Targeting T_{regs} in Tumors

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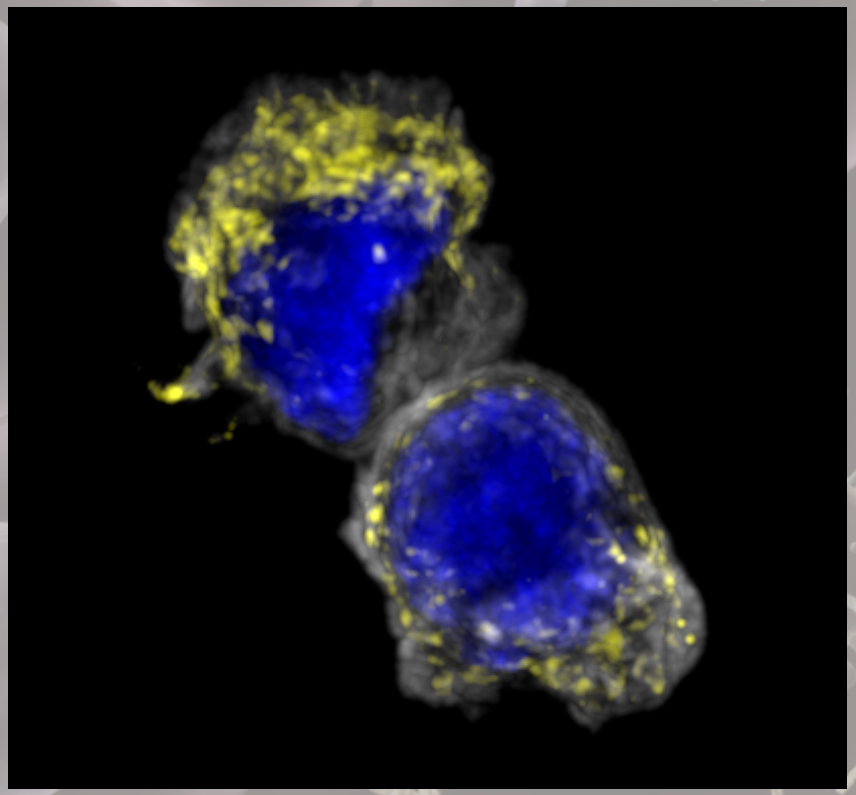
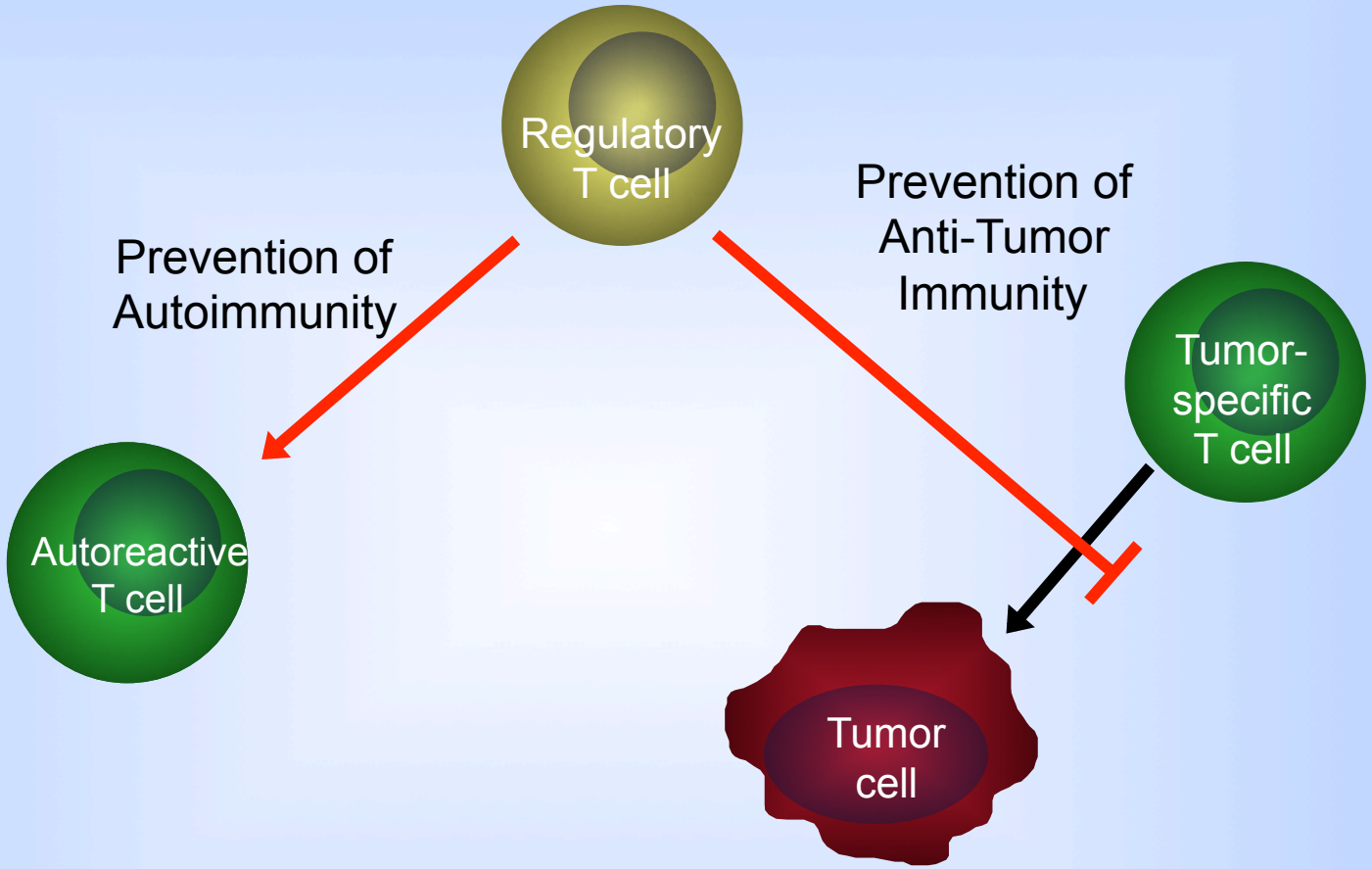


***Conflict Disclosure Statement*: D.A.A.V. has submitted patents on LAG-3, IL-35 and Nrp1/Sema4a that are granted or pending and is entitled to a share in net income generated from the licensing of these patent rights for commercial development.**

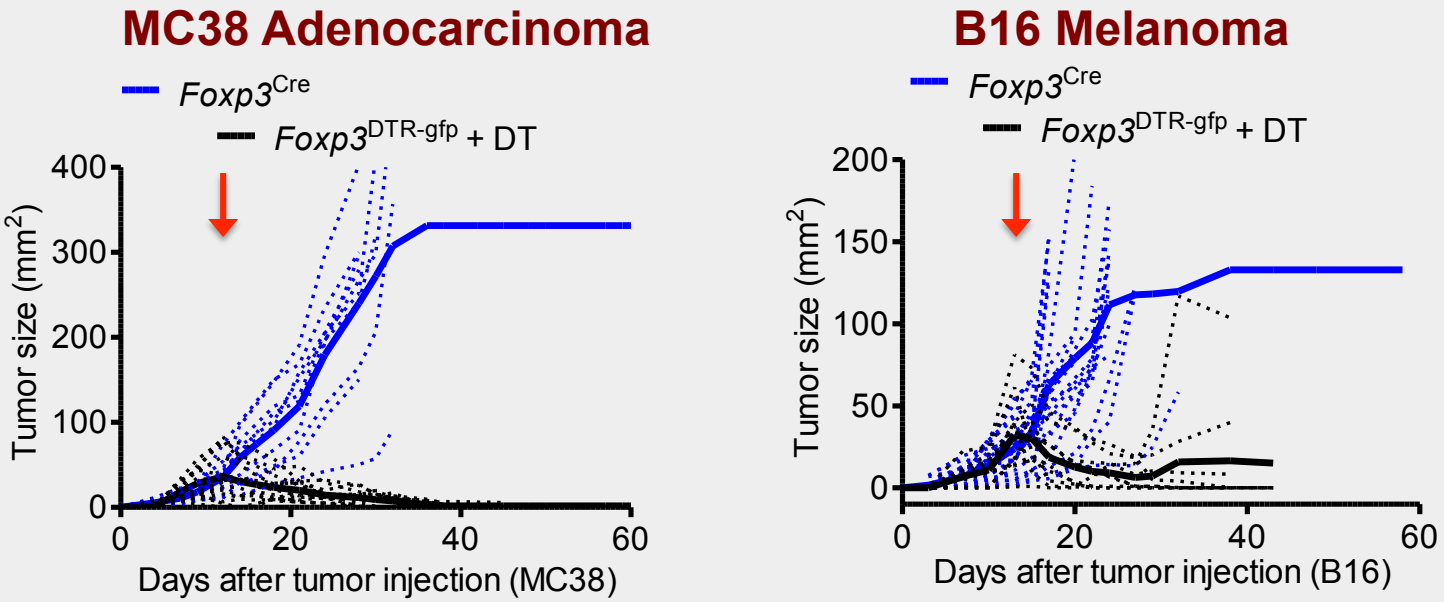
D.A.A.V. is a co-founding scientist and SAB member of Potenza Therapeutics Inc., serves on the SABs of F-Star and Tempero/GSK, and has consultation agreements with several companies.

Regulatory T cells - The Master Controller



Is it possible to limit the activity of T_{regs} in tumors without inducing autoimmune or inflammatory reactions?

What is the impact of T_{regs} on tumor growth?

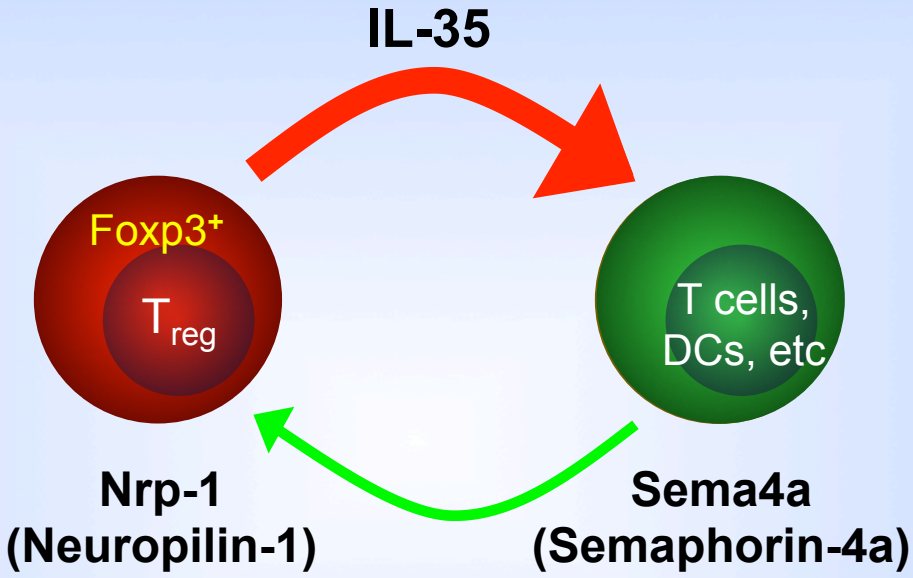


Is it possible to limit the activity of T_{regs} in tumors without inducing autoimmune or inflammatory reactions?

Nature 501:252 (2013)

Meghan Turnis, Greg Delgoffe

Potentiating T_{reg} function and survival



1. *What is the impact of IL-35 on the tumor microenvironment?*
2. *What are the consequences of Treg instability in the tumor microenvironment?*

Nature 450:566 (2007),
JI 182:6121 (2009), JI 187:4987 (2011),
Nature Immunology 11:1093 (2010),
Nature Immunology 13:290 (2012),
Nature 501:252 (2013).

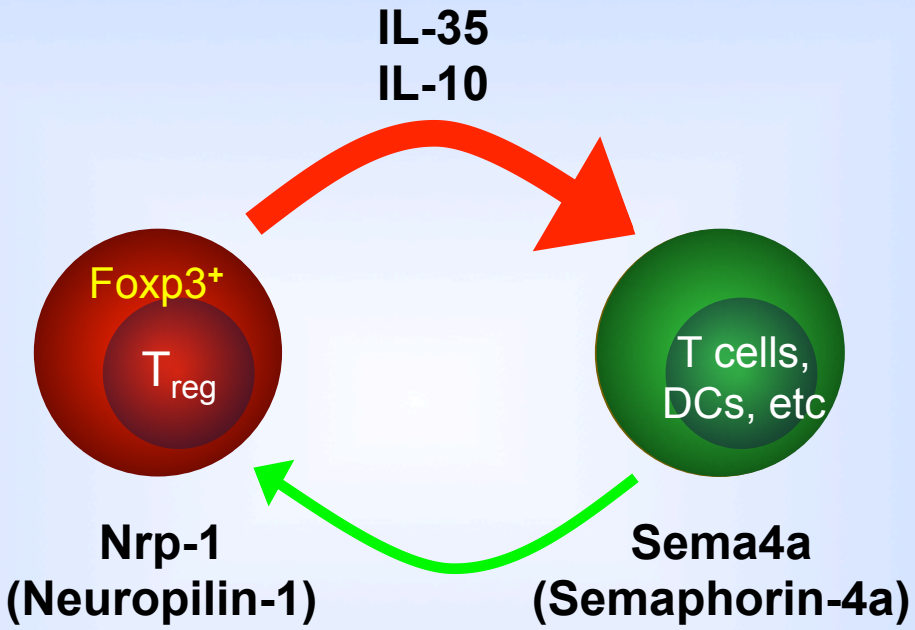
Lauren Collison, Greg Delgoffe,
Seng-Ryong Woo, Creg Workman

What are the consequences of T_{reg} instability in the tumor microenvironment?

Greg Delgoffe

Seng-Ryong Woo

Potentiating T_{reg} function and survival

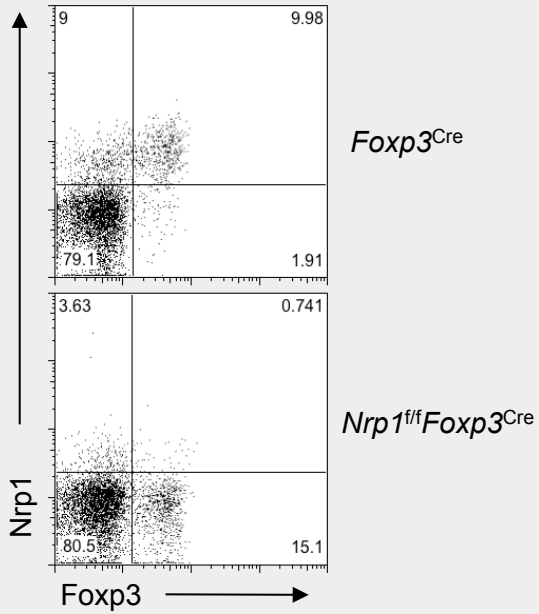


Nature 501:252 (2013).

Greg Delgoffe, Seng-Ryong Woo

Is Nrp1 required for T_{reg}-mediated immune homeostasis?

- Generated *Nrp1*$^{fl/fl}$.*Foxp3*^{Cre} mice
- *Nrp1*$^{fl/fl}$.*Foxp3*^{Cre} mice don't get sick (> 1 year).
- *Nrp1*$^{fl/fl}$.*Foxp3*^{Cre} mice have no inflammatory lesions (11 months).



The Nrp1 pathway is not required for normal immune homeostasis

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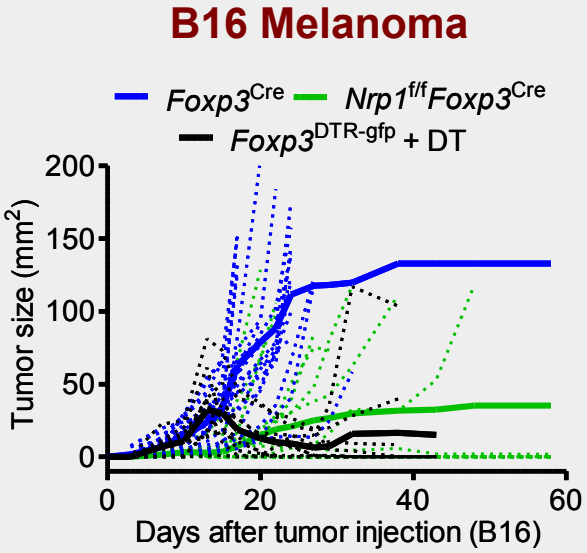
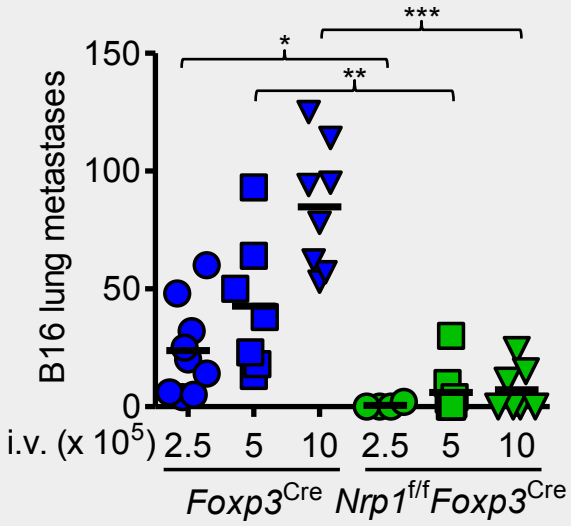
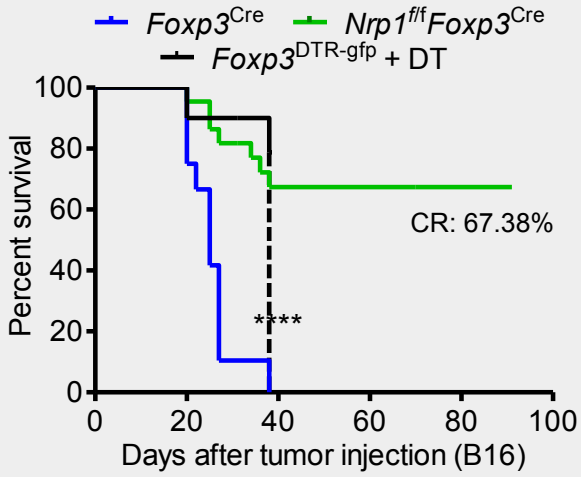
Greg Delgoffe, Matt Bettini, Amy McKenna

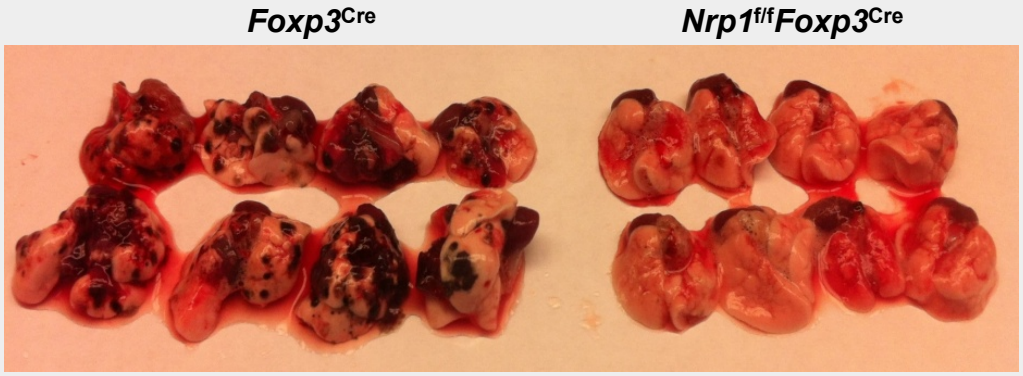
Nrp1-deficient T_{regs} cannot mediate tumor-induced tolerance





Nrp1 is required by T_{regs} to limit anti-tumor immunity

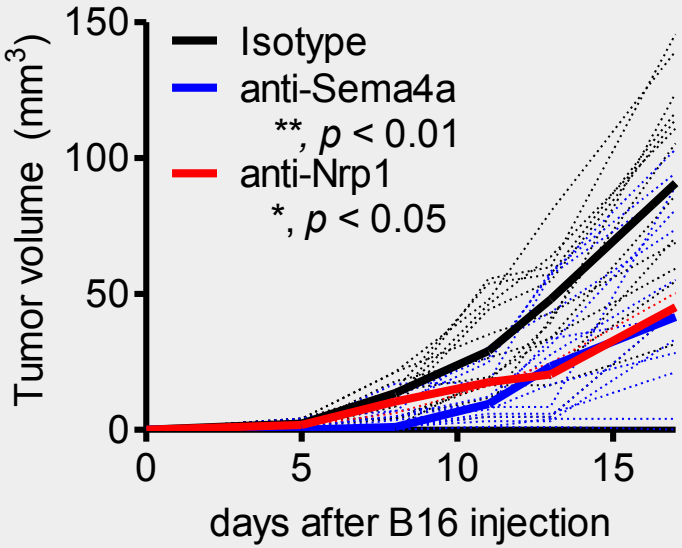


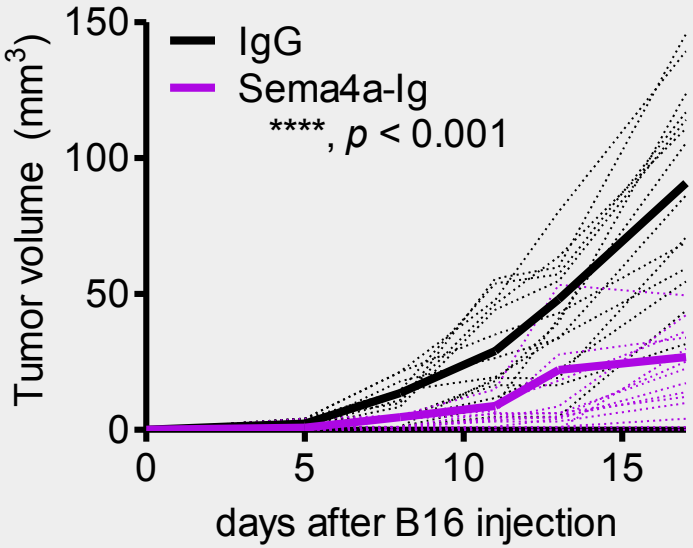


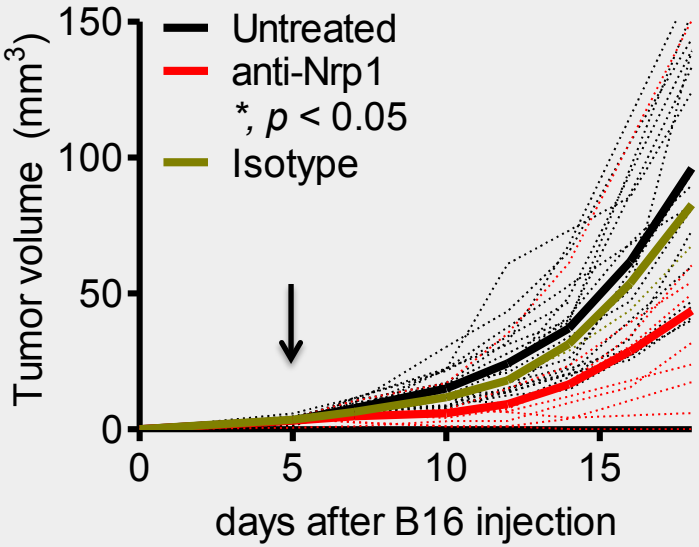
Nature 501:252 (2013)

Meghan Turnis, Greg Delgoffe

Does the Sema4a:Nrp1 axis mediate tumor-induced tolerance?

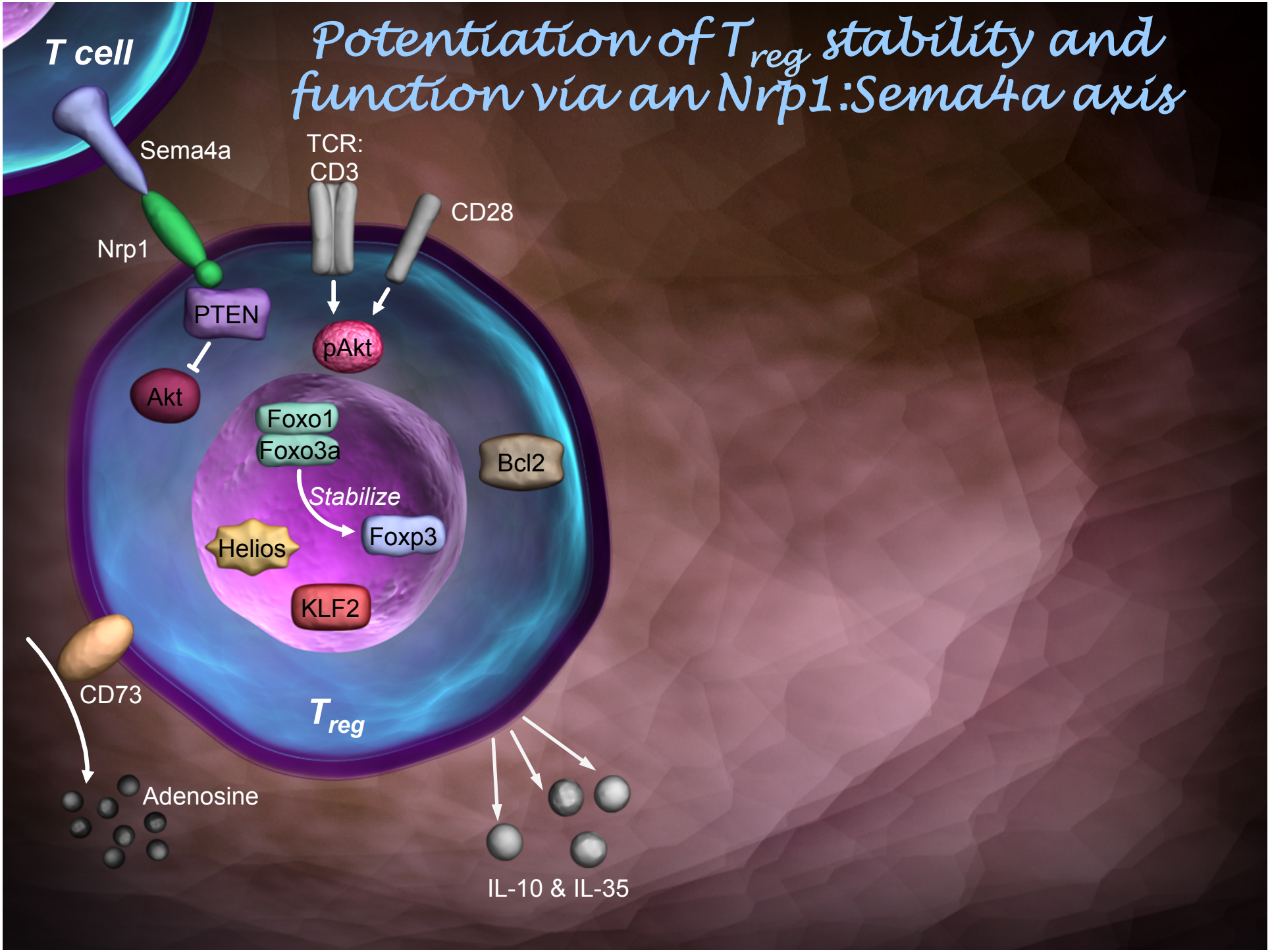




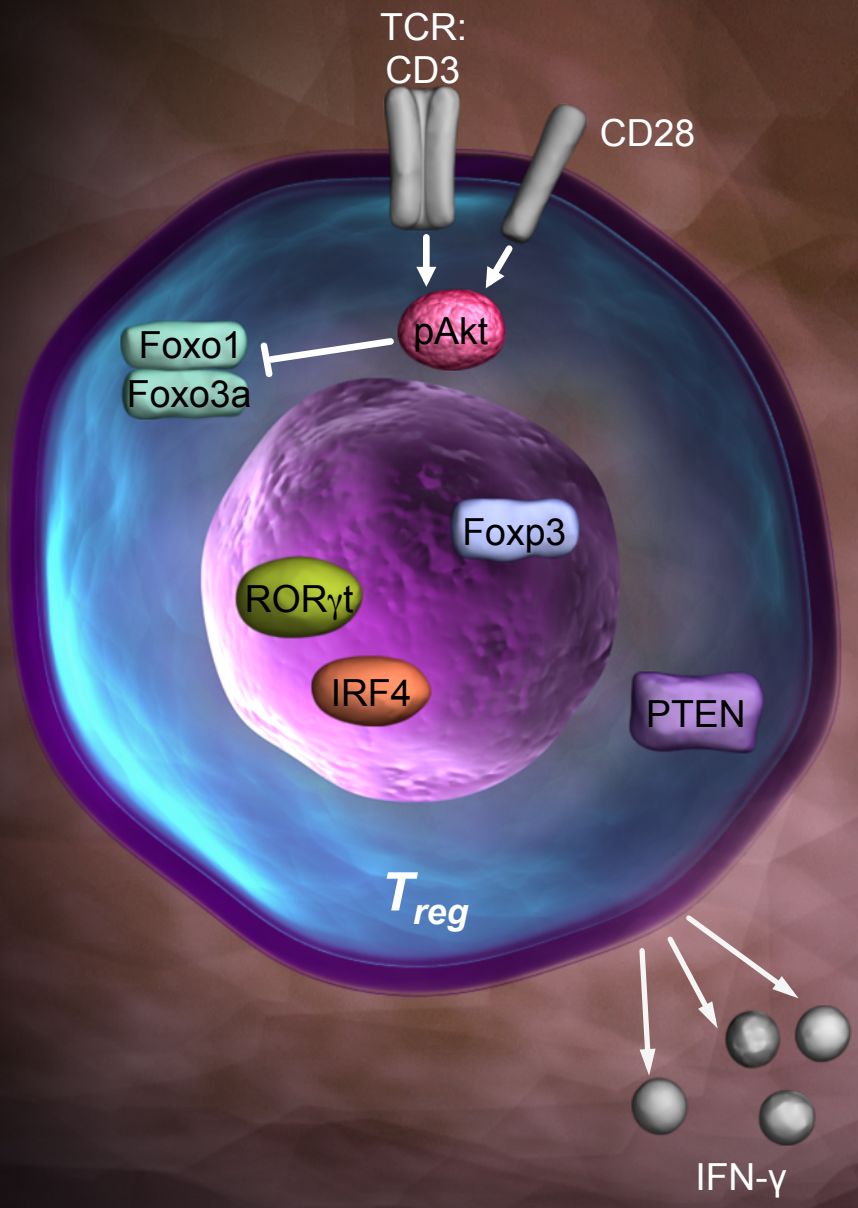


- **Prophylactic reduction in tumor growth with anti-Nrp1 and anti-Sema4a.**
- **Prophylactic reduction in tumor growth with Sema4a-Ig.**
- **Therapeutic reduction in tumor growth with anti-Nrp1.**

Meghan Turnis, Greg Delgoffe


Potentiation of T_{reg} stability and function via an Nrp1:Sema4a axis
T cell
Sema4a
Nrp1
TCR:
CD3
CD28
PTEN
pAkt
Akt
Foxo1
Foxo3a
Stabilize
Bcl2
Foxp3
Helios
KLF2
CD73
T_{reg}
Adenosine
IL-10 & IL-35

Potentiation of T_{reg} stability and function via an Nrp1:Sema4a axis



- Nrp1 ligation by Sema 4a enforces T_{reg} stability and function in inflammatory sites, but is dispensable for the maintenance of immune homeostasis.
- Nrp1 may be a viable therapeutic target to limit T_{reg} function.