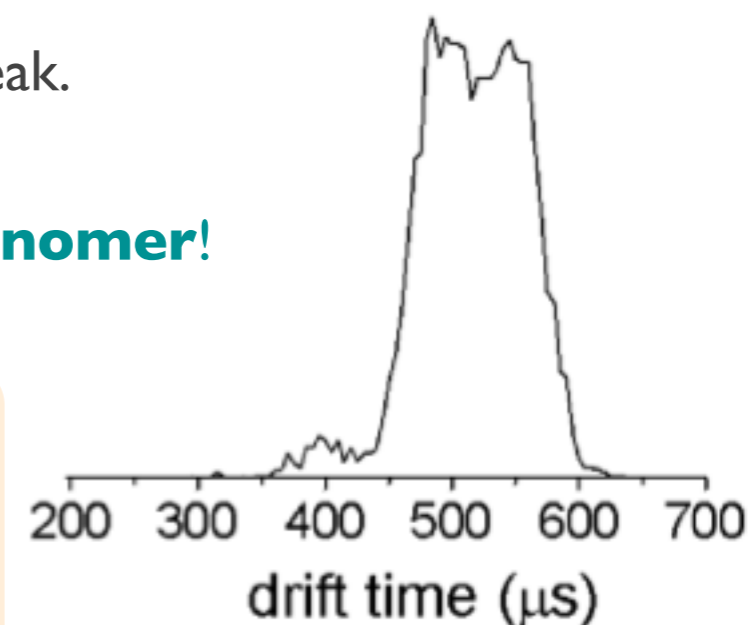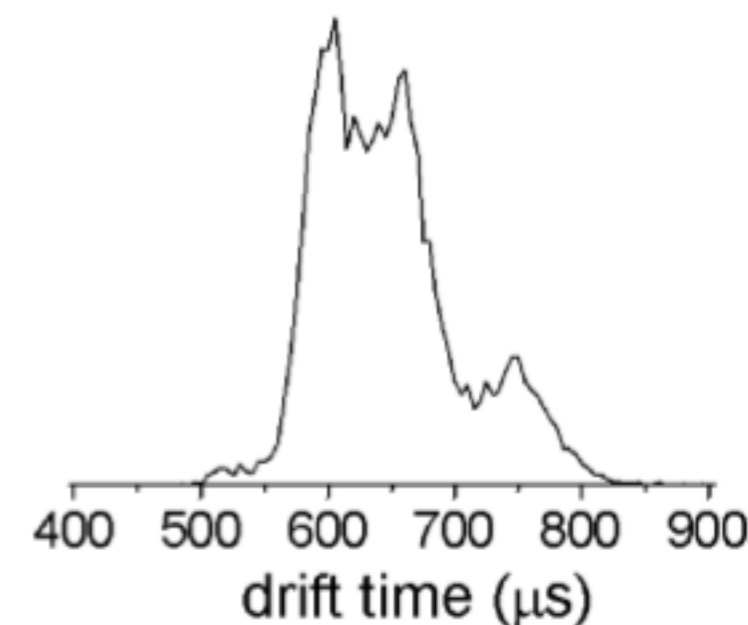
- ATD of "z/n=−2" charge state (injection energy = 40 mV)

  ○ From ^{13}C isotope distributions, this is a mixture of oligomers and in fact, ATDs shows several peaks.

m/z 2231 (−2)

drift time (μs)

S. Bernstein, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 2075.

Assignment of Peaks in ATD (2)

- injection energy dependence of the "z/n=−2" charge state

  ○ As the injection energy increases, the peak at 740 μs becomes dominant and **no additional peaks were observed at longer drift times**.

  ○ Injection with high energy gives the ion higher energy, thus dissociation or conformation change occurs.
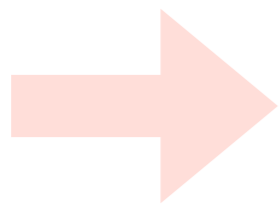
  ➡ 740 μs peak would be the **monomer**.

  ○ Other peaks are assigned as dimer, trimer and tetramer.

  ⎛ This assignment is reasonable because CID-conducted
  ^{13}C isotope distributions shows the existence of dimer.
  Also, native ^{13}C isotope distribution clearly shows the
  ⎝ existence of larger oligomer than dimer.

S. Bernstein, M. Bowers *et al.*,
J. Am. Chem. Soc. **2005**, *127*, 2075.

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(a) 30 eV

(b) 60 eV   Tr   D

Te   M

(c) 140 eV

400   500   600   700   800   900

drift time (μs)

Assignment of Peaks in ATD (3)

- ATD of "z/n=−5/2" charge state (injection energy = 40 mV)

m/z 1785 (-5/2)
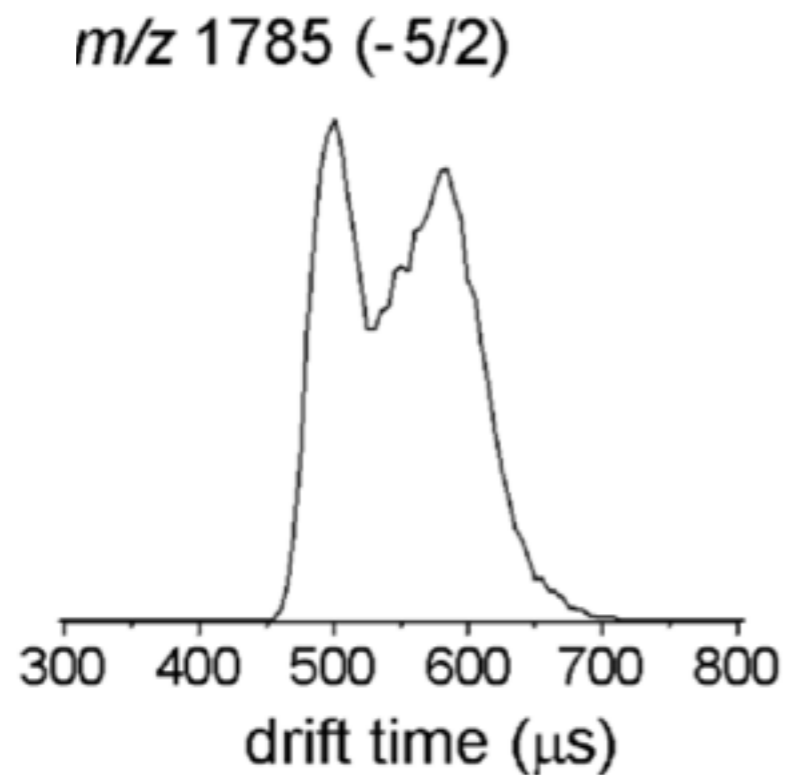
drift time (μs)

S. Bernstein, M. Bowers *et al.*,
J. Am. Chem. Soc. **2005**, *127*, 2075.

- injection energy dependence

(a) 23 eV Te
(b) 50 eV D Te
(c) 100 eV D
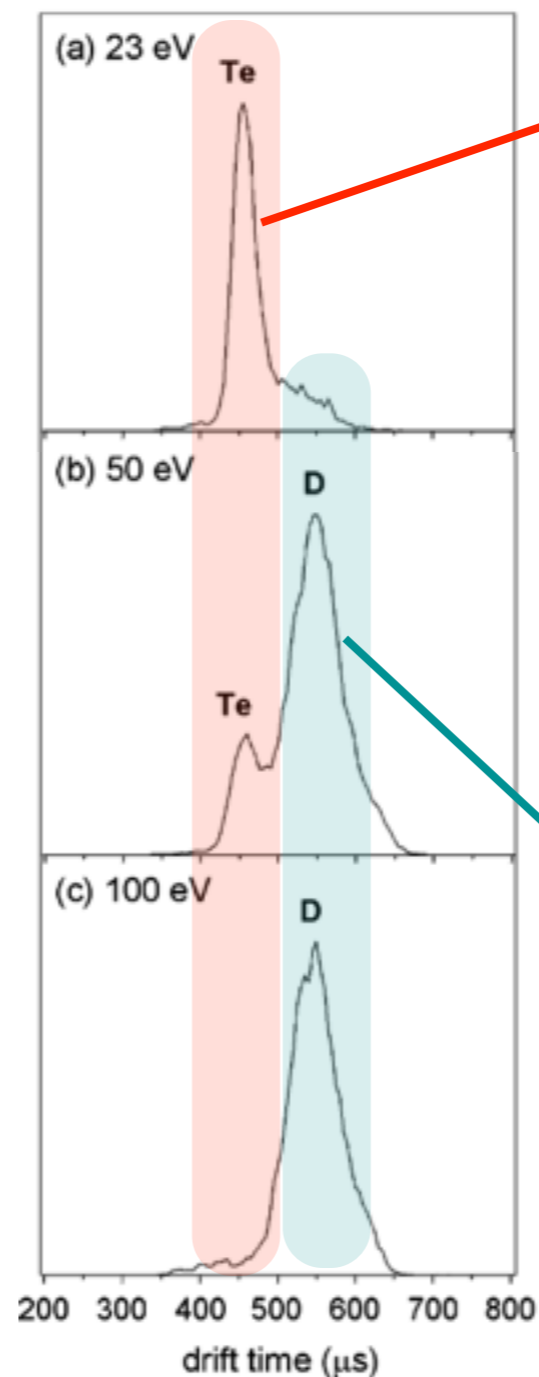
drift time (μs)

- ○ Trimers can't be involved.
- ○ bigger than dimer
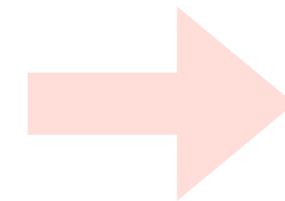
tetramer

- ○ Monomers can't be involved.
- ○ No peak with longer drift time was observed.
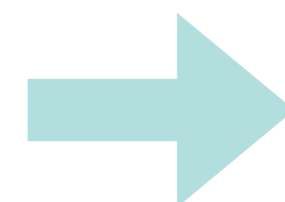
dimer

Short Summary

- flow chart of IM-MS analysis

1) analyze the **MS chart**
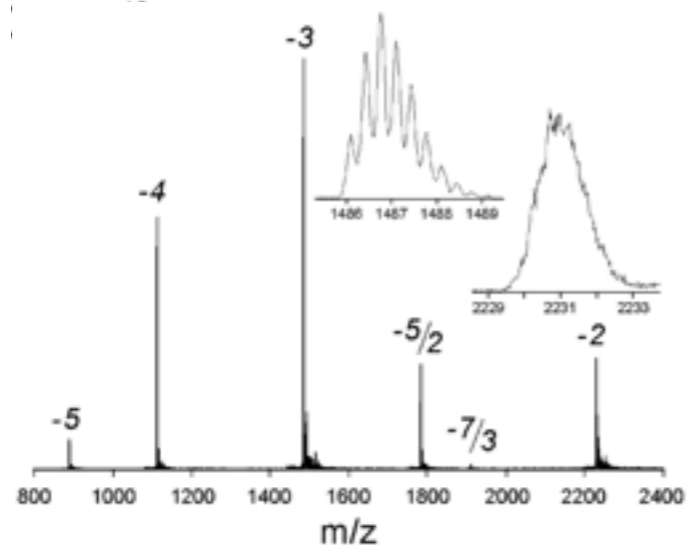
2) analyze the **ATD** of z/n
which you are interested in

m/z 1785 (−5/2)
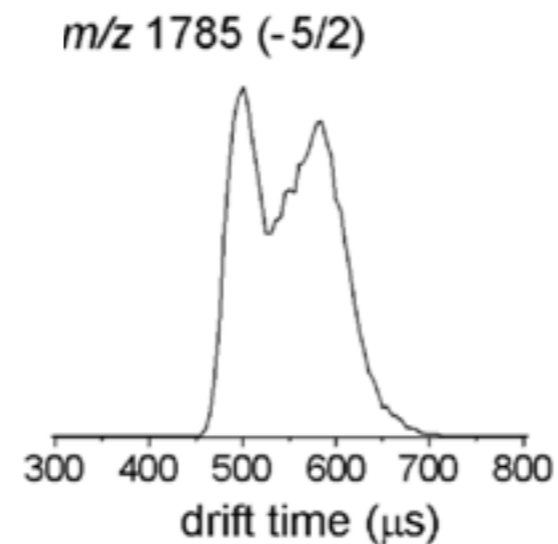
→ ***Structural Information***

- ○ ^{13}C isotope distributions
- ○ Collision-Induced Dissociation

- ○ injection energy dependence
- ○ **CCS calculation** and **comparison of it with theoretical CCS** obtained from modeling.

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Subject of this Section

Amyloid-β protein oligomerization and the importance of tetramers and dodecamers in the aetiology of Alzheimer's disease

Summer L. Bernstein[1], Nicholas F. Dupuis[1], Noel D. Lazo[2], Thomas Wyttenbach[1], Margaret M. Condron[3], Gal Bitan[3], David B. Teplow[3,4], Joan-Emma Shea[1], Brandon T. Ruotolo[5], Carol V. Robinson[5] and Michael T. Bowers[1]*

IM-MS Analysis of Aβ40

- mass spectrum and ATDs (z/n = −5/2)
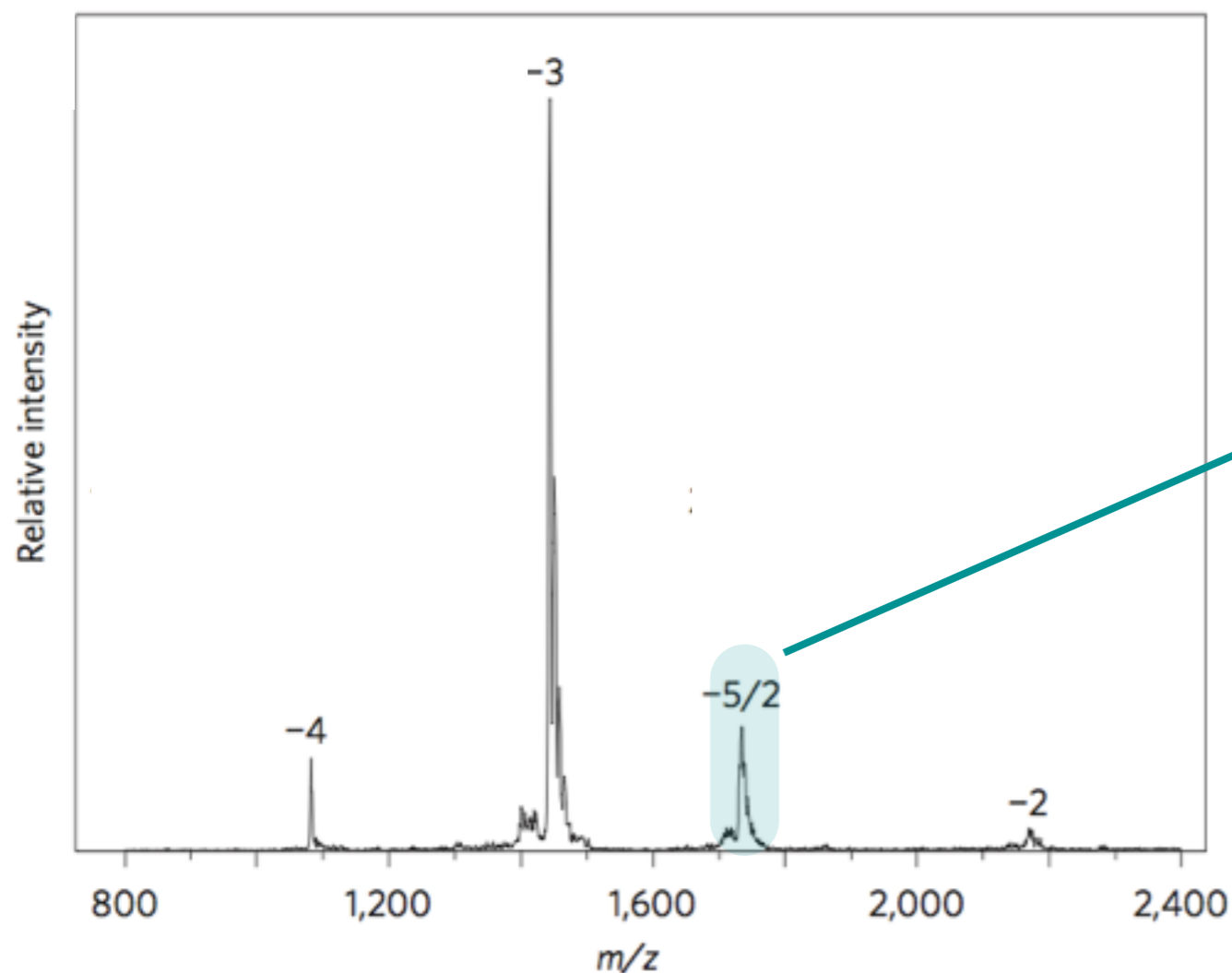
S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.
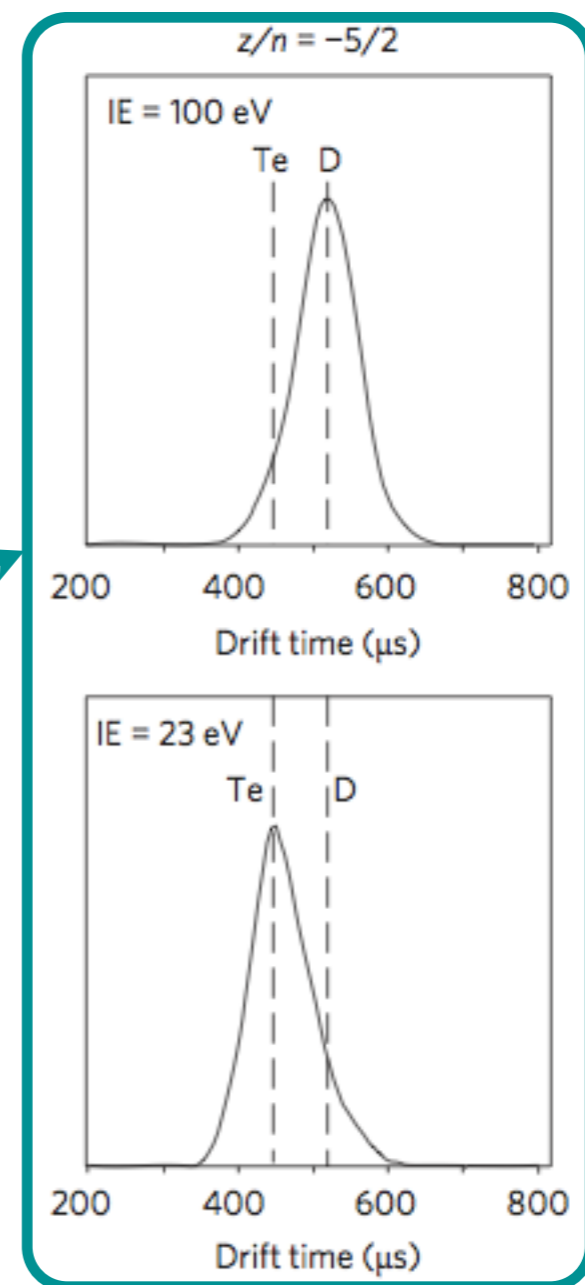
○ As shown here, in "z/n=−5/2" charge state, tetramer and dimer was observed.

IM-MS Analysis of Aβ42

- mass spectrum and ATDs (z/n = −5/2)
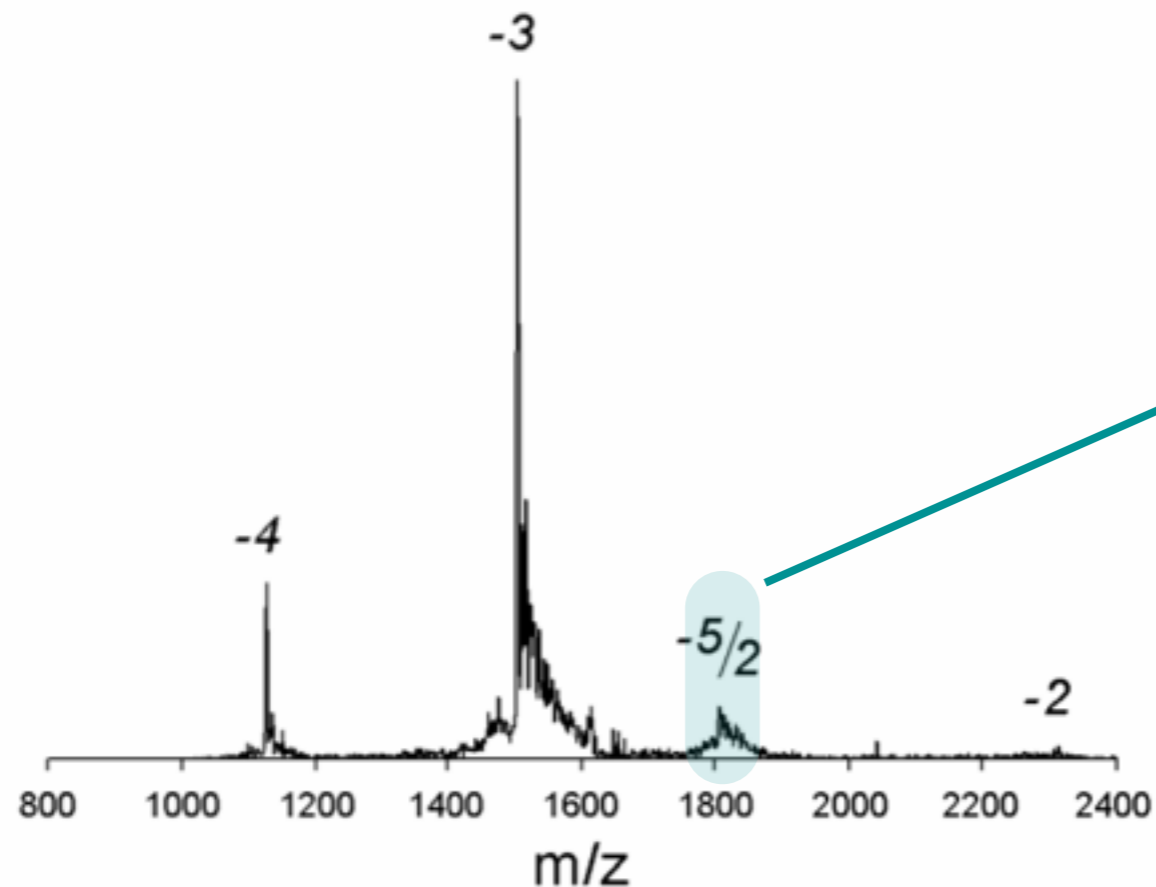
○ As shown here, in "z/n=−5/2" charge state, dimer, tetramer, hexamer, and dodecamer (12-mer) was observed.
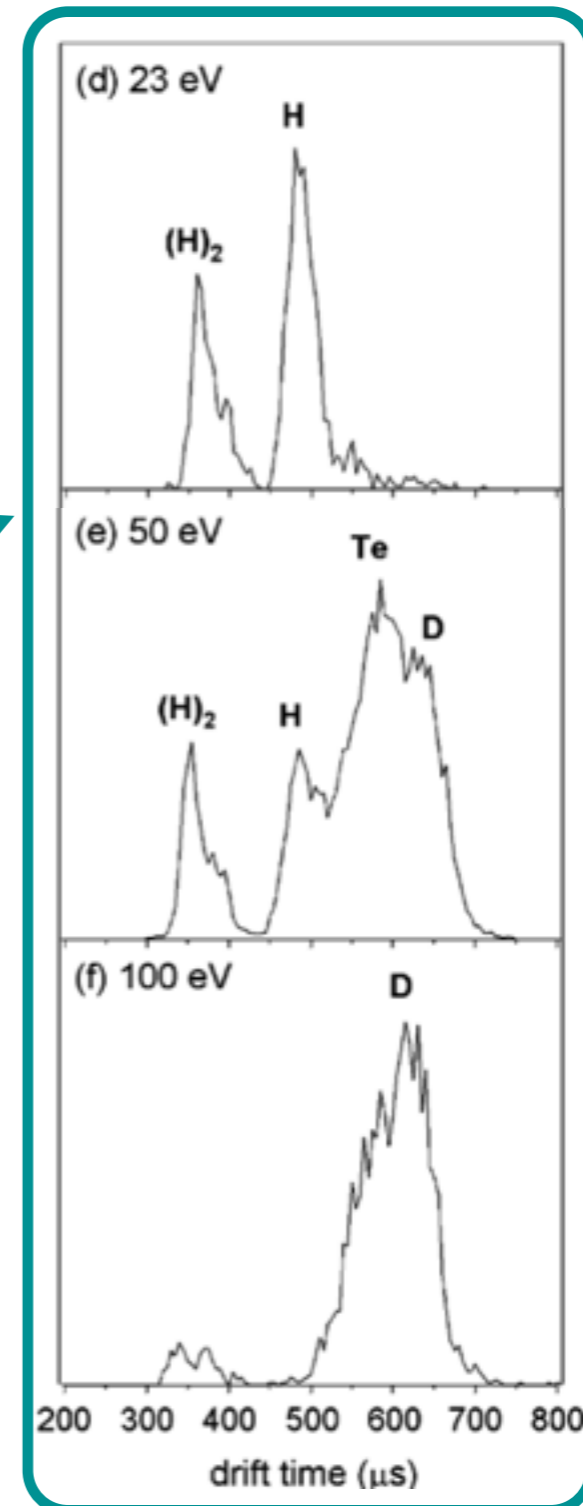
CCS Estimation of Aβ42 Oligomer (1)

- Theoretical CCS for Aβ dimers were obtained as follows.

    <assumption> Aβ monomer has a **spherical shape** (especially hard sphere)

    Based on this, **theoretical CCS for the dimers were calculated**
    with the center-center distance of the two monomers as a variable parameter.
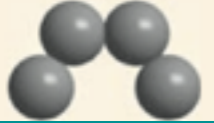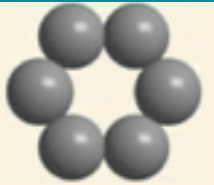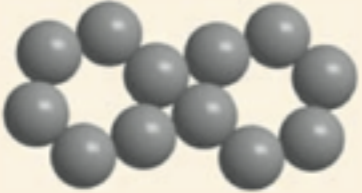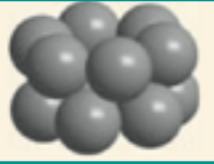
    <calibration> Center-center distance was adjusted to give the experimental dimer CCS.

    CCS of tetramer, hexamer, and dodecamer were calculated based on
    the theoretical dimer (**double hard sphere approximated dimer**).

S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

CCS Estimation of Aβ42 Oligomer (2)

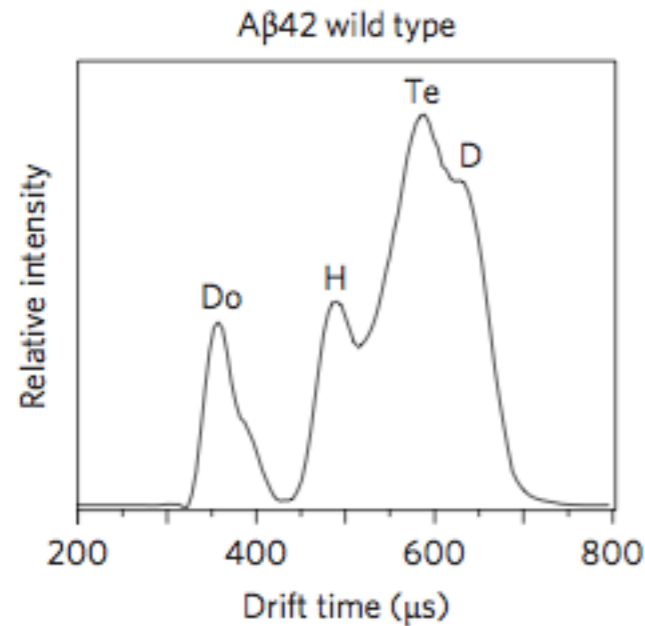- theoretical CCS and experimentally observed CCS for Aβ42 oligomers

← Theoretical CCS was adjusted to observed CCS.

Model structure which had the **most close CCS value to experiment CCS** was successfully obtained.

S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

Comparison between Aβ42 and Aβ40 (1)

- ATDs of Aβ42 and Aβ40 for "z/n = −5/2" charge state

Aβ42 wild type

Aβ40 wild type
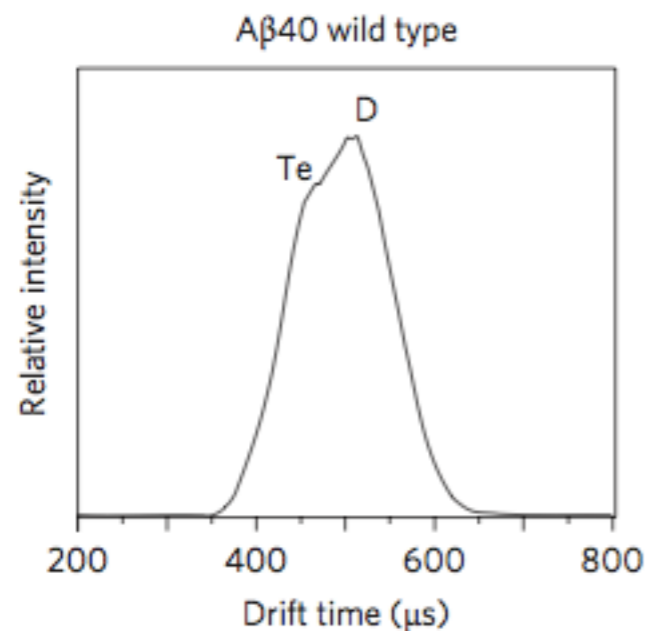
○ In the case of Aβ42, oligomers bigger than tetramer were observed.

○ In contrast, in the case of Aβ40, oligomers bigger than tetramer were not observed at all.

Tetramers can represent the difference between Aβ40 and Aβ42?

S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

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Comparison between Aβ42 and Aβ40 (2)

- comparison of tetramer conformation between Aβ42 and Aβ40
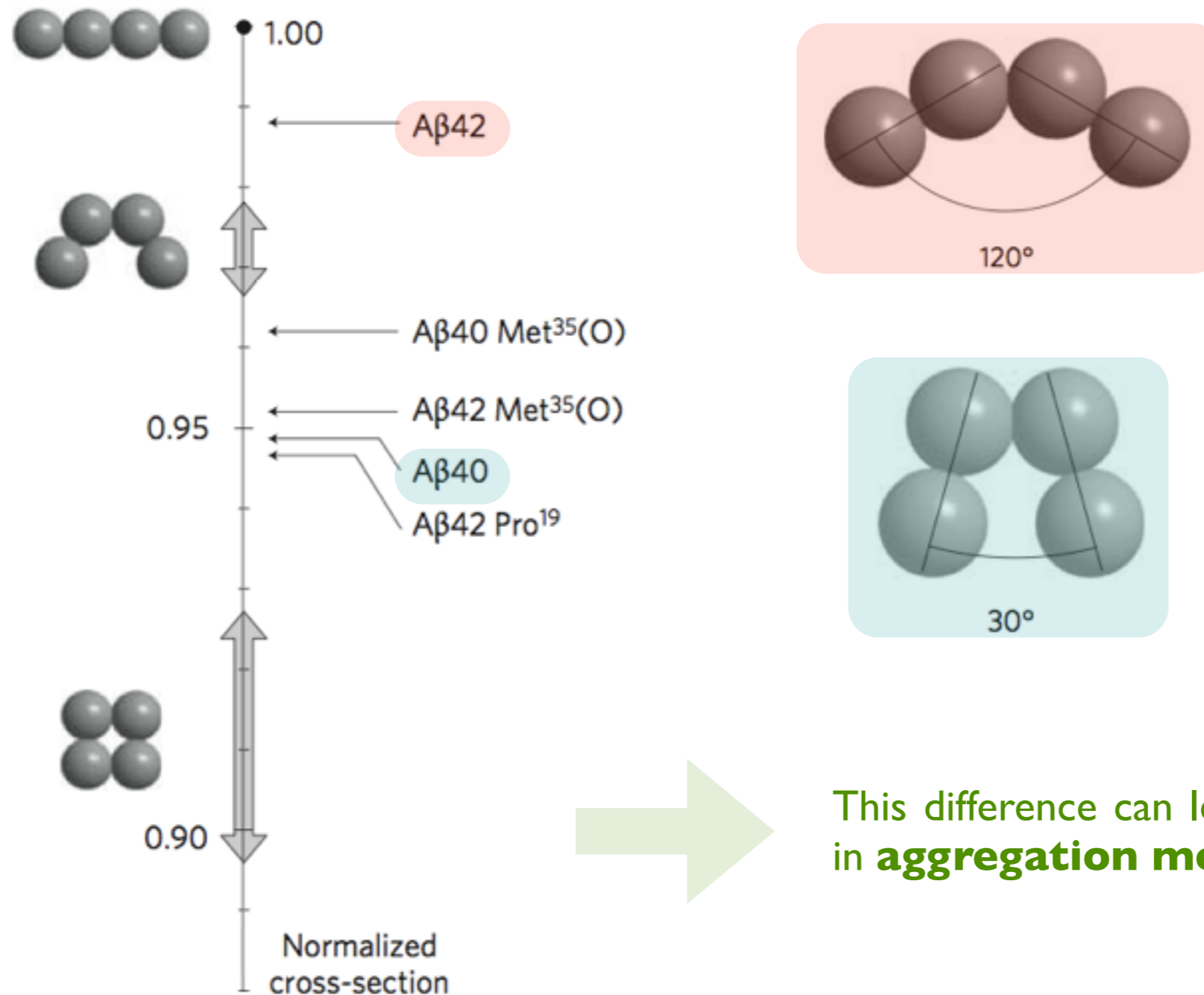
This difference can lead to the difference in **aggregation mechanism**.

S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

Comparison between Aβ42 and Aβ40 (2)

● comparison of aggregation mechanism between Aβ42 and Aβ40
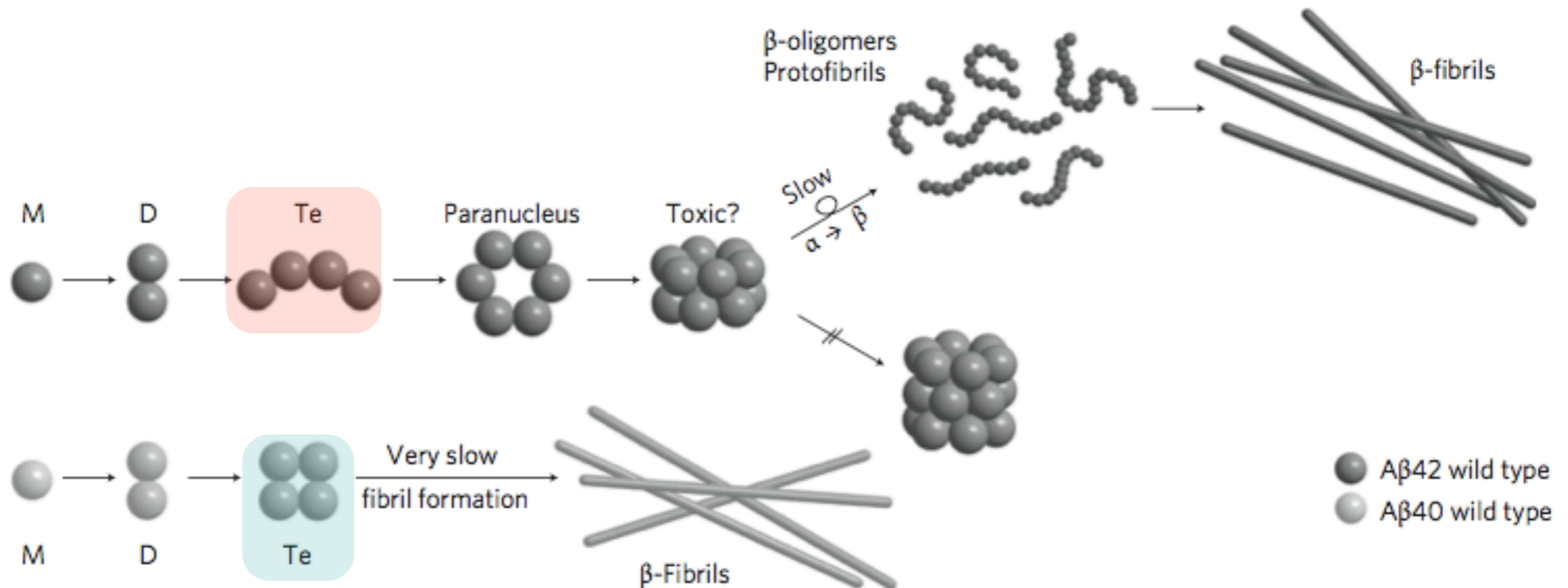
○ Aβ42 tetramer has a room of addition of another dimer to form hexamer or dodecamer. In contrast, Aβ40 tetramer doesn't have a room of addition and doesn't form hexamer.
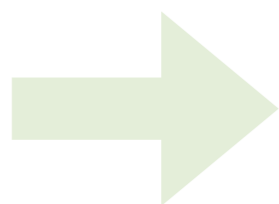
IM-MS could show the difference of aggregation mechanism between Aβ42 and Aβ40!

S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

Short Summary

- Application of IM-MS achieves the mechanistic study of Aβ42 and Aβ40 aggregation based on the difference of tetramer conformation.
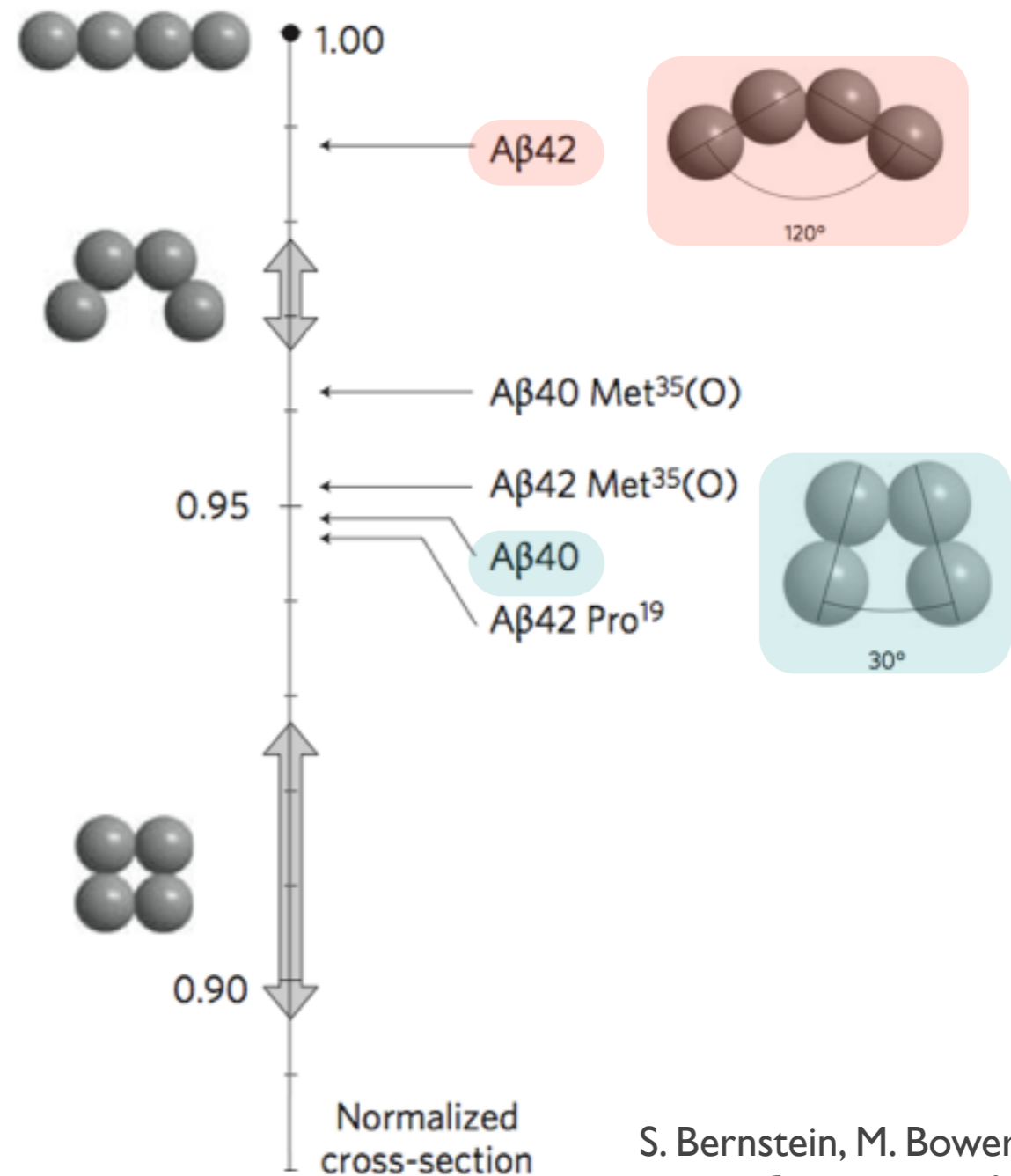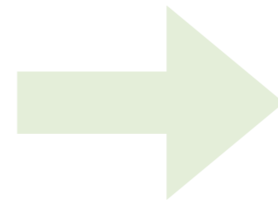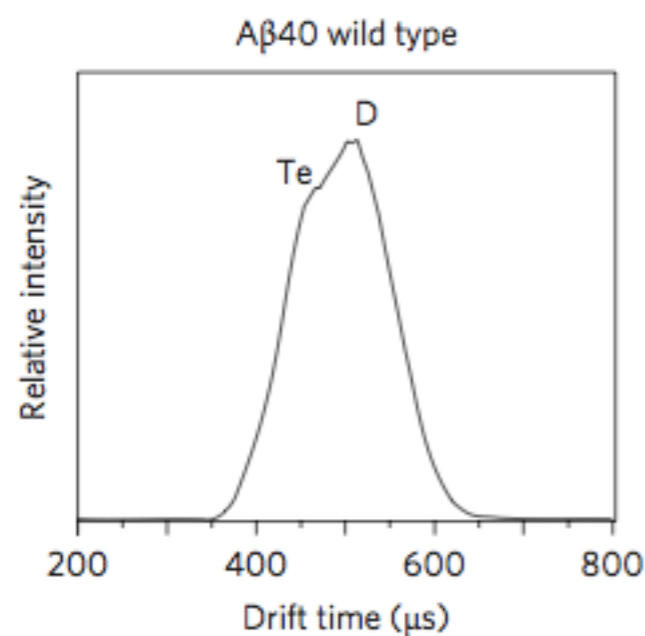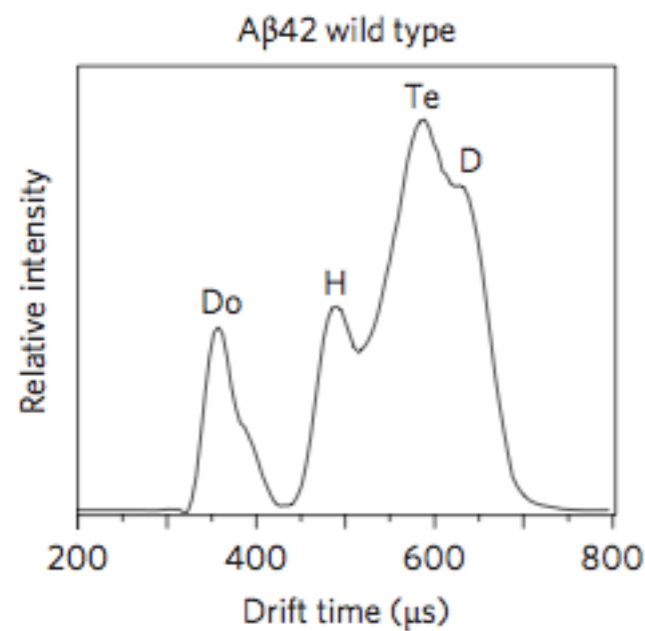
S. Bernstein, M. Bowers *et al.*, *Nat. Chem.* **2009**, *1*, 326.

Table of Contents

Subject of this Section

JACS
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Article

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Ion Mobility Spectrometry Reveals the Mechanism of Amyloid Formation of Aβ(25−35) and Its Modulation by Inhibitors at the Molecular Level: Epigallocatechin Gallate and *Scyllo*-inositol
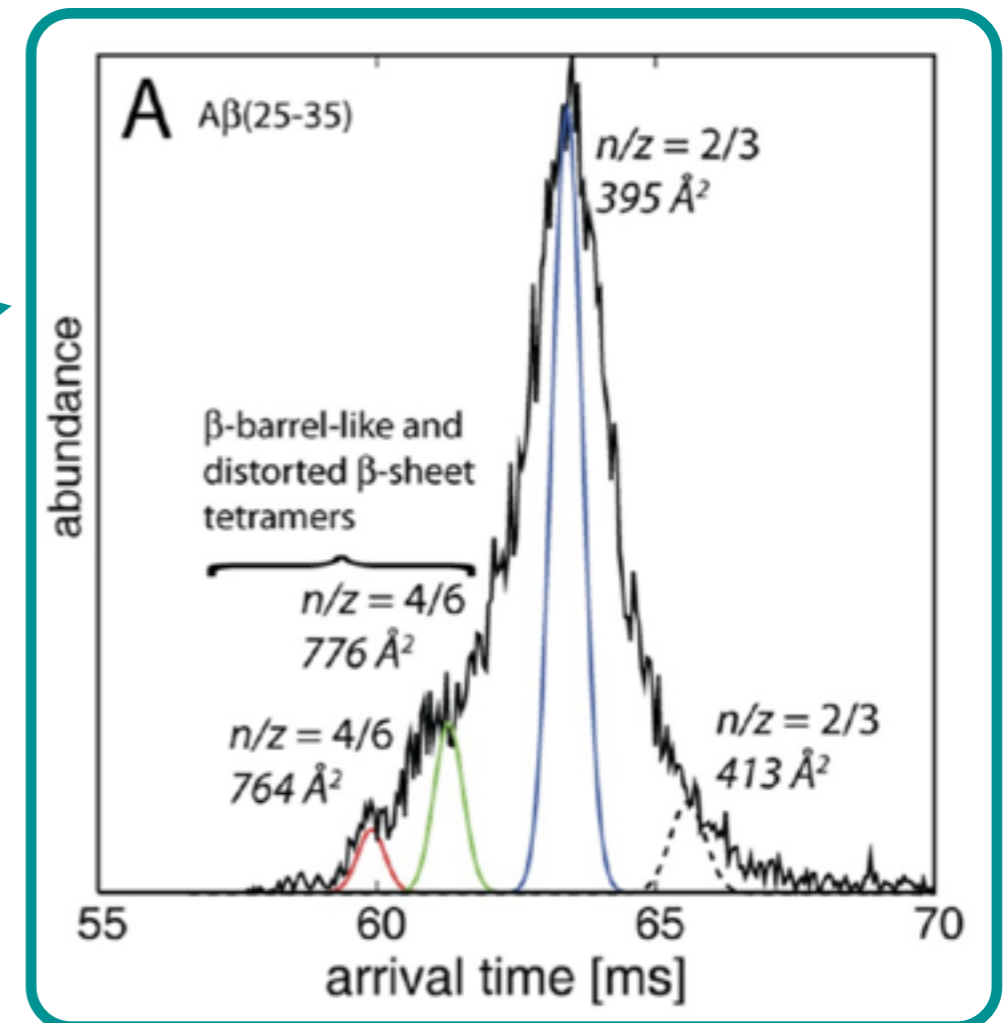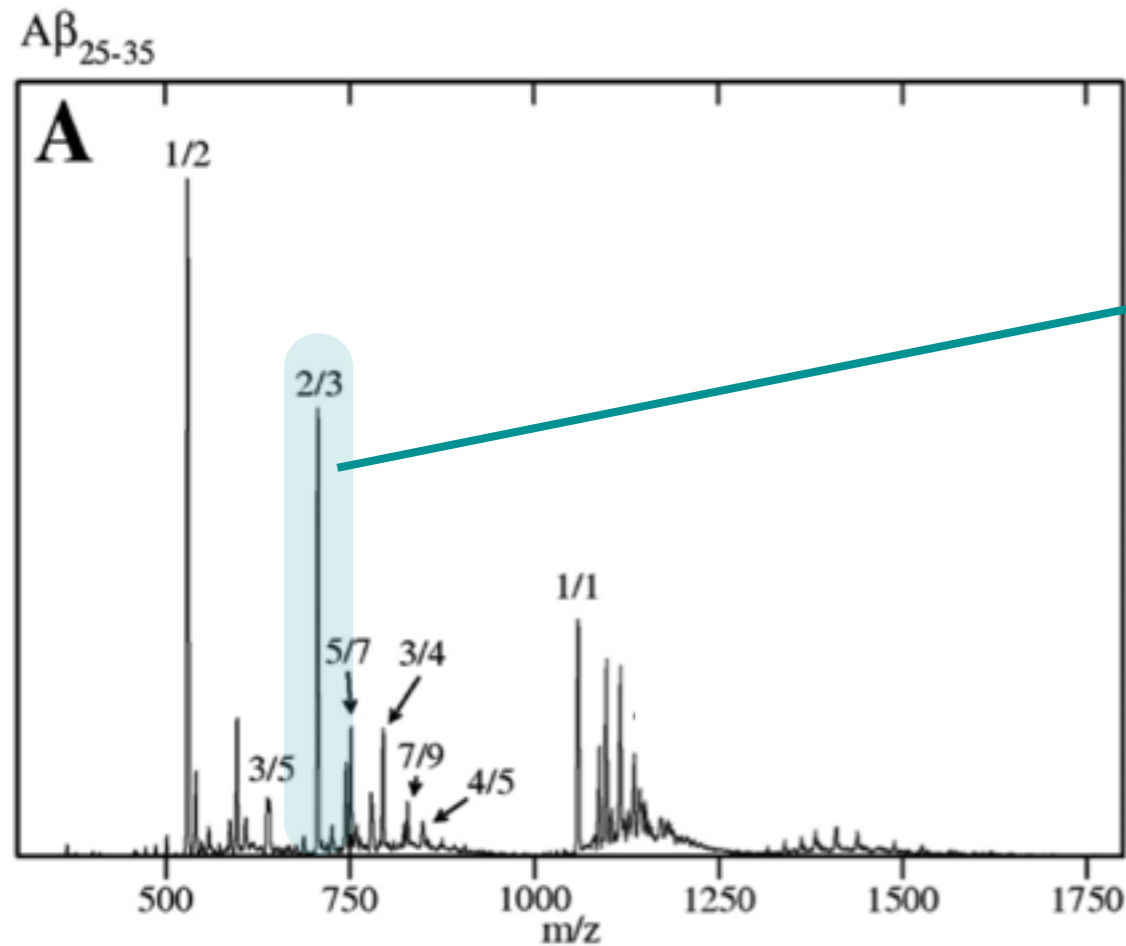
Christian Bleiholder,[†] Thanh D. Do,[†] Chun Wu, Nicholas J. Economou, Summer S. Bernstein, Steven K. Buratto, Joan-Emma Shea, and Michael T. Bowers*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106-9510, United States

IM-MS Analysis of Aβ(25-35)
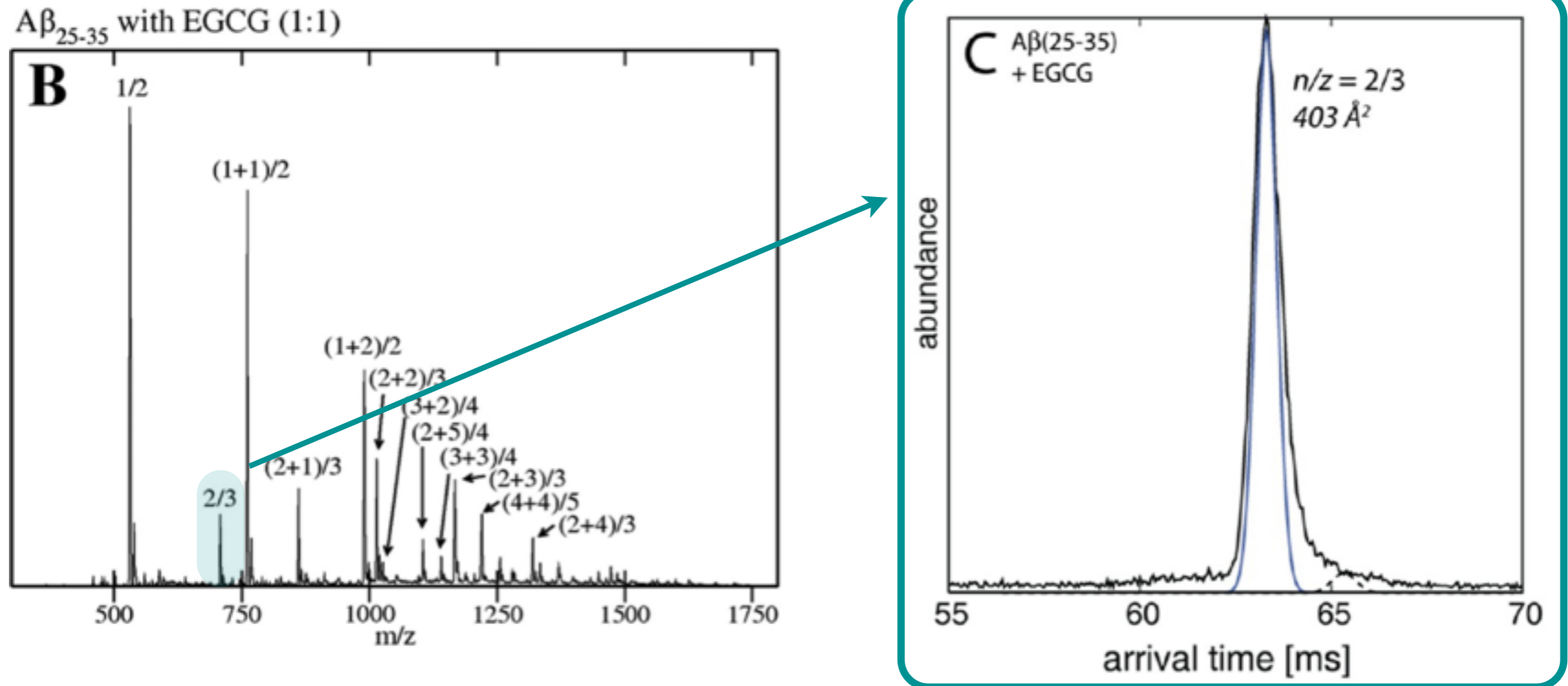
- mass spectrum and ATD for m/z = 707 (n/z = 2/3)

○ Dimers and tetramers were observed.

C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.
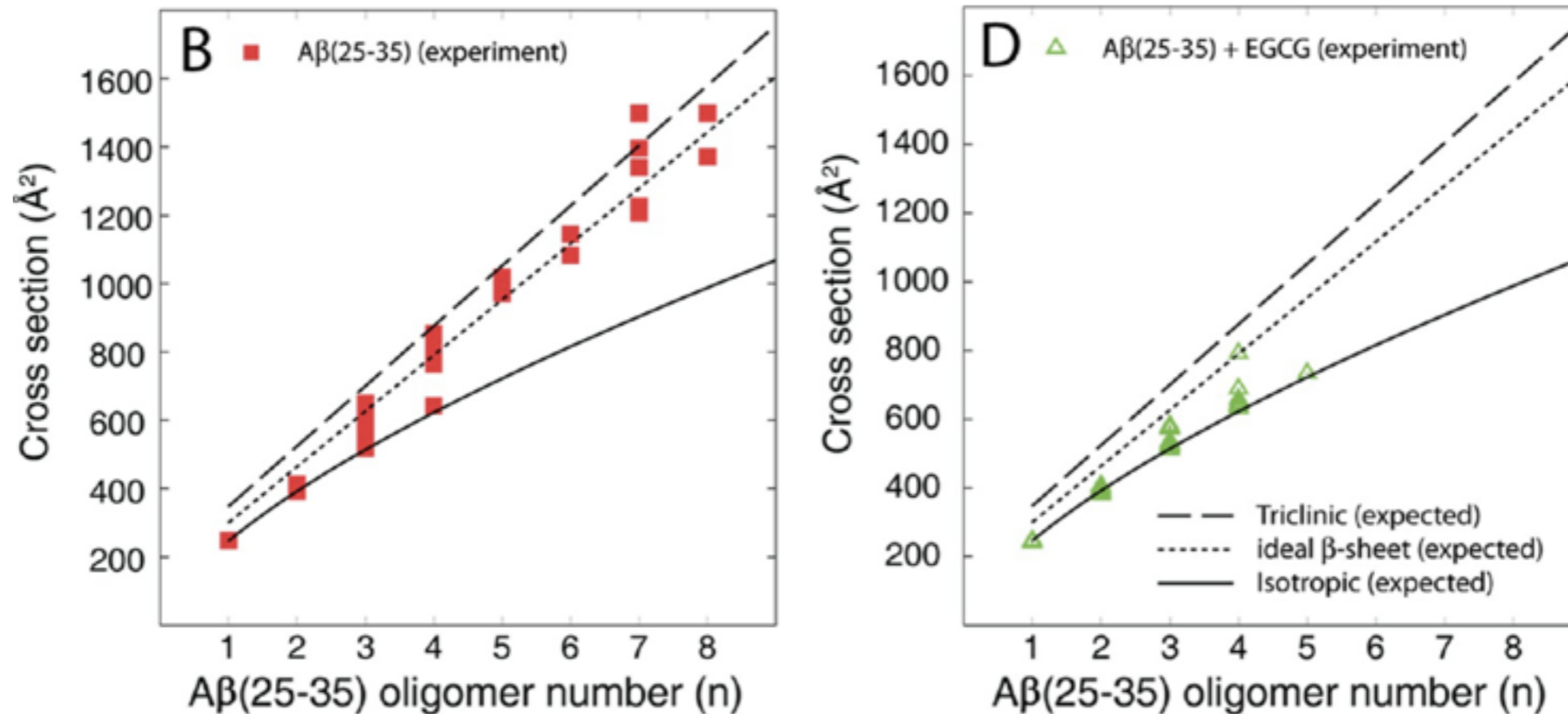
IM-MS Analysis of Aβ(25-35) with EGCG

- mass spectrum and ATD for m/z = 707 (n/z = 2/3)

○ Most peaks observed were hetero-oligomers of Aβ(25-35) and EGCG.

○ **Tetramers were not observed**.

C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.

Oligomer Growth Model (1)

- Correlation with linear line means that observed oligomer had a β-sheet structure.
  - triclinic: ideal out-of-register β-sheet (each monomer chain is shifted by one amino acid residue)
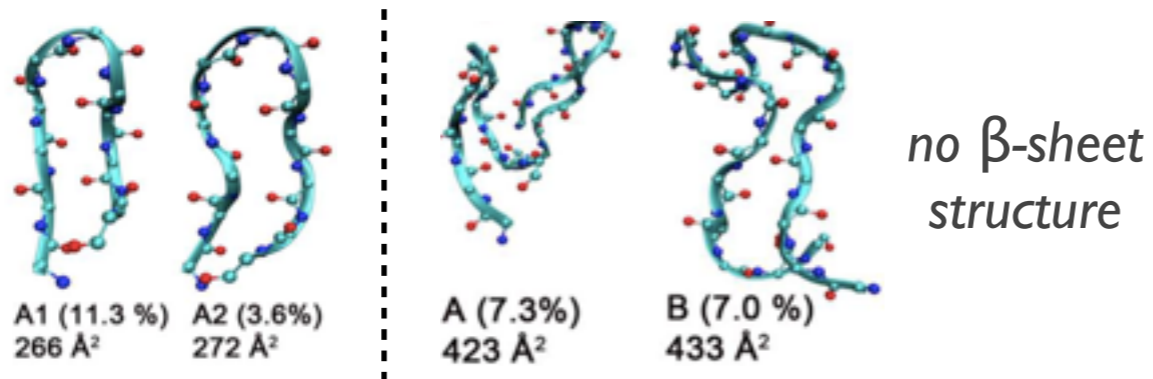 - isotropic: ideal homolytic growth (oligomer grows equally in all spatial dimensions)
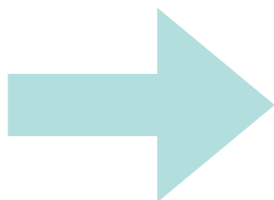
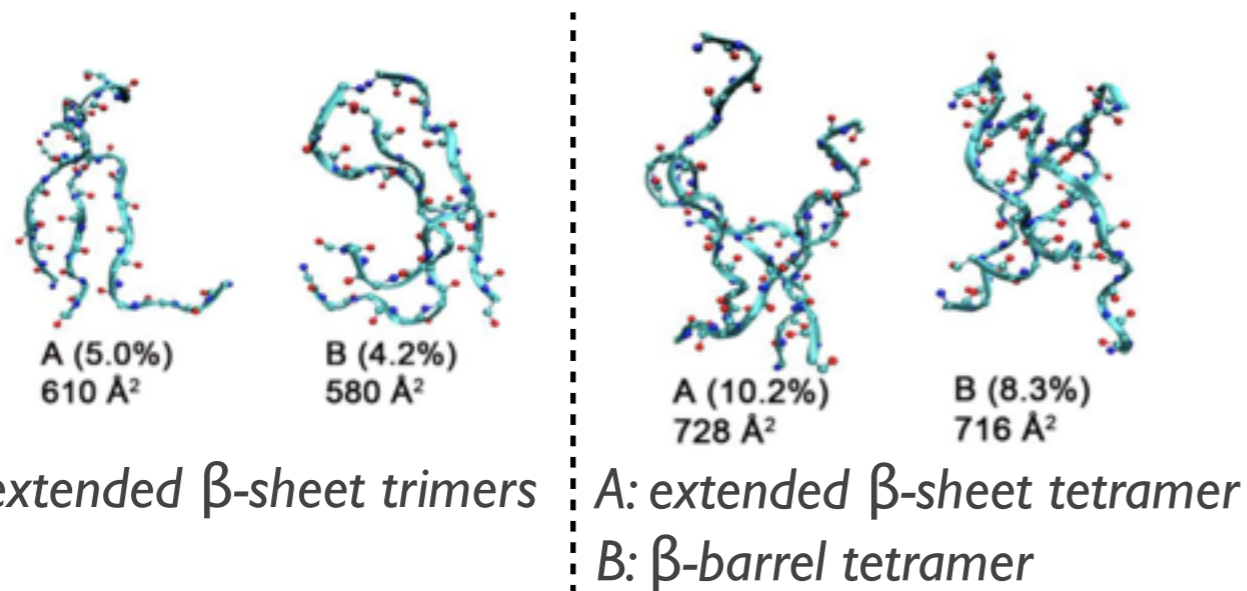**EGCG inhibited the β-sheet conformation appearance.**

C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.

Oligomer Growth Model (2)

- As Aβ(25-35) oligomer grows, β-sheet tendency becomes dominant.

  ○ monomer and dimer: isotropic

  no β-sheet structure
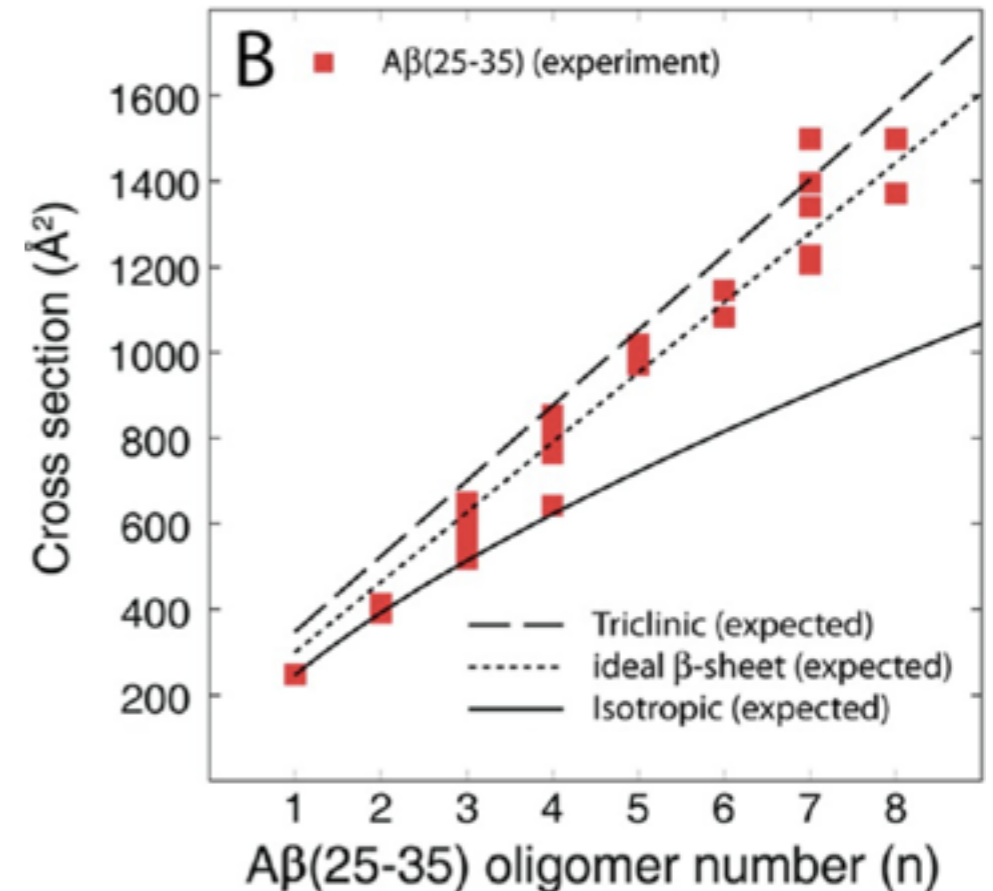
  A1 (11.3 %)   A2 (3.6%)
  266 Å²   272 Å²

  A (7.3%)   B (7.0 %)
  423 Å²   433 Å²

  ○ trimer and tetramer: increasing β-sheet tendency

  A (5.0%)   B (4.2%)
  610 Å²   580 Å²

  A (10.2%)   B (8.3%)
  728 Å²   716 Å²

  extended β-sheet trimers | *A: extended β-sheet tetramer*
  B: β-barrel tetramer

  ○ bigger than pentamer: β-sheet

B ■ Aβ(25-35) (experiment)

Cross section (Å²)

1600
1400
1200
1000
800
600
400
200

1 2 3 4 5 6 7 8
Aβ(25-35) oligomer number (n)

– – Triclinic (expected)
⋯ ideal β-sheet (expected)
— Isotropic (expected)

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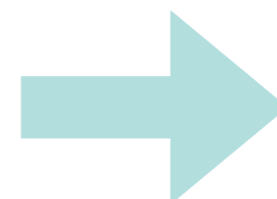
Trimer or tetramer supposed to be essential
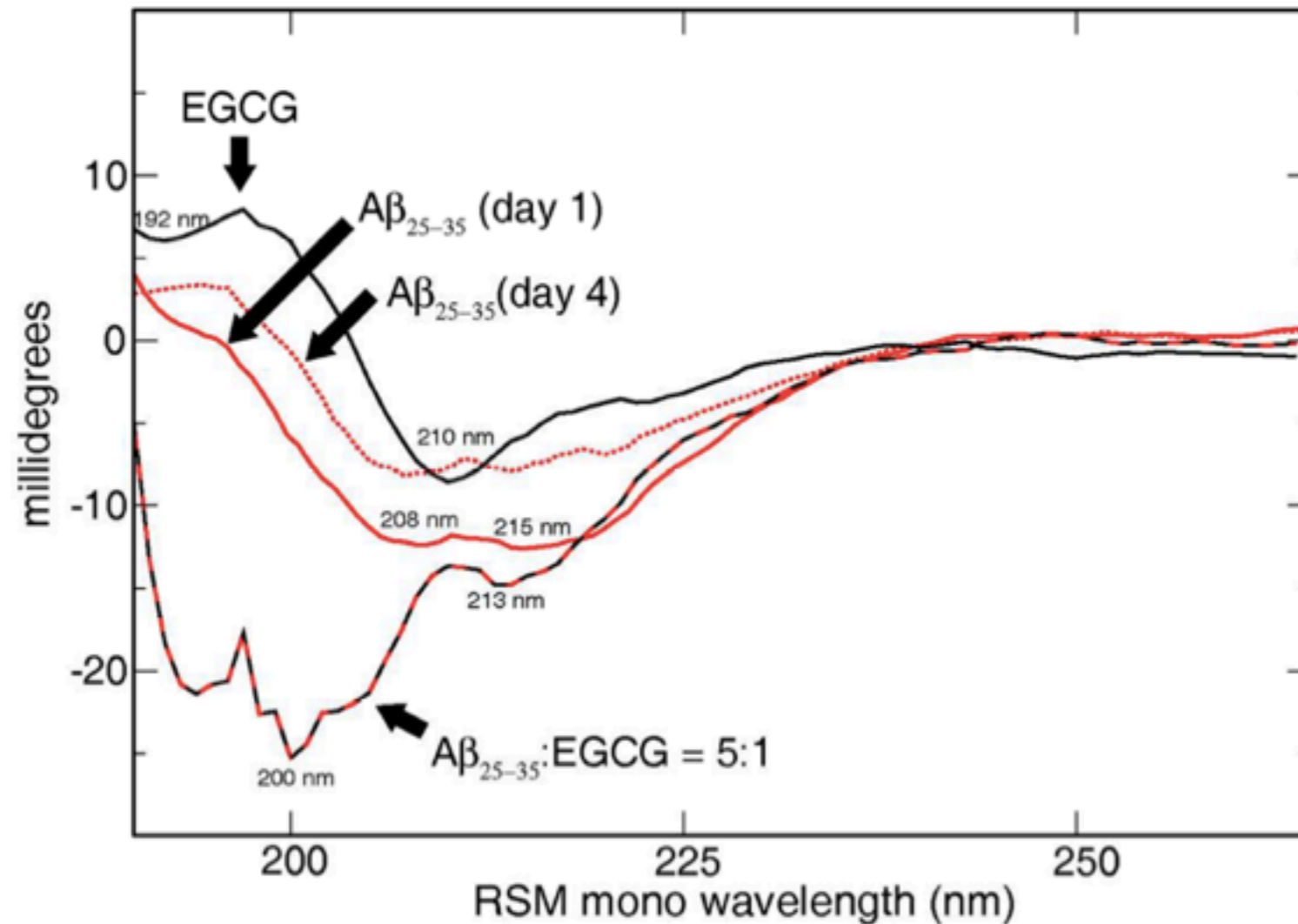for the structural conversion to β-sheet.

ATDs Comparison

- ATDs for m/z = 707 (n/z = 2/3)
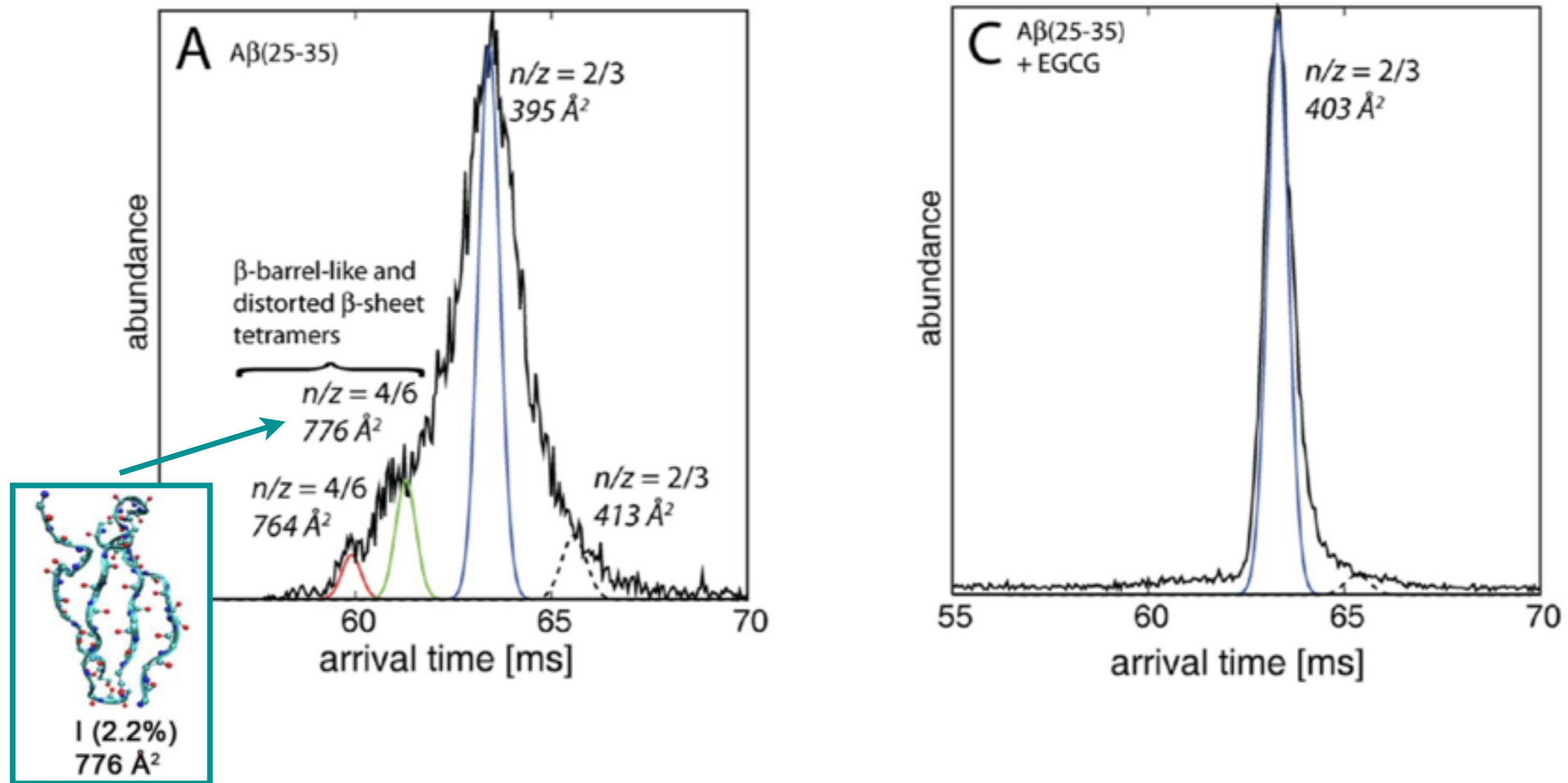
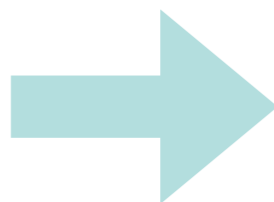
EGCG seemed to **inhibit the formation of β-barrel like tetramer or similar species**.

Circular Dichroism (CD)

- 0.5 mg/mL of Aβ(25-35) was incubated at r.t. with or without 10 mM EGCG (Aβ:EGCG=5:1).

○ Aβ(25-35) spectrum indicated the presence of β-sheet structure.

○ Aβ(25-35) + EGCG spectrum indicated the presence of random-coil structure.

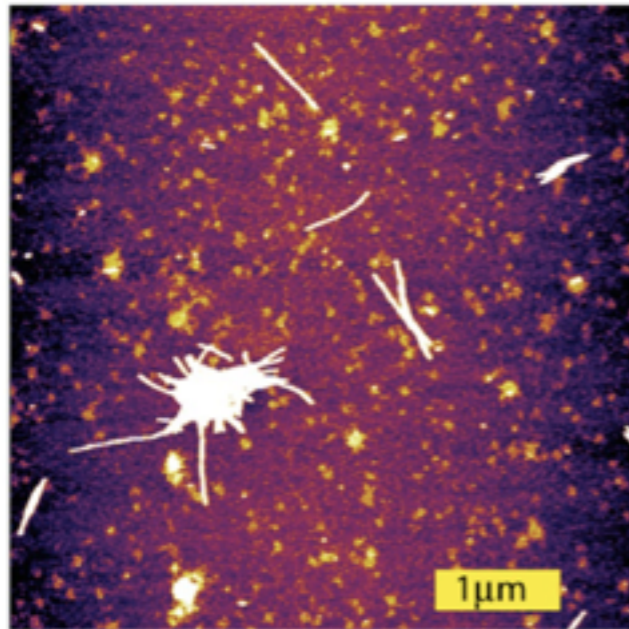This result strongly support the previous IM-MS analysis.
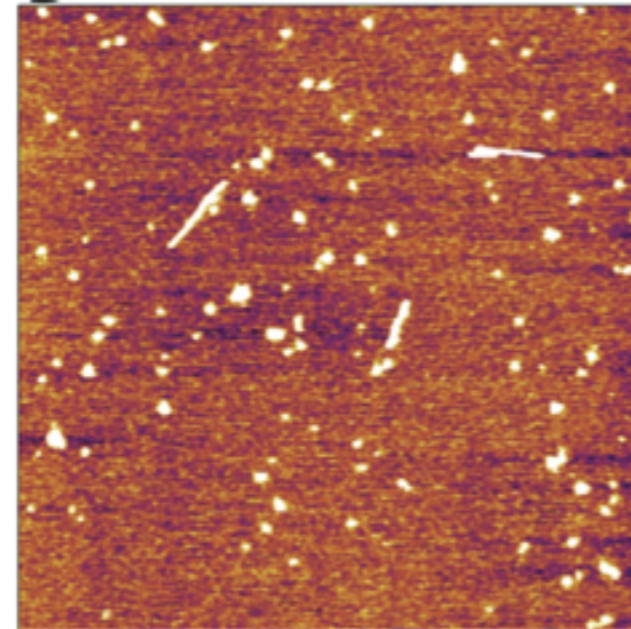
C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.

Atomic Force Microscopy (AFM)

- 200 μM of Aβ(25-35) was incubated at r.t. with or without EGCG (Aβ:EGCG=1:1).
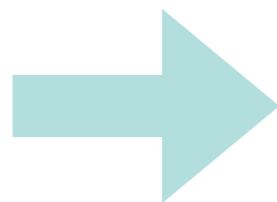
    ○ without EGCG   ○ with EGCG

- Fibril formation was prevented using EGCG.
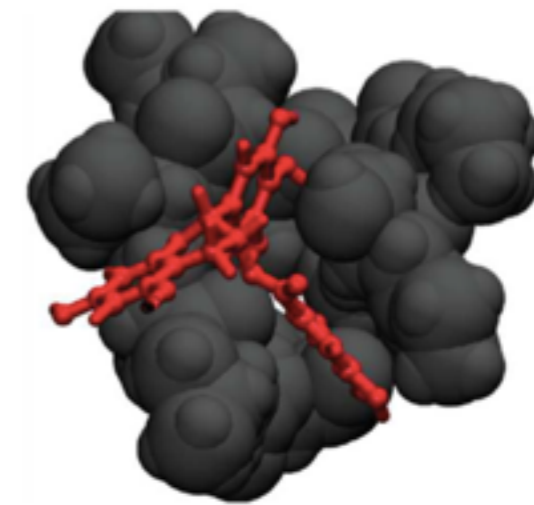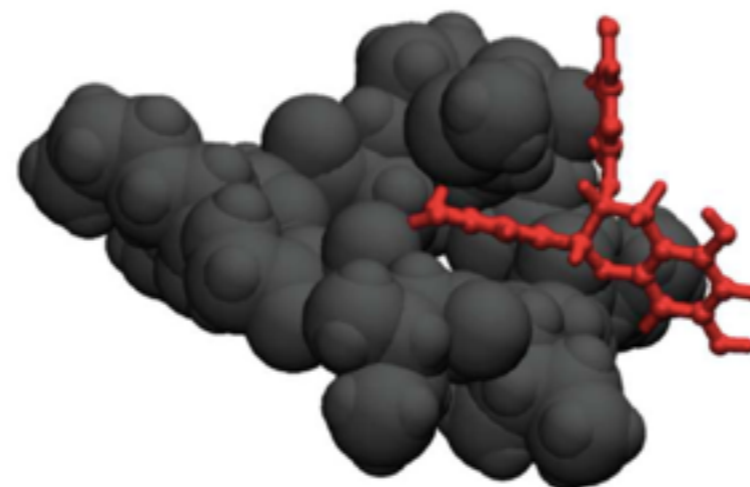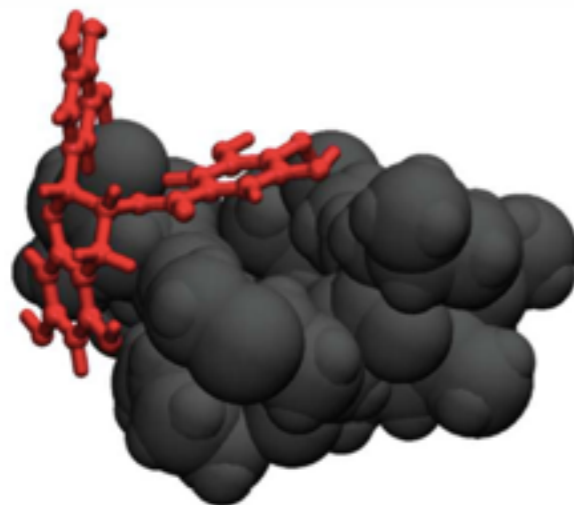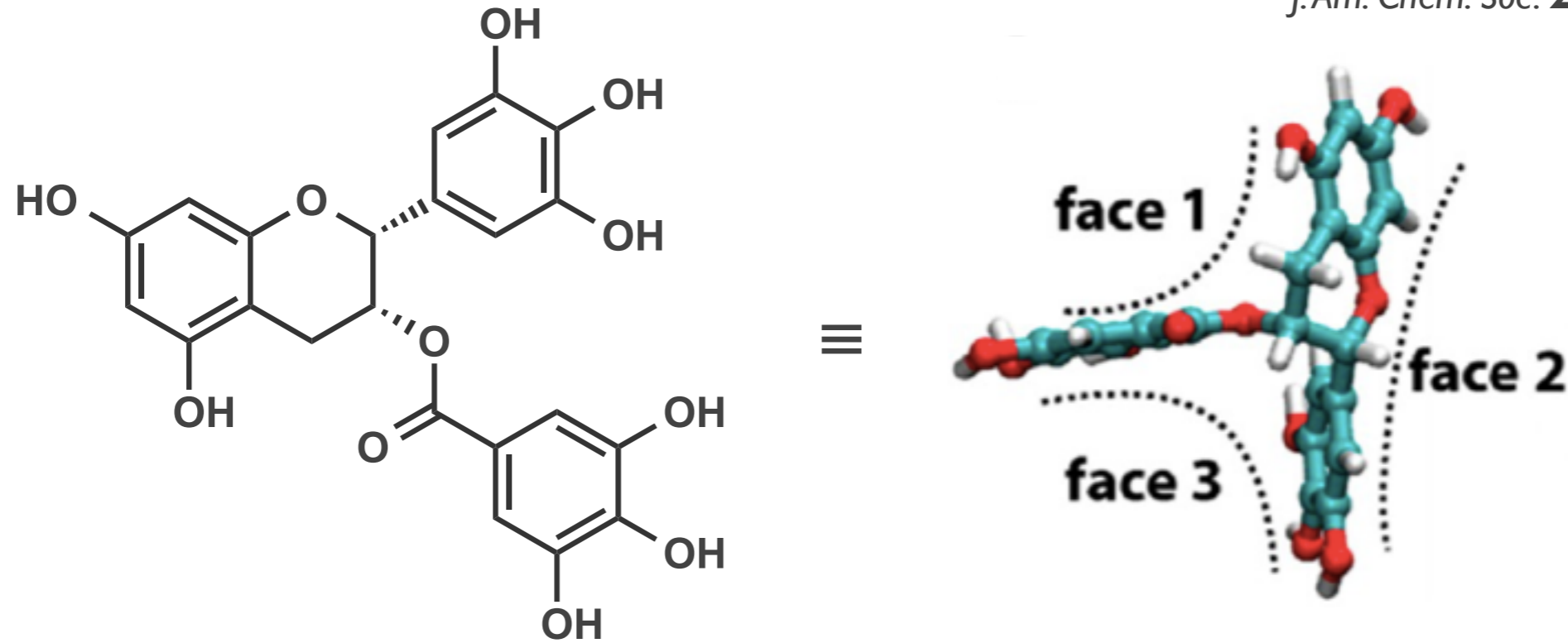
This result also support the previous IM-MS analysis.

C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.

Binding Simulation of EGCG (1)

- three binding sites of EGCG and binding simulation of each site

C. Bleiholder, M. Bowers *et al.*,
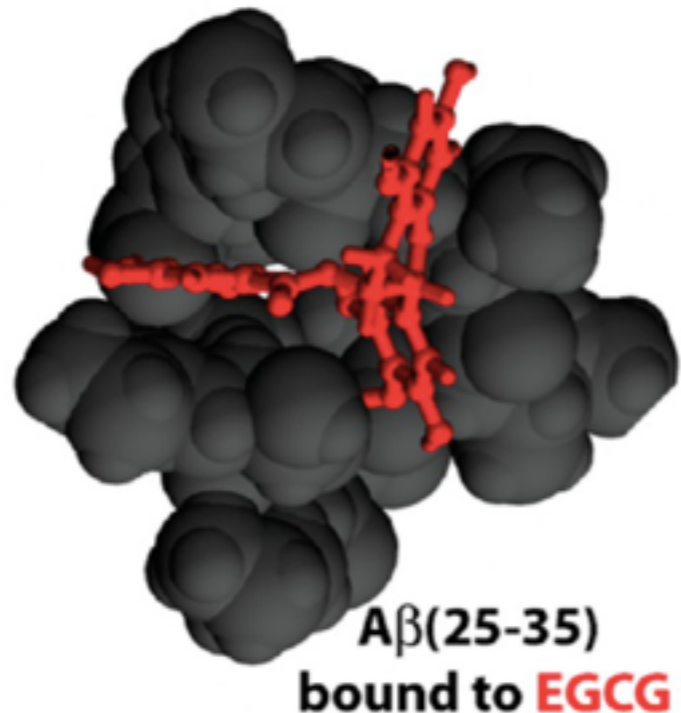*J. Am. Chem. Soc.* **2013**, *135*, 16926.

Binding Simulation of EGCG (2)

- Aβ(25-35) can bind to EGCG using all three binding sites.

Aβ(25-35)
bound to EGCG

○ This tridentate binding mode can only be accomplished when the bound Aβ chain takes on a unordered structure. (data was not shown in the paper...)

➡ **Formation of β-sheet** which is observed in the aggregation of Aβ(25-35) **is prevented**.

➡ **This binding property might inhibit the generation of β-barrel like tetramer strongly** and thus inhibit the formation of fibrils.

C. Bleiholder, M. Bowers *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16926.

Short Summary: Aggregation Pathway of Aβ(25-35)

A) pure Aβ$_{25-35}$

fibrillar aggregates

β-*barrel like tetramers*
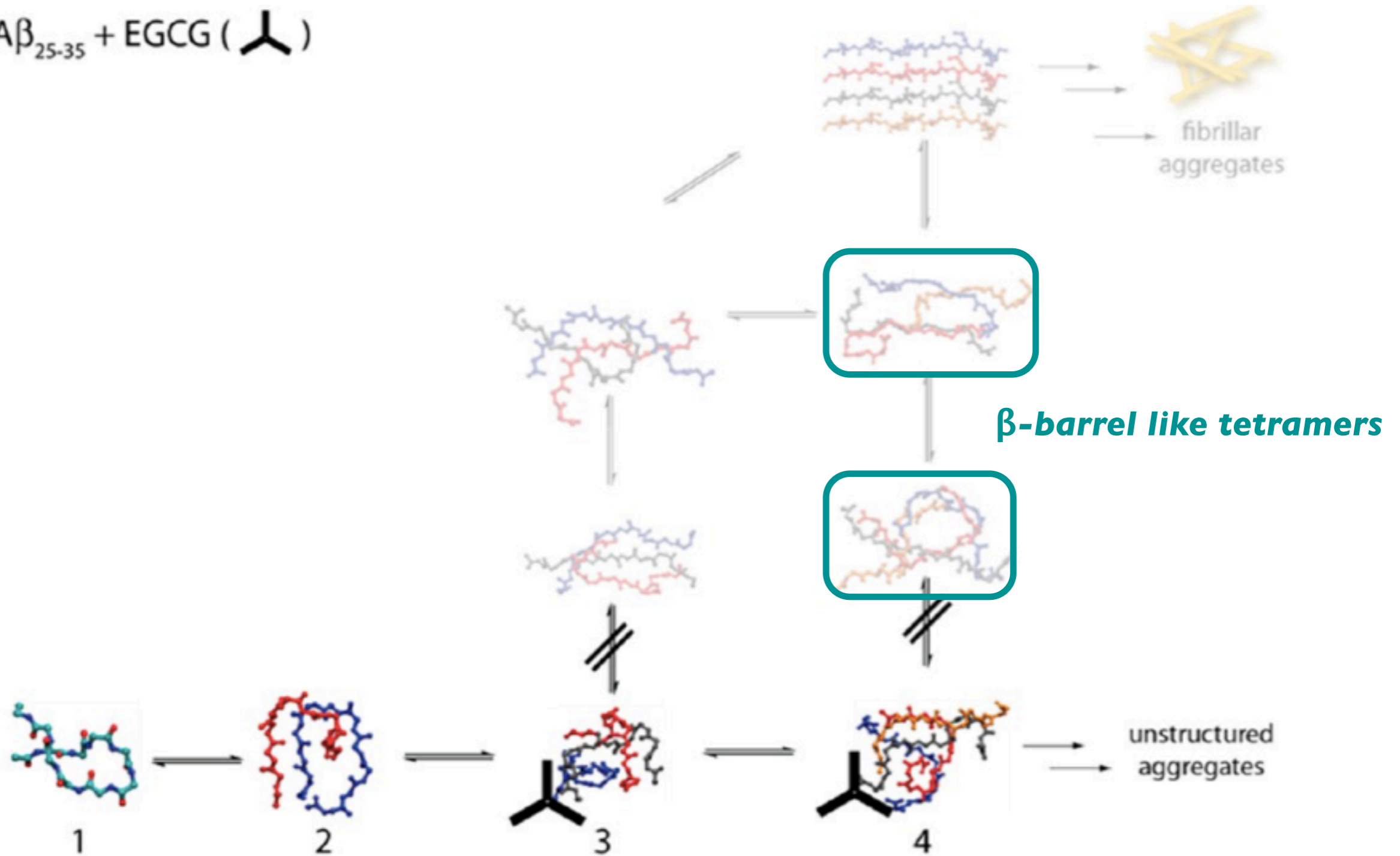
1   2   3   4
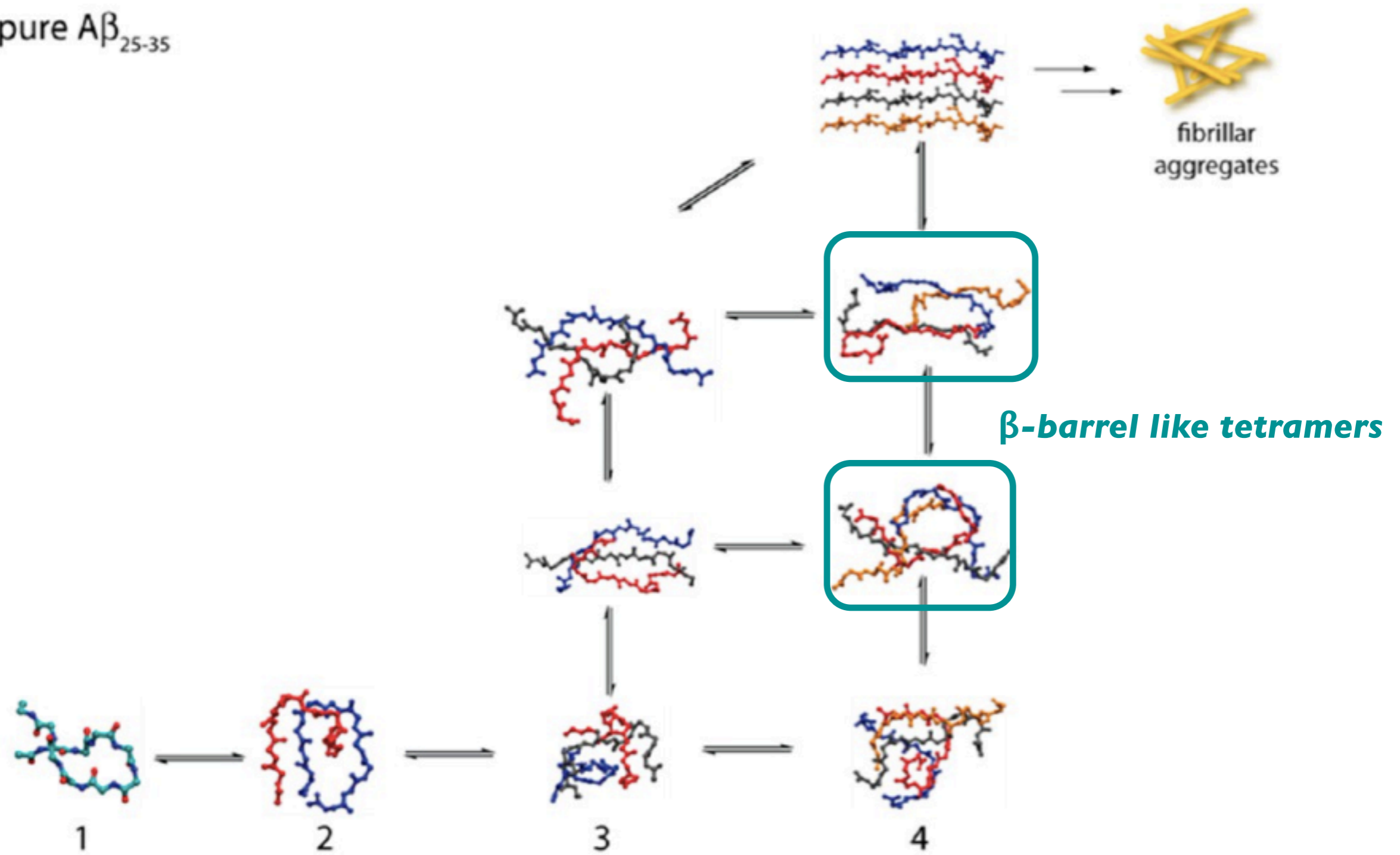
C. Bleiholder, M. Bowers *et al.*,
J. Am. Chem. Soc. **2013**, *135*, 16926.

Short Summary: Aggregate-Inhibiting Pathway of EGCG

B) $A\beta_{25-35}$ + EGCG ( )

β-barrel like tetramers

fibrillar aggregates

unstructured aggregates

1 2 3 4

C. Bleiholder, M. Bowers *et al.*,
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Summary

- application to Aβ42 and Aβ40 oligomerization analysis

  ○ Using appropriate approximation, structure difference between Aβ42 tetramer and Aβ40 tetramer was distinguished.

120°   30°

Aβ42   Aβ40

- application to mechanism analysis of aggregation inhibitor

  ○ Combining MD simulation and IM-MS analysis, advanced information of Aβ(25-35) aggregation and its inhibition by EGCG was obtained.

Aβ(25-35) bound to EGCG
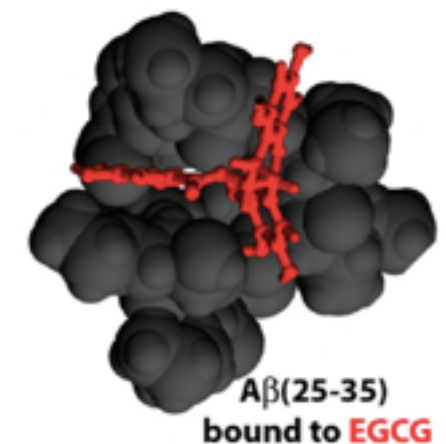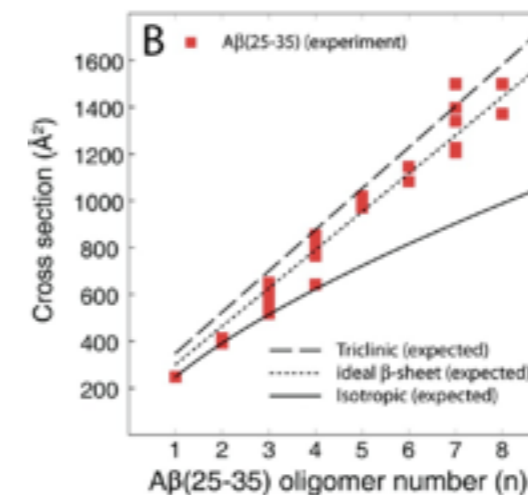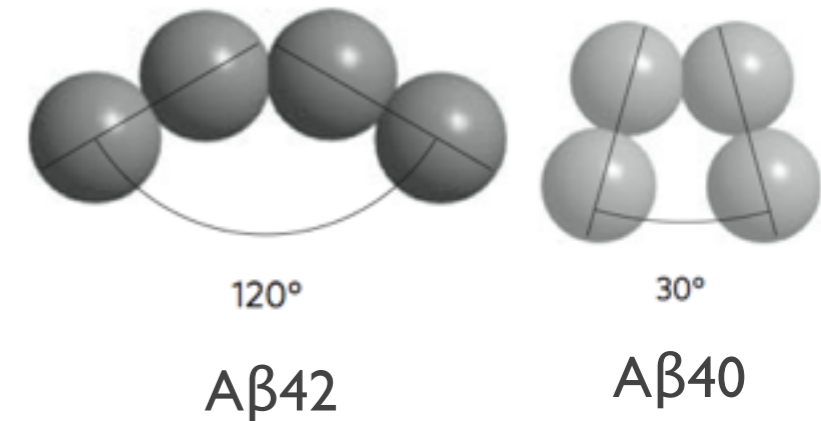
The most important ability of IM-MS to detect intermediates is successfully utilized!

Appendix

Derivation of Mason-Schamp Equation (1)

気相移動度測定においては，イオンの速度は $\dfrac{E}{N}$ に依存した一定の値をとる。特に，低電場極限(電場効果が熱運動に対し無視できるほど小さい)，すなわち

$$\frac{E}{N} \leq 2 \times 10^{-17} \ \left(\mathrm{V}\cdot\mathrm{cm}^2\right) \tag{1}$$

が満たされているとき，イオンは等速運動するようになり，その速度は

$$v_d = KE \tag{2}$$

と書けることが知られている。
　一方，イオンとガス分子との衝突時の運動量変化を解析すると，

$$v_d = qE\tau \left(\frac{1}{m} + \frac{1}{M}\right) \tag{3}$$

が得られる。ここで τ は，「イオンがバッファーガスに衝突する間の時間」であり，

$$\tau = \frac{1}{N \langle |\vec{v_r}| \rangle \Omega} \tag{4}$$

と書ける (分母＝「単位時間でイオンが衝突するバッファーガス分子の数」)。

Derivation of Mason-Schamp Equation (2)

(4) 式を (3) 式に代入すると，下式が得られる。

$$v_d = \frac{qE}{N \langle |\vec{v_r}| \rangle \Omega} \left(\frac{1}{m} + \frac{1}{M} \right) \tag{5}$$

ただし $\langle |\vec{v_r}| \rangle$ は，「全イオンと全バッファーガスの相対速度の絶対値の平均値」である。低電場極限においては，$\langle |\vec{v_r}| \rangle$ に対し熱運動近似を施すことができて，(5) 式は

$$v_d = \frac{1}{\sqrt{3}} \frac{qE}{N} \left(\frac{1}{m} + \frac{1}{M} \right)^{\frac{1}{2}} \left(\frac{1}{k_{\mathrm{B}}T} \right)^{\frac{1}{2}} \frac{1}{\Omega} \tag{6}$$

と書き直すことができる。近似せずより厳密に取り扱うと，

$$v_d = \frac{3}{16} \frac{qE}{N} \left(\frac{1}{m} + \frac{1}{M} \right)^{\frac{1}{2}} \left(\frac{2\pi}{k_{\mathrm{B}}T} \right)^{\frac{1}{2}} \frac{1}{\Omega} \tag{7}$$

となるので，(2) 式とあわせて

$$K = \frac{v_d}{E} = \frac{3}{16} \frac{q}{N} \left(\frac{1}{m} + \frac{1}{M} \right)^{\frac{1}{2}} \left(\frac{2\pi}{k_{\mathrm{B}}T} \right)^{\frac{1}{2}} \frac{1}{\Omega} \tag{8}$$

が得られる (Mason-Schamp equation)。

T. Sugai, *J. Mass Spectrom. Soc. Jpn.* **2010**, *58*, 47.

To Achieve High Resolving Power in DTIMS

半値幅分解能 (近接したピークを高さの半分の高さ位置で分離できること) は

$$R = \frac{1}{4}\sqrt{\frac{q}{k_\mathrm{B}\ln 2}}\sqrt{\frac{V}{T}} \tag{9}$$

で表される。(9) 式は，定数項を考えなければ

$$R \propto \sqrt{\frac{V}{T}}$$

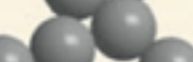となり，分解能は「電位とバッファーガス温度の比に依存する」といえる。
　ゆえに，**高分解能を実現するためには，電位を高く設定すればよい**が，高電位下で
は放電が起こる可能性がある。これを防ぐため，DTIMSでは**バッファーガス圧力が高
く設定されている**。なお，この圧力の高さは，結果的に (8) 式成立の前提である

$$\frac{E}{N} \leq 2 \times 10^{-17} \ \left(\mathrm{V \cdot cm^2}\right) \tag{1}$$

を満たすことにつながっている。また，$V = E \cdot \ell$ であるから，「高電位かつ低電場」
は，**装置を大きくする**ことによっても実現できる。

T. Sugai, *J. Mass Spectrom. Soc. Jpn.* **2010**, *58*, 47.

Gap Study between Model CCS and Exp. CCS

Oligomer	Structure[†]	Cross-section	
		Model	Experiment
Dimer*		1,256	1,256
Tetramer		2,358	
		2,277	2,332
		2,135	
Hexamer		3,450	
		3,100 > 2,898	
		2,578	
Dodecamer		5,824	
		4,562 > 4,308	

*Model cross-section fit to experiment. †Limiting structures of high symmetry.

Model
v
Exp.

Aβ42
● WT
■ Pro[19]
◆ Met[35](O)

σ/n (Å²)

oligomer order (n)
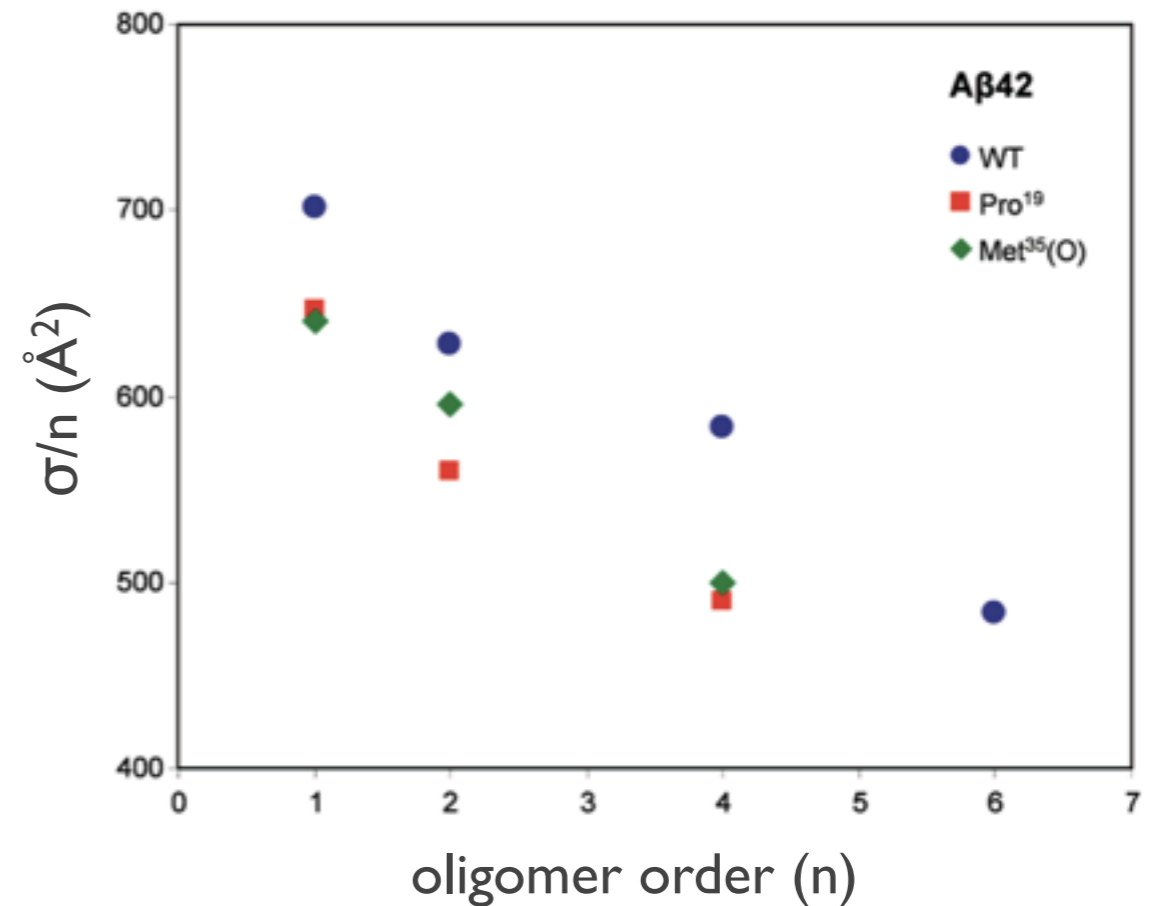
○ As n increases σ/n decreases.

∴ Oligomerization induces a certain amount of structural accommodation...?

○ As model is based on dimer size information, it can overestimate CCS of larger oligomers. Thus, the inequality shown left is reasonable.