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Alzheimer's Disease, Its Causes, Manifold Drugs and Treatment

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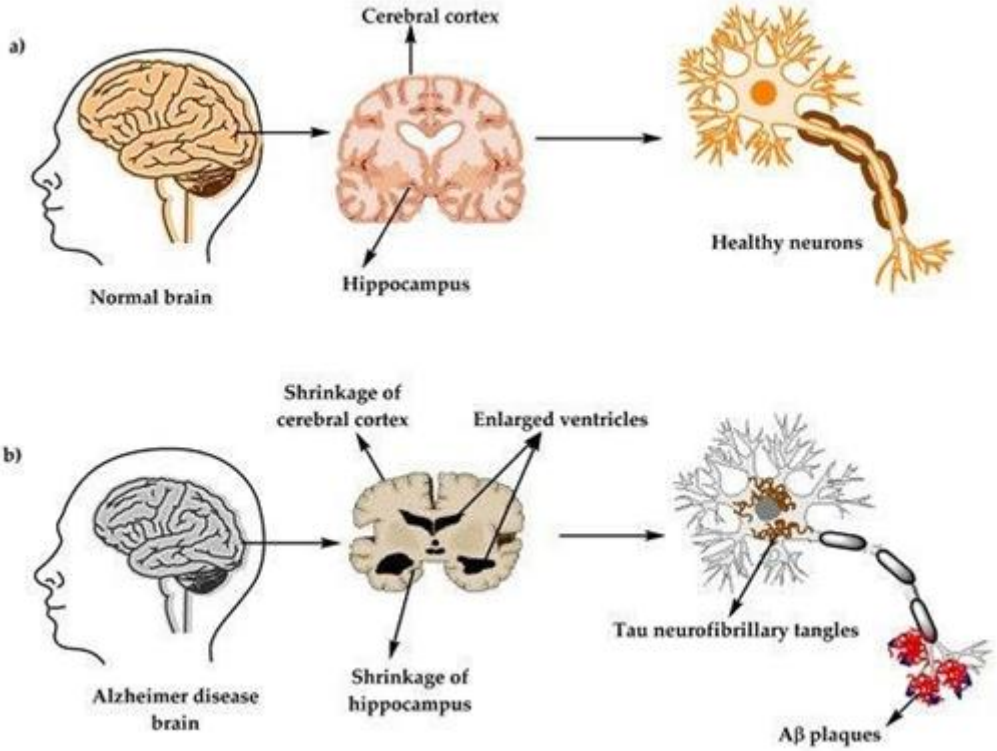
Abstract: ***Alzheimer's disease is viewed from a new perspective, proposing that damaged flows cause the disease and not genes. When microtubules or network of tubules are damaged, it will cause Alzheimer´s disease. Then the search for a new medicine takes a different pathway.***

Keywords: Alzheimer´s disease, treatment, drugs, causes of Alzheimer's

In this paper the principle of relations[1], a new theory, is applied to Alzheimer´s disease. Since the cause of Alzheimer´s is weakly understood, we must try alternative ideas.

First, an overview of the Alzheimer´s disease:



The physiological structure of the brain and neurons in (**a**) healthy brain and (**b**) Alzheimer's disease (AD) brain, from the source: Molecules | Free Full-Text | Comprehensive Review on Alzheimer's Disease: Causes and Treatment | HTML (mdpi. com)

Now the principle, which is based on two stipulated postulates:

1) Nothing exists in isolation; everything exists in relations.
2) Every concept has to represent reality directly and concretely.

The concept relation relates to reality by showing that there are relations between all parts in the human body, where:

1) **a, b, c** … are any system, subsystem, unit, part in any field of the human body, e. g. organs, cells, organelles, nuclei, atoms and molecules.
2) The relation **R** is a flow of packages, p1-n, e. g. neutrons, electrons, photons, proteins, fats, polysaccharides between a, b, c … in any part of the human body, illustrated by this basic model:

Based on the postulate-Nothing exists in isolation; everything exists in relations-in combination with 1 and 2 above, then the principle is

X = aRb,

where X is inflammation and disease[2].

X = Alzheimer´s Disease. When microtubules are damaged and cannot perform intracellular transport of material, huge amount of amyloid beta will be crowded outside the cell and

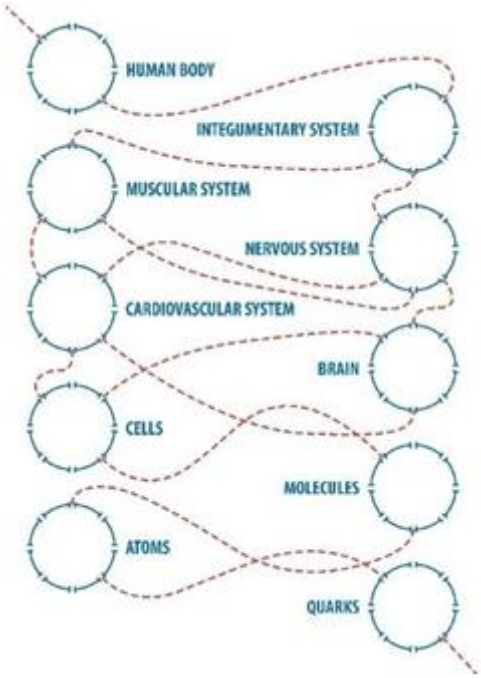
neurofibrillary tangles of tau proteins will occur inside the cell.

The system of the human body consists of flows of packages between different subsystems, i.e., integumentary system, Si, skeletal system, Ss, muscular system, Sm, nervous system, Sn, endocrine system, Se, cardiovascular system, Sc, lymphatic system, Sl, respiratory system, Sr, digestive system, Sd, urinary system, Su and reproductive system, Sre. If SH stands for the system of the human body, then

SH = (aRb)-∞ consists of Si, Ss, Sm, Sc, Sl, Sr, Sd, Su, Sre, Sn and Se, where each S1-11 has its own system of R1-10.

SH = (aRb)-∞ = SiR1SmR2Sc R3SlR4SrR5SdR6SuR7SreR8SnR9Se R10Ss

This is the model of the Human Body, based on the postulate, *nothing exists in isolation; and everything exists in relations:*



Based on the postulates and the Principle X = aRb, we can look into the System of the Human Body. With the language of the principle of relation we can summarize the system, S, for the human body, H, as **SH = (aRb)-∞**

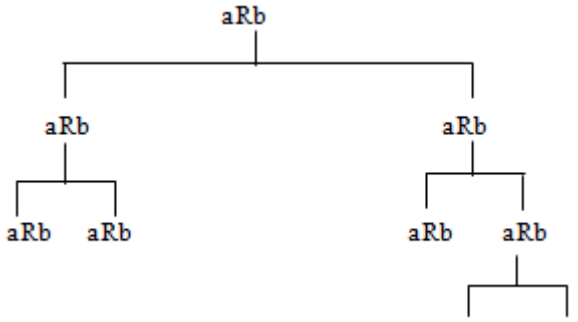
Between all systems and between all parts of any system, S, within the human body, there are continuous flows of packages **p1-n**, i.e., **R = p1-n**. The formula will be found this

S = ap1-nb

R contains p1-n and the function of R is: R = ∑ p1-n = p1 + p2 + p3 …pn

This content will over time change any structure a, b, c in the human body, from the lowest element in the cells to relations between subsystems. Within the body there is complex R1-n.

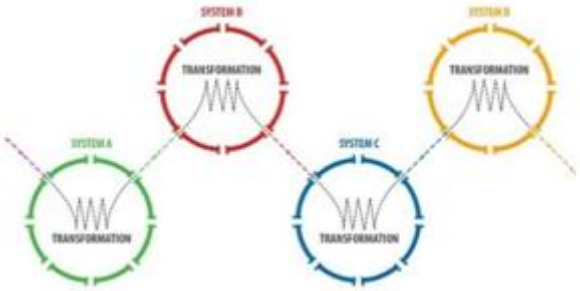
When we apply the principle to the human body, the hierarchy of flows can be illustrated as below:



When any superior and dominate aRb is damaged it will affect related aRb. If any superior aRb collapse, most inferior aRb related will collapse as well. This is the top-down approach.

For each system there are gates, i.e., the transformation mechanism by the transformer, where the content of the packages is transformed for the next level of reality, as illustrated below:

The big challenge is now to identify all the *p* in all relations and to identify, directly and concretely, the logic of the equation S1 = (a1R1b1) R2 (a2R3b2) and illustrated as such:



The size and volume for any system regulate the flows in and out of any system3. When packages leave any system, new packages will come in, i.e., they are needed, since nature abhors vacuum.

Based on the principle X = aRb, we find:

X = Alzheimer´s disease, AD; i.e., AD = aRb, i.e., when any network of tubules is damaged, it will cause AD.

The principle of relations claims that damaged flow dominates causing inflammation, while chronic inflammation causes disease. If damaged flows continue not

being repaired, disease will be chronic, i. e., w*hen any flow is broken or damaged, there will be disorders and diseases, e. g. cancer, AV-block III, Stroke, Alzheimer´s and cardiac infarction*3.

Then, the basic hypothesis for Alzheimer´s disease will be: *When any network of tubules is damaged, it will cause Alzheimer´s disease.*

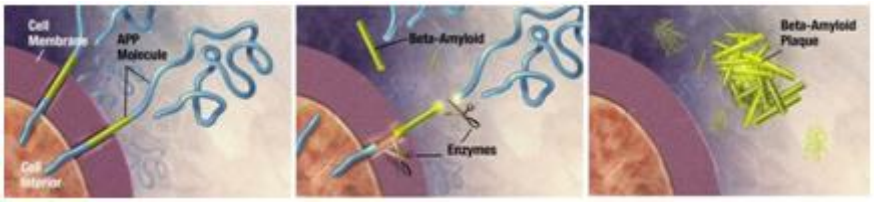
The structure of aRb gives these alternative causes for Alzheimer´s disease, i.e., damaged flows:

1) Gate failure of cell.
2) Microtubule damage.
3) Damaged flow contents.
4) Combination of 1-3.

We know that both amyloid beta and neurofibrillary tangles are involved in the disease. They are told to cause dysfunction within the brains neuronal and their connectivity. When we use aRb viewing the relationship between neuronal function and amyloid plaques/ neurofibrillary tangles the causality will be the opposite, i. e., it is damaged flows between neurons that cause the symptoms of Alzheimer´s disease.

First, the model of flow-block as a cause of Alzheimer´s Disease – AD:

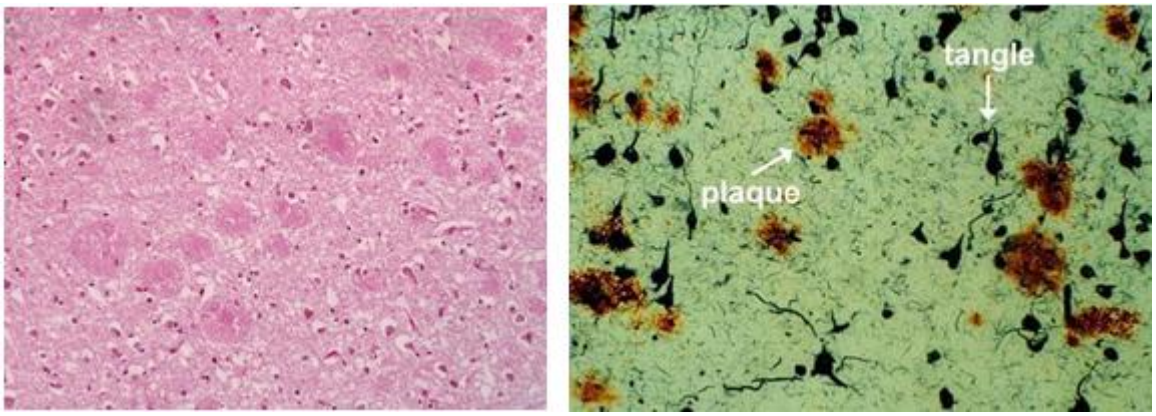
When the gates are closed, no packages can either come into or leave the cell. Then the cell will be destroyed within, and outside the packages will be crowded. Outside the cell, packages are crowded as senile plaques. Inside the cell, genetic disorder will occur. (It is not genetic disorder that causes and disrupts the cell´s normal functioning.) The pictures below will show this:



So far, the facts, based on science, which correspond to the model of aRb, are:

1) Amyloid plaques outside the cell and neurofibrillary tangles inside the cell are involved.
2) Loss of neurons and synapses.
3) Inflammation.
4) Lower levels of Neurotrophic factors and the brain-derived neurotrophic factor, BDNF, (protein). (The activity of the neurotransmitter Alpha-7 nicotinic receptor (protein) is modulated by BDNF.)

In the representations below we can see numerous formations of plaque and tangles within the neuropil; to the left cerebral autopsy specimen of a patient diagnosed having Alzheimer Disease. In the HE stain numerous plaque formations within the neuropil background are visible, (Credit: WIKIPEDIA, CC BY-SA 3.0 and to the right neuropil plaque-Bing):



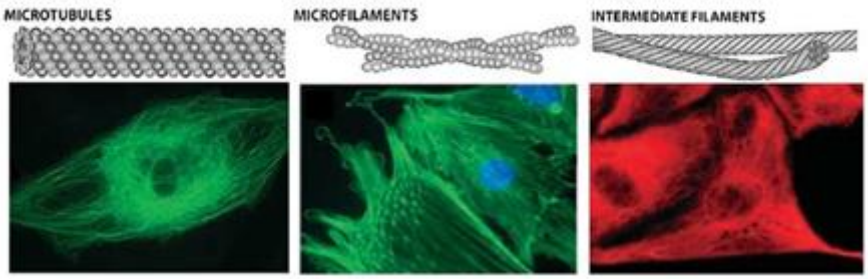
Why do these plaque and tangle occur? How can we find the causes? How can we develop drugs curing the disease?

If we do not have a basic principle and theory understanding the human body, we will be drowned by all information given from massive research. So, by using the principle of relations and the formula X = aRb, we will have some guiding in our search for causes of diseases.

By using the glasses of this principle, we are mostly looking after the R1-n, i.e., networks of relations consisting of flows and its content.[4]

First, we focus the concept and content of cytoskeleton, consisting of microtubules, microfilaments and intermediate filaments. The functions of cytoskeleton are complex, but

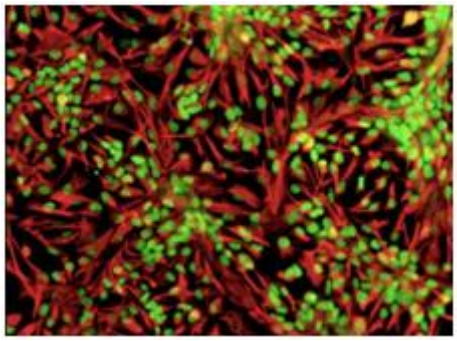
dealing with Alzheimer´s disease, we focus the dynamic network, i.e., the uptake of extracellular material (endocytosis), and organizing organelles. Cytoskeleton consists of filaments and microtubules, as the image below shows:



(Source: Network of cytoskeletal filaments [5, 8]. . . . | Download Scientific Diagram (researchgate. net))

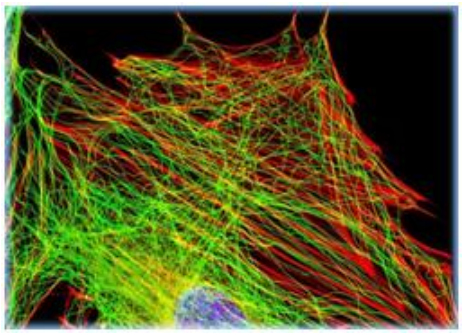
Cytoskeleton holds nucleus enclosed within membranes and connects the cell nucleus with the membrane with protein filaments.

The image below shows this, i.e., "human neural stem cells stained for Sox2, in green, and vimentin, in red. Vimentin is a type III intermediate filament (IF) protein":

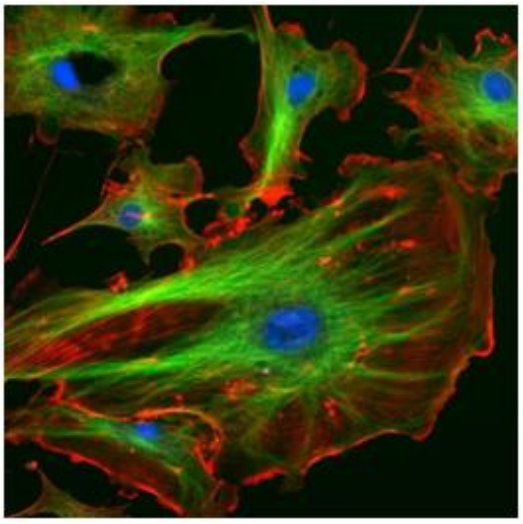


(Source: Intermediate filament-Protein filament-Wikipedia)

Then, when we find the cytoskeleton, which we can imagine it by this image:



(Source: Imaging the Cytoskeletal Network in 3T3 Cell Cultures | Olympus LS (olympus-lifescience. com. cn)) The next image shows actin filaments in red and microtubules in green:

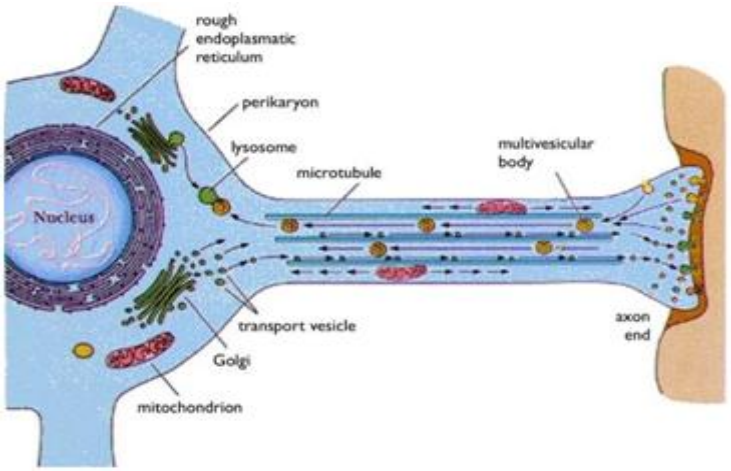


(Source: Fluorescent Cells-Cytoskeleton-Wikipedia)

The logistic system and its flows within the cell

The most important parts and concepts are the following:

1) Cytoskeleton
2) Microtubules
3) Microfilaments
4) Intermediate filaments
5) Axonal transport
6) Integrin

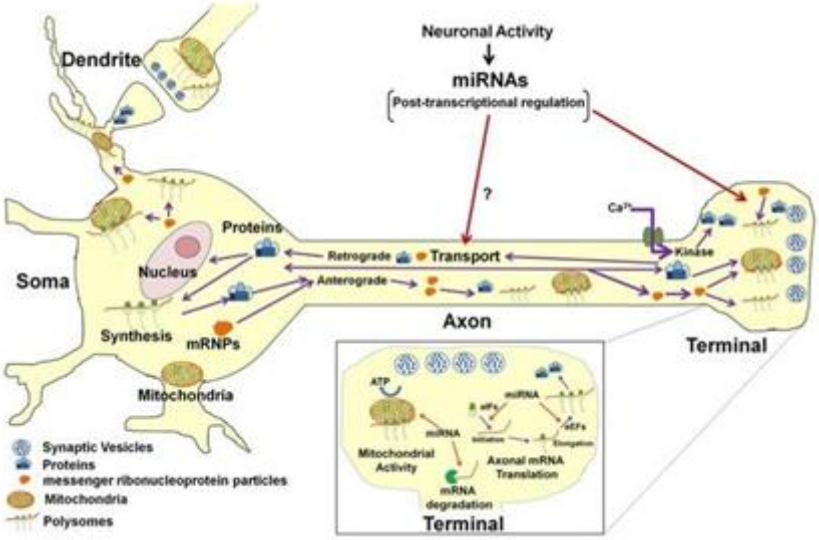


(Source: Axon-Bing images)

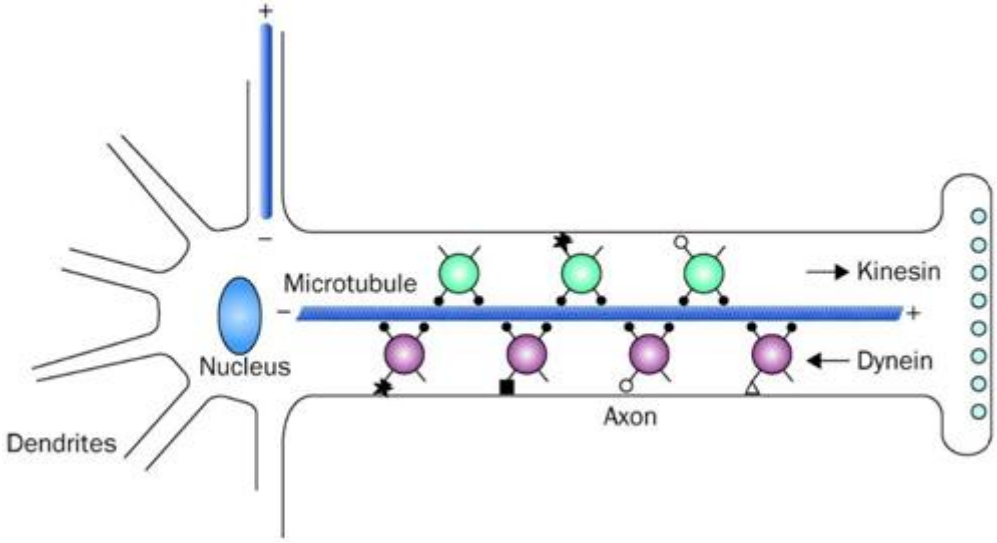
How is it possible finding which part of the logistic system that causes diseases, since there are quite many components to deal with.

Contemporary science mostly tries to find one cause and then develop drugs dealing with that part. But what if we have to find a combination of drugs, which can replace the entire function?

Is it possible to understand exactly which part that is damaged and then direct drugs to that part only?



(Source: axonal transport picture-Bing images)



(Source: axonal transport image-Bing images)

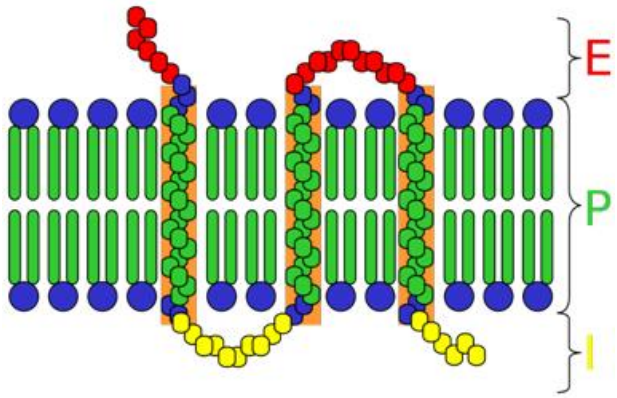
We know that, in normal opening and closing of ion channels, the flow of ions passes through the membrane of a cell. Our first suspicion is that the gate will not open, for some reason. So, how can a gate recover from inactivity?

We will now focus how damaged gates will affect cytoskeleton´s contact with the membrane and extracellular material.

How, then, connect cytoskeleton to extracellular material?

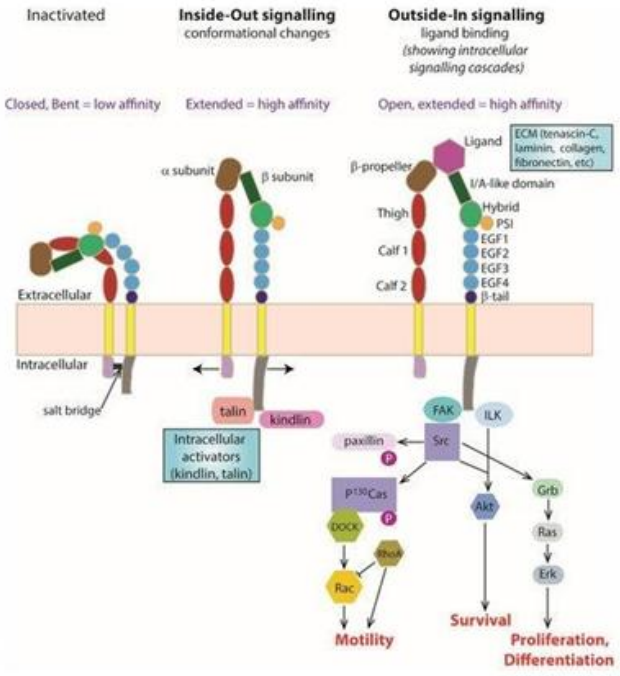
The receptor which connects cytoskeleton to extracellular material is called *integrin*, which looks like a cyclical liaison. Integrins are receptors at the surface of the cell, fulfilling its mediation.

The image below shows how this is made, where E=extracellular space; I=intracellular space; P=plasma membrane, i.e., the function of transmembrane receptor:



(Source: Cell surface receptor-Wikipedia)

Integrin connects cytoskeleton and the extracellular matrix. Based on aRb, damaged flows create Alzheimer´s disease and if the integrin does not function it can be one possible cause for AD. Then, the figure below can guide giving the first possible cause:



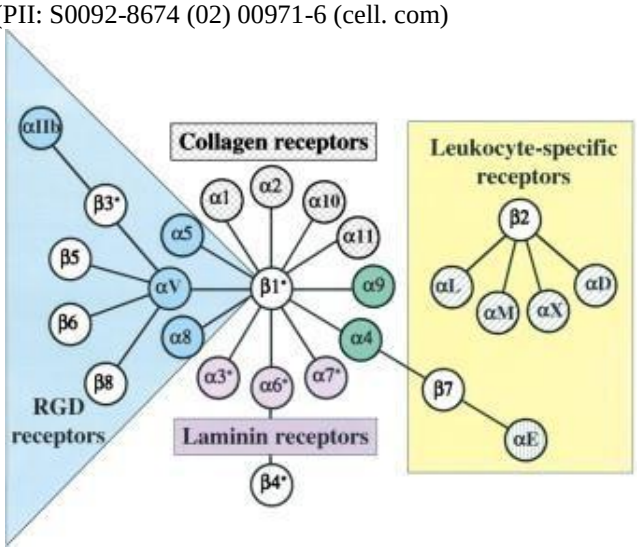
(Source: Cells | Free Full-Text | Integrin Activation: Implications for Axon Regeneration | HTML (mdpi. com))

The figure describes the integrin Structure and Activation. "Activation of integrin heterodimers leads to intracellular signalling cascades and resulting processes such as cell motility, cell survival, cell differentiation, and neurite outgrowth. Schematic representing integrin conformations at the membrane including changes that occur with 'Inside–Out signalling' and 'Outside–In signalling'. An inactivated integrin heterodimer exists with a closed and bent conformation (extracellularly) stabilised by a cytoplasmic salt bridge. This conformation has a very low ligand binding affinity. With Inside–Out signalling, intracellular activators (such as kindlin and talin) bind the β subunit cytoplasmically and interact/destabilise the salt bridge, leading to an open and extended (active) conformation with increased ligand binding affinity. With Outside–In signalling, binding of a ligand (ECM molecules such as laminin, fibronectin, or tenascin) extracellularly occurs as a result of integrin activation leading to a conformational change to an open and extended (active) conformation with high ligand binding affinity. Individual names of the extracellular domain components have been shown in the Outside–In signalling example for simplicity, with further explanation in the main text. " (Source: Cells | Free Full-Text | Integrin Activation: Implications for Axon Regeneration | HTML (mdpi. com))

In the article *Integrin Activation: Implications for Axon Regeneration*, the authors Menghon Cheah and Melissa R. Andrews also conclude that "As integrins are essential for the proper functioning of a normal and healthy nervous system, translational researchers in the field of axon regeneration have been trying to harvest the use of integrins following a central nervous system (CNS) injury, such as spinal cord injury, in order to recapitulate a developmental growth state that could enhance regenerative growth."

But, how can we find out the function of an integrin, when it is large, complex and linked to many sugar trees? (Integrin-Wikipedia)

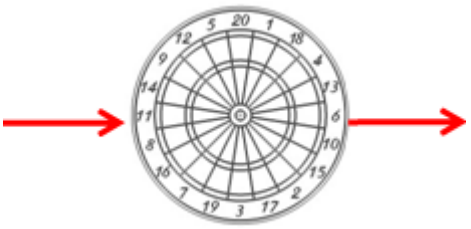
Even after many years of research and hundreds of papers, it is not possible to find the structure of integrins. One attempt is made based on this model, made by Richard O. Hynes. (PII: S0092-8674 (02) 00971-6 (cell. com)



We are told that "integrins are αβ heterodimes; each subunit crosses the membrane once, with most of each polypeptide (>1600 amino acids in total) in the extracellular space and two short cytoplasmic domains (20-50 amino acids) …".

Then, is the answer to the questions of the cause of AD damaged integrin and then, how can reparation of integrins cure AD?

It is obvious that some transformation will fulfill the function of transportation of molecules, but it is not sure integrin has the answer. So, we might as well, based on the principle of relations, create an alternative solution, as told before the name is *transformer*. The shape of a transformer, looking like a paddle wheel, will differ depending on where it is located. The image as below might stimulate our imagination (the size will be measured in nanometres, approximately 50-200 nm), where each number can accept only one specific particle from a molecule, e. g. H, N, P, C and O, at the left side, and then a new molecule will occur, e. g. C10H16N5O13P3, at the right side:



Throughout reality the same principal mechanism of a transformer function, e. g. the Earth, the Sun, the Moon, the Human Body, galaxies, black holes, organs and cells in the Human Body.

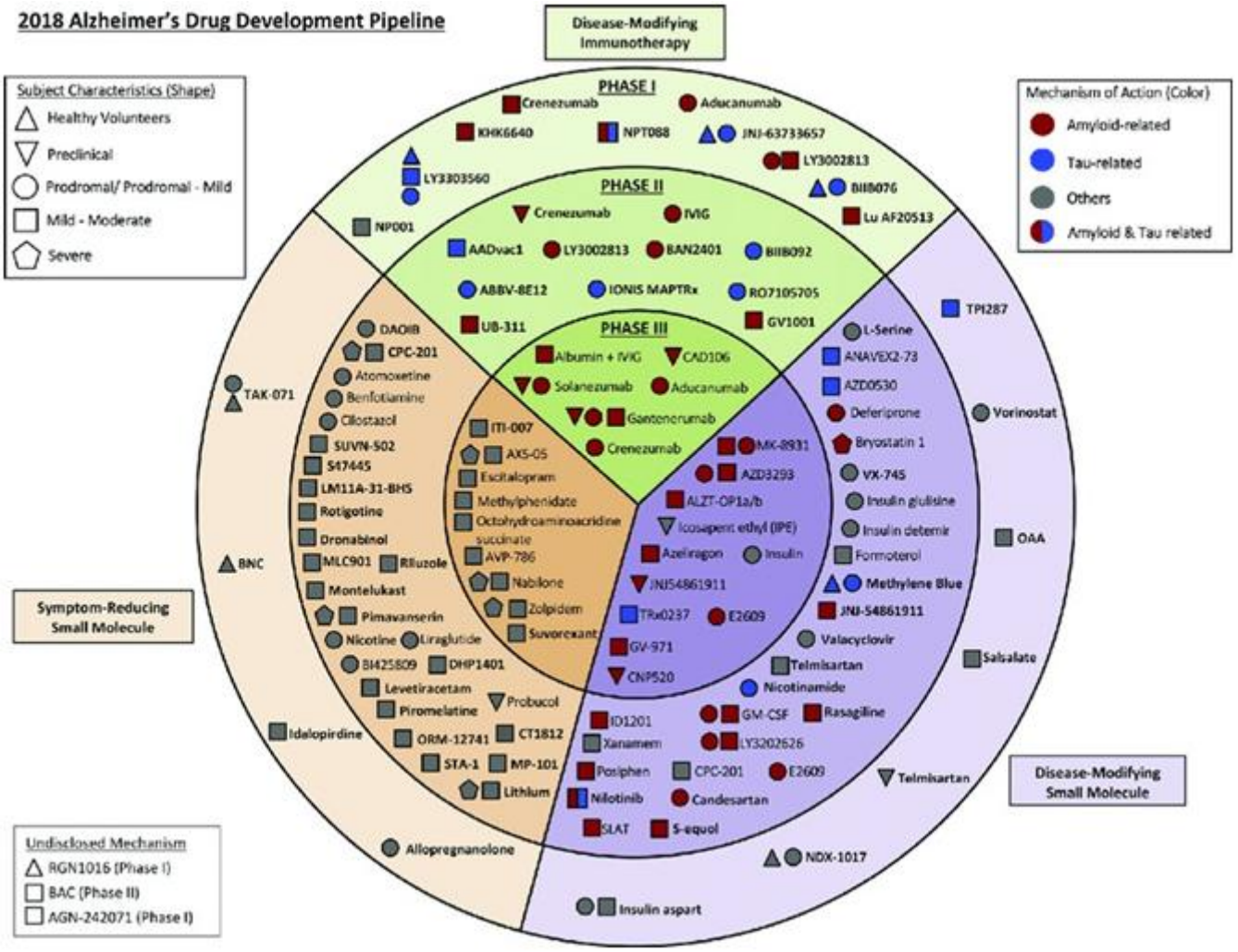
Now, let´s deal with a possible drug curing AD, called a manifold drug.

A manifold drug for Alzheimer´s Disease

How can we find drugs for Alzheimer´s disease?

In this paper a new method finding drugs is proposed. We have seen how many factors can be the cause of AD, so we have to create a manifold drug, i.e., a combination of integrin protein, kinesin, dynein …

Contemporary science often uses this model for clarifying status dealing with drugs for Alzheimer´s disease:



(Source: alzheimer's drugs in clinical trials-Sök (bing. com))

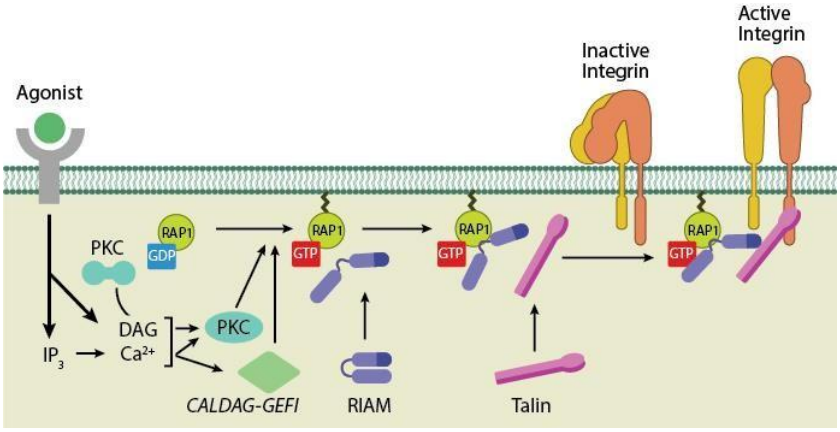
This model shows how different approaches try to handle inflammation and targeting the tau protein tangles which are linked to and occur in Alzheimer´s disease, but the cause of AD is still not yet known, so drugs cannot successfully be developed.

We have to test another angle finding medicine for AD. If we focus on multifactorial drugs, then the content of the medicine might be:

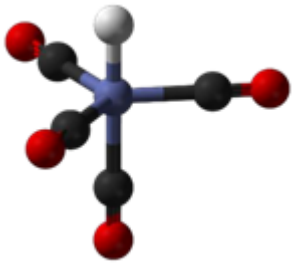
- Kindlin-3, which has a role in the function of integrin activation.
- Talin,
- Ligand,
- Salt bridge.

Kindlin-3 is also known as FERM3. Below in the figure we find how it works out dealing with the integrin (Source: The kindlin family: functions, signaling properties and implications for human disease | Journal of Cell Science | The Company of Biologists):

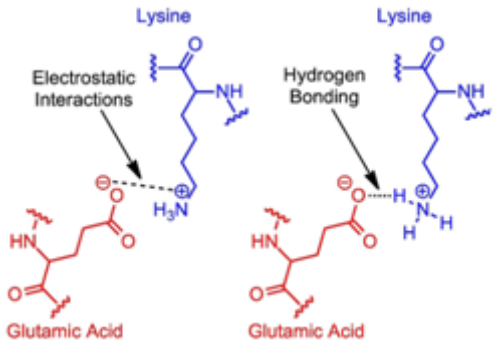
The COOH represents carboxyl group, and the most common organic acids are organic carboxylic acids. Talin activation and membrane recruitment, by engaging:



Below a cobalt complex HCo (CO) 4 with five ligands:



The figure below is an example of salt bridge between acids glutamic acid and lysine.

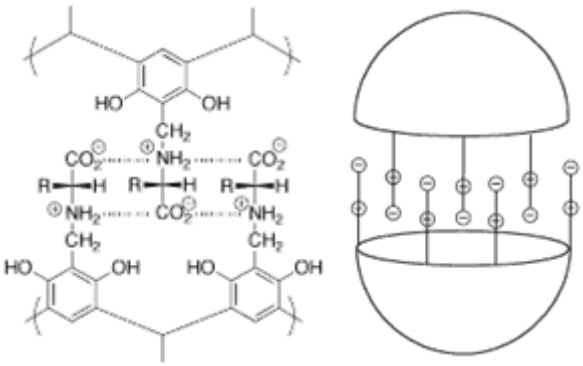


Source: Next Revisit Glutamic Acid Lysine salt bridge-Salt bridge (protein and supramolecular)-Wikipedia How then can we create a manifold drug and treatment for AD?

Starting with molecules and their atoms, then we create a new molecule as drug for AD.

The atoms and the molecules are the following:

1) Glutamic acid using the atoms C, H, N, O and its formula C5H9NO4
2) Ligands using the atoms H, C, O, o and its formula HCo (CO) 4
3) Lysine uses the atoms N, H and its formula $^{+}-NH3$
4) The salt bridge uses the atoms H, O, N, R and its formula and function can be seen in these two figures, connecting two halves of the molecular capsule:



It seems obvious that the understanding of how mass a move in the human body is not fully understood.5 Then we have two choices dealing with drugs and treatment for AD:

1) By a combination of atoms and molecules, based on what has been told above, create the drug.
2) Accept one superior aRb and by its activation repair the cell.

We have to find the dominant and superior aRb, which dictates the process. We must implement a system for

fulfilling flows of atoms and molecules. The flow of C – H – N – O – H – C-O – N – H – H must be reassured.

Now we have to find out how to organize this chain C – H – N – O – H – C-O – N – H – H.

Then we have to produce the molecule and find out how to inject it in the human body, i. e., how to put it in to the brain.

This is a demanding iterative process engaging hundreds of scientists and thousands of lab tests and clinical trials before the molecule becomes a drug seen as a masterpiece.

To be continued …

Notes

1) The theory was first published by Cambridge Scholars Publishing: *The Principle of Relations*.2018. The theory has been developed in the book *The Theoretical Foundation of Physical Reality*, authorHOUSE, 2020. Then the book *Reality and the Paradigm of Relations* was published 2021 by Nova Science Publisher in New York.
2) What is Inflammation? (ijsr.net)
3) The Scientific Illusion of Homeostasis (ijsr.net) and How Mass Moves in the Human Body (ijsr.net)
4) Thomas S. Kuhn: *The Structure of Scientific Revolutions*.2012: "…when paradigms change, the world itself changes with them. Led by a new paradigm, scientists adopt new instruments and look in new places. Even more important, during revolutions scientists see new and different things when looking with familiar instruments in places they have looked before. "
5) How mass moves in the human body IJSR.pdf