



anavex

LIFE SCIENCES Corp.

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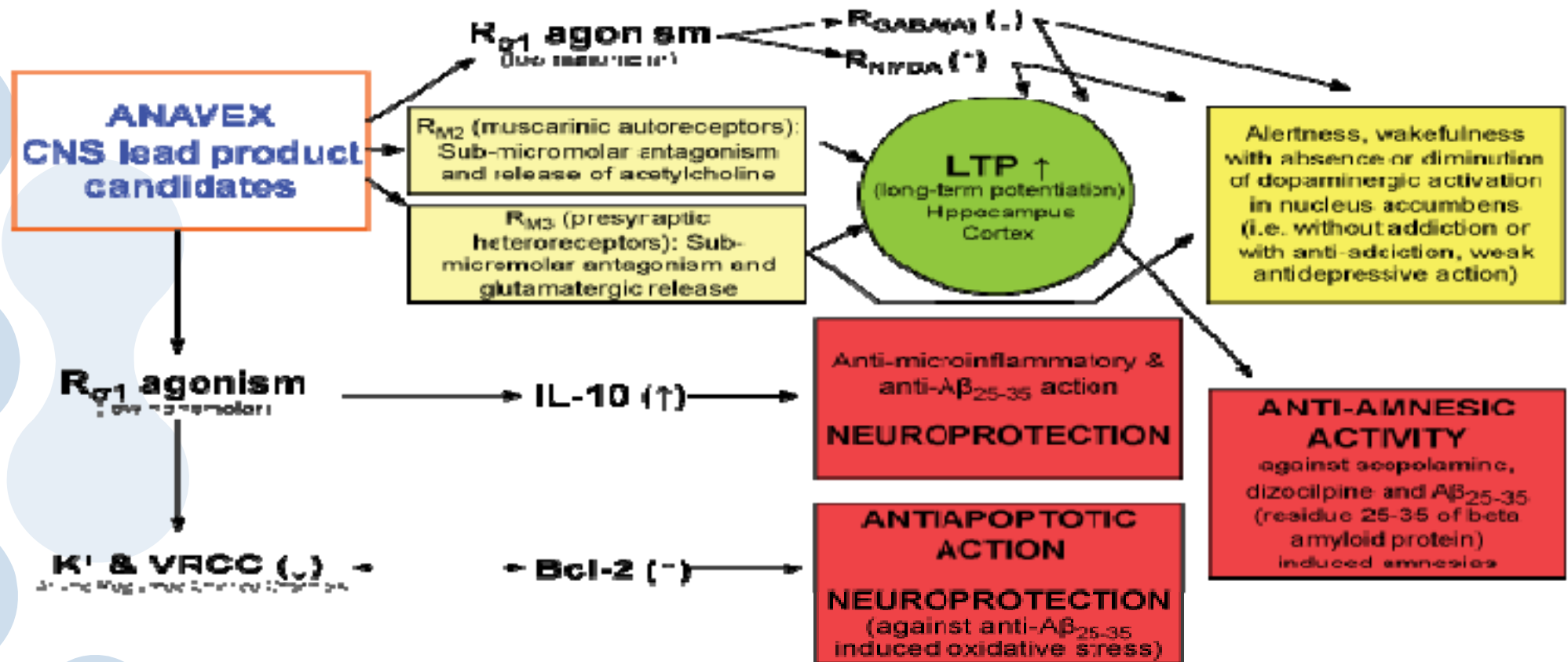
Sigma Receptors: Clinical Importance

- Sigma-1 and sigma-2 receptor ligands are capable of modulating multiple pathways involved in CNS conditions and cancer
- There is independent and validated evidence for ANAVEX sigma receptor ligands in treating CNS disorders including Alzheimer's disease and epilepsy:
 - **disease-modifying properties (not only symptomatic improvement)**
 - **neuroprotective, anti-amnesic and anti-epileptic action**
 - **anti-apoptotic activity and prevention of oxidative stress (which leads to neuronal death)**
- There is independent and validated evidence for ANAVEX sigma receptor ligands in treating cancer:
 - **selective apoptosis (programmed cell death) of cancerous cells without affecting healthy cells**

Mechanism of Action (MOA) of ANAVEX 2-73

(Tetrahydro-N, N-dimethyl-2, 2-diphenyl-3-furanmethanamine hydrochloride)

Central Nervous System: Neurodegenerative diseases



- Selective ligand for σ-1 receptors with a high nanomolar affinity (pKi=6,3)
- No affinity for σ-2 receptors
- Anti-amnesic action (antagonistic action against scopolamine and dizocilpine (MK-801) induced amnesia or amyloid peptide β25-35 (Aβ25-35), at low doses)
- Anti-oxidative stress via agonistic action on σ-1 receptors (ER and mitochondria)
- Excellent safety and toxicological data

Competitive Major MOAs

MOA	Example company/compound	Status	Comments
Oxidative stress/sigma-1 agonist, cholinergic effects via muscarinic receptors/NMDA modulation	ANAVEX (2-73) , Pfizer/Eisai (ARICEPT), Eisai (SA4503)	Clinically VALIDATED (MARKETED: Aricept)	2-73 works by all three mechanisms, driven by oxidative stress. Sigma-1 includes marketed product leader (ARICEPT) from Pfizer/Eisai, plus follow-on product from Eisai.
NMDA receptor modulation	ANAVEX (2-73) , Evotec (EVT-101), Nippon Chemiphar (3459), Forrest (NAMENDA)	Clinically VALIDATED (MARKETED: Namenda)	MOA includes marketed product, 2-73 has therapeutic effect via this MOA and sigma-1
Cholinesterase inhibitor	Novartis (EXELON), Pfizer/Eisai (ARICEPT), Janssen (RAZADYNE)	Clinically VALIDATED (MARKETED: Aricept, Exelon, Razadyne)	MOA has several marketed products that treat symptoms only. Leading pharmaceutical companies need follow-on disease-modifying compounds with new MOA to maintain and grow category post LOE.
Clearance of amyloid beta/secretase inhibitor and anti-amyloid	Neurochem (Alzamed), Myriad (Flurizan), Wyeth/Elan (bapanizumab, ACC-001) CoMentis, Lilly (LY450139), NeuroHitech, Prana (PBT-2), TorreyPines (posiphen), Transition (AZD-103), Nymox (statins), TorreyPines (posiphen), Lilly (LY450139)	Not validated; Phase III failures	All later-stage products have failed in Phases II or III; investor fatigue, increasing KOL skepticism and growing literature dismissing amyloid as cause and viable target
Clearance of tau	REMBER/methylene blue (TauRx), Allon (AL-108)	Not validated	Questionable data analysis, lack of reproducibility or results, KOL skepticism
Nicotinic receptor agonist	Astra-Zeneca/Targacept (TC-1734), Memory (MEM-3454)	Not validated	Failed in Phase II
Unknown/mitochondrial pore blocker	Medivation (Dimebon)	Not validated	?data analysis, lack of reproducibility of results when tested by NIH
Unknown/neuroprotection	Baxter (IgG)	Not validated	Uncertain MOA, KOL skepticism

External Value Drivers

Competitive environment remarkably favorable for ANAVEX

- Competitors experiencing spectacular failures in Phases II and III
- Many programs target mechanisms of action recently shown to be potentially erroneous
- 400+ AD clinical studies – most are reformulations, fewer than 50 are novel compounds

Market dynamics

- AD is a fast growing category
- Huge unmet need for sustainable efficacy, fewer adverse events and disease modifying (vs. symptomatic) treatments
- Four currently marketed meds all off patent within five years

Big pharma dynamics

- ANAVEX already attracting big pharma attention
- AD is a 'must-invest' area for big pharma
- Big pharma eager to do deals in high-growth, high unmet need categories such as AD; internal programs often unproductive
- No opportunities left for big pharma to partner Phase III assets in AD
- 3 or 4 candidates available for big-pharma licensing deals in Phases I/II