Investigate immunotherapy for Alzheimer's disease.

Figure 6 of Bitan's paper describes a mechanism for the formation of amyloid, a culprit of Alzheimer's disease.


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Consider the following mechanism, where monomers eventually form fibrils.

\[
\begin{align*}
&k_{mn} := 1 \quad k_{no} := 1 \quad k_{op} := 1 \quad k_{pf} := 1 \\
&\text{monomer (M) } \xleftarrow{k_{mn}} \text{ paranuclei (N)} \xrightarrow{k_{no}} \text{ large oligomers (O)} \xrightarrow{k_{op}} \text{ protofibrils (P)} \xrightarrow{k_{pf}} \text{ fibril (F)} \\
&k_{nm} := 1 \quad k_{on} := 1 \quad k_{op} := 0.5
\end{align*}
\]

Bitan et al. also consider the following 2 paths leading to protofibrils (P)

\[
\begin{align*}
&k_{mp} := 0.1 \\
&k_{np} := 0.1
\end{align*}
\]

monomer (M) \xrightarrow{k_{mp}} protofibrils (P)

paranuclei (N) \xrightarrow{k_{np}} protofibrils (P)

We propose a means of reducing fibril by "mopping" away one of the precursors, say, protofibrils (P), with a monoclonal antibody (A).

\[
\begin{align*}
&k_{ap} := 1 \\
&A + P \xleftarrow{k_{ap}} AP
\end{align*}
\]

Elementary reaction kinetics

\[
\begin{align*}
&dM dt := -k_{mn} M - k_{nm} N - k_{mp} P \\
&dN dt := k_{mn} M - k_{nm} N - k_{no} N + k_{on} O - k_{op} O \\
&dO dt := k_{op} O - k_{po} P - k_{op} P - k_{pf} P + k_{mp} M + k_{np} N - k_{ap} A \cdot P + k_{pa} A \cdot P \\
&dP dt := k_{pf} P \\
&dA dt := -k_{ap} A \cdot P + k_{pa} A \cdot P \\
&dAP dt := k_{ap} A \cdot P - k_{pa} A \cdot P
\end{align*}
\]

Combine all ODEs into a standard vector form

\[
\begin{align*}
&\text{dydt}(t, y) := \begin{pmatrix}
dM dt \\
\vdots \\
dAP dt
\end{pmatrix} \\
&y \text{ init} := \begin{pmatrix}
1 \\
0 \\
0 \\
0 \\
0 \\
0
\end{pmatrix}
\end{align*}
\]
With immunotherapy, (curve F=without antibody A; curve f=with antibody A), the amount of fibril decreased slightly (but remained significant) at clinical endpoint of t=10 compared to that without immunotherapy. Thus, with the given kinetic parameters and antibody dosage, immunotherapy is not effective.
**Design an antibody that binds stronger and faster to P**, \(k_{ap} := 100\) \(k_{pa} := 0.1\)

\[
dPdt(M,N,O,P,F,A,AP) := k_{op} \cdot O - k_{po} \cdot P - k_{pf} \cdot F + k_{mp} \cdot M + k_{np} \cdot N - k_{ap} \cdot A \cdot P + k_{pa} \cdot AP
\]

\[
dAdt(M,N,O,P,F,A,AP) := -k_{ap} \cdot A \cdot P + k_{pa} \cdot AP
\]

**Combine all ODEs into a standard vector form**

\[
dydt(t,y) :=
\begin{bmatrix}
    dMdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\
    dNdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\
    dOdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\
    dPdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\
    dAdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\
    dAPdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6)
\end{bmatrix}
\]

**Solve the ODEs with antibody (A)**

\[ty := rkfixed(y_{init}, 0, 10, 1000, dydt)\]

**Without Immunotherapy**

**With Immunotherapy**

**Fibril (f) formation is greatly suppressed.** Hopefully a stronger-binding antibody can delay the onset of Alzheimer’s disease long enough.

What if the antibody targeted other species in the amyloid pathway instead: monomer (M), paranuclei (N), or large oligomers (O)? What if we start immunotherapy at t=1, 2, or 3 instead of t=0? (Can early detection be the key?)