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Translacijska istraživanja u neuroznanosti

Goran Šimić

Medicinski fakultet Sveučilišta u Zagrebu



Sažetak izlaganja

- Osvrt na razvitak ideje o važnosti translacijskog pristupa istraživanjima u neuroznanosti
- Neki novi časopisi orijentirani na objavljivanje rezultata translacijskih istraživanja
- Časopis *Translational Neuroscience*

Brojna nova otkrića, ali bez (brze) dobrobiti za bolesnike

mef.hr

translacijska istraživanja

translacijska istraživanja

Translacijska istraživanja Alzheimerove bolesti jučer, danas i sutra

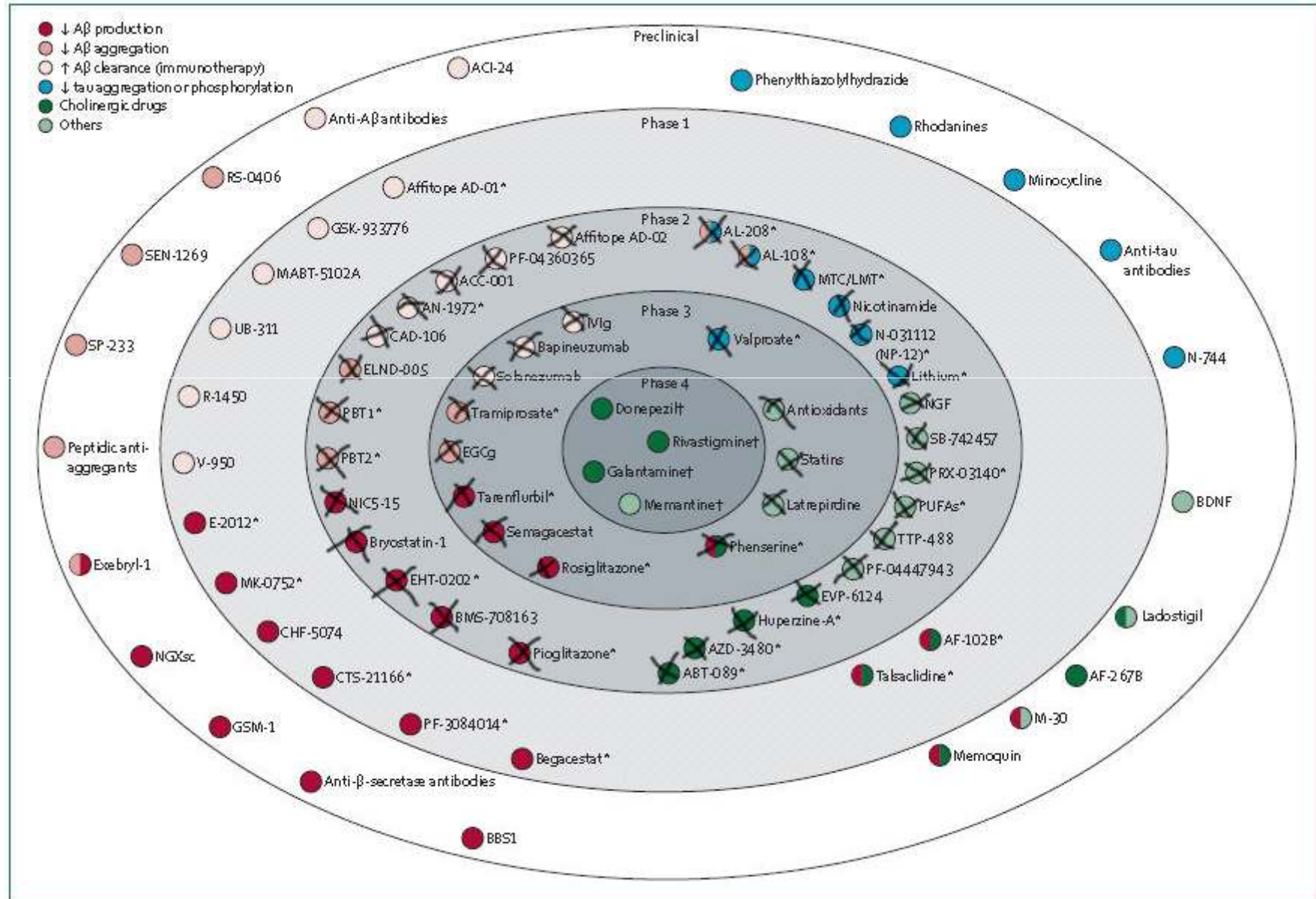
Što smo prije dvadeset godina znali o Alzheimerovoj bolesti (AB) i kako smo je liječili?

S obzirom na nastanak AB, od njezina prvog opisa pa do današnjih dana bilo je rasprostranjeno vjerovanje o postojanju jedinstvenog uzročnika bolesti. To se svojstvo osamdesetih i devedesetih godina pripisivalo isključivo amiloidu, kao središnjem činitelju u nastanku AB, a moguć slijed događaja koji dovode do bolesti nazvan je amiloidnom kaskadnom hipotezom.

Sve do 1991. godine većina znanstvenika, čak i onih koji su se aktivno bavili proučavanjem AB, nije vjerovala da ova bolest čiji se simptomi i znakovi pojavljuju tako kasno u tijeku života može nastati zbog jednog jedinog „krivog“ slova u genomu koji broji nekoliko milijardi slova. Tada je pronađena prva mutacija gena za amiloidni prekursori protein – APP (tzv. Londonska mutacija). Do danas je

treba odmah reći da je i danas liječenje simptomatsko, a ne uzročno. Razvoj i registracija lijekova uobičajeno kasne za znanstvenim spoznajama, u prosjeku 10 – 15 godina. Otkada su Whitehouse i suradnici dokumentirali propadanje bazalne jezgre (čiji se neuroni projiciraju u moždanu koru, a koriste neurotransmiter acetilkolin) u oboljelih od AB 1981. godine, smatralo se da bi se pospješerenjem djelovanja acetilkolina moglo liječiti AB. Trebalo je 12 godina do registracije takrina 1993., 16 godina do registracije donepezila 1997., 19 godina do registracije rivastigmina 2000., odnosno 20 godina do registracije galantamina 2001. godine. U međuvremenu je jasno pokazano da je propadanje živčanih stanica bazalne jezgre samo sekundarna i relativno kasna posljedica propadanja živčanih stanica u moždanoj kori, pa ne čudi činjenica da ti lijekovi samo prolazno i kratkotrajno usporavaju napredovanje bolesti, i to samo u nekih bolesnika u početnim stadijima bolesti.

posljedica normalnog starenja, ne može dokazati ako se u analizu ne uključe i mlade odrasle osobe. S druge strane, kad se na gubitak neurona koji pripisujemo samom starenju pridoda broj neurofibrilarnih snopica u AB, neka područja mozga, kao što su hipokampus i entorinalni korteks, pokazuju veći gubitak neurona nego što bi se on mogao objasniti samo neurofibrilarnim promjenama. To je dokaz da u AB postoje različiti mehanizmi propadanja živčanih stanica. Jedan od ključnih problema jest i činjenica da je gotovo nemoguće razviti dobar životinjski model za proučavanje bolesti koja je karakteristična za čovjeka, a traje 20 – 30 godina prije nastanka prvih kliničkih simptoma. Ne tako davno svjedočili smo da je nedostatak temeljnih spoznaja o mehanizmima nastanka AB rezultirao katastrofalnim neuspjehom pokušaja liječenja bolesti imunizacijom 360 bolesnika cijelom molekulom beta-amiloida (vakcina AN1792). Zbog aktivacije potpornih stanica te upale mozga i moždanih ovojnica umrlo je tridesetak bolesnika uklju-



Svi su se navedeni spojevi:

- Pokazali obećavajućima u eksperimentalnim istraživanjima na životinjama
- Pokazali obećavajućima u prvoj fazi kliničkih istraživanja (na malom broju ispitanika)
- ALI...
se nakon toga moralo odustati od njihove daljnje primjene
- ZAŠTO (i kako su uspjeli proći sve prethodne faze)?

Glavni razlozi za neuspjeh translacije istraživanja u nove načine liječenja su:

1. Upotreba životinjskih modela bolesti koji ne odražavaju dovoljno precizno patogenezu dotičnih bolesti u ljudi
2. Činjenica da je mala vjerojatnost objavljivanja negativnih, nesignifikantnih ili neutralnih rezultata dobivenih u predkliničkim istraživanjima

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Elias A. Zerhouni, M.D.

N ENGL J MED 353;15 WWW.NEJM.ORG OCTOBER 13, 2005

- **...“At no other time has the need for a bidirectional information flow between basic and translational scientists been so necessary.”**
- **...“Genomics, proteomics, transgenic animal models, structural biology, biochemistry, and imaging technologies offer unprecedented prospects for advancing knowledge of human disorders in a translational context”**
- **...”In an attempt to address these concerns, ... the NIH has funded facilities, resources, or both (...36% of its budget) to bolster translational research. ...Yet, the concerns persist, and more must be done.”**
- **...”The scope of knowledge and expertise needed to be an effective translational scientist can no longer be acquired “on the job”, as was done in the past.”**

Lost in Translation

Facing Up to Translational Research

James Levine

DIABETES, VOL. 56, DECEMBER 2007

- **...”Currently, in science, we have our buzz word: “translational research”...Whichever academic center you visit and whatever despairing grant review panel you sit on, I guarantee that the term “translational research” will surface. In fact, I bet that somewhere on earth at every second of every day, somebody somewhere is using the term “translational research” because they are tacitly aware of the fact that there is an urgent need to think out of the box...”**
- **...”The wonderful thing about translational research is that every one knows exactly what it means – the only trouble is that none of them have the same definition.”**
- **...”linear, hypothesis-driven research is almost extinct; ...hypotheses now represent observing the effect of 10,000 genes on scenario X or examining how 50,000 proteins respond to soup Y?... Perhaps, I should turn off the computer and toss my PDA if it will give me the time to do what I am supposed to do as a scientist: take a look at the world and think.”**

Translational research in environmental health sciences

- **...”Clearly, a need exists to translate more quickly the myriad of discoveries in biomedical research into more effective applications relevant to human health and disease.”**
- **...”Translating research and patient data should be viewed as an interconnecting and multidirectional network, with information that flows back and forth among basic scientists, clinicians, epidemiologists, engineers, and policy makers.”**
- **...”The concept of translational research is not meant to push academic scientists into starting biotech companies or to be totally product driven. Translation should be viewed as both an opportunity and in some ways an obligation, so that the general public receives some tangible benefit for supporting the vast research enterprise.”**
- **...”The importance of translational research relative to the broad research enterprise is perhaps best summed up by the following quote from Goethe: “Knowing is not enough; we must apply. Willing is not enough; we must do.””**

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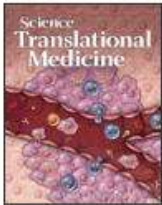

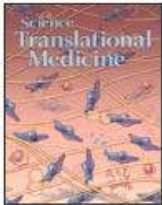

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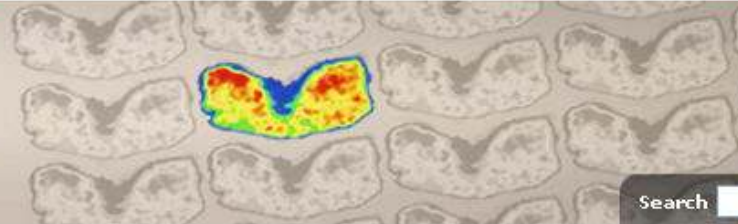
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Introducing the journal "Translational Neuroscience"

Although the last two decades have brought an amazingly rapid accumulation of information concerning all aspects of neuroscience, promising applications of this expanding knowledge have only slowly been realized. In other words, there has been an unprecedented necessity to translate more quickly the discoveries in biomedical research into more effective applications relevant to human health and disease.

With this in mind, several of my colleague scientists, and here I wish to thank particularly Professor Patrick R. Hof from Mount Sinai School of Medicine in New York (now the Senior Advisory Editor of the journal) and myself started to think of responding to this real need in the scientific community by launching a journal devoted to translational neuroscience. After several months of discussions, at the beginning of this year we launched the journal "Translational Neuroscience". The journal is published by Versita and co-published by Springer Verlag publishers.

"Translational Neuroscience" is an international peer-reviewed journal published quarterly in paper (p-ISSN 2081-3856) and electronic (e-ISSN 2081-6936) versions. The language of the journal is English. The web site of the journal is <http://www.versita.com/science/medicine/tn>.

I'm pleased to let you know that Springer has approved to begin distributing the journal "Translational Neuroscience" worldwide from 2011 and will also host the 2010 volume on SpringerLink <http://www.springerlink.com>. I welcome all submissions, comments and suggestions you might have in order to improve our Journal.


Sincerely,

Goran Šimić, M.D., Ph.D.

Translational Neuroscience, Editor-in-Chief and Managing Editor

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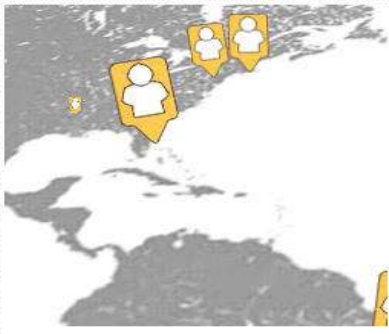
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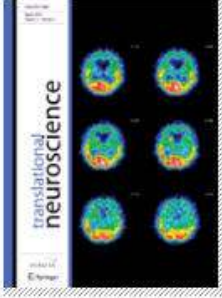
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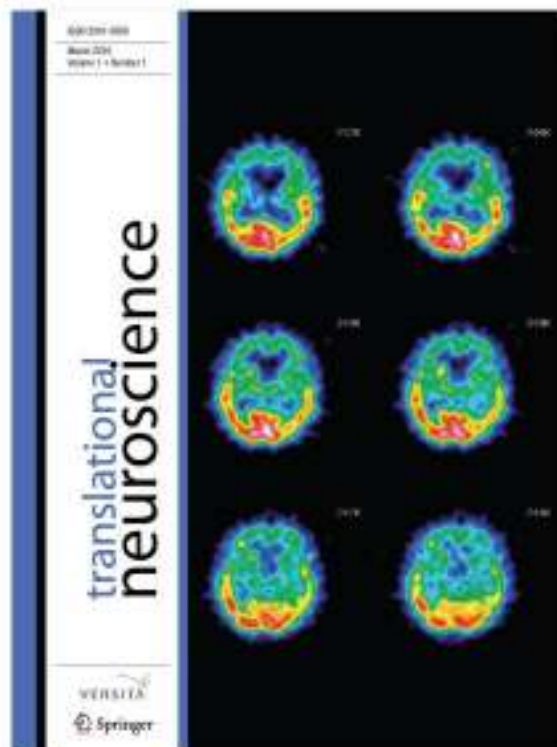
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