

Background and  
Significance  
Institutional Commitment

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There are many categories of grants:

- Mentored grant - e. g., NRSA, K-series
- Individual investigator - RO1
- “Innovative/feasibility” grants - R21
- Industry, foundation or “local” grants

Different grant applications require different approaches:

BUT THERE ARE

General Issues that you can control 100%

**Collaborators/references** - expertize, reagents, support - get letters

**Reviewers** - cite potential reviewers (study section)

**Budget** - justify personnel, supplies, etc. Usually, no equipment

**Check spelling and grammar** - nice style, consistency of style & terms

**Plan ahead** - coordinate with administrator and Grants Management

For a **HOT** grant,

Use **STEAM**

- ✓ Science
- ✓ Training
- ✓ Environment
- ✓ Applicant
- ✓ Mentor

I'm sooo excited  
to write this grant



## Mentored Grants - NIH (K), Foundations, Foreign

1. **Science** - high quality, feasibility, focus, not ambitious, preliminary data, can overlap with mentor (initially)
2. **Training plan** - personalized plan from mentor and yourself
3. **Environment\*** - nurturing, prior success, other faculty, facilities/equipment, other support, courses, workshops
4. **Applicant** - track record, publications, promise, letters are critical (specific personal anecdotes are powerful)
5. **Mentor** - track record, experience, previous mentees, funding success, knowledge of applicant!

**\* - MGH IS OUTSTANDING - slam dunk!!**

## Institutional Commitment

Institutional Commitment to the Candidate's Research Career Development - **should be very detailed**

**Reviewers ALWAYS find any holes in the plan that are not specifically addressed:**

**BAD** - Dr. XX will be provided with adequate laboratory space

**GOOD** - Dr. XX will be guaranteed one **16 ft** work bench with **two** associated **4 ft** desk areas, computers, filing cabinets and shelves. She will be provided with a shared **120 sq ft.** office within the next **12** months.

**BAD** - Dr. XX will be promoted in the future

**GOOD** - Dr. XX will be recommended for promotion to the junior faculty position of **Instructor** of Medicine at Harvard Medical School **upon completing her fellowship training.** Based on her progress, she will then be nominated, as appropriate, for a position of **Assistant Professor** within the subsequent **3-4 years.**

## Institutional Commitment

**BAD** - Dr.XX will be given opportunities to present her work at lab meetings

**GOOD** - The PMB has, in addition, a weekly research meeting each Monday morning between 9.00 - 10.30 am where trainees and faculty present and discuss data and research plans. Dr. XX gave her last formal presentation to this group in June 2004 prior to beginning her clinical year in July 2004, and summed up her progress and results up to that time. After giving her a few months to re-establish her workflow upon returning to the lab in late July 2005, she is scheduled to give her next presentation on February 6, 2006 and will then provide formal presentations to the full PMB faculty and staff at 6-monthly intervals, like all other fellows.

**BAD** - There are many special training workshops at MGH for Dr. XX to attend

**GOOD** - Special symposia and workshops are regularly arranged by the MGH Research Council, usually 4-5 per year, and are attended by many trainees. Those topics that were discussed in the past year, were "How to write a grant", "How to get a manuscript published", "How do I get a promotion" and "The Ethical Conduct of Research". Early this year, the MGH leadership approved a new office for research faculty development, which indicates the increasing commitment of MGH to its research faculty.

## Grant writing tips and help from NIH

[http://grants.nih.gov/grants/grant\\_tips.htm](http://grants.nih.gov/grants/grant_tips.htm)

## Help with background and significance

[http://www.niaid.nih.gov/ncn/grants/write/write\\_k1.htm](http://www.niaid.nih.gov/ncn/grants/write/write_k1.htm)



## Background and Significance

Convince the reviewer that your studies will fill defined gaps in knowledge. Point out your own work clearly (WE HAVE SHOWN, not IT HAS BEEN SHOWN)

**DO NOT** write a long and boring chapter on the subject - it must contain information about your own work and what you will do to alleviate disease, in the context of existing data.

Convey the significance of your research to:

1) increasing scientific knowledge

2) improving public health

\* Tell reviewers how your work suits the NIH mission to improve health through science -- just moving science forward is not enough.

# Example introduction to BS from my PPG grant

Vasopressin (VP) is the major antidiuretic hormone involved in the regulation of water reabsorption by the mammalian kidney. The apical plasma membrane of kidney collecting duct principal cells is remarkably impermeable to water in the "resting" state, but after VP stimulation it shows a rapid and dramatic increase in water permeability. This allows urinary concentration to occur by osmotic equilibrium of luminal fluid with the renal interstitium. A considerable amount of work over the past two decades, including many studies from our own laboratory, has established that VP causes the steady state distribution of the AQP2 water channel to shift from cytoplasmic vesicles to the plasma membrane of collecting duct principal cells. The experiments outlined in this proposal are aimed at elucidating several aspects of the mechanism of recycling of this physiologically important water channel, in particular the role of phosphorylation and the actin cytoskeleton, with the ultimate aim of bypassing the defective V2R in X-linked nephrogenic diabetes insipidus (NDI) to allow these patients to concentrate their urine to normal levels.

“Tell reviewers why testing your hypothesis is worth NIH's money, why you are the person to do it, and how your institution can give you the support you'll need to get it done”

## 1) Nephrogenic Diabetes Insipidus (NDI)

Much of the work proposed is aimed at understanding the cell biology of the AQP2/V2R signaling/trafficking process in order to generate novel therapeutic strategies to alleviate the symptoms of NDI - a condition associated with decreased cell surface AQP2 expression and the inability to maximally concentrate urine in response to AVP.

This was appreciated by Dr. Daniel Bichet in his recent JASN editorial (8) . While discussing our recent findings, he stated: *“These new developments could help bypass defective V2-receptors (X-linked nephrogenic diabetes insipidus) or the complex signaling defect of lithium-induced nephrogenic diabetes insipidus.”*

*Start out with a bang - don't be boring - use statements of other experts in your favor*

## 2) Role of phosphorylation in AQP2 trafficking

AQP2 contains a number of sites that could be phosphorylated by a variety of kinases, including PKA, PKG, PKC, casein kinase II and ERK . Here, we will ask how phosphorylation of AQP2 results in a shift in AQP2 distribution from intracellular vesicles to the cell surface. The problem was succinctly stated in a recent review by Valenti et al. (97) who comments *"Despite this plethora of evidence indicating phosphorylation as a key event in regulating different steps in AQP2 intracellular trafficking, nobody has so far demonstrated a direct interaction of p-AQP2 with any motor or regulatory proteins. That would be the challenge of investigators in the field in the years to come."*

We completely agree with this assessment, and indeed this is the goal of Specific Aim 1 of this proposal.

### 3) Role of the actin cytoskeleton in AQP2 trafficking. Compartmentalization of actin remodeling?

The literature on the role of actin in water channel trafficking dates back over three decades, but **its role in this process still remains unclear.**

The aim of the present studies **is not to unravel all of the vast array** of potential mechanisms by which actin might be involved in exo- and endocytosis, **but is rather to examine the hypothesis** that vesicle cargo – the AQP2 water channel in particular – might be critically involved in local regulation of the actin cytoskeleton to effect VP-induced plasma membrane accumulation and recycling of AQP2.

FOCUS

FOCUS

FOCUS

FOCUS

FOCUS

#### 4) Pathways for bypassing the V2R to achieve AQP2 membrane accumulation: PDE5 inhibitors and statins

Based on a variety of studies from our laboratory and others, we are in a strong position to explore several strategies to bypass the dysfunctional V2R in order to achieve plasma membrane AQP2 accumulation. Thus, Aim 3 of this application is designed to explore some (practical) approaches to achieve VP-independent urinary concentration. While we are directing our efforts towards bypassing the V2R to achieve cell surface expression of AQP2, an alternative line of research pursued by others is to learn how to cause the misfolded, defective V2R to be expressed at the cell surface. Perhaps a combination of both approaches will ultimately be the most successful in the human condition.

Acknowledge work of others - suggest alternatives - be fair

For a **HOT** grant,

Use **STEAM**

Yippee,  
I'm funded



- ✓ Science - exciting/innovative
- ✓ Trainng - superb
- ✓ Environment - outstanding
- ✓ Applicant - stellar
- ✓ Mentor - brilliant/caring