How to write successful proposals

(Bio-medical research)

a personal perspective

by

Israel Vlodavsky

Scientific part

- ***ABSTRACT***
- ***Table of contents***
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Administrative part

Biosketch

Budget & Budget justification

Vertebrate animals

Appendix (Support letters)

Novelty & Credibility

Main idea: should be novel & **significant**

- Propose a meaningful idea
- Stay away from marginal or incremental work; referees do not want to fund such things

➢ First publish several papers with just your own team, gain credibility, and then go ahead and propose new experimental effort.

M. Segev

ABSTRACT

The Abstract is the first part of the proposal

The reviewers will read and first impressions count. This may decide how much time and how closely the reviewer will look at your proposal.

Get your point across:
What is the innovation / Breakthrough?
How does it exceed the State of the art?
What is the impact?

ABSTRACT

Try to include the following items:

Background

Mammalian heparanase, heparan sulfate degrading endoglycosidase, first cloned and characterized in our laboratory, is preferentially expressed in human tumors and its over-expression in tumor cells confers an invasive phenotype in experimental animals. Heparanase also releases ……

Rationale

These observations, the anti-cancerous effect of heparanase gene silencing and inhibitory molecules, and the unexpected identification of a single functional heparanase, indicate that the enzyme is a promising target for anti cancer drug development. The proposed research combines basic and clinical aspects of …….

Specific aims

In continuation of our studies on the involvement of heparanase in cancer metastasis and angiogenesis, we propose to address the following specific aims: I) Regulation of ……..

Expected results & Significance

Precise structure/function analysis of the heparanase protein will pave the way for rational design of ……

Feasibility (available research tools)

The proposed research stems from studies performed during the last 5 years of research supported by the NCI and the development of molecular tools (i.e., …….) and collaborative arrangements (i.e., ……..) to carry out and accomplish each of the proposed specific aims.

Example

Table of contents

SPECIFIC AIMS

Include: Short introduction, Rationale, Specific aims & Sub-aims; Final statements (1 page)

Cancer cells genetically engineered to over-express heparanase are characterized by faster tumor take upon *in vivo* inoculation, form larger and more vascularized tumors and readily metastasize to distant organs. These findings are reinforced by clinical observations demonstrating a highly significant correlation between enhanced heparanase expression and plasma levels, metastatic potential, tumor vascularity and reduced postoperative survival of cancer patients. These results and the anti-cancerous effect of heparanase gene silencing and inhibitory molecules indicate that the enzyme is a promising tumor marker and target for anti-cancer drug development. ……..

Our recent studies indicate that apart of its enzymatic activity, the heparanase protein exerts non-enzymatic functions that further promote tumor angiogenesis, growth, survival and metastatic dissemination. The proposed research focuses on basic and clinical aspects of …….

Aim 1. Impact of the tumor microenvironment on regulation and function of heparanase in cancer progression, focusing on: i) Inflammation associated colon carcinoma; **ii)** Radiation-induced heparanase expression in pancreatic carcinoma; and **iii)** Contribution of heparanase residing in the tumor microenvironment. Altogether, Aim 1 emphasizes the impact of host- vs. tumor- derived heparanase on cancer progression.
Aim 2. Heparanase non-enzymatic activities: i) ……
Aim 3……..

The proposed research stems from studies performed during the last 5 years of research supported by the NCI and the development of molecular tools (i.e., …….) and collaborative arrangements (i.e., …….) to carry out and accomplish each of the proposed specific aims. Precise structure/function analysis of the heparanase protein will pave the way for rational design of inhibitory molecules directed against its enzymatic and non-enzymatic functions**.**

Example

Common Mistakes (NIH):

Problems with significance:

- ✓ Not significant nor exciting nor new research
- ✓ Lack of compelling rationale
- ✓ Incremental and low impact research

Problems with specific aims:

- ✓ Too ambitious, too much work proposed
- ✓ Unfocused aims, unclear goals
- ✓ Limited aims and uncertain future directions

Specific aims/objectives (ERC)

State of the art and objectives: Specify clearly the objectives of the proposal, in the context of the state of the art in the field.

When describing the envisaged research it should be indicated **how and why the proposed work is important for the field, and what impact it will have** if successful, such as how it may open up new horizons or opportunities for science, technology or scholarship.

Specify any particularly challenging or unconventional aspects of the proposal, including multi - or interdisciplinary aspects.

Scientific part

2. BACKGROUND & SIGNIFICANCE

2.1. Heparan sulfate proteoglycans (HSPGs)…….

2.2. Mammalian heparanase……..

2.4. Involvement in tumor angiogenesis and metastasis…….

2.6. Inhibitory compounds……..

2.9. Significance…….

Make sure you have adequate preliminary data

3. PRELIMINARY STUDIES

3.1. Tissue remodeling and morphogenesis…….

3.2. Heparanase processing, uptake, cellular localization and secretion…….

3.3. Transcriptional regulation…….

3.4. Tumoprogression……

i)

ii)

III)

***3.5.* Angiogenesis and lymphangiogenesis…….**

3.8. Inhibitory strategies……..

Summary of preliminary results…….

Be aware that reviewers are very keen to read about any relevant preliminary data you may have generated

Preliminary Results

- Build on your proven strengths & credibility and move forward to new grounds

- Before you write, make sure you have at least some **preliminary results** in (almost) every research topic
- Make a clear statement, in the abstract, on having preliminary results
- Describe the preliminary results in the Detailed Research Plan (include figures & figure legends)

Remember: **credibility** is as important as novelty!

M. Segev

4. RESEARCH DESIGN & METHODS

4.1. Specific Aim 1. ***Regulation and Involvement of heparanase in tumor progression, focusing on: i)*** *inflammation associated colon carcinoma;* ***ii)*** *contribution of heparanase residing in the tumor microenvironment; and* ***iii)*** *Radiation-induced heparanase expression in pancreatic carcinoma*
During the previous years of support provided by the NCI (RO1 CA106456) we have gained experience……

4.1.1. Involvement of heparanase in chronic colitis associated colon tumorigenesis
Rationale and pertinent preliminary results. Colon carcinoma represents a paradigm for the connection.....

Strategy and mode of operation
Impact of HS degradation fragments on tumor associated macrophages. Carcinoma cells…….

4.1.2. Contribution of heparanase residing in the tumor microenvironment
Rational and pertinent preliminary results. The critical importance in carcinogenesis……

Strategy and mode of operation. We propose to apply separately specific siRNAs directed against…….

4.1.3. Radiation-induced heparanase expression in pancreatic carcinoma
Rationale and pertinent preliminary results: The following observations provide the basis for the proposed…..

Strategy and plan of operation. In subsequent studies, the luciferase gene driven by heparanase promoter will be transiently introduced……..

Summary of Aim 1. Aim 1 consists of 3 subaims designed to better elucidate the mode of action and involvement of heparanase in……

Example

4.2. Specific Aim 2. ***Heparanase non-enzymatic activities: i)*** *Involvement and mode of action of the heparanase C-domain in heparanase secretion, non-enzymatic functions and tumor growth; and* ***ii)*** *Activation of EGF receptor (EGFR) by heparanase: mechanisms and consequences*

4.2.1. Involvement and mode of action of the heparanase C-domain in heparanase secretion, non-enzymatic functions and tumor growth

Rational and pertinent preliminary results. Until recently, the involvement of heparanase in cancer metastasis and angiogenesis……..

Strategy and mode of operation

Role of C-domain in heparanase secretion. To more accurately investigate the contribution of the C-domain to heparanase secretion, we will apply…….

4.2.2. Activation of EGF-receptor (EGFR) by heparanase: mechanisms and consequences

Rationale and pertinent preliminary results. In preliminary studies we have noted…….

Strategy and mode of operation. Utilizing A431 human epidermoid carcinoma cells, we found that over expression of heparanase or…….

Cellular consequences. The EGFR has been shown to modulate several fundamental aspects of cell behavior, regulating……..

Clinical significance. U87 glioma cells exhibit elevated levels of EGFR phosphorylation in response to heparanase (not shown)…….

Summary of Aim 2. Aim 2 focuses on non-enzymatic activities of heparanase. Subaim 4.2.1 focuses on the mode of action and significance of…….

Example

4.3. Specific Aim 3. ***Purify, crystallize and establish the 3D structure of the latent (65 kDa) and active (8 + 50 kDa) heparanase proteins***

Rational and pertinent preliminary results. Having overcome substantial obstacles, we have succeeded in producing mg amounts of highly purified recombinant active…….

4.3.1. Purify, crystallize and establish the 3D structure of latent and active heparanase

Strategy and mode of operation. In order to determine

Alternative/complementary approaches

4.3.2. Expression, purification and crystallization of the heparanase TIM barrel- and C-terminus-domains as a chimera with solubility increasing proteins. An alternative approach for obtaining well diffracting crystals is to express individual domains of……..

Summary of Aim 3. The overall objective of Aim 3 is to apply crystallization strategies to unravel the 3D structure of both the active and latent forms of the heparanase protein, as well as of its TIM barrel and C-terminus domains. Clearly,

Foreign justification (NIH)

The 'heparanase-in-cancer' research was initiated by the applicant more than two decades ago. Persistent, systematic and dedicated research led to cloning and expression of the heparanase gene and demonstration of its causal involvement in……..

Bibliography & References cited

1. Bernfield, M., Gotte, M., Park, P. W., Reizes, O., Fitzgerald, M. L., Lincecum, J., and Zako, M. Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem, *68:* 729-777, 1999
2. Iozzo, R. V. Matrix proteoglycans: from molecular design to cellular function. Annu Rev Biochem, *67:* 609-652, 1998.

•Give proper references (these people will be your referees!)

Example

Methodology

Describe the proposed methodology, including, as appropriate, key intermediate goals. Explain and justify the methodology in relation to the state-of-the-art, including any particularly novel or unconventional aspects.

Highlight any intermediate stages where results may require adjustments to the project planning.

Highlight any high risk areas of the research and how you will deal with them; if possible provide an alternative low risk methodology.

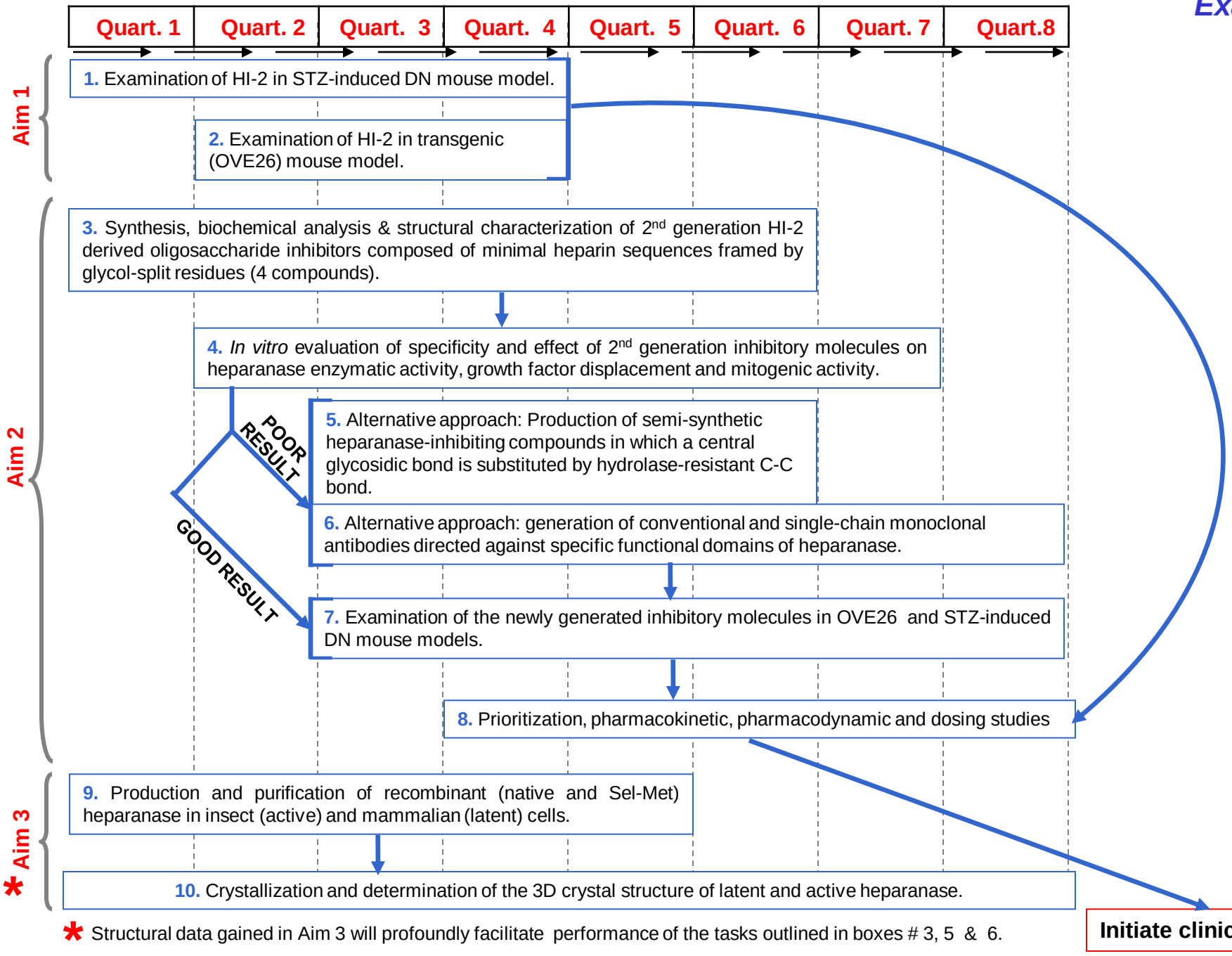
Detail your risk management strategy

Write a reliable time-table

Include a detailed workplan/Gantt for at least the first 2 – 3 years with milestones for your main objectives.

D. MILESTONES AND TIMELINE (in quarterly increments)

Example



* Structural data gained in Aim 3 will profoundly facilitate performance of the tasks outlined in boxes # 3, 5 & 6.

✓ **Write one sentence summarizing the topic sentence of each main section.** Do the same for each main point in the outline.

✓ **Make one point in each paragraph.** This is key for readability. Keep sentences to 20 words or less. Write simple, clear sentences.

✓ **Be realistic.** Don't propose more work than can be reasonably done during the proposed project period.

✓ Include enough background information to enable an intelligent reader to understand your proposed work.

✓ **Use the active, rather than passive, voice.** For example, write "We will develop an experiment, "not "An experiment will be developed ."

✓ Use a clear and concise writing style so that a non-expert may understand the proposed research.

✓ **Use sub-headings,** short paragraphs, and other techniques to make the application as easy to navigate as possible. Be specific and informative, and avoid redundancies.

✓ **Use diagrams, figures and tables**, and include appropriate legends, to assist the reviewers to understand complex information. Make sure the figures and labels are readable in the size they will appear in the application.

Tips to Make Your Research Plan a Winner (Continued):

- Discuss how you will interpret your data.
- Do not overwhelm readers with facts.
- Prioritize your experiments.
- Refer to supportive and conflicting (if any) scientific literature relevant to your work.
- ***Make sure your text is visually easy to read.***
- ***Check your use of English spelling and grammar.***
- Broaden your horizons: Read anything you can get your hands on.

"Your research plan must be adequately focused, and yet at the same time, you must also provide a long-range view of your research goals"

Tips to Make Your Research Plan a Winner:

- Address questions readers may have about your experiments.

- Identify potential weaknesses in your research design.

- Offer alternative methods, in case your primary method fails.
(If Plan A Fails, Here Is Plan B...and Plan C and Plan D ...)

- Show you are capable of adapting future experiments depending upon the results generated.

- Be focused, but put your immediate experiments into the context of the "big picture."

Problems with experimental approach:

- Inappropriate level of experimental detail
- Feasibility of each aim not shown
- Little or no expertise with approach
- Lack of appropriate controls
- Not directly testing hypothesis
- Correlative or descriptive data
- Experiments not directed towards mechanisms

- *No discussion of alternative models or hypotheses*
- *No discussion of potential pitfalls*
- *No discussion of interpretation of data*

RESEARCH DESIGN & METHODS

Don't be afraid to discuss scientific risks. Risk is good and shows what is most challenging about your research. It also helps to reinforce that you have a real understanding of the current scientific and technical state of the art in your field as discussed earlier in your application.

If possible, propose *alternative/complementary approaches*

- **Highlight any high risk areas of the research and how you will deal with them; if possible provide an alternative low risk methodology.**
- **Specify potential pitfalls, groundbreaking results and interpretations and explain how does it all fit together?**

Final comments

Impact of the project such as how it may open up new horizons or opportunities for science, technology or scholarship. ***This should include both your personal vision about what you would do beyond month 60 if you succeed with everything you hope to achieve and what other researchers could do after you have created the new knowledge that you will publish.***

Problems with investigator:

✓ No demonstration of expertise or publications in approaches
✓ Low productivity, few recent papers
✓ No collaborators recruited or no letters from collaborators

Problems with environment:

✓Inadequate institutional support

➢ Stay a couple of steps ahead of the game by offering the answers before reviewers even think to ask the questions

➢ *Much more important than experimental detail is a clear discussion of the design, including the underlying logic, of the proposed experiments*

Research project

Ground-breaking nature and potential impact of the research*: To what extent does the proposed research address important challenges at the frontiers of the field(s) addressed?*

To what extent does it have suitably ambitious objectives, which go substantially beyond the current state of the art?

Methodology:

To what extent does the possibility of a major breakthrough with an impact beyond a specific research domain/discipline justify any highly novel and/or unconventional methodologies ***("high-gain/high-risk balance")?***

To what extent is the outlined scientific approach feasible?

To what extent is the proposed research methodology (including the proposed timescales and resources) appropriate to achieve the goals of the project? To what extent are the resources requested necessary and properly justified?

Budget

- Allocate mostly to stipends of graduate students & postdoctoral fellows
- Much smaller allocation for equipment (if at all)
- Explain and justify every item!
- Unexplained / unjustified items are not funded even in a successful proposal!

Budget / Resources

Describe the size and nature of the team, indicating, where appropriate, the **key team members and their roles.**

Describe other necessary resources, such as infrastructure and equipment.

Specify any **existing resources** **that will contribute to the project**.

Include a short technical description of the equipment requested, a justification of its need as well as the intensity of its planned use.

State the amount of funding considered necessary to fulfil the objectives for the duration of the project.

Take into account the **percentage of your dedicated time** (minimum 30%) to run the funded activity.

Include a breakdown of the budget subdivided in **personnel costs, equipment and infrastructure, consumables, travel, publication costs, and any envisaged subcontracts.** **State how the costs will be distributed over the duration of the project.**

Budget justification

PERSONNEL

Dr. Israel Vlodavsky, (3.6 cal mos) will supervise the entire project and be actively involved in all aspects of the research. Dr. Vlodavsky will be responsible for co-ordination and evaluation of the experiments described in Aim 2 and will prepare the results for reports and publications. $4,000 salary support is requested, the remaining salary and all fringe benefits are paid by the Technion.

Dr. Neta Ilan (3.0 cal mos) is a senior investigator in the Cancer and Vascular Biology Research Center of the Technion, highly experienced in vascular biology and pathology. Dr. Ilan will be in charge of the cell biology, ……Fringe benefits are calculated as 40% of salary.

Dr. Eyal Zcharia (9.0 cal mos; post-doctoral fellow) is highly experienced in heparanase, heparan sulfate and heparin research. Eyal will perform the experiments on ……..

Dr. Liat Fux (9.0 cal mos) is a post-doctoral fellow, highly experienced in molecular biology and bioinformatics. She will execute the molecular biology studies and the 3-D modeling and structural analysis of…….

Dr. Flonia Levi-Adam (6.0 cal mos) is a post-doctoral fellow…….

Uri Barash (6.0 cal mos) is a Ph.D. candidate, experienced in molecular biology and phage display technology. Together with Dr. Ilan, he will be in charge of the…….

Sari Feld (MSc; Technical Assistance; 6.0 cal mos) is highly experienced in Biochemistry and Cell Biology. She will be responsible for …… Fringe benefits are calculated as 40% of salary.

SUPPLIES

The amount requested ($39,440/year) reflects the high costs of cell culture media, sera & supplements ($7,200/year); cell culture plastics ($4,320/year); radioisotopes (heparanase assay, mitogenic activity) ($3,600/year); biochemicals, antibodies & supplies and glassware ($4,320/year); reagents for molecular biology ($5,560/year); preparation of peptides & antibodies ($14,440/year).

TRAVEL

Funds ($3,000/year) are requested for one trip (travel and accommodation) per year (Dr. Vlodavsky and/or Dr. Ilan) to attend meetings with members of the Ronzoni Institute (Milan, Italy) to monitor and coordinate the collaboration in performing the research proposed in Aims 1 & 2.

OTHER EXPENSES

$2,500/year to cover the costs of publications; $3,000/year for lab services & maintenance; $1,000/year for computer services.

Example

Resources: credibility again..

- Describe all current existing resources & grants
- Do NOT hide it, because the referees will dig it out.

- Existing Technion resources are VERY helpful in establishing credibility

Educational impact

Find an excuse to describe somewhere your educational impact

List your former grad students / post-docs, especially those who are now university profs

M. Segev

BIOGRAPHICAL SKETCH

NAME **Vlodavsky, Israel**	POSITION TITLE: **Professor, Cancer & Vascular Biology Research Center, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel**
Date of birth: **August 31, 1944** Place of birth: **Haifa, Israel**	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Hebrew University, Jerusalem, Israel	B.Sc.	1968	Biology
Hebrew University, Jerusalem, Israel	M.Sc.	1970	Biochemistry
Weizmann Institute, Rehovot, Israel	Ph.D.	1975	Cancer Research
University of California, Los Angeles & San Francisco	Postdoc.	1976-79	Growth factors & ECM

A. Personal Statement

Brief outline of the content and impact of the major scientific contributions

B. Positions & Honors

1979-1981: **Lecturer,** Experimental Oncology, Hebrew University- Hadassah Medical School, Jerusalem.
1981-1984: **Senior Lecturer,** Experimental Oncology; Hebrew University- Hadassah Medical School, Jerusalem.
1985-1986 & 2000: Visiting Professor, Department of Surgical Research, Harvard Medical School, Boston, MA.
1985-1990: **Associate Professor,** Department of Oncology, Hadassah-Hebrew University, Jerusalem, Israel.
1990- 2002: **Professor,** Department of……

1997: Elkeles Prize - Distinguished scientist in Medicine.
2002: Teva Prize - Distinction in Cancer Research.
2005: The Henry Taub Prize for Excellence in Research
2006: The Landau Prize in Medicine
2007: ICRF Professorship Award
2010: US-Israel Binational Science Foundation (BSF) Neufeld Prize

Example

C, Selected peer-reviewed publications

1. …….

2. …….

3. …….

D. Research Support

ACTIVE

2RO1 CA106456 (Vlodavsky) 03/01/09 – 02/28/14
NIH $ 179,143
"Regulation of heparanase in cancer progression"
The major goals of this project are to: i)……

ISF grant # 593/10 (Vlodavsky & Elkin) 10/01/10 – 9/30/14
Israel Science Foundation (ISF) $ 21,500
"Heparanase: one molecule with multiple functions in human disease"
The main objective of this proposal is to investigate the involvement of heparanase and its mode action in non-cancerous inflammatory disorders.

JDRF grant 38-2009-635 (Vlodavsky & Elkin) 09/01/09 – 08/31/11
Juvenile Diabetes Research Foundation (JDRF) $ 98,000
"Heparanase as a promising target in diabetic nephropathy"
The major goal of this project is to: i)……..

COMPLETED

ISF grant # 549/06 I. Vlodavsky (PI) 10/01/2006-09/30/2010
Israel Science Foundation (ISF) $ 37,500/year
"Heparanase as a promising target for therapeutic strategies in cancer"
The overall objective of this proposal is to design……

Example

Before submission: editing

- Try to keep consistent style
- Underline/bold key statements
- Key sentences may/should be repeated in different sections
- Include figures & figure legends
- Append support letters (in appendix)

  (Letters of commitment should clearly spell out the roles of the collaborators)

- Write a submission letter
- List suggested referees & request not to send to competing referees

Get Prepared

➢ Ask your colleagues for copies of successfully completed NIH grant applications. Examine them closely.

➢ Make sure your specific research aims can be accomplished within the proposed time and resources.

➢ Discuss your research idea with colleagues. Request that they review a first draft of your specific aims early in the process. This step can save lots of valuable time.

NIH Peer Review Criteria

➢ **Significance.** Does the project address an important problem or a critical barrier to progress in the field?

➢ **Investigator(s).** Are the PD/PIs, collaborators, and other researchers well suited to the project?

➢ **Approach.** Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?

➢ **Environment.** Will the scientific environment in which the work will be done contribute to the probability of success?

Proofreading and Final Edits

✓ ***Indents and bold print add readability.*** Bolding highlights key concepts and allows reviewers to scan the pages and retrieve information quickly.

✓ If possible, have both experts in your field and those who are less familiar with your science provide **feedback.** The application should be easy to understand by all.

✓ **Have zero tolerance for typographical errors, misspellings,** grammatical mistakes or sloppy formatting. A sloppy or disorganized application may lead the reviewers to conclude that your research may be conducted in the same manner.

✓ Prior to submission, perform **a final proofread** of the entire grant application.

Submit,
and
good luck

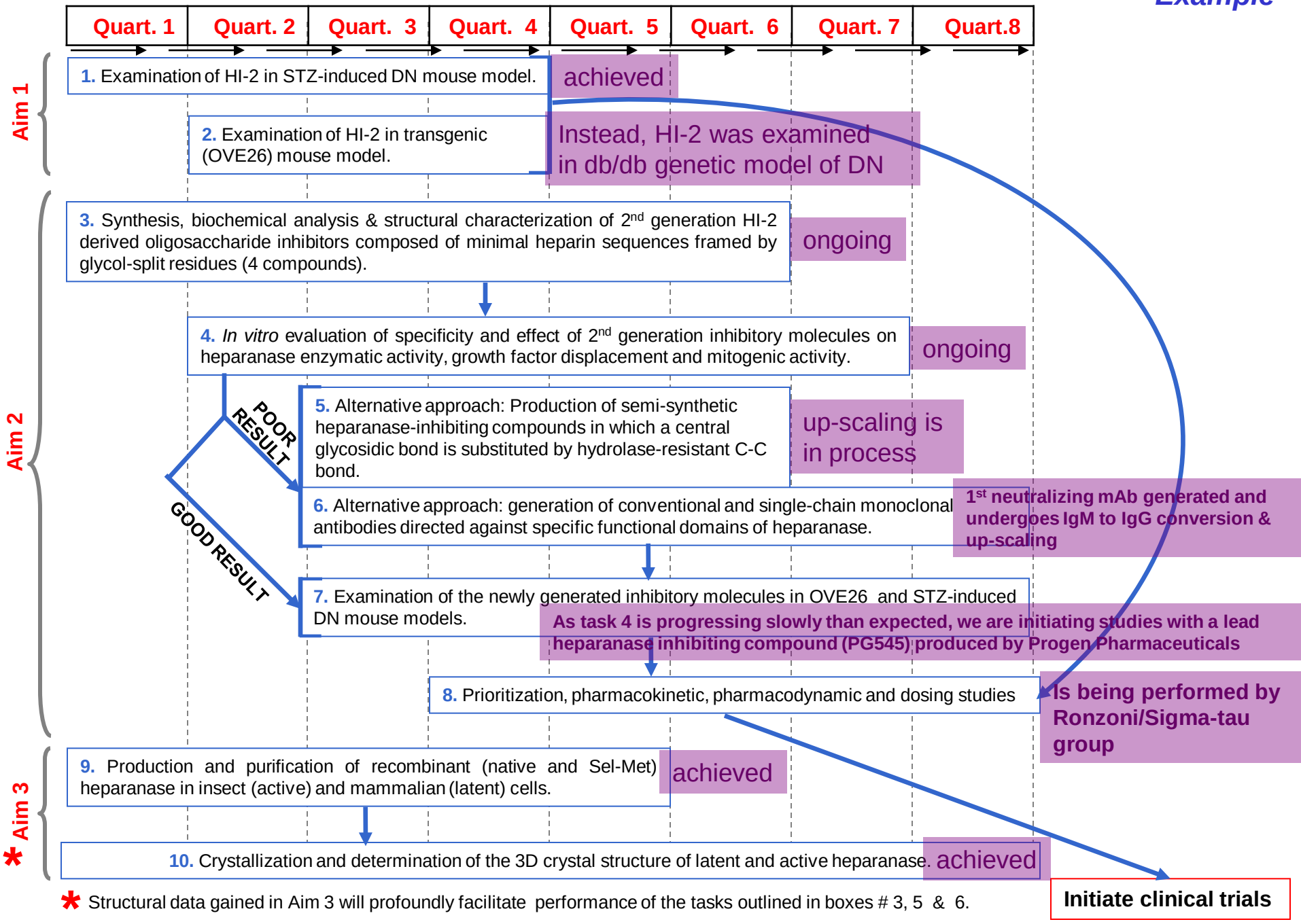
and … if you do not pass,
try again.

Remember: only those who never try,
do not get negative answers
(as in all other areas …)

M. Segev

D. MILESTONES AND TIMELINE (in quarterly increments)

Example



✱ Structural data gained in Aim 3 will profoundly facilitate performance of the tasks outlined in boxes # 3, 5 & 6.