Syllabus: INTD 531 Cell Biology

Units: 4
Course Sessions: Tuesdays and Thursdays
Time: 9:00 am – 11:00 am
Semester: offered each fall semester
Location: McKibben 256 (lectures) & McKibben Annex 149 (exams)

Course Director: Dr. Axel H. Schönthal (schontha@usc.edu)
Teaching Assistant (TA): Jasmin Alves (jalves@usc.edu)

Course Information:
INTD 531 is an advanced graduate-level course in cell biology that is offered on the Health Sciences Campus. Three major areas of active cell biological research will be emphasized:

- Module I: Cellular Growth Control and Regulation
- Module II: The Dynamic Architecture and Composition of Cells
- Module III: Cells In Their Social Context

Each of these areas is covered in a different section of the course and is coordinated by a different faculty member as shown on the course schedule. The course will use the material in the recommended textbook as a starting point, and original recent work and advances in the individual areas will be emphasized.

Course Goals:
Students who successfully complete this course will acquire in depth understanding and advanced knowledge of a range of general and specialized areas in cell biology. They will develop insight into the complexities of cell structure and function, the molecular controls that govern the cells' dynamic properties, and cellular interactions with the organism as a whole.

A further goal of this course is to educate and train the students in grant writing skills. Therefore, an important component of this course will be homework assignments consisting of developing research proposals based on selected hypothesis from the course topics. These assignments will receive written feedback from faculty who will comment on strengths and weaknesses of the students' proposals.

Course Correspondence:
All correspondence between instructors and students will be made using email. All information regarding lectures, reading assignments, and homework will be posted on a Blackboard web site for INTD 531. The Blackboard web site may be entered at https://blackboard.usc.edu/ . Only students who are registered for the course will have access to the Blackboard web site. If you cannot access the web site, inform Dr. Schönthal at schontha@usc.edu

➔ Because much of the correspondence regarding this course will be distributed via email to each student, it is highly recommended to regularly check the quota of your email account; if you are over quota, the USC email system will stop delivering emails to your account. Please note that your inbox, your outbox, as well as your trash folder all count towards your quota; therefore, you must make sure to delete emails regularly, followed by emptying your trash folder.

THE FIRST DAY OF CLASS IS AUGUST 25, 2015
The course will consist of 2 two-hour sessions per week. Classes will meet 9-11 AM on Tuesdays and Thursdays in McKibben 256. The three exams will be held in a different lecture hall: McKibben Annex (MCA) 149.

Textbook:
The recommended text is the Sixth Edition (2015) of *MOLECULAR BIOLOGY OF THE CELL*, by Alberts, Johnson, Lewis, Morgan, Raff, Roberts and Walter. (Garland Science publisher). A copy of this text is on hold in the Norris Medical Library.

Class Format:
The course will consist of 2 two-hour class sessions per week. Classes will meet 9-11 AM on Tuesdays and Thursdays in McKibben 256—except for exams, where class will meet in MCA 149. The lecture schedule and assigned lecturers are listed in the document entitled "Course Schedule" (see below). Lecture dates may vary with advance notice. Homework and pre-class assignments will be required for most classes. Pre-class assignments will be posted on Blackboard. It is advisable that students login to the course on Blackboard and check for updates regularly.

Each class meeting will consist of no more than one hour of lecturing by the instructor. Some instructors may have prerecorded content available on the course Blackboard site in lieu of didactic presentations in class; other instructors may post introductory reading assignment on Blackboard, which students need to review in order to be sufficiently prepared for that class.

About half of the time in each class will be used for interactive exercises that will emphasize data analysis, experimental design, research proposal preparation, or discussion of primary research reports and relevant research methods.

Exams:
Each of the three sections of the course will conclude with a two-part exercise/exam, as follows:

Part 1 will be a take-home assignment, which consists of writing a research proposal. Topics for this research proposal will be given to students about 5 days before the deadline. This typed research proposal must be uploaded (in PDF format) to the course website on Blackboard at the latest by the deadlines listed below. It is advised that each student becomes familiar with Blackboard well in advance of upload deadlines. The students will receive written feedback regarding strengths and weaknesses of their research proposals.

Part 2 will be an exam in the format of a multiple-choice test, based on topics presented during the course section immediately preceding the exam. This exam will be administered on the final day of the respective section of the course and will take up to 2 hours.

Exam Dates for Fall 2014:

Exam for course module I:

- Tuesday, September 29, 9:00 a.m.: Exam for course module I.
- Wednesday, September 30, 11:00 a.m.: Deadline for uploading research proposal.

Exam for course module II:

- Tuesday, November 03, 9:00 a.m.: Exam for course module II.
- Wednesday, November 04, 11:00 a.m.: Deadline for uploading research proposal.

Exam for course module III:

- Wednesday, December 09, 11:00 a.m.: Deadline for uploading research proposal.
- Thursday, December 10, 9:00 a.m.: Exam for course module III.

Grading:
The final grade for each student will be assigned based on the student's performance on the three research proposals and the three multiple-choice tests. Each of these 6 components is worth up to 100 points.

The breakdown of points for each homework assignment (Part 1) and each in-class multiple-choice exam (Part 2) is as follows:

Exam for course module I:

- Part 1: 100 points
- Part 2: 100 points

Exam for course module II:

- Part 1: 100 points
- Part 2: 100 points

Exam for course module III:

- Part 1: 100 points
- Part 2: 100 points

➔ **See following pages for Statement on Academic Conduct and Support Systems.**

➔ **See following pages for schedule of lectures.**

➔ **See following pages for details on homework assignments.**

Statement on Academic Conduct and Support Systems

Academic Conduct

Plagiarism – presenting someone else's ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in *SCampus* in Section 11, *Behavior Violating University Standards* *https://scampus.usc.edu/b/11-00-behavior-violating-university-standards-and-appropriate-sanctions/* Other forms of academic dishonesty are equally unacceptable. See additional information in *SCampus* and university policies on scientific misconduct, http://policy.usc.edu/scientific-misconduct/.

Discrimination, sexual assault, and harassment are not tolerated by the university. You are encouraged to report any incidents to the *Office of Equity and Diversity* http://equity.usc.edu/ or to the *Department of Public Safety* http://adminopsnet.usc.edu/department/department-public-safety This is important for the safety whole USC community. Another member of the university community – such as a friend, classmate, advisor, or faculty member – can help initiate the report, or can initiate the report on behalf of another person. *The Center for Women and Men* http://www.usc.edu/student-affairs/cwm/ provides 24/7 confidential support, and the sexual assault resource center webpage https://sarc.usc.edu/ describes reporting options and other resources.

Support Systems

A number of USC's schools provide support for students who need help with scholarly writing. Check with your advisor or program staff to find out more. Students whose primary language is not English should check with the *American Language Institute* http://dornsife.usc.edu/ali, which sponsors courses and workshops specifically for international graduate students. *The Office of Disability Services and Programs* *https://dsp.usc.edu/* certification for students with disabilities and helps arrange the relevant accommodations. If an officially declared emergency makes travel to campus infeasible, *USC Emergency Information* *http://emergency.usc.edu/* will provide safety and other updates, including ways in which instruction will be continued by means of blackboard, teleconferencing, and other technology.

INTD-531: CELL BIOLOGY — Schedule of Lectures (Course Schedule) 2015

Date	*Topic*	*Lecturer*
Module I:	**Growth Control and Regulation**	
	Section Organizer:	**Dr. A. Schönthal**
Aug. 25	Introduction to Cellular Growth Control and Cell Cycle	Dr. A. Schönthal
Aug. 27	Cell Signaling and Functions Controlled by Kinases	Dr. W. Li
Sept. 01	Cell Signaling and Functions Controlled by Phosphatases	Dr. B. Stiles
Sept. 03	Cell Death and Apoptosis	Dr. P. Feng
Sept. 08	*How To Write A Research Proposal*	Dr. R. Chow
Sept. 10	Senescence and Telomere Function	Dr. A. Goldkorn
Sept. 15	Autophagy	Dr. C. Liang
Sept. 17	Regulation of Stem Cell Self-Renewal and Growth	Dr. Q. Ying
Sept. 22	Introduction to Cancer Cell Biology	Dr. A. Schönthal
Sept. 24	Cancer Stem Cells	Dr. F. Hofman
Sept. 29	Exam for Module I	TA: J. Alves
Module II:	**The Dynamic Architecture and Composition of Cells**	
	Section Organizer:	**Dr. A. Mircheff**
Oct. 01	Some of Nature's Laws	Dr. A. Mircheff
Oct. 06	How Cells Manipulate Nature's Laws to Survive	Dr. A. Mircheff
Oct. 08	Introduction to Cell Membranes	Dr. R. Langen
Oct. 13	Deformation of Cellular Membranes	Dr. R. Langen
Oct. 15	High-Resolution Imaging Techniques in Cell Biology	Dr. R. Chow

Oct. 20	Exocytosis, Endocytosis, and Secretion	Dr. S. Hamm-Alvarez
Oct. 22	Molecular Motors in Cell Biology: *Are the locations of organelles and macromolecules within a cell random*?	Dr. C. Okamoto
Oct. 27	Molecular Motors in Cell Biology: Practical Applications	Dr. C. Okamoto
Nov. 03	Exam for Module II	TA: J. Alves

Module III: Cells In Their Social Context

Section Organizer: Dr. Y. DeClerck

Nov. 05	Overview of the Microenvironment of the Cell	Dr. Y. DeClerck
Nov. 10	The ECM: Structure, Function, and Role in Wound Healing	Dr. T. Tuan
Nov. 12	Cell-Cell and Epithelial-Mesenchymal Interactions	Dr. R. Widelitz
Nov. 17	Cell-Matrix Interactions: Integrins and Other ECM Adhesion Molecules	Dr. S. Swenson
Nov. 19	The Tumor Microenvironment: The Social Environment of the Cancer Cell	Dr. Y. DeClerck
Nov. 24	Inflammation: A Disease of the Social Environment Paper review and discussion session	Dr. Y. DeClerck
Nov. 25-28	Thanksgiving Recess – No class	
Dec. 01	Cell Migration and its Control Mechanisms	Dr. W. Li
Dec. 03	Soluble Factors and Exosomes in Cell-Cell Communication	Dr. M. Fabbri
Dec. 10	Exam for Module III	TA: J. Alves

End of course

Composed by: Axel H. Schönthal, PhD

INTD-531: Instructions and Formatting Guidelines for Research Proposal

1. Format and Sections of Research Proposal

(A) The length of the research proposal is limited to 1 page text + 1 page for diagrams and figures (inclusive of legends) + 1 page references, for an overall length of 3 pages. On all pages, keep the margins (top, bottom, left, right) to at least 0.5 inches. Use single-spaced text with 12-point Times New Roman font (← shown here) or 11-point Arial font (← shown here). Alignment of the text on the right side (flush/not flush) is optional.

(B) The first page of your proposal should contain the following components (in this order):

- **Your name and ID**: LAST NAME IN CAPITAL LETTERS, followed by first name in small letters, followed by your USC student ID.
- **Name of Professor** (whose topic you are presenting)
- Optional: **Project title** (not required)
- **Project summary** (1-2 sentences) – in no more than 2 sentences provide an overview of the topic being studied; mention its overall goal.
- **Background** (quarter page) – briefly present the relevant background of your project.
- **Relevance** (1-2 sentences) – in no more than 2 sentences, describe why your project is important and how it advances scientific knowledge.
- **Specific aims** (less than a quarter page) – list 2-4 specific aims.
- **Methods** (quarter page) – briefly outline your experimental approach to achieve the specific aims.
- **Pitfalls** (2-3 sentences) – present one potential pitfall (a problem that you might encounter in pursuing your specific aims; an experiment that might not yield the expected result), and mention an alternative (how you would deal with the problem; how you would change your experimental approach).

(C) The second page of your research proposal must contain at least 1 diagram or figure. The figure (if any) provided by the professor does not count (you can include that figure, but you must present at least 1 other figure or diagram). For example, you can present a graphical outline of the problem or your experimental approach or your hypothesis. You could also show a figure from the literature in support of your approach or as an example of expected results. Add a figure legend that provides some background of the figure. Make sure you refer to all figure(s) within the text on the first page (e.g., see Fig. 1).

(D) The third page should list all references used. For each reference, provide the names of all authors, the full title of the paper, the journal name, as well as volume, page numbers, and year published. Number the references in the order they appear in the text of pages 1 and 2 of your research proposal. On page 1 and 2, cite the references by referring to their numbers. It is highly recommended that you use a software tool (citation manager) for the insertion and formatting of references, such as Zotero (zotero.org), EndNote, RefWorks, or other. Ask the Norris Medical Library for support and instructions. Some of these programs have tutorials on YouTube.

— over —

2. Content of your Research Proposal

An example of a research proposal is shown on the following pages. In addition, please orient yourself at the lecture given by Dr. Robert Chow during the first section of the course (*How to Write a Research Proposal*) and incorporate suggestions and details as provided by his lecture.

3. Submission of Your Research Proposal

To submit your research proposal, follow these steps:

- Convert your document to PDF format and submit as a 3-page PDF

- Upload your document to Blackboard (3-step process):
  - locate Assignments folder for this course
  - inside this folder, click on the assignment; a new window opens
  - upload your PDF (you can add comments, if you wish) in the new window

- If you cannot figure out how to upload: Make a paper print of your PDF and bring it with you on the exam day
  - hand your hardcopy to the instructor before starting the exam
  - (expect to have points deducted for your inability to manage Blackboard)

There is a video tutorial demonstrating the upload of assignments to Blackboard:

- inside Blackboard, click on Student Help (top row)
- new window: under Getting Started with Blackboard, click on Coursework
- new window: under Coursework, click on Submitting Assignments

4. Deadlines for Submission of Your Research Proposal

You must submit the electronic copy of your research proposal by the time and date outlined further above in the syllabus. There will be a 1-hour grace period, but Blackboard will not accept any more proposals after 12:00 noon on that day.

If you have problems uploading to Blackboard, you can hand-deliver a printed copy of your proposal to Dr. Schönthal. However, paper submissions will incur substantial deductions of points.

5. Example of Research Proposal

The following pages show an example of a research proposal that is formatted according to the above guidelines.

Name: SCHONTHAL, Axel (USC ID: 123456789)

Name of Professor: This is the topic from Dr. Schönthal.

Project title: Novel Therapeutic Approach for Tuberous Sclerosis

Project summary: I propose to determine whether pharmacologic approaches targeting the endoplasmic reticulum (ER) stress response can trigger apoptosis in tuberous sclerosis cells. The overall goal is to develop a novel therapy for tuberous sclerosis.

Background: In general terms, ER stress can be viewed as a cellular "yin-yang" mechanism, where low-level or chronic activation provides profound protection against certain types of stress ("yin"), but were more severe activation will switch to the pro-apoptotic mode of this system and will lead to cell death ("yang") [1]. Most tumor cells (including tuberous sclerosis cells [2]) exhibit low-level, chronic ER stress in a defensive ("yin") mode that ensures their survival under adverse microenvironmental conditions (e.g., hypoxia, low glucose levels, acidity, etc.), and also increases their chemoresistance. The novel therapeutic strategy of my study consists of the controlled pharmacologic aggravation of ER stress to the point where this system overloads and selectively triggers apoptosis in tuberous sclerosis cells (which harbor chronic ER stress), but spares normal cells (which do not have chronic ER stress and therefore are able to adapt and survive treatment with CXB) (see Fig. 1).

Relevance: There is currently no effective treatment for tuberous sclerosis. If my study is successful, it has the potential to create a new therapeutic approach for the treatment of this disease.

Specific Aims: I intend to establish that celecoxib (CXB; Celebrex), a cyclooxygenase-2 (COX-2) inhibitor with known potential to trigger ER stress [3], is able to cause aggravation of ER stress and will result in apoptosis of tuberous sclerosis cells in vitro and in vivo.

Specific Aim 1: Determine whether treatment of tuberous sclerosis cells with CXB in vitro leads to ER stress.

Specific Aim 2: Investigate whether treatment of tuberous sclerosis cells with CXB in vitro leads to apoptosis.

Specific Aim 2: Characterize the effects of CXB on tuberous sclerosis tumors in an animal tumor model.

Methods: For SA1, I will treat tuberous sclerosis cells with increasing concentrations of CXB for 24, 48, and 96 hours, and then harvest total cellular lysate to perform Western blot analysis. I will use antibodies against GRP78 (glucose regulated protein of molecular mass 78 [4]) and CHOP (CCAAT/enhancer binding protein homologous transcription factor [5]). Both of these targets are markers for ER stress; their increased expression is indicative of ER stress. As a control, I will use an antibody against actin; actin is the loading control and will confirm that equal amounts of protein lysate have been used in each lane.

For SA2, I will perform two experiments. Both will be set up similar to the above (with different CXB concentration and different time points). In one part, I will measure cellular survival by using an MTT assay, which determines the viability of cells after treatment with CXB. The other will be a Western blot with antibodies against different caspases, which will reveal whether drug treatment results in the proteolytic cleavage (=activation) of caspases as markers for cells undergoing apoptosis.

For SA3, I will implant tuberous sclerosis cells under the skin of 10 nude mice. After palpable tumors have formed, I will treat 5 mice with CXB (5 mg once daily per gavage). The other 5 mice will form the control group and will receive only salt solution (vehicle) on the same schedule. I will measure tumor growth in both groups of animals over the course of 6 weeks of treatment. Tumor size will be plotted over time in a graph. At the end of the experiment, all animals will be euthanized and the tumors collected. I will perform Western blot analysis of tumor tissue to investigate markers of ER stress and apoptosis (as in SA1 and 2), in order to investigate whether CXB causes ER stress and apoptosis in tuberous sclerosis tumor cells in vivo.

Pitfalls: It is possible that, contrary to my expectation, CXB may not cause ER stress in tuberous sclerosis cells in vitro (or in vivo). If I obtain this outcome, I would then investigate the Akt survival pathway, because CXB is known to down-regulate Akt, and, if I can demonstrate this effect in tuberous sclerosis cells, it would explain how CXB triggers apoptosis without ER stress.

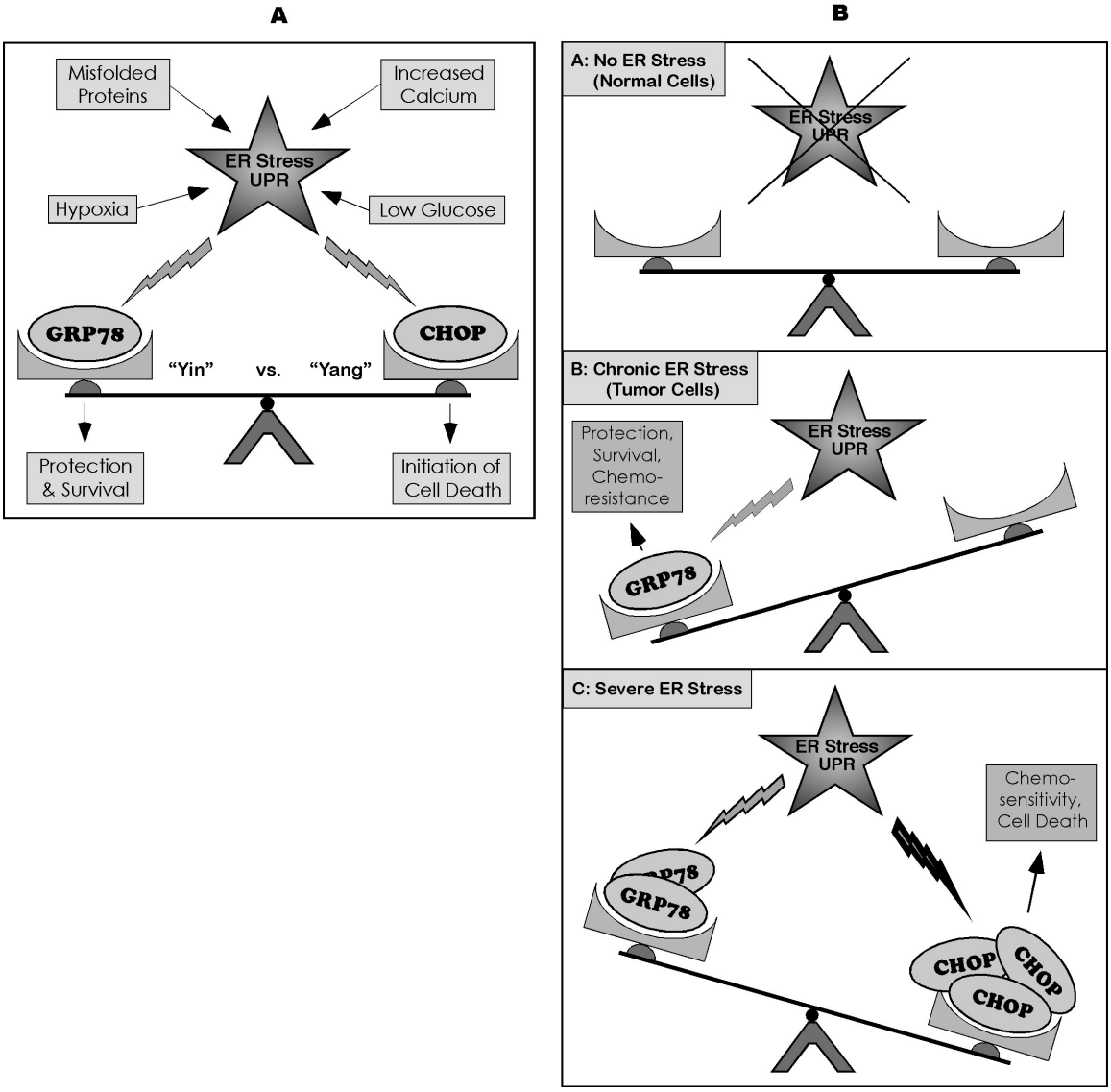

Figure 1: Simplified diagram of the "Yin-Yang" balance of ER stress and how it relates to the project

(**A**) ER stress can be triggered by various unfavorable conditions, such as the accumulation of misfolded proteins, changes in the calcium balance between the ER and the cytosol, low levels of glucose, hypoxia, and others [6; 7]. The ERS response is also called the unfolded protein response (UPR), as some of the above stressors can impinge on proper protein folding [8]. The mechanism of ERS/UPR involves the increased expression of anti-apoptotic GRP78 and pro-apoptotic CHOP, and—depending on the severity of the initial insult—one of these two master executors will gain dominance and decisively determine the resulting consequences, i.e., protection from stress or initiation of cell death.

(**B**) There are three activity levels of the ER stress response system. (A) The "No ER Stress" condition is the default situation in normal cells. (B) In cancer cells, continuous, low-intensity stress generates the "Chronic ER Stress" condition, indicated by elevated levels of GRP78, which, among its various functions, suppresses pro-apoptotic components and thereby supports cellular survival and chemo-resistance. (C) Persistent, high-level stress generates the "Severe ER Stress" situation, where pro-apoptotic components (such as CHOP) dominate and trigger cell death. The protective effort of GRP78 is overwhelmed, which contributes to the chemo-sensitization of tumor cells. Note that thickness of bolts corresponds to the intensity of stimulated expression of GRP78 and CHOP.

➔ I am proposing that CXB is able to convert condition B to condition C (in diagram to the right) and thereby leads to the killing of tuberous sclerosis cells. My research study will investigate this hypothesis.

References

[1] A.H. Schönthal. Targeting endoplasmic reticulum stress for cancer therapy. Front Biosci S4 (2012) 412-431.

[2] U. Ozcan, L. Ozcan, E. Yilmaz, K. Duvel, M. Sahin, B.D. Manning, G.S. Hotamisligil. Loss of the tuberous sclerosis complex tumor suppressors triggers the unfolded protein response to regulate insulin signaling and apoptosis. Mol Cell 29 (2008) 541-551.

[3] H.-C. Chuang, A. Kardosh, K.J. Gaffney, N.A. Petasis, A.H. Schönthal. COX-2 inhibition is neither necessary nor sufficient for celecoxib to suppress tumor cell proliferation and focus formation in vitro. Mol Cancer (2008) 38.

[4] J. Li, A.S. Lee. Stress induction of GRP78/BiP and its role in cancer. Curr Mol Med 6 (2006) 45-54.

[5] S. Oyadomari, M. Mori. Roles of CHOP/GADD153 in endoplasmic reticulum stress. Cell Death Differ 11 (2004) 381-389.

[6] A.S. Lee, L.M. Hendershot. ER stress and cancer. Cancer Biol Ther 5 (2006) 721-722.

[7] A.H. Schönthal. Pharmacological targeting of endoplasmic reticulum stress signaling in cancer. Biochem Pharmacol 85 (2013) 653-666.

[8] J.D. Atkin, M.A. Farg, A.K. Walker, C. McLean, D. Tomas, M.K. Horne. Endoplasmic reticulum stress and induction of the unfolded protein response in human sporadic amyotrophic lateral sclerosis. Neurobiol Dis 30 (2008) 400-407.