FreeMind Group

AI Powered Grant Writing Support

Presenter: Ayal Ronen, CBO

FREEMIND
Non-Dilutive Funding Experts

“AI Won’t Replace Humans — But Humans With AI Will Replace Humans Without AI”

Harvard Business Review

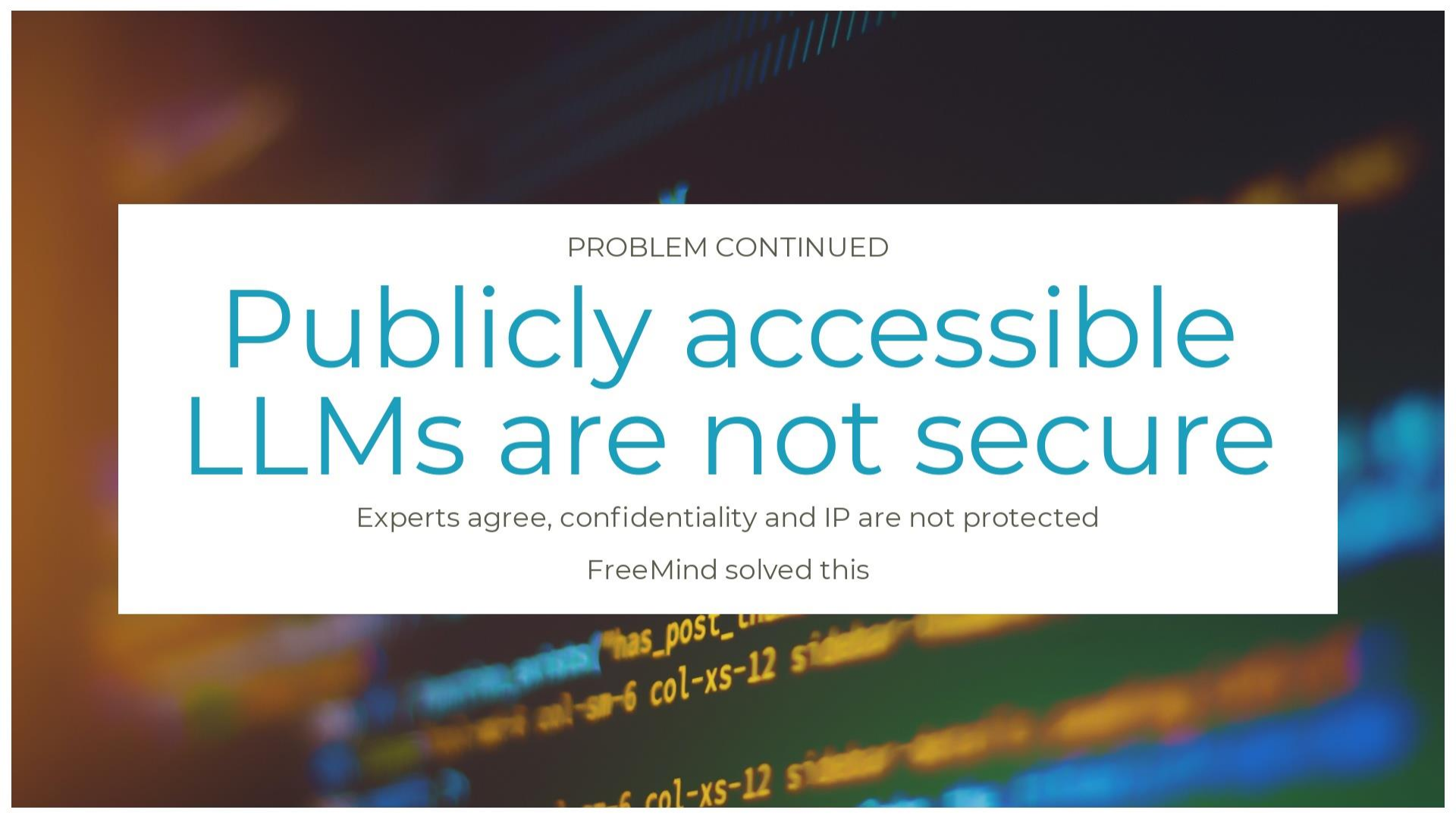
Purpose

To take advantage of the generative AI revolution,
thus propelling grant writing support to new heights

THE PROBLEM:

GenAI exploded into our lives, yet security, reputable data sources, and output accuracy remain a challenge

Need a secure system specifically trained to help write grants



PROBLEM CONTINUED

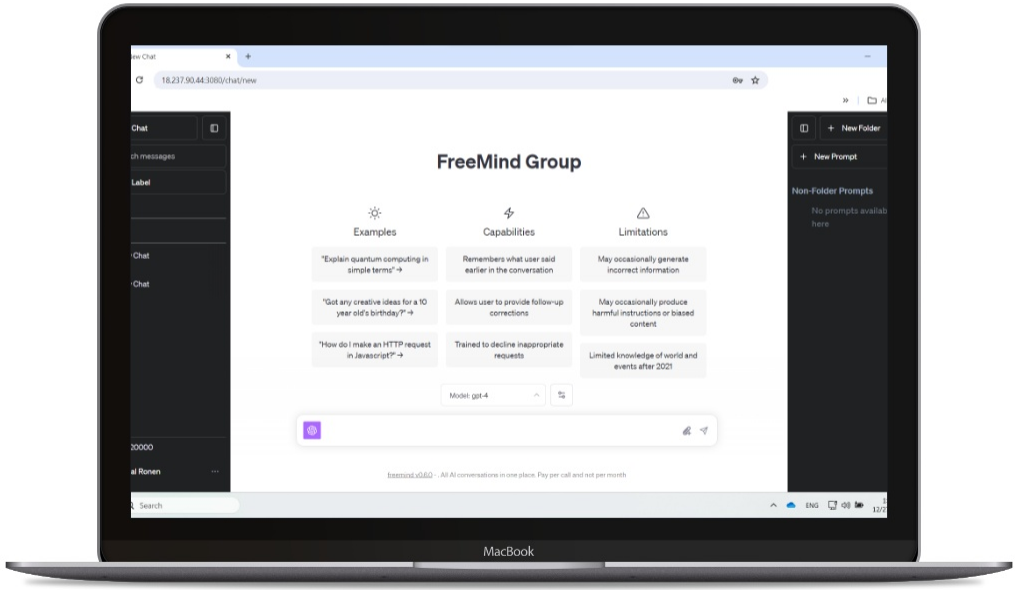
Publicly accessible LLMs are not secure

Experts agree, confidentiality and IP are not protected

FreeMind solved this

100% Secure Generative AI Solution

Custom built solely for in-house use (for now)



Protect your IP and confidentiality

FreeMind grant writers use a custom built in-house GPT

Queries remain secure within the closed system

Results are based on GPT-4's up to date LLM

FREEMIND KNOWS

#1 reason orgs fail to submit grants is bandwidth

We are changing this

Complete A to Z Solution

Suite of AI tools supporting the entire app preparation process

Strategy

- Define pipeline projects
- Automatically identify all available funding opportunities
- Devise a granting strategy

Documents

- Trained on ~5,000 of FMGs submissions and corresponding reviews
- Dedicated tool for each item
- Created by LLMs, validated by professionals

Validation

- Compare to historical submissions
- Identify pitfalls
- Correct in advance of submission
- "Anticipate" a result

Complete A to Z Solution

Suite of AI tools addressing all parts of the application

1 | **Devising a granting strategy**
Defining pipeline projects, identifying all relevant funding opportunities + rank

2 | **Research Approach**
Significance, Innovation, detailed Specific Aims, Future Plans

3 | **Biosketches**
Based on CV, PubMed, USPTO, LinkedIn etc.

4 | **Specific Aims**
Based on Research Approach

5 | **Budget & Justification**

6 | **Commercialization plan**

7 | **Resources**

8 | **Human Subjects**

9 | **Abstract & Project Narrative**
Based on the Specific Aims

10 | **Etc...**

FREEMIND
Non-Dilutive Funding Experts

Created by **LLMs**
Validated by **Professionals**

LLM trained on ~5,000 of FreeMind's submissions, including corresponding reviews

AI Tools

First tools to be deployed

Search

Automated identification and **ranking** of applicable funding opportunities for each pipeline project

Biosketches

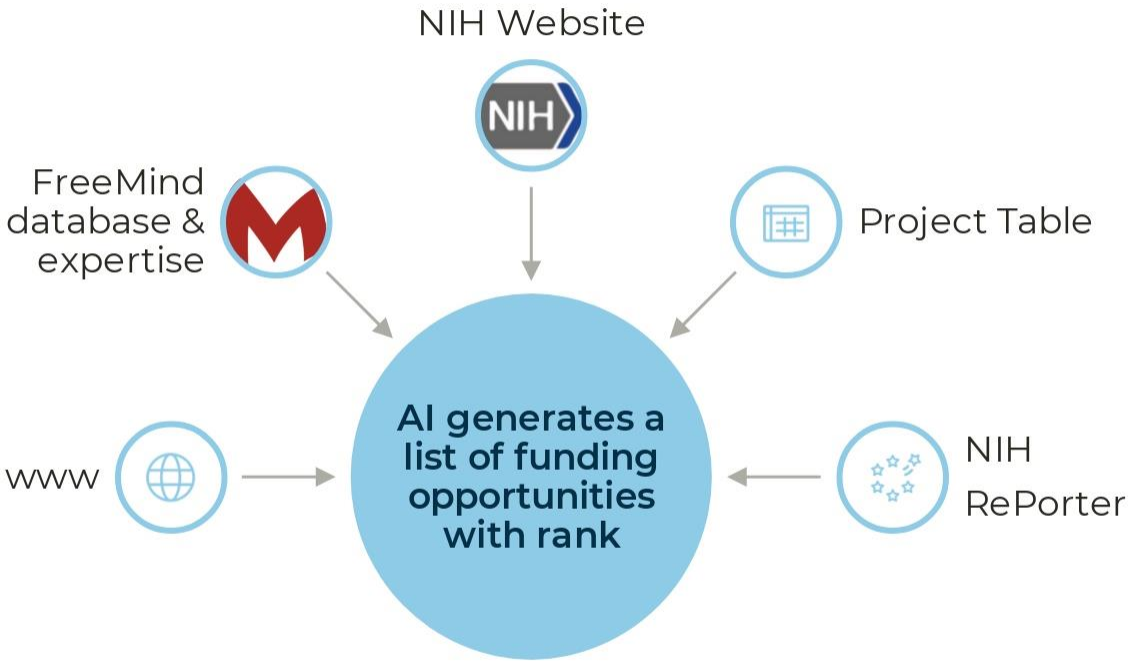
Build a Biosketch at a click of a button

Docs

Specific Aims, Abstract, Project Narrative

LET AI

Search for **funding opportunities**.



Granting strategy is validated by FreeMind Strategists

Devise a Granting Strategy

We trained an AI LLM to identify funding opportunities

Output is based on real-time information available on the web, mainly, the NIH database, as well as FreeMind's knowledgebase and expertise.

Each presented funding opportunity is **ranked**

FREEMIND
Non-Dilutive Funding Experts

- Funding Opportunities
- Project Documents
- Biosketch

Settings

- Profile Settings

Collapse Menu

Funding Opportunities

Your saved projects

New Search

Filters

Search...

Company	Projects	Added at	Version
GenoCure Pharma	3	2023/01/08	2023/01/08
BioPrecision Dx	5	2023/02/05	2023/02/05
CellVista Therapeutics	4	2023/02/09	2023/02/09
NanoHeal Biotech	7	2023/02/01	2023/02/01
ImmunoSolve Pharma	5	2023/02/08	2022/08/08
ImmunoSolve Pharma	5	2023/02/10	2023/02/10
BioSphere Dx	2	2023/09/11	2023/09/11
ProBio Tx	6	2023/11/30	2023/11/30
ProBio Tx	4	2023/12/15	2022/05/15

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Non-Dilutive Funding Experts

- Opportunities
- Project Documents
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Collapse Menu

Step 1 of 4

Funding Opportunities

Add relevant information by uploading files or pasting free text

Import or drop files here

or open from

Salesforce

Sharepoint

or

Insert Text

Files from upload or sources will preview here

Files Added

Files selected will show here.

You have added no files yet

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Step 1 of 4

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Insert Text

Sharepoint

We found files in your salesforce account. Review and select the prospects to add.

Search

Files / Folders

- Accounts
- Account Brand
- ProBio Tx
- Account Contact Role
- Account Feed
- Third Party Account Link
- User Provisional Accounts
- Opportunity
- Lead
- Product
- Campaign
- CustomObject1
- CustomObject2
- CustomObject3

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Name
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document123.txt
project_report_final.docx
image_gallery_2023.jpg
presentation_draft.ppt
code_samples_v2.py
vacation_photos.zip
financial_spreadsheet.xlsx
notes_on_meeting.pdf
march2023.pdf
design_sketches_draft1.png
research_data_set.csv
confidential_notes.txt
software_demo_video.mp4

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ProBio Tx Project Table

Review your added file

Remove

List of pipeline Projects (if possible, in order of priority)

Indication/ Disease	Proposed solution *(name of device/ drug/ biologic /software/ diagnostic)*	High-level bullet point summary of preliminary data accomplished thus far [if there is no preliminary data yet, summarize scientific rationale to back up your project in 1-2 sentences]	Future R&D steps you seek funding for. Please list your specific aims. For example: 1. Develop prototype 2. Validate in mouse model; or 1. Assess safety and efficacy 2. Biomarker analysis in serum	Name the site / facility where the research/ trial will take place and the location (e.g. Mayo Clinic, USA)	Name any additional potential collaborating CROs, Universities, or other parties (e.g. Jackson Laboratory, China)	Priority rank (1 highest -3 lowest
Cervical Carcinoma	E6 small molecule inhibitors to treat HPV-associated cervical carcinomas	• In vitro and in vivo mouse POC data. • ADME + PK complete	• Second species toxicity • PD + MTD • Biomarker design • IND submission • Phase I clinical trial	FreeMind, USA Mayo Clinic USA	Mayo Clinic	1
Broad spectrum HPV-associated cancers **Head and neck, anus and vulva**	E6 small molecule inhibitors to treat HPV-associated head and neck, anus and vulva carcinomas	Discovery	• In vitro POC • In vivo mouse model	FreeMind, USA UCLA, USA Cambridge, UK	UCLA Cambridge	2

Files Added

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- Notes
- ProBio Tx Projects Table
- NCI Deck

File Added

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Step 2 of 4

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Select project details you want to make adjustments to.

Development of E6 Inhibitors for Immunodeficient Patients

Pre-Clinical

Edit Project

Budget: **$700,000**

NCI Country Based: US only

Given the limited effectiveness of current HPV vaccines in immunodeficient individuals, a project could focus on developing specific E6 inhibitors for this demographic. This would involve designing and testing molecules that can effectively disrupt E6 activity in immunocompromised systems, potentially improving treatment outcomes for HPV-associated cancers in these patients.

Activities seeking funding:

1. Molecular design and synthesis of E6 inhibitors,
2. Preclinical testing in immunodeficient models.

Timeline

Start 02/2023, IND submission Q4 2025, Phase 1/2 start Q2 2026

Expanding the Range of HPV Strains Targeted by E6 Inhibitors

Non - clinical

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Budget: **$700,000**

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The current research seems focused on high-risk types of HPV, like HPV16 and 18. A subsequent project could aim to expand the spectrum of HPV types targeted by these therapies. This would involve identifying and characterizing E6 proteins from other HPV strains and developing inhibitors that are effective across a broader range of HPV-associated cancers.

Activities seeking funding:

1. Characterization of E6 proteins from various HPV strains
2. Development and testing of broad-spectrum E6 inhibitors

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The primary objective of this scientific project is to enhance the treatment of HPV-associated cancers in immunodeficient individuals. Recognizing the reduced efficacy of existing HPV vaccines in this demographic, the project aims to create and validate novel E6 inhibitors specifically tailored for immunocompromised systems. By concentrating on the design and experimental assessment of molecules capable of effectively impeding E6 activity, the project seeks to significantly improve treatment outcomes for patients with compromised immune systems suffering from HPV-related cancers.

Cancel | Save

Activities seeking funding:

Go back | Save & Continue

Step 2 of 4

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Text updated

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Timeline

Go back | Save & Continue

Step 3 of 4

Searching for funding opportunities...

Please wait, this may take a few seconds

Step 4 of 4

Matched Opportunities

Select project details you want to make adjustments to.

Find more opportunities

Matched 62 opportunities

Development of E6 Inhibitors for Immunodeficient Patients +3

Expanding the Range of HPV Strains Targeted by E6 Inhibitors +5

Go back | Save | Download File

Step 4 of 4

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Development of E6 Inhibitors for Immunodeficient Patients

+3

90% Match

Impacts of climate change across the cancer control continuum (R21 Clinical Trial Optional)

NIH ,NCI

Link to Grant View Full Details

Activity Codes R21 R01

This Notice of Funding Opportunity (NOFO) aims to support innovative research relevant to advancing the understanding of the effects of climate change across the cancer control continuum, from cancer etiology and cancer risks through survivorship, and ways to prevent or mitigate negative health effects. This includes, but is not limited to, studies to improve knowledge of the impact of climate change related environmental effects on cancer risks, control and behaviors.

Activities included

- Assess the impact of climate change-related environmental changes on cancer risk and cancer outcomes, including carcinogenic exposures and vector-borne diseases.
- Understand and address the susceptibility of cancer survivors to direct and/or indirect climate change effects, such as the spread of vector-borne disease, disruptions in care, and factors that can impact cancer recurrence and/or potential latent effects among childhood cancer survivors.
- Model the magnitude of the impacts of climate change on cancer-related risk factors and health behaviors (e.g. geospatial data linkages).
- Identify and/or characterize communities particularly vulnerable to increased environmental exposures and cancer risk due to climate change-related events and develop interventions to mitigate the impact of social determinants related to climate change and cancer risk.
- Develop and test strategies to enhance the equitable adoption, implementation, and sustainability of evidence-based mitigation or adaptation efforts that reduce the burden of climate change on cancer outcomes.
- Improve understanding of the behavioral, social, and psychological factors that underlie cancer preventive health behaviors implicated in climate change in order to develop approaches to target health behaviors related to both cancer and climate change (e.g., promoting plant-based diets, active transportation).
- Identify, develop, and test behavioral interventions at multiple levels (from the individual to systems-level) to facilitate behavioral strategies and policies that reduce

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Step 4 of 4

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Development of E6 Inhibitors for Immunodeficient Patients

+3

90% Match

Innovation Grants to N… Agent Characterization and In vivo Efficacy Studies (R61/R33 Clinic…

NIDDK ,NIA

Link to Grant View Full…

Activity Codes R16 R3…

This funding opportunity ann… kinetic, and in vivo efficacy studies to demonstrate that proposed therapeutic agent(… urological or neuromuscular disorders that fall under the NINDS mission. Therapeutic agents i… is part of a suite of Innovation Grants to Nurture Initial Translational Efforts (IGNITE)… Blueprint Neurotherapeutics Network or other translational programs.

Activities included

1. Affinity maturation >> Preparation of the therapeutic agent(s) to support proposed activities
2. Human dose modeling >> Studies to inform design and refinement of the PD measure and/or in vivo efficacy models and testing procedures
3. Safety studies >> Characterization of therapeutic agent(s)
4. CD38 pathway characterization >> Limited studies to identify potential pharmacodynamic biomarkers
5. Biomarker development >> Limited studies to identify potential pharmacodynamic biomarkers
6. Additional in vitro efficacy studies >> Limited studies to optimize the candidate therapeutic agent(s) for in vivo efficacy testing
7. In vivo efficacy studies >> Studies to inform design and refinement of the PD measure and/or in vivo efficacy models and testing procedures

Save Matched

Enter Version Name to save your matches

Version

Enter version name

Cancel Save

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Step 4 of 4

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Save Matched

Enter Version Name to save your matches

Version

Project Match

Cancel Save

Go back Save Download File

Opportunities

Lorem Ipsum

Find New Opportunity

Filters

Search...

Company	Projects	Added At	Version
NCI	2	2023/12/31	2023/12/31
GenoCure Pharma	3	2023/01/08	2023/01/08
BioPrecision Dx	5	2023/02/05	2023/02/05
CellVista Therapeutics	4	2023/02/09	2023/02/09
NanoHeal Biotech	7	2023/02/01	2023/02/01
ImmunoSolve Pharma	5	2023/02/08	2022/08/08
ImmunoSolve Pharma	5	2023/02/10	2023/02/10
BioSphere Dx	2	2023/09/11	2023/09/11
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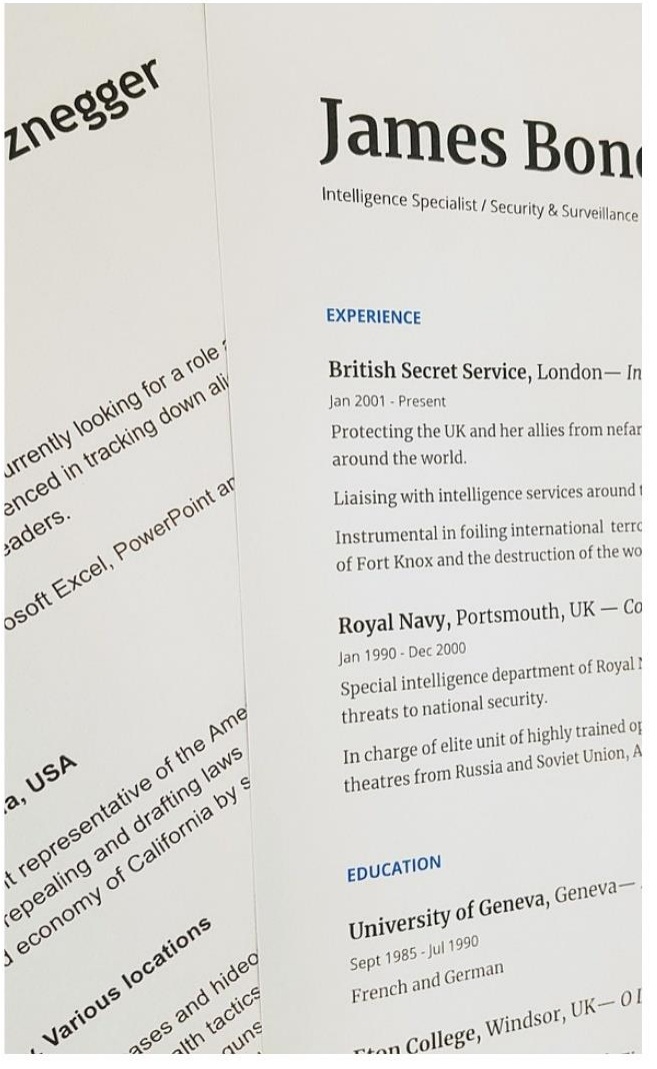

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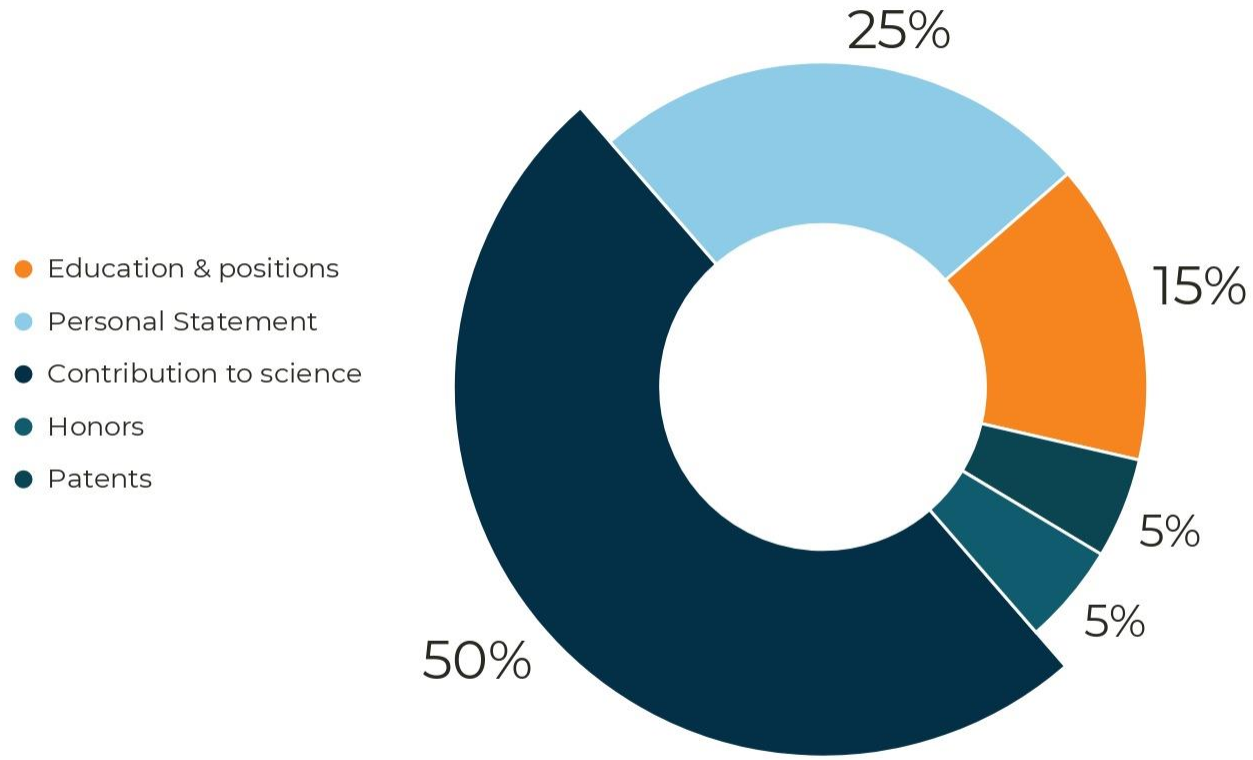

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nechama silverstein

Nechama Silverstein

Senior Client Strategist at FreeMind Group

Israel

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Team Lead

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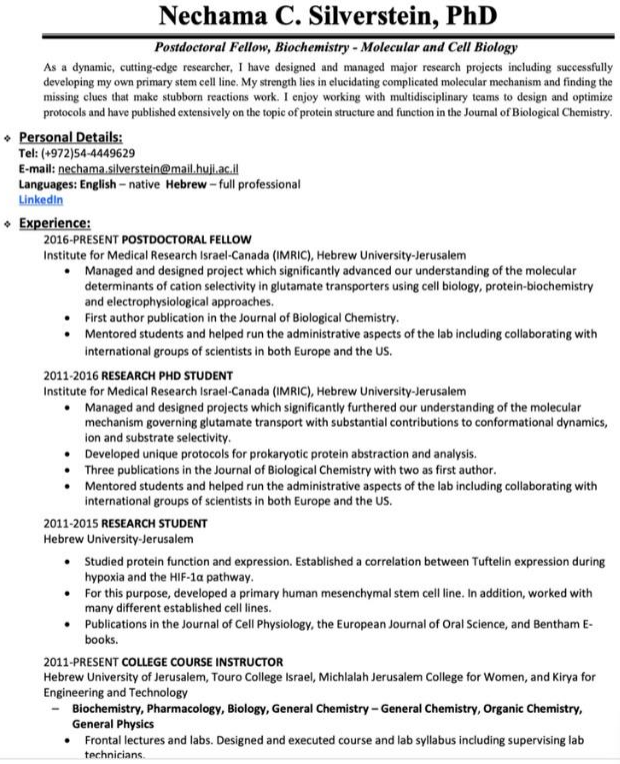

Nechama C. Silverstein, PhD

Postdoctoral Fellow, Biochemistry - Molecular and Cell Biology

As a dynamic, cutting-edge researcher, I have designed and managed major research projects including successfully developing my own primary stem cell line. My strength lies in elucidating complicated molecular mechanism and finding the missing clues that make stubborn reactions work. I enjoy working with multidisciplinary teams to design and optimize protocols and have published extensively on the topic of protein structure and function in the Journal of Biological Chemistry.

Personal Details:
Tel: (+972)54-4449629
E-mail: nechama.silverstein@mail.huji.ac.il
Languages: English – native **Hebrew** – full professional
LinkedIn

Experience:

2016-PRESENT **POSTDOCTORAL FELLOW**
Institute for Medical Research Israel-Canada (IMRIC), Hebrew University-Jerusalem
- Managed and designed project which significantly advanced our understanding of the molecular determinants of cation selectivity in glutamate transporters using cell biology, protein-biochemistry and electrophysiological approaches.
- First author publication in the Journal of Biological Chemistry.
- Mentored students and helped run the administrative aspects of the lab including collaborating with international groups of scientists in both Europe and the US.

2011-2016 **RESEARCH PHD STUDENT**
Institute for Medical Research Israel-Canada (IMRIC), Hebrew University-Jerusalem
- Managed and designed projects which significantly furthered our understanding of the molecular mechanism governing glutamate transport with substantial contributions to conformational dynamics, ion and substrate selectivity.
- Developed unique protocols for prokaryotic protein abstraction and analysis.
- Three publications in the Journal of Biological Chemistry with two as first author.
- Mentored students and helped run the administrative aspects of the lab including collaborating with international groups of scientists in both Europe and the US.

2011-2015 **RESEARCH STUDENT**
Hebrew University-Jerusalem
- Studied protein function and expression. Established a correlation between Tuftelin expression during hypoxia and the HIF-1α pathway.
- For this purpose, developed a primary human mesenchymal stem cell line. In addition, worked with many different established cell lines.
- Publications in the Journal of Cell Physiology, the European Journal of Oral Science, and Bentham E-books.

2011-PRESENT **COLLEGE COURSE INSTRUCTOR**
Hebrew University of Jerusalem, Touro College Israel, Michlalah Jerusalem College for Women, and Kirya for Engineering and Technology
- **Biochemistry, Pharmacology, Biology, General Chemistry – General Chemistry, Organic Chemistry, General Physics**
- Frontal lectures and labs. Designed and executed course and lab syllabus including supervising lab technicians.

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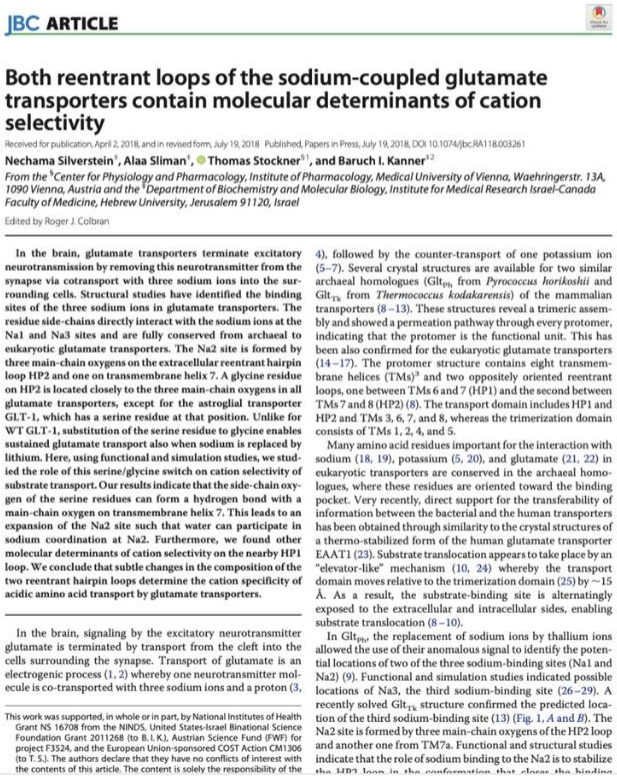

JBC ARTICLE

Both reentrant loops of the sodium-coupled glutamate transporters contain molecular determinants of cation selectivity

Received for publication, April 2, 2018, and in revised form, July 19, 2018 Published, Papers in Press, July 19, 2018, DOI 10.1074/jbc.RA118.003261

Nechama Silverstein[‡], **Alaa Sliman**[‡], **Thomas Stockner**[§1], **and Baruch I. Kanner**[‡2]

From the [§]*Center for Physiology and Pharmacology, Institute of Pharmacology, Medical University of Vienna, Waehringerstr. 13A, 1090 Vienna, Austria and the* [‡]*Department of Biochemistry and Molecular Biology, Institute for Medical Research Israel-Canada Faculty of Medicine, Hebrew University, Jerusalem 91120, Israel*

Edited by Roger J. Colbran

In the brain, glutamate transporters terminate excitatory neurotransmission by removing this neurotransmitter from the synapse via cotransport with three sodium ions into the surrounding cells. Structural studies have identified the binding sites of the three sodium ions in glutamate transporters. The residue side-chains directly interact with the sodium ions at the Na1 and Na3 sites and are fully conserved from archaeal to eukaryotic glutamate transporters. The Na2 site is formed by three main-chain oxygens on the extracellular reentrant hairpin loop HP2 and one on transmembrane helix 7. A glycine residue on HP2 is located closely to the three main-chain oxygens in all glutamate transporters, except for the astroglial transporter GLT-1, which has a serine residue at that position. Unlike for WT GLT-1, substitution of the serine residue to glycine enables sustained glutamate transport also when sodium is replaced by lithium. Here, using functional and simulation studies, we studied the role of this serine/glycine switch on cation selectivity of substrate transport. Our results indicate that the side-chain oxygen of the serine residues can form a hydrogen bond with a main-chain oxygen on transmembrane helix 7. This leads to an expansion of the Na2 site such that water can participate in sodium coordination at Na2. Furthermore, we found other molecular determinants of cation selectivity on the nearby HP1 loop. We conclude that subtle changes in the composition of the two reentrant hairpin loops determine the cation specificity of acidic amino acid transport by glutamate transporters.

In the brain, signaling by the excitatory neurotransmitter glutamate is terminated by transport from the cleft into the cells surrounding the synapse. Transport of glutamate is an electrogenic process (1, 2) whereby one neurotransmitter molecule is co-transported with three sodium ions and a proton (3, 4), followed by the counter-transport of one potassium ion (5–7). Several crystal structures are available for two similar archaeal homologues (Glt_{Ph}, from *Pyrococcus horikoshii* and Glt_{Tk} from *Thermococcus kodakarensis*) of the mammalian transporters (8–13). These structures reveal a trimeric assembly and showed a permeation pathway through every protomer, indicating that the protomer is the functional unit. This has been also confirmed for the eukaryotic glutamate transporters (14–17). The protomer structure contains eight transmembrane helices (TMs)[3] and two oppositely oriented reentrant loops, one between TMs 6 and 7 (HP1) and the second between TMs 7 and 8 (HP2) (8). The transport domain includes HP1 and HP2 and TMs 3, 6, 7, and 8, whereas the trimerization domain consists of TMs 1, 2, 4, and 5.

Many amino acid residues important for the interaction with sodium (18, 19), potassium (5, 20), and glutamate (21, 22) in eukaryotic transporters are conserved in the archaeal homologues, where these residues are oriented toward the binding pocket. Very recently, direct support for the transferability of information between the bacterial and the human transporters has been obtained through similarity to the crystal structures of a thermo-stabilized form of the human glutamate transporter EAAT1 (23). Substrate translocation appears to take place by an "elevator-like" mechanism (10, 24) whereby the transport domain moves relative to the trimerization domain (25) by ~15 Å. As a result, the substrate-binding site is alternatingly exposed to the extracellular and intracellular sides, enabling substrate translocation (8–10).

In Glt_{Tk}, the replacement of sodium ions by thallium ions allowed the use of their anomalous signal to identify the potential locations of two of the three sodium-binding sites (Na1 and Na2) (9). Functional and simulation studies indicated possible locations of Na3, the third sodium-binding site (26–29). A recently solved Glt_{Tk} structure confirmed the predicted location of the third sodium-binding site (13) (Fig. 1, *A* and *B*). The Na2 site is formed by three main-chain oxygens of the HP2 loop and another one from TM7a. Functional and structural studies indicate that the role of sodium binding to the Na2 is to stabilize the HP2 loop in the conformation that closes the binding

This work was supported, in whole or in part, by National Institutes of Health Grant NS 16708 from the NINDS, United States-Israel Binational Science Foundation Grant 2011268 (to B. I. K.), Austrian Science Fund (FWF) for project F3524, and the European Union-sponsored COST Action CM1306 (to T. S.). The authors declare that they have no conflicts of interest with the contents of this article. The content is solely the responsibility of the

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POSITION TITLE: **Co-Investigator**

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	DATE	FIELD OF STUDY
Touro College	B.S.	05/2005	Biology
Hebrew University	M.Sc.	06/2010	Molecular and Cell Biology
Hebrew University	Ph.D.	06/2016	Biomedical Sciences

A. Personal Statement

As Co-Investigator on this project, I will oversee key aspects of research activities assessing combinations of our E6-binding inhibitor spinacine with therapeutic agents TRAIL and cisplatin in a mouse model. My PhD research focused on molecular mechanisms governing neurotransmitter transport and binding. As a postdoctoral fellow, I have published extensively on determinants influencing cation selectivity and substrate interactions in glutamate transporters. My expertise in transporter kinetics, conformational changes, and protein-small molecule binding will be instrumental in elucidating the mechanism of action of spinacine. I have over 10 years' experience managing major research projects and collaborating with leading research groups internationally.

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B. Positions, Scientific Appointments, and Honors

2016-Present

Postdoctoral Fellow, Institute for Medical Research Israel-Canada, Hebrew University

2011-2015

Research PhD Student, Institute for Medical Research Israel-Canada, Hebrew University

2010-2011

Research Student, Hebrew University of Jerusalem

1. My research has elucidated critical molecular determinants that influence cation selectivity and substrate interactions in glutamate transporters. Using functional and simulation studies, I showed that subtle changes in the composition of hairpin loops in glutamate transporters

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Hebrew University	Ph.D.	06/2016	Biomedical Sciences

A. Personal Statement

As Co-Investigator on this project, I will oversee key aspects of the research activities assessing combinations of our E6-binding inhibitor spinacine with therapeutic agents TRAIL and cisplatin in a mouse model. My background in elucidating molecular mechanisms of neurotransmitter and glutamate transporters makes me uniquely qualified to provide critical insights into the mechanism of action of spinacine.

My PhD research focused on investigating the kinetics, conformational changes, and molecular determinants involved in neurotransmitter binding and translocation. As a postdoctoral fellow, I have extensively studied the factors influencing cation selectivity and substrate interactions in glutamate transporters. My expertise in techniques like radioactive transport assays and fluorescence spectroscopy to analyze protein conformational changes and ligand binding will be essential for deciphering how spinacine interacts with target proteins.

Additionally, my over 10 years of experience managing major research projects and collaborating with leading research groups internationally have honed my leadership, organizational, and communication skills. I have a strong track record of elucidating intricacies of membrane transport proteins to advance scientific understanding and therapeutic potential. I will leverage this background to helpcoordinate the research team and provide key insights guiding the direction of experiments to assess spinacine efficacy. My knowledge and technical expertise make me well-positioned to play an integral role driving this research forward.

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Publications and Research Products:

a. Silverstein N, Sliman A, Stockner T, Kanner B. (2018) Both reentrant loops of the sodium-coupled glutamate transporters contain molecular determinants of cation selectivity. J Biol Chem.
b. Tanui R, Tao Z, Silverstein N, Kanner B, Grewer C. (2016) Electrogenic Steps Associated with Substrate Binding to the Neuronal Glutamate Transporter EAAC1. J Biol Chem.
c. Silverstein N, Ewers D, Forrest LR, Fahlke C, Kanner BI. (2015) Molecular Determinants of Substrate Specificity in Sodium-coupled Glutamate Transporters. J Biol Chem.
d. Silverstein N, Crisman TJ, Forrest LR, Kanner BI. (2013) Cysteine scanning mutagenesis of transmembrane helix 3 of a brain glutamate transporter reveals two conformationally sensitive positions. J Biol Chem.
e. Leiser Y, Silverstein N, Blumenfeld A, Shilo D, Haze A, Rosenfeld E, Shay B, Tabakman R, Lecht S, Lazarovici P, and Deutsch D (2010) The induction of tuftelin expression in PC12 cell line during hypoxia and NGF induced differentiation. J Cell Physiol.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

Years	*Position, Place*
2016-Present	Postdoctoral Fellow, Institute for Medical Research Israel-Canada, Hebrew University
2011-2015	Research PhD Student, Institute for Medical Research Israel-Canada, Hebrew University
2010-2011	Research Student, Hebrew University of Jerusalem
2003-2004	Editor in Chief – Touro Science Society Journal

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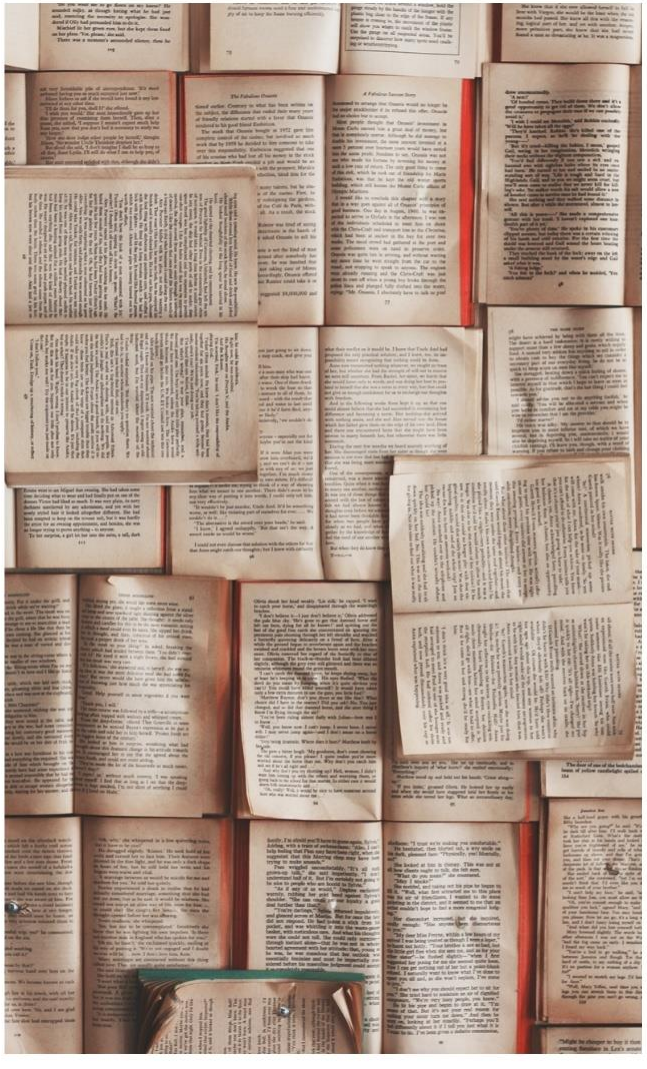

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BioPrecision Dx	5	2023/02/05	2023/02/05
CellVista Therapeutics	4	2023/02/09	2023/02/09
NanoHeal Biotech	7	2023/02/01	2023/02/01
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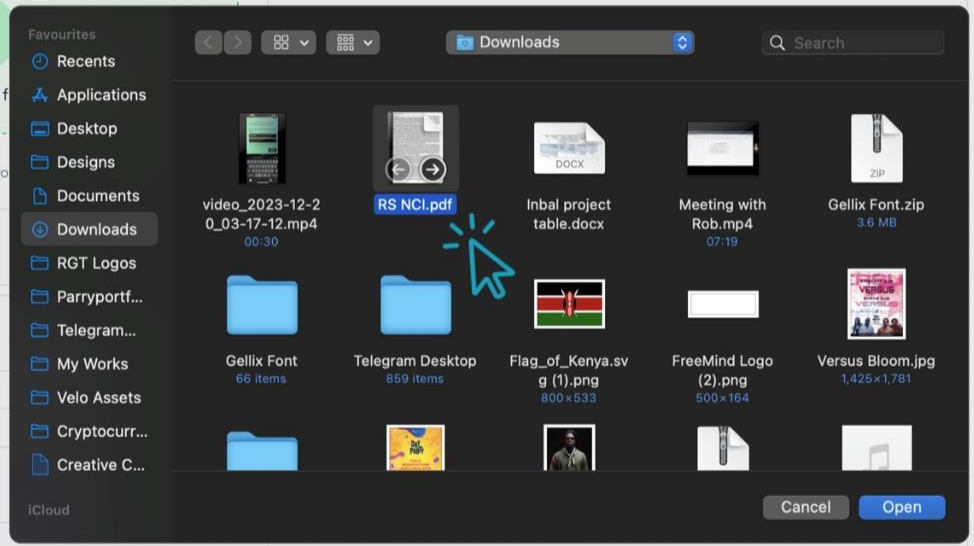

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Contact PD/PI: Filippova, Maria

SIGNIFICANCE

HPV is responsible for nearly all cervical cancers and the majority of head and neck cancers. High-risk types of human papillomavirus (HPV) are responsible for virtually all cases of human cervical carcinoma. Worldwide, this is the second most common cancer in women; over 400,000 women are newly diagnosed with this disease each year, of which approximately half will die [7]. Additional deaths occur due to other HPV-associated malignancies, such as those of the head and neck, anus and vulva. Head and neck (HN) cancers are of particular interest, because the incidence of HPV-mediated HN cancer in the US has dramatically risen [8-10].

Current treatment options for HPV-associated tumors are limited and frequently ineffective. Public health policies and initiatives claim responsibility for significant progress against HPV-mediated cancers in the contexts of infection prevention and early detection. Currently available prophylactic vaccines appear to be both safe and effective [11-13]. Importantly, however, these vaccines are not effective interventions for individuals already infected with HPV, nor are they appropriate for immunodeficient individuals [14]. Further concerns include recent reports regarding side effects of vaccination [15], as well as challenges inherent in making the vaccine available in developing countries. Early detection of cervical cancer is frequently possible through the use of population-wide Pap screening, though an equivalent approach for identifying HN and other HPV-associated tumors is not yet available. Current treatment options focus on removing the tumor, which can be effective when the tumor is detected in time. However, options for tumors detected later are much less effective. Survival is low, due in large part to the activities of the E6 oncoprotein (see below), and patients, especially those who are immunocompromised, frequently relapse [14, 16]. In fact, cervical cancer is highly resistant to chemotherapy, with only 15 – 20% of tumors responding to treatment [17]. The best results thus far have been obtained using combined chemo-radiotherapies, and approaches based on cisplatin, carboplatin, paclitaxel, topotecan, 5-fluorouracil and radiotherapy are frequently combined into regimens drawing on two or even three agents. However, even these combinatorial treatments have limited efficacy and relatively serious side effects [18-20]. Together, these issues point toward the compelling and urgent need to develop better treatment options for patients with cervical cancer and other HPV-associated malignancies.

The E6 oncoprotein encoded by high-risk HPV limits the effectiveness of chemo- and radiotherapies by compromising cellular apoptotic pathways. Most chemo- and radiotherapies are based on the idea that they can damage DNA, and that that damage will then trigger apoptotic death of the cancer cells. Unfortunately, the E6 oncoprotein produced by high-risk types of the virus, such as HPV16 and 18, subverts both the intrinsic and extrinsic apoptotic pathways by accelerating the degradation of key molecular players. This means that apoptosis-inducing treatments are much less effective than they would be in the absence of E6. The first target to be documented was E6AP; the binding of E6 to E6AP leads to rapid degradation of the p53 tumor suppressor, thereby inhibiting the induction of p53-mediated intrinsic apoptosis in HPV-infected cells [1-3]. Since then, our laboratory has demonstrated that TNF R1 [21], FADD [5] and caspase 8 [4], all molecules involved in receptor-mediated apoptosis, are also targets of high-risk E6 oncoproteins.

Treatments based on the TRAIL-mediated apoptosis pathway have the potential to be effective against HPV-mediated malignancies. TRAIL-based therapies, which activate the extrinsic apoptotic pathway, have elicited significant interest, largely due to their ability to kill tumor cells while sparing most normal cells. TRAIL receptors 1 and 2 are highly expressed on a large number of solid and hematologic cancers, making these tumors sensitive to apoptosis induced both by TRAIL itself and by antibodies to the receptor [22-27]. However, TRAIL therapy can be limited in that cancer cells can develop resistance toward TRAIL [28, 29]. In the case of HPV-mediated malignancies, the only cancer-mediated agent is high risk HPV. Our laboratory found that in the case of HPV$^+$-mediated malignancies, E6 is the major factor responsible for resistance to TRAIL [6, 30].

Restoring the level of E6-targeted apoptotic molecules can sensitize HPV$^+$ cells to apoptosis. Our efforts over the past 10-15 years [4-6,30], along with those of others, have implicated E6 as an excellent target for therapeutic intervention. This is because disrupting the binding between E6 and its target proteins can result in restoration of these apoptotic proteins, leading to a re-sensitization of HPV$^+$ cells to apoptotic triggers [4-6, 21, 30-32]. Some progress has been made in identifying small molecules that can interfere with E6 activities [33-38], but no studies have yet combined E6 inhibitors with apoptosis-inducing agents. Our laboratory has identified and tested several small molecules that block E6/caspase 8 interactions, and our preliminary studies provide proof-of principle evidence that molecules that block E6/caspase 8 interactions can, indeed, re-sensitize HPV$^+$ cells to apoptotic triggers [30, 31, 39]. In particular, we found that both myricetin and spinacine, small mole-

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High-risk types of human papillomaviruses (HPV) are responsible for virtually all cases of human cervical car- cinoma, as well as an increasing number of other HPV-associated malignancies, including those of the head and neck, anus and vulva. One growing group of patients particularly affected by HPV includes those with compromised immune systems resulting from HIV infection, other diseases or medical treatments. Perhaps the most noteworthy advance in recent years has been the development of safe and effective vaccines targeted against HPV. However, these vaccines are not beneficial for patients who are already infected, appropriate for use in patients with compromised immune systems, or readily available in all developing countries. Once can- cer has developed, current treatment options are relatively limited and focus on physically removing the cancer through surgery. Unfortunately, tumors frequently return, particularly following late-stage diagnosis and/or if the patient is immunocompromised. Chemo- and radio- therapies that rely on the induction of apoptosis in HPV+ tumor cells are relatively ineffective, primarily due to the actions of a virus-encoded oncoprotein, E6, that sub- verts both intrinsic and extrinsic apoptotic pathways by accelerating the degradation of key molecular players. Therefore, new approaches that can eliminate HPV-containing cells, even in the absence of a functional adap- tive immune system, must be developed.

To meet this need, we propose to combine spinacine, a small, naturally occurring molecule whose E6-inhibiting abilities were recently discovered by our laboratory, with existing therapeutic approaches that function by in- ducing apoptosis. Our laboratory and others have shown that high-risk versions of the HPV E6 oncoprotein induce resistance to both intrinsic and extrinsic apoptosis by mediating the rapid degradation of p53, caspase 8 and FADD [1-6]. The absence of these molecules in turn leads to the protection of infected cells from agents that would otherwise induce programmed cell death. To counter this, we searched for molecules that would inhibit the ability of E6 to bind to its cellular apoptotic partners by screening over 3000 compounds. Spinacine was selected as our lead candidate, because it is able to block the binding of E6 to both caspase 8 and E6AP, thereby sensitizing HPV+ cells to apoptosis triggered by agents such as TRAIL (a ligand that selectively induc- es apoptosis in cancer cells) and

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The long-term goal of our laboratory is to develop novel, effective therapies for patients suffering from HPV- associated malignancies, and the overall objective of this current

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High-risk types of human papillomaviruses (HPV) are responsible for virtually all cases of human cervical car- cinoma, as well as an increasing number of other malignancies including those of the head and neck, anus and vulva. Unfortunately, good treatment options for late-stage HPV+ malignancies are not currently available, in large part because the virus encodes a protein, E6, which disables cellular apoptotic pathways by accelerating the degradation of molecules such as FADD, caspase 8 and p53. This makes it difficult to eliminate HPV+ can- cer cells using conventional inducers of apoptosis. To overcome this obstacle, our laboratory has identified several small molecules that block the binding between E6 and partners such as caspase 8 and E6AP. Ac- cording to our working model, the use of such molecules in a combinatorial manner will greatly increase the effectiveness of standard radio- and chemotherapeutic treatments. Both in vitro binding data and cellular data from our laboratory provide strong data in support of this working model, and it is now time to test our approach in an in vivo context. The overall objective of this current application, therefore, is to move our exciting in vitro and cellular observations into a mouse xenograft model. We will do this by combining spinacine, our best mo- lecular candidate, with two potential therapeutic agents: TRAIL, a biologic, and cisplatin, a more conventional chemotherapeutic, asking whether either of these combinations can reduce or eliminate the growth of HPV+ tumors, of either cervical or head and neck origin, in a nude mouse model. In particular, we will: 1) Determine the toxicity of spinacine in mice. We will assess the toxicity of spinacine in mice, defining the maximum tol- erated dose and identifying the optimum dose with which to carry out experiments designed to test its efficacy, and 2) Evaluate the ability of spinacine to synergize with TRAIL- and/or chemo-based therapies to re- duce or eliminate HPV+ tumor growth. We will assess the ability of spinacine to synergize with hrTRAIL and/or the DNA damaging drug cisplatin to inhibit tumor growth in a xenograft model. At the conclusion of this work, we will have 1) Determined the toxicity of the E6-inhibiting molecule spinacine in mice, and 2) Evaluated the effectiveness of combining spinacine with TRAIL- and cisplatin-based treatments in an animal model. This work has the potential to save the lives of thousands of patients suffering from HPV-associated malignancies.

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High-risk types of the human papillomavirus (HPV) are responsible for nearly all cancers of the cervix, as well as an increasing number of other cancers such as those of the head and neck, anus and vulva. It is difficult to effectively treat late-stage HPV+ cancers, because the virus codes for a protein, E6, which makes cells re- sistant to most therapies. We have found a small molecule, spinacine, which prevents E6 from protecting these cells. We now want to ask if spinacine can be combined with either of two conventional therapies, TRAIL and cisplatin, to reduce or eliminate tumors in a mouse model. If successful, treatment for patients with HPV+ tu- mors could be greatly improved.

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High-risk types of human papillomaviruses (HPV) are responsible for virtually all cases of human cervical car- cinoma, as well as an increasing number of other malignancies including those of the head and neck, anus and vulva. Unfortunately, good treatment options for late-stage HPV+ malignancies are not currently available, in large part because the virus encodes a protein, E6, which disables cellular apoptotic pathways by accelerating the degradation of molecules such as FADD, caspase 8 and p53. This makes it difficult to eliminate HPV+ can- cer cells using conventional inducers of apoptosis. To overcome this obstacle, our laboratory has identified several small molecules that block the binding between E6 and partners such as caspase 8 and E6AP. Ac- cording to our working model, the use of such molecules in a combinatorial manner will greatly increase the effectiveness of standard radio- and chemotherapeutic treatments. Both in vitro binding data and cellular data from our laboratory provide strong data in support of this working model, and it is now time to test our approach in an in vivo context. The overall objective of this current application, therefore, is to move our exciting in vitro and cellular observations into a mouse xenograft model. We will do this by combining spinacine, our best mo- lecular candidate, with two potential therapeutic agents: TRAIL, a biologic, and cisplatin, a more conventional chemotherapeutic, asking whether either of these combinations can reduce or eliminate the growth of HPV+ tumors, of either cervical or head and neck origin, in a nude mouse model. In particular, we will: 1) Determine the toxicity of spinacine in mice. We will assess the toxicity of spinacine in mice, defining the maximum tol- erated dose and identifying the optimum dose with which to carry out experiments designed to test its efficacy, and 2) Evaluate the ability of spinacine to synergize with TRAIL- and/or chemo-based therapies to re- duce or eliminate HPV+ tumor growth. We will assess the ability of spinacine to synergize with hrTRAIL and/or the DNA damaging drug cisplatin to inhibit tumor growth in a xenograft model. At the conclusion of this work, we will have 1) Determined the toxicity of the E6-inhibiting molecule spinacine in mice, and 2) Evaluated the effectiveness of combining spinacine with TRAIL- and cisplatin-based treatments in an animal model. This work has the potential to save the lives of thousands of patients suffering from HPV-associated malignancies.

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ImmunoSolve Pharma	5	2023/02/08	2022/08/08
ProBio Tx	5	2023/02/10	2023/02/10

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In Summary

Secure GPT

Fully secure GPT for internal use ensures client IP is protected and confidentiality kept

Search for funding opportunities

Extracting real-time data from the web, the NIH website and the FreeMind Group data set and expertise enables identification and ranking of funding opportunities for each pipeline project

Trained on ~5,000 submissions

FreeMind trained an LLM using thousands of submissions and corresponding reviews

A to Z suite of tools

FreeMind will continue to develop our suite of AI tools designed to address all parts of any submission type

Predictor

Long term goal is to develop an AI able to predict with a certain degree of certainty the potential outcome of any given submission

“In a world where ChatGPT and other AI apps can do many things humans once needed to do themselves or needed to hire other humans to do, the question of **‘how will I add value?**’ becomes more relevant than ever.”

Hendrith Vanlon Smith Jr