BIOGRAPHICAL SKETCH

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NAME: MINEA, Radu Octavian

eRA COMMONS USER NAME (credential, e.g., agency login): RADUM321

POSITION TITLE: Research Assistant Professor, Department of Neurological Surgery, Keck School of Medicine, University of Southern California

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania	M.D.	1993	Medicine
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania		1995-2000	Surgical Residency
University of California Los Angeles, Los Angeles, California		2001-2002	Immunology and Microbiology (Postdoctoral studies)
University of Southern California, Los Angeles, California		2002-2004	Biochemistry and Molecular Biology (Postdoctoral studies)

A. Personal Statement

Although my professional background is clinical, as a trained M.D. who specialized in abdominal oncological surgery, I have spent the last 14 years in translational cancer research at University of Southern California and with several biotech startup companies being directly involved in the development of novel therapies specifically designed for treating metastatic disease. My research interest lies with the discovery and development of biologics that could potentially revolutionize the treatment of aggressive tumors by exploiting universal mechanisms of metastatic colonization. Toward this goal, I developed an expertise in the field of recombinant protein production and in engineering recombinant expression systems suitable for scalable production of heterologous disulfide-rich biologics with diagnostic and therapeutic value. This work was instrumental in the subsequent design and production of several of recombinant polypeptides that were modeled after a native class of high affinity integrin ligands called disintegrins and originally isolated from snake venoms. Disintegrins function as broad-spectrum integrin ligands and, as potential drug candidates, demonstrate some unique and favorable pharmacologic properties such as extreme stability, lack of toxicity and very high affinities and specificities for several integrin subclasses. Importantly, some of these integrin receptors are also mechanistically involved in metastasis which makes disintegrins extremely valuable drug candidates for tackling metastatic disease. Some of the recombinant polypeptides I had produced and characterized over the years were successfully validated in preclinical models of human breast, ovarian, prostate and brain cancers, including metastatic models. Due to their high stability and solubility, recombinant disintegrins can be easily and stably modified covalently (e.g., fluorescent labeling, radioiodination, etc.) with no loss of activity. I envision a clinical use for recombinant disintegrins as molecular carriers for precision delivery of ablative amounts of beta-emitting radionuclides into metastatic foci, which could potentially

represent a highly effective form of targeted radioablation with minimum off-target effects. Furthermore, disintegrins, specifically because of their high affinity for receptors intimately associated with and involved in multiple metastasis steps, could also be utilized as powerful molecular tools to further our understanding of which molecular drivers and signaling complexes are dynamically operating during metastatic colonization. Additional potential clinical applications for recombinant disintegrins I am currently exploring relate to their usage as sustained release hydrogel formulations for targeting the cancer self-seeding process by during peritoneal or leptomeningeal carcinomatosis in multiple solid tumors including ovarian and breast cancers. Finally, I am interested in exploring the potential of recombinant disintegrins for imagistic applications, as targeting moieties for nanotherapeutic carriers, or as bioadhesives. Together with several basic science investigators and clinicians from the University of Southern California, I co-founded two startup companies with the goal of bringing disintegrin-based cancer theranostics closer to the clinic.

B. Positions and Honors

Positions and Employment

1994-1995 Primary Care Physician, Witing Clinical Hospital, Bucharest, Romania
1995-2000 General and Abdominal Oncology Surgery Resident, Carol Davila University of Medicine and Pharmacy, Fundeni Residency Program in Surgical Oncology, Bucharest, Romania
2000 Visiting Surgery Resident, Lincoln Medical Center, Bronx, NY
2001 Research Associate, Department of Microbiology and Molecular Immunology, University of California Los Angeles, Los Angeles, CA
2002-2004 Research Associate, Department of Biochemistry and Molecular Biology, University of Southern California, Los Angeles, CA
2005-2009 Scientist, Pivotal Biosciences, Inc., Los Angeles, CA
2010-2013 Co-Founder, Principal Scientist, Applied Integrin Sciences, Inc., Thousand Oaks, CA
2014 Co-Founder, Chief Scientific Officer, Disintegrin Therapeutics, Inc., La Canada, CA
2015 Research Assistant Professor, Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA

Entrepreneurship

Co-Founder of Applied Integrin Sciences, Inc., a startup company aimed at developing novel integrin-targeted imaging and therapeutic agents

Co-Founder of Disintegrin Therapeutics, Inc., a startup company aimed at developing disintegrin-based therapeutics for targeted brachytherapy applications and nanoparticle-based solutions for multiple cancer indications

C. Contribution to Science

My main efforts are directed at identifying, designing, and developing first-in-class diagnostic and therapeutic agents with potential impact on altering the progression of advanced, already metastasized human cancers. Toward this goal, one of my contributions, which eventually led to a number of issued patents, was to engineer a bacterial recombinant system suitable for robust and scalable production of disulfide-rich polypeptide biologics with diagnostic and therapeutic value. This system was successfully employed in the production of several recombinant polypeptides belonging to the disintegrin class the first of which, called vicrostatin (VCN), I had modeled after two prototypical snake venom disintegrins to facilitate the incorporation of different structural and functional features from each parental molecule into one chimeric polypeptide with superior activity. This lead to an entirely new biologic with enhanced affinity toward a specific set of human integrins (i.e., multiple αv and α5 subclasses) and novel functionality. This drug candidate has since been extensively tested preclinically and demonstrated potent anti-invasive/anti-metastatic properties in many animal models with very promising results in breast, ovarian, prostate, and brain models of human cancer. Based on its promising efficacy data, favorable stability, pharmacokinetics and toxicology attributes, VCN is currently developed toward its first clinical indication - i.e., to be used for intra-peritoneal delivery in hydrogel formulations in advanced ovarian cancer as a mechanism aimed to stop the intra-peritoneal seeding by ovarian cancer multicellular aggregates. Radioiodinated disintegrins could also potentially function as potent anti-metastatic agents specifically for targeting and treating already established metastatic foci with high specificity (i.e., targeted radioablation) or as contrast-enhancing agents for SPECT/CT imaging to visualize micrometastases and for monitoring the

response of tumors to various therapies. More recently, I developed a biodegradable nanoparticle platform that could be used for gadolinium (Gd, a paramagnetic substance) delivery into metastatic foci in a targeted manner and in conjunction with additional imaging modalities as well as for innovative therapeutic applications in oncology. Listed below are selected publications with this lead molecule:

Issued patents

US Patent 7,754,850 (2010) - **Minea R.** and Markland F.S. Chimeric disintegrin domain

US Patent 8,802,394 (2014) - **Minea R.**, Swenson S., and Markland F.S. Method of expressing proteins with disulfide bridges with enhanced yields and activity

Research papers

Minea R., Helchowski C., Zidovetzki S., Costa F., Swenson S., and Markland F.S. Vicrostatin – An anti-invasive multi-integrin targeting chimeric disintegrin with tumor anti-angiogenic and pro-apoptotic activities; PLoS One 5, e10929, 2010

Minea R., Helchowski C., Rubino B., Brodmann K., Swenson S., and Markland, F.S., Jr. Development of a chimeric recombinant disintegrin as a cost-effective anticancer agent with promising translational potential; Toxicon, 2011, doi:10.1016/j.toxicon.2011.02.020

More recently, I also designed, produced, and partially characterized a library of human-derived disintegrins representing an entirely new class of recombinant polypeptides (called MAPs or 'modified ADAM polypeptides') that were modeled after the disintegrin-like domains of human ADAM (A Disintegrin And Metalloproteinase) proteins; these recombinant polypeptides (comprising 23 drug candidates) are intended to be further developed as novel high-affinity/high-specificity integrin ligands for multiple diagnostic and therapeutic applications as they represent a complex molecular toolbox potentially covering the entire integrin receptor repertoire dysregulated in cancer and in a number of other pathologies (such as multiple sclerosis and Crohn's). While the development of this family of recombinant polypeptides is still in its early stages, a lead human disintegrin called DTI15 and modeled after the disintegrin-like domain of human ADAM15 is currently evaluated preclinically in multiple animal models of cancer. A radioiodinated version of DTI15 will be evaluated for its potential to directly treat metastatic foci in patients with advanced ovarian (high-grade serous) or breast cancers (triple-negative subtype).

Published work

Issued patents

US Patent 7,754,850 (2010) - **Minea R.** and Markland F.S. Chimeric disintegrin domain

US Patent 8,110,542 (2012) - **Minea R.** and Markland F.S. Methods of expressing proteins with disulfide bridges

US Patent 8,338,365 (2012) - **Minea R.** and Markland F.S. Inhibiting integrin receptor binding with non-native monomeric disintegrin or monomeric disintegrin domains

US Patent 8,685,668 (2014) - **Minea R.** and Markland F.S. Method of expressing proteins with disulfide bridges

US Patent 8,802,394 (2014) - **Minea R.**, Swenson S., and Markland F.S. Method of expressing proteins with disulfide bridges with enhanced yields and activity

Pending patents and patent publications

Minea R., Swenson S., Markland F.S. Modified ADAM disintegrin domains polypeptides and uses thereof WO2011100362 and US2013045244 2011

Markland F.S., **Minea R.**, Swenson S., Tiwari V. Compositions and methods for inhibiting viral infection US20130177528 2013

Markland F.S., Swenson S., **Minea R.** Bioadhesive patch for sutureless closure of soft tissue WO2010093976 and US2012142603 2012

Janib S.M., MacKay J.A., Markland F.S., Swenson S., **Minea R.**, Chen T.C. Protein polymers to improve the efficacy of anti-cancer biopharmaceuticals Pending Publication 2014

Markland F.S., Swenson S., and **Minea R.** Compositions and methods for treating and preventing the recurrence of ovarian cancer Pending Publication 2014

Research papers and book chapters

Swenson S., Costa F., **Minea R**., Sherwin R.P., Ernst W., Fujii G., Yang D., and Markland FS Jr. Intravenous liposomal delivery of the snake venom disintegrin contortrostatin limits breast cancer progression; Mol Cancer Ther. 2004 Apr;3(4):499-511

Markland F.S., Swenson S., Costa F., **Minea R.**, Sherwin R.P., Yang D., Ernst W., and Fujii G. A snake venom disintegrin with potent antitumor and antiangiogenic activity; Toxin Reviews 2005; 24(1): 113-142

Minea R., Swenson S., Costa F., Chen C. T., and Markland F.S. Jr. Development of a novel recombinant disintegrin, contortrostatin, as an effective anti-tumor and anti-angiogenic agent; Pathophysiology of Haemostasis and Thrombosis 2005; 34: 177-183

Swenson S., Costa F., **Minea R.**, Fujii G., Ernst W., Markland F. A snake venom disintegrin with powerful anti-angiogenic activity: *in vitro* and *in vivo* studies; Rencontres en toxinologie: Toxines et cancer 2006; 209-218

Helchowski C.M., **Minea R.O.**, Swenson S.D., and Markland F.S., Jr. The use of pepsin in receptor internalization assays; Biochem Biophys Res Commun, 388: 240-246, 2009

Minea R., Helchowski C., Zidovetzki S., Costa F., Swenson S., and Markland F.S. Vicrostatin – An anti-invasive multi-integrin targeting chimeric disintegrin with tumor anti-angiogenic and pro-apoptotic activities; PLoS One 5, e10929, 2010

Swenson, S., **Minea, R.**, and Markland, F.S. Development of integrin targeted anti-angiogenic agents. In Tumor Angiogenesis: From Molecular Mechanisms to Targeted Therapy (Editors: Markland F.S., Swenson S., and Minea R.); ISBN9783527320912, Wiley-Blackwell, 2010

Swenson, S., **Minea, R.**, Zidovetzki, S., Helchowski, C., Costa, F., and Markland Jr. F.S. Anti-angiogenesis and disintegrins. In Toxins and Hemostasis: From Bench to Bedside" (Editors: Kini R.S., Clemetson K.J., Markland F.S., McLane M.A., Morita T. Editors); ISBN9789048192946, Springer, 2010

Minea R., Helchowski C., Rubino B., Brodmann K., Swenson S., and Markland, F.S., Jr. Development of a chimeric recombinant disintegrin as a cost-effective anticancer agent with promising translational potential; Toxicon, 2011, doi:10.1016/j.toxicon.2011.02.020

Janib S.M., Gustafson J.A., **Minea R.O.**, Swenson S.D., Liu S., Pastuszka M.K., Lock L.L., Cui H., Markland F.S., Conti P.S., Li Z., and MacKay J.A. Multimeric disintegrin protein polymer fusions that target tumor vasculature; Biomacromolecules, 2014. **15**(7): p. 2347-58

Chen T.C., Chan N., **Minea R.O.**, Hartman H., Hofman F.M., Schönthal A.H., Rare Stochastic Expression of O6-Methylguanine- DNA Methyltransferase (MGMT) in MGMT-Negative Melanoma Cells Determines Immediate Emergence of Drug-Resistant Populations upon Treatment with Temozolomide In Vitro and In Vivo; Cancers (Basel), 2018. **10**(10), pii:E362; doi: 10.3390/cancers10100362. PMID: 30274152

Swenson S., **Minea R.O.**, Tuan C.D., Thein TZ., Chen T.C. and Markland F.S., A novel venom-derived peptide for brachytherapy of glioblastoma: preclinical studies in mice; Molecules, 2018. **23**(11), pii:E2918; doi:10.3390/molecules23112918. PMID: 30413113

D. Research Support

Active support

NCI R21 1R21 CA223325-01A1 07/01/2018-06/30/2020

NIH-R21 Clinical and Translational Exploratory/Developmental Studies

Minea (PI)

Exploiting the immune microenvironment for radiotargeted destruction of leptomeningeal metastases

This Project is aimed at validating a novel therapeutic strategy which combines precision delivery of beta-emitting radionuclides with the reprograming of the innate immune microenvironment in advanced breast cancer with leptomeningeal metastases

Wright Foundation Research Grant. 07/01/2018-06/30/2019

Minea (PI)

Exploiting the prometastatic effects of chemotherapy for enhanced detection of peritoneal metastases in ovarian cancer

This Project is aimed at developing a novel theranostic for early detection of minimal residual disease after standard of care chemotherapy in advanced ovarian cancer with peritoneal metastases

Completed support

NIH R41-CA168228-01A1 12/2013-11-2014

NIH-STTR Program
Chen (PI); Minea Role: Principal Scientist (Applied Integrin Sciences, Inc.)
A Novel Brachytherapy Agent for Glioblastoma Multiforme (Phase I STTR)
This Project is aimed at development of a targeted delivery strategy for radioactivity in the treatment of diffuse astrocytomas

NIH 3R41CA168228-01A1 12/2013-11/2014

NIH-STTR Program
Calzone (PI); Minea Role: Principal Scientist (Applied Integrin Sciences, Inc.)
Integrin Targeted Therapy for the Treatment of Ovarian Cancer (Administrative Supplement)
This Project was focused on developing a novel route and formulation for vicrostatin, a broad-spectrum integrin ligand, for the treatment of ovarian cancer

NIH 1R41CA168228-01A1 09/2012-8/2013

NIH-STTR Program
Calzone (PI); Role: Principal Scientist (Applied Integrin Sciences, Inc.)
Integrin Targeted Therapy for the Treatment of Ovarian Cancer (Phase I STTR)
This Project was focused on developing a novel route of administration and formulation for vicrostatin, a broad-spectrum integrin ligand, for the treatment of ovarian cancer