# Discovery of a small molecule inhibitor of Burton's Tyrosine Kinase (BTK) for autoimmune diseases

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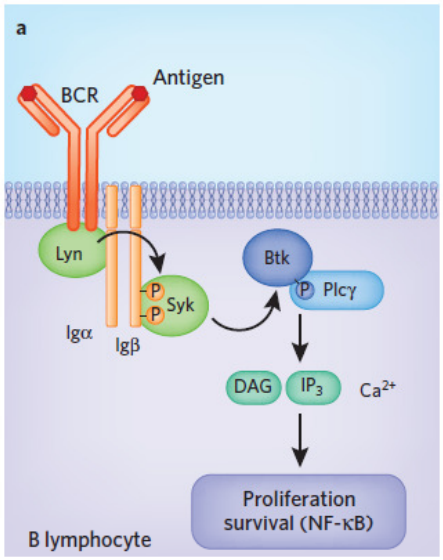
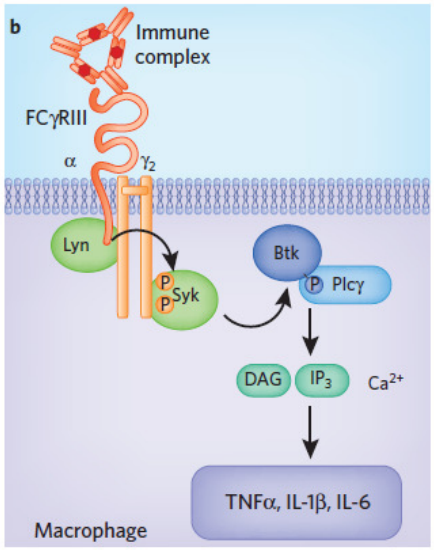
# Bruton's Tyrosine Kinase - Btk

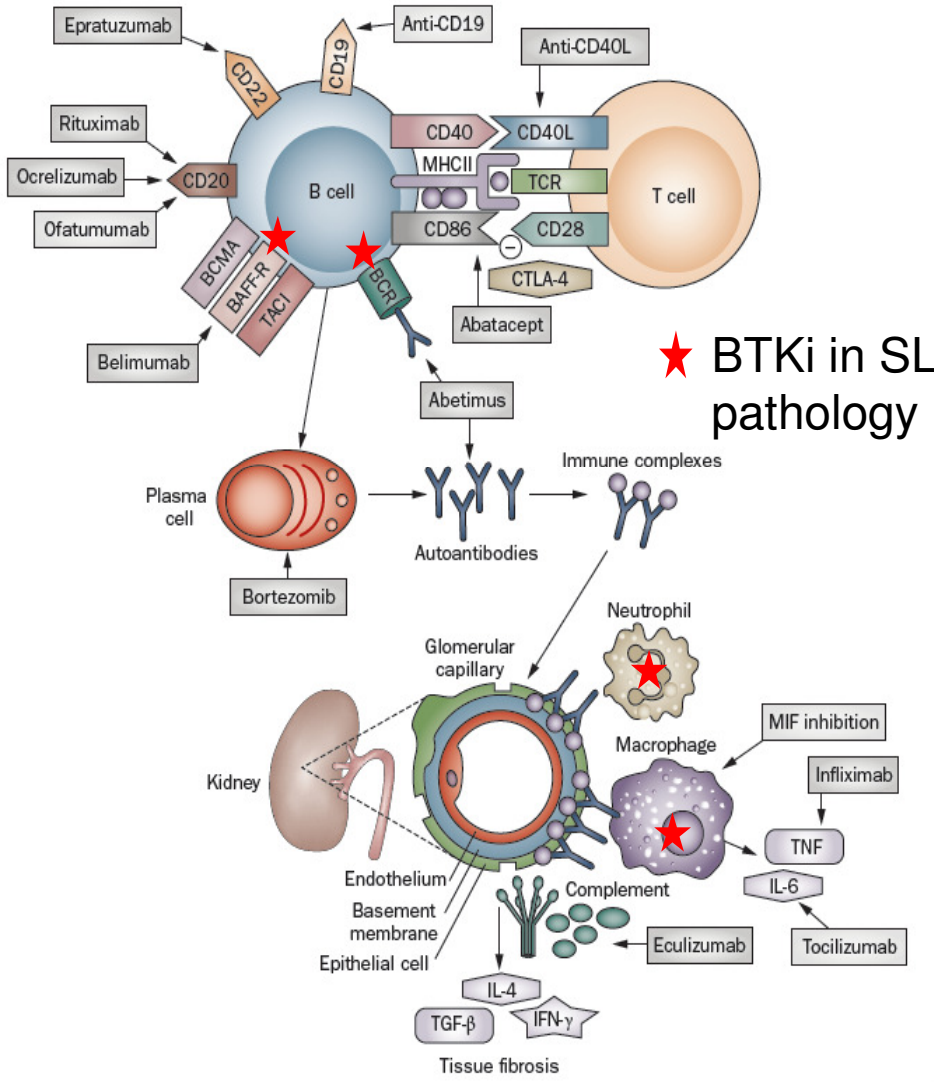



- Tec family kinase required for B-cell receptor signaling in B cells and FCγ receptor signaling in myeloid cells
- Btk is not expressed in T cells
- Aberrant signaling through Btk implicated in the pathogenesis of diffuse large B-cell lymphoma, mantle cell lymphoma and chronic B-cell leukemia
- Ibrutinib (PCI32765) recently approved for the treatment of mantle cell lymphoma

Hendrix, *Nat Chem Biol*. **2011**
Kuppers, *Nature Rev. Cancer,* **2005**, 5, 251-62

# Efficacy and Commercial Opportunity




**Efficacy:** BTKi >> Belimumab and other single axis biologics.

- BTKi has multiple nodes of intervention in SLE pathology
  - Immune-modulation
  - Prevent tissue damage
  - DMARD
  - Faster onset due to activity on multiple nodes
- Small molecules compartmentalize to organs unlike biologics
- Preclinical validation of BTKi for SLE published* – PCI32765

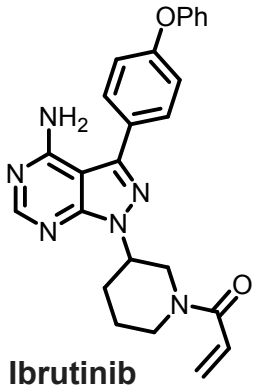
**Commercial Opportunity:**

- Once daily pill >> biologic

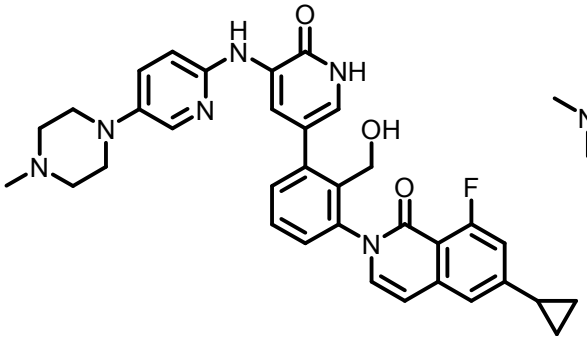
nature reviews rheumatology, volume 6, 2010 pg547

# Published Lead Series

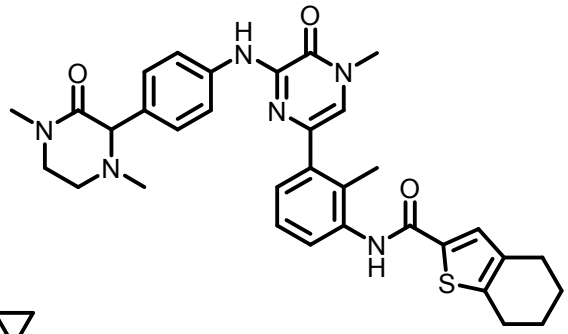
- Published Btk inhibitor series were either covalent or high molecular weight >500 Da and ligand efficiency ≤ 0.3




**Ibrutinib**
**Pharmacyclics**
**Irreversible**




**RN486 Roche**
**Mwt 592 Da**
**Btk Kd 0.3 nM**
**LE 0.30**




**GDC0834 Gilead**
**Mwt 596 Da**
**Btk $IC_{50}$ 6 nM**
**LE 0.27**

- **Our question**: Could a fragment based lead generation approach successfully deliver a reversible BTK inhibitor lead

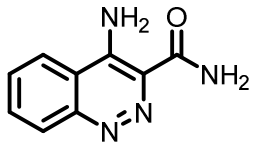


Takeda

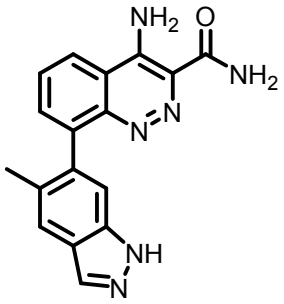
# Fragment and Crystal structure based discovery of BTK inhibitor

**Fragment Hit**

Btk $IC_{50}$ 3.5 µM
LE 0.53

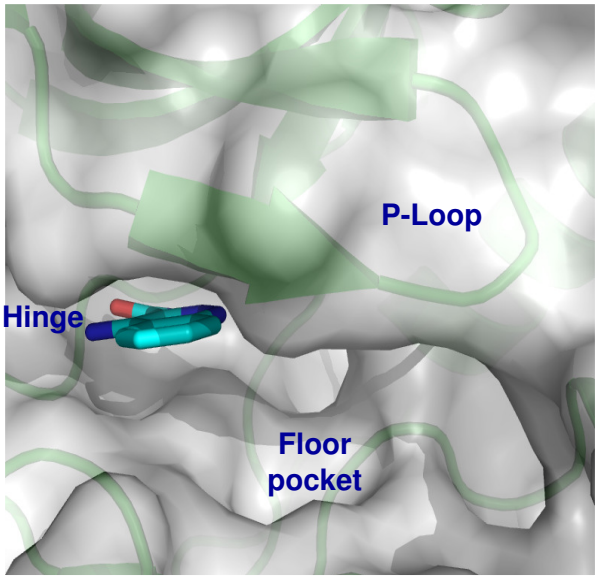


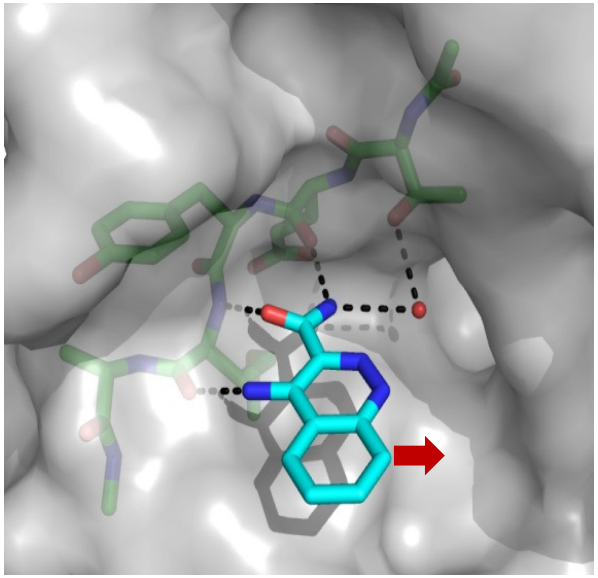

Compound 9

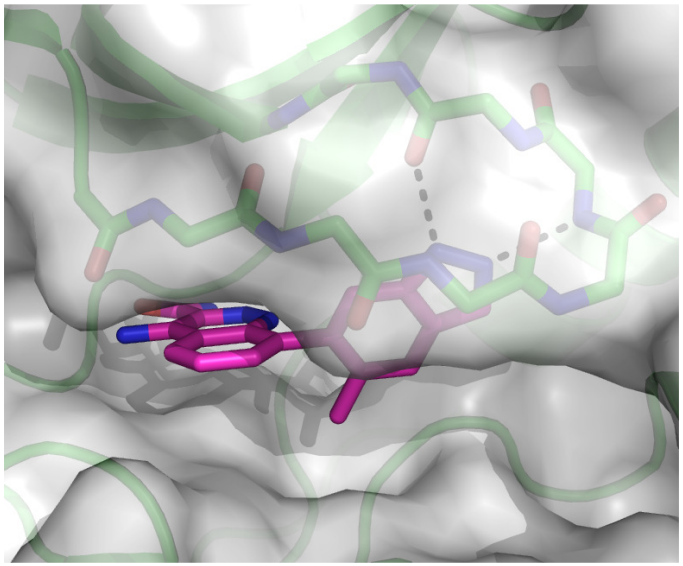



**Mwt 318 Da**
**LogD 1.8**
**tPSA 123 Å**
**pBtk $EC_{50}$ 28 nM**

**X-ray Co-crystal Structure – Btk kinase domain**





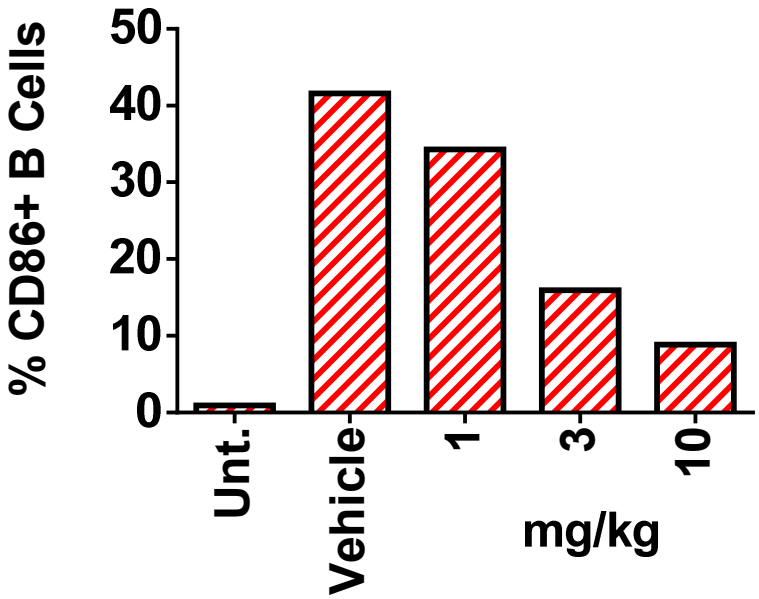
# BTK inhibitor: Pharmacology in vitro

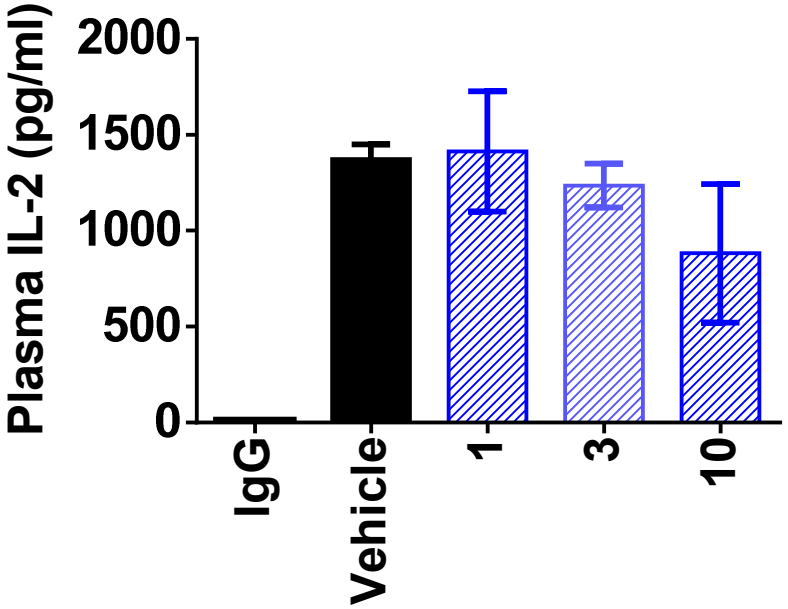
| Compound | pBTK | Rat WB B cells | FceR Mast cells | BAFF B cells | FcgR Macrophages |
|---|---|---|---|---|---|
| **Compound 9** | 42 | 157 | 320 | 733 | 80 |
| **PCI-32765 Ibrutinib** | 3.1 | 30 | 380 | 300 | 10 |

Activity in several pathology nodes

- BCR signaling
- FcεR signaling
- BAFF signaling
- FcγR signaling

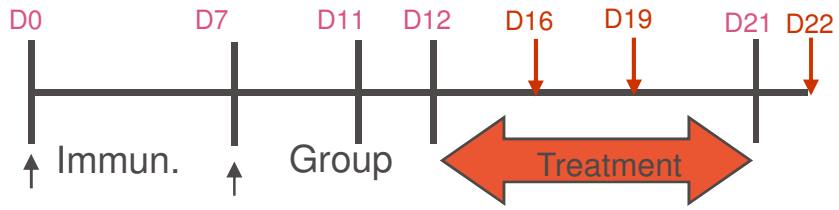
# Demonstrates selective activity to B cell and spares T cells

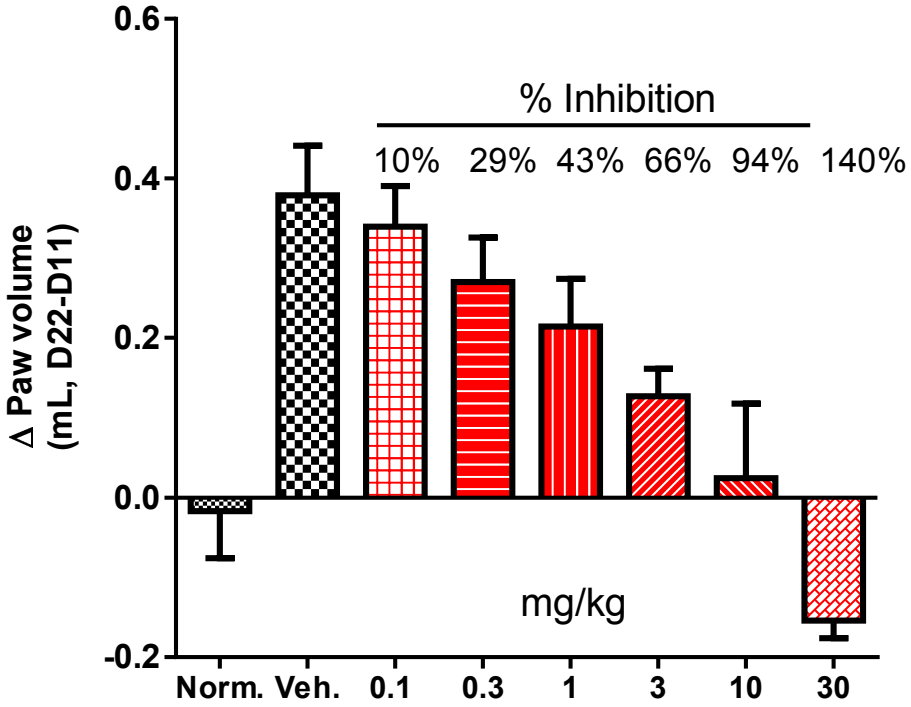


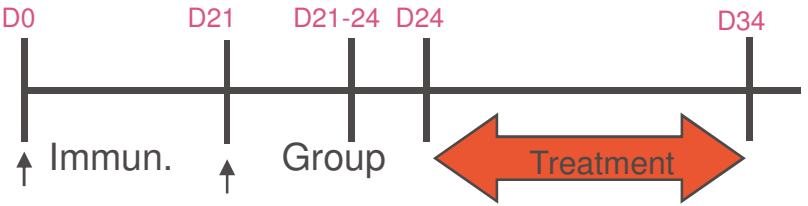
# Efficacy in CIA models

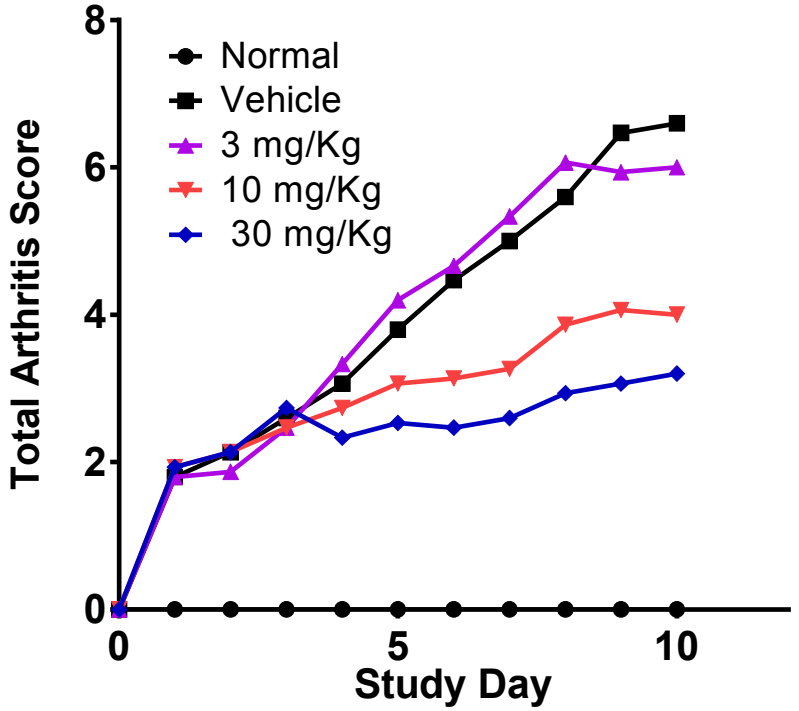
## Rat CIA



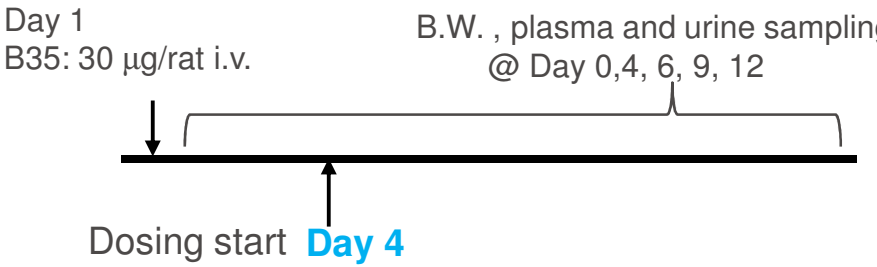



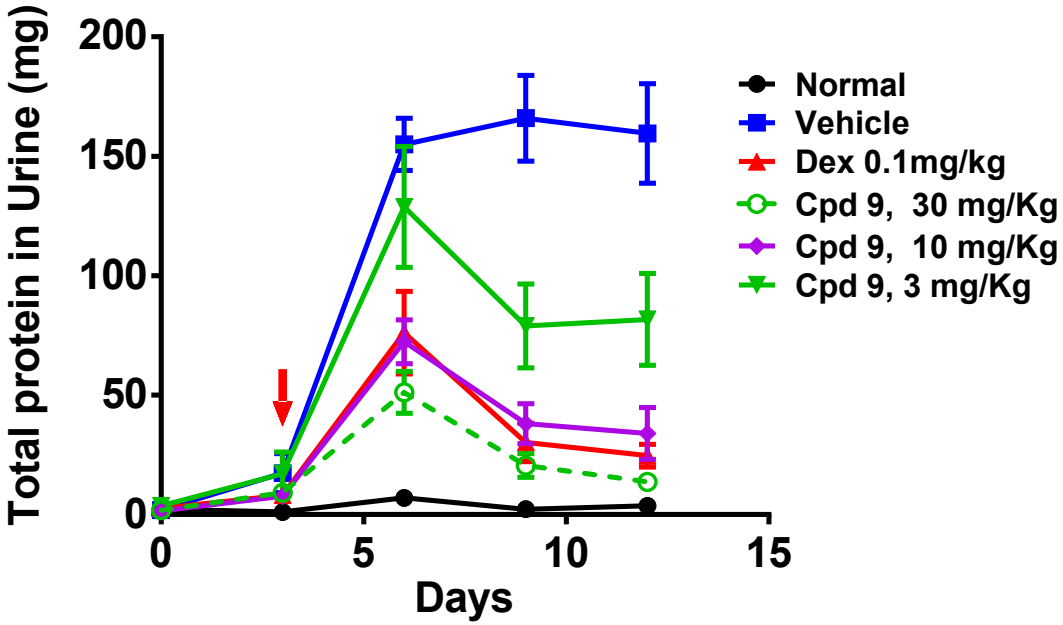

## Mouse CIA



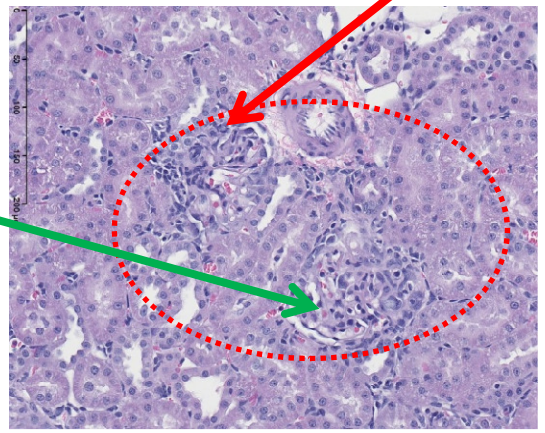
# Efficacy in anti-GBM nephritis model

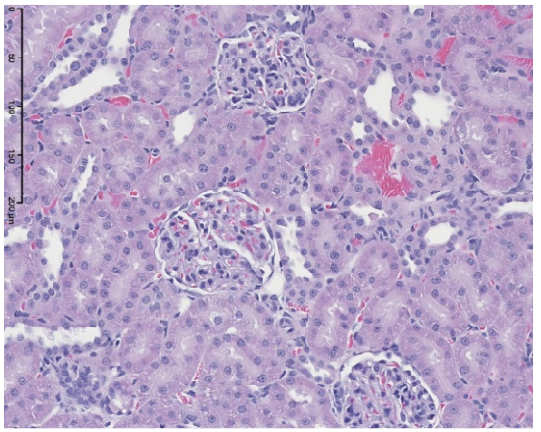



**Infiltration of inflammatory cells**

**Increased prominence of membrane cells (loss of Bowman's space)**





# Summary and Conclusions

- Compound 9 was identified as a potent and selective inhibitor of BTK
- Compound 9 prevented downstream events mediated by BCR and FcR in vitro. Further it also demonstrates the ability to block BAFF mediated B cell survival
- Compound 9 shows no appreciable activity in T cell inhibitory activity
- Compound 9 shows potent and dose dependent inhibition of clinical arthritis in CIA models
- Compound 9 shows unique activity in the IC mediated kidney damage model
- BTK inhibitors are promising approach to treat diseases like RA and nephritis mediated by IC

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