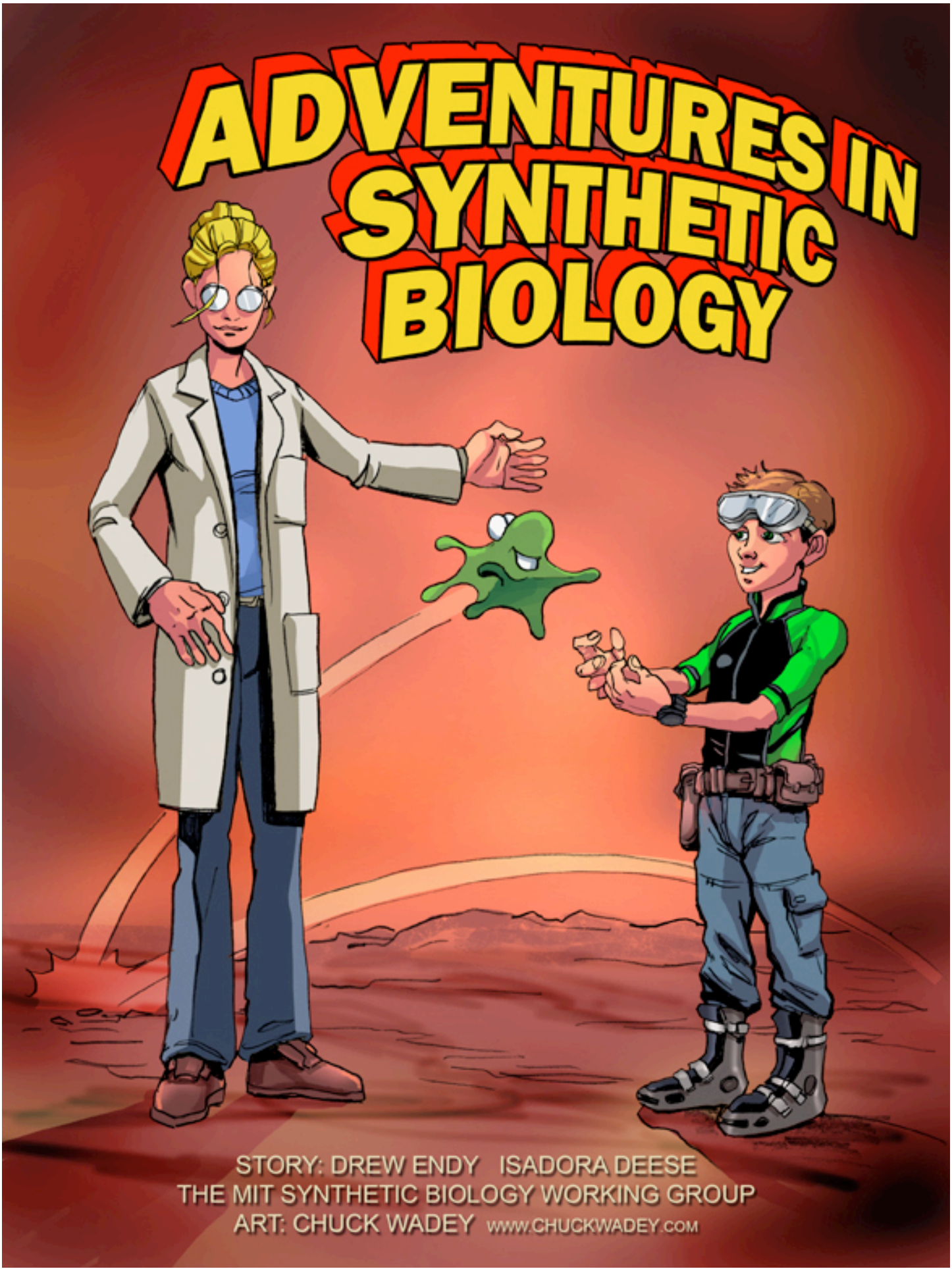
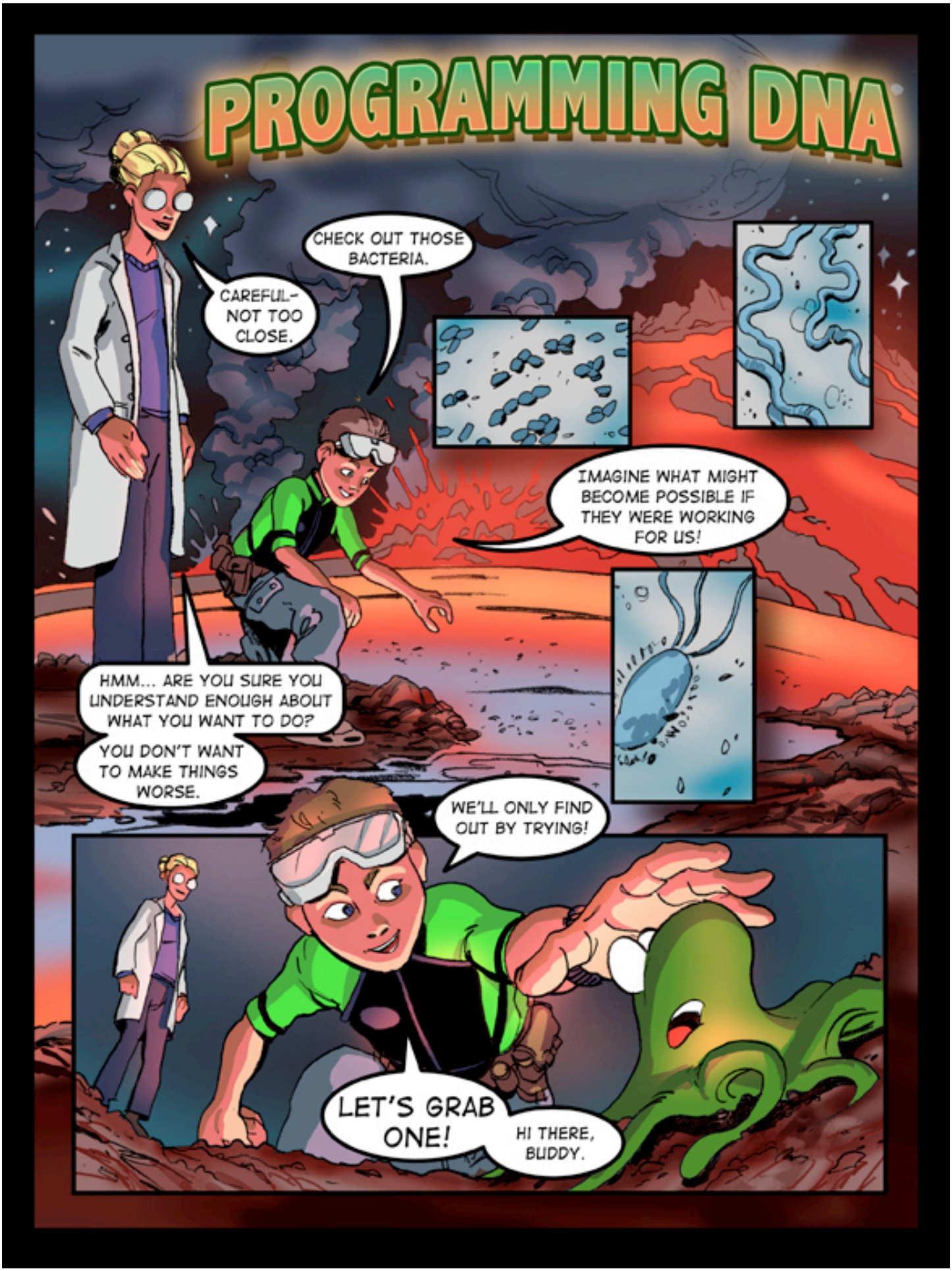
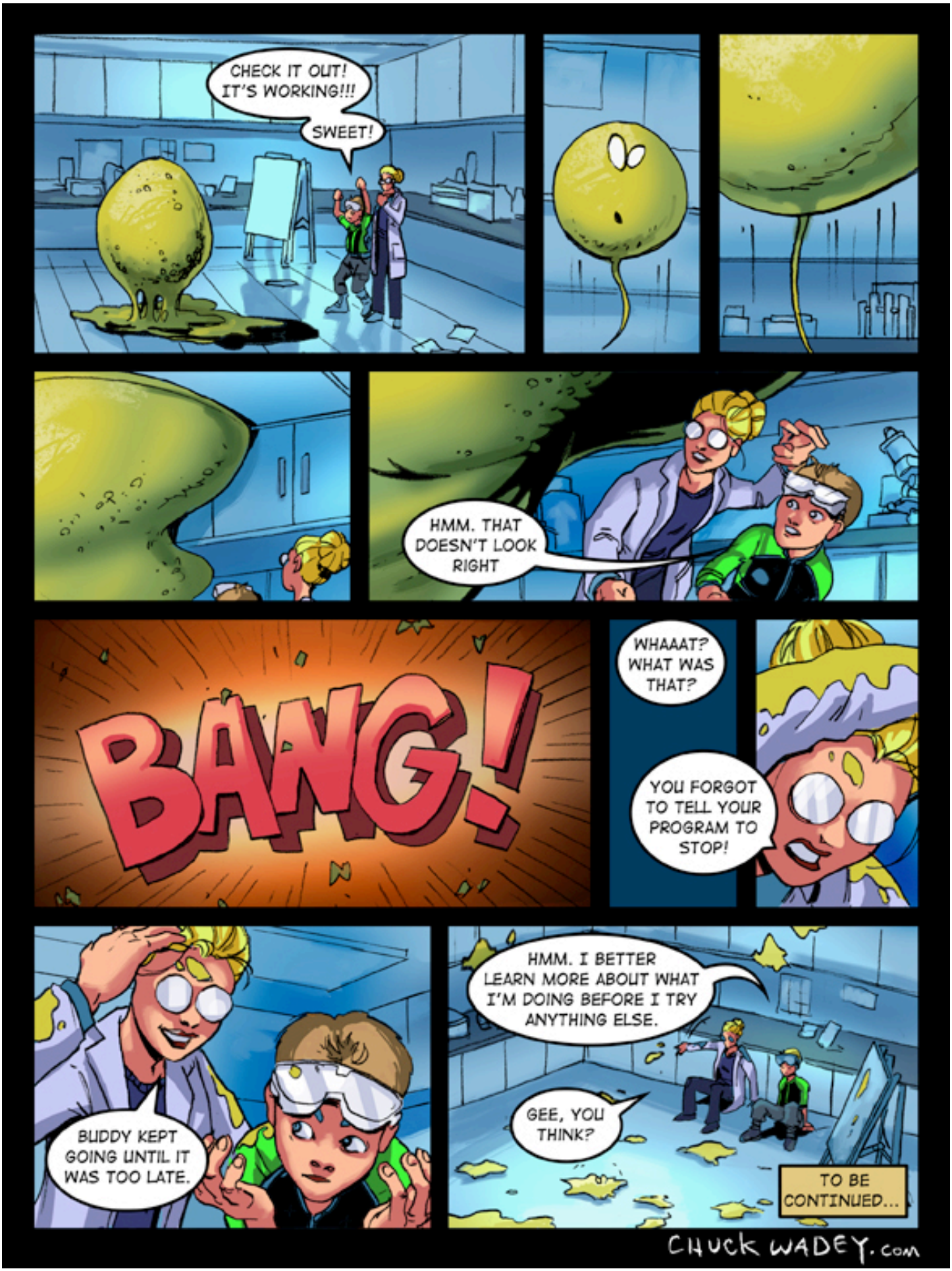

ADVENTURES IN SYNTHETIC BIOLOGY
STORY: DREW ENDY ISADORA DEESE
THE MIT SYNTHETIC BIOLOGY WORKING GROUP
ART: CHUCK WADEY www.CHUCKWADEY.COM


PROGRAMMING DNA
CHECK OUT THOSE BACTERIA.
CAREFUL- NOT TOO CLOSE.
IMAGINE WHAT MIGHT BECOME POSSIBLE IF THEY WERE WORKING FOR US!
HMM... ARE YOU SURE YOU UNDERSTAND ENOUGH ABOUT WHAT YOU WANT TO DO?
YOU DON'T WANT TO MAKE THINGS WORSE.
WE'LL ONLY FIND OUT BY TRYING!
LET'S GRAB ONE!
HI THERE, BUDDY.


HOW DO THESE THINGS WORK ANYWAY?
ALL LIVING THINGS RUN ON PROGRAMS MADE OF DNA.
COME INSIDE, I'LL SHOW YOU!
EACH OF THESE CELLS HAS THEIR OWN DNA PROGRAM, CALLED THE GENOME.
CHECK IT OUT!
WHAT?! WHOAH!
ZZZZT
THERE IT IS - THE GENOME - THE MASTER PROGRAM THAT'S RUNNING THE CELL.
SO THIS IS WHAT WE CHANGE TO REPROGRAM THIS CRITTER?
LOOKS EASY!
CHANGE OR ADD TO IT, BUT IT'S NOT SO EASY,-
-BECAUSE NOBODY COMPLETELY UNDERSTANDS HOW THE PROGRAM WORKS EXACTLY IN THE FIRST PLACE
AH, A WORTHY CHALLENGE. I ACCEPT!
WHAT EXACTLY DID YOU HAVE IN MIND?
HMMM...
ZZZZT


LATER, BACK IN THE LAB.
BACTERIA BALLOONS!
I'M NOT SURE THAT WILL WORK.
WANNA BET?
UH HUH?
ALL I NEED TO DO IS MAKE THEM FORM A CLOSED FILM,-
-THEN START PRODUCING HYDROGEN GAS, THEN...
OK, GOT IT. SO, UH, HOW DO I PROGRAM THIS LITTLE GUY?
FIRST YOU NEED TO ASSEMBLE THE DNA PARTS THAT ENCODE YOUR PROGRAM.
GET THEM FROM THE CATALOG.
ONE BALLOON-O-GENESIS-
-AND ONE GAS-O-MATIC MODULE.
COOL, HERE THEY ARE!
NOW WHAT?
LOAD THE DNA INTO OUR LITTLE FRIEND HERE.
WHAT DO YOU THINK, BUDDY?


DNA'S READY TO GO.
HELP ME CATCH HIM!
MEEP!
-YOU MIGHT WANT TO STAND BACK.
HE'S CHANGING!
POP POP POP


CHECK IT OUT! IT'S WORKING!!!
SWEET!
HMM. THAT DOESN'T LOOK RIGHT
BANG!
WHAAAT? WHAT WAS THAT?
YOU FORGOT TO TELL YOUR PROGRAM TO STOP!
BUDDY KEPT GOING UNTIL IT WAS TOO LATE.
HMM. I BETTER LEARN MORE ABOUT WHAT I'M DOING BEFORE I TRY ANYTHING ELSE.
GEE, YOU THINK?
TO BE CONTINUED...
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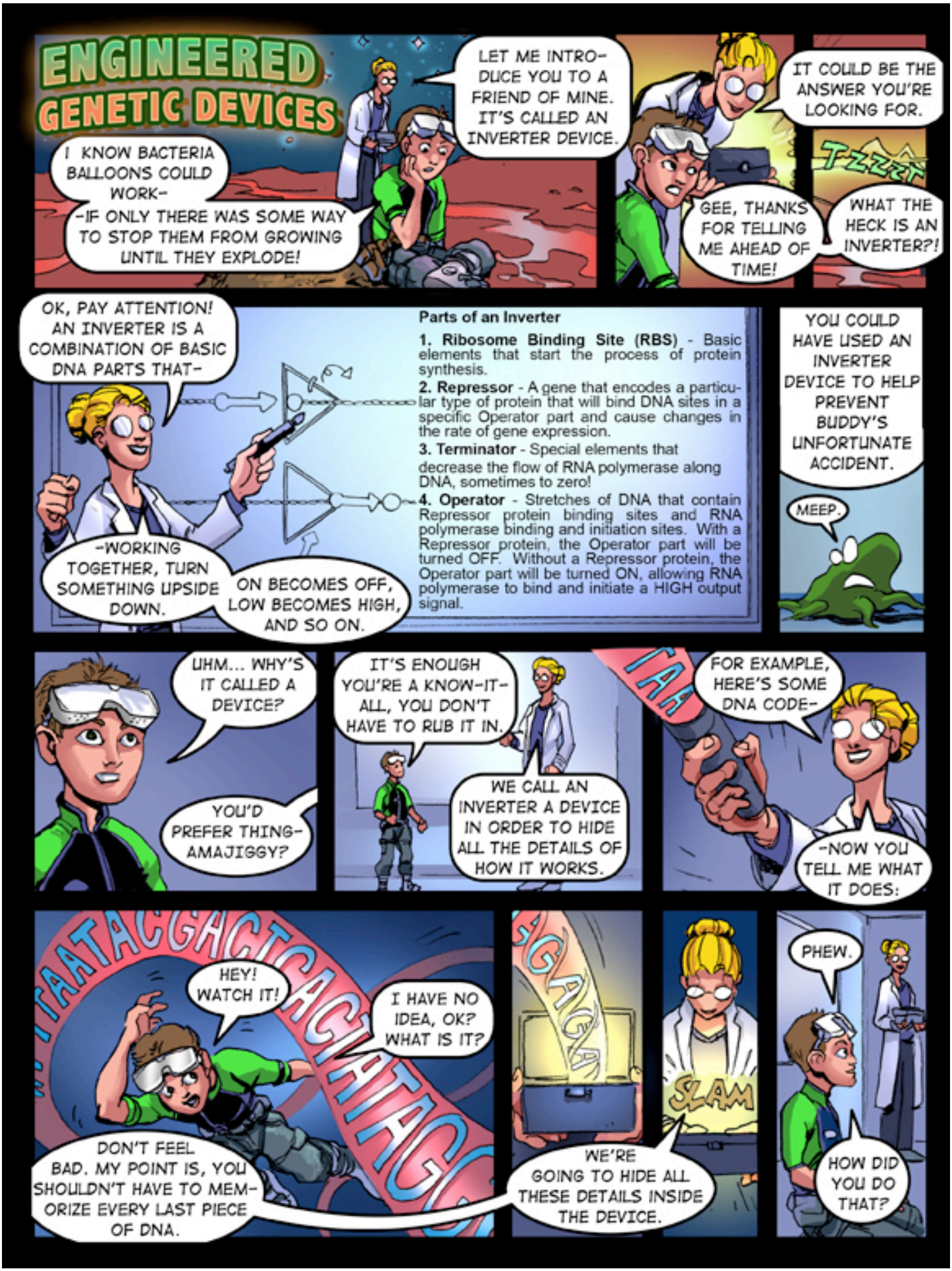
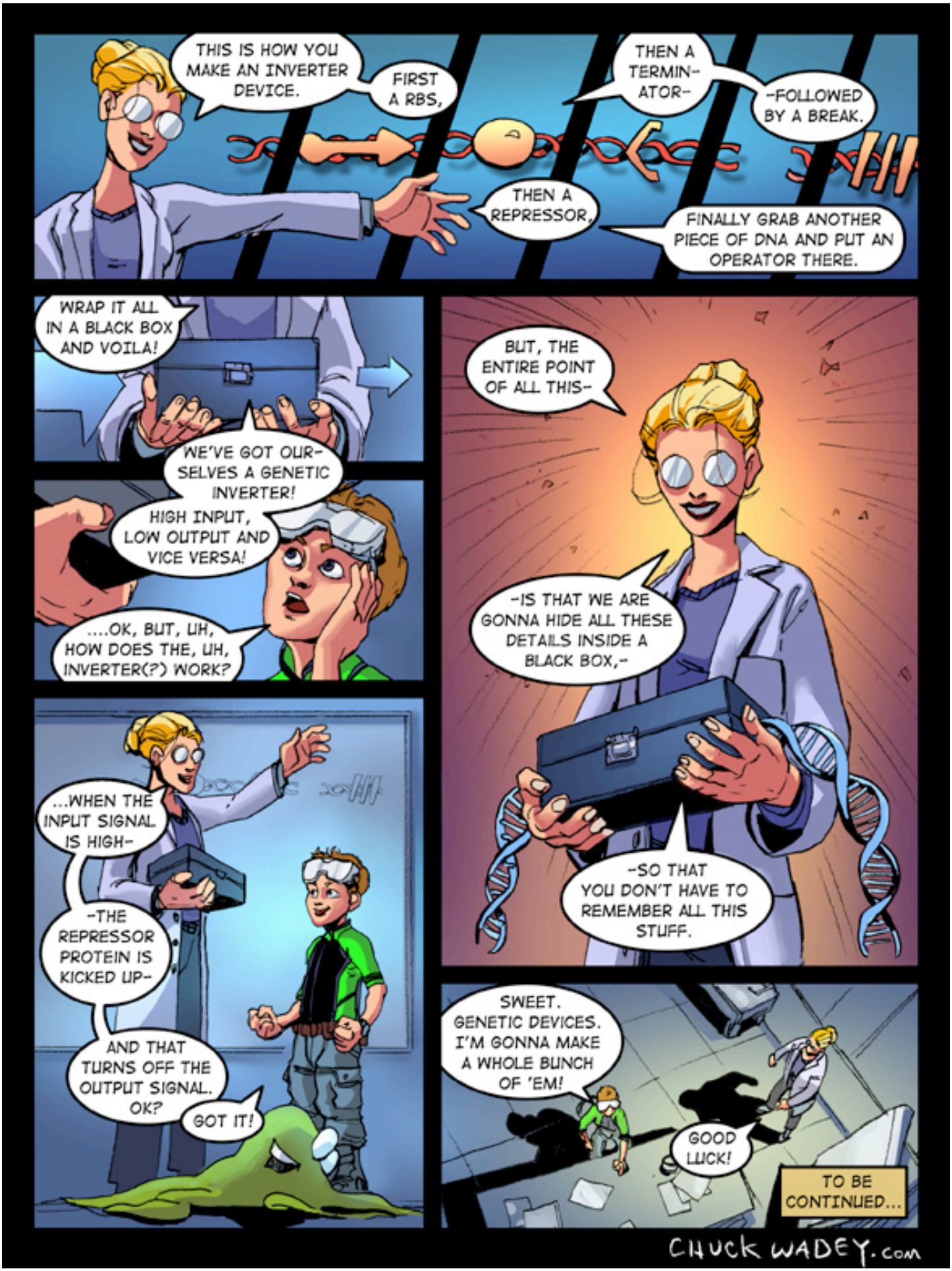

ENGINEERED GENETIC DEVICES
I KNOW BACTERIA BALLOONS COULD WORK-
-IF ONLY THERE WAS SOME WAY TO STOP THEM FROM GROWING UNTIL THEY EXPLODE!
LET ME INTRODUCE YOU TO A FRIEND OF MINE. IT'S CALLED AN INVERTER DEVICE.
IT COULD BE THE ANSWER YOU'RE LOOKING FOR.
Tzzzt
GEE, THANKS FOR TELLING ME AHEAD OF TIME!
WHAT THE HECK IS AN INVERTER?!
OK, PAY ATTENTION! AN INVERTER IS A COMBINATION OF BASIC DNA PARTS THAT-
-WORKING TOGETHER, TURN SOMETHING UPSIDE DOWN.
ON BECOMES OFF, LOW BECOMES HIGH, AND SO ON.
Parts of an Inverter
1. Ribosome Binding Site (RBS) - Basic elements that start the process of protein synthesis.
2. Repressor - A gene that encodes a particular type of protein that will bind DNA sites in a specific Operator part and cause changes in the rate of gene expression.
3. Terminator - Special elements that decrease the flow of RNA polymerase along DNA, sometimes to zero!
4. Operator - Stretches of DNA that contain Repressor protein binding sites and RNA polymerase binding and initiation sites. With a Repressor protein, the Operator part will be turned OFF. Without a Repressor protein, the Operator part will be turned ON, allowing RNA polymerase to bind and initiate a HIGH output signal.
YOU COULD HAVE USED AN INVERTER DEVICE TO HELP PREVENT BUDDY'S UNFORTUNATE ACCIDENT.
MEEP.
UHM... WHY'S IT CALLED A DEVICE?
YOU'D PREFER THING-AMAJIGGY?
IT'S ENOUGH YOU'RE A KNOW-IT-ALL, YOU DON'T HAVE TO RUB IT IN.
WE CALL AN INVERTER A DEVICE IN ORDER TO HIDE ALL THE DETAILS OF HOW IT WORKS.
FOR EXAMPLE, HERE'S SOME DNA CODE-
-NOW YOU TELL ME WHAT IT DOES:
HEY! WATCH IT!
I HAVE NO IDEA, OK? WHAT IS IT?
DON'T FEEL BAD. MY POINT IS, YOU SHOULDN'T HAVE TO MEMORIZE EVERY LAST PIECE OF DNA.
SLAM
WE'RE GOING TO HIDE ALL THESE DETAILS INSIDE THE DEVICE.
PHEW.
HOW DID YOU DO THAT?


THIS IS HOW YOU MAKE AN INVERTER DEVICE.
FIRST A RBS,
THEN A REPRESSOR,
THEN A TERMIN-ATOR-
-FOLLOWED BY A BREAK.
FINALLY GRAB ANOTHER PIECE OF DNA AND PUT AN OPERATOR THERE.
WRAP IT ALL IN A BLACK BOX AND VOILA!
WE'VE GOT OUR-SELVES A GENETIC INVERTER!
HIGH INPUT, LOW OUTPUT AND VICE VERSA!
....OK, BUT, UH, HOW DOES THE, UH, INVERTER(?) WORK?
BUT, THE ENTIRE POINT OF ALL THIS-
-IS THAT WE ARE GONNA HIDE ALL THESE DETAILS INSIDE A BLACK BOX,-
-SO THAT YOU DON'T HAVE TO REMEMBER ALL THIS STUFF.
...WHEN THE INPUT SIGNAL IS HIGH-
-THE REPRESSOR PROTEIN IS KICKED UP-
AND THAT TURNS OFF THE OUTPUT SIGNAL. OK?
GOT IT!
SWEET. GENETIC DEVICES. I'M GONNA MAKE A WHOLE BUNCH OF 'EM!
GOOD LUCK!
TO BE CONTINUED...
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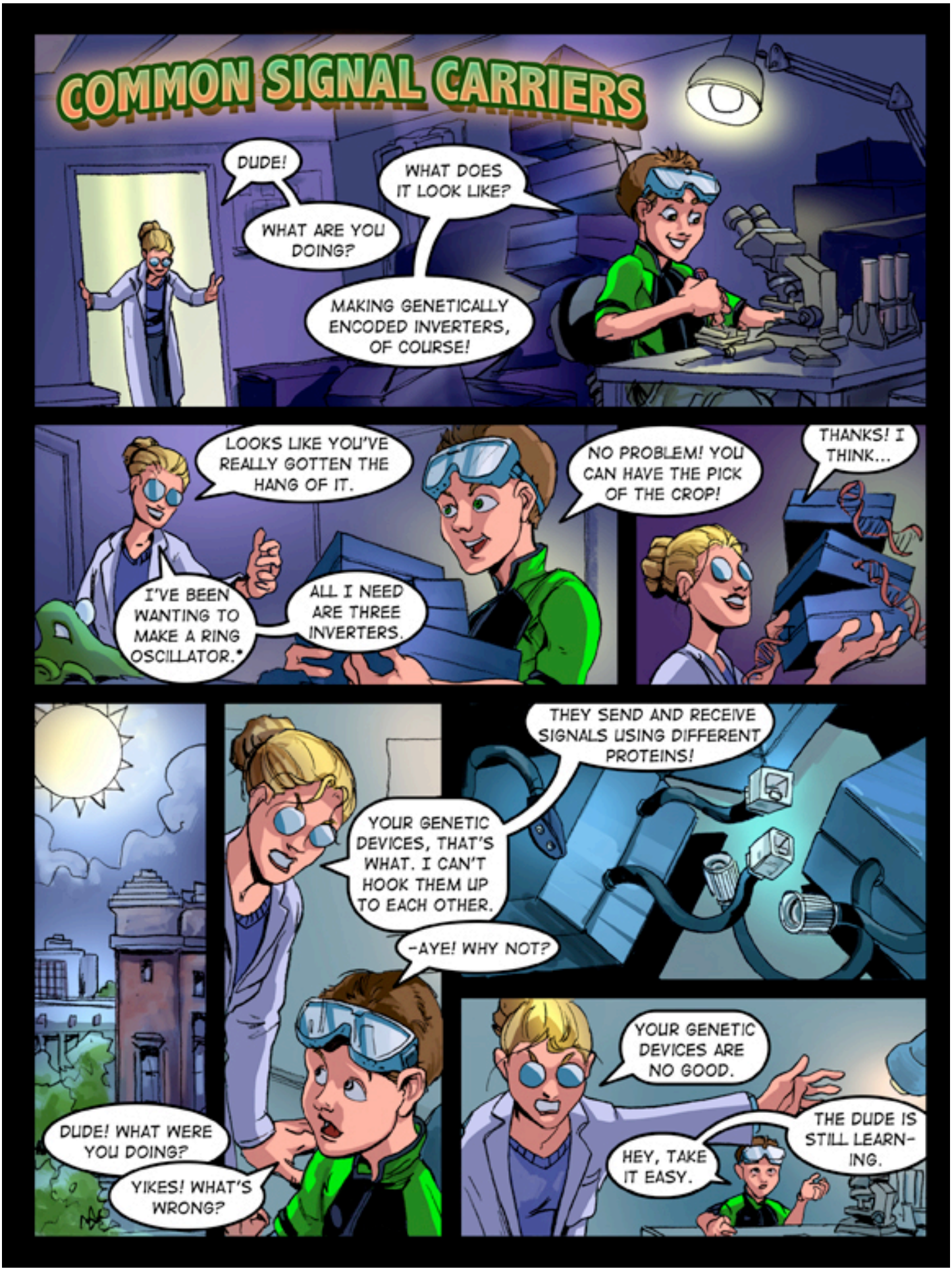
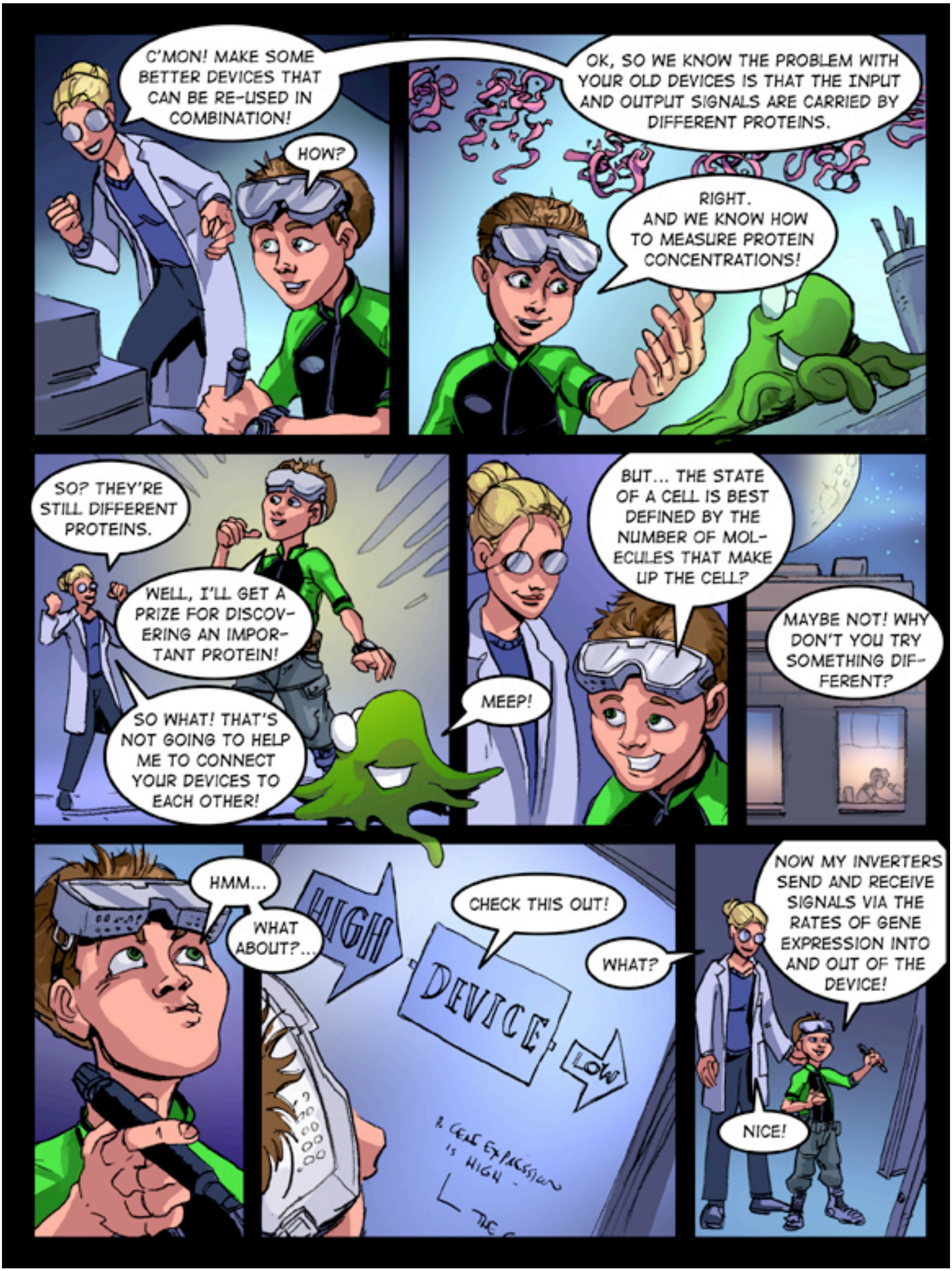
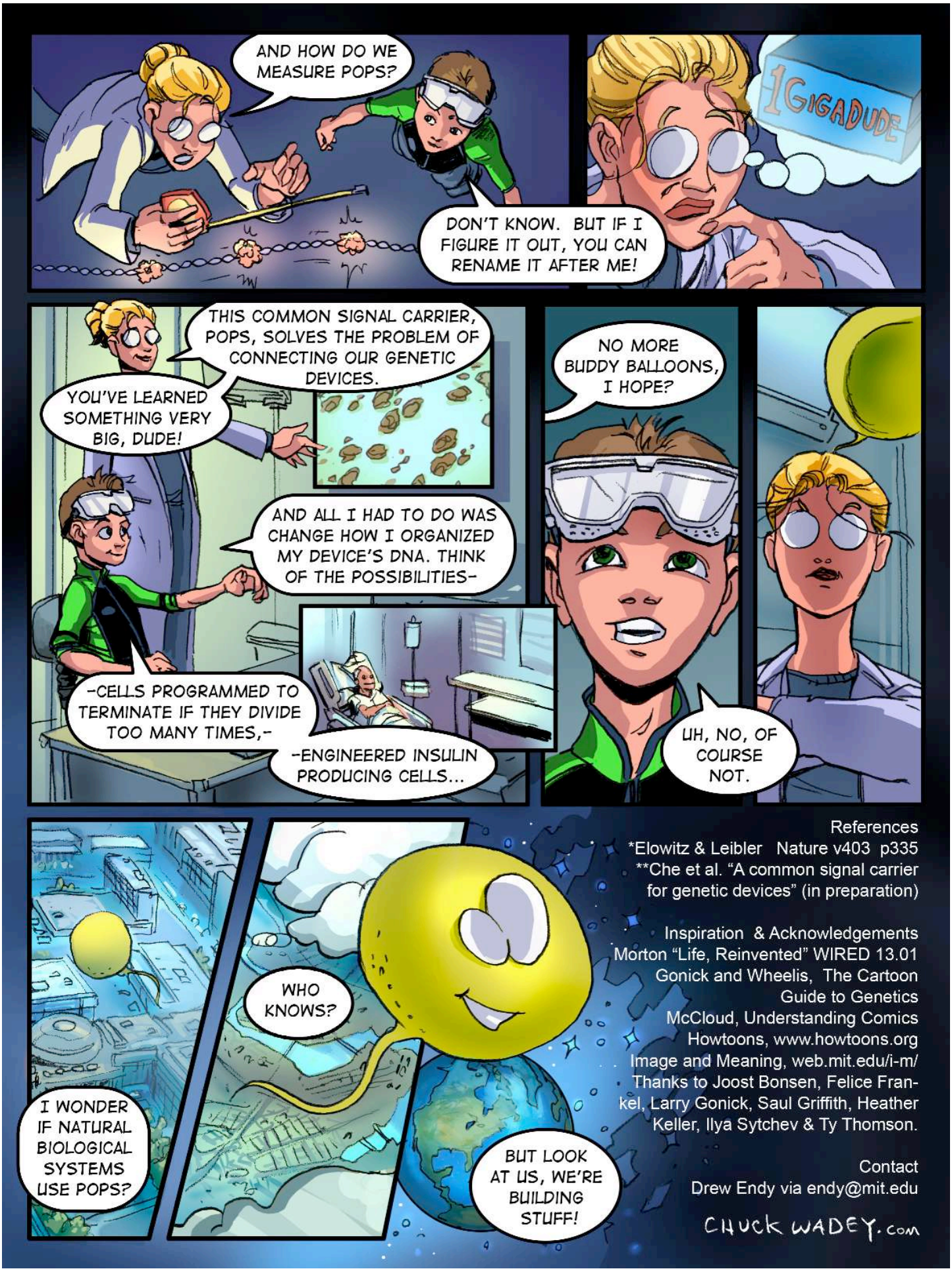

COMMON SIGNAL CARRIERS
DUDE!
WHAT ARE YOU DOING?
WHAT DOES IT LOOK LIKE?
MAKING GENETICALLY ENCODED INVERTERS, OF COURSE!
LOOKS LIKE YOU'VE REALLY GOTTEN THE HANG OF IT.
I'VE BEEN WANTING TO MAKE A RING OSCILLATOR.*
ALL I NEED ARE THREE INVERTERS.
NO PROBLEM! YOU CAN HAVE THE PICK OF THE CROP!
THANKS! I THINK...
DUDE! WHAT WERE YOU DOING?
YIKES! WHAT'S WRONG?
YOUR GENETIC DEVICES, THAT'S WHAT. I CAN'T HOOK THEM UP TO EACH OTHER.
-AYE! WHY NOT?
THEY SEND AND RECEIVE SIGNALS USING DIFFERENT PROTEINS!
YOUR GENETIC DEVICES ARE NO GOOD.
HEY, TAKE IT EASY.
THE DUDE IS STILL LEARN-ING.


C'MON! MAKE SOME BETTER DEVICES THAT CAN BE RE-USED IN COMBINATION!
HOW?
OK, SO WE KNOW THE PROBLEM WITH YOUR OLD DEVICES IS THAT THE INPUT AND OUTPUT SIGNALS ARE CARRIED BY DIFFERENT PROTEINS.
RIGHT. AND WE KNOW HOW TO MEASURE PROTEIN CONCENTRATIONS!
SO? THEY'RE STILL DIFFERENT PROTEINS.
WELL, I'LL GET A PRIZE FOR DISCOVERING AN IMPORTANT PROTEIN!
SO WHAT! THAT'S NOT GOING TO HELP ME TO CONNECT YOUR DEVICES TO EACH OTHER!
BUT... THE STATE OF A CELL IS BEST DEFINED BY THE NUMBER OF MOLECULES THAT MAKE UP THE CELL?
MEEP!
MAYBE NOT! WHY DON'T YOU TRY SOMETHING DIFFERENT?
HMM...
WHAT ABOUT?...
CHECK THIS OUT!
HIGH
DEVICE
LOW
WHAT?
If Gene Expression is HIGH
NOW MY INVERTERS SEND AND RECEIVE SIGNALS VIA THE RATES OF GENE EXPRESSION INTO AND OUT OF THE DEVICE!
NICE!


WHEN THE INPUT RATE IS HIGH, THE REPRESSOR PROTEIN GETS MADE, IT SHOOTS UP AND LANDS ON THE OPERATOR SITE, AND THUS THE OUTPUT RATE IS LOW-
-WHEN THE INPUT RATE IS LOW, NO REPRESSOR GETS MADE, SO THE OUTPUT IS HIGH!
HIGH
DEVICE
LOW
VERY GOOD! BUT WHAT EXACTLY IS THE RATE?
RATE OF GENE EXPRESSION.
WHAT DO YOU MEAN EXACTLY?
RATE OF GENE EXPRESSION IS THE NUMBER OF RNA POLY-MERASE MOLECULES THAT TRUNDLE PAST YOU EACH SECOND.
LET'S CALL THIS POLYMERASE PER SECOND OR POPS!**
AH, THE STUDENT BECOMES THE MASTER.
PRETEND YOU ARE STANDING ON THE DNA WHERE THE INPUT SIGNAL ARRIVES.
GOOD. NOW WHAT?
EXCELLENT!
POPS IS THE "FLOW" OF RNA POLYMERASE ALONG MY DNA WIRE.
KINDA LIKE ELECTRICAL CURRENT!
YES!!



References
*Elowitz & Leibler Nature v403 p335
**Che et al. "A common signal carrier for genetic devices" (in preparation)

Inspiration & Acknowledgements
Morton "Life, Reinvented" WIRED 13.01
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