NEUREYE

New molecules to counteract neurodegenerative ocular pathologies

Main partners involved

Coordinator: A. Pascale, Drug Sciences Department, Section of Pharmacology, University of Pavia.

Main collaborators within the Department of Drug Sciences:

1) Pharmacology Section: S. Govoni, M. Amadio; A. Barbieri;

2) Medicinal Chemistry & Technology Section: S. Collina, D. Rossi, C. Bonferoni and F. Ferrari.

Main collaborators from other Universities:

1) University of Catania:

-Department of Biomedical and Biotechnological Sciences, F. Drago & C. Bucolo team;

-Department of Drug Sciences, R. Pignatello.

2) University of Eastern Finland, Kuopio, Department of Ophthalmology, K. Kaarniranta.

CONTACT

Alessia Pascale:
alessia.pascale@unipv.it

The problem

Diabetic retinopathy (DR) and age-related macular degeneration (AMD) are neurodegenerative pathologies that affect the retina and represent the major causes of irreversible visual impairment in the elderly.
Vascular Endothelial Growth Factor A (VEGF) is a crucial element in RD and AMD forms characterized by new vessels formation, and its inhibition via anti-VEGF antibodies represents an effective therapeutic approach. Although these drugs exhibit excellent safety profiles, ocular and systemic complications remain a concern due to the suppression of VEGF basal activity, necessary to accomplish fundamental physiological functions (i.e. neurotrophic activity and tissue repairing). Moreover, these drugs are expensive, also due to the lack of alternative molecules.

The solution

The project is based on an innovative strategy: to modify the amount of fundamental cellular proteins acting through a new class of proteins named ELAV. The ELAV proteins family interacts with specific sequences within target mRNAs, mainly positively affecting their stability and/or rate of translation into protein. As mentioned, a key protein, which is produced in excessive quantity in some stages of these ocular pathologies, is VEGF whose mRNA is a target of ELAV proteins.
Within this context, in the rat retina, we documented that the ELAV/HuR protein binds to VEGF mRNA and that, following experimentally-induced diabetes, increases the amount of VEGF protein. Moreover, we found that nanosystems loaded with a commercially available siRNA (a short RNA that interferes with the expression of specific genes) that switches off HuR expression when injected into the eye of diabetic rats are able to reduce, without suppressing, VEGF basal levels. These data indicate that

the ELAV/HuR may be a new therapeutic target useful to counteract pathologies implicating VEGF alteration.

Goals

- *In silico* screening studies to identify molecules able to interfere with ELAV/HuR activity.
- Design and synthesis of new ELAV/HuR interfering compounds.
- Preparation of nanosystems loaded with these new molecules.
- Proof of the biological effectiveness of these nanosystems through pharmacological *in vitro* and *in vivo* studies.
- Search for funding to create fellowships for young researchers involved in the project.

Publications within the field

1) "PKC βII/HUR/VEGF: A NEW MOLECULAR CASCADE IN RETINAL PERICYTES FOR THE REGULATION OF VEGF GENE EXPRESSION". Amadio M., Scapagnini G., Lupo G., Drago F., Govoni S. and Pascale A. *Pharmacological Res.* 57(1): 60-66, 2008.

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3) "THE PKCβ/HUR/VEGF PATHWAY IN DIABETIC RETINOPATHY". Amadio M., Bucolo C., Leggio G.M., Drago F., Govoni S. and Pascale A. *Biochem. Pharmacol.* 80: 1230-1237, 2010.

4) "PROTECTING THE RETINAL NEURONS FROM GLAUCOMA: LOWERING OCULAR PRESSURE IS NOT ENOUGH". Pascale A., Drago F. and Govoni S. *Pharmacological Res.* 66(1): 19-32, 2012.

5) "PROTEIN KINASE C ACTIVATION AFFECTS, VIA THE mRNA-BINDING Hu-ANTIGEN R/ELAV PROTEIN, VASCULAR ENDOTHELIAL GROWTH FACTOR EXPRESSION IN A PERICYTIC/ENDOTHELIAL COCULTURE MODEL". Amadio M., Osera C., Lupo G., Motta C., Drago F., Govoni S. and Pascale A. *Molecular Vision* 18: 2153-2164, 2012.

6) "AUTOPHAGY ACTIVATION CLEARS ELAV1/HUR -MEDIATED ACCUMULATION OF SQSTM1/P62 DURING PROTEASOMAL INHIBITION IN HUMAN RETINAL PIGMENT EPITHELIAL CELLS". Viiri J., Amadio M., Marchesi N., Hyttinen J.M.T., Niko Kivinen N., Sironen R., Rilla K., Akhtar S., Provenzani A., D'Agostino V.G., Govoni S., Pascale A., Agostini H., Petrovski G., Salminen A. and Kaarniranta K. *PLoS One* 8(7): e69563, 2013.

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8) "INDUCTION OF VEGFA mRNA TRANSLATION BY CoCl2 MEDIATED BY HUR". Osera C., Martindale J.L., Amadio M., Kim J., Yang X., Moad C.A., Indig F.E., Govoni S., Abdelmohsen K., Gorospe M., Pascale A. *RNA Biol.* 12(10):1121-30, 2015.

9) "TARGETING VEGF IN EYE NEOVASCULARIZATION: WHAT'S NEW? A COMPREHENSIVE REVIEW ON CURRENT THERAPIES AND OLIGONUCLEOTIDE-BASED INTERVENTIONS UNDER DEVELOPMENT". Amadio M., Govoni S., Pascale A. *Pharmacol Res.* 103:253-69, 2016.

10) "NANOSYSTEMS BASED ON siRNA SILENCING HUR EXPRESSION COUNTERACT DIABETIC RETINOPATHY IN RAT". Amadio M., Pascale A., Cupri S., Pignatello R., Osera C., D'Agata V., D'Amico A.G., Leggio G.M., Ruozi B., Govoni S., Drago F., Bucolo C. *Pharmacol Res.*111:713-20, 2016.