Communicating Research to the General Public

The WISL Award for Communicating PhD Research to the Public launched in 2010, and since then over 100 Ph.D. degree recipients have successfully included a chapter in their Ph.D. thesis communicating their research to non-specialists. The goal is to explain the candidate's scholarly research and its significance—as well as their excitement for and journey through their area of study—to a wider audience that includes family members, friends, civic groups, newspaper reporters, program officers at appropriate funding agencies, state legislators, and members of the U.S. Congress.

WISL encourages the inclusion of such chapters in all Ph.D. theses everywhere, through the cooperation of PhD candidates, their mentors, and departments. WISL offers awards of $250 for UW-Madison Ph.D. candidates in science and engineering. Candidates from other institutions may participate, but are not eligible for the cash award. WISL strongly encourages other institutions to launch similar programs.

Wisconsin Initiative for Science Literacy

The dual mission of the Wisconsin Initiative for Science Literacy is to promote literacy in science, mathematics and technology among the general public and to attract future generations to careers in research, teaching and public service.

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Growth Hormone Disruption and Its Therapeutic Potential in Models of Prostate and Breast Cancer

By

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This Is Just To Say: Growth Hormone Disruption has Therapeutic Potential in Prostate and Breast Cancer

Scientific communication is becoming a lost art and, because of that, scientific literacy is suffering. This cause and effect is creating an unfortunate divide in beliefs between scientists and non-scientists. The responsibility of thoroughly explaining the nuance and importance of the scientific method rests squarely on the researchers who conduct the experiments at the foundation of that endeavor. Too opaque is the window through which the public may peer into the world of scientific research.

The demand for effective scientific communication is what drove Dr. Bassam Shakhaskiri to call on Wisconsinites in varying capacities—scientists, elected officials, teachers, business and community leaders—to contribute to increasing science literacy. The development of the Wisconsin Initiative for Science Literacy (WISL) is grounded in the mission to enhance the public's ability to understand science, math, and technology. My appreciation of this mission has pushed me to include this chapter in hopes that it contributes to the public understanding of science via my favorite medium: poetry!

My love of poetry originated in my high school Advanced English class in which we were instructed to produce a collection of personally written poems. Through my undergraduate career, my poetry reading and writing waxed and waned, but it never left me. My time in the research lab at the University of Wisconsin-Madison reintroduced me to my enjoyment of writing poetry and I soon began a poetry blog entitled "This Is Just To Say". Additionally, I took upon the New Year Resolution to write one poem a day in 2018, one poem a week in 2019, one poem a month in 2020,

and, finally, one epic poem for the entirety of 2021. This practice increased my volume and quality of poems and inspired me to use this chapter as another challenge in writing poetry.

I take inspiration here and in my personal writings from poets such as Rudyard Kipling, Emily Dickinson, Charles Bukowski, and my personal favorite, William Carlos Williams (whose poem "This Is Just To Say" inspired the title of my poetry blog and this chapter). Williams himself was a proponent of connecting science and poetry, often writing about the medical subjects he witnessed while practicing as a physician (1).

Others have identified the value in connecting science to written verse. Dr. Sam Illingworth of Edinburgh Napier University produces weekly poems in his collection titled *The Poetry of Science* that is dedicated to connecting scientists and non-scientists in a discussion on various scientific topics. The University of Wisconsin-Madison's Ebling Library for the Health Sciences publishes a biannual collection of art titled *Corpus Callosum* which includes short stories, photography, drawings, and poems that focus on health science. My very own "An Ode to Francis Collins" was published in the Fall 2021 issue of *Corpus Callosum* (2). I continue my attempts to connect science and poetry with this entry into the WISL Award for Communicating Doctoral Research to the Public.

Meter is the rhythm with which poetry is spoken. The body of this chapter has been written loosely in iambic pentameter, meaning that each line of the poem consists of five sets of two syllables following an unstressed, stressed pattern (with some flexibility in areas where iambic pentameter could not be strictly followed). An example of iambic pentameter can be found in John Milton's *Paradise Lost* in which he writes: "Fast by the Oracle of God: I thence//Invoke thy aid to my adventurous Song//That with no middle flight intends to soar//Above th' Aonian Mount, while it pursues…". The rhyme scheme in this chapter roughly follows an ABAB pattern (again with

some liberties where necessary). Rudyard Kipling's "If" is my favorite example of this rhyme scheme. Kipling writes: "If you can make one heap of all your winnings//And risk it on one turn of pitch-and-toss,//And lose, and start again at your beginnings//And never breathe a word about your loss".

Note that there are some citations found throughout this chapter in (numbers in parentheses), but do not pronounce them during your recitation of the poem as this will surely throw off the intended rhyme scheme. So, corral your loved ones and stand tall while you regale them with "This Is Just To Say: Growth Hormone Disruption has Therapeutic Potential in Prostate and Breast Cancer".

Enjoy.

Introduction

A growing body of literature
Slowly builds from decades of study,
Thought, and deliberate research
To implicate growth hormone in the body.
In recent years GH and its connections,
Like proteins—namely IGF-1—
Link to some cancers, in fact a precise section:
Those driven by hormones.

Cancers of the prostate and the breast
Are largely driven by hormonal steroids,
But even worse (and certainly not best)
That steroid need they can avoid.
Humans express GH receptors widely—
On liver, kidneys, even on the bone (3)—
But how they give to cancer isn't entirely
Obvious or even known.

Prostate cancer cells express GHR
At levels more than one would expect (4)
Compared to normal tissue maybe they are
Dependent on GH to grow unchecked.
Same with breast in terms of GH impact,
Receptor's higher in women with disease (5).
Now we look to GH as a target to attack
With therapy for hormone independency.

Cancer

Cancer as a disease discussed
    Is described as uncontrollable division
In tissues whose genetics thrust
    Them into only one decision:
To continue growing where they’re not welcome
    Or even where they know they shouldn’t be
(Metastases to lung or bone are seldom
    Offered solace with a cup of tea).

Prostate Cancer

The prostate may be foreign to a joe
Like you or me, but (trust me) to a cell
It's the Holy Grail, Everest, or Big Show
For turning to a tumor to cause Hell:
A fifth a million men will get this cancer,
A few dozen thousand more will likely die (6)
From an inconspicuous organ below the bladder
That, till now, merely made semen and stood standby.

Prostate cancer's driven by transduction
Cascading forth beyond testosterone,
An androgen who needs no introduction,
But whose cover in disease is early blown.
Advanced cancers can metastasize
(Move from site to site, summarily).
Men with prostate cancer often die
From lung and bone metastases.

So early castration and deprivation
Of androgens is often utilized
To treat this cancer and on occasion
Is paired with radiation from time to time.
This works! (Of course, until it doesn't,
At which point harsher treatments are required
To effectively combat what once wasn't
Until that, too, fails and men expire.)

Docetaxel—DTX—is a chemo drug
Designed to stop the cells from replicating,
Placating to their greedy, (in essence, smug)
Desire to continue recreating.
In prostate cancer, DTX succeeds
In killing cancer castration couldn't kill.
But beware hair loss, nausea, toxicity,
For if cancer doesn't kill you, chemo will.

Breast Cancer

Breasts serve humans as our milk-producing ducts
In which cancers unfortunat'ly are common.
It's affected millions of women and, thus,
Is the deadliest cancer seen in women (7).
While breast cancers are commonly corrupted
By estrogen or progesterone signals,
More aggressive forms don't need this disruption.
Triply negative breast cancer's a death committal.

But fear not! for a chemo drug can help!
Doxorubicin—DOX—stops the spread of cancer,
But not without toxins patients felt
While developing resistance to this answer.
Ninety percent of patients grow immune
To the aid of which DOX contributes action (8).
It's here where science sorely swoons
To find a complementary attraction.

Treating Cancer

The basis of treating cancer rests
In attempts to stop cells in their tracks:
Prevent replication and, in effect,
Stop the spread of cancer…a daunting task.
When hormones are no longer needed
In cancers of the prostate and the breast,
Tried and true therapies are heeded:
Chemo agents, DOX and DTX.

But even these chemo treatments
In cancer often meet resistance
Through an unknown mechanistic sequence
That require us to think different:
Alternative therapies are seen
As a cancer care that needs to be.
One target possibility
Is the GH/IGF-1 axis.

The GH/IGF-1 axis

The axis is the main culprit for growth
In bone and other tissues
Such as muscle, liver, and other boasts
But this may also cause some issues.
A norm'ly functioning axis
Spurs growth without it overdone.
Internal regulation acts as
A safety valve (see Figure 1).

But abnormal sign'ling does occur
Either too much or too little:
Giants are the result of an axis spurred
While dwarves come from axes noncommittal.
Other diseases have axes corrupted—
Some in cancer or diabetes—
But when the axis is disrupted
There seems to be protection from diseases:

In Ecuador lives a population
Of dwarves with mutations that act as treaties
That grant immunity without stipulation
From cancer and diabetes (9).
We suspect that by blocking GH
Cancer patients stand a chance
Of fighting aggressive cancer cases
That would be dismissed for treatment in the past.

GH Disruption in Prostate and Breast Cancer

Our current studies lay the fodder
For disrupting GH in disease.
One prostate cancer model
Is driven by a protein, namely “T”.
T-antigen binds to tumor suppressors
In the mouse prostate where it accrues
Driving cell growth as an aggressor
Soon it becomes cancerous (see Figure 2).

A study done some years ago had
Shown that prostate cancer didn’t grow
In mice with T-antigen (known as TAg)
And mutated GH receptor code (10).
That study was important proof
That prostate cancer needs GH.
However, dwarves are the least likely
To have prostate cancer in the first place.

Our study takes the TAg mouse model
And makes it susceptible to drugs
That essent’ly deletes GH function
Giving us control to when the axis runs.
We found that after cancer forms,
Disrupting GH stops progression
Of the cancer (far from prostate norm)
And even hints at cell regression.

Further studies target growth hormone
With a drug that blocks its function well
And found it didn't really have effect
In human prostate cancer cells (11).
The problem with their model, though,
Is that human cells were in a rodent.
Mouse GH cannot stimulate nor grow
Human cells (not for a moment).

Our studies apply the same drug—that'd be
Pegvisomant—to a system we
Knows appreciates species specificity.
A mouse cell from culture (see Figure 3).
When we took in account for this nuance
We found that this GH-blocking scheme
Slowed the growth of cells not human
And in the process changed their genes (12).

The goal of all of this research
Is to find a different treatment so
Less toxic side effects appear
When getting treated with chemo.
Our lab helped verify a prodrug
(That is, a drug that's initially inactive)
That's effective at fighting cancer,
Not toxic, quite attractive (13).

See Figure 4 for more of that,

But even better yet would be

A treatment that could juice the bats

Of current chemos with no toxicity.

A study back at UIC had claimed

That rat mammary tumors were dependent

On GH to form in a tumor model named

"MNU" after what made it tumorigenic (14).

In that model, rats with mutations that subdued

The axis we routinely mention,

Developed tumors when rescued

With GH supplemented.

But when that supplementation stopped

Those tumors went away,

Showing that, at least in rats,

Mammary cancers need GH.

But iterations of this study

Showed some tumors had persisted

Beyond the need for GH treatment

And continued growth insistent.

But, what we found is that persisting tumors,

When treated with a chemo (in this case DOX),

Shrunk while tumors in normal rats resumed

To grow after DOX's initial stop (15).

Synergy Between Chemotherapy and GH Disruption

Synergy is the idea that two drugs work better than one:
The whole is better than the sum of all parts, for instance.
GH disruption seems to be a prime example bar none,
Considering its contribution to chemotherapy resistance:
GH has been found to regulate expression
Of key genes involved in pumping drugs
Out of the cell, in essence suppress them
(We know melanoma as a cancer does) (16).

The way in which chemo and GH disruption
Can synergize comes in three key steps:
One: stop the cell from replication
By blocking GH's promotion, thus enhancing chemo's effects;
Two: be pro-apoptotic, or pro-cell death,
Block GH's survival and enhance chemo's scythe;
Three: keep the drug in the cell where it's meant
Block the pumping out of chemo and maintain chemo's might.

These three mechanisms combined have the potential
To enhance chemo treatments in aggressive cancers
That no longer feed off hormones. Now consequential
We may adopt GH disruption to find the answers.

Conclusions

Pegvisomant's a drug that's FDA-approved.
It blocks GH function in mouse and humans both.
Pegvisomant's approved to treat giants who
Have too active an axis, slowing their growth.
In mice and other preclinical trials
Pegvisomant's promising, showing results
In slowing cancers of endometrial,
Prostate, and breast cancer graft insults.

This safe and effective drug changes the axis
In a positively negative way:
Shutting it down and, in turn, blocking cancers
From hijacking the axis to do as they may.
The studies rhymed about here support stud'ying the axis
As a viable target alongside DOX and DTX
In attempts to lower the often-toxic chemo practice
That right now's the treatment that serves us best.

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FIGURES

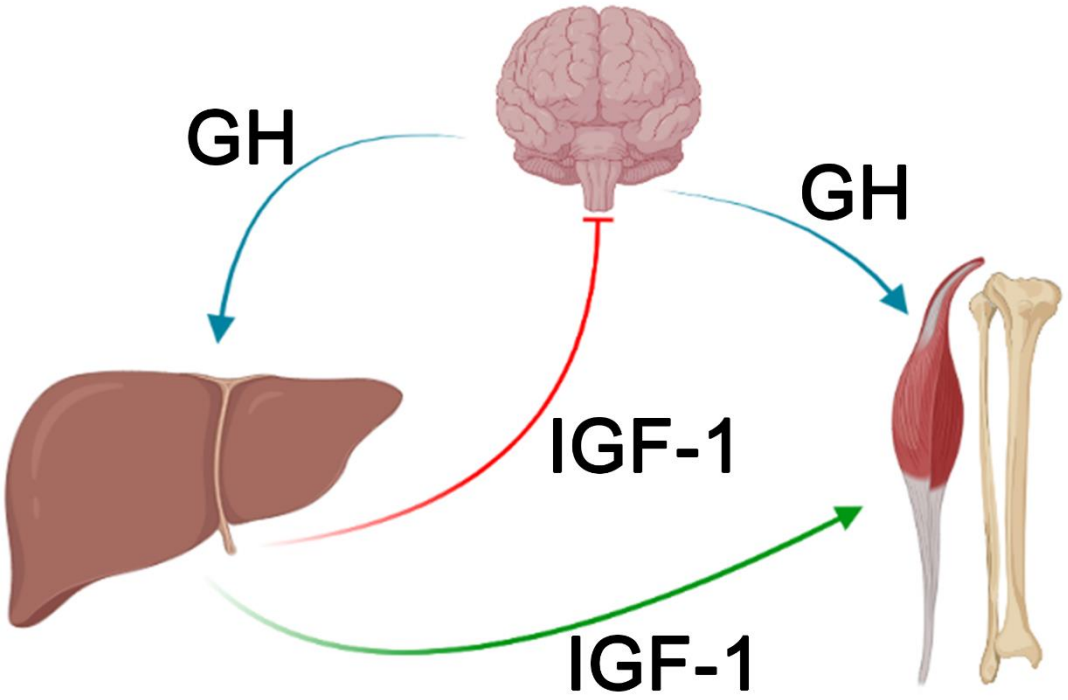

Figure 1. The GH/IGF-1 axis

GH contributes most of its function by signaling within the GH/IGF-1 axis. The pituitary (a small, hormone-producing gland in the brain) is the body' major producer of GH. After release, GH binds to receptors on tissues such as the liver. That binding triggers the production of IGF-1 which then binds to its receptor on tissues throughout the body such as muscle and bone, inducing growth. IGF-1 also binds to its receptor in the pituitary gland. This IGF-1 binding shuts down production of GH which keeps the axis in check. GH can also act directly on tissue to induce growth. Figure created at BioRender.com.

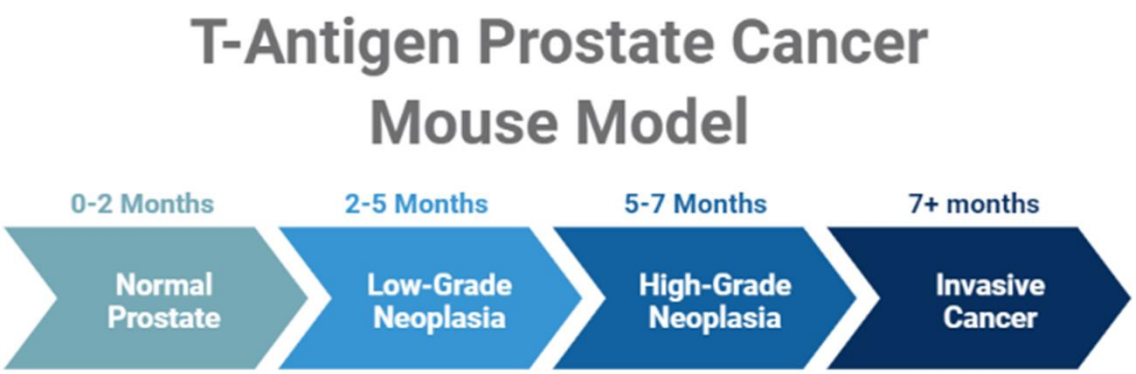

Figure 2. The T-antigen prostate cancer mouse model

T-antigen protein expression in the mouse prostate drives prostate cancer in our model through progressive stages of prostate transformation into invasive cancer. Through 2 months of age, mouse prostates are considered normal. At 2 months, mice possess a less severe version of abnormal prostate cell growth (neoplasia). At 5 months, mice develop a more severe version of neoplasia, and at 7 months, abnormal prostate cells invade their surrounding tissues (cancer). Figure created at BioRender.com.

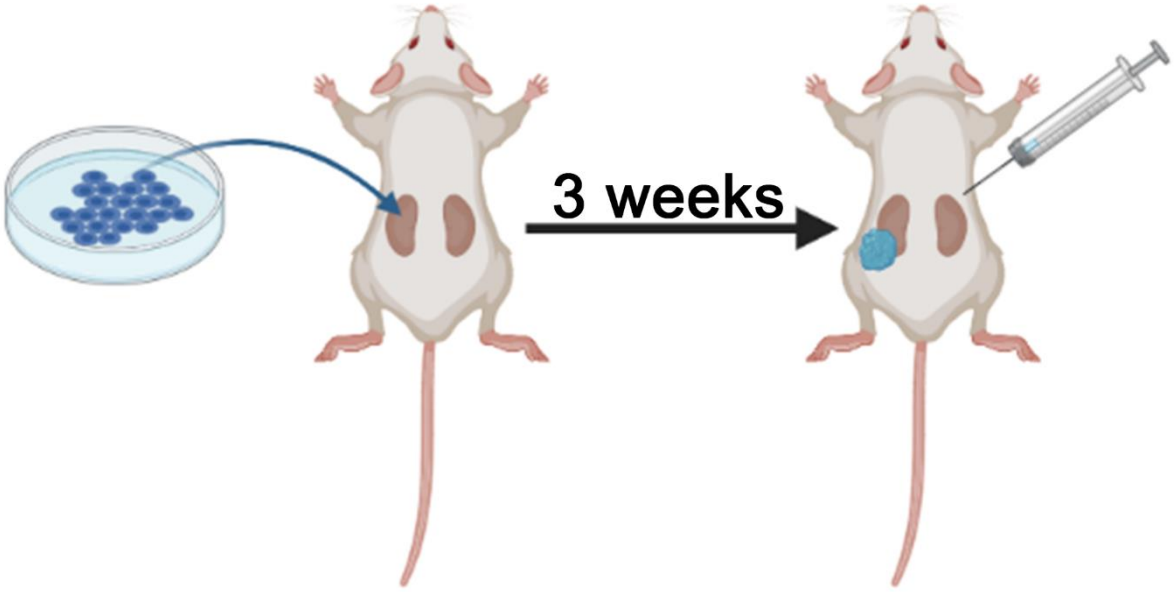

Figure 3. Prostate cancer cell grafts on mouse kidneys to assess drug efficacy

We surgically grafted mouse prostate cancer cells grown in culture onto the kidneys of mice. We left these cells to grow for 3 weeks at which point we treated the mice with a drug regimen to test whether blocking GH function can stop cancer cell growth. Figure created at BioRender.com.

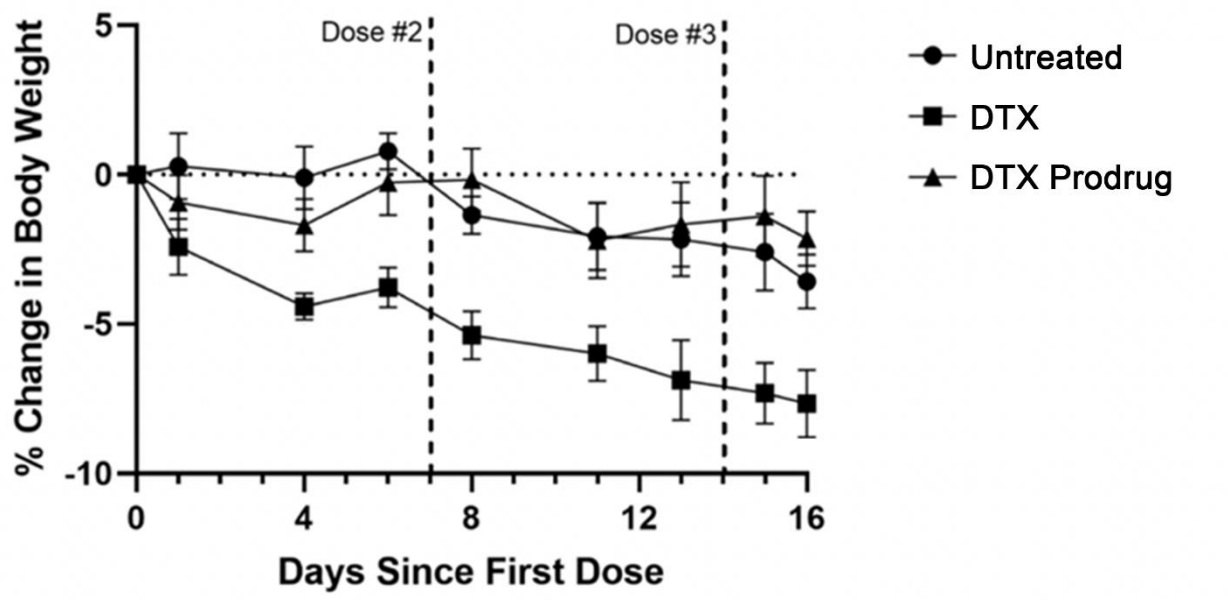

Figure 4. Drug toxicity as determined by body weight change

Mice harboring human prostate cancer cells grafted onto their kidneys went through a two-week drug-dosing regimen with the chemotherapeutic drug DTX or a DTX prodrug that we developed. At the end of the trial, mice treated with the DTX prodrug lost less weight (comparable to mice not treated with drug) than those treated with DTX. This result indicates that the DTX prodrug is less toxic to mice than DTX.