Thoughts about putting together a good grant application

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Everything I am talking about is not an absolute. This is just my experience.
Dr. Otto Warburg

Antrag

Ich benötige 10 000 (zehntausend) Mark

Otto Warburg
### Change in payline in NCI over the years

<table>
<thead>
<tr>
<th>Period</th>
<th>Percentage</th>
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<tr>
<td>1970th</td>
<td>25-30%</td>
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<td>1980th</td>
<td>20-25%</td>
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<td>1990-1995</td>
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<td>2000-2005</td>
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<td>2005-2010</td>
<td>10-15%</td>
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<td>2010-</td>
<td>7-9%</td>
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Doubling of the NIH budget

My experience – 80% are useless, 20% are worthy.
How to scale these 20%?

Current NCI decision making – 7% for sure, and chose few more grants in the range 8-14%
Scientific Projects

Government Funding
What is expected from the grant?

- big piece of research
- rapid breakthrough in the field
- practical applications

NIH R01

NIHR21, DOD

DOD

specialized foundations
industry

1. Find the program that fits.
2. Consider how many grants are awarded. This may be more important than percentile.
3. Make sure that your research fits the program exactly.
Who are reviewers?

They are not specialists in your field!
If you have a choice of study section, find one that has specialists in the field. This is more important than the fear of competition.

What should be done to be in 20% of worthy grants?
Two critical components of grant idea –
1. It should solve a serious biological or medical problem (excitement comes from the realization that this research will save the world)
2. You need to dissociate yourself from the rest of the crowd, i.e. to show that your grant is unique (not standard).

Questions like “what does this protein that I discovered do in a cell?” are not funded anymore. If you find a novel pathway explain why this pathway is more important than others.

Your goal - the grant must be given to you, and not to other people.
Reviewers do not have time, and have very short attention span.

Clarity of writing is critical. Absolutely no excessive information, i.e. introduction should be minimal, only relevant experiments in preliminary data.

Long introduction is a very common mistake!
Sections of the grant:

Specific Aims
Significance
Innovation
Approach (including preliminary data)

Reviewers comment on:

Significance
Applicant
Innovation
Approach (including preliminary data)
Environment
Importance of the work for biology or medicine is what makes it exciting.

Significance and Innovation are extremely important sections of the grant. They define the attitude of the reviewer.

Hint – reviewers need to comment on Significance and Innovation in the review. Put words in their mouth, i.e. write in a way that they will simply be able to cut and paste to their review.
Age-dependence of breast cancer

Significance: Cancer is generally considered to be an age-related disorder, although different types of cancer show different modes of age-dependency (i.e. emerge at late, middle, or young age).

Though certain factors that are involved in the organism aging can affect cancer development (e.g. IGF-1), overall the cause of the age-dependency of cancer is not understood. We believe that the lack of understanding results from a lack of the systematic mechanistic approach and uncertainty with adequate animal models.

The latter factor is most critical since all xenograft models and many existing transgenic models do not recapitulate age-dependency of cancer.

Based on population analysis of the cancer incidence, we argue that unlike other models, mouse models of the Her2-positive breast cancer can recapitulate the age-related effects, and therefore investigation of this type of cancer in animals could clarify aging effects seen in humans.

Here, we propose a pilot project to understand aging factors affecting cancer development, focusing on the aggressive Her2-positive breast cancer. In this project, we will apply a model with inducible expression of Her2 to the study of the molecular nature of the age-related effects. Another significant outcome of this project will be the identification of critical signaling mediators implicated in age-dependency of cancer incidence.
Innovation: The major innovation in this pilot proposal is establishing adequate models of breast cancer that allow investigation of the age-dependency of tumorigenesis in mice. Another important innovation is a novel concept that links the Her2-p21 and the epithelial to mesenchymal transition (EMT) pathways, and establishes its central role in mediating aging effects in tumor development.
Determinants of hyperthermia sensitivity in colorectal cancer cells

Significance The inverse association between acute infections and cancer is supported by epidemiological data, recorded bacterial treatments of cancer patients, and in vivo experimental work in animal models of cancer (1,2). In 1874 in England, Dr. Campbell De Morgan presented evidence that in some cases cancer regresses after infections and, particularly, after the onset of tuberculosis (3). In 1890, during a review of records in Memorial Hospital (New York), Dr. William Coley found a case in which erysipelas cured a cancer patient (4). In 1891, Coley replicated this outcome by utilizing Streptococcus pyogenes and inducing erysipelas in a patient with sarcoma (5). Subsequently, Coley switched to a heat-inactivated mixture of bacteria, and increased the dosage until a fever of 39°C or higher was developed by the patients (4,6,7). Most of Coley’s patients had late stage cancers that did not respond to conventional treatments and yet, retrospective analyses of these cases report five-year survival in more than 44% of the patients (7). In the 1960s, by not “grandfathering” Coley’s treatment, FDA stopped its use in the U.S. A later unsuccessful attempt to revive the therapy utilized a mixed bacterial vaccine (Vaccineurin); however, the treatments were of short duration and without the objective of achieving fever, which may explain the vaccine’s failure, as the curative effect is likely initiated by fever (8). The significance of developing high body temperature was confirmed in a more recent clinical trial in Germany with a mixed bacterial vaccine (9). Reminiscent of Coley’s approach are the promising studies with Clostridium novyi reported by the group of Dr. Vogelstein in Johns Hopkins (10,11). Epidemiological analyses also support an inverse association between acute infections and cancer incidence. For example, individuals with a history of three or more infections with fever above 38.5°C have a 40% lower risk for melanoma (12), and the anamnesis of cancer patients compared to the medical history of infectious diseases in cancerfree patients has been confirmed (13). In contrast to the inverse association between acute infections and cancer, chronic inflammations increase the risk of cancer (1).

A significant difference between the two conditions is that acute inflammations lead to high fever compared to chronic inflammations (2). Therefore, fever might be the critical anti-cancer factor, since high body temperature kills preferentially cancer cells (8), and the release of internal cancer-specific antigens from the dying cells can elicit anticancer immune response. Therapeutic response to hyperthermia consists of two steps: a signaling response at the cancer cell level, and an immune response at the level of the organism (2,13). Our project focuses on the mechanisms of the first step, since cell signaling differences may explain the distinct sensitivity of cancers to hyperthermia.
**Innovation** The application of hyperthermia as an anti-cancer therapy is currently not guided by the cancer mutation profile, and this could be one reason for the variable performance of hyperthermia as an anti-cancer therapy. Establishing a causative association between oncogenic mutations and cancer cell sensitivity to hyperthermia will allow for informed, mutation profile-guided application of hyperthermia.

A little problem with Innovation – hyperthermia has been in trials/clinical use for 50 years, and results are not great.
**Approach:**
It must be absolutely clear what is the question in each experiment, and what information will you gain.

Therefore, each section must start with the question and end with conclusion explaining how the result of the experiment will teach you about the next experiment.

**Example**
As suggested by the analyses of tumor curves, the existing MMTV-neuT mouse model seems to recapitulate effects of aging on tumor emergence. However an alternative possibility still remains that the effect associates not with age of the host but rather with time after Her2 expression. Therefore, it will be essential to utilize a model with inducible expression of Her2 that can directly assess age-dependency of tumorigenesis. Availability of such a model would be important for experiments to investigate the mechanism of the age-dependent effects.

These experiments will clearly dissect whether tumor emergence in this model is affected by a putative age-dependent factor or whether a time period after Her2 expression is necessary for tumor emergence. Furthermore, they will lay the basis for the mechanistic study of the aging effect.
If you study a pathology, you must explain how results of your research will teach medical practice.

This study may provide an important benefit in cancer risk assessment. A prediction from our model is that Her2 positive ductal carcinoma in situ (DCIS) with low expression of p21 can harbor cells that underwent EMT and have higher probability to progress to full blown cancer than DCIS lesions with high p21 levels. Clarifying these options will help defining the treatment strategy, e.g. the necessity of mastectomy. If this pilot program is successful, in the future study we will use human biopsies to evaluate this possibility.
IF you study a disease, e.g. cancer....

**Present yourself** not as a molecular biologist who happen to work with breast cancer, but as a breast cancer specialist who studies this type of cancer by molecular methods.

You need to show that you know specifics of breast cancer, i.e. basal and luminal; triple negative, Her2-positive, etc.; DCIS and invasive...

Make sure that you know specifics related to clinical samples. If you use human samples make sure that taking this samples is feasible from treatment and patient perspectives. **Always consult with clinicians.**

Example 1: you cannot take biopsies after chemotherapy if tumors are surgically removed prior to the therapy.

Example 2: you cannot take biopsies if they are not part of standard treatment protocol without a VERY STRONG justification.
Required level of details is very unclear.

It very much depends on the reviewer.

Tendency now is that people know what they are doing and they should not write what pH will be in their buffer.

Yet, you cannot just say “We will assess apoptosis”. Say how you will do that, e.g. caspase, annexin staining, etc.

Make sure that your experiments are feasible.
Absolutely do not just say that we will do such and such tests. Explain WHY you do each test.

Example 1: “… We shall measure apoptosis by caspase cleavage, annexin staining and propidium iodine staining.” Why three methods? Why these methods?

Example 2: “… We shall test toxicity of this drug on HeLa, BT474, MCF7, MCF10 and HEK293 cells.” Why that many lines? Why cell lines? Why these cell lines? These days generality of effects becomes less and less important (though there are different opinions). I would focus on one specific cancer type, and comment that it may be useful for others.

Example 3: “… in these experiments we will utilize PyMT model of breast cancer.” Do you know that more human cancer-relevant models exist? Do you have a special rationale using this model?
Real example from a grant:

...We will test the hypothesis in three different models; glioma initiating cells (GIC), glioma cell lines, and transplantable human glioma xenografts.

Adherent cell lines U373 and U87MG will be studied to build on the findings in HEK293 and A-172 cell lines.

GIC lines 0913 and 0627 30 will be studied because GIC are generally less responsive to IR and thereby responsible for recurrence.

The advantage of both adherent and GIC cell lines is that there is a stable knockdown of Tet1. The disadvantage is that long-term cell culture could have affected gene expression.

To compensate for this disadvantage, a patient-derived xenograft (PDX) model be studied that originated from human surgical specimens 31.
Hints for a disease research:

If you study a gene and want to link it to medicine, there seem to be ONLY two possibilities - you can use it to improve treatment or to improve diagnostics.

You may want to either apply it to drug design as a target or develop as biomarker.

1. Biomarkers of disease or disease stage (for diagnostics),
2. Biomarkers for rapid testing of new drugs in animal models
3. Predictive biomarker of drug sensitivity

If you have a novel compound, do not rush to promote it in your grant for a clinical application. Everyone knows that chances of success are 1-2% in Biotech, and way below 1% in Academia.

You have a chance to convince reviewers only if the compound is relatively developed (i.e. works at the low-mid nanomolar range and have good pharmacological properties), and you have a good collaborator in medicinal chemistry.

If you compound is not at this level, promote it as an investigative tool.
Put together a strong team.

In a grant that covers several fields, e.g. mouse genetics, drugs and biochemistry, you need to have specialists in each field on your grant.

Preferably have a leader in the field as active participant of your grant. You will have to sacrifice part of money, but your chances of getting the money will be much higher.

Even if you consider yourself a leader in the field, still it make sense to invite another leader.
Writing hints

No negativity, e.g. “if this experiment does not work...”, or “if my hypothesis is incorrect...”. Instead put a positive spin, e.g. “if protein expression is insufficient, we will use a stronger promoter...”.

Absolutely avoid sentences like “it would be interesting to test...”. You are doing science not for the sake of your interest.

Make sure that all pieces are written perfectly, including consumer-oriented parts.

Make paragraphs short. Clearly separate them.

Highlight main statements/ideas by underlying or coloring.
Good Luck