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NC TraCS/NC State RFA Description and Goals

Description of RFA and areas of focus

- - Functional tissue engineering/regenerative medicine
- - Development and utilization of large animal models for translational medicine
- - Manufacturing and scale up of biomaterials
- - Evaluating the potential of naturally occurring disease models for therapeutic discovery
- - Development and testing of medical devices
- - Improvement of imaging technologies
- - Antimicrobial resistance
- - Zoonotic diseases
- - Tissue-on-chip model systems

https://tracs.unc.edu/docs/pilotprogram/NC_TraCS-NC_State_Collaborative_RFA.pdf

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Large Animal Models in Comparative Medicine

- Induced models. *Dr. Anthony Blikslager*
- Genetically modified models. *Dr. Jorge Piedrahita*
- Naturally occurring models. *Dr. Duncan Lascelles*

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Opportunities. Induced Animal Models

Anthony Blikslager, DVM, PhD

Professor, Equine Surgery and Gastroenterology
Director, Large Animal Models Core,
Center for Gastrointestinal Biology and Disease

Anthony_Blikslager@ncsu.edu
919-513-7725

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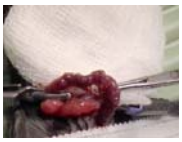
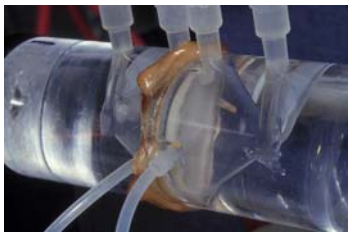
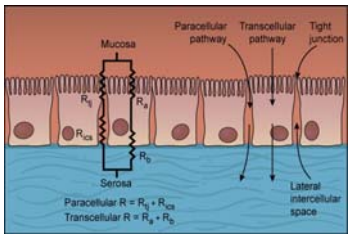
Opportunities. Induced Animal Models

Comparative mechanisms of ischemia/ reperfusion injury







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Opportunities. Induced Animal Models

Availability of facilities, equipment, and know-how for large animal research at the College of Veterinary Medicine

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Opportunities. Induced Animal Models

Use of both research and veterinary clinical facilities to research models of human disease

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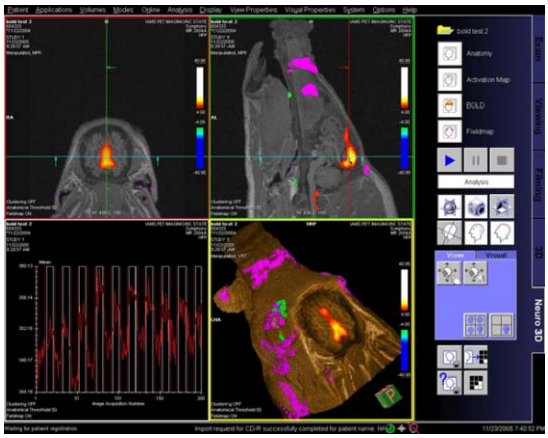
Opportunities. Induced Animal Models

Use of state-of-the-art techniques to strengthen model development



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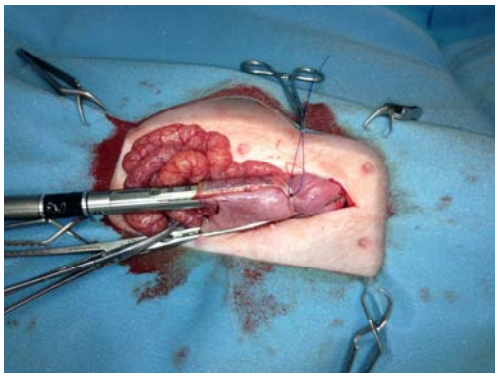
Opportunities. Induced Animal Models

Surgical techniques to model human disease



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Opportunities. Induced Animal Models

Pros and Cons of Large Animal Inducible Models

Advantages
- Physiological similarities to human beings
- Advantage of size of the animal
- Crossover knowledge for veterinary or agricultural knowledge

Disadvantages
- Expense
- Availability of reagents
- Fundability

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Opportunities. Transgenic Pig Models

- *Dr. Jorge Piedrahita*
- *MSC, PhD*
- *Professor of Translational Medicine*
- *Director, Comparative Medicine Institute*

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Why a transgenic pig?

- Similar anatomy, physiology, metabolism, and pathology.
- Similar size.
- Large litters and short generation intervals compared to primates.
- Can do complex genetic manipulations.

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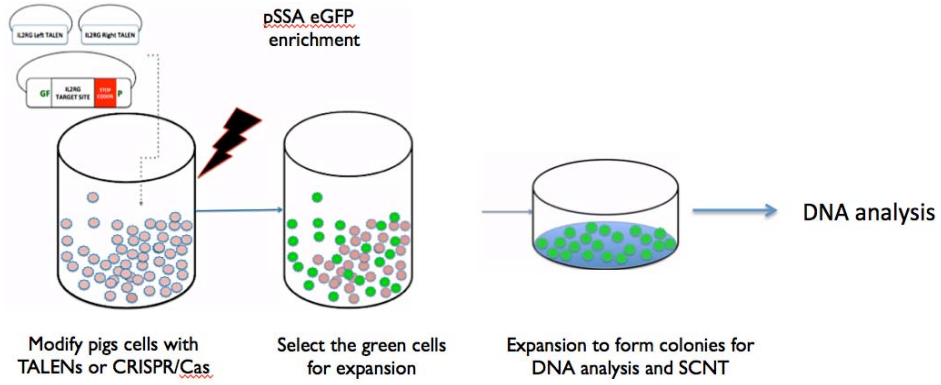
When to make a pig

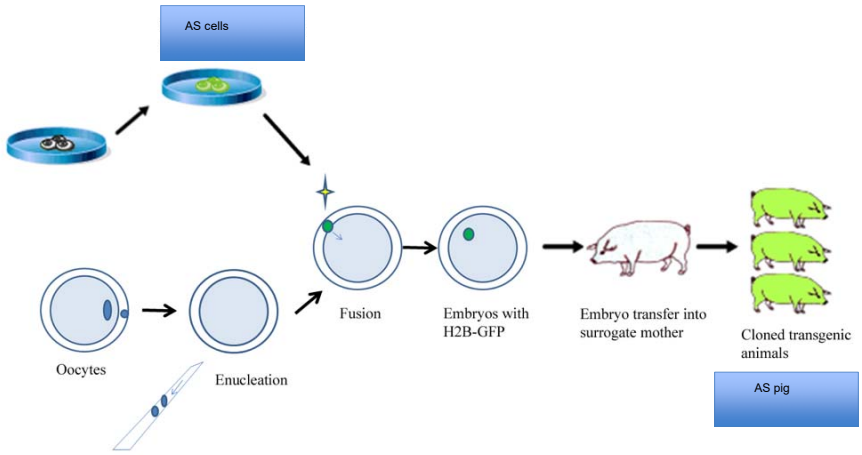
- Mouse mutant does not recapitulate human disease (cystic fibrosis).
- Pig size or physiology has a distinct benefit when compared to mice/rats (regenerative medicine, cardiology).
- Additional costs can be justified.

How do we make transgenic pigs?

Making a TG pig using SCNT

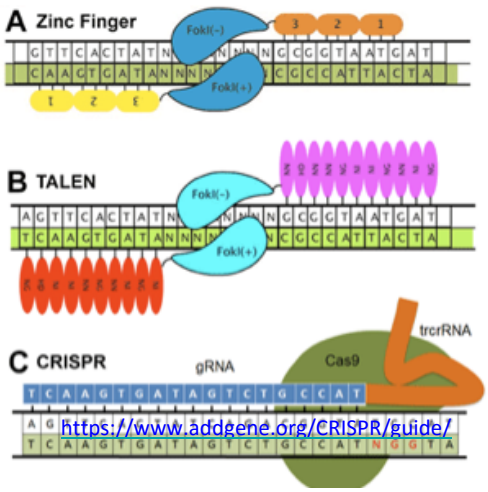


Making a TG pig using SCNT



Step 2. Making the pig using somatic cell nuclear transfer(SCNT).

Meganucleases



https://www.addgene.org/CRISPR/guide/

Zinc Finger Nucleases (ZNF)

Tal Effector Nucleases (TALENs)

CRISPR-Cas9

All same concept. A DNA binding domain linked to a nuclease

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Homing Endonucleases (HE)

PRE-HE

- Rates averaging 1 event per million cells
- Need enriching/selectable markers
- Need complex targeting constructs
- In pigs would take 1-2 years
- For double KOs would need breeding or 2 rounds of SCNT

POST-HE

- Rates as high as 1/1 (100%)
- No need for enriching/selectable markers
- No needs for complex targeting constructs
- In pigs takes 6-9 months
- For double KOs no need to breed. Drastically reduces generational intervals

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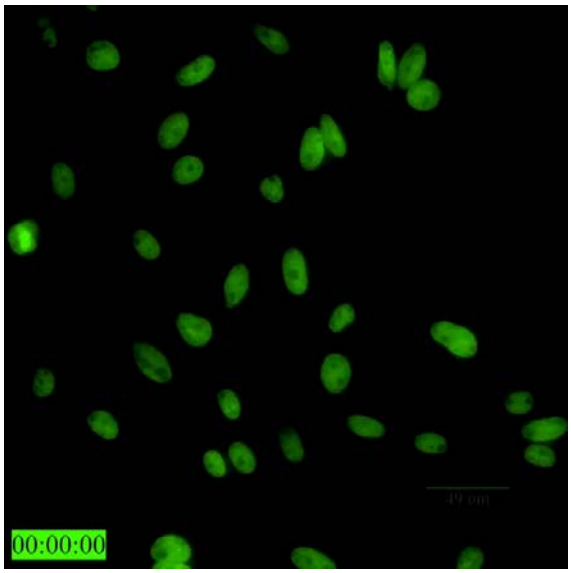
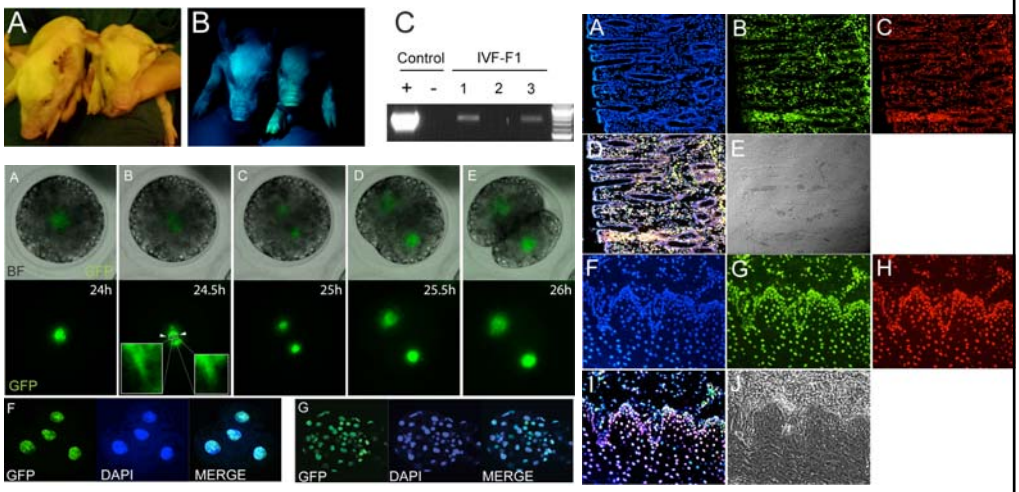
H2B-GFP pigs for cell tracking. "Knock in"



Cell tracker TG pig

H2B-GFP pigs for cell tracking. "Knock in"



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Pig model of dwarfism "Knock out"

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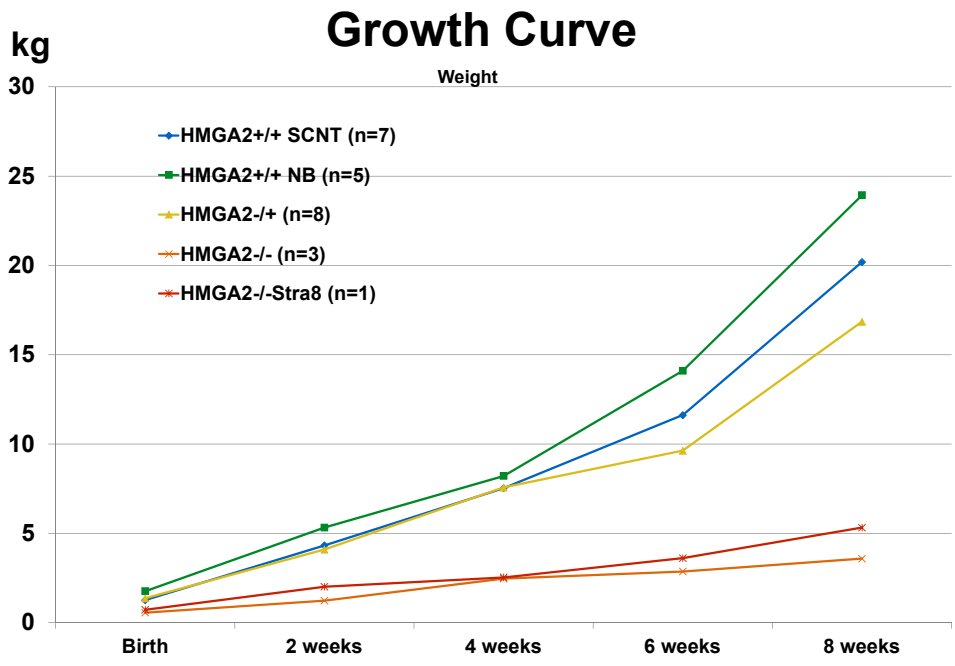
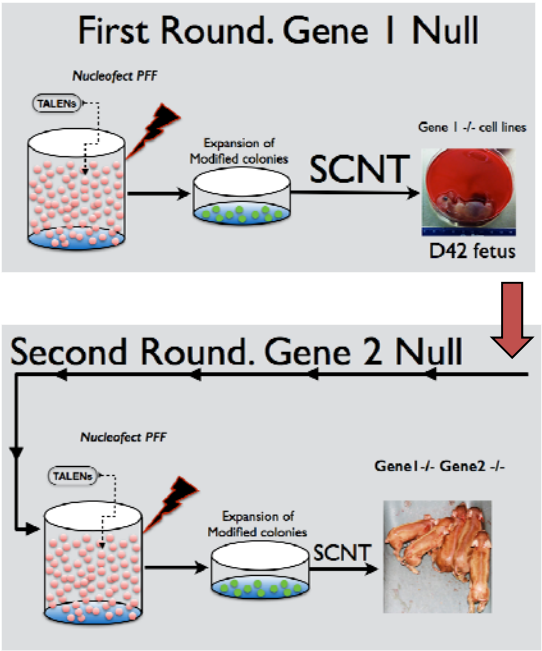


Humanized pig. "Double Knock out"



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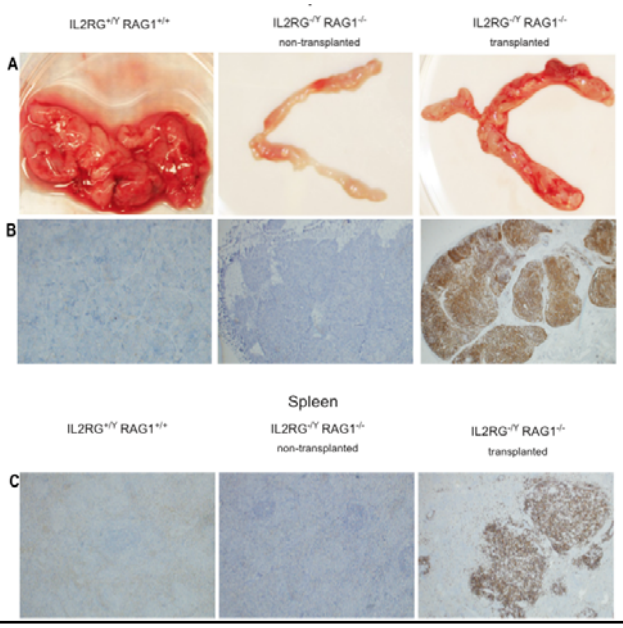
Humanized pig. Double Knock out



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When to make a pig

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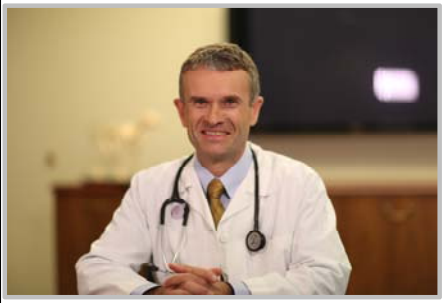
Opportunities. Companion Animal Models



- *Dr. Duncan Lascelles*
- *PhD. MRCVS, CertVA, DSAS (ST), DECVS, DACVS*
- *Professor of Small Animal Surgery and Pain Management*
- *Associate Director, Comparative Medicine Institute*

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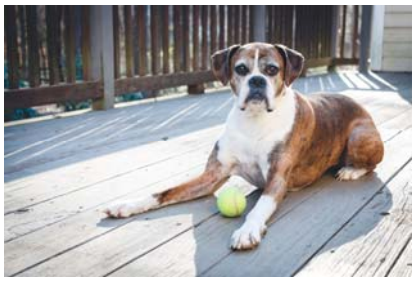
Opportunities. Companion Animal Models



Diseases in pets that accurately reflect the target disease in humans (*fidelity* or *face validity* with the target disease)

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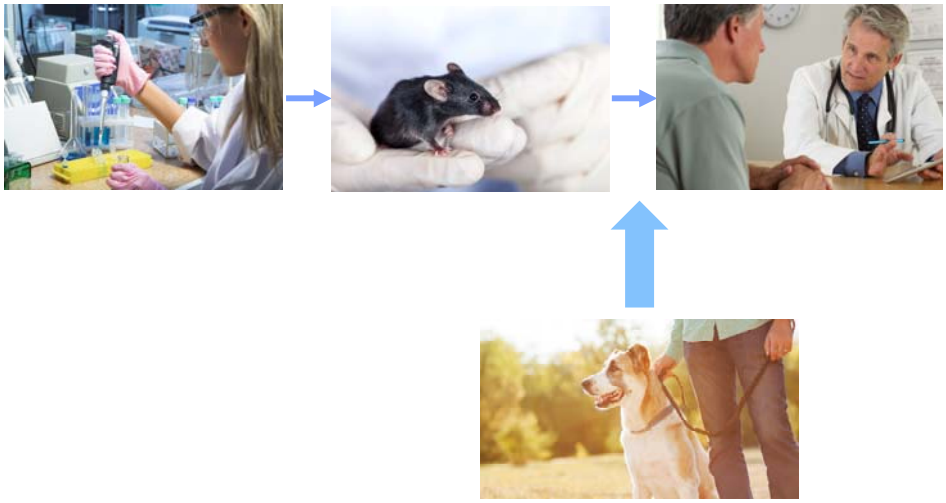
Opportunities. Companion Animal Models



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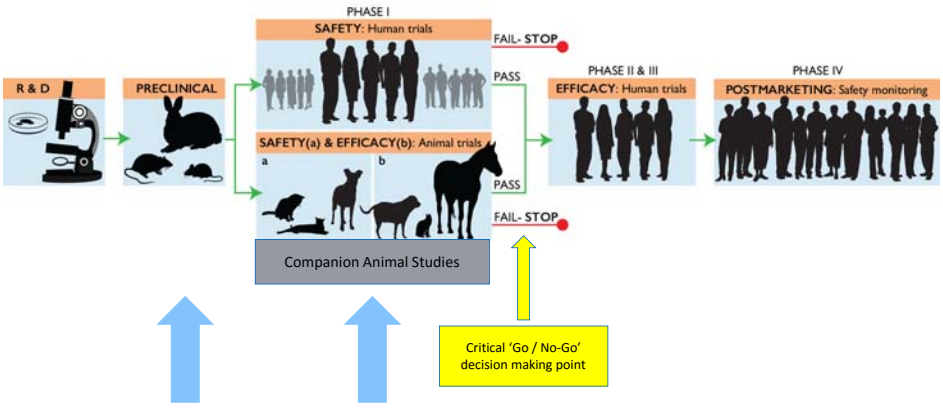
Opportunities. Companion Animal Models



Adapted from Kol 2015 Sci Trans Med

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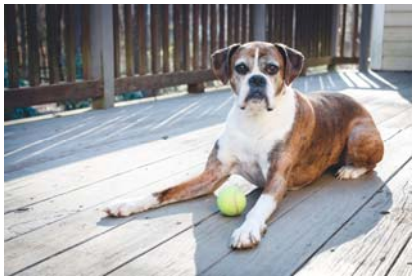
Opportunities. Companion Animal Models



PROOF OF CONCEPT TESTING OF THERAPEUTICS OR DEVICES IN PETS with diseases that accurately reflect the target disease in humans (*fidelity* or *face validity* with the target disease)

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Opportunities. Companion Animal Models

Cardiac disease

Hypertrophic cardiomypoathy (C); Dilated cardiomyopathy (D)

Musculoskeletal disease

Osteoarthritis (D,C,H); Tendon injuries (H); ACL tear (D)

Neurological disease

Acute spinal cord injury; chronic paralysis (D); Chiari malformation/neuropahtic pain (D); Eiplepsy (D)

Cancer

Osteosarcoma (D); Melanoma (D); Non-Hodgkin's lymphoma (D)

Others……..

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Opportunities. Companion Animal Models

Concerns:

Lack of validated outcome measures

Lack of access to subjects

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Opportunities. Companion Animal Models

Outcome Measures

e.g. osteoarthritis pain: Validated Measures of the Functional Impact of Pain

Activity

Somatosensory Function

Sleep quality

Limb use

Pain; Function

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Opportunities. Companion Animal Models

Access to subjects:

66% of owners are very willing to participate in **research studies and trials**

- Sampling; novel therapeutics
- Clinical trials on pets often performed

NC State CVM/CMI Clinical Studies Core:

Facilitates the use of client-owned pets for

- Sampling;
- Clinical trials of novel therapeutics or devices
- *All under informed owner consent and IACUC approval*

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https://tracs.unc.edu/docs/pilotprogram/NC_TraCS-NC_State_Collaborative_RFA.pdf

Oct 18th Deadline

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